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Venous thromboembolism and pregnancy

Edited by
Bernard Tardy and Laurent Bertoletti

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Venous thromboembolism and pregnancy

Topic editors

Bernard Tardy — Inserm CIC1408, France

Laurent Bertoletti — Centre Hospitalier Universitaire (CHU) de Saint-Étienne, France

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Hugo Ten Cate,
Maastricht University Medical Centre, Netherlands

*CORRESPONDENCE
Bernard Tardy
bernardtardy@yahoo.fr

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Editorial: Venous thromboembolism and pregnancy

Bernard Tardy[1]* and Laurent Bertoletti [2]

[1]Clinical Investigation Center, Inserm CIC1408, Saint-Étienne, France, [2]Université Jean Monnet, Department of Médecine Vasculaire et Thérapeutique, University Hospital of Saint-Etienne, Mines Saint-Étienne, INSERM, U 1059, CIC1408, Saint-Étienne, France

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Editorial on the Research Topic
Venous thromboembolism and pregnancy

Around 700 women die each year in the U.S., from conditions related to or associated with pregnancy or childbirth (the highest rate among developed nations) (1), and over 50,000 women experience severe maternal morbidity (SMM) (2). In addition to this alarming finding, overall pregnancy-related mortality is increasing, and the scientific community is still unclear as to why this is occurring. The World Health Organization defines maternal morbidity as any health condition attributed to and/or aggravated by pregnancy and childbirth that has negative outcomes on the woman's wellbeing (3). As with maternal mortality (MM), maternal morbidity has also seen increasing numbers. Excluding blood transfusions, the rate of SMM increased by ~20% from 1993 to 2014 in the U.S. (2).

In response, the NIH Office of the Director (OD), the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), ORWH, and other NIH Institutes, Centers, and Offices have developed the trans-NIH Implementing a Maternal health and PRegnancy Outcomes Vision for Everyone (IMPROVE) initiative to support research into how to reduce preventable MM; improve health for women before, during, and after delivery; and promote health equity in the United States. "Any maternal death is one too many," said NICHD Director Diana W. Bianchi, M.D., co-lead of the IMPROVE Task Force. "Areas of research include heart disease, hemorrhage or bleeding, and infection (the leading causes of U.S. maternal deaths); contributing conditions, such as diabetes, obesity, mental health disorders, and substance use disorders; and structural and health care system factors that may contribute to delays or disruptions in maternal care."

It is for this reason that we are pleased to see the appearance of this Research Topic, which provides a recent update on the various aspects of venous thromboembolism (VTE) risk in pregnant and postpartum women.

Pregnancy represents a unique situation, increasing the risk of thrombosis both throughout the pregnancy and during the postpartum period. The main risk factors have been clarified thanks to the epidemiological studies, summarized by Gris et al. It is thus possible to separate pre-existing risk factors, transient risk factors, and risk factors specifically associated with pregnancy. It is likely that with the change in populations and the development of medically assisted reproduction, the risk factors may change in the coming years. Thus, other studies such as the case-control study conducted by Alsheef et al. are welcome, in order to be able to inform possible changes in the epidemiology.

These epidemiological data have allowed the development of scores aimed at predicting the risk of venous thrombosis disease during pregnancy. Raia-Barjat, Chauleur et al. remind us of the main scores, as well as their different levels of validation. The individualization of patients with a higher risk of developing venous thromboembolic disease has made it possible to propose the implementation of a venous thromboembolic disease prevention strategy. Particular attention is paid by Blondon and Skeith to the prevention of venous thromboembolism during the postpartum period, which appears to be the period of greatest risk for thromboembolic events.

Despite prevention strategies, we still have to manage pregnant women with a suspicion of pulmonary embolism. Great progress has been made in recent years for these patients, who were previously excluded from the main diagnostic tests. Robert-Ebadi et al. examine the different algorithms currently validated, allowing physicians to reject the hypothesis of pulmonary embolism without the need for thoracic imaging.

Although the prevalence of pulmonary embolism is relatively low in pregnant women suspected of having a pulmonary embolism, specific situations such as high-risk PE may be challenging, as discussed by Hobohm et al., or for patients known to have antiphospholipid syndrome, as discussed by Killian and van Mens. The use of inferior vena cava filters is also a potential issue, as presented by Bistervels et al. It is important to note that the rate of complications directly related to the filter is nearly one woman in five.

The final article, by Raia-Barjat, Ni Ainle et al., deals with the problem of pre-eclampsia in the case of venous thromboembolic disease, recalling the vascular role of the placenta and the current discussions on the possibilities of its prevention.

As brilliantly illustrated by the HIGHLOW study (4), evaluating the efficacy and safety of an intermediate dose of low molecular weight heparin in the prevention of venous thromboembolic disease in high-risk women, being pregnant is no more a reason to not be included in trials. This opens the way to make progress on many aspects of VTE in pregnant and postpartum women. Thromboprophylaxis aims to protect patients from venous thromboembolism, but at the risk of an increased risk of bleeding, which may occur in different manners during pregnancy and post-partum (5). During the post-partum, the use of direct oral anticoagulants may also be challenging, as it is associated with an increased risk of genitourinary bleeding (6), a setting that may need dedicated assessment tools (7). In these situations, the potential of anti-Factor XI (8) deserves specific consideration. Notably, both DOACs and small peptides may not be used during lactation. Future work should also address the management of superficial venous thrombosis, as data are limited in the field (9). Finally, long-term follow-up is needed, to assess the risk of vascular sequelae, particularly pulmonary sequelae (10). We very sincerely hope you enjoy reading this Research Topic as much as we enjoyed accompanying the authors through production.

Author contributions

Both authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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MINI REVIEW
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Risk of Thrombosis, Pregnancy Morbidity or Death in Antiphospholipid Syndrome

Martin Killian[1,2] *and Thijs E. van Mens*[3]*

[1] CIRI – Centre International de Recherche en Infectiologie, Team GIMAP, Université de Lyon, Université Jean Monnet, Université Claude Bernard Lyon 1, Inserm, U1111, CNRS, UMR530, Saint-Étienne, France, [2] Internal Medicine Department, Saint-Etienne University Hospital, Saint-Étienne, France, [3] Amsterdam UMC, Department of Vascular Medicine, Amsterdam Cardiovascular Sciences, Amsterdam Reproduction and Development, University of Amsterdam, Amsterdam, Netherlands

The antiphospholipid syndrome is an autoimmune disease characterized by thrombosis and pregnancy morbidity. The manifestations are caused by antibodies targeting cell membrane phospholipids and/or associated proteins. The triggers leading to these antibodies' production are unknown but recent work suggests cross-reactivity between the autoantigens and peptides produced by the intestinal microbiome. Work on how the autoantibodies could cause clinical manifestations implicates different mechanisms. Binding to surface proteins of different cell types can induce intracellular signaling leading to cell activation and tissue factor expression. Complement activation and neutrophil extracellular-traps are also involved, and recent evidence implicates endothelial protein C receptor-lysobisphosphatidic acid complex. Pregnancy is a high-risk situation for antiphospholipid syndrome patients due to the increased risk of thrombosis and obstetric complications. Epidemiological and clinical research on APS is hampered by heterogeneity in populations, testing and treatment strategies. About one in 10 to one in fifty APS pregnancies is complicated by thrombosis, despite treatment. Pregnant patients with prior thrombosis are prescribed therapeutic dose heparins and low dose aspirin. Without prior thrombosis a prophylactic dose is used. The most frequent obstetrical manifestation is recurrent early pregnancy loss. The association of APS antibodies with late pregnancy loss is stronger, however. Prevention of recurrence is achieved with aspirin and prophylactic dose heparin, although the evidence is of low certainty. The third obstetrical classifying manifestation comprises preterm delivery due to placenta-mediated complications and is treated in subsequent pregnancies with aspirin with or without prophylactic dose heparin, again based on low quality evidence. New therapies are under investigation.

Keywords: pregnancy morbidity, obstetric antiphospholipid, antiphospholipid syndrome, venous thromboembolism (VTE), antiphospholipid antibodies

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Edited by:
Avi Leader,
Rabin Medical Center, Israel

Reviewed by:
Fionnuala Ni Ainle,
University College Dublin, Ireland
Quitterie Reynaud,
Hospices Civils de Lyon, France

***Correspondence:**
Thijs E. van Mens
t.e.vanmens@amsterdamumc.nl

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INTRODUCTION

Antiphospholipid syndrome (APS) is a rare autoimmune disease, whose key features are recurrent vascular thrombosis and obstetrical complications, but can also be responsible for thrombocytopenia, haemolytic anemia, cardiac valvular disease, renal thrombotic microangiopathy, neurological symptoms, cognitive impairment or pulmonary hypertension (1). It is also frequently associated with systemic lupus erythematosus, and its approximate prevalence is 40 per 100 000 individuals (2, 3).

APS-specific autoimmune response is targeting components of the cell membrane i.e., phospholipids (e.g., cardiolipin) and/or their associated proteins (mainly β2-glycoprotein-I [β2GPI]) in its phospholipid-bound "activated" open conformation which is exposing cryptic epitopes in its first domain (4–6). Antiphospholipid antibodies (aPL; see **Table 1**), have historically been described in 1983, in Syphilis, as well as in multiple infectious diseases since (20). In such infectious setting, aPL are usually thought of as transient and non-thrombogenic, however thombotic complications have been reported in a small number of aPL-positive infection cases, possibly in autoimmunity-prone individuals (21, 22). Interestingly, aPL have recently been reported in a significant proportion (up to 30–50%) of acute COVID patients, especially in severe cases, but it is still debated whether they could be contributing to the disease prothrombotic state independently of the several potentially confounding factors (23). Of note, the aPL epitope specificity is different in COVID (i.e., rarely targeting β2GPI domain I) (24), and the autoantibody persistence over time ($\geq$ 2 positive testing, 12 weeks apart) seems to be absent in most COVID cases (23, 25), in line with what has been described in infection-related cases (26).

Detecting aPL is primordial for diagnosing APS, but determining if these autoantibodies are culprits (aPL positivity with an APS-compatible clinical setting) or innocent bystanders (aPL positivity alone) can be complicated (23, 27). Classification criteria have been formulated during International Congresses on APS in Sapporo and Sydney, and subsequently published as consensus statements in 1999 (28) and 2006 (29), respectively. The 2006 revised classification criteria for definite APS are met when at least one clinical criterion (vascular thrombosis or pregnancy morbidity), and one biological criterion (Lupus Anticoagulant [LAC], IgM/IgG anti-cardiolipin [aCL], and/or IgM/IgG anti-2GPI positivity) are present. These criteria, which were never intended for diagnostic use, have significant drawbacks: non-inclusion of the less frequent but well-identified APS manifestations (30) or non-inclusion of "non-criteria" autoantibodies (e.g., anti-prothrombin, anti-annexin V, anti-phosphatidylserine…) (31, 32).

The objective of this mini review article is to provide a clear but concise summary regarding pregnancy-related complications in APS, particularly focusing on recent insights, research gaps and future concepts in the pathogenesis, epidemiology, prevention, and treatment of thrombotic and non-thrombotic manifestations.

ORIGIN OF APS AUTOANTIBODIES

APS pathogenesis is thought to rely upon both genetic and environmental factors, which would explain why several microorganisms can trigger transient aPL, whereas only few predisposed individuals will develop definite APS (33). Like other autoimmune diseases, the exact trigger for autoantibodies is unknown. Several theories exist however, including recent work identifying an intestinal microbe as a source of cross-reactive antigens thought to trigger APS autoimmunity (34, 35). A comparison of known APS epitopes within β2GPI with intestinal microbiome metagenomic data, identified *Roseburia Intestinalis* as a gut microbe with "mimotope" peptides for both B and T-cells, and cross-reactivity was experimentally confirmed in humans and mice. Moreover, a *Roseburia Intestinalis*-induced APS phenotype was reported in APS-prone mice.

On another note, some non-β2GPI-specific aPL could be natural antibodies (i.e., polyreactive, non-immunization induced and B1 cell-secreted) (36), whose pathogenicity could be secondarily induced or enhanced by antigen-driven mutation (37).

Regarding the genetic background, different human leukocyte antigen (HLA) gene polymorphisms have been associated with the occurrence of certain types of aPL: HLA-DR5 and HLA-DRw53 with aCL and LAC; HLA-DPB1*0301 and HLA-DPB1*1901 with anti-β2GPI; HLA-DQB1*0301, HLA-DQA1*03, and HLA-DRB1*04 with anti-prothrombin; HLA-DRB1*08 with anti-annexin V, and HLA-DQB1*0301 with anti-phosphatidylserine (38). These findings suggest that the way these autoantigens—or microbial antigens, through molecular mimicry (21, 34)—are presented to the immune system, is important for the generation of the corresponding autoantibodies. Interestingly, another potential autoantibody-generating mechanism has been described for HLA class II molecules and their ability to aberrantly present cellular misfolded proteins [i.e., exposing cryptic epitopes (5) or creating neoantigens (12)] to the cell surface without processing to peptide (39). In line with this, anti-β2GPI/HLA-DR complex antibodies were recently reported in 83% cases of APS (12), and 20% cases of unexplained recurrent pregnancy loss (13).

PATHOPHYSIOLOGY OF THROMBOTIC MANIFESTATIONS

According to the 2006 revised classification criteria for APS, the "vascular thrombosis" criterion is met with the occurrence of $\geq$1 episode(s) of objectively (i.e., *via* appropriate imaging or histopathology) confirmed arterial, venous, or small vessel thrombosis, in any tissue or organ, excluding superficial venous thrombosis (29).

The exact underlying pathogenic mechanisms behind APS have not yet been fully elucidated (40), but multiple leads linking coagulation and autoimmunity have been described:

- aPL direct interference with the endogenous anticoagulant systems e.g., decrease in protein C/S and thrombin plasma levels (41).

TABLE 1 | Spectrum of the main autoantibodies associated with antiphospholipid syndrome.

Specificity	LAC	aCL	Anti-β2GPI	Anti-β2GPI Domain 1	Anti-β2GPI/HLA-DR	Anti-PS	Anti-PT	Anti-PS-PT complex	Anti-Annexin V	Anti-Annexin II
Known isotypes	NA	IgG, IgA, IgM	IgG, IgA, IgM	IgG	IgG	IgG, IgA, IgM	IgG, IgA, IgM	IgG, IgA, IgM	IgG, IgM	IgG, IgM
Approximate prevalence in definite APS	30–80% (7, 8)	10–50% (8, 9)	5–45% (9, 10)	50–60% (8, 11)	80% (12, 13)	45–85% (11, 14)	15–55% (15, 16)	25–75% (7, 8)	15–40% (7, 17)	25–40% (18, 19)
In Classification	Yes	Yes (IgG, IgM)	Yes (IgG, IgM)	No	No	No	No	No	No	No

LAC, lupus anticoagulant; aCL, anti-cardiolipin; anti-PS, anti-phosphatidylserine; anti-PT, anti-prothrombin; PE, anti-phosphatidylethanolamine; NA, not applicable.

- inhibition of β2GPI-stimulated fibrinolysis by anti-β2GPI autoantibodies (42).
- anti-β2GPI antibody-dependent activation of the classical complement pathway in the "standard" thrombotic manifestations of APS (43, 44), but also of the alternative pathways in its catastrophic form due to additional germline mutations in complement regulatory genes (45).
- autoantibody-mediated activation (including C5a and C5b9-related mechanisms) of endothelial cells (46–48), platelets (48–52) and monocytes (53, 54), particularly leading to tissue factor pathway-dependent procoagulant activity *via* various [and sometimes paradoxical (55)] mechanisms (56).
- release of neutrophil extracellular traps (NETs) by activated neutrophils (57).
- endothelial protein C receptor (EPCR)-lysobisphosphatidic acid (LBPA) engagement by aPL, leading to thrombosis and driving dendritic cell interferon-α production for the expansion of aPL-secreting B1 cells (56).

These autoantibodies' pathogenic effects are frequently referred to as the "first hit," inducing a persistent thrombophilic state, which requires a "second hit," usually an inflammatory and/or a prothrombotic condition, to elicit the clinical manifestations (40). Pregnancy can be viewed as such, because of its well-described associated hypercoagulable state, including overlapping mechanisms such as acquired activated protein C resistance or increased tissue factor expression and activation (58).

PATHOPHYSIOLOGY OF PREGNANCY MANIFESTATIONS

According to the 2006 revised classification criteria for APS, the "pregnancy morbidity" criterion is met with the occurrence of at least one of these events (without any alternative cause): (1) ≥1 unexplained death(s) of a morphologically normal fetus (≥10th week of gestation). (2) ≥1 premature births of a morphologically normal neonate (<34th week of gestation) because of eclampsia, severe pre-eclampsia or placental insufficiency. (3) ≥3 unexplained consecutive spontaneous abortions (<10th week of gestation) (29).

Interestingly, whereas high titres and multiple aPL positivity are usually associated with thrombotic manifestations in APS, low titres aPL have been frequently reported in obstetric APS (59, 60). The fact that high levels of β2GPI can be found in the placenta is a possible explanation for this, moreover direct effects (notably through complement, Toll Like Receptors and inflammasome pathways) on trophoblast cell and endometrium differentiation have been reported for aPL (61–65). The recently described anti-β2GPI/HLA-DR antibodies may have a pathogenic role in obstetric APS by inducing complement-dependent cytotoxicity-mediated damaging in vascular endothelial cells of the placental decidua (12). Similarly, the EPCR/LBPA complex is involved in aPL signaling in embryonic trophoblast cells, and using an anti-EPCR/LBPA-blocking antibody was protective from fetal loss in a relevant mouse model (56). Other non-criteria aPL have been

reported in obstetric APS, including anti-Annexin antibodies (66) or aPL of the IgA isotype (67).

CLINICAL IMPLICATIONS OF PREGNANCY IN APS

A current or planned pregnancy demands careful counseling and therapeutic decision making in APS patients. Unfortunately, clinical research on APS is hampered by equivocal data from both epidemiological studies and clinical trials. General reasons for this include heterogeneity in APS testing, cut-off values, patient selection, and treatment protocols. The mainstay of treatment for pregnant APS patients—despite the evidence for a coexisting role of non-thrombotic processes in the pathogenesis—is anticoagulant therapy. This applies to both thrombotic and obstetric APS. Bleeding complications are the main drawback. Bleeding risk was investigated in a *post-hoc* analysis of one retrospective and one prospective cohort of pregnant APS patients receiving low dose aspirin (LDA) and/or low molecular weight heparin (LMWH) (68). The incidence of bleeding events was 25% in the retrospective cohort, with major bleedings, all early post-partum, occurring in 3% of pregnancies. In the prospective cohort only a single bleeding event (1.2%) was recorded. Major bleeding was defined as requiring intervention for hemostasis or blood transfusion, or during the peripartum period >500 mL. A control group was not included in this study, but the rates do not clearly exceed those in untreated pregnant women. Heparin-induced thrombocytopenia and allergic reactions also seem rare (69).

PREGNANCY-RELATED VENOUS THROMBOSIS

Epidemiology

Pregnancy is a prothrombotic state, due to physiological changes in anatomy and circulating hormones and coagulation proteases (70). Hence, pregnancy forms an additional risk factor for thrombosis in APS patients. An estimated one in four thrombotic events in APS are pregnancy related (71). The absolute risk for thrombosis during pregnancy and the postpartum period is variously reported from 1 to 12% (72–74). Not all patients in these studies had APS according to the currently accepted criteria. The reported thrombotic events, mostly venous thrombosis, occurred under different treatment regimens including with and without heparins. Despite these limitations, pregnancy carries a high risk for thrombosis in APS. The risk is further determined by the patients' antibody profile. A high-risk profile comprises persistent positivity for LAC or a combination of at least two of the three aPL, with the general concept of higher titers conferring a higher risk (75). Another major risk factor is a previous thrombosis, and traditional venous thromboembolism (VTE) risk factors likewise apply to the pregnant APS patient.

Patients with purely obstetric APS also have an increased risk for future thrombotic events. Patients with recurrent miscarriage had a thrombotic event rate of 19.3% after a mean follow-up of 7.3 years in one study, with no thrombosis in the group with idiopathic recurrent miscarriage (76). Another case control study in obstetric APS patients reported a approximatively doubled VTE risk when compared to idiopathic controls (77).

Pregnancy can also trigger the most severe form of the syndrome, called catastrophic APS. This rare manifestation is characterized by multiorgan thrombosis, often in the microvasculature, occurring within a single week. Pregnancy is the precipitating factor in an estimated eight percent of cases, half of which occur during the pregnancy and half after (78, 79). Both maternal and perinatal mortality were high in one case-series, around fifty percent.

Interestingly, aPL do cross the placenta and newborns from APS mothers can test postive for these antibodies. Fortunately, this does not appear to cause thrombosis in the infants. Neurodevelopmental disorders have been observed but it is unclear whether there is an increased risk, let alone a causal relation (78, 80).

Prevention and Treatment of Venous Thrombosis

The risk for pregnancy-related thrombosis necessitates prevention using anticoagulants. No trials have assessed different strategies for secondary thrombosis prophylaxis specifically in pregnant APS patients. But even under dual anticoagulant therapy with LDA and LMWH, pregnancy carries a high risk for thrombosis recurrence (81). Experts agree on treating all APS patients with previous thrombosis with therapeutic dose LMWH and LDA during pregnancy (75, 82). Women with obstetric APS are treated with a prophylactic dose during pregnancy and the puerperium. Vitamin K antagonists cross the placenta and can be teratogenic and cause fetal hemorrhage (83). They should therefore be replaced with LMWH as soon as pregnancy is confirmed. Based on data from animal studies, direct oral anticoagulants are also deemed unsafe during pregnancy and lactation (84). Moreover, data from clinical trials outside of pregnancy suggests these anticoagulants have inferior effectiveness compared to vitamin K antagonists, and at least for high-risk patients with arterial thrombosis they are not recommended (85, 86). Direct oral anticoagulants, if prescribed to APS patients, are ideally replaced by LMWH preconceptionally. This recommendation is largely based on the uncertainty about the teratogenicity of these agents (84), which may leave room for an alternative approach in patients with regular menses. If there is a strong preference to avoid long duration LWMH treatment (from the undefined preconceptional period until postpartum), frequent pregnancy testing in case of delayed menses and direct switching to LWMH upon a positive test may be preferred by a well-counseled patient.

New thrombosis occurring during pregnancy in an obstetric APS patient is also treated with LWMH. Catastrophic APS triggered by pregnancy is treated with a combination of intravenous heparin, glucocorticoids and either intravenous immunoglobulins or plasma exchange. Due to the nature of this manifestation, no trials are available, and treatment is based on

expert opinion (87). Delivery should be considered, although it is not known whether this improves outcomes (88).

APS patients undergoing assisted reproductive technology procedures are also at high-risk for thrombosis (89). LMWH is recommended, at the same dose as what would be prescribed during a pregnancy in that individual patient (75, 82). The thrombotic risk is thought to be caused by the high estrogen levels. For this same reason, estrogen containing contraception is discouraged in women with APS (75, 82).

PREGNANCY MORBIDITY

Epidemiology

The other clinical hallmark of APS aside from thrombosis, is obstetrical morbidity. A systematic review of the literature on APS antibody frequencies has shown that 6% of patients with APS related pregnancy morbidity are antibody positive (90). When restricting the analysis to studies that confirmed the diagnosis according to current criteria, the frequency ranged from 0 to 29%. The strength of the association seems to differ between the different obstetrical manifestations. In a European registry study of aPL-positive women, most of whom had APS according to the classification criteria, 54% had a history of recurrent miscarriage (91). However, the baseline risk of a single recognized pregnancy ending in miscarriage is already as high as 13% (92). Although recurrent miscarriage is a part of the classification criteria, the association with aPL is a matter of debate (93). Comparisons of observational studies on the topic are hampered by variation in the number and timing of pregnancy losses, aPL testing, and whether other causes for miscarriage were excluded. An extensive systematic review of these studies does suggest that the risk of early pregnancy losses is tripled in the presence of LAC and/or aCL (94). The same study reported risk increases with LAC for second trimester [OR 14.3 (95% CI 4.7–43.2)] and third trimester [OR 2.4 (95% CI 0.81–7.0)] pregnancy loss, and with aCL for third trimester loss [OR 3.3 (95% CI 1.6–6.7)]. A recent systematic review found odds ratios for late pregnancy loss ranging from 4.3 to 23, depending on the type of antibody (95). The third obstetric classifying manifestation of APS are placenta-mediated complications leading to premature birth, specifically pre-eclampsia, eclampsia and placental insufficiency. The frequency of pre-eclampsia in APS pregnancies is reported from 10 to 48% (96). Conversely, about 1 in 7 cases of pre-eclampsia may be APS-associated. The frequency of placental insufficiency is about 30%.

Prevention of Pregnancy Morbidity

One question related to therapy for obstetric APS is whether a single treatment strategy is optimal for all the different manifestations. The 2020 American College of Rheumatology (ACR) Guidelines on the topic strongly recommends treating pregnant women with APS without prior thrombosis, with prophylactic heparin or LMWH, together with LDA (82). No distinction is made between prior APS manifestations. For patients with $\geq$ 2 prior early losses the evidence is summarized by a Cochrane Review (69). Meta-analysis of five trials produced a relative risk of live birth of 1.3 (95% CI 1.1–1.5) for heparin plus aspirin vs. aspirin alone. The certainty of evidence was judged low. Aspirin is started preconceptionally and heparin as soon as pregnancy is confirmed. LMWH are usually prescribed instead of unfractionated heparin because of convenience. A direct comparison in two small trials showed no difference (97, 98).

The European Alliance of Associations for Rheumatology does differentiate in its recommendations between women with late or recurrent early losses and women with preterm delivery due to placenta mediated complications (75). For the former, the recommendation parallels the recommendations made by the ACR. For the latter, it recommends either aspirin alone or in combination with prophylactic dose heparin. For this patient subgroup, one trial randomized between the two treatment strategies. It was unfortunately underpowered due to recruitment issues and did not show a difference in efficacy. There were no events in the LMWH plus aspirin group and two in the aspirin only group (99).

In analogy to systemic lupus erythematosus and based on a retrospective observational study, the ACR also recommends treating pregnant APS patients with hydroxychloroquine. This strategy is being evaluated in ongoing trials (100). Interestingly LMWH and LDA are also thought to act through non-antithrombotic (i.e., immunomodulatory) functions (101, 102), as hydroxychloroquine (103), but evidence is not conclusive to date (104). Another immunomodulatory therapeutic strategy under investigation is TNF-alpha inhibition by certolizumab pegol (NCT03152058).

DISCUSSION

Despite clear classification criteria, APS remains a complex disease, as highlighted by the large body of work implicating a wide range of cell types, signaling pathways and plasma proteases in its pathophysiology. A single key event within the pathophysiological pathway has however not yet been undisputedly pinpointed, although recent work does identify a new cell membrane lipid complex which links the antibody formation with induction of thrombosis and pregnancy morbidity.

Likewise, the exact origin of aPL remains an open question. Molecular mimicry has been suspected for a long time, but robust evidence linking the targeted autoantigens with intestinal microbe-expressed proteins were only recently reported and deserve further investigation.

Pregnancy is an important second hit in APS. It frequently provokes thrombosis, requiring secondary and sometimes primary thromboprophylaxis. A careful risk assessment is required. Similarly, in women in whom APS previously presented with pregnancy morbidity, secondary thromboprophylaxis is essential.

Trials have been performed to determine the optimal treatment strategy, but overall did not produce unequivocal results. Variations in patient populations, aPL testing

and treatment are part of the explanation. Given the suboptimal efficacy and safety of anticoagulants and the non-coagulation-related mechanisms also involved in the pathophysiology, new non-anticoagulant based treatments are under investigation.

AUTHOR CONTRIBUTIONS

MK and TM wrote sections of the manuscript. Both authors contributed to manuscript revision, read, and approved the submitted version.

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Preeclampsia and Venous Thromboembolism: Pathophysiology and Potential Therapy

Tiphaine Raia-Barjat[1,2], Osasere Edebiri[3] and Fionnuala Ni Ainle[3,4]*

[1] Department of Gynecology and Obstetrics, Centre Hospitalier Universitaire de Saint-Étienne, Saint-Étienne, France, [2] INSERM U1059, SAINBIOSE, Université Jean Monnet, Saint-Étienne, France, [3] Department of Haematology, Mater Misericordiae University Hospital, Rotunda Hospital, Dublin, Ireland, [4] UCD School of Medicine, University College Dublin, Dublin, Ireland

Preeclampsia (PET) is a multisystem inflammatory disorder that represents a leading cause of feto-maternal morbidity and mortality, complicating 2–5% of all pregnancies. PET incurs an increased risk of venous thromboembolism, which is one of the leading causes of death in pregnancy and in the postpartum period. This prothrombotic phenotype is attributable to the maternal phase of PET, which is characterized by a systemic inflammatory response and coagulation activation. Research continues to be undertaken in terms of preventative measures, however, currently revolves around pharmacological low dose aspirin initiated in the first trimester of pregnancy for those with risk factors. Treatment involves antenatal corticosteroids for fetal lung development in preterm birth, parenteral magnesium sulfate for fetal neuroprotection and maternal seizure prophylaxis, and timely birth of the fetus and placenta being the only definitive treatment of PET. Patients with a venous thromboembolism (VTE) risk deemed to be > 1–3% are treated with pharmacological thromboprophylaxis in the form of low molecular weight heparin. Completing each woman's VTE risk assessment is crucial, particularly in the setting of PET, as there is also a proven associated competing hemorrhagic risk.

Keywords: preeclampsia, PET, pregnancy, thrombosis, risk

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Bernard Tardy,
INSERM CIC1408, France

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Renee Eslick,
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****Correspondence:***
Tiphaine Raia-Barjat
tiphaine.barjat@chu-st-etienne.fr

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INTRODUCTION

Preeclampsia (PET) complicates 2–5% of all pregnancies and represents a leading cause of feto-maternal morbidity and mortality worldwide (1–3). PET is a multi-system inflammatory disorder and is estimated to account for 15% of maternal mortality worldwide (3–5). The classical clinical presentation of PET consists of the new onset of hypertension and proteinuria after 20 weeks gestation or other maternal organ dysfunction (6–8). Complications of PET include intra-uterine growth restriction (IUGR), fetal death (1–2% of cases), preterm birth, hepatic and renal dysfunction, thrombosis, coagulopathy, eclampsia (a severe manifestation of PET characterized by severe hypertension and generalized seizures) and maternal death (up to 70,000 deaths annually worldwide) (8–10).

Risk factors for PET include history of PET, chronic hypertension, pregestational diabetes mellitus, multiple pregnancy, obesity, and antiphospholipid syndrome (11, 12). Women with a history of VTE were also at increased risk of placenta-mediated complications (13). PET pathophysiology is considered to occur in two stages: abnormal placentation in the first

trimester followed by maternal endothelial dysfunction in the second trimester (14). Crucially, hypertensive disorders in pregnancy are associated with a higher risk of arterial cardiovascular diseases (myocardial infarction and ischemic stroke) in later life (15–17). Moreover, PET is characterized by alterations in pro and anticoagulant pathways (18), beyond the physiological hypercoagulable state that occurs in pregnancy (19, 20). This hypercoagulable state may increase venous thromboembolism (VTE) risk (1), a major contributor to maternal morbidity and mortality (21–24). VTE is therefore not only a risk factor but also a consequence of PET (13).

PATHOPHYSIOLOGY OF PREECLAMPSIA

Preeclampsia pathophysiology is considered to occur in two stages in the first trimester and 2nd/3rd trimester (**Figure 1**).

Under normal physiological circumstances, the uteroplacental arteries are invaded by endovascular trophoblasts. The caliber of the spiral arteries widens, which facilitates a progressive increase of uteroplacental blood flow; and the tunic of the artery becomes toneless without maternal vasomotor control (25, 26). In PET, placental histology is characterized by impaired trophoblast invasion and failure of vascular remodeling (27). Although hypotheses have been proposed, underlying mechanisms remain poorly characterized. *Reduced oxygen tension and persistent hypoxia* appear to play an important role (28). With impaired spiral artery remodeling, trophoblast cells are exposed to a chronic intermittent hypoxia and reoxygenation phenomenon (29), leading to oxidative stress. *Oxidative stress* is associated with antioxidant depletion, oxidative damage and an inflammatory response (30, 31). *Immune mechanisms* at the maternal–placental interface may be multifactorial, involving a deficiency of natural killer cells at the beginning of placentation (32), and abnormal allorecognition of paternal HLA-C by the maternal killer Ig-like receptors (33). *Imbalances of angiogenic factors* have also been postulated to play a role, in particular vascular endothelial growth factor (VEGF) which plays a role in vascular remodeling (34). Overall PET heritability is estimated at 55%, with 30–35% maternal and 20% fetal *genetic* contributions to risk (35, 36). Emerging mechanisms hypothesized also to play a pathophysiological role include *epigenetic factors*, including dysregulation at the Fms-like tyrosine kinase 1 locus in the fetal genome (37, 38) or a maternal genome-wide susceptibility locus at rs9478812, which is an intronic region of protein PLEKHGI implicated in blood pressure regulation (39). These myriad pathogenetic processes may also be affected by maternal pre-existing characteristics, environmental and physiological factors (40, 41). It is plausible that a combination of mechanisms interact to initiate early changes that result in the clinical spectrum of PET.

Circulating factors that enter the maternal circulation as a consequence of abnormal placentation interact with endothelial cells, stimulating structural and functional changes that include altered vascular reactivity to vasomodulator substances, activation of the coagulation cascade and an increase in capillary permeability (14, 42, 43). Hypertension develops as a consequence of the maternal response to antiangiogenic factors, vasospasm and agonistic autoantibodies that bind to the angiotensin II type 1 receptor (AT1-AAs) (44). In the maternal preeclamptic circulation, excess levels of antiangiogenic factors including soluble Fms-like tyrosine kinase 1 (sFLT1) and soluble endoglin (sENG), coupled with a decrease in physiological levels of proangiogenic proteins including VEGF and placental growth factor (PlGF) result in an overall antiangiogenic state. These markers are used clinically during PET screening in the first trimester, and later as diagnostic or prognostic biomarkers (42, 45–51). The International Federation of Gynecology and Obstetrics (FIGO) recommend the use of this biomarkers in a first- trimester "screen and prevent" strategy for PET (52). Preeclamptic women exhibit a vasoconstrictive state secondary to the release of vasoactive agents such as prostacyclin, thromboxane A2, nitric oxide, and endothelins. Moreover, PET is also a proinflammatory state secondary to (1) systemic release of apoptotic and necrotic trophoblastic placental debris (53), (2) dysregulation in the balance of IL-10 and proinflammatory cytokines including IL-12 and IL-18 (54), and to (3) elevated complement level (55).

Collectively, these processes lead to systemic vascular and maternal organ dysfunction with long-term cardiovascular (56), cognitive (57) and renal (58) effects.

