Parental smoking as a risk factor for wheezing and early onset asthma

Z. Živković

Children's hospital for lung diseases and TB Medical Center “Dr Dragiša Mišović”, Belgrade
US MEDICAL SCHOOL, EUROPEAN UNIVERSITY OF BELGRADE
Disclaimer

- I have nothing to declare
- No financial or pharmaceutical conflicts for my presentation
Risk factors for development of asthma

Almost nothing is known about the role of intrauterine factors and fetal environment that might have been implicated in asthma development. 

Influences in utero:
- immune responses
- inadequate oxygenation
- lung maturation
The most important risk factors for early life respiratory events

- Maternal smoking during pregnancy
- Reduced lung function at birth
- Atopy
- Viral infections
- Ethnic background
- Gender
- Genetics
- Environmental factors
Voltaire

"The role of the doctor is to amuse the patient, while nature takes its course"

Francois Marie Arouet, 1694-1778
Influence of Environmental Tobacco Smoke on Characteristics of Childhood Asthma

Snežana Radić¹, Zorica Živković¹, Nada Erdeljan², Sofija Cerović¹, Jasmina Jocić-Stojanović¹
¹Centre for Children’s Respiratory Diseases and Tuberculosis, Belgrade, Serbia; ²University Children’s Hospital, Belgrade, Serbia

SUMMARY

Introduction  We compared characteristics of asthma in children from smoking and non-smoking families.

Objective  To examine if there was any difference in asthma in children exposed and not exposed to environmental tobacco smoke (ETS).

Methods  We examined 231 asthmatic children and their parents. According to the questionnaire and carbon monoxide (CO) values in exhaled air measured by Smokerlyzer, we divided the children in two groups: children from smoking and children from non-smoking families. We compared birth weight, birth length, the occurrence of the first broncho-obstruction, the number of respiratory infections and exacerbations per year, asthma severity, the number of hospitalizations, total IgE, Skin prick test and allergic manifestations. We examined the influence of parental educational level on smoking behaviour and how much money a smoking family spent on cigarettes.

Results  The children’s average age was 10.6 years, there were 49% of boys and 51% of girls. We had 77% of smoking families, 45.9% of active smoking mothers and 51% of active smoking fathers. Smoking was more common among lower educated parents. A smoking family spent 7.3% of the family budget on cigarettes. The children from smoking families had more allergic manifestations. The children of smoking mothers had more respiratory infections (without a statistic difference in the second and third year) and more asthmatic exacerbations with a statistic difference after the third year. With parents who smoked, children had more severe asthma. There was no statistical difference in the following: birth weight, birth length, Skin prick test, total IgE, the first wheezing episode and the number of hospitalizations. However, in the group of 26 children with exhaled CO values higher than 6ppm, birth weight was lower (3250 g vs. 3550 g), the first wheezing episode occurred earlier (2 years vs. 3.7 years) and total IgE was higher (702 IU/ml vs. 563 IU/ml) by more than two normal ranges (60 IU/ml).

Conclusion  It is necessary to protect children with asthma from ETS because it has a negative impact on their illness.

Keywords: asthma; children; environmental tobacco smoke
<table>
<thead>
<tr>
<th>Period</th>
<th>Smoking mother</th>
<th>Number</th>
<th>$\bar{X}$</th>
<th>$SD$</th>
<th>$SE$</th>
<th>$t$</th>
<th>$df$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. година</td>
<td>He No</td>
<td>125</td>
<td>2.94</td>
<td>2.60</td>
<td>0.23</td>
<td>3.25</td>
<td>229</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>Da Yes</td>
<td>106</td>
<td>4.28</td>
<td>3.67</td>
<td>0.36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-3. година</td>
<td>He No</td>
<td>125</td>
<td>4.30</td>
<td>3.05</td>
<td>0.27</td>
<td>1.79</td>
<td>229</td>
<td>0.07</td>
</tr>
<tr>
<td>2nd to 3rd year</td>
<td>Da Yes</td>
<td>106</td>
<td>5.13</td>
<td>3.97</td>
<td>0.39</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-7. година</td>
<td>He No</td>
<td>118</td>
<td>4.36</td>
<td>2.87</td>
<td>0.26</td>
<td>2.05</td>
<td>215</td>
<td>0.04</td>
</tr>
<tr>
<td>4-7th year</td>
<td>Da Yes</td>
<td>99</td>
<td>5.24</td>
<td>3.44</td>
<td>0.35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>После 7. године</td>
<td>He No</td>
<td>89</td>
<td>4.09</td>
<td>2.12</td>
<td>0.23</td>
<td>2.58</td>
<td>165</td>
<td>0.01</td>
</tr>
<tr>
<td>After 7th year</td>
<td>Da Yes</td>
<td>78</td>
<td>5.72</td>
<td>5.51</td>
<td>0.62</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Graph 2. Number of exacerbations per year in children of nosmoking and smoking mothers

