Venous Thromboembolism and Route of Delivery – Review of the Literature

Tromboembolismo venoso e via de parto – revisão da literatura

Matheus Schimidt Evangelista[1] Karina Slompo[1] Jorge Rufino Ribas Timi[2]

[1] Faculdade de Medicina, Universidade Federal do Paraná, Curitiba, PR, Brazil
[2] Division of Vascular Surgery, Department of Surgery, Hospital de Clínicas da Universidade Federal do Paraná, Curitiba, PR, Brazil

Address for correspondence Matheus Schimidt Evangelista, Medical Student, Universidade Federal do Paraná, Rua Cel. Pedro Scherer Sobrinho, n° 426, Ap 115, 80050-470, Cristo Rei, Curitiba, PR, Brazil (e-mail: matheusschimidt@gmail.com).

Rev Bras Ginecol Obstet 2018;40:156–162.

Abstract

Venous thromboembolism events are important causes of maternal death during pregnancy and the postpartum period worldwide. A review of the literature with the objective of evaluating venous thromboembolism events in the puerperium according to the route of delivery was performed through a bibliographic survey in the Medline, LILACS and Scielo databases. We observed that patients submitted to cesarean sections present a significantly higher risk of developing venous thromboembolism when compared with those who undergo spontaneous vaginal delivery. The pathophysiological bases for this difference were explored and described in this review, as well as the indications of prophylaxis and treatment. Doctors and health professionals must be continuously vigilant regarding this condition, since it is associated with high morbidity and mortality.

Keywords
- venous thromboembolism
- venous thrombosis
- natural childbirth
- cesarean section
- postpartum period

Resumo

Os eventos de tromboembolismo venoso são causas importantes de morte materna durante a gravidez e o período do pós-parto em todo o mundo. Foi realizada uma revisão da literatura com o objetivo de avaliar os eventos de tromboembolismo venoso no puerpério de acordo com a via de parto utilizada, por meio de uma pesquisa bibliográfica nas bases de dados Medline, LILACS e Scielo. Observou-se que as pacientes submetidas a cesariana apresentam um risco significativamente maior de desenvolver tromboembolismo venoso do que aquelas que se submetem a parto vaginal espontâneo. As bases fisiopatológicas desta diferença foram exploradas e descritas nesta revisão, bem como as indicações de profilaxia e tratamento. O alerta contínuo dos médicos e profissionais de saúde é necessário, uma vez que se trata de uma condição comum associada a alta morbidade e mortalidade.

Palavras-chave
- tromboembolia venosa
- trombose venosa
- parto normal
- cesárea
- período pós-parto

Introduction

Venous thromboembolism (VTE) is a problem during pregnancy, delivery and the puerperium. Thromboembolic events represent an important cause of maternal death, occurring both in women who undergo cesarean delivery and in those who undergo vaginal delivery.[1]

Brazil is the country that performs most cesarean sections in the world, with 45.9% of all births being caesarean sections.[2] According to the Brazilian Ministry of Health, the percentage of cesarean deliveries is 40% in the public network, reaching 84% in supplementary health. There are several campaigns aimed at reducing this proportion; however, the Brazilian Federal Medical Council (CFM, in the

received
October 16, 2017
accepted
December 12, 2017
published online
February 23, 2018

DOI https://doi.org/10.1055/s-0037-1621742.
ISSN 0100-7203.

Portuguese acronym) recommends that the obstetrician should respect the decision of elective caesarean section by the patient (Resolution 2144/2016).[3]

The objective of this review is to evaluate the events of VTE in the puerperium according to the chosen route of delivery.

Methods

Data were obtained through a bibliographic survey in the Medline, LILACS and Scielo databases. All articles were searched using the terms *thromboembolism*, *thrombosis*, *cesarean*, *vaginal*, and *delivery*. We included all articles that had data on the occurrence of VTE in populations of pregnant or postpartum women in medical follow-up, with a description of the type of delivery and postpartum follow-up. The studies that did not mention the occurrence of VTE events in pregnant and/or puerperal patients and those that did not mention the type of delivery chosen were excluded.

