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Risk factors for pre-eclampsia in a large cohort of Latin American and Caribbean women

Agustin Conde-Agudelo *Perinatal Researcher*, **José M. Belizán** *Director*

Latin American Centre for Perinatology and Human Development, Division of Health Promotion and Protection, Pan American Health Organisation, World Health Organisation, Montevideo, Uruguay

Objective To study risk factors for pre-eclampsia in a large cohort of Latin American and Caribbean women.

Design Retrospective cross-sectional study from the Perinatal Information System, the database of the Latin American Center for Perinatology and Human Development, Montevideo, Uruguay.

Setting Latin America and the Caribbean, 1985–1997.

Population 878,680 pregnancies at 700 hospitals; of these 42,530 were complicated by pre-eclampsia and 1872 by eclampsia.

Main outcome measures Crude and adjusted relative risks (RR) of risk factors for pre-eclampsia. Adjusted relative risks were obtained after adjustment for potential confounding factors through multiple logistic regression models based on the method of generalised estimating equations.

Results The following risk factors were significantly associated with increased risk of pre-eclampsia: nulliparity (RR 2·38; 95% CI 2·28–2·49); multiple pregnancy (RR 2·10; 95% CI 1·90–2·32); history of chronic hypertension (RR 1·99; 95% CI 1·78–2·22); gestational diabetes mellitus (RR 1·93; 95% CI 1·66–2·25); maternal age ≥ 35 years (RR 1·67; 95% CI 1·58–1·77); fetal malformation (RR 1·26; 95% CI 1·16–1·37); and mother not living with infant's father (RR 1·21; 95% CI 1·15–1·26). Pre-eclampsia risk increased according to pre-pregnancy body mass index (BMI). In comparison with women with a normal pre-pregnancy BMI (19·8 to 26·0), the RR estimates were 1·57 (95% CI 1·49–1·64) and 2·81 95% CI 2·69–2·94), respectively, for overweight women (pre-pregnancy BMI = 26·1 to 29·0) and obese women (pre-pregnancy BMI > 29·0). Cigarette smoking during pregnancy and a pre-pregnancy BMI < 19·8 were significant protective factors against the development of pre-eclampsia. The pattern of risk factors among nulliparous and multiparous women was quite similar.

Conclusions Risk factors for pre-eclampsia observed among Latin American and Caribbean women are similar to those found among North American and European women.

INTRODUCTION

Pre-eclampsia is one of the most important primary cause of maternal and perinatal mortality and morbidity in both developed and developing countries[1-4]. Around 585,000 women die each year of pregnancy-related causes, 95% of them in developing countries[5]. Thirteen percent of these maternal deaths are due to hypertensive disorders of pregnancy, particularly eclampsia[5]. In some Latin American countries such as Colombia, Brazil, Venezuela, and Mexico, it is estimated that 22%–35% of all maternal deaths are associated with pre-eclampsia[6]. Pre-eclampsia is also associated with high rates of preterm delivery, infants being small for gestational age, and perinatal death over the world[7]. The aetiology of pre-eclampsia remains unknown. Current hypotheses suggest placental ischaemia, immune maladaptation, genetic predisposition, and vascular mediated factors as contributing to the development of this disease[8].

Risk factors for pre-eclampsia have been studied extensively in many settings. Nevertheless, no studies have addressed this topic among Latin American and Caribbean pregnant women. Moreover, the majority of risk factors for pre-eclampsia have been identified in studies with a small sample size and the actual independent contribution of some of these factors to the risk of pre-eclampsia remains controversial.

The objective of the present study was to identify maternal demographic and clinical characteristics associated with the development of pre-eclampsia in a large cohort of Latin American and Caribbean women and to determine whether these factors differ in nulliparae and multiparae.

Correspondence: Dr A. Conde-Agudelo, Hospital de Clinicas, Piso 16, Casilla de Correo 627, 11000 Montevideo, Uruguay.

