Optimising the management of asthma during pregnancy

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Errata and Addendum

Chapter 2, page 50 under the section "strengths and limitations of this review" Add para 1 – *Even though a thorough search was conducted, there may be still a chance that some studies were not identified in our search. Non-English studies would also have been missed.*

Chapter 2, page 50, add at the end of para 2 in the section "Discussion" – *The only large, well powered randomised controlled trial included in this review was conducted on budesonide. This was compared to placebo and provided more evidence for its safety than those studies comparing budesonide to other asthmatic drugs. In addition, the majority of the recent trials included in the review have been conducted on budesonide. Many trials have been conducted on beclomethasone as well but perhaps due to the decreasing popularity of this drug over the years, the drug has not been able to move up the ADEC rankings.*

Chapter 2, page 53, add at the start of para 2 in section "Strengths and limitations of the review" – *Every attempt was made to include all studies in our review despite study design, author or outcome. Publication bias was minimised by having two authors read all articles that were included and a panel review the data extracted. Only one researcher (AL) conducted the study selection which could raise the possibility of selection bias but could not be avoided due to time constraints. Authors were contacted to retrieve full texts of articles and English versions of non-English articles were requested to ensure more articles were included. Abstracts and unpublished articles were not included if we could not obtain full texts. This is a limitation and a review should be conducted every 4-5 years to provide health professionals with up to date evidence of the literature. This could lead to a change in ADEC rankings for some medications and improving adherence.*

Chapter 4, page 70, Add start of para 2 in section "Strengths and limitations" – *The authors recognize that the low response rate can also limit the generalisability of the results.*

Chapter 8, page 115, under 8.3 Future directions, add end of para 2 – *In the general asthma population, interventions to improve asthma control are significantly affected by attendance rates.[104] The advantage of conducting interventions in the antenatal setting is that the women have appointments at set times so follow up study appointments can occur at these times. Studies have shown that a model of care incorporating self-monitoring, regular medical review and a written action plan improved many patient outcomes including the number of hospitalisations, unscheduled visits to doctors, days off work or study, and bouts of nocturnal asthma.[105] Gerald et al.[106] has shown that supervised school based therapy participants (n=240) were 1.57 times less likely to experience an episode of poor asthma control. The parameters for assessing poor asthma control in most of these studies were identical to those used to assess poor asthma control in non-pregnant patients (i.e. absence from school/days off work due to asthma, use of rescue medication, and peak flow meter readings).[105] Generally, the average follow up time for an asthma intervention in a*

non-pregnant population is 12 months. During pregnancy follow up is generally limited to six months as it is difficult to recruit participants before the end of first trimester.

Interventions aiming to improve the management of other chronic diseases in pregnancy are few and far in between. The majority of studies use a surrogate outcome measure instead of a particular perinatal outcome. Recently, a study by Ortiz Collado et al.[107] tested a novel psychosomatic programme, consisting of ten antenatal sessions with their partner (n=184 couples), in depressed women who were at risk of postpartum depression to reduce depression symptoms and risk of associated prematurity. Their primary outcome was depressive symptoms on the Edinburgh Postnatal Depression Scale (EPDS). Results showed that postpartum depression risk was 11.2% lower in the intervention group and they were four times less likely to have a premature baby than the control group. This study only analysed 127 cases and could only speculate this change could lead to a decrease in risk of poor perinatal outcomes.

Another study by Secher et al.[108] showed no improvement in perinatal outcomes in their real time continuous glucose monitoring intervention in pregnant women with type 1 diabetes. The authors were disappointed as this intervention has been proven to be effective in non-pregnant participants, they stated this negative finding could be due to their cohort having lower baseline HbA_{1c} than those trials in the non-pregnant population.[108] This trial suggested that just because this intervention showed little benefit to those who were already managing their type 1 diabetes well; it should be tested again in pregnant participants who were not managing their type 1 diabetes as well. Similarly, this theory holds true in regards to asthma management interventions during pregnancy. If outcome parameters are same and similar interventions have been shown to be effective in the non-pregnant population, they should be just as effective in target groups in the pregnant population.

A recent qualitative study showed that pregnant women with chronic diseases are under more stress when their disease is altered by being pregnant, which can lead to poor perinatal outcomes and deterioration in management of their chronic disease.[109] These women may greatly benefit from interventions that help support their chronic diseases so they can also enjoy what they truly desire – "a normal pregnancy."[109] A randomised controlled trial evaluating an intervention to improve chronic disease management, with a large enough magnitude to show a difference in perinatal outcomes is yet to be reported. In summary, more interventional studies in pregnant women with larger sample sizes and with earlier recruitment and thus a longer follow up are warranted to help prevent poor perinatal outcomes and inform policy change. These interventions could replicate those which have been successful in the non-pregnant population, but accounting for baseline severity is needed when interpreting results.

104. Abdulwadud O, **Abramson** M, Forbes A, James A, Light L, Thien F, Walters EH: **Attendance at an asthma educational intervention: characteristics of participants and non-participants.** *Respir Med* 1997, **91**(9):524-529.

105. Gibson PG, Coughlan J, Wilson AJ, et al. **Self-management education and regular practitioner review for adults with asthma.** *Cochrane Database Syst Rev* 2009 (1): CD001117.

106. Gerald LB, McClure LA, Mangan JM, Harrington KF, Gibson L, Erwin S, Atchison J, Grad R. **Increasing adherence to inhaled steroid therapy among schoolchildren: randomized, controlled trial of school-based supervised asthma therapy.** *BMC Pregnancy Childbirth* 2014, **14**(1):22

107. Ortiz Collado MA, Saez M, Favrod J, Hatem M. **Antenatal psychosomatic programming to reduce postpartum depression risk and improve childbirth outcomes: a randomised controlled trial in Spain and France.** *J Obstet Gynecol Neonatal Nurs* 2014, **43**(1):25-37.

108. Secher AL, Ringholm L, Andersen HU, Damm P, Mathiesen ER. **The effect of real-time continuous glucose monitoring in pregnant women with diabetes: a randomised controlled trial.** *Diabetes Care* 2013, **36**(7):1877-1883.

109. Tyer-Viola LA, Lopez RP. **Pregnancy with chronic illness.** *J Obstet Gynecol Neonatal Nurs* 2014, **43**(1):25-37.

Chapter 8, page 111, under 8.1 Overall summary of research findings, add at the start of para 2 – *The majority of studies investigating the safety of asthma medications during pregnancy were not adequately powered, making it difficult to draw any conclusion because there are many factors such as other chronic illnesses, genetics, diet, injury, physiological changes that can contribute to poorly controlled perinatal outcomes. A large randomised controlled trial is needed to account for all these variables.*

Chapter 8, page 115 under 8.3 Future directions, add at the end of para 2 – *Randomising women earlier in pregnancy would be more desirable. This could be done by recruiting from general practitioner clinics, assisted fertility clinics, family planning clinics or posting advertisements in the media or pharmacies near the pregnancy testing section to try and capture women earlier in their pregnancy.*

The MOOSE checklist has now been completed and has been added as Appendix 31.

This thesis is dedicated to my mum and dad who have done everything humanly possible to provide the best life for me

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List of abbreviations

ACAAI	American College of Allergy, Asthma and Immunology
ACOG	American College of Obstetricians and Gynecologists
ACQ	Asthma Control Questionnaire
ADEC	Australian Drug Evaluation Committee
AFV	Asthma Foundation of Victoria
ANZCTR	Australian New Zealand Clinical Trials Registry
BBQ	Beliefs and Behaviour Questionnaire
BDA	Beclomethasone Dipropionate Aerosol
BTS	British Thoracic Society
CI	Confidence Interval
CMUS	Centre for Medicine Use and Safety
ED	Emergency Department
FDA	Food and Drug Administration
F_ENO	Fraction of exhaled Nitric Oxide
FEV	Forced Expiratory Volume
FEV_1	Forced Expiratory Volume in one second
FEV_6	Forced Expiratory Volume in six seconds
FVC	Forced Vital Capacity

GINA	Global Initiative for Asthma
GP	General Practitioner
HDR	Higher Degree by Research
ICS	Inhaled Corticosteroid
IQR	Interquartile Range
IUGR	Intra-Uterine Growth Restriction
L	Litres
LABA	Long-Acting $Beta_2$ Agonist
LBW	Low Birth Weight
LTRA	Leukotriene Receptor Antagonist
MAMMA©	Multidisciplinary Approach to Management of Maternal Asthma
MBW	Mean Birth Weight
mcg	Micrograms
MCG	Multidisciplinary Care Group
mg	Milligrams
MHW	Mercy Hospital for Women
MIGR	Monash Institute of Graduate Research
MMR	Medication Management Review
MUHREC	Monash University Human Research Ethics Committee
NAC	National Asthma Council of Australia

NHLBI	National Heart, Lung and Blood Institute
NPS	National Prescribing Service
OR	Odds Ratio
PBS	Pharmaceutical Benefits Scheme
PEFR	Peak Expiratory Flow Rate
RCT	Randomised Controlled Trial
RR	Relative Risk
RWH	Royal Women's Hospital
SABA	Short-Acting $Beta_2$ Agonists
SD	Standard Deviation
SGA	Small for Gestational Age
SPSS®	Statistical Package for Social Sciences
UCG	Usual Care Group
TABS	Tool for Adherence and Behaviour Screening
TGA	Therapeutic Goods and Administration
USA	United States of America

Definitions

APGAR score

APGAR (named after Dr Virginia Apgar) stands for Appearance, Pulse, Grimace, Activity and Respiration. This score is determined from a test performed at 1 and 5 minutes after birth. The 1-minute score is to see how well the baby tolerated the birthing process. The 5-minute score assesses how well the newborn is adapting to the new environment. The rating is based on a total score of 0 to 10, with 10 suggesting the healthiest infant.

General practitioners/ Family physicians/ Family practice physicians

Doctors who do not specialise in a particular area of medicine but who attend to everyday medical needs of individuals within a community and refer to specialists when the management is beyond their scope of expertise

Low birth weight

Neonate weighing less than 2500g (5.5 lbs) at birth

Premature

Neonate born before 37 weeks gestation

Shared-care general practitioners

Doctors who provide antenatal care to pregnant women in conjunction with the doctors/midwives at the hospital, and who are generally seen by pregnant women who find attending the regular antenatal appointments at their hospital inconvenient and would like their maternity care shared between their general practitioner and obstetrician/midwife

Singleton pregnancy

A singleton intrauterine pregnancy is a normal pregnancy with one baby / fetus, developing in the uterus

Acknowledgements

This PhD has showed me how lucky I am to have such a great support network inclusive of family, friends and colleagues who now I can call my friends. I take this time to say thank you to the main people who have contributed to my PhD journey; without them, this could not have been achieved.

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Statement of originality

In accordance with Monash University Doctorate Regulation 17 Doctor of Philosophy and Master of Philosophy regulations, the following declarations are made:

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

I declare no conflicts of interest.

Signature:  **Date:** 01 July 2013

Declaration for thesis based or partially based on conjointly published or unpublished work

General Declaration

In accordance with Monash University Doctorate Regulation 17 Doctor of Philosophy and Research Master's regulations the following declarations are made:

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes five original papers published in peer reviewed journals and one manuscript that has been submitted for publication. The core theme of the thesis is **"optimising asthma management during pregnancy."** The ideas, development and writing up of all the papers in the thesis were the principal responsibility of Angelina Lim, the candidate, working within the **Centre for Medicine Use and Safety, Monash University** under the supervision of Dr Johnson George, A/Prof Kay Stewart and Prof Michael Abramson.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of chapters two to seven my contribution to the work involved the following:

Thesis chapter	Publication title	Publication status	Nature and extent of candidate's contribution
2	A systematic review of the safety of regular preventive asthma medications during pregnancy	PUBLISHED	Conducted literature search, reviewed articles, extracted data, analysed data, facilitated review meetings and prepared first and final drafts of manuscript
3	Asthma drugs in pregnancy and lactation: practice points	PUBLISHED	Conducted literature review and prepared first and final drafts of manuscript
4	Management of asthma in pregnant women by general practitioners: A cross sectional survey	PUBLISHED	Designed and validated survey tool, conducted survey, entered and analysed data and prepared the first and final drafts of manuscript
5	Asthma during pregnancy: The experiences, concerns and views of pregnant women with asthma	PUBLISHED	Developed topic guide, conducted interviews, participated in data analysis and prepared first and final drafts of manuscript
6	Multidisciplinary approach to management of maternal asthma (MAMMA©): A randomised controlled trial THE PROTOCOL	PUBLISHED	Participated in study design, and prepared first and final drafts of manuscript
7	Multidisciplinary approach to management of maternal asthma (MAMMA©): A randomised controlled trial	SUBMITTED	Conducted trial, entered and analysed data and prepared first and final drafts of manuscript

I have clearly stated the contribution of others to my thesis as a whole, including study design, statistical assistance, data analysis, editorial advice, and any other original research work used or reported in my thesis. I acknowledge that copyright of all material contained in my thesis resides with the copyright holder of that material.

I have included published papers in their original format as they appear in the respective journals and manuscripts in preparation in the format in which they were submitted to the respective journals.

Signature:  **Date:** 1st July 2013

Journal publications and Conference presentations

Journal publications

1. **Lim A**, Konig K, Stewart K & George J. A systematic review of the safety of preventive asthma medications during pregnancy. Annals of Pharmacotherapy 2011, **45**:391-945

2. **Lim A,** Stewart K, Abramson M, George J. Management of Asthma in pregnant women by general practitioners. BMC Family Practice 2011, **12:** 121

3. **Lim A**, Stewart K, Abramson M, Ryan K, George J. Asthma during pregnancy: the views, experiences and concerns of pregnant women with asthma Journal of Asthma 2012, **49**:474-479

4. **Lim A**, Stewart K, Abramson M, Walker S, George J. Multidisciplinary Approach to Management of Maternal Asthma (MAMMA©): The Protocol. BMC Public Health 2012, **12**:1094

5. **Lim A**, Abramson M, Hussainy S. Asthma drugs in pregnancy and lactation. (Invited editorial) Australian Prescriber 2013, **36**:150-153

6. **Lim A**, Stewart K, Abramson M, Walker S, George J. Multidisciplinary Approach to Management of Maternal Asthma (MAMMA©) Thorax Submitted 28th August 2013

Presentations

1. **Lim A**, Stewart K, Abramson M, George J. Management of pregnant asthmatic women by Australian general practitioners. Poster presentation at the Primary Health Care Conference Australia, Brisbane. July 2011.

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3. **Lim A**, Stewart K, Abramson M, George J. Management of pregnant asthmatic women by Australian general practitioners. Poster presentation at the Pharmacy Australia Congress, Melbourne. October 2011.

4. **Lim A**, Stewart K, Abramson M, Ryan K, George J. Asthma during pregnancy; the views, experiences and concerns of pregnant women with asthma. Oral presentation at the Australasian Pharmaceutical Science Association Annual Conference, Adelaide. December 2011.

5. **Lim A**, Stewart K, Abramson M, Ryan K, George J. Asthma during pregnancy; the views, experiences and concerns of pregnant women with asthma. Oral presentation at the National Medicines Symposium, Sydney. May 2012.

6. **Lim A**, Stewart K, Abramson M, Ryan K, George J. Facilitators of and barriers to optimal asthma management during pregnancy. Poster presentation at the International Social Pharmacy Workshop, Phuket. July 2012. Abstracted in Journal of Research in Social and Administrative Pharmacy 2012, **8**:e6-e7.

7. **Lim A**, Stewart K, Abramson M, Ryan K, George J. Facilitators of and barriers to optimal asthma management during pregnancy. Poster presentation at the Monash University Faculty of Pharmacy Higher Degree by Research Symposium. Melbourne. September 2012.

8. **Lim A**, Stewart K, Abramson M, Ryan K, George J. Optimising asthma management during pregnancy. Oral presentation at the Monash University Faculty of Pharmacy Higher Degree by Research Symposium, Melbourne. September 2012.

9. **Lim A,** Stewart K, Abramson M, Walker S, Wolke L, George J. Managing pregnant women with asthma. Poster presentation at the American Society of Health System Pharmacists Clinical Meeting and Exhibition, Las Vegas. December 2012.

10. **Lim A**, Stewart K, Abramson M, Walker S, George J. A multidisciplinary approach to managing maternal asthma. Oral presentation at the National Asthma Conference, Canberra. March 2013. Abstracted in Respirology 2013**, 18 (Suppl 2)**:45

11. **Lim A**, Stewart K, Abramson M, Walker S, George J. A multidisciplinary approach to managing maternal asthma. Poster presentation at the Thoracic Society of Australia and New Zealand Annual Conference, Darwin. March 2013.

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Abstract

Background:

Uncontrolled asthma during pregnancy is associated with the maternal hazards of asthma exacerbation, and perinatal hazards including intrauterine growth restriction and preterm birth. Interventions directed at achieving better asthma control during pregnancy should be considered a high priority in order to optimise both maternal and perinatal outcomes. Poor adherence to asthma medication regimens during pregnancy and suboptimal prescribing in pregnant women have both been shown to jeopardise asthma control. These barriers need to be understood in order to inform the development of interventions for resolving these problems. The aim of this PhD was firstly to ascertain the safety of preventive asthma medications during pregnancy, then explore barriers to and facilitators of maternal asthma management and finally, to design and evaluate an informed intervention to optimise asthma management during pregnancy.

Methods:

A four phase project was conducted to contribute to optimising asthma management during pregnancy. Phase 1 was a systematic review of the safety of preventive asthma medications during pregnancy. Phase 2 involved investigating asthma management and prescribing trends during pregnancy through a postal survey of general practitioners (n=842) involved in shared maternity care at the three largest maternity hospitals in Victoria, Australia. Phase 3 explored the factors associated with adherence to asthma medications and experiences of pregnant asthmatic women through in-depth interviews (n=23). Finally, Phase 4 brought the results together in a randomised controlled trial testing a Multidisciplinary Approach to Management of Maternal Asthma (MAMMA©) in pregnant women with asthma (n=60). Both intervention and control (usual standard care) groups were followed prospectively and their asthma control was assessed at 3 and 6 months using the Asthma Control Questionnaire (ACQ) to evaluate the effectiveness of the intervention. Pregnant women

with asthma were recruited from antenatal clinics and/or databases from two maternity hospitals in Victoria, Australia (Mercy Hospital for Women, and The Royal Women's Hospital).

Key findings:

- **Phase 1 (Chapter 2):** current safety data have not been able to establish a direct association between asthma medication use during pregnancy and poor outcomes, whereas there is an abundance of literature supporting the risks of uncontrolled asthma. Women should not refrain from taking their asthma medications during pregnancy.

- **Phase 2 (Chapter 4) :** Over a quarter of general practitioner respondents may be advising patients to reduce or discontinue their asthma medications during pregnancy when it is unnecessary for them to do so (i.e. patient's asthma adequately controlled on current therapy), putting them at risk of uncontrolled asthma. Furthermore, lack of knowledge in regards to management of deteriorating asthma during pregnancy became evident, with over 12% of respondents being unsure about what to do.

- **Phase 3 (Chapter 5):** By interviewing participants, it became apparent that many pregnant women were unaware of the risks of poorly controlled asthma. Consequently, they were discontinuing their current asthma therapy and increasing the risks of poor asthma control during pregnancy and poor perinatal outcomes. Reasons behind their decisions revolved around lack of support and information about what to do, concerns about the safety of the medications, past experiences, and desire for an "all natural" pregnancy. Asthma monitoring was also found to be poor or nonexistent in pregnancy.

- **Phase 4 (Chapters 6 and 7):** MAMMA© involved many interventions by the trial pharmacist aimed at improving asthma control in the intervention participants. These included initiation of asthma action plans (n=7), restarting of preventers (n=5), initiation of preventers (n=5), increase in preventer doses (n=4) and referral to a respiratory specialist (n=1). The Asthma Control Questionnaire (ACQ) score in the intervention group (n = 29) decreased by a mean (SD) of 0.46 (1.05) at 3 months and 0.89 (0.98) at 6 months. The control group (n = 29) had a mean decrease of 0.15 (0.63) at 3 months and 0.18 (0.73) at 6 months. The difference between groups, adjusting for baseline, was -0.22 (95%CI: -0.54 to 0.10) at 3 months and -0.60 (-0.85 to -0.36) at 6 months. The difference at 6 months was statistically significant ($p<0.001$) and clinically significant (>0.5). No asthma-related oral corticosteroid use, hospital admissions, emergency visits or days off work were reported during the trial.

Conclusion:

These findings confirm the safety of preventive asthma medications, the importance of health professionals, such as pharmacists, monitoring asthma management during pregnancy, and the value of a multidisciplinary model of care involving education, regular monitoring and follow-up in routine antenatal care. This thesis has promoted more awareness of the risks of poorly controlled asthma in pregnancy and clarifies the need for future research in this area.

Keywords:

Antenatal care, Asthma, Asthma education, Attitudes, Inhaled corticosteroids, Intervention Lung function tests, Maternal asthma, Medication adherence, Multidisciplinary care, Perceptions, Pharmacist, Pregnancy, Qualitative, Randomised Controlled Trial, Systematic review

Chapter 1: Introduction

1.1 The epidemiology of asthma during pregnancy

Asthma is one of the most common chronic health conditions among pregnant women in Australia, complicating up to 12.3% of pregnancies.[1] Indeed, Australia has the highest overall prevalence of asthma in the general population, with one in every ten people having asthma.[2] The death rate due to asthma in Australia is high by international standards and the mortality rate in females is almost double that in males.[2] Indigenous Australians have poorer asthma outcomes than the rest of the Australian population.[2]

Internationally, asthma has been known to complicate 3.0% to 8.4% of pregnancies in Canada, New Zealand, Europe and the United States of America (USA).[3] Approximately 38.5% of pregnant women with asthma in the USA reported experiencing at least one asthma attack in the previous year.[4] Survey prevalence data are heavily dependent on self-reports of asthma diagnosis and have been shown to vary from country to country depending on ethnicity and availability of data. Therefore rates of asthma prevalence may be even greater than what is reported.

The prevalence of asthma and its severity have been associated with lower socioeconomic status and education.[3] Similarly, younger and unmarried women experience more asthma attacks or asthma-related emergency visits during pregnancy than older and married women.[3]

The prevalence of asthma is increasing in women of childbearing age.[4] With such a high prevalence of asthma worldwide and continually rising statistics, asthma management during pregnancy has become an important topic for health professionals involved in antenatal care.

1.2 Physiological and cellular changes in the respiratory system during pregnancy

During pregnancy, the enlarging uterus progressively elevates the diaphragm, thereby decreasing the height of the thoracic cavity.[5] This is compensated for by an increase in the anterioposterior and transverse diameters of the chest.[5] Accompanying these anatomic alterations are hormonal changes in progesterone, oestrogen and prostaglandins, among others. Studies examining the effect of pregnancy on pulmonary function have shown that the tidal volume increases, the functional residual capacity and expiratory reserve volume decrease but forced expiratory volume in one second (FEV_1) is essentially unchanged.[6-8] Thus spirometry and using comparisons with FEV_1 measurements in non-pregnant women is a suitable method of monitoring lung function in pregnancy.

During pregnancy there is physiological suppression of the immune system to protect the foetus from the mother when paternally originated antigens are expressed.[9] There is a high T-helper cell type 2 (Th2)/ T-helper cell type 1 (Th1) cytokine response in pregnancy and asthma is categorised as a Th2-predominant state.[10] High Th2/Th1 cell ratios were present in blood samples of healthy women without asthma during pregnancy and in non-pregnant women with asthma, but no further increases in this ratio were found in pregnant women with well-controlled asthma.[11] This suggests that pregnancy does not further augment an inflammatory response in already atopic individuals and that cellular responses may change, especially in a disease with variation in activity (i.e. poorly controlled asthma). Contrasting studies have found an increase in T cells in pregnant women with asthma compared to non-pregnant women with asthma of the same severity.[12] This may partly explain why asthma worsens, improves or remains stable in equal proportions of women during pregnancy.[14]

1.3 The effect of pregnancy on asthma control

It has long been suggested that one third of women experience a worsening of asthma during pregnancy, one third have no change, and one third have an improvement in their asthma symptoms during pregnancy.[13] However, Belanger *et al.*[14] disputed this theory and argued that asthma during pregnancy is of similar severity to the year before pregnancy

and that women who discontinue their medication during pregnancy can experience an increase in the severity of their asthma, even if they only have mild asthma. Indeed, worsening of asthma seems to be the more likely event in pregnancy. In an internet survey study by Beckmann *et al.,*[15] 13.9% of women from North America, Asia and Europe stated that their asthma became better during pregnancy, 34.9% said it remained the same and 41% said it became worse (10% missing data).

According to the classification of asthma by the National Asthma Council (adapted from The Global Initiative for Asthma guidelines 2004), there are four classes of asthma severity: intermittent, mild persistent, moderate persistent and severe persistent.[16] The study by Belanger *et al*.[14] found that, compared with women who had intermittent asthma pre-pregnancy, those who had mild persistent asthma were 50% more likely to experience severe asthma during pregnancy. Among women with moderate or severe asthma before pregnancy, the risk of exacerbations rose almost threefold during pregnancy.[14] Another prospective study conducted at the University Central Hospital of Helsinki, Finland showed that during pregnancy, 40% of patients were managed with the same anti-asthmatic medication as before pregnancy, 18% needed less and 42% needed more medication than before pregnancy.[13]

Specific periods during gestation when asthma could become worse has also been a subject of debate, although a general improvement is often seen in the last four weeks of pregnancy.[17] Explanations for the variability of maternal asthma between women have been speculated. The balance between free cortisol (which improves respiratory outcomes) and progesterone, aldosterone and deoxycorticosterone (which compete with cortisol for pulmonary glucocorticosteroid receptors) could vary between individuals, thus explaining the differences in asthma severity changes during pregnancy.[18] The rarity of asthma symptoms during labour and delivery could be related to a further rise in cortisol reported to occur at this time.[18] Certain types of respiratory infections may occur more commonly

in patients who are pregnant and the frequency of symptoms during pregnancy may be the same as before pregnancy.[3]

The course of asthma during pregnancy has also been shown to be similar in successive pregnancies.[18] Unfortunately, emergency visits for asthma still occur in those whose asthma improved during pregnancy.[18, 19] This indicates that, even though improvement from baseline is seen, overall control may not be achieved and careful monitoring is needed throughout pregnancy.

1.4 Acute asthma during pregnancy

Asthma crises or exacerbations during pregnancy can be life threatening for both the mother and child, as impaired oxygenation is a major concern.[20] A study from Columbia University, United States of America, found that during pregnancy, 6.7% of pregnant women needed emergency care for their asthma, of whom 1.6% required hospitalisation.[3] A prospective study in Finland found 9.3% of 504 pregnant asthmatic women who were followed up in a pulmonary clinic, required emergency treatment for asthma during pregnancy.[19] Another multicentre study conducted in the USA found that 12.6% of asthmatic pregnant women presented to emergency departments, with 1.5% requiring hospitalisation.[21] Severe attacks requiring hospitalisation may be seen during all stages of pregnancy, but they often occur at 21-24 weeks.[21]

Viral infections are one of the main inducers of asthma attacks during pregnancy as at other times.[21] In addition, discontinuation of inhaled corticosteroids (ICSs) can lead to hyper-reactivity of the airway towards respiratory tract irritants.[22]

An unusual case study from Japan reported a young woman who had been pregnant seven times before, but almost every time her asthma control had worsened, spontaneous abortion resulted, so she had only one child.[23] It is important for asthmatic pregnant women to know the consequences of poor asthma control.

1.5 Outcomes of poor asthma control during pregnancy

It has been well established that uncontrolled asthma during pregnancy puts women and their unborn children at risk. Maternal asthma can induce hypoxia combined with respiratory alkalosis that decreases the placental blood flow.[24] Lack of oxygen to the foetus and the long-term effect of hypoxemia could affect foetal growth and development.[25]

1.5.1 Perinatal adverse outcomes

It is difficult to separate the effect of asthma itself from the adverse effects of medications. Many studies that have evaluated the outcomes of pregnancy in women with and without asthma have suggested that maternal asthma may increase the risk of several adverse perinatal outcomes.[26-29] Poorly controlled asthma can lead to an increased risk of pre-term births, low birth weight (LBW) babies, caesarean sections, still births, intrauterine growth restriction (IUGR), congenital malformations (e.g. ventricular and atrial septal malformation, spina bifida), small for gestational age (SGA) babies, pre-eclampsia, chorioamnionitis, low APGAR scores and gestational diabetes.[27, 30-34] Foetal hypoxia, also a result of poorly controlled asthma during pregnancy, can lead to severe risks of neonatal respiratory difficulties, foetal brain ischemia and cerebral palsy.[35]

Congenital malformations

A large population-based cohort study revealed that maternal asthma was significantly associated with a 30% and a 34% increased risk of any and major congenital malformations, respectively.[36] Maternal asthma was significantly associated with an increased risk of any malformation (OR=1.30; 95%CI: 1.20-1.40) and malformations of three specific systems of the body: nervous system (excluding spina bifida: OR=1.83; 1.37-2.83); respiratory system (OR=1.75; 1.21-2.53); and digestive system (OR=1.48; 1.19-1.85).[36] Other studies have also demonstrated specific congenital malformations among women with asthma.[37-39]

Low birth weight, small for gestational age, premature delivery

LBW babies and premature delivery are major contributors to perinatal mortality and morbidity. Mothers with asthma during pregnancy are more likely to have SGA, LBW, or pre-term birth infants than non-asthmatic women.[40] A study investigating 13,007 asthmatic pregnancies found mothers with severe and moderate asthma during pregnancy have a higher risk of SGA babies than those with mild asthma (severe asthmatics OR 1.48 [95%CI: 1.15-1.91] vs moderate asthmatics OR 1.30 [95%CI: 1.10-1.55]).[41] Similarly, another study found maternal asthma to be associated with an increased risk of LBW (RR 1.46, 95%CI 1.22-1.75), SGA (RR 1.22, 95%CI 1.14-1.31) and preterm delivery (RR 1.41, 95%CI 1.22-1.61). The relative risks of pre-term delivery and pre-term labour were reduced to non-significant levels by active asthma management (RR 1.07, 95%CI 0.91-1.26 for preterm delivery; RR 0.96, 95% CI 0.73-1.26 for pre-term labour).[34]

Maternal asthma exacerbations have especially been shown to have a significant effect on LBW (RR 3.02, 95%CI 1.87-4.89) and preterm delivery (RR 1.54, 95%CI 1.15,1.35).[42] Inadequate control of asthma symptoms has been shown to lead to an 11% prevalence of pre-term delivery compared with 6% in all cases, increasing to over 16% when hospitalisation is required (independent of oral steroid use).[43]

Clifton *et al.* investigated impaired placental function and foetal growth in offspring of maternal asthmatic mothers and suggested that the effect of maternal asthma on foetal development might be sex specific with female foetuses at greater risk of developing metabolic diseases than males.[44] However, Murphy *et al.* found maternal asthma to contribute to lower birth weight in male babies than females.[45]

1.5.2 Pregnancy and delivery complications

As well as effects on the offspring, pregnancy and delivery complications have also been demonstrated among women with asthma. By screening a Canadian medical database Liu *et al.*[27] found several adverse outcomes associated with maternal asthma: pre-eclampsia, transient hypertension of pregnancy, pregnancy-associated hypertension, chorioamnionitis

and caesarean delivery. Using a medical records database in Tennessee, Enriquez *et al.,*[33] reported several complications that were more prominent in mothers with asthma than without: hypertensive disorders, ante-partum haemorrhage, membrane-related disorders, gestational diabetes and caesarean section. A more recent study using an even larger medical records database of 223,512 singleton deliveries encompassing nine districts in the USA, showed that maternal asthma increased the risk for nearly all outcomes studied in a general obstetric population: pre-eclampsia, gestational diabetes, placental abruption and previa, caesarean section delivery, hemorrhage and pulmonary embolism.[46]

Conversely, maternal asthma that is carefully managed has not been associated with an increased risk of complications.[13, 30] In a prospective observational study in Finland, 198 pregnancies in 181 pregnant women with asthma who were optimally treated for their asthma as well as being carefully monitored for the progress of pregnancy and condition of the foetus were matched with a control group of 198 pregnant women without asthma.[13] There were no differences between asthmatic and control subjects with regard to length of gestation, birth weight, incidence of perinatal deaths, APGAR scores, neonatal respiratory difficulties, hyperbilirubinaemia or malformations. This suggests that well-controlled asthma can avoid the poor neonatal outcomes in mothers with asthma. Similarly, a study in India that followed up 182 asthmatic pregnant women over a ten year period, found no significant differences in antenatal course, labour, delivery or perinatal outcomes in women with well-controlled asthma compared with a control group of 364 pregnant women without asthma.[47]

An acute asthma attack during pregnancy that is promptly treated is unlikely to have a serious effect on the pregnancy, delivery, or the health of a newborn infant.[19] Asthma exacerbations can generally be medically managed and continuation of pregnancy is possible. However, refractory cases may necessitate caesarean delivery, especially in life threatening cases of status asthmaticus.[48] Greater perceived control of asthma reduces

the risk of subsequent exacerbations, caesarean delivery without labour and pre-term birth, while increased anxiety increases the odds of subsequent exacerbations.[49]

1.5.3 Long term adverse outcomes

Asthma exacerbations during pregnancy pose not only short term risks but also long term risks for the newborn. In a study of 10,512 pregnancies in asthmatic women, children whose mothers had moderate to severe uncontrolled asthma during pregnancy had an increased risk of developing asthma compared with children of mothers with mild, controlled asthma (adjusted OR 1.27, 95% CI 1.06-1.52).[50] No increase in the incidence of developing asthma, however, was observed for children of mild uncontrolled and moderate to severe controlled mothers.[50] Maternal asthma during pregnancy has been associated with an increased risk of atopic dermatitis, but this was not dependent on asthma control or severity.[51]

Moreover, foetal growth restriction and premature birth have been associated with the child developing ischaemic heart disease, hypertension, and type 2 diabetes in adulthood.[52]

1.6 Optimal therapy and recommendations for asthma management during pregnancy

Treatment of asthmatic pregnant women requires special consideration to protect the foetus from hypoxic injury. In Australia, asthma management during pregnancy is similar to the stepwise management of asthma in adults (Figure 1).

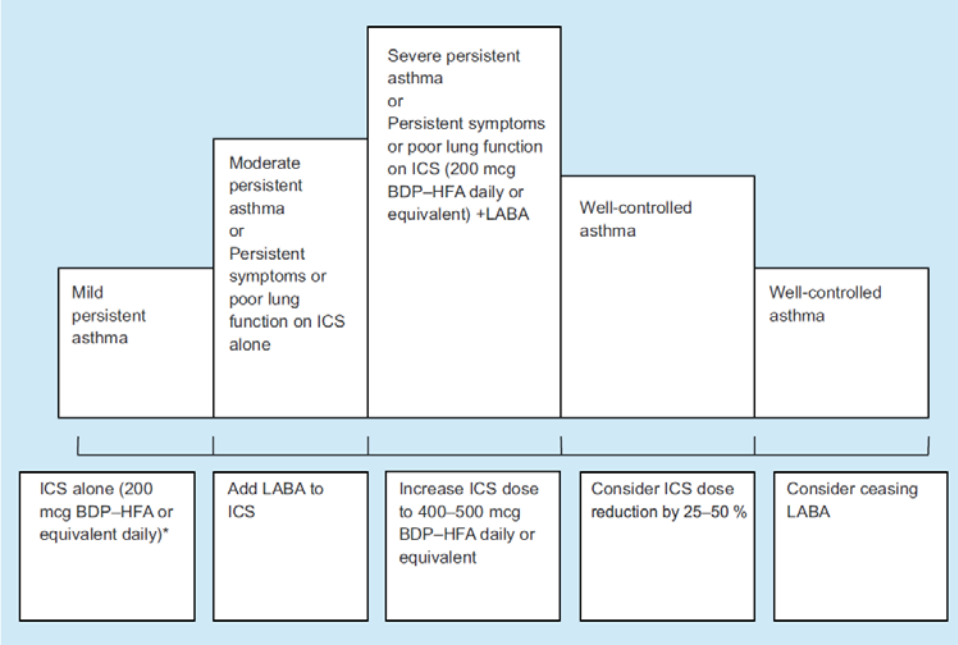

Figure 1. Management of mild, moderate and severe persistent asthma[53]

The National Asthma Council of Australia (NAC)[54] recommends that, for women who are planning a pregnancy and who are already using an inhaled corticosteroid (ICS), a change to budesonide should be considered as it is rated category A by the Australian Drug Evaluation Committee (ADEC) (Table 1).[55] Category A is the safest pregnancy risk category (Table 2).[56] Asthma exacerbations in pregnant women should be managed in the same way as an exacerbation in a nonpregnant patient and oral corticosteroids should be used if needed. Salmeterol and eformeterol should not be stopped if a pregnant woman is already using them, but if possible, they should be avoided during the first trimester as it is the most vulnerable trimester for the baby's development.[54]

Similarly, the majority of asthma guidelines around the world [54, 57-61] suggest continuing pregnant women on the asthma therapy they used prior to the pregnancy if their asthma is well controlled on that regimen (Table 1). ICSs are the first choice for mild to moderate persistent asthma according to all guidelines[54, 57-59, 61] except the American College of Obstetricians and Gynecologists (ACOG) and American College of Allergy, Asthma and Immunology (ACAAI) joint position statement.[60] ACOG recommend cromolyns as first line, although evidence surrounding cromolyn use during pregnancy is limited. Doses of ICSs should be the minimum necessary to control symptoms and maintain best lung function. Peak expiratory flow monitoring and regular review of asthma should be done every 4-6 weeks.[59] Spirometry is a safe and useful way of measuring pulmonary function in pregnant women and results may be compared with nonpregnant reference values.[62]

Table 1. Recommendations for pharmacological treatment of asthma during pregnancy [63-68]

Type of asthma	National Asthma Council of Australia (NAC)	National Heart, Lung and Blood Institute (NHLBI)	British Thoracic Society (BTS)	American College of Obstetricians and Gynaecologists (ACOG) and the American College of Allergy, Asthma and Immunology (ACAAI)	Global Initiative for Asthma (GINA)
Intermittent asthma	Keep women on existing asthma therapy if well controlled, however a change to budesonide is preferred. Salmeterol and eformoterol should not be discontinued if asthma is well controlled on this regimen but avoided if possible in first trimester.	Salbutamol when necessary	Continue women on existing asthma therapy. All asthmatic drugs should be used as normal during pregnancy; oral corticosteroids should not be withheld if needed. LABAs should be used with an inhaled corticosteroid ideally as a combination product. LTRAs may be continued as a last option in women who have demonstrated significant improvement with asthma control prior to pregnancy.	SABAs when necessary	Optimise therapy with asthma medications
Mild persistent		Daily low dose ICS is first line, preferably budesonide LTRAs are an alternative but not preferred treatment for pregnant women whose asthma was successfully controlled with this medication prior to their pregnancy Theophylline if careful titration of the dose and regular monitoring is maintained, aiming for a serum concentration range of 5-12mcg/ml		Inhaled cromolyn or nedocromil as first line therapy, substituting an ICS only if treatments with either of them are inadequate. Zafirlukast and montelukast should be only considered when pregnant women are resistant to other asthma treatment who have shown a uniquely favourable response before pregnancy.	
Moderate persistent		Either a combination of low dose ICS and a LABA or increasing the dose of inhaled corticosteroid to the medium dose range		ICSs are first line. Budesonide and beclomethasone being the preferred ICSs and budesonide even more favoured when patients require a high dose of ICS.	
Severe persistent		Check adherence and administration technique Increase ICS dose to the high dose range, again budesonide is preferred Systemic corticosteroids may be if management is still insufficient		Salmeterol therapy is recommended for consideration in pregnant women with moderate or severe asthma who have responded well to the agent before pregnancy or whose disease is not adequately controlled with a medium-dose ICS.	

ICS- Inhaled corticosteroid; LABA- long acting beta agonist; LTRA- Leukotriene receptor antagonist; SABA- short acting beta agonist

Finally, lifestyle changes should be considered and trigger factors should be avoided or minimised. Obesity has been shown to be associated with poor asthma control.[69] Pregnant women with asthma smoke more than women without asthma.[70] Pregnant patients who smoke should always be encouraged to receive advice and medical support for smoking cessation.[59] Pregnant women with asthma are more likely to have upper respiratory or urinary tract infections than pregnant women without asthma.[70] The close relationship between allergic rhinitis and asthma in nonpregnant patients has been well documented, supporting the need to aggressively manage rhinitis in pregnant women as a potential means for improving asthma control.[71]

Aggressive treatment of asthma during pregnancy, including the use of systemic corticosteroids if necessary, has been advocated to achieve asthma control and to avoid exacerbations. Acute interventions in the emergency department and other settings should be guided by pulmonary function tests, vital signs, chest and heart examinations and the patient's subjective assessment of dyspnea.[20] The goals of emergency treatment are to ensure adequate oxygen for the mother and foetus and the use of multidrug regimens is common. Supplemental oxygen, inhaled $beta_2$ agonists, systemic corticosteroids, and inhaled anticholinergic agents when indicated, are the mainstays of asthma treatment in the emergency department. [21]

Active management strategies which focus on identifying patient-specific risk factors, patient and provider education, and targeted treatment interventions can improve asthma care for women during pregnancy.[71]

1.7 Safety of asthma medications during pregnancy

It is difficult to conduct well-designed trials testing the safety of medications in pregnant women due to ethical and safety reasons. Hence many of the preventive asthma medications are categorised as B3, citing limited evidence regarding safety in pregnancy (Table 2).[56] Studies examining the safety of asthma medications during pregnancy are constantly being criticised for their small sample sizes, inadequate power to assess perinatal outcomes, neglecting confounders such as comorbidities and concomitant use of other

medications.[72] Another major flaw with these studies is that it is hard to distinguish whether the adverse outcomes are due to those medications or the severity of asthma itself.

Table 2. Australian Drug and Evaluation Committee categorisation of risk of asthma drugs in pregnancy[56]

Category	Definition	Asthma medication
A	Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed	budesonide terbutaline salbutamol prednisolone
B1	Drugs which have been taken by a limited number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage.	nedocromil montelukast sodium cromoglycate
B2	Drugs which have been taken by a limited number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed. Studies in animals are inadequate or may be lacking, but available evidence show no evidence of an increased occurrence of foetal damage.	
B3	Drugs which have been taken by a limited number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.	beclomethasone ciclesonide fluticasone eformoterol salmeterol
C	Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Specialised texts should be consulted for further details.	
D	Drugs which have caused are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Specialised texts should be consulted for further details.	
X	Drugs which have such a high risk of causing permanent damage to the foetus that they should not be used in pregnancy or when there is a possibility of pregnancy	

Short-acting beta$_2$ agonists (SABAs) have been shown to be safe to use during pregnancy.[73] Long-acting beta$_2$ agonists (LABAs) have been shown to increase the risks of cardiac and other congenital malformations in the foetus; however, this is confounded by asthma severity or chance alone and more research is required to confirm those associations.[73]

Low to moderate doses of ICSs have been found safe to use during the first trimester, but high doses of ICSs have been associated with a risk of congenital malformations. However, residual confounding by asthma severity is possible.[74] The risk of perinatal mortality was not found to be significant with ICS use during pregnancy.[75]

There are limited safety data on the use of cromolyns, leukotriene receptor antagonists (LTRAs) and anticholinergics during pregnancy; however, there is no evidence to indicate they are unsafe.[72, 76]

Since there is little information confirming the negative effects of asthma medications on the foetus and an abundance of information on the danger uncontrolled asthma poses to both the mother and offspring, pregnant women should be advised to adhere to asthma management guidelines and continue asthma medications as directed to reduce the risk to herself and the unborn child.

1.8 Asthma medication use during pregnancy

Adherence, according to the World Health Organisation (WHO) is "the extent to which a person's health behaviour (taking medication, following a diet, and/or executing lifestyle changes) corresponds with agreed recommendations from a health care provider" and emphasises the need for agreement between the patient and health care provider.[77]

In general, the adherence rate for asthma medicines in the general population is 57%, indicating under use of asthma medicines.[78] Australia was identified as one of the western countries with low adherence rates to asthma medications (48%).[79] The main

causes of nonadherence to asthma medications have been identified as inadequate knowledge about asthma and its treatment; inconvenience of using asthma medicines; fear of side effects after long term usage; and disbelief in the need to use asthma medicines.[78, 80-85] With the mean adherence rate in pulmonary conditions being already low; factors such as pregnancy could further reduce this.[78]

Patient adherence to chronic medications, such as asthma medications, during pregnancy has not been studied in depth. A pilot study carried out at the Royal Women's Hospital in Melbourne in early 2009 identified a few issues associated with the management of asthma during pregnancy, such as worsening of asthma symptoms, inadequate review of asthma management and underutilisation of asthma medicines.[86] A decline in the use of pharmacological treatment during pregnancy, despite worsening of day-time and night-time symptoms, was also observed in some patients. In addition, having asthma was found to be one of the predictors of self-reported nonadherence in pregnant women attending antenatal clinics of a large maternity hospital in Melbourne.

