Chapter

VTE Prophylaxis in Cesarean Section

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Abstract

Venous thromboembolism (VT is a major cause of maternal mortality and severe morbidity. Pharmacological and non-pharmacological methods of prophylaxis are therefore often used for women considered to be a risk including women who have given birth by cesarean section. The risk is potentially increased in women with a personal or family history of VTE, women with genetic or acquired thrombophilia, and another risk factors like sickle cell disease, inflammatory bowel disease, active cancer, obesity, preeclampsia·and SARS COVID 19 infection. However, a specific score in obstetrics has not yet been well defined. Recommendations from major society guidelines for post-cesarean section (C/S) thromboprophylaxis differ greatly; the safety and efficacy of drug prophylaxis - mainly low molecular weight heparins - has been demonstrated, but large scale randomized trials of currently-used interventions should be conducted. The purpose of this chapter is to discuss the indications and contraindications for VTE prophylaxis in cesarean sections, prophylaxis regimens and potential adverse events.

Keywords: VTE, DVT, cesarean section, thromboprophylaxis, heparin

1. Introduction

Venous thromboembolism (VTE) is a major cause of maternal morbidity and mortality. The risk of VTE is particularly elevated during the postpartum period and especially after cesarean section (CS) delivery. The risk of VTE was fourfold greater following CS than following vaginal delivery; seemed independent of other VTE risk factors; and was greater following emergency CS than following elective procedures [1].

Although a number of risk factors have been identified, the size of the increases in risk attributable to these factors is generally poorly quantified and there is considerable variation in the approach to prophylaxis of venous thromboembolism after CS [2–5].

In women with risk factors a combination of pharmacological and non-pharmacological methods are recommended. There is limited literature on the effect of mechanical methods for postpartum thromboprophylaxis, however benefit has been shown in other clinical areas [2, 4].

Antithrombotic prophylaxis are based on unfractionated heparin (UFH), low-molecular weight heparin (LMWH). LMWH was associated with fewer adverse effects when compared with UFH. Therefore, LMWH is considered to be a safe and effective in for postpartum thromboprophylaxis, although high-quality evidence is not available [1, 2].

In this chapter we will discuss the risk factors for VTE, their interactions and potential risk scores, as well as the prophylaxis alternatives and international guidelines for the prevention of VTE.

2. Epidemiology of VTE in pregnancy and puerperium

Women during pregnancy and the immediate puerperal period are considered at risk for VTE and there is a substantially higher prevalence that in non-pregnant women of the same age. A case- control study reported that compared with non-pregnant women, the risk of VTE was increased five-fold during pregnancy, and by 60-fold during the first three months after birth. However the absolute risk remains low, estimated at around one to two in 1000 pregnancies [6, 7].

The incidence of VTE, especially Pulmonary Embolism (PE), is believed to be much higher during the immediate puerperal period - mostly associated with cesarean section - with between 40% and 60% of all acute PE cases reported to occur postpartum(with a estimated 15-fold increased risk of PE postpartum compared with during pregnancy). In a systematic review the risk of VTE was fourfold greater following CS than following uncomplicated vaginal delivery; and was greater following emergency CS than following elective CS. On average, was estimated that three in 1,000 women will develop a VTE following CS [6, 7].

However a decline overall in deaths associated with VTE in recent years has been observed since publication and more adherence to prevention guidelines for obstetric population [2, 6].

Currently there one reported study on incidence of Deep venous thrombosis (DVT) in women receiving thromboprophylaxis using heparin after CS. This study found that the incidence of asymptomatic DVT among women at high risk of VTE was 3.9%. In patients without thromboprophylaxis symptomatic DVT was detected in 0.04% and 0.5% [7–9].

3. Risk factors for VTE in pregnancy and puerperium

Some groups of women have a higher risk of developing VTE. The most important individual risk factor for VTE in pregnancy is a personal history of thrombosis without a trigger factor and/or following use of estrogen-based hormonal therapy. For women who have had a previous thrombosis in pregnancy, the risk of VTE increases considerably in subsequent pregnancies if antenatal thromboprophylaxis is not used, with an estimated increased risk of recurrence of three- to four-fold [1–4].

