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Risk Factors for Preeclampsia: Results from a Cohort of Over 5000 Pregnancies in Spain

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Abstract

Objective: To determine the incidence of preeclampsia (PE) and preterm PE in Spain and to identify the risk factors for developing the disease.

Methods: This is a multicenter prospective cohort study performed at six maternity units across Spain. Women with singleton pregnancies attending their first-trimester routine visit at the hospital were offered participation. Maternal and pregnancy characteristics, including mean arterial pressure, as well as ultrasound findings were recorded. Univariate and multivariate logistic regression analyses were performed to identify independent risk factors for subsequent development of PE.

Results: A total of 5868 pregnancies were recruited for this study, including 174 (3.0%) cases of PE, 47 (0.8%) cases of preterm PE and 127 (2.2%) cases of term PE. Median maternal age was 33.9 years (interquartile range: 30.1 to 36.9) and median gestational age at the routine visit was 12.7 weeks (interquartile range: 12.3 to 13.0). However, 293 (5.0%) of the women were on aspirin treatment during pregnancy, likely reducing the true incidence of the disease. As expected, increasing body mass index ($P < 0.001$), uterine artery pulsatility index ($P = 0.011$) and mean arterial pressure ($P < 0.001$), assisted conception ($P = 0.013$), previous personal ($P < 0.001$) or family history of PE ($P = 0.024$) and chronic hypertension ($P = 0.001$) were identified as independent risk factors for developing subsequent PE during pregnancy. Screening for PE by maternal factors alone leads to a detection rate of 36.8% (64/174) at 10.0% (587/5868) screen positive rate.

Conclusion: In Spain, 3.0% of singleton pregnancies are complicated by PE and 0.8% require delivery before term due to its severity. Screening of PE by risk factors alone is only able to detect about 40% of total PE at 10% screen-positive rate.

Keywords: Pre-eclampsia; Aspirin; Risk factors; Screening

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Introduction

Preeclampsia (PE) is a common complication in pregnancy that occurs in 2% to 5% of all pregnancies and is one of the leading causes of maternal and neonatal morbidity and mortality.[1] The risk of adverse perinatal outcomes is worse in those cases when the disease is severe and early onset, requiring delivery before 37 weeks of gestation (preterm PE) as compared to those cases when it is possible to reach term.[2,3]

Classically, PE was defined by the onset of hypertension and proteinuria after 20 weeks of gestation. Recently this definition has been modified. PE is defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg on at least two measurements, separated in 4 hours, in previously normotensive women after 20 weeks of gestation, and is accompanied by proteinuria, evidence of maternal organ dysfunction or uteroplacental dysfunction.[4]

There are different models to identify women at high risk of developing PE. Some clinical guidelines establish a list of single risk factors and consider a woman is at high risk when they present with one or a combination of the listed risk factors.[5,6] Early recognition of these factors is useful to identify women at risk in clinical practice and this is the screening strategy adopted in many countries and recommended by several professional bodies like the Royal College of Obstetricians and Gynecologists in the UK or the American College of Obstetricians and Gynecologists

in the US. However, this approach is insufficient for an effective prediction of PE and several models which include various biomarkers like arterial blood pressure, sonographic measurements or maternal serum analyses have reported better performance.[7–13] Following this screening, women identified at high risk of developing PE should receive aspirin prophylaxis starting at 11^{+0}–14^{+6} weeks of gestation at a dose of 150 mg to be taken every night until 36 weeks of gestation, when delivery occurs or when PE is diagnosed, since its value in significantly reducing the incidence of preterm PE has been well demonstrated by the ASpirin for evidence-based PREeclampsia prevention (ASPRE) trial.[14]

In Spain, a national screening program for PE is not settled and that was the reason why a collaborative study across the country was designed. The aim of the First-trimester screening for PREeclampsia: Spanish multicenter VALidation (PREVAL) study, an observational multicenter study, is first, to select the best method to screen for PE, adapted to the characteristics of the Spanish population, and second, to develop appropriate national recommendations and guidelines. In order to do this, it is mandatory to firstly know the type of population that will take part in screening and their risk factors to develop the disease as well as its prevalence. Subsequently, different screening models will be applied, including maternal history and biophysical/biochemical markers. Finally, predictive performance and value of each risk factor, biomarker and, therefore, the screening method used, will be evaluated in the studied population.[15–17]

Many different risk factors that contribute to the development of PE have been identified. The absolute and relative importance of one risk factor over another has been assessed in a systematic review.[18]

This is the first interim analysis from the PREVAL study, which aims to determine the incidence of PE in our country (both term and preterm) and to identify the risk factors for developing PE in our population.