1.8.1 Adherence to asthma medications during pregnancy

Even though all clinical guidelines promote the use of asthma medications during pregnancy and safety data also advocate their use, there is still underutilisation of asthma medications during pregnancy. On average, 83.1% of women use at least one medicine at some stage in their pregnancy.[87] Prescription medicine use has been shown to decline in pregnancy,[88] suggesting women may perceive nonprescription medicines to be less harmful. Higher education, religion and geographic location are all factors associated with changes in use of medications during pregnancy.[89] Except for drugs used for chronic diseases, a general reluctance among Chinese women to use western medicine and resort to Chinese traditional medicine has been reported.[90] A six-month pilot study conducted at the antenatal clinics in the Royal Womens Hospital, Melbourne found that 59.1% of pregnant women who were taking at least one prescription medication during pregnancy, were not adherent.[91]

A decrease in the use of preventers, symptom controllers and combinations of asthma medicines, and an increase in the use of relievers during pregnancy have been observed.[92] This supports the hypothesis that women are not controlling their symptoms by optimal use of their regular asthma medicines, but relying on reliever therapy. An internet survey conducted in the USA found that only 17% of pregnant women were taking asthma medication on a preventive/maintenance schedule, while the vast majority took medications only as needed.[15] Among women who used any asthma medication, on average 3.4 reliever medications were dispensed for every symptom controller or preventer medication.[15] Similarly, another prescription database study in the Netherlands showed prescriptions for controller therapies were reduced by 30% during the first months of pregnancy compared with the months before pregnancy.[93] Of 647 pregnancies with at least three prescriptions of asthma medication during the year before pregnancy, 247 (38.2%) did not have a prescription for any asthma medication during the first trimester of pregnancy.[93] In a recent database study in the United Kingdom, low persistence to ICSs (defined as a gap of >60 days between prescriptions) was seen to be common in pregnancy even when 41.2% of 12,828 pregnant women were on ICS therapy.[94]

Data based on 4920 pregnancies from administrative claims databases in Québec, Canada, 50% of women either stopped or reduced their doses of ICSs during pregnancy, even though the doses were already quite low before pregnancy.[95] Murphy *et al*.[96] found that 40% of pregnant women (n=211) reported nonadherence to ICSs whilst recruiting women for an asthma management skills intervention study at antenatal clinics in New South Wales, Australian. On further assessment, 16% of women were found to have inadequate inhaler technique and 42% had inadequate asthma medication knowledge. Peak flow monitoring was performed by only 3% of the subjects and 15% had a written asthma action plan. Only about half of the women who took controller medications before pregnancy took them during pregnancy.[3] Only about half of the women who had daily symptoms during pregnancy took any controller medications in pregnancy.[3] Younger and less educated

women were less likely to take controller medications regularly during pregnancy than older and more well-educated women.[3]

Poorer outcomes have been associated with decreased use of preventive asthma medications. A USA database study (using a managed care patient centric database) found that patients previously receiving medication for asthma decreased their use of asthma medications and increased their asthma-related emergency department visits, whereas patients not being treated for their asthma before pregnancy demonstrated an even greater increase in asthma-related ED visits after confirmation of their pregnancy.[97] Olesen *et al.*[98] showed that after adjusting for smoking status, age, gender of child and cohabitation status, women who decreased their asthma medication during pregnancy, compared with the reference group who did not decrease their asthma medication during pregnancy, gave birth to babies with lower mean gestational age, birth weight and length at birth. Furthermore, women who decreased their ICS medication, had offspring with lower mean birth weight and length. A recent study showed an association between SABA dispensing and preterm birth and LBW, but not preventive medications. This supports the hypothesis that uncontrolled asthma, rather than medications, may be leading to these poor perinatal outcomes.[99]

Anxiety surrounding asthma medication use during pregnancy can affect asthma control.[100] Women overestimate the teratogenic risk of ICS use during pregnancy, which affects adherence to ICS and asthma control.[100] A survey of 501 asthmatic women of childbearing age reported that 82% of women who used ICSs were concerned about their effects on the foetus, as well as consequences of discontinuing medication on their own health. Despite this, 39% had discontinued medication while pregnant, without consulting their physician.[101]

1.8.2 Prescribing asthma medications during pregnancy

Not only do pregnant women struggle with limited information about the use of medications during pregnancy, but obstetricians may also struggle. Obstetricians'

knowledge about the risks and safety of medication use during pregnancy has been shown to vary. Obstetricians who have been in practice for an average of thirteen years or less were more likely to deem medications to be unsafe in pregnancy and were less likely to contemplate a risks versus benefits assessment than their older colleagues.[102] Many obstetricians indicated the greatest barriers to prescribing during pregnancy were lack of a single comprehensive source of information on management, lack of time and the fact that information is outdated rapidly. Older obstetricians were less likely to use online clinical resources than younger obstetricians.[102] The same study also found that obstetricians and physicians were very dependent on pregnancy safety categories.[102] This overdependence was criticised, as these categories ignore the need for individualising treatment based on risk-benefit analysis. Physicians' and obstetricians' heavy reliance on the Food and Drug Administration (FDA)/ADEC pregnancy risk categories, in combination with their reluctance to weigh risks versus benefits of medication use in pregnancy, may be contributing to under-treatment of asthma during pregnancy.

There is little information available regarding prescribing trends for asthma medications in pregnant women. Despite the overwhelming consensus that pregnant women with asthma need to be stringently managed and drug therapy should be stepped up when appropriate, doctors still under-prescribe. A study from Yale University School of Medicine found that 65% of pregnant asthmatic women were under-treated for asthma for three or more months of pregnancy. The figure included 40% of mild, 86% of moderate and 83% of severe asthma cases.[101] This is alarming as 40% of women said they would be more likely to continue taking their asthma medication during pregnancy if their obstetrician recommended it,[101] showing that prescribers have a vital role in patients' adherence.

In another study from the USA, pregnant women were significantly less likely than non-pregnant women to be given oral corticosteroids either in an emergency department or on discharge from hospital.[92] The pregnant women were also three times more likely than non-pregnant women to report an ongoing asthma exacerbation following discharge.[92]

Similarly, another survey study showed that in the emergency department, doctors were less likely to prescribe corticosteroids to pregnant women than to non-pregnant women both initially (44% vs 66%) and on discharge (38% vs 64%).[102] If inadequate prescribing is one of the main contributors to the decline in use of asthma preventive medications during pregnancy, prescriber education is crucial and more research is needed to investigate its role in optimising the management of pregnant women with asthma.

1.9 Interventions in pregnant women with asthma

Healthcare interventions targeted at pregnant women with asthma are few and far between. Murphy *et al*.[96] aimed to improve asthma outcomes during pregnancy using asthma education. Before this study, no published studies had reported the use of asthma education programs specifically for pregnant subjects and the efficacy of self-management education during pregnancy remained unknown. Murphy *et al.*[96] set out to improve asthma self-management skills and knowledge in a group of 211 pregnant subjects with mild, moderate and severe asthma attending antenatal clinics in New South Wales, Australia, using educational sessions. The sessions not only assessed medication use, inhaler technique and adherence, but also provided education about asthma control and management skills, including trigger avoidance, assistance with developing an asthma action plan, and smoking cessation. Also, unstable asthmatics were referred to their primary care physician or a respiratory physician and further educational sessions were offered, if required.

The intervention was well received, as there were significant reductions in nocturnal asthma symptoms as well as a substantial reduction in SABA usage from the first to last visit. The proportion of patients with severe asthma who were nonadherent to their ICSs fell from 40% to 21% after the education sessions. In addition, there was a drop from 16% to 4% in the number of mild asthmatics who had poor inhaler technique, an increase from 58% to 95% in asthma medication knowledge, an increase from 3% to 35% in peak flow monitoring and an increase in the number of women who possessed an asthma action plan (15% to 75%) after the education sessions. Subjects with moderate and severe asthma who had an

asthma management plan, had substantially higher birth weight female babies than those who did not have a plan. The authors concluded that pregnant subjects with asthma have poor self-management skills, regardless of asthma severity, and that asthma education may improve outcomes for both the mother and child. They proposed that severe asthmatics should be a target for self-management education in the future, as they are most at risk of adverse outcomes. The positive results from the study suggest that knowledge and skills may be greatly improved by a specific asthma education program. There was, however, no comparison group of pregnant asthmatics who did not receive asthma education, nor was the study powered to assess perinatal outcomes. The authors of this study recommended that asthma education should be integrated into routine antenatal care.[96]

More recently, a "Managing Asthma during Pregnancy (MAP) study" using an algorithm based on a fraction of exhaled nitric oxide (F_ENO), to reduce exacerbations by 50%.[103] Although the sample was not large enough to assess perinatal outcomes, rates of pre-term delivery and neonatal intensive care admissions were decreased in the intervention group.[103] F_ENO guided therapy was able to detect small changes in airway obstruction before exacerbations occurred. Basing pharmacotherapy on the F_ENO algorithm was able to reduce SABA use, increase the frequency of use of ICSs, but at a lower total daily dose, and introduce LABAs early into medication regimens, leading to better overall asthma control in the intervention group.[103] F_ENO is yet to be integrated into routine antenatal care due to costs and maintenance.

Adherence to asthma medications during pregnancy has not been studied in depth. More research is needed to identify the main factors associated with poor adherence to preventive asthma medications during pregnancy so they can be addressed. Prescribing during pregnancy also needs to be evaluated and issues need to be addressed. With that knowledge, a multi-faceted intervention targeting pregnant women and their health professionals needs to be developed and evaluated to addresses poor asthma knowledge, awareness and management during pregnancy.

Thesis aim and objectives

AIM:

To contribute to optimising the management of asthma during pregnancy

OBJECTIVES:

1. To systematically review the literature and ascertain the safety of preventive asthma medications during pregnancy to make recommendations about their use in future phases. **(Phase 1)**

2. To investigate the management of maternal asthma by shared care general practitioners with a view to developing strategies to address suboptimal care. **(Phase 2)**

3. To explore asthma experiences and medication use in pregnant women with asthma to inform the development of strategies to improve asthma management during pregnancy **(Phase 3)**

4. To develop, implement and evaluate an intervention for improving asthma medication use during pregnancy targeting both prescribers and patients **(Phase 4)**

Project overview

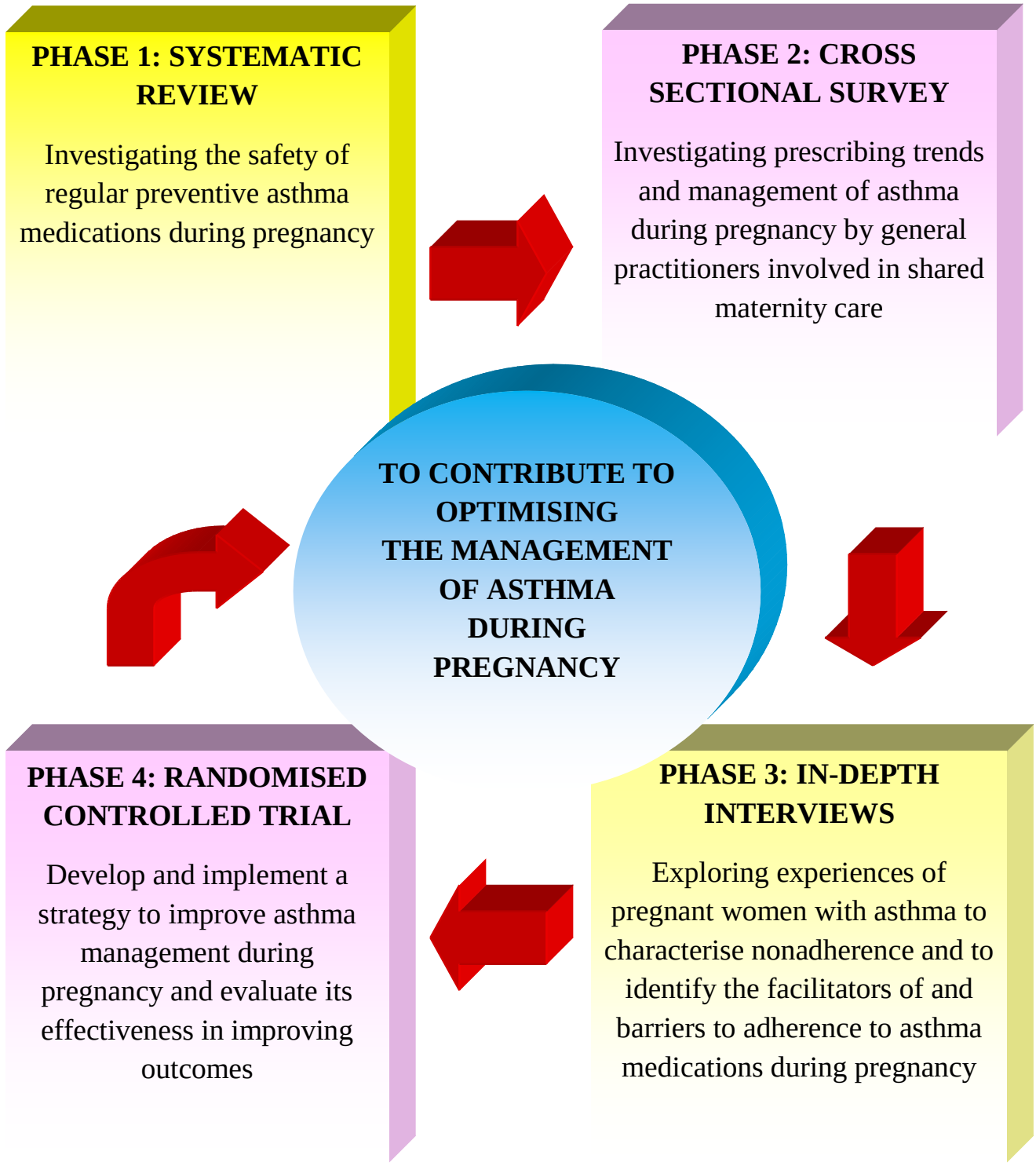

Figure 2. Project overview

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Chapter 2: A systematic review of the safety of regular preventive asthma medications during pregnancy

(Phase 1)

2.1 Preamble

Before exploring the use of asthma medications during pregnancy and making recommendations to patients about medication use, it was vital to ascertain their safety during pregnancy. This chapter summarises the research that has been conducted in pregnant women with asthma with a focus on the safety of preventive asthma medications during pregnancy.

Limited studies have been conducted in this area and evidence comes from small clinical trials with many confounders. Consequently, the best way to present an overview of currently available evidence was by undertaking a systematic review. Other previously published reviews are now outdated and/or have focused on specific medications or outcomes. Encompassing all relevant outcomes was necessary to help plan future phases of research for this thesis, but precluded a meta-analysis.

The aim of this phase was to ascertain the safety of preventive asthma medications during pregnancy to make recommendations about their use in future phases.

The specific objectives were to:

- undertake an up-to-date systematic review of the safety of preventive asthma medications during pregnancy; and
- provide a comprehensive compiled source of information for practitioners to refer to when managing pregnant women with asthma

What this manuscript adds to current knowledge

The manuscript has been published in **The Annals of Pharmacotherapy**. This manuscript has highlighted the limitations of the trials included in the systematic review and demonstrated that more information is needed regarding the safety of asthma medications during pregnancy. Currently, hard evidence on negative outcomes associated with preventive asthma medication use during pregnancy is lacking.

Recommendations from this review may improve prescriber adherence to asthma management guidelines when treating pregnant women with asthma, use of preventive asthma medications and in turn better asthma control. Potential readers of this manuscript include pharmacists, general practitioners and consumers. Readers of this article may recognise the importance of gathering more evidence on the safety of asthma medications during pregnancy, which could potentially lead to re-classification of preventive asthma medications to safer pregnancy risk categories by the Food and Drug Administration and/or Therapeutic Goods Administration. This might improve the use of these medications by both prescribers and pregnant women with asthma and improve asthma control during pregnancy.

2.2 Authors' declaration

MONASH University

Declaration by candidate for paper 1 titled:

A systematic review of the safety of regular preventive asthma medications during pregnancy

The undersigned hereby certify that:

1. The above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors;
2. They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
3. They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
4. There are no other authors of the publication according to these criteria;
5. Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
6. The original data are stored at the following location and will be held for at least five years from the date indicated below:

Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences,
Monash University
Victoria, Australia

Date: 1st July 2013

The nature and extent of candidate's contribution to the work was:

Nature of contribution	Extent of contribution
Conducted literature search, reviewed articles, extracted data, analysed data, facilitated review meetings and prepared first and final drafts of manuscript	80%

Candidate's signature: [redacted] **Date:** 1st July 2013

The contributions of co-authors to the work were:

Name of co-author	Nature of Contribution
Dr Johnson George	Reviewed articles, assisted with data extraction, data analysis and manuscript preparation
A/Prof Kay Stewart	Assisted with data analysis and manuscript preparation
Dr Kai König	Advised on study materials and assisted with manuscript preparation

Co-author's signature [redacted] **Date:** 1st July 2013

(Dr Johnson George)

Co-author's signature [redacted] **Date:** 1st July 2013

(A/Prof Kay Stewart)

Co-author's signature [redacted] **Date:** 1st July 2013

(Dr Kai König)

2.3 Manuscript

ARTICLES

Asthma

Systematic Review of the Safety of Regular Preventive Asthma Medications During Pregnancy

Angelina Lim, Kay Stewart, Kai König, and Johnson George

OBJECTIVE: To review the safety of regular preventive asthma medications during pregnancy.

DATA SOURCES: The following databases were searched from inception to February 2011: Ovid MEDLINE, PubMed, Cochrane Library, EMBASE and CINAHL Plus.

STUDY SELECTION AND DATA EXTRACTION: The search was limited to human studies published in the English language. Titles of all articles were screened for relevance. Abstracts of relevant articles were scrutinized to confirm relevance before obtaining full text.

DATA SYNTHESIS: Selected articles were read by 2 authors and the accuracy of the data extracted was confirmed.

RESULTS: Thirty-three articles were included in the final review. Small sample size, missing data, inadequate control for confounding factors, and poor documentation of dosage range were common limitations of the studies reviewed. The use of inhaled corticosteroids, cromolyns, and long-acting β_2 agonists during pregnancy was not associated with any particular adverse event, although the fluticasone/salmeterol combination has been associated with poor outcomes in postmarketing studies. Congenital malformations have been reported with leukotriene receptor antagonist exposure during pregnancy, but those women also had exposure to other medications, including oral corticosteroids.

CONCLUSIONS: Some negative outcomes of preventive asthma medications have been reported, although their direct link with medication use is inconclusive. Selection of preventive medications for asthma management during pregnancy should be based on an assessment of the risks and benefits of medication use versus the risks of poorly controlled asthma.

KEY WORDS: asthma, medication safety, neonatology, obstetrics, pregnancy.

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Asthma is a common condition reported during pregnancy internationally.[1] The following asthma management guidelines have highlighted the importance of optimizing the use of asthma medications during pregnancy: American College of Obstetricians and Gynecologists (ACOG) and American College of Allergy, Asthma and Immunology (ACAAI)[2]; British Thoracic Society (BTS)[3]; Global Initiative for Asthma (GINA)[4]; National Asthma Council of Australia (NAC)[5]; and National Heart, Lung and Blood Institute (NHLBI).[6,7]

Poorly controlled asthma can lead to an increased risk of preterm birth, low birth weight, cesarean section, intrauterine fetal death, intrauterine growth restriction, congenital malformations (eg, ventricular and atrial septal malformation, spina bifida), small for gestational age (SGA), preeclampsia, chorioamnionitis, low Apgar scores, and gestational diabetes.[8-12] Fetal hypoxia, also a result of poorly controlled asthma during pregnancy, can lead to severe risks of neonatal respiratory difficulties, fetal brain ischemia, and cerebral palsy.[13] Children exposed to uncontrolled maternal asthma during gestation have also been shown to develop asthma later in life.[14] Moreover, fetal growth restriction has been associated with the child developing ischemic heart disease, hypertension, and type 2 diabetes in adulthood.[15] Conversely, well-controlled maternal asthma has been shown to decrease the risks of congenital malformations and birth and delivery complications.[16] An acute asthma attack during pregnancy, if promptly treated, is unlikely to have a serious effect on pregnancy, delivery, or the health of a newborn infant.[17]

Upon realizing they are pregnant, some women may choose to discontinue or decrease their asthma therapy for fear of harm associated with their asthma medications.

Author information provided at end of text.

Chambers[18] found that 39% (n = 501) of women discontinued or reduced their asthma medications during pregnancy. In one study, nearly two thirds of pregnant women with asthma were found to be undertreated for 3 or more months of pregnancy.[18] These subtherapeutic regimens could be explained by prescribers heavily relying on the Food and Drug Administration (FDA) pregnancy categories[19] when prescribing asthma medications during pregnancy.[20] The possibility of fetal harm appears to be remote with the FDA-designated category A, as controlled studies have failed to demonstrate a risk to the fetus in the first trimester (and there is no evidence of risk in later trimesters). Risk of the use of category B and C drugs is debatable, as there are limited controlled studies confirming their safety in pregnancy, although category C drugs have shown adverse fetal outcomes in animal studies. Because of evidence of negative fetal outcomes, category D and category X drugs are not recommended in pregnancy. Heavy reliance on these FDA pregnancy risk categories may cause a prescriber's reluctance to weigh risks versus benefits of drugs for asthma treatment.[20]

Previous reviews on this topic are outdated or have focused on specific outcomes.[21-24] Our objective was to conduct an updated systematic review of the safety of regular preventive asthma medications during pregnancy to guide optimal management of asthma during pregnancy.

Data Sources

The following databases were searched from inception to February 2011: Ovid MEDLINE, PubMed, Cochrane Library, EMBASE and CINAHL Plus. The search terms used were pregnan* and asthma*. Further searches were conducted in PubMed and Ovid MEDLINE using the key words pregnan* and foet*/fet* and each of eformoterol, formoterol, salmeterol, budesonide, ciclesonide, beclomethasone, fluticasone, triamcinolone, nedocromil, cromolyn, chromone, montelukast, zafirlukast, leukotriene antagonist, corticosteroid, LTRA, LABA, and ICS. A MeSH search was also conducted in PubMed, using pregnancy and asthma as the key words.

Study Selection and Data Extraction

The searches were limited to human studies published in the English language. Methylxanthines, oral corticosteroids, short-acting β_2 agonists (SABAs), and anticholinergics were not included, as these are not recommended for regular preventive use by asthma guidelines.[2-7]

The steps in the study selection process are summarized in Figure 1 and were performed by 1 author (AL). Data from studies identified in the search were extracted and tabulated separately by one author (AL) according to drug class. Similarities and differences in results were identified and methodologic strengths and limitations of studies were considered. All the articles identified in step 4 were read by a second author (JG), who independently extracted data. Any discrepancies were discussed and consensus was reached.

Data Synthesis

Thirty-three articles were included in the final review; some studies included more than 1 drug class. There were 30 inhaled corticosteroid (ICS) entries,[8,17,25-46] 2 combination therapy entries,[46,47] 7 long-acting β_2 agonist (LABA) entries,[37,39,45,48-51] 5 leukotriene receptor antagonist (LTRA) entries,[37,52-55] and 5 cromolyn entries.[29,37,39,45,50] Study designs included cohort studies (n = 28), randomized controlled trials (n = 2), case-control studies (n = 2), and case series (n = 1).

Inhaled Corticosteroids

Many ICS studies were retrieved (Table 1).

The rates of pregnancy-induced hypertension (17%) and cesarean delivery (30%) were higher in pregnant women hospitalized with asthma exacerbations (n = 72) compared with the general obstetric population (13% and 17%, respectively).[28] Posthospitalization, a 55% reduction in asthma exacerbations and subsequent hospital admissions was observed in women who used inhaled beclomethasone (n = 34) compared to those who did not (n = 31).[28] Furthermore, Wendel et al.[28] have shown very low incidences of perinatal adverse events regardless of beclomethasone use. Dombrowski et al.[30] compared inhaled beclomethasone with oral theophylline and found similar rates of asthma exacerbations and outcomes in the 2 groups; however, doses of beclomethasone were higher than the average dose range used by the general population (100-400 µg/daily). The randomized controlled trial by Silverman et al.[33] showed similar incidences of adverse events in the budesonide group (400 µg/daily) and the placebo group; healthy children were delivered in 81% of all budesonide-exposed pregnancies (n = 196) and 77% for placebo (n = 117). Other studies reported no significant increases in adverse events; Namazy et al.[38] and Kallen et al.[31] reported that the rates of adverse events, such as gastroschisis, oral clefts, cardiac defects (eg, ductus arteriosus), spina bifida, and chromosomal anomalies, were no greater than that expected in the general population. Greenberger and Patterson[26] related their incidence of congenital malformations (2.3%; 45 pregnancies) to the incidence in the general population (1.0-6.5%). Alexander et al.[8] found a statistically significant increased risk of antepartum hemorrhage, as well as pregnancy-induced hypertension and hyperbilirubinemia with steroid use (oral or inhaled).

Unfortunately, comparative studies of ICSs are lacking and no human studies on ciclesonide were found in our

search. Dombrowski et al.[27] found fewer hospital admissions for the triamcinolone group compared to those treated with beclomethasone and a lower trend for low-birthweight infants. Birth weight differences among the 3 groups were not statistically significant. A mean neonatal intensive care stay of 2.7 ± 7.0 days was reported, but it was not stated how many infants were admitted to neonatal intensive care. The authors acknowledged that the small sample size precluded any meaningful analysis.

Comparisons of ICS doses were also not widely studied. However, Blais et al.,[44] in an exposure study including beclomethasone, budesonide, and fluticasone, found that women who used more than 1000 µg/day of ICS (beclomethasone diproprionate-chlorofluorocarbon equivalent) in the first trimester were 63% more likely to have a baby with congenital malformation (musculoskeletal and cardiac malformations being most prominent) than women who used none or up to 1000 µg/day. Conversely, infants of women who used none or up to 1000 µg/day in the first trimester were not at any greater risk of malformation than those of mothers who did not use ICSs. Multiple pregnancies, diabetes mellitus, and receipt of social assistance were risk factors for the outcome, whereas other covariates, such as maternal sociodemographic characteristics, were neither confounders nor risk factors. Women who used high doses of ICSs during the first trimester were older, less likely to have a singleton pregnancy, and less likely to have a chronic disease other than asthma. Women who were using high doses of ICSs were likely to have had more severe and uncontrolled asthma. Many studies did not specify a dosage range; thus, a dosage threshold above which adverse events were more likely to occur was not evident.

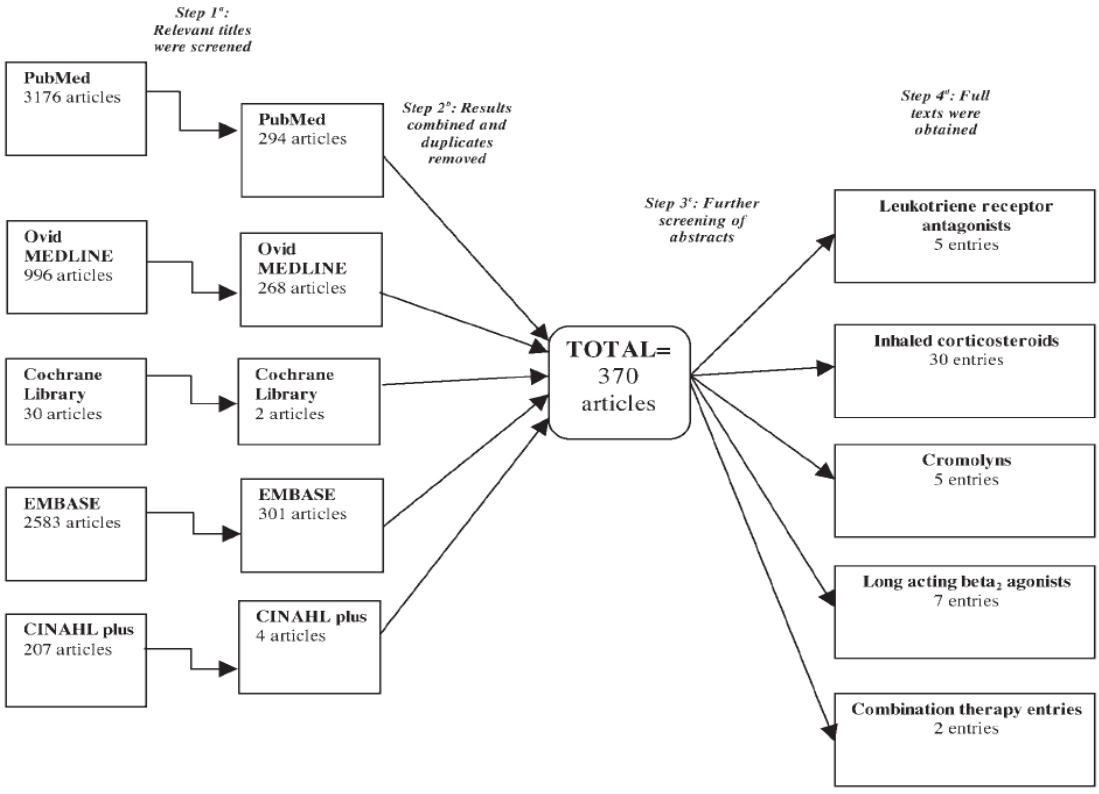

Figure 1. Steps in the study selection process. [a]Articles from each database were imported into a separate EndNote (version 3, Thomson Reuters) library because of the volume; all titles were screened for their relevance. The results from the PubMed MeSH search were combined with the PubMed key word search results and duplicates were removed. Titles were selected if they included specific drug names, class names or key words pertaining to asthma and medications. Review articles and those outside the scope of the topic question were also removed. [b]Selected articles from the various databases were imported and combined into 1 EndNote library and duplicates were removed. [c]Abstracts of relevant articles were scrutinized to confirm relevance and matching to the study inclusion criteria before obtaining their full text. [d]The reference lists of published reviews on the topic were manually searched to ensure that relevant original articles were not missed.

Table 1. Studies on the Safety of ICSs

Reference	Design	Groups (n)	D and DF	Outcomes for Exposed Group
Beclomethasone dipropionate (pregnancy risk category C)[19]				
Morrow-Brown (1974)[25]	Cohort	Exposed: asthmatic pregnant women (N = 20)	D: ~450 µg/day; a few pts. required 600 µg/day DF: inhaled (technique checked until satisfactory)	No spontaneous or therapeutic abortions; all women delivered healthy children
Greenberger (1983)[26]	Cohort	Exposed: asthmatic pregnant women (N = 40; 45 pregnancies; 37 also received oral corticosteroids)	D: 168-672 µg/day DF: inhaled	Preeclampsia (n = 1), hypertension (n = 3), spontaneous abortion (n = 3/33), congenital malformation (n = 1) (cardiac malformation); MBW 3233 g; no fetal or maternal deaths; low birth weights (1820-2458 g) with use of higher doses (6-16 puffs/day)
Dombrowski (1996)[27]	Cohort	Exposed: asthmatic pregnant women (n = 14) Asthmatic pregnant women using inhaled triamcinolone (n = 15) Asthmatic pregnant women using oral theophylline (n = 25)	D: NR DF: inhaled	No incidence of anomalies, grade 3 or 4 intraventricular hemorrhages, or sepsis; MBW 2798 ± 759 g, mean gestational age 38.0 ± 3.1 wk, mean Apgar scores at 5 min 8.6 ± 0.9, mean cord arterial pH 7.24 ± 0.11, mean neonatal intensive care stay 4.8 ± 9.4 days
Wendel (1996)[28]	Cohort (women hospitalized for asthma exacerbation; within an RCT)	Exposed: asthmatic pregnant women (n = 34) Unexposed: asthmatic pregnant women (n = 31)	D: 4 puffs twice daily (µg/puff NR) DF: inhaled	Cohort did not show increased incidence of preterm delivery, low birth weight, pathologic acidemia (umbilical artery blood pH <7), perinatal mortality
Schatz (1997)[29]	Cohort	Exposed: asthmatic pregnant women (n = 137) Unexposed: nonasthmatic pregnant women (n = 1430)	D: NR DF: inhaled	Preeclampsia (10.9%), preterm delivery (7.8%), low birth weight (4.7%); exposure without concomitant oral corticosteroids not associated with these factors
Dombrowski (2004)[30]	RCT	Asthmatic pregnant women using inhaled beclomethasone and placebo theophylline (n = 194) Asthmatic pregnant women using theophylline and placebo beclomethasone (n = 190)	D: 504 µg/day DF: inhaled	Chorioamnionitis (n = 10), preeclampsia (n = 16), preterm delivery (n = 40), hemorrhage (n = 12), cesarean delivery (n = 30), oligohydramnios (n = 7); no significant differences between groups in obstetric outcomes
Namazy (2004)[38]	Cohort	Exposed: asthmatic pregnant women (n = 201 of 396 exposed to ICSs)	D: mostly 92-600 µg/day[a] DF: inhaled	MBW 3421 ± 37.5 g; for all ICSs; low birth weight (<2500 g: 3.3%), preterm delivery (6.1%), congenital malformation (n = 4: gastroschisis, oral cleft, hypospadias, hypoplastic kidney); ICS use not shown to reduce intrauterine growth
Budesonide (pregnancy risk category C)[19]				
Kallen (1999)[31]	Cohort	Infants whose mothers were exposed to inhaled budesonide in early pregnancy (N = 2014)	D: NR DF: inhaled	Congenital malformations: orofacial cleft (n = 4), cardiac defect (n = 16) (includes 2 preterm babies with ductus arteriosus), other structural defects (n = 16, including spina bifida and microcephaly), chromosomal anomaly (n = 5); no increase in general rate of malfor mations over the population rate (3.8% vs 3.5% respectively)
Norjavaara (2003)[32]	Cohort	Asthmatic pregnant women using 1. only budesonide (n = 2968) 2. other antiasthmatic drugs (not inhaled or oral corticosteroids) (n = 7719) 3. oral corticosteroids plus budesonide (n = 103)	D: NR DF: inhaled	Similar rates of stillbirth, multiple birth, MBW, and mean birth length between groups; increased rate of caesarean birth regardless of treatment (group 1: 13.1% vs 16.2%, group 2: 13.3% vs 14.7%, group 3: 30.8% vs 21.6% for girls and boys, respectively) vs all women (11.3% for girls vs 12.2% for boys)
Namazy (2004)[38]	Cohort	Exposed, pregnant asthmatic women (n = 43 of 396 who used ICSs)	D: most 92-600 µg/daya DF: inhaled	MBW 3393 ± 69 g; for all ICSs: infants with low birth weight (<2500 g; 3.3%), preterm delivery (6.1%), congenital malformation (n = 4: gastroschisis, oral cleft, hypospadias, hypoplastic kidney); ICS not shown to reduce intrauterine growth

Silverman (2005)[33]	RCT	Exposed: asthmatic pregnant women (n = 196) Unexposed: asthmatic pregnant women (n = 117)	D: 400 µg/day DF: inhaled	Healthy children delivered in 81% of exposed pregnancies vs 77% of unexposed pregnancies; no increased risk of adverse events: unspecified congenital malformations (3/196 vs 4/117), spontaneous abortion (23/196 vs 11/117), extrauterine pregnancy (4/196 vs 3/117), induced abortion (6/196 vs 6/117), other outcomes (2/196 vs 3/117), hypertension (1/96 vs 2/117)
Clifton (2006)[46]	Cohort	Asthmatic pregnant women using budesonide alone (n = 14), fluticasone alone (n = 18), or fluticasone/salmeterol (n = 9) Pregnant nonasthmatic women (n = 20)	D: 1092.8 µg/day[b] DF: inhaled	No significant differences in gestational age (39.7 vs 40.2 wk), MBW (3824.6 vs 3423.3 g), mean birth length (52.8 vs 51.8 cm), head circumference (35.3 vs 34.2 cm) with budesonide vs nonasthmatic women, respectively
Flunisolide (pregnancy category C)[19]				
Namazy (2004)[38]	Cohort	Exposed: asthmatic pregnant women (n = 25 of 396 exposed to ICSs)	D: most 92-600 µg/day[a] DF: inhaled	MBW 3452 ± 120.3 g; for all ICSs: low birth weight (<2500 g) (3.3%), preterm delivery (6.1%), congenital malformation (n = 4; gastroschisis, oral cleft, hypospadias, hypoplastic kidney; ICSs not shown to reduce intrauterine growth
Fluticasone propionate (pregnancy risk category C)[19]				
Namazy (2004)[38]	Cohort	Exposed: asthmatic pregnant women (n = 132 of 396 exposed to ICSs)	D: most 92-600 µg/day[a] DF: inhaled	(n = 4: gastroschisis, oral cleft, hypospadias, hypoplastic kidney); ICSs not shown to reduce intrauterine growth
Clifton (2006)[46]	Cohort	Pregnant asthmatic women using budesonide alone (n = 14) fluticasone alone (n = 18) fluticasone/salmeterol (n = 9) Nonasthmatic pregnant women (n = 20)	D: 971.05 µg/day[b] DF: inhaled	No significant differences in gestational age (39.6 vs 40.2 wk), MBW (3441.7 vs 3423.3 g), mean birth length (51.6 vs 51.8 cm), head circumference (34.9 vs 34.2 cm) with fluticasone vs nonasthmatic women, respectively
Choi (2007)[34]	Case series	Exposed: pregnant women with respiratory illness (N = 12)	D: 1-2 puffs/day (µg/puff NR) DF: inhaled/intranasal	Abortions (n = 3; 1 spontaneous, 2 requested); no evidence of major congenital malformations or neurodevelopmental delay at birth or 1 wk postdelivery; 3 premature births (34^{+3} wk [twins] and 36^{+4} wk)
Perrio (2007)[35]	Cohort	Exposed: asthmatic pregnant women (N = 55)	D: 50-250 µg DF: inhaled	Spontaneous abortion (n = 5), elective abortion (n = 2), congenital abnormalities associated with extreme prematurity (n = 1), ventricular septal defect with neonatal jaundice and clicky hips (n = 1), bilateral hydroceles (n = 1), clicky hips (n = 1), positional talipes (n = 1), prune belly syndrome (n = 1)
Triamcinolone acetonide (pregnancy risk category C)[19]				
Dombrowski (1996)[30]	Cohort	Exposed: asthmatic pregnant women (n = 15) Asthmatic pregnant women using inhaled beclomethasone (n = 14) Asthmatic pregnant women using oral theophylline (n = 25)	D: NR DF: inhaled	No anomalies, grade 3 or 4 intraventricular hemorrhages, sepsis; MBW 3300 ± 678 g, mean gestational age 39.2 ± 2 wk, mean neonatal intensive care stay 2.7 ± 7 days, mean cord arterial pH 7.3 ± 0.1, mean Apgar 5-min score 8.8 ± 0.9
Namazy (2004)[38]	Cohort	Exposed: asthmatic pregnant women (n = 81 of 396 women exposed to ICSs)	D: most 92-600 µg/day[a] DF: inhaled	MBW 3508 ± 60.1 g; for all ICSs: low birth weight (<2500 g) (3.3%), preterm delivery (6.1%), congenital malformation (n = 4; gastroschisis, oral cleft, hypospadias, hypoplastic kidney); ICSs not shown to reduce intrauterine growth

D = dosage; DF = dosage form; ICSs = inhaled corticosteroids; IGF = insulin-like growth factor; IGFBP = insulin-like growth factor binding protein; MBW = mean birth weight; NR = not reported; RCT = randomized controlled trial; SABAs = short-acting β_2 agonists.

[a]Average daily dose was expressed in beclomethasone dipropionate-chlorofluorocarbon equivalent using an algorithm developed and used in previous studies and recognized by the Canadian Asthma Consensus Guidelines.

[b]Average daily dose was expressed in budesonide equivalent.

[c]IGF-1 and IGF-2 are polypeptides with a sequence related to insulin, which have mitogenic properties inducing somatic cell growth and proliferation and are required for optimal fetal and placental growth. IGFBP-3 correlates with birth weight and IGFBP-1 correlates inversely with birth weight in term or preterm infants. IGF axis is a major contributor to fetal and placental development.

(continued on page xxx)

Table 1. Studies on the Safety of ICSs (continued)

Reference	Design	Groups (n)	D and DF	Outcomes for Exposed Group
Inhaled corticosteroids (nonspecific)				
Stenius-Aarniala (1996)[17]	Cohort	Asthmatic pregnant women who had ICS exposure during pregnancy only after an acute episode (n = 177) used ICSs throughout pregnancy (n = 257) started ICSs at various stages during pregnancy, but before any acute episode (n = 70) Healthy nonasthmatic pregnant women (n = 237)	D: beclomethasone 0.05-3 µg, budesonide 0.2-4 µg DF: inhaled	No significant differences among groups in congenital malformations, premature rupture of membranes, length of gestation, premature uterine contractions, premature separation of placenta, Apgar scores, relative birth weight, hypoglycemia, jaundice, admissions to hospital during the first week of life
Alexander (1998)[8]	Cohort	Exposed: pregnant asthmatic women with or without other drugs (n = 139) Asthmatic pregnant women on no drugs (n = 375) Asthmatic pregnant women on β_2 agonists only (n = 303) Unexposed: pregnant, nonasthmatic women (n = 13,709)	D: NR DF: inhaled or oral (not specified)	Outcomes for asthmatic pregnant women: increased risk of antepartum hemorrhage (15.2%, 11.6%, 10.0%, 8.0%), pregnancy-induced hypertension (18.1%, 13.7%, 11.1%, 10.5%), hyperbilirubinemia (16.1%, 8.6%, 8.5%, 8.8%)
Olessen (2001)[36]	Cohort	Exposed: asthmatic pregnant women (n =108) Unexposed: pregnant women who did not purchase prescription drugs (n = 8717); asthma status NR	D: NR DF: inhaled	Mean gestational age 276.3 ± 15.5 days, MBW 3357.0 ± 524.9 g, mean length at birth 51.2 ± 2.5 cm; no significant difference in these variables between exposed vs reference group
Bracken (2003)[37]	Cohort	Exposed: pregnant asthmatic women (n = 176) Unexposed: pregnant nonasthmatic women (n = 2065)	D: NR DF: inhaled	No increased risk of intrauterine growth restriction (5.9% of 136 exposed vs 7.7% of 2065 not exposed); no increased risk of preterm delivery (8.5% of 176 exposed vs 6.7% of 2029 not exposed)
Schatz (2004)[39]	Cohort	Exposed: asthmatic pregnant women (n = 722) Unexposed: pregnant asthmatic women (n = 1401)	D: NR DF: inhaled	Gestational hypertension (11.2%), preterm delivery (16.2%), low birth weight (13%), small for gestational age (7.1%), unspecified major malformations (1.9%); no significant differences between adverse perinatal outcomes and use of ICSs
Bakhireva (2005)[40]	Cohort	1. Exposed: asthmatic pregnant women (n = 438), including fluticasone, beclomethasone, budesonide, triamcinolone, flunisolide 2. Unexposed: nonasthmatic pregnant women (n = 303) 3. Unexposed: asthmatic pregnant women who used only SABAs (n = 103) 4. Unexposed or exposed: asthmatic pregnant women with concomitant systemic corticosteroids (majority, burst therapy) (n = 113)	D: NR DF: inhaled	No significant differences in MBW (3524 vs 3540 g), mean birth length (51.3 vs 51.6 cm), mean head circumference (34.7 vs 34.7 cm) in group 1 vs 2 Significantly low prevalence of major structural anomalies in group 2 (0.3%); however, similar prevalence in groups 1, 3, and 4 (2.7-4.1%)
Martel (2005)[41]	Case-control	Pregnancy-induced hypertension (n = 302) Preeclampsia (n = 165) Matched controls: pregnancy-induced hypertension (n = 3013), preeclampsia (n = 1643)	D: 0 to >500 µg/day[a] DF: inhaled	No significant difference in risk of pregnancy-induced hypertension in cases vs controls 1-200 µg/day: 35% vs 33% 201-500 µg/day: 10% vs 9% >500 µg/day: 5% vs 5% No significant difference in risk of preeclampsia in cases vs controls 1-200 µg/day: 35% vs 30% 201-500 µg/day: 12% vs 9% >500 µg/day: 5% vs 5%
Blais (2007)[43]	Cohort	Asthmatic pregnant women (n = 4561) using 1. no ICSs (n = 2740) 2. >0-500 µg/day ICSs (n = 1582) 3. >500-1000 µg/day ICSs (n = 167) 4. >1000 µg/day ICSs (n = 72)	D: 0 to >1000 µg/day[a] DF: inhaled	Moderate doses (>500-1000 µg/day) during first trimester significantly associated with a 59% reduction in risk of all congenital malformations vs no ICS use; no increased risk of all malformations/major malformations with first-trimester use of ICSs (groups 1-4: 9.4%/6% vs 9.0%/6.4% vs 5.4%/3.6% vs 12.5%/9.7)

Tata (2008)[45]	Case-control	Children with ≥1 reported major malformation (n = 5124); 220 mothers exposed to ICSs Children with no malformations, matched by year of birth, general practice and singleton or twin delivery (n = 30,053); 1209 mothers exposed to ICSs	D: NR DF: inhaled	No increased risk of congenital malformations (4.3% cases vs 4.0% controls)
Blais (2009)[44]	Cohort	Exposed: asthmatic pregnant women using 1. no ICSs (n = 8734) 2. >0 to ≤1000 µg/day of ICSs (n = 4392) 3. >1000 µg/day of ICSs (n = 154)	D: 0 to >1000 µg/day[a] DF: inhaled	Group 3 not 63% more at risk of delivering an infant with a malformation vs group 2; group 2 not more at risk of delivering an infant with a malformation vs group 1; crude prevalence of all malformations/major malformations (groups 1-3): 9.6%/5.9% vs 9.0%/5.7% vs 14.3%/9.7%
Clifton (2010)[42]	Cohort	Exposed: asthmatic pregnant women (n = 107) Unexposed: nonasthmatic women (n = 38)	D: NR DF: inhaled	ICSs did not affect cord plasma IGF-1, IGF-2, IGFBP-1, IGFBP-3, IGF axis[c]

D = dosage; DF = dosage form; ICSs = inhaled corticosteroids; IGF = insulin-like growth factor; IGFBP = insulin-like growth factor binding protein; MBW = mean birth weight; NR = not reported; RCT = randomized controlled trial; SABAs = short-acting β_2 agonists.

