Published in final edited form as:

J Asthma. 2010 March ; 47(2): 145–149. doi:10.3109/02770900903483774.

Influence of Maternal Asthma and Asthma Severity on Newborn Morphometry

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This work has been presented at the 25th Annual Meeting of the Society for Maternal-Fetal Medicine, February 7-12, 2005, Reno, Nevada, USA.

DECLARATION OF INTEREST

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

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Abstract

Objective—To determine if maternal asthma or asthma severity affects newborn morphometry.

Study Design—A secondary analysis was performed on data collected in a multicenter prospective observational cohort study of asthma in pregnancy. Patients enrolled included women with asthma stratified by severity of disease and controls. Asthma severity was defined according to the classification proposed by the National Asthma Education Program (NAEP) Report of the Working Group on Asthma and Pregnancy, modified to include medication requirements. Newborn morphometry measurements included birth weight (BW) and multiples of the median birth weight (BW-MOM), head circumference (HC), length (L), HC:BW ratio, and ponderal index (PI).

Results—Of 2480 patients there were 828 nonasthmatic controls, 828 with mild, 775 with moderate, and 49 with severe disease. Comparing all groups, there were statistically significant differences in maternal age ($p < .001$), race ($p = .005$), parity ($p = .006$), prepregnancy weight ($p = .028$), and medical care source ($p = .001$), with the severe asthma group having the highest mean maternal age (25.7 years), and proportion of African Americans (71.4%), proportion of multiparous patients (63.3%), and proportion of patients receiving government assistance (85.7%). When the control group was excluded from the comparisons, differences in prepregnancy weight and medical care source were no longer significant. BW-MOM and L did not differ between groups. The HC:BW ratio increased with asthma severity ($p = .029$) and was increased compared to controls ($p = .010$). This remained significant after controlling for confounding variables (both $p < .001$). HC was statistically significantly different between all groups ($p = .032$), as well as among women with varying degrees of asthma severity ($p = .013$), which was not clinically significant. After covariates adjustment, HC was not significantly different among all groups ($p = .228$), nor the asthma groups ($p = .144$).

Conclusion—Asthma severity is associated with an increased HC:BW ratio. Severity was not found to impact HC, BW-MOM, L, or PI independently. However, the magnitudes of the effects were too small to suggest a clinically significant effect of asthma on neonatal morphometry in this large prospectively studied sample.

Keywords

asthma; neonatal morphometry; pregnancy

INTRODUCTION

Asthma is a common medical complication of pregnancy, affecting approximately 6% of pregnant women (1). Previous studies have found inconsistent effects of asthma on birth weight. In some reports, maternal asthma increased the risk for low-birth-weight (LBW;

birthweight < 2500 g) and small-for-gestational-age (SGA; birthweight <10th% for gestational age) neonates compared to controls (2–4), whereas others found no such differences between these groups (1, 5). Attempts have also been made to differentiate neonatal outcomes as they relate to maternal disease based on medication usage (1, 2, 5). Whether or not differences in newborn morphometry can be attributed to differences in disease severity has not been thoroughly investigated until recently. The Maternal-Fetal Medicine Units (MFMU) multicenter study found that infants born to mothers with severe asthma tended to be SGA, but this was not statistically significant (6). If the trend towards SGA infants in women with more severe disease is presumed to be secondary to disease status, one possibility is that women with severe asthma may have more poorly controlled disease and more frequent episodes of decompensation and hypoxia.

Pregnant women living at high altitudes have been studied to determine the effects of maternal-fetal hypoxia during pregnancy. Their newborns have lower birth weights (BW) (7–9) and an increased head circumference (HC):birth weight (HC:BW) ratios (10). Fetal growth surveillance in pregnant women living at high altitude showed a greater reduction in abdominal circumference (AC) than in HC, suggesting an asymmetric-type of growth impairment (11). Using neonatal morphometric measurements applied to high-altitude populations as a model for in utero hypoxia in women with asthma, we can apply this methodology to determine the effects of asthma severity. The degree of hypoxia is presumed to be dependent upon the severity of asthma. The purpose of this study was to determine if differences in the BW, HC, length (L), head circumference:birthweight (HC:BW) ratio, multiples of the median birth weight (BW-MOM), and ponderal index (PI; birth weight/length³) exist among women with asthma, and whether these differences are associated with disease severity.

