In utero exposure to cigarette smoking influences lung function at birth

K.C. Lødrup Carlsen*, J.J.K. Jaakkola**+, P. Nafstad+, K-H. Carlsen++

In utero *exposure to cigarette smoking influences lung function at birth. K.C. Lødrup Carlsen, J.J.K. Jaakkola, P. Nafstad, K-H. Carlsen. ©ERS Journals Ltd 1997.*
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 (C_{rs}) and resistance (R_{rs}) 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 (t_{PEF}/t_E)), and C_{rs} were significantly lower with active as well as passive maternal smoking compared to nonexposure to UTS. Respiratory rate and R_{rs} were not significantly influenced by UTS exposure. However, in linear regression analysis adjusted for confounding factors (including respiratory rate), t_{PEF}/t_E and C_{rs}, but not R_{rs}, were related to maternal active but not passive daily smoking. One daily cigarette corresponded to a change in t_{PEF}/t_E of -0.0021 (95% confidence interval (95% CI) -0.0040 to -0.0002) and a change in C_{rs} of -0.026 mL·cmH$_2$O (95% CI -0.045 to -0.007 mL·cmH$_2$O). 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.
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*Dept of Paediatrics, Ullevål Hospital, Oslo, Norway, **Environmental Epidemiology Unit, Dept of Public Health, University of Helsinki, Helsinki, Finland. +Section of Epidemiology, Dept of Population Health Sciences, National Institute of Public Health, Oslo, Norway. ++Voksentoppen Centre for Asthma and Allergy, Ullveien, Oslo, Norway.

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

Exposure to tobacco smoke products in early life has been reported to adversely affect respiratory health during childhood. Increased airways responsiveness was found among young infants born to atopic and/or smoking mothers [1], and airflow at functional residual capacity ($V'_{max,FRC}$) was diminished in babies of mothers who smoked during pregnancy, compared to babies of mothers who did not [2]. Also, an increased risk of asthma was reported at 8–11 yrs of age in children exposed to maternal smoking only whilst *in utero* compared to nonexposed children [3]. Thus, early exposure to tobacco smoke appears to be a risk factor for reduced lung function as well as obstructive airways disease (OAD).

Implications of reduced lung function soon after birth are not well established. Premorbid flow limitation has been reported during the first months of life among children who subsequently wheezed by 2 yrs of age [4], and changes in the shape of tidal flow-volume (TFV) loops (ratio of time to reach peak expiratory flow to total expiratory time (t_{PEF}/t_E)) predicted wheezy illness by 3 yrs of age [5], but not asthma at the age of 6 yrs [6].

At present, insufficient data exist to establish the effect upon lung function of uterine tobacco smoke (UTS) exposure compared to postnatal exposure to tobacco smoke. To avoid possible confounding effects of exposure after birth, measurements should, ideally, be obtained within the first days of life, also considering the effects of age and birth weight [7–9].

In 1992–1993, a large prospective cohort study ("Environment and Childhood Asthma"), designed to investigate possible influences of environmental and genetic factors upon the development of OAD in young children, was established in Oslo. One aim of the study was to describe lung function by tidal breathing in healthy newborn babies (previously reported in 803 awake neonates [8]) The study was also designed to assess possible influences of environmental factors upon lung function at birth. Thus, in the present paper, we report the assessment of uterine tobacco smoke exposure upon tidal breathing parameters and respiratory mechanics in relation to maternal active and passive smoking.

Methods

Study population

A cohort of 3,754 newborns was established in Oslo, Norway, during 15 months (from January 1, 1992) at

the two main birth clinics, Ullevål and Aker Hospitals [8], after obtaining consent from the Regional Ethics Committee. Inclusion criteria were: permanent Oslo address; minimum birth weight 2,000 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 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 the day, throughout 1992, restricted only by the time available.

