

Original Article

How Maternal BMI Modifies the Impact of Personalized Asthma Management in Pregnancy

Vanessa E. Murphy, BMedChem (Hons), PhD^a, Megan E. Jensen, BNutrDiet (Hons), PhD^a, Annelies L. Robijn, BSc, MSc^a, Thomas K. Wright, BSc (Hons), BMed^b, Joerg Mattes, MD, PhD^{a,c}, Adam Collison, PhD^a, and Peter G. Gibson, MBBS, DMed^{b,d}
 Callaghan and Newcastle, NSW, Australia

What is already known about this topic? Fractional exhaled nitric oxide–based asthma management reduces exacerbations in pregnancy and infant bronchiolitis.

What does this article add to our knowledge? Effects are attenuated among obese mothers and those with excess gestational weight gain.

How does this study impact current management guidelines? Weight management is important for contributing to improved asthma management in pregnancy.

BACKGROUND: Maternal asthma is associated with perinatal complications and respiratory illness in offspring. Obesity increases asthma exacerbation risk in pregnancy and risk of wheeze in offspring.

OBJECTIVES: In this secondary analysis of a randomized controlled trial, we investigated the influence of maternal body mass index, gestational weight gain (GWG), and fractional exhaled nitric oxide (F_ENO)-based management on asthma exacerbations in pregnancy and offspring wheeze.

METHODS: A total of 220 women were randomized to asthma treatment adjustment according to symptoms (control group), or F_ENO and symptoms (F_ENO group). Exacerbations were recorded prospectively. Height and weight were measured at baseline, and in late pregnancy. GWG was categorized according to Institute of Medicine guidelines. A validated parent-completed questionnaire assessed infant wheeze-related outcomes.

RESULTS: F_ENO-based management was associated with a significantly lower incidence rate ratio for maternal exacerbations in nonobese mothers (0.52, 95% confidence

interval [CI], 0.31-0.88, $P = .015$, $n = 129$), and women with GWG within recommendations (0.35, 95% CI, 0.12-0.96, $P = .042$, $n = 43$), but not for obese mothers (0.59, 95% CI, 0.32-1.08, $P = .089$, $n = 88$), or women with excess GWG (0.58, 95% CI, 0.32-1.04, $P = .07$, $n = 104$). Recurrent bronchiolitis occurred in 5.3% ($n = 1$) of infants born to non-overweight mothers, 16.7% ($n = 3$) of infants of overweight mothers, and 21.7% ($n = 5$) of infants of obese mothers in the control group. In the F_ENO group, 2 infants of obese mothers had recurrent bronchiolitis (7.1%, $P = .031$).

CONCLUSIONS: The benefits of F_ENO-based management are attenuated among obese mothers and those with excess GWG, indicating the importance of weight management in contributing to improved asthma management in pregnancy. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;■:■-■)

Key words: Asthma; Pregnancy; Exhaled nitric oxide; Fractional exhaled nitric oxide; F_ENO; Bronchiolitis; Wheeze; Obesity; Maternal BMI

^aPriority Research Centre GrowUpWell™ and Hunter Medical Research Institute, Faculty of Health and Medicine, The University of Newcastle, Callaghan, NSW, Australia

^bPriority Research Centre for Healthy Lungs and Hunter Medical Research Institute, Faculty of Health and Medicine, The University of Newcastle, Callaghan, NSW, Australia

^cDepartment of Paediatric Respiratory and Sleep Medicine, John Hunter Children's Hospital, Newcastle, NSW, Australia

^dDepartment of Respiratory and Sleep Medicine, John Hunter Hospital, Newcastle, NSW, Australia

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Corresponding author: Vanessa E. Murphy, BMedChem (Hons), PhD, Level 2 West, Hunter Medical Research Institute, Lot 1, Kookaburra Circuit, New Lambton Heights, NSW 2310, Australia. E-mail: vanessa.murphy@newcastle.edu.au.

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Abbreviations used

ACQ- Asthma Control Questionnaire
 BMI- Body mass index
 CI- Confidence interval
 ED- Emergency department
 F_ENO- Fractional exhaled nitric oxide
 GIA- Growing Into Asthma
 GWG- Gestational weight gain
 IRR- Incidence rate ratio
 MAP- Managing Asthma in Pregnancy
 OCS- Oral corticosteroids

Asthma is the most common chronic health disorder experienced during pregnancy,¹ affecting 3% to 12% of women.¹⁻³ Maternal asthma is associated with numerous perinatal and neonatal complications,^{4,5} and increases the likelihood that offspring will develop respiratory illnesses such as bronchiolitis⁶ and asthma.⁷ In those who suffer from asthma, 8% to 65% will experience an exacerbation during pregnancy,^{8,9} which is associated with a greater risk of complications such as low birth weight.¹⁰

Obesity increases the risk of asthma exacerbations in pregnancy,^{11,12} and is also an independent risk factor for wheeze and asthma in offspring.¹³ This is of particular concern given that one third of Australian women are overweight, obese, or morbidly obese during pregnancy.¹⁴ Obesity is particularly prevalent in women with asthma, who are more likely to be obese before¹⁵ and during pregnancy¹¹ than women without asthma. Therefore, both asthma and obesity pose significant health risks for women during pregnancy and their offspring, and measures to attenuate these risks need to be assessed.

The fraction of exhaled nitric oxide (F_ENO) is a surrogate marker of IL-13-dependent type 2 airway inflammation, and can be used to guide the treatment of asthma.¹⁶ F_ENO-based management has been shown to reduce maternal exacerbations of asthma during pregnancy,¹⁷ and improve respiratory outcomes of offspring in early life, including lower rates of neonatal hospitalisation,¹⁷ bronchiolitis,¹⁸ and asthma.¹⁹ Some reports suggest that obesity may independently affect F_ENO levels, which suggests that obesity may confound the interpretation of F_ENO and F_ENO-based management. F_ENO levels are reported to be significantly lower in obese asthmatics compared with nonobese asthmatics.²⁰⁻²² However, several studies report no association between obesity and F_ENO.²³⁻²⁶ We therefore questioned whether F_ENO-based management would be effective for obese pregnant women with asthma. We hypothesized that the efficacy of F_ENO-based management of asthma in pregnancy on maternal exacerbations, infant bronchiolitis, and infant health care utilization for wheeze would differ based on maternal body mass index (BMI) category or gestational weight gain (GWG).

Using data from the Managing Asthma in Pregnancy (MAP) study¹⁷ and Growing Into Asthma (GIA) birth cohort,^{18,19} we investigated the influence of maternal BMI and GWG on F_ENO-based asthma management on maternal exacerbations during pregnancy, and wheeze-related outcomes in offspring during the first 12 months of life.