MATERIAL AND METHODS

Secondary analysis was performed on data collected from 16 university hospital centers participating in a prospective, observational cohort study of asthma in pregnancy conducted by the MFMU Network sponsored by the National Institute of Child and Human Development (NICHD) and the National Heart, Lung, and Blood Institute (NHLBI) between December 1994 and March 1999. Obstetric patients were questioned about ever having physician-diagnosed asthma as entrance criteria. Written informed consent was obtained from all participants. Local Institutional Review Board approval was received for the secondary analysis.

Exclusion criteria included intrauterine fetal demise, known multiple gestation, major congenital abnormalities, active pulmonary disease other than asthma, inability to schedule an ultrasound for gestational age confirmation, gestational age of or greater than 26 weeks at intake, or participation in the asthma randomized clinical trial or other interventional studies. Exclusion criteria for the control group also included any prior physician diagnosis of asthma.

In the primary study, demographic, social, and medical information was collected, including age, ethnicity, smoking status (defined as any within the preceding week), prepregnancy

weight, miscarriage/abortion, history of preterm delivery, insurance type, education, marital status, and chronic hypertension (defined as systolic blood pressure more than 140 mm Hg or diastolic blood pressure more than 90 mm Hg on at least two occasions 4 or more hours apart when not pregnant or less than 20 weeks of gestation, or if the patient was on an antihypertensive medication when not pregnant or at less than 20 weeks of gestation). In this secondary analysis, factors that might impact intrauterine growth and neonatal morphometry were considered. These included maternal age, parity, race, smoking status, prepregnancy weight, and insurance type as a measure of socioeconomic status.

Maternal asthma severity was determined at the time of enrollment into the study. Classification of asthma severity was based on the National Asthma Education Program (NAEP) Report of the Working Group on Asthma and Pregnancy, modified to include medication use (Table 1) (12, 13). Daily medication was defined as at least one of the following: 2 puffs per day of inhaled β -agonist, cromolyn, nedocromil, or inhaled steroids, or at least 4 puffs per day of inhaled ipratropium, or at least 1 dose per day of theophylline. Using daily or every other day oral corticosteroids for at least 4 weeks prior to study entry was considered regular use.

Neonatal measurements were abstracted from the newborn record by trained research personnel. The measurements included in this analysis were HC, L, HC:BW ratio, PI (birth weight/length³), and BW expressed as multiples of the median based on growth references previously reported (14).

The Biostatistics Center of George Washington University maintained and analyzed data using SAS 8.2 (SAS Institute, Cary, NC) statistical software. The Kruskal–Wallis test was used for continuous variables and Chi-Square test was used for discrete variables. Multivariate linear model was used to control for confounding demographic variables with regards to neonatal morphometry and the p values for group effect were calculated based on the type III sum of squares. Data were analyzed within the asthma group across severity, as well as across the severity within the asthma group compared to controls. Significance was defined at $p < .05$.

RESULTS

In the primary study there were 881 nonasthmatic controls, 873 patients with mild asthma, 814 with moderate asthma, and 52 with severe asthma (6). For this secondary analysis, neonates with missing morphometric measurements were not included. Therefore, this analysis included 2480 patients of whom 828 were nonasthmatic controls, and the asthmatic cohort included 828 with mild, 775 with moderate, and 49 with severe disease, respectively.

Maternal demographics are presented in Table 2. In the asthma group, maternal age increased with increasing disease severity ($p < .001$), and as a group, those with asthma were older than the controls ($p < .001$). A larger proportion of women with severe asthma were African American, both within the asthma study group ($p = .003$) and compared to controls ($p = .005$). More women with severe asthma were multiparous, both among the asthma groups and among all groups ($p = .045$ and $.006$, respectively). Comparing all groups, women in the control group had the lowest prepregnancy weights ($p = .028$). However, there

was no difference in prepregnancy weight among the women with asthma ($p = .383$). Government assistance was the most common source of health care insurance in asthmatic participants compared to controls ($p = .001$), but this did not vary with disease severity ($p = .056$). The rate of smoking was similar among women with asthma ($p = .491$) and as compared to controls ($p = .682$).

