



Research article

Risk factors and fetal outcomes for preeclampsia in a Colombian cohort

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ABSTRACT

In Latin America and the Caribbean, hypertensive pregnancy disorders are responsible for almost 26% of all maternal deaths [1] and, in Colombia, they account for 59% of all severe maternal morbidity (SMM) cases, and 59.7% of all SMM cases in adolescents [2]. One of the most important hypertensive pregnancy disorders is preeclampsia (PE). Lives can be saved, if PE is prevented, or detected early and properly managed. Prevention and detection depend on identifying the risk factors associated with PE, and, as these have been shown vary by population, they should be determined on a population-by-population basis. The following study utilized the nested case-control model to evaluate 45 potential PE risk factors of a cohort in Bogotá, Colombia, making it perhaps the most comprehensive study of its kind in Colombia. It found PE to have a statistically significant association with 7 of the 45 factors evaluated: 1) pre-gestational BMI >30 kg/m², 2) pregnancy weight gain >12 kg, 3) previous history preeclampsia/eclampsia, 4) previous history of IUGR-SGA (Intrauterine Growth Restriction-Small for Gestational Age), 5) maternal age <20 or ≥35 years (20–34 was not associated), and 6) family history of diabetes. Finally, prenatal consumption of folic acid was found to lower the risk of PE. We recommend that, in Colombia, factors 1–6 be used to identify at risk mothers during pregnancy check-ups; that mothers be encouraged to take folic acid during pregnancy; and, that Colombia's health system and public policy address the problem of pregestational obesity.

1. Introduction

Preeclampsia (PE) is a hypertensive pregnancy disorder of unknown etiology and physiopathology [3], which has been estimated to complicate 2–8% of all pregnancies worldwide [4, 5] and to increase the likelihood of illness and death for fetus, infant, and mother alike. In 2014, the World Health Organization (WHO) systematically reviewed the socio-demographic characteristics of 276,388 women from 24 countries and found that a maternal age >30 years and low educational level were associated with a significantly higher risk of PE/eclampsia. High body mass index (BMI), nulliparity, absence of antenatal care, chronic hypertension, gestational diabetes, heart or kidney disease, pyelonephritis or urinary tract infection, and severe anemia were also found to be significant risk factors for PE and unfavorable to neonatal outcome. The study

further showed that PE/eclampsia was a significant risk factor for maternal and perinatal death, preterm birth, and low birthweight [6]. Additionally, a meta-analysis by Bartsch *et al* showed that anti-phospholipid syndrome, prior PE, pregestational diabetes, chronic hypertension, assisted reproductive technology, and high BMI were the risk factors most strongly associated with PE [7].

As the above studies show, PE is associated with several risk factors. These, however, have been found to vary among populations. In other words, not all populations share the same risk factors and, if they do share a risk factor, its effect may be different on each population. For this reason, researchers have recommended determining PE risk factors, and their corresponding effects, on a population-by-population basis [8]. Once accurately determined for a given population, this knowledge can be used to increase diagnosis of early-term PE in high-risk women, thus

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improving case management and decreasing maternal and perinatal morbidity and mortality [9].

In Latin America and the Caribbean, hypertensive pregnancy disorders are responsible for almost 26% of all maternal deaths [1] and, in Colombia, they account for 59% of all severe maternal morbidity (SMM) cases, and 59.7% of all adolescent SMM cases [2]. These statistics underscore the importance of determining the PE risk factors which affect Colombian mothers and their offspring. The only known study attempting to make this determination in Colombia was performed by Reyes et al in 2012 [10]. They found that body mass index $>31 \text{ kg/m}^2$, high levels of triglycerides, HDL, glycemia and primigravidae were associated with the development of PE. While Reyes et al succeeded in bringing to light the foregoing, a review of the relevant literature, including the WHO studied cited above, showed that there are many other possible PE risk factors, which they were unable to examine, including the following: nulliparity, absence of antenatal care, chronic hypertension, heart or kidney disease, pyelonephritis or urinary tract infection, severe anemia, and the possible protective effect of >8 antenatal care visits. The purpose of the current study was to determine PE risk factors and fetal outcomes for a Colombian cohort more comprehensively by investigating a broader, more extensive range of possible risk factors and fetal outcomes.

2. Materials and methods

2.1. Patients

A nested case-control (NCC) study was chosen as the most suitable framework for the present study. The study protocol was approved by the Institutional Ethics Review Board of the Faculty of Medicine at Pontificia Universidad Javeriana/Hospital Universitario San Ignacio (Bogotá, Colombia), and proceeded as follows. All women who came to Hospital Universitario San Ignacio (HUSI) for their initial pregnancy check-up between July 2017 and November 2018 were attended by gynecologists according to standard procedures. Following each initial appointment, a researcher trained in data collection read the clinical history and categorized the case into one of three groups: case, control, or unsuitable for the current study. All women who were diagnosed with PE, as defined by ACOG guidelines [11], were included in the case group, irrespective of whatever other complications they had (including hypothyroidism, diabetes, and/or multiple gestations). All women who showed signs of a normal pregnancy with no complications were tentatively included in the control group. Finally, those who did not have PE, but evinced other complications, were excluded from the study.

