Perinatal Exposure to Tobacco and Respiratory and Allergy Symptoms in First Years of Life

Bibiana Fríguls, Óscar García-Algar, Carme Puig, Cecilia Figueroa, Jordi Sunyer, and Oriol Vall

ARTICLE INFO

Background and objectives: To analyse the relationship between prenatal and postnatal tobacco exposure and the development of respiratory and allergy symptoms during the first 4 years of life.

Patients and methods: Prospective and multicentred cohort study that included the subjects belonging to AMICS (Asthma Multicentred Infant Cohort Study) located in Ashford (England), Barcelona and Minorca (Spain). We recruited 1611 children, followed from the pregnancy to the 4th year of life, whose parents annually answered a questionnaire on their tobacco consumption and their children’s respiratory and allergy health. In the Barcelona cohort (n=487) a tobacco exposure biomarker (cotinine) was analysed on several matrices.

Results: Prenatal tobacco exposure is associated with a greater risk of hospitalisation due to respiratory infection, particularly in the second year of life, whereas postnatal tobacco exposure is associated more strongly with the presence of late wheezing presence and increases in the chance of being diagnosed with asthma at 4 years of age. The children prenatally and postnatally exposed had more persistent wheezing, persistent roncus, early cough, a higher number of upper respiratory infections per year and a greater number were diagnosed with asthma. The higher the levels of cotinine measured, the higher was the risk for wheezing. No relationship was seen between tobacco exposure and atopic symptoms.

Conclusions: Passive smoke exposure during pregnancy and childhood has very distinct clinical respiratory effects in children. Therefore, smoking cessation of childbearing age women must be a priority of preventive medicine.

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Introduction

Paediatric respiratory diseases are extremely common and account for a high percentage of morbidity, medical visits and hospital admissions, as well as placing a high monetary cost on the public health system. The most frequent causes of lower respiratory disease are infections and asthma. Asthma, the most common chronic illness in children, is a significant global public health problem with a high prevalence rate, and it is on the rise in industrialised areas. The rapid increase in juvenile asthma prevalence leads us to believe that environmental exposure plays an important role in this disease’s aetiology, and that one of those key environmental factors in its development could be exposure to tobacco smoke.

In the last two decades, different studies have been carried out with the aim of defining the association between tobacco smoke and asthma. There is conclusive evidence as to the relationship between exposure to tobacco smoke and the development of respiratory symptoms, particularly wheezing. Today, much emphasis is placed on identifying the most critical periods for exposure to tobacco smoke by studies that mainly examine in utero or postnatal exposure. In this respect, there are currently few studies that compare effects of pre- and postnatal tobacco smoke exposure, and the few that do so provide contradictory results. The AMICS project (Asthma Multicentric Infant Cohort Study) which combines efforts by centres in Ashford, Barcelona and Menorca, proposes an excellent framework for researching the most damaging periods for exposure to tobacco smoke and relating those periods with the respiratory symptoms which then arise.

Patients and Methods

Between 1994 and 1998, three cohorts were created in three different European locations: Ashford (UK), Barcelona and Menorca (Spain). Follow-up was carried out for all children included in the study from the pre-natal period up to four years of age by means of annual questionnaires to obtain information about parents’ tobacco use before, during and after pregnancy, and about any respiratory and allergic symptoms the children presented. The children’s anthropomorphic measurements were taken at birth and at four years of age.

Paediatricians who followed standard criteria in normal clinical practice established the numerous diagnoses based on the questionnaire and a review of the clinical history. We employed the working definition used by paediatricians at the 3rd International Paediatric Consensus group, which defines asthma as the presence of “episodic wheeze and/or cough in a clinical setting where asthma was likely and other, rarer conditions had been discarded”. This definition is more applicable to infants and toddlers. The term “wheezing” was also used to define different clinical patterns for this disease: transient early wheezing, late-onset wheezing and persistent wheezing.

Based on the brand of cigarettes consumed by mothers and other adults in the child’s household, we calculated the mother’s daily nicotine intake (DNI) and the child’s daily exposure to nicotine (DEN) by adding the DNIs of the mother and other adults in the household in the following manner: DNI = number of cigarettes per day × mg nicotine per cigarette, DEN = sum of DNIs for each smoker × hours per day spent with smoker/24.

A fluoro-immunosassay (Pharmacia CAP System) was used to measure total immunoglobulin E concentrations (IgE) in umbilical cord blood at birth and in the child’s venous blood in its fourth year. The same technique was also used to analyse specific IgEs for dust mite and cat hair antigens in the children’s blood plasma when they were four years old. The variables total IgE and specific IgE were treated as a continuous logarithmic distribution.

