Prenatal origins of bronchiolitis: protective effect of optimised asthma management during pregnancy

Objective Maternal asthma is the most common chronic disease complicating pregnancy and is a risk factor for bronchiolitis in infancy. Recurrent episodes of bronchiolitis are strongly associated with the development of childhood asthma.

Methods We conducted a follow-up study of infants born to women with asthma who completed a double-blind randomised controlled trial during pregnancy. In this trial, pregnant women with asthma were assigned to treatment adjustment by an algorithm using clinical symptoms (clinical group) or the fraction of exhaled nitric oxide (FeNO group) and we showed that the FeNO group had significantly lower asthma exacerbation rates in pregnancy.

Results 146 infants attended the 12-month follow-up visit. Infants born to mothers from the FeNO group were significantly less likely to have recurrent episodes of bronchiolitis in the first year of life (OR 0.08, 95% CI 0.01 to 0.62; p=0.016) as compared with the clinical group.

Conclusions Optimised management of asthma during pregnancy may reduce recurrent episodes of bronchiolitis in infancy, which could potentially modulate the risk to develop or the severity of emerging childhood asthma.

Infants born to mothers with asthma have more often bronchiolitis[1] and croup[2] but the effect of asthma management during pregnancy on these outcomes is unknown. We have conducted a double-blind randomised controlled trial and showed that the frequency of asthma exacerbations during pregnancy is reduced by ~50% when treatments are guided by a management algorithm based on measurements of the fraction of exhaled nitric oxide (FeNO group) as compared to clinical symptoms (clinical group).[3] Here we report the effects of this optimised asthma management strategy during pregnancy on respiratory outcomes in infancy.

SUBJECTS AND METHODS

Of the 220 women who completed the clinical trial 79% (n=174) consented in writing to participate in the follow-up birth cohort study that was approved by the Hunter New England Health and University of Newcastle Human Research Ethics Committees. An examination of the infant and interview of the primary carer was conducted by the investigator (JM) who was blinded with respect to management group and pregnancy outcomes. A questionnaire was completed by the parent,[4] which

Table 1 Relative risk of recurrent episodes of bronchiolitis or croup at 12 months of age in infants born to mothers from the clinical versus FeNO group employing regression analyses

Bronchiolitis (multiple versus one or none episode)

	Clinical	FeNO	Univariate regression N=128		Multivariate regression* N=122	
	n/N (%)	n/N (%)	OR (95% CI)	p Value	OR (95% CI)	p Value
Clinical vs FeNO group	10/61 (16.4%)	1/67 (1.5%)	0.08 (0.01 to 0.62)	0.016	0.08 (0.01 to 0.66)	0.019
Female vs male	35/61 (57.4%)	35/67 (52.3%)	1.02 (0.29 to 3.54)	0.975		
Gestational age (weeks)	38.3 (2.7)†	38.9 (2.2)†	0.81 (0.67 to 0.97)	0.021	0.81 (0.67 to 0.99)	0.043
Mother LABA during pregnancy	12 /61 (19.7%)	28/67 (41.8%)	1.95 (0.56 to 6.82)	0.295		
Mother exacerbated during pregnancy	30/61 (49.2%)	20/67 (29.9%)	3.01 (0.57 to 7.35)	0.093		
Mother Caesarean section	19/58 (32.8%)	18/64 (28.1%)	0.85 (0.21 to 3.40)	0.817		

Croup (multiple versus one or none episode)

	Clinical	FeNO	Univariate regression N=129		Multivariate regression* N=128	
	n/N(%)	n/N(%)	OR (95% CI)	p Value	OR (95% CI)	p Value
Clinical vs FENO group	7/62 (11.3%)	1/67 (1.5%)	0.12 (0.01 to 0.99)	0.050	0.15 (0.02 to 1.33)	0.089
Female vs male	36/62 (58.1%)	36/67 (53.7%)	1.38 (0.31 to 6.03)	0.672		
Gestational age (weeks)	38.1 (3.0)†	39.0 (2.2)†	0.87 (0.71 to 1.05)	0.154		
Mother LABA during pregnancy	13/62 (21.0%)	28/67 (41.8%)	0.18 (0 to 1.21)	0.084		
Mother exacerbated during pregnancy	31/62 (48.1%)	19/67 (28.4%)	5.25 (1.02 to 27.14)	0.048	3.88 (0.73 to 20.71)	0.113
Mother caesarean section	20/59 (33.9%)	18/64 (28.1%)	2.38 (0.56 to 10.08)	0.238		