All women whose pregnancies had been included in the case or control group were invited to complete an in-depth pre-eclampsia/eclampsia risk factor survey and to allow the researchers access to their clinical history until they were discharged from Hospital Universitario San Ignacio. Participation in PE screening and subsequent monitoring was entirely voluntary; all participants gave written informed consent prior to participating; and all women invited to participate chose to do so. All pregnancies initially categorized in the case group continued in this group until the study's close. However, those initially accepted into the control group were later transferred to one of the other two groups, if the pregnancy evinced any of the following characteristics subsequent to PE screening. The pregnancy was transferred to the case group, if PE developed, and the pregnancy was excluded from the study altogether, if: 1) any complications whatsoever, other than PE, appeared prior to birth, 2) the newborn's weight was lower/big than normal for its gestational age, and 3) congenital malformations occurred. The answers to PE screening questions and pregnancy outcomes were recorded in Research Electronic Data Capture (REDCap).

2.2. Definition of main outcome variables

PE and eclampsia were defined according to ACOG guidelines [11] and its actualization [5], with eclampsia being the convulsive

manifestation of the disease characterized by "new-onset tonic-clonic, focal, or multifocal seizures in the absence of other causative conditions such as epilepsy, cerebral arterial ischemia and infarction, intracranial hemorrhage, or drug use."

2.3. Definitions of independent variables

Based on an extensive review of the PE literature, including the WHO study alluded to above, the following 45 PE risk factors were investigated, on the basis that it each had been shown to be associated with PE in one or more of the studies reviewed. Where appropriate, information regarding these factors for each pregnancy was obtained from the PE survey mentioned above. Otherwise, it was obtained from the clinical history.

2.3.1. Maternal family history (as far as 2nd generation relatives)

Preeclampsia or eclampsia (yes/no); IUGR-SGA (yes/no); stillbirth (yes/no); miscarriage (yes/no); abortion (yes/no); preterm delivery (yes/no); cardiovascular diseases (yes/no); diabetes (yes/no); cancer (yes/no).

These family antecedents were self-reported by the mother at the time in the PE survey; direct access to the family members' medical history was not available.

2.3.2. Parental demographics

Maternal age (<20 , $20-34$, ≥ 35 years); paternal age (<20 , $20-34$, $35-44$, ≥ 45 years); parental age ≥ 35 years (yes/no); maternal education level (less than high school or high school or beyond); maternal socioeconomic level according to Colombian socioeconomic stratification (low, middle, high); mother employed during pregnancy (yes/no); maternal marital status (single, married, divorced, separated, widowed, or cohabiting with infant's father); time of cohabitation (<6 or ≥ 6 months), if applicable.

2.3.3. Parental antecedents

Nulliparity (yes/no); Primipaternity (yes/no); age of menarche (≤ 12 or >12 years); parity {0, 1, >1 }; history of stillbirth or miscarriage (yes/no); aborted first pregnancy (yes/no); abortions (count); intergenetic period (≤ 2 , >2 years); prior preeclampsia or eclampsia (yes/no); prior IUGR-SGA (yes/no); polycystic ovary syndrome (yes/no); pregestational body mass index (BMI in kg/m^2) (≤ 18.5 , $18.5-24.9$, $25-29.9$, ≥ 30).

2.3.4. Maternal health and habits during pregnancy

Weight gain (<9 , $9-12$, >12 kg); smoking (yes/no); urinary tract infection (yes/no); asthma (yes/no); allergic rhinitis (yes/no); folic acid intake (yes/no); anemia (yes/no); migraine (yes/no); atopic dermatitis (yes/no).

2.3.5. Pregnancy characteristics

Number of antenatal visits, where ranges are those defined by the WHO (0, 1-3, 4-8, or >8); weeks during which UtA pulsatility index was performed (<10 , 11-14, 15-19, 20-24, >25); altered uterine artery doppler (yes/no); gestational age at delivery.

2.3.6. Birth characteristics (Neonatal outcomes)

Pre-term delivery (yes/no); birth weight (median); fetal/newborn's sex (male/female); Apgar score at 5 min (median), IUGR-SGA fetus/newborn (yes/no). An IUGR-SGA fetus/newborn was considered to be one with a birth weight in the lower 10th percentile of previously published normal curves [12], and perinatal mortality was defined as the death of either the fetus or of the newborn between the 28th week of pregnancy, or birth weight ≥ 500 g, and the first week of life (7 days). Low birthweight was defined as <2500 g for a live-born infant, and preterm birth was considered to be live-birth occurring earlier than the 37th week [13].

Birth characteristics were included in the below analysis for singleton pregnancies only, so as not to skew results.