In the Barcelona cohort, cotinine was measured in umbilical cord blood, maternal urine, and foetal urine at birth, as well as in the child’s urine at four years of age using the radioimmunoassay technique.

Statistical Analysis

The χ² and ANOVA tests were used for bivariate analyses, while linear or logistic regression was used for multivariate analyses depending on the variable type. All statistical analyses were performed with Stata software, version 8.

Results

The Ashford cohort included 634 mothers and 642 children; in Barcelona, 480 mothers and 487 children; and in Menorca, 475 mothers and 482 children.

Characteristics of Maternal Tobacco Use

The group percentages according to maternal tobacco use were as follows: Never, 41.8%; always (pre- and postnatal) 26.8%; only before and during pregnancy (prenatal) 3.3%; only before pregnancy (pre-conception) 10.9%; only before and after pregnancy (pre-conception and postnatal) 12.2%; and only after pregnancy (postnatal) 5.2%.

The Barcelona cohort had the highest number of persistent smokers, while Menorca had the highest number of non-smokers. Greater tobacco consumption was observed among the lower social classes. The persistent smokers were younger than the non-smokers. There was a lower presence of atopy among persistent smokers than that among non-smokers. There were no significant differences in asthma prevalence between smokers and non-smokers. Persistent smokers registered a DNI of 20mg/day, double that of those who were occasional smokers before pregnancy. In general, the percentage of women who stopped smoking upon becoming pregnant was 40.1%. 30.1% of the mothers smoked during pregnancy. Of the women continuing to smoke during pregnancy, daily consumption decreased by 70% on average compared to previous consumption habits. After delivery, their tobacco use rose to 80% of the amount initially consumed. The prevalence of maternal tobacco use throughout the first four years of motherhood ranged between 30 and 40%.

Respiratory Symptoms

Prenatal exposure. The group of children exposed to tobacco only during the prenatal period presented a higher incidence rate of hospitalisation due to respiratory infection than children of non-smokers. This was true for both the first and second years of life...
Atopic symptoms and Immunoglobulin E

Atopic mothers’ children who are exposed to tobacco smoke in the postnatal period have a 3.7 times higher risk (95% CI, 1.1-11.24) of presenting allergic rhinoconjunctivitis between the ages of one and two; by the age of four, this risk is 2.61 times higher (95% CI, 1.29-4.72), three (OR = 2.51; 95% CI, 1.43-4.37) and four (OR = 1.84; 95% CI, 1.13-3.01) than children with no exposure. No statistically significant differences between children with and without exposure to tobacco were found for the number of otitis cases.

**Table 1**
Association between maternal tobacco use and wheezing patterns

<table>
<thead>
<tr>
<th>Groups</th>
<th>Early wheezing</th>
<th>Persistent wheezing</th>
<th>Late-onset wheezing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.46 (0.98-2.18)</td>
<td>2.18 (1.49-3.20)</td>
<td>1.41 (0.80-2.48)</td>
</tr>
<tr>
<td>2</td>
<td>0.72 (0.25-2.02)</td>
<td>1.16 (0.45-2.96)</td>
<td>1.07 (0.76-2.22)</td>
</tr>
<tr>
<td>3</td>
<td>0.85 (0.53-1.36)</td>
<td>0.79 (0.47-1.31)</td>
<td>1.15 (0.58-2.31)</td>
</tr>
<tr>
<td>4</td>
<td>0.80 (0.50-1.28)</td>
<td>1.14 (0.71-1.81)</td>
<td>1.42 (0.96-2.88)</td>
</tr>
<tr>
<td>5</td>
<td>1.08 (0.56-2.08)</td>
<td>0.96 (0.47-2.08)</td>
<td>2.48* (1.08-5.71)</td>
</tr>
</tbody>
</table>

The values express the odds ratio (95% confidence interval). Analysis adjusted for location, sex, breastfeeding, maternal asthma, paternal tobacco use, birth weight, number of siblings and number of people in household. Maternal age and social class do not affect the model. The maternal tobacco use groups according to reporting on the questionnaire are: 1: always; 2: only prenatal; 3: only pre-conception; 4: only before and after pregnancy; 5: only postnatal.

*p < 0.05 with regard to the control group (no consumption).

