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Prevention of Venous Thromboembolism in Pregnancy: A Review of Guidelines, 2000–2011

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Abstract

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Disclosure Statement

No competing financial interests exist.

Guidelines Used

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Introduction—Pregnant women are four to five times more likely than nonpregnant women to develop venous thromboembolism (VTE). The aim of this review is to provide an overview of guidelines in the literature on VTE risk assessment, screening for thrombophilias, and thromboprophylaxis dissemination among pregnant women.

Methods—We performed a review of the published literature to identify evidence-based guidelines published between the years 2000 and 2011. We searched for guidelines from U.S. and international organizations that identified clinically based practice recommendations to healthcare providers on how VTE risk should be assessed, thrombophilias screened, and thromboprophylaxis disseminated among pregnant women.

Results—We found nine guidelines that met our requirements for assessing VTE risk and found seven guidelines addressing thrombophilia screening. Seven of the nine agreed that all women should undergo a risk factor assessment for VTE either in early pregnancy or in the preconception period. Seven of the nine agreed that pregnant women with more than one additional VTE risk factor be considered for thromboprophylaxis, and five of the seven groups addressing thrombophilia screening agreed that selected at-risk populations should be considered for thrombophilia screening.

Conclusions—There is some agreement between U.S. and international guidelines that women should be assessed for VTE risk during preconception and again in pregnancy. Although there is agreement that the general population of women should not be screened for thrombophilias, no agreement exists as to the clinical subgroups for which screening should be done.

Introduction

Pregnant women are four to five times more likely than nonpregnant women to develop venous thromboembolism (VTE), a term that encompasses both deep vein thrombosis (DVT) and pulmonary embolism (PE).[1] According to the 2003 *Morbidity and Mortality Weekly Report* on pregnancy-related mortality, unspecified embolism was the leading cause of maternal death, at 20%.[2] In 2008, Clark et al.[3] published an updated list of causes of maternal death; they were able to distinguish PE from amniotic fluid embolism and found amniotic fluid embolism to be the second most common cause of death at 14%, while PE was the fifth leading cause of death, at 9%. Published estimates of maternal mortality from DVT or PE are 1.1–1.5 deaths per 100,000 deliveries in North America and Europe.[1,4]

Approximately 60%–80% of all VTE related to pregnancy are DVT,[5] and women who experience DVT during pregnancy are more likely to have poorer pregnancy outcomes.[6] Women who have experienced VTE during pregnancy may develop long-term sequelae that range from edema and skin changes to recurrent thrombosis and ulceration.[7] Furthermore, VTE is more difficult to diagnose in pregnant women[8]; its associated signs and symptoms, such as dyspnea and peripheral edema, are nonspecific and are often seen in pregnancy, making diagnosis difficult. Regardless, a high index of suspicion for VTE is prudent for all pregnant patients because of the underlying physiologic risk, especially in situations in which other risk factors for VTE are present.[5]

Some VTE risk factors for pregnantwomen include previous VTE, age > 35, obesity (body mass index [BMI] > 30 kg/m^2), African American race, grand multiparity, and bed rest for

such conditions as preterm labor, premature rupture of membranes (PROM), and preeclampsia.[9] Other risk factors include immobility, medical conditions (e.g., lupus, diabetes, sickle cell disease, congestive heart failure, and renal disease), surgery (e.g., cesarean sections), trauma, and inherited thrombophilias.[8,10,11] Inherited thrombophilias (e.g., factor V Leiden and antithrombin deficiency) have been reported as the leading cause of maternal thromboembolism.[12] Data from Greer[13] and Rosendaal[14] suggested that at least 50% of cases of VTE in pregnant women of European ancestry are associated with inherited thrombophilias.

To improve survival, avoid recurrence, prevent complications, and reduce healthcare costs, the risk of VTE in pregnancy must be assessed.[16] Clinical practice guidelines have been developed to provide algorithms to identify women who would benefit from thromboprophylaxis.[17] The purpose of this review is to provide an overview of guidelines available in the literature on VTE risk assessment, screening for thrombophilias, and thromboprophylaxis dissemination for VTE among pregnant women.

Materials and Methods

We performed a review of the published medical literature to identify evidence-based guidelines, searching MEDLINE, PUBMED, Embase, and the Cochrane Database of Systematic Reviews for English-language, evidence-based articles published between the years 2000 and 2011. We searched for guidelines from U.S. and international organizations that offered clinically based practice recommendations to healthcare providers on how VTE risk should be assessed and how thromboprophylaxis should be given among pregnant women. We also searched for guidelines aimed at healthcare providers that gave clinically based recommendations on whom to screen or test for thrombophilias both in the general population and specifically among women before or during pregnancy.