2.4. Statistical analysis

Continuous variables are presented in terms of median and range, while categorical variables are presented as absolute and relative frequencies (%). Continuous parameters were compared using the U Mann-Whitney test, where a *P*-value of <.05 was considered statistically significant. Bivariate and multivariate logistic regression analyses were performed to calculate the odds ratio (OR) and adjusted odds ratio (AOR) of each potential risk factor. Lastly, multivariable analysis using backwards stepwise logistic regression was utilized to determine which variables were independently associated with PE. To be included in the bivariate and multivariable analysis, variables had to be without collinearity and have a *p*-value of <0.2 in the univariate model. Analyses were performed with STATA v.16 and GraphPad Prism v.8 softwares.

3. Results

Between July 2017 and November 2018, 1,498 women came to Hospital Universitario San Ignacio for an initial pregnancy check-up. Of these pregnancies, 236 women developed preeclampsia but 215 qualified for the case group (case pregnancies) (the other 21 women were not available for interview) and, at the end of the study, after all exclusions had been made, 265 qualified for the control group (control pregnancies). The other 997 pregnancies were excluded from the study (Figure 1). Moreover, in the course of the study's 16-month duration, 15.8% of all pregnancies at the hospital were case pregnancies afflicted with PE and were included. Furthermore, the ratio of case pregnancies to control pregnancies was 1–1.2. Of the 215 women with case pregnancies, 2 developed eclampsia; 20 had HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome; 12 had multiple gestations; and 49 had newborns with IUGR-SGA.

38 independent variables were included in the bivariate analysis and, of these, 20 had *p*-value <0.20 and 14 were found to be associated with PE. These 20 variables were then tested in the multivariate analysis, which resulted in only 6 being associated with PE (4 were omitted from the multivariable analyses due to collinearity, namely maternal age (<20 and >34 years), primigravida, anemia, and altered uterine artery Doppler). Finally, after multivariate step-wise elimination, 2 of variables remained associated with PE. The frequencies of the variables included in the bivariate and multivariate analyses are summarized in Table 1. Table 2 shows their crude odds ratio (OR) and adjusted odds ratio (AOR), and Table 3 displays the results of step-wise regression and Table 4 describe the results about neonatal outcome.

Variables associated with PE after the bivariate analysis were: 1) maternal age ≥35 years, 2) maternal age <20 and >34 years, 3)

pregestational BMI >25 kg/m², 4) pregestational BMI >30 kg/m², 5) weight gain during pregnancy < 9kg, 6) parental age ≥35 years, 7) nulliparity, 8) age of menarche ≥12 years, 9) previous history of preeclampsia/eclampsia, 10) previous history of IUGR-SGA, 11) family history of abortions, 12) family history of diabetes, 13) antenatal care visits <3 and 14) non-prenatal folic acid intake.

Variables associated with PE after the multivariate analyses were: 1) family history of diabetes, 2) previous history of preeclampsia/eclampsia, 3) previous history of IUGR-SGA, 4) pregestational BMI >30 kg/m², 5) maternal weight gain during pregnancy >12 kg, and 6) non-prenatal folic acid intake.

Variables associated with PE after stepwise elimination were: previous history preeclampsia/eclampsia and BMI ≥30 kg/m².

4. Discussion

All of the independent variables evaluated in this study had previously been shown by other studies to be associated with PE in one or more populations, both globally and in Latin America [6, 7, 10]. Therefore, none of the risk factors determined above, in and of themselves, are a novel finding. What is distinct about the current study's results, is the set of risk factors found. The first was conducted by Conde-Agudelo et al in 2000 [14], and is of special importance because of its scope. It investigated 15 possible PE risk factors in 834,278 pregnant women in 18 Latin American and Caribbean countries, making its sample population one of the largest studied in the region. The second study, performed Reyes et al in 2012 [10], evaluated 201 cases and 201 controls in various cities around Colombia, excluding Bogotá, however, where the present study was conducted.

These results show that PE risk factors for Colombian mothers may be distinct from those experienced by Latin American mothers in general. A key fact to keep in mind when observing the differences in the current study was different from others, including the Conde-Agudelo and Reyes studies, in the following way. These studies, whether cohort or case-control, have tended to be retrospective, i.e. they have taken data from clinical histories or meta-analysis-studies. In the current study, on the other hand, information was obtained directly from pregnant women and their clinical histories. To the best of our knowledge, this is the largest epidemiological study examining parental and pregnancy factors associated with PE performed in Colombia.

The bivariate analysis identified various PE risk factors, which, however, did not pass the filter of the multivariate test. These include: maternal age ≥35 years, paternal and maternal age ≥35 years, pregestational BMI ≥25 kg/m², weight gain during pregnancy ≤ 9kg, nulliparity, age of menarche ≥12 years, family history of abortions, nulliparity, and antenatal care visits <3. Of these variables, it is important to note that some have been identified as PE risk factors in other studies, namely: maternal age ≥35 years [6, 7, 14, 15, 16, 17, 18, 19, 20] and nulliparity [7, 10, 14, 20]. No differences were found in maternal age

