SHORT COMMUNICATION

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Venous thromboembolism in women

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INTRODUCTION

Pregnant women have all the following three etiopathogenic components of Virchow's triad: (a) venous stasis, caused by compression of the inferior 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; and (c) endothelial injury, which occurs during nidation, endovascular remodeling of the uterine spiral arteries, and expulsion of the placenta[1,2].

During pregnancy, the risk of venous thromboembolism (VTE) increases by 5–10 times and can be 35 times higher during puerperium when compared with the rate among non-pregnant women of the same age. After delivery, the frequency reduces rapidly, but there is a residual risk for up to 12 weeks. Approximately two-thirds of deep venous thrombosis (DVT) occurs during the gestational period, equally distributed across the three trimesters. However, 43–60% of pulmonary embolism episodes occur during the first 6 weeks of the puerperium[1,2].

Among pregnant women, when compared with non-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[1,2].

The main risk factors for VTE during pregnancy are overweight, obesity, age of 35 years or more, inherit or acquired thrombophilias, long-distance travel, immobility, hospital admission during pregnancy, certain comorbidities (inflammatory intestinal disease, urinary tract infection, systemic lupus erythematosus, pregnancy-induced systemic arterial hypertension or pre-eclampsia, and non-obstetric antenatal surgery), obstetric hemorrhage, and hyperemesis.

Prevention of VTE in pregnancy by means of application of guidelines and implementation of mechanical and/or pharmacological prophylaxis is still the best strategy for reducing the rate of these events[1,2].

PECULIARITIES OF ANTICOAGULANT TREATMENT DURING GESTATION AND PUERPERIUM

Administration of warfarin between the 6th and 12th weeks of gestation can induce fetal embryopathy (nasal hypoplasia and/or stippling of the epiphyses), abnormalities of the central nervous system (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 fetal bleeding. However, warfarin is safe while breastfeeding[3].

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Despite the existing direct oral anticoagulants (apixaban, dabigatran, edoxaban, and rivaroxaban), they are contraindicated in pregnancy because they cross the placental barrier and in breastfeeding because they pass into breast milk[3].

Therefore, the treatment of VTE in these periods should preferably be done with heparins, preferably low molecular weight heparins (LMWH) or fondaparinux, when there are restrictions on their use[3].

CHOICE OF DELIVERY IN ANTICOAGULATION WOMEN

The choice of delivery route is obstetric, and there is no contraindication against artificial cervical ripening or induction of labor. Delivery of an anticoagulated pregnant woman should be scheduled for 37–40 weeks. LMWH should be withdrawn 12 h before delivery if given at prophylactic dosages or 24 h before if administered at intermediate or full dosages, enabling safe administration of spinal or epidural anesthesia. The patient should continue wearing antiembolism stockings throughout the procedure, regardless of the mode of delivery chosen[4,5].

Although the risk of VTE associated with caesarean in isolation is low, the rate of VTE occurrence becomes significant when other risk factors exist, and so thromboprophylaxis should be prescribed, based on risk stratification with a risk assessment model[4,5].

RISK STRATIFICATION

Stratification of VTE risk in pregnancy should be performed for all women who intend to become pregnant or as soon as they become pregnant and should be 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[4].

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, the Society of Obstetricians and Gynaecologists of Canada, the Royal College of Obstetricians and Gynaecologists, and the American College of Chest Physicians[1-5].

VENOUS THROMBOEMBOLISM AND CONTRACEPTION

In Brazil, one in every five women uses oral contraceptives (OCs), which offers benefits that go beyond contraception, such as reduction of menstrual bleeding, dysmenorrhea, premenstrual syndrome, migraine, acne, and hirsutism. The long-term benefits of OCs include reduced rates of endometrial, ovarian, and colorectal cancer[4].

OCs 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[3,4]. 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[4].

