



Multidisciplinary Approach to Management of Maternal Asthma (MAMMA)

A Randomized Controlled Trial

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Background: Uncontrolled asthma during pregnancy is associated with maternal and perinatal hazards. A pharmacist-led intervention directed at improving maternal asthma control, involving multidisciplinary care, education, and regular monitoring to help reduce these risks, was developed and evaluated.

Methods: A randomized controlled trial was carried out in the antenatal clinics of two major Australian maternity hospitals. Sixty pregnant women < 20 weeks gestation who had used asthma medications in the previous year were recruited. Participants were randomized to either an intervention or a usual care group and followed prospectively throughout pregnancy. The primary outcome was Asthma Control Questionnaire (ACQ) score. 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 a mean $\pm$ 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 (95% CI, -0.85 to -0.36) at 6 months. The difference at 6 months was statistically significant ($P < .001$) and clinically significant (> 0.5). No asthma-related oral corticosteroid use, hospital admissions, emergency visits, or days off from work were reported during the trial.

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

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Abbreviations: ACQ = Asthma Control Questionnaire; APGAR = appearance, pulse, grimace, activity, respiration; MAMMA = Multidisciplinary Approach to Management of Maternal Asthma; MCG = multidisciplinary care group; UCG = usual care group

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 recognized 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 these important adverse perinatal outcomes and that proper asthma management among pregnant women should be regarded as a leading priority in antenatal care.

Antiinflammatory asthma medications (preventers) at regular doses have been shown to be safe to use during pregnancy, with the risks of reduction or discontinuation of these medications being far worse.^{9,10} Asthma guidelines around the world strongly recommend that women continue their asthma medications during pregnancy to maintain adequate control.^{11–15} However, some women cease their asthma medications

during pregnancy, many without consulting their physicians.^{5,16} Reasons for discontinuation 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 asthma management.¹⁷

Prescribers may be hesitant to prescribe and endorse the use of asthma medications during pregnancy. More than one-fourth of family physicians would instruct their pregnant patients to decrease or discontinue asthma medication during pregnancy when asthma was well controlled by current therapy,¹⁸ potentially jeopardizing asthma control.

The uncertainty and anxiety surrounding medication use and asthma control during pregnancy emphasizes the crucial role of physicians, 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.^{19,20} Using the positive results of these trials, the present study investigated the feasibility of a more practical and sustainable option for routine care. The aim was to evaluate an intervention that incorporated regular patient self-monitoring and a multidisciplinary health professional approach to asthma management (Multidisciplinary Approach to Management of Maternal Asthma [MAMMA]). It was hypothesized that participants receiving the MAMMA intervention would have better asthma control than those receiving usual care at 3 and 6 months from baseline.

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MATERIALS AND METHODS

A single-blind randomized controlled trial was carried out in the antenatal settings of two large maternity hospitals in Victoria, Australia, to evaluate MAMMA intervention. The detailed protocol is published elsewhere.²¹ The study design and flow of participants are shown in Figure 1.

Participants

All pregnant women (up to 20 weeks gestation) with asthma attending antenatal outpatient clinics who could communicate in English were considered. Patients aged < 18 years or who had no asthma symptoms (wheeze, chest tightness, use of reliever asthma medication) in the previous 12 months were excluded. Those who were unlikely to meet the demands of the trial (eg, planning to relocate) were also excluded. Potential participants were approached by the trial pharmacist (A. S. L.) for recruitment while waiting for their antenatal appointments. Identification of potential participants was through advertisement posters, referrals from midwives or physicians, 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 and 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 four-item nonadherence subscale of the Beliefs and Behavior Questionnaire²²), were collected by the trial pharmacist at baseline. Each item on the nonadherence scale was answered on a five-point Likert scale (never = 1 to always = 5); higher scores suggested poorer adherence. This scale has been used in previous studies of pregnant women with asthma.⁵