Neonatal morphometry is presented in Table 3. There was no statistically significant difference in the multiples of the median of BW or L of infants among women with asthma or compared to controls. The HC:BW ratio was increased among the newborns of women with asthma ($p = .029$) and compared to controls ($p = .010$). This remained significant within the study group ($p < .001$) and compared to controls ($p < .001$) after multivariate analysis controlled for confounding variables: maternal age, parity, prepregnancy weight, race, medical care source, and smoking status. HC was statistically significant when comparing the asthmatics and controls ($p = .032$), as well as among women with asthma ($p = .013$). Although these differences were found to be statistically significant, the actual measurements differ by less than 1 cm. HC was not significantly different among all groups ($p = .228$), nor the asthma groups ($p = .144$) after adjusting for covariates. The PI was significantly different across the asthma groups ($p = .031$), but not in comparison to controls ($p = .057$). Once again, the clinical significance of this difference in PI is in question, as the numerical differences between the asthma subgroups is less than one tenth. Furthermore, the PI was no longer significant among asthmatics ($p = .718$) nor compared to controls ($p = .451$) when confounding variables were controlled in the multivariate analysis.

COMMENT

This study failed to find a significant difference in BW between the neonates of women with asthma and controls, supporting data from previous studies (1, 5, 6). Furthermore, there was no significant difference in BW among women with asthma stratified by disease severity. This would indicate a lack of effect of disease severity on BW. Neonatal L was also not effected by the presence or severity of asthma.

Head circumference measurements were found to be statistically significantly different both among all groups, including controls as well as among the women with differing severity of asthma. Although the difference in head circumference is significantly different among women with asthma and in comparison to controls, the actual average difference in HC measurement was less than 1 cm. Presumed hypoxic effects of high altitude compared to sea level in two Peruvian populations showed mean fetal head circumference measurements at 40 weeks to have a difference of approximately 12 mm (11). Although the changes in HC in this study were consistent with an effect of hypoxia, the clinical significance is most likely negligible. Furthermore, after controlling for confounding variables, there was no significant difference in HC either among women with asthma or compared to controls.

Asthma severity is correlated with an increased HC:BW ratio, which mimics the asymmetric growth restriction seen in women living at high altitudes (10, 11). This increased HC:BW ratio also parallels or is analogous to the cranial sparing seen sonographically in the head-to-abdomen circumference ratio of growth restricted fetuses (15). Maternal disease severity

may correlate with an increased risk of in utero fetal hypoxia exposure. Perhaps women with milder disease maintain better oxygenation throughout pregnancy and this phenomenon is not seen as clearly. Given that the components of this ratio analyzed separately show no clinically significant differences in head circumference or birth weight between women with asthma and controls, or among women with varying severity of asthma, the significance of this finding remains uncertain. However, increased HC:BW ratio may serve as a model of what to expect in women with uncontrolled disease. Perhaps HC:EFW (estimated fetal weight) ratio can be used as a marker for antenatal fetal surveillance in women with asthma.

Socioeconomic status has been ruled out as a contributor to the morphometric findings in neonates born at high altitudes (8, 10). In our study, this may be a confounding variable as women with asthma tended to be of African American race and receiving government assistance. Other factors that might contribute to altered birth weight, such as smoking, were not different between the groups, and prepregnancy weight was actually higher in patients with asthma compared to controls. Again, the increased HC:BW ratio seen in women with severe asthma remained significant after controlling for maternal demographic factors.

Dombrowski et al. (6) suggested that the prospective nature of this study may have contributed to the favorable outcomes in these patients. This might also contribute to the lack of clinically significant differences in neonatal morphometry between these groups. However, the differences in the altered HC:BW ratio appear to be a valid finding. The value of the potential application of this finding to the antenatal management of women with asthma is unknown and will need to be studied further.

Acknowledgments

Supported by grants from the National Institute of Child Health and Human Development (HD21410, HD21414, HD21434, HD27869, HD27917, HD27905, HD27889, HD27860, HD27861, HD27915, HD27883, HD34122, HD34116, HD34210, HD34208, HD34136, HD19897, and HD36801) and the National Heart, Lung, and Blood Institute.

The authors thank Mitchell P. Dombrowski, M.D., for his assistance in the design of the study and his role as the Primary Protocol Subcommittee Committee Chair.