THROMBOEMBOLIC RISK AND PREECLAMPSIA

Venous thromboembolism (VTE) remains a leading cause of death in pregnancy and in the postpartum period (59). During 2014–2016, VTE was reported to be the top cause of direct maternal death in the United Kingdom and Ireland, occurring in 1.39 (95% CI 0.95–1.96) per 100,000 pregnancies (60). Women diagnosed with PET are reported to have a variable VTE risk, depending on their pregnancy stage (the highest-risk phase being the postpartum period) and PET severity (likely due to balanced alterations in pro and anticoagulant pathways). However, under some circumstances, women may have an up to five-fold increased risk of VTE compared to the normal pregnancy-associated VTE risk reported in the population (10).

Under normal physiological circumstances, pregnancy is characterized by the development of a hypercoagulable state, characterized by an increase in procoagulant factor activity and a down-regulation of endogenous anticoagulant and fibrinolytic pathways. It is postulated that this hypercoagulable state develops to limit the risk of major bleeding associated with labor and birth (61, 62). Although this pregnancy-associated hypercoagulability may reduce the risk of major peripartum bleeding, the shift toward a procoagulant phenotype also confers an increased risk of VTE.

This baseline pregnancy-associated elevated thromboembolic risk is increased in the presence of additional VTE risk factors. These risk factors may pre-date pregnancy, arise during pregnancy or occur peripartum, highlighting the crucial importance of performing a VTE risk assessment at several

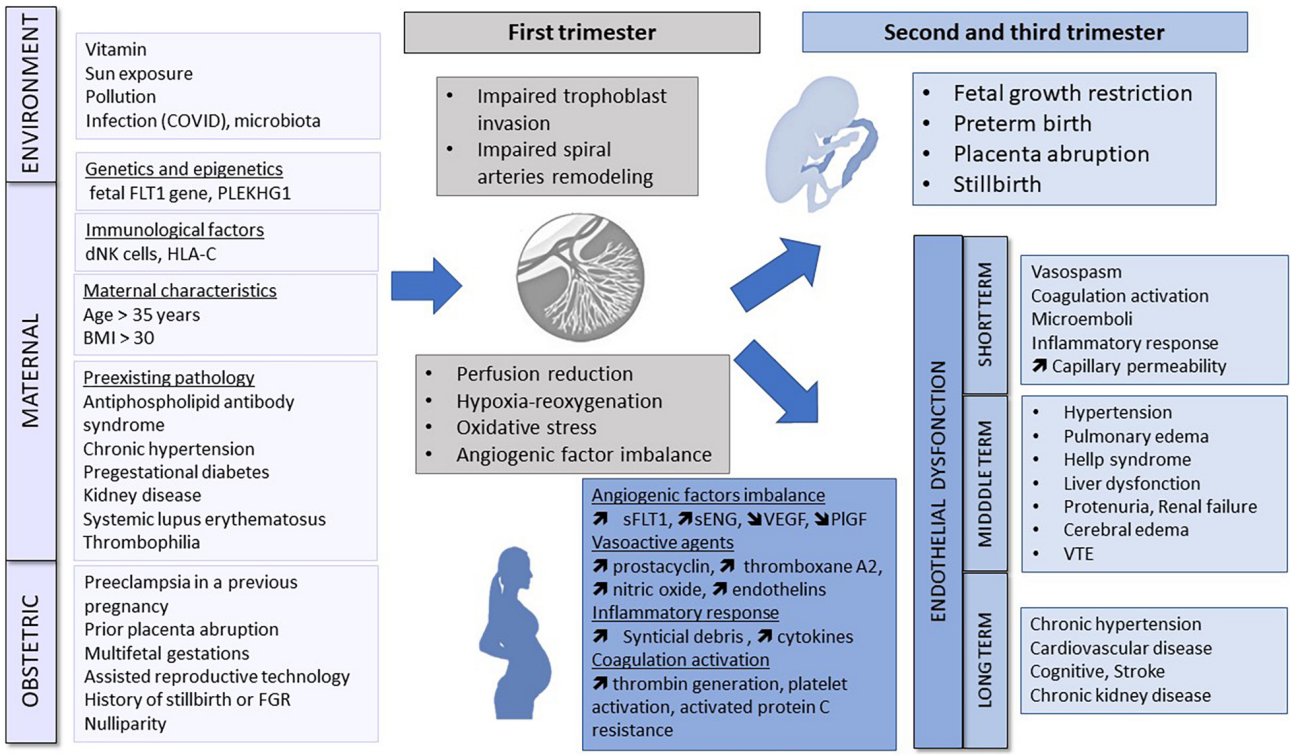

FIGURE 1 | Pathogenesis of pre-eclampsia. Environment, genetic and epigenetic, immunological, maternal and obstetric factors may cause abnormal placentation in the first trimester. Placental ischemia leads to the release of antiangiogenic factors, vasoactive agents, inflammatory response and coagulation activation responsible for endothelial dysfunction and maternal organs dysfunction. FLT1, Fms-like tyrosine kinase; dNK, decidual natural killer; BMI, body mass index; FGR, fetal growth restriction; sFLT1, soluble fms-like tyrosine kinase 1; sENG, soluble endoglin; VEGF, vascular endothelial growth factor; PlGF, placental growth factor; VTE, Venous thromboembolism.

times during pregnancy and at labor and birth. A Norwegian register-based case-control study including 600,000 pregnancies reported a four-fold increased risk of VTE in patients with PET in the postpartum period, however, no association was identified between VTE and PET in antepartum period (63). These results are supported by several studies that reported similar results, assigning greatest VTE risk to the postpartum period (64); mechanisms underlying this observation are not fully characterized (10). Nevertheless PET is still considered as a risk when deciding if a woman needs antenatal thromboprophylaxis in the Royal College of Obstetricians and Gynaecologists (RCOG) guideline (65). An additive effect on the overall postpartum VTE risk was associated with PET complicated by intrauterine growth restriction (IUGR), incurring a seven-fold increased risk (66). In addition, the extent of hemostatic derangement and hypercoagulability appears to be further exacerbated by disease severity and stage; with early-onset PET (EOP) (onset before 34-weeks gestation) having an observed risk of a more severe phenotype (67).

Mechanisms which may underly this prothrombotic phenotype can be attributed to the maternal phase of PET which is characterized by a systemic inflammatory response accompanied by coagulation activation (10). The increased risk of VTE is thought to be multifactorial, involving endothelial dysfunction, coagulation and platelet activation among others (10).

Under normal physiological conditions, the endothelium includes an intact, negatively charged, and non-adhesive glycosaminoglycan layer which acts to inhibit thrombin generation and the adhesion of platelets and leucocytes (68). This endothelial layer expresses a number of anticoagulant proteins such as thrombomodulin (TM), the endothelial protein C receptor (EPCR), and tissue plasminogen activator (tPA) (69). Endothelial dysfunction and damage is extensively reported in PET, and may contribute to impaired activated protein C anticoagulant activity at the endothelial surface and increased exposure of sub-endothelial tissue factor, which is the primary activator of blood coagulation. This, coupled with increased expression of adhesion molecules such as ICAM-1, is postulated to promote the adhesion of inflammatory cells and increased release of endothelial extracellular vesicles (EVs). EVs have also been shown to have a pro-inflammatory and prothrombotic effect activating several pathological signaling pathways on leucocytes, neutrophils, and platelets. Placental-derived factors in PET appear to be key pathological mediators in the process of endothelial damage (67).

Aside from endothelial dysfunction, relative to normal pregnancy, PET is characterized by alterations in circulating

platelet-derived microparticle (MP) and extracellular vesicle (EV) profiles, which may contribute to the PET-associated VTE risk, although a proven mechanistic association has not yet been defined (67).

PREVENTIVE AND CURATIVE TREATMENT FOR PREECLAMPSIA

Preeclampsia prevention and treatment continues to be investigated in ongoing studies. Simpler approaches have explored hygienic and dietetic strategies. Measures including bed rest (70), sodium restriction (71), folic acid (72), antioxidant (combined vitamin C and E therapy) (73), fish oil (74), and garlic (75) have failed to demonstrate a clinical benefit. Studies have suggested that exercise (76), and vitamin D (77) supplementation may reduce the PET, however, these studies are hampered by severe methodological limitations and a beneficial effect for these measures has not been proven. A Cochrane review suggests that in areas with a low calcium intake, high-dose calcium supplementation halves the risk of PET (78). Although there are some limitations to the evidence, the World Health Organization endorses the use of supplemental elemental calcium for pregnant women to reduce the PET risk.

Currently, PET prevention centers around low dose aspirin. In 2019, a Cochrane meta-analysis of 77 trials (40,249 women) determined that the risk of pre-eclampsia was 18% lower with low dose aspirin (95% CI, 12–23%) (79). In the ASPRE trial, aspirin 150 mg daily was administered to pregnant women at high-risk of pre-eclampsia as defined by a screening algorithm consisting of clinical, imaging and blood parameters (80). This trial reported a 62% reduction of the risk of pre-term PET and a 28% reduction in the combination of pre-term and term PET. In the recently published ASPIRIN randomized control trial (RCT), low-dose aspirin was commenced between 6 and 13 + 6 weeks of pregnancy and continued until 36 + 6 weeks. A significant reduction in the incidence of preterm birth before 37 weeks in nulliparous women was observed (RR 0.89, 95% CI, 0.81–0.98), along with reduced birth before 34 weeks in women with hypertensive disorders of pregnancy (RR 0.38, 95% CI, 0.17–0.85). Moreover, perinatal mortality (RR 0.86), fetal loss (RR 0.86), and early preterm birth before 34 weeks (RR 0.75) was also reduced (81).

Optimal timing of initiation and dose remain uncertain (82). Most evidence supports earlier initiation of aspirin prior to 20 weeks' gestation and ideally prior to 16 weeks at (83, 84). Some authors suggest that aspirin administered at bedtime is more efficacious than awakening administration but this concept has not been included in all the recommendations (84–86). The combination of aspirin with low molecular weight heparin (LMWH) is not more efficient than aspirin alone in pregnant women with previous severe preeclampsia diagnosed before 34 weeks of gestation to prevent PET recurrence (87) without maternal or neonatal side effects.

Determining which women should be started on aspirin prophylactically is very challenging. Current evidence shows that no single test predicts pre-eclampsia with sufficient accuracy to be clinically useful (88), and thus signifies the need for improved risk stratification tools.

Preeclampsia without severe features is managed expectantly until 37 weeks, in the presence of severe features in those <34 weeks it may be managed expectantly with birth indicated at any time with deterioration of fetal and maternal status. The pharmacological management of mild to moderate hypertension (systolic <160 and diastolic <110) is not currently recommended by the ACOG, as it does not appear to attenuate disease progression and may increase the risk of fetal growth restriction. As this mild to moderate hypertension may be associated with a 4% risk of stroke, its treatment is still subject to debate (89). Treatment currently revolves around antenatal corticosteroids for fetal lung development in patients <34 weeks, and parenteral magnesium sulfate for fetal neuroprotection and maternal seizure prophylaxis; with timely birth of the fetus and placenta remaining the only definitive treatment of PET (12). The efficacy of magnesium sulfate to prevent seizures in women with preeclampsia with severe features and eclampsia is proven but is more debated in cases of moderate preeclampsia (83, 90, 91).

PREVENTION OF THROMBOEMBOLIC RISK IN PREECLAMPSIA

Despite the fact that pre-eclampsia complicates a significant number of pregnancies and is the leading cause of morbidity and mortality in pregnancy, therapeutic strategies remain poorly characterized (10). The elevated baseline pregnancy-associated VTE risk is further increased by additional maternal, pregnancy and birth characteristics (such as PET) (9, 21, 92–98), highlighting the importance of VTE risk assessment to detect risk factors in early pregnancy, at birth and if risk factors change (65). VTE risk assessment protocols are based on the cumulative presence of multiple risk factors, of which preeclampsia is one component. Guidelines suggest consideration of thromboprophylaxis, particularly in the postnatal period and in the context of additional risk factors such as early onset PET and intrauterine growth retardation, when the overall VTE risk is >1–3% (99). Currently, pharmacological thromboprophylaxis, when it is indicated, is typically achieved through administration of low molecular weight heparin (67). Patient selection is determined based on VTE risk assessment, that should be conducted antepartum and postpartum. However, data supporting the optimal risk threshold at which thromboprophylaxis should be instituted, along with the optimal duration of anticoagulation are lacking, despite how commonly VTE risk factors in the postpartum period arise. As a broad principle, the benefit of pharmacological VTE prophylaxis should outweigh the risk of bleeding and other fetal complications (100). Completing each woman's VTE risk assessment is crucial, particularly in the setting of pre-eclampsia as there is also a proven associated competing hemorrhagic risk. A nationwide cohort study in the Netherlands, reported that 7.4% of woman with pre-eclampsia developed postpartum hemorrhage, compared to 4.2% in those without pre-eclampsia (101). Therefore, determining which patients are more likely to

be affected by bleeding complications is of great importance, and not fully elucidated.

The authors of a 2014 Cochrane review concluded that "there is insufficient evidence on which to base recommendations for thromboprophylaxis during pregnancy (and that) large scale, high-quality randomized trials of currently used interventions are warranted" (102). However, the experience of the PROSPER investigators has demonstrated that conducting RCTs for women with (in this case, postpartum) VTE risk factors can prove extremely challenging (103, 104).

Consequently, to date, guideline recommendations are mainly based on expert opinion rather than high-quality evidence (65, 99, 105–107). This can be extremely challenging for care providers, particularly given the competing risks and challenges of pharmacological thromboprophylaxis, which are relatively common and include bleeding, bruising, skin reactions, pain, and in many jurisdictions, high out-of-pocket costs. Data published to date suggest that women who have a strong thrombophilia or a history of previous VTE are likely to benefit from postpartum thromboprophylaxis. However, guideline recommendations regarding thromboprophylaxis strategies for women with more commonly occurring risk factors such as PET vary widely, with much controversy, in light of uncertainty regarding the optimal strategy. This knowledge gap is currently being addressed by the pilot PARTUM randomized controlled trial (Postpartum Aspirin to Reduce Thromboembolism Undue Morbidity; NCT04153760), a pilot trial that will evaluate the feasibility of conducting a larger multinational trial, in which postpartum women with VTE risk factors will be randomized to low-dose aspirin daily or placebo for 6 weeks.

DISCUSSION

Both PET and VTE remain a leading cause of maternal morbidity and mortality, complicating a significant number of pregnancies (2, 54). Underlying pathophysiological mechanisms modulate the baseline hypercoagulable state of pregnancy, influencing both pro and anticoagulant pathways such that some women exhibit and overall increased procoagulant state relative to normal pregnancy, particularly in the post-partum period (19, 20). Despite this fact, therapeutic strategies remain poorly characterized (8). Urgent research priorities include personalized risk prediction for PET development and PET-associated VTE risk along with continued refinement of PET prevention strategies. Addressing these knowledge gaps has the potential to result in reduced morbidity and mortality for both mothers affected by PET and their infants.

AUTHOR CONTRIBUTIONS

TR-B and OE wrote the sections of the manuscript. FN revised the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Pulmonary Embolism and Pregnancy—Challenges in Diagnostic and Therapeutic Decisions in High-Risk Patients

Lukas Hobohm[1,2]*, *Ioannis T. Farmakis*[2], *Thomas Münzel*[1,3], *Stavros Konstantinides*[2,4] and *Karsten Keller*[1,5]

[1] Department of Cardiology, University Medical Center of the Johannes Gutenberg-University, Mainz, Germany, [2] Center for Thrombosis and Hemostasis (CTH), University Medical Center of the Johannes Gutenberg University, Mainz, Germany, [3] German Center for Cardiovascular Research (DZHK), Partner Site Rhine Main, Mainz, Germany, [4] Department of Cardiology, Democritus University of Thrace, Komotini, Greece, [5] Medical Clinic VII, University Hospital Heidelberg, Heidelberg, Germany

Diagnosis of acute PE in pregnant women with haemodynamic instability is following the general integrated risk-adapted diagnostic algorithm and starts with bedside echocardiography to assess RV function. If RV dysfunction is identified, a prompt and immediate reperfusion without further imaging should be initiated. Although pregnancy is listed as a relative contraindication of systemic thrombolysis, in pregnant women with acute PE and haemodynamic instability thrombolysis must be considered. In those cases, other treatment strategies as surgical embolectomy or catheter-directed low-dose thromboylysis or percutaneous thrombectomy should be taken into consideration as well. A multidisciplinary team with experience of PE management in pregnancy should be consulted to reach consensus on the best treatment approach.

Keywords: pulmonary embolism, pregnancy, thrombolysis, outcome, venous thromboembolism

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***Correspondence:**
Lukas Hobohm
lukas.hobohm@unimedizin-mainz.de

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INTRODUCTION

Venous thromboembolism (VTE) is considered globally as the third most frequent acute cardiovascular syndrome and is an umbrella term for the clinical entities of acute pulmonary embolism (PE) and deep vein thrombosis (DVT) (1). For PE, annual incidence rates range from 39 to 115 per 100,000 population; for DVT, annual incidence rates between 53 and 162 per 100,000 population were reported (2, 3).

Although an overall decreasing trend in PE-related mortality over the past two decades was observed in a recent analysis of vital registration data in Europe, more than 1% of all deaths in women aged 15–50 years are caused by PE (3, 4). VTE occurs and complicates one of 500–3,000 pregnancies and acute PE is still one of the leading causes of maternal death, also in high-income countries with highly developed medical health services (5, 6). Data from the UK and Ireland demonstrated that thrombosis and thromboembolism were the most common causes of direct maternal death in the years 2013–2015 resulting in 1.13 deaths per 100,000 maternities (7). Additionally, based on current epidemiological data from Germany, PE-related deaths in hospitalized women accounted for almost 14% of all maternal deaths (8).

The management of acute PE during pregnancy is challenging since:

- symptoms of PE (particularly dyspnoea) as well as DVT (especially leg swelling) in pregnant women can in part be difficult to distinguish from "physiological" symptoms of pregnancy,
- lower threshold of PE suspicion,
- fewer publications on validation of PE diagnostic algorithms,
- potential concerns regarding the harm of radiations or iodine contrast exposure regarding PE diagnostics and
- lack of direct evidence from interventional trials regarding PE reperfusion treatment, notably systemic thrombolysis, surgical embolectomy or catheter-directed treatment options (9–11).

Initial risk stratification is based on assessment of the patient's vital/haemodynamic parameters. In haemodynamically stable patients, significant progress has been made in the validation of clinical and biochemical criteria, which are generally considered to apply to pregnant patients as well (7). In contrast, haemodynamic instability in acute PE indicates a high risk of early death and, therefore, rapid reperfusion treatment is recommended, which can however be challenging due to a high risk of bleeding complications in pregnant women.

Aim of this review is to provide a framework for the management of pregnancy- associated PE, especially focusing on critically ill patients.

DIAGNOSTIC STRATEGIES IN ALL PATIENTS VS. PREGNANT WOMEN WITH SUSPECTED PE IN THE 2019 ESC GUIDELINES

The diagnostic management of PE in pregnancy is particularly challenging due to the fact that pregnant women often have clinical symptoms, such as shortness of breath or tachycardia, which could point to the suspicion of PE, but can also be present as physiological changes during pregnancy (12). Moreover, overlooking and missing a PE diagnosis could have fatal consequences for mother and child (8), while, on the other hand, thoughtless use of imaging tests could lead to harmful radiation to both mother and fetus (13).

All patients with suspected PE and signs of haemodynamic compromise have a high-risk of death during the first hours and days (14). Thus, initiation of heparin anticoagulation is recommended without delay in patients with high or intermediate clinical probability of PE, while diagnostic workup is in progress (7). The recent published European Society of Cardiology (ESC) guidelines for the diagnosis and management of acute PE underline the importance of a bedside transthoracic echocardiography (TTE) examination in patients with haemodynamic instability. Acute right ventricular (RV) dysfunction can rapidly be detected by TTE if acute PE is the cause of patient's haemodynamic deterioration. If no signs of RV dysfunction exist, other causes of haemodynamic deterioration such as cardiac tamponade, acute coronary syndrome, aortic dissection, acute valvular dysfunction and/or hypovolaemia could be assessed by TTE as well. Additionally, bedside compression ultrasound (CUS) can be used as a further radiation-free diagnostic approach to detect or exclude proximal DVT. If PE is (in)directly confirmed, in all PE patients with haemodynamic instability a rescue thrombolytic treatment is recommended, if no absolute contraindications for systemic thrombolysis are present (7). If these do exist, alternative treatment strategies such as (percutaneous) thrombectomy should be considered. However, there are occasions as haemodynamic collapse with concomitant cardiac arrest and the necessity of cardio-pulmonary resuscitation (CPR) given very limited treatment options. Even if pregnancy is listed as a relative contraindication for systemic thrombolysis, guidelines recommend to consider thrombolysis or surgical embolectomy as the first reperfusion option in these patient group (7, 15). Recent data demonstrated that one third of haemodynamically unstable pregnant women with PE received systemic thrombolytic treatment (8).

In contrast to pregnant women with haemodynamic instability, the diagnostic algorithm for normotensive pregnant women may occasionally vary from that used for patients without pregnancy. A pre-test clinical probability assessment along with high-sensitivity D-dimer testing as well as bilateral lower limb CUS are in the center of the diagnostic algorithm for normotensive pregnant women with suspected PE. If there is a high or intermediate pre-test probability, empirical heparin anticoagulation should be administered before diagnostic imaging is initiated (**Figure 1**). If there are signs/symptoms of DVT, CUS should be performed. If CUS identifies DVT, the diagnosis of PE is—per definition—confirmed indirectly. If no proximal DVT is present or the CUS is inconclusive, chest X-ray followed (in the absence of parenchymal pulmonary changes) by ventilation/perfusion scintigraphy (V/Q scan), or computed tomography pulmonary angiography (CTPA), should be considered to rule out suspected PE (**Figure 1**).

The overall prevalence of confirmed PE among women is low (2 to 7%) and underlines the diagnostic challenges (16–18). Because of this, and due to the weak level of evidence, current guidelines vary in their approach to diagnosing PE in pregnancy (19). However, recently, two prospective studies have investigated a diagnostic algorithm in women with suspected PE during pregnancy (9, 10). A multicentre prospective diagnostic management study validated the combination of pre-test clinical probability assessment based on the Geneva score, high-sensitivity D-dimer testing, CUS and CTPA in a diagnostic strategy for pregnant women with suspected PE (10). With a low or intermediate pre-test clinical probability and a negative D-dimer result, PE was excluded. All other patients underwent lower limb CUS and, if results were negative, CTPA was performed. In total, 395 women were included and among these, PE was diagnosed in 28 (7.1%) and excluded in 367 (92.9%). The rate of symptomatic venous thromboembolic events was 0.0% (95% CI, 0.0 to 1.0%) among untreated pregnant women after exclusion of PE on the basis of negative

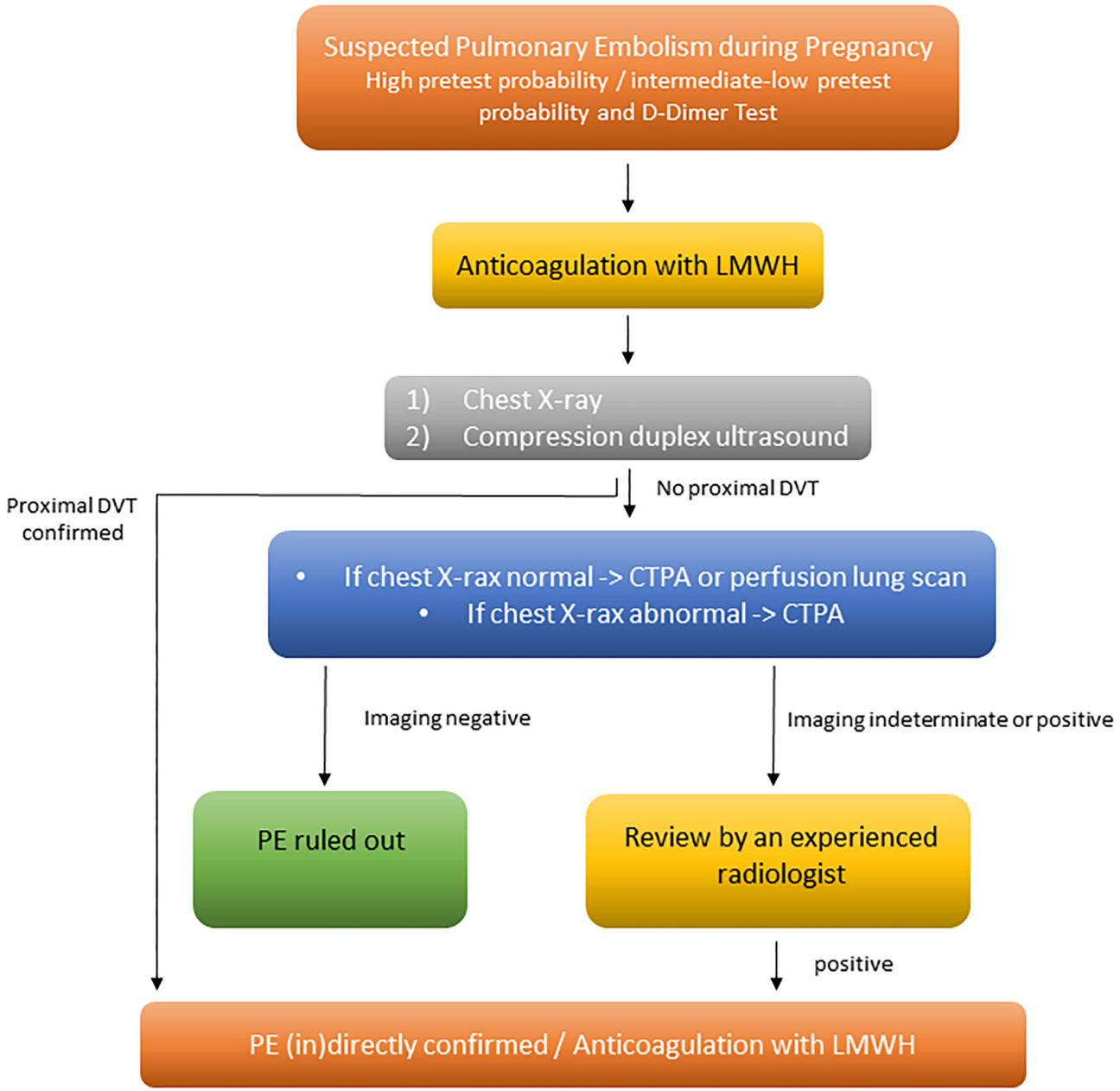

FIGURE 1 | Diagnosis and management of women with suspected acute PE, modified from Konstantinides et al. (7). CTPA, computed tomography pulmonary angiography; DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; PE, pulmonary embolism.

results on the diagnostic work-up. Therefore, this diagnostic algorithm involving sequential assessment of pre-test clinical probability based on the Geneva score, D-dimer measurement, lower limb CUS and CTPA or V/Q scan is able to safely rule out PE in pregnancy (10). Another prospective study involving pregnant women with suspected PE assessed three criteria from the so-called YEARS algorithm (clinical signs of DVT, haemoptysis, and PE as the most likely diagnosis), also taking the D-dimer levels into account. A total of 498 women were included in this study and of these, PE was diagnosed in 20 (4.0%) of the examined patients and excluded in 478 (96%) women.

The current ESC guidelines recommend to perform an X-ray in pregnant women with suspected PE. If the X-ray is normal, V/Q scan should be performed, due to the fact, that V/Q scan is associated with low fetal and maternal radiation exposure. If the X-ray is abnormal, showing, for example, pulmonary infiltrates, then CTPA should be performed directly (7, 17) (**Figure 1**).

DIAGNOSTIC STRATEGIES ACROSS GUIDELINES AND SOCIETIES IN PREGNANT WOMEN WITH SUSPECTED HIGH-RISK PE

International medical society guidelines address new evidence of diagnostic strategies in pregnant women with suspected PE (7, 20–25). In line, to the aforementioned 2019 ESC guidelines, the American Thoracic and Radiology Society (ATS-STR), Society of Thrombosis and Haemostasis (GTH) and Royal College of Obstetricians and Gynaecologists (RCOG) guidelines begin with administering empirical therapeutic anticoagulation, if haemodynamic instability is present, even before any diagnostic work-up is started. The RCOG (24) and ESC (7) guidelines recommend early treatment for all patients suspected of PE with high- or intermediate clinical probability, while diagnostic workup is in progress. GTH (23) and ATS-STR (21) guidelines recommend empirical treatment in patients with a high clinical probability of having PE only (26). The remaining guidelines of Australasian Society of Thrombosis and Haemostasis and the Society of Obstetric Medicine of Australia and New Zealand (ASTH-SOMANZ), European Association of Nuclear Medicine (EANM), and Society of Obstetricians and Gynaecologists of Canada (SOGC) do not mention any empirical treatment (20, 22, 25). The ESC guidelines, as the only one, recommend the use of echocardiography as a first risk assessment strategy in all patients with haemodynamic instability (7).

TREATMENT OF ACUTE PULMONARY EMBOLISM IN PREGNANT WOMEN—HIGH-RISK VS. NOT HIGH-RISK

Especially high-risk PE in pregnancy can be a devastating event with a high case-fatality rate up to 37% (8). In patients with haemodynamic instability, unfractionated heparin (UFH) is used as a first-line medication. If the haemodynamic status aggravates, thrombolytic agents may be necessary to administer. Immediate thrombolytic treatment is recommended unless absolute contraindications for systemic thrombolysis are present (7). Besides thrombolysis, other treatment options of high-risk PE as surgical or percutaneous thrombectomy in should be taken into account. If necessary also extra-corporeal membrane oxygenation (ECMO) can be considered for depressurize the right ventricle and pulmonary circulation (27). Although pregnancy is reported as a relative contraindication of thrombolysis, haemodynamic collapse with concomitant cardiac arrest and the necessity of CPR leave the clinician with limited alternative treatment options (7). Recent data demonstrated that one third of unstable women with PE receive systemic thrombolytic treatment (8). Thrombolysis might be associated with a favorable outcome (94 and 88% of maternal and fetal survival, respectively) (27). However, other data of retrospective nature provide a more ominous prognostic depiction of thrombolysis in the context of high-risk PE. A mortality rate of 42.6% were reported among 67 pregnant women who received thrombolysis (8). Furthermore, in the same study, thrombolysis was sparsely used and regarded as a last resort option; even in the presence of haemodynamic collapse, only 37.8% of patients received thrombolysis.

Bleeding complications are reported as a common adverse event after thrombolytic treatment in 18 to 58% cases during pregnancy and in the post-partum period, respectively (27). Maternal major bleeding was reported in 3 out of 10 cases. Most of them were vaginal or abdominal C-section associated occurring in the early post-partum period. Especially the peripartum phase as well as spinal or epidural anesthesia are associated with high risk of bleeding (7). Therefore, thrombolytic therapy should be used peripartum in a life-threatening context only. The risk for the fetus is low, because a transplacental crossing of fibrinolytic drugs is very unlikely due to the fact that their components are larger than 1,000 Dalton (28, 29). However, the lack of prospectively designed controlled studies precludes conclusions regarding the efficacy and safety profile of thrombolysis in high-risk pregnancy-associated PE. Thus, causalities of fatal maternal and fetal outcomes cannot be deduced to the administration of the thrombolytic agent only.

In the case of absolute contraindications, alternative treatment strategies such as surgical embolectomy or percutaneous low-dose thrombolysis (CDT) or thrombectomy should be considered (30) (**Table 1**). Results of several studies confirm that CDT, a novel treatment modality for high- and intermediate high-risk PE, is associated with a favorable outcome regarding bleeding complications in comparison to systemic thrombolysis in patients with PE (31). However, randomized studies using standardized clinical outcomes such as mortality and recurrent VTE are missing. In order to close this gap, CDT is currently being evaluated in a phase III clinical trial (NCT04790370). However, pregnancy constitutes an exclusion criterion of the trial and only few cases of pregnant women treated with CDT have been published in literature yet (27, 45, 46). Surgical embolectomy or percutaneous thrombectomy are reasonable treatment options, when needed in the immediate postpartum period, to avoid the bleeding risks of thrombolysis. However, these methods are limited in their availability and are used as last life-saving therapy option only (27). However, if reperfusion treatment is not effective or not available in the setting of haemodynamic instability, data indicate that the temporary use of mechanical circulatory support via ECMO as a bridging therapy might improve outcomes until pharmacological or mechanical thrombolysis or embolectomy is applied (47). In patients with acute PE and pregnancy ECMO has not been widely used. In a systematic review of 21 pregnant women with PE and ECMO support, the maternal survival rate was 76%, while the fetal survival rate was 63% (48).

An additional treatment option for pregnant women with absolute contraindications for anticoagulation could be the placement of an inferior vena cava (IVC) filter (7). Data on this preventive approach is limited. A systematic review including 124 pregnant women with DVT, in whom an IVC filter was inserted, were analyzed. No fatal PE occurred after filter placement and retrieval complication rates appeared comparable to those in the general population (49). However, even if

TABLE 1 | Therapeutic strategies for catheter-directed treatment adapted from Hobohm et al. (31).

Technique	Description	Device (company)	Evidence
Catheter-directed thrombolysis	The catheter is inserted directly into the pulmonary artery and the thrombolytic agent released close to the location of the thrombus occlusion.	Cragg-McNamara® (Ev3 Endovascular); UniFuse® (AngioDynamics): Multi-sidehole pigtail catheter with 4–5 French	Observational studies and one randomized trial (31–33)
Ultrasound-assisted catheter-directed thrombolysis	A second catheter lumen contains low-energy ultrasound transducers which should loosen the clot structure to facilitate thrombolytic penetration.	EkoSonic® (BTG) 5.2 French device	Prospective, single group studies and prospective randomized trials (34–36)
Catheter-directed embolectomy by fragmentation	The pigtail is inserted into the distal part of the thrombus and rotating while retracting at the proximal part.	Pigtail 5 French fragmentation plus thrombectomy with Aspirex® 8/10 French	Observational studies (37, 38)
Catheter-directed embolectomy, rheolytic	High-pressure jet streams disrupt the thrombus, which is then trapped in a low-pressure zone and aspirated in the catheter.	AngioJet® (Boston Scientifics) 6 French catheter	Observational studies (39, 40)
Catheter-directed embolectomy by suction	The thrombus is aspirated via a pump, reintroducing excess aspirated blood via a veno-venous bypass system or with mechanical clot engagement.	AngioVac® (AngioDynamics) suction cannula with 26 French access; Indigo (Penumbra) 8 French vacuum-assisted aspiration system	Observational studies (41, 42)
Catheter-directed embolectomy by entrapment	Self-expanding nitinol disks are placed into the thrombus, ensnare it by expanding, and are retracted into the catheter.	FlowTriever® (Inari) 20 French device	Observational studies and one single-arm phase II trial (43, 44)

the authors concluded that IVC filters can be used effectively in pregnancy to prevent PE, there is currently not enough evidence to suggest that IVC filters should be used routinely (50–52). In exceptional cases with absolute contraindications for anticoagulation, or if recurrent PE is present despite adequate therapeutic anticoagulation, IVC should be taken into consideration (7). Overall, the evidence for advanced treatment options in high-risk PE during pregnancy is poor. A prospective international registry investigating the effectiveness and safety of advanced methods in massive pregnancy-related PE is currently underway (MAPP registry endorsed by the International Society on Thrombosis and Haemostasis) (53). Due to the diagnostic and treatment complexity, a multidisciplinary team (with experience in PE management in pregnancy) should be consulted to evaluate the best and treatment approach (7).