*SM* – smoking mother; *noSM* – nosmoking mother

* p<0.05 after 3rd year
Графикон 3. Тежина астме деце мајки пушача и непушача
Graph 3. Asthma severity in children according to smoking and no-smoking mothers

$p<0.05$; SM – мајка активни пушач; noSM – мајка непушач
$p<0.05$; SM – smoking mother; noSM – nosmoking mother
Табела 8. Деца неизложена дуванском диму средине (ДДС) у односу на децу с вредностима CO већим од 6 ppm у издахнутом ваздуху.

<table>
<thead>
<tr>
<th>Параметар</th>
<th>Број испитаника</th>
<th>( \bar{X} )</th>
<th>SD</th>
<th>SE</th>
<th>t</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Тежина на рођењу</td>
<td>Дече неизложена ДДС</td>
<td>54</td>
<td>335.38</td>
<td>609.86</td>
<td>75.64</td>
<td>1.37</td>
<td>89</td>
</tr>
<tr>
<td>Birth weight</td>
<td>Дече са CO&gt;6 ppm</td>
<td>26</td>
<td>3251.54</td>
<td>635.09</td>
<td>140.63</td>
<td>1.36</td>
<td>54.76</td>
</tr>
<tr>
<td>Прва опструкција</td>
<td>Дече неизложена ДДС</td>
<td>54</td>
<td>2.02</td>
<td>3.80</td>
<td>0.47</td>
<td>1.81</td>
<td>89</td>
</tr>
<tr>
<td>First wheezing</td>
<td>Дече са CO&gt;6 ppm</td>
<td>26</td>
<td>3.73</td>
<td>4.70</td>
<td>0.92</td>
<td>1.66</td>
<td>38.74</td>
</tr>
<tr>
<td>Укупни ниво IgE (IU/ml)</td>
<td>Дече неизложена ДДС</td>
<td>54</td>
<td>563.95</td>
<td>560.20</td>
<td>69.48</td>
<td>0.96</td>
<td>89</td>
</tr>
<tr>
<td>Total level of IgE (IU/ml)</td>
<td>Дече са CO&gt;6 ppm</td>
<td>26</td>
<td>702.85</td>
<td>757.87</td>
<td>148.63</td>
<td>0.85</td>
<td>36.44</td>
</tr>
</tbody>
</table>
## TOBACCO EXPOSURE AND ASTHMA IN PRESCHOOL AGES

<table>
<thead>
<tr>
<th></th>
<th>MS</th>
<th>MNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>No RI</td>
<td>&lt;5 (84,4%)</td>
<td>&lt;5 (86,7%)</td>
</tr>
<tr>
<td>No wheezing</td>
<td>&lt;5 (82,2%)</td>
<td>&lt;5 (88,4%)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>&lt;3 (29,5%)</td>
<td>&lt;3 (32,1%)</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>ICS 75,5%</td>
<td>ICS 55,3%**</td>
</tr>
<tr>
<td>SPT</td>
<td>+ (94,4%)</td>
<td>+ (93,6%)</td>
</tr>
<tr>
<td>Serum IgE</td>
<td>442IU/ml</td>
<td>509IU/ml</td>
</tr>
<tr>
<td>Eczema</td>
<td>+ (42%)</td>
<td>+ (43%)</td>
</tr>
</tbody>
</table>

