Maternal smoking

Preterm delivery and exposure to active and passive smoking during pregnancy: a case–control study from Italy

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Summary

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The aim of this study was to assess the relationship between preterm/early preterm delivery and active smoking as well as environmental tobacco smoke (ETS) exposure in a sample of pregnant Italian women. A case–control study was conducted in nine cities in Italy between October 1999 and September 2000. Cases of preterm birth were singleton babies born before the 37th gestational week; babies born before the 35th gestational week were considered early preterm births. Controls were babies with gestational ages $\geq$ 37th week. A total of 299 preterm cases (including 105 early preterm) and 855 controls were analysed. A self-administered questionnaire was used to assess active smoking and ETS exposure, as well as potential confounders. Multivariable logistic regression analysis showed a relationship between active smoking during pregnancy and preterm/early preterm delivery [adjusted ORs: 1.53; 95% CI 1.05, 2.21 and 2.00; 95% CI 1.16, 3.45, respectively]. A dose–response relationship was found for the number of cigarettes smoked daily. The adjusted ORs were 1.54 and 1.69 for preterm babies and 1.90 and 2.46 for early preterm babies for 1–10 and >10 cigarettes/day respectively. ETS exposure was associated with early preterm delivery [adjusted OR 1.56; 95% CI 0.99, 2.46] with a dose–response relationship with the number of smokers in the home. Smoking during pregnancy was strongly associated with preterm delivery with a dose–response effect. ETS exposure in non-smoking women was associated only with early preterm delivery.

Keywords: *preterm delivery*, *maternal smoking*, *environmental tobacco smoke*.

Introduction

Preterm birth is an important cause of neonatal morbidity and mortality, and active smoking during pregnancy is a recognised risk factor for preterm delivery. There is good epidemiological evidence to support an association between smoking during pregnancy and increased risk of premature rupture of membranes, abruptio placentae, placenta praevia and a modest increase in risk for preterm delivery.[1] A recent meta-analysis of 20 prospective studies reported a pooled odds ratio (OR) for preterm delivery of 1.27 [95% confidence interval (CI) 1.21, 1.33] in smoking vs.

non-smoking pregnant women, although not all individual studies reported significantly elevated risks.[2] On the whole, data from epidemiological studies show that there is a dose-related impact of smoking on preterm birth with reported ORs ranging from 1.6 to 1.8 in pregnant women who smoke >10 cigarettes/day compared with non-smokers.[3–6]

Preterm delivery has also been associated with exposure to environmental tobacco smoke (ETS) exposure during pregnancy. The California Environmental Protection Agency recently reviewed the major findings for developmental toxicity of ETS and suggested that there is evidence of an association between ETS exposure and preterm delivery.[7] However, even though a number of studies have shown that ETS exposure during pregnancy increases the risk for preterm delivery, the observed ORs are generally low or limited to specific categories of women such as those older than 30 years or multiparous.[8–10]

We studied the association between the occurrence of preterm and early preterm delivery and maternal active smoking and ETS exposure during the last trimester of pregnancy in a sample of Italian women. The study was conducted within a larger investigation of several risk factors for adverse pregnancy outcomes.[11,12]

Methods

A case–control study with incident cases was carried out between October 1999 and September 2000 in nine Italian cities (Genoa, Udine, Modena, Parma, Siena, Rome, L'Aquila, Naples and Catania). In Modena, Udine, Parma, Siena and L'Aquila, the participating obstetric clinics covered nearly 100% of total births that occurred in the municipal areas, while in Rome, Genoa, Naples and Catania the coverage ranged from 40% to 60% of total births. We considered babies born from mothers who were Caucasian, born in Italy and resident in the investigated cities eligible for inclusion. Multiple pregnancies and newborns with congenital malformations were excluded.

Eligible cases of preterm birth were singleton, live-born children born before the 37th completed week of pregnancy (i.e. before 259 days from first day of last menstrual period); among these subjects we classified all singleton babies born before the 35th week of pregnancy as early preterm births. Controls were enrolled from among singleton births that occurred in the same hospitals 1–2 days after delivery of the case, with a gestational age >37th week of pregnancy.

