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ORIGINAL ARTICLE

Clinical utility of thrombophilia, anticoagulant treatment, and maternal variables as predictors of placenta-mediated pregnancy complications: an extensive analysis

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ABSTRACT

Objective: The objective of this study is to analyze the usefulness of thrombophilia and antithrombotic drugs in combination with materno-fetal characteristics to generate a predictive model of placenta-mediated pregnancy complications (PMPC) for counseling treatment.

Methods: A retrospective analysis was performed in women with singleton pregnancy that required a thrombophilia study, including 222 patients with unknown cause PMPC and 151 women with no complications at current pregnancy in Hospital Clínico Universitario, Lozano, Blesa, Zaragoza, Spain. Chi-squared and Mann–Whitney test were applied to analyze univariate risk factors. Multivariate analysis was performed using logistic regression model with candidate variables: maternal characteristics, obstetric history, thrombophilia, and treatment with low-molecular-weight heparin (LMWH) and/or with acid acetylsalicylic (ASA). The calibration, discrimination, and best cutoff point for the clinical application of the model was analyzed.

Results: Maternal characteristics showed differences in median body mass index (BMI), odds ratio (OR): 0.4, smoking habit, OR: 8.5, and hypertension, OR: 11.4, appearing all of them as risk factors. In our study, a prior pregnancy that ended in a child alive was a protective factor OR: 0.02–0.4, and having a previous preterm child was a strong risk factor OR: 4.2. Thrombophilia was not a risk factor. Patients under LMWH treatment (15%) and/or ASA (6.2%) had better pregnancy outcomes, showing both as protective factors: ASA OR: 0.32 and LMWH OR: 0.16. The model has an AUC value of 0.847, with good calibration. A nomogram and an app is provided for this adjusted model with high discrimination ability in internal validation (AUC = 0.833). Our clinical utility analysis guide us to choose 40% as the best threshold probability.

Conclusions: We found risk and protective factors associated with PMPC, but our data were not conclusive to demonstrate its relation with maternal thrombophilia. However, the challenger finding is the clinical utility of antithrombotic drugs as a protective factors in PMPC prevention. It is possible to identify patients with high risk of PMPC through a combined predictive model, for counseling treatment.

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Antithrombotic treatment; growth restriction; placental abruption; preeclampsia; pregnancy; stillbirth; thrombophilia

Introduction

A right balance of placental hemostasis is essential for optimal human embryo development. Unfortunately, placenta-mediated pregnancy complications (PMPC) are relatively common (up to one in six pregnancies) [1], often causing harmful effects on pregnancy, with significant maternal and fetal morbidity and mortality. Thus, the term PMPC represents a heterogeneous group of adverse pregnancy outcomes: recurrent pregnancy loss (RPL), preeclampsia (PE), intrauterine growth restriction (IUGR), pregnancy loss, small for gestational age (SGA), and placental abruption (PA) [2].

PMPC etiology is multifactorial, as many conditions have been related with them. Final causes are unknown, but at least partly share hemostasis activation in the placental surface that triggers thrombosis of placental vessels and abnormal placental development, although the vasculature affected seems to be different in each clinical situation [3].

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The link between the coagulation system and PMPC is not limited to the thrombotic effects that can cause placental insufficiency, but coagulation activation may play a role in the insufficiency onset, which might be attributed to poor placental development and inflammatory events rather than to a vascular thrombosis [4]. The presence of thrombophilia during pregnancy is important because it can aggravate the physiological hypercoagulable state, being closely associated with venous thromboembolism (VTE). Moreover, in recent years various studies have related thrombophilia to some type of pregnancy complications [5]. In this scenery, prevention of diseases resulting from abnormal placentation is one of the most important challenges for modern obstetrics [6], and antithrombotic drugs might be effective in preventing PMPC [7].

>Although previous studies analyze risk factors associated with PMPC, few of them have combined those factors in order to build a predictive model for pregnancy complications. The aim of this study is to provide a nomogram that combines the clinical and pathological variables associated with the development of PMPCs and more specifically, to analyze the clinical utility of our model to apply it in daily clinical practice.

Material and methods

A retrospective analysis was performed in 373 women with singleton pregnancy who required a thrombophilia test between March 2012 and May 2013 in the Obstetrics Department, Lozano Blesa University Hospital in Zaragoza (Spain). The Ethics Committee for Clinical Research of Aragon (CEICA) favorably informed this biomedical research project on April 2012.

Patients in the control group had been tested for thrombophilia at their first obstetric control as they were considered at risk for developing pregnancy complications because of personal or family history of thrombosis (first-degree relatives presenting VTE under the age of 50 years), or a previous adverse pregnancy outcome, defined as PMPC. All of them ended the current pregnancy in the study period without an adverse pregnancy result.

The case group was offered to enter in the study after developing a PMPC in the study period. Informed consent was obtained. Pregnancies complicated by multiple gestations or fetal anomalies related with IUGR such as chromosomopathy or infection, and preterm delivery due to cervical incompetence were excluded. The control group included 151 pregnant women from 2073 women that were visited in 2012 in our hospital, while the case group, selected during the immediate postpartum period because of having a PMPC in the current pregnancy, met 222 women. More specifically, this study group was distributed as 86 RPL, 9 PA, 58 IUGR, 34 SGA, 23 PE, and 12 fetal loss. Criteria required to be included in these groups are detailed in Table 1. A term pregnancy was defined as 37 weeks of gestation establish by ultrasound crown-rump length (CRL) calculator at first trimester.