**SN
# TOBACCO EXPOSURE AND ASTHMA IN PRESCHOOL AGES

<table>
<thead>
<tr>
<th></th>
<th>MS</th>
<th>MNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>No RI</td>
<td>&lt;5 (84.4%)</td>
<td>&lt;5 (86.7%)</td>
</tr>
<tr>
<td>No wheezing</td>
<td>&lt;5 (82.2%)</td>
<td>&lt;5 (88.4%)</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>&lt;3 (29.5%)</td>
<td>&lt;3 (32.1%)</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>ICS 75.5%</td>
<td>ICS 55.3%**</td>
</tr>
<tr>
<td>SPT</td>
<td>+ (94.4%)</td>
<td>+ (93.6%)</td>
</tr>
<tr>
<td>Serum IgE</td>
<td>442IU/ml</td>
<td>509IU/ml</td>
</tr>
<tr>
<td>Eczema</td>
<td>+ (42%)</td>
<td>+ (43%)</td>
</tr>
</tbody>
</table>

**SN
Allergic sensitization during fetal life - facts -

• Gestation and early childhood - the most influential periods with regard to atopic expression

• Higher total IgE levels in cord blood associated with increased risk for atopic disease in infancy - including atopic dermatitis, urticaria, food allergy **BUT not for asthma**

• Maternal IgE does not cross the placenta
Influences of the fetal environment

- In utero exposure to maternal smoking without postpartum exposure to environmental tobacco smoke increases the risk of childhood asthma, although exposure to environmental tobacco smoke during childhood was related to wheeze but not asthma.

Asthma in mothers

• Umbilical artery flow velocity was found to be significantly reduced at 18 weeks' gestation in moderately and severely asthmatic mothers.

• Intrauterine exposure to beta agonists and poorly managed maternal asthma have been associated with asthma development in children.


Growth and development of the respiratory system

• Take place mainly during the pre-natal and early post-natal periods

• Adverse effects of pre-natal exposures, such as tobacco smoking of the mother, on lung development are well documented

Impact of air pollution on lung development

If present at an early developmental stage are suggestive of:

• respiratory need due to increased resistance (smaller airways),
• decreased compliance (smaller or stiffer airways) and/or
• factors influencing control of breathing (hypoxia)
Possible hypothesis

Inflammation of the mother’s airways after exposure to air pollution may affect the blood-air barrier

- reduced fetal breathing movements
- decreased alveolarisation
- decreased placental blood flow
- reduced transfer of nutrients to the foetus
Tobacco smoke exposure

Maternal smoking
Smoking and Nicotine

• Increased airway resistance in term babies and decreased conductance in premature babies with smoking mothers (Stocks 98,99)

• Nicotine in fetal monkeys reduced alveoli and increased airway collagen (Sekhon et al 1999)

• Rats pups of smoking mothers have reduced alveolar development (Massaro 1996)
Maternal smoking is associated with impaired neonatal toll-like-receptor-mediated immune responses

P.S. Noakes, J. Hale, R. Thomas, C. Lane, S.G. Devadason and S.L. Prescott

ABSTRACT: Infants of smokers have much higher rates of respiratory infection, asthma and airway disease. The current study assessed the effects of maternal smoking in pregnancy on neonatal toll-like-receptor (TLR)-mediated immune responses as a possible contributing factor to the elevated rates of respiratory illness.

In a prospective birth cohort, the cord blood immune responses of neonates of smoking and nonsmoking mothers were compared. Maternal and cord serum cotinine were measured to confirm the level of cigarette smoke exposure. Neonatal cytokine responses were assessed to optimal doses of TLR2, TLR3, TLR4 and TLR9 ligands.

Cotinine levels confirmed maternal reporting of cigarette smoking in pregnancy, with significantly higher cotinine levels in maternal and cord blood compared with the nonsmoking group. Infants of smoking mothers showed significantly attenuated innate TLR-mediated responses compared with infants of nonsmokers.

The current findings indicate that in addition to effects on developing airways, maternal smoking also has significant immunological effects in pregnancy, which could contribute to the well recognised, subsequent increased risk of respiratory infections and asthma. These effects appear to be mediated through effects on toll-like receptor-mediated innate response pathways, which also promote regulatory pathways in the inhibition of allergic immune responses in the postnatal period, suggesting that other environmental interactions are highly relevant to the “hygiene hypothesis”.
Important effect of maternal smoking

- 60 newborns - smoking mothers compared with 62 newborns - non-smoking mothers
- Cord blood mononuclear cell (CBMC) responses to toll-like receptor (TLR) ligands were attenuated for tumour necrosis factor α, IL-6 and IL-10
- In utero exposure affects future wheeze susceptibility via an effect on the innate immune system
- Reduced natural immunity to early respiratory viral infections

In utero exposure to cigarette smoking influences lung function at birth


ABSTRACT: To avoid the possible confounding effects of postnatal exposure to tobacco smoke, we investigated possible effects of uterine tobacco smoke (UTS) exposure upon infant lung function shortly after birth.