The present study population comprised those 803 healthy neonates with measurements of tidal breathing parameters (n=802) and/or passive respiratory mechanics (n=663), as reported previously [8]. Mean age was 2.7 days (range 1–9 days). Eighty four per cent of the children were measured on day 2 (n=354) or 3 (n= 319) of life. Mean birth weight and gestational age (according to last menstrual period and maturity estimation by a paediatrician) of all the subjects were 3.6 kg (range 2.0–5.2 kg) and 39.8 weeks (range 34–42 weeks), respectively. Further characteristics of the children have been reported previously [8]. None of the infants had signs of disease that might affect respiration at the time of measurement, with the exception of a few infants with rapid respiratory rates, but with no other sign of disease during testing or in the subsequent few days.

Outcome measures

The main outcomes were tidal breathing parameters and passive respiratory mechanics. Tidal breathing parameters were determined by the TFV ratios, t_{PEF}/t_E and V_{PEF}/V_E, which have been shown to differ according to obstructive airways disease; t_{PEF}/t_E [10–12] and V_{PEF}/V_E [10, 11, 13, 14] have also predicted wheeze in children under 3 yrs of age (t_{PEF}/t_E) [5]. Respiratory mechanics were determined as: compliance of the respiratory system (C_{rs}) as a measure of tissue and airways elasticity; and resistance of the respiratory system (R_{rs}) as a measures of airways size.

Measurements of TFV loops, as well as passive respiratory mechanics (single-breath occlusion technique) (SensorMedics 2600; SensorMedics Corp., Anaheim, CA, USA) [8], were performed in all infants whilst awake by only two investigators, blinded to parental smoking habits. Measurements were performed as described previously [7, 8], with a face mask (Vital Signs Inc., Totowa, NJ, USA), connected to a pneumotachograph (8311 series, Hans Rudolph, Missouri, USA) with a flow range of 0–10 L·min⁻¹. The dead space of the system was 2.4 mL, and of the face mask 8.4–11 mL.

Four TFV loops were stored for the final analysis, selected from eight temporarily stored curves according to specified selection criteria [8]. Details of ratio calculations have been described previously [7, 8] A mean of four (range 2–14) flow-volume curves after occlusion for passive respiratory mechanics (four or more in >90% of the children) were stored for analysis as described previously [7, 8].

Exposure assessment

Foetal exposure to UTS was separated into mother's active and passive smoking, as reported by the mother (±the father) in questionnaires completed at the birth clinic. Active smoking was expressed as a numerical variable describing the average daily smoking rate (cigarettes·day⁻¹), and a categorical variable classified into: no smoking; occasional smoking; daily smoking of 1–9 cigarettes·day⁻¹, and ≥10 cigarettes·day⁻¹. Information regarding maternal tobacco smoking during pregnancy was not available in four children, who were subsequently excluded from analysis in the present study.

A good agreement was shown between high and low levels of cord blood biomarkers and daily and non-smoking mothers in a different sample of the cohort [15], indicating that the mothers reported the smoking habits adequately. Maternal passive smoking was a categorical variable only, dichotomized into unexposed and exposed based upon the presence or absence of daily smoking by the spouse or other family members. No attempt was made to specify the period of exposure.

An estimation of increased exposure level was attempted as: no exposure (no active or passive smoking); passive smoking only; occasional smoking (regardless of passive smoking); active smoking 1–9 cigarettes·day⁻¹; active smoking ≥10 cigarettes·day⁻¹; and both active and passive daily smoking. However, when performing analysis of the data, this categorization was not used due to the uncertainties of exposure level (*e.g.* maternal active smoking of 4 cigarettes·day⁻¹ may represent a higher exposure to the baby than two actively and two passively smoked cigarettes·day⁻¹).

Covariates

Information on maternal education, family income, and parental history of atopy was obtained by questionnaire. Atopy in this context was considered positive if one or both parents reported asthma and/or hay fever at any time.

