Venous thromboembolism in women: new challenges for an old disease

Tromboembolismo venoso na mulher: novos desafios para uma velha doença

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Abstract

In countries that have controlled classic causes of maternal death, such as eclampsia and hemorrhage, venous thromboembolism (VTE) has become the major concern. Prevention of VTE during pregnancy and postpartum by applying guidelines and implementing pharmacoprophylaxis is still the best strategy to reduce occurrence of this complication. Hormonal contraceptives and hormone replacement therapy also increase the risk of VTE, but women cannot be deprived of their benefits, which increase their freedom at childbearing age and reduce their symptoms at menopause. Both indiscriminate use and unmotivated prohibition are inappropriate. Contraceptive and hormone replacement methods should be chosen with care, evaluating the patients' contraindications, eligibility criteria, and autonomy. This article presents a nonsystematic review of recent literature with the aim of evaluating and summarizing the associations between VTE and clinical situations peculiar to women.

Keywords: thrombosis; contraceptive agents; pregnancy; hormone replacement therapy; women; pulmonary embolism.

Resumo

Nos países que controlaram as causas clássicas de óbito materno, como eclâmpsia e hemorragia, o tromboembolismo venoso (TEV) passou a ser a principal preocupação. A prevenção do TEV na gestação e no puerpério, por meio de diretrizes e da instituição de farmacoprofilaxia, é ainda a melhor estratégia para reduzir essa complicação. Os contraceptivos hormonais e a terapia de reposição hormonal também aumentam o risco de TEV; porém, as mulheres não podem ser privadas dos benefícios dessas terapias, que as tornam mais livres na idade fértil e menos sintomáticas na menopausa. Tanto o uso indiscriminado quanto a proibição imotivada são inadequados. A escolha dos métodos contraceptivos e de reposição deve ser feita por criteriosa seleção, avaliando as contraindicações, os critérios de elegibilidade e a autonomia das pacientes. O presente artigo apresenta uma revisão não sistemática da literatura recente visando a avaliar e resumir a associação entre TEV e situações clínicas peculiares ao sexo feminino.

Palavras-chave: trombose; anticoncepcionais; gravidez; terapia de reposição hormonal; mulheres; embolia pulmonar.

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VENOUS THROMBOEMBOLISM IN PREGNANCY

Modern obstetrics is faced by a bleeding-thromboembolism duality dilemma. If, in the not too distant past the greatest dread among those who cared for women giving birth was accidental hemorrhage, nowadays, this fear is compounded by another complication: venous thromboembolism (VTE).[1,2]

Pregnant women have all three etiopathogenic components of Virchow's triad: a) venous stasis, caused by compression of the vena cava and left common iliac vein by the gravid uterus and by reduced venous tone because of the myorelaxant action of progesterone; b) hypercoagulability, secondary to induction of hepatic synthesis of coagulation factors VII, VIII, and X by placental estriol, increased levels of fibrinogen and plasminogen activator inhibitor types I and II, and reduced synthesis of protein S; c) endothelial injury, which occurs during nidation, endovascular remodeling of uterine spiral arteries, and expulsion of the placenta.[3]

During pregnancy, the risk of VTE increases by between five and ten times, and can be 35 times higher during the puerperium, when compared with the rate among women of the same age who are not pregnant.[4] After this period, the frequency reduces rapidly; but there is a residual risk for up to 12 weeks after delivery.[5]

Deep venous thrombosis (DVT) in the lower limbs is responsible for 75 to 80% of VTE episodes in pregnancy. Approximately two-thirds of DVTs occur during the prenatal period, equally distributed across the three trimesters of gestation. However, 43 to 60% of pulmonary embolism (PE) episodes occur during the first 6 weeks of the puerperium.[6] When compared with women who are not pregnant, among pregnant women DVTs in the left lower limb (90% vs. 55%) and the iliofemoral segment (72% vs. 9%) are even more predominant. This is because of the accentuated compression of the left common iliac vein against the fifth lumbar vertebra by the right common iliac artery, caused by the gravid uterus.[3]

The prevalence of VTE is in the range of 0.5 to 2.2 cases per 1,000 deliveries, depending on the study population,[7] and the absolute incidence of VTE during pregnancy and the puerperium was 107 per 100,000 woman-years in the United Kingdom (UK)[8] and 175 per 100,000 woman-years in Denmark and in Canada.[9] There are no official data on maternal VTE mortality for Brazil.[6]

Although PE remains the number one cause of direct maternal death in the UK, there was a significant fall in the rate linked with vaginal deliveries, from 1.56 per 100,000 deliveries in 2003-2005 to 0.70 per 100,000 deliveries in 2006-2008, which can be attributed to application of the first version (2004) of the Royal College of Obstetricians and Gynaecologists' (RCOG) guideline on reducing the risk of VTE in pregnancy and the puerperium.[10] Prevention of VTE in pregnancy, by means of application of guidelines and the consequent implementation of mechanical and/or pharmacological prophylaxis is the best strategy for reducing the rate of these events.[6]

RISK FACTORS FOR VTE DURING PREGNANCY

Overweight and obesity

Obesity (body mass index [BMI] > 30 kg/m^2) is an important risk factor for VTE in pregnancy and the risk grows as BMI increases,[11] reaching as much as 14.9 times higher than the risk for women who are not obese.[12] Sixty percent of the pregnant women who died from PE in the UK from 2003 to 2008 were obese.[10] While maternal overweight (BMI from 25 to 29.9 kg/m^2) is common, it is considered a less important risk factor for pregnancy-related VTE.[12]

Age

Data extracted from studies with case-control designs suggest that women over the age of 35 years are at double the risk.[13] In a study conducted in the UK, using a broad cohort of women who were not pregnant, those aged 35 to 44 years had a 50% higher risk of VTE when compared with those aged 25 to 34 years. The prenatal VTE rate did not increase with age, but women aged 35 to 44 years exhibited a 70% greater risk in the puerperal period when compared with those aged 25 to 34 years (an increase in absolute risk of 1.6 per 1,000 person-years).[8] In general, age of 35 years or more is considered an antenatal and postnatal risk factor.[14]

Thrombophilias

Although there is an association between hereditary thrombophilias and VTE, systematic work-up for thrombophilias should not be conducted for all women, but restricted to patients with prior episodes or family history of thrombophilias with greater potential for complications, such as antithrombin deficiency and homozygosis of factor V Leiden and the 20210 prothrombin mutation, which may need VTE prophylaxis. Depending on the circumstances,

this may be prescribed from the start of pregnancy up to puerperium, from the 28th week onwards, or just during puerperium. It is important to point out that clinical history is of greater relevance for this decision than the results of laboratory tests. In turn, the association between thrombophilias of genetic causes and uteroplacental thrombosis causing miscarriage, fetal growth restriction, or placental abruption, remains a controversial subject.[15-17]