Anticoagulation remains the mainstay of treatment in pregnancy and must be administered to all patients with high-risk suspicion of PE and confirmed PE (7). Since heparins do not pass the placenta and are not associated with teratogen effects on the fetus, they can be safely administered in pregnant women. Low molecular weight heparins (LMWH) are the agents of choice, because they have a predictable pharmacodynamic profile (54). In contrast, vitamin K antagonists (VKAs) can cause teratogenicity and fetal bleeding during the first and the third trimester and should therefore not used during those periods (55). Due to the insufficient safety data, direct oral anticoagulants (DOACs) are also contraindicated during pregnancy (56, 57). UFH may be associated with heparin-induced thrombocytopenia, resulting in restriction of recommendation regarding their use. However, in pregnant women heparin-induced thrombocytopenia is extremely rare ($<0.1\%$) (58). UFH is used predominantly for patients with severe renal impairment, extreme body weight, high-risk PE, and PE occurring very close to delivery (59). Dosing strategies of LMWH generally follow these of the non-pregnant population, as there is a lack of specific randomized data (60). Although evidence suggest that most anticoagulated patients lie in a sub-therapeutic range, anti-Xa level monitoring has not be shown to be beneficial. LMWH use is currently recommend only for patients with severe renal impairment and extremes of body weight (61–63). However, therapeutic use of LMWH or UFH has a 3 and 2% incidence risk for antepartum and postpartum hemorrhagic complications, respectively (64). Approaching delivery, LMWH is usually converted to a continuous UFH infusion $\geq$36 h prior to delivery, especially if neuraxial anesthesia is planned. Finally, UFH should be paused 4–6 h prior to delivery. The timeframe of the post-partum re-initiation of LMWH should be decided by a multidisciplinary team and depends on the mode of delivery as well as the thrombotic and bleeding risk profile of the patient. Importantly, re-initiation of LMWH should not start 4 h after the epidural catheter has been removed (7). If there is an allergy or adverse response to LMWH, Fondaparinux is given as an alternative drug, although solid data are lacking and minor transplacental passage has been demonstrated (65).

CONCLUSION

Diagnosis of acute PE in pregnant women with haemodynamic instability

- is following the general integrated risk-adapted diagnostic PE algorithm PE and

- starts with bedside echocardiography to assess RV function. If RV dysfunction is identified, a prompt and immediate reperfusion without further imaging should be initiated.

Although pregnancy is listed as a relative contraindication of systemic thrombolysis, in pregnant women with acute PE and haemodynamic instability

- systemic thrombolysis must be considered and
- other treatment strategies as surgical embolectomy or catheter-directed low-dose thromboylysis or percutaneous thrombectomy should be taken into consideration as well.

A multidisciplinary team with experience of PE management in pregnancy should be consulted to reach consensus on the best treatment approach.

AUTHOR CONTRIBUTIONS

All authors: conception and design of the study, data collection, analysis of the data, interpretation of data, drafting of the manuscript and revising of the manuscript critically for important intellectual content, and final approval of the manuscript submitted.

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REVIEW
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Diagnostic Management of Pregnant Women With Suspected Pulmonary Embolism

Helia Robert-Ebadi[1]*, *Grégoire Le Gal*[2,3] *and Marc Righini*[1]

[1] *Division of Angiology and Hemostasis, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland,* [2] *Department of Medicine, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON, Canada,* [3] *EA3878 University of Brest, Brest, France*

Pulmonary embolism (PE) is one of the most common causes of severe morbidity and mortality during pregnancy. PE diagnosis during pregnancy remains a true challenge for all physicians, as many of the symptoms and signs associated with PE are often reported during physiological pregnancy. The fear of missing a PE during pregnancy leads a low threshold of suspicion, hence to a low prevalence of confirmed PE among pregnant women with suspected PE. This means that most pregnant women with suspected PE do not have the disease. Until recently, international guidelines suggested thoracic imaging in all pregnant women with suspected PE. Two recent prospective management outcome studies based on clinical probability assessment, D-dimer measurement, venous compression ultrasonography of the lower limbs (CUS) and computed tomography pulmonary angiography (CTPA) proved the safety of such strategies, with a very low failure rate. For the first time, these studies also demonstrated that the association of a clinical prediction rule and D-dimer measurement allowed a safe exclusion of PE in a significant proportion of pregnant women, without the need for radiating imaging tests. These two prospective studies pave the way to further improvements in the diagnostic strategies. Indeed, both specific clinical prediction rules and possibly D-dimer cutoffs adapted to pregnant women could help to further reduce the proportion of patients needing thoracic imaging. As an imaging test will still ultimately be necessary in a significant proportion of women, further technical advances in CT scans protocols could reduce the radiation dose to both the fetus and the mother, an important step to reassure clinicians. Finally, educational efforts should be encouraged in the future to pass the challenge of implementing these validated diagnostic strategies in everyday clinical practice.

Keywords: pulmonary embolism, diagnostic strategy, D-dimer, clinical probability, pregnancy, computed tomography pulmonary angiography, ventilation-perfusion lung scan

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Eli Westerlund,
Karolinska Institutet, Sweden
Nina Olausson,
Danderyd University Hospital, Sweden

***Correspondence:**
Helia Robert-Ebadi
helia.robert-ebadi@hcuge.ch

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INTRODUCTION

Pregnancy represents a period at risk of venous thromboembolism (VTE) in women of child bearing age who are otherwise at low risk of developing VTE. The overall incidence of VTE is estimated at 1/1'000 pregnancies, and in western countries, pulmonary embolism (PE) remains a leading cause of maternal mortality (1, 2). The risk is highest during the third trimester and the 6 to 12 weeks following delivery (3).

Clinical Suspicion of PE During Pregnancy

PE diagnosis during pregnancy remains a true challenge for physicians, as many of the symptoms and signs frequently reported during physiological pregnancy–such as shortness of breath or tachypnea–may also suggest the diagnosis of PE (4). This is also true for symptoms and signs suggestive of the presence of a deep vein thrombosis (DVT). Indeed, lower limb pain and/or edema is often reported by pregnant women, especially during the second half of pregnancy (5). It is therefore particularly difficult to set a threshold between what can be considered physiological and what should raise the suspicion of VTE and lead to further investigations.

Prevalence of Confirmed PE Among Pregnant Women With Suspected PE

Although VTE risk is increased 7 to 10-fold during pregnancy compared to age-matched controls, the absolute incidence remains low (around 1/1'000) (6). Nevertheless, the fear of missing a PE during pregnancy leads to a low threshold to suspect the disease. This results in a very low prevalence of confirmed events among suspected patients even in the setting of clinical trials. Compared to the PE prevalence observed in diagnostic trials outside pregnancy (10–20% depending on geographic location) (7, 8), the reported PE prevalence in pregnant women is much lower at around 2–7% (4, 9, 10). In other words, the vast majority of pregnant women in whom PE is suspected do not have PE. Therefore, the main focus of diagnostic strategies is–even more than outside pregnancy–to *rule out* the diagnosis. This is an important information to bear in mind when considering the use of radiating imaging tests, and highlights the necessity of finding alternative strategies to minimize the proportion of pregnant women who need chest imaging.

DIAGNOSTIC APPROACH TO PREGNANT WOMEN WITH SUSPECTED PULMONARY EMBOLISM

Historically, all pregnant women with suspected PE underwent a thoracic imaging test. In the 1990's, ventilation-perfusion scintigraphy (V/Q scan) was assessed in the PIOPED trial in the general population of patients with suspected PE (11), and perfusion only scans were rapidly adopted in clinical practice in pregnant women, albeit without previous scientific validation. Interestingly, in a study assessing the appropriateness of diagnostic management of patients with suspected PE, pregnancy was by far the strongest predictor of inappropriate management: 69% of pregnant women with suspected PE were indeed not appropriately managed (12). The lack of solid prospective data specific to this patient population is highly likely to have contributed to this observation published in 2006 (12).

Since then, two prospective management outcome studies have assessed two different strategies, and were published in 2018 (9) and 2019 (10). These two studies represent the first prospective scientific validation of PE diagnostic strategies during pregnancy and will be described in detail below.

Is There Any Clinical Pre-test Probability Assessment Tool I Could Use During Pregnancy?

In patients with suspected PE, the assessment of clinical pre-test probability (PTP) is the first step of all current diagnostic management strategies and is strongly encouraged in international guidelines (13, 14). It allows identifying a subgroup of patients with a low prevalence of the disease in whom a negative D-dimer safely rules out PE without imaging. It is also sometimes used for the final diagnostic interpretation of V/Q scan results.

Available clinical decision rules (CDRs) have not been derived or validated in pregnant women (15). This has been one of the reasons brought by some physicians for not using D-dimer in this setting. The CT-PE pregnancy and ARTEMIS studies assessed diagnostic strategies in the specific setting of pregnant women with suspected PE (9, 10). These studies used two different PTP assessment tools–the Geneva score and a pregnancy-adapted YEARS model- that had not been previously derived nor validated in a pregnant population. Nevertheless, these two CDRs both proved efficient and accurate in integrated diagnostic algorithms (see **Figure 1**) (9, 10).

Further steps were taken in the validation process of pregnancy-adapted CDRs with the external validation of the YEARS model in the CT-PE pregnancy population, confirming the safety of this model in a second cohort of patients (16). Moreover, a novel PTP assessment tool-the Pregnancy-Adapted Geneva Score (PAG score)–was recently developed. The PAG score contains only *objective* items that are all relevant to pregnant women (see **Table 1**) (17). It allows classifying pregnant women with suspected PE in three categories of PTP that correspond to increasing prevalence of the disease (see **Table 1**). However, before advocating its large scale use in clinical practice, the PAG score needs to be prospectively validated.

Should I Use D-Dimer to Exclude PE During Pregnancy?

In clinical practice, D-dimer testing tends to be more often skipped in pregnant women than in the general population because of the knowledge of gradually increasing D-dimer levels during pregnancy. Physicians therefore tend to consider D-dimer as "useless" in this setting. Another reason which likely contributes to a reluctance to use D-dimer during pregnancy is, as said above, the lack of clinical PTP assessment scores specifically developed and validated in pregnant women. Finally, the safety of excluding PE by a negative D-dimer during pregnancy has been challenged by some authors (18).

Nevertheless, the safety of a negative D-dimer associated with a non-high/unlikely PTP to exclude PE without imaging is widely accepted outside pregnancy (7, 8, 19). There is no biological rationale which could support the hypothesis of a lower sensitivity of D-dimer during pregnancy. The CT-PE pregnancy and ARTEMIS studies have both confirmed the safety of excluding PE during pregnancy by a negative D-dimer test in stepwise diagnostic algorithms (see **Figure 1**).

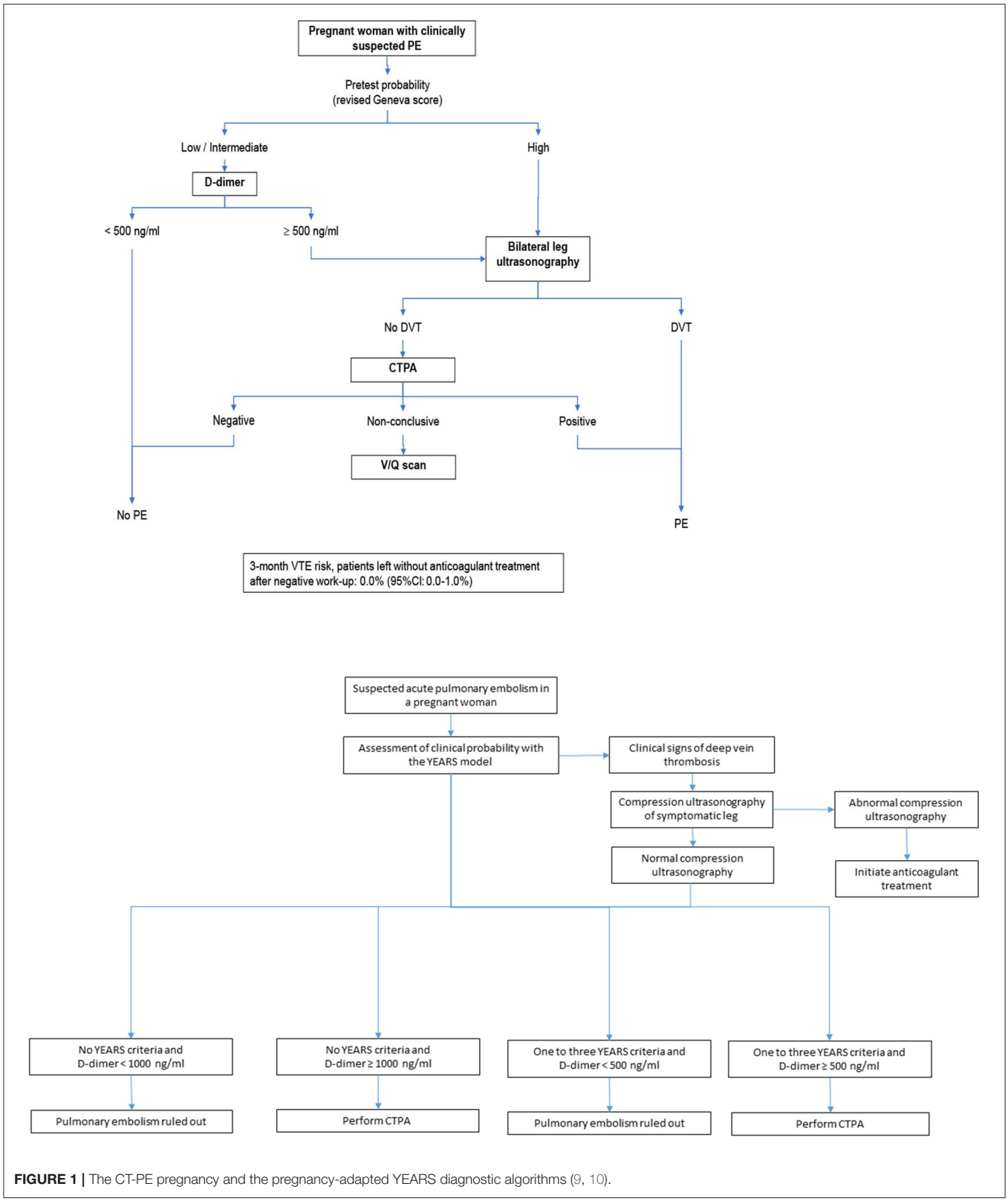

FIGURE 1 | The CT-PE pregnancy and the pregnancy-adapted YEARS diagnostic algorithms (9, 10).

The number of patients remains limited in these studies and needs to be extended and enriched by data from future prospective trials. Nonetheless, a recent meta-analysis reported a high negative predictive value of D-dimer to exclude PE during pregnancy. The pooled estimate values were indeed 99.5% for sensitivity (95% CI 95.0–100.0%)

TABLE 1 | The Pregnancy-Adapted Geneva score for assessment of pre-test clinical probability of PE in pregnant women (17).

The Pregnancy-Adapted Geneva score			
Item			**Points**
Age 40 years and older			+1
Surgery (under GA) or lower limb fracture in past month			+2
Previous DVT or PE			+3
Unilateral lower limb pain			+3
Haemoptysis			+2
Pain on lower limb palpation and unilateral oedema			+4
Heart rate > 110 bpm			+5
Maximal point number			20
Points	**PTP category**	**PE prevalence in development cohort**	**95% CI**
0–1	Low	2.3%	1.0–4.9 %
2–6	Intermediate	11.6%	6.9–18.9%
≥7	High	61.5%	35.5–82.2%

and 100% for negative predictive value (95% CI 99.19–100.0%) (20).

While awaiting additional data, the clinician should bear in mind that the percentage of pregnant women in whom PE diagnosis can be safely excluded by a non-high PTP and negative D-dimer without any additional tests (CUS or thoracic imaging) was of 12% in the CT-PE-pregnancy study, which corresponds to a number of patients needed to test to exclude one PE of 8.3 (9). In a setting where minimizing radiating tests is a central concern, this efficiency is not negligible. Avoiding radiation exposure by a simple blood test in 1 out of 8 pregnant women with suspected PE is already highly appealing. Of note, although the risk of developing PE is highest during the post-partum and the third trimester, the chances of obtaining a negative D-dimer test decreases with advancing pregnancy. In the CT-PE pregnancy study, the proportion of negative D-dimer results was 25% during the first trimester, 11% during the second trimester, and 4% during the third trimester.

The ARTEMIS study also showed a high efficiency of the diagnostic algorithm to avoid thoracic imaging (39%). However, the non-invasive strategy tested in this study was not solely based on PTP and D-dimer but included the pre-exclusion of DVT by lower limb CUS in patients with lower limb symptoms, and so represented a more complex selection of "low-risk" women in whom a higher D-dimer cutoff was used to exclude PE (see **Figure 1**) (10). When pooling all the available evidence to address this question, the recent meta-analysis mentioned above demonstrated an overall efficiency of 34% of D-dimer to safely exclude PE (95% CI 15.9–55.23%) (20). Giving the chance to a pregnant woman with suspected PE to avoid a radiating test should therefore not be neglected, and in spite of the controversies in international guidelines (21), we believe that the use of D-dimer in this setting should be strongly encouraged.

Should I Refer My Patient for Lower Limb Compression Ultrasound Before Chest Imaging?

The information required to answer this question is provided by the CT-PE pregnancy and the ARTEMIS studies. Bilateral lower limb compression ultrasound (CUS) was indeed part of the diagnostic strategies of both studies (see **Figure 1**). In the CT-PE pregnancy study, CUS was performed in 75% of the overall population, and proximal DVT was diagnosed in 2% of patients without leg symptoms and 9% of patients with leg symptoms (9). In the ARTEMIS study, CUS was performed in 88% of the overall population, and DVT was confirmed in 1% of patients without leg symptoms and 7% of patients with leg symptoms (10). CUS seems thus mainly useful in pregnant women with lower limb symptoms (lower limb pain and or edema). Nevertheless, focusing again on the need to maximize the number of avoidable radiating tests rather than on cost-effectiveness, the yield of 1–2% avoided radiating tests provided by screening pregnant women with CUS is considered worthwhile by some. Depending on the structure of medical care facilities, obtaining a CUS can however be more challenging that obtaining a CTPA and represents an obstacle to the implementation of a sequential testing strategy (15). Another potential limitation is the difficulty to assess iliac veins and diagnose isolated iliac DVT, which is however mainly a problem in pregnant women with suspected DVT with no concomitant PE suspicion. Interestingly, international guidelines currently recommend bilateral CUS in pregnant women with suspected PE in whom PE diagnosis could not be excluded by the combination of PTP and D-dimer, in whom further testing is needed, before pursuing to chest imaging (13).

What Chest Imaging Modality Should I Choose in Pregnant Women and Why?

In spite of all the efforts described above to minimize chest imaging, a significant proportion of pregnant women with suspected PE (around 2/3) will ultimately need thoracic imaging in their diagnostic management (20). Radiation exposure to the mother and to the fetus are both matters of concern (22). CTPA and V/Q scan are the two chest imaging modalities studied on a large scale basis outside pregnancy. Due to its high diagnostic accuracy and accessibility, CTPA has become the new "gold standard" for the diagnosis of PE and is the most widely used test in clinical practice (23). Another advantage of CTPA is the possibility to identify an alternative diagnosis such as aortic dissection, pneumonia, pneumothorax, which can be missed by V/Q scan.

This has even led to major concerns about over-testing and over-diagnosis, which are beyond the scope of the present paper. In pregnant women, radiation exposure and the rate of non-diagnostic tests remain the two central matters of concern.

A recent meta-analysis comparing all the available data on these two imaging techniques in pregnant women could not conclude on the relative risk of radiation of CTPA vs. V/Q scan due to lack of homogeneity in the calculation methods and the scan protocols used (22). The important message conveyed by this work is however that all reported radiation measurements for both tests were clearly below the commonly accepted harmful threshold of 100 mGy, in spite of the inclusion of older studies preceding the implementation of adapted imaging protocols in pregnant women (22). Moreover, as previously stated by scientific societies and experts, the risks associated with either test is by far lower than the potential risks of inappropriate diagnostic management leading to a missed diagnosis (with the risk of death) or to an unjustified anticoagulant treatment based on a "clinical" diagnosis (with the risk of bleeding and the long term consequences on delivery and subsequent pregnancies of a unduly confirmed PE) (24, 25). Regarding the proportion of inconclusive tests, the pooled rates of non-diagnostic results were similar between CTPA (14%) and V/Q scan (12%), but the range of reported rates was very broad (0–57% for CTPA and 1–40% for V/Q scan) across the included studies (22).

The technical evolution of CTPA has considerably decreased radiation exposure, and pregnancy-adapted CTPA protocols include a reduced anatomical coverage of the scan and reduced kilovoltage. These specific protocols also include a high-concentration, high-volume and high-rate of injection of contrast media followed by saline flush as well as shallow inspiration breath-hold to avoid a Valsalva manoeuver, in order to optimize arterial opacification and avoid non-diagnostic tests (26). The technical evolution of nuclear medicine imaging modalities, including tomographic lung scintigraphy (SPECT) may also be promising, albeit not yet supported by prospective management outcome data. A prospective study comparing SPECT to CTPA and V/Q scan in non-pregnant patients is currently ongoing (NCT02983760), and SPECT may possibly be a promising technique in the future for pregnant women.

In spite of the optimization of CTPA protocols for pregnant women, the historical belief of significantly higher radiation doses to the mother's breast tissue of CTPA compared to V/Q scan still influences some physicians in their choice toward scintigraphy. Because of a very low likelihood of pulmonary comorbidity in this population, a two-step protocol is used in some centers: a perfusion scan is performed; PE is excluded in case of a normal perfusion scan. Ventilation sequences are only performed in case of an abnormal perfusion pattern to seek for a mismatch suggestive of PE. It should be noted that such a stepwise strategy has however not been validated in prospective trials. Caution is required in particular in the positive diagnosis of PE based on a perfusion scan alone, without having objectively confirmed that the perfusion abnormality is not associated with any parenchymal/ventilation abnormality.

The 2018 American Society of Hematology (ASH) guidelines for the diagnosis of VTE are highly driven by the willingness to avoid radiation even in the general population, and thus advocate for V/Q scan for patients likely to have a diagnostic scan and in centers where V/Q scans are available with expertise to interpret the results in a timely manner (14). The latest European Society of Cardiology (ESC) 2019 Guidelines provide specific recommendations for pregnant women. In terms of imaging test, their recommendation states "perfusion scintigraphy or CTPA with a low-radiation dose protocol" with a Class IIa, level C recommendation (13).

CURRENT DIAGNOSTIC ALGORITHMS

As said before, to date, only two prospective management outcome studies have been published in pregnant women with suspected PE, reflecting the challenges of leading clinical trials in this setting.

CT-PE Pregnancy Algorithm

The CT-PE pregnancy study published in 2018 (9) included 395 women with suspected PE and applied a diagnostic algorithm based on the sequential assessment of clinical PTP, D-dimer with the standard 500 ng/mL cutoff, lower limb venous CUS regardless of the presence of leg symptoms or signs, and CTPA as the first-line chest imaging technique (see **Figure 1**). PE prevalence was 7%, the failure rate of the strategy was 0.0% (95% CI 0.0–1.0%) and the percentage of patients managed without thoracic imaging 12%.

ARTEMIS Algorithm

The ARTEMIS study published in 2019 (10) included 498 women with suspected PE and applied an adapted YEARS model (see **Figure 1**). PE prevalence was 4%, the failure rate of the strategy was 0.21% (95% CI 0.04–1.2%) and the percentage of patients managed without thoracic imaging 39%.

The detailed description of the respective strengths and limitations of these studies have been described elsewhere and are beyond the scope of this paper (15). The important message here is that such prospective outcome studies are gradually filling the knowledge gap in the optimal diagnostic management of pregnant women with suspected PE, and will certainly contribute to increase the appropriateness of these patient's management in the future.

REMAINING CONTROVERSIES

Despite the recently published prospective data and evidence, controversies regarding the optimal diagnostic strategy for PE in pregnant women are still alive and the topic remains highly debated. As an example, the CT-PE pregnancy and ARTEMIS models have been challenged in an analysis performed on a UK cohort of 219 patients (DiPEP study) which includes pregnant women having PE diagnosed primarily by imaging. The authors concluded that both strategies were not safe (18). However, the original DiPEP study this retrospective analysis was performed on, suffered from many limitations. In particular, the DiPEP cohort was not a purely prospective cohort, different D-dimer tests with variable cutoffs were used, and there was no standardized diagnostic algorithm (27). The reported inferences from the recent analysis performed on this partly

retrospective cohort are probably not as robust as the prospective management outcome trials, and the message advocating against D-dimer use based on this data should therefore be interpreted with caution.

Regarding the imaging test of choice, the major concern surrounding the use of any diagnostic test is the risk of maternal and fetal radiation exposure. While fetal exposure seems to be in the same range with both tests, CTPA is more radiating for the mother's breasts. Although no increased risk of early-onset breast cancer was observed in a large population cohort study with a median follow-up of almost 6 years after CTPA and of 7.3 years after V/Q scan, these findings might be considered as insufficiently reassuring, due to the limited length of follow-up (28). Also, the cumulative effect of repeated chest imaging is not well known. Importantly, the previously reported 12% rate of inconclusive CTPAs was not confirmed in the CT-PE pregnancy and in the ARTEMIS studies (reported rates of 7 and 0%, respectively) (9, 15), so that repeat chest imaging during the same diagnostic workup remains exceptional.

Despite these limitations, the risks associated with radiation exposure of both CTPA and V/Q scan are lower than the risk of missing a PE or of exposing unduly a pregnant woman to an anticoagulant treatment. As emergency access to V/Q scan is becoming difficult even in University Hospitals, CTPA will likely become the most used diagnostic test for most pregnant women with suspected PE who could not have the diagnosis excluded by PTP and D-dimer. Noteworthy, the radiation dose to the maternal breast with modern CTPA techniques is steadily decreasing and will probably reassure prescribing physicians in the near future. Ongoing prospective studies on this topic include the OPTICA study (NCT 04179487) whose aim is to assess the usefulness and safety of a low-dose CTPA protocol in pregnant patients with suspected PE (29).

In conclusion, despite the important recent advances in the field, there is room for further refinements and improvements of diagnostic strategies for suspected PE in pregnant women. Educational efforts should be strongly encouraged to pass the challenge of implementing validated diagnostic strategies in everyday clinical practice.

AUTHOR CONTRIBUTIONS

HR-E drafted the paper. GL and MR revised it critically for important intellectual content. All authors provided final approval of the version to be published.

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Venous Thromboembolism Risk Score and Pregnancy

Tiphaine Raia-Barjat[1,2]*, *Osasere Edebiri*[3] and *Céline Chauleur*[1,2]

[1] Department of Gynecology and Obstetrics, Centre Hospitalier Universitaire de Saint-Étienne, Saint-Étienne, France, [2] INSERM U1059 SAINBIOSE, Université Jean Monnet, Saint-Étienne, France, [3] Departments of Haematology, Mater Misericordiae University Hospital and Rotunda Hospital, Dublin, Ireland

Venous thromboembolism (VTE) is a major contributor to maternal morbidity and mortality worldwide. Pregnancy is associated with the development of a baseline hypercoagulable state. The two strongest risk factors for pregnancy-associated VTE are previous VTE and/or high risk thrombophilia. The others risk factors for VTE during pregnancy are well known such as maternal, pregnancy and delivery characteristics. Considering the variation in recommendation in guidelines and low-quality evidence on the prevention, diagnosis and treatment, practice differs between countries and clinical institutions. Some authors developed risk scores, enabling individualized estimation of thrombotic risk during pregnancy, and permitting implementation of a risk-adapted strategy for thromboprophylaxis during pregnancy and postpartum. This review describes the existing VTE risk scores during the antenatal and postnatal period. The important message beyond the score used is that all women should undergo VTE risk factor assessment. The use of a Computerized Clinical Decision Support System for VTE risk assessment should be explored in obstetrics.

Keywords: venous thromboembolism, pregnancy, risk score, guidelines, thrombosis

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INSERM CIC1408, France

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***Correspondence:**
Tiphaine Raia-Barjat
tiphaine.barjat@chu-st-etienne.fr

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INTRODUCTION

Pregnancy is a physiological hypercoagulable state (1, 2), such that venous thromboembolism (VTE) is a major contributor to maternal morbidity and mortality accounting for 13.8% of maternal deaths in developed regions and 3.2% worldwide (3). The absolute incidence of VTE in pregnancy is 1 or 2 cases per 1,000 pregnancies, with 1 death per 100 000 pregnancies. Pulmonary embolism (PE) is one of the three leading causes of maternal death (4, 5). The risk of VTE was 5-fold increased during pregnancy and 60-fold increased during the first 3 months after delivery compared with non-pregnant women (4, 6). The risk factors for VTE during pregnancy are well-known such as maternal characteristics (age, BMI, thrombophilia, tobacco, co-morbidities...), pregnancy characteristics (twin pregnancy, preeclampsia…) and delivery characteristics (cesarean section, hemorrhage...) (7, 8). Pre-existing and acquired factors throughout pregnancy mean that the risk is individual and evolving over time. The cumulative weight of these risk factors made it possible to establish prediction scores for the occurrence of VTE during the antenatal or postnatal period. These scores make it possible to initiate thromboembolic prophylaxis and prevent the occurrence of VTE. However, there are many scores and recommendations on the subject which can be confusing for clinicians. Care was considered non-optimal in 59% of deaths caused by VTE complication and the rate of preventability was 34.8% (9). The important message beyond the score used is that all women should undergo VTE risk factor assessment continuously before, during and after pregnancy (10, 11).

Thromboembolic Risk Change by Pregnancy State

The mechanisms of venous thrombosis were described by Virchow, and describe three etiopathogenic components: venous stasis, hypercoagulability and tissue damage. These three mechanisms are often concomitant, the role of each being more or less prevalent (12). Pregnant women have all components of Virchow's triad (13). Venous stasis is secondary to physiological vasodilatation and compression of the vena cava and left common iliac by the gravid uterus (14). Pregnancy is a physiological hypercoagulable state secondary to the increase of clotting factor concentrations, inhibition of fibrinolysis and a reduction in anticoagulant agent levels (15). Finally, tissue damage occurs with endothelial damage to the pelvic vessels during delivery.

Thrombotic events occur throughout pregnancy, with half occurring in the antenatal period and half in the postnatal period (8). VTEs correspond to deep vein thrombosis 3 times higher than pulmonary embolism in pregnancy (4). Two-thirds of deep vein thrombosis occur in the antenatal period while two-thirds of pulmonary embolism occur in the postnatal period (16). Approximately 80% of postpartum thromboembolic events occur in the first 3 weeks after delivery (8, 17). An increased risk persists until 12 weeks after delivery (18).

Deep-vein thrombosis in pregnant women occurs more frequently in the left leg (85%) compared to those in non-pregnant individuals (55%), and is more often proximal with 72% in the iliofemoral veins compared to 9% in those who are not pregnant (19). Pregnant women have also a greater risk of embolic complications and post-thrombotic syndrome (20).

Risk Factors for Venous Thromboembolism During Pregnancy

The two strongest risk factors both in antenatal and postnatal period are previous VTE and thrombophilia (11). An odds ratio (OR) of 24.8 (95% confidence interval [CI] 17.1–36) for previous VTE, 51.8 (95% CI 38.7–69.2) for thrombophilia and 15.8 (95% CI 10.9–22.8) for antiphospholipid syndrome were reported in a large study (5). The risk of VTE recurrence during pregnancy is increased 3.5 times compared with recurrence in the non-pregnant period. This risk of recurrence appears to be constant over the whole course of pregnancy (21). In pregnancy, the risk of recurrence is very low if VTE was provoked by transient risk factors such as surgery, trauma, or immobility unrelated to estrogen or pregnancy. The risk of recurrence is greater if previous VTE was unprovoked due to no identified precipitating factor present, or if prior VTE was in pregnancy or associated with hormonal contraception (22, 23). Increased VTE risk depending on the type of thrombophilia, the association with personal or family VTE history and additional risk factors. The Royal College of Obstetricians and Gynecologists (RCOG) defined low risk thrombophilia as heterozygous for factor V Leiden or prothrombin G20210A mutations; and high risk thrombophilia as antithrombin deficiency, protein C or S deficiency, compound or homozygous for low-risk thrombophilia (24). A recent meta-analysis confirmed that the absolute risk of VTE exceeded 3% only for women with antithrombin, protein C, and protein S deficiencies, or homozygosity for factor V Leiden (25). The risk of VTE in women with antiphospholipid syndrome without VTE history is poorly described but seems increased and to be considered as a low risk thrombophilia (5, 24).

The other risk factors could be divided into maternal, pregnancy and delivery characteristics. Maternal characteristics that moderately influence the VTE risk are body mass index (BMI) $\geq$40 kg/m^2, or 25 kg/m^2 with antepartum immobilization and a medical co-morbidity like sickle cell disease or preexisting diabetes (26, 27). Maternal characteristics associated with low increase VTE risk are: age $\geq$35 years, BMI $\geq$25 to 40 kg/m2, parity $\geq$3, smoking, assisted reproductive technology, varicose veins and family history of VTE. Pregnancy characteristics such as, hospital admission, surgery, immobility/long-distance travel, systemic infection, and ovarian hyper stimulation syndrome moderately influence VTE risk. Hyperemesis, multiple gestation, intrauterine growth restriction, and preeclampsia have a small influence on risk. For delivery characteristics, emergency cesarean section and postpartum hemorrhage >1,000 mL or blood transfusion moderately increase risk. Stillbirth, preterm delivery <37weeks' gestation, prolonged labor >12 h, planned cesarean delivery, operative vaginal delivery and manual removal of the placenta are mild risk factors (28). The weight of each of these risk factors differs between studies. More than three-quarters of women had at least 1 VTE risk factor (78%) and more than 40% had multiple (2 or more) VTE risk factors (29).

