Does smoking in pregnancy modify the impact of antenatal steroids on neonatal respiratory distress syndrome? Results of the Epipage study

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Objectives: To assess the relation between cigarette smoking during pregnancy and neonatal respiratory distress syndrome (RDS) in very preterm birth, and to analyse the differential effect of antenatal steroids on RDS among smokers and non-smokers.

Design: A population based cohort study (the French Epipage study).

Setting: Regionally defined births in France.

Methods: A total of 858 very preterm liveborn singletons (27–32 completed weeks of gestation) of the French Epipage study were included in this analysis. The odds ratio for RDS in relation to smoking in pregnancy was estimated using a logistic regression to control for gestational age. The odds ratio for RDS in relation to antenatal steroids was estimated taking into account an interaction between antenatal steroids and cigarette smoking, using multiple logistic regression to control for gestational age, birthweight ratio, main causes of preterm birth, mode of delivery, and sex.

Results: The odds ratio for RDS in relation to smoking in pregnancy adjusted for gestational age (aOR) was 0.59 (95% confidence interval (CI) 0.44 to 0.79). The aOR for RDS in relation to antenatal steroids was 0.31 (95% CI 0.19 to 0.49) in babies born to non-smokers and 0.63 (95% CI 0.38 to 1.05) in those born to smokers; the difference was significant (p = 0.04).

Discussion: We found that maternal smoking was associated with a lower risk of RDS independently of known risk factors of RDS such as gestational age, birth weight, causes of preterm birth mainly maternal hypertension[32] or bleeding,[22 23] sex, and mode of delivery.[14 33] Moreover, the protective effect of antenatal steroids on RDS was more effective in non-smokers in late pregnancy than in smokers; similar results were observed for hospital mortality.

The strengths of this study are that it was geographically defined and provided comprehensive preterm birth registration, restricting selection bias, and it included a large sample of patients. To the best of our knowledge, it is one of the few to have studied the effect of smoking on RDS in very preterm neonates,[14] and the first to have tested a differential effect of antenatal steroid treatment on fetal lung maturation in smokers and non-smokers while taking into account potential confounders.

Nevertheless, possible limitations have to be discussed. We analysed only singleton live births at 27-32 weeks, which may explain the relatively low incidence of RDS (41%). The high rates of both antenatal steroids (71%) and maternal smoking (40%) in our cohort may also explain this low rate of RDS.[27]

Information on smoking was collected by interview after birth, which may have led to under-reporting. However, differential under-reporting in combination with RDS status is very unlikely,

as many babies without RDS had other serious complications. Besides, there is some evidence that misclassification on smoking status in pregnancy is limited and is unlikely to have a large influence on risk estimates.[34-36]

In our study, the mothers who did not smoke were more likely to have received antenatal steroid treatment. However, we checked that the indications assessed through gestational age, birthweight ratio, and main causes of preterm birth did not differ between smokers and non-smokers. Moreover, we checked that the differential relation of antenatal steroids to RDS in smokers and non-smokers did exist whether or not hypertension, intrauterine growth retardation, or caesarean section occurred.

Our study confirms the protective effect of smoking against RDS observed previously in moderate[9-11 13] and very[14] preterm neonates. There is some biological evidence to support such an effect. Foetuses exposed to smoke reach sufficient lung maturity to minimise the risk of RDS about one week earlier than unexposed fetuses.[37] Wuenschell et a/[38] have shown in vitro that nicotine induces stimulation of surfactant gene expression.

The crude odds ratio of RDS in relation to antenatal steroids that we observed is equivalent to the effect of one week of gestation and is similar to that described in Crowley's meta-analysis.[15] Steroids enhance the synthesis of different proteins of surfactant in type II pneumocytes, stimulate activity of key enzymes of phospholipid synthesis, and accelerate the clearance of fetal lung.[39] Our study suggests that the benefit of antenatal steroids may be reduced when fetal lungs have already been matured by cigarette smoking. To the best of our knowledge, none of the randomised trials on antenatal steroid treatment included in the meta-analysis of Crowley[15] analysed the effectiveness of antenatal steroids on RDS after stratification on smoking status. Both antenatal steroids and smoking accelerate the maturation of fetal lung, but it is not known whether steroids and cigarette smoking act on the same metabolic pathways of the fetal lung maturation: if they do, this could explain why steroids appear to be less efficient in smokers. However, as well as RDS, antenatal steroids have been shown to reduce the risk of several other complications of prematurity, such as intraventricular haemorrhage and necrotising enterocolitis.[15] Whether smoking in pregnancy would also modify these effects is not known.

Our study suggests that geographic or sociodemographic variations in the incidence of maternal smoking behaviour could partially explain the differences in incidence of RDS among studies. In trials, the random allocation of antenatal steroid treatment should provide balanced smoking rates in treated and untreated groups. However, our study suggests that further observational studies on RDS should take maternal smoking into account to ensure that the effect of some preventive treatments on RDS are not partially due to some confounding effect of smoking.

Further studies will have to assess if the differential effect of smoking on the association between RDS and steroids also exists in extremely preterm babies (22-26 weeks gestation) in whom RDS is more common and antenatal steroid treatment given less often.[40] However, it has to be kept in mind that the surprising short term beneficial effect of maternal smoking on neonatal lung function is counteracted by the long term effects of smoking on infant lung function.[41-44] Besides, maternal smoking increases the risk of very preterm birth[3-6] and thus the number of neonates at risk of RDS; even though preterm neonates born to smokers are less likely to have RDS than those born to non-smokers, their risk of RDS remains high, and, on the whole, smoking contributes to the level of this disease in the population.

Conclusions: Cigarette smoking during pregnancy is associated with a decrease in the risk of RDS in very preterm babies. Although antenatal steroids reduce the risk of RDS in babies born to both smokers and non-smokers, the reduction is smaller in those born to smokers.

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