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"The TEAM Project" Results on Management of Placenta-Mediated Pregnancy Complications (PMC): The Impact of Thrombophilia Test and Thromboprophylaxis with Low-Molecular-Weight-Heparin on Recurrences of PMC

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Abstract

Aim: In placenta-mediated pregnancy complications, evidence-based guidelines are based on studies with controversial results or expert opinion. In this context, the implementation of those guidelines is quite different among physicians. Our aim was to analyze the management of PMC in a real-world scenario.

Methods: From 2010 until 2016, we started the "TEAM Project" as a nested project within a working group of the Spanish Society of Thrombosis and Hemostasis (SETH : Sociedad Española de Trombosis y Hemostasia).

Results: We included 666 women with PMC, including recurrent pregnancy loss (50%), fetal death (25%), pre-eclampsia-eclampsia (20%), intrauterine growth restriction (5%) and placental abruption. Although a thrombophilia test was indicated in more than 80% of these patients, antiphospholipid antibodies were tested in less than 70% cases. The presence of PT20210A mutation and positive antiphospholipid antibodies were the most common findings observed. Among the 257 women with previous PMC who were assessed for thrombotic risk, 88.7% received antithrombotic prophylaxis, most frequently (46.8%) low molecular weight heparin (LMWH)+aspirin (AAS) and recurrence was observed in 14% of women.

Conclusion: This is the first observational, multicentric and multidisciplinar phase IV study analyzing the real-life clinical management of PMC and other hemostatic/thrombotic events in women from Spain and Uruguay. Our results evidence a lack of homogeneity in the management of these complications as a result of the wide discordance among the existing guidelines, as well as a need for a call to action in fetal-maternal medicine.

Keywords: Antiphospholipid antibodies; Pre-eclampsia; Intrauterine growth restriction; Placental abruption; Thrombophilia test

Introduction

Despite gestational morbidity and mortality in women being one of the highest priorities for the World Health Organization (WHO) and improving maternal health one of their eight primary objectives in the 21st century, placenta-mediated pregnancy complications (PMC), that include preeclampsia/eclampsia, fetal loss (FL), intrauterine growth restriction (IUGR) and placental abruption (PA) and sometimes also recurrent pregnancy loss, defined as two or more pregnancy losses; continue being leading causes of fetal and maternal morbidity and mortality and well-known risk factors for cardiovascular disease [1,2]. These PMC may also occur simultaneously and the risk of recurrence in subsequent pregnancies is high, while their causes remain controversial. Therefore, understanding the etiology of PMC and developing effective strategies for the prevention and management of these complications remain unsolved issues [3-11].

Current guidelines on the management of PMC are a useful tool for physicians in the routine clinical practice, but they are entirely based on observational studies, opinions of experts or meta-analysis, and their recommendations vary widely, sometimes even contradicting one another [12-16]. The lack of randomized studies in pregnant women [17], has led to an ambiguous field where crucial decisions such as testing for thrombophilia or the use of thromboprophylaxis are based on the scarce evidence available and sometimes even on the patient's choice [18]. In this scenario, it is difficult to establish protocols to standardize the better option based on a reliable level of evidence, being PMC the best paradigm of a potentially life- threatening situation

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where no standard recommendations are available.

The difficulties inherent to conducting randomized clinical trials in pregnant women leave us with the pragmatic observational studies as nearly the only option to record useful data from the real-world clinical practice, in order to better understand the factors associated with prognosis as well as to identify effective practices for the management of the thrombotic and/or hemorrhagic complications during pregnancy. In this context, we started the TEAM project (TEAM stands for "Trombosis En el Ámbito de la Mujer", namely women-related risk factors for thrombosis) [19], as an observational, prospective, International Phase IV study designed to provide data on thrombophilia and PMC from an unselected population of pregnant women in real-world clinical practice.

Methods

Design, study participants and data collection

From 2010 until 2016, we performed the TEAM initiative as a nested project in a working group of the Spanish Society of Thrombosis and Hemostasis. Data were obtained in a standardized form, registered in the online database. A minimum number of items were mandatory: Demographics, personal and/or familiar history of thrombosis, clinical vital signs, an objective diagnosis of PMC such as a histological study of the placenta or a hospital record, and both plasma and genetic laboratory testing.

Institutional research and ethical approval was obtained in each center before the implementation of the study and all included participants signed an informed consent prior to the inclusion into the study. Thirty centers from Spain and Uruguay participated and actively included patients.

