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Advances in Anticoagulation Therapy for Preeclampsia: A Systematic Review

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Abstract: Preeclampsia (PE) is a multisystem pregnancy disorder. Several pathological processes, such as vascular endothelial dysfunction, an imbalance between coagulation and anticoagulation, and changes in trophoblast characteristics, are involved in the development of PE. The article discusses the pathogenesis of PE. In the third trimester, a protective hypercoagulable state typically develops in normal pregnancies. However, in PE, this state is exacerbated, resulting in a thrombotic phenotype characterized by a systemic inflammatory response and activation of the clotting cascade. This article examines the potential mechanisms involved. The present treatment emphasizes the timely delivery of the fetus. The investigation of anticoagulant therapies is still ongoing, mainly focusing on aspirin and the use of low-molecular-weight heparin for drug-induced thrombosis prevention. In this review, we will summarize the recent findings of reported and ongoing anticoagulation therapy in the treatment of PE. This anticoagulant treatment strategy is essential for the improvement and prevention of PE.

Keyword: Preeclampsia; Therapy; Anticoagulation; Thrombosis; Coagulation monitoring; Heparin

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1. Overview of preeclampsia

Preeclampsia (PE) is a serious complication of pregnancy that affects 3-8% of pregnancies worldwide and is a major cause of fetus-maternal mortality and morbidity [1]. In PE, hypertension and proteinuria can lead to extensive end-organ damage [2]. This complex process involves multiple organ systems, including proteinuria, acute kidney injury, liver dysfunction, hemolysis, thrombocytopenia, and, less frequently, liver rupture, epilepsy, stroke, and death [3]. The pathogenesis of PE remains incompletely understood, but it is believed to involve multiple mechanisms, such as endothelial dysfunction, endovascular inflammation, syncytial trophoblast stress, immunomodulatory disorders, and microembolism [1,4–7].

PE manifests changes in procoagulant and anticoagulant pathways beyond the protective hypercoagulation experienced during pregnancy. There are intravascular agglutination, microvascular thrombosis and

hysteroplacental circulatory disturbance associated with the ischemic and oxidative damage of the placenta. The underlying mechanism of this prothrombotic state is influenced by endotheliopathy, achieved by inducing abnormal regulation of coagulation, platelets, and adhesion ligands [8].

Currently, the only treatment for PE is to terminate the pregnancy, but this is often associated with an iatrogenic preterm birth. Although the risk of immediate death decreases after death, health risks for both mother and fetus increase after birth [3,6]. Therefore, research efforts are focused not only on the treatment of preeclampsia, but also on ways to prevent its occurrence [3]. Early identification and treatment of prothrombotic states can improve the maternal and maternal prognosis of PE. This makes anticoagulation therapy for PE a major research focus. Recent studies have demonstrated that anticoagulant drugs possess anti-inflammatory, anti-apoptotic, and promote the growth and development of trophoblast cells.

In this review, we provide an overview of the significance of anticoagulant therapy in the management of PE, examine the mechanism of action of current anticoagulant therapy and its application in PE.

2. Anticoagulation therapy in preeclampsia

Recent studies have begun to explore the potential of anticoagulation therapy as an innovative approach for managing PE [9]. This therapeutic strategy may not only mitigate the thrombotic risks associated with PE but also alleviate its symptoms and reduce the incidence of complications through mechanisms such as improving placental perfusion, reducing vascular endothelial inflammation, and inhibiting thrombus formation [10]. Anticoagulants commonly employed include aspirin and low-molecular-weight heparin.

Aspirin, particularly at doses exceeding 100 mg when initiated before 16 weeks of gestation, has demonstrated significant efficacy in reducing the incidence of preterm PE, with reductions exceeding 60%. A secondary analysis of data from the Aspirin Evidence-Based Prevention of PE trial further revealed that this intervention led to a 68% reduction in the length of stay in the neonatal intensive care unit, primarily due to fewer cases of PE occurring before 32 weeks of gestation [11].

The combination of low-dose aspirin (LDA) and low-molecular-weight heparin (LMWH) has emerged as a particularly effective regimen. Studies have shown that this combination not only enhances clinical efficacy but also reduces adverse reactions compared to LDA monotherapy [12]. This is especially important for pregnant women with comorbidities, as LDA alone may be insufficient to address the clotting disorders that can affect the placenta and fetus [13].

Despite these promising findings, research on anticoagulation therapy for PE is still in its early stages. Further high-quality clinical trials and fundamental research are essential to validate these results and optimize treatment protocols. Future studies should focus on elucidating the mechanisms underlying the therapeutic effects of anticoagulants and identifying the most effective combinations and dosages for different patient populations.