[a]Average daily dose was expressed in beclomethasone dipropionate-chlorofluorocarbon equivalent using an algorithm developed and used in previous studies and recognized by the Canadian Asthma Consensus Guidelines.

[b]Average daily dose was expressed in budesonide equivalent.

[c]IGF-1 and IGF-2 are polypeptides with a sequence related to insulin, which have mitogenic properties inducing somatic cell growth and proliferation and are required for optimal fetal and placental growth. IGFBP-3 correlates with birth weight and IGFBP-1 correlates inversely with birth weight in term or preterm infants. IGF axis is a major contributor to fetal and placental development.

Asthma severity can be a serious confounding factor, as it is difficult to establish whether the adverse events are attributable to the medications or uncontrolled asthma. Some studies attempted to control for asthma severity.[17,26,28,30,35,37,40-42,46] Analyses in both the mild and moderate-severe asthma groups indicated no effect on fetal growth.[46] Greenberger and Patterson[26] evaluated pregnant women with severe asthma who were exposed to beclomethasone and found only 1 infant with a cardiac malformation, including a double ventricular septal defect, patent ductus arteriosus, and subaortic stenosis. The infant's mother had schizophrenia, asthma and diabetes, and was taking a cocktail of chronic long-term medications, including antipsychotics. Namazy et al.[38] found a nonsignificant trend of increasing incidence of SGA infants with increasing doses of ICS after controlling for factors such as race, smoking, and acute asthma episodes. Choi et al.[34] stated that during pregnancy, none of their 12 ICS-exposed participants experienced uncontrolled asthma.

The relationship between gestational exposure time and adverse events has not been explored in depth.[29,31,32,34,35,43,44,47] Perrio et al.[35] found that 17 of 18 babies exposed to fluticasone in the first trimester were born at term. One baby had a congenital abnormality associated with extreme prematurity; another had a ventricular septal defect, clicky hips, and neonatal jaundice, which was attributed to the mother's antibodies; and 3 babies were born with minor congenital abnormalities. All babies exposed to fluticasone in the second or third trimester were born at full term; 1 baby was born with prune belly syndrome (time of exposure uncertain). Norjavaara et al.[32] found no significant differences in birth weight, length, and gestational age when comparing budesonide exposure in early pregnancy with any time during pregnancy.

Systemic absorption of ICSs following inhalation is generally minimal. Inhaled budesonide has an estimated lung bioavailability of 34% of the inhaled dose and, once absorbed, it becomes a weak systemic steroid.[56] Triamcinolone, fluticasone, ciclesonide, and beclomethasone have low to undetectable plasma concentrations when inhaled.[57] It is uncertain the extent to which these drugs can cause adverse events, considering such low systemic absorption after inhalation.

Oral corticosteroid burst therapy was administered in most studies, which would have added to the corticosteroid concentrations and increased the likelihood of an adverse event. In the study by Namazy et al.,[38] at least 1 course of oral corticosteroids for acute asthma episodes was required by 31.1% of women in the ICS-exposed group (n = 123), of whom 10.6% (n = 13) had SGA babies.

Most of the retrieved ICS studies had small sample sizes and did not control for other contributing risk factors. More adequately powered studies showing a strong correlation between ICS use and an adverse event would be needed before their use during pregnancy should be discouraged.

Combination Therapies

Limited information is available on combination therapies (Table 2). No studies were retrieved on the eformoterol/formoterol and budesonide combination. Clifton et al.[46] found that neonatal birth weight percentile and length were significantly reduced in women using fluticasone/salmeterol (n = 9) compared to budesonide (n = 14). The authors speculated that this may be due to the effects of salmeterol, as fluticasone alone was not associated with these effects. However, this study had a very small sample size and indicated that asthma alone had the greatest negative effect on neonatal outcome. Perrio et al.[47] conducted a postmarketing surveillance study and listed the adverse outcomes without relating them to a control group or to the general population. Neither study provided enough evidence to discourage use of combination asthma preventive therapies.

Long-Acting β_2 Agonists

Overall, the use of LABAs during pregnancy was not associated with any particular adverse event (Table 3). Maternal plasma concentrations after absorption of inhaled salmeterol or formoterol/eformoterol are very low or undetectable.[57] With such low plasma concentrations, it is debatable whether adverse events could be attributed to LABA use.

Mann et al.[49] reported an incident of Aarskog syndrome in an infant whose mother had used salmeterol in the first 4 months of pregnancy. Aarskog syndrome, also known as faciodigitogenital syndrome, is an X-linked syndrome characterized by ocular hypertelorism, anteverted nostrils, broad upper lip, peculiar scrotal "shawl" above the penis, and small hands.[58] However, several of the infant's family members also had this syndrome and the infant had concomitant exposure to ICS and oral corticosteroid, making it impossible to assign this event to any particular drug or to genetics.[49] Jones et al.[51] also reported malformations (bicuspid aorta with penoscrotal fusion, bilateral and unilateral inguinal hernia) in the exposed group; however, the rates of malformations in the exposed (n = 126), unexposed (n = 91), and nonasthmatic (n = 115) groups were 4.7%, 3.9%, and 1.9%, respectively, and were in the range expected in the general population. Seventy-five percent of women were using ICSs concomitantly, but controlling for ICS use did not change the results.

Many studies did not analyze LABAs specifically or control for concomitant use of other asthma medicines. As the use of LABAs during pregnancy with other medications has not shown any increase in harm to the mother or infant, their use alone would be unlikely to pose any risk. While there is currently no established risk with LABA use during pregnancy, more reliable evidence is needed.

Table 2. Studies on the Safety of Combination Asthma Prophylaxis Drugs

Reference	Design	Groups (n)	D and DF	Outcomes for Exposed Group
Fluticasone proprionate + salmeterol (pregnancy category C)[19]				
Clifton (2006)[46]	Cohort	Exposed: pregnant asthmatic women using 1. budesonide (n = 14) 2. fluticasone (n = 18) 3. fluticasone + salmeterol (n = 9) Control: pregnant nonasthmatic women (n = 20)	D: fluticasone 783.3 µg/day,[a] salmeterol 108.3 µg/day (third trimester) DF: inhaled	No significant differences in gestational age (39.9 vs 40.2 wk), MBW (3283.0 vs 3423.3 g), mean birth length (50.2 vs 51.8 cm), head circumference (34.9 vs 34.2 cm) with fluticasone + salmeterol vs control Significant differences in birth weight (34.8 vs 74) and length (51.0 vs 88.9) percentile with fluticasone + salmeterol vs group 1
Perrio (2007)[47]	Cohort	Exposed: pregnant asthmatic women (N = 41)	D = fluticasone 50-250 µg + salmeterol 25 µg DF: inhaled	Spontaneous abortion (n = 4), missed abortion (n = 1) Perinatal outcomes: nonketotic hyperglycemia (n = 1), systolic murmurs and small ventricular septal defect (n = 1), apnea episodes thought to be secondary to liquor aspiration (n = 1), undescended right testis (n = 1)

D = dosage; DF = dosage form; MBW = mean birth weight.
[a]Average daily dose was expressed in budesonide equivalent.

Table 3. Studies on the Safety of LABAs

Reference	Design	Groups (n)	D and DF	Outcomes for Exposed Group
Eformoterol, Formoterol (pregnancy category C)[19]				
Wilton (2002)[48]	Cohort	Pregnant asthmatic women (N = 33)	D: NR DF: inhaled	Prematurity (n = 5), congenital abnormalities (1 infant with fetal heart rate anomaly, 1 infant with pyloric stenosis)
Salmeterol (pregnancy category C)[19]				
Mann (1995)[49]	Cohort	Pregnant asthmatic women (N = 65)	D = 100 µg/day on average DF: inhaled	Aarskog (faciodigitogenital) syndrome (n = 1); asthma during infancy (n = 2)
Wilton (1998)[50]	Cohort	Pregnant asthmatic women (N = 91)	D: NR DF: inhaled	With first trimester use, ectopic pregnancy (n = 2), spontaneous abortion (n = 7), induced abortion (n = 4), congenital malformation for full-term births (n = 1) (Aarskog syndrome) Congenital anomalies for premature infants (n = 3)
Jones (2002)[51]	Cohort	Exposed: pregnant asthmatic women (n = 126) Unexposed: pregnant asthmatic women using SABAs (n = 91) Unexposed: pregnant nonasthmatic women (n = 115)	D: NR DF: inhaled	Similar rates of malformations (4.7%, 3.9%, 1.9%, respectively); all within the range expected in the general population Malformations in exposed group: bicuspid aorta with penoscrotal fusion (n = 1), bilateral inguinal hernia (n = 1), unilateral inguinal hernia (n = 3) No significant differences among groups in MBW, length, or head circumference of full-term infants or SGA infants
LABAs (nonspecific)				
Bracken (2003)[37]	Cohort	Exposed: pregnant asthmatic women (n = 64) Unexposed: pregnant nonasthmatic women (n = 2153)	D: NR DF: inhaled	No increased risk of IUGR (exposed: 8.3% of 48; unexposed: 7.6% of 2153) No increased risk of preterm delivery (exposed: 10.9% of 64; unexposed: 6.8% of 2141)
Schatz (2004)[39]	Cohort	Exposed (eg, salmeterol, albuterol): pregnant asthmatic women (n = 1828) Unexposed: pregnant asthmatic women (n = 295)	D: NR DF: inhaled	Gestational hypertension (11.8%), preterm delivery (15.8%), low birth weight (13.5%), SGA (7.1%), major malformations (2%, underpowered) No significant relationship between adverse perinatal outcomes and β_2 agonist use
Tata (2008)[45]	Case control	Children with ≥1 major malformation (n = 5124); 25 mothers exposed to LABAs Children with no malformations, matched by year of birth, general practice, singleton or twin (n = 30,053); 131 mothers exposed to LABAs	D: NR DF: inhaled	No increased risk of congenital malformations (<0.5% in both groups)

D = dosage; DF = dosage form; IUGR = intrauterine growth restriction; LABAs = long-acting β_2 agonists; MBW = mean birth weight; NR = not reported; SABAs = short-acting β_2 agonists; SGA =small for gestational age.

Leukotriene Receptor Antagonists

In recent years, several LTRA safety studies[53-55] have been published (Table 4), although doses were often not specified. LTRAs are generally taken in combination with other asthma medications; hence, it is not surprising that not many studies have analyzed this drug class exclusively. Bakhireva et al.[55] stated that 99% of subjects in their LTRA group (n = 96) used SABAs, 40% used oral corticosteroids (majority as burst therapy), and 39% used ICSs at some time during pregnancy. Although 5 major structural defects (Sturge-Weber syndrome, congenital hip dislocation, bilateral club foot, neurofibromatosis type 1, and imperforate anus) were reported in the LTRA group, all 5 mothers also had exposure to ICSs and SABAs, and 2 mothers also had exposure to oral corticosteroids at some time during pregnancy (duration not reported). The prevalence of major structural anomalies at birth in the LTRA group (n = 96) was 5.95% compared with 3.9% among exclusive SABA users (n = 122) and 0.3% among controls (those without asthma; n = 346). Only malformations from the LTRA group were reported, and these major structural defects may have been due to exposure to other medications such as ICSs. In all cases, the mother had used LTRAs throughout pregnancy. Sarkar et al.[53] found a significant decrease in birth weight in the LTRA group, but a subanalysis of women who continued LTRAs throughout pregnancy showed no significant differences in birth weights. Given that 52.6% of participants discontinued LTRAs after the first trimester, the authors suggested that continual LTRA use during pregnancy gave better control of asthma and decreased the risk of low-birth-weight babies.

In the study by Tata et al.[45] (Table 5), LTRAs were combined with cromolyns in a category called "antiinflammatory agents" when reporting adverse events. Among the 36 antiinflammatory agent users, only 1 was exposed to montelukast (control group).

Safety data on LTRAs are limited because large, well-designed studies are lacking.

Cromolyns

Few studies are available on the safety of cromolyns during pregnancy (Table 5). Only the study by Schatz et al.[29] had a reasonably large sample size (n = 243), but the drugs used included inhaled (n = 158), intranasal (n = 113), and ophthalmic (n = 23) forms of cromolyns. As with other studies of preventive asthma drugs during pregnancy, patients were allowed to use oral corticosteroids during periods of exacerbation in all the cromolyn studies. Tata et al.[45] identified 9 cases of congenital malformations with cromolyn use, including congenital hip dislocations and shortening of the legs, imperfect fusion of the skull, defect of the lacrimal passages, cleft palate with bilateral cleft lip, hypospadias, and Down syndrome with ventricular septal defect. However, this study used children born to mothers without asthma as controls and was significantly underpowered, making it difficult to distinguish whether these adverse events could have been due to asthma versus the drugs.

More evidence is needed to link cromolyn use with adverse events given that systemic absorption after inhaled cromolyn delivery is low even after continual dosing.[57]

Discussion

This review has identified few reports of negative outcomes; however, there was no clear, direct association with medication use in most of these cases. Many of the adverse events could have been the result of poorly controlled asthma, rather than medications. A few studies noted poorly controlled asthma as a confounding factor.[8,39,43,44,55] Many studies prospectively followed women who continued their existing asthma treatment and did not control for multiple agents. Other medications not used for asthma were also not controlled for. More safety data are available for older ICSs (eg, beclomethasone and budesonide) and cromolyns, compared to newer medications such as LABAs and LTRAs. Further evidence from large, well-designed studies is essential to confirm the safety of LTRAs and LABAs in pregnant women.

ICSs are the most commonly used preventive asthma medications and are the recommended first-line therapy in moderate to severe persistent asthma during pregnancy by most global organizations (BTS, GINA, NAC, and NHLBI)[3-7]; ACOG and ACAAI[2] recommend cromolyns. Treatment of asthma with ICSs during pregnancy decreased asthma-related physician visits compared to prepregnancy and was not associated with adverse outcomes.[59] The only large study of cromolyns did not show any relationship between major malformations and use of cromolyns in the first trimester.[29] Comparative safety studies of cromolyns and ICSs are lacking, making it difficult to recommend one over the other during pregnancy.

To our knowledge, no data on the budesonide and eformoterol/formoterol combination are available. With low incidences of adverse events from using these agents separately, ICS/LABA combinations would not be expected to cause significant harm. Nevertheless, more safety information on ICS/LABA combinations is warranted.

Evidence for the safety of LTRAs is limited; therefore, some guidelines recommend these agents during pregnancy in cases of inadequate control with first-line antiinflammatory agents and/or if previous or current use of LTRAs has demonstrated efficacy.[2,6,7]

Limitations of Studies Included in the Review

Patient adherence to study medication(s) was taken for granted in most studies, although adherence to asthma

Table 4. Studies on the Safety of LTRAs

Reference	Design	Groups (n)	D and DF	Outcomes for Exposed Group
Montelukast (pregnancy category B)[19]				
Merck Registries (2006)[52,a]	Cohort	Pregnant asthmatic women (N = 203)	D: NR DF: inhaled	8 Major congenital anomalies: absent left hand allegedly secondary to amniotic bands (n = 1), hypospadias (n = 2), chordee (n = 1), calcaneal valgus (n = 1), triploidy 69XXY that resulted in termination at 12 gestational wk (n = 1), polydactyly (n = 1), cystic kidney disease (n = 1), bilateral hydroceles (n = 1), cleft tongue (n = 1) No increased risk of spontaneous abortions, low-birth weight, or preterm delivery relative to expected number in general population
Sarkar (2009)[53]	Cohort	1. Exposed: pregnant asthmatic women (n = 180) 2. Unexposed: pregnant asthmatic women using ICSs and inhaled β_2 agonists) (n = 180) 3. Unexposed: pregnant nonasthmatic women exposed to nonteratogens and other innocuous substances (eg, hair dye) (n = 180)	D: NR DF: oral	Outcomes for groups 1 and 2 similar; significant differences between groups 1 and 3 for MBW (3214.1 ± 685.8 g vs 3355.9 ± 657.5 g vs 3424.7 ± 551.1 g), gestational age (37.8 ± 3.1 wk vs 37.6 ± 4.4 wk vs 39.3 ± 2.4 wk), infants with fetal distress (n = 41 vs 22 vs 14) No significant differences in rate of live births, miscarriages, fetal deaths, elective abortions Major malformation in group 1: 1 twin with patent ductus arteriosus, atrial septal defect, congestive heart failure
Zafirlukast (pregnancy category B)[19]				
Twaites (2007)[54]	Cohort	Pregnant asthmatic women (N = 28)	D: NR DF: inhaled	Live births without abnormalities (n = 9), spontaneous abortion (n = 4), therapeutic termination (n = 1)
Leukotriene receptor antagonists (nonspecific)				
Bracken (2003)[37]	Cohort	Exposed: pregnant asthmatic women (n = 9) Unexposed: pregnant nonasthmatic women (n = 2196)	D = montelukast 10 mg daily; zafirlukast 20 mg twice daily DF: inhaled/oral	No increased risk of IUGR (exposed: 16.7% of 6; unexposed: 7.6% of 2195). No increased risk of preterm delivery (exposed: 22.2% of 9; unexposed: 6.8% of 2196)
Bakhireva (2007)[55]	Cohort	1. Exposed: pregnant asthmatic women (n = 96) 2. Unexposed: pregnant asthmatic women who used only SABAs throughout pregnancy (n = 122) 3. Unexposed: pregnant nonasthmatic women (n = 346)	D: NR DF: inhaled/oral	Lower adjusted MBW full-term infants in group 1 (3384 ± 72 g) vs group 2 (3533 ± 68 g) vs group 3 (3529 ± 54 g) 5 Major structural defects reported in group 1: Sturge-Weber sequence (zafirlukast; n = 1), congenital hip dislocation (zafirlukast; n = 1), bilateral club foot (montelukast; n = 1), neurofibromatosis type 1 (montelukast; n = 1), imperforate anus (montelukast; n = 1)

D = dosage; DF = dosage form; ICS = inhaled corticosteroids; IUGR = intrauterine growth restriction; LTRAs = leukotriene receptor antagonists; MBW = mean birth weight; NR = not reported; SABAs = short-acting β_2 agonists.

[a]Secondary evidence from Bakhireva et al.[55]

Table 5. Studies on the Safety of Cromolyns

Reference	Design	Groups (n)	D and DF	Outcomes for Exposed Group
Nedocromil (pregnancy category B)[19]				
Wilton (1998)[50]	Cohort	Pregnant asthmatic women (N = 81)	D: NR DF: inhaled	With first-trimester exposure, spontaneous abortion (n = 1), elective abortion (n = 8), congenital heart disease anomaly (n = 1)
Schatz (2004)[39]	Cohort	Exposed: pregnant asthmatic women (n = 60) Unexposed: pregnant asthmatic women (n = 2063)	D: NR DF: inhaled	Preeclampsia (13.3%), preterm delivery (21.7%), low birth weight (20%), SGA (16.7%, underpowered), major malformations (3.3%, underpowered) No significant relationship between adverse perinatal outcomes and cromolyn use
General cromolyns (nonspecific)				
Schatz (1997)[29]	Cohort	Exposed: pregnant asthmatic women (n = 243) Unexposed: pregnant nonasthmatic women (n = 1247)	D: NR DF: various	No significant relationships between major congenital malformations and first-trimester use (exposed: 6.0% of 151; unexposed: 5.0% of 1348) or anytime use (exposed: 6.2% of 243; unexposed: 4.9% of 1247)
Bracken (2003)[37]	Cohort	Exposed: pregnant asthmatic women (n = 22) Unexposed: pregnant nonasthmatic women (n = 2183)	D: NR DF: various	No increased risk of IUGR (exposed: 0% of 18; unexposed: 7.7% of 2183) Increased risk of preterm delivery (exposed: 18.2% of 22; unexposed: 6.8% of 2183)
Tata (2008)[45]	Case control	Children with ≥1 major malformation (n = 5124); 9 mothers exposed to cromolyns or LTRAs Children with no malformations, matched by year of birth, general practice, and singleton or twin (n = 30,053); 27 mothers exposed to cromolyns or LTRAs	D: NR DF: inhaled	No increased risk of system-specific malformations, apart from a large relative increase in musculoskeletal system malformations in children with prenatal exposure to cromolyns Congenital hip dislocation (n = 3), congenital shortening of leg (n = 1), imperfect fusion of skull (n = 1), defect of lacrimal passages (n = 1), cleft palate with bilateral cleft lip (n = 1), Down syndrome with ventricular septal defect (n = 1), hypospadias (n = 1)

D = dosage; DF = dosage form; IUGR = intrauterine growth restriction; LTRAs = leukotriene receptor antagonists; NR = not reported; SGA = small for gestational age.

medications has been shown to decrease in pregnancy.[18] Sarkar et al.[53] found that 52.6% of their subjects discontinued montelukast after the first trimester. Adherence was measured only in a few studies. Dombrowski et al.[30] used self-reports, serum theophylline concentrations, pill counts, and beclomethasone canister weights to measure adherence, while Bakhireva et al.[40] conducted phone interviews to inquire about actual use, frequency, and dosage in accordance with medical records. Several studies reviewed here used prescription records as a means to follow a subject's medication use.[35,47,48-50,54] Prescription event monitoring (PEM) studies are also heavily reliant on prescribers' documentation, as outcomes are measured using questionnaires that are filled in by treating physicians, which may not always be reliable. Health-care providers may have also been underprescribing, especially when confronted with an asthmatic pregnant patient. Not adhering to asthma management guidelines could also be the cause of poor asthma control, which could be linked to some of the adverse events documented.

Asthma severity may worsen during pregnancy.[1] Most studies included participants with a range of asthma severities; however, few controlled for asthma severity. Dombrowski et al.[30] only included participants with moderate asthma and excluded those with unstable or severe asthma; Greenberger and Patterson[26] targeted pregnant women with severe asthma; Wendel et al.[28] targeted severe asthmatic pregnant women who had been hospitalized; and Stenius-Aarniala et al.[17] included only pregnant women with acute asthma. Women with uncontrolled or severe asthma can also be considered as having a high-risk pregnancy, which could have been the reason for a high incidence of cesarean births.[60] Other confounding factors, such as smoking, illicit drug use, diet, ethnicity, comorbidities and other medications, including nonprescription medications, may have contributed to the negative outcomes reported in many studies. Understandably, nearly all studies permitted subjects to use oral corticosteroids and SABAs when needed for exacerbations. It is impossible to attribute an adverse event to a particular drug when participants are using multiple medications.

Reporting of participant characteristics and outcomes also varied among studies. Some studies listed all the adverse events, but did not clearly state whether more than one of those events was associated with the same pregnancy.[39,46,48,49,55] Kallen et al.[31] listed malformations categorically without an indication of whether multiple malformations occurred in the same infant. The relationship between gestational exposure time and adverse event was not explored in depth; however, a few studies identified most of the adverse events occurring due to exposure in the first trimester.[49,50] Dosage ranges were also poorly documented in the majority of studies, and more than 1 dosage form

was sometimes included.[29,34,37,39,45,55] Furthermore, sample sizes in many studies were small. Missing data and loss to follow-up were also evident in many studies, further skewing the results.

Strengths and Limitations of the Review

This is an up-to-date review of the safety of preventive asthma medications during pregnancy. The review team comprised respiratory and neonatal physicians and pharmacists. A thorough and comprehensive search was conducted to ensure that all relevant articles were identified. To minimize the chances of missing studies, reference lists of already published reviews were also reviewed. However, data from the Merck report[52] were extracted from a secondary source because the original documentation was not available. Two authors reviewed each article and verified the data extracted to reduce the potential for bias in the interpretation of data.

The majority of studies were carried out in North America and Europe; asthma medication safety studies during pregnancy from other parts of the world were limited, which makes the review less generalizable to patients from other regions, especially ethnic minorities.

Message for Practitioners

Until further evidence from large, well-designed studies in pregnant women is available, health-care providers should follow asthma guidelines produced by various professional organizations for the management of asthma during pregnancy (ACOG and ACAAI, BTS, GINA, NAC, and NHLBI).[2-7] A conservative approach would be to use the lowest effective dose of medications with more safety data, such as ICSs and cromolyns. However, health-care providers should not hesitate to increase doses or introduce additional medications as needed, but only after verifying patient adherence and inhaler techniques. The negative outcomes reported in some studies should not discourage prescribers from making appropriate dosage increases of ICSs or introducing other agents, such as LABAs, during pregnancy. A collaborative approach involving an obstetrician, a respiratory specialist, and other health-care providers should be considered in complicated cases.

Summary

Some negative outcomes of preventive asthma medicines have been reported, although there is no clear, direct association with medication use in most of these cases. More safety data are available for older ICSs and cromolyns compared to newer medications such as LABAs and LTRAs. Selection of preventive drugs for asthma management during pregnancy should be based on an assessment of the risks and benefits of medication use versus the risks of poorly controlled asthma for the mother and the unborn child.

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Chapter 3: Asthma drugs in pregnancy and lactation: practice points

(Supplement to Phase 1)

3.1 Preamble

An invitation was received from **Australian Prescriber** *(No reported impact factor)* to write a summary of the findings from our research and to offer recommendations for better practice. *Australian Prescriber*, published by NPS Medicine Wise, an independent, non-profit organisation, is Australia's national independent journal of drugs and therapeutics providing medicines information and resources for health professionals, consumers, members and stakeholders involved in Quality Use of Medicines. The purpose of Australian Prescriber is to help health professionals make informed choices when prescribing, including whether to prescribe a drug or not.

The aim was to provide evidence for translation of research findings into practice.

The specific objectives of this phase were to:

- present practitioners with a succinct summary of clinical points to be considered when managing pregnant and lactating women with asthma;
- highlight the results of the systematic review; and
- provide evidence-based recommendations on management of pregnant women with asthma.

What this manuscript adds to current knowledge

This manuscript provides the target audience (including doctors, dentists, pharmacists and healthcare students) with practice points to consider when managing pregnant and lactating women with asthma, it is anticipated that this information will help support practice and lead to better asthma management during pregnancy.

3.2 Authors' declaration

MONASH University

Declaration by candidate for paper 2 titled:

Asthma drugs in pregnancy and lactation: practice points

The undersigned hereby certify that:

1. The above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors;
2. They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
3. They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
4. There are no other authors of the publication according to these criteria;
5. Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
6. The original data are stored at the following location and will be held for at least five years from the date indicated below:

Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences,
Monash University,
Victoria, Australia
Date: 1st July 2013

The nature and extent of candidate's contribution to the work was:

Nature of contribution	Extent of contribution
Conducted literature review and prepared first and final drafts of manuscript	80%

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3.3 Manuscript

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ARTICLE

Asthma drugs in pregnancy and lactation

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beta agonists, breastfeeding, corticosteroids

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SUMMARY

Uncontrolled asthma during pregnancy poses many short and long-term risks to the mother and her baby. It is therefore important that optimal asthma control is maintained during pregnancy, but studies of drug safety are limited.

Inhaled short-acting beta agonists are safe to prescribe throughout pregnancy. Long-acting beta agonists need not be stopped in the first trimester if they are required to maintain asthma control and can be used in the second and third trimesters if needed to maintain adequate asthma control.

Inhaled corticosteroids, particularly budesonide, at recommended doses are safe to use during pregnancy and breastfeeding. Oral corticosteroids, at the doses used to treat asthma exacerbations, do not appear to pose a significant risk to the mother or child.

Pregnant women tend to overestimate the risk of using asthma drugs, but they are often unaware of the greater risks of uncontrolled asthma. They put themselves at unnecessary risk of acute exacerbations by discontinuing or reducing therapy.

Women with asthma should be advised to continue to take their treatment while breastfeeding. Spacing the dose and feed time may be necessary when using oral corticosteroids.

Introduction

Approximately 8–13% of pregnant women have asthma.[1] Asthma control varies during pregnancy, but it can deteriorate in over one third of women.[2] Continuing therapy and monitoring is essential during pregnancy to maintain optimal control and prevent acute exacerbations. Pregnant women often accept frequent symptoms at the expense of less medication, but underestimate the harm an exacerbation may have on the pregnancy.

There are limited well-designed studies about asthma drugs during pregnancy and breastfeeding. The studies that assessed safety did not assess the drugs individually and rarely controlled for other drugs or medical conditions. Adverse events have also been attributed to worsening asthma, rather than its treatment.

In contrast, there is ample evidence of the risks associated with poorly controlled asthma during pregnancy.[3] These include an increased risk of preterm births, low birthweight, pre-eclampsia, malformations and poor fetal brain development.[3-5] Survivors of preterm birth and fetal growth restriction face an increased risk of cardiovascular complications in later life.[6] Optimal asthma control is therefore vital during pregnancy and a harm–benefit assessment should be done for each patient.

Women with asthma who smoke should be encouraged to quit as smoking can reduce their response to preventive therapy.[7]

Non-adherence to asthma treatment

Almost a third of pregnant women discontinue or reduce their asthma preventing drugs during pregnancy and overcompensate with short-acting relieving drugs, jeopardising asthma control.[1] The connotations of the word 'steroid' distresses many women and they overestimate the harm steroids could have on their unborn child.[8] In addition, women who are unaware of the risks of poorly controlled asthma and not properly advised, turn to unreliable resources, such as the internet, which often exaggerate the risks of treatment without highlighting its benefits.[8]

The uncertainty and anxiety surrounding the treatment of asthma during pregnancy emphasises the important roles of doctors, pharmacists, asthma educators and midwives in encouraging adherence to treatment. The first antenatal visit is an opportunity to discuss the benefits of continuing treatment and to review the patient's asthma management plan.[9] Any harmful effects from the drugs used to prevent asthma will be outweighed by maintaining good control and avoiding acute exacerbations.

Inhaled beta agonists

Salbutamol and terbutaline are safe to use during pregnancy.[10] In the Australian categorisation of risk they are classified as category A (Table 1).

Limited studies are available on long-acting beta agonists such as salmeterol and eformoterol,[11] which are thus categorised as B3 (Table 1). As the majority of these studies analysed long-acting beta agonists

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in combination with other asthma drugs and have not shown any significant increase in harm, they are unlikely to pose a risk.[11] Furthermore, maternal plasma concentrations after inhaled salmeterol or eformoterol are very low or virtually undetectable.[12] The Asthma Management Handbook of the National Asthma Council Australia discourages starting treatment with long-acting beta agonists in the first trimester, but does not advocate withdrawing them if they are necessary to control the patient's symptoms.[13]

Inhaled corticosteroids

Using inhaled corticosteroids during pregnancy has been associated with a decreased risk of low birthweight babies.[14] A study of women with asthma exacerbations found a 55% reduction in subsequent exacerbations and hospital admissions in those who used beclomethasone compared to those who did not.[15] Women should be advised to continue their preventive drugs during pregnancy.

Budesonide is a category A drug. The Asthma Management Handbook recommends switching to budesonide before pregnancy.[13] Ciclesonide, fluticasone and beclomethasone are category B3 (Table 1) with less evidence for safety during pregnancy.

Comparisons between different inhaled corticosteroids and doses are limited. In one study including beclomethasone, budesonide and fluticasone, women who used more than 1000 micrograms daily in the first trimester were more likely to have a baby with congenital malformations (relative risk 1.63; 95% confidence interval 1.02–2.60).[16] However women on high-dose inhaled corticosteroids were likely to have more severe asthma, so adverse outcomes could have been associated with worsening asthma and oral corticosteroid use.[11] The negative outcomes reported should not discourage prescribers from increasing the dose of inhaled corticosteroids when necessary, as the risks of harm may be greater if the patient has uncontrolled asthma. Before increasing the dose it is important to check the patient's adherence and inhaler technique. The relationship between gestation and adverse events has not been explored in depth, but available studies suggest there is no greater risk with using inhaled corticosteroids in any particular trimester.[11]

Table 1 **Australian categorisation of risk of asthma drugs in pregnancy** [29]

Category	Definition	Drugs
A	Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed	budesonide terbutaline salbutamol prednisolone
B1	Drugs which have been taken by a limited number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.	nedocromil montelukast sodium cromoglycate
B2	Drugs which have been taken by a limited number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed. Studies in animals are inadequate or may be lacking, but available evidence show no evidence of an increased occurrence of fetal damage.	
B3	Drugs which have been taken by a limited number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.	beclomethasone ciclesonide fluticasone eformoterol salmeterol
C	Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Specialised texts should be consulted for further details.	
D	Drugs which have caused are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Specialised texts should be consulted for further details.	
X	Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy	

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Oral corticosteroids

Prednisolone, the oral corticosteroid mainly used in the treatment of exacerbations of asthma, has been shown to be under-prescribed in acute asthma exacerbations during pregnancy, leading to persistent and recurrent asthma symptoms two weeks later.[17] The risk of poorly-controlled asthma and the potential for another acute exacerbation during pregnancy is dangerous and acute asthma needs to be treated adequately.

There have been reports of an increased risk of cleft lip with or without cleft palate from first trimester use, however, the data were from studies of small sample size that included corticosteroid use for other conditions that generally needed higher and more frequent doses.[18] It is also difficult to separate the potential effects of oral corticosteroids from the potential effects of poorly controlled maternal asthma as oral corticosteroids are generally indicated for severe asthma.

It is necessary to monitor blood glucose if oral corticosteroids are used in pregnancy, especially if there is gestational diabetes.

Cromolyns and leukotriene receptor antagonists

Inhaled cromolyns are probably safe to use in pregnancy.[10] No well-designed studies have assessed the sole use of leukotriene receptor antagonists, such as montelukast, during pregnancy. Studies have shown an increase in adverse events with use, but these studies did not exclusively test montelukast during pregnancy.[11] Montelukast should be used in pregnancy only if clearly indicated and only after considering more effective and safer treatment, especially given its prescribing restrictions in the Pharmaceutical Benefits Scheme.[10]

Anticholinergics

Currently there are no published controlled human data on the use of inhaled anticholinergics during pregnancy and their use should be reserved as a last option. Nebulised ipratropium bromide with inhaled beta agonists and intravenous corticosteroids has been recommended for management of acute asthma during pregnancy.[19]

Lactation

Asthma control in the postpartum period is important for the same reasons as it is in healthy, non-pregnant women, and the exacerbation risk is similar in the two groups of women. There are limited studies about the safety of asthma drugs during breastfeeding. Published studies in the postpartum period have been small case series with generally short follow-up. Systemic absorption of inhaled drugs is generally minimal and causes little harm to the infant.[13] The infant's exposure is 10 to 1000 times less than during pregnancy.[20] The amount ingested through the mother's milk is far below the therapeutic level for an infant – mostly under 3% of a therapeutic dose per kilogram bodyweight.[21]

Short-acting beta agonists may be used at the usual doses.[10] Maintenance doses of inhaled budesonide (200 microgram or 400 microgram twice daily) result in negligible systemic exposure for the breastfed infant.[22] Once absorbed, inhaled budesonide is a weak systemic steroid and it is unlikely that clinically relevant concentrations would be transferred to the infant.[12] Similarly, only 30% of fluticasone is absorbed systemically and the majority is metabolised by first-pass metabolism.[23] No studies are available for the safety of ciclesonide and cromolyn (milk:plasma ratios unknown) in breastfeeding mothers, but in vitro studies show that the infant would be exposed to virtually undetectable concentrations so is unlikely to be at risk.[12]

There are no human studies of montelukast in breastfeeding, but animal studies have detected excretion into milk. Alternative treatment with short-acting beta agonists, long-acting beta agonists or inhaled corticosteroids should be considered during breastfeeding, particularly as montelukast is taken orally.[10]

Prednisolone at recommended doses is thought to be safe since the amount excreted in human milk is low with daily doses up to 80 mg.[10] It is recommended to withhold feeds for four hours after each dose to reduce infant exposure.[10] Prednisolone is preferred over prednisone, as prednisone is converted to prednisolone in vivo, causing a double peak of parent medicine and metabolite.[10]

Conclusion and recommendations

Due to the limited evidence from large, well-designed prospective studies in pregnant and breastfeeding women, there is often a lack of confidence amongst health professionals when deciding the most appropriate asthma therapy. Optimal asthma control should always be the first priority.

Australian and international guidelines recommend that women continue with the same therapy they used before pregnancy, especially if this regimen adequately controlled their asthma, and that they monitor their asthma monthly.[13,24-26] A switch to budesonide could be considered if the patient is planning a pregnancy and is already taking another inhaled corticosteroid.[13]

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Most of the asthma drugs are safe to use in breastfeeding. Women should be encouraged to continue their treatment during lactation.

Severe or difficult to treat asthma and asthma in women who continue to smoke may require a multidisciplinary approach with a respiratory specialist and more intensive monitoring.

Researchers are currently looking into markers of asthma control during pregnancy.[27] For now, spirometry is recommended for monitoring during pregnancy.[28] ≪

Michael Abramson holds an investigator initiated grant from Pfizer for unrelated research.

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SELF-TEST QUESTIONS

True or false?

1. The risk of fetal malformations is increased by treating acute exacerbations of asthma with oral corticosteroids.
2. Inhaled budesonide can be used during lactation.

Answers on page xx

Chapter 4: Management of asthma in pregnant women by general practitioners: A cross sectional survey

(Phase 2)

4.1 Preamble

Suboptimal prescribing in pregnancy is a major contributing factor to nonadherence to preventive asthma medications during pregnancy. Understanding prescriber perceptions associated with preventive asthma medication use during pregnancy and knowledge about the implementation of recommendations could provide useful background information for designing interventions to improve care.

Since little was known about this topic, an anonymous postal survey was undertaken as it was the most efficient way to reach a wide audience to elicit a range of responses. Furthermore, it was a relatively efficient way of recruiting general practitioners and allowed for anonymity, which may be desirable to prescribers.

General practitioners involved in shared maternal care were the targeted participants as they play a major role in managing asthma in pregnant women in the Victorian antenatal care model. Most obstetricians and midwives refer women to a general practitioner to discuss asthma concerns.

The aim was to investigate the management of maternal asthma by shared care general practitioners with a view to developing strategies to address suboptimal care.

The specific objectives of this phase were to:

- investigate prescribing trends for preventive asthma medications in pregnancy; and

- explore management strategies for various hypothetical clinical scenarios of pregnant women with asthma with a view to developing strategies to address suboptimal care

What this manuscript adds to current knowledge

To the best of my knowledge, this was the first study to investigate the management of pregnant women by general practitioners (also known as family physicians). This study provides essential information regarding the asthma management guidelines followed by prescribers, their management of pregnant women with asthma, and their preferences for different medication classes.

Publishing this manuscript in the open access online journal **BioMed Central (BMC) Family Practice** allowed targeting the appropriate audience to highlight the need for better asthma management during pregnancy.

4.2 Authors' declaration

MONASH University

Declaration by candidate for paper 3 titled:

Management of asthma in pregnant women by general practitioners: A cross sectional survey

The undersigned hereby certify that:

1. The above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors;
2. They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
3. They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
4. There are no other authors of the publication according to these criteria;
5. Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
6. The original data are stored at the following location and will be held for at least five years from the date indicated below:

Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences,
Monash University,
Victoria, Australia
Date: 1st July 2013

The nature and extent of candidate's contribution to the work was:

Nature of contribution	Extent of contribution

Conceived idea, designed and validated survey tool, conducted survey, entered and analysed data and prepared the first and final drafts of manuscript	80%

Candidate's signature: [redacted] **Date:** 1st July 2013

The contributions of c- authors to the work were:

Name of co-author	Nature of Contribution
Dr Johnson George	Advised on study design, survey tool development and data analysis and assisted with manuscript preparation
A/Prof Kay Stewart	Advised on study design, survey tool development and data analysis and assisted with manuscript preparation
Prof Michael Abramson	Advised on study design, survey tool development and data analysis and assisted with manuscript preparation

Co-author's signature [redacted] **Date:** 1st July 2013

(Dr Johnson George)

Co-author's signature [redacted] **Date:** 1st July 2013

(A/Prof Kay Stewart)

Co-author's signature [redacted] **Date:** 1st July 2013

(Prof Michael Abramson)

4.3 Manuscript

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BMC Family Practice

RESEARCH ARTICLE Open Access

Management of asthma in pregnant women by general practitioners: A cross sectional survey

Angelina S Lim[1], Kay Stewart[1], Michael J Abramson[2] and Johnson George[1*]

Abstract

Background: Poorly controlled asthma can lead to maternal and fetal complications. Despite the known risks of poorly controlled asthma during pregnancy and the need for stepping up therapy when appropriate, there are concerns that management is suboptimal in primary care.
Our objective was to investigate the management of asthma during pregnancy by general practitioners providing shared maternity care.

Methods: A pre-piloted, anonymous mail survey was sent to all general practitioners (n = 842) involved in shared maternity care at six maternity hospitals in Victoria, Australia. Respondents were asked about their perceived safety of individual asthma medications during pregnancy. Approach to asthma management during pregnancy was further explored using scenarios of pregnant women with stable and deteriorating asthma and poor medication adherence.

Results: Inhaled corticosteroids (ICS) were perceived to be the safest and were the preferred preventive medication in first trimester (74.1%), whilst leukotriene receptor antagonists were the least preferred (2.9%).
A quarter (25.8%) of respondents would stop or decrease patients' ICS doses during pregnancy, even when their asthma was well controlled by current therapy. In addition, 12.1% of respondents were not sure how to manage deteriorating asthma during pregnancy and opted to refer to another health professional. Almost half the respondents (48.9%) reported encountering medication nonadherence during pregnancy.

Conclusion: A lack of confidence and/or knowledge among general practitioners in managing deteriorating asthma in pregnancy was observed despite a good understanding of the safety of asthma medications during pregnancy, compliance with evidence-based guidelines in the selection of preventive medications, and self reported good asthma knowledge.

Background

Optimal asthma control during pregnancy is vital for the well-being of both mother and fetus. Poorly controlled asthma increases the risk of pre-term birth, low birth weight, cesarean section, stillbirth, intrauterine growth restriction (IUGR), congenital malformations (e.g. ventricular and atrial septal defects, spina bifida), small for gestational age (SGA) infants, pre-eclampsia, chorioamnionitis, low APGAR scores and gestational diabetes [1]. Fetal hypoxia, also a result of poorly controlled asthma during pregnancy, can lead to severe risks of neonatal respiratory difficulties, fetal brain ischemia and cerebral palsy [2]. Moreover, fetal growth restriction has been associated with the development of ischemic heart disease, hypertension, and type 2 diabetes in adulthood [3-7]. Conversely, maternal asthma that is well managed has not been associated with any increased risk of complications [8,9]. A promptly treated acute asthma attack during pregnancy is unlikely to have a serious effect on the pregnancy, delivery, or the health of the infant [10].

A decrease in the use of inhaled anti-inflammatory agents (preventers) [inhaled corticosteroids (ICS)], symptom controllers [long-acting beta agonists (LABA)] and their combinations, but an increase in the use of relievers [short-acting $beta_2$ agonists (SABA)] during pregnancy has been reported [11]. Chambers found that two in five women discontinued or reduced their asthma medication during pregnancy, leaving them at risk of uncontrolled

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asthma [12]. Women who decreased their ICS medication have been shown to deliver offspring with lower mean birth weight and length than women who did not [13].