METHODS**Study design and participants**

This is a secondary analysis of data from the MAP study¹⁷ and GIA birth cohort,^{18,19} the methods of which have been published in detail previously. The MAP study was a double-blind, parallel group, randomized controlled trial conducted between June 2007 and December 2010. Women aged over 18 years with doctor-diagnosed asthma, confirmed by a respiratory physician's diagnostic interview, and who required inhaled therapy for asthma in the past year were recruited.¹⁷ The GIA birth cohort was a prospective, double-blind, longitudinal, observational follow-up of the offspring of women enrolled in the MAP study.¹⁸

Ethics statement

All participants gave written informed consent for participation in these studies. The Hunter New England Area Health Service and University of Newcastle Research Human Ethics Committees approved the studies (MAP approval number 07/02/21/3.06, GIA approval number 12/06/20/4.03), and the MAP study was registered with the Australian New Zealand Clinical Trials Registry ACTRN 12607000561482.

Procedures and outcomes of the MAP study

The primary outcome of the MAP study was the total number of asthma exacerbations, defined as events for which the participant sought medical attention (unscheduled doctor visits, presentation to the emergency department [ED], admission to hospital, or use of oral corticosteroids [OCS]).¹⁷ Eligible participants were randomized 1:1 to either the control or intervention group before 22 weeks of gestation. The intervention group was managed with an algorithm that used F_ENO levels as well as clinical symptoms to adjust inhaled corticosteroid and β_2 -agonist therapy, whereas the control group was managed with an algorithm that used clinical symptoms alone. Clinical symptoms were assessed using the Asthma Control Questionnaire (ACQ).²⁷ All exacerbations after randomization were recorded prospectively. Participants had inhaled corticosteroid delivered as a budesonide turbuhaler (AstraZeneca, North Ryde, New South Wales, Australia). Participants were reviewed at monthly antenatal clinics by a research assistant who collected data on clinical symptoms, ACQ score, current treatment, F_ENO levels, and forced expiratory volume in 1 second. Data were sent to a statistician who applied the relevant algorithm before sending the treatment recommendation back to the research assistant to inform the participant. If asthma symptoms remained uncontrolled despite maximum treatment, participants were seen in the antenatal clinic by a respiratory physician who was a member of the study team. Participants were contacted by telephone 2 weeks after each antenatal clinic visit to assess symptoms and exacerbations, and to encourage adherence to the study protocol.

Maternal height and weight were measured at the first visit, and BMI was calculated and categorized as non-overweight (<25 kg/m²), overweight (25-29.9 kg/m²), and obese ($\geq$ 30 kg/m²). GWG was calculated as the average weight gain over the second and third trimester (kg/week) between the first and last study visit. GWG was compared with Institute of Medicine guidelines,²⁸ which recommend that women with a healthy BMI gain up to 0.45 kg/week, overweight women gain up to 0.27 kg/week, and obese women gain up to 0.23 kg/week, and categorized as GWG below or within guideline recommendations, or above guideline recommendations.

TABLE I. Baseline subject characteristics of pregnant women with asthma, by intervention group and maternal BMI

	Control group (C)			F _E NO group (F)			P value
	Non-overweight (n = 29)	Overweight (n = 31)	Obese (n = 46)	Non-overweight (n = 33)	Overweight (n = 36)	Obese (n = 42)	
Demographics							
Maternal age (y)*	29.0 (6.5)	29.2 (5.0)	28.6 (5.4)	26.3 (4.5)	28.6 (5.8)	29.0 (5.0)	.264
Gestational weight gain†	n = 18	n = 22	n = 31	n = 22	n = 20	n = 33	.485
Below/within guideline recommendations	5 (28%)	5 (23%)	12 (39%)	6 (27%)	3 (15%)	12 (36%)	
Above guideline recommendations	13 (72%)	17 (77%)	19 (61%)	16 (73%)	17 (85%)	21 (64%)	
Exsmoker‡	10 (38%)	8 (32%)	22 (49%)	10 (30%)	16 (46%) n = 35	15 (38%) n = 40	.601
Pack years§	3.0 [1.1, 8.0]	5.3 [3.5, 13.9]	2.1 [1.0, 6.0]	2.9 [2.0, 5.0]	2.5 [1.0, 7.0]	3.3 [1.0, 5.5]	.642
Gestational age (wk) at randomization§	20 [18, 21]	20 [19, 21]	20 [19, 21]	20 [19, 21]	20 [18, 22]	21 [19, 22]	.767
Parity§	0 [0, 1]	1 [0, 1]	1 [0, 2]	0 [0, 1]	1 [0, 1]	1 [0, 2]	<.001
Australian born‡	25 (89%) n = 28	28 (97%) n = 29	39 (89%) n = 44	27 (87%) n = 31	31 (94%) n = 33	38 (97%) n = 39	.470
Employed†	24 (86%)	22 (76%)	26 (59%)	18 (58%)	22 (67%)	16 (41%)	.004
Atopy‡	19 (76%) n = 25	25 (81%)	31 (74%)	26 (79%)	23 (72%) n = 32	30 (75%) n = 40	.971
Asthma history (past 2 y)*							n = 41
Hospitalizations for asthma (per person)	0.10 (0.41)	0.06 (0.36)	0.04 (0.21)	0.09 (0.52)	0	0	.598
Emergency department visits (per person)	0.17 (0.60)	0.32 (0.70)	0.13 (0.40)	0.52 (1.80)	0.06 (0.23)	0.12 (0.64)	.244
OCS courses (per person)	0.24 (0.58)	0.65 (1.11)	0.43 (1.33)	0.36 (0.78)	0.11 (0.32)	0.37 (0.83)	.270
Lung function*							
FEV ₁ % predicted	95.4 (14.7)	92.4 (13.7)	97.1 (14.8)	92.5 (12.8)	94.6 (15.0)	96.5 (11.6)	.579
FVC % predicted	104.7 [93.4, 113.6]	101.4 [95.5, 110.0]	105 [94.2, 112.8]	103.4 [92.0, 114.0]	106.0 [97.2, 113.0]	103.8 [97.2, 115.9]	.918
FEV ₁ :FVC	0.83 [0.76, 0.87]	0.81 [0.74, 0.83]	0.82 [0.75, 0.85]	0.75 [0.71, 0.84]	0.78 [0.73, 0.83]	0.81 [0.76, 0.85]	.239
F _E NO (ppb)§	15.0 [9.1, 33.0] 28	16.6 [9.1, 37.7]	13.4 [7.8, 26.1]	19.1 [7.2, 34.3]	20.3 [6.3, 53.5] 35	14.8 [6.0, 26.9]	.837
Asthma medication							
β ₂ -Agonist use (d/wk) n§	0 [0, 6] n = 28	2 [0, 7] n = 30	2 [0, 7] n = 44	1 [0, 3]	1 [0, 7] n = 31	0 [0, 3] n = 40	.292
ICS use†	8 (28%)	11 (35%)	15 (33%)	6 (18%)	9 (25%)	16 (38%)	.465
ICS dose (beclomethasone dipropionate equivalent) among users (μg/d)§	650 [450, 800]	800 [400, 1600]	800 [40, 2000]	800 [500, 1000]	1000 [800, 1000]	900 [800, 1400]	.448
Quality of life§							
	n = 28	n = 30	n = 45	n = 32	n = 34	n = 40	
SF-12 Physical¶	52.9 [40.7, 55.6]	46.3 [40.4, 53.6]	49.1 [43.4, 52.3]	49.3 [43.5, 54.8]	49.6 [45.9, 52.8]	49.0 [41.5, 51.8]	.173
SF-12 Mental¶	53.5 [46.0, 57.9]	49.5 [42.8, 56.2]	55.0 [49.1, 58.7]	55.2 [48.4, 57.8]	56.3 [54.9, 57.9]	56.4 [44.9, 59.9]	.114
AQLQ-total#	0.8 [0.3, 1.3]	1.3 [0.8, 2.0]	1.0 [0.5, 1.6] n = 42	0.8 [0.5, 1.1] n = 30	0.6 [0.4, 1.4] n = 33	0.9 [0.4, 1.6] n = 38	.103