3. Mechanisms of anticoagulant therapy

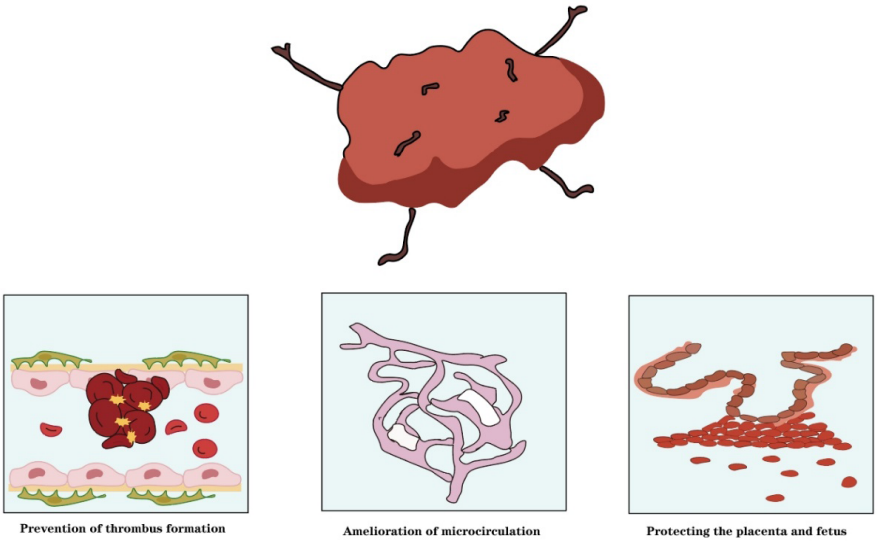

Figure 1. Schematic representation of anticoagulant therapy mechanisms.

3.1. Prevention of thrombus formation

Anticoagulant therapy is designed to prevent thrombus formation by inhibiting clotting factors or disrupting the coagulation cascade while preserving hemostasis.

FXa is central to both intrinsic and extrinsic coagulation pathways, driving prothrombin to thrombin conversion. Development of specific FXa inhibitors can halt thrombin production, achieving an anticoagulant effect while minimizing disruption to primary hemostasis. Thrombin inhibitors block the activation of factors V, VIII, XI, and XIII, inhibiting fibrinogen conversion and platelet activation, thereby preventing clot formation. Heparin activates antithrombin III (AT III) through a key pentasaccharide, inhibiting thrombin and other clotting factors (e.g., XIIa, IXa, XIa, Xa) [14]. Low-molecular-weight heparin (LMWH) preferentially targets FXa, reducing thrombin generation [15].

Inhibition of Factor XI (FXI) and Factor XII (FXII) reduces hemorrhagic complications while maintaining efficacy. FXI inhibition affects both intrinsic and extrinsic pathways, whereas FXII disruption impacts only the initial contact phase [16]. Platelet aggregation is crucial for thrombus formation. Synthetic compounds like 7-N-Acetylamino-4-methylcoumarin derivatives inhibit platelet aggregation by suppressing cyclooxygenase-1 (COX-1) and reducing thromboxane A2 (TXA2) levels [17]. APAC, a proteoglycan analog, blocks collagen- and thrombin-mediated platelet activation, reducing platelet and fibrin deposition in thrombosis models.

Endothelial cells synthesize antithrombin III (ATIII) and produce nitric oxide (NO), promoting vascular relaxation [18]. Heparin enhances endothelial NO availability and inhibits PECAM-1 function, reducing vascular inflammation [19]. Activated protein C (APC) inhibits intrinsic tenase and prothrombinase complexes, with additional anti-inflammatory and cytoprotective functions via interactions with EPCR and PAR-1. Tissue factor pathway inhibitor (TFPI) inhibits the tissue factor (TF)-VIIa complex, reducing thrombin generation [20]. These strategies highlight the multifaceted approach to preventing thrombus formation while balancing anticoagulation and hemostasis.

3.2. Amelioration of microcirculation

The microcirculation, a complex network of minuscule blood vessels, serves as the terminal vascular network of the systemic circulation, intricately delivering oxygenated blood to tissues and organs by their metabolic demands [21]. This network, comprising arterioles, capillaries, and venules, is the final destination of the cardiovascular system, where oxygen transfer from red blood cells to parenchymal cells occurs. The microcirculation is also essential for the regulation of solute exchange between the intravascular and tissular spaces, the distribution of hormones and nutrients to cells, the facilitation of immune responses, and the maintenance of hemostasis [22]. However, the presence of stable heteroaggregates in the absence of physiological shear stress can increase local blood viscosity and the likelihood of thrombus formation [23]. Excessive activation of the coagulation cascade, coupled with the deterioration of anticoagulant and fibrinolytic functions, exacerbates microcirculatory impairment, leading to tissue necrosis and thrombosis [23]. Such impairments are implicated in conditions like PE, highlighting the importance of developing methods to enhance microcirculatory function for maternal and fetal well-being.