Asthma management during pregnancy should follow the stepwise management of asthma in adults. The British Thoracic Society (BTS),[14] Global Initiative for Asthma (GINA),[15] National Asthma Council of Australia (NAC) [16] and National Heart, Lung and Blood Institute (NHLBI)[17] recommend continuing pregnant women on the same asthma therapy used prior to the pregnancy, if their asthma is well controlled on that regimen. ICS are the recommended first line agents for the treatment of mild to moderate persistent asthma in most guidelines except those of the American College of Obstetricians and Gynecologists and the American College of Allergy, Asthma and Immunology (ACOG & ACAAI),[18] which recommend cromones ahead of ICS. A switch to budesonide is recommended for women who are planning a pregnancy and already using an ICS, as it has more evidence for safety during pregnancy [16].

Even though evidence is lacking for the safety of some asthma medications during pregnancy, the risks of uncontrolled asthma during pregnancy are very clear. The authors recently conducted a systematic review of the safety of regular preventive asthma medications during pregnancy and reported some negative outcomes, but also noted many factors confounding the trials [19]. It was concluded that asthma preventive medications did not cause poor perinatal outcomes. Health care providers should not hesitate to increase doses or introduce additional medications as needed. Selection of preventive medications for asthma management during pregnancy should be based on an assessment of the risks and benefits of medication use versus the risks of poorly controlled asthma [19].

The main barrier reported when prescribing in pregnancy was access to current information about medication effects on the foetus, due to lack of a single comprehensive source of information, lack of time to access information and rapidly outdated information [20]. Physicians' and obstetricians' heavy reliance on the United States Food and Drug Administration (FDA) pregnancy risk categories, in combination with their reluctance to weigh risks versus benefits of medication use in pregnancy in individual patients, may be contributing to low prescribing rates during pregnancy [20]. In one study from the United States, pregnant asthmatic women were significantly less likely to be prescribed oral steroids either in the emergency department or on discharge from hospital than were non-pregnant asthmatic women [11]. The pregnant women were also three times more likely than non-pregnant women to report ongoing asthma exacerbations following hospital discharge [11].

There is little information available regarding prescribing trends in pregnant women with asthma in primary care. Despite the overwhelming consensus that pregnant women with asthma should be rigorously managed, doctors still under-prescribe. Due to the increased risk of poor perinatal outcomes, pregnant asthmatic women are recommended to have their asthma monitored at least once a month and their therapy should be increased when appropriate [17]. A study from Yale University found that two-thirds of pregnant asthmatic women were under-treated for asthma for three or more months of pregnancy [12]. Pregnant women were concerned about using steroids during pregnancy due to the perceived effects on the unborn child. Two in five women said they would be more likely to continue taking their asthma medication during pregnancy if their prescriber had recommended it, showing that prescribers have a vital role in encouraging patient adherence to treatment recommendations. Understanding the prescribing practices of physicians providing care to pregnant women with asthma would provide valuable information to optimise asthma management during pregnancy.

The objective of this study was to describe the management of asthma during pregnancy by general practitioners, with a view to informing initiatives for improving asthma management, leading to improved maternal and fetal outcomes.

Methods

An anonymous mail questionnaire was sent to all general practitioners involved in shared maternity care (n = 842) at six public maternity hospitals in Melbourne, Australia. Shared care general practitioners are affiliated with one or more maternity hospitals and review women with uncomplicated pregnancies regularly until delivery, rather than having them attend maternity hospital out-patient antenatal clinics. Any general practitioner, who is accredited at a maternity hospital as a Shared Maternity Care Affiliate, can provide maternity shared care. To find out more about this model of care and the accreditation processes, please refer to http://www.health.vic.gov.au/maternitycare/smcaguidelines.pdf

The questionnaire was designed by the authors using items derived from the literature and discussion with pharmacists and respiratory consultants. Face and content validity was established through review by other experienced researchers (n = 13) and general practitioners (n = 4). Minimal changes were made to the questionnaire based on feedback. The final questionnaire (see additional file 1) consisted of three sections: The first section had 9 items on demographics and the prescriber's practice. The second section asked respondents to rank their preferences for prescribing preventive asthma medication

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during pregnancy and to indicate their perceived safety of different asthma medications in each trimester. The third section aimed to gauge respondents' likely approach to asthma management in pregnant women with the help of two scenarios.

Initially, an explanatory letter, questionnaire and reply-paid envelope were mailed by administrative staff in charge of shared maternity care at each hospital. Due to the anonymous nature of the survey, a blanket reminder letter, questionnaire and reply-paid envelope were sent to all general practitioners six weeks later. As an incentive, potential participants were advised that a small donation would be made to the Asthma Foundation of Victoria for each completed survey returned to the investigators.

This study was endorsed by The Asthma Foundation of Victoria and approved by the Monash University Human Research Ethics Committee (Approval no. CF10/2750 - 2010001557). Permission to contact participants was also sought from all participating institutions.

Statistical analysis

For a population of 850 general practitioners, 144 responses were required to ensure that the sample proportions would be within ±5% of the true values with a 90% level of confidence. Data were analysed using SPSS, version 19.0 (IBM, Somers, NY, USA, 2010). Chi square and independent sample t-tests were performed to investigate relationships between prescriber demographics and prescribing appropriateness, which was identified for the vignettes according to global asthma guidelines [14-18]. Significance level was set at $P < 0.05$.

Results

A total of 176 questionnaires were returned (response rate 20.9%); two were excluded from the analysis as more than 20% of items were unanswered. Respondents were mostly female (70.7%), practising in the metropolitan region (84.5%) and had practised as general practitioners for a median of 19 years. Approximately one-third of respondents had encountered asthma in more than 10% of their pregnant patients. The characteristics of respondents are shown in Table 1.

ICS (74.1%) were the preferred preventive medication for a pregnant woman with worsening asthma in the first trimester, while leukotriene receptor antagonists (LTRA) (2.9%) were the least preferred agents (Table 2). At normal adult doses, ICS and beta$_2$ agonists (short- and long-acting) were perceived to be safe in all trimesters by the majority of respondents, while participants had concerns about the safety of LTRA during all trimesters (Table 3).

Table 1 Demographics and practice information of respondents (n = 174)*

Characteristic	n (%)
Gender	
Female	123 (70.7%)
Years of practice as a Family Practitioner	
≤10years	23 (13.2%)
11-20years	63 (36.1%)
21-30years	63 (36.1%)
>30years	24 (13.7%)
Current practice location	
Metropolitan	147 (84.5%)
Regional	15 (8.6%)
Rural	11 (6.3%)
Proportion of pregnant women cared for who have asthma	
None	6 (3.4%)
<10%	108 (62.1%)
11-20%	52 (29.9%)
>20%	4 (2.3%)
Assistance with asthma management	
None	120 (69.0%)
Practice nurse	34 (19.5%)
Asthma educator	4 (2.3%)
Both an asthma educator and practice nurse	3 (1.7%)
Perceived asthma knowledge	
Poor	1 (0.6%)
Average	56 (32.2%)
Good	81 (46.6%)
Very good	35 (20.1%)

*Some numbers do not add up to 174 due to missing data

Preferred management of asthma in pregnant women

Case vignette one part one (stable asthma in pregnancy)

A quarter of respondents would stop or reduce the dosage of preventive asthma medication during pregnancy, even though the patient's asthma was well controlled on the regimen prior to pregnancy (Table 4). A single agent therapy rather than the combination was preferred by 20.3% of respondents; but one respondent preferred to use ICS

Table 2 Preferences for asthma preventive medication use in pregnancy (n = 174)

Asthma preventive medication class	n (%)	
	First preference	Second preference
Cromones	13 (7.5%)	22 (12.6%)
Leukotriene receptor antagonists (LTRA)	5 (2.9%)	3 (1.7%)
Inhaled corticosteroids (ICS)	129 (74.1%)	24 (13.8%)
Long-acting beta$_2$ agonists (LABA)	10 (5.7%)	11 (6.3%)
LABA/ICS combination	36 (20.7%)	73 (42.0%)

*Some numbers do not add up to 174 due to missing data

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Table 3 Perceived safety of asthma medications during pregnancy in different trimesters (n = 174)

	n (%)					
	First trimester		Second trimester		Third trimester	
Drug	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
Cromones						
Nedocromil	88 (50.9%)	41 (23.6%)	102 (59.0%)	22 (12.6%)	100 (57.8%)	23 (13.2%)
Sodium Cromoglycate	112 (64.4%)	29 (16.7%)	125 (71.8%)	15 (8.6%)	123 (70.7%)	17 (9.8%)
Inhaled corticosteroids						
Beclomethasone	132 (75.9%)	23 (13.2%)	140 (80.5%)	16 (9.2%)	142 (81.6%)	15 (8.6%)
Budesonide	154 (88.5%)	6 (3.4%)	159 (91.4%)	3 (1.7%)	156 (89.7%)	3 (1.7%)
Ciclesonide	111 (63.8%)	31 (17.8%)	120 (69.0%)	23 (13.2%)	121 (69.5%)	21 (12.1%)
Fluticasone	133 (76.4%)	26 (14.9%)	144 (82.8%)	14 (8.0%)	147 (84.5%)	11 (6.3%)
Leukotriene receptor antagonists						
Montelukast	47 (27.0%)	79 (45.4%)	60 (34.5%)	67 (38.5%)	59 (33.9%)	68 (39.1%)
Zafirlukast	29 (16.7%)	83 (47.7%)	40 (23.0%)	73 (42.0%)	40 (23.0%)	73 (42.0%)
Long-acting beta$_2$ agonists						
Eformoterol	101 (58.0%)	46 (26.4%)	120 (69.0%)	21 (12.1%)	121 (69.5%)	23 (13.2%)
Salmeterol	105 (60.3%)	44 (25.3%)	124 (71.3%)	20 (11.5%)	125 (71.8%)	22 (12.6%)
Oral corticosteroids						
Prednisolone	141 (81.0%)	20 (11.5%)	151 (86.8%)	8 (4.6%)	149 (85.6%)	12 (6.9%)
Short-acting beta$_2$ agonists						
Salbutamol	167 (96.0%)	0 (0.0%)	164 (94.3%)	0 (0.0%)	164 (94.3%)	1 (0.6%)
Terbutaline	146 (83.9%)	5 (2.9%)	144 (82.8%)	4 (2.3%)	144 (82.8%)	6 (3.4%)

*Some numbers do not add up to 174 due to missing data

alone. A few (4.0%) decided to decrease the dose of the salmeterol/fluticasone combination.

Case vignette one part two (deteriorating asthma in pregnancy)

Only 62.6% of general practitioners opted to increase the dosage of the current regimen on deterioration of symptoms (Table 4). A few respondents (4.6%) decided to continue the same regimen and not intervene, leaving the patient at risk of uncontrolled asthma.

Patterns of prescribing and management had no association with the proportion of pregnant women treated per year, years in practice, clinical setting, the availability

Table 4 Responses for case vignette one (n = 174)

Case vignette one:
A patient of yours has recently become pregnant. She has moderate asthma which is well controlled with salmeterol/fluticasone (250/25), one puff twice daily, and salbutamol inhaler as required. She has no other medical conditions nor is she taking any other medications. Part one (Stable asthma in pregnancy): She wonders whether she should continue these medications during pregnancy. What is your intended action?

Responses for (i)	**n (%)**
Continue her on the same medications	123 (70.7%)
Decrease her dose	43 (24.7%)
Refer	5 (2.9%)
Stop her medication	2 (1.2%)

Part two (deterioating asthma in pregnancy): A few weeks pass by and your patient returns. You notice that her asthma is deteriorating. She tells you that she has been using her salbutamol inhaler more than three times per week. She has been compliant with the salmeterol/fluticasone and has had no changes to her asthma medication regimen nor has she had any changes in lifestyle. What is your intended action?

Responses for (ii)	**n (%)**
Increase her dose	116 (66.7%)
Refer	21 (12.1%)
Continue her on the same regimen and just monitor her asthma more closely	15 (8.6%)
Add another agent	10 (5.7%)
Decrease ICS regimen	9 (5.2%)

*Some numbers do not add up to 174 due to missing data

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of help from a practice nurse or asthma educator, perceived knowledge, or asthma management guidelines followed (P values all greater than 0.05).

Case vignette two (nonadherent asthmatic pregnant patient)

Over three quarters of respondents (82.2%) would reinforce the need to use the eformoterol/budesonide combination by the 18 weeks pregnant woman with concerns about the safety of this combination, given her history of poor adherence (Table 5). Only two respondents chose not to reinforce the need to adhere to the asthma regimen and a few (12.4%) chose to switch her to another preventive medication that allowed more convenient dosing.

Almost half of the respondents (48.9%) reported encountering patients with poor adherence to preventive asthma medications during pregnancy, putting them at risk of complications. Strategies they employed for improving adherence were: providing education on risks associated with nonadherence to asthma medications during pregnancy and poor asthma control (46.6%); providing education focusing on the safety of asthma medications during pregnancy (42.0%); organising regular visits to monitor asthma control (36.2%); organising regular return visits to monitor adherence (27.6%); referral to another health professional to monitor asthma control (8.6%) and referral to another health professional to monitor adherence (4.6%).

Discussion

This study has shown a strong preference for ICS as first line preventive therapy, which is the recommended agent for pregnant women by most guidelines, including the NAC guidelines [14-17]. In reporting perceived safety of asthma medications in each trimester, ICS were regarded as safe throughout pregnancy. Uncertainty about the safety of LTRA throughout pregnancy was evident. This could possibly be attributed to limited safety data available on these newer medications and/or prescribers' lesser familiarity with these drugs.

It is comforting to know that prescribers are confident addressing poor adherence when confronted with the situation; all respondents listed strategies they have used to improve adherence when noncompliance was encountered. However, it is well known that patients do not normally admit nonadherence and prescribers rarely ask about adherence during consultations [21].

The majority of respondents opted to keep the woman who recently became pregnant on the same asthma regimen as that prior to conception. However, a considerable number of prescribers would either decrease or stop her medication or refer her to another health professional, even though her asthma was well controlled on a fluticasone/salmeterol regimen. Not surprisingly, more prescribers opted to refer when her asthma started deteriorating. Although referral was not an inappropriate action, the case presented did not warrant referral according to the Asthma Management Guidlelines[22] e.g. life threatening asthma attacks, no response to therapy, need for frequent courses of oral corticosteroids. This suggests a lack of confidence and/or knowledge among general practitioners in managing deteriorating asthma in pregnancy. Prescribers apparently feel more comfortable referring these patients; this is surprising in light of the fact that two-thirds of respondents rated their asthma knowledge as good or very good.

There were no differences between experienced and less experienced prescribers in the appropriateness of asthma medicines selected. This is evidence against the suggestion that less experienced prescribers would be more likely to under-prescribe and deem medications unsafe in pregnancy [23]. The proportion of pregnant women treated per year, the clinical setting, support from a practice nurse or asthma educator, perceived knowledge, and use of

Table 5 Responses for case vignette two (n = 174)

Case vignette two

One of your regular patients is 18 weeks pregnant and she asks you for a new prescription for salbutamol inhaler, as she is a health care card holder and can get them cheaper on script. However, you notice that she got a script for salbutamol inhaler only last month. Upon asking, you find out that she has stopped her budesonide/eformoterol inhaler because she fears it will harm her unborn child. Instead she has been using her salbutamol inhaler more frequently to compensate. She has no other medical conditions nor is she taking any other medications.

(i) **Part one (nonadherent asthmatic pregnant patient):** What is your intended action?*

Participants could only tick one response for part one

Responses for (i)	n (%)
Give script for salbutamol and reinforce the need to continue her preventive medication	143 (82.2%)
Give script for salbutamol but change her onto a different preventive medication	21 (12.4%)
Give script for salbutamol and refer	6 (3.5%)
Give script for salbutamol with no further questions	2 (1.2%)
Do not give the salbutamol script and refer patient	0 (0.0%)

*Some numbers do not add up to 174 due to missing data

guidelines were not found to predict appropriate prescribing, but interpretation was limited by low sample size. Some prescribers who said they followed a particular guideline for asthma management still commented that they would like more information regarding management for this population. Morgan *et al.* found that the major barriers to prescribing during pregnancy were lack of a single comprehensive source of information, lack of time and the fact that information gets outdated rapidly [23].

Limited data were available on the study population, but most characteristics were in line with the general population of Australian general practitioners, with the majority practicing in the metropolitan area (84.5% vs. 71% as the national average in 2009-10) [24]. No statistics are available on the characteristics of general practitioners involved in shared maternity care. Our sample had a considerably higher proportion of females than in the Australian population of practicing general practitioners (70.7% vs 44%); [24] shared maternity care may be more attractive to female general practitioners. Our respondents were more likely to have a nurse in their practice than reported in the national statistics (21.2% vs 9.0%);[24] however, patients attending nurse-run asthma clinics based in Australian general practice did not show a greater improvement in quality of life or lung function compared with those receiving usual care [25].

Strengths and limitations

This study has provided information about general practitioners' likely management of asthma in pregnant women. To the best of our knowledge, a survey of this nature has not been previously reported. The study population comprised general practitioners providing shared maternity care in affiliation with all the major Victorian maternity hospitals, including the largest maternity hospital in Australia. Our findings should make general practitioners more aware of under utilization of preventive asthma medications during pregnancy and improve the management of women with asthma.

Our study had a modest response rate; however, this level of response is typical for a postal survey directed to general practitioners [26]. As the study was anonymous, we were unable to follow up the non-respondents to improve the response rate or to compare their characteristics with those of the respondents. Responses were received from general practitioners with a range of characteristics; nevertheless, it is possible that the respondents were more knowledgeable than their counterparts, in which case the extent of poor practice observed would be an underestimation. Thus, it is possible that the perception of general practitioners and poor management of pregnant asthmatic women could be underestimated. There is limited information on women's experiences of asthma management during pregnancy; however, the authors are currently conducting a qualitative study with pregnant asthmatic women in each trimester and with varying asthma severity to address this gap in the literature.

The authors are developing interventions and strategies to promote awareness of poor asthma management during pregnancy targeting both pregnant women with asthma and their health professionals. These interventions may take the form of educational modules that can be used for continuing education of health care providers, or antenatal clinics specifically for pregnant women with asthma.

Conclusion

Overall, general practitioners had a good understanding of the safety of asthma medications during pregnancy, complied with evidence-based guidelines in the selection of preventive medications, and self reported good asthma knowledge. Despite this, a lack of confidence and/or knowledge among general practitioners in managing deteriorating asthma in pregnancy was observed. The findings from this survey will inform the development of future interventions and strategies to optimize asthma management and outcomes in pregnant women.

Additional material

Additional file 1: Management of pregnant women with asthma survey. This is the questionnaire used in our study to investigate prescribing patterns and management strategies of pregnant women with asthma by general practitioners. This survey was given to all our participants and endorsed by the Asthma Foundation of Victoria.

List of abbreviations

ACOG & ACAAI: American College of Obstetricians and Gynecologists & the American College of Allergy; Asthma and Immunology; APGAR: Named after Dr Viginia Apgar (calculated by scores of the newborn's activity; pulse; grimace; appearance; respiration usually at 1 to 5 minutes after delivery); BTS: British Thoracic Society; FDA: Food and Drug Administration; ICS: Inhaled corticosteroids; IUGR: Intrauterine growth restriction; GINA: Global Initiative for Asthma; LABA: Long-acting $beta_2$ agonists; LTRA: Leukotriene receptor antagonists; NAC: National Asthma Council of Australia; NHLBI: National Heart; Lung and Blood Institute; SABA: Short-acting $beta_2$ agonist; SGA: Small for gestational age.

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Authors' contributions
AL proposed the original concept and developed it with input from JG, KS and MA. AL was responsible for data collection and entry. All authors were involved in data analysis, interpretation and manuscript preparation. All authors approved the final manuscript.

Competing interests
The authors declare that they have no competing interests
Conflicts of interest: Angelina Lim - none, Kay Stewart - none, Michael Abramson - was a member of the scientific committee for a meeting sponsored by GlaxoSmithKline, Johnson George - none
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Chapter 5: Asthma during pregnancy: The experiences, concerns and views of pregnant women with asthma (in-depth interviews)

(Phase 3)

5.1 Preamble

In addition to investigating asthma management from the prescribers' viewpoint, it is important to understand the behaviour of pregnant women in relation to medication use. They have been shown to discontinue their asthma medications or reduce dosages without consulting their health professionals. Information about what barriers and facilitators affect adherence is required to develop patient-centered, tailored strategies to improve asthma management in pregnant women.

Because there was limited evidence available on asthma medication use in pregnancy, especially from the women's perspective, in-depth interviewing was more suitable than semi-structured or structured interviews in order to gain comprehensive information regarding pregnant women's attitudes and behaviours in regard to asthma management. Medication use can be a sensitive topic, for which a focus group may not encourage open discussion.

The aim was to explore asthma experiences and medication use in pregnant women with asthma to inform the development of strategies to improve asthma management during pregnancy.

The specific objectives of this phase were to:

- understand the perceptions and experiences of asthmatic pregnant women in regard to medication use; and
- elicit the facilitators for and barriers to adherence to asthma medications during pregnancy

What this manuscript adds to current knowledge

The information obtained by interviewing pregnant women with asthma has demonstrated the need for interventions to improve asthma management during pregnancy. The findings of this study support the literature surrounding nonadherence to asthma medications during pregnancy and improve understanding of why women are nonadherent.

The results of this study have not only been published in the peer-reviewed **Journal of Asthma** but also have been presented orally at many conferences attended by relevant health care professionals, such as midwives, asthma educators, pharmacists and general practitioners, and consumers. A number of media reports have arisen from this article.

This study has not only provided information to help support practice but has also helped to justify the need for more services to improve asthma management during pregnancy.

5.2 Authors' declaration

MONASH University

Declaration by candidate for paper 4 titled:

Asthma during pregnancy: The experiences, concerns and views of pregnant women with asthma

The undersigned hereby certify that:

1. The above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors;
2. They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
3. They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
4. There are no other authors of the publication according to these criteria;
5. Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
6. The original data are stored at the following location and will be held for at least five years from the date indicated below:

Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Parkville, Victoria 3052
Date: 1st January 2013

The nature and extent of candidate's contribution to the work was:

Nature of contribution	Extent of contribution
Conceived idea, designed topic guide, conducted interviews, analysed data and prepared first and final drafts of manuscript	80%

Candidate's signature: [redacted] **Date:** 1st July 2013

The contributions of co-authors to the work were:

Name of co-author	Nature of Contribution
Dr Johnson George	Advised on study design and topic guide and assisted with manuscript preparation
A/Prof Kay Stewart	Reviewed interviews, assisted with interview training, data analysis and manuscript preparation
Prof Michael Abramson	Advised on study design and topic guide and assisted with manuscript preparation
A/Prof Kath Ryan	Assisted with interview training and manuscript preparation

Co-author's signature [redacted] **Date:** 1st July 2013

(Dr Johnson George)

Co-author's signature [redacted] **Date:** 1st July 2013

(A/Prof Kay Stewart)

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(Prof Michael Abramson)

Co-author's signature [redacted] **Date:** 1st July 2013

(A/Prof Kath Ryan)

5.3 Manuscript

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Asthma during Pregnancy: The Experiences, Concerns and Views of Pregnant Women with Asthma

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Objective. To investigate how pregnant women manage their asthma during pregnancy and factors influencing their behavior. *Methods*. In-depth interviews (telephone or face-to-face) with a purposive sample of 23 asthmatic women at various stages of pregnancy and with varying severity of asthma. *Results*. Five major themes were discerned relating to health behavior of pregnant women with asthma. Many of the participants decreased or discontinued their asthma medications themselves and refrained from taking doses when necessary during pregnancy without consulting their doctors. Reasons behind their decisions revolved around lack of support and information about what to do, concerns about the safety of the medications, past experiences, and desire for an "all natural" pregnancy. Asthma monitoring during pregnancy was seen as a low priority for some women and their doctors. Communication between pregnant women and health professionals regarding asthma management was poor. The health behavior of pregnant women with asthma could be explained using the Health Beliefs Model. *Conclusions*. Pregnant women are not well supported in managing asthma during pregnancy, despite being concerned about outcomes. Interventions, education, and more support are warranted and wanted by pregnant women with asthma to optimize pregnancy and neonatal outcomes.

Keywords adherence, inhaled corticosteroids, obstetrics, in depth interviewing

INTRODUCTION

Asthma during pregnancy should be a high priority for health professionals as one in eight pregnant women has asthma (1). Furthermore, poor asthma management during pregnancy is hazardous for both mother and child, leading to increased risk of complications and poor outcomes, such as premature births, low birth weight, preeclampsia, impaired fetal brain development, and malformations (2–4). Prematurity has also been linked to an increased risk of heart disease in adulthood (5, 6). Optimal asthma control during pregnancy is vital to reduce risks; pregnant women should have their asthma monitored at least monthly (7).

Our recent systematic review highlighted a low incidence of adverse events when taking regular preventive asthma medication during pregnancy (8); studies that reported adverse events with asthma medication had numerous confounding factors and a direct association could not be drawn between medications and negative outcomes. Globally, asthma guidelines strongly recommend that women continue their asthma medications during pregnancy to maintain adequate control (7, 9–13). Furthermore, potential benefits of improved fetal growth (14), a reduction in asthma exacerbations (15, 16), and a reduction in the risks of malformations can arise from using asthma preventive medication during pregnancy (17). Despite this evidence, disseminating this information to women and improving adherence is clearly a problem.

Adherence to asthma medications during pregnancy is a significant problem, with over one-third of women discontinuing their asthma medications during pregnancy, many without consulting their doctors (18, 19). Reasons for nonadherence to asthma medications during pregnancy and poor asthma management during pregnancy have not been explored in depth. Women have been shown to be more reliant on their bronchodilators (reliever therapy) and refrain from using their anti-inflammatory medications (preventive therapy) (18). Women who decreased their inhaled corticosteroid (ICS) had babies with lower mean birth weight and length than women who did not (14).

Two in five women are more likely to continue their asthma medication during pregnancy if recommended by their doctor (19). This suggests the crucial role of doctors in ensuring patient adherence to asthma medications during pregnancy. Our recent survey of family physicians' prescribing patterns, however, found that over a quarter would instruct their pregnant patients to decrease or discontinue asthma medication during pregnancy when asthma was well controlled by current therapy (20), potentially jeopardizing asthma control.

Pregnant asthmatic women may not be well supported in regard to their asthma and may be unaware of the risks of uncontrolled asthma during pregnancy. The views and experiences of asthmatic pregnant women were explored

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with a view to developing strategies to improve asthma management during pregnancy.

METHODS

Interviews

Interviews (5 face-to-face and 18 by telephone) were conducted with pregnant asthmatic women about their asthma control and management during pregnancy. The topic guide included perceptions about asthma medications, asthma symptoms during pregnancy, medication use, and support from health professionals.

Participants

Participants were recruited from a large maternity hospital in Australia through a database that identified all outpatient pregnant women with asthma. Participants were excluded if they were under 18 years of age, were non-English speaking, or had no asthma symptoms during the previous 10 years. Selection was also based on a pre-interview questionnaire which enabled us to select women with varying asthma severity (using questions derived from the Asthma Control Questionnaire (ACQ) (21) and classification according to the National Asthma Management handbook (22)) and at various stages of pregnancy (second trimester, third trimester, or delivered within the previous 5 weeks). Medication adherence prior to pregnancy was recalled using the Tools for Adherence Behaviour Screening (TABS), a subscale of the Beliefs and Behaviour Questionnaire (BBQ) (23).

Ethics Approval

This study was approved by the Mercy Health Human Research Ethics Committee and the Monash University Human Research Ethics Committee.

Data Collection and Analysis

Data collection and analysis ran concurrently. One trained researcher (AL) conducted all interviews, which were audio-recorded and transcribed verbatim. Transcripts were organized using NVivo Version 9.0 (QSR International, Doncaster, Australia). Two researchers (AL and KS) coded the transcripts independently for relevant content using the framework approach (24). Results were discussed to establish emerging themes and aid future direction of interviews. This process continued until data saturation was apparent.

RESULTS

Participants

From 179 potential participants, a purposive sample of 23 women was selected for interview. Participants (age range 21–43 years) had a range of demographic and obstetric characteristics and asthma severity (Table 1). Three participants were health-care card holders (25), indicating a lower than average household income. All participants reported they were non-smokers at the time of interview.

TABLE 1.—Characteristics of participants ($n = 23$).

Characteristic	*N*
Country of birth	
Australia	17
Other (China, England, Greece, New Zealand, Pakistan)	6
Gestation period	
Second trimester	7
Third trimester	12
Delivered	4
Other health conditions	
None	18
Allergic rhinitis	2
Depression	1
Eczema	1
Gestational diabetes	1
Sciatica	1
Time since asthma first diagnosed	
≤15 years	4
16–30 years	16
>30 years	3
Asthma medications	
SABA only	8
SABA + ICS	3
SABA + LABA/ICS	12
Asthma severity classification[a]	
Intermittent asthma	3
Mild persistent asthma	3
Moderate persistent asthma	8
Severe persistent asthma	9

Notes: ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; SABA, short-acting beta-agonist.
[a]According to the National Asthma Council classification (22).

Seven participants were primigravidae and the remaining were multigravidae, including three participants who had previous miscarriages. The sample included one assisted pregnancy (in vitro fertilization).

While participants had varying asthma severity, most were long-term moderate-to-severe persistent asthmatics who self-reported good adherence to their medications. The majority of participants ($n = 13$) experienced no changes to their asthma control during pregnancy, but some ($n = 7$) reported worsening of symptoms, mostly due to ceasing or reducing their preventive asthma medications.

Interview Themes

Five major themes relating to asthma management during pregnancy and changes in behavior emerged:

Risks versus Benefits. Perceived risks of uncontrolled asthma were overshadowed by concerns about medication use during pregnancy, especially anxiety about steroid use. However, for some individuals, the perceived risks of uncontrolled asthma distressed them more than the risks of medication use.

Concern for any medication use during pregnancy. Many women, especially those who opted for a home birth or a drug-free delivery, wanted to avoid medication use altogether during pregnancy:

> Just the fact it was medication … I don't even take [paracetamol] when I'm pregnant. (#23, 33 years, severe persistent asthma, second trimester)

Steroid phobia. The connotations of "steroid" distressed many women and deterred them from using their preventive asthma medications during pregnancy:

> The fact that it's a steroid and . . . no-one was really able to tell me that it was safe for the baby. (#20, 30 years, moderate persistent asthma, delivered)

Most participants could not name specific effects of steroids; however, they were seen to be detrimental to fetal growth and development:

> It could influence things like the growth of the baby and have impacts on hormonal and sex development. (#9, 36 years, mild persistent asthma, second trimester)

Some participants limited the use of their preventive medication during pregnancy because of this concern:

> I didn't with both pregnancies use my preventive [ICS] unless I was at the desperate stage. (#1, 28 years, severe persistent asthma, third trimester)

Concern about steroid use was most apparent in the first trimester as it was seen as a critical period of development and growth:

> Especially the first trimester . . . it's such a formative crucial stage when all the main development is happening . . . I was really cautious of using it [ICS] then. (#6, 30 years, severe persistent asthma, third trimester)

The limited absorption and placental transfer likely to result from inhaled route did not alleviate concerns, as participants still linked adverse events with inhaled use:

> The baby kicks a lot after my night time medication [ICS]. I can't imagine the baby is not affected. (#10, 33 years, moderate persistent asthma, third trimester)

Preference for alternative therapies. Some participants reported trying alternative therapies, before reaching for their asthma medications, to minimize medication use:

> I didn't use it [ICS] at all during the first trimester. I would try just slowing down, doing different breathing. I even tried steam in the shower. (#1, 28 years, severe persistent asthma, third trimester)

Lack of confidence in the benefits of medication use. Interestingly, some participants were starting to lose faith in the benefits of asthma medications altogether:

> I went on a course, just an info session . . . called Buteyko (26) . . . and it kind of made me question the validity of the use of asthma medication as the first port of call. (#9, 36 years, mild persistent asthma, second trimester)

Participants did their own risk/benefit assessment of using the medications and decreased their preventive therapy:

> I didn't think my asthma was that bad. I didn't think it was necessary to be taking the preventer [ICS] every day. (#13, 23 years, mild persistent asthma, delivered)

Perceived risks of uncontrolled asthma during pregnancy. No specific risks were identified, but the idea of decreased oxygen availability to the baby was a recurring theme. The risks became more concerning to those participants who had encountered poor neonatal outcomes:

> I'm more concerned about the lack of oxygen to the baby more so than the medication . . . the asthma attack is going to do more harm to the baby than keeping up preventers. (#3, 38 years, severe persistent asthma, third trimester)
>
> My daughter was born with extra digits . . . I actually thought that I had caused that, being off the asthma medication. (#20, 30 years, moderate persistent asthma, delivered)

Other asthma medicines. Relievers (short-acting bronchodilators) were seen as completely safe to use or unavoidable; many participants did not even bother checking their safety during pregnancy:

> I wouldn't think twice about using my [salbutamol] . . . we use asthma puffers on really young kids anyway. (#1, 28 years, severe persistent, third trimester)

Many women appeared happy to rely heavily on their reliever therapy and decrease their preventive therapy:

> I was having [salbutamol] anywhere up to eight puffs a night. (#23, 33 years, severe persistent asthma, second trimester)

Self-Efficacy. Self-management of asthma. Participants were mostly long-term asthmatics and felt quite confident in making their own decisions about their asthma:

> To be honest, I probably haven't had my asthma monitored properly for a good five to six years . . . I've had it for so long, I know when I can control it with [salbutamol]. (#5, 28 years, severe persistent asthma, second trimester)

Dealing with changes to asthma control during pregnancy. Many participants were unaware that pregnancy could change their asthma control and were not equipped to cope with changes. Asthma was described by some participants as significantly worse in their third trimester, although it was difficult for some to distinguish signs of worsening asthma from breathlessness associated with increasing uterine size. This made it difficult for some participants in deciding how to use their bronchodilator appropriately:

> The last trimester is the worst because of the uterus compression, pressing on the lungs; you get that shortness of breath. (#3, 38 years, severe persistent asthma, third trimester)

> It's a little bit unclear separating shortness of breath with asthma symptoms. (#23, 33 years, severe persistent asthma, second trimester)

Although worsening asthma could be attributed to ceasing or decreasing preventive medication, many participants thought it was unnecessary to restart their preventer:

> So whether my asthma worsened because I stopped taking my preventive or my asthma worsened because of the pregnancy, I can't tell you. (#5, 28 years, severe persistent asthma, second trimester)

Asthma as a Priority. Impact of symptoms and severity. If participants had mild asthma or did not experience any symptoms, they were indifferent about asthma monitoring and management during pregnancy:

> It [asthma] became a low priority, which means it wasn't bothering me very much. (#3, 38 years, severe persistent asthma, third trimester)

It was only when they experienced deterioration in control that they started to pay attention to their asthma:

> I didn't even think about going to the GP about my asthma . . . but the asthma attack frightened me. (#17, 39 years, severe persistent asthma, third trimester)

The exception was severe asthmatics who were more concerned about their asthma management:

> I've been hospitalised with it several times when I was young, so yeah, it's still a priority for me. (#17, 39 years, severe persistent asthma, third trimester)

Lack of concern for asthma by their GP. In many cases, if the GP did not bring up the topic of asthma, it was usually ignored:

> The GP never really asked about my asthma to be honest. (#12, 31 years, moderate persistent asthma, second trimester)

Competing priorities. Other medical conditions overshadowed asthma management during pregnancy:

> Other issues with my pregnancy have just taken precedence. (#4, 31 years, moderate persistent asthma, second trimester)

The limited time in appointments with their GP was thought to be better spent on discussions about diet, labor, and so on:

> You have lots of questions . . . it might have actually just gone on the backburner. (#2, 36 years, severe persistent asthma, third trimester)

Past experiences. Participants were likely to be more cautious about their medication if it was their first pregnancy or they had a history of miscarriage:

> It took me two years to get pregnant, so I was quite concerned about using the ICS. (#12, 31 years, moderate persistent asthma, second trimester)

Support and Guidance. Participants complained about the lack of information available on asthma during pregnancy and related topics:

> I wasn't given any information, that's why I was so concerned . . . It would have been good to know what effects different medications have [on the fetus]. (#13, 23 years, mild persistent asthma, delivered)

With the safety of asthma medications in pregnancy not clearly established, women were dissatisfied with the support they received regarding their medication:

> I went to the doctor a couple of times, I talked to the pharmacist, the nurses at the hospital . . . I found it quite frustrating because no one would give me an exact answer . . . I didn't feel like I really got any advice that I could feel confident about. (#20, 30 years, moderate persistent asthma, delivered)

This lack of evidence and support forced women to make their own choices about medication management, sometimes unfortunately wrong decisions:

> I felt I had to make a decision and the decision for me was not to take the [ICS]. (#5, 28 years, severe persistent asthma, second trimester)

Participants wanted more information on medication effects on the fetus, what to expect in regard to asthma changes during pregnancy and labor, medication reviews, regular asthma monitoring, asthma action plans for pregnancy, and alternative therapies. Participants preferred easily accessible information as they found it inconvenient to consult their GPs:

> It would have been good just to know a bit more information than just having to go to the GP, which is hard to book in . . . and they've got to see you so quickly. (#13, 23 years, mild persistent asthma, delivered)

Participants requested authoritative information from key stakeholders such as the Asthma Foundation or their hospitals:

> I think there needs to be definitely information from the Asthma Foundation. (#2, 36 years, severe persistent asthma, third trimester)

Influences on Medication Use. Sources of information. The Internet was a major source of information for many participants, although some had doubts about the quality of information:

> [If information was available from respectable organizations] either through an email or through a webpage, at least I'd know that it's from a reliable source and it's reliable information. (#12, 31 years, moderate persistent asthma, second trimester)
>
> I've already lost two [babies, through miscarriages], so I didn't want to blindly Google for the third. (#8, 32 years, moderate persistent asthma, third trimester)

The Internet led some women to making the wrong decisions:

> I did my own research, just because there wasn't any information available. So I went online and just Googled "asthma medication whilst pregnant" and it came back (that) I couldn't take [fluticasone–salmeterol combination] . . . so I just took myself off it before I even consulted my doctor because I found enough evidence on the Internet to say it's better not to be on it. (#2, 36 years, severe persistent asthma, third trimester)

Some participants had support from family members who had medical or nursing backgrounds:

> I talked to my mum over the phone and she said you shouldn't be using [salbutamol] that much. She's a nurse. (#15, 30 years, moderate persistent asthma, second trimester)

DISCUSSION

This is the first study using in-depth interviewing to explore the experiences of pregnant asthmatic women regarding their asthma management. Many of the participants decreased or discontinued their asthma medications or withheld doses during pregnancy, without consulting their doctors. Their decisions revolved around lack of support and information in regard to what to do, concerns about safety of the medications, past experiences, and a desire for an "all natural" pregnancy.

Lack of proactive support was a definite barrier to gaining optimal asthma control during pregnancy for these women. Asthma had been largely ignored by their health professionals, leading the women to believe that asthma was a low priority. In spite of this, women were concerned about steroid use during pregnancy, and made independent inquiries, for example, via the Internet, which sometimes resulted in confusing or incorrect information. It was clear from the interviews that women felt it would have been helpful if asthma had been brought up more by their health professionals, providing opportunities for pursuing more reliable information.

Along with barriers, the other themes discerned in these interviews concur with the six constructs of the Health Belief Model (25). This model postulates that the likelihood of an individual taking up a health-related behavior is dependent on their assessment of *perceived susceptibility*, *severity*, *barriers*, *benefits*, *cues to action*, *and self-efficacy*. Our results showed that pregnant women were more likely to be more diligent with their asthma management during pregnancy if they were aware of the risks of poorly controlled asthma (*perceived susceptibility*), aware of the advantages of optimal asthma control during pregnancy (*perceived benefits*), and felt they had enough information to make informed decisions about their health (*self-efficacy*).

It was disappointing to note that some participants relied on incorrect information. Cases of poor asthma management were apparent when participants did not perceive uncontrolled asthma as a potential for causing poor outcomes during pregnancy (*perceived severity*), desired a drug-free pregnancy (*perceived barriers*), lacked support, and were not well informed about the risk of the condition (*cues to action*). Association between the themes and model was particularly demonstrated through changes to medication use. Those who did not perceive asthma to be a contributing factor to poor outcomes and perceived the effects of the medication use to be more dangerous discontinued or reduced their medications. This was evident in mild asthmatics, who either did not perceive or were led to believe that asthma was not a high priority. This is concerning as mild asthmatics can experience severe asthma exacerbations during pregnancy (26).

Perceived effects of medication use resulted in most participants avoiding steroid medications but, ironically, they had no qualms about using beta-agonist medications, thus jeopardizing their asthma control. Similar results were reported by Powell et al., who found that many women perceived teratogenic risks with oral (42%) and inhaled (12%) steroids but fewer perceived risks with short-acting beta-agonists (5%) (27). Women's anxiety over these perceived risks, and lack of knowledge of the benefits of ongoing use, could prevent them from achieving optimal asthma control.

Participants included a wide variety of pregnant women, in terms of gestation, severity of asthma, and other parameters, thus enabling us to elicit a range of views. Participants did not, however, include any women in the first trimester of pregnancy as most presented to the outpatient clinic after 12 weeks gestation. Participants easily recalled their management and experiences during the first trimester. Recruitment was only from one maternity hospital but the catchment of women was widespread (metropolitan, rural, and regional participants were approached). Participants included women from various ethnic groups and varying socioeconomic status. No participants were taking leukotriene receptor antagonists or cromolyns, which are not commonly used during pregnancy. Also no participants self-reported smoking during pregnancy. It was difficult to identify and recruit smokers because only 7.8% of pregnant women with asthma in Melbourne have been shown to smoke (1). In addition, given that smokers may feel uncomfortable about their habit, it is not surprising that none volunteered to be interviewed. It may be that their views and experiences would have been different from those of non-smokers.

With such limited independent information and resources for women to guide their asthma management

during pregnancy, more education is warranted. More information could be provided regarding asthma medication safety and changes in asthma during pregnancy, even to women with mild asthma who may be unaware of the potential effects of pregnancy on asthma control. Regular monitoring should be performed (7). The authors are currently developing an educational intervention targeting pregnant women and their health professionals for implementation in both hospital and community practice.

Conclusions

Asthma management during pregnancy can be explained using the Health Belief Model. Women are not well informed about or supported in their asthma management during pregnancy, despite concerns of both health professionals and women about asthma and safety of preventive asthma medications. Communication between pregnant women and health professionals regarding asthma management is also poor. Strategies for optimizing asthma management during pregnancy should be developed and evaluated in prospective studies.

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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Chapter 6: Multidisciplinary approach to management of maternal asthma (MAMMA©): A randomised controlled trial

THE PROTOCOL

(Phase 4)

6.1 Preamble

The previous phases of this PhD research found the following:

- Asthma medications are safe to use during pregnancy but many women are still nonadherent *(Chapters 2 and 5)*;
- Shared care general practitioners lack confidence in regard to asthma management during pregnancy *(Chapter 4)*;and
- Pregnant women are not well supported in managing asthma during pregnancy, despite being concerned about outcomes *(Chapter 5)*.

Interventions, education, and more support for asthma management to optimise pregnancy and neonatal outcomes are warranted. Taking these points into consideration, a pharmacist-led multidisciplinary approach to managing asthma in pregnancy was developed, incorporating education and regular monitoring. In addition, the trial explored the feasibility of asthma self-management with regular home monitoring of lung function. Evaluation of the efficacy of the intervention was by a randomised controlled trial.

The aim was to describe the study design and protocol of a Multidisciplinary Approach to Managing Maternal Asthma (MAMMA©).

The specific objectives of this phase were to:

- implement a pharmacist-led multidisciplinary approach to managing pregnant women with asthma;
- improve adherence to asthma medications and asthma control during pregnancy, and thus reduce hazards associated with asthma exacerbation and poor perinatal outcomes;

- explore the feasibility of asthma self-management with regular home monitoring of lung function; and
- justify more support and services for pregnant women with asthma and potentially a greater role for pharmacists in the antenatal setting.

What this manuscript adds to current knowledge

With many women highlighting the lack of support from health professionals in regards to asthma management, this approach would appear to be appropriate for improving maternal asthma control. If successful, this intervention could justify more support services for these women e.g. antenatal asthma clinics.

This protocol published in **BMC Public Health** has described a simple intervention which could contribute to better asthma management in pregnant women. By publishing the protocol ahead of the trial's commencement, other researchers, clinicians and consumers could be informed that a trial was being conducted and the study design was able to be shared in greater detail.

