

Perinatal risk factors for recurrent wheeze in early life

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The possible value of tidal flow volume (TFV) loops measured at birth in relation to the risk of developing recurrent or persistent bronchial obstruction within two years of life was assessed. TFV loops were measured at a mean age of 2.7 days in 802 neonates enrolled in the 'Environment and Childhood Asthma' (ECA) study in Oslo. Of these, 77 children developed recurrent or persistent bronchial obstruction (cases) and were included in a nested case-control study within the ECA study; 88 controls (the child born closest in time to the case), with no history of bronchial obstruction in the first two years of life, were also included. Information on socio-economic factors, parental atopic diseases and parental smoking habits during the pregnancy was collected from a questionnaire completed by the parents in the maternity ward, and cord blood IgE (CB-IgE) was determined as part of routine sampling in the delivery ward. Mean t_{PTEF}/t_E (time to reach peak flow to total expiratory time) was slightly lower in cases (0.31; 95% CI 0.28–0.34) than in controls (0.33; 0.31–0.35) (difference not significant), whereas geometric mean CB-IgE was significantly higher among cases (0.39; 0.30–0.52) than controls (0.27; 0.23–0.33). No significant differences between cases and controls were found for respiratory rate, peak tidal expiratory flow or expiratory volume. However, the odds ratio for developing recurrent or persistent bronchial obstruction was 3.5 (1.1–11.6) if t_{PTEF}/t_E was < 0.20 and 4.1 (1.1–14.5) with maternal daily smoking during the pregnancy, after adjusting for age, weight, sex, CB-IgE, parental atopy, maternal education and family income. The TFV parameter $t_{PTEF}/t_E < 0.20$ measured within the first week of life as well as maternal daily smoking during pregnancy are significant, independent risk factors for developing recurrent or persistent bronchial obstruction within the first two years of life.

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Despite many studies assessing factors associated with the development of asthma during childhood (1–6), only risk factors, but not predictors very early in life, have been identified which are associated with the later development of asthma. Adding to this, there is no consensus as to definition of asthma during early childhood. Consequently, many studies have used the symptom/sign of wheeze or recurrent wheeze as an outcome measure.

Reduced lung function measured early in life has been reported to predict the development of obstructive airways disease (OAD) during the first three years of life (7,8), but not asthma at the

age of 6 years (9). Also, maternal smoking has been reported as a significant risk factor for transient, recurrent wheeze during early childhood (9), and several studies have demonstrated that maternal smoking may cause diminished lung function shortly after birth (8,10,11). Based upon these studies (7–9), it has been speculated (12) that transient recurrent wheeze during the first few years of life may be due to small-dimension airways, and that the impact of lower respiratory infections becomes less pronounced as the airways grow larger. If this is correct, then diminished airway size should be present and detectable at birth. However, lung function

measurements in most studies (7–10) were performed within the first three months of life, at a time where environmental factors could possibly have exerted an adverse effect on the airways. Little is known about the possible value of lung function measurement immediately after birth in relation to later OAD.

We therefore assessed lung function as soon as possible (and as soon as lung function was stabilized (13)) after birth in a large cohort which was followed to two years of age for the development of obstructive airways disease (the 'Environment and Childhood Asthma' study in Oslo 1992–1993 (14,15)). The aim of the present study was, after completion of the study in 1995, to retrospectively compare initial lung function among those who subsequently developed recurrent or persistent wheeze with that of the controls. Second, an attempt would be made to estimate possible risk of recurrent or persistent bronchial obstruction based upon the level of lung function at birth, adjusting for known and possible risk factors for asthma.

Subjects and methods

Study design

A cohort of 3754 newborns was established in Oslo during 15 months (from 1 January 1992) at the two main birth clinics, Ullevål and Aker Hospitals (14), after consent from the regional ethics committee. Inclusion criteria were: permanent Oslo address, minimum birth weight 2000 g, absence of illness likely to impair respiration (severe respiratory, cardiovascular, neuromuscular or metabolic disease), no requirement for assisted ventilation or oxygen therapy after 6 h of life, at least one Norwegian-speaking family member and the child living with at least one biological parent. In the largest maternity ward at Ullevål Hospital (mainly healthy babies and mothers), lung function measurements were performed in as many of the enrolled babies as possible during daytime throughout 1992. Details of enrolment into the lung function cohort have been described previously (14). A total of 803 healthy neonates with measurements of tidal breathing parameters ($n = 802$) and/or passive respiratory mechanics ($n = 663$), as previously reported (14), were included into a 'lung function cohort' from which the present study population was recruited.