**Table 2**
Anthropometric parameters in newborns and children aged four years according to maternal tobacco use habits

<table>
<thead>
<tr>
<th></th>
<th>Never (n=250)</th>
<th>Always (n=234)</th>
<th>Prenatal (n=228)</th>
<th>Before pregnancy</th>
<th>Before and after pregnancy</th>
<th>Postnatal (n=228)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (mothers)</td>
<td>644</td>
<td>413</td>
<td>47</td>
<td>169</td>
<td>185</td>
<td>81</td>
</tr>
<tr>
<td>Males (%)</td>
<td>52.3</td>
<td>55.6</td>
<td>51.0</td>
<td>50.0</td>
<td>52.4</td>
<td>49.3</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3.306±0.530</td>
<td>3.133±0.479*</td>
<td>3.241±0.547</td>
<td>3.434±0.508</td>
<td>3.320±0.622</td>
<td>3.379±0.545</td>
</tr>
<tr>
<td>Length at birth (cm)</td>
<td>50.3±3.0</td>
<td>49.3±2.5*</td>
<td>49.0±2.3*</td>
<td>50.8±2.8</td>
<td>50.2±3.6</td>
<td>51.6±3.0</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>34.2±1.5</td>
<td>33.9±1.5*</td>
<td>34.3±1.6</td>
<td>34.3±1.5</td>
<td>33.9±1.9</td>
<td>34.0±1.4</td>
</tr>
<tr>
<td>Premature (&lt;37 weeks)</td>
<td>6.7</td>
<td>6.1</td>
<td>6.3</td>
<td>5.3</td>
<td>4.8</td>
<td>8.6</td>
</tr>
<tr>
<td>Low birth weight (&lt;2500 g)</td>
<td>6.5</td>
<td>9.0</td>
<td>10.6</td>
<td>1.7</td>
<td>7.0</td>
<td>7.4</td>
</tr>
<tr>
<td>Breastfeeding (%)</td>
<td>78.8</td>
<td>64.5*</td>
<td>63.8*</td>
<td>70.9</td>
<td>73.3</td>
<td>60.7</td>
</tr>
<tr>
<td>Weight at 4 years old (kg)</td>
<td>17.6±2.5</td>
<td>17.7±2.8</td>
<td>18.6±3.5</td>
<td>17.7±2.5</td>
<td>17.7±2.3</td>
<td>17.0±2.2</td>
</tr>
<tr>
<td>Height at 4 years old (kg)</td>
<td>104.7±5.3</td>
<td>103.9±5.1*</td>
<td>105.4±4.7</td>
<td>104.6±5.1</td>
<td>104.6±4.4</td>
<td>102.8±4.8</td>
</tr>
</tbody>
</table>

Values expressed as percentages or means (standard deviation).

*p < 0.05 with respect to no consumption.
Values express the odds ratio (95% confidence interval). Analysis adjusted by sex, maternal asthma, number of siblings and number of people in household. Maternal age and social class do not affect the model.

### Table 3

<table>
<thead>
<tr>
<th>Tobacco use groups</th>
<th>Cotinine in umbilical cord blood (ng/ml) Mean</th>
<th>GM</th>
<th>Cotinine in maternal urine (ng/ml) Mean</th>
<th>GM</th>
<th>Cotinine in newborn’s urine (ng/ml) Mean</th>
<th>GM</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.65</td>
<td>1.79</td>
<td>9.31</td>
<td>12.20</td>
<td>7.87</td>
<td>7.49</td>
</tr>
<tr>
<td>1</td>
<td>53.15</td>
<td>35.98</td>
<td>897.0</td>
<td>312.9</td>
<td>379.4</td>
<td>188.9</td>
</tr>
<tr>
<td>2</td>
<td>5.94</td>
<td>9.31</td>
<td>126.85</td>
<td>71.73</td>
<td>81.20</td>
<td>86.39</td>
</tr>
<tr>
<td>3</td>
<td>1.87</td>
<td>2.15</td>
<td>7.87</td>
<td>7.85</td>
<td>8.56</td>
<td>7.37</td>
</tr>
<tr>
<td>4</td>
<td>1.63</td>
<td>2.04</td>
<td>10.22</td>
<td>12.32</td>
<td>10.26</td>
<td>9.59</td>
</tr>
<tr>
<td>5</td>
<td>1.18</td>
<td>0.99</td>
<td>15.60</td>
<td>15.27</td>
<td>9.90</td>
<td>6.34</td>
</tr>
</tbody>
</table>

GM: geometric mean adjusted by mother’s age, sex of the child and paternal tobacco consumption. Maternal tobacco use groups according to self-reporting on questionnaire: 0: never; 1: always; 2: only prenatal; 3: only pre-conception; 4: only pre-conception and postnatal; 5: only postnatal.

*p < 0.05.