Long-distance travel and immobility

There are limited data on immobility and long-distance travel in pregnant women, so it is necessary to extrapolate from studies of populations women pregnant who are not.[18] Guidelines from the UK's National Institute of Health and Care Excellence (NICE)[19] and the recommendations of the RCOG on flying during gestation state that flights with duration exceeding 4 hours increase the risk of VTE. A Norwegian case-control study identified an increased risk of VTE in pregnant women with BMI > 25 kg/m^2 and prepartum immobilization (defined as confinement to bed for a period greater than or equal to 1 week before birth or before diagnosis of VTE), showing a multiplication effect on prenatal and postnatal risk of VTE.[11]

Hospital admission during pregnancy is associated with an 18-times increase in the risk of VTE compared with the baseline risk outside of hospital and the risk remains elevated after birth, for the next 28 days. When admitted to hospital, the risk is higher in the third trimester of pregnancy and in women over the age of 35 years.[20]

Others

Certain comorbidities have been associated with increased risk of VTE during pregnancy. These include inflammatory intestinal disease, urinary tract infection, systemic lupus erythematosus, heart diseases, pregnancy-induced systemic arterial hypertension or pre-eclampsia, and non-obstetric antenatal surgery.[21] In an analysis of data from 1,475,301 discharges from Scottish hospital maternity units, Kane et al. found that risk factors associated with VTE included three or more previous gestations, obstetric hemorrhage, and pre-eclampsia.[21] Hyperemesis increases prenatal and postnatal risk of VTE 4.4 times.

This information has important implications, since many thromboembolic events are fatal and occur during the first trimester, often before the first prenatal consultation, when antenatal prophylaxis may be initiated.[22]

Factors related to anticoagulant treatment during gestation and puerperium

Administration of warfarin during pregnancy can induce placental abruption, embryopathy, abnormalities of the central nervous system (CNS), and fetal bleeding. Warfarin embryopathy is characterized by nasal hypoplasia and/or stippling of the epiphyses and is associated with exposure to warfarin between the sixth and twelfth weeks of gestation.[23] Central nervous system abnormalities associated with use of warfarin include dysplasia of the dorsal midline with agenesis of the corpus callosum, atrophy of the cerebellar midline, dysplasia of the ventral midline with optical atrophy and amaurosis, and hemorrhage, and can occur after exposure to warfarin at any phase of the gestation. Warfarin is safe when breastfeeding.[24]

Two approaches can be taken to reduce the risk of warfarin use in women who need anticoagulation and intend to become pregnant. The first is to maintain warfarin and conduct pregnancy tests frequently. As soon as pregnancy is detected, before the sixth week, low molecular weight heparin (LMWH) should be introduced to replace warfarin. The other approach is to withdraw warfarin and start LMWH as soon as the decision to become pregnant is taken.[24-28]

Although existing direct oral anticoagulants (apixaban, dabigatran, edoxaban, and rivaroxaban) have enabled major advances in prophylaxis and treatment of VTE in many clinical situations, they are contraindicated in pregnancy, because they cross the placental barrier, and in breastfeeding, because they pass into breast milk.[6,23-25]

Caesarean

Although the risk of VTE associated with caesarean in isolation is low, the rate of VTE occurrence becomes significant when there is a relationship with other risk factors, and so thromboprophylaxis should be prescribed.[29] Delivery of anticoagulated pregnant woman should be scheduled for 37 to 40 weeks. Low molecular weight heparin should be withdrawn 12 hours before delivery if given at prophylactic dosages, or 24 hours before if administered at intermediate or full dosages, enabling safe administration of spinal or epidural anesthesia. Pregnant women on LMWH should be instructed not to administer the dose if they experience contractions or release of liquids.[23]

The choice of delivery route is obstetric and there is no contraindication against artificial cervical ripening or induction of labor. The patient should continue wearing antiembolism stockings throughout the procedure, regardless of whether delivery is vaginal or caesarean.

Risk stratification

Stratification of VTE risk in pregnancy is based on assessment of each patient and should be performed for all women who intend to become pregnant or as soon as they become pregnant. It is recommended that assessments are repeated throughout the prenatal period, since new risk factors could emerge. The patient's preferences and views should be taken into account when choosing thromboprophylaxis, even though the treatment options are restricted in this situation.[26]

The recommendations suggested are based on individual variations between patients and are intended to inform, rather than substitute, the physician's clinical judgment, which should determine the appropriate management for each case in the final analysis. The most relevant guidelines on the subject of diagnosis, prophylaxis, and treatment of VTE in pregnancy are those published by the American College of Obstetricians and Gynecologists (ACOG),[30] the Society of Obstetricians and Gynaecologists of Canada (SOGC),[31] the RCOG,[27] and the American College of Chest Physicians (ACCP).[28,29]

Summary of guidelines

As mentioned above, the objective of the guidelines is to set out the most appropriate conduct on the basis of publications available in the literature. Notwithstanding, atypical situations are common and demand different treatment. The major guidelines are summarized below.

ACOG: intermittent pneumatic compression (IPC) before caesarean if the patient is not on thromboprophylaxis.[30]

SOGC: drug-based thromboprophylaxis is recommended postpartum in the following situations: prior VTE, high risk thrombophilia (antiphospholipid antibody syndrome, antithrombin deficiency, homozygosis of factor V Leiden or the G20210A mutation of the prothrombin gene, or combined thrombophilias), confinement to bed for 7 or days or more before delivery, bleeding exceeding 1 L during peripartum or postpartum, transfusion of blood products, postpartum surgery, and infection during peripartum or postpartum.[31]

Pharmacological thromboprophylaxis should be considered in the presence of two or more of the following: BMI ≥ 30 kg/m^2 at first prenatal consultation, smoking > 10 cigarettes/day, preeclampsia, fetal growth restriction, placenta previa, emergency caesarean, bleeding exceeding 1 L during peripartum or postpartum or transfusion of blood products, low-risk thrombophilia (deficiency of protein C or S, heterozygosis of factor V Leiden or the 20210A mutation of the prothrombin gene), maternal cardiac disease, systemic lupus erythematosus, sickle-cell anemia, intestinal inflammatory disease, varicose veins of the lower limbs, gestational diabetes, premature delivery, stillbirth; or three or more of the following risk factors: age > 35 years, parity ≥ 2, any type of assisted reproduction technique, multiple gestation, placental abruption, premature rupture of membranes, elective caesarean, or maternal cancer.

