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Prothrombotic risk factors in pregnancy

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Summary. Pregnancy and puerperium have historically been associated with a significant increase – five- and tenfold vs non-pregnant women, respectively – of the thromboembolic risk, which in turn is the main cause of maternal mortality. Predisposing factors for thrombosis include components of the so-called Virchow's triad: venous stasis, hypercoagulability and endothelial damage/dysfunction. Venous stasis is secondary to the compression that the uterus exerts on the inferior vena cava and the pelvic veins, to the reduction of the progesterone-mediated venous tone and to the development of varicose veins in the lower limbs; and, sometimes, to a prolonged immobilization. Furthermore, there is a physiological tendency to hypercoagulability, caused by an imbalance between procoagulant and anticoagulant factors, which on the one hand counters the postpartum hemorrhagic risk, while on the other increases the thromboembolic risk. The hypercoagulable profile may be confirmed via global coagulation assessment tests, such as thrombin generation and thromboelastometry/-graphy. The presence of a thrombophilic state – the tendency to develop thrombosis from an inherited or acquired condition – may contribute, alone or in association with other compounding factors, to the added thrombotic risk described in pregnancy. Pregnancy, especially if complicated, also involves endothelial activation, which may trigger thrombotic events, as confirmed by the increased levels of various plasma markers. Finally, the Virchow's triad is often exacerbated by several thrombotic risk factors, such as a personal history of venous thrombosis, advanced age, obesity, plurality, smoking, hypertension, blood group A and caesarean section.

Key words. Pregnancy, prothrombotic risk factors, maternal mortality.

Fattori di rischio protrombotici in gravidanza

Riassunto. Gravidanza e puerperio sono storicamente associati a un significativo aumento, rispettivamente di 5 e 10 volte rispetto alla donna non gravida, del rischio tromboembolico, a sua volta principale causa di mortalità materna. Fattori predisponenti per trombosi sono gli elementi ascrivibili alla cosiddetta triade di Virchow, ovvero stasi venosa, ipercoagulabilità e danno/disfunzione endoteliale. La stasi venosa è secondaria alla compressione dell'utero sulle vene cava inferiore e pelviche, alla riduzione del tono venoso progesterone-mediata, allo sviluppo di varici agli arti inferiori e, talora, ad una prolungata immobilizzazione. Per di più, si crea una fisiologica tendenza all'ipercoagulabilità, meccanismo volto a contrastare il rischio emorragico nel post-partum, e risultante da uno squilibrio tra fattori procoagulanti (aumentati) ed anticoagulanti e fibrinolitici (ridotti). Il profilo ipercoagulabile è avvalorato dai risultati di test di valutazione globale della coagulazione come la generazione di trombina e la tromboelastometria/grafia. La presenza di un'eventuale trombofilia, ovvero una tendenza a sviluppare trombosi sulla base di un disordine ereditario o acquisito dell'emostasi, concorre, da sola o in associazione, e in misura variabile a seconda del tipo di alterazione, all'aumento del rischio trombotico anche in gravidanza. La gravidanza, soprattutto se complicata, comporta inoltre un'attivazione endoteliale, che può contribuire alla genesi di eventi trombotici, come confermato dall'aumento di alcuni marcatori plasmatici. Infine, a tali condizioni si accompagnano spesso diversi fattori di rischio trombotico, come storia personale di trombosi venosa, età avanzata, obesità, pluriparità, fumo, ipertensione, gruppo sanguigno A e taglio cesareo.

Parole chiave. Gravidanza, fattori di rischio protrombotici, mortalità materna.

Introduction

Pregnancy significantly increases the risk of a thromboembolic event in women.[1,2] Studies published in the literature so far report that, for a pregnant woman, the risk of developing a thromboembolic event is about fivefold that of a non-pregnant woman – with a further increase up to tenfold during the puerperium.[3,4] Notably, venous thromboembolic disease is recognized as one of the main causes of mortality during pregnancy and puerperium.[2,5] There is a wide consensus that the increased thrombotic risk during pregnancy strongly correlates with the presence of predisposing conditions, such as: 1) venous stasis; 2) hypercoagulability; 3) endothelial damage/dysfunction – all of which are components of the so-called Virchow's triad (Table 1). In addition, several other risk factors – such as age, obesity, smoking, previous thromboembolic episodes and fertility treatments – may also contribute to the increased thrombotic risk observed in pregnancy.

