

Smoking and other pre-gestational risk factors for spontaneous preterm birth

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Tabagismo e outros fatores de risco pré-gestacional para nascimento espontâneo prematuro

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Abstract

Objectives: to investigate pre-gestational risk factors for spontaneous preterm birth and, the role of smoking and its cumulative effects on prematurity.

Methods: a case-control study analyzed a data set of all births occurring in a tertiary maternity hospital between April 2002 and July 2004. Spontaneous preterm births of single and live newborns without malformations were selected as cases. Controls were all the term births of live and single newborns without malformations during the same period. Three outcomes were studied: all preterm births (<37 weeks), less than 35 weeks and less than 32 weeks of gestational age. Logistic regression was used to obtain the independent effect of pre-gestational risk factors.

Results: maternal age of less than 20 years, low schooling, low maternal pre-gestational body mass index and smoking showed significant, independent association with spontaneous preterm birth for the three outcomes. For all these risk factors, excepting maternal smoking, odds ratios increased with decreasing gestational age at birth and this trend was significant for low maternal age and low pre-gestational body mass index.

Conclusions: the cumulative effects of smoking calls for the need to encourage smoking cessation among pregnant women, especially those who are underweight and in the older age groups, because of the increased risk of delivering premature babies.

Key words Preterm, Risk factors, Smoking

Resumo

Objetivos: investigar fatores de risco pré-gestacional para nascimento espontâneo prematuro e o papel do tabagismo e seus efeitos cumulativos na prematuridade.

Métodos: um estudo transversal baseado em um banco de dados maternos e perinatais, analisou todos os nascimentos ocorridos, em um hospital terciário, no período de abril de 2002 a julho de 2004. Nascimentos prematuros, únicos e espontâneos, de nascidos vivos, sem malformações, foram selecionados como casos. Controles foram selecionados como nascidos vivos e a termo, únicos e sem malformações durante o mesmo período. Três desfechos foram estudados: todos nascimentos prematuros com menos de 37 semanas, aqueles com menos de 35 e 32 semanas de gestação. Regressão Logística foi utilizada na determinação do efeito independente de cada um dos fatores de risco.

Resultados: idade materna de menos de 20 anos, baixa escolaridade, baixo índice de massa corporal pré-gestacional e tabagismo se mostraram independente e significativamente associados com nascimento espontâneo e prematuro para os três desfechos. Para todos os fatores de risco, exceto tabagismo materno, as razões de chance aumentaram linearmente com o decréscimo da idade gestacional. O teste para tendência linear se mostrou significativa para idade materna de menos de 20 anos e para baixo índice de massa corporal pré-gestacional.

Conclusões: os efeitos cumulativos do tabagismo apontam para a necessidade de incentivar o abandono do hábito de fumar entre as gestantes, especialmente entre aquelas com baixo índice de massa corporal e em idade mais avançada, devido ao risco aumentado de prematuridade neste grupo específico.

Palavras-chave Prematuridade, Fatores de risco, Tabagismo

Introduction

Preterm birth is an important cause of perinatal mortality and long-term morbidity both in developed and developing countries.^{1,2} Cerebral palsy, epilepsy, and visual and mental impairment are some of life-long problems faced by survivors. Advances in neonatal care have been successful in reducing neonatal mortality, but the prevention of long-term consequences of preterm birth has not been so successful, especially in extremely preterm babies.²

Preterm birth is a condition of multiple aetiology and has been classified into the following subtypes: those occurring spontaneously after preterm labour or preterm rupture of membranes, and those medically recommended.^{3,4}

There is extensive literature on the risk factors for preterm birth. Studies cover sociodemographics and pre-gestational health, maternal reproductive antecedents, gestational health and the characteristics of the fetus.⁴

The results of a meta-analysis concluded that smoking during pregnancy is a significant and preventable factor associated with ectopic pregnancy, placental abruption, placenta previa, and preterm premature rupture of the membranes. However, the exact mechanism underlying this is still unclear.⁵ The developmental toxicity of nicotine has been reported, as well as the effects of maternal smoking on the placenta.⁶ Animal studies demonstrate the effects of nicotine on fetal and placental development, although it is not known whether the physiological effects of smoking on fetal growth are due to the vasoconstrictive properties of nicotine on uterine blood or the reduced oxygen availability caused by carbon monoxide.^{7,8} Further research is needed to better understand the impact and aetiology of tobacco-related effects on the maternal-fetal interface throughout pregnancy.

The purpose of this study was to identify pre-gestational risk factors for spontaneous preterm birth at a tertiary care hospital in southern Brazil, in particular the role of smoking and its cumulative effects on prematurity.