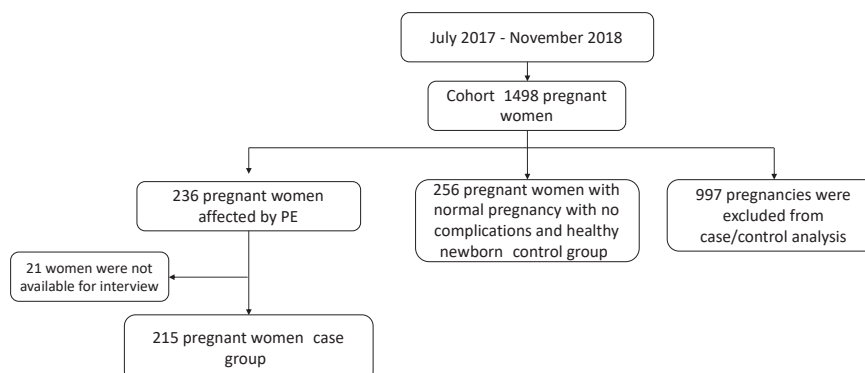


Figure 1. Flow chart of the study population.

Table 1. Overall distribution of risk factors for preeclampsia.

	Preeclampsia group n = 215	Control group n = 265	p value
Gestational age at delivery (weeks)			
Median	36	39	<0.001
Range	22–40	37–41	
Maternal age (years)			
Median	27	27	0.349
Range	15–45	14–52	
Classification of maternal age (n (%))			
<20	18 (8.4)	17 (6.4)	0.086
20–34	148 (68.8)	206 (77.7)	
≥35	49 (22.8)	42 (15.9)	
Maternal age			
<20 and >34 years	67 (31.1)	59 (22.3)	0.027
20–34 years	148 (68.9)	206 (77.7)	
Pregestational maternal body mass index (kg/m²)			
Median	24.3	23.0	<0.001
Range	15.8–46.6	17.1–40.1	
Pregestational maternal body mass index (n (%))			
<18 kg/m ²	6 (2.9)	8 (3.1)	<0.001
18–24.9 kg/m ²	107 (51.4)	189 (72.4)	
25–29.9 kg/m ²	65 (31.2)	53 (20.3)	
≥30 kg/m ²	30 (14.5)	11 (4.2)	
ND = 11			
Weight gain during pregnancy (kg)			
Median	12	12	0.407
Range	0–104	1–90	
Weight gain during pregnancy (n (%))			
≤9 kg	51 (24.5)	38 (14.5)	0.006
9–11.9 kg	56 (26.9)	98 (37.4)	
≥12 kg	101 (48.6)	126 (48.1)	
ND = 10			
Socioeconomic index (n (%))			
Low	126 (59.4)	138 (52.1)	0.085
Middle	85 (40.1)	121 (45.7)	
High	1 (0.5)	6 (2.2)	
ND = 3			
Working during pregnancy			
Yes	135 (63.4)	87 (33.3)	0.455
No	78 (36.6)	174 (66.7)	
ND = 6			
MA ≥35, PA ≥35			
Yes	37 (17.2)	27 (10.2)	0.024
No	178 (82.8)	238 (89.8)	
Nulliparity (n (%))			
Yes	120 (55.8)	117 (44.2)	0.011
No	95 (44.2)	148 (55.8)	
Primigravida (n (%))			
Yes	93 (43.3)	166 (62.6)	0.189
No	122 (56.7)	99 (37.4)	
Primipaternity (n (%))			
Yes	127 (59.1)	151 (57)	0.644
No	88 (40.9)	114 (43)	
Menarche age			
Median	12	13	0.003
Range	9–19	9–19	
Age of menarche at ≥ 12 years (n (%))			
Yes	111 (52.1)	102 (38.9)	0.004
No	102 (47.9)	160 (61.1)	

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Table 1 (continued)

	Preeclampsia group n = 215	Control group n = 265	p value
ND = 5			
Previous abortions			
Yes	55 (25.6)	60 (22.6)	0.453
No	160 (74.4)	205 (77.4)	
Abortions (n (%))			
0	160 (74.4)	205 (77.4)	0.710
1	45 (20.9)	51 (19.2)	
2	8 (3.7)	7 (2.3)	
3	2 (0.9)	1 (0.4)	
6	0 (0)	1 (0.4)	
Abortion in first pregnancy (n (%))			
Yes	31 (14.4)	39 (14.7)	0.926
No	184 (85.6)	226 (85.3)	
Smoking during pregnancy (n (%))			
Yes	6 (2.8)	15 (5.6)	0.897
No	209 (97.2)	250 (94.4)	
Urinary tract infection (n (%))			
Yes	70 (32.6)	83 (31.3)	0.772
No	145 (67.4)	182 (68.7)	
Asma			
Yes	6 (2.8)	8 (3)	0.882
No	209 (97.2)	257 (97)	
Allergic rhinitis (n (%))			
Yes	6 (2.8)	10 (3.8)	0.548
No	209 (97.2)	255 (96.2)	
Anemia (n (%))			
Yes	4 (1.9)	1 (0.4)	0.104
No	211 (98.1)	264 (99.6)	
Polycystic ovary (n (%))			
Yes	5 (2.3)	3 (1.1)	0.310
No	210 (97.7)	262 (98.9)	
Migraine (n (%))			
Yes	17 (7.9)	16 (6)	0.422
No	198 (92.1)	249 (96)	
Atopic dermatitis (n (%))			
Yes	2 (0.9)	4 (1.5)	0.565
No	213 (99.1)	261 (98.5)	
History of previous preeclampsia (n (%))			
Yes	28 (23.1)	6 (3.7)	<0.001
No	93 (76.9)	158 (96.3)	
NA = 195			
History of previous IUGR-SGA (n (%))			
Yes	11 (10.0)	5 (3.0)	<0.001
No	110 (90.0)	159 (97.9)	
NA = 195			
Marital status (n (%))			
Married/cohabiting with the infant's father	179 (91.7)	223 (84.1)	0.791
Single/divorced/separated/widowed	36 (8.3)	42 (15.9)	
Maternal education (n (%))			
less than high school	30 (14.1)	22 (8.4)	0.050
high than high school	183 (85.9)	239 (91.6)	
ND = 6			
Time of sexual cohabitation before conception (months)			
Median	36	36	0.983
Range	0–348	0–300	
Time of sexual cohabitation before conception (n (%))			
<6 months	22 (10.3)	22 (8.3)	0.457
≥6 months	192 (89.7)	243 (91.7)	

