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Review Article

Peripartum Cardiomyopathy and Thrombosis – A Match Made In Hell!

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ABSTRACT

Pregnancy with peripartum cardiomyopathy (PPCM) is associated with a prothrombotic state. The procoagulant system is activated, signaled by the elevated levels of clotting factors. The natural anticoagulation mechanisms are suppressed, along with the fibrinolytic system. Heart failure (HF) is also known to activate platelets favoring thrombus formation. HF with reduced ejection fraction secondary to multi-factorial etiology in PPCM predisposes to intracardiac thrombus formation and embolic complication, jeopardizing maternal and fetal safety. Anticoagulation with heparin for thrombo-prophylaxis and treatment can prevent the formation and extension of the clot. Risk stratification, prompt identification of patients with intracardiac thrombus, and timely initiation of anticoagulation can mitigate the catastrophic thromboembolic episodes.

Keywords: Anticoagulation, Low-molecular-weight heparin, Peripartum cardiomyopathy, Thrombosis, Thromboembolism

INTRODUCTION

Pregnancy, a physiological process, is accompanied by adaptations in the maternal body orchestrated by hormonal changes for the thriving of the fetus till delivery. The hematological system also undergoes a transformation in all three major components – increased red cell mass, leukocytosis, and thrombocytopenia.[1] The hemostatic profile is also in constant flux throughout the gravid state. The levels of procoagulant factors such as fibrinogen, clotting factors, and von-Willebrand factors are elevated with increasing gestational age. At the other end of the spectrum, protein C and S concentrations dwindle, cumulatively leading to a hypercoagulable state.[2] Peripartum cardiomyopathy (PPCM), a rare type of dilated cardiomyopathy, is the commonest cause of heart failure (HF) in pregnancy. It is diagnosed in late pregnancy or within 6 months postpartum. The incidence is highest in African American women. The decrease in global ventricular systolic function and the prothrombotic state due to pregnancy further compounded by PPCM predisposes to stasis and risk of thromboembolic complications and maternal as well as fetal morbidity and mortality.

PPCM AND THROMBOSIS

PPCM significantly exaggerates the risk of both arterial and venous thromboembolism, which is evident from the high percentage (4–6%) of patients reported from various

registries.[3] Pregnancy is a perfect scenario to replicate Virchow's triad – hypercoagulability, venous stasis, and endothelial injury [Figure 1].[4] Recent research elucidating the pathophysiology of PPCM reveals the complex interplay between prolactin, oxidative stress, and soluble Fms-like tyrosine kinase-1 released from the placenta, inhibiting vascular endothelial growth factor promoting endothelial cell (EC) dysfunction. The 16 KiloDalton prolactin subfragment promotes micro ribonucleic acid-146a expression, induces EC apoptosis, promotes vasoconstriction, and inhibits EC migration and proliferation.[5] The hemostatic milieu is shifted toward a prothrombotic state, with an attenuated fibrinolytic system. The systolic dysfunction, cardiac chamber dilatation, and low cardiac output contribute to intracardiac blood stasis and thrombus formation.

HF AND PLATELET DYSFUNCTION

Congestive HF is also associated with changes in platelets in the form of platelet activation. Consequently, there is whole blood aggregation, increased mean platelet volume, and elevated expression of platelet-bound and soluble p-selectin, platelet/EC adhesion molecules, and β-thromboglobulin.[6,7] Interacting with leukocytes and EC, they serve as mediators of inflammation. Platelet to leucocyte ratio particularly with monocytes and lymphocytes could usher as a novel marker of inflammation. PPCM is also a form of HF with reduced ejection fraction (EF). In a retrospective study, elevated platelet count was found to be associated with left ventricular (LV) thrombus formation.[8] Further studies are required to validate the role of platelet count and function for thrombosis in PPCM.

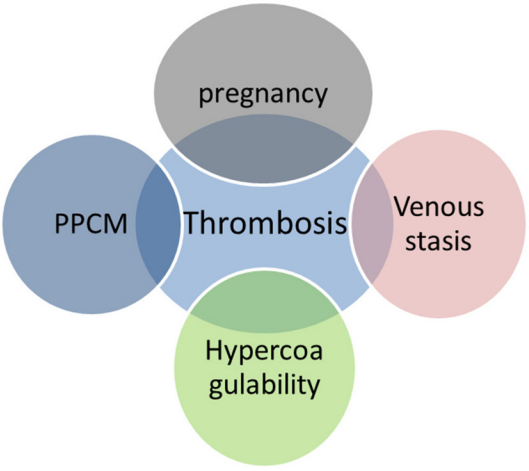

Figure 1: Venn diagram depicting the inter-relationship between pregnancy, peripartum cardiomyopathy (PPCM), venous stasis, and hypercoagulability in thrombotic complications.