Statistical analysis

The means of tidal breathing parameters and measures of respiratory mechanics were compared in the different categories of active and passive smoking, and differences assessed for statistical significance (two-tailed) using t-test (with calculation of 95% confidence intervals (95% CI) of the means). Wilcoxon's rank test was used when applicable. The relationships between the outcomes and exposure to UTS were estimated in linear regression analysis, adjusting for potential confounders. Indicator variables (coded 1/0) were constructed to represent polytomous covariates in the models. The following core covariates were fitted in all the models: age; gender; birth weight (with and without) gestational age (for respiratory mechanics only); maternal education (1: <12 yrs, 2: 12–15 yrs, and 3: >15 yrs); family income (low: <200,000 Norwegian Kroner (NKr), medium: 200,000–500,000 NKr, and high: >500,000 NKr); parental atopy; and either active or passive smoking.

Birth length was fitted as an optional covariate and retained in case it would change the estimates of interest. Potential modification of the effect of smoking by gender and atopy was assessed by introducing interaction terms and retaining them on the basis of statistical significance of the regression coefficients (p-value less than 0.05 as the limit). A residual analysis of the final models was carried out to assess the fit of the model, and to evaluate the role of possible outliers.

Results

Active daily smoking was reported by 17% of mothers, whereas 10% reported both daily active and passive smoking. Occasional active smoking was reported by 6% of mothers, and occasional smoking with daily passive exposure by 3%. No active smoking was reported by 61% of mothers, but 12% of all mothers reported daily passive, but no active smoking. The median number of cigarettes smoked per day was 11 among both mothers and fathers who reported daily smoking.

Mean birth weight (3.6 ± 0.51 ($\pm$SD) kg) and birth length (50.9 ± 2.2 cm) among boys were larger than among girls (3.5 ± 0.46 kg and 49.6 ± 2.9 cm, respectively; p<0.005), and were reduced by 299 g and 1.9 cm, respectively (both p<0.001) among boys exposed to active and passive maternal smoking compared to nonexposed boys. In girls, the corresponding reductions were 210 g (p=0.03) and 1.0 cm (p=0.02) (characteristics at birth are given for all subjects in table 1). Postnatal age did not differ significantly according to exposure groups.

Tidal breathing parameters

The 82 children exposed *in utero* to active and passive maternal daily smoking had significantly lower mean t_{PEF}/t_E (p=0.04) compared to the 486 nonexposed children (table 2). Similar results were found for the volume ratio V_{PEF}/V_E (p=0.02) (results not shown). The ratios declined with increasing exposure, grouped as: nonexposed; passive maternal exposure only; occasional maternal smoking; active daily smoking 1–9 cigarettes·day^{-1}; active daily smoking $\geq$10 cigarettes·day^{-1}; and maternal active and passive daily smoking (fig. 1). The difference was significant only when comparing babies exposed to active and passive maternal smoking to nonexposed babies (p=0.04).

Respiratory frequency (f_R), however, did not differ significantly according to tobacco smoke exposure (table 2), and there was no significant correlation between f_R and t_{PEF}/t_E.

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

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

Data are presented as percentages, or as mean and SD in parenthesis. Active: only the mother smoked daily; Passive: someone else in the household, but not the mother, smoked daily; Both: mother and father (or someone else in the household) smoked daily; Parental atopy: reported asthma and/or rhinoconjunctivitis at some time in their lives in one or both parent(s); Education: refers to maternal education, 1=<12 yrs, 2=12–15 yrs, and 3=>15 yrs; Income group: reflects family's total income, 1=low, 2=medium, 3=high. [+]: p=0.04; [†]: p<0.005; ***: p<0.001, compared to nonexposed infants.