Venous Thromboembolism Risk Score During Pregnancy

Some authors developed risk-scoring systems, enabling individualized estimation of thrombotic risk during pregnancy, and permitting implementation of a risk-adapted strategy for anti-thrombotic prophylaxis during pregnancy and puerperium. We have found seven scores allowing an assessment of the VTE risk during pregnancy and the postpartum period (**Table 1**). In these studies, individual risk factors were allocated a weighted score. Variations among these scores exists in their development, target population, risk factors and the weight of risk assigned to each risk factor.

Four scores are addressed to a population at high risk of VTE. Lindqvist et al. was the first to propose a risk score for VTE during pregnancy (40, 41). Estimates of absolute risk of pregnancy-related VTE were calculated by multiplying reported prevalence-adjusted odds ratios by the given variables. With this VTE risk estimation, more women at high risk can be identified in the postpartum period. The authors did not detail the decision threshold for thromboprophylaxis, and this unvalidated score cannot therefore be used routinely. The score was modified in Swedish guidelines but was not validated (30). Dargaud et al. proposed a practical risk score called "the Lyon VTE score" (31–33). This score was established according to data from the literature and validated in two prospective studies on 286 and 566 patients with thrombophilia or VTE history. The effectiveness of this score has not yet been demonstrated in clinical practice to reduce the incidence of VTE. Using a Delphi approach, Chauleur et al. developed an easy-to-use tool, the "STRATHEGE score," enabling individualized estimation of thrombotic risk during

TABLE 1 | Venous thromboembolism risk score during pregnancy and postpartum period.

	Antenatal and postnatal risk scores						
Scores	**Lindqvist et al. (30)**	**Dargaux et al. (31–33)**	**Chauleur et al. (34–36)**	**Schoenbeck et al. (37)**	**RCOG (24)**	**Testa et al. (38)**	**Chau et al. (39)**
First published	**2002–2011**	**2005**	**2008**	**2011**	**2015**	**2015**	**2019**
Country	**Sweden**	**France**	**France**	**United Kingdom**	**United Kingdom**	**Italy**	**France**
Population	**High risk VTE**	**Thrombophilia and/or a VTE history**	**High risk of VTE**	**High risk of VTE**	**Unselected**	**Unselected**	**Unselected**
Personal history of VTE							
Recurrent personal VTE events	Very high risk	3	12				6
VTE during childhood		6					6
VTE in previous pregnancy, cerebral VTE, or massive pulmonary embolism	≥4	6	6	2	4	3	6
Spontaneous or estrogen-induced or proximal VTE	≥4	3	6	2	4	3	6
Spontaneous or estrogen-induced distal DVT	≥4	2	3	2	4	3	6
Proximal VTE with transitory risk factor	≥4	2	3	1	3	3	3
Distal VTE with transitory risk factor	≥4	1	0	1	3	3	3
Residual venous thrombi with clinical signs of post-thrombotic syndrome		3	0				
Recent VTE history <2 years		2					
Familial history of VTE							
Family history (1st degree) of proximal VTE without risk factors	1		2		1	1	3
Family history (1st degree) of proximal VTE recurrent or severe	1	1	2	0.5 (two or more)		1	
Family history of non-severe VTE: distal or triggering factor or >60 years			0			1	
Thrombophilia							
Antithrombin III deficiency	Very high risk	1	10	3	3	3	3

(Continued)

TABLE 1 | Continued

	Antenatal and postnatal risk scores						
Scores	**Lindqvist et al. (30)**	**Dargaux et al. (31–33)**	**Chauleur et al. (34–36)**	**Schoenbeck et al. (37)**	**RCOG (24)**	**Testa et al. (38)**	**Chau et al. (39)**
First published	**2002–2011**	**2005**	**2008**	**2011**	**2015**	**2015**	**2019**
Country	**Sweden**	**France**	**France**	**United Kingdom**	**United Kingdom**	**Italy**	**France**
Population	**High risk VTE**	**Thrombophilia and/or a VTE history**	**High risk of VTE**	**High risk of VTE**	**Unselected**	**Unselected**	**Unselected**
Protein C or protein S deficiency	2	3	4	C: 1.5, S: 1	3	3	1
Factor V Leiden or prothrombin G20210A (factor II) homozygosity	3	1	5	3	3	3	3
Factor V Leiden or prothrombin G20210A (factor II) heterozygosity	1	3	3	1	1	2	1
Combined thrombophilia		1	4		3	3	3
Obstetrical Antiphospholipid syndrome	≥4		9	1	1	3	6
Maternal, pregnancy, and delivery characteristics							
Age (>35 years), Obesity, Parity ≥3, Smoking, varicose veins, Multiple pregnancy	Age>40: 1 Obesity: 1	Age >35 years: 1 Obesity:1 Multiple pregnancy:1	Parity >4: 0 Varicose veins: 0	Age>35: 0.5 Obesity: 0.5	1 for each Except BMI≥30: 1 ≥40: 2	Age>35: 0.5 Obesity: 1 Varicose veins: 0.5 Parity >4: 0.5 HTA/diabète:0.5	1 for each
Heterozygous sickle-cell trait, Inflammatory bowel disease, Nephrotic syndrome, Lupus	IBD: 1		Lupus: 0		3	2 for each	1 for each
OHSS (first trimester only)					4	1	
Hyperemesis					3	0.5	
IUGR, PE, placental abruption, ART	PE: 1 Placental abruption: 1				PE: 1 ART: 1	PE: 0.5	IUGR:1 PE: 1
Bed rest, immobilization, Sepsis	Bed rest: 2	Bed rest: 2			1 for each	Bed rest: 3 sepsis: 1	2 for each
Emergency cesarean delivery	1				2	0.5	2

(Continued)

TABLE 1 | Continued

	Antenatal and postnatal risk scores						
Scores	**Lindqvist et al. (30)**	**Dargaux et al. (31–33)**	**Chauleur et al. (34–36)**	**Schoenbeck et al. (37)**	**RCOG (24)**	**Testa et al. (38)**	**Chau et al. (39)**
First published	**2002–2011**	**2005**	**2008**	**2011**	**2015**	**2015**	**2019**
Country	**Sweden**	**France**	**France**	**United Kingdom**	**United Kingdom**	**Italy**	**France**
Population	**High risk VTE**	**Thrombophilia and/or a VTE history**	**High risk of VTE**	**High risk of VTE**	**Unselected**	**Unselected**	**Unselected**
Elective cesarean section, Mid-cavity or rotational operative delivery, Prolonged labor (>24 h), PPH (>1 liter or transfusion), Preterm birth < 37 + 0 weeks in current pregnancy, Stillbirth in current pregnancy					1 for each	Blood transfusion: 2	PPH >500 mL: 1
Hemostatic hysterectomy, embolization, or arterial ligation					3		3
Total score	Weighted risk score	Weighted risk score	Weighted risk score	Weighted risk score	Weighted risk score	Weighted risk score	Weighted risk score
Thromboprophylaxis A. 1 conservative management, 2 Compression B. prophylactic LMWH from delivery 1 until 6 weeks postpartum 2 short duration C. prophylactic LMWH from 28 weeks until 6 weeks postpartum D. prophylactic LMWH from diagnosis of pregnancy until 6 weeks postpartum E. Adjusted dose LMWH	0–1: A 2: B2 3: B1 ≥4: D Very high risk: E	<3: B1 3–5: C ≥ 6: D	1–3: B1 4: C 5-11: D ≥12: E	<1.0: A 1.0–1.5: B1 2.0–2.5: C 3.0 or more: D	*Antenatally* 3: C ≥4: D *Postnatally* Low-risk thrombophilia + familial VTE history: B ≥ 2: B2	0–1: A1 1.5–2: A2 ≥2.5: LMWH as described by RCOG	0: A1 1–2: A2 3–5: B1 ≥6: D

VTE, Venous thromboembolism; IBD, Inflammatory bowel disease, IUGR, intrauterine growth restriction; PE, preeclampsia; ART, assisted reproductive technology; OHSS, ovarian hyper stimulation syndrome; PPH, postpartum hemorrhage; LMWH, low molecular weight heparin; RCOG, Royal college of Obstetricians and Gynecologists.

pregnancy and permitting implementation of a risk-adapted strategy for anti-thrombotic prophylaxis during pregnancy and postpartum (34–36). The score is intended for pregnant women at risk of VTE and placental vascular complications. In a prospective multicenter before-after study on 2,000 patients at risk, the use of the score reduced the risk of VTE (RR 0.68 [0.55; 0.83]) especially during pregnancy (RR 0.30 [0.14; 0.67]) without any significant increase in bleeding. In the united Kingdom in 2011, a multidisciplinary group of physicians, hematologists, and obstetricians established the "Thromboprophylaxis Scoring System" (37). The scoring system improved the consistency of advice and increased the mean duration of thromboprophylaxis, but no effect on reducing the incidence of VTE could be highlighted because the patient cohort was too small.

Three other scores are addressed to an unselected pregnant population. The RCOG propose a risk assessment for VTE based on adjusted odds ratios for risk factors (24, 42). This score has not been validated, but there is evidence that the implementation of these practice guidelines in the United Kingdom decreased mortality from VTE. Maternal mortality rates decreased from 1.94 deaths per 100,000 births from 2003 to 2005, to 1.01 from 2011 to 2013 (42, 43). A working group of hematologists, internists and gynecologists in Italy created a model to evaluate the risk of VTE in pregnancy called "Pregnancy Health-care Program" (38). The score determined whether or not to initiate heparin thromboprophylaxis, however in the event of required heparin treatment, the score refers to the RCOG recommendations. The score was validated on 1,800 patients in Italy but its effectiveness has not been demonstrated. The most recent score from 2019 is that of Chau et al. The score was validated in a study on 1,000 patients, comparing its effectiveness via, one retrospective period for the population before implementation of the score, and one prospective period post implementation of the score. Use of the VTE risk score at the first consultation in pregnancy increased the likelihood of appropriate treatment (OR 1.5, 95% CI 1.2–1.9; $P = 0.002$) and reduced the risk of undertreatment (OR 0.5, 95% CI 0.4–0.7; $P < 0.001$). No effect on reducing the incidence of VTE could be highlighted.

The feasibility of routine use of the VTE risk score by clinicians and safety in the absence of increased risk of bleeding has been proven. All the VTE risk scores are finally very close. Two studies have shown a promotion of appropriate thromboprophylaxis with the use of VTE risk scores (33, 39). Only one study showed an effectiveness of these risk scores in reducing the incidence of VTE (36). Indirect evidence of the effectiveness of the RCOG score exists through the reduction in VTE mortality seen in the UK.

Venous Thromboembolism Risk Score in Postpartum Period

All the previous scores allowed the calculation of a score from which followed a course of action to be taken in the postpartum period. Three scores allowing an assessment of the VTE risk only in the postpartum period will be discussed. These scores are for very different populations, with different risk factors considered and with different contribution of each risk factor to the overall risk of VTE. Emergency cesarean delivery, stillbirth, varicose veins, PE/eclampsia, postpartum infection, and comorbidities were the strongest predictors of VTE in the final multivariable model based on data from 433 353 deliveries. The sensitivity of the model to predict VTE is 68% while that of RCOG is only 63% at similar thresholds (44). The disadvantage of this score is that it quantifies absolute risk of postpartum venous thromboembolism and does not give guidance in terms of thromboprophylaxis. The French National College of Gynecologists and Obstetricians proposed a score adapted from existing recommendations. For every cesarean delivery, mechanical thromboprophylaxis with elastic stockings is recommended with or without the addition of LMWH according to the presence of additional risk factors. The score is determined by multiplying the adjusted Odds-Ratio for major and minor risk factors. The treatment is necessary when the combined OR of added risk factors is > 10 (45). The disadvantage of this score is its complex calculation by multiplication. In the recommendations of the American College of Chest Physicians (ACCP) (11), thromboprophylaxis was implemented in the postpartum period when the risk of VTE was >3% (11). None of these scores showed an effectiveness of these risk scores in reducing the incidence of VTE.

DISCUSSION

Several international organizations have published recommendations on the prevention of VTE during pregnancy by giving priority to prophylaxis in the event of previous VTE and thrombophilia (11, 24, 46, 47). Variation exists in the risk factors considered, the contribution of each risk factor to the overall risk, and the threshold at which a woman is at risk of VTE. It remains unknown whether risk factors are additive or multiplicative. A 5-fold difference in the number of women who would theoretically receive a recommendation for postpartum thromboprophylaxis by various international guidelines was observed, which ranged from 7% under ACOG to 37% under RCOG guidelines (29). These variations could be explained by the low quality evidence on the effectiveness of thromboprophylaxis that led to use expert opinion and consensus-derived guidelines. These discrepancies in the recommendations and their complexity may discourage their routine use by primary care practitioners and gynecologists less familiar with VTE. The utilization of thromboembolism prophylaxis adapted to individualized risk assessment remains unused in many countries (48, 49).

The important message is that it is recommended that all women undergo a documented assessment of risk factors for VTE in early pregnancy or pre-pregnancy. Risk assessment should be repeated if the woman is admitted to hospital for any reason or develops other intercurrent problems (24). Risk assessment should be repeated intrapartum or immediately in postpartum. The National Partnership for Maternal Safety under the guidance of the Council on Patient Safety in

Women's Health Care propose a safety bundle organized into four domains, readiness, recognition and prevention, response and reporting and systems learning (1). *Readiness* discusses the use of a standardized VTE risk score (2). *Recognition* is divided into the identification of appropriate patients for thromboprophylaxis, as well as education for patients and health care workers (3). *Response* suggests the use of standardized recommendations for mechanical thromboprophylaxis, dosing of anticoagulation and for appropriate timing of pharmacologic prophylaxis with neuraxial anesthesia. Finally (4) *Reporting and systems learning* recommend to review all thromboembolism events (50).

The introduction of VTE risk scores and electronic health records aims to reduce variation in care and improve the reliability of action in the prevention of VTE. Yet no standardized VTE risk score exists. It seems necessary to differentiate in the scores, high-risk patients (with previous VTE and/or with thrombophilia) from other patients, and to carry out antenatal and postnatal assessments given evolving risk factors. Clinicians do not uniformly use existing risk-stratification tools and, when used, clinicians often use the tools incorrectly, producing an underestimation of a patient's risk for VTE. However, the complexity of the risk assessment signifies the need for an automatic computerized system (51). Some studies have used Computerized Clinical Decision Support Systems (CCDSS) to stratify the patient according to VTE risk and make suggestions for thromboprophylaxis outside the context of pregnancy. A CCDSS is a rule- or algorithm-based software that can be integrated into an electronic health record and uses data to present evidence-based knowledge at the individual patient level. In a systematic review, the use of CCDSS was associated with a 2-fold increase in the rate of ordering prophylaxis for VTE when compared with controls (odds ratio, 2.35; 95% CI, 1.78–3.10; $P < 0.001$) and a significant decrease in the risk of VTE events (risk ratio, 0.78; 95% CI, 0.72–0.85; $P < 0.001$) (51). Further research and data using large study cohorts reporting the use of CCDSS in obstetric settings is required.

AUTHOR CONTRIBUTIONS

TR-B wrote the different parts of the review. CC designed the manuscript and supervised the progress of the review. OE verified the English. All authors contributed to the article and approved the submitted version.

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Preventing Postpartum Venous Thromboembolism in 2022: A Narrative Review

Marc Blondon[1]* *and Leslie Skeith*[2]

[1] Division of Angiology and Hemostasis, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland, [2] Division of Hematology and Hematological Malignancies, Department of Medicine, University of Calgary, Calgary, AB, Canada

The postpartum period represents the most critical time for pregnancy-associated venous thromboembolism (VTE), which is responsible for substantial morbidity and an important cause of maternal mortality. The estimated risk of postpartum VTE of about 1/1,000 deliveries can be modulated with the knowledge of maternal and obstetrical risk factors, although a precise estimate remains challenging in individuals. The use of postpartum low-dose low-molecular-weight heparins are tailored at intermediate and high-risk groups to reduce the thrombotic burden, despite the lack of dedicated randomized controlled trials. In this review, we will highlight the contemporary evidence on the risk of postpartum VTE, its stratification and its prevention. We will also discuss our knowledge on the values and preferences of women for postpartum thromboprophylaxis and their adherence to treatment.

Keywords: postpartum, thrombosis, pulmonary embolism, prevention, heparin, preferences

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***Correspondence:**
Marc Blondon
marc.blondon@hcuge.ch

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INTRODUCTION

Pregnancy-associated venous thromboembolism (PA-VTE) is responsible for about 10% of VTE in women (1). Activation of the coagulation system, endothelial trauma and venous stasis all contribute to the increased risk during pregnancy. Endogenous hormones induce a hypercoagulability characterized by increased levels of coagulation factors (fibrinogen, factors VII, VIII, X and von Willebrand factor), decreased levels of antithrombotic factors (protein S, protein C), an acquired resistance to the inhibition by protein C, and a decrease in fibrinolytic acitivty (decreased tissue plasminogen activator activity and an increase in plasminogen activator inhibitors 1 and 2) (1). Blood stasis is mediated through venous dilation and compression of the iliac veins (2), especially the left common iliac vein. Finally, vascular damage arises from delivery.

The clinical relevance of PA-VTE is underlined by its mortality and morbidity. Approximately 1/100'000 pregnant women dies from pulmonary embolism in the Western World (3). Compared to the non-pregnant setting, deep vein thromboses (DVT) are more commonly proximal with involvement of the iliofemoral veins. Postpartum DVT is complicated by a high rate of post-thrombotic syndrome, which reduces long-term quality of life (4, 5). Further, because direct oral anticoagulants are contra-indicated during breastfeeding, there is the necessity to use low-molecular-weight heparins or vitamin K antagonists in the postpartum, each with their associated constraints.

The biggest potential impact of PA-VTE prevention (thromboprophylaxis) is in the postpartum period, defined as the 6 weeks after delivery, with the peak incidence of PA-VTE in the first 2 weeks after delivery (6). Compared with non-pregnant women, women in the postpartum period have up to a 22–60-fold increased risk of VTE (7, 8). However,

because the absolute VTE risk remains low in the short-term, identification of individuals who may benefit from preventive measures is needed but can be complex, such as through risk stratification. In this narrative review, we will summarize the current knowledge on risk factors and risk stratification for postpartum VTE, on our knowledge of the benefit and risk of mechanical and pharmacological thromboprophylaxis, and on patients' preferences and values relating to postpartum thromboprophylaxis. These topics will be put in the perspective of a hypothetical postpartum situation.

Case Presentation

A 35-year old woman has delivered today her first newborn of 3,600 grams, at 39 weeks of gestation. Because of fetal distress during labor, an emergency cesarean section (C-section) was performed. The mother has no prior history or family history of VTE, and apart from obesity (BMI 32.7 based on pre-pregnancy weight 89 kg and height 165 cm) has no other medical conditions. Both mother and newborn are doing well a few hours after delivery. The mother asks about the need for prevention of venous thromboembolism.

OVERALL RISK OF POSTPARTUM VTE

The absolute risk of VTE in the 6 weeks postpartum is low, based on population-based studies from several countries. A major strength of population-based studies is their large sample size and generalizability, but the definition of VTE commonly relies on administrative codes and/or some signal of anticoagulation use, without adjudication for VTE, so there is a potential for misclassification. In the UK, >200,000 pregnancies without a prior history of VTE were identified in a network of 255 general practices between 1987 and 2004, with a risk of postpartum VTE of 0.5/1,000 deliveries (8). In Denmark, a nationwide prospective cohort studied >900,000 pregnancies between 1995 and 2009, and after exclusion of women with a prior VTE, the risk was 0.35/1,000 deliveries (9). In California, between 2005 and 2010, among >1,600,000 pregnancies, the risk was 2.8/1,000 deliveries (10). In Canada, among >3,800,000 pregnancies, the risk was 1.2/1,000 deliveries between 1991 and 2006 (11). Finally, a cohort of Medicaid and private insurances in the United States between 2005 and 2011 found a risk of 1.6/1,000 deliveries (12). Underestimation of risks is likely in the first 2 studies (0.35–0.5/1,000 deliveries) due to exclusion of women with prior VTE and an unknown sensitivity of the algorithm of identification of VTE outcomes. Overestimation is possible in the 2 last studies (1.2–2.8/1,000 deliveries) due to broad diagnostic codes with suboptimal positive predictive value. Overall, these studies suggest that about 1/1,000 women will experience a VTE in the postpartum period, with a proportion of 40% of patients experiencing pulmonary embolism (6). This means that women without any VTE risk factors and women combining several risk factors will have a risk lower and >0.1%, respectively.

A 0.1% risk of postpartum VTE is 10–50 times lower than that of medical inpatients deemed at high risk of VTE (1–5%) with an indication for thromboprophylaxis (13). It is also >10 times lower than the VTE incidence after hip or knee replacement therapy (14). Although the actual number of postpartum VTE events is large because of a huge denominator of >10 million deliveries per year in Europe and North America, universal postpartum thromboprophylaxis cannot be advised for this uncommon event: in an optimistic scenario of a 70% relative reduction of VTE by short-term low-molecular-weight heparin (LMWH), one should need to treat about 1,500 women to prevent 1 VTE event. This number needed to prevent is likely too high from the perspective of healthcare costs and likely women themselves. The key is to stratify women at different risk levels, to avoid treating women at very low risk and to reduce the thrombotic risk in women at high risk, to find the optimal balance of reducing VTE while minimizing cost and possible side effects of pharmacologic thromboprophylaxis.

RISK STRATIFICATION

There is surprisingly little direct data to quantify the absolute postpartum VTE risk among patients with additional transient or pregnancy-specific risk factors. Most of the available data used to support clinical practice guidelines has been derived from large population-based registries or case-control studies. While not an exhaustive list, we highlight the type and level of data available when trying to predict postpartum VTE risk.

Previous VTE

Undoubtedly, a history of any prior VTE represents the most important risk factor, with a relative risk >20–50 and an absolute risk of postpartum VTE of 6–8% without thromboprophylaxis (15, 16).

Cesarean Delivery

In a comprehensive meta-analysis that evaluated both case-control and cohort studies published up to 2015, the postpartum VTE risk after cesarean delivery was increased >3 times, compared with vaginal deliveries (17). The absolute risk from prospective studies was 2.6–4.3/1,000 deliveries, or about 1 in 230–380 deliveries. This risk was greater in urgent/emergency cesarean deliveries than planned/elective cesarean deliveries. Significant heterogeneity was observed in the meta-analysis, reflecting not only differences in research methodology but also in clinical contexts and the occurrence of other risk factors.

Elevated BMI

There is a positive gradual association between postpartum VTE risk and BMI. In a hospital-based case control study that compared women with objectively verified VTE during pregnancy or postpartum vs. controls, the risk of postpartum VTE was modestly higher among women with a BMI $\geq$ 25 kg/m^2 at the beginning of pregnancy [adjusted Odds Ratio (aOR)2.4, 95% CI, 1.7–3.3] (18). Other studies have looked at different pre-pregnancy BMI cut-offs found that compared to a normal BMI, categories of increasing BMI had progressively increased VTE risk, with class III obesity (BMI $\geq$40 kg/m^2) having the highest risk (aOR 4.0, 95% CI, 2.7–6.3) (19). Excess weight gain during pregnancy has been less studied, and whether it is a risk factor for postpartum VTE or not is inconsistent (18, 19). Due

to its increasing prevalence and its strength of association with VTE, obesity carries an important population attributable risk for postpartum VTE.

Markers of Placental Disease

Intrauterine growth restriction (IUGR), pre-term birth and pre-eclampsia are well-recognized risk factors for postpartum VTE. In a population-based case-control study, postpartum women who delivered neonates with low birth weight (<2,500 grams) had a 3-fold increased risk of VTE that persisted after adjusting for possible confounding variables (aOR 2.98, 95% CI 1.80–4.93) (20). In other studies, IUGR, preterm birth (defined as <37 weeks), and pre-eclampsia showed similar VTE risk (18, 21, 22). How preeclampsia or IUGR is defined, including what growth restriction reference standard or what percentile cut-offs are used, remains unclear and may change across countries.

Additional VTE Risk Factors

Many other VTE factors exist, with minor or intermediate associations with postpartum VTE, such as postpartum hemorrhage, infection, current or recent smoking, or medical conditions including diabetes. While bedrest during pregnancy is a known VTE risk factor, indications for strict bedrest are now uncommon (18). Also, the relationship of thrombophilia and family history with VTE is complex and goes beyond the scope of this review, but has been recently meta-analyzed (23) and detailed in guidelines (24).

Two areas of uncertainty are worth discussing. First, the timing of postpartum VTE may vary according to the type of VTE risk factors. In a UK database study, those with preterm birth or postpartum hemorrhage had increased VTE incidence rate only in the first 3 weeks postpartum. In comparison, those with an elevated BMI $\geq$30 kg/m^2 or those having cesarean delivery had a risk that persisted up to 6 weeks postpartum (22). Given the multiple risk factors to evaluate and the numbers of patients and VTE cases needed, little information is still known about the timing of postpartum VTE events for different risk factors. Second, the impact of combined risk factors needs to be clarified, especially because almost half of women carry multiple risk factors in the puerperium (25). For example, when a patient has an elevated BMI $\geq$ 25 kg/m^2 and with strict antepartum immobilization, the aOR for postpartum VTE may be as high as 40-times, compared with a patient who has normal BMI and no antepartum immobilization.

Currently, guidelines suggest to risk stratify using empiric schemes of levels or combination of risk factors in several categories: no thromboprophylaxis or mechanical thromboprophylaxis only, short-term pharmacologic thromboprophylaxis (days) and 6-weeks of pharmacologic thromboprophylaxis. Importantly, such guidelines (ACOG (26), RCOG (27), ASH (24)), which are detailed elsewhere, diverge dramatically in the proportion of women with advised thromboprophylaxis, between 7 and 40% for all deliveries (28) and 0.2–73% for cesarean deliveries (29). Logically, a higher prevalence of use of thromboprophylaxis is associated with lower risks among those with thromboprophylaxis, and greater numbers needed to treat to prevent 1 VTE.

A recent innovation in this field is the development of a risk score for postpartum VTE ("Maternity Clot Risk"), combining in complex forms the following 11 maternal and obstetrical factors: age, BMI, varicose veins, co-morbidities, smoking, pre-eclampsia, bleeding, infection, delivery method, parity and infant birth weight (30). The score allows estimation of postpartum VTE risk in individual women with VTE risk factors, and so may help focus prevention efforts on women above a certain threshold of risk. This score does not apply to women with a prior VTE or take into account thrombophilia. It was externally validated using a Swedish database and a UK primary care database (31), however with some limitations (32). Further validation effort would be welcome, and meanwhile it has not been incorporated into clinical practice guidelines yet.

Case Discussion

The patient has two intermediate risk factors for VTE: obesity (BMI = 32.7 kg/m^2) with a relative risk of 2.5 (19), and emergency C-section with a relative risk of about 4. Assuming a baseline risk among women without any risk factors of 0.05%, we could broadly estimate, with a combination of risk factors between 5.5 (additive model) or 10 (multiplicate model), that her personal postpartum VTE risk is around 0.3–0.5%. The use of the Maternity Clot Risk calculator yields a lower estimate of risk of 0.1%. We inform the patient that her risk of postpartum VTE lies around 0.1–0.5%, or about 1 in 200–1,000 deliveries.

HOW CAN WE PREVENT POSTPARTUM VTE IN HIGH-RISK SITUATIONS?

Strong evidence shows that low-dose heparins, either unfractionated heparin or LMWH, reduces the risk of DVT and pulmonary embolism in medical or surgical inpatients, by about 50–70% (33). In the obstetric setting, the level of evidence is close to null, and has been recently summarized in an updated Cochrane systematic review as having a "very uncertain effect" (34). Indeed, all available randomized trials included small sample sizes, and some were only pilot randomized trials to test feasibility. No conclusion can be drawn with regards to the efficacy and safety of heparins in this population. Further, most concluded that the feasibility of a large-scale randomized trial was poor due to barriers and low recruitment of postpartum participants (**Table 1**).

Although non-randomized, a large monocentric trial in Iraq sequentially allocated to 6 days of low-dose bemiparin or enoxaparin or no treatment among women after vaginal or cesarean deliveries who were deemed at intermediate risk of postpartum VTE according to the RCOG guidelines (**Table 1**) (41). Quite surprisingly, the investigators reported the inclusion of 7,020 participants, with an extremely low 0.5% refusal to participate, and a 0% loss to follow-up. Enoxaparin and bemiparin were associated with a 89–95% relative reduction in the risk of symptomatic VTE, which was not adjudicated. This corresponded to a 0.3% absolute risk reduction (number

TABLE 1 | Published (pseudo)-randomized trials of heparins vs. placebo or no treatment to prevent postpartum venous thromboembolism.

	Study type	Country	Population	Intervention	Control	Risk of VTE (intervention / control)	Risk of bleeding[a] (intervention / control)
Segal et al. (35)	Monocentric RCT	Israel	210 postpartum women with varicose veins	UFH 5000 IU s.c. (4–5d)	No treatment	0.8/5.3%[b]	Not reported
Hill et al. (36)	Pilot RCT	UK	50 women after elective CS	UFH 1000 IU b.i.d. (5d)	Saline b.i.d. (5d)	0/0%	4/8%
Burrows et al. (37)	Pilot RCT	Australia	76 women after CS	Dalteparin 2500 IU o.d. (5d)	Placebo o.d. (5 d)	2.6/0%	0/0%
Gates et al. (38)	Multicenter pilot RCT	UK	141 women after CS	Enoxaparin 40 mg o.d. (max 14d)	Placebo o.d. (max 14d)	1.5/0%	0/0%
Rodger et al. (39)	Multicenter pilot RCT	USA-Canada	25 women at intermediate risk	Dalteparin 5000 IU o.d. (3w)	Placebo o.d. (3w)	0/0%	0/0%
Rodger et al. (40)	Multicenter pilot RCT	USA-Canada	37 women at intermediate risk	Dalteparin 5000 IU o.d. (10d)	No treatment	0/0%	6.3/0%
Alalaf SK et al. (41)	Monocentric sequential clinical trial	Iraq	7,020 women at intermediate risk based on RCOG guidelines	Bemiparin 3500 IU o.d. / enoxaparin 40 mg o.d. (6d)	No treatment	0.1/0.4%	Not reported

a Various definitions according to individual studies.
b Clinical diagnoses of VTE.
RCT, randomized controlled trial; UK, United Kingdom; CS, cesarean section; UFH, unfractionated heparin; d, days; w, weeks.

needed to treat of 333). This study brings hope that short-term LMWH may efficiently reduce postpartum VTE, but no firm interpretations should be made based on its limitations of methodology, the unknown external validity and the lack of reports on safety (bleeding complications).

We have limited evidence from observational studies. Recently, two monocentric studies from the USA did not show a reduction in VTE events after implementation of standardized postpartum LMWH protocols for postpartum women with VTE risk factors, despite an increase in the use of postpartum enoxaparin from <1– >30% among 9,766 deliveries (42) and from 1 to 16% among 24,299 deliveries (43). Importantly, there was also an increased risk of wound hematomas and unplanned procedures noted in the post-LMWH protocol implementation group in one of the studies (43). Limitations to these studies include a retrospective study design evaluating a pre- and post-intervention over time that is not randomized, and the lack of VTE and bleeding event independent adjudication. These contradictory studies highlight the uncertainty still present and need for more research in the area.

Another drug of interest is low-dose aspirin. Its main advantages are its oral route and known safety profile including with breastfeeding, with a demonstrated benefit of VTE in other settings [surgical thromboprophylaxis (14), secondary prevention of VTE (44)], although with a potential lower VTE risk reduction than that of LMWH. Aspirin is currently not recommended in the postpartum period but is the subject of an ongoing trial (pilot PARTUM trial, described below).

Direct oral anticoagulants should be avoided in breastfeeding women due to safety, and there is currently no data for VTE prevention in postpartum non-breastfeeding women. With previous safety signals reported for increased heavy menstrual bleeding for women taking direct oral anticoagulants for VTE management, further research is still needed on the safety of this approach in postpartum non-breastfeeding women.

Mechanical thromboprophylaxis, in particular intermittent pneumatic compression (IPC), may also reduce the risk of VTE after surgery (45). Unfortunately, as there are no clinical data to evaluate IPC in the postpartum period, the role of mechanical thromboprophylaxis in this setting is unclear. Also, one study pointed out a low adherence with compression stockings, after hospital discharge, highlighting its burden despite its safety (46).

Case Discussion

With the use of short-term LMWH (up to 10 days), we believe that the risk of postpartum VTE of our patient may be halved, however, the true benefits of LMWH are still unknown. In other words, 400–2,000 women would have to be treated to prevent 1 VTE event. We communicate these estimates to the patient, including the large uncertainty, possible LMWH side effects, and the suggestion by some guidelines (but not all) to prescribe LMWH in her situation. We also acknowledge that each of the authors has a different approach, including a variation in the duration of LMWH ranging from the hospital stay only (47), up to 10 days postpartum (27).

WHAT DO WOMEN THINK OF POSTPARTUM PHARMACOLOGICAL THROMBOPROPHYLAXIS?

Views and opinions of patients are critical in this area of current uncertainty. Strikingly, we know very little on the preferences and values of women about thromboprophylactic strategies and which threshold of VTE risk they believe should justify the use of short-term postpartum LMWH, but this could be critically helpful.

Patient preferences and values for decision-making about antepartum thromboprophylaxis have been explored in an international multicenter study (40, 48). Using a series of different exercises (direct choice, utilities for health states and probability trade-off), the authors interviewed 123 women with a history of VTE who were pregnant or considering pregnancy. There were only ∼80% of women who would consider taking antepartum LMWH for a VTE risk of 10%, which is above a threshold that most physicians would recommend thromboprophylaxis. This highlights the contrast between the vision of VTE specialists and that of women with a history of VTE. While this study does not apply to a primary thromboprophylaxis decision (women without a history of VTE) in the postpartum period, it underlines the importance of shared decision-making about VTE risk.

To our knowledge, and quite surprisingly, the value and preferences of women toward postpartum thromboprophylaxis or postpartum VTE research have not been explored. We are unaware of the preferred threshold of VTE risk that would justify the use of postpartum LMWH according to pregnant women, how decisions are made that take into account the burden and side effects of LMWH, and how these views' may differ from their healthcare providers. Additionally, how patients' views should be incorporated into clinical practice guidelines is largely unknown.

Today, a large difference of VTE risks to justify postpartum LMWH exists between experts' opinion (formulating guidelines) and the actual practice from these guidelines. When using the Maternity Clot Risk to indirectly estimate VTE risk used in guidelines, in a sample of parturients from the Geneva University Hospitals (28), we found that the 2015 RCOG and the 2018 ACOG guidelines suggested thromboprophylaxis at a risk of 0.12 and 0.20%, respectively. This contrasts dramatically with experts, who advocate for a VTE risk of 1–3% to justify postpartum VTE (24). Clearly, more research is needed in this field, to better appreciate women's preferences and values, and ensure that the use of postpartum LMWH achieves an acceptable number needed to prevent a VTE event, while minimizing harm.