Thrombophilia testing was conducted in early pregnancy in controls and in postpartum period, in two different stages, for cases. In the first stage, since genetic thrombophilia test is not altered by pregnancy status, a blood test was requested at patient inclusion. This venepuncture also offered an opportunity to evaluate the anemic status of the women. The second stage was conducted 3 months after the first analysis, as it is known that plasmatic thrombophilia (mainly protein S level) can be altered during pregnancy and puerperium period [8]. Genetic and plasmatic thrombophilia variables included in the study are detailed in Table 1. In addition, thrombophilia summative scores were considered. Also, maternal characteristics—age, body mass index, blood type and Rh factor, smoking habits, maternal comorbidity, gynecological and obstetric history, obstetric pregnancy outcome, personal or family history of VTE, and anticoagulant treatment during pregnancy detailed in Table 1 were included in the study. Pregnant women were on anticoagulant treatment (heparin and/or low dose aspirin) either because of VTE risk (according to guidelines recommendations) [9] or because of previous PMPC (even though controversy about the benefit of the therapy) [10]. Treatment was started as soon as they were assessed in the first visit. Patients with a high VTE risk were treated with low-molecular-weight heparin (LMWH), with previous PE with acid acetylsalicylic (ASA) starting before 16 weeks and patients with RPL were treated empirically with LMWH and ASA, though this management has not been validated in recent meta-analysis [11].

Chi-squared and Mann–Whitney test were applied to establish differences between PMPC and no PMPC in the study groups. In addition, odds ratios were estimated and predictive ability of variables was analyzed using a multivariate logistic regression model. Calibration and discrimination for this model was analyzed using the calibration curve and the area under the ROC curve (AUC) [12]. A nomogram and an app risk calculator (https://pmpcriskcalculator.shinyapps.io/PMPC/) were provided for an easy use of the

Table 1. Genetic and plasmatic thrombophilia study.

Study of genetic thrombophilia	Normal values
Factor V mutation R506Q (Leiden)	No mutation is detected
Factor V mutation H1299R (R2)	No mutation is detected
Prothrombin mutation G20210A	No mutation is detected
MTHFR mutation C677T	No mutation is detected
MTHFR mutation A1298C	No mutation is detected
Factor XIII. Variable sequence V34L	V34L normal
Plasminogen activator inhibitor. Polymorphism: 4G/5G.	Unknown standard value
ITGB3 integrin beta-3 Variables allelic: a/a, a/b	Unknown standard value
Fibrinogen beta polymorphism 455$G > A$	Unknown standard value
Angiotensin converting enzyme Ins/delec. I/D	Unknown standard value
APOB mutation R3500Q	Unknown standard value
APOE genotype ApoE	Unknown standard value
Study of plasmatic thrombophilia	**Normal values**
Antithrombin	80–120%
Amyloid protein functional C	70–120%*
Free protein S	55–150%*
Resistance to activated protein C	Ratio 2–4
Thrombin time	15–28 s
Anticardiolipin antibodies (IgG)	0–20 UI/mL
Anticardiolipin antibodies (IgM)	0–10 UI/mL
Ratio Ac. Lupus Rusell (S/C)	Ratio 0.8–1.2
Beta 2 glycoprotein I (IgG)	0–20 UI/mL
Maternal comorbidity	**Possible values**
Heart disease	Categorical: yes/no
Anemia	Hb < 11 mg/dL
SLE	Categorical: yes/no
Cancer	Categorical: yes/no
Nephrotic syndrome	Categorical: yes/no
Diabetes	Categorical: pregestational diabetes diagnosis, yes/no
Symptomatic varicose veins	Yes/no
HBP	Categorical: systolic >140 or diastolic >90 mmHg, yes/no
Gestational diabetes	Categorical: two altered values in TTOG, yes/no
TORCH infections	Categorial: toxoplasmosis, rubeola, CMV, HSV, HIV. Yes/no
Systemic infections	Categorical: yes/no
Long immobilization	Categorical: More than 1 week in bed, yes/no
Maternal variables	**Type**
Age	Continuous
BMI	Continuous
Smoking	Categorical: yes, no
Blood type	Categorical: 0, A, AB, B
RH	Categorical: negative, positive
Obstetric history	**Type**
Pregnancies	Categorical: 1, 2, >2
Term new-born	Categorical: 0, 1, 2, 3, >3
Alive children	Categorical: 0, 1, >1
Miscarriages	Categorical: 0–1, 2, >2
Preterm new-born	Categorical: 0, >0
Treatment	**Type**
LMWH	Categorical: yes, no
ASA	Categorical: yes, no
PMPC	**Definition**
Preeclampsia	Systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg associated with proteinuria or adverse conditions occurring after 20-week gestation and no preexisting hypertensive disorder.
PA	Premature separation of the placenta and is diagnosed clinically by antepartum bleeding and evidence of retroplacental thrombus
SGA	Fetal weight <10th percentile with normal Doppler study
RPL	Two or more consecutive pregnancy loss
IURG	Fetal weight <10th percentile with altered Doppler study or fetal weight <3rd percentile.
Late pregnancy loss	Fetal death after 28 weeks

*Reference values outside pregnancy.

developed model and an internal validation of the model was performed using 1000 bootstrap samples [13].