Randomization

Asthma severity was determined in accordance with the National Asthma Council classification.²³ Participants were stratified into two groups: mild to intermittent asthma and moderate to severe persistent asthma. Within these two strata, participants were randomized in blocks of four and six using the sealed opaque envelope method. Numbered envelopes were opened by the trial pharmacist to allocate participants to the usual care group (UCG) or the multidisciplinary care group (MCG). Stratification and block randomization ensured 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 that included asthma education, monitoring, feedback, and follow-up as integral components of the monthly intervention. At baseline, the trial pharmacist, who was also an accredited asthma educator, reviewed medications (prescription and over the counter), including inhaler device technique; offered advice on trigger avoidance; and provided smoking cessation support, if relevant. To encourage home monitoring of lung function, each participant in the MCG was given a handheld, portable, electronic spirometer (PiKo-6; nSpire Health, Inc) for measuring FEV₁, FEV₆, and FEV₁/FEV₆ daily. At baseline, participants were trained by the trial pharmacist on how to use the PiKo-6 meter and interpret results. Technique was corrected if participants were seen to be using the meter incorrectly at face-to-face visits. Participants were also instructed to contact the trial pharmacist if their lung function deteriorated (FEV₁/FEV₆ < 0.75).

In addition, every month, participants in the MCG were contacted by the trial pharmacist either by phone or in person at their antenatal appointment to assess their asthma control based on a short data collection form that included the seven-item Asthma

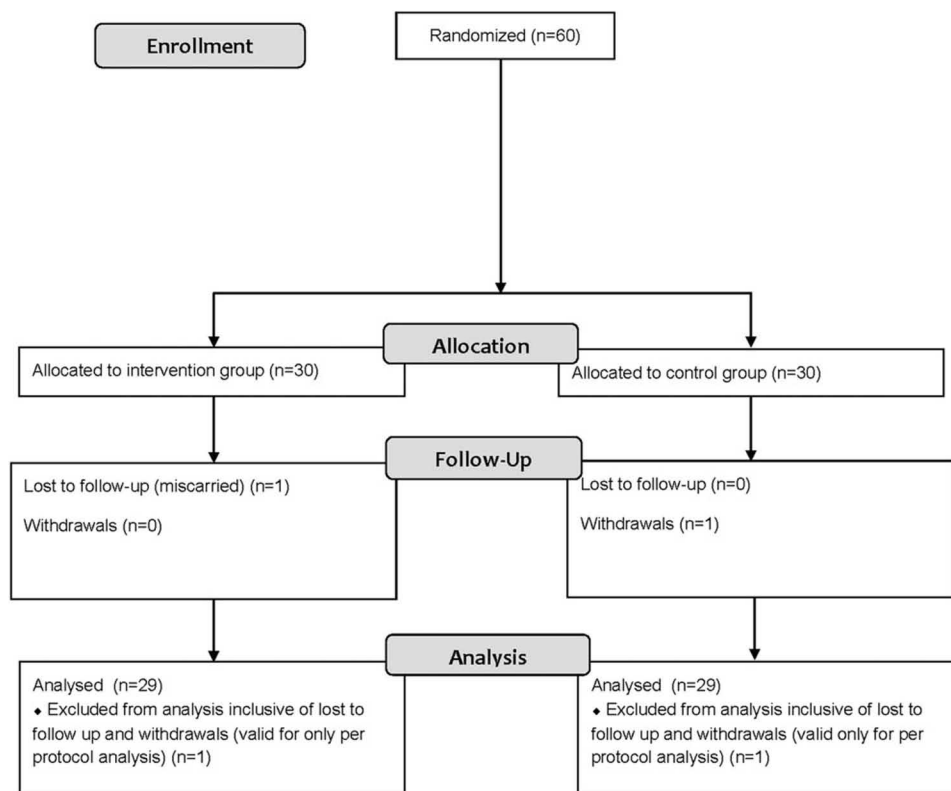


FIGURE 1. CONSORT (Consolidated Standards of Reporting Trials) diagram of participant flow.

Control Questionnaire (ACQ),²⁴ oral corticosteroid use, asthma-related hospital admissions, days off from work, and any recent changes to pharmacotherapy. If participants were contacted by phone, the questionnaire was read to them, and the participants used the PiKo-6 meter to report lung function. Assessments took approximately 30 min. The seven-item ACQ was used because it has been shown to be superior to its shortened versions²⁵ and includes an objective measure (FEV_1) in the score to complement the self-reported symptom data. An increase in ACQ score of ≥ 0.5 suggested a clinically significant deterioration of asthma control.²⁴ The trial pharmacist contacted the participant's nominated family physician if the ACQ score increased by ≥ 0.5 , there was a documented exacerbation since the last monthly visit, or both. Further individualized education was provided to each participant, if needed.