Methods

A case-control study was conducted between April 2002 and July 2004 in the Maternity Unit of the University Hospital of the Federal University of Santa Catarina (HU/UFSC), in Florianópolis, Brazil. The HU/UFSC is one of the two main public maternity hospitals in Florianópolis, admitting women from the government-funded Brazilian national

health insurance system (SUS).

Data from the Perinatal Information System Database, concerning all births during this period in this maternity hospital were used. Such secondary data are routinely collected using the protocol devised by the Latin American Centre for Perinatology and Human Development (CLAP).

All spontaneous preterm births, of single and live newborns, without malformation, occurring between 20 and 37 weeks of gestation, taking place from April 2002 to July 2004 in the HU/UFSC Maternity Unit, were defined as cases and included in the analysis. A birth was included in the case group when gestational age was estimated to lie within this range by physical examination of the newborn and, by date of the last menstrual period. When only one of these measures was available, those babies weighing more than 2500g were excluded. For further calculations, the estimated gestational age according to physical examination of the newborn was the measure of choice. Estimation of gestational age by physical examination of the newborn was calculated using Ballard's method for those infants weighing less than 1500 g or, when estimated according to the last menstrual period or when early ultrasound indicated less than 34 weeks. Capurro's method was used for more mature infants. Multiple or medically indicated preterm births were excluded, as well as stillbirths and births resulting in a newborn with a malformation. The controls were all other births at the same hospital between 37 and 42 complete weeks of gestation, as estimated according to both physical examination of the newborn and date of the last menstrual period. Multiple births, stillbirths and births resulting in a newborn with a malformation were also excluded from the control group.

The cases were categorized according to three outcomes: all preterm births of less than 37, those of less than 35 and those of less than 32 full weeks of gestation.

The main pre-gestational variables indicating a risk factor, as previously reported in the literature, were available in more than 95% of cases and controls in the database. Although the variables related to smoking in the database referred to smoking during the pregnancy, we considered it also to be a pre-gestational factor, as a woman who smoked during pregnancy was most probably a pre-gestational smoker. The following pre-gestational risk factors were analysed: maternal age, schooling, marital status, body mass index (BMI), smoking and parity. Odds ratios (ORs) and 95% confidence intervals [CI] were calculated. The significance level was

set at $p < 0.05$. Risk factors with an increased odds ratio at a level of significance of 90% were included in the final model using logistic regression. When a linear trend for the three outcomes was observed, the Mantel-Haenszel test for linear trend was performed. The SPSS 12.0 software was used for statistical analysis.

The cumulative effect of pre-gestational smoking on spontaneous preterm birth, was obtained by stratifying smokers according to age using 25 years as a cut-off point, assuming that most smokers start in early adolescence⁹ and that age was positively associated with exposure.

This study was approved by the Human Research Ethics Committee of the Federal University of Santa Catarina (CEPSH/UFSC) – Process n° 11158 FR:383612.

Results

The selection process resulted in 146 cases (<37 weeks of gestation) and 2198 controls. Of the cases, 69 had a gestational age of less than 35 weeks and 26 of less than 32 weeks. Table 1 shows the distribution of cases and controls according to maternal variables and gestational age.

Table 2 shows the results of the univariate analysis. Women below the age of 20 years, those with a lower level of education, and those with low BMI and who were smokers during pregnancy presented an increased risk of spontaneous preterm birth for all three outcomes.

A significant linear trend for age was also observed in those women with less than 32 weeks of gestation, with risk of preterm birth increasing inversely with age.

In this study, the risk associated with schooling, i.e. those women not reaching a secondary level of education which, in Brazil, occurs at 13 years of age. Low schooling was associated with a significant risk of spontaneous preterm birth. A linear trend was observed, although it was not significant (Table 2).

Pre-gestational BMI lower than 20 kg/m² was also significantly associated with an increased risk of spontaneous preterm birth for the three outcomes and a significant linear trend with increasing rates among low BMI women in the lower gestational age groups (Table 2).

Smoking posed an increased and significant risk of prematurity, for all three gestational age outcomes, compared to non smokers. When taking into account the number of cigarettes smoked per day, the risk increased significantly with increased exposure, although this was not significant among those with less than 32 weeks of gestation.

Table 3 shows the results of the multivariable analysis using logistic regression. The final model including those variables with a significant odds ratio indicated that an increased risk of spontaneous preterm birth remained for all three outcomes, for women of a lower age, lower schooling and lower BMI and smokers.