Also of interest is the adherence to postpartum thromboprophylaxis, which may be suboptimal. In a 2018 study completed in Israel at a tertiary center, 250 postpartum women completed a telephone interview at the end of their planned postpartum thromboprophylaxis (48). While in-hospital adherence with LMWH was 100% in-hospital, 33% had injected <80% of the planned mean 7 days of LMWH after discharge, and 18% had injected none. Women were more likely to be compliant if they had used LMWH in the past or antenatally, and women who felt they had received good technical explanations about injections were more likely to be compliant. The two main reasons for non-adherence were the belief that LMWH was not necessary and challenges with injections at home. These reasons were similar to the reasons described for non-participation in the pilot feasibility randomized trial PROSPER, that evaluated the role of 10–21 days of post-discharge LMWH vs. no LMWH for women with intermediate VTE risk factors (40).

Three prospective studies from the UK suggest more optimistic estimates of adherence (46). Among 51 women who completed a prospective diary of postpartum LMWH injections for a duration of 7 days to 6 weeks, 82% had not missed more than most 1 dose. Among 95 women who had an indication for both antenatal and postnatal LMWH, mostly at a prophylactic dose, 98% in the antepartum and 93% in the postpartum had an adherence ≥80% (49). Similarly, another prospective cohort from the UK indicate an 83% proportion of complete adherence with postpartum LMWH (50). The selection of highly motivated women willing to participate in clinical studies in the two first studies and the overall prospective design likely boosted the level of adherence. Whether such a high adherence is representative of the general population is doubtful. Together, these studies highlight the importance of discussing the benefit of LMWH and the technique of LMWH injections prior to discharge for those who benefit.

Case Resolution

The patient has understood her risks, possible benefits of LMWH and the overall uncertainty to guide the decision of thromboprophylaxis. While she would have met inclusion criteria for the pilot PARTUM trial (described below), this study was not available at her center. After shared decision making, she decides to use low-dose LMWH for 10 days to further reduce her risks of VTE. She receives training on subcutaneous injections.

DISCUSSION

Throughout this review, we have tried to highlight several areas in critical need for high-quality data.

With regards to risk stratification, the advent of an estimator of individual risks (the Maternity Clot Risk) may be of great help to clinicians in the future, but needs, in our opinion, further validation, ideally in a population of women with intermediate VTE risk factors who have not received postpartum thromboprophylaxis. Individual-patient data meta-analyses of observational studies may help increase the power to detect clinically significant interactions of common risk factors. The identification of the mode of combination (additive, multiplicative, supra-additive) requires large sample sizes, which may emanate from individual patient analysis meta-analyses. Lastly, further research is needed to better understand patient experience and associated preferences and values, to better guide research and clinical practice guidelines in the area of postpartum thromboprophylaxis.

It is a clear paradox that, only in the UK, close to 300,000 women receive postpartum thromboprophylaxis every year, but that pilot randomized trial of subcutaneous LMWH

concluded on the unfeasibility of a large-scale trial of 10,000–20,000 women. The COVID-19 pandemic has brought into light the challenges of recruitment, but also the possibility of international collaborations that can bring answers to clinically important questions through large randomized trials, and we should not stop our effort for postpartum VTE. The pilot PARTUM trial, an ongoing pilot randomized trial testing the feasibility of conducting a large trial of low-dose aspirin vs. placebo for postpartum women at intermediate risk of VTE, led by one of the authors, is a great example of such a global effort (https://partumtrial.ca; clinicaltrials.gov ID: NCT04153760). Randomized trials of low-dose LMWH vs. no treatment are still desperately needed to provide high-quality data to support current thromboprophylaxis practice patterns for postpartum women at intermediate risk of VTE. Not only will such randomized trials allow to draw conclusions on the efficacy of these different drugs, but also on their safety and the actual risks of VTE in control groups.

AUTHOR CONTRIBUTIONS

MB and LS drafted the review, revised it critically, and provided approval for publication of its content.

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The Risk of Thrombosis Around Pregnancy: Where Do We Stand?

Jean-Christophe Gris[1,2,3,4]*, *Florence Guillotin*[1], *Mathias Chéa*[1], *Chloé Bourguignon*[1,3] and *Sylvie Bouvier*[1,2,3]

[1] Department of Hematology, Nîmes University Hospital, Nîmes, France, [2] Department of Hematology, Faculty of Pharmaceutical and Biological Sciences, Montpellier University, Montpellier, France, [3] UMR UA11 INSERM-Montpellier University IDESP, Montpellier, France, [4] Department of Obstetrics and Gynecology, First Ivan Setchenov Medical University, Moscow, Russia

Pregnancy and puerperium increase the relative risk of venous thromboembolism (VTE) and the absolute risk remains low, around 1 per 1,000, with induced mortality of around 1 per 100,000. Analysis of large databases has helped specify the modes of presentation and risk factors (RF) whose impact is greater after than before childbirth, since VTE during pregnancy and post-partum obey different RFs. The evolution of the population concerned (mostly women over 35, obese, of multi-ethnicity undergoing medically assisted reproduction) affects the frequency of these RFs. Pulmonary embolism (PE) is over-represented after childbirth, but 30% of PE in pregnancy occurs without any RFs. Recommendations for prevention, mainly from expert groups, are heterogeneous and often discordant. Low molecular weight heparins (LMWH) are the mainstay of pharmacological thromboprophylaxis, in a field where randomized controlled studies are definitely lacking. VTE risk assessment in pregnancy must be systematic and repetitive. Risk assessment methods and scores are beginning to emerge to guide thromboprophylaxis and should be used more systematically. In the future, analyzing observational data from huge, nationwide registries and prospective cluster clinical trials may bring to light clinically relevant outcomes likely to feed comprehensive guidelines.

Keywords: pregnancy, puerperium, thrombosis, risk factor, prophylaxis

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Bernard Tardy,
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Mathilde Nijkeuter,
University Medical Center Utrecht, Netherlands
Alessandra Bura Riviere,
Centre Hospitalier Universitaire de Toulouse, France
Per Morten Sandset,
University of Oslo, Norway

***Correspondence:**
Jean-Christophe Gris
jean.christophe.gris@chu-nimes.fr

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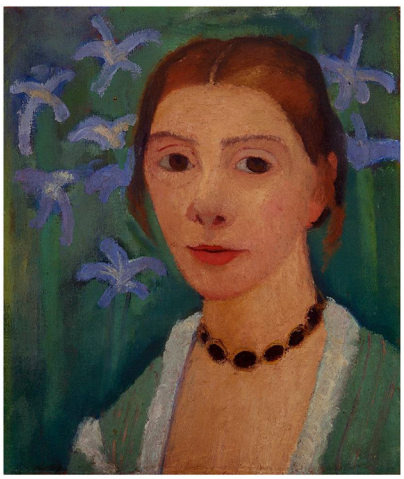
INTRODUCTION

Although the epidemiology and risk factors of venous thromboembolism (VTE) associated with pregnancy and puerperium have become more familiar, its efficient, medically-economical, individual prevention remains unclear.

Pregnancy, and the 3 months following childbirth, increase the average relative risk of VTE by 4 to 5 (1, 2). The absolute risk of VTE during pregnancy and puerperium, estimated per thousand deliveries, is however limited: 1.4 (1.0–1.8), divided into 1.1 (1.0–1.3) for deep vein thrombosis (DVT) and 0.3 (0.3–0.4) for pulmonary embolism (PE) (1, 2). Induced mortality ranges from 0.8 to 1.9 per 100,000 deliveries, or 8–10% of maternal mortality in industrialized countries (**Figure 1**; see Author's note at the end).

DVT mainly affects the left lower limb (88 vs. 55%), is more often proximal (iliofemoral axis: 72 vs. 9%; compression effect of pelvic engagement of the fetal head at the end of pregnancy) and more often generates a post-thrombotic syndrome (3).



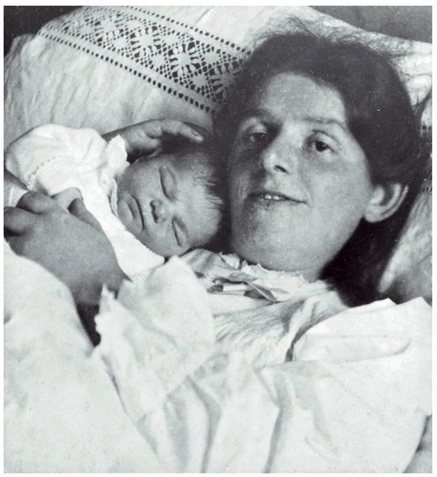


FIGURE 1 | Paula Becker (February 8, 1876–November 20, 1907), German painter, one of the most important representatives of early expressionism. Self-portrait and photography after giving birth.

The risk increases with the progression of pregnancy, peaks after delivery and normalizes 12 weeks later. Although two thirds of events occur before delivery and half during the third trimester, a quarter are diagnosed in the 3 weeks following delivery: postpartum is characterized by the highest daily incidence (1).

PEs occur mainly after delivery (60% of cases in the 2001–2006 Australian series involving over 500,000 pregnancies: 1 per 2,220 deliveries) (4) with 2% mortality and French data from 2013 show a PE/VTE ratio over 3 times higher in weeks 2–7 after delivery than during pregnancy (5).

RISK FACTORS FOR VTE AROUND PREGNANCY

In 2008, using a case-control approach on hospital enrolments, the Norwegian Jacobsen et al. (6) was the first to show that clinical risk factors (RFs) were different before and after delivery. These risk factors can be classified as pre-existing, intercurrent-transitory and pregnancy-specific. Adding them together qualifies the individual risk, which may therefore change and require regular assessment. With regards to ante-partum RFs, immobilization -in relation with multiple pregnancy, or a diagnosis of placenta praevia and premature rupture of membranes-, defined as a strict bed rest 1 week or more prior to delivery or to the diagnosis of VTE, was associated with the highest adjusted risks, with a striking multiplied risk effect in women with a high body mass index (BMI), defined as higher than 25 $kg.m^{-2}$ (6). The same was observed for postnatal VTE, with a significant effect of antepartum immobilization, and again high BMI in combination with antepartum bed rest being associated with the stronger risk for postnatal VTE (6). In both cases, the VTE risk associated with immobilization was stronger than the one associated with overweight (6).

The 1995–2009 UK cohort, analyzing over 280,000 women and 375,000 pregnancies (7), confirmed that the RFs for VTE before and after delivery differ, and the risk per patient-year is 4 times higher after delivery than before. Significant RFs only have a very modest effect on the incidence of VTE during pregnancy (**Table 1A**) and are present in 70% of PEs occurring at that time. Significant RFs for the post-partum period have a more sustained absolute effect but the average effect is <2, or 3% at the most. The same team also showed that the duration of risk associated with post-partum RFs was variable: 3 weeks for preterm birth and hemorrhage in labor and 6 weeks for Cesarean section, pre-eclampsia, obesity and acute infections (8). VTE risk factors during pregnancy have been recently reviewed by the Working Group in Women's Health of the German Society of Thrombosis and Haemostasis (9) (**Table 1B**), showing the striking impact of a personal history of VTE among preexisting RFS, of ovarian hyperstimulation syndrome and of the multiplicative interaction between antepartum immobilization and pre-pregnancy overweight among transient risk factors, and to a lesser extent of transfusion among pregnancy-associated risk factors.

Blondon's meta-analysis of the risk associated with Cesarean section certainly showed a four times higher increase in risk, and even more so in the event of urgent procedures but with an average of hardly 3 thrombotic events per 1,000 Cesareans (10).

The Australian group focusing on the risk factors for postpartum PE (4) identified planned Cesarean section (relative risk RR: 3.2), Cesarean section during labor (RR: 3.7), red blood cell transfusion (RR: 3.9), stillbirth (RR: 6.0), other transfusions and infusion of procoagulant fractions (RR: 8.2) and, finally, lupus (RR.8.8). However, in that setting, a relative risk of 6, means hardly one PE per 1,000 deliveries fulfilling the corresponding clinical criteria.

Moving from these data to prevention, first, it cannot target women who develop a pulmonary embolism during their pregnancy in the absence of any identifiable risk factor

TABLE 1 | Risk factors (RFs) for venous thromboembolism (VTE) around pregnancy.

(A) RFs identified in the UK population cohort, 1995-2009 (7).

	Mean variation in the relative risk*	Absolute risk, %: mean value (upper value)**
Antepartum VTE		
Medical comorbidities Urinary infections	+80%	0.11 (0.16)
Varicose veins	+120%	0.16 (0.21)
Inflammatory bowel disease	+250%	0.22 (0.75)
Pre-existing diabetes mellitus	+250%	0.21 (0.42)
PostpartumVTE, 6 weeks postpartum		
Body mass index > 30 $kg.m^{-2}$	+245%	0.70 (1.17)
Medical comorbidities Varicose veins	+290%	1.00 (1.48)
Inflammatory bowel disease	+300%	1.14 (2.73)
Cardiac disease	+430%	1.69 (7.75)
Pregnancy complications Cesarean delivery	+90%	0.48 (0.59)
Premature childbirth	+130%	0.64 (0.84)
Obstetrical hemorrhage	+150%	0.72 (1.34)
Stillbirth	+300%	1.83 (4.10)

*Reference: criterion-free pregnant woman. **For a hundred 9-month-long pregnancies meeting the criterion.

(B) Classification of RFs during pregnancy with their corresponding adjusted odds ratios (95% confidence intervals) (OR, 95%CI) in the review performed by the Working Group in Women's Health of the German Society of Thrombosis and Haemostasis (GTH), 2020 (8).

Preexisting RFs	OR, 95%CI	Transient RFs	OR, 95%CI	Pregnancy-associated RFs	OR, 95%CI
Parity > 3	1.0 (0.6–1.8)	*In vitro* fertilization	2.7 (2.1–3.6)	Weight gain > 21 kg	1.6 (1.1–2.6)
Age > 35 years	1.5 (1.1–2.2)	Ovarian hyperstimulation syndrome	87.3 (54–141)	Cesarean section	2.1 (1.8–2.4)
Smoking*	2.1 (1.3–3.4)			Multiple pregnancy	2.7 (1.6–4.5)
Familial VTE**	2.2 (1.9–2.6)	Antepartum immobilization^{+}		Preterm delivery$^{\circ}$	2.7 (2.0–6.6)
Anemia	2.6 (2.2–2.9)	If no overweight^{++}	7.7 (3.2–19)	Preeclampsia	3.1 (1.8–5.3)
Varicose veins	2.7 (1.5–4.7)	If overweight^{++}	62.3 (11.5–337)	Severe peripartum hemorrhage$^{\circ\circ}$	4.1 (2.3–7.3)
Obesity***	4.4 (3.4–5.7)			Postpartum infection	4.1 (2.9–5.7)
Prior VTE	24.8 (17.1–36)			Stillbirth	6.2 (2.8–14.1)
				Transfusion	7.6 (6.2–9.4)

**Defined as 10-30 cigarettes per day prior to or during pregnancy. **Family history of VTE in any relative. ***Defined as a body mass index value > 30 $kg.m^{-2}$. $^{+}$Defined as a strict bed rest > to 1 week. $^{++}$Defined as pre-pregnancy body mass index value > 25 $kg.m^{-2}$. $^{\circ}$Defined as before 37 weeks. $^{\circ\circ}$Defined as > 1L of blood loss.*

(30% of cases in the British group). Nor can it be directly applied to women with only one risk factor: an enormous prescribing effort would be required for prevention in the event of one single postpartum RF for VTE as identified by the UK group. For instance, based on an 80% efficacy of low-molecular weight heparins (LMWH), the number of women to treat during 6 weeks for avoiding one VTE event would be 1,598 in case of preeclampsia. The therapeutic intervention, in terms of the number of injections required to avoid a VTE event, is considerable (in the previous case of a woman with pre-eclampsia: 67,116 injections to avoid one VTE event) and thus of dubious medico-economic efficiency, with the risk of inducing a hemorrhagic becoming significant. The ideal solution would be to target only those women who have accumulated such a high risk of VTE that the absolute risk incurred exceeds the consensus threshold, outweighs the iatrogenic risks incurred and retains a medico-economic virtue.

Risk assessment is also carried out within a changing population, with more and more obese pregnant women, higher age of first pregnancy and more pregnant women over the age of 35, increasing use of medically-assisted procreation (MAP: *in vitro* fertilization and other methods and techniques based on the laboratory manipulation of reproductive cells; i.e., assisted reproduction techniques), more and more Cesarean deliveries and increasing multi-ethnicity. MAP is accompanied by an increased risk in the first trimester, mainly after ovarian hyperstimulation syndrome (11, 12), with an absolute risk of 1.7% and, in the USA, the risk of thrombosis during pregnancy is lower in patients of Asian origin and higher in Afro-American women (13). One large study conducted at a hospital

in Dublin on 21,000 deliveries (14) showed that age over 35 years, overweight or Cesarean section were present in one third of the women for each of the three criteria, with three quarters of them having at least one post-partum risk of VTE, with the application of international recommendations leading to prevention measures being prescribed for 7 to 37% of cases!

In women with a personal history of VTE, pregnancy also carries a risk of VTE recurrence. The RIETE registry restricted to women affected by VTE during pregnancy showed a 3.3% (1.5–5%) risk of recurrence at 2 years i.e., 2.3 recurrences per 100 patient-years (15). In the 2002 Vienna study, a new pregnancy increased that risk (RR: 3.5 (1.5–7.8) (16). The study by Brill-Edwards et al. (17) on a limited group of patients, suggests that the risk of recurrence during pregnancy was low (0% although the maximum calculated was 8%) if the first event was caused by a transient RF and if thrombophilia screening was negative.

The question of risk of a first VTE event in pregnancy in a patient with previously asymptomatic thrombophilia is frequently raised. The latest Bayesian meta-analysis identifies high-risk traits (18). Antithrombin deficiency induces an absolute risk in pregnancy of 7.3% (1.8–15.6%) and of 11.1% (3.7–21%) during puerperium. For protein C deficiency, the risk is 3.2% (0.6–8.2%) in pregnancy and 5.4% (0.9–13.8%) in the postpartum period. For protein S deficiency: 0.9% (0.0–3.7%) in pregnancy and 4.2% (0.7–9.4%) after delivery. For homozygous factor V Leiden polymorphism, it is 2.8% (0.0–8.6%) in pregnancy and 2.8% (0.0–8.8%) in puerperium. On the other hand, the cumulative risk (pregnancy + post-partum) of heterozygous V Leiden, of heterozygous FII 20210A and of their combination are all <3% (18) and we will see that this absolute risk threshold is proposed to justify thromboprophylaxis during postpartum.

THE PRECARIOUS PATHWAY FROM RISK FACTORS TO THROMBOPROPHYLAXIS

It is not easy to move on from an epidemiological approach describing the RFs for VTE during pregnancy and postpartum to an informed, balanced therapeutic proposal for prophylaxis which is both medically and economically acceptable. No placebo-controlled trials can be used to consolidate one particular approach. A large number of expert recommendations are available but these often disagree and are not regularly updated. Critical analysis using the AGREE II instrumental score (19) highlights their variable quality, inconsistencies, questionable methodologies and insufficient independence from the drug industry. One remarkable American single-center study (20) assessed the percentages of post-partum pharmacological thromboprophylaxis that would result from applying the recommendations of the American College of Obstetricians and Gynecologists (ACOG), the American College of Chest Physicians (ACCP) and the Royal College of Obstetricians and Gynecologists (RCOG) on 293 Cesarean section cases. The values obtained vary significantly (1, 35, and 85%, respectively).

The absolute thrombotic risk threshold justifying thromboprophylaxis has not been definitively decided.

During pregnancy itself, the available recommendations are still evasive.

During the postpartum period, extrapolating from general surgery patients, the ACCP experts (21) first evaluated the balance of desirable and undesirable consequences of a LMWH-prophylactic treatment, second focused on pregnancy-specific considerations then defined an absolute risk of VTE suggesting prophylaxis. The postpartum risk of major bleeding was estimated to be 0.3% (0–1%). The case-fatality rate of major VTE was estimated 1% (0.9–2.2%), the one of major bleeding under prophylactic anticoagulants 3.6% (3.2–3.9%). From these data, it was estimated a postpartum VTE risk $\geq$ 1% to *possibly* provide a net clinical benefit, and a postpartum VTE risk > 3% to *likely* provide net benefit.

After delivery, the ACCP thus stipulates 3% (i.e., for situations associated with an odds ratio of >10 after vaginal delivery, for which the risk is 0.3%, and >6 after Cesarean delivery, for which the average risk is 0.5%) (21).

In 2018 the American Society of Hematology (ASH) (22) and in 2014 the Society of Obstetrics and Gynecology of Canada (SOGC), estimated it as 1%. The arguments why these societies have chosen a different thrombotic risk threshold are not clearly supported.

In 2015 the RCOG and the ACOG in 2018 (American College of Obstetrics and Gynecology), did not set a threshold but categorized situations into levels of risk, with suggestions per level. It should be noted that, to avoid one VTE during the 6 weeks postpartum for a hundred women with an absolute risk of 3%, and if low molecular weight heparins (LMWHs) are 80% effective, 1,750 injections should be given. For women with an absolute risk of 1%, 5,250 LMWH injections should be given to 125 women to avoid one VTE.

A particular clinical issue is the prevention of recurrence during pregnancy or postpartum in a woman with a personal history of VTE, the strongest individualized preexisting RF for VTE (**Table 1B**). All women with such a history should be assessed before starting a pregnancy, with information on the risks involved, means of prevention, known data and risk assessment. Postpartum thromboprophylaxis for at least 6 weeks is recommended by almost all the available experts-driven international guidelines, regardless of the mode of occurrence of the prior VTE event. Recommendations are more variable during the pregnancy itself.

In case of an unprovoked or a hormone-related VTE (i.e., associated with an estrogen-containing hormonal contraception or with a prior pregnancy), thromboprophylaxis is recommended during pregnancy. However, the optimum LMWH dosages are still uncertain.

In case of a VTE provoked by a non-hormonal transient RF, and in absence of any other VTE RF, some discrepancies still exist, from thromboprophylaxis only in the third trimester of pregnancy, to postpartum only thromboprophylaxis.

Regarding pharmacological thromboprophylaxis methods before/after childbirth, unfractionated heparins are impractical before, but can be applied after. Although LMWHs are the

gold standard, the use of weight-adjusted preventive doses is increasingly suggested on pharmacological grounds, but no work has ever demonstrated its clinical relevance. Pentasaccharide is occasionally used before, but can be used after. Vitamin K antagonists (VKAs) are reserved for women with mechanical heart valves before delivery and can be used afterwards. Direct oral anticoagulants (DOACs) should not be used during pregnancy as they may be teratogenic, nor should they be used afterwards in breastfeeding women. Aspirin crosses the placenta but can be used before and after delivery. However, its effectiveness is highly questionable. Thrombolytics are reserved, before and after, for life-threatening thrombotic situations. The question of LMWH and epidural anesthesia is frequently raised. Local anesthesia techniques should not be applied <12 h after the last preventive injection, and <24 h after the last therapeutic dose injection. LMWH should not be administered within 6 h of epidural anesthesia or after the catheter has been removed. The cannula should not be removed <10–12 h after the most recent injection.

The development of objective Risk Assessment Methods (RAMs) has led some teams to propose scores to guide thromboprophylaxis.

The most notable one is that of the British group, focusing on the assessment of postpartum risk, whose extensive epidemiological studies have led to the publication of a model based on derivation and then validation cohorts (23). This model making it possible to extrapolate the absolute risk for a patient from selected clinical data (23): we have developed a practical online calculable version of this model in our university hospital, http://is.gd/postpartum_risk. The model appears to be more effective than the national guidelines, both British and Swedish, but the area under the ROC curve is still average, slightly over 0.70.

The group in Lyon prospectively described and validated a VTE risk score for pregnancy in 445 heterogeneous women with a history of VTE or with constitutive thrombophilia, accumulating 542 pregnancies (24), the value of the score leads to graduated therapeutic proposals applied to pregnancy, with preventive LMWH systematically prescribed during the postpartum period. The observed incidence of VTE is 8/542: 1.47%, which is at least 10 times higher than the natural incidence of VTE during pregnancy, with no comparison of prophylactic therapeutic modalities.

Another approach, proposed by the Strathège group coordinated in Saint-Etienne (25), was initially based on a national DELPHI method for selecting risk factors and means of prevention (26), constructing a score and proposing progressive prophylactic strategies indexed on that score. Applying a methodological approach before/after use of score-guided prevention in 2,085 pregnant women at risk of VTE or placental vascular complications reduced the incidence of the composite primary outcome [at least one VTE or placental vascular complication: from 19 to 13%, with a reduction of the incidence of DVT: RR 0.30 (0.14–0.67)] without increasing the risk of bleeding (from 3.2 to 4.5%). Placental vascular complications comprised mainly preeclampsia, which relative risk was also reduced: RR 0.52 (0.36–0.75).

These convincing approaches are not yet widely accepted by prophylaxis prescribers, who find them far too complex. However, these methods are full of objective promise and deserve clinical investment. The English algorithm provides an absolute risk value (22) that puts the treatment decision in perspective, particularly in the clinical records. Despite an obvious conflict of interest, we believe that the use of the Saint-Etienne score-guided prophylaxis suggestions has the advantage of having been tested prospectively and shown to be clinically useful (25, 26).

Furthermore, there is no convincing work in clinical biology or laboratory medicine to suggest that the use of functional or genetic laboratory data will make it possible to gain (in terms of relevance and efficiency) in the identification of women who are likely to develop VTE during pregnancy and in the following weeks.

The importance of women's values and preferences with regards to thromboprophylaxis must be discussed and taken in account. A multicenter, international study in women with a history of VTE compared women's choices using a holistic approach in which they were presented all of the relevant information (direct-choice) vs. a personalized decision analysis in which a mathematical model incorporated their preferences and VTE risk to make a treatment recommendation (27). A high degree of discordance between the two decision approaches was observed: 72% of the 72 women for whom the decision model recommended against thromboprophylaxis chose LMWH and 12% of the 51 women for whom the decision model recommended thromboprophylaxis chose not to take LMWH. A cross-sectional, international multicenter study included women with a history of VTE planning pregnancy or being pregnant (28) and determined their values and preferences, and the choices. More women at high risk (defined as women with prior unprovoked VTE or VTE associated with minor transient risk factor with 8 weeks prior to event) than those at low risk of recurrence chose to use LMWH (86 vs. 60%. Given a 16% risk of VTE without prophylaxis, the median threshold reduction in VTE at which women were willing to accept use of LMWH was 3%, interquartile range 1% to 6%. Given the wide variability in patients' values and preferences, patients with similar probabilities of the same consequences will make different choices. Individualized shared decision making is thus needed in the clinical encounter, and weak recommendations for LMWH must be suggested by guideline panels that make necessary the need for individualized shared decision making (28).

FOR OR AGAINST A BROADER USE OF HEPARIN PROPHYLAXIS?

How to best improve thromboprophylaxis around pregnancy remains highly controversial, with strong disagreements between experts and guidelines. Two main practical situations are central to this discussion: pregnant women hospitalized for an antepartum complication (the VTE risk being 17.5 times that of an outpatient pregnancy in the UK study) and Cesarean delivery, both at a high relative risk of VTE events. Some experts do

believe that more frequent use of heparin prophylaxis should be encouraged (29) and the best data supporting the safety and efficacy of heparin prophylaxis comes from the UK, with a decline in maternal deaths from VTE in the subsequent 2006–2008 Saving Mothers' Lives triennial report (30), with no associated increased risk of death from hemorrhage being evidenced. Other experts are against a more frequent use of heparins due to costs, lack of evidence and safety concerns [mainly the risk of wound hematomas (31)]. In the ideal situation, a prophylactic regimen based on the conclusions of relevant randomized clinical trials (RCTs) would be recommended. However, we will never have these RCTs because the feasibility of recruitment for such studies is nil, and rare attempts have been failures (32). The analysis of observational data from huge, nationwide registries and prospective cluster clinical trials in which the unit of randomization is not the patient but groups of patients defined, for example, according to the medical ward (hospital) in which they are followed and treated following local prophylactic regimens, might help to qualify/quantify certain clinically-relevant outcomes exploitable for future guidelines.

Going to the Clinicaltrial.gov website, some current studies in pregnant women are found which can draw what to expect in the next future. The NCT01828697 "Highlow" compares low and intermediate dose LMWH to prevent recurrent VTE in pregnancy and results will be soon communicated. The NCT03659708 "Prescot" conducts a medico-economic study to evaluate the efficiency of an innovative strategy integrating the Lyon-VTE-score (24) in the management of pregnant patients with venous thromboembolism risk vs. standard care. The NCT05066867 evaluates LMWH compliance among pregnant and postnatal women undergoing VTE thromboprophylaxis. The NCT01019655 investigate whether heparin is an effective treatment in pregnant women at risk for thrombosis and other pregnancy-associated complications, due to thrombophilia. The NCT02600260 evaluates in-hospital pregnant women through the application of a thromboprophylaxis protocol with risk assessment score. Some new answers will thus be soon available.

CONCLUSION

It is therefore clear that, although we have a better understanding of the epidemiology of VTE in pregnancy, its rarity makes its accurate prevention difficult. Conducting therapeutic trials in pregnancy is always a challenge. Making a decision on pharmacological prophylaxis is easy in the most caricatured cases that accumulate risk factors, but remains approximate most of the time. Many points remain unknown: in particular, the precise definition of the populations of women in whom the benefit-risk ratio is acceptable and when to begin prevention during pregnancy and after delivery in the event of obstetric hemorrhage. Also the type of antithrombotic: the use of DOACs after delivery seems to need further exploration, particularly as regards the return home, and perhaps even during breastfeeding as the concentrations of rivaroxaban in milk, for example, do not seem to exceed 10% of that present in maternal blood, and are therefore not clinically relevant. Finally, the dosages and durations need to be better defined.

The heterogeneous expert recommendations show their limits but, as the French humorist Francis Blanche used to say, *"a camel is a horse drawn by a committee of experts."* The use of "RAMs" (see above) seems to give us great encouragement. Systematic, repetitive assessment of individual thrombotic risk around the time of pregnancy has become compulsory. Teams should finally specify and choose one single common approach whose relevance should be regularly retrospectively evaluated. As randomized trials are unlikely to be conducted here, data from registries and large cohorts of patients are of major help. Finally, we may recall a discussion by Greene-Morton and Minkler (33) on cultural competence and cultural humility in 2020. They stated that believing that one should choose one thing over another would be a poor choice as, in medicine, both concepts have been generated by the professionals' understanding and must consider the biases therein.

AUTHOR'S NOTE

On November 2nd, 1907 at the age of 31, the artist Paula Becker (**Figure 1**), an early figure of German expressionism, gave birth to her daughter Mathilde with great difficulty. After 2 days of labor ending with chloroform, she finally delivered by forceps. Her doctor ordered her to stay in bed. She got up for the first time on November 20th, only to collapse and die of a pulmonary embolism.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

J-CG developed the idea, supervised, wrote the first draf, and reviewed all subsequent drafts. FG and MC helped in collecting and analyzing the relevant published data. CB and SB reviewed all subsequent drafts. All authors contributed to the article and approved the submitted version.

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EDITED BY
Luca Spiezia,
University of Padua, Italy

REVIEWED BY
Yafei Wu,
Xiamen University, China
Lifan Zhang,
Sichuan University, China

*CORRESPONDENCE
Kai Huang
huangk37@mail.sysu.edu.cn
Junmeng Zheng
zhengjm27@mail.sysu.edu.cn

†These authors have contributed equally to this work

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Machine learning-based prediction of the post-thrombotic syndrome: Model development and validation study

Tao Yu[1†], Runnan Shen[2†], Guochang You[2†], Lin Lv[2†], Shimao Kang[2], Xiaoyan Wang[2], Jiatang Xu[3], Dongxi Zhu[2], Zuqi Xia[2], Junmeng Zheng[2,3*] and Kai Huang[2,3*]

[1]Department of Emergency, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China, [2]Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou, China, [3]Department of Cardiovascular Surgery, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China

Background: Prevention is highly involved in reducing the incidence of post-thrombotic syndrome (PTS). We aimed to develop accurate models with machine learning (ML) algorithms to predict whether PTS would occur within 24 months.

Materials and methods: The clinical data used for model building were obtained from the Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis study and the external validation cohort was acquired from the Sun Yat-sen Memorial Hospital in China. The main outcome was defined as the occurrence of PTS events (Villalta score $\geq$5). Twenty-three clinical variables were included, and four ML algorithms were applied to build the models. For discrimination and calibration, F scores were used to evaluate the prediction ability of the models. The external validation cohort was divided into ten groups based on the risk estimate deciles to identify the hazard threshold.

Results: In total, 555 patients with deep vein thrombosis (DVT) were included to build models using ML algorithms, and the models were further validated in a Chinese cohort comprising 117 patients. When predicting PTS within 2 years after acute DVT, logistic regression based on gradient descent and L1 regularization got the highest area under the curve (AUC) of 0.83 (95% CI:0.76–0.89) in external validation. When considering model performance in both the derivation and external validation cohorts, the eXtreme gradient boosting and gradient boosting decision tree models had similar results and presented better stability and generalization. The external validation cohort was divided into low, intermediate, and high-risk groups with the prediction probability of 0.3 and 0.4 as critical points.

Conclusion: Machine learning models built for PTS had accurate prediction ability and stable generalization, which can further facilitate clinical decision-making, with potentially important implications for selecting patients who will benefit from endovascular surgery.

KEYWORDS

deep vein thrombosis, machine learning, post-thrombotic syndrome, prognosis, endovascular

Introduction

Post-thrombotic syndrome (PTS) is a common sequela of deep vein thrombosis (DVT), which is caused by chronic venous insufficiency (CVI), secondary to prior DVT, and can affect up to 50% of patients with proximal DVT within 2 years (1, 2). However, its pathophysiology remains unclear. Nonetheless, similar to other forms of CVI, PTS is mostly caused by venous hypertension, which is attributed to an irreversibly fibrosed vein wall, valvular damage, or residual venous obstruction after acute DVT (3). The clinical symptoms of PTS can manifest as heaviness, pain, edema, pruritus, and spasticity of the lower extremities, which are often aggravated during standing or walking and relieved while resting or lying down (4). PTS heavily affects the quality of life and has an effect comparable to that of heart failure or diabetes mellitus (5), which could cost an estimated annual direct cost of US $200 million and an annual loss of 2 million workdays in the United States (6, 7). Existing treatment options for PTS remain limited despite its severe harm to health and a high socioeconomic impact (8). Preventative interventions remain a key measure to reduce the incidence, impact on quality of life, and treatment cost of PTS.