The trial pharmacist and the family physician also collaborated on appropriate step-up therapy for the participant. If the step-up therapy did not require a new prescription, the pharmacist communicated this to the participant; otherwise, the participant was asked to return to her family physician for a prescription. This close monthly monitoring aimed to maintain the participant's asthma as well controlled during pregnancy.

Asthma action plans were also recommended by the trial pharmacist and drafted alongside a respiratory physician at the discretion of the participant's family physician, who signed off on the final plan. Participant self-report of adherence to recommendations made by the trial pharmacist and asthma action plan were assessed informally at the next follow-up.

Control (UCG Participants)

Control group participants received usual antenatal care and were provided with written information from the Asthma Foun-

dation on the management of asthma in pregnancy.²⁶ They did not receive the additional monitoring or education sessions offered to MCG participants but were assessed at 3 and 6 months with the ACQ. If asthma control had deteriorated, evidenced by two or more documented exacerbations without increasing preventer dose since the prior assessment, or if their ACQ score exceeded 2, UCG participants were advised by study staff to contact their family physicians.

Outcomes

The primary outcome of the trial was the change in baseline ACQ score at 3 and 6 months. Secondary outcomes included asthma exacerbations defined as having asthma-related hospital visits, emergency visits, days off from work, or use of oral corticosteroids. Pregnancy and neonatal outcomes were also collected, but the trial was not powered to assess these outcomes. These outcomes included mode of delivery; gestational age and birth weight centile; APGAR (appearance, pulse, grimace, activity, respiration) scores; admission to the neonatal ICU or special care nursery; the development of antenatal complications, such as hypertensive disorders of pregnancy, antepartum hemorrhage, and gestational diabetes; and postnatal complications.

Follow-up

Blinded assessments were performed at 3 and 6 months for participants in both groups during their antenatal appointment. ACQ scores, asthma-related hospital admissions, emergency visits, days off from work, and oral corticosteroid use were assessed at 3 and 6 months by a research assistant blinded to participant group allocation. Pregnancy and neonatal outcome data were obtained from medical records shortly after delivery.

Sample Size

A conservative SD of 0.66 was used to detect a mean change in ACQ score of ≥ 0.5 between groups. A sample size of 29 per arm was needed to provide 80% power with a two-sided α of 5%, assuming equal variance.

Statistical Analysis

An intention-to-treat analysis was conducted with SPSS, version 20 (IBM) statistical software. Continuous baseline variables were compared between groups using a two-sample *t* test for normally distributed data and the Mann-Whitney *U* test for nonnormal data. Categorical variables were compared using Fisher exact test. For the primary analysis, differences in the primary outcome at 3 and 6 months were compared between groups using linear regression modeling adjusted for baseline ACQ scores. A secondary analysis considered variables that appeared different at baseline as potential confounders in the primary models. Because no evi-

dence of confounding was found, only the primary analysis is presented. Primary results are presented as estimated differences with 95% CIs. All tests were two tailed, and $P < .05$ was considered statistically significant.

Ethics

This trial was approved by the human research ethics committees of the participating hospitals (Mercy Hospital #R12/13, Royal Women's Hospital #12/22) and Monash University (#2012000921). All participants gave written informed consent before taking part.

RESULTS

Sixty participants from a range of ethnic and socioeconomic groups were recruited into the trial. At baseline, the groups were well matched (Table 1). All