AQLQ, Asthma Quality of Life Questionnaire; BMI, body mass index; F_ENO, fractional exhaled nitric oxide; FVC, forced vital capacity; ICS, inhaled corticosteroid; OCS, oral corticosteroids; SF-12, 12 item short form survey.

Data are mean (standard deviation), median [interquartile range], or n (%) as appropriate.

Bold indicates statistical significance ($P < .05$).

*Analysis of variance.

† χ^2 test.

‡Fisher exact test.

§Kruskal-Wallis test.

||Control nonoverweight vs F_ENO obese significantly different ($P < .05$).

¶Low = 0, high = 100.

#Good = 0, poor = 10.

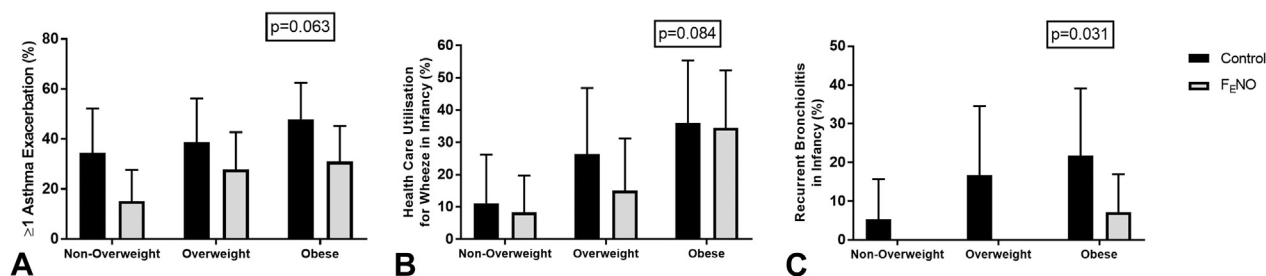


FIGURE 1. The proportion of women with asthma exacerbations (**A**), and children with health care utilization for wheeze in infancy (hospitalization; emergency department visits; unscheduled GP visits; oral corticosteroid use) (**B**) or recurrent bronchiolitis (more than once) in infancy (**C**) born to mothers with non-overweight, overweight, and obese BMIs who were managed throughout pregnancy according to either an F_ENO-based or a symptoms-based (control) algorithm. *BMI*, Body mass index; *F_ENO*, fractional exhaled nitric oxide; *GP*, general practitioner.

Procedures and outcomes of the GIA cohort follow-up

Children, parents/carers, and study personnel who undertook follow-up visits were blinded to the treatment group allocated during pregnancy. When infants were 6 and 12 months of age, the primary carer completed a validated parent-report questionnaire with 50 questions on patterns of wheeze and other respiratory symptoms, respiratory infections, family history of allergic diseases, breastfeeding, immunization, and socioeconomic status.^{29,30} We analyzed data on any health care utilization for wheeze (hospital admission, ED presentation, attending or calling the general practitioner in an emergency, or referral to a consultant), and episodes of infant bronchiolitis (reported as none, once, or more than once), by the maternal intervention group, BMI, and GWG category.

Statistical methods

Data were analyzed on an intention-to-treat basis. Statistical analysis was conducted using Stata version 14 (StataCorp LLC, College Station, Tex). Participants were categorized based on treatment group allocation (F_ENO group or control group), BMI category (non-overweight, overweight, and obese), and GWG category (below/within recommendations or above recommendations). The number of women with at least 1 exacerbation was compared using χ^2 tests with Bonferroni adjusted *P* values for multiple comparisons. The exacerbation rate difference (incidence rate ratio [IRR]) between the treatment groups and the interaction with BMI or excessive GWG was compared with a Poisson regression model, after which the aforementioned *a priori* determined groups were used in the Poisson regression to identify attenuation of the treatment effect. Potential confounders were identified and added to the regression analysis.

Quality-of-life variables as reported in the original randomized controlled trial¹⁷ were analyzed using analysis of covariance with adjustment for baseline values. For other continuous variables, analysis of variance (Tukey-Kramer or Fisher-Hayter pairwise comparison) or Kruskal-Wallis tests were performed as appropriate. Categorical variables were analyzed using χ^2 tests or Fisher's exact test. Multiple comparisons were Bonferroni adjusted. Significance was accepted when *P* < .05.

RESULTS

Effect of maternal BMI category

Table I shows the subject characteristics at baseline, when categorized by intervention group and maternal BMI. Data on BMI were available for 217 women, of whom 62 (29%) were non-overweight, whereas 67 (31%) were overweight and 88 (41%) obese. Groups were balanced regarding maternal age, categorized GWG, smoking status, gestational age at randomization, place of birth, atopy, asthma history and medication, lung function, and quality of life.

The proportion of women with exacerbations during pregnancy was higher in overweight (39%) and obese (48%) women, compared with non-overweight women (34%) in the control group (Figure 1, A; Table II). Similarly, in the F_ENO group, the proportion of women with exacerbations was higher in the overweight (28%) and obese (31%) women compared with non-overweight women (15%, Figure 1, A; Table II; *P* = .067 all 6 groups). The interaction between the treatment group and BMI was not significant (*P* = .419) and remained not significant after adjusting for parity (interaction *P* = .474). The magnitude of the F_ENO-based management effect was summarized as the IRR for maternal exacerbations (adjusted for parity), and greatest in the non-overweight subgroup (IRR = 0.38, 95% confidence interval [CI], 0.14-1.07, *P* = .067, *n* = 62), followed by the overweight subgroup (IRR = 0.48, 95% CI, 0.24-0.99, *P* = .048, *n* = 67) and the obese subgroup (IRR = 0.59, 95% CI, 0.32-1.08, *P* = .089, *n* = 88) (χ^2 for trend *P* = .029). When combined, the IRR for maternal exacerbations was different between management groups for nonobese (non-overweight and overweight) mothers (0.52, 95% CI, 0.31-0.88, *P* = .015, *n* = 129).