Table 1

Mean and standard deviation of quantitative variables, in controls and in the cases of the three outcomes: spontaneous preterm birth at less than 37, 35 and 32 weeks of gestation. University Hospital of the Federal University of Santa Catarina, Florianópolis, Santa Catarina, Brazil, 2002-2004.

Variables	Controls (n=2198)		Cases					
			<37 weeks (n=146)		<35 weeks (n=69)		<32 weeks (n=26)	
	n	$\bar{X} \pm SD$	n	$\bar{X} \pm SD$	n	$\bar{X} \pm SD$	n	$\bar{X} \pm SD$
Gestational age* (weeks)	2198	39.4 ± 1.2	146	33.8 ± 2.6	69	31.8 ± 2.5	26	29.3 ± 2.6
Maternal age (years)	2194	25.3 ± 6.2	145	23.9 ± 6.9	68	23.6 ± 7.0	26	21.1 ± 6.0
Pre-gestational BMI (kg/m ²)	2110	22.5 ± 4.1	140	22.1 ± 4.3	64	21.8 ± 4.8	24	21.3 ± 4.6
Previous pregnancies	2196	1.3 ± 1.5	146	1.3 ± 1.6	69	1.5 ± 1.9	26	1.5 ± 2.0
Cigarettes per day	2184	1.2 ± 4.1	145	3.1 ± 7.6	69	3.6 ± 8.5	26	2.8 ± 8.7

* Preferably estimated by clinical examination of the newborn; BMI= body mass index.

Table 2

Odds ratio (OR) and 95% confidence intervals [95% CI] for the association of maternal pre-gestational characteristics and spontaneous preterm birth of less than 37, 35 and 32 weeks of gestational age. University Hospital of the Federal University of Santa Catarina, Florianópolis, Santa Catarina, Brazil, 2002-2004.

Variables	Controls		<37 weeks		<35 weeks		<32 weeks		Mantel-Haenszel (p) ^a			
	n	%	Cases	OR (95%CI)	Cases	OR (95%CI)	Cases	OR (95%CI)				
Maternal age at delivery (years)												
≤19	412	18.8	44	30.3	1.94 (1.30 - 2.89)***	24	35.3	2.49 (1.42 - 4.35)***	14	53.8	4.88 (2.05 - 11.68)***	0.03
20 - 34	1579	72.0	87	60.0	1.0	37	54.4	1.0	11	42.4	1.0	
≥35	203	9.2	14	9.7	1.25 (0.66 - 2.32)	7	10.3	1.47 (0.59 - 3.53)	1	3.8	0.71 (0.00 - 5.37)	ns
Schooling (secondary level)												
Reached	1007	46.2	49	33.8	1.0	21	30.9	1.0	6	23.1	1.0	
not reached	1171	53.8	96	66.2	1.68 (1.16 - 2.45)**	47	69.1	1.92 (1.11 - 3.37)**	20	76.9	2.87 (1.08 - 8.07)*	0.29
Marital status												
not single	1941	89.0	134	92.4	1.51 (0.78 - 2.99)	62	91.2	1.28 (0.52 - 3.33)	23	88.5	1.05 (0.27 - 4.0)	ns
Single	240	11.0	11	7.6	1.0	6	8.8	1.0	3	11.5	1.0	
BMI (kg/m²)												
≤19	468	22.2	44	31.4	1.61 (1.06 - 2.45)*	27	42.2	2.55 (1.42 - 4.59)***	12	50.0	3.27 (1.27 - 8.55)**	0.04
20 - 23	1149	54.4	67	47.9	1.0	26	40.6	1.0	9	37.5	1.0	
≥24	493	23.4	29	20.7	1.01 (0.63 - 1.62)	11	17.2	0.99 (0.45 - 2.12)	3	12.5	0.78 (0.16 - 3.17)	ns
Smoking (cigarettes/day)												
Non-smokers	1926	88.2	108	74.5	1.0	48	69.6	1.0	19	73.1	1.0	
All smokers	258	11.8	37	25.5	2.56 (1.68 - 3.88)***	21	30.4	3.27 (1.85 - 5.73)***	7	26.9	2.75 (1.03 - 7.05)*	ns
1 - 10	180	8.2	23	15.9	2.28 (1.37 - 3.77)**	15	21.8	3.34 (1.74 - 6.33)***	5	19.3	2.82 (0.90 - 8.18)	ns
11 - 20	71	3.3	10	6.8	2.51 (1.17 - 5.23)*	3	4.3	1.70 (0.41 - 5.89)	1	3.8	1.43 (0.00 - 10.42)	ns
>20	7	0.3	4	2.8	10.19 (2.44-39.88)**	3	4.3	17.20 (3.37-77.78)**	1	3.8	14.48 (0.00 - 130.17)	ns
Parity (number of previous pregnancies)												
0	825	37.6	60	41.1	1.0	28	40.6	1.0	10	38.5	1.0	
1 or 2	992	45.2	57	39.0	0.79 (0.53 - 1.17)	27	39.1	0.80 (0.45 - 1.42)	11	42.3	0.91 (0.36 - 2.35)	ns
3 or 4	303	13.8	20	13.7	0.91 (0.52 - 1.58)	8	11.6	0.78 (0.32 - 1.82)	2	7.7	0.54 (0.08 - 2.69)	ns
>4	76	3.4	9	6.2	1.63 (0.72 - 3.58)	6	8.7	2.33 (0.83 - 6.19)	3	11.5	3.26 (0.69 - 13.33)	ns