METHODS

This research is based on the Perinatal Information System database in Montevideo, Uruguay. This system was devised by the Latin American Center for Perinatology and Human Development in 1983, and it consists in the basic perinatal clinical record, its complementary forms and charts, the perinatal card, and a software package for personal computers[9]. In 1985, the Perinatal Information System was adopted by many Latin American and Caribbean hospitals, and is now used by over 700. From 1985 to 1997, the Perinatal Information System recorded the births of 1,008,954 infants to women who were themselves born in Uruguay (25·3%), Argentina (24·1%), Peru (9·4%), Colombia (8·6%), Honduras (8·2%), Paraguay (6·9%), El Salvador (4·2%), Chile (2·8%), Bolivia (2·3%), Costa Rica (2·2%), Panama (1·4%), Republica Dominicana (1·3%), Nicaragua (1·2%), Brazil (0·8%), Ecuador (0·6%), Mexico (0·4%), Bahamas (0·2%), and Venezuela (0·1%).

Detailed descriptions of the database have been published elsewhere[10,11]. Briefly, from the first antenatal visit until discharge of both mother and her infant, the attendant physicians or nurses collect data in the perinatal clinical record in check-box format which includes demographic information, reproductive history, maternal characteristics, prenatal care, labour management, maternal complications during pregnancy, delivery, and the puerperium, and neonatal outcomes. Then, data are entered into an on-site computer and quality control is conducted. Later, these data are sent to the Latin American Centre for Perinatology and Human Development where further data entry, quality control checks, and validation are performed.

All information was obtained from the Perinatal Information System database. We included all pregnancies ending in live births and stillbirths of at least 20 weeks of gestation or at least 500 g birthweight. Pregnancies with missing information on the dependent variable (12·9%) were excluded. Thus, the study population included 878,680 pregnancies.

Dependent variable

Women were classified as having pre-eclampsia according to the English version of the International Classification of Diseases, tenth revision (ICD-10)[12]. The diagnosis of pre-eclampsia in ICD-10 is based on criteria proposed by Davey and MacGillivray[13]. Pre-eclampsia (ICD-10 code O14) is defined as a diastolic blood pressure of at least 90 mmHg on two or more consecutive occasions ≥ 4 hours apart or a diastolic blood pressure of at least 110 mmHg on any one occasion plus proteinuria (one 24-hour urine collection with a total protein excretion of at least 300 mg or ≥ 1+ on a urine dipstick). Eclampsia (ICD-10 code O15) is defined as the occurrence of generalised convulsions together with pre-eclampsia. In the present analysis the pre-eclamptic pregnancies were analysed together with the eclamptic pregnancies.

Independent variables

Maternal age, mother's education, marital status, parity, history of induced or spontaneous abortion, history of chronic hypertension (ICD-10 code I10), gestational age at first antenatal visit, maternal height, pre-pregnancy body mass index, mother's Rh status, cigarette smoking, type of birth (single or multiple), infant's gender, fetal malformations, and gestational diabetes mellitus (ICD-10 code O24·4) were evaluated as potential risk factors for pre-eclampsia. Maternal age was defined as completed years at time of delivery. It was categorised into three groups: < 20 years, 20–34 years, and > 34 years. Mother's education was categorised into none, elementary, secondary, and university. Marital status was dichotomised between those who did and did not live with infant's father. Maternal height and pre-pregnancy weight were recorded at the woman's first antenatal visit in centimeters and kilogrammes, respectively. Maternal height was categorised, according to centiles of our study population, into four groups: ≤ 152 cm (corresponding to 25th centile and lower); 153–157 cm (corresponding to the 26th to 50th centile); 158–161 cm (corresponding to the 51th to 75th centile); and ≥ 162 cm (corresponding to the 76th centile and higher). Body mass index (BMI) defined as pre-pregnancy weight in kilogrammes divided by height in meters squared, was categorised as follows: underweight (BMI < 19·8); normal weight (BMI = 19·8–26·0); overweight (BMI = 26·1–29·0); and obese (BMI > 29·0)[14]. Information on cigarette smoking was also recorded at the first visit to antenatal care, and categorised into nonsmoker (i.e. nondaily smoker), moderate smoker (1–9 cigarettes per day), and heavy smoker (≥ 10 cigarettes per day). Since the database consists of only one variable for cigarette smoking, changes in smoking behavior during pregnancy are not recorded. Hence, if women quit smoking during the latter stages in pregnancy but were classified as smokers early in gestation, they were considered as smokers. Fetal malformations included congenital malformations, deformations, and chromosomal abnormalities (ICD-10 codes Q00 to Q99).