Cord blood immunoglobulin E (CB-IgE) was sampled in as many as possible of the whole cohort, but due to technical and sampling error, results were available only from 57 of the

subsequent cases and 75 of the subsequent controls.

Questionnaires regarding health of the child, family history of disease, socio-economic factors, and exposure to various pollutants and allergens were completed by the parents every 6 months from birth through to the child's second birthday. In seeking to examine and include as cases all children from the cohort with recurrent or persistent wheeze, several measures were instituted: the questionnaires were assessed for possible symptoms suggestive of OAD, the participating parents were encouraged to liberally report symptoms or signs suggestive of recurrent or persistent wheeze, all local family doctors and well-baby clinics were informed and asked to refer children with possible or established OAD to the project doctor, and special cards (returned and replaced every six months) with boxes for each of five signs related to OAD were distributed to the parents to be completed by any doctor who examined the child during a respiratory tract illness. Any of these events would lead to an invitation to bring the child to the clinic for examination and subsequent inclusion as a case if the criteria were fulfilled.

A nested case-control design was chosen (as resources did not allow clinical investigation of all 3574 children) to assess possible influencing factors upon the health of children developing recurrent or persistent wheeze compared to children who did not have a history of lower respiratory tract disease. Cases for the nested case-control study were defined as soon as they had experienced at least two episodes of bronchial obstruction or persisting bronchial obstruction for at least 4 weeks. At least one episode of bronchial obstruction had to be verified by a doctor, with a history highly suggestive of a further bronchial obstruction. A control was chosen as soon as possible after definition of a case. The control was the child with no history suggestive of bronchial obstruction born closest in time to the case. If the cases were recruited from the lung function cohort, we initially intended to include an additional control from the same cohort, if the selected control child had not had lung function measured at birth. However, due to limited resources, this turned out not to be feasible. Thus, many of the cases from the lung function cohort had controls from the total cohort, and vice versa. Consequently, in the present study, the cases and controls were not matched, as this would decrease the number of subjects available for analysis.

Verification of eligibility of case and control status was performed at completion of the study

Table 1. Characteristics of newborn babies who subsequently developed recurrent or persistent bronchial obstruction within the first two years of life (cases), controls with no history suggestive of bronchial obstruction, as well as the entire cohort in whom lung function was measured at birth

	Cases (n = 77)	Controls (n = 88)	Cohort (n = 803)
Postnatal age (days)	2.8 ± 1.2	2.6 ± 0.8	2.7 ± 0.9
Gestational age (weeks)	39.7 ± 1.5	39.8 ± 1.4	39.8 ± 1.3
Birth weight (kg)	3.60 ± 0.58	3.49 ± 0.49	3.57 ± 0.49
Birth length (cm)	50.2 ± 2.9	49.8 ± 3.4	50.1 ± 2.0
Percentage boys	53.2	55.7	53.1
Percentage with parental atopy	63.6	58.0	58.0
Percentage maternal smoking	32.9*	17.2	26.1

*p = 0.05 (between cases and controls) Values are given as mean ± SD. Parental atopy is given as a positive response to ever having asthma, eczema or rhinoconjunctivitis in one or both parents. Maternal smoking is given as a positive response to a question of daily or occasional smoking during pregnancy.

by a group of senior paediatricians at Ullevål Hospital to ensure that inclusion and exclusion criteria were met appropriately.

Subjects

Subjects in the present study comprised those 77 children who at the age of 2 years were defined as cases as well as the 88 children who were selected as controls from the initial lung function cohort. Characteristics of the cases, controls and whole cohort of 803 children (as reported previously (14)) are given in Table 1. Mean postnatal age at the time of lung function measurements was 2.8 and 2.6 days among cases and controls, respectively (not significant), ranging from 1–9 days. Gestational age was estimated according to last menstrual period and maturity estimation by a paediatrician, with a range of 34–42 weeks. None of the infants had signs of disease which might affect respiration at the time of measurement, except a few infants with rapid respiratory rates but with no other sign of disease during testing or the subsequent few days.