Results

A total of 34 articles published between 2000 and 2016 fulfilled the inclusion criteria. The information was analyzed for the consistency of the data, the year of publication, and the quality of the study.

Incidence of Venous Thromboembolism

Venous thromboembolism events, including deep venous thrombosis (DVT) and pulmonary thromboembolism (PTE), are present in up to 3 out of 1,000 pregnancies, with pregnancy-associated pulmonary embolism being a major cause of maternal morbidity and mortality in the Western world.[4–7] In addition, VTE is considered one of the most serious complications of pregnancy, accounting for 10% of maternal deaths in the United States through the occurrence of PTE. In addition, pregnancy-related DVT causes significant morbidity, along with a long-term risk of post-thrombotic syndrome (PTS), leg ulcers and a documented decrease in quality of life.[8,9]

It has been found that the incidence of VTE increases about 4-5 times in pregnant women and $\sim$ 20 times in the postpartum period.[5–7,9–15] This risk may be even higher: 1 study demonstrated a 60-fold increase in the risk of VTE in the first 3 months after delivery compared with non-pregnant women.[16]

In developing countries, the incidence of VTE has increased, with a ratio of 1 case per every 16 pregnancies per year. This represents an incidence rate of 1.4% of VTE, with 1.1% manifesting as DVT and 0.3%, as PTE.[4,6,10,13,17]

Given the high maternal mortality due to PTE, early diagnosis and treatment should be prioritized.[7]

Risk Factors

Thrombophilia is the most important risk factor for venous thrombosis during pregnancy.[5] Other risk factors include history of VTE, obesity, obstetric hemorrhage, presence of varicose veins, heart disease, increased maternal age ($\geq$ 35 years), eclampsia, preeclampsia, intrauterine growth restriction, preterm labor, surgical history, multiparity ($\geq$ 3 children), anemia and smoking.[4,9,14,15,18,19]

Pathophysiology of the Thrombus

Pregnancy, due to hypercoagulability, venous stasis and endothelial injury, is considered a typical example of the Virchow triad, with pregnant women having a potential 5-fold higher possibility of developing a thrombogenic status when compared with non-pregnant women of the same age group.[4–6] Hypercoagulability occurs due to the increase in coagulation factors such as fibrinogen, factors II, VII, VIII and X, and the decrease in coagulation inhibitors, such as fibrinolytic activity. Venous stasis occurs as a result of decreased venous return caused by compression of the gravid uterus on the iliac veins and inferior vena cava, and endothelial injury may occur during vaginal delivery, and it may be exacerbated during cesarean delivery. All of this represents the physiological preparation to protect women from bleeding during childbirth or abortion.[4–6,10]

In relation to the postpartum period, the type of delivery and postnatal mobility are fundamental components in the pathophysiology of thromboembolism. The risk of thromboembolism after vaginal delivery is $\sim$ 1 per 1,000, while this risk reaches 3 per 1,000 after elective cesarean section, and the mortality associated with VTE after cesarean section is increased 10-fold compared with women who undergo vaginal delivery.[20,21] The reasons for such a difference in outcome between the different delivery routes can be explained by several factors, among them, a greater immobility after cesarean section when compared with vaginal delivery. A study even showed that on the 7th day, postpartum women who underwent vaginal delivery were almost twice as mobile as those who had undergone cesarean section.[16]