Also, the clinical utility was explored estimating the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for different threshold points. Probability density functions [12] and clinical utility curves [14] were provided in order to choose the best threshold point for the model.

Statistical analyses were performed using R programing language v.3.3.2 (The R Foundation for Statistical Computing, Vienna, Austria) [15].

Results

The median age of women was 33 years old. Univariate analysis (Table 2) showed that BMI (OR: 0.94) and having a child who is alive (OR: 0.70) significantly decrease the risk of PMPC. Maternal comorbidity related with VTE risk was poorly represented in the sample. None of the likely variables studied showed association with PMPC. In contrast, hypertension (HBP) (OR: 6.6), smoking habits (OR: 8.8), and having a child at term pregnancy (OR: 0.62) increased the risk of PMPC.

In addition, the obstetrics outcome analysis showed a 26% rate of abortions, 4% of elective cesarean section, 16.9% of urgent cesarean, and 52.8% of vaginal deliveries in the study sample, with more vaginal deliveries in the control group (82.1 versus 32.9% in women with PMPC). From the total number of cesarean, the percentage of elective and urgent cesarean was 40 and 71% for the group of women with PMPC. Thus, the percentage of deliveries was superior in the control group and the number of urgent cesarean was clearly more frequent in the case group.

We also analyzed family and personal history of VTE as a risk factor for maternal side placental thrombosis, which would be a treatable cause of PMPC. Only a 1.6% of women had a family history of VTE and 1.6% of women had a personal history of VTE. We did not find significant differences between cases and controls. Focusing the association between thrombophilia and PMPC, we found that neither genetic nor plasmatic thrombophilia had a significant association with PMPC.

In our study, 15% of patients were on LMWH and 6.2% on ASA treatment. Both drugs have been shown as protective factors, ASA with an OR: 0.25 and LMWH with an OR: 0.16. Indications for treatment were based on previous obstetric adverse outcomes, personal or familiar history of thrombosis, VTE risk factors, and infertility. Univariate results were confirmed in multivariate analysis. Table 3 show variables that have been statistically significant in the model. BMI (OR: 0.45), having at least an alive children [OR: 0.02 (1)–0.04 (>1)], LMWH administration (OR: 0.16), and ASA (OR 0.32) were protective factors. Specifically, the best relationship with BMI was achieved by using restricted cubic splines. By contrast, a previous preterm newborn (OR: 4.24), HBP (OR: 11.42), and smoking habit (OR: 8.47) were risk factors for PMPC. This model has a good discriminatory ability, with an AUC of 0.847. Also, the model had a good calibration (Figure 1), and the internal validation using 1000 bootstrap samples decreased the AUC value to 0.833, very similar to the original.

Also, Figure 2 shows the nomogram associated and, an app named (https://PMPCriskcalculator.shinyapps.io/PMPC/) is provided for an easy use of the model.

Moreover, clinical utility of the model was analyzed. Figure 3 shows the probability density functions. We have chosen 40% as the point that provides graphically the best separation between PMPC/non-PMPC groups. This threshold shows that the density function for non-PMPC group decrease meanwhile the line for PMPC group begins to increase. Figure 4 shows the Clinical utility curve. For different threshold points, it can be seen two different graphs; in blue line, the percentage of PMPC patients that are not correctly diagnosed below the cutoff point, and in red line, it can be seen the percentage of patients that are not classify as PMPC patients. Choosing 40% as the probability threshold point, only 13.5% PMPC women are not correctly diagnosed and 33% are saved treatments. Finally, Table 4 shows the accuracy of the model for different threshold points.

Discussion

The purpose of this article was to provide a predictive model of PMPC useful from the first trimester of pregnancy, exploring mainly the relationship between thrombophilia and PMPC. The available literature in this field is contradictory [16] as heterogeneity observed between studies, trial design, and methodological limitations may have introduced bias. Thus, thrombophilia does not seem to be accepted universally as a direct causal factor [17]. Seeking to provide a more complete analysis, our study was extended to include other risk factors for obstetric outcome during pregnancy.

Our selection of the case group with known thrombophilia was justified by the fact that PMPC may share some pathogenic mechanisms as activation of hemostasis in the placental surface and abnormal placental

Table 2. Univariate analysis.