Table 1—Baseline Participant Characteristics With Comparisons Between Groups

Characteristic	MCG (n = 29)	UCG (n = 29)	P Value
Demographic			
Age, y	31.97 $\pm$ 4.33	31.38 $\pm$ 5.14	.64
Height, cm	165.12 $\pm$ 6.49	162.10 $\pm$ 5.54	.06
Gestational age at baseline, wk	11.59 $\pm$ 2.96	11.97 $\pm$ 2.01	.68
Ex-smokers	4 (13.3)	6 (20.0)	.71
Health-care concession cardholders	8 (26.6)	4 (13.3)	.93
Nulliparous	12 (40.0)	14 (46.6)	.79
Highest level of education			.09
Secondary	13 (43.3)	7 (23.3)	
Tertiary	17 (56.7)	23 (76.7)	
Ethnic background			.86
Australian/New Zealander	22 (73.3)	21 (70.0)	
Asian	2 (6.7)	4 (13.3)	
European	2 (6.7)	3 (10.0)	
Middle Eastern	3 (10.0)	2 (6.7)	
South African	1 (3.3)	0 (0.0)	
Other medical conditions			
Anxiety/depression	1 (3.3)	1 (3.3)	> .9
Thyroid disorders	1 (3.3)	2 (6.7)	> .9
GERD	1 (3.3)	1 (3.3)	> .9
Asthma history			
Asthma severity			
Mild to intermittent	14 (48.3)	15 (51.7)	> .9
Moderate to severe persistent	15 (51.7)	14 (48.3)	> .9
Asthma medications			.51
SABA only	11 (36.7)	16 (53.3)	
SABA + ICS	5 (16.7)	3 (10.0)	
SABA + ICS + LABA	13 (43.3)	11 (36.7)	
Changes made to medication regimen during pregnancy (prior to trial entry)			.22
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 nonadherence score	8 (6-11)	7.5 (6-10)	.34
Spirometry			
FEV ₁ , L	2.68 $\pm$ 0.69	2.39 $\pm$ 0.75	.14
FEV ₁ , % predicted	82 $\pm$ 19	77 $\pm$ 22	.16
FEV ₁ /FEV ₆	0.78 $\pm$ 0.15	0.79 $\pm$ 0.12	.79
Asthma exacerbations during current pregnancy (prior to trial entry)			
Asthma-related hospital visit	4 (13.3)	1 (3.3)	.35
Course of oral corticosteroids	3 (10.0)	2 (6.6)	.67
Asthma-related days off from work	6 (20.0)	3 (10.0)	.47

Data are presented as mean $\pm$ SD, No. (%), or median (interquartile range). GERD = gastroesophageal reflux disease; ICS = inhaled corticosteroid; LABA = long-acting β -agonist; MCG = multidisciplinary care group; SABA = short-acting β -agonist; UCG = usual care group.

participants reported that they were nonsmokers or had quit smoking upon confirmation of pregnancy. At the baseline interview, 42 participants (70%) revealed that they were unaware of the risks of poorly controlled asthma, and 19 (32%) reported ceasing or reducing their medications since becoming pregnant. Sixteen participants (27%) (10 in MCG, six in UCG) reported ceasing their asthma medications since becoming pregnant, and three (5%) (one in MCG, two in UCG) reduced their medication doses. Some participants reported asthma exacerbations during pregnancy but prior to trial commencement.

One participant from each arm was lost to follow-up (Fig 2). In the MCG, 23 of 30 participants (77%) received from the asthma educator/pharmacist-family

practitioner team an adjustment in their asthma management to optimize control: three (11%) required initiation of a preventer; eight (27%) the reinstatement of a preventer; four (14%) escalation of preventer dosage; seven (23%) initiation of an asthma action plan (with three of these seven [43%] self-reporting that they used their given plans); and one (3%) being referred to a respiratory specialist. Baseline ACQ scores improved (decreased) at both 3 and 6 months for both groups (Fig 3, Table 2).

The ACQ score in the intervention group decreased by a mean $\pm$ SD of 0.46 ± 1.05 at 3 months and 0.89 ± 0.98 at 6 months. The UCG 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

