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Running head: Asthma exacerbations after inhaled steroid changes

Exacerbations of asthma following step-up and step-down inhaled corticosteroid and long acting beta agonist therapy in the Managing Asthma in Pregnancy study

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ABSTRACT

Guidelines for asthma management contain a consensus recommendation that inhaled corticosteroid (ICS) dose should not be stepped down in pregnancy. However, this is not consistent with consumer preferences and pharmacological principles to minimize medication exposure during pregnancy. We investigated exacerbations after changes to ICS and long acting beta agonist (LABA) therapy in pregnant women with asthma.

Pregnant women (n=220) were recruited to a randomised controlled trial (RCT) where maintenance treatment was adjusted monthly based on either symptoms (control group), or fractional exhaled nitric oxide (FeNO, to alter ICS) and symptoms (to alter LABA, FeNO group). Exacerbations were monitored prospectively.

ICS were used by 137 (62.3%) women at some time during pregnancy. ICS dose remained unchanged in 16 women (11.7%, 95% confidence interval [CI] 7-18%), increased in 37 women (27%, 95%CI 20-35%), decreased in 34 women (24.8%, 95%CI 18%-33%), or both increased and decreased in 50 women (36.5%, 95%CI 29-45%). Exacerbations occurred within 14 days of ICS step-down in 11 women (13%, 95%CI 7.5%-22%). This was not significantly different from exacerbations occurring within 14 days of step-up, in 7 women (8.1%, 95%CI 4%-16%, P=0.294). There were no differences between management groups. Exacerbations occurred within 14 days of step-down in 14.7% (95%CI 7%-30%) of women in the control group, and in 12% (95%CI 6%-24%) of women in the FENO group.

ICS step-down could be considered when eosinophilic inflammation or symptoms are low, and may be a useful management approach for women, doctors, and midwives wishing to minimize ICS exposure during pregnancy.

Key words: fractional exhaled nitric oxide, asthma management, inhaled steroid titration

Abbreviations: FeNO (fractional exhaled nitric oxide), ICS (inhaled corticosteroid), OCS (oral corticosteroid), SABA (short acting beta agonist), LABA (long acting beta agonist), ACQ (asthma control questionnaire), RCT (randomised controlled trial), ATS (American Thoracic Society), ECO (exhaled carbon monoxide), BMI (body mass index), IQR (interquartile range), FEV₁ (forced expiratory volume at 1 second).

Introduction

Asthma is a chronic inflammatory disease of the lower airways which affects 8-12% of pregnancies worldwide.¹⁻³ The prevalence of asthma during pregnancy is on the rise, and pregnancy may lead to a worsening of asthma for many women, with studies indicating that 33-45% of women have exacerbations during pregnancy which require medical intervention.^{4,5} Maternal asthma carries increased perinatal risks compared to women without asthma, including significantly increased risks for low birth weight, preterm delivery, gestational diabetes, pre-eclampsia, placental abruption, caesarean section and congenital malformations.⁶⁻⁸ Asthma exacerbations during pregnancy are also associated with further increases in risk for low birth weight and preterm delivery.^{9,10}

Pregnancy is a time associated with a change in medication taking behaviour, with studies showing high rates of non-adherence to ICS¹¹ and a decline in prescriptions for short acting beta agonists (SABA), ICS and oral corticosteroids (OCS) in the first trimester.¹² Other large database studies have demonstrated a decline in prescription filling in early pregnancy, followed by an increase in mid-gestation,^{13,14} possibly associated with the increased risk of exacerbations at this time.^{5,15} A survey of 500 women of childbearing age found that 82% of women who used ICS were worried about their effects on the fetus, and 36% indicated that they would discontinue ICS use if pregnant without consulting their doctor, even though they had concerns about their own health.¹⁶ A more recent Australian qualitative study also found that women made decisions to stop their medication during pregnancy without consulting a doctor, due to concerns about medication safety and a lack of support or information about what to do about their asthma during pregnancy.¹⁷ Some women expressed a lack of confidence in the benefits of medication use and performed their own risk/benefit assessment, choosing to decrease their medication.¹⁷ These data suggest that women voluntarily step-down their dose, and that management strategies that target treatment to the level of airway inflammation may be a useful approach in pregnancy to maintain asthma control at the minimum dose required.