Regarding hemostatic differences in the puerperium, hypercoagulability is observed for at least 2–3 weeks postpartum. Reactive thrombocytosis is a common occurrence during the postpartum period, regardless of the chosen route of delivery, and it is associated with an increased incidence of thrombosis.[22] There is also an increase in tissue factor (TF) levels in the postpartum period, which is directly associated with an increase in activated factor VII (FVIIa) levels and markers of thrombin generation. However, there is no significant difference between vaginal delivery and cesarean section in the activation of TF-dependent coagulation. The introduction of TF in the maternal blood leads to a rapid formation of the TF-FVIIa complex, which is the main route of initiation of the hemostatic system. Through activation of TF and factor X (FX), minimal amounts of thrombin can be formed, which results in the activation of platelets and cofactors activated factor V (FVa) and activated factor VIII (FVIIIa), causing a rapid amplification of the coagulation response. All of this contributes to the development of thrombosis in the puerperium.[5]

In addition, an increase in the concentration of plasma homocysteine, which is responsible for the inhibition of endothelial nitric oxide (NO) production and consequent endothelial dysfunction, was observed in women after cesarean section as opposed to women after vaginal delivery.

Maternal erythrocyte glutathione levels, an indicator of oxidation and reduction balance, have also been shown to increase significantly after full-term vaginal delivery, while this has not occurred after elective cesarean delivery. Oxidative stress through the production of oxygen-free radicals contributes to NO depletion and eventually leads to endothelial dysfunction. These observations suggest that vaginal delivery promotes endothelial function, while cesarean delivery impairs it.[23]

Another parameter to be analyzed is the mean platelet volume (MPV), a factor related to cardiovascular complications, cerebrovascular disorders, and low-grade inflammatory conditions. The increase in MPV contributes to the development of arterial and venous thrombosis and to the pathogenesis of thromboembolic complications reported in patients who gave birth by cesarean section and not by vaginal delivery.[24]

Groups of Higher and Lower Risk

Ethnic factors interfere with the risks of VTE in the postpartum period. Compared with white women, black women have a 50% higher risk, and Asian women have a 30% lower risk, while Hispanic women also have a lower risk. The increased risk of postpartum VTE for black women is only observed after cesarean section, while the lower risk for Hispanic women is apparent only after vaginal delivery.[8]

The postpartum thromboembolic mortality rate of African-American women is 4.5 times higher than that of Caucasian women: 4.1/100,000 live births and 0.9/100,000 live births respectively.[25]

Prophylaxis Techniques

After acknowledging the increase in maternal deaths due to thromboembolism and a widespread failure of the clinicians to follow existing guidelines for prophylaxis based on identified risk factors, experts have advocated universal prophylaxis for all women undergoing cesarean section.[26]

Post-cesarean thromboprophylaxis has been shown to reduce maternal VTE-related morbidity and mortality. Sequential mechanical compression devices, simple graduated compression socks, low molecular weight heparin (LMWH), and fractionated heparin (FH) and unfractionated heparin (UFH) demonstrated to be effective in this issue.[4,6,10–12,20,21,23,26–29]

In 2011, the American College of Obstetricians and Gynecologists (ACOG)[30] published an opinion supporting the routine use of perioperative pneumatic compression devices during cesarean section. Sequential compression devices reduce the risk of VTE by increasing femoral blood flow through mechanical compression of the lower limbs, as well as by stimulating fibrinolysis through an increase in tissue plasminogen activator concentration and a decrease in inhibitor levels. However, in order to effectively prevent venous thrombosis, devices should be used continuously, since their beneficial effects are lost within 10 minutes of their removal.[4,6,10,12,27,29]

The prophylactic use of LMWH in low-risk post-cesarean women is still controversial. The current guidelines do not recommend LMWH thromboprophylaxis in this situation without any additional risk factors. However, the "Confidential Inquiry into Maternal Deaths" (CEMACH) report showed that risk factors were absent in more than 20% of women who died from venous thromboembolism events.[21]

The Norwegian Society of Gynecology and Obstetrics recommends prophylaxis with low-molecular weight heparin for 4 to 8 days after all cesarean sections. On the other hand, the Royal College of Obstetrics and Gynecology (RCOG) classifies women who underwent cesarean section in three degrees, and recommends thromboprophylaxis only for those women classified as having a medium or high risk of thrombosis.[23]