Mothers of cases and controls were recruited during their hospital stay just after delivery by trained interviewers. After informed consent and before hospital discharge, mothers were asked to complete a structured, validated and self-administered questionnaire.[11] This collected information about sociodemographic variables (e.g. mother's age, educational level), medical and reproductive history (e.g. parity, previous miscarriages and stillbirth, hypertension, diabetes) and lifestyle habits such as coffee, beer and alcohol consumption. Maternal and infant medical records were reviewed to obtain clinical data about mother's health at the delivery and birth outcomes (infant sex, gestational age and infant birthweight). Data on gestational age were obtained from medical records according to the last menstrual period. We considered the following variables as confounders: gender, maternal age, marital status, education, parity, previous preterm delivery, miscarriages and stillbirths, hypertension and diabetes, working in pregnancy, antenatal class attendance and moderate physical activity during pregnancy. Confounding variables were assessed by both questionnaire and clinical records.

The study protocol was reviewed and approved by the Research Ethics Boards in all obstetric clinics.

Exposure assessment

Information on active smoking habits and ETS exposure was based on maternal self-reporting. We collected information about smoking habits before pregnancy (yes, no), the number of cigarettes smoked per day and the period of smoking habits before pregnancy.

Data on smoking habits during pregnancy concerned whether the mother had smoked during the last trimester of pregnancy (yes, no) as well as the number of cigarettes smoked per day; all smokers reported they had smoked for the entire period of pregnancy.

ETS exposure was grouped into two categories based on the number of smokers in the home during the period of pregnancy (none, one or more smokers).

Statistical analyses

Univariable and multivariable regression procedures were applied to estimate the associations between maternal smoking and ETS exposure during pregnancy and preterm and early preterm birth. We estimated ORs and 95% CIs using logistic regression. The

Table 1. Basic characteristics of cases: preterm (<37 weeks) and early preterm (<35 weeks) delivery, and controls delivered at term

	Controls $n = 855$ %	Early preterm $n = 105$ %	Preterm $n = 299$ %
Gender of baby			
Male	48	47	54
Female	52	53	46
Maternal age (years)			
≤20	1	4	2
21–30	39	36	39
31–40	58	56	54
>40	1	4	4
Marital status			
Married/de facto	96	90	94
Single	2	5	3
Separated/divorced	2	5	3
Education			
Primary/middle school	30	34	29
High school	49	48	48
University	22	18	23
Parity			
Primiparous	50	51	51
Multiparous	50	49	49
Previous preterm deliveries			
No	95	84	84
Yes	4	16	15
Miscarriages			
No	83	74	77
Yes	17	26	23
Stillbirth			
No	99	97	97
Yes	1	3	3
Diabetes			
No	99	91	94
Yes	1	9	6
Hypertension			
No	96	78	84
Yes	4	22	15
Working in pregnancy			
No	29	28	30
Yes	71	72	70
Antenatal class attendance			
No	51	66	60
Yes	49	34	40
Moderate physical activity			
No	29	28	30
Yes	71	72	70
Active smoking			
No	85	76	80
Yes	15	24	20
ETS exposure			
No	65	53	63
Yes	35	47	37

Percentages may not add to 100 because of rounding or missing information for some subjects.

Table 2. Smoking habits of cases (preterm and early preterm delivery) and controls before and during pregnancy

	Early preterm delivery <35 weeks gestation		Preterm delivery <37 weeks gestation	
	Cases/controls	Adjusted OR[a] [95% CI]	Cases/controls	Adjusted OR[a] [95% CI]
Smoking during pregnancy				
No	80/721	1.00 Reference	239/721	1.00 Reference
Yes	25/125	2.00 [1.16, 3.45]	60/125	1.53 [1.05, 2.21]
Cigarettes/day during pregnancy				
None	80/721	1.00 Reference	237/721	1.00 Reference
<10/day	16/89	1.90 [1.01, 3.56]	40/89	1.54 [1.01, 2.35]
10+/day	9/36	2.46 [1.05, 5.76]	20/36	1.69 [0.91, 3.13]
Smoking before and during pregnancy				
Neither	62/595	1.00 Reference	187/595	1.00 Reference
Yes, only before pregnancy	18/128	1.19 [0.63, 2.24]	50/128	1.20 [0.81, 1.79]
Yes, both before and during pregnancy	25/125	1.43 [1.09, 1.89]	60/125	1.25 [1.04, 1.50]

[a]Adjusted for maternal age, previous preterm deliveries, hypertension, diabetes, antenatal class attendance and moderate physical activity.

regression models were adjusted for the following potential confounders: maternal age, previous preterm deliveries, hypertension, diabetes, antenatal class attendance and moderate physical activity. These variables were associated with case status ($P < 0.05$) in univariable analyses. Statistical analyses were performed with SPSS 10.0 for Windows (SPSS 2000).[13]