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Table 1 (continued)

	Preeclampsia group n = 215	Control group n = 265	p value
ND = 1			
Intergenic period (years)			
Median	60	72	0.462
Range	0–252	12–252	
Intergenic period (n (%))			
≤2 years	33 (29.7)	34 (21.2)	0.113
>2 years	78 (70.3)	126 (78.8)	
NA = 192 [†]			
ND = 17			
Family history of pre-eclampsia (n (%))			
Yes	52 (24.2)	46 (17.4)	0.065
No	163 (75.8)	219 (82.6)	
Family history of IUGR-SGA (n (%))			
Yes	15 (7)	17 (6.4)	0.806
No	200 (93)	248 (93.6)	
Family history of cardiovascular disease (n (%))			
Yes	38 (17.7)	40 (13.6)	0.446
No	177 (82.3)	255 (86.4)	
Family history of abortions (n (%))			
Yes	30 (13.9)	20 (7.5)	0.022
No	185 (86.1)	245 (92.5)	
Family history of stillbirth (n (%))			
Yes	13 (6)	11 (4.1)	0.345
No	202 (94)	254 (95.9)	
Family history of preterm birth (n (%))			
Yes	35 (16.3)	35 (13.2)	0.344
No	180 (83.7)	230 (86.8)	
Family history of diabetes (n (%))			
Yes	72 (33.3)	60 (22.6)	0.011
No	144 (66.7)	205 (77.4)	
Family history of cancer (n (%))			
Yes	37 (17.2)	57 (21.5)	0.236
No	178 (82.8)	208 (78.5)	
Antenatal care visits (n)			
Median	7	8	0.012
Range	0–20	0–16	
Antenatal care visits (n (%))			
0–3	26 (12.6)	15 (5.9)	0.041
4–8	126 (61.2)	163 (64.4)	
>8	54 (26.2)	75 (29.6)	
ND = 21			
Altered uterine artery doppler (n (%))			
Yes	37 (50)	0 (0)	Non evaluable
No	37 (50)	13 (100)	
ND = 393			
Weeks at uterine artery doppler (weeks)			
Median	25	20.5	0.239
Range	11–37	7–37	
Weeks at uterine artery doppler (n (%))			
<10 weeks	0 (0)	1 (7.1)	0.190
11–14 weeks	10 (13.7)	2 (14.3)	
15–19 weeks	9 (12.3)	2 (14.3)	
20–24 weeks	16 (21.9)	4 (28.6)	
>25 weeks	38 (52)	5 (35.7)	
Paternal age (years)			
Median	31	30	0.330
Range	18–56	16–58	
Paternal age (n (%))			

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Table 1 (continued)

	Preeclampsia group n = 215	Control group n = 265	p value
<20	6 (2.8)	6 (2.3)	0.291
20-34	137 (64.3)	173 (66.0)	
35-44	59 (27.7)	66 (25.2)	
≥45	11 (5.2)	17 (6.5)	
ND = 4			
Prenatal vitamins			
Yes	83 (71.5)	139 (84.2)	0.020
No*	33 (28.5)	26 (15.8)	

ND: no data; NA: not applicable.

† Nulliparous women and with PE plus RCIU were excluded.

‡ Nulliparous women were excluded.