Women with persistent risk factors should be given pharmacological thromboprophylaxis for a minimum of 6 weeks postpartum, while those with transitory factors during prepartum and peripartum should be given pharmacological thromboprophylaxis up to hospital discharge, or 2 weeks postpartum.[25]

RCOG: emergency caesarean, for 10 days postpartum with prophylactic doses of LMWH; for all other patients delivered by caesarean, consider 10 days of LMWH at prophylactic doses if other risk factors are present.[27]

ACCP: in the absence of additional risk factors, early mobilization; in the case of one major risk factor or two or more minor ones (or one minor factor if emergency caesarean has been performed), prophylaxis with LMWH after delivery is suggested while the patient is still in hospital (in the presence of contraindications to anticoagulation, use mechanical prophylaxis with antiembolism stockings or IPC); in extremely high-risk cases, with additional risk factors that remain during puerperium, combine LMWH with antiembolism stockings and/or IPC; selected high risk patients with additional risk factors that remain during puerperium should be given up to 6 weeks extended pharmacological thromboprophylaxis after hospital discharge.[28,29]

Venous thromboembolism and contraception

In Brazil, one in every five women use (OC).[32] Oral contraceptives offer benefits that go beyond contraception, such as reduction of menstrual bleeding, dysmenorrhea, treatment of premenstrual syndrome, menstrual migraine, acne, and hirsutism. The long-term benefits include reduced rates of endometrial, ovarian, and colorectal cancer.[30] Oral contraceptives are well-tolerated, serious side effects are rare, and compliance with use is high.[31]

Venous thromboembolism is a rare complication of OCs.[31] The first report of increased risk of VTE associated with use of OCs was in 1961[32] and since then many different studies have confirmed an increase of two to six times in the risk of VTE. The thromboembolic risk of OCs depends on the estrogen dosage and the type of progestogen combined with it.[33,34] Oral contraceptives increase the risk of VTE from a baseline rate of 5/10,000 woman-years among non users

to 9 to 10/10,000 woman-years among users.[34] To keep this risk in perspective, it is important to remember that the risk of VTE is 29/10,000 during pregnancy and 300-400/10,000 in puerperium.[35] These impressive figures confirm that, in many clinical situations, health professionals advising women not to take OCs verges on the irresponsible.

Older OCs, with high estrogen levels (> 50 µg of ethinylestradiol) are linked with a greater risk of VTE than modern OCs (< 50 µg of ethinylestradiol). Notwithstanding, no reduction of risk was confirmed with pills containing 20 µg of ethinylestradiol compared with pills containing 30µg of ethinylestradiol.[34] Although OCs with less than 35 µg ethinylestradiol provoked fewer side effects related to estrogen, such as nausea and increased breast sensitivity, during the first months of use, a reduction in risk of VTE was not demonstrated.[36]

The risk of VTE among women on OCs is attributed to changes in hemostasis.[37] Estrogen increases serum concentration of coagulation factors (prothrombin, factors VII, VIII, and X, and fibrinogen) and reduces concentration of anticoagulant factors (protein S and antithrombin).[38] These changes can have a clinical impact in women with hereditary thrombophilias.[39] The risk of VTE associated with OCs increases with the estrogen dose, with increased body weight and age, and with reintroduction or change of OC after a withdrawal exceeding 4 weeks.[34] The type of progestogens also influences the risk of VTE, and second-generation progestogens (levonorgestrel [LNG] and norethisterone) are safer than third and fourth-generation ones.[40] The new generations of progestogens are partly responsible for the non-contraceptive benefits of OCs.[31] Oral contraceptives containing third-generation progestogens have fewer androgenic effects and possibly lower metabolic and cardiovascular risk, but possibly with an increased risk of VTE.[31]

Among users of OCs, those with hereditary thrombophilia, smokers, and the obese are at higher risk of VTE. Recognizing this increased risk, the World Health Organization (WHO) advises against use of OCs by women with these factors. However, because of the low prevalence of hereditary thrombophilias and the high cost of screening for them, routine testing for thrombophilias is not recommended by the WHO.[41]

Presence of a family history of VTE is a strong and common risk factor for OC-linked VTE, even in the absence of hereditary thrombophilias.[42] The risk of VTE for a woman who takes OC and has a family history of VTE is 15.3 times higher than for a woman who do not take OCs and does not have a family history of VTE.[43]

There is no consensus on the best OC to prescribe. There is, however, an understanding that second-generation progestogens should be the first choice for the majority of women.[44,45]

Non-oral contraceptives, including patches and vaginal rings, are also associated with increased risk of VTE, raising the risk of VTE by 7.9 and 6.5 times, respectively.[45] Several different studies report that the risk of VTE is higher during the first year of use, probably because of undiagnosed thrombophilias.[46] Coagulation does not exhibit significant changes with progesterone-only OCs, implants containing LNG, or medroxyprogesterone injection in depot form.[47] Normal or increased sensitivity to active C protein was reported 3 months after insertion of the levonorgestrel intrauterine system (LNG-IUS), indicating that this contraceptive does not have pro-thrombotic effects.[48]

Venous thromboembolism and assisted fertilization

Infertility affects more than 10% of couples worldwide.[49,50] In vitro fertilization (IVF) is a process in which ovarian cells are fertilized by spermatozoa outside of the body and is the most widely-used technique for human reproduction in infertile couples.[51,52] Venous thromboembolism is a rare complication in women who undergo IVF and occurs in 0.1 to 2.4% in each fertilization cycle.[53-57] The risk of VTE is double during prenatal period after IVF (odds ratio [OR] 2.18; 95% confidence interval [95%CI] 1.63-2.92), when compared with the baseline risk of other pregnant women. This is because of a five-to-ten-times increase in the risk of VTE during the first trimester of gestations after IVF, partly because of the very high risk of VTE in ovarian hyperstimulation syndrome (OHS), which is a iatrogenic and potentially fatal complication that occurs in 33% of all cycles generated by IVF.[58] The incidence of VTE after IVF is 0.1% in cycles without OHS and from 0.8% to 2.4% of those in which OHS occurs.[53-57] Women who have OHS are at 100 times greater risk of VTE[59] and, in severe OHS, thromboprophylaxis with LMWH reduces 26 cases of VTE for every 1,000 women treated (number necessary to treat [NNT] is 39, based on a baseline VTE risk of 4%), without significant increase in bleeding.[24] Venous thromboembolism occurs with greatest frequency between the 40th and 42nd days after transfer of the embryo. In vitro fertilization also increases the risk of arterial thrombosis, which occurs earlier, on average on the 10th day after transfer of the embryo.[58,60,61]

Venous thromboembolism associated with IVF has a propensity to sites in the upper extremities and

the cervical region, rather than in the left lower limb, as is more common in spontaneous pregnancies.[60-67]

In addition to OHS, other obstetric complications are related to a greater risk of VTE in patients who undergo IVF: multiple gestations, prematurity, fetal death, preeclampsia, and prenatal and postpartum hemorrhage.[58-65,68]

Venous thromboembolism and hormone replacement therapy

Venous thromboembolism is an uncommon event before menopause, but incidence increases considerably after this period, at around one event per 1,000 woman-years at around 50 years of age, and mortality is 10% in these cases.[69-73]

Risk factors for VTE include genetic predisposition (hereditary thrombophilias), constitutional factors (age, overweight, and obesity), comorbidities (cancer, heart failure, active systemic lupus erythematosus, antiphospholipid antibody syndrome, inflammatory polyarthropathy, inflammatory intestinal disease, nephrosis, diabetes mellitus type I with nephropathy, sickle-cell anemia, and intravenous drug use), use of tamoxifen, immobility, and surgery.