Infants with no major disease, in one maternity ward in Oslo, Norway, participating in a cohort study established in 1992/1993, were included in the present study (n=803). Exposure information, assessed as maternal active and passive smoking during pregnancy and other personal and environmental factors, was obtained by questionnaire. Tidal flow-volume (TFV) loops (n=802) and compliance (Crs) and resistance (Rrs) of the respiratory system (n=663) were measured at a mean age of 2.7 days.

In girls, the TFV ratio (time to reach peak expiratory flow to total expiratory time (tPEF/tE)), and Crs were significantly lower with active as well as passive maternal smoking compared to nonexposure to UTS. Respiratory rate and Rrs were not significantly influenced by UTS exposure. However, in linear regression analysis adjusted for confounding factors (including respiratory rate), tPEF/tE and Crs, but not Rrs, were related to maternal active but not passive daily smoking. One daily cigarette corresponded to a change in tPEF/tE of -0.0021 (95% confidence interval 95% CI -0.0040 to -0.0002) and a change in Crs of -0.026 mL·cmH2O (95% CI -0.045 to -0.007 mL·cmH2O). The decrease was 0.023 and 0.29, respectively, in infants of an average smoker.

Maternal smoking during pregnancy adversely affected tidal flow-volume ratios in healthy newborn babies, as well as the compliance of the respiratory system in girls, independently of the reduced body size also resulting from maternal smoking. Eur Respir J 1997; 10: 1774–1779.

*Dept of Paediatrics, Ullevål Hospital, Oslo, Norway, **Enviro-medicine Unit, Dept of Public Health, University of Helsinki, Helsinki, Finland, ***Section of Epidemiology, Department of Health Sciences, National Public Health, Oslo, Norway. Open Centre for Asthma and Allergy, Ullevål, Oslo, Norway.

Correspondence: K.C. Lødrup Carlsen
Dept of Paediatrics
Ullevål Hospital
N-0407 Oslo
Norway

Keywords: In utero newborn infants passive respiratory mechanics tidal flow-volume loops tobacco smoke exposure

Received: November 7 1996
Accepted after revision April 1997

The study was supported by the Norwegian Research Council.

The study was supported by the Norwegian Research Council.
In utero exposure to cigarette smoking influences lung function at birth

Table 1. – Characteristics of the study population in relation to daily tobacco smoke exposure

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No</th>
<th>Active</th>
<th>Passive</th>
<th>Both</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight kg</td>
<td>3.6 (0.49)</td>
<td>3.4 (0.55)†</td>
<td>3.5 (0.46)+</td>
<td>3.4 (0.39)***</td>
<td>3.6 (0.49)</td>
</tr>
<tr>
<td>Birth length cm</td>
<td>50.6 (2.5)</td>
<td>49.7 (2.3)†</td>
<td>50.4 (2.1)</td>
<td>49.1 (3.2)***</td>
<td>50.1 (2.0)</td>
</tr>
<tr>
<td>Gestational age weeks</td>
<td>39.9 (1.8)</td>
<td>39.5 (1.6)</td>
<td>39.6 (1.5)</td>
<td>39.8 (1.3)</td>
<td>39.8 (1.3)</td>
</tr>
<tr>
<td>Parental atopy %</td>
<td>54</td>
<td>25</td>
<td>21</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>Boys %</td>
<td>55</td>
<td>40</td>
<td>57</td>
<td>41</td>
<td>53</td>
</tr>
<tr>
<td>Education 1/2/3 %</td>
<td>5/41/54</td>
<td>12/55/31</td>
<td>8/44/48</td>
<td>16/58/26</td>
<td>7/45/48</td>
</tr>
<tr>
<td>Income group 1/2/3 %</td>
<td>15/66/18</td>
<td>33/53/14</td>
<td>30/61/10</td>
<td>14/78/8</td>
<td>18/66/15</td>
</tr>
</tbody>
</table>
**In utero** exposure to cigarette smoking influences lung function at birth