Table E1 (available in this article's Online Repository at www.jaci-inpractice.org) outlines perinatal outcomes for the cohort, categorized by the intervention group and maternal BMI. Data were available for 211 children, of whom 60 (28%) were born to mothers who were of non-overweight BMI, 66 (31%) to mothers who were overweight, and 85 (40%) to mothers who were obese. Groups were balanced for infant sex, gestational age at birth, birth length and head circumference, and labor and delivery outcomes. Infants born to mothers in the control group with a non-overweight BMI weighed significantly less at birth (median, 3350 g) compared with infants born to obese mothers in the F_ENO intervention group (median, 3770 g; Table E1,

TABLE II. Efficacy outcomes according to intervention group and maternal BMI in women with asthma followed during pregnancy

	Control group (C)			F _E NO group (F)			P value
	Non-overweight (n = 29)	Overweight (n = 31)	Obese (n = 46)	Non-overweight (n = 33)	Overweight (n = 36)	Obese (n = 42)	
Experienced ≥1 exacerbation during pregnancy*	10 (34%)	12 (39%)	22 (48%)	5 (15%)	10 (28%)	13 (31%)	.067
Exacerbation types,† mean (standard deviation)							
Unscheduled doctor visits	0.37 (0.69)	0.59 (0.98)	0.67 (0.75)	0.17 (0.38)	0.34 (0.55)	0.37 (0.63)	.183
OCS use	0.11 (0.32)	0.45 (1.0)	0.10 (0.30)	0.03 (0.19)	0.17 (0.38)	0.08 (0.27)	.072
Hospitalization	0.07 (0.27)	0	0.02 (0.15)	0	0	0	.098
Emergency department (ED) presentation	0.04 (0.19)	0	0.02 (0.15)	0	0.03 (0.19)	0.05 (0.23)	.433
Quality of life‡	n = 26	n = 29	n = 38	n = 28	n = 28	n = 36	
SF12-Physical§	50.9 [40.4, 54.7]	45.6 [35.5, 49.0]	46.1 [37.9, 50.7]	46.5 [43.4, 53.0]	48.9 [42.7, 52.2]	44.2 [37.4, 50.5]	.802
SF12-Mental§	55.1 [47.3, 56.4]	53.3 [46.0, 57.8]	54.6 [44.6, 57.5]	55.8 [47.0, 59.2]	57.8 [55.5, 60.2]	56.6 [47.9, 59.3]	.076
AQLQ-M-total	0.63 [0.4, 1.3] n = 25	1.1 [0.5, 1.9] n = 28	1.0 [0.5, 1.6]	0.9 [0.4, 1.4]	0.6 [0.5, 1.0] n = 26	0.9 [0.5, 1.0]	.569
Lung function‡	n = 26	n = 28	n = 41	n = 27	n = 28	n = 38	
FEV ₁ (L)	3.0 (0.4)	3.0 (0.4)	3.1 (0.6)	3.0 (0.5)	3.2 (0.5)	3.0 (0.4)	.706
FEV ₁ % predicted	95.8 (11.7)	93.9 (12.6)	96.2 (14.4)	94.6 (13.7)	96.6 (11.0)	97.7 (11.0) n = 37	.861
FVC (L)	3.7 (0.4)	3.8 (0.5)	3.8 (0.7)	3.8 (0.6)	3.9 (0.5)	3.7 (0.5)	.493
FVC %	103.9 (11.3)	103.1 (13.2)	102.2 (14.2)	104.1 (13.5)	104.8 (11.0)	103.6 (11.0) n = 37	.971
FEV ₁ :FVC	0.80 (0.06)	0.79 (0.04)	0.82 (0.06)	0.79 (0.06)	0.81 (0.07)	0.82 (0.04)	.171
Inflammation							
F _E NO (ppb)¶	12.3 [5.6, 21.8]	14.9 [7.4, 23.8] n = 29	8.6 [5.9, 14.2]	11.5 [5.4, 16.4] n = 29	13.3 [6.5, 23.1] n = 29	10.8 [5.6, 15.6]	.279
Treatment	n = 27	n = 29	n = 42	n = 29	n = 29	n = 38	
β ₂ use past week (d/wk)¶	1 [0, 3] n = 25	1 [0, 3]	1 [0, 5]	1 [0, 3]	1 [0, 5] n = 28	1 [0, 3]	.979
ICS use*	11 (41%)	15 (52%)	19 (45%)	22 (76%)	19 (66%)	27 (71%)	.017#
ICS dose (beclomethasone dipropionate equivalent, ICS users) (μg/d)¶	800 [400, 800]	800 [400, 1600]	800 [400, 1600]	400 [200, 800]	400 [400, 1600]	400 [200, 1600]	.068
ICS/LABA use**	3 (11%)	5 (17%)	9 (21%)	10 (34%)	10 (34%) n = 29	19 (50%)	.006††

AQLQ-M, Asthma Quality of Life Questionnaire — Marks; BMI, body mass index; F_ENO, fractional exhaled nitric oxide; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long acting beta agonist; OCS, oral corticosteroids; SF-12, 12 item short form survey.

Data are mean (standard deviation), median [interquartile range], or n (%) as appropriate.

Bold indicates statistical significance ($P < .05$).

* χ^2 test.

†Poisson regression.

‡Analysis of covariance/analysis of variance.

§Low = 0, high = 100.

||Good = 0, poor = 10.

¶Kruskal-Wallis test.

#No significant subgroups.

**Fisher.

††Control nonoverweight vs F_ENO obese ($P < .01$), control overweight vs F_ENO obese ($P = .03$), control obese vs F_ENO obese ($P = .04$).

TABLE III. Baseline subject characteristics by intervention group and maternal gestational weight gain (GWG), in women with asthma followed during pregnancy