Although recent data show that the risks could outweigh the benefits for women who take hormone replacement therapy (HRT), many are still prescribed estrogens to minimize symptoms of the menopause, which can be an additional risk factor for VTE. Women who have a uterus are also given progestogens to neutralize the risk of endometrial cancer.[69,74,75]

A great variety of HRT can be used for women going through the menopause and the preparations can differ in terms of their adverse effects. There is evidence that the risk of VTE among users is dependent on the route of estrogen administration. In fact, the transdermal route is not associated with an increased risk of VTE among postmenopausal women.[71,75-86] Additionally, the type of concomitant progestogens was recently identified as an additional VTE risk factor in women who take HRT.[75,87]

Observational studies, systematic reviews, and metanalyses consistently report a two to three times greater risk of VTE among postmenopausal women on HRT.[71,75,88-93] Women who have used HRT in the past have a similar VTE risk to those who have never used the treatment and, among those on HRT, risk is greatest during the first year of treatment. However, there are no consistent data on risk of VTE according to the method of HRT, including type and dose of estrogens, route of administration, and the potential role of progestogens.[69,75]

In order to prevent VTE in women who request HRT, it is important to identify susceptible subsets. Hereditary thrombophilias are well-established risk factors for VTE, increasing the risk by three times in postmenopausal women (OR 3.3; 95%CI 2.6-4.1).[88] The combination of these mutations with estrogen taken orally increases the risk of VTE (OR 8.0; 95%CI 5.4-11.9) compared to the risk among women without these mutations and not taking estrogen.[75] However, there was no difference in risk of VTE among women using the transdermal route when compared with women who did not use HRT.[88]

Women with a personal and family history of VTE are considered high risk and, therefore, are not candidates for HRT with oral route estrogen. Oral route estrogen provokes procoagulatory changes, such as increased resistance to active C protein, by reducing serum concentration of protein S, probably because of passage of estrogen through the liver and reduction of fibrinolytic activity.[75,94]

These changes are not observed with the transdermal route. The impact of progestogens in postmenopausal women on HRT has been studied little.[95-97]

The Menopause, Estrogen and Venous Events Study (MEVE) investigated the association between transdermal estrogen and risk of VTE recurrence in 1,023 postmenopausal women with prior history of VTE.[98] The results suggest that transdermal estrogen is safe with regard to VTE recurrence and confirmed that oral estrogen increased the risk of recurrence (relative risk [RR] 6.4; 95%CI 1.59-27.3).

Hormone replacement therapy is the most effective treatment for climacteric symptoms associated with falling estrogen levels after menopause.[74,75] After evaluation of the risks and benefits, HRT should be prescribed with the lowest estrogen dose and shortest duration possible. Current data do not support its use for primary or secondary prevention of cardiovascular diseases or dementia.[71,75,98] Since PE is the greatest cause of death attributed to HRT among postmenopausal women aged 50-59 years, the reduced risk of VTE linked with HRT using transdermal estrogen alone or combined with micronized progestogen indicates that this is the most recommended strategy for improving the risk-benefit relationship of HRT.[71] This strategy is confirmed in the North American Menopause Society and the European Menopause Society guidelines.[75,99,100]

■ CONCLUSIONS

Venous thromboembolism is a current challenge in obstetric practice, particularly after the reductions in hemorrhagic complications and infectious during pregnancy and puerperium observed in more developed settings. Preventative interventions of a mechanical and pharmacological nature reduce occurrence of VTE and its short and long-term complications.

The implementation of several prophylaxis guidelines and protocols reflect concern with the quality of care provided to pregnant women. Irrespective, adequate attention to contraception and HRT also demand maturity and knowledge. Simply prohibiting use of OCs and HRT without carefully assessing risk factors and family and personal history, does not decisively combat occurrence of VTE and unnecessarily exposes woman to a risk of reduced quality of life.

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Tromboembolismo venoso na mulher: novos desafios para uma velha doença

Venous thromboembolism in women: new challenges for an old disease

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Resumo

Nos países que controlaram as causas clássicas de óbito materno, como eclâmpsia e hemorragia, o tromboembolismo venoso (TEV) passou a ser a principal preocupação. A prevenção do TEV na gestação e no puerpério, por meio de diretrizes e da instituição de farmacoprofilaxia, é ainda a melhor estratégia para reduzir essa complicação. Os contraceptivos hormonais e a terapia de reposição hormonal também aumentam o risco de TEV; porém, as mulheres não podem ser privadas dos benefícios dessas terapias, que as tornam mais livres na idade fértil e menos sintomáticas na menopausa. Tanto o uso indiscriminado quanto a proibição imotivada são inadequados. A escolha dos métodos contraceptivos e de reposição deve ser feita por criteriosa seleção, avaliando as contraindicações, os critérios de elegibilidade e a autonomia das pacientes. O presente artigo apresenta uma revisão não sistemática da literatura recente visando a avaliar e resumir a associação entre TEV e situações clínicas peculiares ao sexo feminino.

Palavras-chave: trombose; anticoncepcionais; gravidez; terapia de reposição hormonal; mulheres; embolia pulmonar.

Abstract

In countries that have controlled classic causes of maternal death, such as eclampsia and hemorrhage, venous thromboembolism (VTE) has become the major concern. Prevention of VTE during pregnancy and postpartum by applying guidelines and implementing pharmacoprophylaxis is still the best strategy to reduce occurrence of this complication. Hormonal contraceptives and hormone replacement therapy also increase the risk of VTE, but women cannot be deprived of their benefits, which increase their freedom at childbearing age and reduce their symptoms at menopause. Both indiscriminate use and unmotivated prohibition are inappropriate. Contraceptive and hormone replacement methods should be chosen with care, evaluating the patients' contraindications, eligibility criteria, and autonomy. This article presents a nonsystematic review of recent literature with the aim of evaluating and summarizing the associations between VTE and clinical situations peculiar to women.

Keywords: thrombosis; contraceptive agents; pregnancy; hormone replacement therapy; women; pulmonary embolism.