The databases were searched using relevant Medical Search Headlines (MeSH) terms and other terms as deemed pertinent. The principal terms used were pregnancy, pregnant women, puerperium, thrombosis, pulmonary embolism, thrombophilia, postpartum thrombosis, deep vein thrombosis, blood clots, practice guidelines, evidence-based guidelines, prevention, heparin prophylaxis, prophylaxis, postpartum, compression stockings, inpatient, thromboprophylaxis guidelines, primary prevention recommendation on testing for thrombophilia, consensus guidelines, screening for thrombophilia, counseling for thrombophilia, consensus statement, and preconception.

We included only those articles in which the guideline development was based on a systematic review of the literature or consensus expert opinion. We excluded review articles but included both U.S. and international guidelines from organizations that commissioned the development of guidelines. We also excluded articles not addressing all thrombophilia types and not providing recommendations for pregnant women.

Results

We found nine guidelines for providers' assessment of VTE risk and thromboprophylaxis dissemination for pregnant women and seven guidelines for thrombophilia screening in

women (Table 1, supplementary material available on line at www.liebertonline.com).The mechanism for gathering and grading the level of evidence used in making recommendations differed among organizations (Appendix, supplementary material available on line at www.liebertonline.com). For instance, whereas the British Committee for Standards in Haematology (BCSH) and the National Institute for Health and Clinical Excellence (NICE) used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to rank their evidence, the American College of Obstetricians and Gynecologists (ACOG) used the U.S. Preventive Services Task Force (USPSTF) system for grading evidence (Appendix, supplementary material available on line at www.liebertonline.com).

After reviewing the selected guidelines, recommendations for VTE risk assessment and thromboprophylaxis were grouped as follows: general recommendations, cesarean sections, prior VTE, thrombophilia and no prior VTE, thrombophilia and prior VTE, and thrombophilia screening (Table 2, supplementary material available on line at www.liebertonline.com).

General recommendations

Eight of the nine organizations—the American College of Chest Physicians (ACCP), the European Genetics Foundation (EGF), the Queensland Maternity and Neonatal Clinical Guidelines Program (QMNC), the Royal College of Obstetricians and Gynaecologists (RCOG), NICE, the French Society for Anesthesiology and Intensive Care (SFAR), the Scottish Intercollegiate Guidelines Network (SIGN), and the Society of Obstetricians and Gynaecologists of Canada (SOGC)—agreed that all women should undergo risk factor assessment for VTE either in early pregnancy or in the preconception period. RCOG, EGF, and NICE added that the assessment should be repeated if a pregnant woman is admitted to the hospital for any reason or develops a complication (e.g., preeclampsia). Similarly, the majority of the organizations (ACCP, RCOG, EGF, NICE, SIGN, SFAR, and QMNC) thought that pregnant women with more than one additional known VTE risk factor (e.g., reducedmobility for ≥3 days or age > 35 years or obese) should be considered for thromboprophylaxis. However, there were variations among organizations about the risk factors to include and how they should be used in the assessment of pregnant women.

Cesarean section

With regard to how to prevent VTE after cesarean section, there was variation in the guidelines among organizations. ACCP recommends against the use of specific thromboprophylaxis other than early mobilization after cesarean section in women with no additional thrombosis risk factors, whereas ACOG recommends placement of pneumatic compression devices before cesarean delivery for all women not already receiving thromboprophylaxis. NICE recommends offering combined (pharmacologic and mechanical) VTE prophylaxis to women who are pregnant and undergoing cesarean section. For women with additional risk factors, such as obesity, who will undergo a cesarean section, four of the nine organizations (ACCP, RCOG, SIGN, and SOGC) recommend initiation of thromboprophylaxis.

Prior VTE

For women with a prior VTE, some of the relevant recommendations depended on whether the VTE was considered provoked, meaning associated with a risk factor other than increased estrogen, unprovoked, or estrogen dependent. The ACCP, ACOG, RCOG, and SIGN make this distinction and recommend postpartum thromboprophylaxis for all women with a prior VTE, regardless of this categorization. For women with a prior provoked VTE, ACCP, ACOG, RCOG, and SIGN do not recommend routine antepartum prophylaxis. In fact, ACCP and ACOG recommend only antepartum surveillance for this group of women. ACOG, RCOG, and SIGN agree that in women with unprovoked or estrogendependent VTE, antepartum prophylaxis should be offered. ACCP differs in its recommendations, offering either antepartum prophylaxis or surveillance for women with unprovoked or estrogen-dependent VTE. QMNC and SOGC do not distinguish between provoked and unprovoked VTE. QMNC and ACOG recommend thrombophilia screening for women with a prior VTE. QMNC and SOGC also recommend antepartum and postpartum prophylaxis. QMNC includes antepartum surveillance and use of postpartum compression stockings in their recommendations for women with a prior VTE.