Another important individual risk factor for VTE in pregnancy is the presence of an inherited or acquired thrombophilia (a condition that predisposes individuals to developing thromboses) [2–4].

The risk of a thromboembolic event occurring during pregnancy has been shown to differ according to the nature of the thrombophilia, with estimates of risk varying from 5–33% (Homozygotic mutations or multiple thrombophilias) [3, 7, 8].

Other pregnancy-related factors shown to increase the risk of VTE include multiple gestation, pregnancy induced hypertension, prolonged active fase of labour and cesarean section (mainly in the emergency and or after labor). In a case–control study the overall risk of VTE was 0.09%, with a higher risk of events in the postnatal period following cesarean birth; and the authors verified that the risk in the antenatal period was estimated as 0.18% following cesarean section compared with 0.03% without cesarean section [2, 6, 7].

Obesity, smoking, advanced maternal age, severe heart disease, sickle cell disease, inflammatory bowel disease, active cancer, family history of VTE, and prolonged immobilization are other commonly reported risk factors [2].

VTE risk factors vary in their association with but appear to be common. In a recently published cross-sectional study of prospectively collected data from 21 019 sequential postpartum VTE risk assessments in a hospital setting the most prevalent VTE risk factors related to maternal and delivery characteristics included overweight and obesity (36%), age ≥ 35 (35%) and cesarean section (32%). Over three-quarters of women had at least 1 VTE risk factor (78%), and over 40% had multiple (2 or more) VTE risk factors. An important finding is the fact that in 19% of women all VTE risk developed during delivery or in the post-partum period (and were not present prior to the peripartum period) highlighting the critical importance of performing continuos VTE risk assessment even after delivery [8, 9].

COVID-19 is new disease with potentially impact in pregnancy and pueperium. The evidence addressing the issues of coagulopathy and thrombosis in pregnancy in association with COVID-19 is sparse and so far, there is no available high-quality studies at this moment.. However, given the possible association between the hypercoagulability characteristic of pregnancy and the risk increase in COVID-19-related VTE, the International Society of Thrombosis and Haemostasys (ISTH), as well as the Ministry of Health in Brazil, suggest that all pregnant and postpartum women admit had at the hospital for COVID-19 (i.e., severe and moderate cases) receiving pharmacological prophylaxis [10, 11].

4. Interaction of VTE risk factors and potencial risk scores

The interaction of VTE risk factors remains an important knowledge gap. However in a large hospital- based case–control study, including 559 women with objectively verified VTE during pregnancy or the postpartum period and 1229 controls, some risk factors exhibited additive interaction (as observed with the combination of assisted reproductive technology with multiple pregnancy, and emergency cesarean section with infection), while others appeared to act as multipliers, as with the combination of antepartum immobilization and elevated body mass index [12, 13].

In particular, understanding how these VTE risk factors translate into absolute PA-VTE is essential. A risk prediction model for postpartum VTE was recently developed using large data on 433 353 deliveries. This model was externally validated using another data sets of 662 387 deliveries. Emergency cesarean section, stillbirth, varicose veins, preeclampsia/eclampsia, infection, and medical comorbidities were the strongest VTE predictors in the final multivariable model. The risk prediction model was able to discriminate postpartum women with and without VTE with statistical significance [C statistic of 0.70 (95% CI, 0.67-0.73)] [13].

The risk assessment models in surgical patients (e.g., Caprini and Padua) to predict VTE after cesarean delivery has not been adequately studied suggesting the establishment of a maternal clinical registry and more extensive research to identify optimal models with which to predict VTE risk in the obstetrical population [4, 13].

At the Maternity Hospital of the Hospital das Clínicas, Universidade de São Paulo in Brazil – a tertiary referral service provider for obstetric pathologies - a risk score for VTE was developed since 2014. Since the establishment of this risk score, there have been no more maternal deaths from PE during hospitalization or up to three months postpartum. Among patients who received prophylaxis with enoxaparin, 0.4% had VTE (failure of treatment); in the untreated (that is, low risk) group had 0.06% of VTE. In our institution we have adapted this score since

3 points High risk factors	2 points Moderate risk factors	1 point Low risk factors
Previous VTE associated with pregnancy and or hormonal treatment	Previous VTE with a trigger factor	—
High Risk Thrombophilia	Low risk Thrombophilia	—
Covid 19 severe cases Sickle cell anemia Severe cardiovascular disease Active Cancer	Previous cancer Severe infections Obesity Severe bleeding with transfusion of blood products	Preeclampsia Multiple pregnancy C-Section or any surgical procedure Massive varicose veins
Obesity with Imobilization >4 days Inflammatory Bowel Disease Nephrotic Proteinuria		Severe hyperemesis Severe smoking

Adapted from: [14].