### Table 4A

<table>
<thead>
<tr>
<th>Cotinine in umbilical cord blood (ng/ml)</th>
<th>Early wheezing</th>
<th>Persistent wheezing</th>
<th>Late-onset wheezing</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1-14</td>
<td>1.45 (0.45-3.14)</td>
<td>0.71 (0.35-4.76)</td>
<td>0.83 (0.22-7.74)</td>
</tr>
<tr>
<td>&gt; 14</td>
<td>1.72 (1.12-6.18)</td>
<td>1.42 (0.70-6.16)</td>
<td>1.78 (0.82-5.06)</td>
</tr>
</tbody>
</table>

Values express the odds ratio (95% confidence interval). Analysis adjusted by sex, maternal asthma, number of siblings and number of people in household. Maternal age and social class do not affect the model.

*p < 0.05 with regard to the control group (cotinine < 1 ng/ml).

### Table 4B

<table>
<thead>
<tr>
<th>Cotinine in urine (ng/ml)</th>
<th>Wheezing at 4 years old:</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1</td>
<td>1</td>
</tr>
<tr>
<td>10-50</td>
<td>0.88 (0.56-4.18)</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>3.02 (1.71-4.27)</td>
</tr>
</tbody>
</table>

Values express the odds ratio (95% confidence interval). Analysis adjusted by sex, maternal asthma, number of siblings and number of people in household. Maternal age and social class do not affect the model.

*p < 0.05 with regard to the control group (cotinine < 10 ng/ml).

### Discussion

## Respiratory Infections

Data obtained in our study indicate that tobacco use during pregnancy increases the prevalence of hospitalisation due to lower respiratory infections, particularly during the first two years of life, and this effect does not depend on postnatal exposure to tobacco, as other authors have also stated.6

Other studies conclude that postnatal exposure has a decisive influence on the child’s developing respiratory infections, and that tobacco use during pregnancy alone represents an added risk for developing this type of infection.8,13

This increase found in the frequency of infections (probably viral) in children exposed to tobacco smoke during the prenatal period can be explained by their decreased ability to neutralise viruses.13 We have also seen that tobacco use during pregnancy affects the development and maturation of the pulmonary immune system.14 Foetal development is a critical moment of pulmonary vulnerability, which is why smoking during pregnancy is associated with decreased pulmonary function during the neonatal period.15 Likewise, it has been suggested that the effect of prenatal exposure to tobacco on respiratory function may be indirect, by means of a negative effect on anthropometric parameters, which would lead to a decrease in airway size.16 All of these pulmonary changes in the newborn would contribute to the appearance of respiratory infections during the first years of life.

## Wheezing and Asthma

Our study found no association between prenatal exposure to tobacco and wheezing, nor did it find a significant increase in the prevalence of children diagnosed with asthma. However, the consumption of tobacco during the postnatal period only was associated with the appearance of late onset wheezing and the diagnosis of asthma by the child’s fourth year. In an extensive transversal study, Cunningham et al8 also observed an association between postnatal exposure and wheezing. This would indicate that the passive exposure to the child during its infant state would have a greater effect on bronchial hyperreactivity than inflammation. Contrary to our data, Gilliland et al16 conclude that in utero exposure is associated with increased prevalence of diagnosed asthma, a history of wheezing and persistent wheezing, while postnatal exposure is related to both intermittent and persistent wheezing, but not to the diagnosis of asthma. In addition, the Avon9 study observes that both pre- and postnatal exposure, independently, increase the risk of developing wheezing. Similarly, Jaakkola et al8 found that asthma and wheezing are associated with prenatal exposure, and with early postnatal exposure as well.

Our study also detected that environmental exposure to tobacco increases the frequency of medically diagnosed asthma and wheezing, especially when the mother has a history of atopy. On this subject, children with a family history of atopy will be more susceptible to tobacco smoke, and their bronchial hyperreactivity will appear earlier, as some authors indicate.20

According to our results, permanent exposure to tobacco smoke from the gestation period to early childhood is associated with increased prevalence of persistent wheezing, persistent rhonchus, nocturnal cough, common cold episodes per year and a higher risk of being diagnosed with asthma. These observations coincide with...
most published studies. Some mechanisms by which pre- and postnatal tobacco exposure may induce asthma include an irritant effect with an inflammatory response by the mucosa, followed by the appearance of coughing and rhoncus; increased bronchial hyperreactivity with the onset of wheezing; and changes in pulmonary function and increased sensitivity to allergens. Our study did not detect any association between the number of otitis episodes and maternal exposure to tobacco smoke, although some studies conclude that tobacco smoke exposure during infancy is a factor that favours the development of ear infections. One possible limitation in this study could be the presence of biases related to the variability of medical practice and the definitions for different clinical profiles. However, the numerous diagnoses were performed based on the questionnaire and reviewing clinical history according to standardised criteria, and they were compared on an individual basis. Furthermore, we followed the same diagnostic criteria as in the rest of the publications having to do with the AMICS project.