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TROMBOEMBOLISMO VENOSO NA GESTAÇÃO

A obstetrícia moderna enfrenta o dilema da dualidade sangramento-tromboembolismo. Se, no passado não muito remoto, o grande temor dos que assistiam à parturiente era a hemorragia acidental, hoje esse receio é acrescido de mais um complicador: o tromboembolismo venoso (TEV)[1,2].

A gestante apresenta os três componentes etiopatogênicos da tríade de Virchow: a) estase venosa, devido à compressão das veias cava e ilíaca comum esquerda pelo útero gravídico e à diminuição do tônus venoso por causa da ação miorrelaxante da progesterona; b) hipercoagulabilidade, secundária à indução da síntese hepática dos fatores VII, VIII e X de coagulação pelo estriol placentário, aumento do fibrinogênio e do inibidor do ativador do plasminogênio tipo I e II, e diminuição da síntese de proteína S; c) lesão endotelial, que ocorre na nidação, na remodelação endovascular das artérias uteroespiraladas, e na dequitação[3].

Durante a gestação, o risco de TEV aumenta de cinco a dez vezes, podendo chegar a 35 vezes no puerpério, quando comparado ao de mulheres não gestantes de mesma idade[4]. Após esse período, a frequência diminui rapidamente; porém, um risco residual permanece por até 12 semanas após o parto[5].

A trombose venosa profunda (TVP) de membros inferiores é responsável por 75 a 80% dos episódios de TEV na gestação. Aproximadamente dois terços das TVPs ocorrem no período antenatal e distribuem-se igualmente nos três trimestres. Entretanto, de 43 a 60% dos episódios de embolia pulmonar (EP) ocorrem nas primeiras 6 semanas do puerpério[6]. Nas gestantes, as TVPs predominam ainda mais no membro inferior esquerdo (90% *versus* 55%) e no segmento íleo-femoral (72% *versus* 9%), quando comparadas às não gestantes. Esse fato pode ser explicado pela acentuação da compressão da veia ilíaca comum esquerda pela artéria ilíaca comum direita contra a quinta vértebra lombar, causada pelo útero gravídico[3].

A prevalência do TEV é de 0,5 a 2,2 casos para cada 1.000 partos, dependendo da população estudada[7], e a incidência absoluta de TEV na gestação e no puerpério foi de 107 por 100.000 mulheres-ano no Reino Unido (RU)[8] e de 175 por 100.000 mulheres-ano na Dinamarca e no Canadá[9]. No Brasil, não há dados oficiais sobre a mortalidade materna por TEV[6].

A EP permanece como a principal causa de morte materna direta no RU; porém, houve uma queda significativa no parto vaginal, de 1,56 por 100.000 partos em 2003-2005 para 0,70 por 100.000 partos em 2006-2008, justificada pela aplicação da primeira versão (2004), das diretrizes do *Royal College of Obstetricians and Gynaecologists* (RCOG) para redução do risco de TEV na gestação e no puerpério[10]. A prevenção do TEV na gestação, por meio da aplicação de diretrizes, e a consequente instituição de profilaxia mecânica e/ou farmacológica, é a melhor estratégia para reduzir essa intercorrência[6].

FATORES DE RISCO DE TEV DURANTE A GESTAÇÃO

Sobrepeso e obesidade

A obesidade [índice de massa corporal (IMC) > 30 kg/m^2] é um importante fator de risco para TEV na gestação, e esse risco cresce à medida que o IMC aumenta[11], chegando a ser 14,9 vezes maior quando comparado ao de mulheres não obesas[12]. Entre as gestantes que morreram de EP no RU entre 2003 e 2008, 60% eram obesas[10]. O sobrepeso materno (IMC entre 25 e 29,9 kg/m^2), apesar de comum, também é considerado um fator de risco menos importante para TEV relacionado à gestação[12].

Idade

Dados extraídos de estudos do tipo caso-controle sugerem aumento de risco de duas vezes para mulheres acima de 35 anos[13]. Em estudo conduzido no RU, em que se utilizou uma coorte ampla de mulheres fora da gestação, aquelas com idade entre 35 e 44 anos apresentaram risco 50% maior de TEV quando comparadas com aquelas entre 25 e 34 anos. A ocorrência de TEV não aumentou com a idade no período anteparto; contudo, mulheres em fase puerperal entre 35 e 44 anos apresentaram risco 70% superior quando comparadas àquelas entre 25 e 34 anos (um aumento de risco absoluto de 1,6 por 1.000 pessoas-anos)[8]. De modo geral, considera-se a idade de 35 anos ou mais como fator de risco antenatal e puerperal[14].

Trombofilias

De fato, existe a associação entre trombofilias hereditárias e TEV; porém, a pesquisa sistemática de trombofilias não deve ser realizada, e sim restrita à pacientes com episódio progresso e história familiar de trombofilia com maior potencial de complicação, como deficiência de antitrombina e homozigose do fator V Leiden e mutação 20210 da protrombina, que podem exigir a profilaxia do TEV. Esta, a depender das circunstâncias, poderá ser indicada desde o início da gravidez até o puerpério, a partir da 28ª semana, ou apenas durante o puerpério. É importante ressaltar que a história clínica é mais relevante para essa decisão do que o resultado da pesquisa laboratorial. Quanto à associação entre trombofilias de causas

genéticas e trombose uteroplacentária que ocasione perda fetal, pré-eclâmpsia, restrição de crescimento fetal ou descolamento prematuro de placenta, é um assunto ainda controverso[15-17].

Viagens de longa distância e imobilidade

Os dados relacionados à imobilidade e a viagens de longa distância em gestantes são limitados, sendo necessária a extrapolação de estudos de populações não gestantes[18]. As diretrizes relativas a cuidados antenatais do Instituto Nacional de Excelência em Saúde e Cuidados (*National Institute of Health and Care Excellence*, NICE)[19] e as recomendações do RCOG sobre viagens aéreas durante a gestação estabelecem que voos com duração superior a 4 horas aumentam o risco de TEV. Um estudo de caso-controle norueguês apontou aumento do risco de TEV em gestantes com IMC > 25 kg/m^2 e imobilização anteparto (definida como restrição ao leito por tempo igual ou superior a uma semana antes do parto ou antes do diagnóstico de TEV), mostrando efeito multiplicador sobre o risco de TEV anteparto e pós-parto[11].

A admissão hospitalar durante a gravidez é associada a aumento de 18 vezes no risco de TEV em comparação ao risco basal fora do hospital, e o risco permanece elevado após o parto, nos 28 dias seguintes. Na internação hospitalar, o risco é maior no terceiro trimestre de gravidez e em mulheres acima de 35 anos[20].