Material and methods

Study design and population

This is a prospective cohort study performed at six maternity units in Spain (Hospital Universitario de Torrejón, Hospital Universitario Quirón and Hospital Universitario Fundación de Alcorcón in Madrid, Hospital Clínico Universitario Virgen de la Arrixaca in Murcia, Complejo Hospitalario Universitario A Coruña in Galicia and Hospital Universitari Vall d'Hebrón in Catalonia). In the participating centers, all pregnant women attend for a routine ultrasound examination at 11^{+0}–13^{+6} weeks' gestation. At that visit, all women over 18 years with a singleton pregnancy are invited to participate in the study and written informed consent is obtained upon acceptance. For this interim analysis we included patients recruited between September 2017 to May 2019. Eligibility criteria were women >18-year-old with a life fetus at 11^{+0} to 13^{+6} weeks', without major fetal malformations or diagnosed chromosomal defects who signed the informed consent to participate in research. Cases without complete pregnancy outcome as well as termination of pregnancies and miscarriages before 24 weeks were excluded for analysis. The study was approved by the local Research Ethics Committee (Hospital Universitario de Getafe, A07/17).

Study procedures

Prior to the commencement of the study, all research teams were trained for all research procedures and certificate of competence from the FMF was mandatory for uterine artery pulsatility index (UtA-PI) measurement.

During the first-trimester hospital visit, patient's characteristics and medical history were recorded, ultrasound examination was carried out to assess viability, diagnose major defects, date the pregnancy according to the fetal crown-rump length (CRL) and measure fetal nuchal translucency thickness and, as part of our research study, UtA-PI was also determined.[19] Combined screening for aneuploidies was offered and maternal blood for measurement of serum free β-human chorionic gonadotropin (β-hCG) and serum pregnancy-associated plasma protein-A was collected during the same visit or a few days earlier.

We recorded the following patient's characteristics: maternal age, weight, height, body mass index (BMI) racial origin (White, Black, South Asian, East Asian, and mixed), method of conception (natural or assisted conception requiring the use of ovulation drugs or in-vitro fertilization), cigarette smoking during pregnancy (yes or no), parity (parous or nulliparous if no previous pregnancy at ≥24 weeks' gestation), medical history of diabetes mellitus and chronic hypertension (yes or no) and details on previous pregnancies, if any. We also took special care in recording aspirin intake during pregnancy and the reason for it at every hospital visit and during collection of data on pregnancy outcome. All these variables as well as results of the ultrasound investigations, blood tests, arterial blood pressure and pregnancy outcome were recorded in a secure computer database with ViewPoint® software (GE Healthcare; Munich, Germany).

Arterial blood pressure was measured with automated and validated devices, with the woman in a sitting position, with their arms well supported at the level of the heart, using an appropriate-sized adult cuff, after resting for 5 minutes. Blood pressure was measured in both arms simultaneously and at least two sets of recordings were made with at least 1-minute intervals between them.[20] Mean arterial pressure (MAP) was automatically calculated by the software using the following formula: diastolic blood pressure + (systolic blood pressure − diastolic blood pressure) / 3.