Table 1. Virchow's triad in pregnant women

1. Venous stasis	
Compression of endoabdominal vessels due to growing fetus Progesterone-mediated reduced venous tone Varicose veins Reduced mobilization	
2. Hypercoagulability	**Main laboratory markers**
Increased procoagulant factors	VII, VIII, X, fibrinogen and von Willebrand
Decreased anticoagulant factors	Protein S
Impaired fibrinolysis	PAI-1 and -2
Classic thrombophilia	Antithrombin, protein C and S FV Leiden, prothrombin variant Antiphospholipid antibodies
3. Endothelial damage/dysfunction	
	t-PA and PAI-1 von Willebrand factor exosomes and microparticles matrix metalloproteinases (MMPs) vascular cell adhesion molecule (VCAM) intracellular cell adhesion molecule (ICAM) reactive oxygen species (ROS) reactive nitrogen species (RNS) microRNAs

PAI: plasminogen activator inhibitor; t-PA: tissue-type plasminogen activator.

Venous stasis

From a mechanical perspective, the increase in intraabdominal pressure caused by the growing fetus results in an abnormal compression of the endoabdominal vessels – mainly the inferior vena cava and the pelvic veins – with a subsequent blood stagnation in the lower limbs, which might favor the development of thrombosis.[6-8] Moreover, the decreased venous tone secondary to the higher plasma levels of progesterone in pregnant women may predispose to venous stasis. The pressure that the uterus applies on the vena cava may also further contribute to the development of varicose veins in the legs, one of the main known risk factors for superficial venous thrombosis.[9] Finally, some pregnant women may require prolonged immobilization, especially in the final stages, which may further increase the incidence of thrombotic events.[10] Graduated elastic compression stockings could be considered the main useful tool to prevent and alleviate venous stasis, though their effectiveness in actually reducing the risk of thrombosis has not been definitively proved yet.[11,12]

Hypercoagulability

The plasma concentrations of several coagulation factors change during pregnancy, to achieve a hypercoagulable state.[13-16] While this acts as a natural adaptive mechanism to prevent postpartum bleeding, it however exposes women to an increased thrombotic risk. Several procoagulant proteins, such as factors VII, VIII, X, fibrinogen and von Willebrand factor, increase during pregnancy.[13] Concomitantly, the plasma levels of coagulation inhibitors such as protein S drop noticeably from the early stages of pregnancy.[17] Moreover, there are reports of a reduced activity of the fibrinolytic system, mainly due to an increase of the type 2 placenta-derived plasminogen activator inhibitor (PAI-2).[18] Global assays for blood clotting evaluation, such as thrombin generation (TG) and thromboelastometry/-graphy (TEM/TEG), have been able to accurately confirm the peculiar hypercoagulable state described in pregnant women. In particular, several papers published in literature have reported a significant increase in endogenous thrombin potential (ETP) – one of the main TG parameters – both in healthy and pathological pregnancies.[17,19-21] Also, viscoelastic tests conducted on whole blood were able to identify – in pregnant women vs non-pregnant women – a hypercoagulable profile, mainly characterized by a faster activation of the coagulation cascade and a stronger clot firmness.[22,23] It is still up for debate whether abnormal results from traditional laboratory tests and/or global assays can reliably identify pregnant women most at risk of developing thrombotic events. Hence the inability to determine which patients should receive thromboprophylaxis.