Statistical analysis

Estimates of crude relative risk with 95% confidence interval were computed as measures of the association between pre-eclampsia and the independent variables. Adjusted odds ratios were derived through logistic

regression models as estimates of adjusted relative risks. Those variables that were indicated in the literature as important risks factors for pre-eclampsia or that produced a point estimate at a P value of $< 0{\cdot}10$ on the univariate analysis were entered into a multiple logistic regression model. Variables that were selected by regression procedures were included in the final model. In addition, all one-way interaction terms with parity were included to determine whether risk factors differed between nulliparae and multiparae. Geographic area (Andean region [Colombia, Peru, Ecuador, Bolivia, and Venezuela], Central America [Honduras, El Salvador, Costa Rica, Panama, Nicaragua, Mexico, Republica Dominicana, and Bahamas], and Southern cone [Uruguay, Argentina, Chile, Paraguay, and Brazil]), hospital type (tertiary, secondary, and primary hospitals) and year of delivery (1985 to 1989, 1990 to 1994, 1995 to 1997) were included for adjustments in all the analyses. Dummy variables for missing information were constructed for each of those variables with information missing on more on 10%.

Statistical analyses in the present study are based on data that span 13 years (1985 to 1997), thus allowing for the possibility of including several pregnancies for a woman. Because women with pre-eclampsia are at increased risk for repeating this disorder in subsequent pregnancies[15], an analysis of more than one pregnancy to the same women violates the assumption of the usual methods of estimation and testing for multiple logistic regression model. To address this problem, we performed statistical analysis using the generalised estimating equations model[16] to incorporate dependence among the variables from the same woman and to provide robust variance estimates of the regression coefficients. Since information on both cigarette smoking during pregnancy (routinely recorded since 1990), and pre-pregnancy BMI was missing for 53% and 36% of the women, respectively, several models were undertaken to assess the effects of adjustment for these variables for each independent variable.

The first model was based on the entire data set, without adjustment for the two variables. Two other models were based on the women for whom data on cigarette smoking and pre-pregnancy BMI were available. One model adjusted for these variables and the other did not. This approach allowed to determine whether the inclusion of these variables in the model altered the effects of the remaining factors.

In the several multivariate analyses performed, we found no evidence of confounding of the effect of independent variables on pre-eclampsia by cigarette smoking and pre-pregnancy BMI. The patterns yielded were similar, although the widths of the confidence intervals slightly increased. Therefore, and in order to increase the precision of our analyses, we excluded cigarette smoking and pre-pregnancy BMI from subsequent models. In addition, the rates of pre-eclampsia were 5·1% among women for whom information about cigarette smoking was available and 5·0% among those for whom it was missing. The corresponding rates of pre-eclampsia for women with data missing about pre-pregnancy BMI and women with complete data about that variable were 4·8% and 5·1%, respectively. All analyses were done using the SPSS 8·0 program package (SPSS Inc, Chicago, Illinois, USA) and the SAS statistical package (SAS Institute, Cary, North Carolina, USA).

RESULTS

A total of 878,680 women were included in the present analysis. Of these, 42,530 women (4·8%) developed pre-eclampsia and 1872 (0·2%) were complicated by eclampsia. Hence, for our analyses, we considered 44,402 women suffering from pre-eclampsia. The mean (standard deviation) age was 26·3 (7·2) years in women with pre-eclampsia and 25·3 (6·4) ($P < 0{\cdot}0001$) in women with normal pregnancies. On average, the pre-pregnancy BMI was higher in women with pre-eclampsia than in those with normal pregnancies (27·2 (5·2) *vs* 25·0 (4·2); $P < 0{\cdot}0001$). The mean weight before pregnancy was also higher among women with pre-eclampsia compared with normal pregnancies (61·4 kg (12·5) *vs* 57·2 kg (10·2); $P < 0{\cdot}0001$). The mean gestational age at delivery was significantly lower for women with pre-eclampsia compared with normal pregnancies (38·3 (2·5) *vs* 38·9 (2·1) weeks, respectively; $P < 0{\cdot}0001$).

