Original Article

Influence of Maternal Body Mass Index and Macrophage Activation on Asthma Exacerbations in Pregnancy

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What is already known about this topic? Obesity is a risk factor for exacerbations of asthma.

What does this article add to our knowledge? Maternal overweight/obesity and systemic macrophage activation increase exacerbation risk for asthma during pregnancy.

How does this study impact current management guidelines? This study highlights the potential importance of pre-pregnancy weight reduction for improving asthma outcomes, as well as perinatal outcomes, during pregnancy.

BACKGROUND: Obesity is a risk factor for exacerbations of asthma, but the mechanisms of this effect in pregnancy are unknown.
OBJECTIVE: This study determined the influence of maternal body mass index, gestational weight gain, eosinophilic inflammation, and systemic macrophage activation on the risk of exacerbations during pregnancy.
METHODS: Women with asthma (n = 164) participated in the study. Body mass index recorded at baseline (17 weeks gestation) was categorized as healthy weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), or obese (>30 kg/m^2). Exacerbations requiring medical intervention were recorded prospectively. Asthma control, medication use, and fractional exhaled nitric oxide were assessed monthly; additional visits occurred during exacerbations. Peripheral blood was collected at baseline for the measurement of eosinophils, soluble CD-163, C-reactive protein, and IL-6.
RESULTS: Exacerbations occurred in a higher proportion of overweight (51.1%) and obese (48.4%) women compared with healthy weight women (25%; $P = .026$). Excess weight gain during pregnancy was not associated with exacerbation risk. Macrophage activation (elevated serum soluble CD-163) was associated with exacerbations requiring oral corticosteroids ($P = .043$), whereas high peripheral blood eosinophils or fractional exhaled nitric oxide were not associated with exacerbation or oral corticosteroid use.
CONCLUSIONS: Being overweight or obese confers a greater risk of asthma exacerbation during pregnancy, and may be due to systemic macrophage activation. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: *Asthma; Pregnancy; Exacerbation; Macrophage; CD163; Inflammation; Eosinophil; Exhaled nitric oxide*

Asthma affects 8% to 12% of pregnant women worldwide,[1,2] and up to 45% of these women have exacerbations requiring medical intervention during pregnancy.[3] Asthma contributes to an increased risk of poor perinatal outcomes including preterm birth,[4] and neonatal hospitalizations,[5] with some outcomes, such as low birth weight, linked to exacerbations.[6] Obesity is now known to adversely impact asthma.[7] In pregnancy, obesity can occur as a preexisting condition (elevated body mass index [BMI]) or because of excessive gestational weight gain (GWG).

The prevalence of overweight and obesity among pregnant women has greatly increased in recent years.[8] Only 1 previous study has examined the relationship between maternal obesity and asthma exacerbations in pregnancy.[9] Hendler et al[9] studied a cohort of American women with asthma from 1994 to 1999 and found that obese women with a pre-pregnancy BMI of 30 kg/m^2 or more were 30% more likely to have an exacerbation requiring medical intervention during pregnancy than women who were nonobese (adjusted odds ratio, 1.3; 95% CI, 1.1-1.7).[9] However,

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Project grant funding was provided by the National Health and Medical Research Council (NHMRC, project grant ID 455593). V.E.M. was the recipient of an Australian Research Training Fellowship (part-time, grant ID 455626) and Career Development Fellowship from the NHMRC (grant ID 1084816). P.G.G. was the recipient of a Practitioner Fellowship from the NHMRC.
Conflicts of interest: V. E. Murphy has received research support from the National Health and Medical Research Council and is employed by and has received travel support from the University of Newcastle. P. G. Gibson has received lecture fees from AstraZeneca and GlaxoSmithKline. The rest of the authors declare that they have no relevant conflicts of interest.
Received for publication October 27, 2016; revised March 13, 2017; accepted for publication March 31, 2017.
Available online ■■
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2213-2198

http://dx.doi.org/10.1016/j.jaip.2017.03.040

Abbreviations used
BMI- Body mass index
CRP- C-reactive protein
FENO- Fractional exhaled nitric oxide
GWG- Gestational weight gain
ICS- Inhaled corticosteroid
OCS- Oral corticosteroid
sCD-163- Soluble CD-163

the mechanisms involved in this association have not been explored.

Inflammation has been proposed as a key mediator of adverse pregnancy outcomes associated with obesity.[10] Inflammation in asthma is often associated with allergen-driven eosinophilic airway inflammation. However, obesity itself is a proinflammatory state where macrophages in adipose tissue are increased and exhibit an activated proinflammatory (M1) phenotype that results in secretion of cytokines such as IL-6 and TNF-α.[10] IL-6 leads to increased liver production of C-reactive protein (CRP), which is a typical feature of systemic inflammation in obesity. Toll-like receptor activation by fatty acids induces cleavage of the macrophage surface marker CD-163, which results in increased circulating soluble CD-163 (sCD-163), a marker of macrophage activation.[11] In addition, macrophages have an important role in the placenta, with significantly more placental macrophages in obese compared with nonobese women, accompanied by increased expression of proinflammatory cytokines including IL-6, and higher gene expression of macrophage markers including CD-68.[12]

This study tested the hypothesis that the risk of asthma exacerbation would be greater among overweight or obese pregnant women compared with healthy weight women, and that exacerbations would be driven by systemic inflammation rather than eosinophilic airway inflammation.