Table 2. Tidal breathing parameters ($f_R$ and $t_{PEF/TE}$) and respiratory mechanics ($C_{rs}$ and $R_{rs}$) in relation to maternal active or passive smoking whilst pregnant

<table>
<thead>
<tr>
<th>Active</th>
<th>Passive</th>
<th>n</th>
<th>$f_R$</th>
<th>$t_{PEF/TE}$</th>
<th>$C_{rs}$ mL·cmH$_2$O$^{-1}$</th>
<th>$R_{rs}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All</td>
<td>Girls</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>483</td>
<td>58.4</td>
<td>0.32</td>
<td>4.18</td>
<td>4.19</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(57.2–59.6)</td>
<td>(0.31–0.33)</td>
<td>(4.07–4.30)</td>
<td>(4.01–4.37)</td>
</tr>
<tr>
<td>Occ.</td>
<td>No</td>
<td>51</td>
<td>60.1</td>
<td>0.32</td>
<td>4.12</td>
<td>4.11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(55.9–64.4)</td>
<td>(0.28–0.35)</td>
<td>(3.80–4.45)</td>
<td>(3.62–4.61)</td>
</tr>
<tr>
<td>Daily</td>
<td>No</td>
<td>52</td>
<td>56.9</td>
<td>0.31</td>
<td>3.92</td>
<td>3.79</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(52.9–60.8)</td>
<td>(0.28–0.34)</td>
<td>(3.59–4.25)</td>
<td>(3.06–4.52)</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>105</td>
<td>60.2</td>
<td>0.33</td>
<td>3.83</td>
<td>4.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(57.4–63.0)</td>
<td>(0.31–0.36)</td>
<td>(3.91–4.52)</td>
<td>(3.70–4.70)</td>
</tr>
<tr>
<td>Occ.</td>
<td>Yes</td>
<td>27</td>
<td>56.9</td>
<td>0.30</td>
<td>4.03</td>
<td>4.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(52.0–61.7)</td>
<td>(0.28–0.34)</td>
<td>(3.49–4.71)</td>
<td>(3.40–4.20)</td>
</tr>
<tr>
<td>Daily</td>
<td>Yes</td>
<td>78</td>
<td>60.7</td>
<td>0.29</td>
<td>3.78</td>
<td>3.97</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(57.4–64.0)</td>
<td>(0.27–0.31)*++</td>
<td>(3.51–4.04)+$</td>
<td>(3.24–3.78)*++$</td>
</tr>
</tbody>
</table>
In utero exposure to cigarette smoking influences lung function at birth

KC Lodrup Carlsen, ERS 1997

Fig. 1. – a) t\textsubscript{PER/FE}; and b) C\textsubscript{rs} in newborn babies in relation to maternal smoking. Values are presented as mean and 95% confidence interval. No: no active or passive maternal smoking; P: daily passive (but not active) maternal exposure to tobacco smoke in the household; Occ.: occasional maternal smoking (+passive smoking); UTS: uterine tobacco smoke exposure; 1–9: maternal active (but not passive) smoking of 1–9 cigarettes-day\textsuperscript{-1}; ≥10: maternal active (but not passive) smoking of ≥10 cigarettes-day\textsuperscript{-1}; A+P: both active and passive daily smoking. t\textsubscript{PER/FE}: ratio of time to reach peak expiratory flow to total expiratory time; C\textsubscript{rs}: compliance of the respiratory system. +: p=0.04; †: p<0.005, compared to nonexposed group.
Health effects of passive smoking · 1

Parental smoking and lower respiratory illness in infancy and early childhood

David P Strachan, Derek G Cook

Abstract

Background - A systematic quantitative review was conducted of evidence relating parental smoking to acute lower respiratory illness in the first three years of life.

Methods - Fifty relevant publications were identified after consideration of 692 articles selected by electronic search of the Embase and Medline databases using keywords relevant to passive smoking in children. The search, completed in April 1997, identified 24 studies ascertaining illnesses in a community setting, including five surveys of schoolchildren with retrospective ascertainment of early chest illness, and 17 studies of admissions to hospital for lower respiratory illness in early life. Thirty eight studies were included in a quantitative overview using random effects modelling to derive pooled odds ratios.

Keywords: parental smoking, tobacco smoke pollution, lower respiratory illness, infancy, childhood.

