Maternal-Fetal Management in Trombophilia Related and Placenta-Mediated Pregnancy Complications

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It is widely accepted that thrombophilia in pregnancy greatly increases the risk of venous thromboembolism. Pregnancy complications arise, at least partly, from placental insufficiency. Any change in the functioning of the gestational transient biological system, such as inherited or acquired thrombophilia, might lead to placental insufficiency. In this research we included 64 pregnant women with trombophilia and 70 cases non-trombophilic pregnant women, with or without PMPC, over a two-year period. The purpose of this multicenter case-control study is to analyze the maternal-fetal management options in obstetric thrombophilia, the impact of this pathology on the placental structure and possible correlations with placenta-mediated pregnancy complications. Maternal-fetal management in obstetric thrombophilia means preconceptional or early diagnosis, prevention of pregnancy morbidity, specific therapy as quickly as possible and fetal systematic surveilance to identify the possible occurrence of placenta-mediated pregnancy complications.

Keywords: obstetric trombophilia, maternal-fetal interface, acetylsalicylic acid , low molecular weight heparin, folic acid.

Placenta-mediated pregnancy complications (PMPC) such as preeclampsia, intrauterine growth restriction (IUGR), birth of a small-for gestational age infant, obstetric morbidity and recurrent pregnancy loss, stillbirth or placental abruption, are significant causes of maternal and fetal poor outcome [1]. These complications are believed to result due to thrombophilia, and therefore from thrombosis within the placental angioarchitecture [1-3].

The etiology of placenta-mediated pregnancy complications is likely multifactorial and may include abnormal coagulation activation of the maternal-fetal interface [4].

Normal pregnancy is a state of physiological hypercoagulability involving complex changes in blood fluid-coagulation balance, from primary haemostasis to fibrinolysis and natural anticoagulant mechanisms [5].

Therefore, any disruption of this balance may interfere with the maternal-fetal interface and cause pregnancy complications.

It is widely accepted that thrombophilia in pregnancy greatly increases the risk of venous thromboembolism [6, 7]. Thus, it is speculated that thrombophilia may compromise the slow low-pressure circulation in the placenta due to micro and macro-vascular thrombosis and possibly abnormal placentation [6-8].

Thrombophilia can be inherited or acquired, and the major hereditary forms include deficiency of one of the natural anticoagulant proteins and mutations in genes that encode coagulation factor V (Leiden mutation, G1691A) or coagulation factor II (mutation G20210A) [1, 5, 9].

The most commonly acquired maternal thrombophilia is the obstetric antiphospholipid syndrome (OAPS) defined as the association of thrombotic events or obstetric morbidity in patients persistently positive for antiphospholipid antibodies (aPL) [1, 10, 11].

Furthermore, hyperhomocysteinemia, which can be hereditary or acquired, is a risk factor for diseases that primarily affect the arteries [1, 12].

PMPC could affect over 5% of pregnancies and can result in significant maternal and perinatal morbidity and mortality [13]

Duffett et al. in 2015, suggest that these pregnancy complications arise, at least partly, from placental insufficiency, possibly as a result on inappropriate coagulation activation, this pathophysiological association leading to the hypothesis that anticoagulant therapy, such as low molecular weight heparin (LMWH), might reduce their occurence [13].

LMWH has been proposed as a potential preventive therapy for a number of PMPC including preeclampsia and IUGR [14].

The use of acetylsalicylic acid (ASA), widely accepted as aspirin, and heparin has improved the pregnancy outcome in OAPS and approximately 70% of pregnant women with this syndrome have a successful pregnancy outcome [11].

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The purpose of this paper is to analyze the maternal-fetal management options in obstetric thrombophilia, the impact of this pathology on the placental structure and possible correlations with PMPC.

Experimental part

In this multicenter (see affiliation of the authors) case-control study we included 64 pregnant women with thrombophilia and 70 cases non-thrombophilic pregnant women, with or without PMPC, over a two-year period.

All the patients included in the study were routinely or due to obstetric history, tested for thrombophilia (table 1).

The first line in the diagnosis of obstetric thrombophilias was represented by the standard screening tests, and then, depending on the results, specific tests followed.

The clinical characteristics of the patients in the study, as well as the tests used according to their profile are presented in table 2.