6.2 Authors' declaration

MONASH University

Declaration by candidate for paper 5 titled:

Multidisciplinary approach to management of maternal asthma (MAMMA©): the PROTOCOL for a randomised controlled trial

The undersigned hereby certify that:

1. The above declaration correctly reflects the nature and extent of the candidate 's contribution to this work, and the nature of the contribution of each of the co-authors;
2. They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
3. They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
4. There are no other authors of the publication according to these criteria;
5. Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
6. The original data are stored at the following location and will be held for at least five years from the date indicated below:

Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University,
Victoria, Australia
Date: 1st July 2013

The nature and extent of candidate's contribution to the work was:

Nature of contribution	Extent of contribution
Conceived idea, designed trial, conducted trial, entered and analysed data and prepared first and final drafts of manuscript	80%

Candidate's signature: [redacted] **Date:** 1st July 2013

The contributions of co-authors to the work were:

Name of co-author	Nature of Contribution
Dr Johnson George	Advised on study design, in charge of product purchases and assisted with manuscript preparation
A/Prof Kay Stewart	Advised on study design and assisted with manuscript preparation
Prof Michael Abramson	Advised on study design and participant's asthma action plans and assisted with manuscript preparation
Prof Susan Walker	Advised on study design and assisted with manuscript preparation

Co-author's signature [redacted] **Date:** 1st July 2013

(Dr Johnson George)

Co-author's signature [redacted] **Date:** 1st July 2013

(A/Prof Kay Stewart)

Co-author's signature [redacted] **Date:** 1st July 2013

(Prof Michael Abramson)

Co-author's signature [redacted] **Date:** 1st July 2013

(Prof Susan Walker)

6.3 Manuscript

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BMC Public Health

STUDY PROTOCOL Open Access

Multidisciplinary approach to management of maternal asthma (MAMMA [copyright]): the PROTOCOL for a randomized controlled trial

Angelina Lim[1], Kay Stewart[1], Michael J Abramson[2], Susan P Walker[3] and Johnson George[1*]

Abstract

Background: Uncontrolled asthma during pregnancy is associated with the maternal hazards of disease exacerbation, and perinatal hazards including intrauterine growth restriction and preterm birth. Interventions directed at achieving better asthma control during pregnancy should be considered a high priority in order to optimise both maternal and perinatal outcomes. Poor compliance with prescribed asthma medications during pregnancy and suboptimal prescribing patterns to pregnant women have both been shown to be contributing factors that jeopardise asthma control. The aim is to design and evaluate an intervention involving multidisciplinary care for women experiencing asthma in pregnancy.

Methods/design: A pilot single-blinded parallel-group randomized controlled trial testing a Multidisciplinary Approach to Management of Maternal Asthma (MAMMA©) which involves education and regular monitoring. Pregnant women with asthma will be recruited from antenatal clinics in Victoria, Australia. Recruited participants, stratified by disease severity, will be allocated to the intervention or the usual care group in a 1:1 ratio. Both groups will be followed prospectively throughout pregnancy and outcomes will be compared between groups at three and six months after recruitment to evaluate the effectiveness of this intervention. Outcome measures include Asthma Control Questionnaire (ACQ) scores, oral corticosteroid use, asthma exacerbations and asthma related hospital admissions, and days off work, preventer to reliever ratio, along with pregnancy and neonatal adverse events at delivery. The use of FEV_1/FEV_6 will be also investigated during this trial as a marker for asthma control.

Discussion: If successful, this model of care could be widely implemented in clinical practice and justify more funding for support services and resources for these women. This intervention will also promote awareness of the risks of poorly controlled asthma and the need for a collaborative, multidisciplinary approach to asthma management during pregnancy. This is also the first study to investigate the use of FEV_1/FEV_6 as a marker for asthma control during pregnancy.

Trial registration: Australian New Zealand Clinical Trials Registry (ACTRN12612000681853)

Keywords: Asthma, Pregnancy, Inhaled corticosteroids, Randomized controlled trial, Antenatal care, Intervention, Lung function tests, Multidisciplinary care

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Background

Preterm birth and intrauterine growth restriction remain leading contributors to perinatal mortality and morbidity. Preterm birth is the leading cause of neonatal death, and over half of term stillbirths are associated with impaired fetal growth. Beyond the perinatal period, survivors of preterm birth and fetal growth restriction face a range of long term adverse health outcomes through infancy and childhood [1], and many adult diseases are now recognised to have their origins in fetal life [2-4]. Accordingly, continued efforts are necessary to identify interventions that may reduce the burden of preterm birth, and improve in utero fetal growth.

Poorly controlled asthma during pregnancy has been shown to be associated with an increased risk of preterm birth, low birth weight, and pre-eclampsia [5,6]. This data suggests that improved asthma control may be a means of reducing these important perinatal outcomes and that proper asthma management among pregnant women should be regarded as a health priority. In general, they should be managed in the same way as non-pregnant women with asthma, with the exception their asthma should be monitored at least monthly, as pregnancy can have a significant effect on asthma control [7,8]. A lack of knowledge amongst women regarding the risks of uncontrolled asthma during pregnancy is evident. Furthermore, there is a lack of confidence amongst health professionals when deciding the best management strategy for these women [9]. These concerns need to be addressed, as a starting point to optimise asthma control during pregnancy. Strategies to improve asthma management during pregnancy are warranted.

Preventive asthma medications at regular doses have been shown to be safe to use during pregnancy and the risks of reduction or discontinuation of these medications are far worse [10,11]. Asthma guidelines around the world strongly recommend that women continue their asthma medications during pregnancy to maintain adequate control [7,8,12-18]. However, women are still choosing to cease their asthma medications during pregnancy, many without consulting their doctors [19-21]. Reasons for this include concern over using any medication use during pregnancy, a desire for alternative therapies, perceptions of negative outcomes associated with steroid use, lack of support and guidance from health professionals regarding what to do with their asthma medications and the risks of poorly controlled asthma during pregnancy [22]. Moreover, women overestimate the teratogenic risks of asthma medication especially the steroid medications, with one report citing women perceived a 42% teratogenic risk for oral corticosteroid versus 12% risk for inhaled corticosteroid [23].

Prescribers have also been shown to be hesitant to prescribe and encourage use of asthma medications during pregnancy. Over a quarter of family physicians have said they would instruct their pregnant patients to decrease or discontinue asthma medication during pregnancy, when asthma was well controlled by current therapy [9], potentially jeopardizing asthma control. Pregnant women are also less likely to be treated with systemic corticosteroids for acute asthma exacerbations than non-pregnant women (50.8% versus 72.4%) [24].

The uncertainty and anxiety surrounding medication use and asthma control during pregnancy emphasise the crucial role of doctors, pharmacists and midwives in ensuring patient adherence to asthma medications during pregnancy and educating them on the risks of uncontrolled asthma during pregnancy. A collaborative approach between the pregnant women, doctors, midwives and pharmacists is needed to maintain adequate asthma control. Monthly monitoring has been recommended by guidelines [25] to maintain optimal asthma control as different stages of pregnancy can have an effect on asthma control [8]. We aim to test an intervention that allows for regular patient self-monitoring and a multidisciplinary health professional approach for asthma management during pregnancy; if successful it could justify funding for more support services for these women.

There also needs to be more detailed guidelines and objective measures for monitoring lung function for the treatment of pregnant women with asthma. The exhaled fraction of nitric oxide (FeNO) has been investigated as a marker for asthma control during pregnancy, but is expensive and not easily accessible [26]. Forced Expiratory Volumes in one and six seconds (FEV_1/FEV_6) has shown to be effective in detecting airway obstruction in the elderly and could be helpful in pregnancy [27]. FEV_1/FEV_6 may be a way of differentiating the shortness of breath associated with pregnancy from worsening asthma symptoms and a more convenient and affordable way of monitoring and guiding therapy in pregnant asthmatic women.

Objective

To determine whether a multidisciplinary approach involving asthma education and regular monitoring during pregnancy will decrease asthma exacerbations with associated maternal and perinatal benefits. We hypothesis that the intervention group will have a better mean asthma control score than the control group at three and six months.

Methods/design

Study design

This is a single-blinded parallel-group randomized controlled pilot trial which will be conducted in the antenatal setting. It will test and evaluate a Multidisciplinary Approach to Management of Maternal Asthma (MAMMA©)

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which will involve education and regular monitoring by patients and their health professionals. The flow of the study design is outlined in Figure 1. Recruited participants, stratified by disease severity, will be allocated to the intervention or the usual care group in a 1:1 ratio. Both groups will be followed prospectively throughout pregnancy, and outcomes will be compared between groups at three and six months from baseline to evaluate the effectiveness of this intervention.

Inclusion and exclusion criteria

All pregnant women with asthma attending antenatal outpatient clinics who are in their first or second trimester, and who can communicate in English will be considered. Patients who are under the age of 18 years or who have not had asthma symptoms (wheeze, chest tightness and/or use of their reliever asthma medication) in the last year will be excluded. Participants who are also unlikely to meet the demands of the trial will be excluded (e.g. planning to relocate during the trial). Furthermore, participants who were previously involved in our previous qualitative exploratory study conducted at the same maternity hospital, titled "Asthma during pregnancy; the experiences, concerns and views of pregnant women with asthma" [22] will also be excluded. Lastly, in the event of a miscarriage or termination of pregnancy, the participant will be excluded from the trial. Participant characteristics will be described in Table 1.

Recruitment

Participants will be recruited from antenatal clinics of two major Victorian women's hospitals. Four recruitment methods will be used to ensure the sample size is reached efficiently:

1. Pregnant women who have self reported asthma will be approached at their antenatal outpatient appointment.
2. Advertisement posters publicising the trial will be placed in the outpatient department alongside an 'expression of interest' box where participants can leave their contact details. Study packs (including an explanatory statement with an expression of interest form and a reply paid envelope) will also be available in the outpatient department so potential participants can take the information home to read and post back expression of interest forms.
3. Midwives will also be asked to help identify eligible pregnant women with asthma during their first outpatient visit. They will be asked to approach any woman who has indicated they are asthmatic and hand them a study pack, which will be available in the outpatient department.

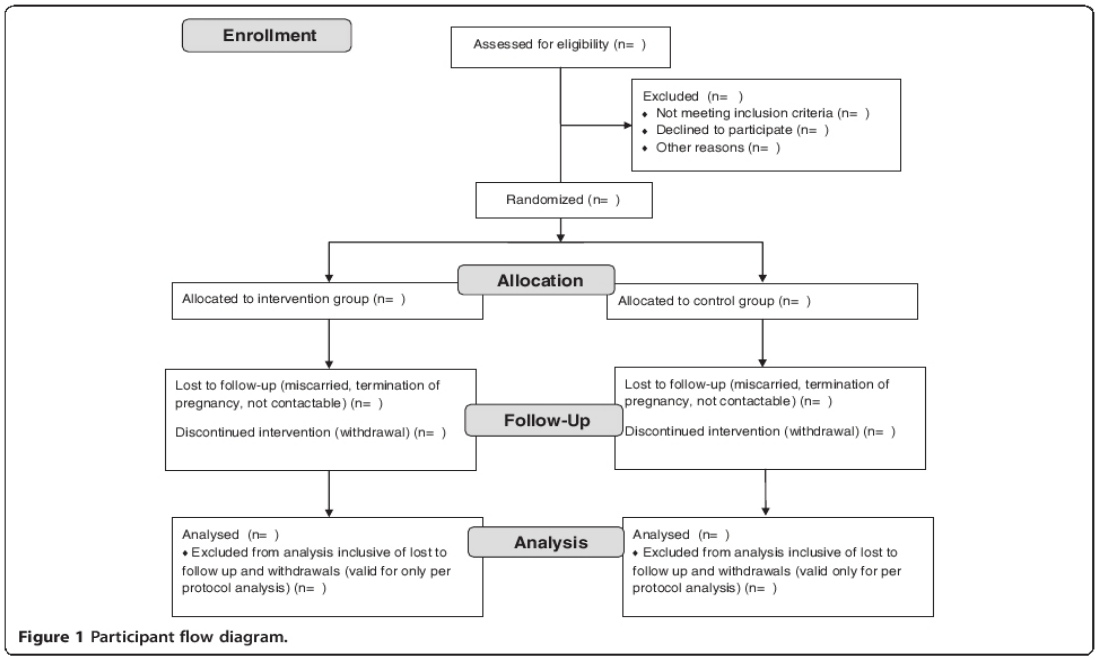

Figure 1 Participant flow diagram.

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Table 1 Demographic and clinical characteristics of the study population at baseline

Characteristic	Intervention group (n=30)	Control group (n=30)
Patient information		
Age in years Mean [SD]		
Parity		
Gravidity		
Gestational age at first visit in weeks Mean [SD]		
Height in cm Mean [SD]		
Adherence Score Median [IQR]		
Ethnicity		
Australian		
Arabic		
Asian		
European		
Other		
Asthma severity[+]		
Intermittent to Mild		
Moderate to Severe		
Asthma medication		
SABA only		
ICS+SABA		
ICS/LABA + SABA		
FEV_1 in litres Mean [SD]		
FEV_1%predicted Mean [SD]		
FEV_1/FEV_6 Mean [SD]		
Co-morbidity		
Gestational diabetes		
Hypertension in pregnancy		
Anxiety/depression		
Other		
Smokers		
Health Care Concession Card holders		

ICS – inhaled corticosteroid, LABA- Long acting beta agonist, SABA – short acting beta agonist.
[+]Asthma severity classified by National Asthma Handbook [28].
Values are given as number (percentages) unless specified.

4. A list of pregnant asthmatic women who have had their first outpatient visit will be generated weekly from the medical records database which stores antenatal information for all hospital patients. Study packs will be posted to the women who are on the weekly list.

Written informed consent will be obtained from all participants. All participants will be over the age of 18 years and will have competency to consent. During the recruitment phase, each participant will be asked to nominate her preferred family physician (general practitioner) to be involved in the trial who will be the lead clinician responsible for her asthma management during pregnancy.

Group allocation

Participants will be asked basic questions to determine their asthma severity in accordance with the National Asthma Council Management Handbook [28] classifications. Participants will be stratified into two groups: mild intermittent asthmatics and moderate-severe persistent asthmatics. Within these two strata, block randomization using random blocks of four and six will be conducted using the sealed opaque envelope method. A random sequence of numbers will be generated using the Random allocation software program® by an external researcher who is not part of the research team. Only this researcher will be aware of the allocation sequence. Numbered envelopes will be opened by the leading investigator AL to allocate participants to the usual care group (UCG) or the multidisciplinary care group (MCG) at time of recruitment and will enrol the participant into the study. Stratification and block randomization are included to ensure a balance of asthma severities between groups and an even number of participants per group. Outcome assessors will be blinded to participant group allocation.

Intervention (MCG participants)

The Multidisciplinary Approach to Management of Maternal Asthma (MAMMA©) intervention will embrace a collaborative approach involving the participant's family physician, pharmacist and asthma educator. Details of the intervention are described in Figure 2. Asthma education, monitoring, feedback and follow-up are integral components of the monthly intervention. Every month, participants in the intervention group will be contacted by the trial's nominated pharmacist for an hourly session to assess their asthma control by administrating the Asthma Control Questionnaire (ACQ) [29] and a short data collection form which inquires about oral corticosteroid use, asthma related hospital admissions, days off work and preventer to reliever use ratio. The ACQ states that an increase in a score of 0.5 is a clinically significant deterioration of asthma control [29]. The trial pharmacist will provide feed back to the participant's nominated family physician if the ACQ score has increased by 0.5 or greater and if there has been a documented exacerbation since the last monthly visit. The pharmacist and family physician will then collaborate on appropriate step up therapy for the participant. It is anticipated that this close monthly monitoring will maintain the participant's asthma under closer control during pregnancy. Each participant in the MCG will be given a handheld device (PiKo-6) to use as they please for home monitoring of lung function and instruction in the use of PiKo-6. They will also receive pharmacist led medication management

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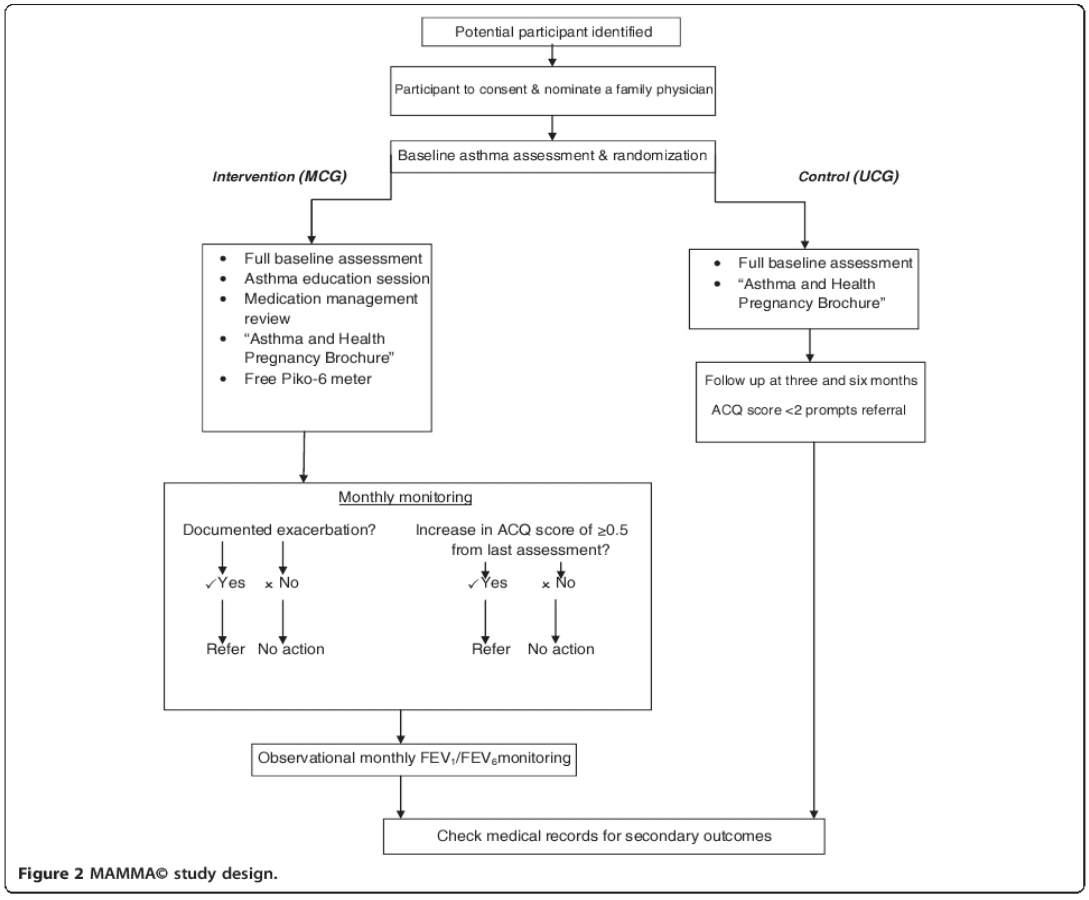

Figure 2 MAMMA© study design.

review at the beginning of the trial, periodic review of inhaler device technique by asthma educator, trigger avoidance and smoking cessation support (if relevant). The MCG will also have their FEV_1/FEV_6 measured monthly during the trial. Adherence and uptake of the intervention will be described in Table 2.

Table 2 Adherence to intervention by intervention and control groups

	Intervention group n(%)	Control group n(%)
No. of reviews recommended by intervention pharmacist		
No. of asthma action plans up taken		
No. of recommended medication changes up taken		

Control (UCG participants)

The control group will receive usual medical care; this normally includes their regular antenatal visits ranging from weekly to monthly depending on trimester and other complications. They will not receive the intervention, any additional monitoring or education sessions like participants in the MCG. If during follow ups at three and six months, their asthma control becomes a concern (2 or more documented exacerbations without resolution (i.e. increasing preventer dose) since prior assessment or their ACQ score exceeds 2, the participant and their family physician will be notified (with participant permission). This notification will be taken into account when we do the analysis.

Both groups will be given a summarised version of the "Asthma and Healthy Pregnancy" brochure from the Asthma Foundation of New South Wales, Australia

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which is a pamphlet on basic asthma facts to avoid unfair disadvantage to participants in the control group and to minimise the risks of poorly controlled asthma.

Outcomes

The primary outcome of the trial will be the ACQ score. It is hypothesised that the MCG will have a higher average ACQ score than the UCG at 3 and 6 months. Secondary outcomes will include asthma-related hospital visits and days off work, oral corticosteroid use and preventer to reliever use ratio. Pregnancy outcomes to be collected will be the development of antenatal complications, such as hypertensive disorders of pregnancy, antepartum haemorrhage, gestational diabetes and gestational age at delivery. Neonatal outcomes will include gestational age and birth weight percentile, Appearance Pulse Grimace Activity and Respiratory (APGAR) scores, admission to neonatal intensive care or special care nursery, mode of delivery and any postnatal complications. The study is not powered to assess the effect of the intervention on pregnancy and neonatal outcomes; however, these outcomes will still be documented as there is an abundance of information available highlighting poorly controlled asthma during pregnancy leading to maternal and perinatal hazards. Results of outcomes will be described in Table 3.

Follow up

ACQ scores, asthma-related hospital visits and days off work, oral corticosteroid use and preventer to reliever use ratios will be compared at three and six months between groups. Both groups will be assessed using the same data collection form at 3 and 6 months (once in their second trimester and once in their third trimester) and the results will be compared. The assessor collecting the data at three and six months in both groups will be different from the intervention pharmacist and will be blinded to participant group allocation. The assessor will not be given any clinical information about each participant and will be unaware of the study protocol (including details of the intervention) just in case a participant inadvertently discloses details to the assessor. Pregnancy and neonatal outcomes will be confirmed via medical records shortly after delivery.

Sample size calculation

This is a pilot study, however sample size was still calculated to guide recruitment. Using a conservative standard deviation of 0.66, to detect a change in ACQ score of 0.5 or more between groups,[18] a sample size of 29 per arm would have 80% power with a two sided 5% significance level assuming the two variances are the same. To allow for 20% attrition, 35 participants will be recruited in each arm.

Data analysis

The primary analysis will be intention to treat. Per protocol analyses will also be conducted. The baseline characteristics of participants in the intervention and control groups will be compared using Chi-square, Student *t*-test or Mann–Whitney tests if distributional assumptions are not satisfied. ACQ scores at baseline, three and six months will be compared using Mann–Whitney test. Secondary outcomes will be listed as descriptive statistics and analysed using similar tests. FEV_1/FEV_6 trends will be described as these are observational data only. Sensitivity and predictive validity of the ACQ would also be investigated.

Ethics

This trial has been approved by the Mercy Health Research Ethics Committee, The Royal Women's Hospital Research Ethics Committee and Monash University Human Research Ethics Committee. The trial has also been registered with the Australian and New Zealand Clinical Trial Registry ACTRN12612000681853.

Discussion

The proposed intervention has the potential to improve health outcomes in pregnant women with asthma, by reducing the incidence and severity of maternal exacerbations, and potentially reducing the perinatal morbidity associated with preterm birth and impaired fetal growth. These interventions have the potential to reduce health

Table 3 ACQ scores and asthma outcomes at Baseline, 3 and 6 months

	Baseline		At 3 months		At 6 months	
Result	Intervention group (n=30)	Control group (n=30)	Intervention group (n=30)	Control group (n=30)	Intervention group (n=30)	Control group (n=30)
ACQ score						
No. of asthma related hospital visits						
Days off work						
No of days of asthma related oral corticosteroid use						
Preventer to reliever ratio						

Values are given as mean (SD) or number (percentages).

care costs through fewer asthma-related unplanned medical and emergency department visits for pregnant women. In addition, the costs associated with poor pregnancy and neonatal outcomes that can result from poorly controlled asthma i.e. pre-term births and low birth weight babies (parenteral nutrition costs, Neonatal Intensive Care admissions, assisted ventilation etc.) would be reduced. The interventions could also have a positive impact on the health of future generations. If the proposed intervention is successful and cost-effective, it may justify additional support services for pregnant women with chronic health conditions such as asthma. These support services could readily be made available and accessible in the community as well as hospital settings.

The trial is also the first to investigate the use of FEV_1/FEV_6 monitoring during pregnancy. This trial is powered to assess the primary asthma symptom-related endpoint, but not sufficient enough to draw conclusions in regards to maternal and perinatal outcomes. It has been expressed that it is difficult to distinguish between the shortness of breath associated with pregnancy and the airway obstruction associated with asthma [22]. Observational findings from this trial could help examine patterns and trends of FEV_1/FEV_6 values. It is suggested that overweight individuals have a lower FEV_1 and the expanding uterus during pregnancy may further reduce this by decreasing lung volumes [30]. However, significant changes in FEV_1 coupled with reduced FEV_1/FEV_6 ratios are likely to be due to deteriorating asthma control.

Moreover, as the lung function of a pregnant woman differs from that of a non-pregnant woman [30], a target range for FEV_1/FEV_6 measurements during pregnancy could be identified and prompt further research in using this ratio as a marker for asthma control during pregnancy. FEV_1/FEV_6 could be a simple and easier method of assessing asthma control and help prescribers better distinguish between asthma symptoms and the shortness of breath associated with pregnancy. Women will have the convenient option of monitoring their asthma at home using a handheld spirometer and adjusting therapy or management according to an individualised asthma action plan.

Conclusion

The MAMMA trial will investigate the role of participant self-monitoring and multidisciplinary team care in the management of asthma during pregnancy. The use of FEV_1/FEV_6 as a measure of lung function in pregnancy will also be explored. Empowering women to take control of this common chronic health condition and a multidisciplinary approach to management could potentially reduce the burden of asthma during pregnancy.

Abbreviations

ACQ: Asthma Control Questionnaire; APGAR: Appearance, Pulse, Grimace, Activity, Respiratory; FEV_1: Forced Expiratory Volume in one second; FEV_6: Forced Expiratory Volume in six seconds; ICS: Inhaled Corticosteroid; MCG: Multi-disciplinary Care Group; UCG: Usual Care Group.

Competing interests

Dr Johnson George and Prof Michael Abramson had an investigator-initiated research (IIR) grant from Pfizer for a separate research project which targets smoking cessation. All other authors declare no competing interests.

Authors' contributions

Angelina Lim (PhD candidate) developed and designed the trial with input from all the other authors (AL, JG, KS, MA and SW). Ms Lim wrote the first draft of the protocol and refined it based on comments and feedback from all the other authors. All authors read and approved the final manuscript.

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Chapter 7: Multidisciplinary approach to management of maternal asthma (MAMMA©): A randomised controlled trial

RESULTS

(Phase 4)

7.1 Preamble

A pharmacist-led Multidisciplinary Approach to Managing Maternal Asthma (MAMMA) in pregnancy was developed, incorporating education and regular monitoring. Evaluation of the efficacy of the intervention was by a randomised controlled trial. This chapter presents the results of the MAMMA trial.

What this manuscript adds to current knowledge

With many women highlighting the lack of support from health professionals in regard to asthma management, the multidisciplinary approach would appear to be appropriate for improving maternal asthma control. By publishing the results in Thorax (or another respiratory or obstetric journal), the success of this intervention could be widely disseminated, and could justify more support services (e.g. antenatal asthma clinics run by pharmacist-midwife teams) for these women.

Relaying the results to key stakeholders such as hospital administrators, The National Asthma Council and Asthma Australia, pregnancy advice hotlines and organisations such as the Society of Hospital Pharmacists and the Pharmaceutical Society of Australia, could encourage more support and services for managing maternal asthma and stimulate policy changes to allow for pharmacist-led asthma antenatal clinics.

In addition, presenting the results locally and internationally and publishing them in high impact journals will promote awareness for better asthma management during pregnancy. This trial was conducted as a pilot study and has been shown to be practical and efficacious.

Future research could involve expanding the trial by increasing the sample size and duration of follow-up to demonstrate improvements in maternal and perinatal outcomes. There is already interest from one of the maternity hospitals in Melbourne in adopting this model of care for pregnant women with asthma. Intervention studies in pregnant women with asthma are few and far between and this trial could boost the interest of researchers to conduct more trials in this area.

7.2 Authors' declaration

MONASH University

Declaration by candidate for paper 6 titled:

Multidisciplinary approach to management of maternal asthma (MAMMA©): A randomised controlled trial

The undersigned hereby certify that:

3 The above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors;
4 They meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
5 They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
6 There are no other authors of the publication according to these criteria;
7 Potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
8 The original data are stored at the following location and will be held for at least five years from the date indicated below:

Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences,
Monash University,
Victoria, Australia
Date: 1st July 2013

The nature and extent of candidate's contribution to the work was:

Nature of contribution	Extent of contribution
Conceived idea, designed trial, conducted trial, entered and analysed data and prepared first and final drafts of manuscript	80%

Candidate's signature: [redacted] **Date:** 1st July 2013

The contributions of co-authors to the work were:

Name of co-author	Nature of Contribution
Dr Johnson George	Advised on study design, in charge of product purchases and assisted with manuscript preparation
A/Prof Kay Stewart	Advised on study design and assisted with manuscript preparation
Prof Michael Abramson	Advised on study design and participant's asthma action plans and assisted with manuscript preparation
Prof Susan Walker	Advised on study design and assisted with manuscript preparation
Catherine Smith	Conducted statistical analysis on primary outcomes and assisted with manuscript preparation

Co-author's signature [redacted] **Date:** 1st July 2013

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(Prof Susan Walker)

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(Catherine Smith)

7.3 Manuscript

Thorax (Submitted 28th August 2013)

Multidisciplinary Approach to Management of Maternal Asthma (MAMMA©): A Randomised Controlled Trial

A Lim, K Stewart, M Abramson, S Walker, C Smith, J George

Abstract:

Background: **Uncontrolled asthma during pregnancy is associated with maternal and perinatal hazards.**

Objective: **The aim was to evaluate a pharmacist-led intervention directed at improving maternal asthma control involving multidisciplinary care, education and regular monitoring to help reduce these risks.**

Design: **A randomised controlled trial allocated participants to either an intervention or usual care group and followed them prospectively throughout pregnancy.**

Setting: **Antenatal clinics of two major Victorian Maternity Hospitals, Australia.**

Participants: **Sixty pregnant women <20 weeks gestation who have used asthma medications in the past year were recruited.**

Main outcome measures: **The primary outcome was Asthma Control Questionnaire (ACQ) score. Secondary outcomes were asthma-related oral corticosteroid use, hospital admissions, emergency visits and days off work. Mean changes in ACQ scores from baseline were compared between groups at 3 and 6 months to evaluate intervention efficacy.**

Results: **The ACQ score in the intervention group (n = 29) decreased by mean (SD) of 0.46 (1.05) at 3 months and 0.89 (0.98) at 6 months. The control group (n = 29) had a mean decrease of 0.15 (0.63) at 3 months and 0.18 (0.73) at 6 months. The difference between groups, adjusting for baseline, was -0.22 (95%CI: -0.54 to 0.10) at 3 months and -0.60 (-0.85 to -0.36) at 6 months. The difference at 6 months was statistically significant (p<0.001) and clinically significant (>0.5). No asthma-related oral corticosteroid use, hospital admissions, emergency visits or days off work were reported during the trial.**

Conclusion: **A multidisciplinary model of care for asthma management involving education and regular monitoring could potentially improve maternal and perinatal outcomes and be widely implemented in clinical practice.**

Trial registration: **The trial was registered with the Australian and New Zealand Clinical Trial Registry ACTRN12612000681853 June 2012.**

Keywords: Asthma, Pregnancy, Antenatal Care, Multidisciplinary, Intervention

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Submitted to Thorax 28th August 2013

Preterm birth and intrauterine growth restriction remain leading contributors to perinatal mortality and morbidity. Beyond the perinatal period, survivors of preterm birth and fetal growth restriction face a range of long term adverse health outcomes through infancy and childhood.[1] Many adult diseases are now recognised to have their origins in fetal life.[2-4] Asthma is among the most common medical conditions affecting pregnant women, with the prevalence reported to be up to 12% in some countries.[5] [6] Poorly controlled asthma and asthma exacerbations during pregnancy have been shown to be associated with an increased risk of preterm birth, low birth weight, and pre-eclampsia.[7] [8] These data suggest that improved asthma control may be a means of reducing those important adverse perinatal outcomes and that proper asthma management among pregnant women should be regarded as a leading priority in antenatal care.

Anti-inflammatory asthma medications at regular doses have been shown to be safe to use during pregnancy and the risks of reduction or discontinuation of these medications are far worse.[9] [10] Asthma guidelines around the world strongly recommend that women continue their asthma medications during pregnancy to maintain adequate control.[11-19] However, some women cease their asthma

medications during pregnancy, many without consulting their doctors.[20-22] Reasons for this include concerns about using any medication during pregnancy, a desire for alternative therapies, perceptions of negative outcomes associated with 'steroid' use, and lack of support and guidance from health professionals regarding what to do with their asthma medications and the maternal and perinatal risks of poorly controlled asthma.[23] Moreover, women overestimate the teratogenic risks of asthma medication, particularly steroid medications. One report found 42% of women perceived a teratogenic risk when using oral corticosteroids during pregnancy versus 12% in relation to inhaled corticosteroids.[24]

Prescribers have also been shown to be hesitant to prescribe and endorse use of asthma medications during pregnancy. Over a quarter of family physicians would instruct their pregnant patients to decrease or discontinue asthma medication during pregnancy, when asthma was well controlled by current therapy,[25] potentially jeopardising asthma control. Pregnant women are also less likely to be treated with systemic corticosteroids for acute asthma exacerbations than non-pregnant women (50.8% versus 72.4%).[26]

It is generally recommended that pregnant women with asthma should be managed in the same way as non-pregnant women, except that more frequent monitoring is necessary since pregnancy can have a significant adverse impact on asthma control.[18 19] Women tend to underestimate the risks of uncontrolled asthma during pregnancy. [23] Primary care clinicians, trying to balance optimising control with minimising fetal exposure to medication, lack confidence in optimal management regimens in pregnancy.[25] Education is thus a crucial component of any intervention to optimise asthma management in pregnancy.

The uncertainty and anxiety surrounding medication use and asthma control during pregnancy emphasise the crucial role of doctors, pharmacists and midwives in ensuring patient adherence to medication regimens during pregnancy and educating them on the risks of uncontrolled asthma during pregnancy. Only two interventional studies aimed at improving asthma control in pregnant women have been conducted.[27 28] Using the positive results of these trials, the present study was designed to investigate the feasibility of a more practical and sustainable option for routine care. The aim was to test an intervention that incorporated regular patient self-monitoring and a multidisciplinary health professional approach to asthma management during pregnancy.

Objective

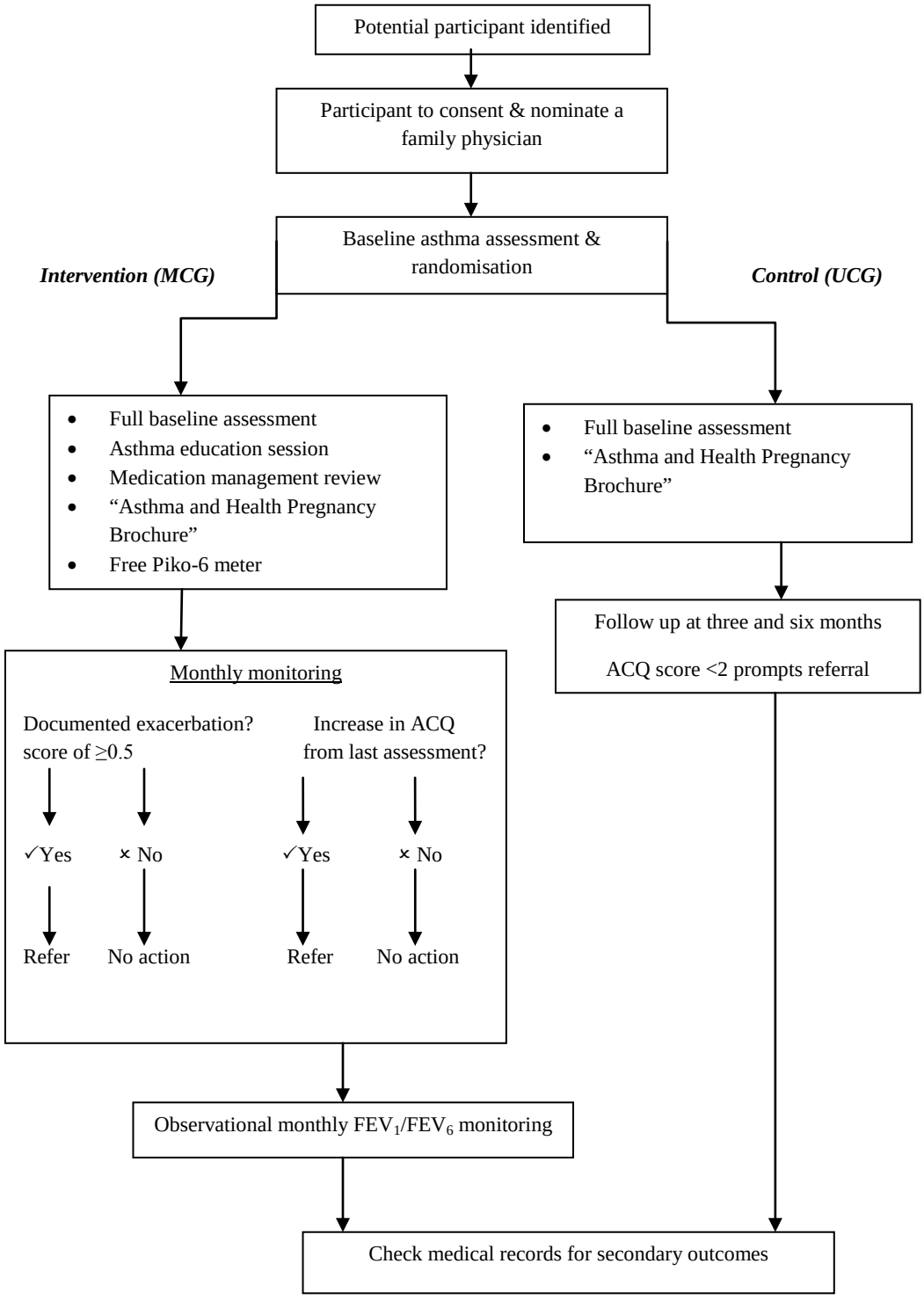
The aim was to evaluate the effectiveness of a Multidisciplinary Approach to Management of Maternal Asthma (MAMMA©). It was hypothesised that participants receiving the MAMMA© intervention would have better asthma control than those receiving usual care at 3 and 6 months from baseline.

Methods

TRIAL DESIGN

The trial was a single-blinded randomised controlled trial conducted in the antenatal setting of the two largest maternity hospitals in Victoria, Australia. It evaluated MAMMA©, which involved education and regular monthly follow-up of maternal asthma. The study design and follow up of participants are outlined in Figure 1. Full trial protocol can be accessed at http://www.biomedcentral.com/1471-2458/12/1094 .

Figure 1. MAMMA© study design



PARTICIPANTS

All pregnant women, up to 20 weeks gestation, with asthma attending antenatal outpatient clinics, who could communicate in English, were considered. Patients under the age of 18 years or who had no asthma symptoms (wheeze, chest tightness and/or use of reliever asthma medication) in the previous 12 months were excluded. Those who were unlikely to meet the demands of the trial (e.g. planning to relocate) were also excluded. Potential participants were approached AL for recruitment while waiting for their antenatal appointments. Identification of potential participants was through advertisement posters, referrals from midwives or doctors, and screening of medical records. During the recruitment phase, each participant was asked to nominate her preferred family physician to be involved in the trial, who would be the lead clinician responsible for asthma management during pregnancy. General demographics, medication history, asthma history, obstetric history and treatment adherence (using the Beliefs and Behaviour Questionnaire[29]), were collected AL at baseline.

RANDOMISATION

Asthma severity was determined in accordance with the National Asthma Council classification[30]. Participants were stratified into two groups: mild-intermittent asthmatics and moderate-severe persistent asthmatics. Within these two strata, participants were block randomised using random blocks of four and six and the sealed opaque envelope method. Numbered envelopes were opened by AL to allocate participants to the usual care group (UCG) or the multidisciplinary care group (MCG). Stratification and block randomisation were included to ensure a balance of asthma severity between groups and an equal number of participants per group.

INTERVENTION (MCG participants)

MAMMA© was a multidisciplinary pharmacist-led intervention, which included asthma education, monitoring, feedback and follow-up as integral components of the monthly intervention. At baseline, the trial pharmacist (AL, an accredited asthma educator) conducted a review of medications (prescription and over-the-counter) including inhaler device technique, offered advice on trigger avoidance and provided smoking cessation support, if relevant. In addition, every month, participants in the intervention group were contacted by the trial pharmacist to assess their asthma control using a short data collection form that included the Asthma Control Questionnaire (ACQ)[31], oral corticosteroid use, asthma-related hospital admissions, days off work and any recent changes to pharmacotherapy. An increase in ACQ score of 0.5 or more suggested a clinically significant deterioration of asthma control.[31] The trial pharmacist contacted the participant's nominated family physician if the ACQ score had increased by ≥0.5 and/or there had been a documented exacerbation since the last monthly visit. The pharmacist and family physician collaborated on appropriate step-up therapy for the participant. This close monthly monitoring aimed to maintain the participant's asthma well controlled during pregnancy. In addition, to encourage home monitoring of lung function, each participant in the MCG was given a handheld portable, electronic spirometer (PiKo-6, Nspirehealth®, USA) for measuring FEV_1, FEV_6 and FEV_1/FEV_6 daily. Participants were given instructions to contact the trial pharmacist if their lung function deteriorated ($FEV_1/FEV_6<0.75$).

CONTROL (UCG participants)

Members of the control group received usual antenatal care, and were also provided with written information from The Asthma Foundation on management of asthma in

pregnancy.[32] They did not receive the additional monitoring or education sessions offered to participants in the MCG, but were assessed at 3 and 6 months using the ACQ. If asthma control had deteriorated, evidenced by two or more documented exacerbations without increasing preventer dose since prior assessment, or if their ACQ score exceeded 2, participants were advised to contact their family physicians by study staff.

OUTCOMES

The primary outcome of the trial was the change in baseline ACQ score at 3 and 6 months. Secondary outcomes included asthma-related hospital visits, emergency visits, days off work and oral corticosteroid use. Pregnancy and neonatal outcomes were also collected, but the trial was not powered to assess these outcomes. These included mode of delivery, gestational age and birth weight centile, APGAR scores, admission to neonatal intensive care or special care nursery, the development of antenatal complications, such as hypertensive disorders of pregnancy, antepartum haemorrhage, gestational diabetes, and any postnatal complications.

FOLLOW UP

ACQ scores, asthma-related hospital admissions, emergency visits, days off work and oral corticosteroid use were assessed at 3 and 6 months by a research assistant blinded to participant group allocation. Pregnancy and neonatal outcomes were confirmed from medical records shortly after delivery.

SAMPLE SIZE CALCULATION

Using a conservative standard deviation of 0.66, to detect a mean change in ACQ score of 0.5 or more between groups,[18] a sample size of 29 per arm was needed to provide 80% power with a two-sided alpha of 5% assuming equal variance.

STATISTICAL ANALYSIS

An intention to treat analysis was conducted using SPSS® Version 20 (IBM, Armonk, NY). P values less than 0.05 were considered statistically significant. Differences in the primary outcome at 3 and 6 months were compared between groups using linear regression modeling adjusting for baseline ACQ scores. Results are presented as estimated differences with 95% confidence intervals.

ETHICS

This trial was approved by Mercy Health Human Research Ethics Committee (Approval no 12/13), The Royal Womens Hosptial Human Research Ethics Committee (Approval no. 12/22) and Monash University Human Research Ethics Committee (Approval no. 2012000921). All participants gave informed consent before taking part. The trial was registered with the Australian and New Zealand Clinical Trial Registry ACTRN12612000681853 June 2012.

FUNDING

This project received no external funding.

Results

Sixty participants were recruited into the trial. However, one participant from each arm was lost to follow-up (Figure 2). At baseline, the groups were well matched (Table 1).

Participants were from a range of ethnic and socioeconomic groups. All participants reported that they were non-smokers or had quit smoking upon confirmation of pregnancy. At baseline, 42/60 (70%) participants revealed they were unaware of the risks of poorly controlled asthma, and 19/60 (32%) reported ceasing or reducing their medications since becoming pregnant; 16/60 (27%) (MCG:10, UCG:6) participants reported ceasing their asthma medications

since becoming pregnant and 3/60 (5%) (MCG:1, UCG:2) reduced their medication doses. Asthma exacerbations during pregnancy, but prior to trial commencement, were reported by some participants. Of women in the MCG, 23/30 (77%) received an adjustment in their asthma management to optimise control from the pharmacist-family practitioner team; 3/30 (11%) required initiation of a preventer, 8/30 (27%) reinstatement of preventer, 4/30 (14%) escalation of preventer dosage, 7/30 (23%) initiation of an asthma action plan, and 1/30 (3%) referral to respiratory specialist.