Outros

Algumas comorbidades têm sido associadas ao aumento do risco de TEV durante a gestação, entre elas estão: doença intestinal inflamatória, infecção do trato urinário, lúpus eritematoso sistêmico, cardiopatias, hipertensão arterial sistêmica induzida pela gestação ou pré-eclampsia, e cirurgia antenatal não obstétrica[21]. Na análise de dados de 1.475.301 altas hospitalares em maternidades escocesas, Kane et al. encontraram fatores de risco associados ao TEV que incluíam três ou mais gestações anteriores, hemorragia obstétrica e pré-eclâmpsia[21]. A hiperêmese aumenta o risco de TEV ante e pós-natal em 4,4 vezes.

Essas informações têm importantes implicações, já que muitos eventos tromboembólicos são fatais e ocorrem no primeiro trimestre, frequentemente antes da primeira consulta pré-natal, quando poderia ser instituída a profilaxia antenatal[22].

Fatores relacionados ao tratamento anticoagulante durante a gestação e o puerpério

O uso da varfarina na gestação pode induzir o descolamento prematuro da placenta, a embriopatia, anormalidades do sistema nervoso central (SNC)

e o sangramento fetal. A embriopatia varfarínica é caracterizada pela hipoplasia nasal e/ou pela não consolidação das epífises, e está associada à exposição à varfarina entre a sexta e a 12ª semanas de gestação[23]. As anormalidades do SNC associadas com o uso da varfarina incluem displasia da linha média dorsal com agenesia do corpo caloso, atrofia da linha média cerebelar, displasia da linha média ventral com atrofia óptica e amaurose, e hemorragia, podendo ocorrer após a exposição varfarínica, em qualquer fase da gestação. A varfarina é segura na amamentação[24].

Duas abordagens podem ser adotadas para diminuir o risco do uso de varfarina em mulheres que necessitam de anticoagulação e desejam engravidar. A primeira é manter a varfarina e realizar testes de gravidez frequentes. Tão logo a gravidez seja diagnosticada antes da sexta semana, a heparina de baixo peso molecular (HBPM) deve ser introduzida no lugar da varfarina. A outra abordagem é suspender a varfarina e iniciar a HBPM logo que a decisão de tentar engravidar seja tomada[24-28].

Apesar de trazerem grandes avanços à profilaxia e ao tratamento do TEV em diversas situações clínicas, os anticoagulantes orais diretos existentes (apixabana, dabigatrana, edoxabana e rivaroxabana) são contraindicados na gestação, por cruzar a barreira placentária, e na amamentação, por passar para o leite materno[6,23-25].

Cesariana

Embora o risco de TEV associado à cesariana isoladamente seja baixo, a ocorrência de TEV passa a ser significativa quando há relação com outros fatores de risco, e deve-se indicar a instituição de tromboprofilaxia[29]. Na gestante anticoagulada, o parto deve ser programado entre 37 e 40 semanas. A HBPM deve ser suspensa 12 horas antes do parto se administrada em dose profilática, ou 24 horas antes se administrada em doses intermediária ou plena, o que permitirá a realização da raquianestesia ou da peridural com segurança. Gestantes em uso de HBPM devem ser orientadas a não administrar a dose do fármaco caso apresentem contrações ou perda de líquido[23].

A indicação da via de parto é obstétrica, não havendo contraindicação à maturação artificial do colo nem à indução do trabalho de parto. Sendo a via de parto vaginal ou cesárea, a paciente deve permanecer com uso de meias antitrombo durante o procedimento.

Estratificação de risco

A estratificação de risco de TEV na gestação baseia-se na avaliação de cada paciente e deve ser realizada em todas as mulheres com intenção de engravidar ou logo que engravidam. Recomenda-se

repeti-la ao longo do pré-natal, diante do surgimento de novos fatores de riscos. As preferências e as considerações das gestantes devem ser levadas em conta no momento da escolha da tromboprofilaxia, muito embora, nesse cenário, as opções terapêuticas sejam restritas[26].

As recomendações sugeridas dependem de variações individuais entre as pacientes e têm o intuito de informar, e não de substituir, o julgamento clínico do médico, que em última análise deve determinar a conduta apropriada para cada caso. As diretrizes mais relevantes na área de diagnóstico, profilaxia e tratamento do TEV na gestação são as das entidades *American College of Obstetricians and Gynaecologists* (ACOG)[30], *Society of Obstetricians and Gynaecologists of Canada* (SOGC)[31], RCOG[27] e *American College of Chest Physicians* (ACCP)[28,29].

Resumo das diretrizes

Como mencionado anteriormente, as diretrizes têm por objetivo ordenar as condutas mais apropriadas em função das publicações disponíveis na literatura. Todavia, situações atípicas são frequentes e exigem um tratamento diferenciado. A seguir serão apresentadas as principais diretrizes.

ACOG: compressão pneumática intermitente (CPI) antes da cesariana se a paciente não fizer uso de tromboprofilaxia[30].

SOGC: recomenda-se farmacoprofilaxia no pós-parto diante das seguintes situações: TEV prévio, trombofilia de alto risco (síndrome do anticorpo antifosfolipídeo, deficiência de antitrombina, homozigose do fator V de Leiden ou mutação do gene G20210A da protrombina ou trombofilias combinadas), restrição ao leito antes do parto por 7 ou mais dias, sangramento maior que 1 L no periparto ou no pós-parto, transfusão de hemoderivados, cirurgia pós-parto e infecção no periparto ou no pós-parto[31].

Deve-se considerar o uso de farmacoprofilaxia na ocorrência de duas ou mais das seguintes situações: IMC ≥ 30 kg/m² na primeira consulta pré-natal, tabagismo > 10 cigarros/dia, pré-eclâmpsia, restrição de crescimento fetal, placenta prévia, cesariana de emergência, sangramento maior que 1 L no periparto ou no pós-parto ou transfusão de hemoderivados, trombofilia de baixo risco (deficiência de proteínas C ou S, heterozigose do fator V de Leiden ou mutação 20210A do gene da protrombina), doença cardíaca materna, lúpus eritematoso sistêmico, anemia falciforme, doença inflamatória intestinal, varizes de membros inferiores, diabetes gestacional, parto prematuro, parto de natimorto, ou três ou mais dos seguintes fatores de risco: idade > 35 anos, paridade ≥ 2, qualquer técnica de reprodução assistida, gestação múltipla, descolamento prematuro de placenta, ruptura prematura de membranas, cesariana eletiva ou câncer materno.

Mulheres com fatores de risco persistentes devem receber farmacoprofilaxia no mínimo por 6 semanas pós-parto, já as com fatores transitórios no anteparto e intraparto devem receber farmacoprofilaxia até a alta hospitalar, ou até 2 semanas após o parto[25].