METHODS

This is a secondary analysis of pregnant women with physician-diagnosed asthma, recruited from the John Hunter Hospital antenatal clinics, between April 2007 and November 2009, to a prospective study of exacerbations of asthma during pregnancy.[13] Concurrently, some women also participated in a randomized controlled trial (the Managing Asthma in Pregnancy Study, Australian and New Zealand Clinical Trials Registry: 12607000561482) in which women in the control group had their asthma treatment adjusted monthly according to symptoms and lung function, whereas women in the intervention group had their asthma treatment adjusted monthly according to fractional exhaled nitric oxide (FENO) as well as symptoms and lung function.[14] Inclusion and exclusion criteria were given in detail in previous publications[13,14]; women with preexisting diabetes or hypertension were not excluded. Ethics approval was provided by the Hunter New England Area Health Service and the University of Newcastle Research Ethics Committees and women provided written informed consent for participation.

Data were included from all women who had height and weight measurements made at the baseline study visit, with a BMI of 18.5 kg/m^2 or more. Women with an early pregnancy BMI from 18.5 to 24.9 kg/m^2 were considered healthy weight, those with a BMI of 25 to 29.9 kg/m^2 were considered overweight, and those with a BMI of 30 kg/m^2 or more were considered obese, according to the Institute of Medicine guidelines.[15]

GWG was calculated as the average weight gain (kg/wk) over the second and third trimesters (from study recruitment to the final visit) and compared with Institute of Medicine guidelines for rate of weight gain in pregnancy. These guidelines recommend that women with a BMI in the healthy weight range gain 0.45 kg body weight per week in the second and third trimesters (total weight gain, 11.3-15.9 kg), while those who are overweight and obese have a recommended weight gain of 0.27 kg/wk (total weight gain, 6.8-11.3 kg) and 0.23 kg/wk (total weight gain, 5.0-9.7 kg), respectively.[15]

This study involved monthly clinical visits, phone calls between visits (every 14 days), and additional visits during asthma exacerbations. Exacerbations requiring medical intervention were recorded prospectively and defined as hospitalization, emergency department presentation, unscheduled doctor visit, and/or a prescribed course of oral corticosteroids (OCSs). Exacerbations that occurred at least 14 days apart were considered separate events. Each month, and during asthma exacerbations, asthma control was assessed using the validated Asthma Control Questionnaire (ACQ-7)[16]; lung function was measured by spirometry (EasyOne Spirometer, NicheMedical, North Sydney, Australia); and inhaled corticosteroid (ICS) use was assessed by direct questioning of prescribed dose and adherence. Smoking was assessed by self-report, and confirmed by urinary cotinine at visit 1 or 2 (≥level 5 or 2840 nmol/L, Nicalert, NYMOX, Saint-Laurent, Quebec, Canada), and exhaled carbon monoxide measurements (≥10 ppm, piCO Smokerlyzer Breath CO Monitor, Bedfont, UK) at monthly visits. Perinatal outcomes were extracted from medical records after delivery.

The inflammatory profile was assessed using FENO; it was assessed using the Ecomedics chemiluminescence analyzer (Ecomedics, Duernten, Switzerland), at a controlled flow rate of 50 mL/s, and serum measurements. Blood samples were collected via venepuncture at baseline (early second trimester) and tested for sCD-163 (Trillium Diagnostics, IQ Products, Groningen, The Netherlands), IL-6 (high sensitivity ELISA, R&D Systems, Minneapolis, Minn), and CRP (high sensitivity ELISA, MP Biomedicals, Solon, Ohio) using ELISA. Peripheral blood eosinophil counts were measured by Hunter Area Pathology Service (Newcastle, NSW, Australia) using an automated analyzer (Beckman Coulter LH780, Miami, Fla). The baseline sample was used to assess atopy as previously described.[14] Subjects were considered atopic if the specific serum IgE to aeroallergen was 0.35 kUA/L or more.

Statistical analysis was performed using Stata 11 (StataCorp, College Station, Texas) and GraphPad Prism 6 (GraphPad Software, Inc, La Jolla, Calif). Results are presented as mean ± SD or median (interquartile range) with Student *t* test or Mann-Whitney test, and ANOVA or Kruskal-Wallis test applied as appropriate. The STATA kwallis2 test was used to test for post hoc significance.[17] The chi-square test was used to compare proportions. Two-sided tests with $P < .05$ were considered significant.

RESULTS

One hundred sixty-eight pregnant women with asthma were recruited to the primary study. Three women were excluded from the secondary analysis because they were underweight (BMI < 18.5 kg/m^2), and 1 woman was excluded because of a missing baseline weight measurement. Of the 164 women remaining, 45 were healthy weight (27.4%), 53 were overweight (32.3%), and 66 were obese (40.2%). Most subjects were also