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Venous Thromboembolism Risk Score and Pregnancy

Tiphaine Raia-Barjat^{1,2*}, Osasere Edebiri³ 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.

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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) ≥ 40 kg/m², or 25 kg/m² 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 ≥ 35 years, BMI ≥ 25 to 40 kg/m², parity ≥ 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 <37 weeks' 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.

Scores	Antenatal and postnatal risk 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

Scores	Antenatal and postnatal risk 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	0–1: A	<3: B1	1–3: B1	<1.0: A	<i>Antenatally</i>	0–1: A1	0: A1
A. 1 conservative management, 2 Compression	2: B2	3–5: C	4: C	1.0–1.5: B1	3: C	1.5–2: A2	1–2: A2
B. prophylactic LMWH from delivery	3: B1	≥ 6: D	5–11: D	2.0–2.5: C	≥4: D	≥2.5: LMWH as described by RCOG	3–5: B1
1 until 6 weeks postpartum	≥4: D		≥12: E	3.0 or more: D	<i>Postnatally</i>		≥6: D
2 short duration	Very high risk: E				Low-risk thrombophilia + familial VTE history: B ≥ 2: B2		
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							

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 Healthcare 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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