Variable	PMPC 222 (60%)	NO PMPC 151 (40%)	Total 373 (100%)	*p* value	OR	CI 95%
Maternal variables						
Maternal age (years), average (IC 95%)	32.5 (31.8–33.2)	33.4 (32.7–34.2)	32.9 (32.4–33.4)	.066	0.96	0.92–1.01
Median (p25–p75)	33 (29–36)	34 (30–37)	33 (30–36)			
Min–Max	17–46	18–45	17–46			
BMI (kg/m^2)						
Average (IC 95%)	24.8 (24.1–25.4)	25.9 (25.2–26.7)	25.3 (24.8–25.7)	.008	0.94	0.9–0.98
Median (p25–p75)	23.6 (22–26.3)	25 (23.2–27.9)	24.1 (22.3–27.1)			
Min – Max	16.5–48.4	17.7–41.9	16.5–48.4			
Smoking						
No	210 (94.6%)	150 (99.3%)	360 (96.6%)	.030	9.93	1.93–181.84
Yes	12 (5.4%)	1 (0.7%)	13 (3.4%)			
Blood type						
0	105 (47.3%)	71 (47%)	176 (47.2%)	.176	Ref.	–
A	76 (34.2%)	62 (41%)	138 (37%)	.696	0.91	0.58–1.43
AB	6 (2.7%)	3 (2%)	9 (2.4%)	.533	0.65	0.15–2.54
B	32 (14.4%)	14 (9.3%)	46 (12.3%)	.079	1.86	0.94–3.82
Unknown	3 (1.4%)	1 (0.7%)	4 (1.1%)	–	–	–
Rh						
Negative	36 (16.2%)	27 (17.9%)	63 (16.9%)	.706	Ref.	–
Positive	183 (82.4%)	123 (81.4%)	306 (82%)	.546	1.18	0.68–2.03
Unknown	3 (1.4%)	1 (0.7%)	4 (1.1%)	–	–	–
Maternal comorbidity						
Heart disease						
No	222 (100%)	150 (99.3%)	372 (99.7%)	.225	–	–
Yes	0 (0%)	1 (0.7%)	1 (0.3%)			
Anemia						
No	218 (98.2%)	150 (99.3%)	368 (98.7%)	.347	3.18	0.46–62.54
Yes	4 (1.8%)	1 (0.7%)	5 (1.3%)			
SLE						
No	221 (99.5%)	150 (99.3%)	371 (99.5%)	.783	0.78	0.03–19.92
Yes	1 (0.5%)	1 (0.7%)	2 (0.5%)			
Cancer						
No	220 (99%)	151 (100%)	371 (99.5%)	.242	–	–
Yes	2 (1%)	0 (0%)	2 (0.5%)			
Nephrotic syndrome						
No	222 (100%)	150 (99.3%)	372 (99.7%)	.224	–	–
Yes	0 (0%)	1 (0.7%)	1 (0.3%)			
Diabetes						
No	219 (98.6%)	150 (99.3%)	369 (98.9%)	.526	2.37	0.3–48.23
Yes	3 (1.4%)	1 (0.7%)	4 (1.1%)			
Symptomatic varicose veins						
No	218 (98.2%)	148 (98%)	366 (98.1%)	.897	1.05	0.23–5.38
Yes	4 (1.8%)	3 (2%)	7 (1.9%)			
HBP						
No	194 (87.4%)	147 (97.4%)	341 (91.4%)	<.001	6.18	2.36–21.23
Yes	28 (12.6%)	4 (2.6%)	32 (8.6%)			
Gestational diabetes						
No	211 (95%)	143 (94.7%)	354 (94.9%)	.882	1.08	0.43–2.86
Yes	11 (5%)	8 (5.3%)	19 (5.1%)			
TORCH infections						
No	221 (99.5%)	149 (98.7%)	370 (99.2%)	.353	0.39	0.01–4.09
Yes	1 (0.5%)	2 (1.3%)	3 (0.8%)			
Systemic infections						
No	219 (98.6%)	149 (98.7%)	368 (98.6%)	.982	1.17	0.19–9.03
Yes	3 (1.4%)	2 (1.3%)	5 (1.4%)			
Long immobilization						
No	220 (99%)	150 (99.3%)	370 (99.2%)	.8	1.57	0.14–34.06
Yes	11 (5%)	8 (5.3%)	19 (5.1%)			
Obstetric history						
Pregnancies						
1	77 (34.7%)	48 (31.8%)	125 (33.5%)	.421	Ref.	–
2	76 (34.2%)	34 (22.5%)	110 (29.5%)	.033	1.77	1.04–3.04
≥3	69 (31.1%)	69 (45.7%)	138 (37%)	.4836	0.84	0.2–1.36
Term new-born						
0	90 (40.5%)	8 (5.3%)	98 (26.3%)		Ref.	
1	91 (41%)	96 (63.6%)	187 (50%)	<.0001	0.08	0.04–0.18
2	31 (14%)	36 (23.8%)	67 (18%)	<.0001	0.08	0.03–0.18
3	7 (3.1%)	7 (4.7%)	14 (3.8%)	.0002	0.09	0.02–0.32
≥4	3 (1.4%)	4 (2.6%)	7 (1.9%)	.0014	0.07	0.01–0.35
Alive children						
0	71 (32%)	4 (2.6%)	75 (20.1%)	<.001	Ref.	–
1	106 (47.7%)	96 (63.6%)	202 (54.2%)	<.001	0.29	0.15–0.53
≥2	45 (20.3%)	51 (33.8%)	96 (25.7%)	<.001	0.24	0.12–0.46

(*continued*)

Table 2. Continued.

