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Exposure to active and passive smoking during pregnancy and severe small for gestational age at term

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Abstract

Objective. The objective of this study was to assess the relationship between active smoking as well as environmental tobacco smoke (ETS) exposure and severe small for gestational age (SGA) at term in a sample of pregnant Italian women.

Methods. A case–control study was conducted in nine cities in Italy between October 1999 and September 2000. Cases of severe SGA were singleton, live born, at term children with a birth weight $\leq 5^{th}$ percentile for gestational age. Controls (10:1 to cases) were enrolled from among singleton at term births that occurred in the same hospitals one or two days after delivery of the case, with a birth weight $> 10^{th}$ percentile for gestational age. A total of 84 cases of severe SGA and 858 controls were analyzed. A self-administered questionnaire was used to assess active smoking and ETS exposure, as well as potential confounders.

Results. Multivariate logistic regression analysis showed a relationship between active smoking during pregnancy and severe SGA (adjusted odds ratio (OR) 2.10, 95% confidence interval (CI) 1.13–3.68). ETS exposure was associated with severe SGA (adjusted OR 2.51, 95% CI 1.59–3.95) with a dose–response relationship to the number of smokers in the home.

Keywords: *Severe small for gestational age at term, active smoking, environmental smoke exposure, Italy, case–control study*

Introduction

Low birth weight is an important cause of fetal mortality as well as neonatal morbidity and mortality in developed countries [1], and active smoking is the major modifiable risk factor contributing to limited birth weight [2].

There is documented and unequivocal epidemiological evidence to support an association between active smoking during pregnancy and preterm delivery, premature rupture of the membranes, low birth weight (LBW), intrauterine growth restriction (IUGR), small for gestational age (SGA), placenta previa, abruptio placentae, and sudden infant death syndrome (SIDS) [3,4].

The general acceptance of the association between smoking and impairment of fetal growth is illustrated by numerous studies: maternal smoking retards fetal growth, causes an average reduction in birth weight of 165 g [5], and is associated with an increased risk of SGA (adjusted odds ratio (OR) 2.41, 95% confidence interval (CI) 1.78–3.28) [6,7].

On the whole, data from several studies show that there is a dose–response effect of smoking on both mean birth weight and the incidence of LBW infants with an adjusted OR of 2.3 (95% CI 2.0–2.04) for smoking pregnant women compared to non-smokers [8,9].

Decrements in birth weight have also been associated with environmental tobacco smoke (ETS) exposure during pregnancy. A recent meta-

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analysis of 16 studies reported a pooled OR for either LBW or SGA of 1.22 (95% CI 1.10–1.35) in exposed versus unexposed pregnant women [10]. Moreover, a strong dose-effect has been observed: in a recent study, in mothers heavily exposed to ETS both at home and at work, infant birth weight was lower by 189 g in comparison with the group of non-exposed, never smoking mothers and even 70 g compared with mothers smoking during pregnancy [11].

We studied the association between the occurrence of an impairment of fetal growth such as severe SGA 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 [12].

Methods

A population-based 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 the 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 where 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 babies with an impairment of fetal growth were singleton, live born, at term children with a birth weight $\leq 5^{th}$ percentile for gestational age, considered severe SGA babies. Controls (10:1 to cases) were enrolled from among singleton at term births that occurred in the same hospitals one or two days after delivery of the case, with a birth weight $> 10^{th}$ percentile for gestational age.

Mothers of cases and controls were recruited during their hospital stay, which lasted 48–72 hours after delivery, by trained interviewers. Interviewers recruited cases (and controls) 1–2 days/week, excluding holidays, in a random fashion. After informed consent and before hospital discharge, mothers were asked to complete a structured, validated, and self-administrated questionnaire [13]. The questionnaire collected information on maternal socio-demographic status (mother's age, educational level, etc.), obstetric history (parity, previous miscarriages and stillbirth, gestational hypertension and diabetes, etc.), and lifestyle habits such as coffee, beer, and wine consumption. Maternal and infant medical records were reviewed to obtain clinical data on mother's health at delivery and birth outcomes (infant sex, gestational age, and infant birth weight). Data on gestational age were obtained from medical records according to the last menstrual period. We considered the following variables as confounders: infant gender, maternal age (years), marital status ('with' or 'without' a partner), education, parity, previous LBW, previous preterm deliveries, miscarriage, stillbirth, antenatal class attendance, urinary tract infections (UTI), gestational diabetes and hypertension, proteinuria, edema, anemia and treatment for anemia, wine, beer, and coffee consumption, working activities in pregnancy, and moderate physical activity. Confounding variables were assessed both by questionnaire and clinical records.

The study protocol was reviewed and approved by the research ethics boards of all the obstetric clinics.