Table 1.
Risk factors for VTE in hospitalization of pregnant women and puerperal women.

2020 and The National Specialized Commission on Thromboembolism of the Febrasgo (CNE-TEV), based on this national experience proposes the risk score for pregnant women and hospitalized mothers in Brazil. The risk factors were divided into high, medium and low risks, which score, respectively, 3, 2 or 1 point. The fine score occurs by the sum of the values attributed to each factor present in the patient. Pharmacological anticoagulation with is indicated for patients with a score risk of VTE greater than or equal to three [14, 15].

The score is summarized in **Table 1**.

5. Considerations for VTE prophylaxis in cesarean section

A Cochrane's systematic review concluded that there is insufficient evidence of post-cesarean thromboprophylaxis due to the small number of studies and different comparison criteria. Although the risk of VTE associated with cesarean section is low, when there is a relationship with other risk factors, the occurrence of VTE becomes significant and the institution of thromboprophylaxis should be indicated [1, 2].

Based on observational data, some authors have attempted to calculate the number needed to treat (NNT) to prevent 1 episode of VTE during the postpartum period, and reported that among women deemed at high risk for VTE postpartum, 640 as high as 4000 would require prophylaxis to prevent 1 episode of VTE [13].

The potential benefit of pharmacologic prophylaxis needs to be weighed against the potential for adverse outcomes associated with the intervention. The use of pharmacologic VTE prophylaxis after cesarean delivery has been associated with increased rates of wound morbidity. The number needed to harm (NNH) with the use of pharmacologic VTE prophylaxis after cesarean delivery has been reported to be as low as 200. Due to inadequate sample calculation in the available studies the optimal risk threshold for initiating pharmacological thromboprophylaxis in the antepartum and postpartum periods, particularly in women with lower-risk thrombophilic traits and multiple (common) VTE risk factors remains to be established [16].

Another question is optimal optimal time to start and duration of thromboembolism prophylaxis after a cesarean delivery. Recent guidelines have addressed the optimal interval between neuraxial anesthesia and initiation of pharmacologic VTE

prophylaxis to prevent the development of spinal or epidural hematomas take in consideration the time of insert and removal of epidural catheter [5, 15, 16]. Prophylactic doses of enoxaparin (40 mg subcutaneously every day) may be started postoperatively as early as 4 hours after catheter removal but not earlier than 12 hours after the block was performed [4, 15, 17]. Another complication to be considered is iatrogenic postoperative bleeding. The risk of bleeding with prophylactic doses are usually mild, such as wound hematomas, and rarely life-threatening hemorrhagic complications [16–21]. In cases with significant intraoperative bleeding complications, the decision of when to start pharmacologic prophylaxis (if indicated) must be individualized according with the clinical and surgical scenarios [2, 3, 21].

Although the evidence is scarce Women with risk factors should receive thromboprophylaxis at minimum for 6 weeks postpartum; women with transient risk factors in the antepartum and intrapartum should receive thromboprophylaxis until hospital discharge or up to 2 weeks after delivery [2–5].

In SARS COVID-19 given the potential increase in VTE risk a weight-adjusted VTE prophylaxis with low molecular weight heparin (LMWH) should be considered in all pregnant and post partum women admitted to hospital (in the absence of active bleeding and with a platelet count above 30 × 109/L or indication for immediate delivery). In case of indicated or emergency delivery VTE prophylaxis should be evaluated individually [10, 11].

6. Pharmacologic agents for prophylaxis of VTE

The 2 most common agents used for prophylaxis of VTE are LMWH and Unfractionaded Heparin (UFH). Recent guidelines recommend LMWH (most recomended enoxaparin) as the first-line pharmacologic agent. Enoxaparin has a half-life of 4 to 6 hours and is eliminated by the kidney and it is not recommended in patients with significant impaired renal function but has the advantage of better bioavailability, longer half-life, more predictable anticoagulation effect, less bleeding risks, and less risk of heparin-induced thrombocytopenia and osteopenia [2–5, 17, 18].