Thrombophilia

The term "thrombophilia" refers to the presence in the blood of a congenital or acquired predisposition to thrombosis. The most known congenital thrombophilic conditions are the FV Leiden mutation, the prothrombin variant and the reduction of natural coagulation inhibitors (eg. protein C, protein S and antithrombin).[24] The most common acquired thrombophilic condition is the antibody antiphospholipid syndrome.[25] Clores et al recently conducted a systematic review of several studies on the risk of pregnancy-associated venous thromboembolism (VTE) in women with thrombophilia.[26] There have been reports that women with a heterozygous FV Leiden mutation carry a 4- to 16-fold increased risk of thromboembolic disease during pregnancy, which may further increase up to 40-fold in women with FV Leiden homozygosity. Depending on the prothrombin variant, the risk of thromboembolic disease may increase 3- to 15-fold. With regard to antithrombin, protein C and protein S deficiencies, most of the data

on the risk of thromboembolic disease in pregnancy derive from small family studies, precisely due to the rarity of these thrombophilic abnormalities. The risk of venous thromboembolism in pregnancy seems particularly high in women with antithrombin deficiency, with an annual incidence estimated at 30-40%, but is considerably lower in women with protein S or protein C deficiencies, with an annual incidence estimated at 6-13%. Finally, the antiphospholipid antibody syndrome is a systemic autoimmune disorder characterised by venous or arterial thrombosis and/or pregnancy morbidity (eg. one or more unexplained deaths of a morphologically normal fetus; one or more premature births or three or more consecutive spontaneous pregnancy losses), in the presence of persistent laboratory evidence of antiphospholipid antibodies (aPL).[27] Antiphospholipid antibodies are a heterogeneous group of autoantibodies directed against negatively charged molecules and towards a combination of phospholipids and plasma proteins. They are divided into three classes: anticardiolipin (aCL), antibeta2glycoprotein1 (antiβ2GPI) and lupus anticoagulant (LAC). Their antibody action is directed against various combinations of phospholipids, proteins with a high affinity for phospholipids or phospholipid-protein complexes. According to the literature, the presence of aPL has been confirmed in approximately 10% of pregnant women with deep vein thrombosis.[28,29]

An aspect that is always much debated is which pregnant woman may benefit most from thrombophilia screening. Furthermore, considering the aforementioned changes in the coagulation factors, it would be advisable, when possible, to conduct the thrombophilia study before pregnancy. Based on a consensus paper published by the Italian Society for Hemostasis and Thrombosis (SISET) in 2009, Table 2 presents a summary of the women who should or should *not* receive a thrombophilic screening.[30] Another highly debated issue is the optimal pharmacological prophylaxis for asymptomatic (i.e. with no prior VTE and/or obstetric complications) pregnant women with hereditary thrombophilia. Following SISET recommendations, women with a major thrombophilic defect (eg. deficiency of protein C or protein S, double heterozygous carriers of FV Leiden and prothrombin variant or homozygous carriers of FV Leiden or prothrombin variant) should receive prophylactic doses of low molecular weight heparin (LMWH) antepartum and for 6 weeks after delivery.[30] Women with antithrombin deficiency should receive moderate doses of LMWH antepartum and for 6 weeks after delivery, and the use of antithrombin concentrates at the time of delivery should be considered.[30] Finally, heterozygous carriers of FV Leiden of prothrombin variant should receive postpartum prophylactic doses of LMWH for 6 weeks after delivery.[30]

Table 2. Screening for thrombophilia in pregnancy according to the Italian Society for Hemostasis and Thrombosis 2009 consensus

Screening suggested in:
Asymptomatic women with family history of: ■ venous thromboembolism (grade D). ■ inherited thrombophilia (grade C).
Women with history of venous thromboembolism (grade C).
Recurrent pregnancy loss or prior unexplained IUFD (grade C).
Women with prior preeclampsia, HELLP syndrome, *abruptio placentae*, FGR (grade D).
NO screening suggested in:
Asymptomatic women without family history of: ■ venous thromboembolism (grade C) ■ obstetric complications (rade D).

IUFD: intrauterine fetal death; HELLP: hemolysis, elevate liver enzymes, low platelet count; FGR: fetal growth restriction.