The thromboembolic risk of OCs depends on the estrogen dosage and the type of progestogen combined with it. Old OCs with high estrogen levels (>50 µg of ethinylestradiol [EE]) are linked with a greater risk of VTE than modern OCs (<50 µg of EE). Notwithstanding, no reduction of risk was confirmed with OCs containing 20 µg of EE compared with pills containing 30 µg of EE[4].

The type of progestogen also influences the risk of VTE, and second-generation progestogens (levonorgestrel [LNG] and norethisterone) are safer than third- and fourth-generation ones[4].

The risk of VTE associated with OCs increases with body weight and age and with reintroduction or change of OC after a withdrawal exceeding 4 weeks[4].

Among users of OCs, those with hereditary thrombophilia are at higher risk of VTE. However, because of the low prevalence of hereditary thrombophilias and the high cost of screening for them, routine testing is not recommended[4] and the presence of a personal or family history of VTE is a stronger and more common risk factor for OC-linked VTE[4].

Non-oral contraceptives, including patches and vaginal rings, are also associated with an increased risk of VTE, raising the risk of VTE by 7.9 and 6.5 times, respectively[4].

Coagulation does not exhibit significant changes with progesterone-only OCs, implants containing LNG, LNG intrauterine system, or medroxyprogesterone injection in depot form; therefore, the use of these is safe in this situation[4].

VENOUS THROMBOEMBOLISM AND ASSISTED FERTILIZATION

In vitro fertilization (IVF) is the most widely used technique for human reproduction in infertile couples, and VTE is a rare complication of this technique, occurring in 0.1–2.4% in each fertilization cycle[4].

The risk of VTE is two times higher during the prenatal period after IVF, when compared with the baseline risk of other pregnant women, due to a 5–10 times increase in the risk during the first trimester of gestations after IVF, partly secondary to ovarian hyperstimulation syndrome (OHS),

which is an iatrogenic and potentially fatal complication that occurs in 33% of all cycles generated by IVF[5]. Women who have OHS are at 100 times greater risk of VTE, and, in severe OHS, thromboprophylaxis with LMWH reduces VTE without significant increase in bleeding[4].

VTE associated with IVF has a propensity to sites in the upper extremities and the cervical region rather than in the left lower limb[4].

IVF also increases the risk of arterial thrombosis, which occurs earlier, on average on the 10th day after the transfer of the embryo[4].

VENOUS THROMBOEMBOLISM AND HORMONE REPLACEMENT THERAPY

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 climacteric, which can be an additional risk factor for VTE, particularly during the first year[4].

Observational studies, systematic reviews, and meta-analyses consistently report a 2–3 times greater risk of VTE among postmenopausal women on HRT[4].

There is evidence that the risk of VTE among users is dependent on the route of estrogen administration. Oral route estrogen provokes procoagulant changes, such as increased resistance to active C protein, by reducing serum concentration of protein S, probably because of the passage of estrogen through the liver and reduction of fibrinolytic activity; these changes are not observed with the transdermal route[4].

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. The combination of these mutations with estrogen taken orally increases the risk of VTE compared to the risk among women without these mutations and not taking estrogen[4].

Women with a personal and family history of VTE are considered high-risk and, therefore, are not candidates for HRT with oral route estrogen[4].

HRT is the most effective treatment for climacteric symptoms associated with falling estrogen levels after menopause[6], and after evaluation of the risks and benefits, HRT should be prescribed with the lowest transdermal estrogen dose alone or combined with micronized progestins and the shortest duration possible[4].

VENOUS THROMBOEMBOLISM IN TRANSGENDER WOMEN

The terms transgender and gender nonconformity describe a situation in which a person's gender identity differs from the external sexual anatomy they were born with. The objectives of gender affirmation in transgender women are to suppress male characteristics and induce female characteristics to the extent possible. Gender affirmation can encompass hormone therapy (HT) and affirmation surgery[7].

Provision of physician-guided gender affirmation HT has shown improved quality of life, and it reduces the disorders observed in this population, including VTE[7].