Inherited thrombophilias and no prior VTE

The ACCP, EGF, QMNC, RCOG, SIGN, and SOGC all recommend close surveillance antenatally and that anticoagulant prophylaxis be offered after delivery. Exceptions to these recommendations are made for women with anti-thrombin deficiency, with more than one thrombophilic defect, or with additional risk factors. For these high-risk groups, EGF, QMNC, RCOG, SIGN, SOGC, and ACOG recommend antepartum prophylaxis and postpartum anticoagulation therapy. In contrast, ACCP recommends that women with antithrombin deficiency receive anticoagulation prophylaxis (not therapy) in both the antepartum and postpartum periods. For women with other thrombophilias and no prior VTE, ACCP recommends either routine surveillance or prophylaxis during pregnancy and anticoagulation postpartum.

Thrombophilias and prior VTE or recurrent VTE

For this high-risk population of women, there was agreement among the recommendations of six organizations (ACCP, ACOG, EGF, QMNC, RCOG, and SOGC), who advise that antenatal and postpartum thromboprophylaxis should be offered to women with a thrombophilia and a previous or recurrent VTE.

Thrombophilia screening

There was agreement among most organizations that addressed thrombophilia screening not to recommend thrombophilia screening of the general population of pregnant women in order to assess venous thrombosis risk—ACOG, the College of American Pathologists (CAP), EGF, the French Group for Haemostasis and Thrombosis (GEHT), and the Italian Society for Haemostasis and Thrombosis (SISET). ACOG, CAP, EGF, and SISET also agreed that nonpregnant women with a prior VTE, whose only other risk factor was estrogen exposure, should be tested for thrombophilias.

Other thrombophilia-related recommendations

- Women with a history of VTE who have not had a complete evaluation of possible underlying etiologies should be tested for both antiphospholipid antibodies and inherited thrombophilias (ACOG).
- All patients with an inherited thrombophilia should undergo individualized risk assessment (ACOG).
- Thrombophilia testing must be supervised by experienced laboratory staff, and the clinical significance of the results must be interpreted by an experienced clinician who is aware of all relevant factors that may influence individual test results (BCSH).
- Screening for thrombophilias should be done before pregnancy. If screening is performed during pregnancy, the results should be interpreted with great caution (SISET).
- Testing at the time of acute venous thrombosis is not indicated (BCSH).

Discussion

There is broad agreement among the guidelines from U.S. and international organizations that all women should be assessed for VTE risk during preconception and again during pregnancy. With regard to thrombophilia screening, there is agreement that the general pregnant population should not be screened but rather that screening should be done selectively; however, no agreement exists on the exact population in which screening should be performed.

Our review of the available guidelines and consensus statements identified a number of issues that warrant concern. First, most are inconsistent in both the way in which the quality of evidence is rated and the way in which the strength of recommendations is graded. Second, the statements often vary in their recommendations on whom to screen. Third, most of the primary studies used to make the recommendations were conducted in populations of women of European descent, so the risks identified are not necessarily generalizable to non-European populations. Finally, some of the guidelines have not been updated recently.

Our review of guidelines and consensus statements follows in the footsteps of Clark and Bates,[18] who reviewed guidelines for antithrombotic therapy in pregnancy from both North American and British organizations. We expanded on this approach and considered organizations in North America, Britain, and other countries, and we included available screening guidelines for thrombophilias in pregnant women.

Although studies have evaluated adherence to thromboprophylaxis in the general population, no study has yet addressed adherence specific to pregnant women. Furthermore, despite the availability of these guidelines and consensus statements, their implementation is inconsistent. The Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting (ENDORSE) study found 58.5% adherence to thromboprophylaxis among surgical patients at risk and only 39.5%

adherence for medical patients at risk.[19] Similarly, the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) study found that only 61% of at-risk medical patients in the United States and in other countries received some form of prophylaxis.[20]

Based on the results of several studies, the reasons for guideline underuse include underestimation of the risks of VTE, failure to perform individual risk assessments, and lack of awareness of relevant guidelines.[21,22] Although underuse is extensive, studies have shown that increasing DVT prophylaxis rates can decrease the rate of hospital-acquired DVT[23,24] or DVT and PE.[25] We hope this article will raise provider awareness of relevant available guidelines for assessing risk of VTE in women before and during pregnancy.

Conclusions

U.S. and international guidelines and consensus statements on thromboprophylaxis and screening pregnant women for VTE and thrombophilias showed agreement on some points but not on others. There is agreement that pregnant women should be assessed for VTE risk during pregnancy and that the general population of pregnant women should not be screened for thrombophilias. However, there is a lack of overall agreement about which groups of women should be offered thromboprophylaxis during or after pregnancy or offered testing for thrombophilias. This review demonstrates that partial agreement exists, and efforts should be made to establish more areas of agreement through collaborative documents.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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