INDICATION FOR ANTICOAGULATION

There lacks an universal consensus on the threshold for administering anticoagulation in PPCM and the duration of treatment. Low EF is a major determinant of the necessity of anticoagulant use. The American Heart Association 2016 guidelines propagate anticoagulation in LVEF <30%.[9] The European Society of Cardiology (ESC) 2016 guidelines suggest using LVEF <35% as the cutoff value. Its 2019 position statement states the use of anticoagulation in prophylactic dose in reduced EF,[10] but "reduced EF" has not been specifically defined. Therapeutic anticoagulation is recommended in patients with visualization of intracardiac thrombus on imaging, systemic embolism, and paroxysmal or persistent atrial fibrillation. There are also conflicting data on bromocriptine used in the postpartum period aggravating the thrombotic risk including, cerebrovascular, and myocardial infarction. The ESC 2018 guideline on the management of cardiovascular diseases in pregnancy recommends prophylaxis with heparin in females on bromocriptine.[11]

ANTICOAGULATION DURING PREGNANCY AND POSTPARTUM

Heparin in both unfractionated and low-molecular-weight forms is the drug of choice for anticoagulation in pregnancy. Low–molecular-weight heparin (LMWH) is derived from the depolymerization of unfractionated heparin (UFH) resulting in the formation of fragments that are about one-third the size of UFH molecule.[12,13] These LMWHs, such as enoxaparin and dalteparin, also activate antithrombin III but predominantly act on factor Xa versus thrombin. Therefore, their activity is best monitored using anti-Xa assays and not with activated clotting time/activated partial thromboplastin time, as with UFH.[14,15] LMWH supersedes UFH due to its long half-life, allowing once or twice daily dose, predictable anticoagulation response, and decreased heparin-induced thrombocytopenia and heparin-induced osteoporosis incidence.[16] UFH is usually reserved for patients requiring urgent delivery, surgery, or thrombolysis.[17] Other anticoagulants have either an unacceptable risk of embryopathy or are not adequately evaluated in this population [Table 1]. However, Vitamin K antagonist can be employed post-delivery.

DISCUSSION

PPCM is a pro-thrombotic state, with a heightened risk of thrombosis during pregnancy. The thromboembolic risk continues unabated in the postpartum period, conspicuous from the prevalence of complications even after delivery. No cardiac chamber/great vessel are immune from thrombus

Table 1: Safety of anticoagulants during pregnancy.

Anticoagulant	Safety	Reason
LMWH	Data present supporting use in pregnancy	Do not cross placenta, dosing to be adjusted during delivery, and central neuraxial blockade
UFH	Data present supporting use in pregnancy	Do not cross placenta, shorter half-life, and preferred when urgent delivery is imminent
VKA	Avoided; Extreme caution in 2nd and 3rd trimester	Warfarin crosses placenta, embryopathy, and risk of fetal malformation
NOAC	Avoided	Contraindicated; scarce data
Synthetic Pentasaccharide	Avoided	Limited data to support use during LMWH allergy/adverse reactions

LMWH: Low molecular weight heparin, UFH: Unfractionated heparin, VKA: Vitamin K antagonist, NOAC: Novel oral anticoagulants; : Indicated; : Avoided

formation. Intracardiac thrombus can develop in both the left (17%)[18] and right ventricle, atria, aorta, pulmonary artery, and superior vena cava. The major cause of morbidity and mortality is cerebrovascular embolism. Deep venous thrombosis and catastrophic pulmonary embolism have also been reported.[5,19] Biventricular thrombus was found in a 32 year, gravida seven patient, 2 months after delivery, echo revealed an EF of 15–20%. She was treated with heparin infusion and subsequently transitioned to apixaban for 4 months.[20] In a retrospective study involving 123 PPCM patients, 22 were found to harbor intracardiac thrombus, after multivariable logistic regression analysis-LVEF, hemoglobin, and thrombocyte count were associated with the prediction of LV thrombus formation.[8] In another case, a 32-year-old postpartum patient suffered a cerebral infarct due to a large thrombus in the aortic root.[21] Comparatively lower thromboembolism episode (TEE) rates were observed in a population given thromboprophylaxis to a substantial percentage (16%) of patients.[22] Lower-segment cesarean section delivery and post-operative status were associated with higher TEE.

FUTURE RESEARCH AND DELIBERATIONS

The use of novel biomarkers in both diagnosis and prognosis in PPCM has been on a rising trend in the current decade.[23] *Plasminogen Activator Inhibitor-1* (*PAI-1*) gene plays a crucial role in regulating fibrinolysis. Elevated levels of *PAI-1* can increase the risk of thrombosis. *PAI-1* has been studied for its potential role in vascular impairment through the urokinase plasminogen activator receptor/nuclear factor kappa B Cells (uPAR/NF-kB/miR-146a) pathway on endothelial activation. Polymorphism in the *PAI-1* gene can decode the variability in the thrombotic episodes in PPCM. The 4G allele is associated with higher *PAI-1* levels compared to the 5G allele.[24]

The pertinent questions that still remain unanswered with respect to anticoagulation – LVEF below which anticoagulation be initiated during pregnancy, duration of anticoagulation, and anticoagulant agent after postpartum. Although novel oral anticoagulants (NOAC's) are used after delivery, the 2019 position statement of ESC mentions rivaroxaban being found in breast milk, although in a small amount in a single case study, mandating further confirmation of NOAC safety in the postpartum group.[25] With the current understanding of PPCM, serial echocardiograms in females with low EF can detect thrombus formation in the early stages, restricting its growth and chances of embolism. Thus, TEEs are a potential threat in PPCM and the use of LMWH can significantly decrease this risk.

CONCLUSION

Although substantial progress has been made in understanding of etiology, pathophysiology, and treatment options in PPCM, a major lacuna regarding identifying risk factors for TEE's and optimal preventive and treatment strategies looms over safe pregnancy, puerperium, and postpartum period. Regular surveillance in high-risk patients can promote timely identification and initiation of thromboprophylaxis. Further prospective studies are required for risk stratification of pregnant females with PPCM benefiting from anticoagulation.

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