Baseline ACQ scores improved (decreased) at both three and six months for both groups. (Table 2 and Figure 3).

Figure 2. CONSORT Participant flow diagram

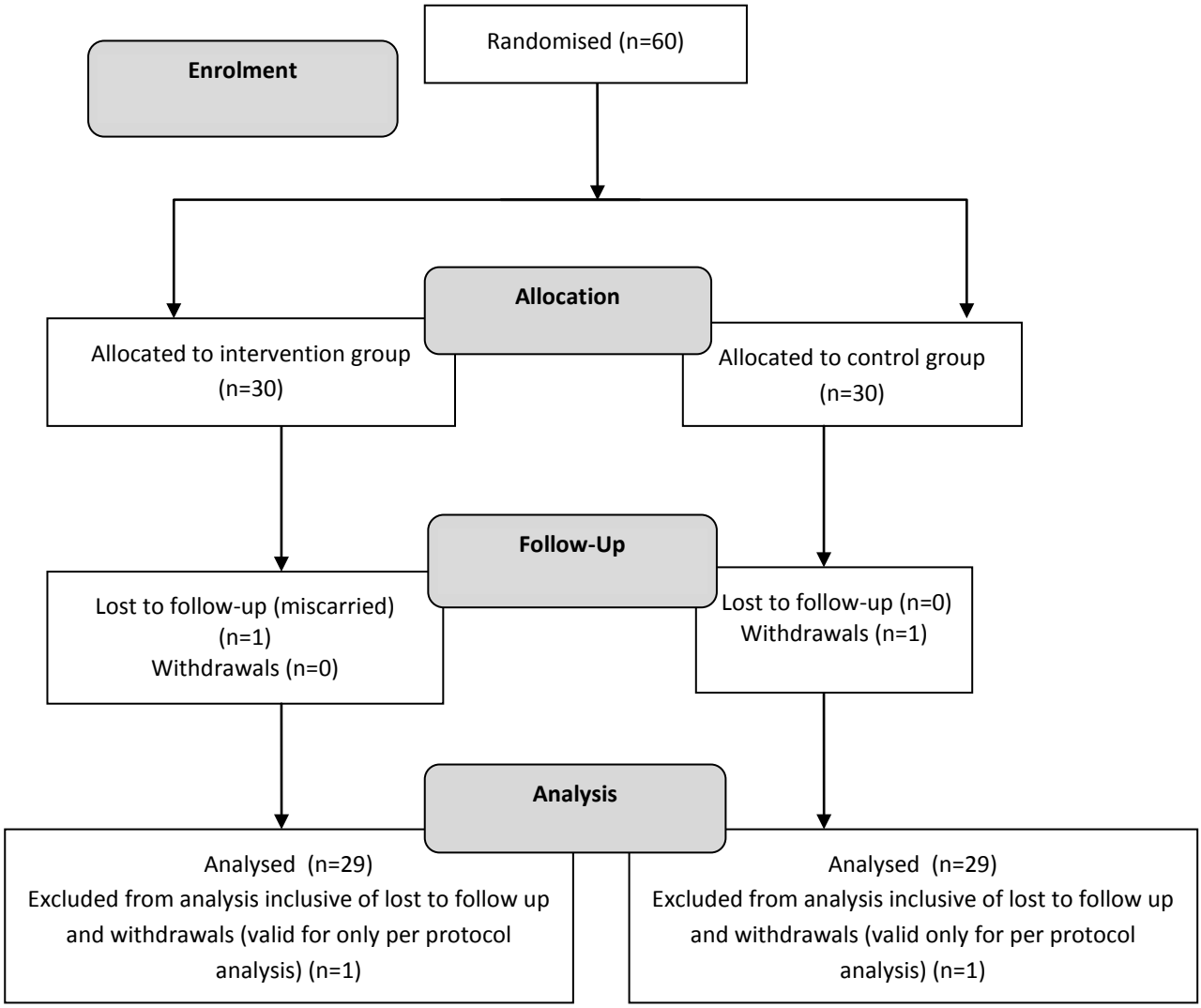


Table 1. Baseline participant characteristics

Characteristic	MCG (n=30)	UCG (n=30)
Demographic		
Age (years) (Mean [SD])	31.97 [4.33]	31.38 [5.14]
Ex-smokers (n [%])	4 [13.3]	6 [20.0]
Health care concession card holders (n [%])	8 [26.6]	4 [13.3]
Nulliparous (n [%])	12 [40.0]	14 [46.6]
Highest level of education		
Secondary (n [%])	13 [43.3]	7 [23.3]
Tertiary (n [%])	17 [56.7]	23 [76.7]
Ethnic background		
Australian/ New Zealander (n [%])	22 [73.3]	21 [70.0]
Asian (n [%])	2 [6.7]	4 [13.3]
European (n [%])	2 [6.7]	3 [10.0]
Middle eastern (n [%])	3 [10.0]	2 [6.7]
South African (n [%])	1 [3.3]	0 [0.0]
Other medical conditions		
Anxiety/ depression (n [%])	1 [3.3]	1 [3.3]
Thyroid disorders (n [%])	1 [3.3]	2 [6.7]
GORD (n [%])	1 [3.3]	1 [3.3]
Asthma History		
Asthma medications		
SABA only (n [%])	11 [36.7]	16 [53.3]
SABA + ICS (n [%])	5 [16.7]	3 [10.0]
SABA + ICS + LABA (n [%])	13 [43.3]	11 [36.7]
Changes made to medication regimen during pregnancy (prior to trial entry)		
Ceased asthma medications	10 [33.3]	6 [20.0]
Reduced current asthma medication dosage	1[3.3]	2 [6.6]
Possessed current asthma management plan	2 [6.6]	1 [3.3]
Baseline adherence score[29] (Median [IQR])	10 [8,13.5]	9 [7.75,13.0]
Spirometry		
FEV_1 (L) (Mean [SD])	2.68 [0.69]	2.39 [0.75]
FEV_1 % predicted (Mean [SD])	82 [19]	77 [22]
FEV_1/FEV_6 (Mean [SD])	0.78 [0.15]	0.79 [0.12]
Asthma exacerbations during current pregnancy (prior to trial entry)		
Asthma-related hospital visit (n [%])	4 [13.3]	1 [3.3]
Course of oral corticosteroids (n [%])	3 [10.0]	2 [6.6]
Asthma-related days off work (n [%])	6 [20.0]	3 [10.0]

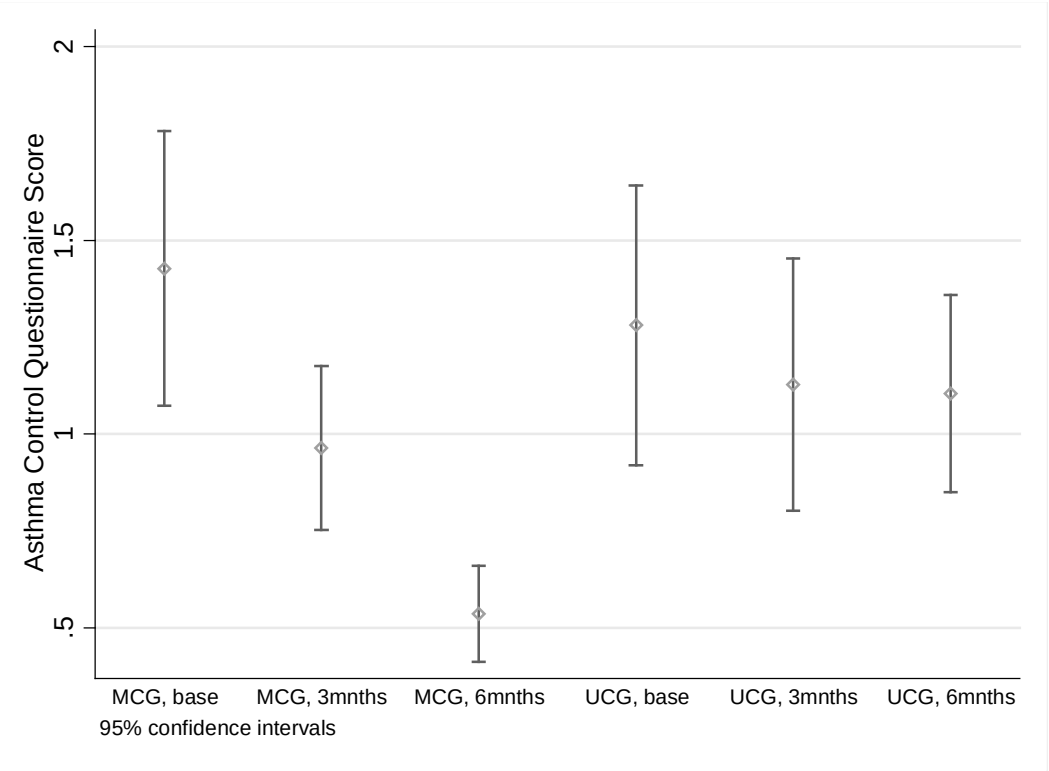
FEV_1=Forced Expiratory Volume in one second; FEV_6=Forced Expiratory Volume in six seconds; GORD= Gastro-oesophageal reflux disease; ICS=inhaled corticosteroid; LABA=long-acting beta agonist; MCG=Multidisciplinary Care Group; SABA=short-acting beta agonist; UCG=Usual Care Group

Table 2: Primary outcome data: ACQ scores at baseline, 3 months and 6 months

Time of ACQ score	MCG (n=29) (Mean [SD])	UCG (n=29) (Mean [SD])
Baseline	1.43 [0.93]	1.28 [0.95]
3 months	0.96 [0.56]	1.13 [0.86]
6 months	0.54 [0.32]	1.10 [0.67]

ACQ= Asthma Control Questionnaire; MCG=Multidisciplinary Care Group; UCG=Usual Care Group

Figure 3. Mean Asthma Control Questionnaire scores and 95% confidence intervals



The ACQ score in the intervention group decreased by mean (SD) of 0.46 (1.05) at 3 months and 0.89 (0.98) at 6 months. The control group had a mean decrease of 0.15 (0.63) at 3 months and 0.18 (0.73) at 6 months. The difference in ACQ scores between groups, adjusting for baseline ACQ, was significant at 6 months, but not at 3 months (Table 3).

Furthermore, all participants in the intervention group had an ACQ score <1.5 indicating adequately controlled asthma, as opposed to 20/29 (69%) in the UCG. No new asthma-related hospital admissions, emergency visits or oral corticosteroid use were reported in either group during the trial.

Table 3: Primary analysis: Mean change in baseline ACQ score at 3 and 6 months and the difference in mean change between groups adjusted for baseline ACQ

Change in ACQ score	Change within group		Difference between groups adjusted for baseline ACQ		
	MCG (n=29) (Mean [SD])	UCG (n=29) (Mean [SD])	Mean difference	95%CI	P-value
3 months - baseline ACQ	-0.46 [1.05]	-0.15 [0.63]	-0.22	(-0.54 to 0.10)	0.2
6 months - baseline ACQ	-0.89 [0.98]	-0.18 [0.73]	-0.60	(-0.85 to -0.36)	<0.001

ACQ= Asthma Control Questionnaire; MCG=Multidisciplinary Care Group; UCG=Usual Care Group

Perinatal outcome data are shown in Table 4. The intervention did not show any difference in mean birth weight, mean gestational age, mode of delivery, APGAR scores or incidence of congenital malformations and low birth weight babies. No pregnancy complications arising from asthma control were reported in either group during the trial.

Discussion

This study has shown that a straight-forward, low cost and well-tolerated intervention – comprising education, surveillance and multidisciplinary management – can successfully overcome barriers to asthma management in pregnancy, translating into improved asthma control in pregnancy. Our findings add to knowledge in this area and have addressed some of the limitations of the previous trials [27 28] targeting pregnant women with asthma. This is a simple, low cost model of care that could be easily implemented in antenatal settings with minimal additional resources. Larger studies are needed to demonstrate that these improvements translate to improved maternal and perinatal outcomes.

An asthma education programme was developed and tested by Murphy *et al.*[27] delivered in an antenatal clinic setting, that involved education and improving self-management skills in a single group study. The intervention was well received and produced significant improvements in self-management skills in women with mild, moderate and severe asthma. Nonadherence to inhaled corticosteroids dropped from 40% to 21%, inadequate inhaler technique decreased from 16% to 4% and asthma medication knowledge increased from 58% to 95%.[27] This uncontrolled study showed a simple educational programme could benefit asthma management during pregnancy, but it did not have any formal assessment of

Table 4: Perinatal outcome data

Outcome	MCG (n=29)	UCG (n=29)
Neonatal data		
Male (n [%])	18 [62.1]	15 [51.7]
Birth weight (g) (Mean [SD])	3456.2 [664.6]	3448.4 [627.8]
Gestation (weeks) (Mean [SD])	38.9 [1.6]	38.9 [2.9]
Head circumference (cm) (Mean [SD])	34.7 [1.8]	35.2 [1.7]
Length (cm) (Mean [SD])	50.8 [2.7]	51.3 [2.0]
APGAR scores		
At 1 minute (Mean [SD])	8.5 [1.1]	7.8 [1.7]
At 5 minutes (Mean [SD])	9.1[0.5]	8.8 [0.9]
Admission to NICU or SCN (n [%])	3 [10.3]	2 [6.8]
Premature (<37 weeks) (n [%])	3 [10.3]	2 [6.9]
Low birth weight (<10th centile for gestational age) (n [%])	1 [3.4]	1 [3.4]
Congenital malformations (n [%])	0 [0.0]	0 [0.0]
Delivery data		
Mode of delivery		
Vaginal delivery (n [%])	21 [72.4]	20 [69.0]
Emergency caesarean (n [%])	2 [6.9]	4 [13.8]
Elective caesarean (n [%])	6 [20.7]	5 [17.2]
Complications		
Hypertension during pregnancy (n [%])	2 [6.9]	0 [0.0]
Gestational diabetes (n [%])	2 [6.9]	0 [0.0]
Macrosomia (n [%])	1 [3.4]	0 [0.0]

This dataset also includes one set of twins in the UCG – in this case, the data of the larger twin was included.
MCG=Multidisciplinary Care Group; NICU= Neonatal Intensive Care Unit; SCN= Special Care Nursery; UCG=Usual Care Group

asthma control. Furthermore, women were not monitored regularly throughout pregnancy as recommended. A more complex intervention targeting doctors was designed by Powell *et al*.[28] which involved monitoring asthmatic women using an algorithm based on the fraction of exhaled nitric oxide (F_ENO) – a marker of airway inflammation. The intervention reduced exacerbations by 50% compared to a symptom-based algorithm. Although F_ENO-guided management was found to be efficacious and safe, it may not be a viable option for routine antenatal care due to operational and maintenance costs.

Two major barriers to optimising management of asthma in pregnancy were identified: 70% of women were unaware of the hazards of poorly controlled asthma and 32% ceased or changed medications during pregnancy without discussing with their health professionals. Overall, our participants appreciated the support and advice they received regarding their asthma management.

Asthma is often ignored during pregnancy as other health conditions take priority; however, asthma causes much anxiety in affected patients.[23 24]

Recruiting participants from the antenatal clinics in their first trimester was a challenge as the majority of pregnant women do not present until late first trimester or early second trimester. By this time many participants had already made incorrect management decisions regarding their asthma (e.g. ceasing asthma medications), which could have affected asthma control at baseline. Severely uncontrolled asthma in the control group (ACQ>2) was brought to the attention of participants, who were advised to get their asthma reviewed by their family physician – this occurred on two occasions at the three month assessment. However, at the six month assessment neither of these participants had followed that advice.

A trial (Hawthorne) effect might have influenced our outcomes, especially those self-reported by participants. However, assessments of primary outcomes were made by independent research assistants who were not involved in the care of participants and were blinded to group allocation. General improvement in asthma control in the last four weeks of gestation has been reported[33]; a third of women naturally have their asthma improve during pregnancy.[34] We could not establish any natural influences on asthma control amongst our participants and assumed that randomisation has balanced this variable across groups. The study was not powered to detect any differences in perinatal or neonatal outcomes, or health resource utilisation. The intervention was admittedly time intensive but this can be reduced by incorporating this model into routine antenatal care and use of technology.

The MAMMA© intervention has the potential to reduce health care costs through fewer asthma-related unplanned medical and emergency department visits for pregnant women, and costs associated with poor perinatal outcomes resulting from poorly controlled asthma. Larger multicentre studies powered to detect improvements in other maternal and perinatal outcomes and cost-effectiveness are warranted. Future studies should also investigate the use of technology (e.g. mobile phone-based applications) to minimise burden on the health professionals and to facilitate participant acceptance. Positive results from such studies would convince policy makers and ensure more support for multidisciplinary asthma management in antenatal settings.

Conclusion

The MAMMA© trial has shown that actively managing asthma through education and regular monitoring using a pharmacist-led multidisciplinary team can improve asthma control during pregnancy. Empowering women to take control of this common chronic health condition and providing them with more support services will reduce the burden of asthma during pregnancy and potentially reduce poor perinatal outcomes associated with exacerbations.

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Chapter 8: Summary of research findings and conclusions

8.1 Overall summary of the research findings

Exploration of factors that influence maternal asthma management, such as medication safety, has been valuable in developing an intervention to help improve asthma control during pregnancy.

The systematic review highlighted that women should not refrain from taking their asthma medications during pregnancy if necessary for adequate asthma control. Current safety data have not been able to demonstrate a direct association between poor outcomes and asthma medication use during pregnancy, whereas there is an abundance of literature supporting the risks of uncontrolled asthma. These recommendations could potentially improve adherence to asthma management guidelines, better use of asthma medications and better asthma control. Pharmacists, general practitioners and consumers are potential readers of this published manuscript. Readers may realise the importance of obtaining more safety data regarding asthma medication use during pregnancy. More evidence could potentially lead to re-classifying these products to a safer category under the Food and Drug Administration or Therapeutic Goods Administration pregnancy risk categories. Again, this could optimise the use of these medications and improve asthma control during pregnancy.

Suboptimal prescribing in pregnancy is a major contributing factor to nonadherence to asthma preventive medications during pregnancy. The plan to implement an educational multidisciplinary intervention to address this warranted the need for investigation into prescribing trends

and management strategies in this particular group of women. Exploring perceptions associated with preventive asthma medication use during pregnancy and what recommendations are being implemented, provided useful background knowledge for designing interventions to improve care. The results showed that prescribers were advising patients to reduce or discontinue their asthma medications during pregnancy when it was unnecessary, putting them at risk of uncontrolled asthma. Furthermore, there was a lack of knowledge in regard to management of deteriorating asthma during pregnancy. The study has drawn media attention and some publicity regarding the importance of stringent asthma management and asthma monitoring during pregnancy.

There was limited evidence available on asthma medication use in pregnancy especially from the pregnant women's perspective, so in-depth interviewing was used to elicit the barriers to and facilitators of adherence and elucidate the asthma experiences of these women. Through these interviews, it was demonstrated that the majority of women were anxious about taking medicines because they were unaware of the risks of poorly controlled asthma. Consequently, many were coming off their current asthma therapy and increasing their risk of poor asthma control during pregnancy and poor perinatal outcomes. This study gave insights into why so many women are nonadherent to their asthma medication during pregnancy and aided the development of the next phase – the intervention.

The final phase of the research was the intervention study, a single-blinded parallel-group randomised controlled trial. The Multidisciplinary Approach to Management of Maternal Asthma (MAMMA©) involved asthma education and regular monitoring by patients and their health

professionals. Both intervention and control groups were followed prospectively throughout pregnancy and outcomes were compared between groups at three and six months from baseline to evaluate the effectiveness of this intervention. The intervention was well received, with many GPs and midwives getting involved. Changes recommended in the intervention group included initiation of asthma action plans, re-introduction of preventers, increase in preventer dosages and referral to a respiratory specialist. Results showed improvements (decrease) in Asthma Control Questionnaire (ACQ) mean scores at three and six months from baseline, for both control and intervention groups. At the six-month assessment, the mean ACQ score was better in the intervention group than the control group and the difference was clinically significant (>0.5). Furthermore, all participants in the control group had an ACQ score <1.5 indicating adequately controlled asthma. No asthma-related hospital admissions, emergency visits or oral corticosteroid use was reported in either group during the trial.

These results confirmed the importance of improving asthma management during pregnancy and validated a feasible model for supporting pregnant women with asthma that could be more widely implemented in routine antenatal care in hospitals. The proposed intervention has the potential to reduce health care costs through fewer unplanned asthma-related medical and emergency department visits for pregnant women. The study was not powered to show a decrease in the risk of poor perinatal outcomes. However, the literature suggests that through better asthma control during pregnancy, the costs associated with poor perinatal outcomes i.e. pre-term births and low birth weight babies (parenteral nutrition costs, Neonatal Intensive Care admissions,

assisted ventilation etc.) could be reduced. This needs to be confirmed in large prospective controlled studies.

8.2 Strengths and limitations

This research has investigated important barriers to and facilitators of optimal asthma management during pregnancy from the perspective of patients and general practitioners. It tested the need for regular monitoring of pregnant women with asthma using a multidisciplinary approach and the role of patient self-management. It increased awareness of negative outcomes associated with poorly controlled asthma among participants, promoted the safety of asthma medications, improved patient adherence to asthma medications during pregnancy, encouraged monitoring of maternal asthma, and thus improved asthma control among participants.

The research was limited by funding and time. Ideally, it would have been more representative to only include moderate to severe asthmatics in our trial who were at least on preventive therapy; however, without sufficient staffing for recruitment, our numbers would have been too hard to reach in the given time frame. This was also the reason why the study was not powered to detect differences in asthma exacerbations as an outcome. In addition, it was not possible to obtain consent from participants' GPs to follow a standard clinical algorithm to ensure all participants in the intervention arm were treated equally. This would not only have slowed down recruitment, but also was queried by the ethics committee as overstepping boundaries of clinical care.

Furthermore, adherence to asthma medications and monitoring was self-reported by the participant as electronic monitoring of adherence was

beyond the scope of this project. Unlike some countries, Australia does not have a prescription record database that is easily accessible.

8.3 Future directions

Maternal asthma management is suboptimal in Australia. Health professionals should be well supported with information to help them guide and optimise therapy. For better understanding of asthma management during pregnancy, the usage of asthma medicines should be studied longitudinally and in more depth in pregnant women. With the prevalence of asthma increasing in women of childbearing age, and with Australia being one of the countries with the highest prevalence of asthma worldwide, more research on this condition is required.

More well-controlled randomised controlled trials assessing asthma medication use in pregnancy are warranted. In addition, more interventions aimed to decrease asthma exacerbations during pregnancy should be developed and tested in this population. Larger intervention studies powered to assess perinatal outcomes are warranted to justify more funding for support services in routine antenatal care.

Markers of asthma control during pregnancy should also be a research priority to help pregnant asthmatic women better guide management and distinguish shortness of breath from asthma symptoms. Further implementation of treatment algorithms e.g. FeNO testing and self-management plans incorporating simple home monitoring of lung function (e.g. FEV_1 and FEV_6) using handheld devices, should be continued to detect changes in lung function during pregnancy to avoid exacerbations.

Lastly, updated guidelines for prescribers and lung function-based step-up therapies during pregnancy should be developed to help support doctors in practice.

8.4 Conclusions

Overall, this thesis has accumulated evidence of poor management of asthma during pregnancy by both health professionals and pregnant women. The thesis promoted greater awareness of the risks of poorly controlled asthma and the need for more attention in this area. In addition, the feasibility of patient self-monitoring of lung function in pregnancy has been established. Empowering pregnant women to take control of this common chronic health condition will reduce the burden of maternal asthma, potentially reducing risks associated with uncontrolled asthma and improving the health of future generations.

Appendices

Appendices for asthma drugs in pregnancy and lactation:

Practice points

(Supplement to Phase 1 – Chapter 3)

Appendix 1 – Australian Prescriber invitation letter

Appendix 1 – Australian Prescriber invitation letter (Chapter 3)

NPS
Better choices ▸ Better health

Australian Prescriber
AN INDEPENDENT REVIEW

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Miss Angelina Lim
Department of Pharmacy Practice
Faculty of Pharmacy and
Pharmaceutical Sciences
Monash University
Victoria 3806

Dear Miss Lim

Australian Prescriber is an independently edited, review of therapeutics which is published six times per year under the auspices of the NPS.

I am pleased, on behalf of the Editorial Executive Committee of *Australian Prescriber,* to invite you to write an article on 'Asthma drugs in pregnancy and lactation' for possible publication in the journal.

Australian Prescriber aims to provide short, direct and didactic reviews on a variety of therapeutic topics which will appeal and be helpful to those perceived by the Editorial Committee as the journal's main readership – the busy doctor in general practice and the community pharmacist.

The article could begin with the concerns that women have about managing their asthma during pregnancy and lactation. It should summarise the evidence regarding the safe and effective, use of drugs for asthma in these women. This should include the use of oral corticosteroids for treating acute exacerbations of asthma. The article can conclude by suggesting what advice can be given to the women.

A nominal fee is payable for contributions and the Editor retains the right to accept or reject an article. All articles published in *Australian Prescriber* are sub-edited by the journal's staff, refereed by a senior consultant and reviewed by the Editorial Committee, and their respective comments may be incorporated. Additional editing is sometimes required to ensure that the articles provide an authoritative review for the majority of readers. All edited articles are returned to authors for approval before publication.

I have attached for your assistance a copy of the guidelines outlining the requirements for articles. Here are some previously published articles about drugs in pregnancy and lactation. http://www.australianprescriber.com/magazine/34/1/8/10 , http://www.australianprescriber.com/magazine/30/5/125/7 Please note that, because of restrictions on space, articles should not exceed 1500 words. Copyright will apply to all material published in *Australian Prescriber.*

I would appreciate your early advice by telephone, facsimile or email as to whether or not you agree to contribute. If you are able to write the article, I would be grateful if it could be received in this office by **Wednesday 29 August 2012**. Please inform me if you intend to work with a co-author.

Should you be unable to accept the invitation, you may care to nominate a suitable colleague.

Yours sincerely

[redacted]
EDITOR
4 July 2012

Appendices for management of asthma in pregnant women by general practitioners:

A cross sectional survey

(Phase 2 – Chapter 4)

Appendix 2 – Monash University Human Research Ethics Committee approval letter

Appendix 3 – Participant explanatory statement

Appendix 4 – Signed consent form from Monash Medical Centre

Appendix 5 – Signed consent form from Mercy Hospital for Women

Appendix 6 – Survey questionnaire

Appendix 2 – Monash University Human Research Ethics Committee ethics approval letter

MONASH University

Monash University Human Research Ethics Committee (MUHREC)
Research Office

Human Ethics Certificate of Approval

Date:	**22 October 2010**
Project Number:	**CF10/2750 - 2010001557**
Project Title:	**A questionnaire on prescribing trends and management of asthma during pregnancy**
Chief Investigator:	**Dr Johnson George**
Approved:	**From: 22 October 2010 To: 22 October 2015**

Terms of approval

1. The Chief investigator is responsible for ensuring that permission letters are obtained, if relevant, and a copy forwarded to MUHREC before any data collection can occur at the specified organisation. **Failure to provide permission letters to MUHREC before data collection commences is in breach of the National Statement on Ethical Conduct in Human Research and the Australian Code for the Responsible Conduct of Research**.
2. Approval is only valid whilst you hold a position at Monash University.
3. It is the responsibility of the Chief Investigator to ensure that all investigators are aware of the terms of approval and to ensure the project is conducted as approved by MUHREC.
4. You should notify MUHREC immediately of any serious or unexpected adverse effects on participants or unforeseen events affecting the ethical acceptability of the project.
5. The Explanatory Statement must be on Monash University letterhead and the Monash University complaints clause must contain your project number.
6. **Amendments to the approved project (including changes in personnel):** Requires the submission of a Request for Amendment form to MUHREC and must not begin without written approval from MUHREC. Substantial variations may require a new application.
7. **Future correspondence:** Please quote the project number and project title above in any further correspondence.
8. **Annual reports:** Continued approval of this project is dependent on the submission of an Annual Report. This is determined by the date of your letter of approval.
9. **Final report:** A Final Report should be provided at the conclusion of the project. MUHREC should be notified if the project is discontinued before the expected date of completion.
10. **Monitoring:** Projects may be subject to an audit or any other form of monitoring by MUHREC at any time.
11. **Retention and storage of data:** The Chief Investigator is responsible for the storage and retention of original data pertaining to a project for a minimum period of five years.

[redacted]
Professor Ben Canny
Chair, MUHREC

cc: Assoc Prof Kay Stewart, Prof Michael Abramson, Miss Angelina Lim

Postal – Monash University, Vic 3800, Australia
Building 3E, Room 111, Clayton Campus, Wellington Road, Clayton
Telephone +61 3 9905 5490 Facsimile +61 3 9905 3831
Email muhrec@adm.monash.edu.au www.monash.edu/research/ethics/human/index/html
ABN 12 377 614 012 CRICOS Provider #00008C

Appendix 3 – Participant explanatory statement

Participant Explanatory Statement

A questionnaire on prescribing trends and management of asthma during pregnancy

8th November 2010

This information sheet is for you to keep

Dear Doctor,

Please help us investigate and optimise the management of asthma during pregnancy. Some women discontinue or reduce the use of their asthma medication during pregnancy. This could lead to complications such as severe exacerbations, low birth weight, pre-term delivery, infections and more seriously, foetal brain damage and cerebral palsy in the infant. A study conducted at The Royal Women's Hospital in 2009 found a decline in the use of pharmacological treatment during pregnancy despite worsening of symptoms.

By completing the enclosed questionnaire, you will help us to understand the prescribing trends and management of asthma during pregnancy by general practitioners, which will inform strategies to optimise outcomes in pregnant women with asthma.

The survey is very simple and will only take less than 15 minutes to complete. It is not designed to test practitioners' knowledge in any way, but only to investigate different practices. This is an anonymous questionnaire. Participation is voluntary; completion

and return of the questionnaire constitutes informed consent to take part in the study. This survey is endorsed by The Asthma Foundation of Victoria.

$1 donation to the Asthma Foundation of Victoria will be made for every survey completed and returned. **Please ignore this invitation if you have already received this survey and completed it already.**

The investigators for this study are Dr Johnson George, A/Prof Kay Stewart, Prof Michael Abramson (all of Monash University) and Ms Angelina Lim (Monash University, The Mercy Hospital).You have been contacted because you are involved in providing maternity shared care through Hospital XXX. We have not obtained any contact details; this invitation has been sent to you by Hospital XXX on behalf of the investigators. This study has been approved by Monash University Human Research Ethics Committee (MUHREC). The data collected from this questionnaire will be stored for at least 5 years and then destroyed. Hard copies will be stored in locked cabinets and electronic copies will be password protected: both will only be accessible by the investigators. Results may be presented at various conferences and in journal publications, but will be fully de-identified. You can contact one of the chief investigators to get a copy of the publication or summary of the study findings by e-mail or post.

There are no foreseeable risks associated with participation in this study. Parent hospitals will be notified the summary results of the study, including any prescribing patterns of concern; however, it will not be possible to identify any individual practitioner, as the survey will be completed anonymously.

Contact details for further enquiries, feedback or complaints in-relation to this project are given below.

If you would like to contact the researchers about any aspect of this study, please contact:	If you have a complaint concerning the manner in which this research (MUHREC Project No: **XXX**) is being conducted, please contact:
Dr Johnson George [redacted] [redacted] Ms Angelina Lim [redacted] [redacted] [redacted]	Executive officer Monash University Human Research Ethics Committee (MUHREC) Building 3e Room 111 Research Office Monash University VIC 3800 [redacted] [redacted] [redacted]

We would very much appreciate your participation. Pre paid reply envelopes are also included.

Yours sincerely,

Angelina Lim (On behalf of Dr. Johnson George, Prof Michael Abramson and A/Prof Kay Stewart)

Appendix 4 – Signed consent form from Monash Medical Centre

MONASH University

Consent Form

Title: **A questionnaire on prescribing trends and management of asthma during pregnancy**

NOTE: This consent form will remain with the Monash University researcher for their records

I, REBECCA FRAPLING (GP liaison officer) on behalf of Southern Health will allow the research team consisting of Angelina Lim, Dr. Johnson George, Assoc/Prof Kay Stewart, Professor Michael Abramson (all of Monash University, Australia) access to contact our general practitioners affiliated with shared care through our mailing system. Contact will be via written communication and will pass through our department and will be under my supervision. No contact details of general practitioners involved in shared care will be given to the research team.

AND

I understand that any data that the researcher extracts from the questionnaire for use in reports or published findings will not, under any circumstances, contain names of individuals or affiliated hospitals.

AND

I understand that the data collected from this questionnaire will be stored for at least 5 years and then destroyed. Hard copies will be stored in locked cabinets and electronic copies will be password protected and both will only be accessible by the research team.

Results will [redacted] on your request and may be presented at various conferences or publications de-identified.

Signature [redacted]

Date

4 / 10 / 10

Appendix 5 – Signed consent form from Mercy Hospital for Women

MONASH University

Consent Form

Title: **A questionnaire on prescribing trends and management of asthma during pregnancy**

NOTE: This consent form will remain with the Monash University researcher for their records.

I, Dr Mary Anne McLean (GP liaison officer) on behalf of Mercy Health will allow the research team consisting of Angelina Lim, Dr. Johnson George, Assoc/Prof Kay Stewart, Professor Michael Abramson (all of Monash University, Australia) access to contact our general practitioners affiliated with shared care through our mailing system. Contact will be via written communication and will pass through our department and will be under my supervision. No contact details of general practitioners involved in shared care will be given to the research team.

AND

I understand that any data that the researcher extracts from the questionnaire for use in reports or published findings will not, under any circumstances, contain names of individuals or affiliated hospitals.

AND

I understand that the data collected from this questionnaire will be stored for at least 5 years and then destroyed. Hard copies will be stored in locked cabinets and electronic copies will be password protected and both will only be accessible by the research team.

Results will be provided upon your request and may be presented at various conferences or publications but will be fully de-identified.

Signature [redacted]

Date 5-10-10

Appendix 6 – Survey questionnaire

MONASH University

THE ASTHMA FOUNDATION Victoria

Section one: You and your practice

The questions in this section are about you and your practice. Please either fill in the gaps or tick (✓) the boxes as appropriate.

1. **Gender:** ☐ MALE ☐ FEMALE

2. **The year you began practising as a General Practitioner** ☐☐☐☐

3. **Did you complete ALL your medical training in Australia?**
Please tick (✓) one (1) box only
☐ Yes

☐ No, Please specify
where_____
(Specify if more than one location is applicable i.e. Australia/United Kingdom)

If NO, how long have you been practising in Australia? _____years

4. **Do you have any areas of expertise (e.g. asthma, women's health, paediatrics)?**
Please tick (✓) one (1) box only
☐ Yes, please specify
_____

☐ No

5. **Your practice setting could be described as?** *Please tick (✓) one (1) box only*
☐ Metropolitan ☐ Regional ☐ Rural

6a. On average, how many pregnant women do you provide shared care in a year?

Please tick (✓) one (1) box only

☐ None (go to question 7) ☐ <10 ☐ 11-20 ☐ >20

6b. Approximately, what proportion of these pregnant women have asthma?

Please tick (✓) one (1) box only

☐ None ☐ <10% ☐ 11-20% ☐ 20-30% ☐ >30%

7. Do you have a practice nurse or asthma educator who assists you in asthma management?

Please tick (✓) one (1) box only

☐ Yes, please specify _____ ☐ No

8. Do you follow any guideline for managing asthma? *Please tick (✓) one (1) box only*

☐ Yes, please specify _____ ☐ No

9. On a scale of very poor to very good, how would you rate your knowledge in managing asthma?

Please tick (✓) one (1) box only

☐ Very poor ☐ Poor ☐ Average ☐ Good ☐ Very Good

Section two: Safety of asthma medications during pregnancy

The two questions in this section are to investigate the perceived safety of different asthma medications during pregnancy.

10. **You need to prescribe a PREVENTIVE medication to a pregnant patient with worsening asthma who is in her <u>FIRST TRIMESTER</u>. She has no other medical conditions nor is taking any other medications. Give your top two preferences.** *(Put a **"1"** in the box of your first preference, and a **"2"** in the box of your second preference. You can have more than one 1st OR 2nd preference)*

    ☐ Cromolyns (nedocromil, sodium cromoglycate)

    ☐ Inhaled corticosteroids (beclomethasone, budesonide, ciclesonide, fluticasone)

    ☐ Leukotriene receptor antagonists (montelukast, zafirlukast)

    ☐ Long-acting $beta_2$ agonists (eformoterol, salmeterol)

    ☐ Long-acting $beta_2$ agonists + inhaled corticosteroid combination (Seretide, Symbicort)

11. At normal adult doses, which of the following asthma medicines do you consider 'safe' for use in a pregnant woman with asthma? *Please tick (✓) either "Yes" or "No" for each drug for each trimester.*

Example:

Drug	First trimester		Second trimester		Third trimester	
	Yes	No	Yes	No	Yes	No
Drug A	✓			✓		✓

Now complete the following table

Drug	First trimester		Second trimester		Third trimester	
	Yes	No	Yes	No	Yes	No
Cromolyns						
Nedocromil						
Sodium Cromoglycate						
Inhaled corticosteroids						
Beclomethasone						
Budesonide						
Ciclesonide						
Fluticasone						
Leukotriene receptor antagonists						
Montelukast						
Zafirlukast						
Long acting beta$_2$ agonists						
Eformoterol						
Salmeterol						
Oral corticosteroids						
Prednisolone						
Short acting beta$_2$ agonists						
Salbutamol						
Terbutaline						

Section three: Management of pregnant women with asthma

This section has two (2) scenarios of pregnant women with asthma. Each scenario is accompanied by some questions.

SCENARIO ONE:

Refer to the following scenario and answer questions 9 and 10

A patient of yours has recently become pregnant. She has moderate asthma which is well controlled with ***Seretide (250/25)*** *(fluticasone /salmeterol) one puff twice daily and Ventolin (Salbutamol) Inhaler as required. She has no other medical conditions nor is she taking any other medications.*

12. She wonders whether she should continue these medications during pregnancy. What is your intended action? *Please tick (✓) one (1) box only*

☐ Continue her on the same medications

☐ Change Seretide to Pulmicort (Budesonide)

☐ Change Seretide to Symbicort (Budesonide/eformoterol)

☐ Change her to a different preventive medication(s), specify which one(s)_____

☐ Stop Seretide

☐ Decrease the dose of Seretide

☐ Refer her to another health professional (e.g. Respiratory specialist)

☐ Other, please specify

_____

13. A few weeks pass by and your patient returns, and you notice that her asthma is deteriorating. She tells you that she has been using her Ventolin inhaler more than three times per week. She has been compliant with the Seretide and has had no changes to her asthma medication regimen nor has she had any changes in lifestyle. What is your intended action? *Please tick (✓) one (1) box only*

☐ Increase the dose of Seretide

☐ Continue with the same regimen and simply monitor her asthma more closely

☐ Change her to another preventive medication, specify which one(s)

_____

☐ Add another preventive medication, specify which one(s)_____

☐ Refer her to another health professional (e.g. Respiratory specialist, obstetrician)

☐ Other, please specify

_____

SCENARIO TWO:

Refer to the following scenario and answer questions 11 and 12

*One of your regular patients is **18 weeks pregnant** and she **asks you for a new prescription of Ventolin inhaler** as she is a health care card holder and can get them cheaper on script. However, you notice that she got a script of **Ventolin Inhaler only last month**. Upon asking, you find out that she has stopped her **Symbicort** (budesonide/eformeterol) inhaler because she fears it will harm her unborn child. Instead she has been using her Ventolin inhaler more frequently to compensate. She has no other medical conditions nor is she taking any other medications.*

14. What is your intended action? *Please tick (✓) one (1) box only*

☐ DO NOT give a script for the Ventolin inhaler, but refer her to a respiratory specialist

☐ Give a script for Ventolin Inhaler and refer her to a respiratory specialist

☐ Give a script for Ventolin Inhaler with no further questions and just monitor her asthma more closely thereafter

☐ Give a script for Ventolin Inhaler, discuss the importance and safety of Symbicort and reinforce the need for her to continue Symbicort

☐ Give a script for Ventolin Inhaler and initiate her on a different preventer, specify which one(s)

_____

☐ Other, specify_____

15a. Have you ever had to intervene and promote compliance (adherence) to preventive asthma medication(s) in a noncompliant (non-adherent) patient during pregnancy? *Please tick (✓) one (1) box only*

☐ Yes ☞ please go on to 12 b ☐ No

15b. If *yes*, which of the following strategies have you employed? *Please tick (✓) as many boxes as appropriate*

☐ Provided education focusing on the safety of asthma medications

☐ Provided education on the risks associated with non-adherence to asthma medications during pregnancy and poor asthma control

☐ Organised regular return visits to monitor adherence to asthma medications

☐ Organised regular return visits to monitor asthma control

☐ Referred them to another health professional (e.g. pharmacist, asthma educator) to monitor their adherence

☐ Referred them to another health professional (e.g. respiratory specialist) to monitor their asthma control

☐ Other, please specify _____

Thank you for your time!

Appendices for Asthma during pregnancy: The experiences, concerns and views of pregnant women with asthma (Phase 3 – Chapter 5)

Appendix 7 – Monash University Human Research Ethics Committee approval letter

Appendix 8 – Mercy Health Ethics Committee approval letter

Appendix 9 – Participant explanatory statement

Appendix 10 – Participant consent form

Appendix 11 – Pre-interview questionnaire

Appendix 12 – Interview topic guide

Appendix 7 – Monash University Human Research Ethics Committee approval letter

MONASH University

Monash University Human Research Ethics Committee (MUHREC)
Research Office

Human Ethics Certificate of Approval

Date:	**22 October 2010**
Project Number:	**CF10/2750 - 2010001557**
Project Title:	**A questionnaire on prescribing trends and management of asthma during pregnancy**
Chief Investigator:	**Dr Johnson George**
Approved:	**From: 22 October 2010 To: 22 October 2015**

Terms of approval

1. The Chief investigator is responsible for ensuring that permission letters are obtained, if relevant, and a copy forwarded to MUHREC before any data collection can occur at the specified organisation. **Failure to provide permission letters to MUHREC before data collection commences is in breach of the National Statement on Ethical Conduct in Human Research and the Australian Code for the Responsible Conduct of Research**.
2. Approval is only valid whilst you hold a position at Monash University.
3. It is the responsibility of the Chief Investigator to ensure that all investigators are aware of the terms of approval and to ensure the project is conducted as approved by MUHREC.
4. You should notify MUHREC immediately of any serious or unexpected adverse effects on participants or unforeseen events affecting the ethical acceptability of the project.
5. The Explanatory Statement must be on Monash University letterhead and the Monash University complaints clause must contain your project number.
6. **Amendments to the approved project (including changes in personnel):** Requires the submission of a Request for Amendment form to MUHREC and must not begin without written approval from MUHREC. Substantial variations may require a new application.
7. **Future correspondence:** Please quote the project number and project title above in any further correspondence.
8. **Annual reports:** Continued approval of this project is dependent on the submission of an Annual Report. This is determined by the date of your letter of approval.
9. **Final report:** A Final Report should be provided at the conclusion of the project. MUHREC should be notified if the project is discontinued before the expected date of completion.
10. **Monitoring:** Projects may be subject to an audit or any other form of monitoring by MUHREC at any time.
11. **Retention and storage of data:** The Chief Investigator is responsible for the storage and retention of original data pertaining to a project for a minimum period of five years.

[redacted]
Professor Ben Canny
Chair, MUHREC

cc: Assoc Prof Kay Stewart, Prof Michael Abramson, Miss Angelina Lim

Postal – Monash University, Vic 3800, Australia
Building 3E, Room 111, Clayton Campus, Wellington Road, Clayton
Telephone +61 3 9905 5490 Facsimile +61 3 9905 3831
Email muhrec@adm.monash.edu.au www.monash.edu/research/ethics/human/index/html
ABN 12 377 614 012 CRICOS Provider #00008C

Appendix 8 – Mercy Health Ethics Committee approval letter

Mercy Health
Care first

31 May 2012

Dr Johnson George
Lecturer
Centre for Medicine Use and Safety
Monash University
381 Royal Parade
Parkville
VIC 3052

Dear Dr George

Re: R12/13: Evaluation of an intervention to improve asthma control in pregnant women. A pilot study.

