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 in infancy 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.

**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, 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

<table>
<thead>
<tr>
<th>Bronchiolitis (multiple versus one or none episode)</th>
<th>Clinical n/N (%)</th>
<th>FeNO n/N (%)</th>
<th>Univariate regression N=128 OR (95% CI)</th>
<th>p Value</th>
<th>Multivariate regression N=128 OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical vs FeNO group</td>
<td>10/61 (16.4%)</td>
<td>1/67 (1.5%)</td>
<td>0.08 (0.01 to 0.62)</td>
<td>0.016</td>
<td>0.08 (0.01 to 0.66)</td>
<td>0.019</td>
</tr>
<tr>
<td>Female vs male</td>
<td>35/61 (57.4%)</td>
<td>35/67 (52.3%)</td>
<td>1.02 (0.29 to 3.54)</td>
<td>0.975</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>38.3 (2.7)†</td>
<td>38.9 (2.2)†</td>
<td>0.81 (0.67 to 0.97)</td>
<td>0.021</td>
<td>0.81 (0.67 to 0.99)</td>
<td>0.043</td>
</tr>
<tr>
<td>Mother LABA during pregnancy</td>
<td>12/61 (19.7%)</td>
<td>28/67 (41.8%)</td>
<td>1.95 (0.56 to 6.82)</td>
<td>0.295</td>
<td></td>
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<tr>
<td>Mother exacerbated during pregnancy</td>
<td>30/61 (49.2%)</td>
<td>20/67 (29.9%)</td>
<td>3.01 (0.57 to 7.35)</td>
<td>0.093</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother Caesarean section</td>
<td>19/58 (32.8%)</td>
<td>18/64 (28.1%)</td>
<td>0.85 (0.21 to 3.40)</td>
<td>0.817</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Croup (multiple versus one or none episode)</th>
<th>Clinical n/N (%)</th>
<th>FeNO n/N (%)</th>
<th>Univariate regression N=129 OR (95% CI)</th>
<th>p Value</th>
<th>Multivariate regression N=128 OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical vs FeNO group</td>
<td>7/62 (11.3%)</td>
<td>1/67 (1.5%)</td>
<td>0.12 (0.01 to 0.99)</td>
<td>0.050</td>
<td>0.15 (0.02 to 1.33)</td>
<td>0.089</td>
</tr>
<tr>
<td>Female vs male</td>
<td>36/62 (58.1%)</td>
<td>36/67 (52.3%)</td>
<td>1.38 (0.31 to 6.03)</td>
<td>0.672</td>
<td></td>
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</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>38.1 (3.0)†</td>
<td>39.0 (2.2)†</td>
<td>0.87 (0.71 to 1.05)</td>
<td>0.154</td>
<td></td>
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</tr>
<tr>
<td>Mother LABA during pregnancy</td>
<td>13/62 (21.0%)</td>
<td>28/67 (41.8%)</td>
<td>0.18 (0 to 1.21)</td>
<td>0.084</td>
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<tr>
<td>Mother exacerbated during pregnancy</td>
<td>31/62 (48.1%)</td>
<td>19/67 (28.4%)</td>
<td>5.25 (1.02 to 27.14)</td>
<td>0.048</td>
<td>3.88 (0.73 to 20.71)</td>
<td>0.113</td>
</tr>
<tr>
<td>Mother Caesarean section</td>
<td>20/59 (33.9%)</td>
<td>18/64 (28.1%)</td>
<td>2.38 (0.56 to 10.06)</td>
<td>0.238</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Bronchiolitis or croup combined (multiple versus one or none episode)</th>
<th>Clinical n/N (%)</th>
<th>FeNO n/N (%)</th>
<th>Univariate regression N=127 OR (95% CI)</th>
<th>p Value</th>
<th>Multivariate regression N=121 OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical vs FeNO group</td>
<td>16/61 (26.2%)</td>
<td>2/66 (3.0%)</td>
<td>0.09 (0.02 to 0.40)</td>
<td>0.002</td>
<td>0.11 (0.02 to 0.53)</td>
<td>0.006</td>
</tr>
<tr>
<td>Female vs male</td>
<td>35/61 (57.4%)</td>
<td>35/66 (53.0%)</td>
<td>1.02 (0.37 to 2.78)</td>
<td>0.968</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>38.8 (2.7)</td>
<td>39.3 (2.2)</td>
<td>0.78 (0.65 to 0.93)</td>
<td>0.006</td>
<td>0.79 (0.64 to 0.98)</td>
<td>0.030</td>
</tr>
<tr>
<td>Mother LABA during pregnancy</td>
<td>12/61 (19.7%)</td>
<td>28/66 (42.4%)</td>
<td>0.81 (0.27 to 2.46)</td>
<td>0.714</td>
<td></td>
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</tr>
<tr>
<td>Mother exacerbated during pregnancy</td>
<td>30/61 (49.2%)</td>
<td>19/66 (28.8%)</td>
<td>5.27 (1.74 to 15.93)</td>
<td>0.003</td>
<td>3.38 (1.02, 11.25)</td>
<td>0.047</td>
</tr>
<tr>
<td>Mother Caesarean section</td>
<td>19/58 (32.8%)</td>
<td>18/63 (28.6%)</td>
<td>1.55 (0.55 to 4.37)</td>
<td>0.409</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 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 V11. 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 birth-weight,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 fetus-maternal interface that favour aberrant immune responses in the foetus.6 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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Acknowledgements The authors would like to thank Kelly Steel and Karen McLaughlin for their assistance.

Contributors JM: had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. He designed the infant study, followed up infants, analysed data and wrote the manuscript. VEM: designed studies, coordinated follow-up, analysed data and edited the manuscript. HP: had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. She analysed data and edited the manuscript. PGG: conceived, supervised and designed studies, analysed data and edited the manuscript.

Funding National Health Medical Research Council (NH&MRC) (VEM 455593, PG 455592), Hunter Medical Research Institute (JM, VEM, PGG), Hunter Children’s Research Foundation (JM, VEM, PGG), NH&MRC Health Practitioner Research Fellowship (JM 455623, PGG 188586), NH&MRC Australian Research Training Fellowship (VEM 455626).

Competing interests None.

Patient consent Obtained.

Ethics approval HNE Human Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

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Received 12 February 2013
Revised 13 August 2013
Accepted 2 September 2013
Published Online First 25 September 2013
doi:10.1136/thoraxjnl-2013-203388

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