The recommended dose of enoxaparin is typically 40 mg subcutaneously once a day. Obese women may require higher doses; some evidence supports the use of intermediate doses of enoxaparin (40 mg subcutaneously every 12 hours) for obese women or a weight-based prophylactic dose of 0.5 mg/kg subcutaneously every 12 hours of enoxaparin in morbidly obese women after cesarean delivery [2, 17].

UFH has a shorter half-life than LMWH of 60 to 90 minutes and is mostly cleared by the reticuloendothelial system, rendering it a good choice in women with renal disease. Recommended prophylactic dosages in the postpartum period is 5000 units subcutaneously every 8 to 12 hours [17].

Fondaparinux is a completely synthetic pentasaccharide heparin analog and the first of a new class of selective indirect antithrombin-dependent factor Xa inhibitors, which inhibits thrombin generation, has some benefit for thromboprophylaxis. Heparin-induced thrombocytopenia (HIT) is an extremely rare situations of fondaparinux in comparison with the UFH and LMWH, suggesting that fondaparinux is an alternative for the treatment of thrombosis associated with HIT [22]. In a small study in Japan short term fondaparinux (2,5 mg/day)appears to be an adequate and safe method for prevention of symptomatic VTE in women at risk after cesarean section [22, 23].

There are insufficient safety and efficacy data to recommend the use of new oral anticoagulants (e.g., apixaban, rivaroxaban, dabigatran) during the postpartum period [24, 25].

7. Contraindications and patient risks for pharmacological prophylaxis

a. Potential contraindications to prescribing enoxaparin or heparin.

Thrombocytopaenia - Low platelet count (<100.000 ui/ml)
High risk of uncontrolled hemorrhage or current bleeding
Adverse reaction/allergy to enoxaparin or heparin
Acute bacterial endocarditis [2]

b. Patient related risk factors for bleeding:

Current active major bleeding with need for transfusion
Current chronic bleeding over 48 hours
Bleeding disorders (e.g. hemophilia)
Recent central nervous system bleeding
Intracranial or spinal lesion
Current renal impairment with secondary coagulation did
Underlying coagulopathy or coagulation factor abnormalities
Thrombocytopaenia.- a platelet count <50000/uL
Severe platelet dysfunction
Active peptic ulcer or active ulcerative gastrointestinal disease
Obstructive jaundice or cholestasis
Recent major surgical procedure with a high bleeding risk [2, 3].

8. Summary of the recommendations

To date, guideline recommendations are mainly based on expert opinion rather than high-quality evidence and provide conflicting recommendations (**Table 2**).

Recently The Society of Maternal Fetal Medicine published a evidence based guideline summarized in **Table 3** [17].

9. Electronic medical records and improvements in the prevention of VTE

Predicting individual VTE risk is extremely challenging because no single variable is strongly predictive, and we are investing on systems that incorporate multiple variables to produce significant predictive values for VTE. The medical records waistband Electronics (EMR) Scoring systems with use of artificial intelligence should be seen as an opportunity to support clinical decision. Some studies indicate that computer alert interventions may increase the adherence to appropriate risk stratification for VTE, reduce costs and avoiding unnecessary thromboprophylaxis in low-risk patients [15].

10. Conclusions

VTE remains an important and preventable cause of maternal morbidity and mortality during the postpartum period [26–29]. Despite absence or robust evidence use of mechanical prophylaxis sequential compression devices is an inexpensive, safe intervention and should be used in all women undergoing