Two articles published in the Lancet in 1974\(^1\) alerted readers to a possible link between parental smoking and the risk of lower respiratory illness in infancy. Although adverse effects from exposure of children to environmental tobacco smoke had been suggested previously,\(^3\) the association with acute chest illness was of immediate and continuing interest because of the suspected long term consequences of early episodes for lung growth, chronic respiratory morbidity in childhood, and adult chronic obstructive lung disease.\(^3\)

During the last two decades many epidemiological studies have reported upon the association of parental smoking and respiratory diseases throughout childhood. In this, the first of a series of systematic and quantitative reviews of health effects of passive smoking, we summarise the evidence relating specifically to acute
Figure 1  Odds ratios and 95% confidence intervals for effect of either parent smoking compared with neither smoking. The pooled odds ratios derived by fixed effects and random effects methods appear at the foot of the figure. The horizontal scale is logarithmic (base 2). Individual studies are denoted thus: circles = studies of lower respiratory illnesses; squares = studies of wheezing illnesses; diamonds = studies of upper and lower respiratory illnesses; open symbols = community studies; filled symbols = studies of hospitalised illnesses.

Figure 3  Odds ratios and 95% confidence intervals for effect of smoking by household members apart from the mother compared with neither parent smoking. Definition of symbols as for fig 1.
Immune responses

Atopy
Immune system

• Impairment of the innate immune system in early life in infants who are likely to wheeze has been noted in those exposed to tobacco smoke and in those with pro-Th2 genotypes.

• Infants destined to become atopic and asthmatic demonstrate a delay in maturation of the immune system in early life.

T-cell response at birth

- At birth, T-cell responses are already different between infants of atopic and non-atopic mothers.
- The levels of Th2 related cytokines produced by CBMC are reduced in infants of atopic mother.
- Th1 and Th2 cytokine levels in cord blood were reduced in infants who later developed asthma.

Genes&Environment

Antenatal determinants of airway branching
Genes and environment

- Genes (ADAM33)
- Maternal and foetal glutathione metabolising enzyme phenotype
- Maternal atopy
- Maternal hypertension
- Maternal use of antibiotics
- Maternal diabetes
- Amniocentesis
Viral infections

RSV BRONCHIOLITIS
Relationship between respiratory syncytial virus bronchiolitis and future obstructive airway diseases

G. Wennergren*, S. Kristjánsson#

*Dept of Paediatrics, Göteborg University, Queen Silvia Children's Hospital, Göteborg, Sweden, and #Dept of Paediatrics, Landspitali University Hospital, Reykjavik, Iceland.

Correspondence: G. Wennergren
Dept of Paediatrics
Göteborg University
Queen Silvia Children's Hospital
SE-416 85 Göteborg
Sweden
Fax: 46 31402424

Keywords: Allergy
asthma
bronchiolitis
infant
outcome
respiratory syncytial virus

Received: March 20 2001
Accepted after revision June 19 2001

ABSTRACT: Evidence from a large number of prospective case-control studies shows that respiratory syncytial virus (RSV) bronchiolitis in infancy is often associated with recurrent wheezing and asthma during subsequent years. However, wheezing tends to diminish and most studies show no significant increase in wheezing compared to controls by school age or adolescence. An unresolved question is whether severe RSV infection during infancy causes the respiratory sequelae or inherent abnormalities predispose an infant to develop severe respiratory infection and sequelae, *i.e.* RSV is associated with the development of pulmonary sequelae.

Studies on long-term outcome of RSV bronchiolitis are reviewed from an evidence-based perspective.

The majority of prospective placebo-controlled studies do not show any long-term beneficial effects of corticosteroid treatment, *i.e.* the risk of subsequent wheezing is not diminished by the treatment. The evidence for an increased risk of allergic sensitization after RSV bronchiolitis is not nearly as strong as the evidence for an increased risk of subsequent wheezing. In fact, most studies do not show any significant increase in atopy after RSV bronchiolitis. This suggests that the increased risk of wheezing after RSV is not linked to an increased risk of atopy. There are some indications that infants who develop severe RSV and subsequent wheezing may have aberrations that predate the RSV infection.

To decide whether respiratory syncytial virus bronchiolitis causes, or is associated with the respiratory sequelae (or with subsequent allergy), it will be necessary to conduct prospective, randomized studies, where the cytokine profile prior to bronchiolitis onset is known. Such studies should preferably include some form of intervention against respiratory syncytial virus. A more complete understanding of the risk factors for severe respiratory syncytial virus infection and the role of respiratory syncytial virus infection in the initiation of asthma is needed as a basis for large-scale and cost-effective programmes to prevent respiratory syncytial virus-related morbidity.