* Women who did not take any micronutrient.

between the study groups, when teenagers and ≥ 35 years pregnant women were evaluated separately, no differences were found, but when teenagers and ≥ 35 years pregnant women were included in a group, we found statistically significant differences. It is believed that women of advanced maternal age have an increased rate of pregnancy complications, because advanced age brings with other PE risk factors such as obesity, diabetes, and hypertension [6, 7, 14, 15, 16, 17, 18, 19, 20]. Teenage pregnancy is largely associated with adverse pregnancy outcomes such as preterm delivery, preeclampsia, anemia, surgical deliveries, postpartum endometritis, postpartum hemorrhage, low birth weight, and perinatal death [21, 22, 23, 24]. Teenage pregnancies represent a high-risk group in reproductive terms due to the double burden of reproduction and growth. Maternal age is not the only risk factor for adverse pregnancy outcomes, but they are more related to poverty, inadequate nutrition, impaired health before pregnancy, marital status, and low education [25]. With respect to nulliparity, although hypotheses related to immune maladaptation have put forth [26, 27, 28, 29, 30], the mechanism by which it is a PE risk factor remains unknown. The multivariate test identified BMI ≥ 30 kg/m², weight gain during pregnancy ≥ 12 kg, history of previous preeclampsia and IUGR-SGA and family history of diabetes as variables associated with preeclampsia.

The one variable which occurs as a PE risk factor in all three studies Conde-Agudelo et al, Reyes et al and this study is pregestational maternal obesity. In addition to this common weight-related factor, the current study found excessive weight gain (>12 kg) during pregnancy to be a PE risk factor. Although not found by Conde-Agudelo et al [14] and Reyes et al [10], Guzman-Juarez et al [16] encountered the same result. They categorized pregnancy weight gain as <6.8 , $6.8-11.3$, or >11.3 kg, with $6.8-11.3$ kg being normal weight gain. Compared with women in the normal range, women in the lower range had a lower risk of developing PE and those in the upper range had a greater risk. While the mechanisms linking pregestational or pregnancy obesity to PE are complex, Spradley et al [31] proposed three possibilities: 1) cytotrophoblast migration and placental ischemia [32, 33, 34]; 2) release of soluble placental factors into the maternal circulation [35, 36, 37, 38, 39]; and 3) maternal endothelial and vascular dysfunction.

Although previous history of PE was not analyzed in the studies by Conde-Agudelo et al and Reyes et al, it has been previously found to be a PE risk factor in Latin American populations by Lopez-Carbajal et al [40], as well as Morgan-Ortiz et al [41]. The reason that previous PE might bring about PE in a subsequent pregnancy may be due to impaired endothelial function, which has been shown to be impaired in women with previous PE. In relation to this, there is evidence that administering antioxidant ascorbic acid may improve endothelial function, which opens up the hypothesis that ascorbic acid intake may reduce the risk of PE [42]. In spite of this, Weissgerber et al suggest that persistent endothelial dysfunction in women who have had PE may be due to risk factors that pre-dated pregnancy. Alternatively, PE could also worsen other

cardiovascular risk factors, increasing a women's probability of having hypertension and cardiovascular disease in the future. Finally, PE may cause lasting damage to the heart and vasculature [43].

We found that the previous history of IUGR-SGA was associated with PE. It should also be noted that PE and IUGR-SGA are considered to be different conditions that share physiopathological mechanisms and even could coexist. With respect to IUGR-SGA, a meta-analysis which evaluated IUGR-SGA in previous pregnancies, found no association between IUGR-SGA and PE (OR 1.4; CI95% 0.6–3.0). Both diseases have been associated to endothelial dysfunction and placenta abnormalities [44]. Due to this, it is plausible that history of IUGR-SGA in previous pregnancies might be a risk factor for PE in subsequent pregnancies. Because the controls recruited in our study were uncomplicated pregnancies and deliveries, it was not possible to assess whether the IUGR-SGA was associated with PE.

The current study shared with other worldwide [45, 46] and Latin American [10, 47] studies the result that PE can be associated with family history diabetes. However, it was not in position to evaluate the effect of maternal diabetes due the fact that, while 6 mothers (2.8%) in the case group had diabetes, mothers with diabetes were excluded from the control group. Even though maternal diabetes was not evaluated, it would be reasonable to include it in PE screenings, as there is considerable evidence connecting it with PE. It is known that hyperinsulinemia stimulates the proliferation of vascular smooth muscle cells [48], enhances acute sympathetic nervous system activity [49], and modifies transmembrane ion transport [50] and renal sodium retention [51]. Moreover, hyperinsulinaemia has been shown to promote the proliferation of muscle cells, which, in turn, activate noradrenaline and adrenaline secretion resulting in increased blood pressure [46]. These alterations in glucose metabolism imbalance, together with hyperinsulinemia being associated with endothelial dysfunction, may contribute to increased blood pressure [52, 53] and, hence, pathogenesis characteristic of PE [47].

This study also found that the use of folic acid with ferrous sulfate, or multivitamin supplements with these, during pregnancy was associated to a lower frequency of preeclampsia. Literature reviews of the benefit of folic acid are, however, mixed. On the one hand, regular vitamin intake beginning at 20 weeks was found to reduce the likelihood of PE by 45% [54] and to reduce the probability of the same by 31% in primiparae women [55]. In contrast, Reyes et al [10] and others [56, 57, 58] found that women with PE were less likely to receive vitamin supplements during prenatal care, while still others [56, 57, 58] found no association of any kind. It is biologically plausible that periconceptional multivitamin use protects against PE [59]. Periconceptional exposures may even influence implantation. Thus, many nutrients found in typical prenatal vitamins and multivitamins may be involved, including vitamins C, E, A, D, folic acid, calcium, iron, zinc, selenium, and copper [54].

