

ORIGINAL ARTICLE

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 ($p = 0.04$).

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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Cigarette smoking during pregnancy causes numerous problems with fetal and infant health, including low birth weight,^{1,2} very preterm birth,^{3–6} sudden infant death syndrome,⁷ and abnormal pulmonary function in infancy.⁸ However, 20 years ago smoking in pregnancy was found to be related to a lower incidence of neonatal respiratory distress syndrome (RDS) in preterm neonates.^{9–10} More recent studies have confirmed this protective effect of maternal smoking,^{11–14} but the relation has remained relatively unexplored and is yet to be documented in the case of very preterm births. Steroids given before preterm birth have been shown to be effective in preventing RDS.¹⁵ However, maternal smoking and its possible protective effect on RDS were neither studied nor separated from the protective effect of antenatal steroids in 16 of the 18 trials analysed by Crowley¹⁵; maternal smoking was not significantly different between the placebo and steroids groups in the remaining two.^{16–17} Many trials of antenatal steroid treatment before this meta-analysis^{18–20} and other studies of risk factors for neonatal RDS did not consider smoking in pregnancy.^{21–23} Therefore, to the best of our knowledge, the differential effect of antenatal steroids on RDS in neonates born to smokers and non-smokers has not yet been studied. In western countries, very preterm births (before 33 completed weeks of amenorrhoea) account for 1–2% of live births.^{24–26} RDS is encountered in 40–70% of very preterm neonates depending on gestational age, with a large contribution to perinatal morbidity and mortality.²⁷ Furthermore in European countries, 20–30% of mothers smoked in the third trimester of pregnancy,²⁸ and mothers of very preterm neonates have been

shown to be more likely to be smokers than mothers delivering at term.^{3–6}

The purpose of this study was firstly to estimate the relation of cigarette smoking during pregnancy to RDS in very preterm neonates, taking pregnancy history and antenatal steroid treatment into account. We secondly tested the hypothesis that the benefit of antenatal steroid treatment on RDS is different in smokers and non-smokers. The alternative hypothesis was that antenatal steroid treatment leads to the same effect, independently of maternal smoking.

METHODS AND DATA COLLECTION

We analysed the relation between maternal smoking and neonatal RDS in a geographically defined population of very preterm singletons in France. The methodology of the French Epipage cohort study has been described previously.^{29–30} The main objective of this survey was to assess mortality and neurological morbidity, health, and development of these children at the age of 5. The survey included all very preterm babies (22–32 completed weeks of gestation) born in 1997, in all the maternity wards of nine French regions. Data were collected using the same questionnaire in the nine regions. Medical data, including obstetric history, pregnancy, delivery, and neonatal examination, were extracted from medical records. The women were interviewed a few days after birth, during their stay in the maternity unit, to collect information on social characteristics and smoking habits.

Abbreviations: PPRM, preterm premature rupture of membranes; RDS, respiratory distress syndrome

Table 1 Respiratory distress syndrome (RDS) according to obstetric and neonatal characteristics

	N	RDS		p Value
		n	%	
Gestational age (weeks)				
27–28	164	113	68.9	0.001
29–30	213	98	46.0	
31–32	481	144	29.9	
Total	858			
IUGR				
Yes	211	89	42.2	0.74
No	643	263	40.9	
Total	854			
Main cause of preterm birth*				
Hypertension	235	126	53.6	0.001
Uterine bleeding	230	95	41.3	
PPROM	172	38	22.1	
Preterm spontaneous labour	152	71	46.7	
Other	69	25	36.2	
Total	858			
Sex				
Boys	458	189	41.3	0.92
Girls	399	166	41.6	
Total	857			
Mode of delivery				
Vaginal	309	102	33.0	0.001
Caesarean section	548	253	46.2	
Total	857			

*Comparison between five exclusive groups of causes defined in the following order: hypertension, either pre-existing or due to pregnancy; maternal bleeding (abruptio placenta, placenta previa, and other uterine bleeding) without hypertension; preterm premature rupture of membranes (PPROM) without hypertension or bleeding; preterm spontaneous labour without hypertension, bleeding, or PPRM; all other causes, excluding hypertension, bleeding, PPRM of preterm spontaneous bleeding.
IUGR, Intrauterine growth retardation defined as a birth weight ratio <0.74.³¹

We studied 956 liveborn singletons of 27–32 completed weeks of gestation, born in five of the nine regions of the Epipage study: Alsace, Franche-Comté, Lorraine, Midi-Pyrénées, and Nord-Pas de Calais. In these areas, information on maternal smoking and social characteristics was available for 90% (858/956) of the infants. Limiting the cases included in the analysis was necessary because women were not interviewed if (a) their neonate was less than 27 weeks gestation or (b) the delivery took place in the four other regions included in the study. This meant that 858 preterm singletons were included in the analysis.