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

| Active | Passive | n | f_R | t_{PEF}/t_E | C_{rs} mL·cmH$_2$O^{-1} | | | R_{rs} |
					All	Girls	Boys	
No	No	483	58.4 (57.2–59.6)	0.32 (0.31–0.33)	4.18 (4.07–4.30)	4.19 (4.01–4.37)	4.17 (4.02–4.31)	0.051 (0.048–0.055)
Occ.	No	51	60.1 (55.9–64.4)	0.32 (0.28–0.35)	4.12 (3.80–4.45)	4.11 (3.62–4.61)	4.13 (3.67–4.60)	0.050 (0.038–0.062)
Daily	No	52	56.9 (52.9–60.8)	0.31 (0.28–0.34)	3.92 (3.59–4.25)	3.79 (3.06–4.52)	4.12 (3.68–4.56)	0.057 (0.044–0.070)
No	Yes	105	60.2 (57.4–63.0)	0.33 (0.31–0.36)	4.23 (3.95–4.52)	4.20 (3.70–4.70)	4.26 (3.92–4.60)	0.051 (0.047–0.056)
Occ.	Yes	27	56.9 (52.0–61.7)	0.30 (0.26–0.34)	4.19 (3.68–4.71)	4.31 (3.40–5.22)	4.11 (3.56–4.65)	0.047 (0.042–0.053)
Daily	Yes	78	60.7 (57.4–64.0)	0.29 (0.27–0.31)*+++	3.78 (3.51–4.04)+$	3.51 (3.24–3.78)*+‡	4.08 (3.63–4.53)	0.049 (0.044–0.053)

Values are presented as mean, and 95% confidence interval in parenthesis. The exposure groups are based upon: the mother's report of smoking habits during pregnancy (Active, never (No), occasionally (Occ.), or daily); and daily smoking or not by others in the household during the pregnancy (Passive). The number of subjects for each group refers to the number in which tidal flow-volume loops were obtained (total of 796 subjects with reported cigarette exposure). As the effect of cigarette exposure upon C_{rs} was significant only in girls, the results are shown for the whole group as well as in girls and in boys. f_R: respiratory frequency; t_{PEF}/t_E: time to reach peak expiratory flow to total expiratory time; C_{rs}: compliance of the respiratory system; R_{rs}: resistance of the respiratory system. *: p<0.05 and $: p<0.005, compared to nonexposed infants; +: p<0.05 and ++: p<0.01, compared to infants who were not exposed to maternal smoking during pregnancy, but were exposed to passive smoking; ‡: p<0.05, compared to infants whose mothers occasionally smoked during pregnancy and who were also exposed to passive smoking.
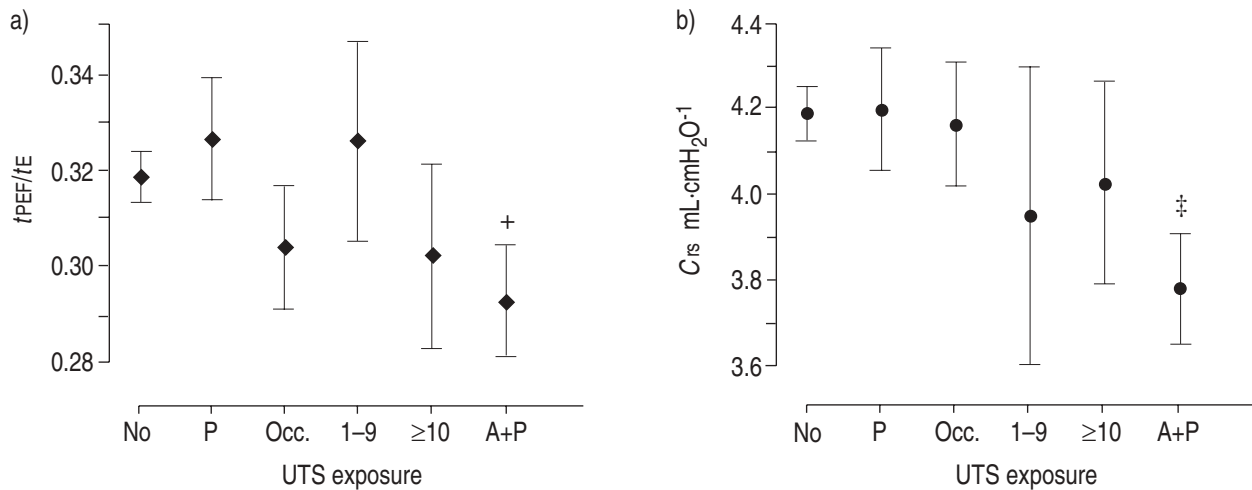
Fig. 1. – a) t_{PEF}/t_E; and b) C_{rs} in newborn babies in relation to maternal smoking. Values are presented as mean and 95% confidence interval. No: no active or passive maternal smoking; P: daily passive (but not active) maternal exposure to tobacco smoke in the household; Occ.: occasional maternal smoking ($\pm$passive smoking); UTS: uterine tobacco smoke exposure; 1–9: maternal active (but not passive) smoking of 1–9 cigarettes·day^{-1}; $\geq$10: maternal active (but not passive) smoking of $\geq$10 cigarettes·day^{-1}; A+P: both active and passive daily smoking. t_{PEF}/t_E: ratio of time to reach peak expiratory flow to total expiratory time; C_{rs}: compliance of the respiratory system. [+]: p=0.04; [‡]: p<0.005, compared to nonexposed group.