We included consecutive women aged>18 years old with a PMC or recurrent pregnancy loss (RPL). PMCs included FL, defined as pregnancy loss after 10th week of gestation; pre-eclampsia (gestational hypertension with proteinuria and/or systemic signs or symptoms, such as thrombocytopenia, impaired liver function, development of renal insufficiency, pulmonary edema or new onset cerebral or visual disturbances); IUGR morphology (fetus weight below the 10th percentile for the gestational age with a pathologic restriction of fetal growth) having been documented by ultrasound scan or direct examination of the fetus, and PA (placental separation from the uterus with bleeding before fetal birth, with or without maternal/fetal compromise). RPL was defined as 2 unexplained consecutive spontaneous abortions before the 10th week of gestation, not caused by maternal anatomic or hormonal abnormalities or by paternal and maternal chromosomal causes. The follow-up period included the whole pregnancy period until three months post-delivery.

Exclusion criteria were: any women less than 18 years old, women with pregnancy losses explained by genetic, infectious, metabolic, anatomic, hormonal factors or other causes. The primary endpoint was to evaluate the routine clinical management of women with PMCs; including the practice of thrombophilia screening and the therapeutic management during next pregnancies. Secondary endpoints were to evaluate the prevalence of thrombophilia in these women and outcomes, in terms of recurrence of PMC in women receiving thromboprophylaxis or not.

Sample size was estimated taking into account the prevalence of PMC and thrombophilia. Therefore, it was assumed that we needed a minimum number of 1000 patients to achieve enough power to observe the prevalence of thrombophilia and in those women receiving LMWH prophylaxis, to demonstrate a reduction from 7 to 4% in the recurrence rate (α=0.05 and β=0.1).

Trombophilia testing

As this study was intended to follow the clinical practice, the indication of the thrombophilia screening and the methodological analysis were performed according to the protocol of each center. Thrombophilia testing was categorized depending on their content. Complete classic thrombophilia testing included: inherited risk factors for venous thrombosis, such as natural anticoagulants antithrombin (AT), protein C (PC), and protein S (PS) and genetic polymorphisms, such as factor V Leiden (FVL) and F2G20210A mutation (PGM), and acquired risk factors as functional fibrinogen, antiphospholipid antibodies (APA), including anti-cardiolipin and anti-b2glycoprotein antibodies, and lupus anticoagulant. We called incomplete thrombophilia testing the one with absence of any of the tests included in the complete thrombophilia study. Advanced thrombophilia studies included other thrombophilic risk factors such as elevated levels of factor VIIIc (FVIIIc), ABO genotype, F12C46T mutation and antithrombin Cambridge II mutation, in addition to the parameters included in the classical test explained above.

Statistical analysis

We used means, standard deviation (SD) medians and interquartile range (IQR) to present continuous baseline variables. For categorical variables, we used frequencies and percentages. We used the Student t test and Chi-Square test (or Fisher exact test when appropriate) to compare continuous or categorical variables. Then, we carried out a multivariable analysis through a logistic regression model trying to identify independent predictors for adverse pregnancy outcome. Covariates entering in the model were selected by a significance level of $p<0.10$ on univariate analysis or an association reported in the literature. Data were analyzed with SPSS version 20 (SPSS, Chicago, IL, USA). A p-value of <0.05 was considered to be statistically significant.

Results

From October 2010 to October 2016 we included 625 women with PMCs. From this group, 368 women had been solely referred for thrombophilia testing and 257 patients with previous PMCs had been referred for thrombophilia testing and to obtain a medical expertise on whether thromboprophylaxis should be proposed during the next pregnancy. Median age was 37 ± 6 years and more than a half were older than 35 years. Main characteristics of the participants are shown in Table 1.

The most frequent complication in both groups was unexplained pregnancy loss, mainly recurrent embryonic loss, that supposed

Characteristics	Value
Age, Median ± SD	37 ± 6
Age>35 years, n (%)	401 (66.7)
Autoimmune disease, n (%)	10 (1.6)
Obesity, n (%)	20 (3.3)
Arterial hypertension, n (%)	9 (1.5)
Diabetes mellitus, n (%)	3 (0.5)
Dyslipidemia, n (%)	3 (0.5)
Smoking, n (%)	42 (6.9)
Family history of thrombosis, n (%)	42 (6.9)
Known thrombophilia, n (%)	111 (18.3)

Table 1: Main clinical characteristics.

more than 30% of PMC group and nearly half of the patients in the prophylaxis group. Most of these women had primary infertility: 196 (70%) women with recurrent embryonic loss and 106 (60%) women with FL were nulliparous. The type of PMC in both groups is given in Table 2.

Thrombophilia testing was performed in 501 (80.16%) women, although interestingly in almost 33% of these women, no APA testing was performed. Complete test was performed in 224 (44.7%) women, incomplete test in 175 (34.9%) and extended test in 102 (20.4%). In 80 (15.9%) cases thrombophilia screening was positive.

Results of thrombophilia test are given in Table 3. The presence of PGM and positive APA were the most common findings observed, but some thrombophilia factors not performed in the routine practice, as F12C46T or FVIII elevation have a high prevalence.