Organization	Recommendation	Risk stratification
American College of Obstetricians and Gynecologists [4]	• Pneumatic compression for all • Women with additional risk factors for VTE may benefit from pharmacologic prophylaxis	A risk scoring system is not endorsed
American College of Chest Physicians [3]	• Early mobilization is recommended in absence of risk factors. Prophylaxis with heparin is suggested when 1 major or 2 or more minor risk factors are present or when 1 minor risk factor is associated with emergent cesarean section In women at very high risk, we suggest ad pharmacologic to mechanical prophylaxis After delivery, prophylaxis is suggested for up to 6 weeks postpartum in the presence of risk factors	Major risk factors for VTE: Immobility (for at least 7 days antepartum) Postpartum hemorrhage with surgical intervention Previous history of VTE Pregnancy induced hypertension with fetal growth restriction Antithrombin deficiency Factor V Leiden or Prothrombin gen mutations Blood transfusion Puerperal infection Active Systemic lupus erythematosus Severe Heart disease Sickle cell disease Minor risk factors: Obesity Multiple pregnancy Postpartum hemorrhage Smoking Pregnancy induced hypertension Protein C or S deficiency
Royal College of Obstetricians and Gynecologists [2]	Women at high risk should receive pharmacologic prophylaxis for 6 weeks after delivery; women at intermediate risk for VTE should receive pharmacologic prophylaxis for at least 10 days after delivery. For women at low risk for VTE, we recommender early mobilization and adequated hydratation	**High-risk patients** Any previous VTE, any woman requiring antenatal LMWH, high-risk thrombophilia, low-risk thrombophilia with family history of thrombosis **Intermediate-risk** Cesarean delivery after labor, Obesity, postpartum hospital readmission, surgical procedures during the puerperium, Maternal diseases - cancer, heart failure, active lupus, nephrotic syndrome, sickle cell disease, type 1 diabetes with nephropathy, inflammatory bowel disease, or Two or more of the following: Age > 35 years, parity 3, obesity, smoker, elective cesarean delivery, family history of VTE, low-risk thrombophilia, varicose veins, current systemic infection, pregnancy induced hypertension, immobility, multiple pregnancy, preterm delivery, stillbirth, operative vaginal delivery, prolonged labor >24 hours, postpartum hemorrhage

Adapted from [17].

Table 2.
Current guidelines on prophylaxis of thromboembolism after C/S.

cesarean delivery until the woman is fully ambulatory [1, 2, 4, 17]. The decision to add pharmacologic prophylaxis depends on the presence or absence of risk factors [2–4, 15, 17]. Women with a previous personal history of deep venous thrombosis or pulmonary embolism and women with a personal history of an inherited thrombophilia (either high-risk or low-risk), and should receive pharmacologic prophylaxis after cesarean delivery [3, 4, 27, 29]. Another risk factors like obesity

	Recommendation	Grade
1	All women who undergo cesarean sectionreceive sequential compression devices starting before surgery and that the compression devices be used continuously until discharge	1C
2	Women with a previous personal history of DVT venous thrombosis or PE submitted to cesarean section receive both mechanical and pharmacologic prophylaxis.. Pharmacological must be maintained for up to 6 weeks postpartum	2C
3	Women with a personal history of an inherited thrombophilia (high-risk or low-risk) but no previous thrombosis submitted to cesarean section receive both mechanical and pharmacologic prophylaxis. Pharmacological must be maintained for up to 6 weeks postpartum	2C
4	Low-molecular-weight heparin is the preferred thromboprophylactic agent in pregnancy and the postpartum period	1C
5	We suggest the use of intermediate doses of enoxaparin in pharmacologic thromboprophylaxis for pregnant women with class III obesity,	2C
6	A patient safety bundle with an institutional protocol for venous thromboembolism prophylaxis must be developed for women who undergo cesarean delivery	Best Practice

Adapted from [17].

Table 3.
SMMF summary of recommendations.

and clinical complications (Sickle cell disease, Hypertension, COVID 19 infections) should be considered. The use of universal or near-universal pharmacological prophylaxis for low risk women undergoing cesarean delivery, cannot be recommended until further studies demonstrate that such a strategy is beneficial [14]. At present, the available VTE risk stratification tools used to decide for or against pharmacologic prophylaxis have not been validated in women undergoing cesarean delivery being a good opportunity for research and development. Individualization of care is recommended for women at very high risk for VfE and institucional safety bundles are recommended as a best practice [14, 15, 17]. In the last half-century, we have made tremendous progress in understanding the epidemiology and prevention of VTE, and it is imperative that these advances be studied and implemented in obstetric care [26].

Conflict of interest

"The authors declare no conflict of interest."

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