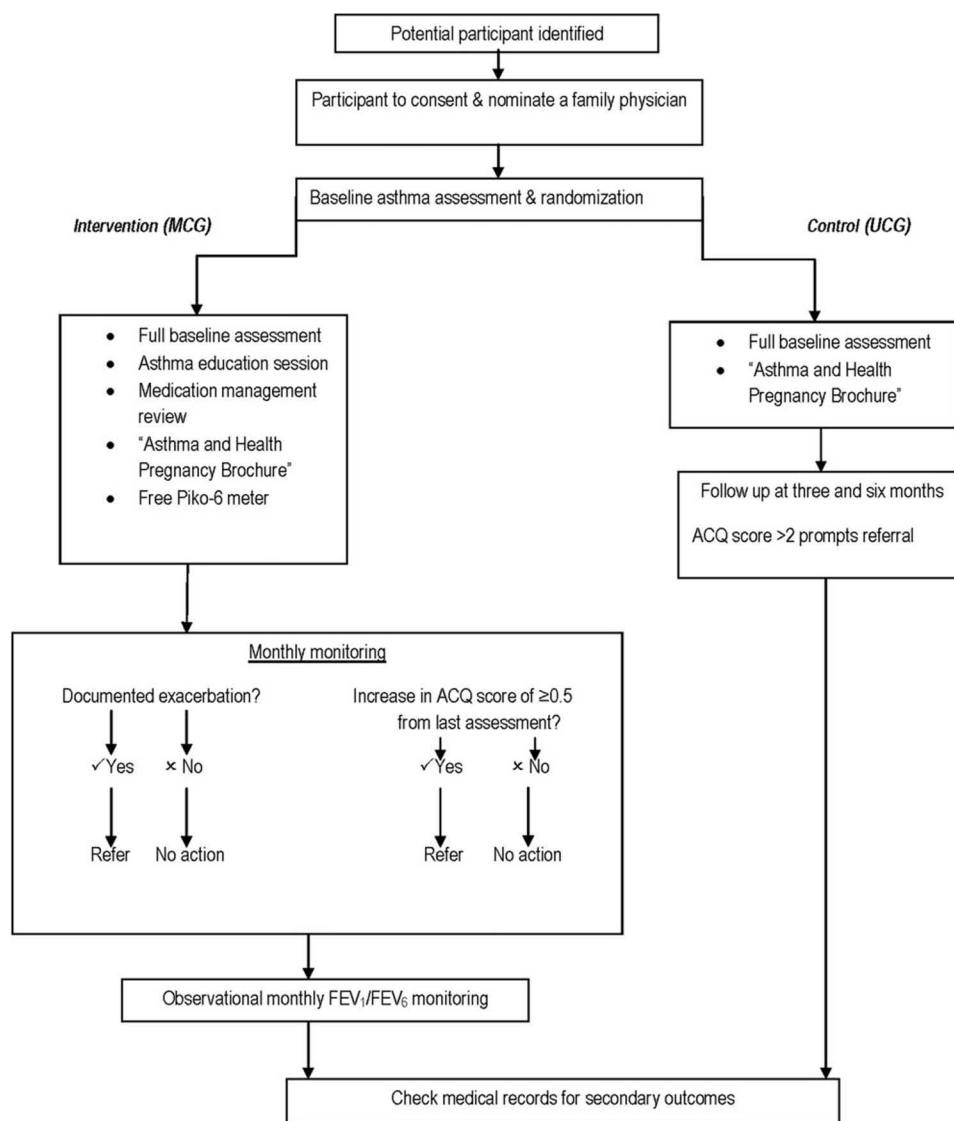


FIGURE 2. Multidisciplinary Approach to Management of Maternal Asthma (MAMMA) study design. ACQ = Asthma Control Questionnaire; MCG = multidisciplinary care group; UCG = usual care group.

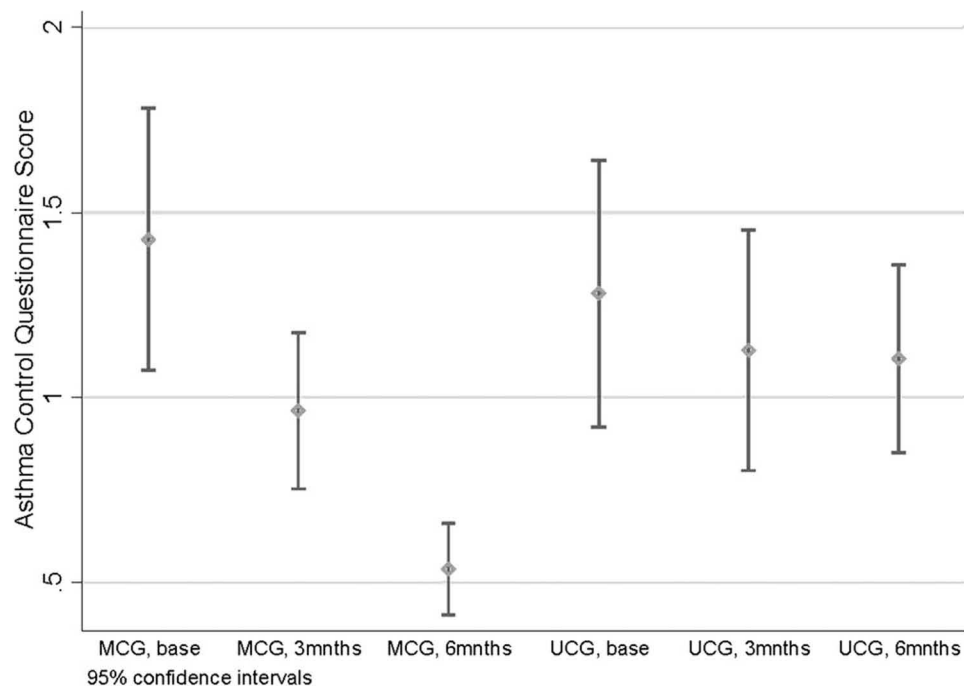


FIGURE 3. Mean ACQ scores and 95% CIs. See Figure 2 legend for expansion of abbreviations.