During pregnancy, guidelines recommend that asthma be managed as for other adults, with the goal of maintaining asthma control and avoiding exacerbations, with 4-weekly review of symptoms and lung function recommended.^{18,19} For pregnant women, preventer medication should be prescribed (and not withheld), if indicated, just as for other adults. Budesonide has the best safety rating of ICS medications for use in pregnancy, while other ICS and ICS/long acting beta agonist (LABA) combination treatments are not contraindicated in pregnancy.¹⁸ However, step-down of ICS is not recommended in pregnancy; the National Asthma Council's Australian Asthma Handbook states that step down of ICS should only be considered if a woman is taking "an inappropriately high dose of a medicine", and indicates that stepping down is not a priority due to the risk of exacerbations.¹⁸ These recommendations are based on expert consensus, not evidence. There are currently no studies which investigate the risk of exacerbation following changes to ICS dose in pregnancy.

In this secondary analysis of a randomised controlled trial (RCT) which compared two active asthma management strategies, we investigated the rate of exacerbations following changes in ICS dose during pregnancy. We hypothesised that exacerbations in the 14 days following an ICS or LABA dose change would not differ among women who had a decrease in dose compared to an increase in dose.

Material and Methods

Study design and participants

This is a secondary analysis from a double-blind, parallel group RCT of fractional exhaled nitric oxide (FeNO)-guided therapy in two antenatal clinics (John Hunter Hospital Newcastle, and Maitland Hospital, NSW, Australia) from June 2007 to December 2010, known as the Managing Asthma in Pregnancy (MAP) Study (Australian and New Zealand Clinical Trials Registry number 12607000561482).²⁰ Participants were at least 18 years of age, non-smokers, 12-22 weeks gestation at randomisation, with doctor-diagnosed asthma and use of inhaled therapy for asthma within the past year.²⁰ Eligible participants (n=220) were randomly assigned before 22 weeks gestation to either a control algorithm, which adjusted medication monthly based on symptoms and lung function (assessed using the asthma control questionnaire, ACQ7),²¹ or a FeNO-based algorithm, which at monthly visits adjusted ICS dose based on FeNO and added LABA when symptoms (ACQ7) remained uncontrolled.²⁰ Cut-points for FeNO which were used for ICS dose reduction (<16 ppb) or increase (>29 ppb) were based on previous studies of pregnant women with asthma²⁰, while the ACQ7 cut-point was the validated score for uncontrolled asthma (>1.5)²¹. Treatment changes occurred monthly, based on the guideline recommendation of monthly review of asthma in pregnant women. Details of this RCT have been described elsewhere.²⁰ Written informed consent was obtained prior to participation and ethics approval was granted by the Hunter New England Health Human Research Ethics Committee (07/02/21/3.06).

Measurements

FeNO was measured according to American Thoracic Society (ATS) criteria²² at a controlled flow rate of 50 ml/s using the Ecomedics chemiluminescence analyser (Ecomedics, Duernten, Switzerland). Lung function was measured using an EasyOne Spirometer (NicheMedical, North Sydney, Australia), and exhaled carbon monoxide (ECO) was measured using a piCO Smokerlyzer Breath CO Monitor (Bedfont, UK).

Perinatal outcomes

Perinatal outcomes including birth weight, gestational age at birth, preterm birth, congenital malformations, mode of delivery, type of caesarean section, pre-eclampsia, gestational diabetes, Apgar score at 5 minutes, neonatal intensive care unit admission and respiratory distress at birth were extracted from the woman's medical records.

Treatment algorithms

Maintenance treatment algorithms were applied at monthly visits during pregnancy from randomisation until delivery, except when women were taking exacerbation treatment.²⁰ Treatment algorithms were applied as follows: Women attended monthly assessments in conjunction with their regular antenatal appointments. FeNO was measured first, followed by ECO and spirometry. The ACQ was completed and ACQ7 calculated. As the study was double blinded, participants, the clinical assessor and the prescribing physicians were unaware of group allocation, and FeNO and ACQ was assessed in all women. Results of the FeNO test, and the ACQ7 score were faxed to a blinded research assistant who applied the appropriate algorithm and sent back a treatment decision. There were eight possible treatment decisions: no change, increase ICS, decrease ICS, increase ICS/LABA, decrease ICS/LABA, increase LABA, decrease LABA and increase ICS/decrease LABA (FeNO algorithm only). Step-down to zero ICS was possible for both algorithms, but in the FeNO algorithm this required women to be eligible for ICS step-down two months in a row, and was not allowed for those on ICS/LABA. To ensure that these treatment decisions were likely to be adopted, free medications, collected from the hospital pharmacy shortly after the appointment, were provided. In addition, telephone follow-ups occurred 2 weeks after each visit and documented

medication adherence, asthma control (ACQ6) and exacerbations requiring medical intervention (hospital admission, emergency department [ED] presentation, course of OCS, or unscheduled doctor visit). Women also attended additional visits at the time of exacerbation.