Preventing PTS remains a huge challenge as symptoms of PTS change gradually during chronic progression. Many previous studies have identified predictors that may help in the risk stratification of patients with PTS. The baseline Villalta Scale score is usually identified as an independent predictor (9). Proximal, recurrent ipsilateral, or provoked DVT; previous varicose vein surgery; body mass index (BMI); age; gender; smoking status; and persistent venous obstruction may be helpful for risk stratification (10, 11). Five prediction models were developed by Huang et al. (12), the two-step model by Amin et al. (13), the SOX-PTS score by Rabinovich et al. (14), the prediction model for the elderly by Méan et al. (15), and a new predictive model by Qiu et al. (16) to determine the probability of PTS more accurately and facilitate clinical decision-making, and the two were validated externally (13, 14). An accurate clinical prognostic model can help patients at high risk of developing PTS receive sufficient clinical education and achieve optimal anticoagulation quality to prevent severe PTS and lower the cost of treatment. However, these models have limitations. First, the SOX-PTS score and two-step model were developed based on a large cohort (762 former, 479 latter); however, they had poor discrimination (13, 14). The SOX-PTS scale yielded C-Statistics of 0.65 (95% CI:0.64–0.67) and 0.63 (95% CI:0.59–0.67) in internal and external validation, respectively (14). For the two-step model, the optimism-corrected) AUCs were 0.71 for the baseline model and 0.60 for the secondary model, and those in the derivation cohort were 0.66 (95% CI:0.63–0.70) and 0.64 (95% CI:0.60–0.69), respectively, in external validation (13). Second, the other three prediction models, including the APTSD score, prediction model for the elderly, and new PTS predictive model by Qiu et al., showed far better prediction ability (AUC varied from 0.71 to 0.79); however, they were developed based on smaller cohorts (107 for APTSD score, 276 for being elderly, and 210 for the new PTS predictive model by Qiu et al.), and all lacked external validation, which made their models less convincing (12, 15, 16). Third, the model developed by Méan et al. was specially built for elderly patients aged >65 years, which undermined the applicability of the model (15). Fourth, these five models were built using traditional Cox or logistic regression (LR). However, some high-dimensional or non-linear relationships between clinical data and outcomes could not be identified.

Machine learning (ML) is a widely accepted computational technique that can overcome some of the limitations of current analytical approaches and capture high-dimensional,

Abbreviations: PTS, post-thrombotic syndrome; ML, machine learning; DVT, deep vein thrombosis; LR, logistic regression; AUC, area under the curve; 95% CI, 95% confidence intervals; XGBoost, eXtreme gradient boosting; GBDT, gradient boosting decision tree; CVI, chronic venous insufficiency; PE, pulmonary embolism; BMI, body mass index; ATTRACT, Acute Venous Thrombosis, Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis; PCDT, pharmacomechanical catheter-directed thrombolysis; BIOLINCC, Biologic specimen and Data Repository Information Coordinating Center; VCSS, venous clinical severity scores; VKA, vitamin K antagonists; LMWH, low-molecular weight heparin; DOAC, direct oral anticoagulation; ISTH, International Society on Thrombosis and Hemostasis; VTE, venous thromboembolism; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; CHF, congestive heart failure; SMOTE, Synthetic Minority Over-sampling Technique; RF, Random Forest; NRI, net reclassification improvement; IDI, integrated discrimination improvement; IQR, interquartile range; ROC, receiver operating characteristic; PMT, percutaneous mechanical thrombectomy; CDT, catheter directed thrombolysis.

non-linear relationships among clinical features to make data-driven outcome predictions (17). ML can also improve the robustness and generalizability of the prediction model by constructing a phenotypically cohort-based risk model (18). The potential to improve prediction accuracy for cardiovascular diseases using ML approaches has been investigated widely (19, 20). In this study, we hypothesized that ML could help improve the prediction accuracy of PTS using numerous multidimensional clinical variables. The clinical data used for model building were obtained from the Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT) study, a phase III, multi-center, dual-arm randomized clinical trial (21). The model was validated in a Chinese cohort to investigate its generalizability.

Materials and methods

Patients and materials

Clinical data of the derivation cohort included in this study were extracted from the ATTRACT study (21). A total of 691 patients with symptomatic proximal DVT, involving the femoral, common femoral, or iliac veins (with or without other involved ipsilateral veins), were randomly assigned to receive either pharmacomechanical catheter-directed thrombolysis (PCDT) with standard anticoagulation therapy or separate standard anticoagulation therapy in a 1:1 ratio. Relevant participant inclusion criteria can be found in the original study. Subjects were enrolled at 30–60 United States Clinical Centers for 4.5 years and followed up for 24 months. Since not every individual in ATTRACT completed a 2-year follow-up, patients with <2 years of follow-up and who did not present with PTS were excluded from this study to reduce the follow-up bias.

Clinical data in the external validation cohort were obtained from the electronic record database of Sun Yat-sen Memorial Hospital. The inclusion criteria were as follows: patients diagnosed with lower-extremity DVT who were admitted to the hospital between 2010 and 2020, and the gold standard for diagnosis was thrombus filling defect detected by Doppler ultrasound in the deep iliofemoral or femoral popliteal veins. Other auxiliary diagnoses included clinical symptoms, D-dimer index, and relative clinical score. As this study was retrospective, the requirement for informed consent was waived under the ethical supervision of the center. The patients were followed up for 2 years, and their Villalta and venous clinical severity scores (VCSS) were calculated. The exclusion criteria were as follows: (1) patients who refused follow-up visits or forgot about their status; (2) patients who had not been followed up for 2 years and did not present with PTS events; (3) patients whose baseline data could not be found in the electronic record database; (4) The patient was diagnosed with DVT but also with small saphenous vein thrombosis, femoral-popliteal vein sclerosis, and others diagnosed using Doppler ultrasonography; and (5) Patients mainly treated with traditional Chinese medicine.

Clinical treatment

The treatment plan in the ATTRACT study can be obtained from the original study or BIOLINCC in detail. The treatment plan of the external validation cohort also included patients undergoing standard DVT treatment with or without PCDT. The basic standard DVT treatment includes anticoagulation, inferior vena cava filter implantation, and physical pressure therapy. Anticoagulation drugs consisted of unfractionated heparin, low-molecular-weight heparin (LMWH), vitamin K antagonists (VKA), and direct oral anticoagulants (DOAC). For patients with DVT, but not cancer, DOACs, such as rivaroxaban or LMWH with VKA, were preferred. For those with cancer, LMWH, as well as VKA or DOAC, was preferred. The use of retrievable inferior vena cava filters is generally recommended for patients at a high risk of pulmonary embolism (PE) (history of PE, planned use of pneumatic compression therapy). Physical pressure therapy includes the use of elastic stockings and intermittent pneumatic compression devices. The treatment plan for PCDT at our center was detailed in our previous study (22). The patients were treated with LMWH twice daily before and after PCDT. The urokinase dosage was adjusted according to the patient's weight. Urokinase was first injected at a bolus dose of 2–3 $\times$ 10^5 U. Urokinase was continuously infused at a dose of 1–1.5 $\times$ 10^4 U/kg/d. Residual thrombi were evaluated daily using ultrasonography or venography. Thrombolysis should generally last for less than 7 days. If the patient experienced a mild, controllable bleeding event, PCDT was paused. If minor bleeding continued, the PCDT was permanently disabled. When anticoagulation was administered, an appropriate antagonist was used, if necessary. The center followed the guidelines of the American College of Chest Physicians for the diagnosis and treatment of DVT (23).

Outcomes and variables definition

In 2009, the International Society on Thrombosis and Hemostasis (ISTH) recommended the Villalta scale for PTS assessment 3–6 months following acute DVT (24). The Villalta score was calculated using five subjective symptoms (pain, spasm, heaviness, itching, and paresthesia) and six clinical signs (edema, redness, induration of the skin, hyperpigmentation, venous distension, and calf compression pain) scored on a scale from 0 (non-existent) to 3 (severe). The main outcome was PTS (binary outcome, which was defined as Villalta score of $\geq$5), whereas moderate-severe PTS (binary outcome, which was defined as Villalta score of $\geq$10) and severe PTS (binary

outcome, which was defined as Villalta score of ≥15) were secondary outcomes.

The VCSS score was also calculated for each patient, if possible. The VCSS score was calculated using 10 items, including pain, varicose veins, venous edema, skin pigmentation, inflammation, induration of active ulcers, number of active ulcers, active ulcer diameter, ulcer duration, and compression therapy, and scored on a scale from 0 (non-existent) to 3 (severe). The SOX-PTS score was also calculated based on the research by Rabinovich et al., which contained three items: iliofemoral DVT (1 score), BMI of ≥35 (2 scores), baseline Villalta score of ≥15 (2 scores), or baseline Villita score of 10–14 (1 score) (14).

Baseline data of the external validation cohort. Age, sex, complications, history of venous thromboembolism (VTE), provoked DVT, and in-hospital diagnoses were obtained from the admission records. The clinical treatment plan was obtained from the doctor's list. Height and weight were obtained from the nursing sheets. The DVT type and leg involved were obtained from the Doppler ultrasonography reports.

Imputation of missing value

Only variables that had missing value rate lower than 5% would be included in the model and filled with imputation. The missing rate of all variables is shown in **Supplementary Table 1**. Given the heterogeneity of the different populations in the derivation and external validation cohorts, imputation was conducted separately in two independent datasets. In this study, a single imputation was conducted to fill in the missing values based on the complete conditional criterion. Missing values were filled using the predictive mean matching method. Each missing variable was estimated using an independent model to ensure its validity (25). To ensure the authenticity of these scores, the Villalta, VCSS, and SOX-PTS scores were not imputed for missing values.

Feature selection and model development

Twenty-three variables were included in the structured dataset: basic demographic information, including age, sex, height, weight, and BMI; DVT-associated variables, including an extension to the iliac vein or isolated femoropopliteal, DVT leg, previous VTE, major surgery, hospitalization, plaster cast immobilization, childbirth, impatient qualifying DVT, baseline Villalta score, and complications, including hypertension, diabetes mellitus, high cholesterol, asthma, chronic obstructive pulmonary disease (COPD), angina or myocardial infarction (MI), congestive heart failure (CHF), DVT treatment type, and aspirin use. The treatment included PCDT with anticoagulation or base anticoagulation only.

As there still exited imbalance in the derivation set (slight for PTS in 24 months: 327 [58.9%], mainly when the outcome was set as moderate-severe PTS in 24 months: 144 [25.9%] and severe PTS in 24 months: 69 [12.4%]), the synthetic minority over-sampling technique (SMOTE) was used to oversample the derivation set, which was intended to synthesize new samples and add them into the derivation cohort to ensure equality between the number of positive and negative examples. Our previous experimental results also had shown that the performance index of the models was improved after oversampling in both primary and secondary outcomes (**Supplementary Table 2**).

To decrease the effect of non-normality on the model performance, the Shapiro-Wilk normality test was conducted to detect the normality of the continued variables in the derivation cohort (including age, height, weight, BMI, and base Villalta score) and none of them showed normality (**Supplementary Table 3**). In the derivation and external validation cohorts, zero-mean normalization of non-normal distribution continued variables was performed to eliminate dimensionality effects and improve comparability among variables.

To select a more suitable model that had a better matching degree with the data, 12 algorithms [including random forest (RF), logistic regression (LR), gradient boosting decision tree (GBDT), extreme gradient boosting (XGB), k-Nearest Neighbors (KNN), iterative dichotomiser 3 (ID3), classification and regression trees (CART), adaptive boosting (ADB), Gaussian naive Bayes (GNB), least absolute shrinkage and selection operator (LASSO), Elasticnet, and support vector classification (SVC)] were conducted to build models, and, finally, models with better performances in both derivation and external validation cohorts, which did not have too much overfitting, were chosen (**Supplementary Table 4**). At last, four ML algorithms, XGBoost, GBDT, and LR based on gradient descent, L1 regularization, and RF, were used for model building. An overview of ML algorithm principles used in this study is shown in **Supplementary Methods**. A grid search method was used to optimize the hyperparameters to improve the prediction ability of the model. Every individual in the derivation and external validation cohorts was given a prediction probability according to the different ML models.

In addition to the primary outcome, models for predicting secondary outcomes were established and validated.

Feature importance

The relative importance of each feature in the four models was calculated and ranked to select the predictor with the greatest impact on each outcome. The feature importance was retrieved using the scikit-learn library and XGBoost package. Based on the different principle of the four model algorithms, we used different methods to calculate the

feature importance. For RF, we used feature_importances_ property of RandomForestClassifier to calculate the feature importances, and the calculation method was based on impurity. For GBDT, we used feature_importances_ property of GradientBoostingClassifier, and the calculation method was based on impurity. For XGBoost, we used feature_importances_ property of XGBClassifier, and the calculation method was based on "gain," which used the average gain across all splits of the feature. For LR, we used coef_ attribute of LogisticRegression, and the calculation method was based on regression coefficient.

Moreover, to explain the interpretability of ML in more depth, permutation importance was calculated by ELI5 package of Python. Partial dependence plots (PDP) were drawn by the sklearn package of Python to show the marginal effect that each feature had on the predicted outcome of a model. Shapley additive explanations (SHAP) values were calculated by the SHAP package of Python, which used a game theoretic approach, to explain the output of ML models. The SHAP force plots and feature importance plots were also plotted.

Evaluation and validation of the model

Evaluation of the model was internally validated with 10-fold cross-validation in the derivation cohort to investigate the stability of the model (derivation cohort was divided into training and internal validation dataset for 10-fold cross-validation), and then external validation was conducted to investigate the generalization ability of the model. AUC and calibration plots were used to evaluate the discrimination and calibration. After determining the cutoff value of the prediction probability by the receiver operating characteristic (ROC) curve, calibration and risk classification results, F scores, negative predictive value, positive predictive value, sensitivity, and specificity were used to evaluate the risk stratification ability of the models. We also externally validated the SOX-PTS score in the derivation and external validation cohorts and used net reclassification improvement (NRI) and integrated discrimination improvement (IDI) to investigate the prediction ability improvement of ML models compared with SOX-PTS.

Risk classification

Patients in the external validation cohort were divided into estimated risk deciles in accordance with the prediction probability yielded by the four models and then grouped into low-, intermediate-, and high-risk groups with thresholds reflecting clinically meaningful gradients in risk from one group to the next. The mean prediction probability and observed probability were calculated for each group.

Statistical analysis

Continuous variables were represented by the median with interquartile range (IQR) and compared using the Kruskal–Wallis test. Categorical variables are expressed as percentages, compared with chi-square tests. A two-sided $P < 0.05$ was considered statistically significant. Data imputation and significance tests were conducted using R software (version 3.6.3). Data preprocessing, model development, and further evaluation and validation were conducted using Python (version 3.8.5).

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Results

After filtration based on the exclusion criteria in this study, 555 patients from the ATTRACT study were finally included in the derivation cohort to build four models with ML methods comprising XGBoost, GBDT, LR, and RF. As for the external validation cohort, 428 patients were diagnosed with DVT between 2010 and 2020, 288 patients refused follow-up or forgot the details of body status, and 117 patients were finally included in the external validation cohort. The study pipeline is illustrated in **Figure 1**. The baseline data of the derivation and external validation cohorts are shown in **Table 1**, and the heterogeneity of different populations can be observed. The prevalence of PTS occurrence within 2 years and previous VTE was higher in the derivation cohort than in the external validation cohort (58.9 vs. 32.5% [$P < 0.001$]; 23.4 vs. 19.7% [$P = 0.446$]). The BMI in the derivation cohort was higher than that in the validation cohort (30.84 [26.98, 36.17] vs. 23.87 [21.31, 26.20], $P < 0.001$), as were basic comorbidities and aspirin use (21.4 vs. 10.3%, [$P = 0.008$]). However, the DVT occurrence age was lower in the derivation cohort than in the external validation cohort (54 [44, 62] vs. 59 [48, 67], $P = 0.002$). A higher prevalence of VTE occurrence, and basic comorbidities, as well as a higher BMI, might be associated with a higher prevalence of PTS occurrence.

The relative importance of the features in the four models was ranked, and a radar plot of the seven most important features for each model is shown in **Figure 2**. The main predictors varied among the four models, which was due to the principle of different algorithms and the method of

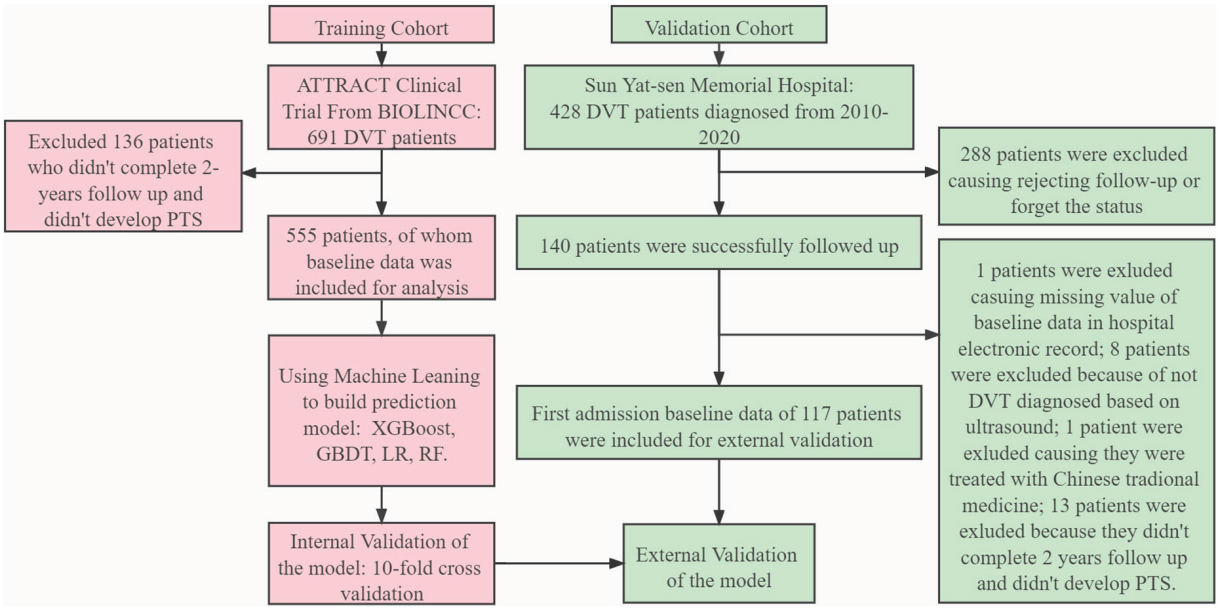

FIGURE 1
Model development and evaluation pipeline. ATTRACT, Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis; BIOLINCC, Biologic Specimen and Data Repository Information Coordinating Center; PTS, post-thrombotic syndrome; XGBoost, eXtreme gradient boosting; GBDT, gradient boosting decision tree; RF, random forest; LR, logistic regression; DVT, deep vein thrombosis.

importance calculation. BMI, diabetes mellitus, baseline Villalta score, and treatment type all appeared on the importance radar of the four models. High-cholesterol level, weight, and history of VTE were observed on radar images in three of the models. In addition, two other radar plots built for predicting the occurrence of moderate-severe PTS and severe PTS are shown in **Supplementary Figures 1, 2**. It is worth noting that BMI, diabetes mellitus, baseline Villalta score, and treatment type were four significant features that appeared in all radar plots, whereas BMI failed to appear in the GBDT model when predicting moderate-to-severe PTS. Thus, there were adequate reasons to believe that these four features were the most important for predicting PTS.

To explain the interpretability of ML in more depth and evaluate the effect of variables on outcome, permutation importance for 3 outcomes was calculated and is shown in **Supplementary Tables 5–7**. Baseline Villalta score got the highest weight in LR and GBDT when predicting PTS in 24 months, while weight and diabetes mellitus got highest in RF and XGB. PDP showed the influence of each feature for 3 outcomes and is shown in **Supplementary Figures 3–5**. The SHAP force plots showed which features have the most influence on the model's prediction for a single observation and are shown in **Supplementary Figures 6–8**. The SHAP feature importance plots are shown in **Supplementary Figures 9–11**, which were similar to permutation importance, showing the effect of each feature on the outcome.

When the models were evaluated and validated, the LR, based on gradient descent and L1 regularization, performed best in external validation (0.83 [95% CI:0.76–0.89]). In the derivation cohort, RF performed best (0.81 [95% CI:0.78–0.84]), whereas LR performed worst (0.73 [95% CI:0.70–0.76]). The ROC curves for the four models for predicting PTS are shown in **Figure 3**. In addition, four models were used to predict moderate-to-severe PTS and severe PTS. In the external validation cohort, LR performed best in predicting moderate-to-severe PTS and PTS, with AUCs of 0.97 (95% CI:0.94–1) and 0.99 (95% CI:0.97–1), respectively. The ROC curves for the prediction of secondary outcomes are shown in **Supplementary Figures 12, 13**.

The calibration plots of the four models for the three outcomes in both the derivation and external validation cohorts were also plotted, as shown in **Supplementary Figures 14–19**.

For other ML performance indices, we paid more attention to the F2 score because the dataset had a degree of imbalance, and the potential cost of missed real cases was higher than that of missed cases. The results showed that all four models had a good predictive ability (F2 score:0.70–0.76 when the threshold was set to 0.3). LR performed best in predicting moderate-to-severe and severe PTS (F2 score:0.76 and 0.91, respectively, when the threshold was set at 0.4). Other performance indices (F1 score, F.5, negative predictive value, positive predictive value, accuracy, sensitivity, and specificity) are shown in **Supplementary Figures 20, 21**. The NRI and IDI results showed that all four models performed better

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TABLE 1 Baseline characteristics and outcome of derivation cohort and validation cohort.

Characteristics and outcome	Derivation cohort (n = 555)	Validation cohort (n = 117)	P-value
Treatment			0.011
Using PCDT with anticoagulation	279 (50.3%)	43 (36.8%)	
Using anticoagulation only	276 (49.7%)	74 (63.2%)	
DVT type			0.055
Extend to Iliac vein	313 (56.4%)	54 (46.2%)	
Isolated femoropopliteal	242 (43.6%)	63 (53.8%)	
Age	54.00 [44.00, 62.00]	59.00 [48.00, 67.00]	0.002
Gender			0.004
Male	349 (62.9%)	56 (47.9%)	
Female	206 (37.1%)	61 (52.1%)	
Comorbidity			
Hypertension	242 (43.6%)	15 (12.8%)	<0.001
Diabetes mellitus	91 (16.4%)	8 (6.8%)	0.012
High cholesterol	176 (31.7%)	8 (6.8%)	<0.001
Asthma	57 (10.3%)	3 (2.6%)	0.013
COPD	22 (4.0%)	2 (1.7%)	0.357
MI	25 (4.5%)	4 (3.4%)	0.783
CHF	26 (4.7%)	1 (0.9%)	0.097
Height	175.00 [165.10, 182.88]	164.00 [156.00, 170.00]	<0.001
Weight	93.00 [80.95, 112.14]	62.50 [57.00, 71.50]	<0.001
BMI	30.84 [26.98, 36.17]	23.87 [21.31, 26.20]	<0.001
DVT leg			0.029
Right	209 (37.7%)	31 (26.5%)	
Left	346 (62.3%)	86 (73.5%)	
Previous VTE	130 (23.4%)	23 (19.7%)	0.446
DVT risk factor			
Major surgery	48 (8.6%)	25 (21.4%)	<0.001
Hospitalization	55 (9.9%)	14 (12.0%)	0.618
Plaster cast immob	15 (2.7%)	3 (2.6%)	1
Childbirth	7 (1.3%)	5 (4.3%)	0.064
Inpatient qualify DVT	92 (16.6%)	17 (14.5%)	0.683
Taken aspirin	119 (21.4%)	12 (10.3%)	0.008
SOX-PTS score	2.00 [1.00, 3.00]	1.00 [0.00, 1.00]	<0.001
PTS in 24 Months	327 (58.9%)	38 (32.5%)	<0.001

PCDT, pharmacomechanical catheter-directed thrombolysis; DVT, deep vein thrombosis; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; CHF, congestive heart failure; BMI, body mass index; VTE, venous thromboembolism; PTS, post-thrombotic syndrome.
All values included in the machine learning model had missing value rate lower than 1%.

than the SOX-PTS score in the derivation and external validation cohorts (NRI and IDI > 0, $P < 0.05$), as shown in Table 2.

The ten divided groups based on the estimated risk deciles of the four models predicting PTS in the external validation cohort are shown in Figure 4. The observed probability also tended to increase with an increase in the prediction probability. According to the risk classification results of XGBoost, LR, and GBDT (RF was excluded because of its poor performance in external validation), we stratified the patients into three risk groups (first to fifth deciles as low risk: prediction probability approximately lower than 30%; sixth to eighth deciles as intermediate risk: prediction probability approximately of 30–40%; and eighth to tenth deciles as high risk: prediction probability approximately higher than 40%). In calibration plots of four models in both derivation and validation cohorts (Supplementary Figure 14), underestimation is shown when predicted probability is higher than 0.4. As a result, defining 0.4 as the high-risk threshold was meaningful. The risk stratification figures for PTS in the derivation cohort are also plotted and shown in Supplementary Figure 22. The risk stratification figures for moderate-to-severe and severe PTS in both the derivation and external validation cohorts are also plotted and are shown in Supplementary Figures 23–26.

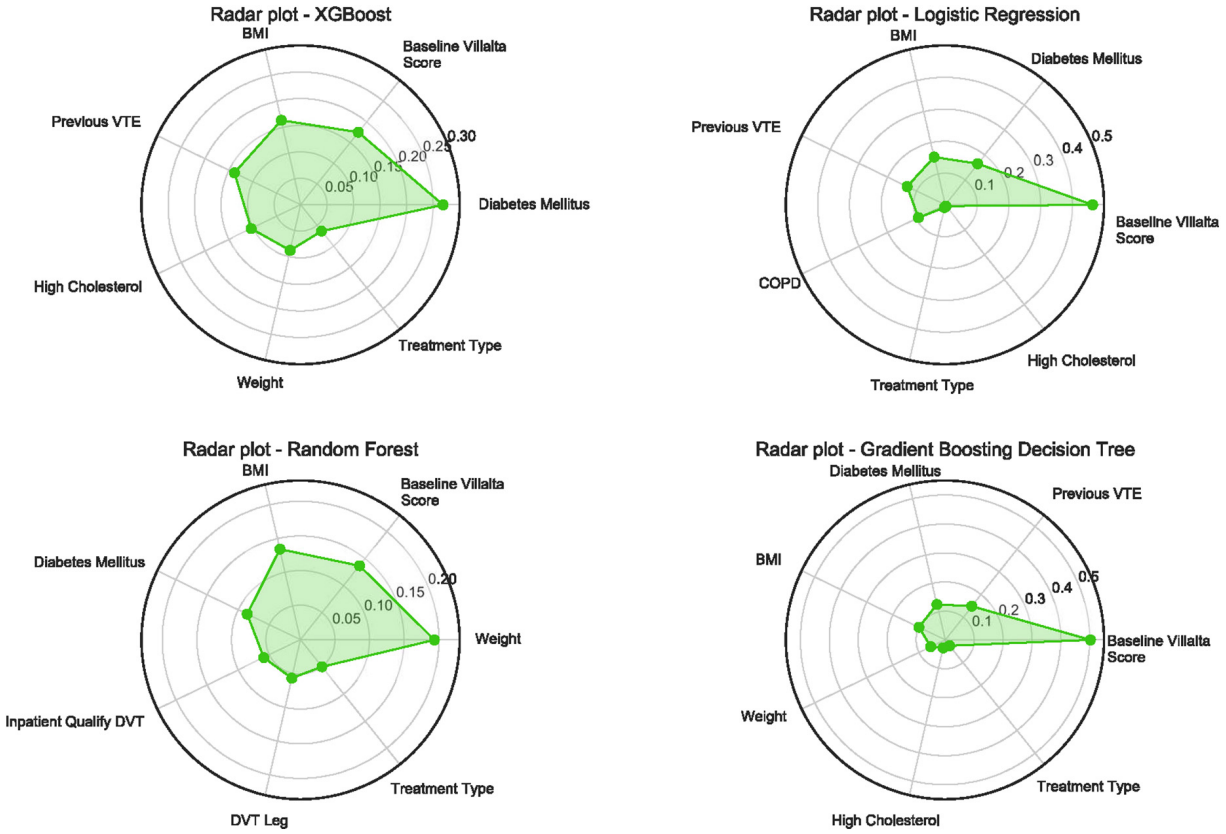

FIGURE 2
Radar plot for the seven important predictors of post-thrombotic syndrome in 24 months. Higher value means more importance of the features determined by different ML algorithms. PTS, post-thrombotic syndrome; XGBoost, eXtreme gradient boosting; VTE, venous thromboembolism; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; ML, machine learning.

To evaluate the risk classification ability of the ML models, the XGBoost model was chosen as an example to investigate the association between risk groups and clinical features. As the derivation group was divided into low-risk, intermediate-risk, and high-risk groups based on the prediction probability of XGBoost, the prevalence of PTS increased (PTS: 14.8% [9/61] low risk vs. 34.3% [12/35] intermediate risk vs. 81% [17/21] high risk; moderate-severe PTS: 0% [0/61] low risk vs. 5.7% [2/35] intermediate risk vs. 28.6% [6/21] high risk; severe PTS:0% [0/61] low risk vs. 0% [0/35] intermediate risk vs. 19% [4/21] high risk). In addition, the related risk scores at different time points showed similar results, as shown in **Table 3**.

Discussion

In this study, 555 patients with DVT were included to build models with different ML algorithms, and the models were validated in a Chinese cohort of 117 patients. The results showed that the models presented good prediction abilities for both the primary and secondary outcomes. When predicting PTS 2 years after acute DVT, LR based on gradient descent and L1 regularization had the highest AUC of 0.83 (95% CI:0.76–0.89) in external validation, whereas RF had the highest AUC of 0.81 (95% CI:0.78–0.84) in the derivation cohort. However, when considering the model performance in both the derivation and validation cohorts, the XGBoost and GBDT models had similar results and presented better stability and generalization. Compared with the SOX-PTS score, all ML models exhibited improved prediction ability, with NRI and IDI indices all significantly higher than zero. After dividing the external validation cohort into ten groups based on the estimated risk deciles of the models, three risk groups were identified. Moreover, a tendency of increase in the risk score and prevalence of PTS occurrence could be found as the risk increased, which indicated good clinical application of the models. Moreover, BMI, diabetes mellitus, baseline Villalta score, and treatment type were identified as important features using ML algorithms in this study. To the best of our knowledge, this study is the first to build models for predicting PTS using ML algorithms and confirm that ML can help improve the prediction ability.

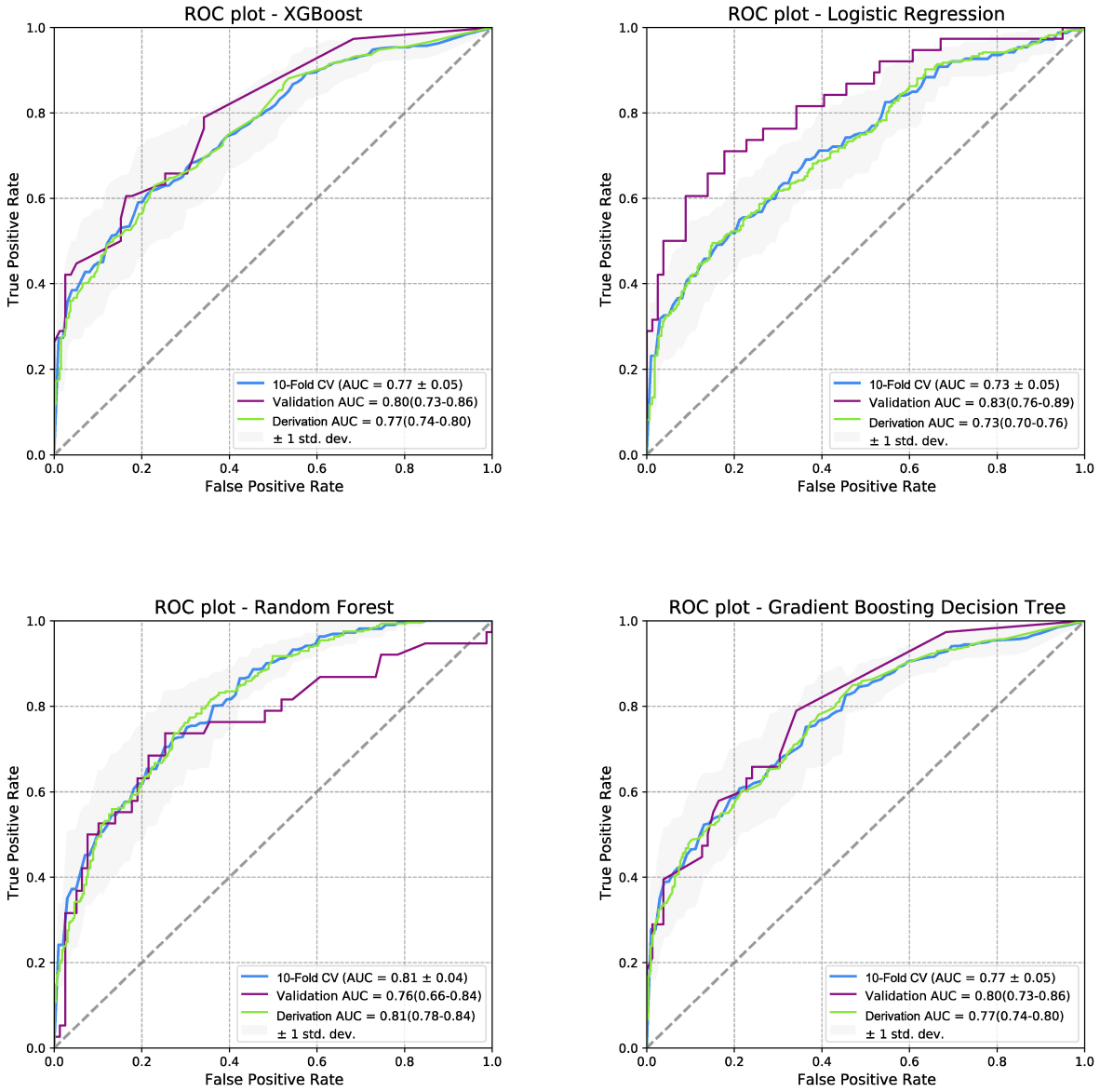

FIGURE 3
Receiver operating characteristic curves for post-thrombotic syndrome at 2-year follow-up. ROC, receiver operating characteristic curve; PTS, post-thrombotic syndrome; AUC, area under the curve; XGboost, eXtreme gradient boosting.

TABLE 2 Net reclassification improvement and integrated discrimination improvement results of machine learning models compared with the SOX-PTS score.