Methods

Information on parental atopy (positive response to the question of ever having had parental asthma, rhinoconjunctivitis and/or atopic dermatitis) as well as maternal smoking history was obtained from the questionnaire completed in the maternity ward (11). Blood from the umbilical cord was sampled for IgE analysis as part of routine practice in the delivery ward, stored in a refrigerator overnight and subsequently frozen before later analysis.

Outcome measures

The main lung function prediction variables were tidal breathing parameters and passive respiratory mechanics, compliance and resistance of the total respiratory system, Crs and Rrs, respectively. The main tidal breathing parameter was

the ratio t_{PTEF}/t_E (time to reach peak flow to total respiratory time) which has been shown to differ with OAD (15–17) as well as predict wheeze in children under 3 years of age (18).

Measurements of TFV loops as well as passive respiratory mechanics (single breath occlusion technique) (SensorMedics 2600) (14), were performed in all infants awake, by two investigators only, blinded to parental smoking habits. Measurements were performed as described elsewhere (13,14), with a face mask (Vital Signs inc.) connected to a pneumotachograph (8311 series, Hans Rudolph, Missouri, USA) with a flow range of 0–10 l/min. Dead-space of the system was 2.4 ml, and that of the face mask was 8.4–11 ml.

Four TFV loops were stored for the final analysis, selected from eight temporarily stored curves according to specified selection criteria (14). Details of ratio calculations are described elsewhere (13,14). Passive respiratory mechanics were sampled and stored for analysis as described previously (13,14).

Statistical analysis

Lung function variables were compared between groups using Student's *t* test. t_{PTEF}/t_E was further categorized into three groups, with the lowest group < 1 SD below the mean for the entire cohort, the middle group from mean–1 SD to the mean, and the upper group above the mean; i.e. $t_{PTEF}/t_E < 0.20$, t_{PTEF}/t_E 0.20–0.31 and $t_{PTEF}/t_E > 0.31$, respectively. This grouping was included into the logistic regression analysis. CB-IgE was analyzed by log transformation to give a geometric mean, and further categorized into groups based upon levels as described by Martinez et al. (9). Categorical variables were analyzed using the Kruskal–Wallis test where appropriate. Odds ratio estimates were performed including numerical and categorical variables into a logistic regression analysis. Several factors were included and retained only if they significantly altered the estimates (such as

Table 2. Lung function measurements at birth and CB-IgE levels in children who subsequently developed recurrent or persistent bronchial obstruction by 2 years of age (cases) and those who did not (controls)

	Cases	Controls
Respiratory rate (breaths/min)	59.5 (56.6–62.4)	58.6 (55.5–61.8)
V_E (ml)	24.2 (23.1–25.3)	24.8 (23.8–25.8)
PTEF (ml/s)	64.7 (61.4–68.0)	65.0 (61.2–68.8)
t_{PTEF}/t_E	0.31 (0.28–0.34)	0.33 (0.31–0.35)
Crs (ml/cm H ₂ O)	3.99 (3.68–4.31)	4.13 (3.87–4.39)
Rrs (cm H ₂ O/ml/s)	0.057 (0.048–0.066)	0.053 (0.043–0.063)
CB-IgE (mU/l)	0.39 (0.30–0.52)	0.27 (0.23–0.33) *

Values are given as mean (95% confidence interval), except for cord blood immunoglobulin-E (CB-IgE) which is given as geometric mean (95% CI). None of the lung function values differed significantly between cases and controls, but CB-IgE was significantly (* $p = 0.03$) higher among cases than controls. (V_E , expiratory tidal volume; PTEF, peak tidal expiratory flow; t_{PTEF}/t_E , ratio of time to reach PTEF to total expiratory time; Crs, compliance of the respiratory system; Rrs, resistance of the respiratory system).

month of birth and passive respiratory mechanics (Crs and Rrs)).