In this secondary analysis, we determined the proportion of women with each type of ICS or LABA dose change (no change, step-down only, step-up only or both step-up and step-down). Exacerbations requiring medical intervention were assessed within 14 or 30 days of the treatment change, and to the end of the study.

Statistical analysis

Statistical analysis was conducted using GraphPad Prism version 7 (GraphPad Software, Inc, La Jolla, CA) and Stata version 15 (Stata Corp, College Station TX, USA). Results are presented as mean $\pm$ standard deviation (SD) or median (interquartile range, IQR) with Student's t-test or Mann Whitney test, as appropriate. The Chi square test or Fisher's exact test was used to compare proportions. Two-sided tests with $P < 0.05$ were considered significant. P values were adjusted for multiple comparisons where appropriate, using the Bonferroni method.

Results

Baseline characteristics

ICS maintenance treatment was used by 137 women (60 control group, 77 FeNO group) at one or more time points during pregnancy (62.3% of cohort); these women were all followed for at least 4 weeks post-randomisation. Table 1 outlines baseline characteristics showing that women from both arms of the RCT had similar gestational age at recruitment, maternal age, body mass index (BMI), asthma control and lung function ($P > 0.05$). Women in both groups had the same total number of visits during pregnancy (median 6, interquartile range 5-6, $P = 0.72$).

Changes to ICS dose during pregnancy

The majority of women (88.3%) had a change to maintenance ICS therapy during pregnancy (from randomisation to birth, Table 2). Overall, 61% of women decreased ICS dose at some stage during pregnancy, while 63% increased ICS dose at some stage during pregnancy. ICS dose was both increased and decreased in 36.5% (95% CI 29.0-45.0%), whereas 27.0% (95% CI 20.0-35.0%) increased ICS dose only, 24.8% (95% CI 18.0-33.0%) decreased ICS dose only and 11.7% (95% CI 7.0-18.0%) of women had no change to ICS dose during pregnancy. Women in the FeNO group were less likely to have no change to their ICS dose (6.5%, 95% CI 2.8-14.3%) compared to women in the control group (18.3%, 95% CI 10.6-29.9%, $P = 0.032$).

Exacerbations after step-up or step-down in ICS dose

During participation in the RCT, 8.0% of women had an exacerbation within 14 days of ICS dose step-up, while 13.1% had an exacerbation within 14 days of ICS step-down (Figure 1, Table 3, $P > 0.05$). In terms of treatment decisions, there were 122 ICS step-up decisions within the cohort, with 7 subsequent exacerbations and 124 ICS step-down decisions, with 11 subsequent exacerbations (Table 3, $P > 0.05$). Of the 7 exacerbation events following ICS step-up therapy, all occurred ≥ 7 days after dose change, 4 resulted in an unscheduled doctor visit, 2 required OCS treatment, and 1 resulted in a hospital admission. Of the 11 exacerbations following ICS step-down therapy, all occurred ≥ 7 days after dose change, 9 resulted in an unscheduled doctor visit, and 2 required OCS treatment.

Exacerbations after step-up or step-down in ICS dose by management group

We examined exacerbations by management group (Table 4) and found that after ICS step-up, exacerbations within 14 days occurred in 14.7% of those in the control group and 3.8% of the FeNO group ($P=0.067$). Following ICS step-down, there were no statistically significant group differences in the proportion of women having exacerbations within 14 days.

When considering a longer time period, up to 30 days after ICS step-up, 20.6% of women in the control group, and 3.9% of women in the FeNO group had an exacerbation ($P=0.026$, Fisher's exact test).

For ICS step-down, there were no significant group differences in the proportion of women having exacerbations up to 30 days after ICS step-down or by the end of the study (Figure 2).