	Control group (C)		F _E NO group (F)		P value
	GWG below/within recommendation (n = 22)	GWG above recommendation (n = 50)	GWG below/within recommendation (n = 21)	GWG above recommendation (n = 54)	
Maternal age (y)*	30.3 (4.6)	27.3 (5.5)	29.8 (5.4)	28.0 (5.2)	.077
Gestational age (wk) at randomization†	20 [19, 21]	20 [18, 21]	20 [18, 21]	20 [19, 21]	.340
BMI category at randomization‡					.577
Non-overweight	5 (23%)	13 (27%)	6 (29%)	16 (30%)	
Overweight	5 (23%)	17 (35%)	3 (14%)	17 (31%)	
Obese	12 (55%)	19 (39%)	12 (57%)	21 (39%)	
Ex-smoker§	9 (43%) n = 21	16 (36%) n = 45	5 (24%)	22 (42%) n = 53	.517
Pack years†	6.0 [2.0, 7.0] n = 9	2.6 [0.4, 4.6] n = 16	1.0 [1.0, 2.0] n = 5	3.0 [1.0, 6.0] n = 22	.198
Parity†	1 [0, 3]	0 [0, 1]	1 [0, 2]	1 [0, 1]	.017
Australian born§	17 (81) n = 21	46 (94) n = 49	13 (76) n = 17	52 (98) n = 53	.008
Employed‡	12 (57) n = 21	39 (80) n = 49	9 (53) n = 17	31 (58) n = 53	.065
Atopy§	17 (85%) n = 20	33 (72%) n = 46	19 (90%)	38 (73%) n = 52	.269
Asthma history in past 2 years*					
Hospitalizations	0.1 (0.5)	0 (0)	0 (0)	0 (0)	.015¶
Emergency department visits	0.3 (0.6)	0.1 (0.5)	0 (0)	0.2 (0.7)	.363
OCS courses	0.7 (1.6)	0.3 (1.0)	0.2 (0.5)	0.3 (0.7)	.259
Lung function*					
FEV ₁ % predicted	90.8 (16.8)	96.0 (14.9)	92.9 (10.3)	95.3 (14.8)	.609
FVC % predicted	99.0 (16.1)	104.8 (14.3)	101.7 (12.5)	106.4 (15.7)	.382
FEV ₁ :FVC	80.2 (6.5)	79.9 (7.5)	79.3 (6.3)	78.4 (8.1)	.686
Airway inflammation					
F _E NO (ppb)†	18.3 [10.9, 34.5]	14.6 [6.7, 31.5] n = 49	15.9 [7.6, 52.8] n = 20	20.5 [7.1, 29.0]	.742
Asthma medication					
β ₂ agonist use (d/wk)†	2 [0, 7] n = 21	0 [0, 7] n = 47	0.5 [0, 4] n = 20	1 [0, 5]	.583
ICS use‡	8 (36%)	14 (28%)	10 (48%)	13 (24%)	.217
ICS dose (beclomethasone dipropionate equivalent) among users (μg/d)†	500 [400, 900]	800 [400, 1000]	900 [800, 1600]	800 [600, 1000]	.281
Quality of life†	n = 22	n = 49	n = 21	n = 52	
SF-12 Physical#	48.6 [34.9, 52.8]	49.3 [44.1]	49.7 [43.9, 54.6]	49.6 [44.7, 53.6]	.721
SF-12 Mental#	52.8 [48.2, 57.9]	52.8 [43.3, 57.9]	55.0 [42.2, 59.3]	55.6 [47.7, 58.3]	.668
AQLQ-total**	1.0 [0.5, 2.0] n = 21	0.9 [0.4, 1.6] n = 48	0.9 [0.19, 1.1] n = 20	0.9 [0.4, 1.6] n = 49	.688

AQLQ, Asthma Quality of Life Questionnaire; BMI, body mass index; F_ENO, fractional exhaled nitric oxide; FVC, forced vital capacity; ICS, inhaled corticosteroid; OCS, oral corticosteroids; SF-12, 12 item short form survey.

Data are mean (standard deviation), median [interquartile range], or n (%) as appropriate.

Bold indicates statistical significance ($P < .05$).

*Analysis of variance.

†Kruskal-Wallis test.

‡ χ^2 test.

§Fisher exact test.

||F_ENO within vs F_ENO above ($P = .0300$).

¶Control within vs control above ($P < .05$) and control within vs F_ENO above ($P < .05$).

#Low = 0, high = 100.

**Good = 0, poor = 10.

available in this article's Online Repository at www.jaci-inpractice.org, $P = .029$).

Health care utilization for wheeze in infancy occurred in 36% of infants of obese mothers in the control group (vs 34% in the F_ENO group), 26% of infants of overweight mothers (vs 15% in the F_ENO group), and 11% of infants of non-overweight mothers (vs 8% in the F_ENO group, $P = .084$ all 6 groups; Figure 1, B). When combined, the proportion of health care utilization for wheeze was 19% for nonobese (non-overweight

and overweight) mothers in the control group (vs 11% in the F_ENO group, $P = .038$ all 4 groups).

Recurrent bronchiolitis (more than once) in infancy was reported for 5% of those of non-overweight mothers, 17% of overweight mothers, and 22% of obese mothers in the control group. Conversely, in the F_ENO group, recurrent bronchiolitis occurred in only 2 infants (7%) of obese mothers ($P = .031$; Figure 1, C). When combined, the proportion of recurrent bronchiolitis was 11% for nonobese (non-overweight and

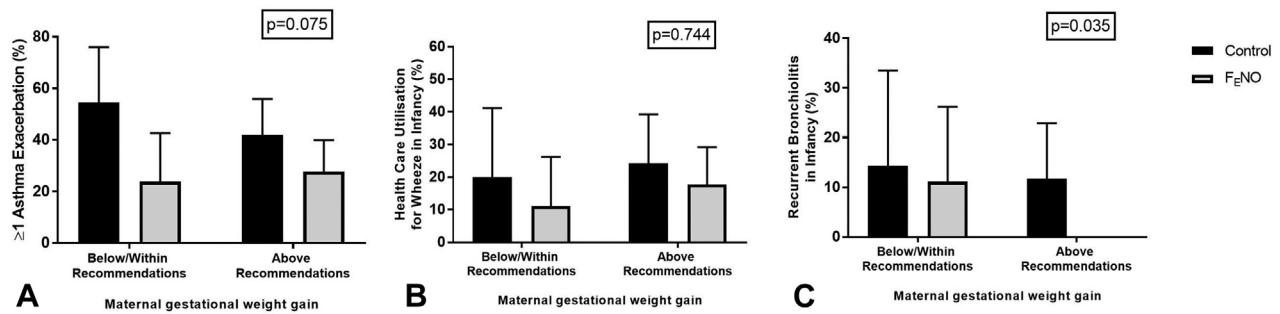


FIGURE 2. The proportion of women with asthma exacerbations (A), and children with health care utilization for wheeze in infancy (hospitalization; emergency department visits; unscheduled GP visits; oral corticosteroid use) (B) or recurrent bronchiolitis (more than once) in infancy (C) born to mothers within and exceeding recommended gestational weight gain limits who were managed throughout pregnancy according to either an F_ENO-based or a symptoms-based (control) algorithm. F_ENO, Fractional exhaled nitric oxide; GP, general practitioner.

overweight) mothers in the control group (vs 0% in the F_ENO group; $P = .008$ all 4 groups).

Effect of maternal GWG

Table III outlines baseline subject characteristics when categorized by the intervention group and maternal GWG. Data were available for 147 women, of whom 43 (29%) were below or within recommended guidelines for GWG, whereas 104 (71%) were above the recommended guideline for GWG. Groups were balanced for maternal age, BMI, smoking history, gestational age at randomization, employment status, atopy, lung function, asthma medication use, and quality of life. A lower proportion of women in the F_ENO group experienced an exacerbation (24% below/within GWG recommendations; 28% above recommendations) compared with the control group (55% below/within GWG recommendations; 42% above recommendations, $P = .072$ all 4 groups) across both GWG categories (Figure 2, A; Table IV). The interaction between treatment groups and excessive GWG was not significant ($P = .215$) and remained not significant after adjustment for hospitalizations in the past 2 years (interaction $P = .389$).