Several different studies have demonstrated an increased risk of VTE in transgender women who are on HT, which is related to the type and dosage of the hormones employed and, primarily, to the route of administration[1]. This can be a determinant factor in the choice of HT, making transdermal administration the preferred route for transgender women with a personal or family history of VTE or those who have thrombophilia[7].

Oral administration induces the hepatic first-pass effect with increased pro-thrombotic factors, whereas non-oral routes and transdermal administration in particular do not appear to induce increased VTE[7].

This can be a determinant factor in the choice of HT, making transdermal administration the preferred route for transgender women with a personal or family history of VTE or those who have thrombophilia[7].

It should be emphasized that HT is not an elective treatment in this population but an absolute necessity to achieve the desired phenotype. In many places, these women are at the margins of society and cannot access professionals who are able to prescribe HT. As a consequence, estrogens are very often obtained illegally and taken on the person's own initiative, without professional guidance on the safest composition, dosage, and route of administration. Another point to be considered is that non-oral HT presentations are normally more expensive than oral preparations and thus inaccessible to the majority of people. One feasible strategy to attenuate the risk of VTE in groups at risk is to initiate prophylactic anticoagulation simultaneously with HT, especially for the first 6–12 months of treatment[7].

VENOUS THROMBOEMBOLISM IN WOMEN WITH CANCER

Breast and cervical cancer are prominent causes of female morbidity and mortality worldwide. Excluding non-melanoma skin cancers, breast cancer is the most common among

women, accounting for 2.1 million new cases and approximately 600,000 deaths in 2018[6,8]. In Brazil, it is the most common cancer in females in all regions of the country[8]. Cervical cancer is the second most frequent cancer among women in the North, Northeast, and Midwest regions, while it ranks fourth and fifth in the South and Southeast regions, respectively[8].

Cancer is widely known to increase the risk of thromboembolic complications. This risk is related to the characteristics of the patient, their comorbidities, and their clinical conditions, in addition to several factors related to the tumor and the phase of treatment. Appropriate prophylaxis for DVT should be based on risk groups and individual patient conditions. In many cases, multiple factors are present, and the risks are cumulative[8]. The risk must be well defined using risk assessment models so that the application of prophylactic recommendations is adequate and effective. In general, the duration of prophylaxis in cancer patients is longer and should always be considered, always remembering the risk stratification, especially in the perioperative and chemotherapy periods[8].

CONCLUSIONS

VTE is a current challenge in obstetric practice, particularly after the reductions in hemorrhagic complications and infectious diseases observed in more developed settings. Preventative interventions of a mechanical and pharmacological nature based on guidelines and protocols reduce its occurrence and its short- and long-term complications.

Irrespective, adequate attention to contraception and HRT also demands maturity and knowledge. Simply prohibiting the use of OCs and HRT without carefully assessing risk factors and family and personal history does not decisively combat the occurrence of VTE and unnecessarily exposes women to a risk of reduced quality of life.

It is important to emphasize that transgender women exhibit peculiarities inherent to the use of HT and difficulties with access to medical services, which, in the final analysis, expose this population to higher incidences of underdiagnosed complications. The occurrence of VTE in the transgender population is one of the many facets that modern medicine must deal with.

AUTHORS' CONTRIBUTIONS

MAM: Conceptualization, Data curation, Formal Analysis, Investigation, Supervision, Validation, Visualization, Writing – review & editing. **JCPO:** Conceptualization, Investigation, Visualization, Writing – original draft. **EEJ:** Conceptualization, Investigation, Visualization, Writing – review & editing. **ALMLO:** Conceptualization, Investigation, Methodology, Visualization. **AJAR:** Conceptualization, Investigation, Visualization, Writing – review & editing. **MLS:** Conceptualization, Investigation, Validation, Visualization. **WJBA:** Conceptualization, Investigation, Supervision, Visualization. **RKAF:** Conceptualization, Formal Analysis, Investigation, Visualization. **BG:** Conceptualization, Investigation, Project administration, Visualization. **APRMP:** Conceptualization, Data curation, Formal Analysis, Investigation, Project administration, Visualization, Writing – original draft.

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