I am pleased to advise that your amendments comply with the requirements of the Human Research Ethics Committee meeting of 3 April 2012 and as such you may now commence with the study. Specifically, the following documentation is approved:

Module One	Version 2 Dated 10 May 2012
Recruitment Poster	Dated 10 May 2012
Participant Explanatory Statement	Version 2 Dated 10 May 2012
Expression of Interest form	Version 2 Dated 10 May 2012
Information given to midwives	Version 2 Dated 10 May 2012
Data Collection form	Version 2 Dated 10 May 2012
Asthma control Questionnaire (ACQ)	Dated 10 May 2012
Asthma during pregnancy education leaflet	Dated 10 May 2012
Participant Consent Form	Version 2 Dated 10 May 2012
General Practitioner Notice- Notification of patient participation	Dated 10 May 2012

The Human Research Ethics Committee is constituted and functions in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007).

Approval by the Mercy Health Board is valid for up to 3 years from the date of this letter. That is, the project should be completed by the approval expiry date, which is **31 May 2015**. Should it become apparent that an extension of the 3-year period is required, the principal researcher should apply, in writing, through the Administrative Officer of the Human Research Ethics Committee. Please note that the research

Mercy Health
Level 2, 12 Shelley Street, Richmond Victoria 3121 Phone: +61 3 8416 7777 Fax: +61 3 8416 7888 mercyhealth.com.au ABN 77 191 901 062

project should be commenced within 12 months from the date of this letter. **Would you kindly advise me the date that you commence your research.**

In accordance with the NHMRC Guidelines, approval is subject to:

1. Immediate notification to the Administrative Officer, The Mercy Health Human Research Ethics Committee and sponsor, of any serious adverse effects on participants;
2. Immediate notification of any unforeseen events that may affect the continuing ethical acceptability of the project;
3. Notification and reasons for ceasing the project prior to its expected date of completion;
4. The completion of a progress report at 6 months and then annually for the duration of the project; (progress report attached);
5. The Mercy Health Human Research Ethics Committee approval of any proposed modifications to the project;
6. The submission of a final report and papers published on completion of the project.

Please also note:

7. Consent Forms must be available for audit by the Mercy Health Human Research Ethics Committee and retained for the period required by law;
8. The Principal Investigator upon leaving the Institution must inform the Mercy Health Human Research Ethics Committee as to the nominated person to replace him/her.

If you have any queries, please do not hesitate to contact me on 8458 4808.

Yours sincerely

[redacted]

Carole Branch
Administrative Officer
Mercy Health Human Research Ethics Committee

Appendix 9 – Participant explanatory statement

Participant Explanatory Statement

Title: Qualitative interviews with pregnant asthmatic women about the management of their asthma during pregnancy

1st March 2011

This information sheet is for you to keep

You are invited to participate in a study that will help improve the management of asthma during pregnancy. Your involvement will provide information that will aid future research. Many women are unsure what to do with their asthma medications during pregnancy and are concerned about how asthma will affect their pregnancy. By sharing your experiences, you will help provide support and informative data for others.

We invite you to participate in an individual, one-on-one interview. You have been selected as you have identified yourself to the outpatient department of Mercy Hospital for Women, Heidelberg, as a pregnant woman with asthma. The interview would be conducted at your preferred location and time as selected on the consent form provided. Conveniently, you have the option of being interviewed when you attend your next appointment at your Mercy Hospital for Women, Heidelberg. **If you chose this option, your parking or public transport costs will be reimbursed.** If you chose to interview over the phone or at another location, there will be no cost to you associated with the interview.

The interview will be simple and straightforward and run from 30mins to an hour. The questions will surround the topic of medication use and asthma management. You are not obliged to answer any question and you may withdraw or leave the interview at any time. There will be no consequences for not answering any given question. Participation is voluntary and the interview is about your experiences with asthma during pregnancy. There are no right or wrong answers. Please return and complete both the pre-interview questionnaire and consent form in the enclosed pre-paid envelope if you are interested in participating. You will be only contacted again if you fill in the consent form. From the pre-interview questionnaire, we will select a sample of participants to interview. If you are chosen, you will be contacted and a suitable time and place for an interview will be arranged.

The investigators for this study are Dr Johnson George, A/Prof Kay Stewart, Prof Michael Abramson (Monash University) and Ms Angelina Lim (Monash University, The Mercy Hospital). This study has been approved by Monash University Human Research Ethics Committee (MUHREC) and the Human Research Ethics Committees of Mercy Hospital for Women, Heidelberg. The interview will be recorded and supplemented with hand-written notes. Both will be stored for at least 5 years and then destroyed. Hard copies will be stored in locked cabinets and electronic copies will be password protected; both will only be accessible by the investigators. Results may be presented at various conferences and in journal publications, but no participants will be able to be identified. You can contact one of the chief investigators to get a summary of the study findings by e-mail or post or download it from www.monash.edu.au/.

There are no foreseeable risks associated with participation in this study. If during the interview, it becomes evident that there is concern with your asthma management, we will notify you and/or your doctor, at your discretion.

By participating in this study, you will help us to understand and improve the management of asthma during pregnancy.

Contact details for further enquiries, feedback or complaints in relation to this project are given below.

If you would like to contact the researchers about any aspect of this study, please contact:	If you have a complaint concerning the manner in which this research is being conducted, please contact either the Monash University Human Research Ethics Committee or the Mercy Hospital for Women Research Ethics Committee:
Dr Johnson George [redacted] [redacted] Ms Angelina Lim [redacted] [redacted] [redacted]	Executive officer Monash University Human Research Ethics Committee (MUHREC) [redacted] [redacted] Mercy Hospital for Women Research Ethics Committee (MUHREC) [redacted] [redacted]

We very much look forward to hearing from you.

Yours sincerely,

Angelina Lim (On behalf of Dr. Johnson George, Prof Michael Abramson and A/Prof Kay Stewart)

Appendix 10 – Participant consent form

Consent Form

Title: Qualitative interviews with pregnant asthmatic women about the management of their asthma during pregnancy

NOTE: This consent form will remain with the Monash University researcher for their records

I, _____ (full name) consent to participating in the project titled "**Qualitative interviews with pregnant asthmatic women about the management of their asthma during pregnancy".** I will undergo an individual interview that will cover topics do to with asthma management, medication use and past pregnancy experiences.

I have the right to withdraw or leave the interview at any time. I am also not obliged to answer any question.

AND

I understand the research team consisting of Angelina Lim, Dr. Johnson George, Assoc/Prof Kay Stewart and Prof Michael Abramson will have access to all the details I provide and the interviews will be tape recorded.

AND

I understand that any data that the researcher extracts from the interview for use in reports or published findings will be fully de-identified.

AND

I understand that the data collected from the interview will be stored for at least 5 years and then destroyed. Hard copies will be stored in locked cabinets and electronic copies will be password protected and both will only be accessible by the research team.

OPTIONAL REQUIREMENT:
(Tick (✓) the appropriate box)
If during the interview, it becomes evident that management of my asthma is a concern, please notify my treating doctor

Yes ☐ No ☐

If ***Yes,*** please supply doctor's name and contact number
_____

Results of the study will be provided upon your request.

Signature _____

Date _____

Appendix 11 – Pre-interview questionnaire

Pre-interview questionnaire

Title: Qualitative interviews with pregnant asthmatic women about their management of their asthma during pregnancy

Please answer the following questions:

Please fill in the gaps

1. How long have you had asthma for? _____years
2. Please state your country of birth

   _____
3. Can you speak English? ***Please tick (✓)one*** Yes ☐ No☐
4. Please state ANY other languages you speak at home

   _____
5. What asthma medications are you currently taking?

   _____

   _____
6. Please list ALL other medications you are currently taking

   _____

   _____

   _____

Please tick (✓) the appropriate box

7. Is this your first pregnancy?

   Yes ☐ No ☐

8. Do you currently smoke?

   Yes ☐ No ☐

9. Do you currently hold a health care concession card?

   Yes ☐ No ☐

10. Who is currently managing your asthma?

    ☐A specialist ☐A general practitioner

    ☐Other, please specify_____

11. How would you describe your asthma day time symptoms?

    ☐Less than weekly ☐Weekly or more, but less than daily

    ☐Daily ☐Daily with restriction of physical activity

12. How would you describe your asthma night time symptoms?

    ☐Less than twice per month ☐Twice per month but less than weekly

    ☐Weekly or more often ☐Very frequently

13. Do you ever forget to take your medications?

    ☐Always ☐Often ☐Sometimes ☐Rarely ☐Never

14. I get confused about my medications

    ☐Always ☐Often ☐Sometimes ☐Rarely ☐Never

15. I make changes in the recommended medication management to suit my lifestyle

    ☐Always ☐Often ☐Sometimes ☐Rarely ☐Never

16. I vary my recommended medication management based on how I am feeling?

☐Always ☐Often ☐Sometimes ☐Rarely ☐Never

17. I put up with my medical problems before taking any action

☐Always ☐Often ☐Sometimes ☐Rarely ☐Never

Please provide your contact details so we can contact you for an interview

Name:_____

Address:_____

Email:_____

Phone no:_____

Please tick (✓) the preferred option:

☐ I would like a phone interview

☐I would like the interview to be held at The Mercy Hospital for Women, Heidelberg*

☐I would like the interview to be held at another venue, please specify address

_____

***Paid parking or public transport will be reimbursed**

Appendix 12 – Interview topic guide

Interview topic guide

Title: Qualitative interviews with pregnant asthmatic women about their management of their asthma during pregnancy

Four topics will be discussed:

Topic one: Asthma severity during pregnancy

This topic will explore the increase/decrease of severity of asthma during pregnancy and how they have dealt with those changes. Experiences and coping strategies will be discussed. Changes to asthma management and whether they have complied with those changes will be discussed.

Topic two: Asthma medication use during pregnancy

This topic will explore the concerns and experiences associated with the safety of using different medications during pregnancy and their thoughts on the importance of continuing them through pregnancy. This topic will also investigate whether there was decreased or increased use in any particular medication and why, and factors contributing to compliance. This topic will also ask participants to compare the use of asthma medications to other medications during pregnancy.

Topic three: Support regarding asthma management during pregnancy

This topic will explore whether women received enough support during pregnancy from their doctors and other health professionals and if they would have liked more support and in what aspects. It will also investigate what resources they used in regards to asthma management, (i.e. books, websites, family, friends). It will explore whether they were confused in regards to what to do with their asthma management initially, or when there was a change in severity.

Topic four: Previous and future pregnancy experiences

This topic will give the opportunity for participants to talk about their previous pregnancy experiences regarding asthma management. The topic will also discuss whether they have changed their behaviour or management from a previous pregnancy and why and whether they think they would change their behaviour in a future pregnancy.

Appendices for a multidisciplinary approach to management of maternal asthma (MAMMA©):

A randomised controlled trial

(Phase 4 – Chapters 6 and 7)

Appendix 13 – Monash University Human Research Ethics Committee approval letter

Appendix 14 – Mercy Health Ethics Committee approval letter

Appendix 15 – Royal Women's Hospital Ethics Committee approval letter

Appendix 16 – Participant explanatory statement

Appendix 17 – Participant consent form

Appendix 18 – Recruitment advertisement poster

Appendix 19 – Asthma Control Questionnaire

Appendix 20 – Baseline demographics data collection form

Appendix 21 – Follow up data collection form

Appendix 22 – Notification letter to general practitioners

Appendix 23 – Feedback form sent to general practitioners

Appendix 24 – National Asthma Council asthma action plan

Appendix 25 – Piko-6 meter information leaflet

Appendix 26 – "Asthma and health pregnancy" brochure

Appendix 13 – Monash University Human Research Ethics Committee approval letter

MONASH University

Monash University Human Research Ethics Committee (MUHREC)
Research Office

Human Ethics Certificate of Approval

Date:	**22 June 2012**
Project Number:	**2012000921**
Project Title:	**Evaluation of an intervention to improve asthma control in pregnant women (pilot study)**
Chief Investigator:	**Dr Johnson George**
Approved:	**From: 22 June 2012 To: 22 June 2017**

Terms of approval

1. The Chief investigator is responsible for ensuring that permission letters are obtained, if relevant, and a copy forwarded to MUHREC before any data collection can occur at the specified organisation. **Failure to provide permission letters to MUHREC before data collection commences is in breach of the National Statement on Ethical Conduct in Human Research and the Australian Code for the Responsible Conduct of Research**.
2. Approval is only valid whilst you hold a position at Monash University.
3. It is the responsibility of the Chief Investigator to ensure that all investigators are aware of the terms of approval and to ensure the project is conducted as approved by MUHREC.
4. You should notify MUHREC immediately of any serious or unexpected adverse effects on participants or unforeseen events affecting the ethical acceptability of the project.
5. **Complaints:** The researchers are required to inform MUHREC promptly of any complaints made about the project, whether the complaint was made directly to a member of the research team or to the primary HREC.
6. **Amendments to the approved project (including changes in personnel):** Requires the submission of a Request for Amendment form to MUHREC and must not begin without written approval from MUHREC. Substantial variations may require a new application.
7. **Future correspondence:** Please quote the project number and project title above in any further correspondence.
8. **Annual reports:** Continued approval of this project is dependent on the submission of an Annual Report. This is determined by the date of your letter of approval.
9. **Final report:** A Final Report should be provided at the conclusion of the project. MUHREC should be notified if the project is discontinued before the expected date of completion.
10. **Monitoring:** Projects may be subject to an audit or any other form of monitoring by MUHREC at any time.
11. **Retention and storage of data:** The Chief Investigator is responsible for the storage and retention of original data pertaining to a project for a minimum period of five years.

[redacted]

Professor Ben Canny
Chair, MUHREC

cc: Assoc Prof Kay Stewart, Prof Michael Abramson, Ms Angelina Lim, Prof Susan Walker

Postal – Monash University, Vic 3800, Australia
Building 3E, Room 111, Clayton Campus, Wellington Road, Clayton
Telephone +61 3 9905 5490 Facsimile +61 3 9905 3831
Email muhrec@monash.edu www.monash.edu/research/ethics/human/index/html
ABN 12 377 614 012 CRICOS Provider #00008C

Appendix 14 – Mercy Health Ethics Committee approval letter

Mercy Health
Care first

31 May 2012

Dr Johnson George
Lecturer
Centre for Medicine Use and Safety
Monash University
381 Royal Parade
Parkville
VIC 3052

Dear Dr George

Re: R12/13: Evaluation of an intervention to improve asthma control in pregnant women. A pilot study.

I am pleased to advise that your amendments comply with the requirements of the Human Research Ethics Committee meeting of 3 April 2012 and as such you may now commence with the study. Specifically, the following documentation is approved:

Module One	Version 2 Dated 10 May 2012
Recruitment Poster	Dated 10 May 2012
Participant Explanatory Statement	Version 2 Dated 10 May 2012
Expression of Interest form	Version 2 Dated 10 May 2012
Information given to midwives	Version 2 Dated 10 May 2012
Data Collection form	Version 2 Dated 10 May 2012
Asthma control Questionnaire (ACQ)	Dated 10 May 2012
Asthma during pregnancy education leaflet	Dated 10 May 2012
Participant Consent Form	Version 2 Dated 10 May 2012
General Practitioner Notice- Notification of patient participation	Dated 10 May 2012

The Human Research Ethics Committee is constituted and functions in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007).

Approval by the Mercy Health Board is valid for up to 3 years from the date of this letter. That is, the project should be completed by the approval expiry date, which is **31 May 2015**. Should it become apparent that an extension of the 3-year period is required, the principal researcher should apply, in writing, through the Administrative Officer of the Human Research Ethics Committee. Please note that the research

Mercy Health
Level 2, 12 Shelley Street, Richmond Victoria 3121 Phone: +61 3 8416 7777 Fax: +61 3 8416 7888 mercyhealth.com.au ABN 77 191 901 062

project should be commenced within 12 months from the date of this letter. **Would you kindly advise me the date that you commence your research.**

In accordance with the NHMRC Guidelines, approval is subject to:

1. Immediate notification to the Administrative Officer, The Mercy Health Human Research Ethics Committee and sponsor, of any serious adverse effects on participants;
2. Immediate notification of any unforeseen events that may affect the continuing ethical acceptability of the project;
3. Notification and reasons for ceasing the project prior to its expected date of completion;
4. The completion of a progress report at 6 months and then annually for the duration of the project; (progress report attached);
5. The Mercy Health Human Research Ethics Committee approval of any proposed modifications to the project;
6. The submission of a final report and papers published on completion of the project.

Please also note:

7. Consent Forms must be available for audit by the Mercy Health Human Research Ethics Committee and retained for the period required by law;
8. The Principal Investigator upon leaving the Institution must inform the Mercy Health Human Research Ethics Committee as to the nominated person to replace him/her.

If you have any queries, please do not hesitate to contact me on 8458 4808.

Yours sincerely,

[redacted]

Carole Branch
Administrative Officer
Mercy Health Human Research Ethics Committee

Appendix 15 – Royal Women's Hospital Ethics Committee approval letter

Mr Arthur Hui
Administrative Officer
Research and Ethics Secretariat
Tel: +61 3 8345 3720
Fax: +61 3 8345 3702
Email: arthur.hui@thewomens.org.au

the women's
the royal women's hospital

ABN 62 787 822 077
Locked Bag 300
Cnr Grattan St & Flemington Rd
Parkville VIC 3052 Australia
Tel +61 3 8345 2000
www.thewomens.org.au

27.8.12

Dr J George
Centre for Medicine Use and Safety
Faculty of Pharmacy and Pharmaceutical Sciences
Monash University (Parkville Campus)
381 Royal Parade, Parkville Vic 3052

Dear Dr George,

Re: Project 12/22 - Evaluation of an intervention to improve asthma control in pregnant women

Thank you for submitting the amendments as requested by the RWH Human Research Ethics Committee.

I confirm the project is now approved.

Enclosed please find Project Approval and Notification of Project Commencement Forms for your record.

Prior to commencement of your project, you are reminded that you must contact the relevant RWH Divisional Directors / Department Heads to confirm your actual commencement date. Failure to inform these RWH personnel may jeopardise their approval and support for your project.

Please return the completed Notification of Project Commencement Form to me when the project begins.

Yours sincerely,

A. C. B. Hui
Administrative Officer
Research and Ethics Secretariat

cc Ms L Wolke

Encl:

Appendix 16 – Participant explanatory statement

Participant Explanatory Statement

Title: Evaluation of an intervention to improve asthma control in pregnant women

27th August 2012

***Sites**: The Royal Women's Hospital, Mercy Hospital for Women*
***Principal Researcher**: Dr Johnson George*
***Associate researcher(s)**: A/Prof Kay Stewart, Lisa Wolke, Prof Michael Abramson, Prof Sue Walker, Angelina Lim*

This information sheet is for you to keep

1. Introduction

You are invited to participate in a study that will test strategies to improve asthma control and decrease the risk of pregnancy complications. You have been selected as you have identified yourself as having a history of asthma. Your involvement in the study will provide information that will assist us improve the management of asthma in pregnant women. Feel free to ask questions about any information in the document. You may also wish to discuss the project with relatives or friends. By signing the consent form, you understand the given information and agree to participate in the research project.

2. What is the purpose of this study?

There have been many cases of poor asthma management during pregnancy and complains of a lack of support. Many women are unsure what to do with their asthma medications during pregnancy and are concerned about how asthma will affect their pregnancy. Unfortunately, some women do not get enough information about asthma management during pregnancy, jeopardising asthma control which can complicate their pregnancy. This trial will test two ways of managing pregnant women with asthma. If one method proves to

be more effective than the other, we will relay this information to funding bodies and policy makers. Information generated from this trial can help prompt more support services and resources for pregnant women with asthma in the future. By participating, you will help evaluate strategies to decrease the risks of uncontrolled asthma in the future. The results of this research will also be used to help Angelina Lim obtain her PhD, which is titled 'optimising the management of asthma during pregnancy'.

3. What does participation in this study involve?

You will be allocated to one of two groups in this study. Both groups will receive the same assessments using a standard questionnaire which assesses asthma control. We also take a measure of your current lung function as part of the questionnaire. Both groups will be administered the questionnaire in each trimester. The only difference between the two groups is that one group will also be asked to use a PIKO-6 meter because we are trialing its use in pregnant women.

The first assessment will be at the beginning of the study, second at three months from baseline and third at six months from baseline. These assessments will be done face to face and can be conducted at your preferred location and time. These will involve answering a few questions about how your asthma is going and your general physical wellbeing and may take 15 – 20 minutes. Conveniently, you have the option of being assessed at your next appointment at the Mercy Hospital for Women or The Royal Women's Hospital. **If you choose this option, your parking or public transport costs will be reimbursed.** The questions will surround the topic of medication use and asthma management and will not be intrusive. You also need to give us permission to speak to your general practitioner as we will be liaising with them on your asthma management.

One group will also be asked to use a PIKO-6 meter. If you have been selected in this group, the PIKO-6 meter you will receive will be free of charge. This device is similar to that of a peak flow meter and is used to measure breathing. You will be contacted monthly via telephone so we can acquire the results from this device and ask about how your asthma is going in general. If there is any concern about the control of your asthma, we will contact your general

practitioner. The Piko-6 meter is also for you to keep and use as often as you like. We will notify you if you are chosen and organise those visits accordingly.

4. Will I or my baby benefit from this study?

All women in the study will be given information and support on asthma management during pregnancy which may improve asthma control leading to better outcomes for you and your baby. However, we cannot promise you any benefits from participation in this study. If this study is successful, findings will justify more support for asthma management during pregnancy, such as asthma antenatal clinics, asthma monitoring programs etc. and help contribute to helping other women in your situation in the future. Data gathered from this study may inform health professionals leading to better management of pregnant women with asthma.

5. Are there risks to me or my baby in taking part in this study?

There are no foreseeable risks associated with participation in this study. The questions are simple and participation does not demand any laborious activity. We will not be asking any intrusive or sensitive questions. You may withdraw from the study at anytime without being disadvantaged. If during the study, it becomes evident that there is a concern with your asthma management, we will notify you and/or your doctor, with your permission.

6. How will my confidentiality be protected?

All data collected from you, your health records, your doctor or your pharmacy will be stored for at least 7 years and then destroyed. Hard copies will be stored in locked cabinets and electronic copies on password protected computers; both will **ONLY** be accessible by the investigators. Results may be presented at various conferences and in journal publications, but no participants, doctors nor pharmacies will be identified. All identifiable information will be de-identified before data storage. Your contact information was only needed to invite you to participate. There will be no possible way for someone outside the research team to identify you.

7. What if new information arises during the research project?

We will let you know if any information comes out that may affect your choice about the study.

8. How will I be informed of the results of this research?

You can contact one of the chief investigators in mid 2013 to get a summary of the study findings by e-mail or post.

9. What if I need further information or I have any problems during the study?

You are more than welcome to contact one of the research investigators or ethics committees named at the end of this explanatory letter.

10. What if I have a complaint?

Mercy Hospital patients.

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a researcher participant, then you may contact either

Carole Branch, administrative officer of Mercy Health Ethics Committee

[redacted]

[redacted]

Royal Women's Hospital patients

Complaints should be directed to the RWH Consumer Advocate,

[redacted]

[redacted]

11. Do I have to take part in this research project?

Participation in any research study is voluntary. If you are interested in participating, please complete and return the consent form in the enclosed reply-paid envelope. You will only be contacted again if you fill in the consent form.

12. Has this research been approved?

The project has been approved by the Mercy Health Ethics Human Research Ethics Committee, The Royal Women's Hospital Human Research Ethics Committee and the Monash University Human Research Ethics Committee. This project will be carried out according to the *National Statement on Ethical Conduct in Research Involving Humans* (2007) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies. In accordance with the National Medical Health and Research Council guidelines, the Mercy Health Human Research Ethics Committee is required to conduct audits of research projects from time to time. It may therefore be possible that the Mercy Health Human Research Ethics Committee which has approved this research will seek to view a copy of your signed consent form, or to contact you, to ensure that the research is being conducted according to the ethical standards required by these guidelines. This research has also been endorsed and supported by the Asthma Foundation of Victoria.

13. Will I be reimbursed for my participation?

All participants will be reimbursed for their travel expenses or receive free on-site parking. Piko-6 meters will be supplied free of charge to chosen participants. Parking or public transport costs will be reimbursed if you chose to have your assessments at either Mercy Hospital for Women.

By participating in this study, you will help us to understand and improve the management of asthma during pregnancy. The investigators for this study are Dr Johnson George, A/Prof Kay Stewart, Prof Michael Abramson (Monash University), Prof Sue Walker (Mercy Health and Melbourne University), Lisa Wolke (The Royal Women's Hospital) and Ms Angelina Lim (Mercy Health and Monash University).

Contact details for further enquiries, feedback or complaints in relation to this project are given below.

If you would like to contact the researchers about any aspect of this study, please contact:	If you have a complaint concerning the manner in which this research is being conducted, please contact either the Monash University Human Research Ethics Committee, the Mercy Health Research Ethics Committee or The Royal Women's Hospital Consumer Advocate.
Dr Johnson George [redacted] [redacted] Ms Angelina Lim [redacted] [redacted] [redacted]	Executive officer Monash University Human Research Ethics Committee (MUHREC) [redacted] [redacted] Mercy Health Human Research Ethics Committee [redacted] [redacted] The Royal Women's Hospital Consumer Advocate [redacted] [redacted]

Yours sincerely,

Angelina Lim, (On behalf of Dr. Johnson George, Prof Michael Abramson, Lisa Wolke, Prof Sue Walker and A/Prof Kay Stewart)

Please separate the expression of interest form from the participant explanatory statement so you may keep all the details of the participant explanatory statement

✂----------

EXPRESSION OF INTEREST FORM:
R12/13 Version 2, 10th May 2012
Project title: R12/13: Evaluation of an intervention to improve asthma control in pregnant women. A pilot study.

Full name:_____

Address: _____

Contact phone number: _____

Email address (optional): _____

Date of birth:___/____/___ Do you speak English? *Please tick (✓) one* Yes ☐ No ☐

1. How many weeks gestation are you? (If not sure, please state a trimester)

_____

2. What asthma medications are you currently taking?

_____

If you are not currently taking any asthma medication, have you had asthma symptoms in the last ten years? Please tick (✓) one

Yes ☐ No ☐

3. How would you describe your asthma day time symptoms?
Please tick (✓) one
☐ Less than weekly ☐ Weekly or more, but less than daily
☐ Daily ☐ Daily with restriction of physical activity

4. How would you describe your asthma night time symptoms?
Please tick (✓) one
☐ Less than twice per month ☐ Twice per month but less than weekly
☐ Weekly or more often ☐ Very frequently

Appendix 17 – Participant consent form

Consent Form

Title: Evaluation of an intervention to improve asthma control in pregnant women

NOTE: This consent form will remain with the Monash University researcher for their records

I, _____ (full name of participant) of

_____

(address of participant)

have read and understood the enclosed participant information form for the project titled "evaluation of an intervention to improve asthma control in pregnant women."

I freely agree to participate in this project according to the conditions in the participant's information. I allow the investigators to monitor my progress during my pregnancy and undergo assessments regarding asthma management and medication use.

AND

I have the right to withdraw or leave the study at any time.

AND

I understand the research team consisting of Angelina Lim, Prof Sue Walker, Dr. Johnson George, Assoc/Prof Kay Stewart, Lisa Wolke and Prof Michael Abramson will have access to all the details I provide in the assessments and medical records.

AND

I understand that any data that the researcher extracts from the study for use in reports or published findings will be fully de-identified.

AND

I understand that the data collected from this study will be stored for at least 7 years and then destroyed. Hard copies will be stored in locked cabinets and electronic copies will be password protected and both will only be accessible by the research team.

AND

I consent to the Mercy Health Human Research Ethics Committee, Royal Women's Human Research Ethics Committee and Monash University Ethics Committee, which approved this study to access my information, or to contact me to ask about my research experience, in order to ensure that the project is being run in accordance with government standards.

Required participant's details

Full name:

Address:

Contact phone number:

Email address (optional):

Please nominate the general practitioner you wish us to contact regarding your asthma management

Name:_____

Clinic name: _____

Clinic's Address:_____

Clinic's phone number: _____

Participants' name (printed)_____

Participant's signature _____

Date_____

Name of witness to Participant's signature (printed)_____

Witness' signature_____Date_____

Declaration by researcher

Researcher's name (printed)_____

Researcher's signature _____

Date_____

Please cut and keep for revocation ✂----------

Revocation of consent form

Title: Evaluation of an intervention to improve asthma control in pregnant women

I hereby wish to WITHDRAW my consent to participate in the research proposal described above and understand that such withdrawal WILL NOT jeopardise any treatment of my relationship with Mercy Health or The Royal Women's Hospital.

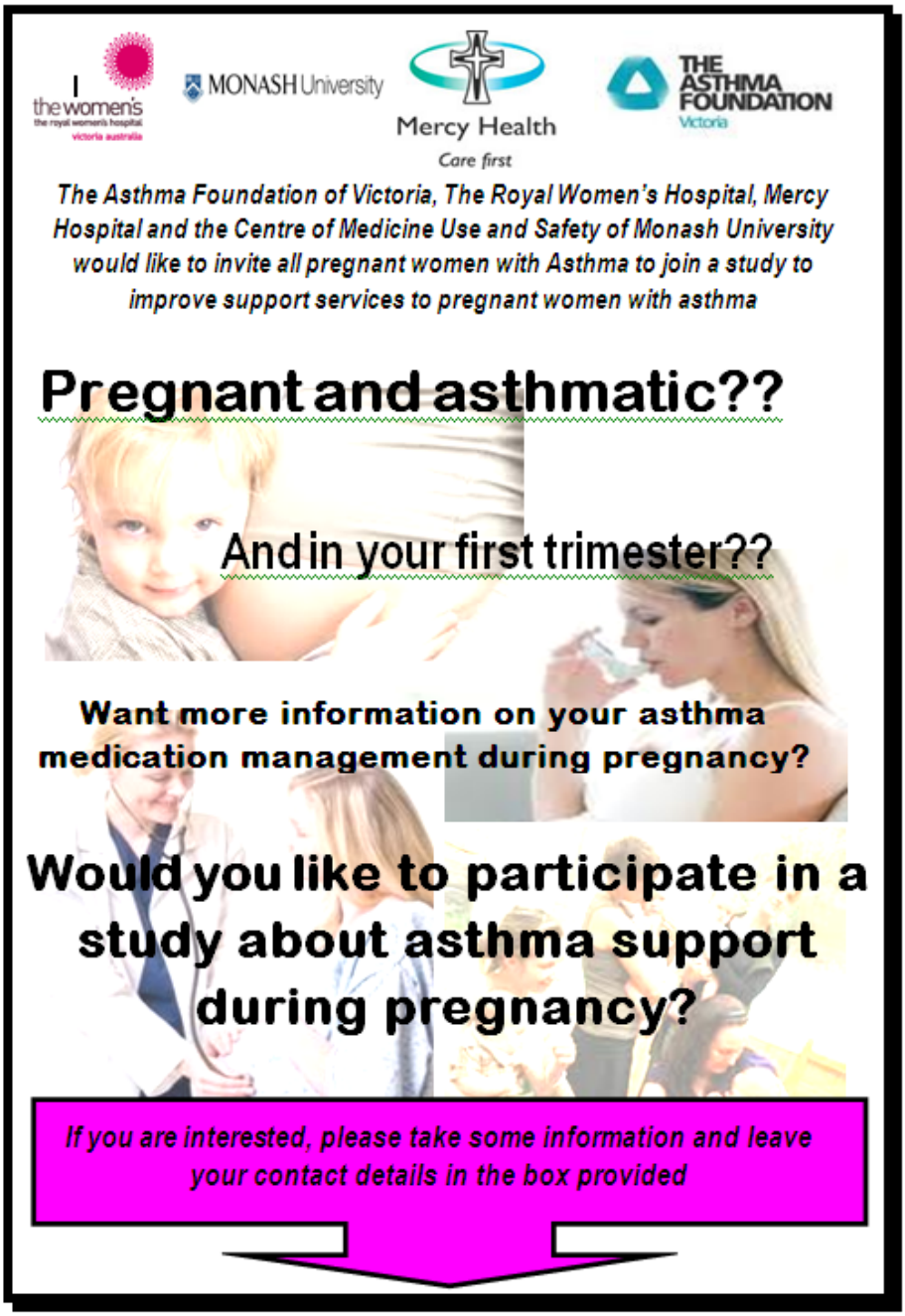
Participant's name (printed)_____

Participant's signature _____

Date _____

Participant's address _____

Appendix 18 – Recruitment advertisement poster



Appendix 19 – Asthma Control Questionnaire

Appendix

ASTHMA CONTROL QUESTIONNAIRE©

Please answer questions 1–6.

Circle the number of the response that best describes how you have been during the past week

1.	On average, during the past week, how often were you **woken by your asthma** during the night?	0	Never
		1	Hardly ever
		2	A few minutes
		3	Several times
		4	Many times
		5	A great many times
		6	Unable to sleep because of asthma
2.	On average, during the past week, how **bad were your asthma symptoms when you woke** up in the morning?	0	No symptoms
		1	Very mild symptoms
		2	Mild symptoms
		3	Moderate symptoms
		4	Quite severe symptoms
		5	Severe symptoms
		6	Very severe symptoms
3.	In general, during the past week, how **limited were you in your activities** because of your asthma?	0	Not limited at all
		1	Very slightly limited
		2	Slightly limited
		3	Moderately limited
		4	Very limited
		5	Extremely limited
		6	Totally limited
4.	In general, during the past week, how much **shortness of breath** did you experience because of you asthma?	0	None
		1	A very little
		2	A little
		3	A moderate amount
		4	Quite a lot
		5	A great deal
		6	A very great deal
5.	In general, during the past week, how much of the time did you **wheeze**?	0	Not at all
		1	Hardly any of the time
		2	A little of the time
		3	A moderate amount of the time
		4	A lot of the time
		5	Most of the time
		6	All the time
6.	On average, during the past week, how many **puffs of short-acting bronchodilator** (eg. Ventolin) have you used each day?	0	None
		1	1–2 puffs most days
		2	3–4 puffs most days
		3	5–8 puffs most days
		4	9–12 puffs most days
		5	13–16 puffs most days
		6	More than 16 puffs most days

To be completed by a member of the clinic staff

7.	**FEV**1 pre-bronchodilator:	0	>95% predicted
		1	95–90%
	FEV1 predicted	2	89–80%
		3	79–70%
	FEV1 % predicted	4	69–60%
	(Record actual values on the dotted lines and score the **FEV**1 % predicted in the next column)	5	59–50%
		6	<50% predicted

Appendix 20 – Baseline data collection form

Data collection form

1. How long have you had asthma for? _____years
2. What was your country of birth?
3. Please state ANY other languages you speak at home
4. What other medications are you currently taking?
5. Is this your first pregnancy?
6. Do you currently smoke?
7. Do you currently hold a health care concession card?
8. Who is currently managing your asthma?

   ☐A specialist ☐A general practitioner

   ☐Other, please specify_____
9. Do you ever forget to take your medications?

   ☐Always ☐Often ☐Sometimes ☐Rarely ☐Never
10. I get confused about my medications

    ☐Always ☐Often ☐Sometimes ☐Rarely ☐Never
11. I make changes in the recommended medication management to suit my lifestyle

    ☐Always ☐Often ☐Sometimes ☐Rarely ☐Never
12. I vary my recommended medication management based on how I am feeling?

    ☐Always ☐Often ☐Sometimes ☐Rarely ☐Never
13. I put up with my medical problems before taking any action

    ☐Always ☐Often ☐Sometimes ☐Rarely ☐Never

Appendix 21 – Follow up data collection form

These questions are coupled with the ACQ

Name of patient:

Date:

FEV_1=

FEV_6=

FEV_1/FEV_6=

Since we last spoke to you…

1. Have you had any recent asthma exacerbations?
2. Have you had any recent asthma related hospital visits?
3. Have you recently had to take any days off due to a worsening in your asthma symptoms?
4. Have you had any recent oral corticosteroid courses prescribed for asthma exacerbations?
5. Have you had any changes made to your asthma medications?
6. Have you complied with those changes?
7. Have you yourself made any changes to your asthma medication regimen?
8. Do you have any concerns about your asthma?

Appendix 22 – Notification letter to general practitioners

Dear [Name of doctor]

This is a courtesy notice to inform you that your patient, [Name of participant] has expressed interest in participating in a study to improve asthma management during pregnancy. This study tests an intervention to improve asthma outcomes in pregnant women via education and monitoring. We will be monitoring asthma using the Asthma Control Questionnaire and spirometry throughout pregnancy monthly as per National Asthma guidelines to maintain stringent asthma control during pregnancy. **This study will not require you to do anything extra on top of your usual practice, but we wanted to let you know that your patient is enrolled in our study because we may contact you** if their asthma control becomes of concern (i.e. documented exacerbations or an increase in ACQ score of 0.5 or greater since last assessment) and may require a change in medication management or at the patient's request. Although we are happy to suggest appropriate changes to asthma management, their medical management will be entirely under your control.

All information obtained in this study will be de-identified.

Enclosed is the participant explanatory statement we have given your patient so you are aware of the information they have received. Our contact details are also on this form. Please do not hesitate to contact us if there are any concerns.

Thank you for your participation.

Yours sincerely,

Angelina Lim (on behalf of Dr Johnson George, Prof Michael Abramson, Prof Sue Walker, Lisa Wolke and A/Prof Kay Stewart)

Appendix 23 – Feedback form sent to general practitioners

RE: Multidisciplinary Approach to Managing Maternal Asthma (MAMMA© Trial)

The following information is regarding the latest assessment of your patient's asthma control. Her responses to the Asthma Control Questionnaire (ACQ) are also attached.

Name of patient:

Date of Assessment:

Results:

FEV_1(L)	FEV_1%	FEV_6(L)	FEV_1/FEV_6

1. Complaints?
2. Exacerbations?
3. Total ACQ score:
4. ACQ score change from last visit:

Recommendations

Review required?

☑No ❑Yes ❑ Yes with urgency

Comments_____

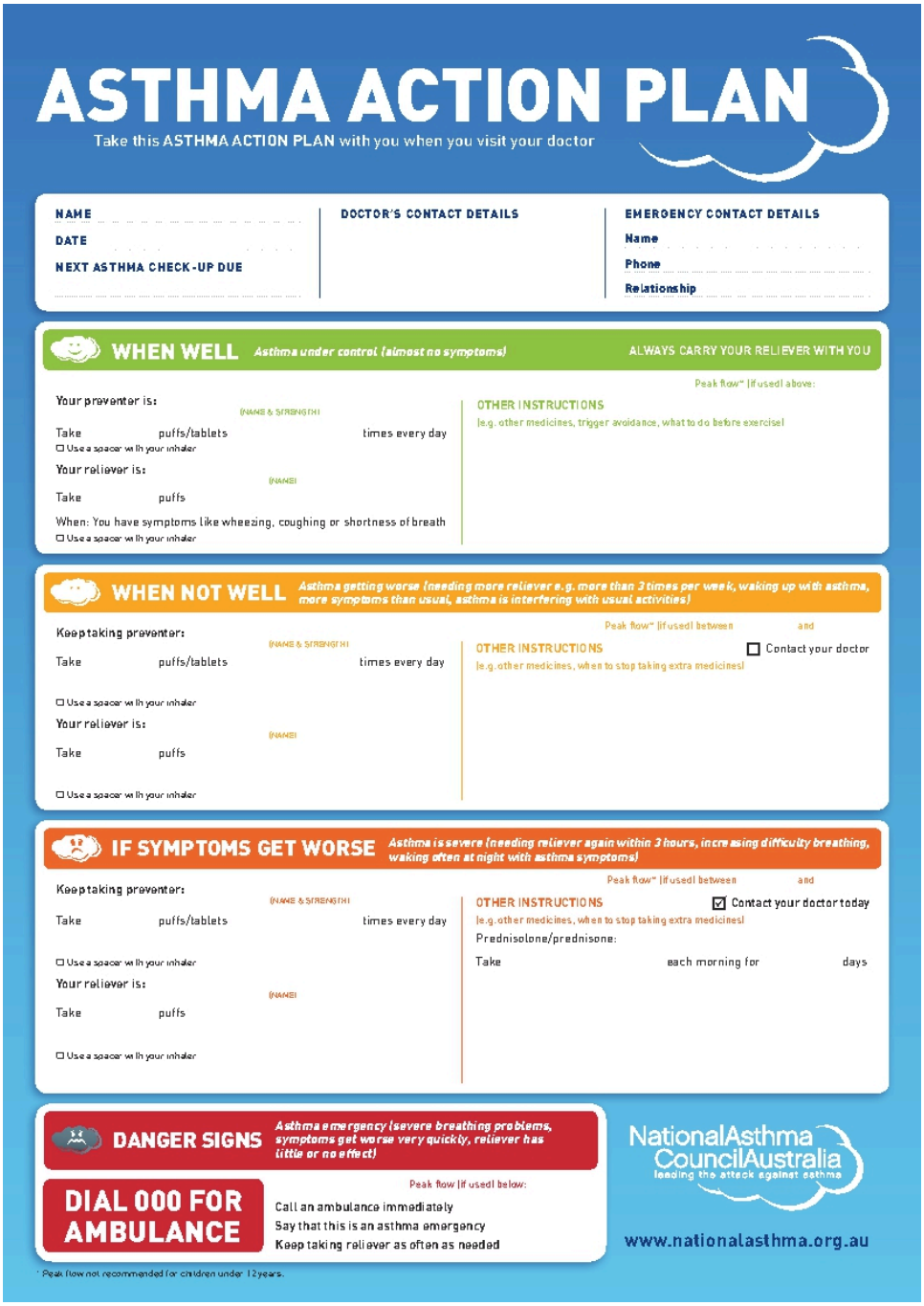
Reference ranges and definitions

ACQ score = *(This is a mean total of the points allocated for each response on the ACQ) An increase of 0.5 or greater has shown to be a significant deterioration in asthma control. An ACQ score of 2 or greater indicates poorly controlled asthma.*

FEV_1%= *>80% indicates well controlled asthma, 60-79% indicates mild asthma, 40-59% indicates moderate asthma, <40% indicates severe asthma*

FEV_1/FEV_6= *Ideally, a score of <0.75 warrants a review of their asthma control*

Appendix 24 – National Asthma Council asthma action plan



ASTHMA ACTION PLAN

Take this **ASTHMA ACTION PLAN** with you when you visit your doctor

NAME . . . . . .
DATE . . . . . .
NEXT ASTHMA CHECK-UP DUE . . . . . .

DOCTOR'S CONTACT DETAILS

EMERGENCY CONTACT DETAILS
Name . . . . . .
Phone . . . . . .
Relationship . . . . . .