In linear regression analysis adjusting for potential confounders (including f_R and the optional covariates), the effect of UTS exposure on tidal breathing parameters was estimated to be a -0.0021 change in t_{PEF}/t_E (p=0.03) per unit increase in daily smoking rate (table 3). Thus, the estimated average decrease in infants of smoking mothers (mean 11 cigarettes·day^{-1}) was 0.023. Tidal breathing parameters were not significantly related to occasional or passive smoking, but were lower in girls, with decreasing birth weight and with increasing postnatal age. Respiratory frequency and parental atopy did not significantly influence t_{PEF}/t_E, but adjusting for maternal education and family income slightly improved the overall fit of the model between exposure and tidal breathing parameters to an r^2 of 0.30.

Respiratory mechanics

Mean C_{rs} was significantly lower among the 66 children exposed to UTS both from active and passive maternal smoking compared to the 422 nonexposed children (p<0.005) (table 2 and fig. 1). The difference was significant only among girls (mean 3.51 *versus* 4.19 mL·cmH$_2$O^{-1}) (p<0.005), (boys 4.08 *versus* 4.17 mL·cmH$_2$O^{-1}; NS). Mean C_{rs}·kg^{-1} in girls (but not boys) exposed to maternal act-

ive and passive smoking (1.08 mL·cmH$_2$O^{-1}·kg^{-1}) was significantly lower than in the nonexposed group (1.22 mL·cmH$_2$O^{-1}·kg^{-1}; p=0.05).

R_{rs} did not vary significantly in relation to UTS exposure (table 2) by any of the analyses performed.

In linear regression analysis, one daily cigarette corresponded to a change in C_{rs} of -0.026 mL·cmH$_2$O^{-1}, (table 3), with an average decrease in C_{rs} among infants of daily smoking mothers of 0.29 mL·cmH$_2$O^{-1}. Postnatal age, birth weight, and f_R also significantly influenced C_{rs} (as reported previously [8]) (table 3). However, C_{rs} was not significantly related to maternal occasional or passive smoking, gender, parental atopy, maternal education, or family income. The latter three did not significantly modify the relationship between tobacco exposure and C_{rs}.

There was no significant association between low C_{rs} in the girls and t_{PEF}/t_E in bivariate correlation analysis.