ICS step-down to zero ICS occurred in 14 women in the control group (23.3%), and of these, 1 had an exacerbation resulting in a GP visit, but this did not occur within 14 days (7.1%, 95% CI 1.3-31.5%). Two women in the FeNO group (2.6%) had ICS stepped down to zero, and neither had an exacerbation within 14 days. ICS step-up within 4 weeks of ICS step-down occurred in 5 participants in the control group (14.7%, 95% CI 6.5-30.1%) and 12 participants in the FeNO group (24%, 95% CI 14.3-37.4%, $P=0.298$).

There were no significant differences in perinatal outcomes for singleton births among women who had any step-down in ICS dose during pregnancy ($n=78$), compared to those without a step-down in ICS dose ($n=50$, Supplement table 1, all $P>0.15$).

Changes to LABA dose during pregnancy

Of those using ICS preventer medication, 79 women (57.7%, 95% CI 49.3-65.6%) used ICS/LABA combination therapy at some time during pregnancy. There was no change to LABA dose during pregnancy in 6.3% (95% CI 2.7-14.0%) of these women, increase(s) only in 32.9% (95% CI 23.6-43.9%), decrease(s) only in 24.1% (95% CI 16.0-34.5%), and both increases and decreases during pregnancy in 36.7% (95% CI 26.9-47.7%) of women. Women randomised to the FeNO group were more likely to step-up in LABA, compared to women in the control group (Table 2).

Exacerbations following changes to LABA dose

There was no significant difference in the proportion of women with exacerbations within 14 days of LABA dose step-up (7.4%) or LABA step-down during pregnancy (14.3%, Figure 3, Table 5).

There were 4 exacerbations within 14 days of LABA dose step-up, out of 71 step-up decisions (Table 5). They were all at least 7 days later, 3 were in the control group and 1 in the FeNO group. Of the 3 exacerbations in the control group, 2 also followed an increase in ICS dose, one was a hospital admission, another a course of OCS and the other an unscheduled GP visit. The exacerbation in the FeNO group followed a decrease ICS/increase LABA treatment decision and resulted in an unscheduled GP visit 7 days later. There were 7 exacerbations following LABA dose step-down, out of 78 decisions (Table 5); all were at least 7 days later, 4 also involved ICS dose decrease, 1 exacerbation was in the FeNO group (14 days later) and 5 resulted in unscheduled doctor visits. The difference between LABA step-up versus step-down was not statistically significant.

Discussion

This study examines for the first time, the consequences of ICS and LABA dose titration during pregnancy for exacerbations. There was no significant difference in the proportion of women having exacerbations following ICS or LABA step-down, compared to ICS or LABA step-up. Exacerbations following ICS or LABA dose step-down were primarily moderate, and occurred at least 7 days after the dose change. Data from the RCT management groups indicated that there was no excess of exacerbations when stepping down ICS dose when FeNO was low (irrespective of symptoms), or when symptoms were controlled. Therefore, these novel data provide reassurance that asthma in pregnancy can be managed using step-up and step-down ICS dose titration, as is also recommended for non-pregnant adults.

This study is the first to examine exacerbation rates following treatment changes during pregnancy. A Finnish study of 55 adults with controlled asthma, showed that exacerbations within 6 weeks occurred in 7% after LABA cessation, 16% after ICS step-down and 46% after ICS cessation.²³ The exacerbation definition differed from that used in our study, being defined by night symptoms, peak flow deviations and bronchodilator use, with all exacerbations managed in the outpatient setting.²³ Predictors of a successful step-down of medication dose were good asthma control (assessed by ACQ6 or ACQ7), and % predicted FEV₁ prior to dose reduction.²³ In our study, dose reduction was only allowed in the control group when asthma was controlled (ACQ7<0.75), while in the FeNO group, dose reduction could occur when FeNO was low, and LABA reduction when symptoms were also controlled²⁰.

A previous study of down-titration of high dose ICS/LABA in 82 adults randomised to receive either ICS alone, or ICS/LABA, found that baseline blood eosinophils were a predictor of failure of ICS dose reduction.²⁴ In another dose reduction study, patients who were able to tolerate ICS cessation for 6 weeks had lower serum eotaxin compared to those who developed severe symptoms.²⁵ These studies suggest that T2 biomarkers are useful predictors of response to ICS step-down, and are consistent with our findings that those managed by a FeNO-guided algorithm had few exacerbations following ICS dose reduction.