Exposure assessment

Information on active smoking habits and ETS exposure was based on maternal self-reporting [13]. 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 were also collected. We collected information about smoking habits during the last trimester of pregnancy (yes/no) as well as the number of cigarettes smoked per day: all smokers reported that they had smoked for the entire period of pregnancy.

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

Statistical analyses

Univariate and multivariate regression procedures were applied to estimate the associations between maternal smoking and ETS exposure during pregnancy and severe SGA. We estimated odds ratios (OR) and 95% confidence intervals (95% CI) using logistic regression. The regression models were adjusted for the following confounders: previous LBW, UTI, gestational hypertension, and treatment for anemia. These variables were associated with case status ($p < 0.05$) in univariate analyses. Statistical analyses were performed with SPSS 10.0 for Windows (SPSS 2000) [14].

Results

A total of 84 cases of severe SGA and 858 controls completed the questionnaire. Overall the participation rate was 96% of those eligible. The distribution of maternal socio-demographic status, obstetric history, and lifestyle habits in pregnancy (including smoking) among cases and controls was considered.

Mothers of severe SGA infants were more likely to have a history of previous LBW, UTI, and

gestational hypertension than mothers of controls. Moreover, mothers of controls (non-severe SGA babies) were more likely to undergo treatment for anemia suggesting a protective role of this therapy towards the reduction in newborn birth weight (Table I).

No association was found with infant gender, maternal age, marital status ('with' or 'without' a partner), education ($>$ or $\leq$ eight years of education), parity (multiparous vs. primiparous), previous preterm deliveries, miscarriage, stillbirth, antenatal class attendance, gestational diabetes, proteinuria, edema, anemia, wine, beer, and coffee consumption, working activities, and moderate physical activity in pregnancy for severe SGA babies compared with control subjects (data not shown). Mothers who had reported active smoking more frequently delivered severe SGA babies compared with non-smoker mothers (14.8%/7.6%). Moreover, 13.8% of mothers who delivered severe SGA babies were exposed to ETS while 6.0% were not. Beer, wine, and coffee intake (no/yes) were not associated with severe SGA babies.

Adjusted ORs and 95% CIs for smoking habits before and during pregnancy are shown in Table II. All risk estimates were adjusted for variables associated with severe SGA in the univariate analyses (previous LBW, UTI, gestational hypertension, treatment for anemia). Multiple regression analysis showed a strong association between severe SGA and smoking during pregnancy. A higher adjusted risk was found for severe SGA babies among mothers who smoked during pregnancy compared to non-smokers with evidence of a dose–response relationship according to the number of cigarettes smoked daily. Smoking only before pregnancy and then stopping did not show a significant risk, while smoking before and during pregnancy showed increased risk of severe SGA.

A positive trend in OR values according to exposure to smoke was observed for severe SGA babies: ETS exposure was associated with a strong increase in risk for severe SGA when the analysis was limited to non-smoking women. When we considered women with both ETS exposure and active smoking habits, the association between smoke exposure and severe SGA became more evident (Table III).

Discussion

Active smoking during pregnancy is strongly associated with severe SGA with a dose–response relationship: the risk doubled when more than ten cigarettes/day were smoked with respect to non-smokers. Only smoking before pregnancy was not associated with the investigated outcome in a significant way.

In this study ETS exposure in pregnant women was significantly associated with a higher risk of severe SGA, and the value was very close to the risk for active smoking women (OR 1.95 vs. 2.10).

Several epidemiological research studies have already evaluated the role of socio-economic factors and behavioral patterns for associations with SGA. In addition to unhealthy behavior (cigarette smoking,

Table I. Basic characteristics of cases (severe SGA, $\leq 5^{th}$ percentile for gestational age) and controls ($>10^{th}$ percentile for gestational age).

Variables	$>10^{th}$ percentile for gestational age ($N=858$)	$\leq 5^{th}$ percentile for gestational age ($N=84$)	OR (95% CI)	*p*-Value
Previous low birth weight (only in multiparous women)			3.54 (1.42–8.82)	0.011
No	556 (90.1%)	61 (9.9%)		
Yes	18 (72.0%)	7 (28.0%)		
Urinary tract infections (UTI)			1.90 (1.02–3.52)	0.061
No	769 (91.7%)	70 (8.3%)		
Yes	81 (85.3%)	14 (14.7%)		
Gestational hypertension			2.14 (1.07–4.26)	0.047
No	795 (91.6%)	73 (8.4%)		
Yes	56 (83.6%)	11 (16.4%)		
Treatment for anemia			1.51 (0.95–2.38)	0.098
Yes (iron, folic acid, or both)	459 (92.7%)	36 (7.3%)		
No	389 (89.4%)	46 (10.6%)		
Active smoking			2.10 (1.27–3.47)	0.005
No	714 (92.4%)	59 (7.6%)		
Yes	144 (85.2%)	25 (14.8%)		
ETS exposure			2.51 (1.59–3.95)	0.000
No	548 (94.0%)	35 (6.0%)		
Yes	306 (86.2%)	49 (13.8%)		

SGA, small for gestational age; OR, odds ratio; CI, confidence interval; ETS, environmental tobacco smoke.