Women in the F_ENO group with GWG below/within recommendations had a significantly lower exacerbation rate compared with the control group (GWG below/within recommendations, IRR 0.35, 95% CI, 0.12-0.96, adjusted for hospitalizations in past 2 years, $P = .042$, $n = 43$). Women in the F_ENO group with GWG above recommendations had a reduction in exacerbation rate compared with the control group with GWG above recommendations, but this failed to reach statistical significance (IRR 0.58, 95% CI, 0.32-1.04, $P = .07$, $n = 104$). Women in the F_ENO intervention group, both those who were below/within or above GWG recommendations, had significantly fewer unscheduled doctor visits than women in the control group who had GWG below/within recommended limits ($P = .003$; Table IV).

Table E2 (available in this article's Online Repository at www.jaci-inpractice.org) outlines perinatal outcomes for the cohort, categorized by the intervention group and maternal GWG. Data were available for 144 children, of whom 41 (28%) were born to mothers below/within the recommended limits for GWG, whereas 103 (72%) were born to mothers above the recommended limit for GWG. Groups were balanced regarding infant

sex, gestational age at birth, birth weight, length and head circumference, labor and delivery outcomes, and maternal and infant complications. There were no significant differences between subgroups.

Health care utilization for wheeze occurred in 20% of infants of mothers with GWG below/within recommendations and 24% of infants of mothers with GWG above recommendations, in the control group (vs 11% and 9%, respectively, in the F_ENO group, $P = .297$ all 4 groups; Figure 2, B).

Recurrent bronchiolitis in infancy was reported for 14% of those in the control group with GWG below/within recommendations, compared with 11% of those in the F_ENO group (GWG below/within recommendations), and in 12% of the control group with GWG above recommendations compared with 0% in the F_ENO group (GWG above recommendations) ($P = .033$ all 4 groups; Figure 2, C).

DISCUSSION

This study examined the effect of maternal BMI and GWG on the efficacy of F_ENO-based management for pregnant women with asthma. The proportion of women who experienced an asthma exacerbation during pregnancy increased with maternal obesity but not with increasing GWG, as previously described.^{11,12} However, this study contributes novel data showing that both obesity and excessive GWG attenuated the beneficial effects of F_ENO-based management on maternal exacerbations. This was demonstrated by a nonsignificant exacerbation rate (IRR) among obese women, and those with excess GWG. For maternal exacerbations, the biggest effects of F_ENO-based management (over symptoms-based management) were demonstrated in mothers with GWG within guideline recommendations (72% decrease), and those who were non-overweight (64% decrease). These effect sizes are greater than the overall effect reported in the original trial (50% decrease in exacerbation rate).¹⁷ This suggests that the optimal efficacy of the F_ENO-based asthma management approach may be achieved among women who are not obese, and who have GWG within recommendations, highlighting the importance of nutritional status in achieving optimal respiratory outcomes in pregnancy.

F_ENO is a marker of eosinophilic and corticosteroid-sensitive airway inflammation, with elevated levels suggesting

TABLE IV. Efficacy outcomes according to intervention group and maternal gestational weight gain (GWG), in women with asthma followed during pregnancy

	Control group (C)		F _E NO group (F)		P value
	GWG below/within recommendation (n = 22)	GWG above recommendation (n = 50)	GWG below/within recommendation (n = 21)	GWG above recommendation (n = 54)	
Experienced ≥ 1 exacerbation during pregnancy*	12 (55%)	21 (42%)	5 (24%)	15 (28%)	.072
Exacerbation types†					
Unscheduled doctor visits	0.82 (1.01)	0.56 (0.76)	0.19 (0.40)	0.33 (0.58)	.003‡
OCS use	0.27 (0.88)	0.16 (0.42)	0.05 (0.22)	0.09 (0.29)	.056
Hospitalization	0.05 (0.21)	0.02 (0.14)	0	0	.184
Emergency department presentation	0.05 (0.21)	0.02 (0.4)	0.05 (0.22)	0.02 (0.14)	.674
Quality of life§	n = 22	n = 47	n = 20	n = 51	
SF12-Physical	45.9 [40.8, 50.9]	47.7 [37.3, 51.7]	43.4 [37.0, 51.8]	47.8 [40.4, 52.5]	.729
SF12-Mental	56.3 [53.5, 57.8]	53.9 [42.8, 57.5]	57.2 [54.0, 59.2]	55.8 [48.5, 59.3]	.953
AQLQM-total¶	0.5 [0.3, 1.0] n = 22	0.9 [0.5, 1.6] n = 46	0.9 [0.4, 1.3]	0.9 [0.4, 1.4] n = 49	.409
Lung function§	n = 21			n = 53	
FEV ₁ (L)	2.9 (0.6)	3.1 (0.4)	2.9 (0.4)	3.1 (0.5)	.138
FEV ₁ %	92.0 (17.6)	96.8 (12.4)	92.9 (9.5)	97.2 (12.5) n = 52	.298
FVC (L)	3.6 (0.7)	3.9 (0.5)	3.6 (0.5)	3.8 (0.5)	.082
FVC %	99.0 (17.2)	104.6 (12.3)	100.8 (9.8)	105.2 (12.3) n = 52	.184
FEV ₁ :FVC	80.7 (5.9)	80.7 (5.9)	80.3 (5.4)	80.5 (5.6)	.996
Airway inflammation					
F _E NO (ppb)#	10.8 [6.6, 22.2]	11.3 [6.7, 17.5]	11.0 [6.0, 15.7]	12.2 [6.0, 19.3]	.949
Treatment					
β_2 use past week (no. of days)#	0 [0, 2] n = 21	1 [0,3]	0 [0, 2]	1 [0,3] n = 53	.374
ICS use*	12 (55%)	21 (42%)	16 (76%)	37 (69%)	.014**
ICS dose (beclomethasone dipropionate equivalent, all women) (μg/d)#	400 [0, 800]	0 [0, 400]	400 [200, 800]	200 [0, 800]	.128
ICS dose (beclomethasone dipropionate equivalent, ICS users) (μg/d)#	800 [600, 1200]	800 [400, 800]	800 [300, 1200]	400 [200, 1600]	.274
ICS/LABA use††	4 (18%)	8 (16%)	7 (33%)	22 (41%)	.025‡‡
Symptom-free days#	7 [5, 7]	5 [1, 7]	7 [5, 7]	6 [4, 7]	.080

AQLQ-M, Asthma Quality of Life Questionnaire — Marks; F_ENO, fractional exhaled nitric oxide; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long acting beta agonist; OCS, oral corticosteroids; SF-12, 12 item short form survey.

Data are mean (standard deviation), median [interquartile range], or n (%) as appropriate.

Bold indicates statistical significance ($P < .05$).

* χ^2 test.

†Poisson regression.

‡Control within vs control above ($P < .01$) and control within vs F_ENO above ($P < .01$).

§ANCOVA/ANOVA.

||Low = 0, high = 100.

¶Good = 0, poor = 10.

#Kruskal-Wallis.

**Control above vs F_ENO within ($P < .05$) and control above vs F_ENO above ($P < .05$).

††Fisher.