Variable	PMPC 222 (60%)	NO PMPC 151 (40%)	Total 373 (100%)	*p* value	OR	CI 95%
Miscarriages						
0–1	130 (58.5%)	96 (63.6%)	226 (60.6%)	.425	Ref.	–
2	56 (25.2%)	28 (18.5%)	84 (22.5%)	.068	1.62	0.97–2.73
≥3	36 (16.3%)	27 (17.9%)	63 (16.9%)	.528	1.19	0.68–2.12
Preterm new-born						
0	185 (83.3%)	140 (92.7%)	325 (87.1%)	.292	Ref.	–
≥1	37 (16.7%)	11 (7.3%)	48 (12.9%)	0.002	2.99	1.52–6.34
Treatment						
LMWH						
No	210 (94.6%)	107 (70.9%)	317 (85%)	<.001	0.17	0.08–0.32
Yes	12 (5.4%)	44 (29.1%)	56 (15%)			
ASA						
No	216 (97.3%)	134 (88.7%)	350 (93,8)	<.001	0.25	0.09–0.63
Yes	6 (2.7%)	17 (11.3%)	23 (6.2%)			
Thrombophilia study						
FVL						
No mutation	214 (96.4%)	146 (96.7%)	360 (96.5%)	.879	1.59	0.49–6.05
Mutation	8 (3.6%)	5 (3.3%)	13 (3.5%)			
FVR2						
No mutation	194 (87.4%)	128 (84.8%)	322 (86.3%)	.469	0.78	0.44–1.43
Mutation	28 (12.6%)	23 (15.2%)	51 (13.7%)			
Prothrombin						
No mutation	216 (97.7%)	144 (95.4%)	360 (96.5%)	.317	0.55	0.16–1.7
Mutation	6 (2.7%)	7 (4.6%)	13 (3.5%)			
Deficiency AT						
No	215 (96.9%)	147 (97.4%)	362 (97.1%)	.777	1.39	0.41–5.37
Yes	7 (3.1%)	4 (2.6%)	11 (2.9%)			
Deficiency PS						
No	186 (83.8%)	129 (85.4%)	315 (84.5%)	.666	0.88	0.50–1.56
Yes	36 (16.2%)	22 (14.6%)	58 (16.5%)			
Deficiency PC						
No	210 (94.6%)	145 (96%)	355 (95.2%)	.526	1.24	0.48–3.45
Yes	12 (5.4%)	6 (4%)	18 (4.8%)			
ACL						
No	218 (98.2%)	147 (97.4%)	365 (97.8%)	.579	0.78	0.18–3.35
Yes	4 (1.8%)	4 (2.6%)	8 (2.2%)			
AL						
No	219 (98.6%)	148 (98%)	367 (98.4%)	.632	0.78	0.14–4.27
Yes	3 (1.4%)	3 (2%)	6 (1.6%)			
B2GPI						
No	220 (100%)	150 (99.3%)	372 (99.7%)	.225	–	–
Yes	0 (0%)	1 (0.7%)	1 (0.3%)			
Combined defect						
No	214 (96.4%)	142 (94%)	356 (95.4%)	.284	0.68	0.25–1.83
Yes	8 (3.6%)	9 (6%)	17 (4.6%)			

GVC: gestational vascular complications; OR: odds ratio; CI: confidence interval; Min: minimum; Max: maximum; SLE: systemic lupus erythematous; HBP: high blood pressure; TORCH: toxoplasmosis, herpes, cytomegalovirus and rubella; LMWH: low molecular weight heparin; ASA: acid acetylsalicylic; FVL: factor V Leiden; AT: antithrombin; PS: protein S; PC: protein C; ACL: anti-cardiolipin; AL: anti-lupic; B2GPI: B2glicoprotein I.

Table 3. Multivariate analysis.

Factors	Category	*p* value	Odds ratio	CI 95%
BMI	p_{75}: p_{25}	<.0003	0.45	0.30–0.67
Alive children	1:0	<.001	0.04	0.01–0.12
	>1:0	<.001	0.02	0.01–0.08
Preterm delivery	≥1:0	.001	4.24	1.79–10.03
HBP	Yes: No	.001	11.42	3.33–39.17
Smoking habits	Yes: No	.046	8.47	1.04–68.81
ASA	Yes: No	.038	0.32	0.11–0.94
LMWH	Yes: No	<.001	0.16	0.07–0.36

CI: confidence interval; BMI: body mass index; HBP: high blood pressure; ASA: acid acetylsalicylic; LMWH: low molecular weight heparin.

development [18]. In recent years, following the observation that thrombotic events of placental vessels may be involves in serious pregnancy complications by impairment of placental perfusion, thrombophilias have gained much attention as risk factor for adverse pregnancy outcome [19].

Regarding our study results, the maternal demographic variables BMI and smoking habit showed association with PMPC. The literature shows that a high BMI in early pregnancy is related with increasing risk of macrosomic fetuses, gestational diabetes, and hypertension [20], while a low BMI can be associated with IUGR and SGA or preterm births [21]. Recent published studies attach more importance to weight gain during pregnancy than to BMI in early pregnancy for the prediction of perinatal outcomes and occurrence of pregnancy complications. Regardless of that, recommendations about weight gain should be offered to women [22].