_Eur Respir J 2001; 18: 1044–1058._
We previously reported an increased risk for bronchial obstructive disease and allergic sensitization up to age 3 in 47 children hospitalized with a respiratory syncytial virus (RSV) bronchiolitis in infancy compared with 93 matched control subjects recruited during infancy. The aims of the present study were to evaluate the occurrences of bronchial obstructive disease and allergic sensitization in these children at age 7½. All 140 children reported for the follow-up, which included physical examination, skin prick tests, and serum IgE tests for common food and inhaled allergens. The cumulative prevalence of asthma was 30% in the RSV group and 3% in the control group (p < 0.001), and the cumulative prevalence of "any wheezing" was 68% and 34%, respectively (p < 0.001). Asthma during the year prior to follow-up was seen in 32%.

We compared prospectively a group of 47 children hospitalized with RSV bronchiolitis in infancy and a matched control group of 93 children at the mean ages of 1 yr and 3 yr (7). Both the frequency of asthma and of allergic sensitization was significantly higher in the RSV group than in the control group. The present study reports the results of a third follow-up of this cohort, at age 7½. We aimed, first, to study the development and course of bronchial disease, clinical allergies, and sensitization and, second, to determine whether any occurrences since the second follow-up affected the comparability of the study groups.

a

Current bronchial obstructive symptoms

% of group

RSV Controls RSV Controls

Any wheezing Asthma

b

Current allergic sensitization

% of group

RSV Controls RSV Controls

SPT Phadiatop

Age □ 1 □ 3 □ 7.5
Prematurity
Low birth weight
Prematurity

- Premature air breathing during the alveolar phase
- Mechanical ventilation
- Corticosteroides in utero
- Surfactant
- Premature birth reason - infection
- Effect on lung development and function
Reduced lung function at birth

What is already known on this topic

- There are no data documenting the lung function of very prematurely born infants wheezy at follow-up.
- Very prematurely born infants with BPD are frequently wheezy at follow-up; limited post-mortem data suggest that they have minimal lung inflammation and fibrosis but have evidence of arrest of alveolar development.

What this study adds

- We have demonstrated, in infants born prior to 29 weeks of gestational age, that gestational age, length at assessment, family history of atopy and a low functional to total lung volume were significantly associated with wheeze at follow-up.
- These data highlight that wheeze at follow-up in very prematurely born infants is associated with gas trapping, suggesting abnormalities of the small airways.

Very prematurely born infants wheezing at follow-up: lung function and risk factors

Simon Broughton, Mark R Thomas, Louise Marston, Sandra A Calvert, Neil Marlow, Janet L Peacock, Gerrard F Rafferty and Anne Greenough

Arch. Dis. Child. 2007;92;776-780
Very prematurely born infants wheezing at follow-up: lung function and risk factors

Simon Broughton, Mark R Thomas, Louise Marston, Sandra A Calvert, Neil Marlow, Janet L Peacock, Gerrard F Rafferty and Anne Greenough

Arch. Dis. Child. 2007;92;776-780

Wheezing in very prematurely born infants wheezing

![Graph showing wheezing in very prematurely born infants]
CURRENT CONCEPTS

Chronic Lung Disease after Premature Birth

Eugenio Baraldi, M.D., and Marco Filippone, M.D.

IN 1967, NORTHWAY ET AL. FIRST DESCRIBED A NEW CHRONIC RESPIRATORY disease, bronchopulmonary dysplasia, that developed in premature infants exposed to mechanical ventilation and oxygen supplementation. Two decades later, the same authors found that clinically significant respiratory symptoms and functional abnormalities persisted into adolescence and early adulthood in a cohort of survivors of bronchopulmonary dysplasia, suggesting that lung injuries early in life may have lifelong consequences. Bronchopulmonary dysplasia is now the most common chronic lung disease of infancy in the United States.