Ultrasound (US) assessment of all the cases in the study (TG - trombophilia group and nTG - - non-trombophilia group) has been performed both via 2D conventional technique and 3D or tomographic US imaging, as well as spectral, color or power Doppler. Obstetrical US assessment included fetal biometry and morphology, as well as placental, umbilical cord and amniotic fluid evaluation, maternal-fetal Doppler profile and in the case of multiple pregnancies, the diagnosis of corionicity and amnionicity.

Placentas from the pregnancies of the study group were sent to the pathology department. The placenta specimens resulting after birth were fixed in 10% buffered neutral formalin, processed by paraffin embedding and Haematoxylin and Eosin staining. The pathological assessment of the specimens, included according to the study protocol, the systemantic analysis for perivillous or subchorionic fibrin depositions, maternal floor infarction/

Table 1
TROMBOPHILIA TESTS

Antithrombin III [15]	- Inhibited enzymes: factors Xa, IXa, IIa, XIIa, XIa VIIa - tissue factor complex; - sampled on Na-citrate 0.105 M (1/9); - chromogenic method.
Protein C [15]	- inactivation of factors V and VIII; - sampled on Na-citrate 0.105 M (1/9); - chromogenic method, snake venom extract.
Protein S [15]	- intensifies the inactivation of factors Va and VIIIa on phospholipid surfaces; - sampled on Na-citrate 0.105 M (1/9); - method - coagulation test that measures the activity of the protein S.
Activated protein C resistance (APCR) [15]	- inability of APC to anticoagulate plasma; - sampled on Na-citrate 0.105 M (1/9); - method - coagulation test with specifically action on prothrombinase complex.
Factor V Leiden Mutation (G1691A) [15]	- abnormal variation of factor V - getting resistant to APC; - mutation on chromosome 1q23; - sampled on EDTA as anticoagulant; - Real-time PCR; genotyping.
Prothrombin 20210 Mutation (Factor II Mutation/ G20210A) [15]	- nucleotide substitutions at base pair 20210, in the untranslated region 3' of the factor II gene; - sampled on EDTA as anticoagulant; - Real-time PCR; genotyping.
Homocysteine [15]	- metabolized by transsulfurization to cysteine (Cystathionine-β-synthase and Vitamin B6) or remethylation to methionine (MTHFR and Methionine synthase; Folic acid and Vitamin B12) - sampled on K3-EDTA as anticoagulant; - enzymatic method.
MTHFR gene (mutations C677T; A1298C) [15]	- enzyme catalysing the reduction of 5,10-methylenetetrahydrofolate to 5-methylenetetrahydrofolate, cofactor in remethylation of homocysteine to methionine; - sampled on EDTA as anticoagulant; - Real-time PCR; genotyping.
Factor XIII mutation (G102T) [15]	- 4G/4G PAI-1, homozygous status for Val34Leu mutation of factor XIII or homozygosity / heterozygosity comprised for both defects is associated with pregnancy losses in the first trimester; - sampled on EDTA as anticoagulant; - Real-time PCR; genotyping.
Plasminogen Activator Inhibitor (PAI gene; 675 4G/5G polymorphism) [15]	- presence of 4G/4G or 4G/5G genotypes is clinically significant for the development of venous thromboembolism in pregnancy; - sampled on EDTA as anticoagulant; - Real-time PCR; genotyping.
Lupus anticoagulants (LA) [15]	- antibodies directed against phospholipid-protein complexes; - sampled on Na-citrate 0.105 M (1/9); double centrifuged; - dRVVT and aPTT using silica activators.
Anti-cardiolipin antibodies (ACA) [15]	- antiphospholipid specific antibodies for anionic phospholipids; - sampled without anticoagulant with/without separator gel; - immunochemical with chemiluminescent detection method.
Ig A, Ig G, IgM Anti-β2-glycoprotein I antibodies (β2GPI) [15]	- antibodies binding to β2 glycoprotein 1 in the absence of phospholipids; - sampled without anticoagulant with/without separator gel; - ELISA.
Endothelial protein C receptor (EPCR) gene [16, 17]	- receptor binds protein C and facilitates the activation of the thrombin-thrombomodulin complex; - sampled on K3-EDTA as anticoagulant; - End-point PCR; molecular probe hybridization.
APC - Activated Protein C; EDTA - ethylenediamine tetraacetic acid; PCR - Polymerase chain reaction; MTHFR - methylenetetrahydrofolate reductase; dRVVT - diluted Russel viper venom test; aPTT - activated partial thromboplastin time; ELISA - enzyme-linked immunosorbent assay.	

