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REVIEW

Venous thromboembolism and pregnancy

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Abstract: In recent decades, the association between a hypercoagulable state and its causes and adverse pregnancy outcome, in particular recurrent pregnancy loss (RPL) has been studied extensively. Although the first studies were focused only on the association between thrombophilia and RPL, subsequent studies underlined also a potential role of antithrombotic treatment to prevent vascular complication such as venous thromboembolism (VTE) during pregnancy. Thromboprophylaxis should be considered also for pregnant subjects carriers of molecular thrombophilia or that previously experienced VTE, in order to prevent VTE during pregnancy, while antithrombotic treatment for VTE should be performed during all pregnant periods.

Keywords: thrombophilia, venous thromboembolism, recurrent pregnancy loss, factor V Leiden

Hypercoagulable state during pregnancy

Recurrent pregnancy loss (RPL) represents a major health problem with two to three or more losses in up to 5% of women of reproductive age and is actually one of the most common causes of female sterility.[1] Several reports identify inherited predisposition to thrombophilia as one of the main causes of RPL in particular if several diseases potentially responsible for RPL have been already excluded such as endocrine diseases (eg, ovarian dysfunction, anovulation, hypopituitarism, diabetes), uterine malformation, genetic alterations (eg, chromosomal aberrations), inflammatory diseases (in particular systemic lupus erythematosus), and infectious diseases.[2–5]

From a pathological point of view, women affected by thrombophilia show during their pregnancy a hypercoagulable state, that is already increased during pregnancy. This combined increase in thrombophilic state may impair placental flow, its function and fetal growth and may predispose to develop venous thrombosis.[6]

During pregnancy we may observe many changes in the haemostatic balance with a trend toward thrombophilia in order to be prompt for the hemostatic challenge of delivery.[2,6,7] Thus, pregnancy is a condition associated to thrombophilia *per se* and for this reason it is associated with the increase of several clotting factors (ie, factor VIII, von Willebrand factor, fibrinogen, factor VII).[7] Moreover, also other markers of a hypercoagulable state are increased during pregnancy, such as D-dimer and/or prothrombin fragment 1 + 2.[7,8] For this reason we may observe episodes of venous thromboembolism (VTE) during pregnancy.[9] So, women carrying further thrombotic risk factors (eg, inherited thrombophilia) show an additional increase in risk of thrombotic events during pregnancy such as venous thromboembolism and/or abortion.[10]

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VTE and pulmonary embolism (PE), in fact, continue to be a leading cause of maternal death during pregnancy or postpartum and may cause significant morbidity of pregnant women. Although DVT and PE occur infrequently during pregnancy, they represent one of the most serious complication and important issues concerning their natural history, prevention and therapy remain unresolved during pregnancy.

This review was focused on the management of venous thromboembolism occurrence and its prophylaxis during pregnancy.

Occurrence of VTE during pregnancy and its causes

VTE is a multifactorial disease which involves acquired and inherited risk factors.[11,12] Molecular thrombophilia, in particular inherited thrombophilia, is involved in the pathophysiology of juvenile VTE, whereas pregnancy is recognized as one of the acquired thrombotic risk factors for VTE.[11] However, not all pregnant women develop VTE during pregnancy, therefore a clear evaluation of the VTE risk is suggested in any case. Data on all types of patients that should have thromboprophylaxis performed during pregnancy are really controversial in the literature. There is only one way to perform thromboprophylaxis during pregnancy, that is, in women that are at high risk of VTE because they are carriers of relevant predisposing factors for VTE. In this field, antithrombin deficiency seems to be the inherited disorder that patients more at risk of VTE during pregnancy show, but other molecular conditions associated with inherited thrombophilia have also been frequently identified.

However, most previous studies evaluating pregnancy-associated thromboembolic events have used clinical criteria only for diagnosis or included few patients.