Endothelial damage/dysfunction

It has been widely reported in the literature that endothelial cell activation may contribute to hypercoagulability, both during physiological, but also – and especially – during pathological pregnancies (eg. gestational diabetes, preeclampsia and hypertension, obesity and hyperlipidemia).[31] In fact, the peculiar structure of the placenta, with its dual endothelial layers (i.e. on the maternal and fetal sides), makes this organ particularly susceptible not only to an alteration of the endothelial function, but also to the activation of the coagulation cascade. The tissue factor (TF)-driven procoagulant role of the trophoblast, phosphatidylserine and fibrin deposition renders the placenta prone to thrombotic risk.[32] Several parameters have been proposed as markers of endothelial dysfunction in pregnant women [eg. tissue-type plasminogen activator antigen (t-PA), plasminogen activator inhibitor-1 (PAI-1), von Willebrand factor antigen, exosomes and microparticles, matrix metalloproteinases (MMP), vascular and intracellular cell adhesion molecules (VCAM and ICAM), reactive oxygen and nitrogen species (ROS and RNS), microRNAs, etc.].[33-36] The main limitation pertaining to the diagnosis of this predisposing factor is the difficulty to carry out laboratory tests that can detect endothelial damage/dysfunction.

Other prothrombotic risk factors

Several clinical studies have identified numerous conditions associated with an increased thrombotic risk in pregnancy, in addition to the aforementioned mecha-

nisms attributable to the Virchow's triad. However, it should be noted that the current literature only allows to establish a nexus between the phenomena (risk factor vs thrombotic event), rather than to identify an etiological connection.

A previous thromboembolic event has been reported as the most important risk factor for antenatal recurrence of venous thrombosis.[37,38] This risk increases if the maternal age is >35[6] or in case of additional independent risk factors, such as obesity,[39] multiple pregnancies,[39-43] or smoking.[39,40,44] Assisted reproductive technologies (ART) have also been identified as a possible risk factor for venous thromboembolism.[45,46] Notably, the ovarian hyperstimulation syndrome (OHSS) is a syndrome characterized by supraphysiological estradiol levels, which induce a sustained activation of the coagulation cascade, resulting in thrombotic events that have been reported to occur weeks after OHSS had resolved.[46,47] During the postnatal period, increasing age,[6,40,48] hypertension (probably due to preeclampsia)[40,48] and blood group A[41,49] appear to be the most important risk factors for venous thromboembolism. Another salient risk factor for thromboembolic disease in puerperium is the caesarean section, which precedes more than 75% of the deaths from puerperium pulmonary embolism.[50,51]

Key messages

- Pregnancy and puerperium have historically been associated with a significant increase of the thromboembolic risk, which is the main cause of maternal mortality.
- During pregnancy, there is a physiological tendency to hypercoagulability, caused by an imbalance between procoagulant and anticoagulant factors, which on the one hand counters the postpartum hemorrhagic risk, while on the other increases the thromboembolic risk.
- There are currently no laboratory tests to ascertain the risk of developing thrombosis. Hence, the challenge in identifying women who may require pharmacological antithrombotic prophylaxis due to their high risk of developing thrombosis.
- Larger prospective studies are warranted to broaden our understanding of the mechanisms which favor the development of thromboembolic events during pregnancy, in order to optimize treatment and reduce the incidence of these potentially fatal complications.

Conclusions

A state of hypercoagulability is a physiological necessity during pregnancy which, compounded by other prothrombotic conditions (eg. immobilization, obesity, smoking, hypertension, etc.), may considerably increase the risk of developing thrombotic events. Although many efforts have been made to clarify the risk of thrombosis in pregnancy, a clear understanding of the underlying mechanisms remains elusive. There are currently no laboratory tests to ascertain the risk of developing thrombosis. Hence, the challenge in identifying women who may require pharmacological antithrombotic prophylaxis due to their high risk of developing thrombosis. Larger prospective studies are warranted to broaden our understanding of the mechanisms which favor the development of thromboembolic events during pregnancy, in order to optimize treatment and reduce the incidence of these potentially fatal complications.

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