Table 2. Crude and adjusted odds ratios (OR) of risk factors for preeclampsia.

	OR	CI95%	Adjusted OR	CI95%
Cases = 215; Controls = 265				
Maternal age				
≤20 years	1.47	0.73–2.95	0.18	0.05–6.36
21–34 years	Reference			
≥35 years	1.62	1.02–2.58	4.57	0.94–22.06
Maternal age				
<20 and >34 years	1.58	1.05–2.37		
20–34 years	Reference			
Pregestational maternal body mass index				
≤18.5 kg/m ²	1.32	0.44–3.91	2.39	0.20–28.36
18.6–24 kg/m ²	Reference			
25–29.9 kg/m ²	2.16	1.40–3.34	2.37	0.79–7.10
≥30 kg/m ²	4.81	2.32–10.00	21.0	1.90–232.58
Weight gain during pregnancy				
≤9 kg	2.34	1.37–4.00	3.14	0.65–15.05
10–11.9 kg	Reference			
≥12 kg	1.40	0.92–2.13	3.67	1.04–12.86
Socioeconomic index				
Low	5.47	0.65–46.13	2.29	0.12–41.42
Middle	4.21	0.49–35.64	3.84	0.19–74.85
High	Reference			
Working during pregnancy				
Yes	1.15	0.79–1.68		
No	Reference			
MA ≥35, PA ≥35				
Yes	1.35	1.03–1.76	0.45	0.07–2.93
No	Reference			
Nulliparity				
Yes	1.59	1.11–2.29	3.83	0.72–20.40
No	Reference			
Primigravida				
Yes	1.27	0.88–1.84		
No	Reference			
Primipaternity				
Yes	1.08	0.75–1.56		
No	Reference			
Age of menarche ≥12 years				
Yes	1.70	1.18–2.46	1.31	0.44–3.90
No	Reference			
Previous abortions				
Yes	1.45	0.90–2.33	0.88	0.24–3.14
No	Reference			
Smoking during pregnancy				
Yes	0.96	0.58–1.59		
No	Reference			
Urinary tract infection				
Yes	1.05	0.71–1.55		
No	Reference			
Asma				
Yes	0.92	0.31–2.69		
No	Reference			
Allergic rhinitis				
Yes	0.73	0.26–2.04		
No	Reference			
Anemia				
Yes	5.00	0.55–45.11		
No	Reference			
Polycystic ovary				

(continued on next page)

Table 2 (continued)

	OR	CI95%	Adjusted OR	CI95%
Yes	2.07	0.49–8.80		
No	Reference			
Migraine				
Yes	1.33	0.65–2.71		
No	Reference			
Atopic dermatitis				
Yes	0.61	0.11–3.37		
No	Reference			
History of previous preeclampsia				
Yes	6.58	2.89–14.97	30.78	2.65–356.73
No	Reference			
History of previous IUGR-SGA				
Yes	4.54	1.85–11.13	11.10	1.60–76.76
No	Reference			
Single/divorced/separated/widowed/other				
Yes	1.06	0.65–1.73		
No	Reference			
Maternal education less than high school				
Yes	1.78	0.99–3.18	2.47	0.30–20.03
No	Reference			
Time of sexual cohabitation before conception <6 months				
Yes	1.26	0.68–2.35		
No	Reference			
Intergenic period ≤2 years				
Yes	1.56	0.89–2.73	2.23	0.67–7.40
No	Reference			
Family history of pre-eclampsia				
Yes	1.51	0.97–2.37	0.91	0.20–4.12
No	Reference			
Family history of IUGR-SGA				
Yes	1.09	0.53–2.24		
No	Reference			
Family history of cardiovascular disease				
Yes	1.20	0.74–1.96		
No	Reference			
Family history of abortions				
Yes	1.98	1.09–3.60	0.96	0.17–5.15
No	Reference			
Family history of stillbirth				
Yes	1.48	0.65–3.38		
No	Reference			
Family history of preterm birth				
Yes	1.27	0.76–2.12		
No	Reference			
Family history of diabetes				
Yes	1.68	1.12–2.52	3.41	1.09–10.67
No	Reference			
Family history of cancer				
Yes	0.75	0.47–1.20		
No	Reference			
Antenatal care visits				
0-3	2.24	1.13–4.41	0.83	0.12–5.37
4-8	Reference			
>8	0.93	0.61–1.41	0.48	0.15–1.54
Altered uterine artery doppler				
Yes	1			
No	Reference			
Paternal age				
≤20	1.26	0.39–4.00		

(continued on next page)

Table 2 (continued)

	OR	CI95%	Adjusted OR	CI95%
21-34	Reference			
35-44	1.12	0.74–1.71		
≥45	0.81	0.37–1.80		
Prenatal vitamins				
Yes	0.22	0.06–0.78	0.22	0.06–0.79
No*	Reference			

MA: maternal age; PA: paternal age; IUGR-SGA: intrauterine growth restriction-small for gestational age.