Table 1 provides information on the association between maternal and pregnancy characteristics and risk of pre-eclampsia through univariate analysis. Nulliparity, history of chronic hypertension, multiple birth, and gestational diabetes mellitus were strongly associated with increased risk of pre-eclampsia. In addition, the risk of this disorder was significantly higher in women younger than 20 years old and those 35 years old or above, women not living with the infant's father, and those who began prenatal care after 27 weeks of gestation. Moreover, there was a significant trend toward increasing risk of pre-eclampsia with higher level of maternal education (χ^2 test for trend = 43·9 with 3 degrees of freedom; $P < 0{\cdot}00001$). Women without previous abortion had a slightly decreased risk of developing pre-eclampsia. A increasing risk of pre-eclampsia was observed in relation to pre-pregnancy BMI, with almost a fourfold difference between lean (BMI < 19·8) and obese (BMI > 29) women (incidence rates of 2·6% and 10·1%, respectively). Overall, cigarette smoking during pregnancy was associated with a 41% reduction in risk of pre-eclampsia (95% CI 38% to 44%). Among smokers, relative risks decreased regularly when the number of cigarettes smoked daily increased.

Table 1. Risk factors for pre-eclampsia among Latin American and Caribbean women (1985–1997): crude relative risks (RR) by univariate analysis.

Characteristic	Total births *n* (%)	Pre-eclampsia *n* (%)	Crude RR (95% CI)
Maternal age (years)			
10–19	180,523 (20·5)	9500 (5·3)	1·16 (1·14–1·19)
20–34	606,220 (69·0)	27,462 (4·5)	Reference
≥ 35	91,937 (10·5)	7080 (7·7)	1·70 (1·66–1·74)
Mother's education			
None	38,505 (4·4)	1300 (3·4)	Reference
Elementary	413,175 (47·0)	18,699 (4·5)	1·34 (1·27–1·42)
Secondary	345,284 (39·3)	20,023 (5·8)	1·72 (1·63–1·81)
University	44,776 (5·1)	2419 (5·4)	1·60 (1·50–1·71)
Missing	36,940 (4·2)	1601 (4·3)	—
Living with infant's father			
No	172,542 (19·6)	9380 (5·4)	1·11 (1·09–1·13)
Yes	686,241 (78·1)	33,625 (4·9)	Reference
Missing	19,897 (2·3)	1037 (5·2)	—
Parity			
0	322,314 (36·7)	22,934 (7·1)	1·88 (1·84–1·91)
≥ 1	556,366 (63·3)	21,108 (3·8)	Reference
Previous abortion			
No	702,541 (80·0)	34,683 (4·9)	0·93 (0·91–0·95)
Yes	163,176 (18·5)	8639 (5·3)	Reference
Missing	12,963 (1·5)	720 (5·6)	—
History of chronic hypertension			
No	866,788 (98·6)	41,510 (4·8)	Reference
Yes	11,892 (1·4)	2532 (21·3)	4·45 (4·29–4·61)
Mother's Rh			
Positive	819,973 (93·3)	41,194 (5·0)	1·04 (1·00–1·07)
Negative	58,707 (6·7)	2848 (4·9)	Reference
Gestational age at first antenatal visit (weeks)			
1–13	223,709 (25·5)	11,465 (5·1)	Reference
14–26	345,287 (39·3)	17,912 (5·2)	1·01 (0·99–1·04)
≥ 27	217,422 (24·7)	12,734 (5·9)	1·14 (1·12–1·17)
Missing	92,262 (10·5)	1931 (2·1)	—
Cigarette smoking			
No	371,942 (42·3)	19,603 (5·3)	Reference
1–9 cigarettes per day	26,160 (3·0)	960 (3·7)	0·73 (0·69–0·78)
≥ 10 cigarettes per day	13,661 (1·6)	279 (2·0)	0·39 (0·34–0·44)
Missing	466,917 (53·1)	23,200 (5·0)	—
Body mass index (kg/m^2)			
< 19·8	86,924 (9·9)	2901 (3·3)	0·72 (0·69–0·74)
19·8–26·0	362,073 (41·2)	16,885 (4·7)	Reference
26·1–29·0	61,601 (7·0)	4264 (6·9)	1·48 (1·44–1·53)
> 29·0	51,172 (5·8)	4749 (9·3)	1·99 (1·93–2·05)
Missing	316,910 (36·1)	15,243 (4·8)	—
Maternal height (cm)			
≤ 152	185,748 (21·2)	10,099 (5·4)	Reference
153–157	178,603 (20·3)	9541 (5·3)	0·98 (0·96–1·01)
158–161	146,024 (16·6)	8103 (5·5)	1·02 (0·99–1·05)
≥ 162	149,462 (17·0)	7862 (5·3)	0·97 (0·94–1·00)
Missing	218,843 (24·9)	8437 (3·9)	—
Type of birth			
Single	862,107 (98·1)	42,326 (4·9)	Reference
Multiple	15,869 (1·8)	1680 (10·6)	2·16 (2·06–2·26)
Missing	704 (0·1)	36 (5·1)	—
Infant's sex			
Male	447,349 (50·9)	22,608 (5·1)	1·02 (1·00–1·04)
Female	422,797 (48·1)	21,017 (5·0)	Reference
Missing	8534 (1·0)	417 (4·9)	—
Fetal malformation			
No	799,793 (91·0)	39,074 (4·9)	Reference
Yes	9562 (1·1)	668 (7·0)	1·43 (1·33–1·54)
Missing	69,325 (7·9)	4300 (6·2)	—
Gestational diabetes mellitus			
No	873,371 (99·4)	43,131 (4·9)	Reference
Yes	5309 (0·6)	911 (17·2)	2·97 (2·78–3·17)
TOTAL	878,680		