*p<0.05; ** p<0.01; *** p<0.001; ns= non-significant at the 95% confidence level; a significance from Mantel-Haenszel test for gestational age at birth linear trend analysis; BMI= body mass index.

Table 3

Adjusted odds ratios and 95% confidence intervals [95% CI] for significant risk factors found in the univariate analysis, for spontaneous preterm birth of less than 37, 35 and 32 weeks of gestational age. University Hospital of the Federal University of Santa Catarina, Florianópolis, Santa Catarina, Brazil, 2002-2004.

Factor	<37 weeks	<35 weeks	<32 weeks
	OR _{adj} (95%CI)	OR _{adj} (95%CI)	OR _{adj} (95%CI)
‡Age < 20 years ^a	1.87 (1.28 - 2.73)	2.37 (1.40 - 4.01)	4.56 (2.04 - 10.15)
‡Low schooling ^b	1.58 (1.09 - 2.30)	1.79 (1.03 - 3.12)	2.43 (0.96 - 6.16)
§BMI < 20 kg/m ² ^c	1.40 (0.92 - 2.13)	2.15 (1.19 - 3.90)	2.44 (0.99 - 6.01)
§Smoking ^d	2.46 (1.52 - 3.98)	2.51 (1.27 - 4.95)	1.48 (0.48 - 4.63)

^a reference category age 20–34 years; ^b less than 9 years in school; ^c reference category BMI 20-24 kg/m²; ^d reference category non-smokers; BMI= body mass index; § Model adjusted for all variables in the table; ‡ Model adjusted for age and schooling.

Discussion

Preterm birth is a heterogeneous condition, with multiple aetiologies. In this study, we examined the effect of potential pre-gestational risk factors on spontaneous preterm birth. We, therefore, only included those births following spontaneous preterm labour or rupture of the membranes. Multiple births, stillbirths and births of a newborn with a malformation were excluded. The purpose of this selection was to obtain an etiologically homogeneous sample, although, even in this group, the pathogenic pathways may be multiple. Cases were divided into three outcomes according to gestational age because the mortality and morbidity of preterm birth are mainly associated with the most immature newborns.² Four pre-gestational risk factors were significantly and independently associated with increased risk of spontaneous preterm birth at less than 37, less than 35 and less than 32 weeks of gestational age: namely, maternal age of less than 20 years, low schooling, pre-gestational BMI of less than 20 kg/m² and smoking.

We found that pregnancy in adolescence is a risk factor for spontaneous preterm birth, and this association was significantly stronger for the earliest births. Adolescents thus had a 5-fold chance of delivering their babies at less than 32 weeks of gestation. These babies are the most susceptible to death or unfavourable outcomes.² Low maternal age as a risk factor has been observed in Brazil¹⁰ and in other countries,¹¹ although it has not been a uniform finding.¹² During recent decades, a troubling increase in the number of pregnancies in adolescence has been observed in some regions of Brazil,¹ especially amongst poorer women.¹³ The mechanism by

which adolescence and preterm birth are associated is not clear. The effect of age could simply reflect other factors related to an adverse environment or could lead to preterm birth as a consequence of the biological immaturity of young women.¹⁴ These two mechanisms could act in association. The multivariable analysis in our study indicated that low maternal age had an effect independent of low schooling, low body mass index and smoking, which suggests that the biological immaturity of young women may play some role in this association. Prenatal variables, such as prenatal care were not covered by this study and inappropriate prenatal care in adolescent women must be considered. A study in Australia demonstrated that prenatal care could reduce the risk of preterm birth in teenagers.¹⁵

