Eur Respir J 2004; 24: 722–723
DOI: 10.1183/09031936.04.00100104

European Respiratory Journal
ISSN 0903-1936

EDITORIAL

The womb and lung function later in life

E.J.L.E. Vrijlandt, J. Gerritsen

The information about the *in utero* influences on the development of the lungs and lung function is limited. No measurements are available at present to objectify this, and all studies in humans describing early determinants of airway function mention placental function, birth weight in relation to gestational age, sex and ethnicity, environmental factors, such as smoking, nutrition of the mother, and respiratory infections of the neonate. In fact, the womb is a black box where many factors influence the development of the foetus and, in particular, the lungs. Another complicating factor is that before birth the lungs are not involved in gas exchange and are not fully expanded.

Negative effects on lung development can result from either: mother-related factors, including hypoxia, intoxications and other causes of intra-uterine stress, like pre-eclampsia, which leads to growth retardation and often to premature birth; or child-related factors, such as foetal diseases like congenital renal abnormalities and diaphragmatic hernias.

In this issue, GREENOUGH *et al.* [1] present interesting data on the effects of intra-uterine growth retardation (IUGR), in children born prematurely, on the severity of lung function impairment. The most important findings of their study include a significant relationship between airway resistance, on the one hand, and IUGR, maternal smoking and bronchopulmonary dysplasia, on the other hand.

Almost no data on the impact of IUGR on lung function during infancy are available, until now, despite the known association between IUGR, subsequent airway function and morbidity in later life. GREENOUGH *et al.* [1] compared children, who were small for gestational age (SGA), with children born with an appropriate weight for gestational age (AGA). The significant differences in body weight, median airways resistance (Raw) and specific conductance (sGaw) compared with AGA children at follow up (6–24 months old) might confirm that pre-natal factors play an important role. Total lung volume measured with the body plethysmograph and with the helium-dilution method were similar in both groups and were significantly related to weight at testing, independently of all other factors *i.e.* also birthweight. Maternal smoking had significant associations with raised Raw and lower sGaw at follow up [1].

A known risk factor for the impairment of lung function at follow up is being SGA and has been confirmed in several studies in different age categories. Reduced airway function, in relation to being SGA, has already been found when measured in early infancy at 6 weeks and, thus, before the onset of any lower respiratory illness. However, it has also been found during school age, or during adolescence [2–5]. The main issue is whether or not diminished airway function is caused by impaired somatic growth. GREENOUGH *et al.* [1] report that low birth weight itself did account for a proportion of the reduction. Also, in children of school age, relatively impaired airway function was observed in the very low birth weight children. However, this was not related to differences in body dimensions, as the dimensions were similar to that of the controls [6]. Another appealing result in the study by GREENOUGH *et al.* [1] is the association between raised Raw and maternal smoking, because smoking is one of the few preventable causes of raised Raw. In other studies, maternal smoking, but not smoking by other members of the household, was independently associated with a reduction in expiratory flow indices [5, 6].

The number of participants in the study by GREENOUGH *et al.* [1] is rather large, taking into account that they had to sedate the infants. This often throws obstacles in the way of getting parental permission to participate. The question crops up whether the present number is large enough to tease out interactions. Other studies have shown dysfunction of the respiratory units and alveolar development [7] and it would be quite interesting to explore why lung volumes are not different in the study by GREENOUGH *et al.* [1]. Normally young males are more susceptible to pre- and post-natal influences than girls; in the study by GREENOUGH *et al.* [1] no differences in lung function between young males and females were found. Reasons for this might be the proportion of male subjects in the study by GREENOUGH *et al.* [1] and the high variability of the methods. Male sex was found to be associated with poor airway function in low birth weight cohort [6], and other authors have reported that young males perform less well at partial expiratory manoeuvres and are more likely to suffer from respiratory problems [8, 9].

Another remarkable point is that infants were measured between 6–24 months of age; the latter is rather old for investigating pre-natal influences. Infants should preferably be as young as possible to allow investigations of pre-natal influences, such as exposure to passive smoking (prior to any post-natal exposures or respiratory infections). Many factors are associated with growth retardation and it is of interest to investigate what the relationship was between the cause of growth retardation and lung function. In other words, do children whose mothers have suffered from, as an example, pre-eclampsia, develop other problems than do children of smoking mothers? Immediately, we admit that it seems rather difficult to evaluate this complex topic because it is possible that, for example, smoking results in, not only IUGR, but also has a direct effect on Raw in infants [10]. Therefore, the number of participants of such a study should be large.