Clinical characteristic/ risk factor	TG	nTG
Age (mean, ±)	27 (±9)	32 (±13)
Singleton pregnancy	63 (98.43)	68 (97.14)
Multiple pregnancy	1(1.56)	2 (2.85)
Hypertension	4 (6.25)	8 (11.42)
Preeclampsia	14 (21.87)	11 (15.71)
Obesity	21 (32.81)	32 (45.71)
Smoking	1 (1.56)	6 (8.57)
Diabetes	-	2 (2.85)
Recurrent miscarriages	18 (28.12)	12 (17.14)
Previous stillbirth	2 (3.12)	1 (1.42)
History of infertility	17 (26.56)	16 (22.85)
Previous thrombosis history	2 (3.12)	-
Trombophilia tests used	**TG**	**nTG**
Thrombophilia screening (LA, Antithrombin III, Protein C, Protein S, APCR, Homocysteine)	64 (100)	70 (100)
Inherited thrombophilia (Antithrombin III, Protein C, Protein S, Factor V Leiden Mutation, Factor II Mutation, MTHFR gene)	55 (85.93)	6 (8.57)
OAPS (LA, ACA, Anti-β2GPI antibodies)	11 (17.18)	9 (12.85)
Factor XIII mutation	5 (7.81)	3 (4.28)
PAI gene	7 (10.93)	1 (1.42)
EPCR gene	57 (89.06)	10 (14.28)

TG - trombophilia group, nTG - non-trombophilia group, LA - lupus anticoagulants, APCR - activated protein C resistance, MTHFR - methylenetetrahydrofolate reductase, OAPS - obstetric antiphospholipid syndrome, PAI - plasminogen activator inhibitor. Values are given as number (%), unless indicated otherwise.

Table 2
CLINICAL CHARACTERISTICS AND PROFILED TESTS

massive basal plate fibrin deposition, placental infarction, subchorial thrombosis, intervillous thrombi or placental calcifications.

The research meets the conditions of the ethical guidelines and legal requirements, and was approved by each Ethical Committee of the Universities of Medicine and Pharmacy (see authors' affiliations). Informed consent was obtained from every patient included in the study.

Results and discussions

Of the 64 pregnant women diagnosed with trombophilia included in the study, 51 (79.68%) had inherited trombophilic disorders, 11 (17.18%) acquired disease and 2 (3.12%) cases hyperhomocysteinemia, which might be either hereditary or acquired (table 3).

Our management in TG cases included maternal-fetal US monitoring starting with the first trimester of pregnancy and the establishment of specific treatment as early as possible. This involved administration of acetylsalicylic acid, folic acid, vitamin B6 and B12 supplements and LMWH (Enoxaparin, Dalteparin, Nadroparin and Tinzaparin) (table 4).

Regarding the association between thrombophilia and PMPC, on our series we observed a relative increase in the incidence of preeclampsia (32.81% vs. 25.71%) or IUGR (37.5% vs. 24.28%), but also a significant increase of recurrent miscarriages, late pregnancy loss (21.87% vs. 4.28%) or stillbirth and placental abruption, in the group of patients associating this condition (table 5).

Gestational age at delivery has been relatively lower in cases of thrombophilia compared to non-thrombophilic cases, the same trend being observed in the case of birth weight (table 5).

Placental pathology analysis revealed rather uncharacteristic aspects between the two groups, with slight increases in incidence of placental infarction and perivillous fibrin deposition, but also more significant increases in the case of intervillous thrombosis (14.06% vs.7.14%) or umbilical cord thrombosis, with regard to the thrombophilia group (table 5, fig. 1-8). Other aspects of the umbilical cord pathology observed in our series were