Diagnosis of PE and ascertainment of pregnancy outcome

Participants were followed-up according to the protocols of each center and all pregnancy complications and delivery data were carefully recorded by reviewing hospital records or contacting delivering hospitals or the general medical practitioners of the women. PE was diagnosed in the presence of hypertension (systolic blood pressure of ≥140 mmHg or diastolic blood pressure of ≥90 mmHg on at least two measurements 4 hours apart, developed after 20 week of gestation in previously normotensive women) and at least one of the following: proteinuria

(≥300 mg/24 h or protein to creatinine ratio ≥ 0.3 or ≥2+ on dipstick testing), liver involvement (blood concentration of transaminases to twice the normal level), renal insufficiency (serum creatinine >1.1 mg/dL or two-fold increase in serum creatinine in the absence of underlying renal disease), thrombocytopenia (platelet count $<100 \times 10^9$/L), neurological complications, or pulmonary edema.[21]

Statistical analyses

Biomarkers were converted into multiples of the median (MoMs) to adjust for maternal and pregnancy characteristics.[22] Descriptive data were expressed as median and interquartile range (IQR) and in proportions (absolute and relative frequencies). Comparisons between PE and non-PE groups were performed by Mann-Whitney *U* test or Fisher-test as appropriate. Level of significance was set at 0.05. Univariate and multivariate logistic regression models were adjusted, using as dependent variable the development of PE. Best model was selected with the Akaike Information Criterion (AIC). Odds Ratio (*OR*), 95% confidence intervals (*CI*) and *P* values are reported. Given the scale of the MAP MoMs, the variable was multiplied by ten, to allow for a more intuitive interpretation of the *OR*, by the decimal instead of by the unit. Area under the receiver operating characteristic (AUC) and its 95% *CI* were computed for the final multivariate logistic regression model. Probability of developing PE was calculated for each patient using maternal factors identified by this model. We used a 10% screen-positive rate to calculate detection rate. All analyses were carried out in software R (R Core Team, Vienna, Austria) in its version 4.0.2.[23]

Results

A total of 5868 pregnancies were included in this study. Baseline characteristics of the study population are shown in Table 1. Of note, 5726 (97.6%) of the total population were of White racial origin. There were 174/5868 (3.0%) cases of PE, including 47/5868 (0.8%) cases of preterm PE and 127/5868 (2.2%) cases of term PE. It is also worth it to note that 293/5868 (5.0%) of the women were on aspirin treatment during pregnancy, including 5/47 (10.6%) of those who developed preterm PE and 11/127 (8.7%) of those who developed term PE, likely reducing the true incidence of the disease. This will have to be taken into account when screening models are evaluated in this population.

Comparison of baseline characteristics of women developing and not developing PE is shown in Table 2. Compared to women who did not develop PE, women developing PE had a significantly higher BMI ($P<0.001$), were more frequently conceived by assisted reproductive techniques ($P<0.001$), had a higher incidence of type 2 diabetes mellitus ($P=0.013$) and chronic hypertension ($P<0.001$) and were more likely to have family history of PE in their first degree relatives ($P=0.009$).

Results from the univariate and multivariate analyses are shown in Table 3. As expected, increasing BMI (*OR*: 1.10, 95%*CI*: 1.07–1.13, $P<0.001$), UtA-PI (*OR*:1.83, 95%*CI*: 1.15–2.91, $P=0.011$) and MAP (*OR*:1.83, 95%*CI*: 1.53–2.17, $P<0.001$), assisted conception (*OR*:1.79, 95%*CI*: 1.13–2.85, $P=0.013$), previous personal (*OR*: 2.83, 95%*CI*: 1.58–5.06, $P<0.001$) or family history of PE (*OR*:2.35, 95%*CI*: 1.12–4.94, $P=0.024$) and chronic hypertension (*OR*:3.46, 95%*CI*: 1.65–7.27, $P=0.001$) were identified as independent risk factors for developing subsequent PE during pregnancy. Interestingly, maternal age was not found to be a risk factor (*OR*:1.03, 95%*CI*: 1.00–1.07, $P=0.060$) after adjusting by other maternal and pregnancy characteristics, neither as a continuous variable nor as a categorical one, (35 years

Table 1

Baseline characteristics of the study population ($n=5868$).