Table 2. Adjusted relative risks (RR) for pre-eclampsia among Latin American and Caribbean women (1985–1997).

Risk factor	Adjusted RR (95% CI)
Maternal age (years)	
10–19	0·94 (0·85–1·04)
20–34	Reference
≥ 35	1·67 (1·58–1·77)
Mother's education	
None	Reference
Elementary	1·05 (0·93–1·19)
Secondary	1·28 (0·98–1·60)
University	1·08 (0·93–1·24)
Living with infant's father	
No	1·21 (1·15–1·26)
Yes	Reference
Parity	
0	2·38 (2·28–2·49)
≥ 1	Reference
Previous abortion	
No	1·13 (0·99–1·26)
Yes	Reference
History of chronic hypertension	
No	Reference
Yes	1·99 (1·78–2·22)
Gestational age at first antenatal visit (weeks)	
1–13	Reference
14–26	1·04 (1·00–1·09)
≥ 27	1·01 (0·96–1·06)
Cigarette smoking	
No	Reference
1–9 cigarettes per day	0·79 (0·73–0·85)
≥ 10 cigarettes per day	0·39 (0·33–0·45)
Body mass index (kg/m^2)	
< 19·8	0·57 (0·52–0·64)
19·6–26·0	Reference
26·1–29·0	1·57 (1·49–1·64)
> 29	2·81 (2·69–2·94)
Type of birth	
Single	Reference
Multiple	2·10 (1·90–2·32)
Fetal malformation	
No	Reference
Yes	1·26 (1·16–1·37)
Gestational diabetes mellitus	
No	Reference
Yes	1·93 (1·66–2·25)

Maternal rhesus status and height, and the gender of the baby were not associated with the risk of pre-eclampsia. Table 2 shows the results of multiple logistic regression analysis. Maternal age ≥ 35 years, mother not living with infant's father, nulliparity, history of chronic hypertension, a pre- pregnancy BMI > 26·0, multiple pregnancy, fetal malformation, and gestational diabetes mellitus were factors independently associated with an increased risk of pre-eclampsia. On the other hand, cigarette smoking during pregnancy and a pre-pregnancy BMI < 19·8 were significant protective factors against the development of pre-eclampsia. Besides, even after adjustment, there was a dose–response relation between cigarettes smoked per day and the reduction in risk of pre-eclampsia.