Table 3
TYPES OF THROMBOPHILIA AND SPECIFIC MARKERS

Inherited trombophilia	**TG (n = 51)**
Antithrombin III deficiency	6 (9.37)
Protein C deficiency	2 (3.12)
Protein S deficiency	18 (28.12)
EPCR mutation - heterozygous	31 (48.43)
EPCR mutation - homozygous	3 (4.68)
Factor V Leiden - heterozygous	4 (6.25)
Factor V Leiden - homozygous	1 (1.56)
Prothrombin 20210A - heterozygous	3 (4.68)
Prothrombin 20210A - homozygous	1 (1.56)
MTHFR C677T - heterozygous	19 (29.68)
MTHFR C677T - homozygous	6 (9.37)
MTHFR A1298C - heterozygous	21 (32.81)
MTHFR A1298C - homozygous	3 (4.68)
PAI-1 gene 4G/5G polymorphism - heterozygous	29 (45.31)
PAI-1 gene 4G/5G polymorphism - homozygous	2 (3.12)
Factor XIII mutation - heterozygous	11 (17.18)
Factor XIII mutation - homozygous	3 (4.68)
Acquired trombophilia	**TG (n = 11)**
LA	10 (15.62)
ACA	8 (12.5)
Anti-β2GPI antibodies	9 (14.06)
Acquired/ inherited trombophilia	**TG (n = 2)**
Homocysteine	2 (3.12)

TG - trombophilia group.

Table 4
OBSTETRIC THROMBOPHILIA SPECIFIC THERAPY

Acetylsalicylic acid (75-100 mg once a day)	
Preconceptionally	16 (25)
< 24 gestational weeks	47 (73.43)
< 36 gestational weeks	16 (25)
> 36 gestational weeks	11 (17.18)
Folic acid (1-5 mg once a day)	
Preconceptionally	19 (29.68)
1st trimester	59 (92.18)
>1st trimester	31 (48.43)
Vitamin B6 supplements	39 (60.93)
Vitamin B12 supplements	39 (60.93)
LMWH	
Enoxaparin 40 mg (0.4 ml) subcutaneous once a day	19 (29.68)
Enoxaparin 20 mg (0.2 ml) subcutaneous once a day	7 (10.93)
Dalteparin 5000 UI subcutaneous once a day	9 (14.06)
Nadroparin 3800 UI (0.4 ml) subcutaneous once a day	7 (10.93)
Tinzaparin 5000 UI subcutaneous once a day	5 (7.81)

PMPC	TG (n = 64)	nTG (n = 70)
Preeclampsia	21 (32.81)	18 (25.71)
IUGR/ SGA	24 (37.5)	17 (24.28)
Recurrent miscarriages	14 (21.87)	3 (4.28)
Late pregnancy loss	6 (9.37)	1 (1.42)
Stillbirth	5 (7.81)	1 (1.42)
Placental abruption	4 (6.25)	2 (2.85)
HELLP syndrome	2 (3.12)	-
Outcome	**TG (n = 64)**	**nTG (n = 70)**
Vaginal delivery	9 (14.06)	28 (40)
Caesarian delivery	55 (85.93)	42 (60)
Gestational age at delivery (weeks; mean, ±)	33.5 (± 5.5)	35 (± 6)
Birth weight (g; mean, ±)	2595 (± 1275)	2950 (± 1170)
Placental findings	**TG (n = 64)**	**nTG (n = 70)**
Placental infarction	19 (29.68)	15 (21.42)
Perivillous fibrin deposition	16 (25)	12 (17.14)
Intervillous thrombosis	9 (14.06)	5 (7.14)
Umbilical cord thrombosis	3 (4.68)	-
Hypercoiled cord	6 (9.37)	8 (11.42)
True cord knot	1 (1.56)	2 (2.85)
Reduced cord coiling	-	1 (1.42)
Excessively long cord	-	2 (2.85)

PMPC - placenta-mediated pregnancy complications; TG - trombophilia group; nTG - non-trombophilia group; HELLP - hemolysis, elevated liver enzymes, low platelets syndrome; Values are given as number (%), unless indicated otherwise.

Table 5
PMPC, PLACENTAL PATHOLOGY AND PREGNANCY OUTCOME

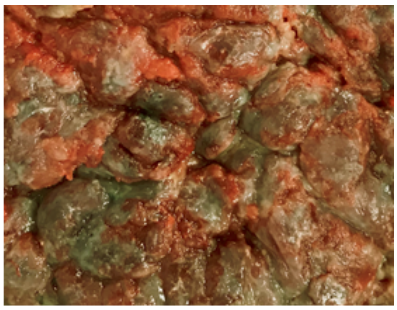

Fig.1. Gross appearance of maternal surface in the placenta from a TG pregnancy demonstrating basal plate fibrin deposition, with a greyish - yellow, gyriform appearance.