Recently, the Registry of Patients with Venous Thromboembolism (RIETE) underlined several interesting aspects of VTE during pregnancy. VTE is more common in the first trimester of pregnancy compared to the second and third trimesters; [13] moreover, this registry underlined the need for starting thromboprophylaxis during pregnancy as soon as possible in pregnant women at risk for thrombotic events.[13] Furthermore, nearly 55% of pregnant patients with VTE during pregnancy were carriers of molecular thrombophilia.[13] In this field, factor V Leiden and prothrombin A20210G are the more common gene variants present in this population.[13] Once therapy was started, VTE recurrences seem to be rare while bleeding complications are more frequent after delivery.[13]

Episodes of acute VTE during pregnancy should be treated as in nonpregnant women (ie, with full doses of unfractionated heparin (UFH) monitored with activated partial thromboplastin time, or with low-molecular-weight heparin (LMWH), twice daily with possible monitoring according to Xa levels.[14–18] However, many variables should be considered during heparin treatment in pregnancy because the several metabolic changes during pregnancy may also modify the plasma concentration and bioavailability of any type of heparin.[17]

Recently other data from RIETE registry confirmed that pregnant women with VTE show few clinical symptoms and frequently do not have comorbidities.[19] The main frequent symptoms of VTE during pregnancy are painful limb and lower limb edema associated to chest pain or dyspnea,[19] and relevant changes in electrocardiography may be found in pregnant women with VTE in particular, such as the presence of negative waves.[19]

Treatment in this report was based mainly on LMWH (nearly 80%) with high daily doses (185 U\Kg daily), while UFH was used in nearly 10% of patients as acute treatment. Vena cava filter was considered only for 4% of patients and thromblysis for 1% of patients. Antivitamin K drugs were administered for long-term treatment in nearly 20% of patients.

Anticoagulant treatment after acute VTE in pregnancy should be continued, in particular if needed for clinical conditions, but it should be stopped when the patient is near to delivery.[2] Anticoagulant treatment should be re-started after delivery in order to avoid recurrences, based mainly on oral anticoagulation according to the required International Normalized Ratio range.[2]

Thrombophilia and VTE thromboprophylaxis during pregnancy

Thromboprophylaxis may be divided into primary prophylaxis for patients that never experienced VTE or secondary prophylaxis in subjects who previously suffered from VTE.

For pregnant women primary thromboprophylaxis is recommended in case of Cesarean section and during the puerperium in most cases.[20]

Moreover, primary thromboprophylaxis is suggested for asymptomatic pregnant women if one of these conditions is present: antithrombin deficiency; more than

one thrombophilic condition (eg, homozygosity for one thrombophilic gene polymorphism or two or more heterozygosities for thrombophilic defects, or the presence of one or more inherited thrombophilic defects associated to one or more acquired thrombophilic defects); and first-degree relative with a history of severe juvenile VTE.[21] Furthermore, primary thromboprophylaxis has been recently suggested for pregnant carriers of thrombophilic conditions without previous history of VTE.[13]

In pregnant women with previous VTE, secondary thromboprophylaxis during pregnancy should be performed.[22,23] According to the data available from the literature we may perform an active pharmacological thromboprophylaxis based on the administration of UFH or LMWH.[22,23]

Furthermore, pharmacological thromboprophylaxis is suggested if further thrombotic risk factors are present during pregnancy (ie, prolonged bed rest, recent surgery, obesity, autoimmune disease with or without antiphospholipid syndrome, infections, nephrotic syndrome, preeclampsia).

However, pharmacological thromboprophylaxis should be considered during the puerperium for about six to eight weeks and based on the administration of UFH or LMWH once daily if several thrombotic risk factors are presence because the frequent appearance of VTE during first weeks of puerperium.[20]

Conclusion

VTE is multifactorial disease that recognizes several risk factors in which pregnancy is included. Although, not all pregnant women develop VTE during pregnancy, VTE is still a cause of maternal death during pregnancy or postpartum and cause also a significant subsequent morbidity. However, in these years most of the protocols for treatment of DVT or PE during pregnancy or postpartum were based on data extrapolated from the nonpregnant population, mainly because these patients have been systematically excluded from participating in clinical trial, so emerging data about treatment and\or prophylaxis for VTE during pregnancy were not universally accepted. In this short review we reported recent data that confirmed a relevant role of molecular thrombophilia in the occurrence of VTE during pregnancy and the efficacy and safety of anticoagulant therapy in pregnant women with VTE. Considering VTE prophylaxis as a clear evaluation of thrombotic risk is suggested because VTE prophylaxis actually is considered only for high-risk patients and further data should be provided by further studies.

Disclosures

The authors report no conflicts of interest in this work.

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