Table II. Smoking habits of cases (severe SGA, $N = 84$) and controls before and during pregnancy.

	Cases	Controls	Adjusted OR* (95% CI)
Smoking during pregnancy			
No	59 (7.6%)	714 (92.4%)	1.00
Yes	25 (14.8%)	144 (85.2%)	2.10 (1.13–3.68) $p = 0.018$
Cigarette/day during pregnancy	$p = 0.012$		
None	59 (7.6%)	714 (92.4%)	1.00
<10/day	18 (15.1%)	101 (84.9%)	1.82 (0.9–3.56) $p = 0.148$ (NS)
≥ 10/day	7 (14.0%)	43 (86.0%)	2.00 (0.78–5.10) $p = 0.078$
Smoking before and during pregnancy	$p = 0.012$		
Neither	50 (7.8%)	593 (92.2%)	1.00
Yes, only before pregnancy	9 (6.9%)	121 (93.1%)	0.95 (0.43–2.14) $p = 0.911$ (NS)
Yes, both before and during pregnancy	25 (14.8%)	144 (85.2%)	2.04 (1.13–3.68) $p = 0.018$

SGA, small for gestational age; OR, odds ratio; CI, confidence interval.
*Adjusted for previous low birth weight, urinary tract infections, gestational hypertension, treatment for anemia.

Table III. ETS exposure of cases (severe SGA, $N = 84$) and controls according to the number of smokers in the home and smoking habits.

	Cases	Controls	Adjusted OR* (95% CI)
Active smoking/ ETS exposure	$p = 0.000$		
No active smoking/ no ETS exposure	30 (5.7%)	499 (94.3%)	1.00
No active smoking/ yes ETS exposure	29 (12.1%)	211 (87.9%)	1.95 (1.05–3.62) $p = 0.035$
Yes active smoking/ yes ETS exposure	20 (17.4%)	95 (82.6%)	2.71 (1.41–5.22) $p = 0.003$

SGA, small for gestational age; OR, odds ratio; CI, confidence interval; ETS, environmental tobacco smoke.
*Adjusted for previous low birth weight, urinary tract infections, gestational hypertension, treatment for anemia.

drug use) [8], the most frequently associated factors are maternal anthropometry, poor nutrition, maternal age, low maternal education, maternal unemployment or heavily working during pregnancy, and absence or poor quality of prenatal and family care [15].

In the actual study, maternal age, marital status, education, moderate physical activity, working, as well as further socio-economic and behavioral factors were not found to be associated with severe SGA. Such discrepancies could possibly be ascribed to the strict definition of SGA we utilized, i.e., birth weight $\leq 5^{th}$ percentile. The common definition of SGA as $\leq 10^{th}$ percentile could overdiagnose the condition. Indeed, SGA is defined according to gestational age and 5–20% of estimates of gestational age are incorrect based on last menstrual period recall [16].

In contrast, some variables from obstetric history and medical records, such as previous LBW, UTIs, gestational hypertension, and treatment for anemia, were found to be associated with the outcome and were adjusted for in the multivariate analysis.

Some methodological limitations, however, 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) this was limited to 40–60% as it was impossible to cover all the obstetric wards in these big cities. However the sample from these areas is to be considered homogeneous as we only involved public hospitals in the present study.

Maternal smoking was based on self-report, leading to potential misclassification. Although many studies have shown agreement between the amount of self-reported smoking and serum or urinary cotinine levels [17], several issues regarding covariates and confounders need to be addressed. However, in our study 40.4% of women with severe SGA and 31% of control women reported that they smoked before pregnancy. These data agree with those from the Italian Institute for Statistical Research [18], who reported that the prevalence of smoking among Italian women aged 25–44 years was 33.5%, similar to our study and refutes the fact, suggested by some authors, that mothers may not report the number of cigarettes smoked in pregnancy accurately, leading to additional misclassification. 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 univocal: a number of studies have found poor to moderate correlation between self-reported information on ETS exposure and cotinine measurements [19–21], while other studies testing the exposure to ETS and cotinine levels have shown a good correlation with a history of this exposure [22,23].

In conclusion, our results add to earlier findings that active smoking during pregnancy increases the

risk for SGA in its severe form. However, stopping smoking before pregnancy reduces this risk.

ETS exposure contributes to the risk of severe SGA to a similar extent as active smoking, and health information on this topic must be addressed to family members of pregnant women.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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