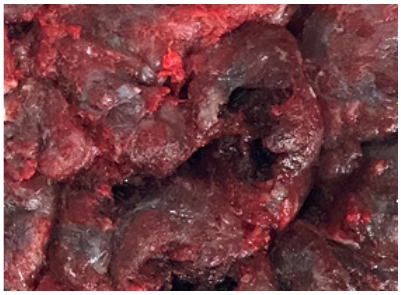

Fig.2. Gross appearance of maternal surface in the placenta from a TG pregnancy demonstrating a few intervillous thrombi with a soft, dark red appearance.

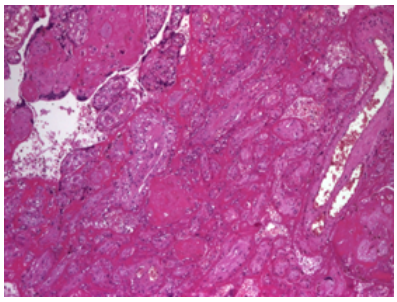

Fig.3. Placental infarction, Haematoxylin - Eosin staining x40.

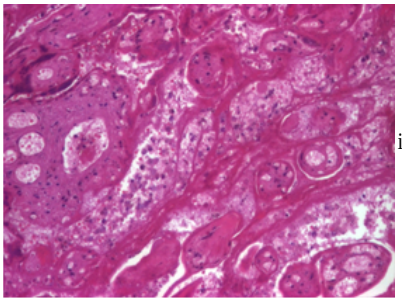

Fig.4. Placental infraction, Haematoxilyn -Eosin staining x 100

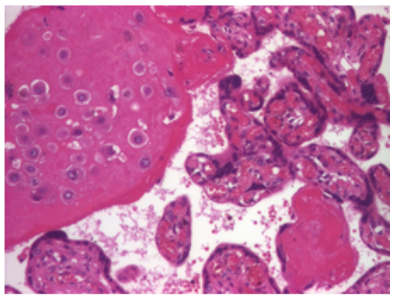

Fig.5. Villous vascular stasis, perivillous fibrin deposition, Haematoxylin - Eosin staining x100.

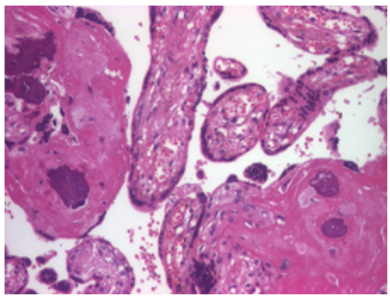

Fig.6. Intermediate mature and terminal villi, fibrin and microcalcifications, Haematoxylin - Eosin staining x100.

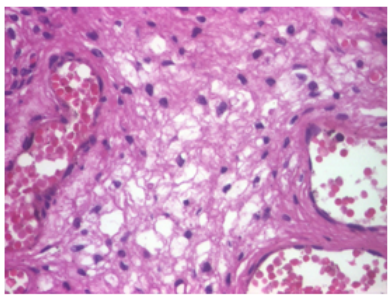

Fig.7. Vascular stasis, edema, extravasated red blood cells, Haematoxylin - Eosin staining x200.

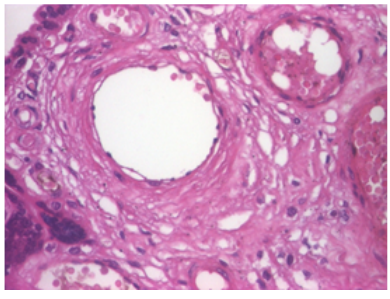

Fig.8. Villous vascular stays and sclerosis, Haematoxylin - Eosin staining x200.

