EDITORIAL

Adverse effects of maternal smoking during pregnancy on innate immunity in infants

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The potentially fatal effects of maternal smoking on infants have been recognised since the 1800s [1]. In the latter half of the 1900s, the link between maternal smoking and the increased rate of lower respiratory infection (LRI) in early life was described [2]. Given the high rates of smoking in many societies [3], the burden of the increase in LRI is substantial. In a meta-analysis of relationships between parental smoking and respiratory disease, Li *et al.* [4] calculated that the odds ratio (OR) for hospitalisation of LRI in infancy or early childhood for those exposed to parental environmental tobacco smoke (ETS) compared with those not exposed was 1.93 (95% confidence interval (CI) 1.66–2.25). The risk was age related, as the ORs of prevalence of serious LRI were 1.71 (95% CI 1.33–2.20) and 1.25 (95% CI 0.88–1.78) for children aged 0–2 and 3–6 yrs, respectively. Li *et al.* [4] concluded that the results of community and hospital studies were broadly consistent, and showed that the child of a parent who smokes is at approximately twice the risk of having a serious respiratory tract infection requiring hospitalisation in early life. Indeed, early respiratory infection is not only a major cause of morbidity in developed countries, but, in developing countries, respiratory infection is also the leading cause of death in children [5].

There have been a large number of studies showing the relationships between maternal smoking and impaired lung function and increases in respiratory symptoms in infants and young children. An effect of maternal smoking on neonatal lung function has been demonstrated in a study performed very soon after birth [6]. In addition, maternal smoking has been associated with increased wheeze [7] in early life and in schoolchildren [8]. However, few studies have been large enough to separate the effects of placental-borne exposure during pregnancy and breast milk, and air-borne exposure after delivery. Studies that have been able to do this have concluded that the most important deleterious effects have occurred before birth. In a cohort study of 12,743 children from the UK, admission rates for lower respiratory diseases in children born to mothers who stopped smoking during pregnancy were as high as in children whose mothers smoked both during and after pregnancy [9]. Admission rates for lower respiratory diseases in children whose mothers smoked only post-natally were no higher than in those with nonsmoking mothers. Post-natal exposure exerted a significant influence on

the incidence of bronchitis, but less than the effect of *in utero* exposure. For impairment in lung function in schoolchildren, similar conclusions regarding *in utero versus* post-natal exposure were reached by a more recent Californian study of 3,357 children [10]. In 5,762 subjects from the same Californian study, maternal smoking during, but not after, pregnancy was associated with an increased incidence of asthma [11].

Thus, the previous studies have established that maternal smoking during pregnancy exerts a highly deleterious effect on the foetus, and that this is reflected by increases in respiratory infection and wheeze, impairment in lung function and perhaps by increases in the future incidence of asthma. The mechanism by which this occurs is not clear, but the systemic levels of the harmful elements of tobacco are as high in the foetus as in active smokers and, therefore, an order of magnitude higher than in passive smoke exposure *via* inhalation [12].

An effect of maternal smoking on atopy and immunoglobulin (Ig)E can now be seen to be an unlikely explanation for the effect of maternal smoking on the observed increases in respiratory infection and wheezing disorders in early life. Studies of cord serum IgE levels were the first to examine the effects of maternal smoking on foetal immunology, but did not produce consistent results. Although a study in 1986 reported that cord serum IgE was increased in newborns if the mother smoked [13], many subsequent studies have not confirmed this [14–16]. A comprehensive longitudinal study did not find an effect of ETS on the development of atopy in early life [17].

More recent evidence has increasingly implicated other aspects of immune function as potentially important mechanisms by which maternal smoking during pregnancy affects offspring. Several studies on cord blood have shown changes in immunological variables in smoking compared with nonsmoking mothers. In one such study, interference with development of the immune system was suggested by a study of 407 Western Australian children showing that maternal smoking was associated with lower cord blood serum concentrations of interleukin (IL)-4 and interferon (IFN)- γ in cord blood, and a higher risk of wheeze at 6 yrs of age [18]. In another study, proliferation of cord blood mononuclear cells (CBMC) in response to house dust mite was increased in those whose mothers smoked *versus* those who did not smoke during pregnancy [19]. Further evidence of altered immune responses from maternal smoking was found in a study of cord blood from another Western Australian birth cohort [20]. In this study, immunological variables in cord blood were compared

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between 17 infants whose mothers smoked during pregnancy and 40 infants with nonsmoking mothers. In the former group compared with the latter, IL-13 responses were increased for CBMC stimulated with both house dust mite and ovalbumen, and in cord blood cell pellets, IFN- γ mRNA responses to phytohaemagglutinin and concanavalin A were reduced. The findings from these immunological studies suggest that maternal smoking can modify aspects of foetal T-helper (Th)-1 and Th-2 cell function. NOAKES *et al.* [20] emphasised the need for further studies in this area to assist in interpreting these findings and, in particular, studies that assess mechanisms.

In the current issue of the *European Respiratory Journal*, NOAKES *et al.* [21] have provided evidence for one of the potential mechanisms by which maternal smoking exerts its adverse effects on the foetus. They studied CBMC responses to toll-like receptor (TLR)2, TLR3, TLR4 and TLR9 ligands in cord blood specimens from 60 newborns whose mothers smoked and 62 newborns of nonsmoking mothers. Significantly attenuated responses were found for tumour necrosis factor- α , IL-6 and IL-10. Not all responses were altered; IL-12 was not affected, perhaps because it is naturally attenuated at birth, and IFN- γ responses were increased in response to TLR9 stimulation. Importantly, maternal allergy did not affect TLR responses. Thus, these results demonstrate that maternal smoking during pregnancy inhibited innate immune responses to a variety of TLR ligands. The authors speculate that their results may have been produced by the previously observed effect of smoking on TLR signalling *via* inhibition of transcription factor expression [22].

Although the results of the study by NOAKES *et al.* [21] need to be confirmed by similar studies in other populations, and many other potentially important immunological pathways need to be examined in more detail [23], they do suggest that infants born to smoking mothers have a significant impairment of their innate immunity. NOAKES *et al.* [21] quite reasonably raise the possibility that their findings might explain, at least in part, the higher rate of infection seen in infants whose mothers smoked during pregnancy. This explanation is also consistent with the observations regarding increased respiratory wheezing in early life, as with increasing age, maternal smoking gradually lessens as a risk factor for wheeze [4]. In addition, the involvement of TLR2, TLR3 and TLR4 would suggest that problems could be encountered in handling both viral and bacterial infections, and the involvement of TLR4 and TLR9 could affect the development of T-regulatory cell function.

Finally, although the new data presented by NOAKES *et al.* [21] do not bear on the existing strong public-health message that smoking during pregnancy is dangerous to the foetus and should be avoided, further study of the effects of smoking on the immune system allows greater insight to be gained into the complex area of early development of the immune system, and the contribution of innate immunity to protection from respiratory infection and wheezing disorders in early life.

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