In addition to the authors, other members of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network are as follow:

Wayne State University—M. Dombrowski, Y. Sorokin, A. Millinder

University of Pittsburgh—R. Phillip Heine, M. Cotroneo, and E. Daugherty

University of Tennessee—W. Mabie, B. Sibai

University of Southern California—R. Paul and Y. Rabello

University of Alabama at Birmingham—W. Andrews, R. Copper, S. Tate, and A. Northen

University of Cincinnati—N. Elder, T. Siddiqi, and V. Pemberton

University of Oklahoma—G. Thurnau, J. Carey, A. Meyer

Wake Forest University Health Sciences—P. Meis, M. Harper, M. Swain, and A. Luper

University of Chicago—P. Jones, M. Brown, and G. Mallett

The Ohio State University—F. Johnson, S. Meadows, and B. Collins

University of Miami—S. Beydoun, C. Alfonso, and J. Potter

University of Texas Southwestern Medical Center—M. Sherman

University of Texas at San Antonio—S. Barker and O. Langer

Thomas Jefferson University—M. DiVito and K. Smith

The National Heart, Lung, and Blood Institute—J. Kiley

The George Washington University Biostatistics Center—E. Thom, E. Rowland, and S. Brancolini

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Table 1

Classification of asthma severity (12).

Classification of asthma	Criteria
Mild	<p>All of the following:</p> <p>Asthma symptoms in the prior 6 months</p> <p>Asthma symptoms fewer than 8 days in prior 4 weeks (except with URI)</p> <p>FEV₁ ≥ 80% predicted</p> <p>Not taking daily asthma medications*</p>
Moderate	<p>Any of the following:</p> <p>Asthma symptoms on 8 or more days during the prior 4 weeks not attributable to a URI</p> <p>FEV₁ 60–79% predicted</p> <p>Use of one or more daily asthma medications*</p>
Severe	<p>Any of the following:</p> <p>FEV₁ < 60% predicted</p> <p>Use of daily or every other day oral corticosteroids for 4 weeks prior to enrollment</p>

FEV₁ = forced expiratory volume of air expired in 1 s, measured at the time of enrollment >4 h post bronchodilator.

* Daily medications included 2 puffs per day of inhaled β -agonist, cromolyn, nedocromil, inhaled steroids, or 4 puffs per day of ipratropium, or 1 dose per day of theophylline. Patients on regular corticosteroids were classified as severe irrespective of their criteria.

Table 2

Maternal demographics.

	Controls (<i>N</i> = 828)	Mild (<i>N</i> = 828)	Moderate (<i>N</i> = 775)	Severe (<i>N</i> = 49)	<i>p</i> value	
					All groups	Asthma groups
Maternal age (years)	24.7(6.1)	22.3(5.2)	24.0(6.1)	25.7(6.3)	<.001	<.001
Race						
% African American	52.1	58.9	51.0	71.4	.005	.003
% Caucasian	36.6	31.0	37.8	20.4		
% Other	11.4	10.0	11.2	8.2		
Multiparity (%)	59.7	51.6	56.9	63.3	.006	.045
Prepregnancy weight (kg)	70.5(19.1)	72.9(21.8)	74.4(22.5)	73.4(19.7)	.028	.383
Medical care source						
Government assistance (%)	73.2	80.7	78.3	85.7	.001	.056
Private (%)	18.5	11.6	15.7	12.2		
None (%)	8.3	7.7	5.9	2.0		
Smoking (%)	19.2	18.7	19.1	12.2	.682	.491

Numerical data presented as mean (*SD*).

Table 3

Neonatal morphometry.

	Controls (<i>N</i> = 828)	Mild (<i>N</i> = 828)	Moderate (<i>N</i> = 775)	Severe (<i>N</i> = 49)	<i>p</i> value	
					All groups	Asthma groups
HC (cm)	33.7 (2.1)	33.6 (2.3)	33.8 (2.4)	32.9 (4.2)	.032	.013
Length (cm)	49.8 (3.5)	49.5 (4.0)	49.5 (3.8)	48.1 (5.7)	.060	.104
Birth weight (MOM)	1.0 (0.2)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)	.219	.483
HC:BW ratio	0.0110 (0.0029)	0.0112 (0.0028)	0.0111 (0.0037)	0.0134 (0.0125)	.010	.029
Ponderal index	2.6 (0.4)	2.7 (2.2)	2.7 (1.4)	2.6 (0.3)	.057	.031

Data presented as mean (*SD*).

HC = head circumference; MOM = multiples of the median; HC:BW ratio = head circumference:birth weight ratio.