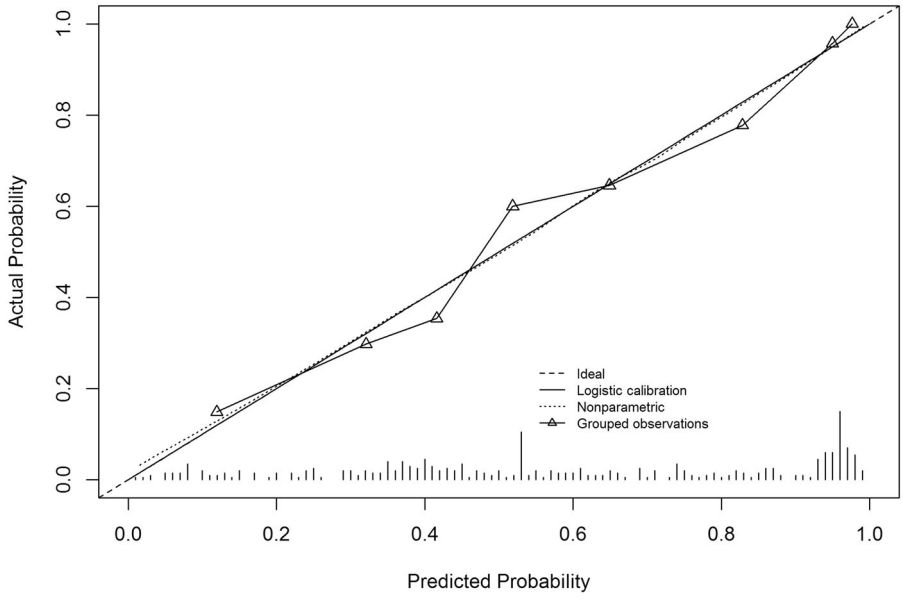

Figure 1. Calibration curve.

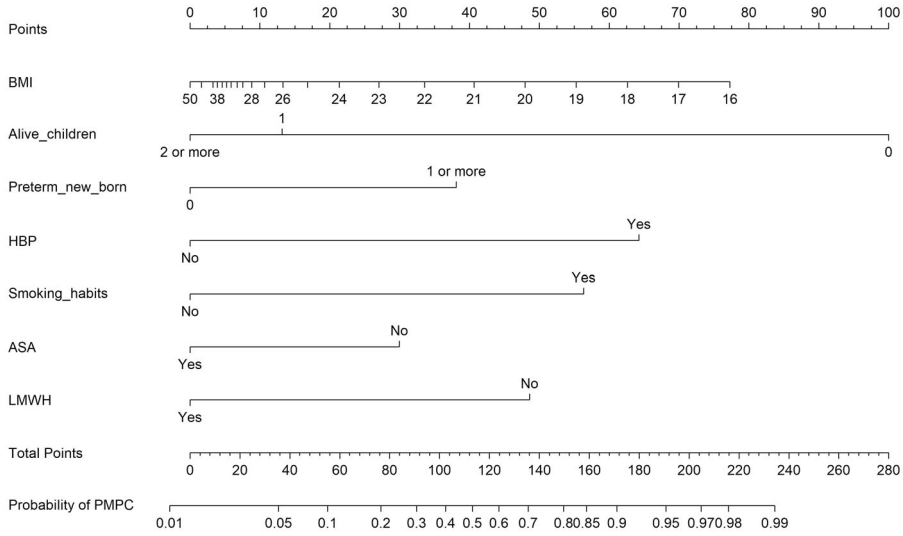

Figure 2. Nomogram. As an example: in the first pregnancy visit, we know a pregnant woman with a previous urgent cesarean because of a severe preeclampsia and fetal growth restriction at 33 weeks. She has high blood pressure, a body mass index of 30 and she does not smoke. She is not under treatment with ASA or LMWH. When we apply the nomogram we get 13 points for and alive children, 38 points for a preterm child, 64 points for HBP, 7 points for a BMI of 30, 49 points for does not be under treatment with LMWH, 30 for does not be with ASA, and 0 points for no smoking, which adds up to a total of 201 points, corresponding to a predicted risk of gestational vascular complication in this pregnancy of approximately 96%. If our patient, would use LMWH and ASA, her score would go down to 122 points, corresponding to a predicted risk of PMPC in this pregnancy of approximately 60%.

Although maternal diseases showed low frequencies in our sample, these conditions can influence the development of complications in pregnancy. Preconception counseling and interdisciplinary management should be essentials to ensure optimal obstetrics results for these women [23]. Nevertheless, HBP appears to be a relevant risk factor and significant differences were found between the two groups. For this reason, the diagnosis of hypertension risk early in pregnancy is very important to ensure a good obstetric outcome. Increasing the frequency of controls and applying preventive measures, such as ASA prescription from the first trimester of pregnancy, should improve placentation and reduce the prevalence of the disease [24].

In our sample, infertility was the more frequent gynecological antecedent. Most of these patients have empirically received antiplatelet and/or antithrombotic