There are many variables associated with exacerbation risk in pregnancy, including smoking⁴, asthma severity^{5,26}, ICS use^{15,27} and obesity²⁸. This study only included non-smokers, and the RCT groups were balanced for obesity and other baseline characteristics including maternal age and parity. ICS use was also similar between groups at baseline, with ICS used by 53% of women in the control group, and 40% of women in the FeNO group. By the end of the study all women in this analysis had required ICS during at least one visit, due to either symptoms (control group), or airway inflammation (FeNO group). It was a limitation of our study that the sample size was relatively small (n=137), and conclusions about endpoints such as exacerbations should be interpreted with caution.

Pregnant women with asthma want to be able to minimise the dose of ICS they take, with previous studies finding that cessation of asthma medication use occurs in early pregnancy¹², often without medical advice^{16,17}. A recent systematic review demonstrated that worldwide, around 41% of pregnant women with asthma use ICS²⁹, and non-adherence to ICS medication is high at around 40%^{11,29}. A recent qualitative study of health professionals who provide antenatal care in Australia (midwives and obstetricians) explored the acceptability of FeNO-based management for asthma in pregnancy, and its acceptability to clinicians³⁰. The participants considered FeNO-based management as a useful way to include the woman in her own healthcare, by providing an objective measurement which could help inform her about the need for medication. One obstetrician commented that the process enabled optimised management “without increasing the risks of steroids”³⁰. Pregnant women with asthma also found the approach acceptable, commenting that being “accurately medicated” helped them feel safe³¹. Understanding the implications of step-down treatment on exacerbations is important to both physicians and pregnant women, and this paper addresses the knowledge gap in this area, providing supporting data to inform individualised management of asthma in pregnancy.

In conclusion, this study demonstrated no difference in the rate of exacerbations following ICS step-up or step-down using either a symptoms-based or FENO-based algorithm. The FeNO-based management approach was able to reduce exacerbations while both stepping up and stepping down therapy, and may therefore be a useful strategy in pregnancy where women wish to minimise their ICS dose.

Declaration of Interest

The authors report no conflicts of interest.

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Table 1: Baseline characteristics of women who used ICS in a secondary analysis of an RCT of asthma management during pregnancy

	Control group (n=60)	FeNO group (n=77)	P value
Gestational age (weeks)	15.9 (14.1, 18.1)	16.7 (14.4, 19.1)	0.213
Maternal age (years)	29.2 (5.3)	28.2 (5.2)	0.265
Height (cm)	164 (160, 170)	165 (161, 169)	0.893
Weight (kg)	78.1 (66.1, 88.1)	78.2 (68.0, 89.6)	0.698
BMI (kg/m ²)	28.6 (24.8, 32.4)	27.9 (24.2, 32.6)	0.860
Parity (no.)	1 (0, 1)	1 (0, 1)	0.959
ACQ7 (score range 0-7)	1.3 (0.7, 1.9)	1.1 (0.4, 1.9)	0.227
Uncontrolled asthma (ACQ7>1.5)	21 (35%)	25 (32.5%)	0.756
% Predicted FEV ₁	91.9 (14.3)	92.8 (17.4)	0.742
ICS use at baseline (%Y)	32 (53.3%)	31 (40.3%)	0.128
ICS Dose (BDP equivalents among ICS users) µg/day	800 (400, 1000)	800 (800, 1100)	0.091

Data are presented as mean (SD), median (IQR), or n (%). Abbreviations used: BMI body mass index, ACQ asthma control questionnaire, FEV₁ forced expiratory volume at 1 second, ICS inhaled corticosteroid, BDP beclomethasone dipropionate, SD standard deviation, IQR interquartile range

Table 2: Changes to ICS and LABA dose during pregnancy following group allocation in a secondary analysis of an RCT of asthma management during pregnancy

	Control group (n=60)	FeNO group (n=77)	P value
No change to ICS dose	11 (18.3%)	5 (6.5%)	0.032
ICS step-up only	15 (25%)	22 (28.6%)	0.640
ICS step-down only	15 (25%)	19 (24.7%)	0.965
Both ICS step-up and ICS step-down	19 (31.7%)	31 (40.3%)	0.300
Using ICS/LABA combination	34 (57%)	45 (58%)	0.835
No change to LABA dose	3 (8.8%)	2 (4.4%)	0.647
LABA step-up only	5 (14.7%)	21 (46.7%)	0.003
LABA step-down only	12 (35.3%)	7 (15.6%)	0.042
Both LABA step-up and step-down	14 (41.2%)	15 (33.3%)	0.474