Results

The results of tidal breathing parameters and passive respiratory mechanics are given in Table 2 for cases and controls. Mean t_{PTEF}/t_E was slightly lower in cases (0.31) than in controls (0.33) but this was not statistically significant, and none of the other lung function values differed significantly between cases and controls.

Among babies of daily smoking mothers, only two children (one case and one control) had $t_{PTEF}/t_E < 0.20$, whereas the remaining 19 babies had $t_{PTEF}/t_E \geq 0.20$ (Table 3).

Significantly more mothers of cases reported daily smoking during the pregnancy than mothers of controls, and significantly more controls than cases were born of non-smoking mothers ($p = 0.02$) (Table 3).

Geometric mean CB-IgE (95% CI) was significantly ($p = 0.03$) higher among cases (0.39 kU/l; 0.30–0.52) than controls (0.27 kU/l; 0.23–0.33), and significantly more cases (15.8%) than controls (8%) had CB-IgE > 0.9 kU/l.

A $t_{PTEF}/t_E < 0.20$ as well as being born to a daily smoking mother both significantly increased the risk of having recurrent or persistent bronchial obstruction within the first 2 years of life, with odd ratios of 3.50 (1.06–11.61, 95% CI) and 4.06 (1.13–14.46), respectively, when corrected for respiratory rate, gender, birth weight, postnatal and gestational age, CB-IgE, parental atopy, maternal education and family income. Excluding maternal smoking from the analysis did not change the estimate of the odds ratio of $t_{PTEF}/t_E < 0.20$, indicating that the two factors act independently. Passive respiratory mechanics did not significantly influence the risk of developing recurrent or persistent bronchial obstruction in this analysis. Adding the number of cigarettes smoked by daily smoking mothers or birth month into the regression analysis did not improve classification or significantly modify the estimates. No interaction was found between the maternal smoking history and lung function in the regression analysis.

Discussion

Although t_{PTEF}/t_E , Crs and Rrs obtained within the first few days of life were not significantly different between subjects who developed recurrent or persistent bronchial obstruction within the first 2 years of life and controls, the odds ratio for bronchial obstruction was 3.5 with $t_{PTEF}/t_E < 0.20$ compared to ≥ 0.20 at birth, and 4.1 if the mother had smoked daily during pregnancy compared to being born to a non-smoking mother. Crs and Rrs was not related to the development of OAD.

A low value of t_{PTEF}/t_E as a risk factor for OAD as found in the present study supports previous reports (7,19). However, the odds ratio of 3.5 for t_{PTEF}/t_E in the present study is substantially lower than the reported odds ratio of 10.1 for OAD by the Tucson group (7), but more in keeping with the results of Yuksel et al. (19) who found a positive predictive value for t_{PTEF}/t_E of 41%. The time of measurements may contribute to these differences. The present

Table 3. Distribution of maternal daily versus non-smoking by pregnant mothers and t_{PTEF}/t_E below compared to equal to or above the mean–1 SD (for 803 neonates) among cases and controls

	Non-smoking mothers t_{PTEF}/t_E *		Daily smoking mothers t_{PTEF}/t_E	
	< 0.20	≥ 0.20	< 0.20	≥ 0.20
Cases	13	38	1	13
Controls	8	64	1	6

* $p = 0.03$ for number of cases versus controls in relation to t_{PTEF}/t_E among babies born to non-smoking mothers, but not among smoking mothers.

population, and that of Yuksel et al. (19) were measured at birth prior to any known adverse environmental exposure, whereas the Tucson children were on average 3 months old with a possible exposure to environmental tobacco smoke (ETS) at home. Consequently, it is possible that an adverse airway development was more advanced among the older children (7), which was reflected by larger differences in the premorbid lung function. However, the optimal time for lung function measurements in a healthy individual neonate or young infant is still not defined, as age is known to influence both the absolute value of TFV ratios (8,13,14,20) and variability of measurements (13,20).

We previously reported from the same cohort of children (11) that maternal smoking during pregnancy influenced lung function at birth. This is supported by other studies demonstrating adverse effects of ETS upon lung function or airway responsiveness in 1–3-month-old infants (with possible postnatal exposure) by use of partial forced expiratory flow volume curves (8,10,21,22). Consequently, it was decided to correct for maternal smoking during pregnancy rather than postnatal parental smoking in the risk estimation.