Data analysed separately for nulliparous and multiparous women are shown in Table 3. Significant risk factors that were found to operate similarly in nulliparous and multiparous women were history of chronic hypertension, cigarette smoking during pregnancy, pre-pregnancy BMI, multiple birth, fetal malformations, and

Table 3. Adjusted relative risks (RR) for nulliparous and multiparous Latin American and Caribbean women (1985–1997).

Characteristic	Nulliparae RR (95% CI)	Multiparae RR (95% CI)
Maternal age (years)		
10–19	0·98 (0·92–1·04)	0·99 (0·94–1·05)
20–34	Reference	Reference
≥ 35	0·94 (0·85–1·04)	1·75 (1·64–1·86)
Mother's education		
None	Reference	Reference
Elementary	1·05 (0·96–1·15)	1·03 (0·97–1·10)
Secondary	1·23 (0·98–1·47)	1·31 (0·96–1·66)
University	1·36 (0·97–1·73)	1·28 (0·96–1·59)
Living with infant's father		
No	1·01 (0·98–1·04)	1·29 (0·97–1·62)
Yes	Reference	Reference
Previous abortion		
No	0·98 (0·92–1·03)	0·96 (0·89–1·02)
Yes	Reference	Reference
History of chronic hypertension		
No	Reference	Reference
Yes	1·76 (1·61–1·93)	2·07 (1·98–2·16)
Gestational age at first antenatal visit (weeks)		
1–13	Reference	Reference
14–26	1·03 (0·98–1·08)	1·06 (0·98–1·13)
≥ 27	1·09 (0·99–1·20)	1·06 (0·97–1·13)
Cigarette smoking		
No	Reference	Reference
1–9 cigarettes per day	0·85 (0·78–0·92)	0·78 (0·67–0·88)
≥ 10 cigarettes per day	0·76 (0·68–0·87)	0·41 (0·34–0·48)
Body mass index (kg/m^2)		
< 19·8	0·51 (0·47–0·56)	0·32 (0·27–0·37)
19·6–26·0	Reference	Reference
26·1–29·0	1·31 (1·24–1·38)	1·34 (1·25–1·44)
> 29	1·83 (1·73–1·94)	2·69 (2·52–2·87)
Maternal height (cm)		
≤ 152	Reference	Reference
153–157	1·12 (0·97–1·26)	1·09 (0·98–1·20)
158–161	1·01 (0·96–1·06)	0·99 (0·94–1·04)
≥ 162	0·85 (0·70–1·01)	0·98 (0·95–1·01)
Type of birth		
Single	Reference	Reference
Multiple	1·44 (1·33–1·55)	1·42 (1·33–1·52)
Fetal malformation		
No	Reference	Reference
Yes	1·23 (1·11–1·35)	1·29 (1·19–1·38)
Gestational diabetes mellitus		
No	Reference	Reference
Yes	1·57 (1·44–1·71)	1·18 (1·07–1·30)

gestational diabetes mellitus. The increased risk of pre-eclampsia with maternal age ≥ 35 years was only observed among multiparae but not among nulliparae

DISCUSSION

The results of the present study indicates that maternal age ≥ 35 years, mother not living with infant's father, nulliparity, history of chronic hypertension, pre-pregnancy BMI > 26·0 kg, multiple pregnancy, presence of fetal malformations, and diabetes mellitus are associated with a significantly increased risk of pre-eclampsia in a large cohort of Latin American and Caribbean women, whereas cigarette smoking and pre-pregnancy BMI < 19·6 were protective factors for this disorder. Except for maternal age ≥ 35 years, the regression models predicting risk of pre-eclampsia were identical for nulliparous and multiparous women. To our knowledge, this is the largest study examining the relation between maternal and pregnancy characteristics and pre-eclampsia.