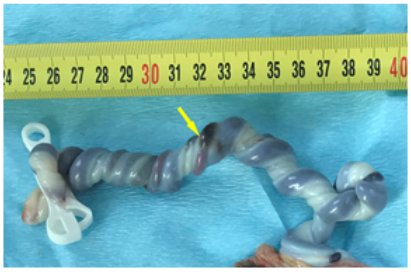

Fig.9. Gross appearance of the umbilical cord from a TG pregnancy, demonstrating hypercoiled cord, false knot and thrombosis (arrow)

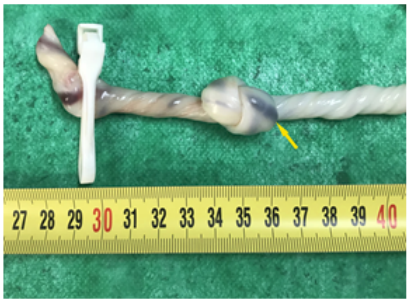

Fig.10. Gross appearance of the umbilical cord from a nTG pregnancy, demonstrating true cord knot, excessive cord twisting and thrombosis (arrow)

hypercoiled cord, true cord knot, reduced cord coiling or excessively long cord (fig. 9, 10).

The pregnancy itself represents a state of acquired hypercoagulability, with an increase in coagulation factors and a decrease in fibrinolysis activity, state which occurs naturally, and which predisposes to deep vein thrombosis, especially as the venous return slows down, by the pressure of the expanding uterus, favoring stasis [18].

Placentation involves trophoblast invasion of nearly one hundred spiral arterioles with subsequent remodelling resuliting in a low resistance placental circulatory system without maternal vasomotor control, and hence, the resulting low resistance utero-placental circulatory system allows for high volume blood flow in the placenta ond fetus [13, 19].

Any change in the functioning of this gestational transient biological system, such as inherited or acquired thrombophilia, might lead to placental insufficiency.

PMPC such as severe preeclampsia, IUGR or still birth are attributed to placental insufficiency [20].

Placental pathology is thought to arise from placental developmental dysfunction in a two-step sequence, meaning failure of trophoblast invasion, followed by systemic endothelial dysfunction, therefore in PMPC, shallow trophoblast invasion is obvious, resulting in a higher placental vascular resistance, decreased placental perfusion and placental ischemia [13, 21, 22].

It is also believed that about half of gestational venous thromboembolisms are associated with inherited thrombophilia, and anticoagulant therapy to prevent adverse pregnancy outcomes are increasingly used [23].

In our series, LMWH (table 4) have been used in 47 (73.43%) of TG cases, the choice of the active substance based on obstetricians' experience, clinical practice, hematological consultation, thus we can assert that the obstetrical outcome is encouraging.

Low-dose acetylsalicylic acid (table 4), together with LMWH or alone, used preconceptionally, in the first part of pregnancy or even to the end of it, brings benefits in the maternal-fetal outcome in thrombophilia in general, and in OAPS in particular.

Many studies to the date stated that the current standard of treatment in OAPS is mainly relying on antithrombotic and antiaggregation treatment, the combination of low-dose acetylsalicylic acid and LMWH (or heparin) has resulted in a live birth rate of 70–80% [11, 24-26].

Furthermore, characterization of biochemical and immunological mechanisms involved in development of PMPC could help to early diagnose, to discover new screening methods, and provide new insights into therapy [27, 28].

Franco et al. [20] consider that the most common placental lesion is infarction of placental villi, whose frequency correlates with disease severity and antenatal test results of placental function, meaning uterine artery Doppler and placental morphology [20, 29].

In our series, placental infarction was the most common pathological finding in both TG and nTG. We believe that in thrombophilia cases, associated or not with PMPC, it can be discussed rather by a combination of pathological changes, not by specific findings.

The present study has some potential strengths and limitations. The strengths of the study mean the complex analysis and correlations obtained in thrombophilia associated or not with PMPC, integrating in a multicentre research data on comprehensive thrombophilia screening and testing, therapeutic management, placental morphology and pregnancy outcome. Our study is limited however, by the rather low number of cases included, and this may impact the statistical power of our analysis.

Conclusions

Pregnancy is a state of physiological hypercoagulability involving complex changes in blood fluid-coagulation, therefore any disruption of this balance may interfere with the maternal-fetal interface and cause pregnancy complications. Maternal-fetal management in obstetric thrombophilia comprises preconceptional or early diagnosis during gestation, prevention of pregnancy morbidity and ensuring of specific therapy as quickly as possible. Fetal systematic surveilance should assess the biometric and haemodynamic profile to identify the possible occurrence of PMPC. Our study suggests that PMPC occurs with a relatively higher incidence in thrombophilia than in nontrombophilic cases. In thrombophilia associated or not with PMPC there is rather a combination of placental pathological changes, not specific findings.

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