Variables	Values
Maternal age (years)	33.9 (30.1, 36.9)
Subgroup 1	
≥ 35	2385 (40.6)
< 35	3483 (59.4)
Subgroup 2	
≥ 40	492 (8.4)
< 40	5376 (91.6)
Body mass index (kg/m^2)	
Underweight (<18.5)	164 (2.8)
Normal weight (18.5 to 24.9)	3319 (56.6)
Overweight (25.0 to 29.9)	1560 (26.6)
Obese or more (≥ 30.0)	825 (14.1)
Conception	
Natural	5356 (91.3)
Assisted	512 (8.7)
Cigarrette smoker	
No	5152 (87.8)
Yes	716 (12.2)
Obstetric history	
Parous with previous preeclampsia	116 (2.0)
Parous without previous preeclampsia	2767 (47.2)
Nulliparous	2985 (50.9)
Racial origin	
White	5726 (97.6)
Black	42 (0.7)
East Asian	14 (0.2)
Mixed	81 (1.4)
South Asian	5 (0.1)
Medical history	
Type 1 Diabetes Mellitus	34 (0.6)
Type 2 Diabetes Mellitus	17 (0.3)
AFS	17 (0.3)
SLE	14 (0.2)
SLE and AFS	1 (0.0)
Chronic hypertension	58 (1.0)
Aspirin intake	
No	5575 (95.0)
Yes-started < 16 weeks of gestation	284 (4.8)
Yes-started > or = 16 weeks of gestation	9 (0.2)
Family History of preeclampsia	
No	5747 (97.9)
Yes	121 (2.1)
Gestational age at ultrasound(weeks)	12.7 (12.3, 13.0)
Uterine artery pulsatility index (MoMs)	1.02 (0.83, 1.24)
Mean arterial pressure (MoMs)	0.98 (0.92, 1.04)

Data are given as median (interquartile range) or *n* (%).

SLE: Systemic lupus erythematosus; AFS: Antiphospholipid syndrome; MoMs: Multiples of the median.

Table 2

Baseline characteristics of women developing and not developing preeclampsia.

Variables	No preeclampsia ($n=5694$)	Preeclampsia ($n=174$)	*P*
Maternal age (years)	33.9 (30.1, 36.8)	34.4 (30.5, 38.3)	0.036
Subgroup 1			0.158
≥ 35	2305 (40.5)	80 (46.0)	
< 35	3389 (59.5)	94 (54.0)	
Subgroup 2			0.017
≥ 40	468 (8.2)	24 (13.8)	
< 40	5226 (91.8)	150 (86.2)	
Body mass index (kg/m^2)			<0.001
Underweight (<18.5)	162 (2.8)	2 (1.1)	
Normal weight (18.5 to 24.9)	3257 (57.2)	62 (35.6)	
Overweight (25.0 to 29.9)	1505 (26.4)	55 (31.6)	
Obese or more (≥ 30.0)	770 (13.5)	55 (31.6)	
Conception			<0.001
Natural	5212 (91.5)	144 (82.8)	
Assisted	482 (8.5)	30 (17.2)	
Cigarrette smoker			0.482
No	5002 (87.8)	150 (86.2)	
Yes	692 (12.2)	24 (13.8)	
Obstetric history			<0.001
Parous with previous preeclampsia	97 (1.7)	19 (10.9)	
Parous without previous preeclampsia	2724 (47.8)	43 (24.7)	
Nulliparous	2873 (50.5)	112 (64.4)	
Racial origin			0.272
White	5558 (97.6)	168 (96.6)	
Black	39 (0.7)	3 (1.7)	
East Asian	13 (0.2)	1 (0.6)	
Mixed	79 (1.4)	2 (1.1)	
South Asian	5 (0.1)	0 (0)	
Medical history			
Type 1 Diabetes Mellitus	31 (0.5)	3 (1.7)	0.079
Type 2 Diabetes Mellitus	14 (0.2)	3 (1.7)	0.013
AFS	17 (0.3)	0 (0)	1
SLE	14 (0.2)	0 (0)	1
SLE and AFS	1 (0.0)	0 (0)	1
Chronic hypertension	47 (0.8)	11 (6.3)	<0.001
Aspirin intake			0.022
No	5417 (95.1)	158 (90.8)	
Yes-started < 16 weeks' gestation	269 (4.7)	15 (8.6)	
Yes-started > or = 16 weeks' gestation	8 (0.1)	1 (0.6)	
Family History of preeclampsia			0.009
No	5582 (98.0)	165 (94.8)	
Yes	112 (2.0)	9 (5.2)	
Gestational age at ultrasound(weeks)	12.7 (12.3, 13.0)	12.8 (12.4, 13.2)	0.014
UtA-PI (MoMs)	1.02 (0.83, 1.24)	1.03 (0.83, 1.36)	0.317
MAP (MoMs)	0.98 (0.92, 1.04)	1.03 (0.97, 1.09)	<0.001