Results from the present study corroborate the findings from earlier reports[17,18] that nulliparous women are at increased risk of pre-eclampsia. It is believed that this high risk is related to the maternal first exposure to chorionic villi, specifically the trophoblast, which is of fetal origin[19]. Previous univariate studies have shown that there is a J-shaped curve for the relation between maternal age and the incidence of pre-eclampsia, with a slightly increased incidence pattern among the young women and a markedly increased incidence among the older women[18,20,21]. We did not find young maternal age (< 20 years) itself to be a risk factor. Undoubtedly, this reflects a confounding factor due to the association of young maternal age with nulliparity. The data from our study indicate that only maternal age ≥ 35 years was significantly associated with pre-eclampsia. However, this risk factor observed in the analysis of all women disappeared in nulliparae when parity was controlled for. The higher risk of pre-eclampsia among women aged ≥ 35 years may be explained by placental ischemia secondary to the increase of sclerotic lesions in the myometrial arteries of this group of women in comparation with younger women[22].

A reduced incidence of pre-eclampsia in women with previous abortion or miscarriage has been reported by some authors[18,23] but not by others[24–27]. We observed that women with previous abortion were not at lower risk of pre-eclampsia than women without that history. However, Campbell *et al.*[28] reported that the incidence of pre-eclampsia after early abortion (less than 13 weeks) was similar to the population incidence in a first pregnancy, but after a late spontaneous abortion the risk of pre-eclampsia was significantly reduced. Thus, it would seem that a previous pregnancy not ending in early abortion would confer some 'immunity' to pre-eclampsia in the next pregnancy.

Unmarried marital status has been implicated as a risk factor for pre-eclampsia in some[21,23] but not all studies[29,30]. We found that mothers not living with infant's father had a significantly higher rate of pre-eclampsia than women living with infant's father. Nevertheless, it is worth noting that this effect disappeared in multivariate analysis by parity.

Like previous studies that have found that chronic hypertension[31,32] and gestational diabetes mellitus[30,33] are risk factors for the development of pre-eclampsia, our study demonstrated that the rate of pre-eclampsia among women with some of these risk factors is about two times higher than that in women without such risk factors. Growing evidence indicates that pre-eclampsia is, at least partially, mediated by insulin resistence which might activate the sympathetic nervous system and lead to an increase in expression of receptors for endothelin, both of which events lead to increased blood pressure[34,35]. The common pathophysiologic factor of insulin resistance in essential hypertension and gestational diabetes mellitus[36] would be the link between these disorders and pre-eclampsia. In addition, the vascular endothelial dysfunction associated with gestational diabetes mellitus may contribute to the increased incidence of pre-eclampsia among these women[37].

We found that a pregnant woman with multiple gestation has two times the risk of developing pre-eclampsia than a woman with a singleton pregnancy. Hyperplacentosis[38], a greater demand of blood and oxygen supply[39], and an increase in the maternal cardiac output[40] have been proposed as underlying mechanisms to explain the increased incidence of pre-eclampsia in multiple pregnancies.

In 1950 De Watteville[41] reported that the incidence of pre-eclampsia was 6·6% in mothers of malformed fetuses, compared with 3% in the general population. Some years later, Nelson[42] found a lower incidence of congenital abnormalities in pre-eclampsia. The data from our study revealed that the presence of fetal malformation was associated with a increased incidence of pre-eclampsia, a finding that is consistent with that of a recent case–control study[43] that included 5261 live and stillborn infants of at least 28 weeks of gestation having a malformation. In addition, these authors showed that malformations of the male genitals and those named 'multiple congenital abnormalities' were the main malformations associated with pre-eclampsia. The underlying mechanism of this association remains unknown, but it has been proposed that impaired placental perfusion could be the common ground for malformations and pre-eclampsia[43].