RCOG: cesariana de emergência, 10 dias após o parto com dose profilática de HBPM; para todas as outras pacientes submetidas a cesariana, considerar 10 dias de HBPM em dose profilática se houver outros fatores de risco[27].

ACCP: na ausência de fatores de risco adicionais, deambulação precoce; no caso de um fator de risco maior ou de dois ou mais menores (um menor se houver cesariana de emergência), sugere-se profilaxia com HBPM após o parto enquanto a paciente permanecer no hospital (se houver contraindicação à anticoagulação, usar profilaxia mecânica com meias antitrombo ou CPI); no caso de risco altíssimo com fatores de risco adicionais que persistem no puerpério, combinar HBPM com meias antitrombo e/ou CPI; as pacientes selecionadas de alto risco com fatores de risco adicionais que persistem no puerpério devem receber até 6 semanas de extensão de farmacoprofilaxia após a alta hospitalar[28,29].

Tromboembolismo venoso e contracepção

No Brasil, uma em cada cinco mulheres utiliza contraceptivo oral (CO)[32]. Os COs oferecem benefícios além da contracepção, como redução do sangramento menstrual, dismenorreia, tratamento da síndrome pré-menstrual, enxaqueca menstrual, acne e hirsutismo. Os benefícios em longo prazo incluem redução na incidência de câncer endometrial, ovariano e colorretal[30]. Os COs são bem tolerados, com raros efeitos colaterais sérios, e apresentam grande adesão ao uso[31].

O TEV é uma complicação rara dos COs[31]. O primeiro relato de aumento de risco de TEV associado ao uso de COs foi em 1961[32], e desde então vários estudos têm confirmado um aumento de duas a seis vezes no risco de TEV. O risco tromboembólico de COs depende da dose de estrógeno e do tipo de progestágeno associado[33,34]. Os COs aumentam o risco de TEV de uma taxa basal de 5/10.000 mulheres-ano em não usuárias para 9 a 10/10.000 mulheres-ano em usuárias[34]. Para não se perder a perspectiva desse risco, é importante recordar que o risco de TEV é de 29/10.000 na gestação e de 300-400/10.000 no puerpério[35]. Esses números expressivos confirmam que, em várias situações clínicas, o desaconselhamento

do uso de COs pelos profissionais de saúde beira a irresponsabilidade.

Os COs antigos, com altos níveis de estrógeno (> 50 μg de etinilestradiol), apresentam risco maior de TEV que os COs modernos (< 50 μg de etinilestradiol). Todavia, a redução de risco de pílulas com 20 μg de etinilestradiol comparadas com as pílulas de 30μg de etinilestradiol não foi confirmada[34]. Os COs com menos de 35 μg de etinilestradiol, apesar de terem menos efeitos colaterais relacionados ao estrógeno, como náuseas e aumento de sensibilidade mamária, nos primeiros meses de uso, não demonstraram redução de risco de TEV[36].

O risco de TEV em mulheres em uso de COs é atribuído às mudanças na hemostasia[37]. O estrogênio aumenta a concentração sérica dos fatores de coagulação (protrombina, fator VII, VIII, X e fibrinogênio) e reduz a dos fatores anticoagulantes (proteína S e antitrombina)[38]. Essas mudanças podem ter um impacto clínico em mulheres portadoras de trombofilias hereditárias[39]. O risco de TEV associado aos COs aumenta com a dose de estrógeno, com aumento do peso corporal e da idade, e com o reinício ou a troca do CO após interrupção superior a 4 semanas[34]. O tipo de progestágeno também influencia no risco de TEV, sendo os progestágenos de segunda geração [levonorgestrel (LNG) e noretisterona] mais seguras que os de terceira e quarta[40]. As novas gerações de progestágeno são, em parte, responsáveis pelos benefícios não contraceptivos dos COs[31]. Os COs contendo progestágeno de terceira geração apresentam menos efeito androgênico e possivelmente menor risco metabólico e cardiovascular, porém com possível risco aumentado para TEV[31].

Entre as usuárias de COs, as portadoras de trombofilia hereditária, tabagistas e obesas apresentam risco maior de TEV. Reconhecendo esse aumento de risco, a Organização Mundial da Saúde (OMS) desaconselha o uso de COs em mulheres nessas condições. Entretanto, devido à baixa prevalência de trombofilias hereditárias e aos altos custos de rastreamento, a pesquisa rotineira de trombofilias não é recomendada pela OMS[41].

A presença de história familiar de TEV é um fator de risco forte e comum para TEV associado ao COs, mesmo na ausência de trombofilias hereditárias[42]. O risco de TEV com uso de CO numa mulher que apresenta história familiar de TEV é 15,3 vezes maior que o de uma mulher não usuária de CO e sem história familiar de TEV[43].

Não há consenso sobre qual o melhor CO a ser prescrito. Todavia, há entendimento de que os progestágenos de segunda geração devem ser a primeira escolha para a maior parte das mulheres[44,45].

Contraceptivos não orais são também associados com aumento de risco de TEV, incluindo os adesivos transdérmicos e o anel vaginal, com aumento de 7,9 a 6,5 vezes de risco de TEV, respectivamente[45]. Vários estudos reportam que o risco de TEV é maior no primeiro ano de uso, provavelmente devido a trombofilias não diagnosticadas[46]. A coagulação não apresenta mudanças significativas com COs exclusivos de progesterona, implantes contendo LNG ou injeção de medroxiprogesterona em forma de depósito[47]. A sensibilidade normal ou aumentada à proteína C ativada foi reportada 3 meses após a inserção de sistema intrauterino de levonorgestrel (SIU-LNG), indicando que esse contraceptivo não tem efeito pró-trombótico[48].

Tromboembolismo venoso e fertilização assistida

A infertilidade afeta mais de 10% dos casais em todo o mundo[49,50]. A fertilização *in vitro* (FIV) é um processo em que as células ovarianas são fertilizadas pelo espermatozoide fora do corpo e é a principal técnica utilizada em reprodução humana de casais inférteis[51,52]. O TEV é uma complicação rara em pacientes submetidas a FIV, e ocorre em 0,1 a 2,4% delas em cada ciclo de fertilização[53-57]. O risco de TEV no anteparto pós-FIV dobra [*odds ratio* (OR) 2,18; intervalo de confiança de 95% (IC95%) 1.63-2.92], quando comparado com o risco basal das outras gestantes. Isso se deve ao aumento de cinco a dez vezes no risco de TEV no primeiro trimestre em gestações pós-FIV, em parte pelo risco muito alto de TEV na síndrome de hiperestimulação ovariana (SHO), uma complicação iatrogênica e potencialmente fatal, que ocorre em 33% de todos os ciclos gerados por FIV[58]. A incidência de TEV após FIV ocorre em 0,1% dos ciclos sem SHO, e em 0,8% a 2,4% daqueles com SHO[53-57]. Mulheres que apresentam SHO têm 100 vezes mais risco de TEV[59] e, na SHO grave, a tromboprofilaxia com HBPM reduz 26 casos de TEV para cada 1.000 mulheres tratadas [número necessário para tratar (NNT) de 39 (dado um risco basal de TEV de 4%)], sem aumento significativo de sangramento[24]. O TEV ocorre com maior frequência entre o 40º e 42º dia após a transferência do embrião. A FIV também aumenta o risco de trombose arterial, que ocorre mais precocemente, em média no 10º dia pós-transferência do embrião[58,60,61].