Regarding women referred for consideration of thromboprophylaxis (n=257), we obtained information from the whole pregnancy in 238 (92%) of them. Most of these patients received pharmacological treatment. Low molecular weight heparin (LMWH)+low dose aspirin (LDA) was the most frequent option and was given in half of them (Table 4).

	PMC, N (%)	PMC Prophylaxis, N (%)
Recurrent Embryonic Loss	125 (34.0)	119 (46.1)
FL	100 (27.2)	81 (31.6)
IUGR	26 (7.1)	4 (1.6)
PE	112 (30.4)	9 (3.5)
PA	5 (1.3)	1 (0.4)
RPL (embryonic and fetal loss)	NA	25 (9.8)
Recurrent embryonic loss and IUGR	NA	2 (0.8)
Recurrent embryonic loss and PE	NA	3 (1.2)
Recurrent embryonic loss and PA	NA	0 (0.0)
FL and IUGR	NA	5 (2.0)
FL and PA	NA	3 (1.2)
FL and PE	NA	5 (2.0)

PE=Preeclampsia/eclampsia; NA: Not Applicable
FL: fetal loss
IUGR: intauterin growth retardation
PE : pre-eclampsia
PA: Abruprio placentae
RPL: recurrent pregnancy loss

Table 2: Type of PMC.

Defect	N/Total (%)
AT Deficiency	6/429 (1.4)
PC Deficiency	1/451 (0.2)
PS Deficiency	17/447 (2.5)
Heterzigous FVL	17/446 (3.8)
Homozigous FVL	0/446 (0.0)
Heterozigous PGM	21/433 (4.8)
Homzigous PGM	0/433 (0.0)
Homozigous F12C46T	7/95 (7.4)
Positive APA	39/423 (8.6)
High homocisteine levels	9/423 (2.1)
High FVIIIc levels	17/141 (12.9)
Genotipo ABO allele A1	15/48 (31.2)

AT: antithrombin
PC: Protein C
PS: protein S.
FVL: factor V Leiden
PGM: ptrotrombin mutation
APA: antiphospholipids

Table 3: Results of Thrombophilia study T.

	LMWH	LMWH+LDA	LDA	No Treatment
Patients, N (%)	58 (24.3%)	120 (50.4%)	19 (7.9%)	41 (17.2%)
Positive trombophilia	25 (43.8%)	27 (47.3%)	0 (0%)	5 (8.7%)
Negative trombophilia	16 (16.1%)	53 (53.5%)	11 (11.1%)	19 (19.2%)
Presence of FVL or PGM	18 (64.35)	8 (28.6%)	0 (0%)	2 (7.1%)
Positive APL	3 (11.5%)	22 (84.6%)	0 (0%)	1 (3.8%)

Table 4: Use of antithrombotic treatments in patients with PMC, according to the presence of thrombophilia.

Low dose aspirin (LDA) alone was used in 19 (7.9%). It is noteworthy that LDA alone was chosen mostly in women with negative thrombophilia. In 41 (17.2 %) cases, no treatment was indicated. Again, most of these women had a negative thrombophilia study. In women with positive thrombophilia LMWH with or without LDA was the treatment, most often used. These women were more frequently treated than non-thrombophilic women (p=0.018). The use of LMWH alone was preferred in women with factor V Leiden or PGM (p=0.002). Most of the women positive for antiphospholipid antibodies received the LMWH+LDA association. It is important to point out that although women with positive thrombophilia received prophylaxis more frequently, more than 70% of women with a negative thrombophilia testing were treated with LMWH+LDA, LMWH alone, and LDA. Only 20% didn't receive any treatment.

In 103 (66.5%) cases, treatment started during the first trimester, in 38 (24.5%) and 14 (9%) during the second and the third trimester, respectively. The LMWHs used included enoxaparin in 107 patients (59.8%), tinzaparin in 55 (30.7%), bemiparin in 15 (4%) and nadroparin in 2 (1.1%). We analyzed PMC recurrences as a composite outcome in the prophylaxis group. Recurrences history of RPL or FL is presented in Table 5.

Recurrences were observed in 34 (19%) patients that received any kind of treatment (8 women received LMWH+LDA, 5 with LDA only and 21 with LMWH only). Recurrences occurred in 2 (6.2%) women that did not receive any treatment. We tried to evaluate the effectiveness of treatment in terms of recurrence, with different regression models, but either the low number of patients as well as the heterogeneity of the treatments and type of PMC did not allow us to establish any conclusion. In terms of safety, one episode of arterial thrombosis (transient ischemic stroke) was observed in one woman with a history of RPL and high levels of FVIIIc receiving prophylactic LMWH. We recorded one major bleeding in a woman receiving prophylactic dosages of LMWH and previous history of RPL, and 2 minor bleedings were reported, one with prophylactic LMWH and other with LDA.