WHEN WELL
Asthma under control (almost no symptoms)
ALWAYS CARRY YOUR RELIEVER WITH YOU

Peak flow* (if used) above:

Your preventer is:
(NAME & STRENGTH)
Take puffs/tablets times every day
☐ Use a spacer with your inhaler

Your reliever is:
(NAME)
Take puffs
When: You have symptoms like wheezing, coughing or shortness of breath
☐ Use a spacer with your inhaler

OTHER INSTRUCTIONS
(e.g. other medicines, trigger avoidance, what to do before exercise)

WHEN NOT WELL
Asthma getting worse (needing more reliever e.g. more than 3 times per week, waking up with asthma, more symptoms than usual, asthma is interfering with usual activities)

Peak flow* (if used) between and

Keep taking preventer:
(NAME & STRENGTH)
Take puffs/tablets times every day
☐ Use a spacer with your inhaler

Your reliever is:
(NAME)
Take puffs
☐ Use a spacer with your inhaler

OTHER INSTRUCTIONS ☐ Contact your doctor
(e.g. other medicines, when to stop taking extra medicines)

IF SYMPTOMS GET WORSE
Asthma is severe (needing reliever again within 3 hours, increasing difficulty breathing, waking often at night with asthma symptoms)

Peak flow* (if used) between and

Keep taking preventer:
(NAME & STRENGTH)
Take puffs/tablets times every day
☐ Use a spacer with your inhaler

Your reliever is:
(NAME)
Take puffs
☐ Use a spacer with your inhaler

OTHER INSTRUCTIONS ☑ Contact your doctor today
(e.g. other medicines, when to stop taking extra medicines)
Prednisolone/prednisone:
Take each morning for days

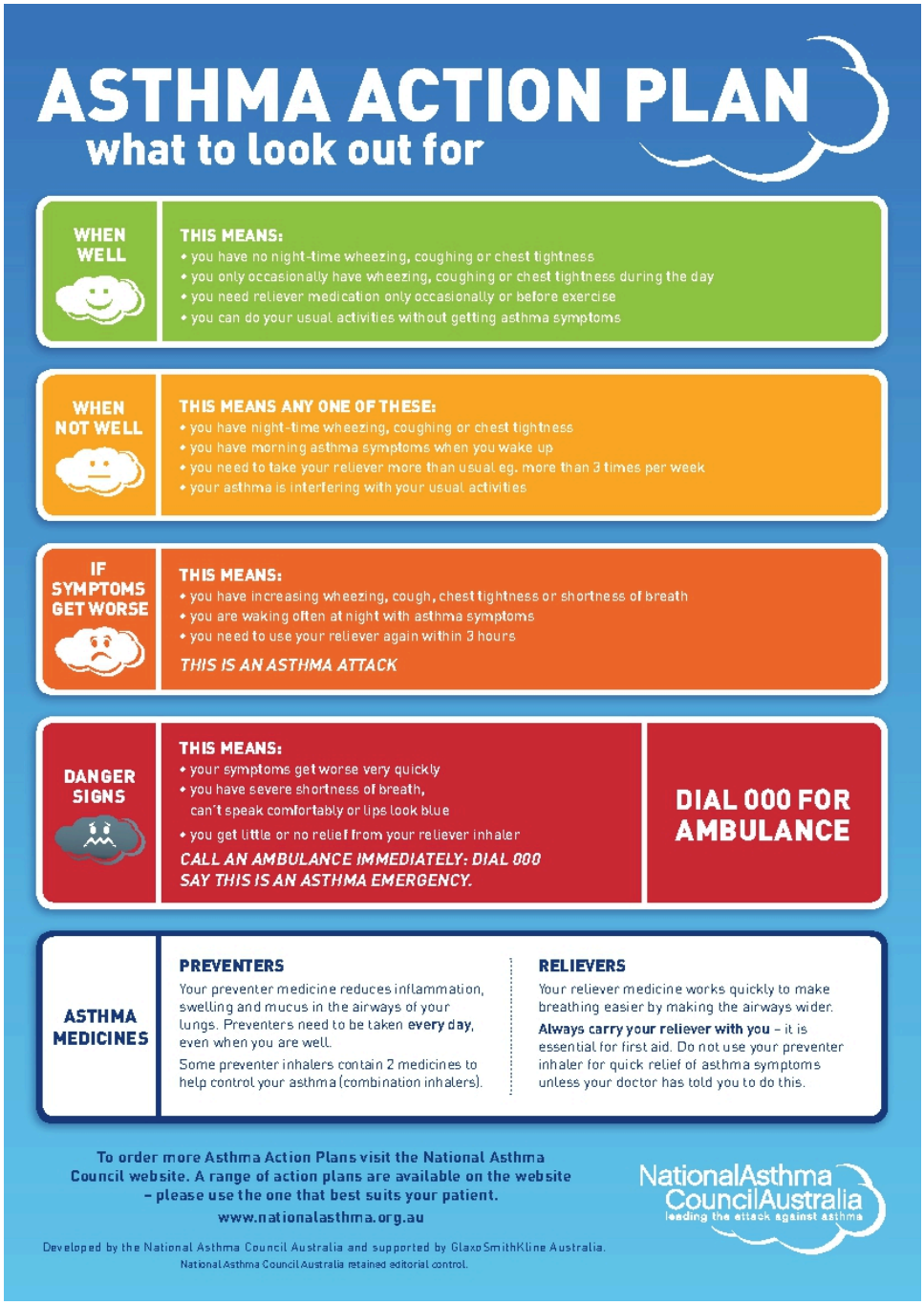
DANGER SIGNS
Asthma emergency (severe breathing problems, symptoms get worse very quickly, reliever has little or no effect)

DIAL 000 FOR AMBULANCE

Peak flow (if used) below:
Call an ambulance immediately
Say that this is an asthma emergency
Keep taking reliever as often as needed

National Asthma Council Australia
leading the attack against asthma
www.nationalasthma.org.au

* Peak flow not recommended for children under 12 years.


ASTHMA ACTION PLAN
what to look out for
WHEN WELL
THIS MEANS:
• you have no night-time wheezing, coughing or chest tightness
• you only occasionally have wheezing, coughing or chest tightness during the day
• you need reliever medication only occasionally or before exercise
• you can do your usual activities without getting asthma symptoms
WHEN NOT WELL
THIS MEANS ANY ONE OF THESE:
• you have night-time wheezing, coughing or chest tightness
• you have morning asthma symptoms when you wake up
• you need to take your reliever more than usual eg. more than 3 times per week
• your asthma is interfering with your usual activities
IF SYMPTOMS GET WORSE
THIS MEANS:
• you have increasing wheezing, cough, chest tightness or shortness of breath
• you are waking often at night with asthma symptoms
• you need to use your reliever again within 3 hours
THIS IS AN ASTHMA ATTACK
DANGER SIGNS
THIS MEANS:
• your symptoms get worse very quickly
• you have severe shortness of breath, can't speak comfortably or lips look blue
• you get little or no relief from your reliever inhaler
CALL AN AMBULANCE IMMEDIATELY: DIAL 000
SAY THIS IS AN ASTHMA EMERGENCY.
DIAL 000 FOR AMBULANCE
ASTHMA MEDICINES
PREVENTERS
Your preventer medicine reduces inflammation, swelling and mucus in the airways of your lungs. Preventers need to be taken every day, even when you are well.
Some preventer inhalers contain 2 medicines to help control your asthma (combination inhalers).
RELIEVERS
Your reliever medicine works quickly to make breathing easier by making the airways wider.
Always carry your reliever with you – it is essential for first aid. Do not use your preventer inhaler for quick relief of asthma symptoms unless your doctor has told you to do this.
To order more Asthma Action Plans visit the National Asthma Council website. A range of action plans are available on the website – please use the one that best suits your patient.
www.nationalasthma.org.au
Developed by the National Asthma Council Australia and supported by GlaxoSmithKline Australia.
National Asthma Council Australia retained editorial control.
National Asthma Council Australia
leading the attack against asthma

Appendix 25 – Piko-6 meter information leaflet

PiKo® Monitors

Electronic Patient Monitoring

Performance and simplicity go beyond expectations to create the world's most effective home health monitor for managing asthma and other respiratory conditions at home.

Redefining Patient Care — *Diagnostic Confidence*

PiKo® monitors measure peak flow, FEV_1, FEV_6, and FEV_1/FEV_6, giving you a reliable solution for asthma and COPD management. Sophisticated features include automatic test quality alerts and electronic data storage of 96 tests. Data can be reviewed via a single operating button, eliminating the errors associated with paper diaries. All tests can be easily downloaded to the companion PiKoNET software.

Redefining Patient Care — *Improving Outcomes*

As a part of our family of asthma and disease management products, PiKo monitors embody years of dedication to advancing the quality of lung health.

We continue redefining patient care so that you can achieve improved patient outcomes, more efficiently, more profitably.

Spire™ Inspiring Respiratory Health

Redefining Patient Care — *Proven Technology*

- **Portable.** PiKo-1™ is the world's first pocket sized electronic peak flow and FEV_1 meter. In addition to FEV_1, the new PiKo-6™ measures FEV_6 and FEV_1/FEV_6.
- **Ease of Use.** Single operating button simplifies testing, while electronic data storage eliminates errors. Color zone personalization, red, yellow, and green zones are automatically displayed.
- **Intelligent Design.** Features test quality alerts and electronic storage of the last 96 readings.
- **Affordable.** Not only the highest performing home health monitor of its type, PiKo is cost comparable to traditional mechanical peak flow meters.
- **Optional Software.** PiKoNET™ for tracking and trending. Available in Professional and Personal versions.

PiKo® Monitors

PiKo Monitors

PiKo-1 ™
Electronic Peak Flow & FEV_1 Meter

PiKo-1 measures peak flow and FEV_1, considered by many asthma specialists to be a more reliable indicator of an impending asthma attack.

Recognized as the Best Over-the-Counter and Self Care Product at the US Medical Design Excellence Awards in 2003, PiKo-1 provides the most accurate peak flow measurement when compared to mechanical peak flow meters and is ATS/EU scale compliant.

PiKo-6 ™
Electronic FEV_6, & FEV_1/FEV_6 Meter

PiKo-6 goes one step further measuring FEV_1, FEV_6, and FEV_1/FEV_6, bringing a new level of effectiveness to the monitoring of COPD, asthma, cystic fibrosis, and lung transplant patients.

An easy and cost-effective solution to patient screening and monitoring, PiKo-6 acts as a reliable indicator of the need for full spirometry and provides continuous assessment of lung function.

(Actual Size)

PiKoNET™ Software

PiKoNET™ Software

Tracking & Trending Software

Easy-to-use, Windows® based PiKoNET software allows viewing and trending of PiKo results for effective monitoring and management of asthma and COPD.

Featuring a small USB interface cradle, PiKoNET software allows single or multiple patient data to be downloaded onto a computer for tracking and trending. All data can be presented in graphical and tabular format and is date and time stamped, eliminating the need for record cards.

- **Simplicity.** Easily download data via infrared ports on PiKo and cradle.
- **Graphical Customization.** Viewed parameters selectable for table and graphs as well as dates, data, scales, and zones. Graphical data selectable for morning, afternoon, or all day.
- **Intelligent Design.** PiKoNET configures PiKos with zones and reference values. Automatically calculates diurnal variation and links serial number(s) of PiKo(s) to the patient record.
- **Reporting.** Reports include patient data, tables, and graphs that can be previewed on screen, printed, or saved as a PDF file on the patient's record.
- **Records.** Patient Records include ID, patient demographics, and reference values.
- **Security.** Password protected databases can be created for storing patient records in groups or for trials.

Redefining Accuracy. Beyond Expectations.

Technical Specifications

PiKo-1 & PiKo-6

Sensor:
Pressure/flow sensor technology, (patented)
Memory:
96 patient test scores
Memory Type:
Non-volatile
Color Zone:
3 Color Zones (Green, Yellow, Red)
Reference Values:
User defined
Quality Factor:
Warning & indicator for cough or abnormal blow
Sounds:
Four patterns for different indications and warnings
Communication:
Bi-directional IR port (RS232 format)
Battery Life:
PiKo-1: One year (based on average of 6 blows per day)
PiKo-6: Six months (based on average of 6 blows per day)
Battery Type:
2 x type 357 silver oxide button cells (or equivalent)
Dimensions:
75 x 35 x 20 mm; 35 grams
Resistance:
<2.5 cmH2O/l/sec at 14 LPS or lower
Operating Temp:
10°C to 38°C (50°F to 100°F)
Storage Temp:
-20°C to 60°C (-4°F to 140°F)
Humidity:
0 - 100% relative humidity
Barometric:
550 to 780 mm Hg
Performance:
ATS 1994 (monitoring), AS/NZS 4237: 1994, EN13826: 2003
Safety:
EN60601-1, EN60601-1-1, EN60601-1-2, and IPX4
Regulatory:
PiKo-6 FDA 510(k); PiKo-1 FDA 510 (k) for OTC; CE 0086, Class I with measurement function
Contracts:
GSA V797P-40634; UK NHS Drug Tariff prescribable on FP10
Patent:
US #6,447,459 B1
Warranty:
Six months (batteries not included)

PiKo-1
PEF:
Range 15 - 999 LPM (1 LPM resolution)
Accuracy 5% or +/- 20 LPM (whichever is greater)
FEV1:
Range 0.15 - 9.99 liter (0.01 liter resolution)
Accuracy +/-3.5% or 0.1 liter (whichever is greater)

PiKo-6
FEV1:
Range 0.15 - 9.99 liter (0.01 liter resolution)
Accuracy +/- 4% or 0.1 liter (whichever is greater)
FEV6:
Range 0.15 - 9.99 liter (0.01 liter resolution)
Accuracy +/- 4% or 0.1 liter (whichever is greater)

PiKoNET software
Definition:
PiKoNET is a reporting package that reads data from a PiKo-1 or PiKo-6 and presents the data in trend format against time. With PiKo-1, PEF and FEV1 are reported. PiKo-6 does not measure PEF.
Parameters reported:
PEF, FEV1, FEV6, FEV1/FEV6, reference values, zone thresholds, diurnal variation (difference between best am and best pm readings for selected parameter). Reference values are used for comparison and the graphs show banded zones relating to percentages of reference values achieved.
Operating Systems:
Windows 98, Windows ME, Windows 2000, Windows XP.
Hardware Requirement:
Minimum of Pentium III, 600 MHz, 64MB RAM, 500MB free space. Supports USB connection to PiKo.
Networks:
This is a single computer-based product; however, if the computer is part of a network, installation requires that the user be logged in as an administrator.
Software Required:
The following will be installed at the installation if required. NET Framework version 1.1 or higher, MDAC version 2.6 or higher, or JET version 4.0 or higher.
Databases:
Multiple databases supported, unlimited patients. Uses Microsoft generic high security format with password protection.
Output:
-PDF: Creates an Adobe Acrobat Portable Document of the entire patient report.
-TXT: Creates as Tab Delimited Text File useful for importing into word processing documents.
-CSV: Creates a comma separated variables text file, suitable for importing easily into Excel or other spreadsheets, databases and statistical analysis programs.
-Inbuilt report preview and print.
Program facility:
Allows PC to program reference and zone thresholds into PiKo.
Study Record:
Allows entry of site ID, study code and comments.
Quality Standards:
Facility to record study properties, for trials etc.

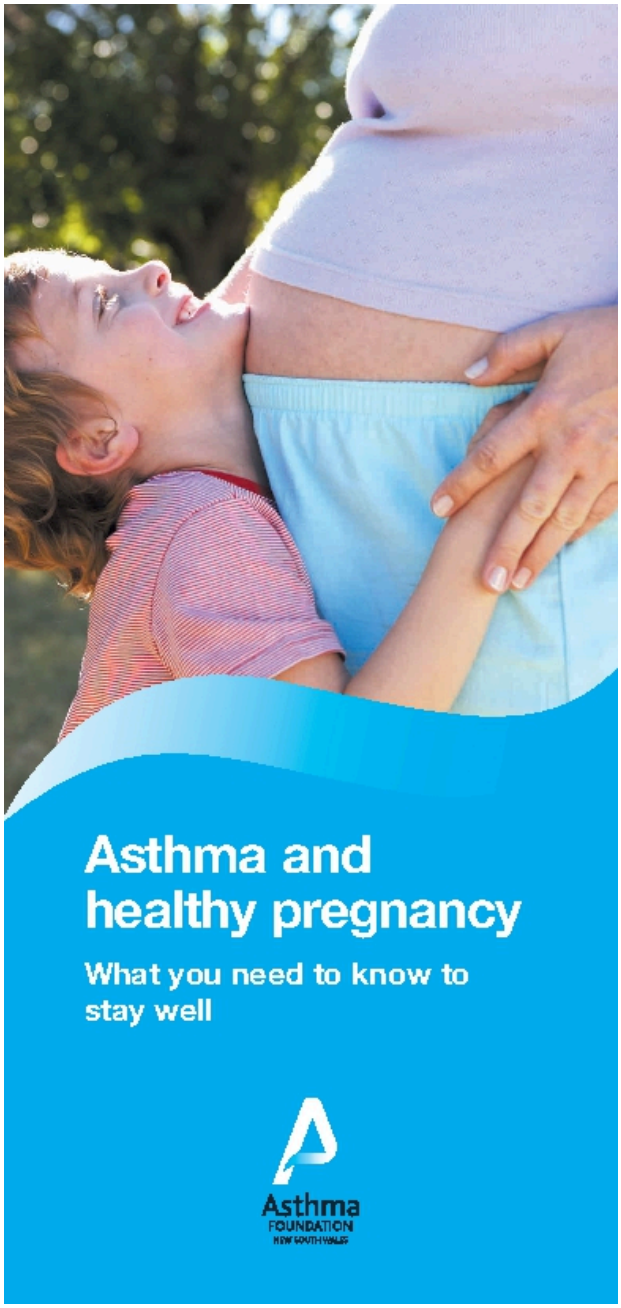
Contact Information

US
Phone: + 1.800.574.7374
Email: sales@nspirehealth.com
UK
Phone: + 44 (0) 1992 526300
Email: info@nspirehealth.com
Germany
Phone: + 49 (0) 9736/8181-0
Email: vertrieb@nspirehealth.com

www.nspirehealth.com

PN 633077 REV A

Appendix 26 – "Asthma and health pregnancy" brochure



Good asthma control is especially important throughout your pregnancy, because you are breathing for your baby as well as yourself. You need to take special care to make sure your lungs are working at their peak so your baby has a good oxygen supply and can grow properly.

About half of Australian women with asthma experience temporary worsening of their asthma while they are pregnant, and some need urgent medical care. The risk of a serious asthma attack is higher for women who stop taking their usual asthma medications while pregnant. It is especially important to keep taking the medications prescribed by your doctor, because uncontrolled asthma puts you and your baby at risk.

With good asthma control, you can expect a normal pregnancy.

See your doctor if you need any information about your medications or the information in this brochure.

Will my asthma get worse while I am pregnant?

- Most women with mild asthma are not troubled by asthma during pregnancy, but still need to have their asthma checked regularly. Women whose asthma was moderately severe or severe before pregnancy have a higher chance of needing emergency care for asthma.
- It is possible for asthma to recur during pregnancy, even in women who have not had asthma symptoms since childhood, but this is not common.
- Asthma control can worsen at any time during pregnancy, but any problems usually occur at around 17 to 36 weeks.
- **The risk of a serious asthma attack is highest for women who stop taking regular preventer medications during pregnancy.**

Keep a close check on your asthma during pregnancy, and see your doctor immediately if your asthma worsens.

Planning a pregnancy

If you have asthma and are planning to become pregnant, now is a good time to talk to your doctor about your asthma and medications. You need to know these key facts:

- You should stop smoking (for help quitting, call the Quitline on 13 78 48).
- Your asthma may become worse while you are pregnant, so see your doctor and make sure it is well controlled before you become pregnant.

- Good asthma control is especially important during pregnancy. Your doctor may arrange to check your asthma every 4–6 weeks while you are pregnant.
- Most asthma medications have no special safety concerns for pregnant women and should be continued during pregnancy. Stopping your medications can put your baby at risk.
- If you don't have an asthma action plan, ask your doctor for one now.

While you are pregnant

If you take regular preventer medication, make sure you keep taking it, because it will help stop asthma troubling you during pregnancy. Stopping your medication during pregnancy increases the chance of serious asthma attacks and puts your unborn baby at risk.

Pay close attention to your asthma, and tell your doctor if you have any asthma symptoms. If you have a viral infection (e.g. a cold), your asthma could worsen, so check your asthma action plan and be ready to follow it.

Sometimes breathlessness can be normal during pregnancy, but if you have asthma you should tell your doctor if you feel breathless.

If you have allergic rhinitis, treating it with effective medications may help control your asthma. Some medications that are used to treat allergic rhinitis are safe in pregnancy. Decongestants (medications to unblock your nose) should not be taken by pregnant women. Do not take antihistamines without asking your doctor or pharmacist for advice. When buying any medications, tell your pharmacist that you are pregnant.

What you can do

It is especially important to avoid asthma attacks while you are pregnant. Here are some tips on how you can stop your asthma from becoming worse:

- Avoid smoking and breathing other people's tobacco smoke. Smoking during pregnancy also increases the risk that your baby will have asthma, respiratory infections, sudden infant death syndrome (SIDS) and other problems.
- Keep taking all your asthma medications.
- Have regular check-ups for your asthma.
- Avoid things that trigger your asthma or worsen allergies.
- Keep an eye on your symptoms and tell your doctor if your asthma becomes worse.
- Work with your GP to keep your asthma action plan up to date, and follow it closely.

If your asthma is difficult to control, or if you have had an asthma attack while pregnant, your doctor may recommend extra ultrasound checks to make sure the baby is healthy and growing properly.

During your pregnancy, if you get asthma symptoms when you do physical activity, see your doctor. You should also ask your doctor about your asthma if you want to do more exercise while you are pregnant.

Warnings and reassurance

The aim of good asthma control is to avoid these problems:

- **Low birth weight** – babies born to women with asthma may have a higher risk of being small at birth. It is best for babies to reach their full weight before being born, because this helps protect them against diabetes, heart disease and other conditions when they are adults.
- **Pre-term babies** – babies born to women with asthma may have a higher risk of being born before reaching full term (pre-term birth). Pre-term birth can cause complications and can be dangerous for the baby's health.
- **Lack of oxygen** – if asthma is not controlled, the mother and unborn baby may not get enough oxygen. This can cause problems during pregnancy and after birth.

Recent studies from Australia and around the world show that all of these problems are more likely in women whose asthma is severe or who have serious asthma attacks while they are pregnant. **The good news is that if you have well-controlled asthma, your risk is no higher than for women without asthma.**

Medical experts now believe that the risk of pre-term birth and low birth weight are mainly due to **asthma attacks** during pregnancy – not just having asthma.

Women with asthma who take regular preventer medication during pregnancy have the same risk of having a small (low birth weight) baby as women without asthma.

After your baby is born

Keep having your regular asthma check-ups. If asthma has worsened during pregnancy, it usually settles back to normal within about 3 months after the baby is born.

If you have asthma and allergies in your family, there is a risk your baby will have asthma too. The best way you can help to reduce this risk is to **avoid tobacco smoke** (e.g. ban smoking in your car and home). Breastfeeding is best for babies, and might also help prevent asthma.

Questions and answers

Will asthma medications harm my baby?

Most medications used to treat asthma have a much lower risk to your baby than having asthma symptoms. It is much safer to use regular inhaled preventer medications that have been taken by a large number of pregnant women around the world than to risk an asthma attack. A severe asthma attack – or some medications that are used to treat severe attacks (prednisolone tablets) – are more likely to harm your baby than regular medications for preventing attacks.

Can I just put up with asthma symptoms while I'm pregnant?

No – this is unsafe and not recommended. Asthma can increase the risk of pregnancy complications and increase the chance that your baby will be born early or with a low birth weight. You can reduce these risks by keeping your asthma under control. Uncontrolled asthma puts you and your baby at risk.

What happens if I have an asthma attack while I'm pregnant?

If you have an asthma attack during pregnancy, it will be treated the same as an attack that occurs at any other time. Tell the emergency centre staff that you are pregnant, but don't worry – most treatments used during asthma attacks are much safer for your baby than an untreated asthma attack.

Will I have an asthma attack while giving birth?

Asthma attacks rarely happen during labour. Any asthma symptoms are usually easily controlled with usual asthma medications.

Like other women, most women with asthma can expect a normal vaginal birth. If you have very severe asthma or asthma that is difficult to control, tell your obstetrician and midwife that you have asthma so that they can talk to the doctor who manages your asthma.

Know your asthma medications

There are three types of asthma medications: relievers, preventers and symptom controllers. Your doctor will prescribe the medication best for you.

- Relievers (Airomir, Asmol, Bricanyl, Epaq and Ventolin) – these medicines provide relief from asthma symptoms within minutes. If you need to use your reliever more than 3–4 times a week (not counting use before exercise), it may be a sign that your asthma is not well controlled and you should tell your doctor immediately.
  Airomir is a different type of reliever. If you normally take Airomir, tell your doctor that you are pregnant.
- Preventers (Alvesco, Flixotide, Inhal, Inhal Forte, Pulmicort, Qvar, Singulair, Tilade) – these medications make the airways less sensitive. Preventers usually need to be taken every day, even when feeling well. If you normally take an inhaled preventer medication, you should keep taking it unless your doctor tells you that you no longer need it.
  If you normally take preventer tablets (Singulair), tell your doctor that you are pregnant.
- Symptom controllers (Foradile, Oxis and Serevent) – these medications act like relievers, but the effects are longer lasting and they are normally taken long term. They should only be taken with a preventer. They should not be taken in an asthma attack. If you normally take a symptom controller, tell your doctor that you are pregnant.
- Combination medications Seretide (Flixotide and Serevent) and Symbicort (Pulmicort and Oxis) – if you normally take a combination medication, tell your doctor that you are pregnant.

If you would like more information on asthma medications in pregnancy, visit www.asthmansw.org.au

For information on medications during pregnancy and breastfeeding please call MotherSafe, Royal Hospital for Women on 02 9382 6539 (Sydney) or 1800 647 848 (NSW outside Sydney).

Asthma Foundation NSW
Level 7, 35 Chandos St
St Leonards NSW 2065
Infoline: 02 9906 3233
www.asthmansw.org.au

This brochure contains general information and is not intended to replace medical advice.

This project was supported by funding from NSW Health
Produced in consultation with the NSW Regional Committee of the Royal Australian & New Zealand College of Obstetricians & Gynaecologists

Appendices for poster presentations

Appendix 27 – Poster 1

Presented at Primary Health Care Conference 2011, Pharmacy Australia Congress 2011 and Higher Degree by Research Symposium, Monash University 2011

Appendix 28 – Poster 2

Presented at International Social Pharmacy Workshop 2012, Pharmacy Australia Congress 2012 and Higher Degree by Research Symposium, Monash University 2012

Appendix 29 – Poster 3

Presented at American Health-System Pharmacists 2012

Appendix 30 – Poster 4

Presented at Thoracic Society of Australian and New Zealand Conference 2013 and European Academy of Allergy and Clinical Immunology World Allergy and Asthma Congress 2013

Appendix 27 – Poster 1

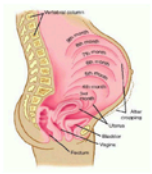
Management of pregnant asthmatic women by Australian General Practitioners (GPs)

A Lim,[1,2] K Stewart,[1] MJ Abramson[1,3] and J George[1]

[1]Centre for Medicine Use and Safety, Monash University, Vic; [2]Mercy Hospital for Women, Vic; [3]Department of Epidemiology and Preventive Medicine, Monash University, Vic

Background

- Poorly controlled asthma during pregnancy is detrimental for both the mother and the foetus, leading to increased risks of pre-term deliveries, stillbirths, infections, foetal hypoxia and cerebral palsy.[1,2]
- Furthermore, pre-term babies have an increased risk of developing heart disease, high blood pressure and diabetes in adulthood.[3]
- Pregnant women tend to reduce or stop their asthma medications during pregnancy due to concerns about safety for their unborn child.[4]



- Two-thirds of pregnant asthmatic women have been shown to be under-treated for asthma for three or more months of pregnancy.[4]
- Two in five women said they would be more likely to continue taking their asthma medication during pregnancy if their prescriber had recommended it.[4]
- Limited data are available on prescribing trends and management in the pregnant asthmatic population.
- Recently, prescribers have been shown to be heavily reliant on pregnancy risk categories, which could explain suboptimal management and deter them from conducting a risk benefit assessment per patient.[5]

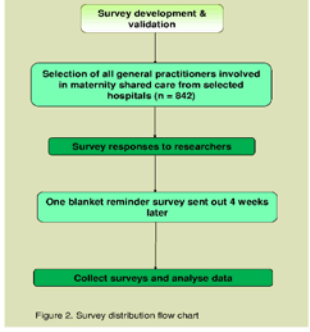


Figure 2. Survey distribution flow chart

Aim:

- To investigate the management of asthma during pregnancy by Australian general practitioners who provide shared maternity care.

Method:

- A pre-piloted, anonymous mail survey (See figure 1) was sent to all GPs (n = 842) involved in shared maternity care at six maternity hospitals in Victoria, Australia (See figure 2).
- Respondents were asked about the perceived safety of individual asthma medications during pregnancy.
- Their approach to asthma management during pregnancy was further explored using scenarios of pregnant women with stable and deteriorating asthma and poor medication adherence.

Table 1. Case vignette one and responses

A patient of yours has recently become pregnant. She has moderate asthma which is well controlled with salmeterol/fluticasone (250/25), one puff twice daily, and salbutamol inhaler as required. She has no other medical conditions nor is she taking any other medications.

Part one (Stable asthma in pregnancy): She wonders whether she should continue these medications during pregnancy. What is your intended action?*

Responses to part one	n (%)
Continue her on the same medications	119 (68.8%)
Decrease her dose	7 (4.0%)
Stop her medication	2 (1.2%)
Change to a different ICS/LABA combination	3 (1.7%)
Change to just one agent (i.e. ICS or LABA only)	35 (20.3%)
Refer	5 (2.9%)

Part two (deteriorating asthma in pregnancy): A few weeks pass by and your patient returns. You notice that her asthma is deteriorating. She tells you that she has been using her salbutamol inhaler more than three times per week. She has been compliant with the salmeterol/fluticasone and has had no changes to her asthma medication regimen nor has she had any changes in lifestyle. What is your intended action?*

Responses to part two	n (%)
Increase her dose	110 (63.6%)
Continue her on the same regimen and just monitor her asthma more closely	8 (4.6%)
Refer	21 (12.1%)
Add another agent	12 (6.94%)
Decrease ICS regimen	8 (4.6%)
Change to another agent	9 (6.2%)

*Participants could only tick one response for part one and part two; responses may not add up to 174 due to missing data.

Figure 1. Survey tool

Conclusions

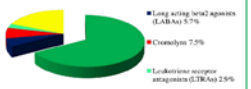
- Overall, GPs complied with evidence-based guidelines in the selection of preventive medications, and self reported good asthma knowledge.

- Despite this, a lack of confidence and/or knowledge in managing stable and deteriorating asthma in pregnancy was observed.
- The findings from this survey will inform the development of future interventions and strategies to optimize asthma management and outcomes in pregnant women.

Results

- 176 responses received; 174 useable (See Table 1)
- **Demographics:** 70.7% females, 84.5% metropolitan GPs, 31.2% encountered asthma in >10% of their pregnant patients, 67.6% rated their asthma knowledge as good or very good, median of 19 years practised as a GP.
- Inhaled corticosteroids (74.1%) were the preferred preventive asthma medication in the first trimester. (See Figure 3)
- 25.8% of respondents would stop or decrease patients' preventer doses during pregnancy, even when asthma control was stable.
- 12.1% of respondents were not sure how to manage deteriorating asthma during pregnancy and opted to refer to another health professional.
- Almost half of the respondents reported encountering nonadherence to asthma medications during pregnancy in their practice.

Figure 3. Asthma preventive agent of choice in pregnancy



Discussion

- GPs' management of asthma in pregnant women can be suboptimal. A considerable number of respondents would either decrease or stop asthma preventive medication or refer patients to another health professional even when asthma is well controlled with current preventive therapy.
- Few respondents rated LABAs and LTRAs as the first choice of preventive asthma medication. Limited safety data and/or the prescribers' lesser familiarity with these newer medications, may result in reluctance to initiate or permit their ongoing use during pregnancy.
- Prescribers who opted to refer when the woman's asthma started deteriorating, may lack confidence and/or knowledge in managing deteriorating asthma in pregnancy.

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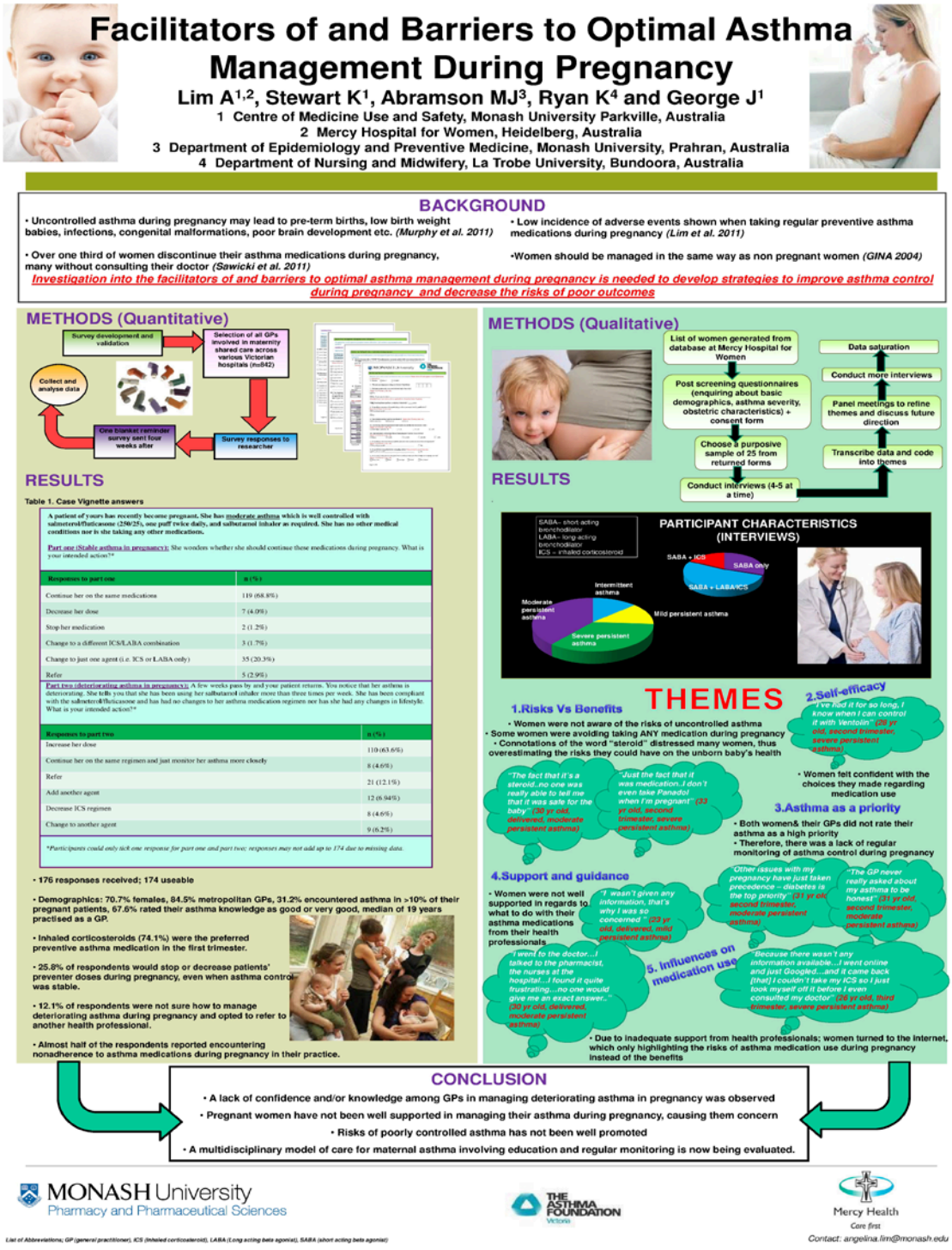
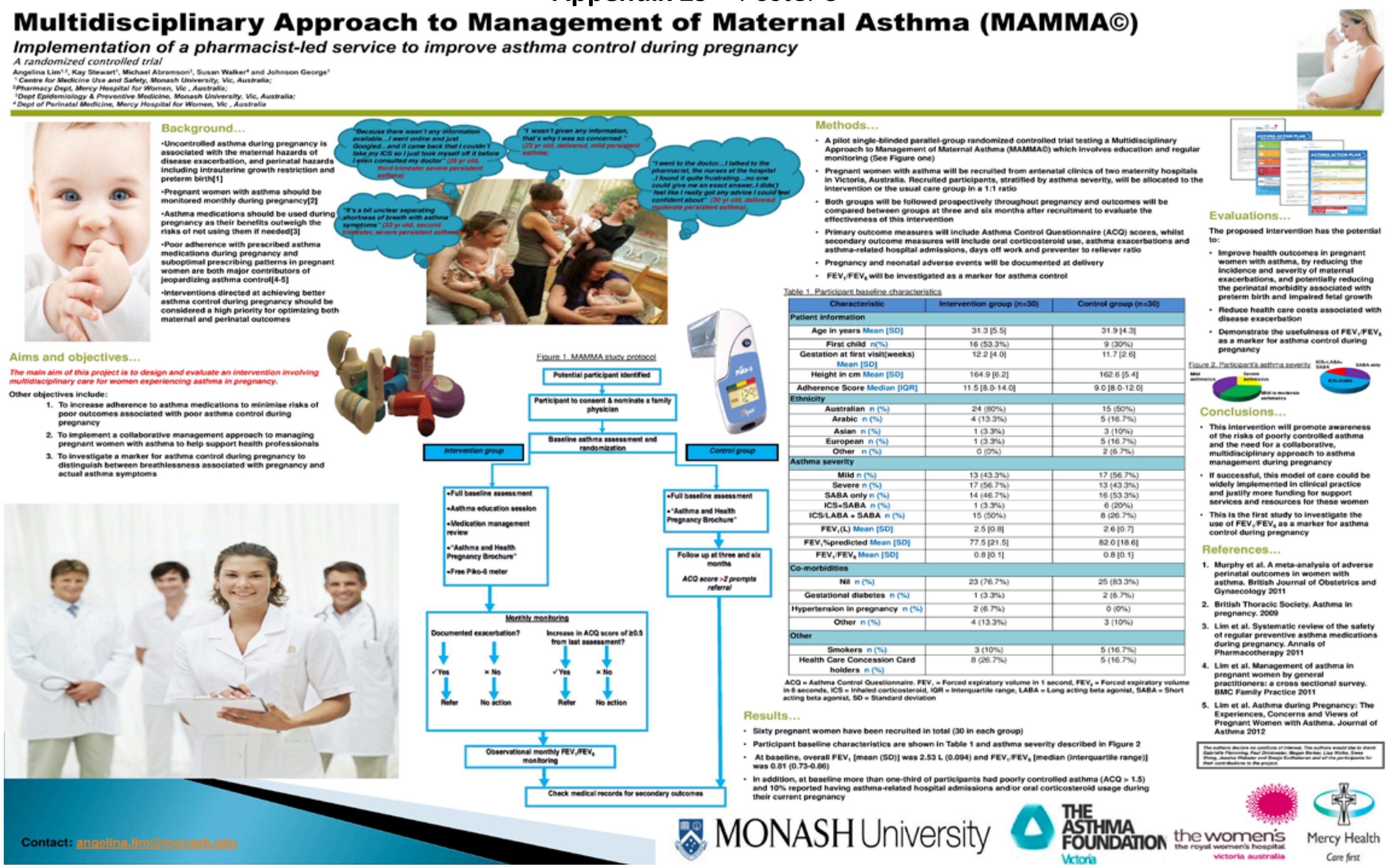
THE ASTHMA FOUNDATION Victoria

Appendix 28 – Poster 2



Appendix 29 – Poster 3



Multidisciplinary Approach to Management of Maternal Asthma (MAMMA©)

Implementation of a pharmacist-led service to improve asthma control during pregnancy

A randomized controlled trial

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Background…

- Uncontrolled asthma during pregnancy is associated with the maternal hazards of disease exacerbation, and perinatal hazards including intrauterine growth restriction and preterm birth[1]
- Pregnant women with asthma should be monitored monthly during pregnancy[2]
- Asthma medications should be used during pregnancy as their benefits outweigh the risks of not using them if needed[3]
- Poor adherence with prescribed asthma medications during pregnancy and suboptimal prescribing patterns in pregnant women are both major contributors of jeopardizing asthma control[4-5]
- Interventions directed at achieving better asthma control during pregnancy should be considered a high priority for optimizing both maternal and perinatal outcomes

"Because there wasn't any information available…I went online and just Googled…and it came back that I couldn't take my ICS so I just took myself off it before I even consulted my doctor" (26 yr old, third trimester severe persistent asthma)

"I wasn't given any information, that's why I was so concerned " (23 yr old, delivered, mild persistent asthma)

"I went to the doctor…I talked to the pharmacist, the nurses at the hospital ..I found it quite frustrating…no one could give me an exact answer..I didn't feel like I really got any advice I could feel confident about" (30 yr old, delivered moderate persistent asthma)

"It's a bit unclear separating shortness of breath with asthma symptoms" (33 yr old, second trimester, severe persistent asthma)

Aims and objectives…

The main aim of this project is to design and evaluate an intervention involving multidisciplinary care for women experiencing asthma in pregnancy.

Other objectives include:

1. To increase adherence to asthma medications to minimise risks of poor outcomes associated with poor asthma control during pregnancy
2. To implement a collaborative management approach to managing pregnant women with asthma to help support health professionals
3. To investigate a marker for asthma control during pregnancy to distinguish between breathlessness associated with pregnancy and actual asthma symptoms

Figure 1. MAMMA study protocol

Potential participant identified
Participant to consent & nominate a family physician
Baseline asthma assessment and randomization
Intervention group
- Full baseline assessment
- Asthma education session
- Medication management review
- "Asthma and Health Pregnancy Brochure"
- Free Piko-6 meter

Monthly monitoring
Documented exacerbation? ✓Yes → Refer; × No → No action
Increase in ACQ score of ≥0.5 from last assessment? ✓Yes → Refer; × No → No action
Observational monthly FEV_1/FEV_6 monitoring

Control group
- Full baseline assessment
- "Asthma and Health Pregnancy Brochure"

Follow up at three and six months
ACQ score >2 prompts referral

Check medical records for secondary outcomes

Methods…

- A pilot single-blinded parallel-group randomized controlled trial testing a Multidisciplinary Approach to Management of Maternal Asthma (MAMMA©) which involves education and regular monitoring (See Figure one)
- Pregnant women with asthma will be recruited from antenatal clinics of two maternity hospitals in Victoria, Australia. Recruited participants, stratified by asthma severity, will be allocated to the intervention or the usual care group in a 1:1 ratio
- Both groups will be followed prospectively throughout pregnancy and outcomes will be compared between groups at three and six months after recruitment to evaluate the effectiveness of this intervention
- Primary outcome measures will include Asthma Control Questionnaire (ACQ) scores, whilst secondary outcome measures will include oral corticosteroid use, asthma exacerbations and asthma-related hospital admissions, days off work and preventer to reliever ratio
- Pregnancy and neonatal adverse events will be documented at delivery
- FEV_1/FEV_6 will be investigated as a marker for asthma control

Table 1. Participant baseline characteristics

Characteristic	Intervention group (n=30)	Control group (n=30)
Patient information		
Age in years Mean [SD]	31.3 [5.5]	31.9 [4.3]
First child n(%)	16 (53.3%)	9 (30%)
Gestation at first visit(weeks) Mean [SD]	12.2 [4.0]	11.7 [2.6]
Height in cm Mean [SD]	164.9 [6.2]	162.6 [5.4]
Adherence Score Median [IQR]	11.5 [8.0-14.0]	9.0 [8.0-12.0]
Ethnicity		
Australian n (%)	24 (80%)	15 (50%)
Arabic n (%)	4 (13.3%)	5 (16.7%)
Asian n (%)	1 (3.3%)	3 (10%)
European n (%)	1 (3.3%)	5 (16.7%)
Other n (%)	0 (0%)	2 (6.7%)
Asthma severity		
Mild n (%)	13 (43.3%)	17 (56.7%)
Severe n (%)	17 (56.7%)	13 (43.3%)
SABA only n (%)	14 (46.7%)	16 (53.3%)
ICS+SABA n (%)	1 (3.3%)	6 (20%)
ICS/LABA + SABA n (%)	15 (50%)	8 (26.7%)
FEV_1(L) Mean [SD]	2.5 [0.8]	2.6 [0.7]
FEV_1%predicted Mean [SD]	77.5 [21.5]	82.0 [18.6]
FEV_1/FEV_6 Mean [SD]	0.8 [0.1]	0.8 [0.1]
Co-morbidities		
Nil n (%)	23 (76.7%)	25 (83.3%)
Gestational diabetes n (%)	1 (3.3%)	2 (6.7%)
Hypertension in pregnancy n (%)	2 (6.7%)	0 (0%)
Other n (%)	4 (13.3%)	3 (10%)
Other		
Smokers n (%)	3 (10%)	5 (16.7%)
Health Care Concession Card holders n (%)	8 (26.7%)	5 (16.7%)

ACQ = Asthma Control Questionnaire. FEV_1 = Forced expiratory volume in 1 second, FEV_6 = Forced expiratory volume in 6 seconds, ICS = Inhaled corticosteroid, IQR = Interquartile range, LABA = Long acting beta agonist, SABA = Short acting beta agonist, SD = Standard deviation

Results…

- Sixty pregnant women have been recruited in total (30 in each group)
- Participant baseline characteristics are shown in Table 1 and asthma severity described in Figure 2
- At baseline, overall FEV_1 [mean (SD)] was 2.53 L (0.094) and FEV_1/FEV_6 [median (interquartile range)] was 0.81 (0.73-0.86)
- In addition, at baseline more than one-third of participants had poorly controlled asthma (ACQ > 1.5) and 10% reported having asthma-related hospital admissions and/or oral corticosteroid usage during their current pregnancy

Evaluations…

The proposed intervention has the potential to:

- Improve health outcomes in pregnant women with asthma, by reducing the incidence and severity of maternal exacerbations, and potentially reducing the perinatal morbidity associated with preterm birth and impaired fetal growth
- Reduce health care costs associated with disease exacerbation
- Demonstrate the usefulness of FEV_1/FEV_6 as a marker for asthma control during pregnancy

Figure 2. Participant's asthma severity

Conclusions…

- This intervention will promote awareness of the risks of poorly controlled asthma and the need for a collaborative, multidisciplinary approach to asthma management during pregnancy
- If successful, this model of care could be widely implemented in clinical practice and justify more funding for support services and resources for these women
- This is the first study to investigate the use of FEV_1/FEV_6 as a marker for asthma control during pregnancy

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Appendix 30 – Poster 4