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 (Table 3). This difference was significant at 6 months ($P < .001$) but not at 3 months.

Furthermore, all participants in the intervention group had an ACQ score < 1.5 , indicating adequately controlled asthma, as opposed to 20 of 29 participants (69%) in the UCG. No new asthma-related hospital admissions, emergency visits, or oral corticosteroid use was reported in either group during the trial. Perinatal outcome data are shown in Table 4.

Statistical analysis of perinatal outcomes showed no significant trends between groups (Table 4). The intervention did not show any differences in mean birth weight, mean gestational age, mode of delivery, APGAR scores, incidence of congenital malformations, or low birth weight.

DISCUSSION

This trial shows that an intervention comprising education, surveillance, and multidisciplinary management can successfully overcome barriers to asthma management in pregnancy, translating into improved asthma control. This intervention is simple and could be easily implemented in antenatal settings with minimal additional resources. Although the intervention was pharmacist led, it could potentially be delivered by any member of the health-care team with additional training in asthma management. Larger studies are needed to demonstrate that the improvements in asthma control translate to improved maternal and perinatal outcomes.

The findings add to the knowledge in this area and address some of the limitations of the previous trials^{19,20} targeting pregnant women with asthma. In a

Table 2—Primary Outcome Data: ACQ Scores at Baseline, 3 Mo, and 6 Mo and the Change From Baseline to 3 and 6 Mo

Time of ACQ Score	Gestational Age, wk	MCG (n = 29)	UCG (n = 29)	P Value Comparing Groups
Baseline	11.7 ± 2.5	1.43 ± 0.93	1.28 ± 0.95	.56
3 mo	23.8 ± 2.5	0.96 ± 0.56	1.13 ± 0.86	.39
6 mo	34.4 ± 2.5	0.54 ± 0.32	1.10 ± 0.67	< .001
3 mo – baseline	...	−0.46 ± 1.05 ^a	−0.15 ± 0.63 ^b	.18
6 mo – baseline	...	−0.89 ± 0.98 ^a	−0.18 ± 0.73 ^b	.003

Data are presented as mean ± SD. ACQ = Asthma Control Questionnaire. See Table 1 legend for expansion of other abbreviations.

^a $P \leq .02$ for within-group change.

^b $P = .2$ for within-group change.

Table 3—Primary Analysis: Mean Change in Baseline ACQ Score at 3 and 6 Mo 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)	UCG (n = 29)	Mean Difference	95% CI	P Value
3 mo – baseline ACQ	–0.46 ± 1.05	–0.15 ± 0.63	–0.22	–0.54 to 0.10	.2
6 mo – baseline ACQ	–0.89 ± 0.98	–0.18 ± 0.73	–0.60	–0.85 to –0.36	< .001

Data are presented as mean ± SD unless otherwise indicated. See Table 1 and 2 legends for expansion of abbreviations.

single-group study, Murphy et al²⁰ developed and tested an asthma education program delivered in an antenatal clinic setting that involved education and improving self-management skills. 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%.²⁰ This uncontrolled study showed that a simple educational program could benefit asthma management during pregnancy, but it did not include a formal assessment of asthma control. Furthermore, participants were not monitored regularly throughout pregnancy as recommended.

A more complex intervention targeting physicians was designed by Powell et al¹⁹ and involved monitoring women with asthma with an algorithm based on the fraction of exhaled nitric oxide, a marker of airway inflammation. The intervention reduced exacer-

bations by 50% compared with a symptom-based algorithm. Although fraction of exhaled nitric oxide-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 optimizing 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 it with their health professionals. Although not formally assessed, many of the MCG participants reported during their monthly assessments that they appreciated the support and advice they received regarding their asthma management. Asthma often is ignored during pregnancy because other health conditions take priority; however, asthma causes much anxiety in affected patients.^{17,27} Recruiting participants from the antenatal clinics in their first trimester was a challenge because the majority of pregnant women did not present until late first trimester or early second trimester. By this