Today, newborns consistently survive at gestational ages of 23 to 26 weeks — 8 to 10 weeks younger than the infants in whom bronchopulmonary dysplasia was first described. New mechanisms of lung injury have emerged, and the clinical and pathological characteristics of pulmonary involvement have changed profoundly, although its natural history and outcome into adulthood are still largely unknown. It is only now that large populations of persons born prematurely are approaching adulthood, and they may be at increased risk for respiratory disease in adult life.
Antenatal Exposures
- Steroids
- Chorioamnionitis
- Intrauterine growth restriction

Genetic susceptibility

Premature delivery

Stages of lung development
- Canaliculr stage: 16 wk
- Saccular stage: 23 wk
- Alveolar stage: 32 wk, 38 wk

Developmental arrest or delay
- New bronchopulmonary dysplasia

Structural injury
- Old bronchopulmonary dysplasia

Postnatal Exposures
- Ventilator-induced lung injury
- Oxidative stress
- Infections
- Steroids
- Pulmonary fluid overload
- Nutritional deficits

Normal development

Figure 1. Stages of Lung Development, Potentially Damaging Factors, and Types of Lung Injury.

In premature newborns, the lungs are often exposed to several sources of injury, both before and after birth. Such exposures — as well as genetic susceptibility to problematic lung development — may cause direct airway and parenchymal damage and induce a deviation from the normal developmental path. Depending on the timing and extent of the exposures, lung injury may range from early developmental arrest (new bronchopulmonary dysplasia) to structural damage of a relatively immature lung (old bronchopulmonary dysplasia). Premature infants born at a gestational age of 23 to 30 weeks (region shaded light red) — during the canalicular and saccular stages of lung development — are at the greatest risk for bronchopulmonary dysplasia.
Figure 3. FEV₁ Values in Children, Adolescents, and Young Adults Who Were Born Prematurely and Had Bronchopulmonary Dysplasia, as Compared with Controls Born at Term.
Figure 4. Theoretical Model of Changes in FEV₁ in Survivors of Bronchopulmonary Dysplasia and Healthy Subjects According to Age.

Theoretical curves are shown for the forced expiratory volume in 1 second (FEV₁) in healthy subjects and survivors of bronchopulmonary dysplasia. Survivors of bronchopulmonary dysplasia may have variable airflow limitation from the first years of life, with little evidence of “catch-up” growth in lung function. In some of these patients, FEV₁ does not reach the normal maximal value in early adulthood, and the phase of declining FEV₁ values starts from a substantially reduced maximal value. Whether the rate of decline with advancing age will parallel that among healthy persons or will be accelerated is not known. The dashed lines represent the potential effect of smoking on the rate of decline of FEV₁ in susceptible subjects. Values for FEV₁ in the first 3 years of life are extrapolated from measurements of maximal flow at functional residual capacity. Adapted from Fletcher and Peto.⁶¹
Asthma

Atopy associated
Persistent
Tucson study - outcome of asthma and wheezing in the first 6 yr of life - follow up through adolescence

Morgan WJ et al. AJRCCM 2005; 172: 1253-1258
Dunedin study – longitudinal population based study of childhood asthma followed to adulthood

Sears MR, NEJM 2003; 349: 1414-1422

**Figure 2.** Mean (± SE) FEV₁:FVC Ratios Measured at 9, 11, 13, 15, 18, 21, and 26 Years in Male (Panel A) and Female (Panel B) Study Members, According to the Pattern of Wheezing.
Change in Weight vs. Change in Lung Function

154 infants from a general population, recruited antenatally, studied at 1 & 12 months

• METHODS
  - Weight gain, VmaxFRC
  - Wheeze symptoms from questionnaires
  - Infant feeding practices determined

Thorax 2008; 63: 234-9
The greater the weight gain, the lower the growth in lung function.
Identify a High Risk Group

• Babies of smoking mothers

• Patterns of weight gain in first year of life

• Smoke exposure postnatally

• Obesity
Key issues to bring home

• Antenatal Indoor Pollution
• Events *in utero*
• Patterns of weight gain
• Viral infections
• New onset of wheezing among females (obese) in adolescence
Action on Smoking—Public Health

- Ban smoking in public places
- Ban all tobacco advertising everywhere
- Ban selling of tobacco to children
- Raise the prices of tobacco

Who smokes a $50 cigarette?
What is our working plan?

• Research on European and local level
• More caution to environmental influences on pregnant women
• Identify children from the risk groups EARLY
• Treatment and all other measures to protect lung function in children
Hvala na pažnji!
Thank you for your attention!