‡‡Clinical above vs F_ENO above ($P < .05$).

uncontrolled disease, and can be used to adjust treatment and improve disease outcomes. F_ENO-based management has been shown to reduce maternal asthma exacerbations during pregnancy¹⁷ and improve offspring respiratory outcomes, including lower rates of bronchiolitis in infancy¹⁸ and asthma at preschool age.¹⁹ The relationship between F_ENO (and F_ENO-based management) and obesity, however, remains unclear. Although some studies indicate that obesity is associated with lower F_ENO levels in asthmatic adults²⁰⁻²² and children,^{31,32} others report that there is no association between F_ENO levels and obesity in either adults²³⁻²⁶ or children³³⁻³⁷ with asthma. The picture is even less clear in nonasthmatic subjects, with obesity associated

with a higher F_ENO level,^{24,33-35,38-41} a lower^{36,42} F_ENO level, or no change in F_ENO.^{21,26,43-45} These mixed results may be accounted for by differences in how obesity was classified, as well as by differences in the numerous confounding variables that influence F_ENO levels.^{46,47} Furthermore, asthma is a heterogeneous disease with different pathological phenotypes, including both eosinophilic and noneosinophilic disease.⁴⁸ Consequently, given that F_ENO is a measure of eosinophilic inflammation, some of the variation in the relationship between obesity and F_ENO may also be explained by differences in the proportion of eosinophilic and noneosinophilic (neutrophilic) populations. Given these uncertainties, and the rising prevalence of obesity,

especially in asthma, it is important to determine whether BMI might influence the efficacy of F_ENO-based management for asthma in pregnancy.

Maternal BMI, but not GWG, was associated with a greater risk of asthma exacerbation during pregnancy, regardless of symptom- or F_ENO-based asthma management, which is consistent with previous studies.^{11,12} Although F_ENO-based management reduced asthma exacerbations across all BMI and GWG categories, the effect was attenuated with increasing BMI and increasing GWG. Of interest, we observed an increase in the proportion of infants with recurrent bronchiolitis in parallel with maternal early-pregnancy BMI; yet, F_ENO-based management reduced both health care utilization for wheeze and recurrent bronchiolitis in infancy across all maternal BMI and GWG categories. This may suggest that F_ENO-based asthma management during pregnancy partially mitigates the negative effects of overweight and obesity on both maternal and infant respiratory health. However, although F_ENO-based management remains beneficial, its efficacy appears to be reduced at a higher BMI and with GWG above the recommended limits. To improve the efficacy of this asthma management approach during pregnancy, early nutritional/lifestyle intervention is required to address obesity in early pregnancy and monitor GWG.

Obesity and excess GWG are both associated with an increased risk of a range of antepartum, intrapartum, and postpartum complications for women, in addition to an increased risk of adverse outcomes for their offspring.⁴⁹⁻⁵² Pre-pregnancy weight loss has been shown to reduce the risk of several obesity-related complications such as gestational diabetes⁵³ and neonatal mortality.⁵⁴ Given the results of our study, targeted preconception counseling and the development of a weight loss program for overweight and obese women with asthma may be beneficial in reducing exacerbations during pregnancy and adverse infant outcomes. Our results also highlight the importance of weight management during pregnancy in women with asthma. This is likely to pose a challenge, however, as GWG recommendations are rarely discussed by health care providers,⁵⁵ and changing outcomes has proven difficult even with intensive intervention.^{56,57}

An alternative approach to improving outcomes for pregnant women with asthma may lie in addressing the question of why F_ENO-based management was less effective with maternal obesity or excess GWG. The major change in obesity is an increase in adipose tissue, a recognized endocrine organ, which produces proinflammatory cytokines, or “adipokines,” such as TNF- α and IL-6.⁴⁹ This is largely driven by a shift in adipose tissue macrophages to the proinflammatory M1 phenotype and results in a low-grade systemic inflammatory state.⁴⁹ sCD-163, a marker of macrophage activation, is significantly elevated in obese women with asthma in pregnancy, and, when elevated, is associated with significantly more exacerbations requiring OCS.¹² Elevated sCD-163 has also been associated with worse asthma control in obese girls⁵⁸ and other complications of pregnancy such as gestational diabetes mellitus.⁵⁹ Asthma exacerbations in obese individuals may therefore be driven, or at least contributed to, by systemic inflammation from macrophages in adipose tissue rather than localized eosinophilic inflammation in the lungs. Given that F_ENO is a marker of eosinophilic airway inflammation rather than systemic inflammation, this could explain the lower F_ENO levels observed in obese

asthmatics^{20-22,31,32} and why F_ENO-based management, which alters medication dosing according to F_ENO levels, is less effective with increasing BMI. Monitoring systemic markers of macrophage activation, such as sCD-163, may therefore prove useful in guiding the management of pregnant women with asthma, but further research is needed to determine how this might influence treatment.

A major limitation of this was the small sample sizes within the subgroups, and the lack of a control group of nonasthmatic women where infant outcomes were evaluated. The Breathing for Life Trial, a multicenter, parallel group, randomized controlled trial of F_ENO-based management versus usual care,⁶⁰ is currently underway, and may allow validation of these findings in a larger cohort (1200 pregnant women with asthma).

In summary, this study indicates that although F_ENO-based management remains beneficial in reducing adverse maternal and infant outcomes of asthma, its efficacy is attenuated with increasing BMI and excess GWG. Consequently, if issues of maternal obesity and GWG are addressed both before pregnancy and during pregnancy, maternal and infant respiratory outcomes may be improved. Furthermore, given that monitoring F_ENO, a marker of eosinophilic inflammation, is less effective in obesity, our study supports the notion that asthma exacerbations may, at least in part, be driven by low-grade systemic inflammation.

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TABLE E1. Perinatal outcomes according to intervention group and maternal BMI, in women with asthma followed during pregnancy