Study variables

Gestational age was the best obstetric estimate using menstrual dates and early ultrasonographic assessment. Birthweight ratio was defined as observed birth weight/theoretical birth weight for gestational age according to ultrasonographic values.³¹ Intrauterine growth restriction (birthweight ratio less than the 25th centile) was observed in our cohort (<0.74). The main causes of preterm delivery were classified into five exclusive groups in the following order: maternal hypertension, defined as a systolic blood pressure higher than 139 mm Hg or diastolic blood pressure higher than 89 mm Hg, either pre-existing or due to pregnancy; maternal bleeding (abruptio placenta, placenta praevia, and other uterine bleeding) without hypertension; preterm premature rupture of membranes (PPROM; rupture of membranes 12 hours or more before onset of labour) without hypertension or bleeding; spontaneous labour without hypertension, bleeding, or PPRM; the fifth group included all other cases. Maternal smoking was defined as consumption of one or more cigarettes a day at the end of pregnancy. RDS (hyaline membrane disease) was defined as clinical symptoms of respiratory distress associated with signs of hyaline membrane disease on chest x ray examination. Information on infants was collected until they were

discharged home or until the date of their death in hospital. Women were considered to have received antenatal steroid treatment whether or not they had received a complete course and whether the treatment was with betamethasone or dexamethasone.

Statistical analysis

The analysis followed five steps. (1) We first ascertained that known risk factors of RDS (gestational age, birth weight, main cause of preterm birth, sex, mode of delivery) and antenatal steroid rates were no different whether or not data on maternal smoking were available. (2) We analysed the distribution of RDS according to the obstetric and neonatal known risk factors of RDS listed above. (3) We compared the rate of antenatal steroid treatment according to the risk factors of RDS listed above and smoking status of the mother. (4) We estimated the odds ratios of RDS according to antenatal steroid treatment among smokers and non-smokers, and compared them after controlling for the confounders listed above. (5) We checked that these results were similar in various subpopulations: neonates born to mothers with and without hypertension; neonates born with and without caesarean section; neonates with or without intrauterine growth restriction. Death rates were compared according to antenatal steroid treatment and maternal smoking status. Bivariate analysis was performed using Pearson's χ^2 test. The distributions of antenatal steroid treatment according to risk factors for RDS in smokers and non-smokers were compared using the χ^2 test for homogeneity. The risk of RDS related to smoking was estimated with odds ratios (ORs) and 95% confidence intervals (CIs). Multivariate analysis used logistic regression, with the presence or absence of RDS as the dependent variable, to investigate the relation of steroids and smoking to RDS and to test for an interaction between these two factors after controlling for the confounders listed above. Analysis was

Table 2 Respiratory distress syndrome according to smoking during pregnancy and antenatal steroids

	N	RDS		OR (95% CI)	aOR (95% CI)	p Value
		n	%			
Smoking						
No	518	235	45.4	1.0		
Yes	340	120	35.3	0.66 (0.50 to 0.87)	0.59 (0.44 to 0.79)	0.001
Antenatal steroids						
No	253	136	53.8	1.0		
Yes	605	219	36.2	0.49 (0.36 to 0.66)	0.47 (0.35 to 0.65)	0.001
Steroids and smoking						
No smoking, no steroids	134	87	64.9	1.0		
No smoking, steroids	384	148	38.5	0.34 (0.23 to 0.51)	0.32 (0.21 to 0.50)	0.001
Smoking, no steroids	119	49	41.2	0.38 (0.23 to 0.63)	0.34 (0.20 to 0.57)	
Smoking and steroids	221	71	32.1	0.26 (0.16 to 0.40)	0.22 (0.13 to 0.35)	

RDS, Respiratory distress syndrome; OR, odds ratio; aOR, adjusted for gestational age (logistic regression performed on 858 infants); CI, confidence interval.

performed with BMDP statistical software (BMDP Corp, Los Angeles, California, USA).

RESULTS

There was no difference in gestational age, birth weight, main cause of preterm birth, mode of delivery, sex, and antenatal steroids between the preterm infants for whom maternal smoking status was known ($n = 858$) and those for whom it was unknown ($n = 98$) (results not shown).

The rate of RDS was significantly higher in the group of lower gestational age and caesarean section (table 1), and in neonates born to non-smokers and to mothers who did not receive antenatal steroids (table 2). After adjustment for gestational age, the ORs for the relation of RDS to maternal smoking (aOR = 0.59, 95% CI 0.44 to 0.79) and antenatal steroids (aOR = 0.47, 95% CI 0.35 to 0.65) were significant.