Bronchiolitis or croup combined (multiple versus one or none episode)

	Clinical	FeNO	Univariate regression N=127		Multivariate regression* N=121	
	n/N (%)	n/N (%)	OR (95% CI)	p Value	OR (95% CI)	p Value
Clinical vs FENO group	16/61 (26.2%)	2/66 (3.0%)	0.09 (0.02 to 0.40)	0.002	0.11 (0.02 to 0.53)	0.006
Female vs male	35/61 (57.4%)	35/66 (53.0%)	1.02 (0.37 to 2.78)	0.968		
Gestational age (weeks)	38.8 (2.7)	39.3 (2.2)	0.78 (0.65 to 0.93)	0.006	0.79 (0.64 to 0.98)	0.030
Mother LABA during pregnancy	12/61 (19.7%)	28/66 (42.4%	0.81 (0.27 to 2.46)	0.714		
Mother exacerbated during pregnancy	30/61 (49.2%)	19/66 (28.8%)	5.27 (1.74 to 15.93)	0.003	3.38 (1.02, 11.25)	0.047
Mother caesarean section	19/58 (32.8%)	18/63 (28.6%)	1.55 (0.55 to 4.37)	0.409		

*Variables p<0.10 included in multivariate regression with stepwise removal for best fit.
†Mean (SD).
FeNO, fractional exhaled nitric oxide; LABA, long-acting β-agonist.

contained a question on bronchiolitis and croup ('Has your child ever had the following conditions:' 'bronchiolitis'/'croup' 'Never'; 'Once'; 'More than once').

Logistic regressions were performed using STATA V.11. Any predictor variable with $p<0.1$ on simple regression is shown in table 1 and was included in a multiple regression model with stepwise removal for best fit. Predictor variables were tested for colinearity using STATA's variance inflation factors post estimation.

RESULTS

One hundred forty six infants (82%) completed follow-up at 12 months of age. There was no difference in prevalence of 'wheeze ever' between the FeNO and the clinical infant group (55.9 vs 52.4%). There was also no difference in wheezing and coughing frequency, triggers and severity between groups as evaluated by the specific domains of the standardised questionnaire.[4] However less infants born to mothers from the FeNO versus clinical group had recurrent episodes of bronchiolitis in the first year of life (table 1). There was also a statistical trend towards less croup episodes (table 1). As expected, greater gestational age was protective against recurrent bronchiolitis (table 1). The agreement between questionnaire data and standardised interview was 97% (0.89, $p<0.0001$) for bronchiolitis. Maternal smoking and number of siblings did not significantly affect the relative risk for recurrent episodes of bronchiolitis (data not shown).

COMMENT

Asthma during pregnancy is associated with both premature birth and low birthweight,[5] which are risk factors for bronchiolitis. However, this did not explain our results because there was no difference in gestational age (table 1) and other pregnancy outcomes between the groups with the exception of reduced neonatal hospitalisation in the FeNO group.[3] The study design makes a reporting or recall bias as well as seasonal effects very unlikely as an alternative explanation for the observed effects even though symptoms and infections were reported retrospectively. We consequently have no data on disease severity, viral aetiology and time of infection in infancy, which are limitations of this study. Asthma exacerbations during pregnancy result in changes at the feto-maternal interface that favour aberrant immune responses in the foetus.[5] Mechanistically, immune and lung function, epigenetic and microbiome studies conducted in this birth cohort in the future all appear of interest. Together, our study identifies asthma in pregnancy as a potentially modifiable determinant in the prenatal origins of bronchiolitis with the prospect to be evaluated as a potential primary preventative strategy that could modulate the risk of childhood asthma.

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