Results

A total of 299 cases of preterm birth (including 105 early preterm cases) and 855 controls completed the questionnaire; the participation rate was 96% of eligible mothers. The distribution of sociodemographic data, lifestyle habits and medical information among cases and controls are shown in Table 1. Mothers of preterm and early preterm deliveries were more likely to be >40 years of age, to have a history of preterm delivery, miscarriage or stillbirth and to have a history of hypertension and diabetes than mothers of controls. No associations were found with other sociodemographic variables such as gender of the baby, marital status, education and working during pregnancy or with antenatal class attendance or moderate physical activity for either preterm or early preterm cases compared with control subjects.

Active maternal smoking was reported more frequently by mothers who delivered either early preterm or preterm babies compared with mothers of term deliveries (24%, 20% and 15% respectively). Forty-seven per cent of mothers who delivered early preterm babies were exposed to ETS; 8.6% of them lived with

Table 3. ETS exposure of cases (preterm and early preterm delivery) and controls in non-smoking women

		Early preterm delivery <35 weeks gestation			Preterm delivery <37 weeks gestation		
ETS exposure (only non-smoking mothers)	Controls *n* (%)	*n* (%)	Crude OR [95% CI]	Adjusted OR[a] [95% CI]	*n* (%)	Crude OR [95% CI]	Adjusted OR[a] [95% CI]
No	507 (71)	47 (59)	1.00 Reference	1.00 Reference	170 (72)	1.00 Reference	1.00 Reference
Yes	210 (29)	33 (41)	1.69 [1.06, 2.72]	1.70 [1.01, 2.86]	67 (28)	0.95 [0.69, 1.32]	0.92 [0.65, 1.31]
Total	717 (100)	80 (100)			237 (100)		

[a]Adjusted for maternal age, previous preterm deliveries, hypertension, diabetes, antenatal class attendance and moderate physical activity.

Table 4. Association between preterm and early preterm delivery and both active maternal smoking and ETS exposure

	Early preterm delivery <35 weeks gestation $n = 105$		Preterm delivery <37 weeks gestation $n = 299$	
Active smoking/ETS exposure	Cases/controls	Adjusted OR[a] [95% CI]	Cases/controls	Adjusted OR[a] [95% CI]
No active smoking/no ETS exposure	47/507	1.00 Reference	170/507	1.00 Reference
No active smoking/yes ETS exposure	33/210	1.71 [1.04, 2.89]	67/210	0.92 [0.65, 1.31]
Yes active smoking/yes ETS exposure	25/125	2.28 [1.16, 4.61]	59/125	1.51 [1.03, 2.20]

[a]Adjusted for maternal age, previous preterm deliveries, hypertension, diabetes, antenatal class attendance and moderate physical activity.

two or more smokers. Coffee, beer, wine and alcohol intake (no/yes) were not associated with the preterm birth (data not shown).

Adjusted ORs and 95% CIs for smoking habits before and during pregnancy are shown in Table 2. All risk estimates were adjusted for variables associated with preterm delivery in univariable analyses (maternal age, previous preterm deliveries, hypertension, diabetes, antenatal class attendance and moderate physical activity). Logistic regression analysis showed a strong association between preterm delivery and smoking during pregnancy. A higher adjusted risk was found for early preterm delivery among mothers who smoked during pregnancy compared with non-smokers with evidence of a strong dose–response according to the number of cigarettes smoked daily. Smoking only before pregnancy and then stopping showed low risks, while smoking both before and during pregnancy showed increased risks of early preterm delivery and preterm delivery.

In non-smoking mothers, ETS exposure was associated with a moderate increase of risk for early preterm delivery, while the risk of preterm delivery on the whole in mothers exposed to ETS was lower and non-significant. (Table 3).

In Table 4 we consider the association with both active smoking and ETS exposure. Early preterm delivery shows a dose–response relationship such that the women with both active and passive exposure show the highest risk, while preterm delivery, is associated with active maternal smoking only.