Steroids alone, smoking alone, and association of smoking and steroids were significantly related to a lower risk of RDS (table 2). However, the protective effects of steroids on neonatal RDS differed in smokers and non-smokers.

Antenatal steroid treatment was more efficient in non-smokers (OR 0.34, 95% CI 0.23 to 0.51) than smokers (OR 0.68, 95%CI 0.43 to 1.07), and the two ORs were significantly different ($p = 0.03$).

Non-smokers were treated with antenatal steroids significantly more often than smokers (74% *v* 65%, $p = 0.01$). The distributions of antenatal steroid treatment according to gestational age, birthweight ratio, main cause of preterm birth, mode of delivery, and sex did not differ significantly among smokers and non-smokers (table 3).

Finally, this differential effect of antenatal steroid treatment on RDS was observed in smokers and non-smokers after adjustment for gestational age, birthweight ratio, main cause of preterm birth, mode of delivery, and sex. Antenatal steroid treatment was more efficient in non-smokers (aOR 0.31, 95%CI 0.19 to 0.49) than smokers (aOR 0.63 (0.38 to 1.05); comparison of the two ORs by the χ^2 test showed significance ($p = 0.04$).

Similar trends were found in the following subpopulations: preterm neonates born to mothers with hypertension or

Table 3 Antenatal steroids according to risk factors of respiratory distress syndrome (RDS) among non-smokers and smokers

	Non-smokers		Smokers		p Value*
	n/N	%	n/N	%	
Antenatal steroids	384/518		221/340		
Gestational age (weeks)					
27–28	62/92	67.4	46/72	63.9	0.63
29–30	100/128	78.1	57/85	67.1	
31–32	222/298	74.5	118/183	64.5	
IUGR†					
Yes	112/137	81.8	52/74	70.3	0.47
No	271/378	71.7	169/265	63.8	
Main cause of preterm birth‡					
Hypertension	157/194	80.9	29/41	70.7	0.29
Bleeding	81/117	69.2	72/113	63.7	
PPROM	74/91	81.3	53/81	65.4	
Spontaneous prelabour	43/81	53.1	41/71	57.7	
Other	29/35	82.9	26/34	76.5	
Caesarean section					
Yes	271/352	77.0	132/196	67.3	0.8
No	112/165	67.9	89/144	61.8	
Sex					
Boys	210/281	74.7	116/177	65.5	0.93
Girls	173/236	73.3	105/163	64.4	

*Comparison of the distribution of antenatal steroids by risk factors of RDS in non-smokers and smokers.

†Intrauterine growth retardation defined as a birth weight ratio <0.74 .³¹

‡Comparison between five exclusive groups of causes defined in the following order: hypertension, either pre-existing or due to pregnancy; maternal bleeding (abruptio placenta, placenta previa, and other uterine bleeding) without hypertension; preterm premature rupture of membranes (PPROM) without hypertension or bleeding; preterm spontaneous labour without hypertension, bleeding, or PPRM; all other causes, excluding hypertension, bleeding, PPRM of preterm spontaneous bleeding.

without hypertension; preterm neonates born by caesarean section or vaginal delivery; preterm neonates with or without intrauterine growth restriction (results not shown).

Hospital mortality was similar in smokers and non-smokers; mortality was lower in neonates whose mother had received steroids (5.0% *v* 9.1%, OR = 0.52, 95% CI 0.29 to 0.95). However, this beneficial effect of steroids on neonatal mortality was significant only in infants of non-smokers (4.2% *v* 11.9%, OR = 0.32, 95% CI 0.15 to 0.70) and not smokers (6.3% *v* 5.9%, OR = 1.08, 95% CI 0.39 to 3.1). This differential effect of antenatal steroids on neonatal mortality by maternal smoking was significant ($p = 0.04$), and this difference remained significant after adjustment for gestational age.

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 hypertension³² 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 very¹⁴ preterm neonates. There is some biological evidence to support such an effect. Fetuses exposed to smoke reach sufficient lung maturity to minimise the risk of RDS about one week earlier than unexposed fetuses.³⁷ Wuenschell *et al*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 Crowley¹⁵ 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.

CONCLUSION

Compared with non-exposed neonates, very preterm neonates exposed to maternal cigarette smoking in pregnancy experience a lower incidence of RDS. Antenatal steroid treatment reduces the risk of RDS in very preterm neonates born to non-smokers as well as to those born to smokers, but the benefit is smaller in smokers than non-smokers. There is no evidence that pregnant smokers at risk of delivering very prematurely should not be offered antenatal steroid treatment.

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APPENDIX

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