Data are presented as n(%). P Values adjusted for multiple comparisons ($P < 0.0055$ considered significant) – significant values in bold. Abbreviations used: ICS Inhaled corticosteroid, LABA long acting beta agonist

Table 3: Exacerbations after step-up and step-down of ICS dose during pregnancy in a secondary analysis of an RCT of asthma management

	ICS Step-up	ICS Step-down	P value
Number of women	n=87	n=84	
Proportion of women with exacerbations within 14 days of ICS change	8% (4.5%-13.8%)	13.1% (7.5%-22.0%)	0.282
Number of treatment decisions	n=122	n=124	
Proportion of treatment decisions with exacerbations within 14 days	5.7% (2.8%-11.4%)	8.9% (5.0%-15.2%)	0.345

Data are presented as n or % (95% CI). Abbreviations used: ICS inhaled corticosteroid

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Table 4: Exacerbations after step-up or step-down in ICS dose by management group in a secondary analysis of an RCT of asthma management during pregnancy

	ICS Step-up			ICS Step-down		
	Control group	FeNO group	P value	Control group	FeNO group	P value
Number of women	n=34	n=53		n=34	n=50	
Proportion of women with exacerbations within 14 days of ICS change	14.7% (6.5%-30.1%)	3.8% (1.0%-12.8%)	0.067	14.7% (6.5%-30.1%)	12.0% (5.6%-23.8%)	0.718
Proportion of women with exacerbations within 30 days of ICS change	20.6% (10.4%-36.8%)	3.9% (1.1%-13.0%)	0.026	20.6% (10.4%-36.8%)	14.0% (7.0%-26.2%)	0.427
Proportion of women with exacerbations by end of study	26.5% (14.6%-43.1%)	17.3% (9.4%-29.7%)	0.307	26.5% (14.6%-43.1%)	28.0% (17.5%-41.7%)	0.877

Data are presented as n or % (95% CI). Abbreviations used: ICS inhaled corticosteroid

Table 5: Exacerbations following changes to LABA dose during pregnancy in a secondary analysis of an RCT of asthma management

	LABA Step-up	LABA Step-down	P value
Number of women	n=55	n=48	
Proportion of women with exacerbations within 14 days of LABA change	7.4% (2.9%-17.6%)	14.3% (7.1%-26.7%)	0.244
Number of treatment decisions	n=71	n=78	
Proportion of treatment decisions with exacerbations within 14 days of LABA change	5.6% (2.2%-13.6%)	9.0% (4.4%-17.4%)	0.436

Data are presented as n or % (95% CI). Abbreviations used: LABA long acting beta agonist

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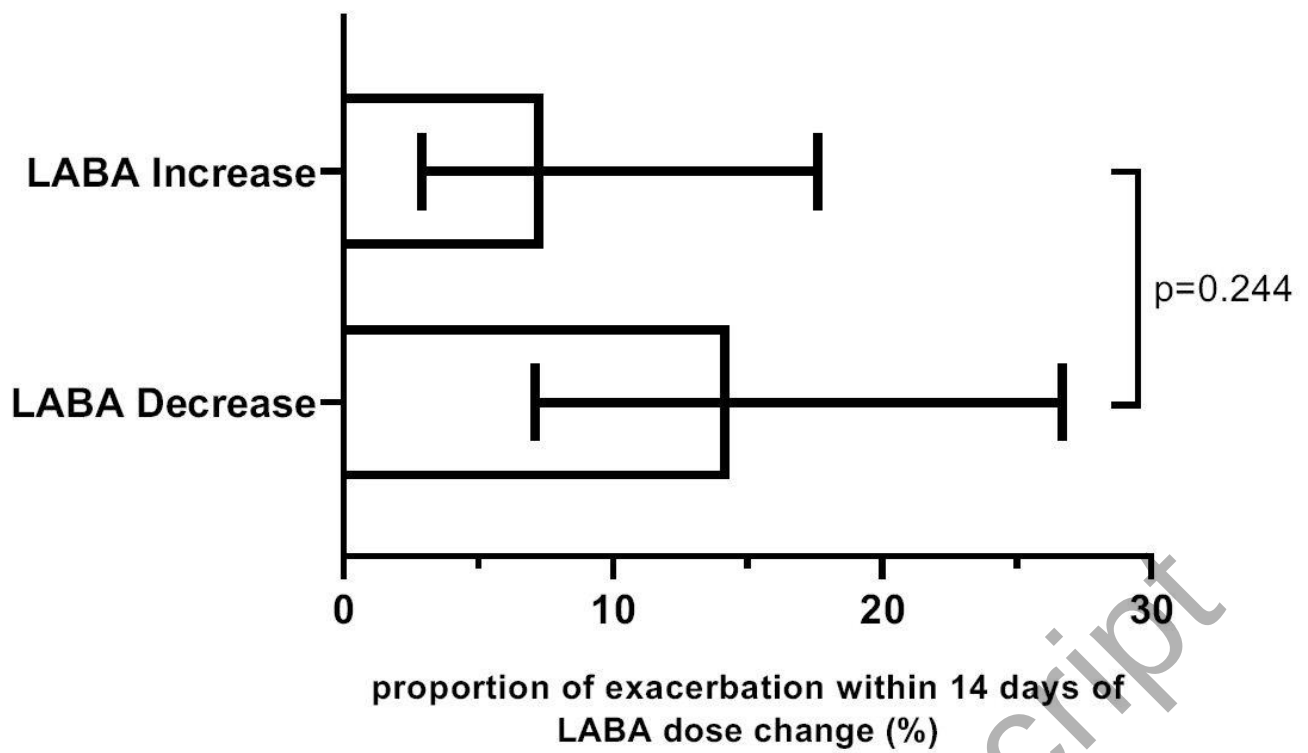