According to the French College of Gynecology and Obstetrics,[20] for all cesarean sections, thromboprophylaxis by compression stockings from the day of delivery until at least 7 days is recommended, with or without the addition of LMWH, depending on the presence and type of risk (higher or lower). Considering that the thromboembolic risk during an elective cesarean section is 3 per 1,000, and that the anticoagulant treatment is indicated for any risk higher than 3%, it is important to know the multiplicative factor of the risk, that is, the odds ratio (OR), for all additional risk factors. Treatment is therefore considered necessary when the OR of the combined risk factors is higher than 10, so that the theoretical risk of 3 per 1,000 for an elective cesarean section exceeds 3%. These additional risk factors were well-studied in obstetric settings, and their ORs were evaluated. These data are presented in ►**Table 1**. When there are several additional risk factors, their ORs are multiplicative. The duration of the anticoagulant treatment depends on the number and, in particular, on the type (major or minor) of associated risk factors: 1) in an emergency cesarean section with no additional minor risk factor, thromboprophylaxis by compression stockings is recommended alone for 7–14 days (by professional consensus); 2) in an emergency cesarean with a minor additional risk factor (resulting in a cumulative OR $>$ 10), thromboprophylaxis by compression stockings plus a preventive dose of LMWH for 7–14 days is recommended (by professional consensus); 3) in an elective cesarean section with no additional risk factors or only a minor one, thromboprophylaxis by compression stockings for 7–14 days is recommended (by professional consensus); 4) in an elective cesarean section with two additional minor risk factors (producing a cumulative OR $>$ 10), thromboprophylaxis with compression stockings and a preventive dose of LMWH for 7–14 days is recommended (by professional consensus); and 5) in all situations, particularly those involving great risk or the presence of additional risk factors, this may result in prolonging the duration of this medication prophylaxis for up to 6 weeks (by professional consensus).[20,29]

Venous filters may be used as a temporary measure in patients with contraindication to anticoagulation.[4] Inferior vena cava (IVC) filters have been used safely and effectively to prevent PTE in pregnant patients with confirmation of DVT in the lower limbs, as well as for prophylactic use in patients with proximal DVT prior to delivery.[10,13] However, there is insufficient evidence to suggest that IVC filters should be

Table 1 Simplified table describing the odds ratio of the main risk factors for venous thromboembolism related to cesarean sections according to the French College of Gynecology and Obstetrics

Risk factor	Adjusted odds ratio
Major risk factors (odds ratio > 10)	
History of thromboembolism with or without adjacent thrombophilia	> 20
High-risk asymptomatic thrombophilia[a]	> 20
Asymptomatic antiphospholipid syndrome	> 20
Complete and prolonged immobility	11
Postpartum hemorrhage with consequent surgical procedure	12
Minor risk factors (odds ratio < 10)	
Age > 35 years	1.4
Obesity (body mass index > 30) or weight > 120 kg	4
Parity > 3	2
Smoking (> 10 cigarettes/day before pregnancy or persistent smoking during pregnancy)	3
Significant varicose veins	2
Sickle cell anemia	4
Important heart disease	7
Disseminated lupus erythematosus	8
Inflammatory bowel disease	4
Low-risk asymptomatic thrombophilia[b]	3
Anemia or bleeding during pregnancy	3
Pregnancy obtained by assisted reproduction technique	4
Preeclampsia	3
Severe or fetal growth restrictive preeclampsia	4
Multiple pregnancies	4
Preterm birth < 37 weeks	3
Emergency cesarean section	3
Severe postpartum hemorrhage (bleeding > 1 L and/or blood transfusion)	3
Postpartum infection	4

Notes: [a]High-risk asymptomatic thrombophilia: antithrombin deficiency, homozygous mutations of factor V Leiden, homozygous mutation of the combined prothrombin deficiency G202010A; [b]Low risk asymptomatic thrombophilia: heterozygous mutation of factor V Leiden, heterozygous mutation of prothrombin G202010A, protein C deficiency, protein S deficiency.