Discussion and Conclusion

Our study is the first observational, multicenter and multidisciplinary phase IV study conducted in Spain and Uruguay in the context of pregnancy-related risk factors for thrombosis and PMC. Our study evidences a lack of homogeneity in real-life management of these complications among clinicians, which is in accordance to the differences; and even discordances among the existing guidelines [12-16]. A good example of this is that most of them are against performing thrombophilia testing, although in real life it is performed in more than 80% of cases. It is also noteworthy that the determination of antiphospholipid antibodies is not performed in all women against the recommendations of guidelines. This situation might reflect an insufficient knowledge in the field of acquired or inherited thrombophilia, and highlights the role of hematologists or experts for counseling or guidance in this controversial field of thrombophilia-related diseases.

	PMC Recurrences N (%)			
Initial diagnosis	**Early pregnancy loss**	**Fetal loss**	**IUGR***	**Preeclampsia**
Recurrent embryionic loss , N=118	7 (5.9)	3 (2.5)	4 (3.4)	0 (0)
Fetal loss, N=81	0 (0)	12 (14.8)	1 (1.2)	0 (0)
Embryonic and fetal losses, N=1	0 (0)	1 (4.0)	0 (0)	0 (0)
Preeclampsia, N=8	0 (0)	0 (0)	0 (0)	3 (37.5)
Preeclampsia and embryonic loss, N=3	1(33.3)	0 (0)	0 (0)	0 (0)
Preeclampsia and fetal loss, N=5	0 (0)	1 (20.0)	0 (0)	1 (20.0)
* IUGR: Intrauterine Growth Restriction				

Table 5: Type of PMC Recurrences in the Prophylaxis Group.

It seems relevant that new thrombophilia markers such as F12C46T polymorphism, elevated FVIIIc, or the A1 allele of the ABO genotype showed a high prevalence. Although they were performed only in 17% of women in the study, it might bring forward an open gate to a personalized PMC-related thrombophilia risk assessment. Very few studies have studied these factors before [20-23].

In our study, more than 90% of women received thromboprophylaxis regardless of the type of PMC presented or the results of the thrombophilia test. In fact, it strikes that more than 50% of women with a negative thrombophilia test were treated with LMWH plus LDA, while only 20% were observed with no prophylaxis. The weaknesses of this type of studies rely on that there are no monitoring and no external control of the data entered so that the management is determined solely by physicians.

Although the causes of PMCs remain controversial and are likely to be multifactorial [4,9,10], there are data suggesting that thrombophilia might be related or even an actual cause of PMC. Similarly, there is *in vitro* evidence of the positive effects that heparin has on both embryo implantation and trophoblast development, which suggests that LMWH prophylaxis might contribute to a reduced risk of PMC in ongoing pregnancies [4,7,24-28]. In addition, it is remarkable how the available clinical studies on PMC differ from one another in both design and results [29-31] and even currently published reviews and meta-analyses propose different conclusions [3,5,8].

Despite its inherent limitations, our study is intended to give some light to the clinicians facing the management of these complications from a realistic perspective that mirrors the actual routine practice. A picture of the real world in the field of women-related thrombosis coming from these data might facilitate the understanding of a number of existing gaps that remain unsolved in this area. On the other hand, one of the strengths of our study are the large cohort of consecutive unselected patients included, showing a wide array of real-life clinical situations, whose data can be useful to both guide the practical management of these complications and to be hypothesis; generating, as much as some registry-based studies have been before [6].

Although randomized controlled trials (RCTs) are the "gold standard" for generating evidence they are difficult to perform in pregnancy-related situations. The field of pregnancy-related diseases poses special difficulties to conduct them, while real-world data from Phase IV studies provide longitudinal and comparative information on clinical practices as well as useful information about their impact on medical costs and use of other resources, pharmaco-economical outcomes and patient-reported outcomes. Therefore, Phase IV studies are still needed in an area of medicine where solid data lack. The results of our Phase IV study evidence an urgent need for a properly designed International project that helps establish useful guidelines to cover all the uncertainties that still remain in this area.

Author Contributions

All authors participated in the work and take public responsibility for the content. M. A. Santamaría and E. Martí designed the study, collected data, performed the statistical analyses, and wrote the manuscript. C. Medina, A. M. Rodríguez, M. Stevenazzi, Y. Mira, M. López, A. M. Redondo and R. Aguinaco collected data, made substantial intellectual contributions to the manuscript and its final approval. A. Oliver performed the statistical analyses and made substantial intellectual contributions to the manuscript and its final approval. A. Santamaria supervised and coordinated all the project, giving the final approval.

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Conflict of Interest

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject discussed in this manuscript.

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