Data are given as median (interquartile range) or *n* (%).

SLE: Systemic lupus erythematosus; AFS: Antiphospholipid syndrome; UtA-PI: Uterine artery pulsatility index; MoMs: Multiples of the median; MAP: Mean arterial pressure.

old threshold (*OR*: 1.28, 95%*CI*: 0.92–1.79, $P=0.139$) or 40 years old threshold (*OR*: 1.54, 95%*CI*: 0.92–2.46, $P=0.085$). However, it was retained in the final model because of the lower AIC. AUC for this model was 0.77 (95%*CI*: 0.74–0.81).

Using only the maternal factors identified by the multivariate model, 587/5868 (10.0%) women would screen positive, including 64/174 (detection rate of 36.8%) cases of PE. Of these, 24/47 (detection rate of 51.1%) would correspond to preterm PE and 40/127 (detection rate of 31.5%) to term PE.

Discussion

Main findings

In this study, we found that first, the incidence of preterm and term PE in our Spanish population is 0.8% and 2.2% respectively, similar to what it was anticipated; second,

Table 3

Results from univariate and multivariate regression analyses.

Variables	Univariate model *OR* (95% *CI*), *P*	Multivariate model *OR* (95% *CI*), *P*
Maternal age (years)	1.03 (1.00–1.06), $P=0.039$	1.03 (1.00–1.07), $P=0.060$
Body mass index (kg/m^2)	1.10 (1.07–1.12), $P<0.001$	1.10 (1.07–1.13), $P<0.001$
Assisted conception	2.23 (1.47–3.30), $P<0.001$	1.79 (1.13–2.85), $P=0.013$
Cigarrette smoker	1.16 (0.73–1.76), $P=0.513$	-
Diabetes type 1	3.21 (0.76–9.09), $P=0.056$	4.02 (1.14–14.16), $P=0.030$
Obstetric history		
Nulliparous	Reference	
Parous with previous PE	5.02 (2.89–8.34), $P<0.001$	2.83 (1.58–5.06), $P<0.001$
Parous without previous PE	0.40 (0.28–0.57), $P<0.001$	0.37 (0.25–0.54), $P<0.001$
Chronic hypertension	8.11 (3.93–15.37), $P<0.001$	3.46 (1.65–7.27), $P=0.001$
Aspirin intake		
Yes - started < 16 weeks' gestation	1.90 (1.06–3.16), $P=0.021$	–
Yes - started > or=16 weeks' gestation	4.29 (0.23–23.56), $P=0.171$	–
Positive family history of PE	2.72 (1.26–5.17), $P=0.005$	2.35 (1.12–4.94), $P=0.024$
UtA-PI (MoMs)	1.51 (0.94–2.39), $P=0.080$	1.83 (1.15–2.91), $P=0.011$
MAP (MoMs)*	1.77 (1.50–2.09), $P<0.001$	1.83 (1.53–2.17), $P<0.001$

OR: Odds ratio; *CI*: Confidence interval; PE: Preeclampsia; UtA-PI: Uterine artery pulsatility index; MoMs: Multiples of the median; MAP: Mean arterial pressure. –: Not applicable.
* *OR* of MAP (MoMs) are to be interpreted for each decimal instead of for each unit.

baseline characteristics as well as biomarkers of women who subsequently developed PE significantly differed from those who did not develop PE; and third, increasing BMI, UtA-PI and MAP, assisted conception, previous personal or family history of PE and chronic hypertension are independent risk factors for developing PE during pregnancy.