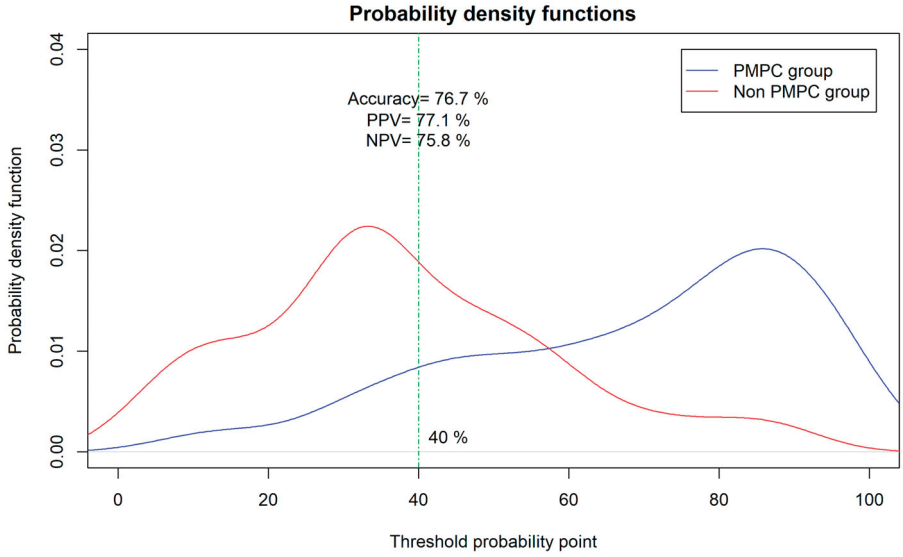

Figure 3. Probability density functions.

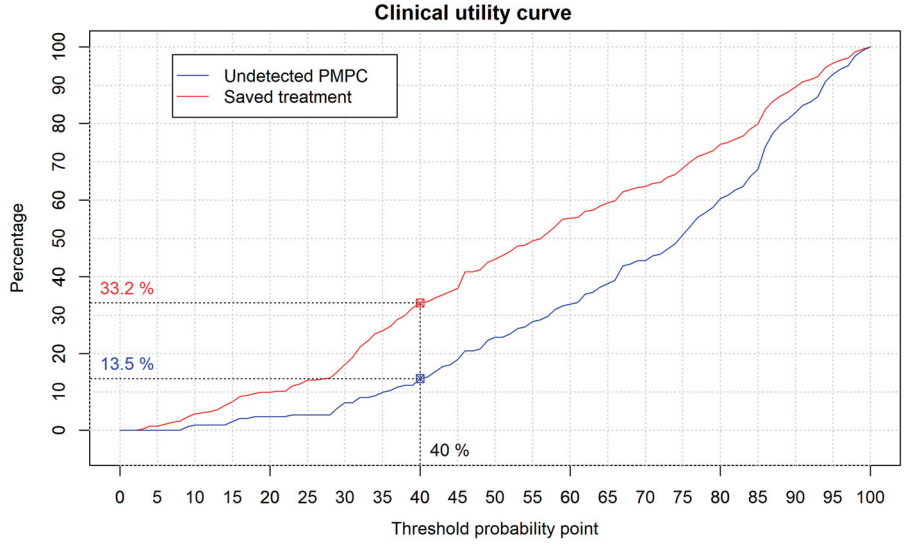

Figure 4. Clinical utility curves.

Table 4. Accuracy measures for different cutoff probabilities of PMPC predictive model.

Cut-off (%)	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)	Accuracy (%)
99	1	100	100	41	41
90	42	97	97	45	50
80	52	95	93	52	62
70	60	90	91	59	71
60	68	84	89	65	76
50	79	71	81	68	75
40	89	56	77	76	77
30	95	32	67	75	68
20	98	24	64	78	65
10	99	12	61	81	62
1	100	0	59	0	59

Sens.: sensitivity; Spec.: specificity; PPV: positive predictive value; NPV: negative predictive value; accuracy=(true positive + true negative)/(positive + negative).

treatment during pregnancy to improve reproductive prognosis, although evidence about the effectiveness of the therapy is scarce [11,25].

Our study shows the relevance of the previous obstetric history in predicting risk in future pregnancies. The greater number of previous pregnancies in the control group might correspond to women who have had a successful outcome in a previous pregnancy and who, for that reason, have sought another pregnancy, once they have demonstrated their biological success in having a healthy child. On the other hand, if a woman has suffered a PMPC and has a high risk of suffering pregnancy complications, then she can reconsider its family planning. In fact, the group

of non-PMPC shows a significantly higher rate of baby born at term than the PMPC and a higher number of children who are alive. The rate of preterm birth (16.7%) in PMPC group is significantly higher than in non-PMPC group (7.3%). This is consistent with the literature that relates PMPC with premature birth in two ways: when a PMPC arises and placenta no longer fulfills its duties properly, the best option to ensure maternal and fetal well-being is often to end the pregnancy and treat the mother and new born separately; on the other hand, other studies try to find the relationship between molecular mechanisms involved in a defective placentation process, which may trigger spontaneous preterm labor. Finally, the numbers of abortions in the two groups explored in this study show no significant differences. In fact, women with previous RPL and an abortion in the current gestation were included in the cases group but, controls included women tested for thrombophilia, some of them because of RPL history, whose current pregnancy ended in an uncomplicated pregnancy, perhaps facilitated by the antithrombotic therapy prescribed.

Moreover, we have found no significant differences between personal and family history of thrombosis in women with PMPC or without them. The interest of this variable lies in the fact that if a relationship between PMPC and thrombophilia was demonstrated, it would be likely that women who suffered PMPC could have a personal or family history of VTE, and it thus it seemed important to know whether these episodes had appeared in the context of a triggering factor.