O TEV associado à FIV tem a propensão de localizar-se em extremidades superiores e na região cervical, em vez de no membro inferior esquerdo, mais frequente nas gestações espontâneas[60-67].

Além da SHO, outras intercorrências obstétricas são relacionadas a um maior risco de TEV em pacientes

submetidas a FIV: gestação múltipla, prematuridade, óbito fetal, pré-eclâmpsia e hemorragia ante e pós-parto[58-65,68].

Tromboembolismo venoso e terapia de reposição hormonal

O TEV é um evento incomum antes da menopausa, mas com aumento de incidência importante após esse período, de cerca de um evento por 1.000 mulheres-ano em torno de 50 anos de idade e mortalidade de 10% desses casos[69-73].

Os fatores de risco para TEV incluem a predisposição genética (trombofilias hereditárias), fatores constitucionais (idade, sobrepeso e obesidade), comorbidades (câncer, insuficiência cardíaca, lúpus eritematoso sistêmico ativo, síndrome do anticorpo antifosfolipídeo, poliartropatia inflamatória, doença intestinal inflamatória, nefrose, diabetes melito tipo I com nefropatia, doença falciforme, uso de drogas intravenosas), uso de tamoxifeno, imobilidade e cirurgia.

Apesar de dados recentes apontarem que os riscos podem exceder os benefícios em mulheres que realizam terapia de reposição hormonal (TRH), muitas ainda recebem prescrição de estrógenos para minimizar os sintomas do climatério, o que pode ser um fator de risco adicional para TEV. As mulheres com útero também recebem progestágenos para neutralizar o risco de câncer de endométrio[69,74,75].

Uma grande variedade de TRH pode ser usada entre as mulheres climatéricas, e essas preparações podem diferir em relação aos seus efeitos adversos. Há evidência de que o risco de TEV entre as usuárias depende da via de administração de estrógenio. De fato, a via transdérmica não está associada ao risco aumentado de TEV entre mulheres na pós-menopausa[71,75-86]. Além disso, o tipo de progestágeno concomitante emergiu recentemente como fator de risco adicional de TEV em mulheres que usam TRH[75,87].

Estudos observacionais, revisões sistemáticas e metanálises relatam consistentemente um risco de duas a três vezes maior de TEV entre mulheres pós-menopáusicas que utilizam TRH[71,75,88-93]. Usuárias pregressas de TRH têm um risco TEV similar ao das que nunca usaram essa terapia, e, entre as usuárias de TRH, o risco é maior durante o primeiro ano de tratamento. No entanto, não há dados consistentes sobre o risco de TEV de acordo com a modalidade de TRH, incluindo o tipo e a dose de estrógenos, a via de administração e o papel potencial dos progestágenos[69,75].

Com o intuito de prevenir o TEV em mulheres que solicitam TRH, é importante identificar os subgrupos suscetíveis. As trombofilias hereditárias são fatores de risco bem estabelecidos para TEV, aumentando o risco em três vezes em mulheres na pós-menopausa (OR 3,3; IC95% 2,6-4,1)[88]. A combinação dessas mutações com estrógeno por via oral aumenta o risco de TEV (OR 8,0; IC95% 5,4-11,9) comparado ao risco de mulheres sem essas mutações e que não usam estrógeno[75]. Todavia, não houve diferença no risco de TEV nessas mulheres quando usaram a via transdérmica quando comparadas às que não usaram[88].

Mulheres com história pessoal e familiar de TEV são consideradas de alto risco e, portanto, não são candidatas à TRH com estrogênio via oral. O estrógeno via oral provoca mudanças pró-coagulantes, como o aumento da resistência à proteína C ativada, por redução da concentração sérica de proteína S, provavelmente pela passagem do estrogênio no fígado e pela diminuição da atividade fibrinolítica[75,94].

Essas alterações não são observadas pela via transdérmica. Em mulheres na pós-menopausa em TRH, o impacto dos progestágenos tem sido pouco estudado[95-97].

O estudo *Menopause, Estrogen and Venous Events Study* (MEVE) investigou a associação entre estrógeno transdérmico e risco de recorrência de TEV em 1.023 mulheres na pós-menopausa e com história pregressa de TEV[98]. Os resultados sugerem que o estrógeno transdérmico é seguro com relação à recorrência de TEV e confirmam que o estrógeno oral aumenta o risco de recorrência [risco relativo (RR) 6,4; IC95% 1,59-27,3].

A TRH é o mais efetivo tratamento para os sintomas climatéricos associados com a queda estrogênica após a menopausa[74,75]. Após avaliação dos riscos e benefícios, a TRH deve ser prescrita com a dose mais baixa de estrógeno e pelo menor período possível. Os dados atuais não suportam seu uso para prevenção primária ou secundária de doenças cardiovasculares ou demência[71,75,98]. Como a EP representa a principal causa de morte atribuída à TRH nas mulheres pós-menopausa com idade entre 50-59 anos, a redução no risco de TEV na TRH com o estrógeno transdérmico isolado ou associado ao progestágeno micronizado demonstra que essa parece ser a estratégia mais recomendada para melhorar a relação de risco-benefício da TRH[71]. Inclusive, essa estratégia é corroborada pelas diretrizes da Sociedade Norte-Americana de Menopausa e da Sociedade Europeia de Menopausa[75,99,100].

◼ CONCLUSÃO

O TEV é um desafio atual na prática da obstetrícia, particularmente após a redução das complicações hemorrágicas e infecciosas do período gravídico e puerperal, observada em cenários de maior desenvolvimento. As intervenções preventivas de natureza mecânica e farmacológica reduzem a ocorrência

do TEV e de suas complicações a curto e longo prazo. A implantação de várias diretrizes e protocolos de profilaxia refletem a preocupação com a qualidade da atenção à parturiente. Independentemente, a atenção adequada à anticoncepção e à TRH também exige maturidade e conhecimento. Simplesmente proibir a utilização de COs e TRH sem avaliar criteriosamente os fatores de risco e a história familiar e pessoal, além de não coibir decisivamente a ocorrência do TEV, expõe a mulher a riscos desnecessários e à perda de qualidade de vida.

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