* Reference group: women who did not take any micronutrients.

Table 3. Stepwise multiple regression analysis of factors related to Preeclampsia.

Risk factor	OR	P value	IC 95%
History of previous preeclampsia	26.91	0.002	3.27–221.18
BMI ≥30 kg/m2	29.90	0.001	3.67–243.30

Table 4. Birth outcomes in singleton deliveries.

	All	Preeclampsia group ^a	Control group	P value
Patients (n (%))	468	203	265	
Birth weight (grams) ^a				
Median	2925	2360	3095	<0.0001
Range	310–5100	310–5100	2530–3580	
Baby's sex (n (%))				
Male	239	106 (52.2)	133 (50.2)	0.732
Female	229	97 (47.8)	132 (49.8)	
Apgar 5 min				
Median	9	9	9	0.0002
Range	3–10	3–10	7–10	

^a 7 perinatal deaths and one case without information.

Vitamin D deficiency has been described as a PE risk factor [60]. In light of this and the fact that residents of the city of Bogotá (where the current study was performed) have been reported to have higher incidence of vitamin D deficiency [61, 62], it is possible that vitamin D supplementation could be serve to help prevent PE in Bogota's population. Unfortunately, we were not able to include vitamin D in the current study, because the length of supplementation and stratification of the control pregnancies by gestational age necessary for a valid result [55] would have been difficult to achieve. We hope to able to capture the effect of Vitamin D in a later study.

In relation to newborn complications, it was found that women with PE had newborns with lower birth weight and Apgar score at 5 min. These results have already been reported previously [6, 20, 41, 63], and the most likely cause is that when there is PE placental dysfunction, the conditions of the intrauterine environment adequate for fetal growth and development are affected [64]. Growth restricted fetuses have increased risk of perinatal outcome, and of neonatal complications. Long-term, newborns are at greater risk of developmental delay and behavioral problems in childhood and of metabolic hypertension and diabetes in adulthood [65]. The common causes of neonatal mortality include pre-term birth complications. Although many neonates, because of the plasticity of their developing brains and improvements in medical care, survive major insults without any evidence of impairment, some suffer varying degrees of long-term neurodevelopmental impairment [66].

It should be noted that we found the two variables that could predict women who will develop PE: PE in previous pregnancies and pregestational obesity. These are two modifiable variables in which public policy might help to prevent and thereby lower the incidence of PE. Furthermore, these factors should be carefully considered in the assessment of

each pregnant mother to determine if she is at high risk of developing PE and might benefit from aspirin use to prevent early-onset PE [5].

A key strength of this study was the accuracy of the data collected. Information was obtained directly from mothers and clinical histories by a researcher trained in data collection. A factor which was both a strength and a limitation was that the control group was composed entirely of healthy mothers with uncomplicated pregnancies. The limitation of this was that it prevented the study of some comorbidities, such as gestational hypertension, diabetes and multiple pregnancy, and for this reason it was not possible to assess and control these confounding factors in the epidemiological model. Other limitation of the study was that the researcher did not have access to the medical records of the mother's relatives and had to rely on her responses for this information. It is important to point out that the aOR confidence intervals are wide in some cases, possibly due to the sample size because collinearity is controlled by stepwise analysis and the same effect is also observed in the bivariate analysis. However, despite the lack of precision, the results that highlight the history of previous pre-eclampsia and high BMI are conclusive. For this reason, the low sample size most be consider as a limitation of the study, so the results should be replicated with a larger sample size. Another limitation was the collection of uterine artery Doppler measurements. While these were obtained directly from medical histories, not all Dopplers were carried out at the same institution. Finally, the relative high number of factors compared to the sample size could lead to problems of model fit and reduced statistical power in factor evaluation. Due to this, the relationship of each factor with the outcome was evaluated independently in a bivariate logistic regression model, then the factors that were statistically significant or had a p-value <0.20 were included in a multivariate logistic regression model. The multivariate

model only included 17 factors, so the potential risk of power and stability loss was reduced.

5. Conclusions

Various PE risk factors were identified that could serve as potential predictors of PE in Bogotá, Colombia, and should, therefore, be included in pregnancy check-ups: previous history of PE, previous history of IUGR-SGA, pregestational obesity, weight gain during pregnancy ≥ 12 kg, consumption of prenatal vitamins and family history of diabetes. Although it has been found that the prioritization of risk factors differs at the level of individual patients [67] from the rest of the population, it is important to generate knowledge about the risk factors in the specific population in order to generate specific interventions. In the light of this type of study, it is recommended that the health system be modified to improve maternal and perinatal health, most especially pregestational obesity. However, further studies for larger samples are needed in order to have a better estimation of the associations.

Declarations

Author contribution statement

P. Ayala-Ramírez: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

R. García-Robles: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

N. Serrano, V. Barrera and J. Bejarano: Performed the experiments.

F. Gil: Analyzed and interpreted the data.

J. Silva, and R. Martínez: Contributed reagents, materials, analysis tools or data.

M. Olaya-C: Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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