used routinely during pregnancy in patients with DVT and, until further studies are performed, their use should be considered following the same absolute indications for the non-pregnant population, or in individuals in whom there are concerns about childbirth. The rates of complications in pregnant patients are comparable to those of the non-pregnant population, and there is no significant fetal morbidity or mortality. Both suprarenal and infrarenal positioning can be used, although there are more theoretical benefits with the suprarenal placement.[31]

For women undergoing cesarean delivery without additional risk factors for VTE, the American College of Chest Physicians (ACCP) recommendations suggest no prophylaxis. For women with one major or two minor risk factors (►**Table 2**), pharmacologic prophylaxis is recommended. For patients at very high risk, combined mechanical and pharmacologic prophylaxis is recommended. The ACCP also supports post-partum pharmacologic prophylaxis for all women with a prior VTE event, and recommends against antepartum pharmacologic prophylaxis for women with a single, provoked, and non-estrogen related event; however, prophylaxis is recommended for all other women with a history of VTE (►**Table 3**).[32]

Therapeutic Measures

Once the diagnosis of VTE is established, the treatment should begin as soon as possible. After initiating the basic care of support and monitoring, anticoagulant therapy is initiated.[6]

According to the ACCP guidelines published in 2016, patients with lower limb DVT or PTE due to surgical procedures should receive anticoagulant therapy for 3 months,

Table 2 American College of Chest Physicians risk factors for venous thromboembolism

Major risk factors
Immobility (strict bed rest for > 1 week in the antepartum period)
Post-partum hemorrhage > 1 L with surgery
Previous venous thromboembolism event
Pre-eclampsia with fetal growth restriction
Thrombophilia
Antithrombin
Factor V Leiden (homozygous or heterozygous)
Prothrombin G20210A (homozygous or heterozygous)
Medical conditions
Systemic lupus erythematosus
Heart disease
Sickle cell disease
Blood transfusion
Post-partum infection
Minor risk factors
Body mass index > 30 kg/m^2
Multiple gestation
Post-partum hemorrhage > 1 L
Smoking > 10 cigarettes/day
Fetal growth restriction
Thrombophilia
Protein C deficiency
Protein S deficiency
Pre-eclampsia

with the drugs of choice being dabigatran, rivaroxaban, apixaban or edoxaban.[33] Since pregnant and lactating women were excluded from studies with such drugs, these recommendations do not apply to them. Thus, in these groups, the use of LMWH is recommended for at least 6 weeks postpartum, with the minimum duration of the anticoagulant therapy being 3 months.[32]

Regarding the management of massive PTE cases in pregnant women with hemodynamic impairment, the treatment strategy remains controversial. More aggressive approaches, such as pulmonary thromboaspiration and thrombolysis, are warranted to save the mother's life.[6]

Thrombolysis is generally contraindicated during gestation and the puerperium due to the high risk of bleeding. However, over the past decade, advances in minimally invasive technologies have stimulated aggressive treatment of DVT using percutaneous techniques. Endovascular treatment using mechanical thromboaspiration alone or in combination with pharmacological thrombolytic agents has received much attention in the literature as a safe and effective means of treating acute postpartum DVT.[34]

Discussion

Venous thromboembolism is the leading cause of maternal death during pregnancy and the postpartum period in developed countries. According to the World Health Organization (WHO), 2% of all maternal deaths in the world are caused by VTE, and 14.9% of maternal deaths in developed countries are related to thromboembolic events, including, among these countries, mainly the United States, due to the higher prevalence of risk factors and lower incidence of maternal death due to causes such as hemorrhage and sepsis.[1]

Approximately 80% of venous thromboembolic events during pregnancy correspond to DVT, and 20% correspond to PTE. Two thirds of the cases of DVT occur during gestation, and are distributed with relative homogeneity in the three trimesters. In contrast, 43% to 60% of pregnancy-related episodes of pulmonary embolism occur in the puerperium.[6]