Different methods compared with SOX-PTS	Derivation cohort		Validation cohort	
	NRI (95% CI/*P*-value)	IDI (95% CI/*P*-value)	NRI (95% CI/*P*-value)	IDI (95% CI/*P*-value)
XGBoost	0.621 (0.461–0.782/<0.001)	0.098 (0.074–0.121/<0.001)	0.351 (0.095–0.607/0.007)	0.176 (0.091– 0.260/<0.001)
LR	0.642 (0.484–0.801/<0.001)	0.082 (0.062–0.103/<0.001)	0.518 (0.264–0.772/<0.001)	0.239 (0.154–0.324/<0.001)
RF	0.664 (0.507–0.820/<0.001)	0.124 (0.099–0.149/<0.001)	0.350 (0.077–0.622/0.012)	0.078 (−0.001–0.157/0.054)
GBDT	0.672 (0.514–0.830/<0.001)	0.102 (0.078–0.125/<0.001)	0.404 (0.141–0.668/0.003)	0.144 (0.062–0.227/<0.001)

XGBoost, extreme gradient boosting; LR, logistic regression; RF, random forest; GBDT, gradient boosting decision tree; NRI, net reclassification improvement; IDI, integrated discrimination improvement.

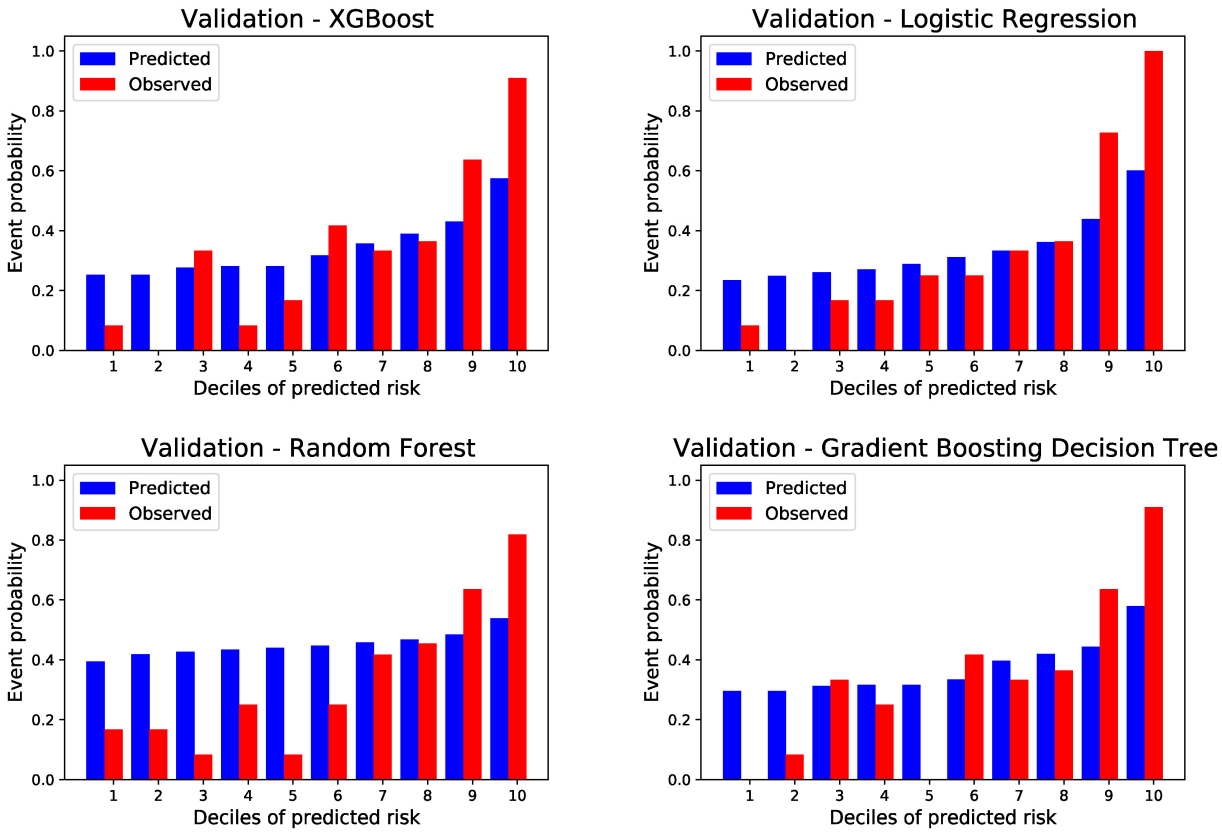

FIGURE 4
Risk of post-thrombotic syndrome within 24 months according to deciles of event probability based on four machine learning models in the validation cohort. PTS, post-thrombotic syndrome; ML, machine learning; XGBoost, eXtreme gradient boosting.

TABLE 3 Outcome in each risk groups defined by prediction probability of the XGBoost model in external validation cohort.

Outcome	Low-risk group ($n = 61$)	Intermediate-risk group ($n = 35$)	High-risk group ($n = 21$)	*P*-value
Risk score				
Baseline Villalta score	1.00 [1.00, 3.00]	2.00 [1.00, 3.50]	9.00 [3.00, 13.00]	<0.001
6 Month Villalta score	0.00 [0.00, 2.00]	1.00 [0.00, 2.25]	5.00 [4.00, 10.75]	<0.001
12 Month Villalta score	0.00 [0.00, 1.00]	0.00 [0.00, 1.50]	4.00 [1.00, 6.00]	0.002
18 Month Villalta score	1.00 [0.00, 1.00]	1.00 [0.00, 2.75]	3.00 [2.00, 6.50]	0.001
24 Month Villalta score	1.00 [0.00, 2.00]	1.00 [0.00, 3.00]	3.00 [0.00, 5.25]	0.073
6 Month VCSS score	0.00 [0.00, 1.00]	1.00 [0.00, 1.25]	3.00 [2.00, 5.00]	<0.001
12 Month VCSS score	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	2.00 [1.00, 3.50]	0.002
18 Month VCSS score	1.00 [0.00, 1.00]	1.00 [0.00, 1.25]	2.00 [1.00, 3.00]	0.004
24 Month VCSS score	1.00 [0.00, 1.00]	1.00 [0.00, 2.00]	2.00 [0.00, 3.25]	0.057
Baseline SOX-PTS score	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	1.00 [1.00, 2.00]	<0.001
Binary outcome				
PTS in 24 months	9 (14.8%)	12 (34.3%)	17 (81.0%)	<0.001
Moderate to severe PTS in 24 months	0 (0.0%)	2 (5.7%)	6 (28.6%)	<0.001
Severe PTS in 24 months	0 (0.0%)	0 (0.0%)	4 (19.0%)	<0.001

Low-risk group was defined as patients whose XGBoost prediction ability is lower than 30%, Intermediate-risk group was defined as patients whose XGBoost prediction ability is between 30 and 40%, High-risk group was defined as patients whose XGBoost prediction ability is higher than 40%.
VCSS, venous clinical severity scores; PTS, post-thrombotic syndrome.

Predicting and preventing PTS remains a challenge to date. There is still no effective treatment, and the management thereof relies more on prevention after DVT (8). Anticoagulation remains the cornerstone of acute DVT treatment. Although it is not the main purpose of treatment, it plays a key role in preventing the development of PTS (26). Physiological and clinical studies have shown that LMWH is preferred over VKA in preventing PTS due to its improved rates of venous recanalization and anti-inflammatory effects (27, 28). However, current guidelines do not recommend specific anticoagulation to prevent PTS in clinical practice (10). Extending anticoagulation therapy also adversely affected the prevention of PTS, and it is recommended that VTE occurrence besides PTS be prevented (29, 30). Early thrombus removal may prevent PTS by reconstructing the microenvironment of blood circulation and preserving venous function (31). However, the results of the ATTRACT study showed that PCDT did not exert a protective effect on PTS (46.7% PCDT vs. 48.2% no PCDT, $P = 0.56$). This might be interpreted as the ATTRACT study, including both femoropopliteal and iliofemoral DVT, and femoropopliteal DVT showed a lower risk of developing PTS (21). Therefore, another study conducted a subgroup analysis of the iliofemoral arm in ATTRACT and showed that PCDT reduced the risk of moderate-to-severe PTS (18% PCDT vs. 28% no PCDT, $P = 0.021$) (32). A recent study investigated the efficacy of different treatment modalities for percutaneous thrombus removal and found that the use of PCDT for treating iliofemoral DVT could provide comparable patient outcomes, comparable vessel patency, an acceptable safety profile, and a reduced overall lytic dose (33). Percutaneous mechanical thrombectomy (PMT) is an alternative method for DVT treatment, and pharmacomechanical thrombectomy refers to a combination of mechanical and pharmacological therapies to achieve thrombolysis. Compared with PCDT or catheter-directed thrombolysis (CDT) alone, pharmacomechanical thrombectomy can lower thrombolytic dosage and procedural time and achieve a more complete resolution of the thrombus. When the prognosis results of PMT ± CDT and CDT alone were compared, the partial thrombolysis rate was higher in the PMT ± CDT group (odds ratio, 2.64; 95% confidence interval, 1.34–5.21; $P = 0.005$) (34). With advancements in endovascular technology, we believe that it can reduce PTS risk in the future. An accurate prediction model can help identify patients who can benefit from endovascular surgery, which we hypothesize is one of the most important implications of our models.

Machine learning is currently an effective method to investigate high-dimensional and non-linear relations between features and outcomes and improves the prediction ability of the prognostic model (17). In this study, ML models reached a higher AUC than previous PTS models and attained an improved prediction ability compared with SOX-PTS. We used an American cohort to build models and a Chinese cohort to validate them to ascertain whether the models were effective in other populations as well. Western and Asian populations are extremely heterogeneous. Previous studies have indicated that VTE occurrence and reoccurrence were not as high in the Chinese cohort as in the Western population (35, 36). In addition to the effect of genes, nutritional status, dietary habits, economic status, and medical status also affect the prognosis of DVT. In this study, we found that the prevalence of PTS occurrence in 2 years and previous VTE was higher in the derivation cohort, which might be associated with higher BMI, higher prevalence of basic comorbidity, and aspirin use (aspirin use also indicated worse health status). However, models built with XGBoost and GBDT still showed good and stable prediction abilities in internal and external validation, which indicated the good stability and generalization of ML.

The chosen four ML models in this study both had their advantages and disadvantages. LR is a kind of discriminative models, which can be used in combination with regularization methods. The linear models have high interpretability compared to most classification algorithms. LR has the advantages of easy implementation and low computational cost. However, when there are a large number of features, LR performances are poor, and LR is easy to cause underfitting. It is mostly used to deal with binary classification problems, and the classes must be linearly separable. The non-linear characteristics need to be transformed before modeling. RF performs well on a lot of datasets. Firs, RF is suitable for highly dimensional features. Second, it has fast calculation speed and easy implementation. Third, the model has strong generalization ability. Fourth, RF has strong anti-interference capability and can also be used when there is a large amount of missing data. Fifth, it has a strong anti-overfitting ability. The disadvantages of RF are the following: poor performances in solving regression problems; the model is similar to the black box, which has poor interpretability; and it may not produce good classification results in small samples or low dimensional data. GBDT has good prediction performances and is suitable for low-dimensional data. It can flexibly handle various types of data and has strong robustness to outliers. However, due to the dependency between weak learners, it is difficult to carry out parallel computing. The calculation complexity will be increased when the data dimension is high. XGBoost is based on GBDT. Compared with GBDT, XGBoost has the following advantages: first, adding the complexity of tree models to the regularization term, the generalization ability is better; second, it uses Taylor expansion on the loss function to accelerate the optimization speed; and third, XGBoost supports parallel processing (37).

The performance metrics for four ML models in predicting different outcomes were shown in **Supplementary Figure 21**. The threshold term indicated the threshold of 0/1 classification of samples according to the model prediction probability, where in the fourth column of each model was the best cutoff value of ROC curve. For PTS in 24 months, performance indices of RF and LR were similar, performance indices of

GBDT and XGBoost are similar, and the former two models performed better than the latter two. For moderate-severe PTS, performance indices of four models were different. LR had the highest F2 score and accuracy, while the other three models had low F2 scores and accuracy. XGBoost had the highest sensitivity and specificity, while LR had the lowest sensitivity and specificity. For severe PTS, LR had the best performance indices, while XGBoost and GBDT had the worst performance indices, because both the accuracy and sensitivity of LR were higher than XGBoost and GBDT.

Area under the curve is an important index to evaluate the discrimination of the models; however, the cut-off value of prediction probability should also be focused on because risk stratification and prevalence identification in each risk group are important for clinical decision-making. Based on the prediction results of the XGboost, three risk groups were identified. PTS occurrence reached up to 81% in the high-risk group and only 14.8% in the low-risk group. Other ML performance indices can also be calculated after the threshold is determined to reflect the effectiveness of the models. The results showed that all four models had good predictive ability (F2 score:0.70–0.76 when the threshold was set to 0.3). LR performed best in predicting moderate-severe and severe PTS (0.76 and 0.91 when the threshold was set as 0.4). The threshold may vary in different populations as the prevalence of disease may differ.

In this study, a more important result was the identification of important features for predicting PTS, including BMI, diabetes mellitus, baseline Villalta score, treatment type, high cholesterol level, and history of VTE. BMI and baseline Villalta score as risk factors have been validated by previous studies and were also the predictive items included in the SOX-PTS score (14). A history of VTE or recurrent DVT is a strong predictor of PTS (38). PCDT was found to be a protective factor in the present study. Therefore, diabetes mellitus and high-cholesterol levels were identified as new risk factors that have not been reported elsewhere. The pathophysiology and epidemiological mechanisms are complex. Diabetes mellitus is associated with an increased risk of DVT and CVI (39, 40), which can be attributed to PTS. Moreover, a hyperglycemic environment can damage the vascular wall and create hypercoagulability (41). High-cholesterol levels are also associated with DVT due to hypercoagulability in the blood and can reduce the rate of thrombosis recanalization (42). Previous studies have shown that statin use was associated with a higher rate of thrombus resolution and could reduce the rate of PTS (38.3 and 48.5% in the statin and control groups, respectively, $P = 0.02$) (43, 44). Hyperglycemic and high-cholesterol levels can also contribute to inflammation and senescent pathological changes in the vasculature (45, 46). However, there are still some confounding factors, such as BMI, diabetes mellitus, and high-cholesterol levels, which are associated with BMI and drug use. The mechanism, by which these two factors contribute to the development of PTS, requires further investigation.

This study has several limitations. First, it had a retrospective design, and the derivation cohort in the ATTRACT study was not designed to build models in the original study. Consequently, some important factors were not included in the model because they were not included prospectively or too many values were missing. For example, some laboratory induces, such as D-dimers, were not included because >20% of the values were missing, which might affect the ability of the model if they were filled using mean values or single imputation. Moreover, previous studies have indicated that previous varicose vein surgery is a strong predictor (13). However, it was not recorded in the ATTRACT database and not included in the model. Second, as varicose veins, iliac vein compression syndrome, and smoking status were not recorded in ATTRACT, other previous scores [including APTSD score by Huang et al. (12), two-step model by Amin et al. (13), the prediction model for elderly by Méan et al. (15), and a new predictive model by Qiu et al. (16)] could not be validated and compared with our models. Although the AUC showed that our ML models improved the prediction ability, it would be more rigorous if they were validated in the same cohort using the NRI and IDI to evaluate the difference in prediction ability. Third, the external validation cohort did not record any bleeding events as a safety outcome. If bleeding events were recorded, the prevalence of PTS and bleeding events could be calculated in each risk group, e.g., using the PRAISE score (20), which could guide further anticoagulation or other treatment. However, the duration of anticoagulation therapy cannot be extended, especially to prevent PTS. In clinical practice, extended anticoagulation should refer to the risk of VTE and bleeding. We believe that this limitation did not affect the value of the model too greatly. Fourth, all four models slightly underestimated the high-risk category when predicting PTS, which negatively impacted the predictive power of the prediction system. In the future, we may consider ways to reduce the underestimation of the current model. For example, adding a penalty during the derivation phase or selecting a different classification threshold. Other ML algorithms, such as neural networks, can be used to build the model or increase the sample size of the derivation data.

In conclusion, we developed and validated models using ML algorithms in large cohorts. This study demonstrated that the ML models had accurate prediction ability and stable generalization, which can further facilitate clinical decision-making, with potentially important implications for selecting patients who will benefit from endovascular surgery.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Informed patient consent was exempted, and the study was approved by the Ethics Committee of Sun Yet-sen Memorial Hospital. Additionally, the study was conducted in accordance with the ethical principles for medical research involving human subjects set out in the Declaration of Helsinki. Data associated with ATTRACT research were requested from the Biologic Specimen and Data Repository Information Coordinating Center (BIOLINCC). According to the purposes of the study, the clinical research protocol was written in advance and reviewed by the Ethics Committee of Sun Yat-sen Memorial Hospital (SYSEC-KY-KS-2020-188) and the Independent Committee of BIOLINCC (BIOLINCC ID:9456). Related baseline data and outcomes were consolidated and extracted using BIOLINCC software.

Author contributions

TY, RS, GY, and KH: conception and design. TY and KH: administrative support. RS, GY, LL, DZ, and JX: provision of study materials or patients. RS and LL: collection and assembly of data. RS, GY, LL, SK, XW, and ZX: data analysis and interpretation. All authors manuscript writing, final approval of manuscript, agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated, and resolved.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.990788/full#supplementary-material

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EDITED BY
Hugo Ten Cate,
Maastricht University Medical Centre, Netherlands

REVIEWED BY
Andrea Vergara,
University of Campania Luigi Vanvitelli, Italy
Donatella Caserta,
Sapienza University of Rome, Italy

*CORRESPONDENCE
Mohammed A. Alsheef
malsheef@kfmc.med.sa

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Predictors of pregnancy-associated venous thromboembolism: A case-control study

Mohammed A. Alsheef[1]*, Alhanouf M. Alabbad[2], Rowida A. Albassam[2], Rawan M. Alarfaj[2], Abdul Rehman Zia Zaidi[1,3], Ouhod A. Alarfaj[4], Mohsen Ayyash[5] and Amani Abu-Shaheen[6]

[1]Department of Medical Specialties, King Fahad Medical City, Riyadh, Saudi Arabia, [2]College of Pharmacy, Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia, [3]College of Medicine, Alfaisal University, Riyadh, Saudi Arabia, [4]Pharmacy Service Administration, King Fahad Medical City, Riyadh, Saudi Arabia, [5]School of Mathematical Sciences, University Sains Malaysia (USM), Gelugor, Malaysia, [6]Scientific Writing Department, King Fahad Medical City, Riyadh, Saudi Arabia

Background: Venous thromboembolism (VTE), manifesting as pulmonary embolism (PE) or deep vein thrombosis (DVT), is the most common cause of morbidity and death during pregnancy and the postpartum period. We conducted this study to describe the predictors of pregnancy-associated VTE (DVT and PE).

Methods: A case-control study was conducted at a tertiary care center in Riyadh. A total of 380 patients were included in this study, 180 of whom were diagnosed with pregnancy-associated thrombosis and 200 of them showed no VTE. Demographic data and data on risk factors of VTE were collected by reviewing the medical charts and the risk assessment tool of the Royal College of Obstetricians and Gynecologists, respectively. The main outcome measures were VTE, manifesting as PE or DVT.

Results: The following factors were identified as the predictors of VTE through multivariate analysis: family history [Odds ratio (OR) = 50.47, 95% Confidence Interval (CI): 6.78–375.64, $P < 0.0001$)], thrombophilia (OR = 21.99, 95% CI: 2.83–170.63, $P = 0.003$), and presence of gross varicose veins (OR = 17.15, 95% CI: 3.93–74.87, $P < 0.0001$).

Conclusions: The findings of this study showed that family history, thrombophilia, and the presence of gross varicose veins were risk factors for VTE, exceeding other transient risk factors. Hence, prophylaxis is highly recommended for those women who present with any of these factors.

KEYWORDS

associated venous thromboembolism, pregnancy, VTE, deep vein thrombosis, DVT and PE

Introduction

Venous thromboembolism (VTE), which may manifest as pulmonary embolism (PE) or deep vein thrombosis (DVT), is a serious medical condition associated with significant morbidity and mortality and is expected to more than double in the next 40 years (1). It is predominantly a disease of old age and rarely occurs before late adolescence (2, 3). VTE incidence rates are slightly higher in women during their childbearing years, while in men it is generally higher after the age of 45 (4).

Age, body mass index (BMI), major surgery, hospitalization for acute illness, trauma, fracture, cancer, central vein catheterization or the presence of a trans-venous pacemaker, prior vein thrombosis, varicose veins, urinary tract infection, and a family history of venous thrombosis have all been found to increase the risk of VTE (5). Among women, additional risk factors for VTE include use of combined hormonal contraceptives (6). hormone therapy, pregnancy, and the postpartum period (7).

In Saudi Arabia, pregnancy poses an even greater risk than surgery, hospitalization, and combined hormonal contraceptive use (8), and the risk of VTE during the postpartum period are about fivefold higher than the risk during pregnancy (7). The overall incidence of pregnancy-associated VTE is currently about 200 per 100,000 women per year (9). According to the Centers for Disease Control (CDC) pregnancy-related mortality surveillance, PE was the leading cause of pregnancy-related deaths at 20%, outnumbering other complications such as hemorrhage, infections, and pregnancy-induced hypertension (10). Additionally, prior superficial vein thrombosis was found to be an independent risk factor during pregnancy or postpartum (11).

The risk of thrombosis is attributed to the homeostatic changes that occur during pregnancy. There is an increase in the concentration of clotting factors, namely, fibrinogen, von Willebrand factor, and factors VII, VIII, IX, X, and XII; which results in a hypercoagulable state. This is intended to protect pregnant women against hemorrhage, simultaneously exposing them to the potential risk of thrombosis (12). In addition to hypercoagulability, several anatomical changes occur during pregnancy: the venous stasis created by the external venous compression due to the growing uterus compromises venous outflow, subsequently increasing the susceptibility to developing thromboembolism in pregnant and postpartum women (13). Although these changes take place during pregnancy and create a higher risk of VTE during it, they also play a key role during the postpartum period (9, 13, 14).

Moreover, pregnancy combined with either heritable or acquired forms of thrombophilia results in the cumulative risk of thrombosis. A meta-analysis of pregnancy-associated thrombophilia concluded that pregnant women with heterozygous factor V Leiden mutation and prothrombin G20210A mutation had an eightfold and sevenfold increase in thrombosis risk, respectively (15). Due to the lack of prior research on pregnancy-induced thrombosis in Saudi Arabia, we conducted this study to describe the predictors of pregnancy-induced VTE (DVT and PE).

Materials and methods

Study design

We carried out a case-control study of patients with objectively confirmed VTE (DVT, PE, or both), induced during pregnancy or postpartum, visiting the thrombosis clinics at a major tertiary care hospital in Riyadh.

Study participants

Cases

Patients who experienced one or more episodes of objectively confirmed VTE (*proximal* DVT or PE or both) during pregnancy or the postpartum period were included. We excluded intra-abdominal (splanchnic) vein, renal, gonadal, and cerebral venous thrombosis, which are often called venous thrombosis of the unusual site due to their rarity and difference in their management strategies (type and duration of anticoagulant therapy). In addition, patients with missing medical records or those with normal diagnostic imaging were excluded from this study. DVT was objectively confirmed by Doppler ultrasound and PE was diagnosed through Ventilation-perfusion (VQ) scan or CT Pulmonary Angiography (CTPA) scan. The study population, including those who developed previous episodes of single VTE, were not taking any anticoagulant therapy before the diagnosis of recurrent VTE.

Controls

A random sample of pregnant women attending the thrombosis clinics who did not develop VTE was selected from high-risk pregnancies. High-risk pregnancies consisted of any chronic medical condition that affected either the pregnant woman or the fetus or both, including diabetes mellitus, hypertension, chronic kidney disease, cardiac disease, inflammatory bowel disease, cancer, multiple sclerosis, and epilepsy. The ratio of controls to cases was ∼1:1.

Demographics and risk factors

Data was collected in a specifically designed strategy by reviewing the chart of the included patients. Demographic information collected included: age, weight, height, BMI before pregnancy, first-degree relative family history of VTE (venous

and/or arterial thrombotic event), previous history of combined hormonal contraceptive use, and pregnancy trimester at the time of VTE diagnosis.

Data on the risk factors of VTE were collected using the risk assessment tool of the Royal College of Obstetricians and Gynecologists (RCOG) (16). Information on the risk factors collected included: C-section and pre-term delivery, postpartum hemorrhage (PPH) or blood transfusion, age, history of VTE, thrombophilia[1], antiphospholipid syndrome (APLS), medical comorbidities, diabetes, hypothyroidism, hypertension (HTN), cardiac and lung disease, systemic lupus erythematosus (SLE), nephrotic syndrome, surgical history, BMI, parity, gross varicose veins [defined as symptomatic or above the knee or with associated phlebitis, edema/skin changes as per the RCOG guidelines (16)], current systemic infection, immobility, immobility type, hospitalization for non-delivery reasons, preeclampsia, dehydration or ovarian hyperstimulation syndrome (OHSS), recurrent abortions, and multiple pregnancies or assisted reproductive therapy (ART).

Sample size estimate

Sample size calculations were performed using the Epi Info^{TM} program (version 7.2.5 Nov. 2021) that is provided by the Centers for Disease Control and Prevention (CDC). Accordingly, to achieve a 95% confidence interval to detect a similar odds ratio with a 5% margin of error, the sample size calculations showed that the minimum required size for the current study was 348 subjects (174 subjects per group).

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 23. Descriptive statistics were carried out by reporting the number and percent for categorical variables, whereas continuous variables were presented as mean and standard deviations (SD). The associations between different categorical variables and VTE and continuous variables and VTE were determined through the chi-square test and student's t-test, respectively. To identify significant predictors of VTE, backward multiple logistic regression (Wald test) analyses were carried out by including all the patients' characteristics and excluding independent variables based on the probability of the Wald statistic. Only variables that showed statistical significance were reported in the results.

1 Thrombophilia is a group of inherited or acquired disorders that increase the risk of venous or arterial thrombosis. Hereditary thrombophilia is due to antithrombin deficiency, protein C or protein S deficiency, factor V Leiden mutation, and prothrombin gene mutation. Acquired thrombophilia is frequently associated with antiphospholipid syndrome and, activated protein C resistance; which is characterized by thrombosis and the presence of lupus anticoagulant, anticardiolipin, and anti-beta2-glycoprotein antibodies.

Results

The current study was conducted among 180 patients diagnosed with pregnancy-associated thrombosis out of a total of 800 VTE cases in our thrombosis clinic registry; 135 (75%) of patients developed DVT, 30 (16.7%) patients developed PE, and 15 (8.3%) developed DVT that progressed to PE. Moreover, a sample of 200 subjects who did not develop VTE was included as controls.

The average ages of the patients in the control and case groups were 29.09 (±5.16) and 29.67 (±6.00) years, respectively, showing no statistically significant difference ($P = 0.31$). Similarly, no significant difference was observed in the average BMIs between the two groups, which were 31.76 (±6.48) kg/cm^2 and 30.93 (±5.25) kg/cm^2 in the case and control groups, respectively ($P = 0.17$). As for family history, there was a significant association between pregnancy and VTE [19.4% of cases had a family history of VTE as compared to 0.5% of the controls ($P < 0.0001$)]. In the case and control groups, 60.6 and 58.5% of the subjects were in their postpartum period, respectively. The remaining 39.4 and 41.5% of the subjects in the case and control groups were pregnant, respectively. VTE cases were almost equally distributed with a slight surge toward the first and third trimesters (13.3 and 12.8%, respectively) (Table 1).

VTE was significantly associated with C- section delivery ($P = 0.03$), single previous VTE ($P < 0.0001$), antenatal previous recurrent >1 VTE ($P < 0.0001$), thrombophilia ($P < 0.0001$), APLS ($P = 0.01$), gross varicose veins ($P < 0.0001$), immobility ($P = 0.001$), hospitalization for non-delivery reasons ($P = 0.003$), and multiple pregnancy or ART ($P = 0.03$) (Table 2).

After entering all the significant variables from the univariate analysis into multivariate analysis, the only variables that remained significant were family history (adjusted OR = 50.47, 95% CI: 6.78–375.64, $P < 0.0001$), thrombophilia (adjusted OR = 21.99, 95% CI: 2.83–170.63, $P = 0.003$), and gross varicose veins (adjusted OR = 17.15, 95% CI: 3.93–74.87, $P < 0.0001$). Thus, VTE is more likely to develop 50.47 times, 21.99 times and 17.15 times in cases with family history, thrombophilia, and gross varicose veins, respectively (Figure 1). We noticed that the adjusted ORs were almost similar to unadjusted ORs. This could probably be due to potential confounders like other unmeasured factors that could not be determined due to data limitations.

Discussion

The results of the present study show that family history increases the risk of developing VTE. These findings are

TABLE 1 Association between baseline characteristics and VTE in cases and controls.

		Group		*p*
		Case *N* = 180	Control *N* = 200	
Age (year)	Mean (SD)	29.67 (6.00)	29.09 (5.16)	0.31
	≤35	149 (82.8%)	174 (87.0%)	0.25
Nationality	Saudi	180 (100.0%)	194 (97.0%)	**0.03**
	No Saudi	0 (0.0%)	6 (3.0%)	
BMI	Mean (SD)	31.76 (6.48)	30.93 (5.25)	0.17
Family history	Yes	35 (19.4%)	1 (0.5%)	**<0.001**
Pregnancy period	Postnatal	109 (60.6%)	117 (58.5%)	Reference
	First trimester	24 (13.3%)	7 (3.5%)	0.003
	Second trimester	18 (10.0%)	35 (17.5%)	0.060
	Third trimester	23 (12.8%)	41 (20.5%)	0.081
	Unknown trimester	6 (3.3%)	–	–
Surgery	Yes	3 (1.7%)	1 (0.5%)	0.35

Significant variables are in bold.

consistent with the findings from a case-control study carried out by Gader et al. (17) among Sudanese pregnant and postpartum patients with VTE (OR: 7.4). Correspondingly, Bezemer et al. (18) and Zoller et al. (19) also reported that a positive family history of VTE increases its risk twofold to fourfold, depending on the number of affected relatives.

Similarly to our results, the significant association of VTE with thrombophilia was also reported by James et al. The latter found that, in pregnant women with thrombophilic abnormalities, the risk of VTE was estimated to be 51.8-fold and 15.8-fold in those with hereditary thrombophilia and APLS, respectively (20). A possible explanation for thrombophilia is the effect of blood abnormalities on the levels of coagulation factors and other circulating blood proteins (participating in the coagulation cascade) (21).

Thrombophilia is defined as the disruption in the balance of "procoagulant" and "anticoagulant" activity, which determines the likelihood of thrombosis in a patient (22). A univariate analysis indicated that recurrent VTE was significantly associated with thrombosis. However, similar results were not observed after a multivariate analysis, which was congruent with previous studies (23, 24). A study conducted by Middeldorp among non-pregnant patients also concluded that no association was found between thrombosis abnormalities and VTE (24). This could be explained by the global increase of thrombotic risk in pregnant women and the synergistic interaction with inherited thrombophilia, allowing for the demonstration of an association that is not statistically significant in the general population. Therefore, inherited thrombophilia seems to be the major cause of adverse pregnancy outcomes including fetal loss, preeclampsia, abruptions, severe intrauterine growth restriction, and early onset (9, 25–27). The most frequent clinically significant inherited thrombophilias are Factor V Leiden and Factor II (prothrombin) G20210A followed by deficiencies in proteins C, S, and antithrombin; dysfibrinogenemia, and hyperhomocysteinemia (15, 25–30). However, previous studies demonstrated a weaker association between inherited thrombophilia [Factor V Leiden and Factor II (prothrombin) G20210A] and pregnancy-associated VTE risk (6). Correspondingly, some studies suggested that inherited thrombophilia had some impact on adverse pregnancy outcomes, suggesting that it is contributory instead of a major cause (25, 29–31). Furthermore, the effect of the changes in hemostatic, fibrinolytic, and anticoagulant proteins during pregnancy expose pregnant women to an increased risk of thromboembolism and, therefore, aggravate the effects of inherited thrombophilia's (9, 15, 26).

The last risk factor found to be significantly associated with VTE was gross varicose veins. Similar to our observations, a significant association between varicose veins and DVT was observed among a general practice population with documented varicose veins, in a study carried out by Muller-Buhl et al., in a primary care center in Heidelberg, Germany. They reported that there were 132 DVT episodes among 2,357 patients with varicose veins (5.6 %) compared to 728 out of 80,588 patients of the cohort without varicose veins (0.9 %) ($P < 0.0001$) (32). This can be explained by the fact that varicose veins cause chronic venous insufficiency and thus becomes a possible risk factor for DVT (33). On the other hand, it was reported by Heit et al. (34) that the risk of DVT imparted by varicose veins is uncertain and appears to vary with the patient's age.

It is important to note that both the case and control groups consisted of pregnant women from the high-risk group. As their characteristics and prognosis were similar, no other factors

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TABLE 2 Association between different risk factors and VTE in cases and controls.