We found that, when the secondary level of schooling was not reached, which usually occurs at 13 years of age in Brazil, the chances of spontaneous preterm birth was significantly higher for the three outcomes and, this was independent of the other factors studied, such as maternal age. Low schooling is an indicator of low socioeconomic status. Studies in northern Brazil¹⁰ and in developed countries¹⁶ have not demonstrated this association, but others have found this to be the case, although most of these did not consider the preterm birth subtypes. In another southern city in Brazil, Barros *et al.*¹³ found that, although literacy improved between 1982 and 1993, the occurrence of preterm birth increased and this trend continues today.¹

Pre-gestational BMI of less than 20 kg/m² significantly increased the chances of spontaneous preterm birth for the three outcomes and this association was stronger for the earliest preterm births, with a significant trend ($p=0.04$) (Table 2). An asso-

ciation between low pre-gestational BMI or body-weight and spontaneous preterm birth has been observed^{17,18} and the mechanism by which this association occurs is a subject of considerable interest.^{19,20} Pre-gestational malnutrition may be a marker for the other factors of an unfavourable environment or could have a more direct effect on preterm birth.

Smoking was one of the main risk factors found in this study. Although the number of cigarettes smoked per day in the database referred to gestational smoking, we considered it a pre-gestational variable, as a pregnant smoker was most certainly a pre-gestational smoker. Thus, as some women may have stopped smoking or cut down on the number of cigarettes per day when planning pregnancy or on becoming pregnant, pre-gestational smoking may be underestimated but not overestimated in our study. Smoking more than 20 cigarettes a day was associated with a much higher Odds Ratios (Table 2). Moore and Zaccaro¹⁹ also found different risks for different numbers of cigarettes smoked per day, but, in a systematic review and meta-analysis, this relationship was not clear.²⁰

Smoking has decreased in the USA²¹ but remains a concern in Brazil, especially among people on a low income and adolescents.⁹ In another southern Brazilian city, the prevalence of smoking among pregnant women decreased in the last three decades but, in 2004, more than a quarter of them smoked.¹ In order to confirm the possible cumulative effect of smoking on spontaneous preterm birth, and assuming that older women have been smoking for longer, since almost all of them start smoking early in adolescence,⁹ we stratified smoking into those women of 25 or more years and in those of less than 25 years of age (Table 3). Although the number of births in each stratum was small, we observed that, for births of less than 32 weeks of gestation, the odds of prematurity among older smokers were significantly higher when compared to those among younger smokers (significance for evaluation of interaction = 0.02), indicating a possible cumulative effect of smoking on spontaneous preterm birth of less than 32 weeks of gestation. In Brazil, as in many other countries, one of the tobacco warning labels on cigarette packages is: "Smoking by pregnant women may result in preterm birth or low birth weight". The general belief seems to be that stopping smoking when planning to become or becoming pregnant will prevent all of its detrimental consequences for the mother and the fetus, including preterm birth. This may, however, not be sufficient to prevent spontaneous birth at less than 32 weeks of gestation in

older women, if one considers the chronic pre-gestational effects of smoking. It could affect the uterine vasculature in a way analogous to its effect on the heart and other organs.²²

Results from other studies show that smoking during pregnancy is associated with ectopic pregnancy, placental abruption, placenta previa, and preterm premature rupture of the membranes. Current research has focused mainly on the deleterious effects of smoking on the fetus and the placenta during pregnancy.²³ Our results suggest that more attention should be paid to the chronic effects of smoking on the reproductive system years before conception as a risk factor for preterm birth. However, more research is needed to better understand the impact and etiology of tobacco-related effects on the maternal-fetal interface throughout pregnancy.

Pre-gestational overweight has been identified as a risk factor for preterm birth.²⁴ We did not observe this for spontaneous preterm birth. Although the odds ratios for the three outcomes were higher for a history of more than 4 previous pregnancies, we did not find a significant association between this and spontaneous preterm birth. Likewise, the study did not find an increased risk of preterm birth among women aged 35 years or more, delayed childbearing, or those who were single, as suggested by other authors.^{13-16,23}

The reduced number of women in the lower gestational groups and, the relatively small number of pre-gestational variables in the secondary data used prevented further analysis. Ethnicity, a variable considered in most studies, was not available in the database at the time of the study. However, the variables most frequently reported by other studies were explored.

The detection of pre-gestational risk factors for spontaneous preterm is important for prevention. Focusing efforts on prenatal efforts alone may not be optimally effective and wider measures, such as providing information on pregnancy in adolescence should be stepped up. The cumulative effects of smoking also suggests the need to encourage smoking cessation among pregnant women, especially those in the older age group and those who are underweight when they become pregnant, because of the increased risk of premature delivery in these groups.

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