Atopic Symptoms

Some publications describe a positive association between parental tobacco use and rhinitis, rhinoconjunctivitis or allergic phenomena in general. On the contrary, our data show that tobacco smoke exposure is not related to most allergic symptoms unless there is a maternal history of atopy. Results from Strachan et al.’s study support our own; they affirm that parental use of tobacco before or immediately after the birth of the child does not increase atopic sensitivity in children. This could be due to symptoms being independent from the irritant, harmful effects of tobacco. Some Norwegian authors observed a negative association between prenatal exposure to tobacco and the prevalence of atopy in children, and they point out that selective avoidance of tobacco by women with a history of atopy could explain the fact that their children, who have a high genetic component, are not exposed to it.

Immunoglobulin E

According to some authors, exposure to tobacco could increase the total IgE value in infancy through an indirect mechanism that would favour the risk of intercurrent infections. However, specific IgE would only be influenced by exposure to the specific allergen, and tobacco would not contribute at all. In our study, passive exposure to tobacco did not change total or specific IgE levels, whether at birth or by the age of four, as other authors have also observed.

Anthropometric Parameters

The adverse effect that tobacco use during pregnancy has on newborns’ birth weight has been known about since 1957. It is believed that this effect is caused by tobacco temporarily decreasing blood flow in the uterus, with the resulting decrease in oxygen provided from the uterus to the placenta; on the other hand, carbon monoxide in tobacco smoke leads to the formation of carboxyhaemoglobin. All of the above factors lead to decreased oxygenation of foetal tissues and a decreased foetal development rate. We observed that all anthropometric parameters at birth are smaller in children whose mothers are persistent smokers; this group is characterised by high nicotine consumption. Children with isolated prenatal exposure are significantly smaller than those without exposure, but we did not detect differences in birth weight. This is because the average DNI in this group is far more moderate. This indicates an anthropometric response which depends on the amount of tobacco used by the pregnant mother, as some authors have indicated.

Despite the deficient growth caused by tobacco use during gestation, we have not observed any significant differences in the weight and height of children with and without tobacco exposure by the fourth year, which indicates that these children recover their weight correctly. According to our results, there is no evidence that pre- and postnatal tobacco smoke exposure has any permanent effects on growth, as other authors have suggested.

Biomarkers

To rule out the possibility of a bias in the questionnaires owing to overestimating or underreporting childhood tobacco exposure, we decided to include objective measurement with biomarkers in the Barcelona cohort. We chose cotinine, the principle metabolite in nicotine, because it is currently considered the biomarker of choice due to having high specificity and a longer mean lifetime than nicotine. Although some authors believe that tobacco consumption information obtained in a questionnaire can be underestimated, most of all due to low sensitivity, others find a reasonable level of coincidence between biomarkers and information collected in the surveys. Studies published by our group have shown that the questionnaire allows us to differentiate between active smokers and non-smokers, but it is not sensitive enough to distinguish between non-smokers exposed to tobacco and non-smokers with no exposure. In our study, we observed an acceptable level of correlation between cotinine measured at birth and group stratification according to the questionnaire. In addition, our group observed that the cotinine in umbilical cord blood enabled us to distinguish between active maternal tobacco consumption and passive exposure; it even allows us to differentiate between different degrees of daily nicotine exposure and different levels of self-reported DNI. We also observed that the child’s urine cotinine during the fourth year can show different degrees of exposure from the mother, different degrees of exposure from the father, and different degrees of exposure from both parents, which indicates that urine cotinine is a highly sensitive value. Despite consensus that maternal tobacco use affects children less than paternal tobacco use, our group is the only one to have quantified this relationship in a recent study. This indicates that the influence of the mother’s tobacco habit is much more harmful to her children, principally because mothers are more often in contact with them.

Conclusions

Exposure to tobacco smoke has harmful effects on a child’s health, and on its respiratory tract in particular. Prenatal exposure alone increases the frequency of lower respiratory infections during the first years of life, while postnatal exposure to tobacco induces late onset wheezing and asthma. In this moment, it is crucial to limit the dangerous effects of tobacco exposure during the prenatal or postnatal periods. Stopping smoking among childbearing age must be a priority for preventative medicine.

References