Discussion

The results of our study are in agreement with previous epidemiological studies that reported that active smoking is associated with preterm delivery.[1–6,14] In this study, the association was even stronger for early preterm delivery, defined as singleton babies born before the 35th week of pregnancy. Epidemiological research has evaluated the role of socio-economic factors and behavioural patterns for associations with preterm delivery. In addition to unhealthy behaviour (cigarette smoking, drug use), the most frequently associated factors were maternal anthropometry, poor nutrition, physically demanding work during pregnancy and absence or poor quality of prenatal and family care. Despite the fact that we did not control for all of these factors, the associations between smoking and preterm delivery remain statistically significant after adjusting for some of these variables including maternal age, marital status and education. On the other hand, factors that protect women from preterm delivery have also been reported. Among these, moderate physical activity including golf, walking, table tennis, swimming as well as participation in prenatal classes were evaluated in our study. Attendance in antenatal classes is believed to have a positive effect in reducing fear and anxiety about labour and delivery and in identifying the most suitable time for coming to the hospital thereby reducing preterm labour emergencies.[15] The protective role of these factors was also confirmed in our population. Nevertheless, active smoking before and during pregnancy remains a significant predictor of preterm delivery. Of paramount importance, our study also confirmed the dose–response relationship with the number of cigarettes smoked daily during pregnancy.

The most widely accepted hypothesis to account for the role of smoking on fetal development is that carbon monoxide and/or nicotine induce fetal hypoxia. Carbon monoxide is known to decrease the oxygen-carrying capacity of haemoglobin. Fetal haemoglobin has a higher affinity for carbon monoxide than adult haemoglobin and the impact on the fetus is more severe than on the mother, since fetal tissues receive

even less oxygen. Nicotine is a vasoconstrictor and appears to reduce placental perfusion leading to fetal hypoxia.[1] However, the association between smoking and preterm birth could have some other explanation, and the pathogenesis of a possible smoking-related increased risk of preterm labour is probably multifactorial.[3,4]

Several methodological limitations should be considered in interpreting the results of our study. The first issue is related to the sample: while in some towns the coverage of preterm births was 100%, in other areas (Rome, Naples and Genoa) it was limited to 40–60% as it was impossible to cover all the obstetric wards in these big towns. However, the sample from these areas is probably homogeneous as we involved public clinics only in the present study.

Maternal smoking was based on self-report, leading to potential misclassification. Although many studies have shown agreement between self-reported smoking amount and serum or urinary cotinine levels,[16] several issues regarding covariates and confounders need to be addressed. Active maternal smoking can act as a confounder in studies of ETS exposure and create misclassification. In our study, the data for ETS exposure during pregnancy were obtained using a structured, standardised questionnaire. Some authors suggest that mothers may not report the number of cigarettes smoked in pregnancy accurately, leading to additional misclassification. However, in our study 37% of women with preterm/early preterm delivery and 30% of control women reported that they smoked before pregnancy. These data agree with those from the Italian Institute for Statistical Reasearch who reported that the prevalence of smoking among Italian women aged 25–44 years was 33.5%, similar to our study.[17] Moreover, in our study a similar reduction in the prevalence of active smoking was observed both for controls (–15%) and for cases (–17%).

The accuracy of the exposure to ETS is difficult to evaluate when data are collected only by self-reported questionnaire. The results obtained from epidemiological studies performed on the validity of self-reported exposure to ETS are not unequivocal: a number of studies have found poor to moderate correlation between self-reported information on ETS exposure and cotinine measurements, while other studies tested the exposure to ETS and the resulting cotinine levels correlated well with a history of this exposure.[18–23]

In conclusion, our results confirm earlier findings that active smoking during pregnancy increases the risk for preterm and early preterm delivery. In addition, we have shown ETS exposure during the third trimester of pregnancy to be associated with early preterm delivery (before the 35th gestational week).

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References

1 US Department of Health and Human Services. *The Health Consequences of Smoking: A Report of the Surgeon General*. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Diseases Prevention and Health Promotion, Office on Smoking and Health, 2004.

2 Shah NR, Bracken MB. A systematic review and meta-analysis of prospective studies on the association between maternal cigarette smoking and preterm delivery. *American Journal of Obstetrics and Gynecology* 2000; **182**:465–472.

3 Burguet A, Kaminski M, Abraham-Lerat L, Shaal JP, Cambonie G, Fresson J, *et al.* The complex relationship between smoking in pregnancy and early preterm delivery. Results of the Epipage study. *BJOG* 2004; **111**:258–265.

4 Kyrklund-Blomberg N, Cnattingius S. Preterm birth and maternal smoking: risks related to gestational age and onset of delivery. *American Journal of Obstetrics and Gynecology* 1998; **179**:1051–1055.