Figure 1: Proportion of women with exacerbations requiring medical intervention within 14 days of ICS dose change

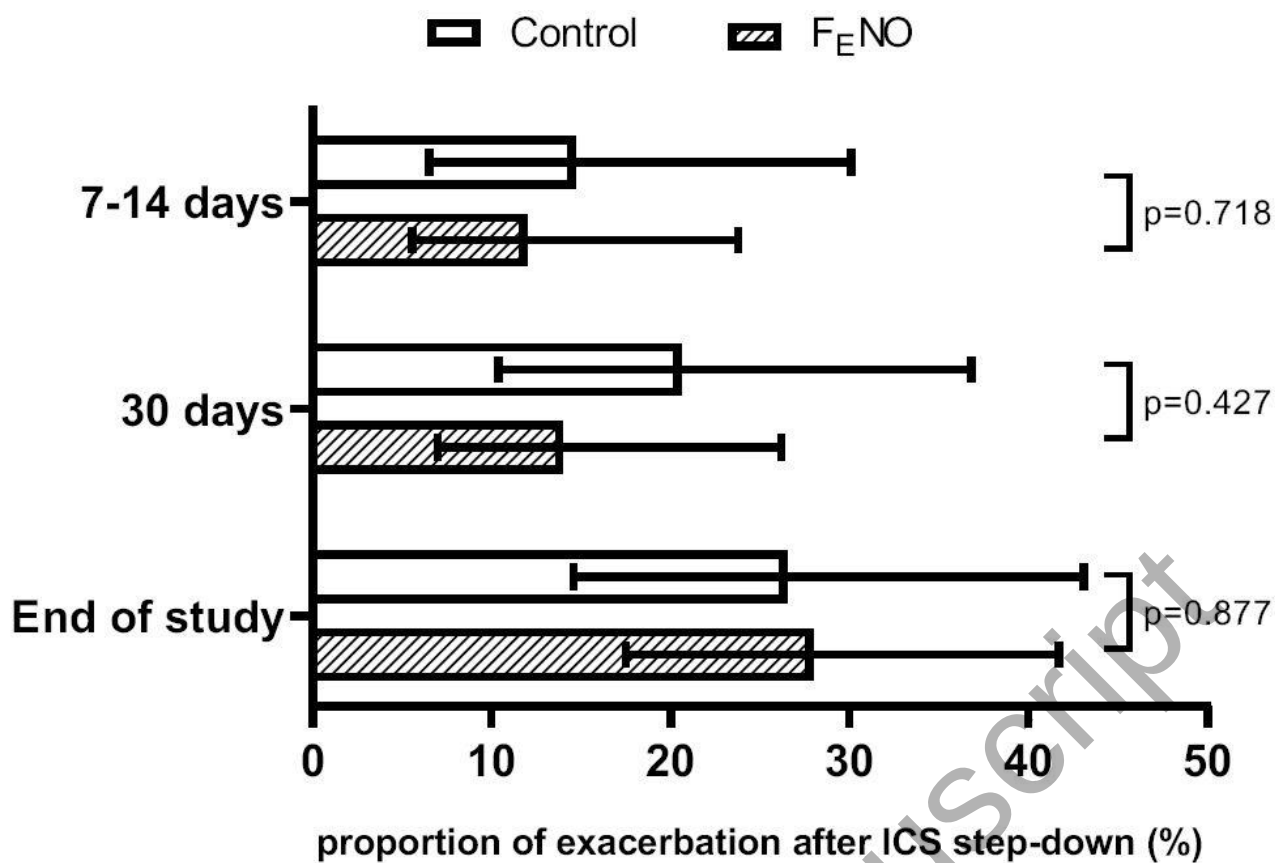


Figure 2. Proportion of women with exacerbations after ICS step-down