Discussion

Tidal breathing parameters (t_{PEF}/t_E and V_{PEF}/V_E) within the first few days of life were significantly lower in children exposed *in utero* to maternal smoking, and the

Table 3. – The effects of maternal active and passive cigarette smoking in pregnancy on tidal flow-volume ratio (t_{PEF}/t_E) and compliance of the respiratory system (C_{rs})

	t_{PEF}/t_E			C_{rs} mL·cmH$_2$O^{-1}		
	B	95% CI	p-value	B	95% CI	p-value
Cigarettes·day^{-1} (daily active)	-0.0021	-0.0040 to 0.0000	0.03	-0.026	-0.45 to -0.007	0.007
Passive smoking (yes=1, no=0)	0.0085	-0.012 to 0.029	NS	0.116	-0.099 to 0.330	NS
Gender (1=boy)	-0.019	-0.035 to -0.002	0.03	-0.108	-0.277 to 0.61	NS
Birth weight	-0.022	0.005 to 0.039	0.01	0.255	0.081 to 0.428	0.004
Postnatal age	-0.027	-0.035 to -0.018	<0.001	-0.143	-0.235 to -0.052	0.002
Respiratory frequency	0.0001	0.000 to 0.001	NS	-0.05	-0.056 to -0.043	<0.001

The partial correlation coefficients (B) (with 95% confidence interval (CI)) are adjusted in linear regression for parental history of atopy, maternal education, family income, and either active or passive smoking. The average number of cigarettes smoked by the daily active smoking mothers was 11. Subsequently the mean decrease in t_{PEF}/t_E in infants of daily smoking mothers was 0.023, with the corresponding decrease in C_{rs} of 0.29 mL·cmH$_2$O^{-1}. NS: nonsignificant. For further definitions see legend to table 2.

decline in ratios was inversely proportional to the reported amount of cigarettes smoked per day. C_{rs} was significantly lower in female babies exposed to UTS *in utero* independent of birth weight. No significant association was found between R_{rs} and maternal active or passive smoking.

To our knowledge, reductions in TFV ratios in children exposed to UTS have not been reported previously. Changes in tidal breathing parameters in the present study are not directly comparable to measures of breathing parameters by partial forced expiration. How-ever, adverse effects of environmental tobacco smoke upon lung function or airways responsiveness in 1–3 month old infants (with possible postnatal exposure) have been reported from Perth and Boston by use of partial forced expiratory flow-volume curves [1, 2, 4, 16].

Theoretically, t_{PEF}/t_E could be influenced by f_R. A correlation has been reported between f_R and both t_{PEF} and t_E [17] in children with recurrent lower airways disease. Furthermore, the observed decline in t_{PEF}/t_E with increasing age was explained entirely by an increase in t_E, (with decreasing f_R) in another study [4]. However, f_R was not significantly reduced according to UTS exposure in the present study, and we found no significant correlation between t_{PEF}/t_E and f_R. Thus, it is unlikely that the decrease in t_{PEF}/t_E found in relation to UTS exposure could be explained by differences in f_R. Moreover, in the regression analysis, f_R, age, gender and birth weight were all adjusted for, strengthening the findings in the group comparisons of an adverse effect of UTS exposure.

It has also been suggested that the t_{PEF}/t_E may, to some extent, reflect expiratory braking [18] in healthy newborn babies, and that this may be associated with respiratory mechanics. In the present study, there was no significant association between R_{rs} or low C_{rs} and t_{PEF}/t_E. Thus, the effects of UTS exposure upon t_{PEF}/t_E seem to be independent of respiratory mechanics obtained by the single-breath occlusion technique.

The present study was designed to obtain measurements as soon as possible after birth to avoid possible confounding effects of even brief postnatal exposure of tobacco smoke [1, 2, 4, 16]. The timing of these measurements was based upon a pilot study performed to assess the optimal time to perform lung function tests within the first few days of life [7], and we therefore assessed the effects of *in utero* (but not postnatal) exposure to tobacco smoke in subjects with a mean age of only 2.7 days. Although HANRAHAN *et al.* [2] found no significant effect of exposure to UTS by stratifying for postnatal tobacco smoke exposure, the numbers of subjects exposed to tobacco smoke in their study was low (21 continuously smoking mothers), and possible influences would thus be difficult to detect. Potential confounders, such as parental atopy, maternal education and family income, were adjusted for in linear regression analysis in the present study. The reduced TFV ratios and C_{rs} in children exposed to tobacco smoke in the present study are, therefore, likely to be a true reflection of adverse effects of exposure *in utero*.