Table 4—Perinatal Outcome Data and the Comparison Between Groups

Outcome	MCG (n = 29)	UCG (n = 29)	P Value
Neonatal data			
Male sex	18 (62.1)	15 (51.7)	.42
Birth weight, g	3,456.2 ± 664.6	3,448.4 ± 627.8	> .9
Gestation, wk	38.9 ± 1.6	38.9 ± 2.9	.25
Head circumference, cm	34.7 ± 1.8	35.2 ± 1.7	.31
Length, cm	50.8 ± 2.7	51.3 ± 2.0	.73
APGAR score			
At 1 min	8.5 ± 1.1	7.8 ± 1.7	.12
At 5 min	9.1 ± 0.5	8.8 ± 0.9	.13
Admission to NICU or SCN	3 (10.3)	2 (6.8)	.48
Premature (< 37 wk)	3 (10.3)	2 (6.9)	.67
Low birth weight (< 10th centile for gestational age)	1 (3.4)	1 (3.4)	> .9
Congenital malformations	0 (0.0)	0 (0.0)	> .9
Delivery data			
Mode of delivery			.85
Vaginal delivery	21 (72.4)	20 (69.0)	
Emergency cesarean	2 (6.9)	4 (13.8)	
Elective cesarean	6 (20.7)	5 (17.2)	
Complications			
Hypertension during pregnancy	2 (6.9)	0 (0.0)	.24
Gestational diabetes	2 (6.9)	0 (0.0)	.24
Macrosomia	1 (3.4)	0 (0.0)	.49

Data are presented as No. (%) or mean ± SD. This dataset also includes one set of twins in the UCG; in this case, the data of the larger twin were included. APGAR = appearance, pulse, grimace, activity, respiration; NICU = neonatal ICU; SCN = special care nursery. See Table 1 legend for expansion of other abbreviations.

time, many participants had already made incorrect management decisions regarding their asthma (eg, ceasing asthma medications), which could have affected asthma control at baseline. Severely uncontrolled asthma in the UCG (ACQ > 2) was brought to the attention of participants, who were advised to have their asthma reviewed by their family physician; this occurred on two occasions at the 3-month assessment. However, at the 6-month assessment neither of these participants had followed the advice.

The participants are representative of pregnant women, including those with asthma, attending the two public maternity hospitals from where they were recruited.^{28,29} However, the effectiveness of the MAMMA intervention in current smokers, those with lower education, and those requiring frequent hospital admissions or emergency visits is unclear. A trial (Hawthorne) effect might have influenced our outcomes, especially those self-reported by participants. However, assessments of key 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 4 weeks of gestation has been reported³⁰; one-third of women naturally experience improvement in their asthma during pregnancy.³¹ We could not establish any natural influences on asthma control among the present participants and assumed that randomization balanced this variable across groups. The study was not powered to detect any differences in perinatal or neonatal outcomes or health resource use. The sample size was small, and cost data were not collected. Admittedly, the intervention was time intensive, but this could be reduced by incorporating the model into routine antenatal care and with the help of technology for self-monitoring.

The MAMMA intervention has the potential to reduce health-care costs resulting from poorly controlled asthma in pregnant women. Larger multicenter studies powered to detect improvements in asthma-related unplanned medical and ED visits for pregnant women and perinatal outcomes are needed; the cost-effectiveness of such interventions should be evaluated. Future studies should also investigate the use of technology (eg, mobile phone-based applications for facilitating patient self-management) to minimize the burden on health professionals and to facilitate participant acceptance. Positive results from such studies could convince policymakers to take action to ensure more support for multidisciplinary asthma management in antenatal settings.

CONCLUSIONS

The MAMMA trial has shown that actively managing asthma through education and regular moni-

toring by 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 health outcomes associated with exacerbations.

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Author contributions: Dr George had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Ms Lim: contributed to the trial design and management, participant recruitment, baseline data collection, data entry, drafting of the manuscript, and editing the manuscript based on comments and feedback from the other authors.

Dr Stewart: contributed to the trial design and review of the manuscript.

Dr Abramson: contributed to the trial design and review of the manuscript.

Dr Walker: contributed to the trial design and review of the manuscript.

Ms Smith: contributed to the trial design and review of the manuscript.

Dr George: contributed to the trial design and review of the manuscript.

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