Risk factor	Case $N = 180$	Control $N = 200$	p	Unadjusted OR (95 % CI)
Antenatal period	71 (39.4%)	82 (41.0%)	0.76	1.07 (0.71–1.61)
Postnatal period	109 (60.6%)	118 (59.0%)		
C-section delivery	52 (47.7%)	40 (33.9%)	**0.03**	**1.78 (1.04–3.04)**
Preterm delivery	7 (6.4%)	4 (3.4%)	0.29	1.96 (0.56–6.88)
PPH or blood transfusion	5 (4.6%)	1 (0.8%)	0.10	5.72 (0.66–49.76)
Family history	35 (19.4%)	1 (0.5%)	**<0.0001**	**48.03 (6.51–354.66)**
Age >35	31 (17.2%)	26 (13.0%)	0.25	1.39 (0.76–2.54)
Single previous VTE	33 (18.3%)	4 (2.0%)	**<0.0001**	**11.00 (3.81–31.73)**
Antenatal previous recurrent > 1 VTE	13 (7.2%)	0 (0.0%)	**<0.0001**	NA
Thrombophilia	21 (11.7%)	1 (0.5%)	**<0.0001**	**26.28 (3.50–197.51)**
APLS	10 (5.6%)	2 (1.0%)	**0.01**	**5.82 (1.26–26.95)**
Medical comorbidities	56 (31.1%)	56 (28.0%)	0.51	1.16 (0.75–1.82)
Diabetes	7 (5.1%)	12 (8.1%)	0.32	0.61 (0.23–1.61)
Hypothyroidism	19 (13.8%)	27 (18.0%)	0.33	0.73 (0.38–1.38)
Hypertension	5 (3.6%)	5 (3.3%)	1.00	1.09 (0.31–3.85)
Cardiac disease	1 (0.7%)	0 (0.0%)	0.48	NA
Lung disease	1 (0.7%)	0 (0.0%)	0.48	NA
SLE	7 (5.1%)	2 (1.3%)	0.09	3.95 (0.81–19.37)
Nephrotic syndrome	1 (0.7%)	0 (0.0%)	0.48	NA
Surgical procedures	3 (1.7%)	3 (1.5%)	1.00	1.11 (0.22–5.59)
Obesity (BMI >30)	73 (40.6%)	93 (46.5%)	0.24	0.78 (0.52–1.18)
Parity ≥3	58 (32.2%)	56 (28.0%)	0.37	1.22 (0.79–1.90)
Gross varicose veins	26 (14.4%)	2 (1.0%)	**<0.0001**	**16.71 (3.91–71.51)**
Current systemic infection	4 (2.2%)	6 (3.0%)	0.75	0.73 (0.20–2.65)
Immobility	9 (5.0%)	0 (0.0%)	**0.001**	NA
Immobility type			NA	NA
Paraplegia	0 (0.0%)	0 (0.0%)		
Long distance	8 (88.9%)	0 (0.0%)		
Travel > 6 h				
PGP	0 (0.0%)	0 (0.0%)		
Other	1 (11.1%)	0 (0.0%)		
Hospitalization for non-delivery reasons	12 (6.7%)	2 (1.0%)	**0.003**	**7.07 (1.56–32.04)**
Preeclampsia	8 (4.5%)	3 (1.5%)	0.09	3.07 (0.80–11.76)
Dehydration or OHSS	3 (1.7%)	0 (0.0%)	0.10	NA
Recurrent abortions	25 (13.9%)	24 (12.0%)	0.58	1.18 (0.65–2.16)
Multiple pregnancy or ART	17 (9.4%)	8 (4.0%)	**0.03**	**2.50 (1.05–5.95)**

VTE, Venous thromboembolism; PPH, Postpartum hemorrhage; APLS, Antiphospholipid syndrome; SLE, Systemic lupus erythematosus; PGP, Pelvic girdle pain; OHSS, Hyperemesis ovarian hyperstimulation syndrome; ART, Assisted reproductive technology. Significant variables are in bold.

would have impeded the results. Additionally, compression ultrasound sonography (CUS) was performed in all patients as the first line for diagnosis of PE (35). If the results of CUS were negative further investigating would be used such as confirmatory diagnostic imaging for PE, to minimize radiation exposure to the patients (36).

Therefore, it is recommended that a formal, written risk assessment of VTE risk factors be performed before pregnancy, at the time of antenatal booking, and at the time of delivery to reduce VTE during pregnancy. Given the ongoing deliberation to introduce universal screening for thrombophilia before pregnancy, this study could play an essential role in helping obstetricians to decide on the use of a prophylactic treatment such as anticoagulant therapy. It is therefore also recommended that obstetricians refer women with gross varicose veins planning for pregnancy to vascular

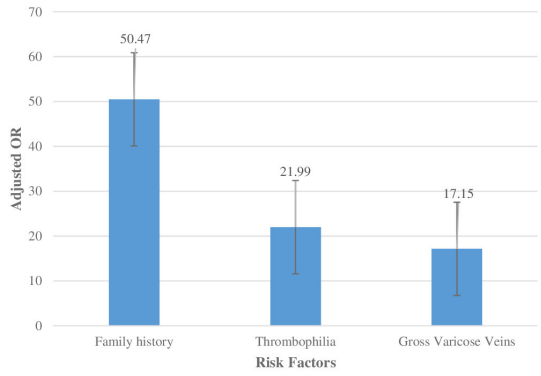

FIGURE 1
Adjusted ORs for each significant factor of VTE in the multiple logistic regression model.

surgeons for proper management of varicose veins before pregnancy where any intervention would be delayed if possible. Additionally, obstetricians are recommended to screen pregnant women for VTE risk factors addressed by RCOG, particularly varicose veins and those with a family history of VTE to help them make more time-sensitive decisions regarding the use of anticoagulant thromboprophylaxis during their patient's pregnancy supported by a multi-disciplinary discussion.

Moreover, prophylaxis is advised for women who are at high risk of pregnancy-associated VTE, such as those with inherited thrombophilias, a strong family or personal history of VTE, and those with gross varicose veins.

The results of this study should be evaluated in light of its strengths and limitations. Being one of the few studies, addressing this important topic in the Middle East is the main strength of our study. The critical limitation of our study was the retrospective design, where potential confounding by other unmeasured factors could not be taken into account due to data limitations.

Conclusion

In summary, the findings of this study show that family history, thrombophilia, and gross varicose veins were the provoking factors for VTE, exceeding other transient risk factors during pregnancy and the postpartum period. Further larger studies using a randomized design need to be conducted to confirm the results of our study and to identify a more predictive risk factor during pregnancy and the postpartum period. Recommendations for including a multidisciplinary team approach to the management of pregnant women or those seeking pregnancies taking into account the VTE risk factors is highly encouraged.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by KFMC IRB. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MAA carried out the study, participated in the study design, and wrote the final manuscript. AA conceived the study and participated in its design and in drafting of the manuscript. RAA participated in the study design, interpretation of data, and drafting of the manuscript. RMA contributed to the design of the study, managed the literature search, and drafted the manuscript. AZ participated in the interpretation of data and drafting of the article. OA, MA, and AA-S participated in the study design, interpretation of data, and drafting of the manuscript. All authors read and approved the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Nicola Mumoli,
ASST Ovest Milanese, Italy

REVIEWED BY
Mi Zhou,
Beijing Jishuitan Hospital, China
Mariam Shariff,
Mayo Clinic, United States

*CORRESPONDENCE
Bernard Tardy
bernardtardy@yahoo.fr

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Inferior vena cava filters in pregnancy: Safe or sorry?

Ingrid M. Bistervels [1,2], Andrea Buchmüller [3,4] and Bernard Tardy [3]*

[1]Department of Vascular Medicine, Amsterdam UMC Location University of Amsterdam, Amsterdam, Netherlands, [2]Amsterdam Cardiovascular Sciences, Pulmonary Hypertension and Thrombosis, Amsterdam, Netherlands, [3]INSERM, Clinical Investigator Center 1408 – Centre Hospitalier Universitaire de Saint-Etienne, Saint-Etienne, France, [4]F CRIN, INNOVTE Network, Saint-Etienne, France

Background: Potential hazards of vena cava filters include migration, tilt, perforation, fracture, and in-filter thrombosis. Due to physiological changes during pregnancy, the incidence of these complications might be different in pregnant women.

Aim: To evaluate the use and safety of inferior vena cava filters in both women who had an inferior vena cava filter inserted during pregnancy, and in women who became pregnant with an inferior vena cava filter *in situ*.

Methods: We performed two searches in the literature using the keywords "vena cava filter", "pregnancy" and "obstetrics".

Results: The literature search on women who had a filter inserted during pregnancy yielded 11 articles compiling data on 199 women. At least one filter complication was reported in 33/177 (19%) women and included in-filter thrombosis ($n = 14$), tilt ($n = 6$), migration ($n = 5$), perforation ($n = 2$), fracture ($n = 3$), misplacement ($n = 1$), air embolism ($n = 1$) and allergic reaction ($n = 1$). Two (1%) filter complications led to maternal deaths, of which at least one was directly associated with a filter insertion. Filter retrieval failed in 9/149 (6%) women. The search on women who became pregnant with a filter *in situ* resulted in data on 21 pregnancies in 14 women, of which one (6%) was complicated by uterine trauma, intraperitoneal hemorrhage and fetal death caused by perforation of the inferior vena cava filter.

Conclusion: The risks of filter complications in pregnancy are comparable to the nonpregnant population, but could lead to fetal or maternal death. Therefore, only in limited situations such as extensive thrombosis with a contraindication for anticoagulants, inferior vena filters should be considered in pregnant women.

KEYWORDS

venous thromboembolism, pregnancy, safety, anticoagulants, vena cava filter

Introduction

Vena cava filters are intravascular devices that trap thrombi migrating from deep veins toward the pulmonary arteries, and therefore prevent new pulmonary embolisms. Currently, major guidelines agree on the recommended use of vena cava filters in patients

with acute venous thromboembolism (VTE, comprising deep vein thrombosis [DVT] and pulmonary embolism) while therapeutic anticoagulant treatment is contraindicated if there is active bleeding or a high risk of bleeding—such as recent or planned surgery or delivery, and in patients with recurrent VTE despite adequate anticoagulant treatment (1–5). Complications occurring directly after insertion of the vena cava filter include access site thrombosis, infection, bleeding and perforation of the vena cava wall (2, 4, 6). Long-term complications of vena cava filters can occur in the days or months after insertion and include filter migration, filter tilt, perforation of the vena cava wall, fracture and embolization of filter struts, or in-filter thrombosis with or without concomitant deep-vein thrombosis (2, 6). These complications have been reported in 7–22% of the nonpregnant population (7, 8). Failure of filter retrieval was reported in 11–12% of nonpregnant patients (8, 9).

When a VTE occurs during pregnancy, the indicated anticoagulant treatment should temporarily be interrupted around time of delivery. This poses hemostatic challenges when VTE is diagnosed shortly prior to the expected date of delivery, since the risk of progression or recurrence of VTE is highest during the first month after diagnosis, while at the same time anticoagulant treatment can worsen peripartum bleeding.

Due to physiological changes that occur during pregnancy, pregnant women may be at increased risk of inferior vena cava filter complications. As a result of the dilated and curved inferior vena cava during pregnancy, the filter might be more likely to tilt and/or migrate, which could make the filter less effective and harder to retrieve. Moreover, the effect of compression of the gravid uterus on the inferior vena cava, contractions and increased intra-abdominal pressure while pushing, has not yet been established. Therefore, evidence-based guidance on the use of vena cava filters in pregnant women is paramount. In this review we aim to provide an overview of the available literature on the use and safety of inferior vena cava filters in pregnant women. We will separately report results for women who got an inferior vena cava filter inserted during pregnancy and for women who became pregnant with an inferior vena cava filter *in situ*.

Inferior vena cava filters for acute venous thromboembolism inserted during pregnancy

In the first part of this review, we aim to evaluate the use, obstetric outcomes, and filter complications of patients who had an inferior vena cava filter inserted during pregnancy.

Literature search—methods

A systematic search of literature published between January 2015 and May 2022 was conducted on Medline and Embase. The search strategy was based on the following keywords: "vena cava filter", "pregnancy" and "obstetrics". We searched for original studies, case series and case reports. No restrictions with regard to study design or geographic location were applied. Articles were included if they reported data on inferior vena cava filters inserted during pregnancy. Information about filter indication, route and timing of filter insertion, filter complications, indwelling time, and maternal and fetal outcomes was collected. All reference lists of included manuscripts were manually searched to identify related articles that were not yet identified.

Results

Literature search yielded 50 articles based on titles and abstracts, and eleven articles were included after full text screening: one cohort study (10), four case series (8, 11–13), five case reports (14–18) and a systematic review with case series and case reports (19). The reasons for excluding the other 39 manuscripts were: review articles without case reports ($n = 12$), not concerning pregnant women (9), postpartum filter insertion ($n = 5$), article not in the English language ($n = 5$), no details provided concerning either the pregnancy or the filter ($n = 6$), and filter insertion prior to pregnancy ($n = 2$) (Figure 1). One of the included articles was a case report accompanied by an overview of the English language literature from January 1970 to 2014 on vena cava filters during pregnancy (14). In this overview (14), a total of 64 cases were reported and all these cases—except for three—were also included in another systematic review on inferior vena cava filters in pregnancy, published in 2016 (19). In a case series published in 2015 (11), 11 of the 20 cases were duplicates of previously published cases (20) included in the systematic review of Harris et al (19). From this article (11) we only retained the nine cases which were never previously published. Hence our systematic search yielded a total of 199 women who had an inferior vena cava filter inserted during pregnancy.

Filter insertion

Of the 199 pregnant women, 45 women (23%) had a permanent filter (36 Greenfield, 4 Cardial, 2 Bird's Nest, 1 TrapEase, 2 undetermined) and 154 women (77%) had a retrievable filter (26 Neuhaus Protect, 20 Günther Tulip, 19 OptEase, 12 Antheor, 10 ALN, 5 Tempofilter, 4 Celect, 2 Recovery, 1 Zontik, 1 Prolyser, 1 Cardial and 53 undetermined) inserted. The filter locations were reported for 138 women:

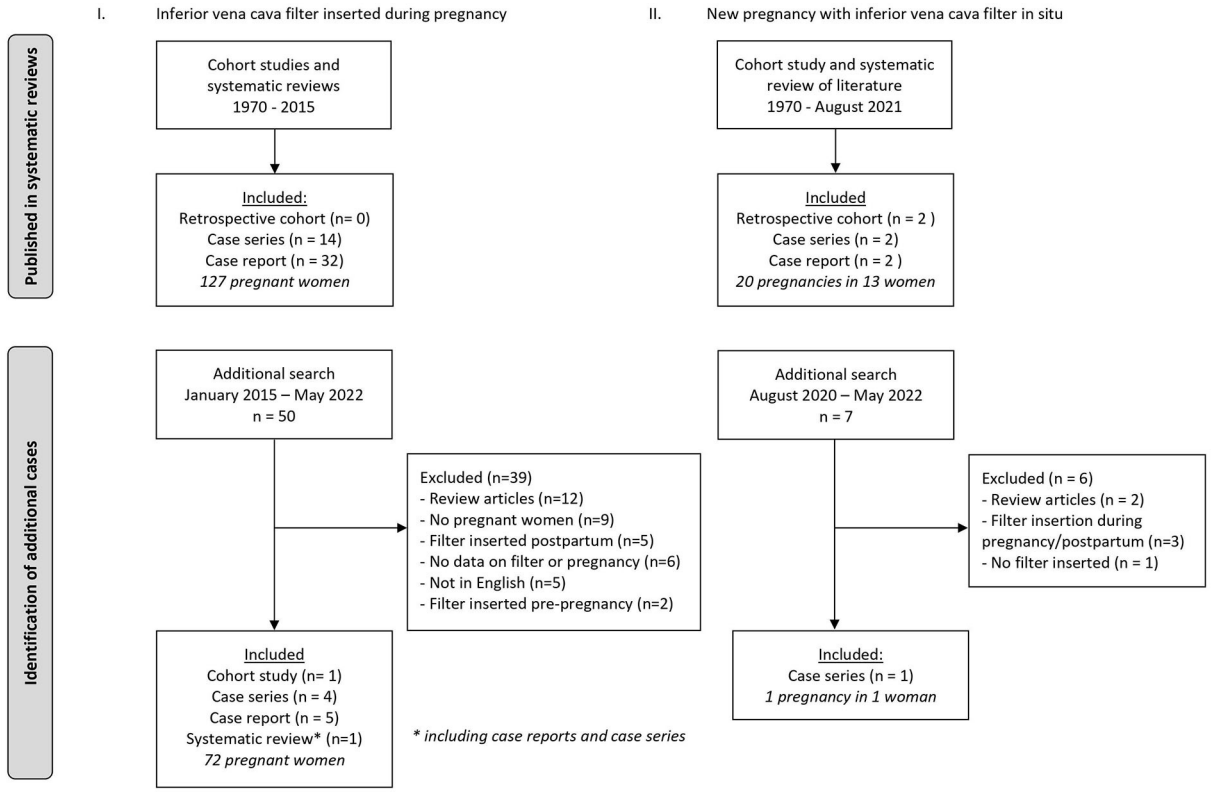

FIGURE 1
Flow chart literature searches.

inferior vena cava filters were inserted in a suprarenal position in 96 women (70%) and in an infrarenal position in 42 women (30%).

The indication for filter insertion in all women was venous thromboembolism during pregnancy: 90 women (45%) had a proximal DVT, 17 women (9%) had pulmonary embolism with or without concomitant DVT, and in 51 women (26%) the exact thrombosis location remained unspecified (Table 1) (8, 10–18, 21–50). Additionally, 27 women (19%) had progression of VTE despite adequate anticoagulant treatment (13–15, 24, 25, 29, 32, 35, 36, 48, 50–59), and 9 women (5%) had a proximal DVT and a contraindication for anticoagulant treatment due to significant risk of bleeding (8, 13, 18, 24, 25, 48, 51). Deep-vein thrombosis and heparin induced thrombocytopenia occurred in 5 women (3%) (24, 25, 35, 51, 60). In more than half of the women (107/199, 54%), an inferior vena cava filter was inserted in the third trimester of pregnancy (Table 1).

Obstetric outcomes

Obstetric outcomes were reported in 162 cases: 73 women (46%) had a vaginal delivery and 85 women (52%) had a caesarean section. Four women (2%) had a medically indicated termination of pregnancy. No fetal deaths were recorded. Two neonates (1%) suffered from mild respiratory distress (51), but data concerning the fetal outcomes were often lacking.

Filter complications

Individual data on follow-up of inferior vena cava filters after insertion in pregnant women were reported for 177 women: at least one complication of the inferior vena cava filter was reported in 33 women (19%). Filter complications are summarized in Table 2. Immediate complications (within 24 h of filter insertion) occurred in three women (2%) and long-term complications (days to months after filter insertion) occurred in 30 women (17%). Two maternal deaths (1%) were reported: one woman had a fatal air embolism during the insertion of a Kimray-Greenfield filter (53), the other woman with an in-filter thrombosis died as a consequence of catastrophic antiphospholipid syndrome (13). The most frequently reported complication was in-filter thrombosis. Some authors reported in-filter thrombosis as a consequence of extended proximal DVT (13, 54, 58, 61), while others described captured thrombi as a successful filter function or

TABLE 1 Characteristics, indications and timing of insertion of inferior vena cava filters during pregnancy.

Indications for filter	1st trimester ($n = 29$)	2nd trimester ($n = 26$)	3rd trimester ($n = 107$)	Trimester not reported ($n = 37$)	TOTAL ($n = 199$)
Filter type, *n*					
Permanent					45
Retrievable					154
Position of filter, *n*					
Suprarenal					96
Infrarenal					42
Not reported					61
Filter shape, *n*					
Umbrella-shaped: *Greenfield, Günther Tulip, ALN, Tempofilter, Celect, Recovery*					102
Spindle-shaped: *TrapEase, OptEase, Neuhaus Protect, Antheor,*					38
Free struts and barbs: *Bird's Nest*					2
Undetermined					57
Indications for filter, *n*					
Proximal DVT	7	10	43	30	90
Pulmonary embolism with/without concomitant DVT	7	3	7	0	17
Venous thromboembolism (location not reported)	6	6	27	0	39
Distal DVT	0	0	1	0	1
DVT (location not reported)	2	0	10	0	12
Pulmonary embolism or extensions of DVT despite anticoagulant treatment for initial DVT	4	5	15	3	27
Proximal DVT and contraindication for anticoagulant treatment because of ongoing bleeding or risk of bleeding	3	2	1	2	8
DVT and heparin induced thrombocytopenia	0	0	3	2	5
Total	29	26	107	37	199

DVT, deep-vein thrombosis.
Proximal DVT was defined as a thrombus involving one or more of the following veins: the popliteal, femoral, iliac veins, the inferior vena cava.
Distal DVT was defined as infrapopliteal DVT without extension to proximal veins (popliteal vein or above) or pulmonary embolism.

as a consequence of discontinuation of anticoagulant therapy (12, 17, 20, 41). Of the 14 in-filter thromboses (8%), concomitant symptomatic pulmonary embolism was reported in one woman (54). These in-filter thromboses or captured thrombi were observed in almost all types of retrievable filters (Celect, Neuhaus Protect, Antheor, OptEase) and in one case with a permanent filter (Greenfield). Filter complications occurred in 21% (20 of 96 women) of suprarenal positioned and in 24% (10 of 42 women) of infrarenal positioned inferior vena cava filters. Overall the complications occurred with all types of filters. Therefore, it is not possible to clearly establish a link between a type of filter and a type of complication. Of note, the level of DVT that justified the need for filter placement in these women was femoral in four women (12, 58), iliofemoral in four women (12, 17, 20, 61), and not specified in six women (13, 18, 41, 54). Among the women with in-filter thrombosis, time since filter insertion was 5 days or less for three women (21%) (12, 61) and 7 days or more for 11 women (79%).

Other complications of the filter were observed in 19 women and included in a descending order of frequency: tilts (six women, 3%), migrations (five women, 3%), fractures (three women, 2%), vena cava perforation (two women, 1%), misplacement (one woman, <1%) and allergy (one woman, <1%). The most important consequence of these complications was the failure of filter retrieval in nine of the women concerned.

Filter retrieval

In the large majority of women with retrievable filters, the vena cava filter could be retrieved (140/154, 91 %). Data on time to filter retrieval was available for 98 women, in 81 women (83%) the inferior vena cava filter was left *in situ* for a maximum of 30 days and in the remaining 17 women (17%) filters were retrieved after 1 month. For eight of these women (47%), time since filter insertion was more than 90 days with a maximum

TABLE 2 Immediate and long-term complications of inferior vena cava filters inserted during pregnancy.

Type	Position of filter	Name and Type of filter	Filter shape	Number of patients	Outcome	Reference
Immediate complication (≤24 h after insertion)						
Air embolism	1 unknown	Greenfield (permanent)	Umbrella	1	Maternal death	(53)
Misplacement of filter (iliac vein)	1 infrarenal	Celect or ALN or Günther Tulip (retrievable)	Umbrella	1	Unsuccessful filter retrieval	(13)
Allergic reaction	1 suprarenal	Neuhaus Protect (retrievable)	Spindle	1	Fully recovered	(11)
Long-term complication (days to months after insertion)						
Filter tilt	3 infrarenal 2 suprarenal 1 suprarenal	3 Günther Tulip (retrievable) 2 OptEase (retrievable) 1 Recovery (retrievable)	Umbrella Spindle Umbrella	6	Unsuccessful filter retrieval: 3 Successful filter retrieval: 3	(37, 39, 57)
Filter migration	1 infrarenal 1 suprarenal 1 suprarenal 2 suprarenal	Recovery (retrievable) Neuhaus Protect (retrievable) Tempofilter (retrievable) ALN (retrievable)	Umbrella Spindle Umbrella Umbrella	5 ¥	Unsuccessful filter retrieval: 2 Successful filter retrieval: 3	(11, 23, 32, 35, 57)
Filter thrombosis including thrombus captured in filter	1 Unknown 2 infrarenal 1 infrarenal (death) + 1 suprarenal 4 suprarenal 1 suprarenal 1 suprarenal 2 suprarenal 1 suprarenal	Neuhaus Protect (retrievable) Neuhaus Protect (retrievable) Celect or ALN or Günther Tulip (retrievable) Unknown Neuhaus Protect (retrievable) Antheor (retrievable) OptEase (retrievable) Greenfield (permanent)	Spindle Spindle Umbrella Spindle Spindle Umbrella Umbrella	14 §	Maternal death: 1* Pulmonary embolism: 1	(12, 13, 17, 18, 20, 41, 54, 58, 61)
Filter fracture	1 Unknown 1 infrarenal 1 suprarenal	Neuhaus Protect (retrievable) Recovery (retrievable) Recovery (retrievable)	Spindle Umbrella Umbrella	3	Unsuccessful retrieval of the filter fragment: 2	(32, 57, 79)
Vena cava perforation	1 infrarenal 1 suprarenal	Greenfield (permanent) Celect (retrievable)	Umbrella Umbrella	2	Unsuccessful filter retrieval: 1 Leading to retroperitoneal haematoma: 1	(8, 80)

¥ Localization of filter migration: right atrium = 2 (one migration to the right atrium resulting in premature ventricular contractions), renal vein = 1, caudal migration = 2.
* Maternal death as a result of catastrophic anti-phospholipid syndrome.
§ captured thrombi > 1 cm was observed in 4 cases.

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of 287 days (15). In nine of the 154 women with a retrievable filter (6%) failed attempts of retrieval were reported (8, 13, 35, 36, 39, 57, 59). *Two* of these retrieval failures (22%) occurred after a very long time after insertion (167 and 659 days), the other six attempts (66%) were performed after an *in situ* time varying between 6 and 73 days, and for one woman (11%) data were missing. In five women (5/154, 3%), no attempt of filter retrieval was made and the filter was left *in situ*. The reasons were persistent extensive DVT despite of anticoagulants (62), in-filter thrombosis (41), filter misplacement into external iliac vein (13) or maternal dead (13). Hence, in total 9% of the filters were not retrieved.

New pregnancy in women with a permanent vena cava filter

In the second part of this review, we aim to evaluate the use, obstetric outcomes, and filter complications of patients who became pregnant with an inferior vena cava filter already *in situ* prior to conception.

Literature search—methods

Similar to the first part of the review, a literature search was conducted. However, a review on this exact same subject has been recently performed and published by one of the authors of this review (63). In that publication a comprehensive search of the English language literature was conducted in MEDLINE, Embase, and abstracts of conferences between 1970 and August 2020 (63). For the current review, we have repeated the same search for the period from August 2020 to May 2022 (Figure 1). No restrictions with regard to study design nor geographic location were applied. Articles were included if they reported data on pregnancies after insertion of an inferior vena cava filter that was left *in situ*. Information about filter indication, route and timing of filter insertion, filter complications, indwelling time, and maternal and fetal outcomes was collected. All reference lists of included manuscripts were manually searched to identify related articles that were not yet identified.

Results

The extended literature search yielded seven new articles based on titles and abstracts, and only one article was included after full text screening. The reasons for exclusion of the six other manuscripts were: review articles ($n = 2$), filter insertion during pregnancy or postpartum ($n = 3$), and no inferior vena cava filter inserted ($n = 1$) (Figure 1). The included study was a case series of Taiwanese patients with inferior vena cava thrombosis (64). This case series included one 46-year old woman who was pregnant and had an unretrieved inferior vena cava filter *in situ*. However, other than the inferior vena cava thrombosis, no details or outcomes of interest were reported. The recently published review (63) revealed one cohort study (13), two case series (36, 48) and two case reports (65, 66). Additionally, the review also reported data from its own cohort. In total, data on 21 pregnancies in 14 women were available.

Filter insertion

Among 14 women, six women (43%) had a permanent vena cava filter (3 Bird's Nest, 1 Greenfield, 2 TrapEase) inserted, six women (43%) had a retrievable inferior vena cava filter (2 Günther Tulip, 2 OptEase, 2 undetermined retrievable filter) inserted, and for two women (14%) the filter type was unknown. Of the women with a retrievable filter, retrieval attempts failed in five women (83%) and in one woman (17%) no attempts were made. The filter position was infrarenal in six women (43%) and was not reported for the other eight (57%) women. Indication for an inferior vena cava filter was pre-pulmonary endarterectomy because of chronic thrombo-embolic pulmonary hypertension in two women (14%) (63), pulmonary embolism or recurrent VTE and contraindication for anticoagulant therapy due to surgery or bleeding in three women (21%) (36, 63, 65), DVT or pulmonary embolism during pregnancy in four women (29%) (13, 36, 63), recurrent VTE despite anticoagulant therapy in two women (14%), and VTE outside of pregnancy in two women (14%) (48, 66). The indication was unknown in one woman (64). Time between filter insertion and pregnancy ranged from <1–8 years.

Obstetric outcomes

Obstetric outcomes were reported for 17 pregnancies: 15 pregnancies (87%) ended in life-births, one pregnancy (7%) ended in miscarriage before the 10th weeks of gestation (63), and one pregnancy (7%) ended in an emergency cesarean section at 24 weeks of gestation (65). The later was the result of a filter complication described below. The fetus died shortly after birth.

Filter complications

Filter complications were reported for 16 pregnancies and summarized in Table 3. In 14 pregnancies (88%) no complications occurred, but follow-up and imaging of the filter was poorly performed. One pregnancy (6%) was complicated by uterine trauma and major intraperitoneal hemorrhage caused by perforation of the vena cava wall and uterus by the inferior vena cava filter's barbs and struts (65). In this case, the infrarenally positioned TrapEase filter was already known to have perforated the inferior vena cava wall prior to pregnancy, but the woman

had been asymptomatic up until the uterine laceration occurred (65). Other filter complications were reported by one other study (64), information was limited to the occurrence of inferior vena cava filter thrombosis. It was not reported whether this was caused by an in-filter thrombosis.

Discussion

Our literatures searches compiled data on 199 women who had an inferior vena cava filter inserted during pregnancy, and data on 21 pregnancies that occurred in 14 women who had an inferior vena cava filter *in situ* prior to conception. In women who had a filter inserted during pregnancy, 77% had a retrievable filter and in more than half of these women the filter was inserted in the third trimester of pregnancy. At least one complication was reported in 19% of women, most women had in-filter thrombosis. Two women died after filter insertion, however for one of them it was unclear whether this was a direct complication of the filter insertion. Retrieval failure was reported in 6%. These numbers are comparable to the nonpregnant population. In women who became pregnant with a filter *in situ*, complications were poorly evaluated but one filter complication resulting in major hemorrhage and fetal death was reported.

Although VTE risk increases up to 7–10-fold during pregnancy compared to age-matched controls, the overall incidence remains low (around 1–2 per 1,000 pregnancies) (67). Consequently, it is not surprising that the number of pregnant women who had an inferior vena cava filter inserted for an acute VTE reported in the English literature was low: only 199 cases have been reported since 1970 and no randomized-controlled trials on the safety and efficacy of inferior vena cava filters in pregnancy have been conducted. Moreover, the very low number of women who became pregnant with an inferior vena cava filter *in situ* was also expected. In the recent American Society of Hematology (ASH) guideline on venous thromboembolism management in pregnant women, the question whether to insert a vena cava filter for the treatment of acute VTE in the third trimester of pregnancy has not been addressed (68). The older American College of Chest Physicians (ACCP) guideline discusses the use of vena cava filters which was restricted to women with very high risk of recurrence, such as women with proven DVT and recurrent pulmonary embolism despite anticoagulant treatment (69).

From the data provided in this review, we can conclude that most women who had an inferior vena cava filter inserted during pregnancy did not meet these indications and should not have had a filter inserted. At most, only 4 % of the women had an absolute contraindication for anticoagulant therapy and failure of anticoagulant treatment was the indication for filter insertion in 14% of pregnant women. The occurrence of VTE was the most frequently reported reason for filter insertion, while patients were not at very high risk of recurrence. This might be based on the fear of a pulmonary embolism occurrence or recurrence related to the temporary withdrawal of anticoagulant treatment peripartum. Higher VTE incidence during the third trimester of pregnancy and in the early postpartum period is well reported (70, 71), but the risk of thrombosis extension or new pulmonary embolism some hours after anticoagulation withdrawal is poorly evaluated in the literature. There is one retrospective study reporting 344 nonpregnant patients with VTE who had a vena cava filter inserted and received no anticoagulants. In 42% of patients there was a contraindication for anticoagulants because of a significant risk of bleeding. These patients were matched using propensity scores with 344 other patients treated with only anticoagulants without having a vena cava filter inserted. After 30 days of treatment, the risk-adjusted pulmonary embolism related mortality rate was lower for filter insertion compared to no filter insertion (1.7 vs. 4.9%; $p = 0.03$), but the risk-adjusted recurrent VTE rates were higher for filter insertion compared to no filter insertion (6.1 vs. 0.6%; $p < 0.001$) (72). The authors concluded that despite an increased risk of VTE events, including in-filter thrombosis, filter insertion did not allow for a large pulmonary embolism to occur (73).

The most frequently reported filter complication was in-filter thrombosis. This is a well-known complication of vena cava filters and usually occurs at long-term use (>30 days) (7, 74). Early in-filter thrombosis has also been described as a captured large thrombus that can appear only a very few days after its insertion (11, 12, 17). These findings argue for optimal peripartum management and require a multidisciplinary approach: the window without anticoagulant therapy should kept as short as possible and both induction of labor and bridging with unfractionated heparin should be considered. Furthermore, anticoagulant therapy should be resumed as soon as possible after delivery and filter retrieval should be planned. The incidence of other filter complications is lower and similar to incidence rates of the nonpregnant population. Some authors suspected that during the second stage of labor and delivery intra-abdominal pressure could cause tilt, fracture and migration of the filter (20, 75). Due to the low number of patients in our review, we were unable to statistically compare such complications for patients with vaginal delivery compared to patient who had a caesarean section. Finally, the rate of filter complications in our review might be overestimated because of selection and publication biases.

The failure rate of filter retrieval is low (6 %) and comparable to the one in nonpregnant population (76, 77). However, in 3% no filter retrieval was attempted. When the filter remains *in situ*, women will be exposed to complications described by Decousus in a nonpregnant cohort with a follow-up period of 8 years (78), these include DVT recurrence and in-filter thrombosis.

In conclusion, only in pregnant women with clear indication such as acute proximal DVT shortly prior to delivery and contraindication for anticoagulant therapy, or progression of DVT despite adequate anticoagulant therapy, should inferior vena filters be considered. When inserted, retrieval should be planned as soon as possible and temporary filters are to be

TABLE 3 Complications of inferior vena cava filters in women with new pregnancy with inferior vena cava filter *in situ*.

Complication	Number of patients	Outcome	Reference
Perforation of vena cava wall and uterus by filter barbs and struts of TrapEase filter in infrarenal position	1	Uterine trauma Massive intra-abdominal bleeding Emergency cesarean section Fetal death	(65)
Inferior vena cava thrombosis	1	Unknown	(64)

preferred over permanent filters. This would help to avoid long-term complications in young women who might be planning future pregnancies.

Author contributions

IB and AB performed the literature searches, interpreted extracted data, and wrote the first draft of the manuscript. BT critically reviewed and revised the manuscript. The final version of the manuscript was approved by all authors.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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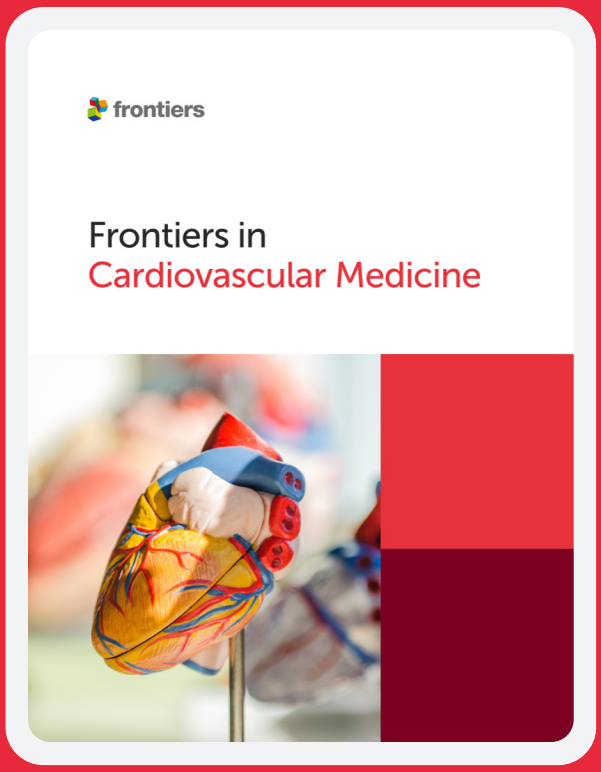

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Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
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