by asthma management group during pregnancy

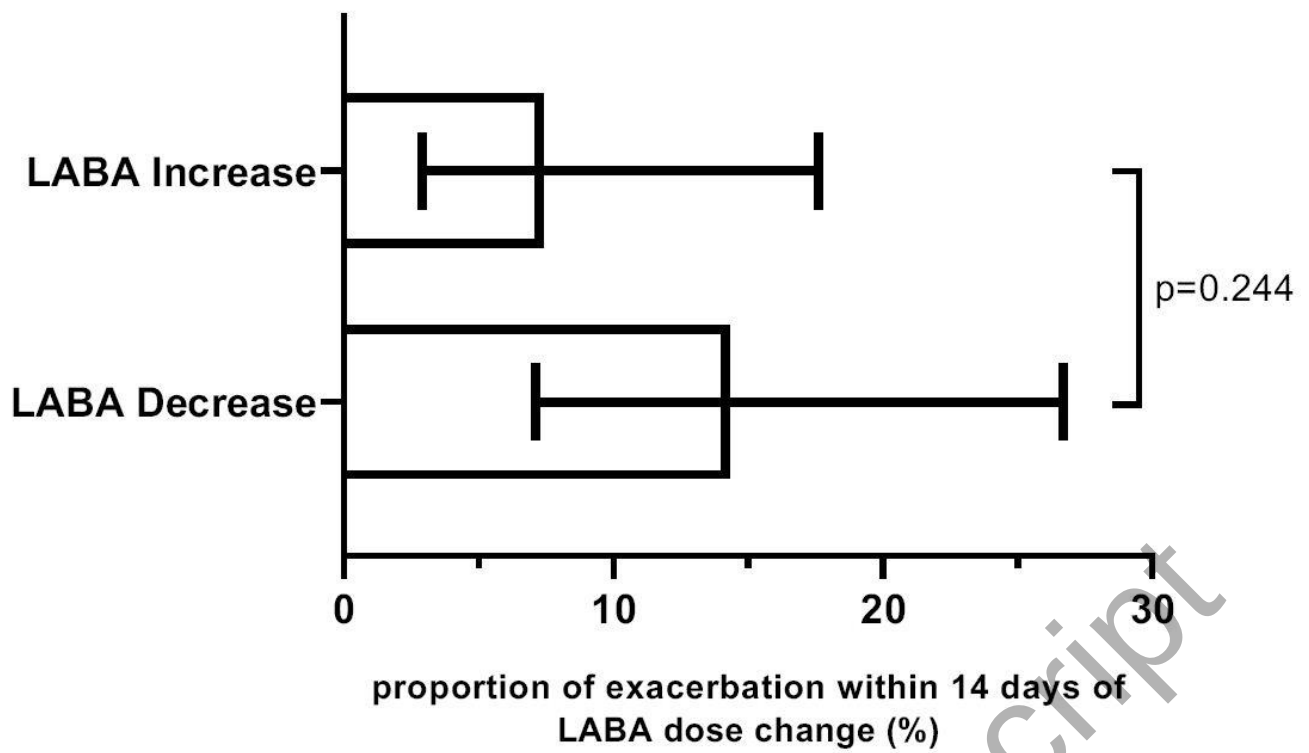


Figure 3. Proportion of women with asthma exacerbations requiring medical intervention within 14 days of LABA dose change during pregnancy