It is clearly demonstrated in the study by GREENOUGH *et al.* [1] that premature infants who suffered IUGR may be at risk of impaired lung function at follow up. The role of birth weight has been stressed in studies concerning the foetal origin hypothesis. This hypothesis suggests that organ function in later life is programmed by impaired foetal nutrition or growth at a critical period of organ development [11]. Infants who are SGA with growth retardation will

Dept of Pediatric Pulmonology, Beatrix Children's Hospital, University Hospital Groningen, Groningen, the Netherlands.

Correspondence: E. Vrijlandt, Beatrix Children's Hospital, Hanzeplein 1, NL 9713 GZ, PO Box 30.001, NL 9700 RB Groningen, the Netherlands. Fax: 31 503614235. E-mail: e.j.l.e.vrijlandt@bkk.azg.nl

consequently be at risk. Malnutrition will affect lung growth pre- and post-natally and will have the greatest effect at the time of rapid alveolar development [12].

In contrast, impaired airway function is not simply due to smaller post-natal body size or poorer post-natal growth. Airway function is diminished in early post-natal life as a consequence of a complex causal pathway, which includes social disadvantage, as indicated by maternal social class, smoking and height, birth weight as a proximal and related consequence of these factors, and a genetic predisposition to asthma [3]. Hence, multiple factors can influence airway and lung function. It is not only prematurity, neonatal disease, its treatment and other post-natal factors which are important, but IUGR also seems to play a major role.

Future studies should be focused on the causal relationship between growth retardation and pre-and post-natal development of the lungs. This information might be important and would create possibilities for early intervention in order to improve the outcome in the long term. This may allow unravelling of the "hen and the egg" question about factors affecting lung development in the womb and post-natally.

References

1. Greenough A, Yuksel B, Cheeseman P. Effect of *in utero* growth retardation on lung function at follow-up of prematurely born infants. *Eur Respir J* 2004; 24: 731–733.
2. Hoo AF, Stocks J, Lum S, *et al.* Development of lung function in early life: influence of birthweight in infants of non-smokers. *Am J Respir Crit Care Med* 2004; 170: 527–533.
3. Dezateux C, Lum S, Hoo AF, Hawdon J, Costeloe K, Stocks J. Low birth weight for gestation and airway function in infancy: exploring the foetal origins hypothesis. *Thorax* 2004; 59: 60–66.
4. Rona RJ, Gulliford MC, Chinn S. Effects of prematurity and intrauterine growth on respiratory health and lung function in childhood. *BMJ* 1993; 306: 817–820.
5. Boezen HM, Vonk JM, van Aalderen WM, *et al.* Perinatal predictors of respiratory symptoms and lung function at a young adult age. *Eur Respir J* 2002; 20: 383–390.
6. Chan KN, Noble-Jamieson CM, Elliman A, Bryan EM, Silverman M. Lung function in children of low birth weight. *Arch Dis Child* 1989; 64: 1284–1293.
7. Hjalmarson O, Sandberg K. Abnormal lung function in healthy preterm infants. *Am J Respir Crit Care Med* 2002; 165: 83–87.
8. Hoo AF, Dezateux C, Hanrahan JP, Cole TJ, Tepper RS, Stocks J. Sex-specific prediction equations for Vmax (FRC) in infancy: a multicenter collaborative study. *Am J Respir Crit Care Med* 2002; 165: 1084–1092.
9. Martinez FD, Morgan WJ, Wright AL, Holberg CJ, Taussig LM. Diminished lung function as a predisposing factor for wheezing respiratory illness in infants. *N Engl J Med* 1988; 319: 1112–1117.
10. Kooi EMW, Vrijlandt EJLE, Boezen HM, Duiverman EJ. Children with smoking parents have a higher airway resistance measured by the interruption technique. *Pediatr Pulmonol* 2004; (In press).
11. Barker DJ. Foetal and infant origins of adult disease. 1st Edn. London, BMJ Publishing, 1992.
12. Gaultier C. Malnutrition and lung growth. *Pediatr Pulmonol* 1991; 10: 278–286.