Comparison with previous studies

In our cohort, women that developed PE during their pregnancy were older, more obese and had more frequently a history of pregestational diabetes, chronic hypertension and/or previous PE (if parous women). In addition, there were more often smokers and had more frequently conceived by assisted reproduction techniques. These risk factors have been previously reported in a meta-analysis published by Barstch *et al.* including 92 studies and more than 25,000,000 pregnancies.[18] They found that previous history of PE increases the risk in current pregnancy eight-fold, as compared to about three-fold increase in our study; pregestational hypertension five-fold, as compared to three-fold increase in our study; assisted reproduction techniques two-fold, as compared to a 10% increase in our study; and maternal age above 35 years about 20%, while we did not find it as a significant risk factor. They also reported that a BMI of over 30 increased the risk three-fold while we adopted a continuous approach, demonstrating a 10% increase every one-unit increase in BMI. These risk factors may have an important role in the physiopathology of PE, probably in relation to the superficial placentation and/or endothelial disfunction that is involved in the clinical appearance of PE.

MAP was previously identified as an important risk factor for PE by Poon *et al.*[20] In our study we indeed identified it as the most important factor, increasing 83% the risk every decimal unit of MAP increase.

Similarly, we found that the UtA-PI was higher in women that develop PE just like Plasencia *et al.* published,[19] increasing 83% the risk with every unit.

Since many of the women at increased risk of PE due to maternal factors where prescribed aspirin during pregnancy, this drug was paradoxically identified as a risk factor from univariate analysis, which was obviously not proven after adjusting by maternal and pregnancy characteristics in this study.

In our population, screening of PE using maternal factors alone yield a detection rate of about 40% at a screen positive rate of 10%, similarly to what it was previously reported by Tan *et al.*[24]

Implications for clinical practice and future research

There is an extensive evidence that PE can be efficiently screened and prevented with aspirin. Although many multimarker algorithms have been proposed to evaluate this risk, there is still no national recommendation from the Spanish Ministry of Health in this respect. Consequently, each center uses a different strategy of screening.

The PREVAL study will help establish the screening strategy and algorithm that best fits our population by assessing each model and biomarker. However, these preliminary findings may still guide clinicians on when to prescribe aspirin based on risk factors until final results are available. As we have shown, a detection rate of about 40% is still expected.

Strengths and limitations

The main strength of this study relates to the large sample size, which allowed us to study a rare condition. Participants were prospectively enrolled across different regions of the country, likely representing the global characteristics of the maternal population in Spain. All

variables were prospectively measured and recorded by the research team, avoiding patients' self-reporting bias derived from questionnaires. Last, pregnancy outcome was ascertained by careful review of pregnancy and delivery hospital records by the same research team, ensuring homogeneity of the criteria when diagnosing the disease.

Nevertheless, our study also has some limitations. The main limitation relates to the low incidence of the disease, with the inevitable wide *CI* associated to several of the reported *OR*. Additionally, some minority ethnic and racial groups may have not been adequately represented due to less access to hospital care and language barriers which may have reduced their participation in this research study.

Conclusions

In Spain, 3.0% of singleton pregnancies are complicated by PE and 0.8% require delivery before term due to its severity. The use of maternal risk factors to screen for this condition in the first trimester of pregnancy may help clinicians identify high-risk women who will benefit from preventive strategies and close monitoring during pregnancy until a better screening method is recommended and implemented by national bodies.

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Author Contributions

The authors confirm contribution to the paper as follows: study conception and design: Maria del Mar Gil, Belen Santacruz; data collection: Diana Cuenca, Katy de Paco Matallana, Nuria Valiño, Rocio Revello, Begoña Adiego, Manel Mendoza, Maria del Mar Gil; analysis and interpretation of results: Diana Cuenca, Maria del Mar Gil, Valeria Rolle; draft manuscript preparation: Diana Cuenca, Maria del Mar Gil, Valeria Rolle. All authors reviewed the results and approved the final version of the manuscript.

Conflicts of Interest

None.

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