	Control group			F _E NO group			P value
	Non-overweight (n = 29)	Overweight (n = 33)	Obese (n = 44)	Non-overweight (n = 31)	Overweight (n = 33)	Obese (n = 41)	
Male infant*	18 (62.0%)	11 (33.3%)	22 (50%)	13 (41.9%)	16 (48.5%)	16 (39.0%)	.354
Gestational age at birth (wk)†	39.6 [38.4, 40.7]	39.9 [37.9, 40.3]	39.6 [38.6, 40.4]	39.6 [38.6, 40.9]	40.3 [38.9, 41.1]	39.6 [39.0, 40.3]	.573
Birth weight (g)†	3350 [2960, 3520]	3475 [2930, 3660] n = 32	3535 [3280, 3980] n = 43	3360 [3040, 3800]	3520 [3020, 3743] n = 32	3770 [3260, 4010]	.029 (control non-overweight vs F _E NO obese)
Birth length (cm)†	50.0 [49.0, 52.0] n = 24	51.5 [49.5, 53.0] n = 25	52.0 [50.0, 53.0] n = 41	51.0 [49.5, 53.0] n = 26	52.0 [51.0, 54.0] n = 31	51.0 [50.0, 53.5] n = 37	.176
Birth head circumference (cm)†	35.0 [33.8, 35.5] n = 28	34.0 [33.0, 35.0] n = 31	35.0 [34.0, 36.0] n = 43	34.6 [34.0, 35.0] n = 30	34.0 [33.0, 35.5] n = 32	35.2 [34.0, 36.0]	.097
Labor type	n = 28	n = 31	n = 44	n = 31	n = 33	n = 40	
Spontaneous*	13 (46%)	18 (58%)	21 (48%)	22 (71%)	22 (67%)	19 (48%)	.168
Induced*	11 (39%)	9 (29%)	13 (30%)	7 (23%)	7 (21%)	13 (33%)	.657
No labor‡	3 (11%)	3 (10%)	8 (18%)	1 (3%)	4 (12%)	7 (18%)	.416
Spontaneous and augmented‡	1 (4%)	1 (3%)	1 (2%)	1 (3%)	0 (0%)	1 (3%)	.948
Delivery type‡							
Vaginal	19 (68%)	21 (68%)	30 (68%)	25 (81%)	28 (85%)	25 (63%)	.258
Forceps	2 (7%)	1 (3%)	4 (9%)	4 (13%)	3 (9%)	2 (5%)	.767
Vacuum	2 (7%)	2 (6%)	0 (0%)	2 (6%)	1 (3%)	0 (0%)	.160
C-section elective	3 (11%)	2 (6%)	8 (18%)	2 (6%)	2 (6%)	8 (20%)	.271
C-section nonelective	4 (14%)	6 (19%)	4 (9%)	2 (6%)	3 (9%)	6 (15%)	.635
Maternal complications‡							
Pre-eclampsia	1 (4%)	1 (3%)	3 (7%)	2 (6%)	0 (0%)	1 (3%)	.727
Gestational diabetes	1 (4%)	4 (13%)	6 (14%)	0 (0%)	1 (3%)	7 (18%)	.046
Hypertension	2 (7%)	3 (10%)	6 (14%)	0 (0%)	0 (0%)	7 (18%)	.022
Postpartum hemorrhage	3 (11%)	0 (0%)	1 (2%)	2 (6%)	1 (3%)	2 (5%)	.415
Premature rupture of membranes	3 (11%)	3 (10%)	2 (5%)	8 (26%)	2 (6%)	2 (5%)	.065
Multiple pregnancy	1 (4%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	.546
Infant complications‡							
Stillbirth	0 (0%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	.726
Preterm delivery	2 (7%)	5 (15%)	2 (5%)	1 (3%)	2 (6%)	3 (7%)	.590

(continued)

TABLE E1. (Continued)

	Control group			F _E NO group			P value
	Non-overweight (n = 29)	Overweight (n = 33)	Obese (n = 44)	Non-overweight (n = 31)	Overweight (n = 33)	Obese (n = 41)	
Intrauterine growth restriction	3 (10%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)	.004
Jaundice	1 (3%)	1 (3%)	1 (2%)	1 (3%)	1 (3%)	1 (2%)	1.000
Neonatal intensive care unit admission	6 (21)	8 (24)	4 (9)	3 (10)	1 (3)	4 (10)	.094

BMI, Body mass index; F_ENO, fractional exhaled nitric oxide.

Data are mean (standard deviation), median [interquartile range], or n (%) as appropriate.

Bold indicates statistical significance ($P < .05$).

* χ^2 test.

†Kruskal-Wallis test.

‡Fisher exact test.

TABLE E2. Perinatal outcomes according to intervention group and maternal gestational weight gain, in women with asthma followed during pregnancy

	Control group		FeNO group		P value
	GWG below/within recommendation (n = 21)	GWG above recommendation (n = 50)	GWG below/within recommendation (n = 20)	GWG above recommendation (n = 53)	
Male infant*	8 (38%)	26 (52%)	6 (30%)	23 (43%)	.317
Gestational age at birth (wk)†	39.0 [38.7, 40.0]	39.7 [38.4, 40.3]	39.6 [38.6, 40.6]	40.0 [39.0, 41.0]	.157
Birth weight (g)‡	3508 [3220, 3805] n = 20	3430 [3000, 3710] n = 48	3525 [3030, 3855]	3520 [3160, 3920]	.615
Birth length (cm)†	51.0 [50.0, 53.5] n = 20	51.5 [49.0, 53.0] n = 40	50.5 [49.0, 52.0] n = 18	51.5 [50.0, 54.0] n = 49	.246
Birth head circumference (cm)†	35.0 [34.0, 36.0] n = 20	34.5 [33.0, 35.5] n = 47	34.6 [34.0, 35.5]	35.0 [34.0, 36.0]	.479
Labor type‡					
Spontaneous	8 (38%)	27 (55%)	9 (45%)	35 (66%)	.119
Induced	5 (24%)	15 (31%)	9 (45%)	10 (19%)	.145
No labor	6 (29%)	6 (12%)	2 (10%)	6 (11%)	.267
Spontaneous and augmented	2 (10%)	1 (2%)	0 (0%)	2 (4%)	.407
Delivery type‡					
Vaginal	10 (48%)	35 (71%)	13 (65%)	40 (75%)	.125
Forceps	0 (0%)	4 (8%)	1 (5%)	5 (9%)	.669
Vacuum	1 (5%)	2 (4%)	1 (5%)	0 (0%)	.324
C-section elective	5 (24%)	6 (12%)	2 (10%)	6 (11%)	.504
C-section nonelective	6 (29%)	6 (12%)	4 (20%)	6 (11%)	.235
Maternal complications‡					
Pre-eclampsia	2 (10%)	1 (2%)	0 (0%)	2 (4%)	.407
Gestational diabetes	2 (10%)	5 (10%)	2 (10%)	3 (6%)	.805
Hypertension	4 (19%)	5 (10%)	2 (10%)	4 (8%)	.527
Postpartum hemorrhage	2 (10%)	1 (2%)	1 (5%)	2 (4%)	.434
Premature rupture of membranes	1 (5%)	5 (10%)	1 (5%)	6 (11%)	.863
Multiple pregnancy	0 (0%)	1 (2%)	0 (0%)	0 (0%)	.629
Infant complications‡					
Stillbirth	0 (0%)	0 (0%)	0 (0%)	1 (2%)	1.000
Preterm delivery	1 (5%)	5 (10%)	1 (5%)	1 (2%)	.301
IUGR	0 (0%)	2 (4%)	1 (5%)	0 (0%)	.334
Jaundice	1 (5%)	2 (4%)	1 (5%)	2 (4%)	1.000
Neonatal intensive care unit admission	2 (10%)	9 (18%)	1 (5%)	3 (6%)	.208

FeNO, Fractional exhaled nitric oxide; GWG, gestational weight gain; IUGR, intrauterine growth restriction.

Data are mean (standard deviation), median [interquartile range], or n (%) as appropriate.

* χ^2 test.

†Kruskal-Wallis test.

‡Fisher exact test.