5 Kolas T, Nakling J, Salvesen A. Smoking during pregnancy increases the risk of preterm births among parous women. *Acta Obstetricia et Gynecologica Scandinavica* 2000; **79**:644–648.

6 Hammoud AO, Bujold E, Sorokin Y, Schild C, Krapp M, Baumann P. Smoking in pregnancy revisited: findings from a large population-based study. *American Journal of Obstetrics and Gynecology* 2005; **192**:1856–1863.

7 Cal/EPA (2004) *Health Effects Assessment for ETS. (Draft)*. Available at: http://www.arb.ca.gov/toxics/ets/finalreport/chap3b.pdf (accessed 17 October 2005).

8 Windham GC, Hopkins B, Fenster L, Swan SH. Prenatal active or passive tobacco smoke exposure and the risk of preterm delivery or low birthweight. *Epidemiology* 2000; **11**:427–433.

9 Jaakkola JJ, Jaakkola N, Zahlsen K. Fetal growth and length of gestation in relation to prenatal exposure to environmental tobacco smoke assessed by hair nicotine concentration. *Environmental Health Perspectives* 2001; **109**:557–561.

10 Kharrazi M, DeLorenze GN, Kaufman FL, Eskenazi B, Bernert JT Jr, Graham S, *et al.* Environmental tobacco smoke and pregnancy outcome. *Epidemiology* 2004; **5**:660–670.

11 Barbone F, Valent F, Brussi V, Tomasella L, Triassi M, Di Lieto A, *et al.* Assessing the exposure of pregnant women to

drinking water disinfection byproducts. *Epidemiology* 2002; **13**:540–544.
12 Aggazzotti G, Righi E, Fantuzzi G, Biasotti B, Ravera G, Kanitz S, *et al*. Chlorination by-products (CBPs) in drinking water and adverse pregnancy outcomes in Italy. *Journal of Water and Health* 2004; **2**:233–247.
13 SPSS Inc. *SPSS for Windows*, Version 10.0. Chicago, IL: SPSS Inc., 2000.
14 Ahern J, Pickett KE, Selvin S, Abram B. Preterm birth among African American and white women: a multilevel analysis of socioeconomic characteristics and cigarette smoking. *Journal of Epidemiology and Community Health* 2003; **57**:606–611.
15 Albizu L, Goni J, Mejias A. Antenatal education and recognition of the onset of labour. *Anales del Sistema Sanitario de Navarra* 2000; **23**:337–342.
16 de Weerd S, Thomas CM, Kuster J, Cikot R, Steegers E. Variation of serum and urine cotinine in passive and active smokers and applicability in preconceptional smoking cessation counselling. *Environmental Research Section A* 2002; **90**:119–124.
17 DOXA (Istituto Italiano per le ricerche statistiche). *Il fumo in Italia 2003*. Available at: http://www.doxa.it/italiano/inchieste/fumo.pdf (accessed 17 October 2005).
18 Rebagliato M, Bolumar F, Florey C du V. Assessment of exposure to environmental tobacco smoke in nonsmoking pregnant women in different environments of daily living. *American Journal of Epidemiology* 1995; **142**:525–530.
19 O'Connor T, Holfor T, Leaderer B. Measurement of exposure to environmental tobacco smoke in pregnant women. *American Journal of Epidemiology* 1995; **142**:1315–1321.
20 DeLorenze G, Kharrazi M, Kaufman F, Eskenazi B, Bernert J. Exposure to environmental tobacco smoke in pregnant women: the association between self-report and serum cotinine. *Environmental Research* 2002; **90**:21–32.
21 Kaufman F, Kharrazi M, DeLorenze G, Eskenazi B, Bernert J. Estimation of environmental tobacco smoke exposure during pregnancy using a single question on household smokers versus serum cotinine. *Journal of Exposure Analysis and Environmental Epidemiology* 2002; **12**:1–10.
22 Riboli E, Preston-Martin S, Saracci R, Haley NJ, Tricopoulos D, Becher H, *et al*. Exposure of non smoking women to environmental tobacco smoke: a 10-country collaborative study. *Cancer Causes and Control* 1990; **1**:243–252.
23 Pickett KE, Rathouz P, Kasza K, Wakschlag L, Wright R. Self-reported smoking, cotinine levels, and patterns of smoking in pregnancy. *Paediatric and Perinatal Epidemiology* 2005; **19**:368–376.