There are several risk factors for the development of VTE in pregnant women, with thrombophilia and the previous history of VTE being the main ones. Age > 35 years is also an important factor, since pregnant women aged ≥ 35 years present a relative increase of 70% in the incidence of VTE when compared with women aged between 25 and 34 years.[6,13]

It has been proven by several studies that the morbidity and incidence of VTE is higher in women who undergo cesarean delivery compared with those who opt for vaginal delivery. A study in Canada, which included women who delivered between April 1991 and March 2005, showed differences between the group of women undergoing planned cesareans and the group of women undergoing planned vaginal delivery, with overall rates of severe morbidity for the entire period of 14 years of 27.3 and 9.0 per 1,000 births respectively. The cesarean group presented a higher risk of developing VTE (OR: 2.2, 95% confidence interval [95% CI]: 1.5–3.2) than the vaginal delivery group.[14] In another study conducted in India between 2003 and 2006, cesarean section was associated with a 3.01-fold increase in the risk of maternal mortality compared with vaginal delivery.[17]

Despite the higher maternal risk of VTE after cesarean section and the numerous campaigns that stimulate vaginal delivery, cesarean rates remain high, reaching 90% in the private sector. The high rates do not correspond to the high number of cesareans performed by medical indication, but by the cesarean sections performed at the request of the mother. The CFM guarantees the patient's autonomy in choosing the type of delivery that best suits her, and the reason most Brazilian women choose cesarean delivery is the absence of pain.[3]

It is also worth noting that, in Brazil, childbirth care does not constitute an exclusively medical act. The public health system admits the nursing professional's performance in the process of childbirth, with legal regulations made by Ordinance no. 163, dated 09/22/1998, of the Health Care Secretariat of the Brazilian Ministry of Health, and by Resolution 223/1999 of the Brazilian Federal Nursing Council.[35]

Table 3 The American College of Chest Physicians (ACCP) recommendations for antenatal and post-partum pharmacologic prophylaxis

	Antepartum	Postpartum
Low-risk thrombophilia without personal or family history of VTE[a]	Vigilance recommended	Vigilance recommended
Low-risk thrombophilia without personal history of VTE; family history positive for VTE	Vigilance recommended	Prophylaxis recommended
Low-risk thrombophilia with single prior VTE event	Prophylaxis recommended	Prophylaxis recommended
High-risk thrombophilia without personal or family history of VTE	Vigilance recommended	Prophylaxis recommended
High-risk thrombophilia with single prior VTE event or family history of VTE	Prophylaxis recommended	Prophylaxis recommended
Single prior VTE, no thrombophilia, idiopathic event, or provoked by pregnancy or estrogen	Prophylaxis recommended	Prophylaxis recommended
Single prior VTE, no thrombophilia, event provoked by non-estrogen-related transient risk factor	Vigilance recommended	Prophylaxis recommended
Multiple prior VTE events	Prophylaxis recommended	Prophylaxis recommended

Abbreviation: VTE, venous thromboembolism.
Note: [a]The ACCP defines high-risk thrombophilias as homozygosity for factor V Leiden or prothrombin 20210A mutation; other thrombophilias are considered low-risk.

Therefore, the adequate preparation of these professionals for the detection of VTE is indispensable.

Conclusion

There is a higher incidence of thromboembolic events in pregnant patients compared with non-pregnant women. In addition, patients undergoing cesarean sections have a significantly higher risk of developing VTE when compared to those who spontaneously deliver vaginally. Obviously, a higher incidence of these events is observed in patients with different risk factors. Venous thromboembolism is an important cause of maternal death worldwide, especially in developed countries, which demonstrates the importance of studies advocating the continuous vigilance of physicians and health professionals who care for pregnant patients with risk factors and/or who will undergo cesarean sections. These thromboembolic events are common, difficult to identify, and of high maternal morbidity and mortality, thus requiring a constant update on the part of the professionals, who must know the correct use of the thromboprophylaxis and treatment techniques.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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