The present study suggests that after adjusting for potential confounding factors (cord-blood IgE, maternal smoking during pregnancy, parental atopy, gender, maternal education and family income, time of birth (by month and by season)), both daily tobacco smoke exposure *in utero* as well as low t_{PTEF}/t_E are independent risk factors for developing OAD within the first 2 years of life. Further data strengthen this assumption; Among children born to non-smoking mothers, a significantly larger proportion of babies with $t_{PTEF}/t_E < 0.20$ ($n = 13/21$) subsequently developed OAD compared to babies born with $t_{PTEF}/t_E \geq 0.20$ (38/102), as demonstrated in Table 3. Such a distribution was not seen among babies of daily smoking mothers, of whom only two subjects (one case) had $t_{PTEF}/t_E < 0.20$. This indicates that the increased odds ratio for maternal daily smoking as a risk factor for developing recurrent or persistent bronchial obstruction within the first 2 years of life is unlikely to be a result of low t_{PTEF}/t_E associated with tobacco smoke exposure *in utero*. Also, excluding maternal smoking from the analysis did not change the risk estimate in relation to $t_{PTEF}/t_E < 0.20$. The lack of modifying effect of the number of cigarettes may be attributed to the relatively low number of subjects included in the analysis. Thus, our data suggest that two separate modes of action may account for the increased

risk of early development of OAD. Reduced t_{PTEF}/t_E at birth on the one hand (whether or not they are exposed to maternal smoking *in utero*) may indicate reduced airway size as suggested by the Tucson group (7) and render the airways more liable to wheeze with respiratory infections. On the other hand, even among children without diminished t_{PTEF}/t_E , maternal smoking during pregnancy induces a significant risk to the baby of subsequent development of early OAD.

It is still not clear how uterine tobacco smoke exposure (UTS) or ETS exposure contributes to the increased risk of OAD in early life. However, several mechanisms have been suggested, such as a 'masculinization' (22) of the UTS-exposed female airways towards lower airway size (23), some degree of emphysema (with loss of elastic component of the lungs) in rats exposed to tobacco smoke (24,25), lung hypoplasia (26), insufficiently extended (atelectatic) lungs with poorly developed type II pneumocytes and surfactant (in newborn rats) (27) and disturbed growth of the airways as a result of depressed fetal breathing movements (28). However, as the mechanisms regulating TFV ratios are not clear, it is difficult at present to infer what the changes in ratios reflect.

The role of CB-IgE in the prediction of asthma is uncertain, especially since various factors may influence the level of CB-IgE (29). In contrast to the findings of Martinez et al. (9) in a similar study, the present study demonstrated higher CB-IgE in children with OAD compared to controls. However, a high CB-IgE (> 0.9 IU/l) was not a significant risk factor for developing early OAD in the present study.

UTS exposure assessed as cotinine in cord blood from the Oslo Birth Cohort study corresponded well to reported smoking habits of mothers (10), in agreement with previously reported studies with a good correlation between questionnaire-reported smoking habits and levels of urinary cotinine (10,30,31).

In the present study, male gender was not a significant risk factor for the early development of OAD. This is explained by girls and boys being almost equally represented among cases and controls in the present study.

Defining the likely etiology or separating children with asthma from those who are more likely to have transient recurrent wheeze (9) were beyond the scope of the present study. However, it is likely that the presented estimates of risk factors would change if the children were studied again at school age with asthma as the outcome measure.

Based upon the results of our study, the value of lung function measured at birth may be twofold. Firstly, it indicates an objectively measured risk factor for later development of lower respiratory disease, thereby indicating possible mechanisms underlying the disease. Another possible value may be screening of certain populations at risk. Although the methods presented in our study are relatively simple to perform, the cost-benefit of screening programmes has yet to be evaluated. At the present time, it is not proven that such measurements would be of benefit in single individuals. However, it is likely that simple lung function measurements at birth could yield important additional information as part of primary or secondary prevention programmes in relation to airways disease.

In conclusion, the present study indicates that both low lung function measured at birth as well as maternal daily smoking during pregnancy are independent risk factors for developing OAD within the first 2 years of life.

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