The main aim of our study was to explore the usefulness of thrombophilia test as a predictor for a successful pregnancy. We have not found any significant differences between the studied groups. Our findings are consistent with the recommendation of *American College of Chest Physicians* guideline where thrombophilia screening is not recommended in women with a history of PMPC [26]. It seems unlikely that thrombophilia can become a major risk factor for most PMPC, but some retrospective studies suggest a link with FVL or prothrombin mutations [27], antithrombin deficiency, and PC and PS deficiency [28]. However, other prospective studies have failed to demonstrate any association [29]. This controversy could suggest a weak association in a high risk population for PMPC. Published works mainly present case-control studies or retrospective cohort studies, small sample size, with heterogeneous population, that unfortunately often provide contradictory results [16].

By the time we planned the study and collected data in 2012, association between PMPC and thrombophilia published had been widely diffused to assistance protocols. This explains why thrombophilia testing took place to such an extent in our hospital. Besides, testing for thrombophilia was commonly performed in patients with thrombotic events in their relatives, as part of the risk assessment, to improve or modify antenatal VTE prophylaxis. Later on, international guidelines have recommended against testing for inherited thrombophilia in women with PMPC, while presence of antiphospholipid antibodies should be investigated for the diagnosis of obstetric antiphospholipid syndrome [26,30]. Yet, thrombophilia testing goes on being very popular between women with pregnancy complications that use internet forums and demand any novel treatment to their doctors.

Although our study has not demonstrated association between PMPC and thrombophilia, we agree with those studies that have shown the potential benefit of antithrombotic therapy to improve perinatal outcomes in women with a history of PMPC with or without thrombophilia [31]. Accordingly, the main findings in our study were the lack of association between PMPC and thrombophilia and the potential benefits of antithrombotic therapy, in agreement with previous studies [32,33]. In our study, we found significant differences in the appearance of PMPC in patients who had not taken LMWH or ASA in comparison with those who had taken it. LMWH seems to add a beneficial effect to ASA, probably because of additional mechanisms of action of heparin other than antithrombotic effect. Its anti-inflammatory and anticomplement effect, and also its early effect at the cellular level decreasing trophoblast apoptosis and increasing proteases involved in the trophoblast invasion of the maternal endometrium, may improve placentation [19] avoiding these pregnancy complications.

To summarize, we can argue that in multivariate analysis we found three risk factors associated with PMPC, namely previous preterm deliveries, HBP, and smoking habits. The first of these provides an OR value of 4.24 but is not applicable to women in their first pregnancy. With regards to hypertension and smoking habits, their OR value of 11.4 and 8.5, respectively, makes them unmistakable risk factors. However, 95% confidence intervals for these variables was large, mainly due to the limited occurrence of cases with hypertension or smoking habits in our sample.

Also, we found five protective factors for PMPC. Two of them were related to the number of previous successful pregnancies, with OR values of 0.04 and 0.02, and the third one was BMI, although its OR value

was only 0.45. The remaining two protective factors were LMWH administration, OR values 0.16 and ASA, OR 0.32. Our findings ratify the results of recent studies that support the benefit of LMWH and ASA in the prevention of pregnancy complications for selected populations [34] but the risk assessment for women who will benefit from such treatment is not well-established. Indeed, not all patients with thrombophilia will develop pregnancy complications [35]. However, some studies conclude that significantly better perinatal outcomes have been obtained in patients with poor obstetric history and thrombophilia by administering anticoagulant therapy. When different treatment regimens were compared, LMWH proved to be more effective than ASA, although combined therapy provided better results than monotherapy [36]. However, before recommending the routine administration of anticoagulant therapy in patients with poor obstetric history, with or without thrombophilia, randomized controlled trials, taken into account benefit and harm of the therapy, should be performed.

We believe that methodological limitations of previous studies prevent conclusive recommendations for high-risk patient population, which is indeed the target group. Well definition of the study groups and analysis of different pathologies with a multifactorial origin separately could find better evidence to prevent the recurrence of severe PMPC. Rodger meta-analysis point that only in severe PMPC heparin is recommended to prevent the recurrence [33].

As a major strength of the study, the model we created has a high discrimination capacity to distinguish between PMPC and non-PMPC with an AUC value closed to 85%. This result shows that our model could be used in clinical practice to predict PMPC appearance and contribute to decide LWMH and ASA prescription to prevent them in an easy and cheap manner, as we included neither biochemical markers nor umbilical artery Doppler that may not be available for all. In addition, we have recommended a cutoff of 40% for clinical use using probability density functions and clinical utility curve.

We can object that our predictive model incudes prophylactic treatments, LMWH and ASA, in its prediction when what we want is to identify high risk PMPC patients to treat. Ethics limitations avoided us to develop our study without prescribing recommend treatments in patients with accepted high risk of PMPC, though we know evidence is limited in some situations. At this point, we have to reflex on how prophylactic treatment contribute on our multivariate model to avoid PMPC in every individual patient, and how necessary it is, in case. The app clarifies this reflexion and help us to make individual clinical decisions.

The limitation of the study lies in the variety of PMPC defined as outcome. This could result in a heterogeneous group that might hinder the extrapolation of our results for each PMPC separately.

We can conclude that our study has compiled a set of maternal variables, maternal thrombophilia, and antithrombotic treatment in a predictive model which should contribute to detect the most important factors involved in the appearance of PMPC and what is more important to successfully, prevent it. A desirable external validation using the app provided would reinforce our findings.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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