We found that cigarette smoking during pregnancy decreases the incidence of pre-eclampsia. Moreover, a

inverse relation between intensity of smoking and this disorder was observed. Recently, we have performed a meta-analysis of 35 cohort and case–control studies that assessed the effects of cigarette smoking on risk of pre-eclampsia. Overall, cigarette smoking during pregnancy was associated with a 32% reduction in risk of pre-eclampsia (95% confidence intervals: 31% to 33% for cohort studies and 19% to 43% for case–control studies) (unpublished observations). However, despite this protective effect, smokers with pre-eclampsia have significantly higher rates of low birthweight, small for gestational age, perinatal mortality, and placental abruption compared with nonsmoking pre-eclamptics[44,45]. The biologic mechanism by which cigarette smoking during pregnancy reduces the risk of pre-eclampsia is not clear. However, the beneficial effect might be mediated by nicotine through inhibition of the cytokines or thromboxane A_2 synthesis[46,47], stimulation of nitric oxide release[48], and antioxidant activity[49].

We observed that pre-pregnancy BMI was strongly associated with the risk of pre-eclampsia, findings which support the results of other studies reporting an increased incidence of pre-eclampsia in both overweight and obese women[7,23,25,26,29,30,50]. We found no relation between pre-eclampsia and height as a single variable, in accordance with other authors[30,42]. The mechanisms linking obesity and pre-eclampsia are complex. Obesity is associated with insulin resistance and hypertriglyceridaemia[51,52]. This results in an increased flux of free fatty acids to the liver which lead to an increased secretion of triglyceride-rich, very low density lipoprotein particles. Increased concentrations of these lipoproteins in the circulation may contribute both directly and, through the generation of small, dense low density lipoprotein, indirectly to endothelial dysfunction and therefore expression of pre-eclampsia[53]. Attempts to decrease incidence of pre-eclampsia through maternal weight reduction before pregnancy should take in consideration that small effects should be expected. For example, if women with a pre-pregnancy BMI of 26·1 or more reduce it to 19·8 to 26·0, we estimate that the rate of pre-eclampsia would be reduced by 13%.

The strength of this investigation is its large sample size which confers the sufficient power to evaluate the relation between maternal and pregnancy characteristics and pre-eclampsia. This large database allowed us to analyse risk factors with a high prevalence and those with a low prevalence, such as fetal malformations, gestational diabetes mellitus, multiple gestation, and history of chronic hypertension. The current study also had the ability to control for the influence of many possible confounding factors.

Several limitations and potential biases of this study also must be considered. Firstly, we were unable to evaluate the risk of pre-eclampsia in relation to some factors previously reported to influence this disorder such as race[23,50], maternal physical activity during pregnancy[54], change in paternity[55], length of sexual cohabitation before conception[56], and familial history of pre-eclampsia-eclampsia[57,58], because these data were not available from the Perinatal Information System database. Secondly, the accuracy of diagnosis of cases of pre-eclampsia registered in the database has not been determined; only local medical record verifications have been performed[59]. As such, these data are limited to a certain extent. Moreover, we were concerned with the diagnosis of pre-eclampsia because the diagnoses were made in relatively heterogeneous settings. However, the overall rate of pre-eclampsia in this data set was similar with those previously reported[30,60,61] which would confirm the accuracy of pre-eclampsia diagnosis in our database. Thirdly, Uruguay and Argentina contributed almost 50% of births registered in the Perinatal Information System, whereas the biggest Latin American country, Brazil, contributed < 1% of data. Thus, our results may not be generalised to the whole of Latin American and Caribbean population. Finally, a potential limitation of our analysis is the high proportion of data missing on pre-pregnancy BMI and cigarette smoking. Nevertheless, to investigate this potential source of bias, we performed multiple analyses of the effects of adjustment for these variables and found no evidence of confounding of the effect of significant risk factors on pre-eclampsia by pre-pregnancy BMI and cigarette smoking. In addition, reproductive history and demographic and pregnancy characteristics were not significantly different between women with complete data and women with incomplete data, suggesting that missing values were missed at random. These findings provide some tranquillity that biases due to data missing may not have influenced our results.

In conclusion, the results from our study indicate the presence of a significant association between several maternal demographic and clinical characteristics and pre-eclampsia. Besides, the risk factors for pre-eclampsia identified in this large cohort of Latin American and Caribbean women were similar to those found among North American and European women.

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