The significant reduction in C_{rs} in newborn girls exposed to UTS has, to our knowledge, not previously been reported, although others have suggested that C_{rs} was lower in 1 month old babies exposed to tobacco smoke [4, 19]. Whereas YOUNG *et al.* [4] reported reduced C_{rs} as well as increased R_{rs} in 19 children with flow limitation (of forced expiratory flow-volume loops) with a history of parental atopy and/or smoking, BROWN *et al.* [19] found nonsignificant reductions in time constant and C_{rs} in 10 infants exposed to maternal smoking *in utero*. The reason why the effect of UTS was greater on girls than on boys is not clear. However, in support of our findings, a greater impact of exposure to UTS on girls than on boys was reported in relation to a decrease in $V'_{max,FRC}$ [16], whereas no gender difference was reported by BROWN *et al.* [19].

The C_{rs} values in the present study of awake neonates were lower than in sedated infants in other studies [4, 19]. This is probably explained by previously observed differences in C_{rs} related to arousal state [20]. However, the present 10% reduction in C_{rs} among girls, as well as 9% lower t_{PEF}/t_E among tobacco smoke-exposed neonates, is in agreement with the estimated 13% reduction in C_{rs} in 10 children (NS) reported by BROWN *et al.* [19].

Regression analysis indicated that the effects of exposure to UTS upon tidal breathing parameters and C_{rs} were independent from the effects upon birth weight. The underlying mechanisms for our findings of decreased TFV ratios and decreased C_{rs} with UTS exposure is not clear. It has been suggested that there may be a "masculinization" [16] of the UTS-exposed female airways, towards lower airway size and/or decreased airway compliance [19]. Animal studies have demonstrated some degree of emphysema (with loss of elastic component of the lungs) in rats exposed to tobacco smoke [21, 22], lung hypoplasia [23], and, in newborn tobacco-exposed rats, the lungs were found to be insufficiently extended (atelectatic) with poorly-developed type II pneumocytes and surfactant [24]. Also, disturbed growth of the airways as a result of depressed foetal breathing movements have been suggested as possible consequences of maternal smoking during pregnancy [25], These experimental data support our finding of a decreased C_{rs}. However, as the mechanisms regulating TFV ratios are not clear at present, it is difficult to infer what the changes in ratios reflect.

All babies in the maternity ward (with generally healthy babies) who met the inclusion criteria were eligible for measurements, which were performed in as many infants as possible during the day, restricted only by the time available. Thus, the risk of selection bias among the infants was minimized, as was the risk of information bias as measurements were performed without knowledge of the family's smoking habits. UTS exposure assessed as cotinine in cord blood from the Oslo Birth Cohort study corresponded well to the reported smoking habits of mothers [2], in agreement with previously reported studies, with a good correlation between questionnaire reported smoking habits and levels of urinary cotinine [2, 26, 27].

The adverse changes in lung function demonstrated in the present study are within the range of interindividual variability in healthy awake newborns. Thus, such measurements are not likely to be of prognostic value in individual babies. However, these methods are important epidemiological tools to detect significant, but relatively weak associations requiring large sample sizes.

In conclusion, measurements in a large study population of healthy, awake, newborn babies demonstrated that maternal active smoking during pregnancy adversely influences tidal breathing parameters, and, in girls, compliance of the respiratory system, independently of the effect upon the size of the baby. This is yet another strong case for urging mothers to cease cigarette smoking not only when rearing a child, but also when bearing one.

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