Inflammation is a significant contributor to microcirculation dysfunction [24]. It can lead to endothelial dysfunction, increased vascular permeability, and leukocyte adhesion, all of which impair microcirculatory flow and contribute to tissue ischemia. Anticoagulants, such as heparin, can modulate the inflammatory process by affecting neutrophil migration, complement activation, and cytokine production [25]. Vitamin K antagonists (VKAs) also influence inflammatory pathways through the inhibition of growth-arrest-specific protein 6, which subsequently activates receptor tyrosine kinases, such as MER and AXL [26].

In the context of pregnancy, heightened inflammation and the initial demise of trophoblast cells can result in deficient placentation. This is characterized by compromised invasion, remodeling of blood vessels, and disruption of microcirculation within the placenta. Unfractionated heparin (UFH) has been shown to inhibit the migratory ability of extravillous trophoblasts induced by hepatocyte growth factor, thereby hindering their differentiation [27]. These findings underscore the intricate interplay between inflammation, microcirculation, and placental development and highlight the need for targeted therapeutic interventions to mitigate these effects.

Heparin exerts multifaceted effects on trophoblasts and microcirculation, which are particularly relevant in the context of PE. It has been demonstrated that heparin can prevent the consumption of trophoblasts by inhibiting matrix metalloproteinases (MMPs)and suppressing the activity of tissue inhibitors of metalloproteinases (TIMPs). Additionally, heparin prevents the activation of the complement system in trophoblasts, thereby mitigating inflammation and apoptosis [28].

During PE, elevated vascular tone in the maternal microvasculature is observed, primarily due to the vasoconstrictive effects of endothelin-1 and angiotensin II [29]. Experimental evidence indicates that women with PE exhibit reduced blood flow area in the choroidal capillaries compared to healthy pregnant individuals, a phenomenon likely mediated by vasospasm [30]. Notably, enoxaparin, a low-molecular-weight heparin, significantly reduces the rate of cerebral infarction linked to vasospasm and decreases the frequency of severe vasospasm [31].

PE impairs microcirculation through endothelial dysfunction and increased vascular resistance [32]. Brain microcirculatory dysfunction in preeclamptic patients is characterized by compromised autoregulation capacity, predisposing the microvasculature to harmful hyperperfusion. Anticoagulant therapy has been shown to reduce maternal vascular reactivity and mitigate vasoconstriction, thereby enhancing microcirculatory function. Therapies that enhance nitric oxide (NO)availability through endothelial nitric oxide synthase(eNOS)upregulation may potentially improve pregnancy outcomes. For instance, administration of unfractionated heparin(UFH)therapy enhances NO bioavailability, as evidenced by increased endothelium-dependent vasodilation mediated by flow-

mediated dilation and alterations in forearm blood flow in response to acetylcholine (ACh) [33]. Furthermore, the combination of LMWH, LDA, and pravastatin exerts a synergistic effect on eNOS, thereby enhancing placental blood flow and improving pregnancy outcomes [34].

3.3. Protecting the fetus

The immune landscape of pregnancy significantly shapes fetal growth and development [35]. LMWH therapy plays a pivotal role in modulating the maternal immune response, preserving fetal immune tolerance, and mitigating the risks associated with abnormal fetal development. By restoring Treg cell homeostasis and enhancing decidual IL-10 mRNA expression, LMWH therapy not only dampens caspase-3 activity but also improves pregnancy outcomes across diverse genetic backgrounds [36].

The therapeutic potential of LMWHs extends beyond mere anticoagulation. Their broad application in preventing early pregnancy loss is underpinned by their theoretical association with placental thrombosis and infarction. LMWHs may bolster placental function through various mechanisms, including modulating trophoblast cell apoptosis and influencing growth factors such as HB-EGF. Additionally, their interaction with molecules like Cyr61 suggests a multifaceted approach to placental health and fetal development [37].

4. Conclusion

A prothrombotic state is a critical pathological alteration. This prothrombotic tendency is associated with endothelial dysfunction, placental ischemia, and systemic inflammation, contributing to the clinical manifestations of PE.

Anticoagulation therapy has emerged as a vital strategy in managing preeclampsia, targeting the prothrombotic state to prevent thrombosis, improve microcirculation, lower blood pressure, protect the fetus, and enhance maternal prognosis. Low-dose aspirin has demonstrated efficacy in reducing the incidence and severity of preeclampsia and is widely recommended for high-risk pregnancies. Although the role of low molecular weight heparin in preeclampsia prevention remains inconclusive, evidence suggests potential benefits in specific high-risk scenarios.

While current anticoagulation therapies primarily focus on interventions within the coagulation system, future breakthroughs will likely require exploring new therapeutic frontiers. These include modulating endothelial cell function, optimizing immune regulatory mechanisms, and innovating interventions in the angiogenic process.

Disclosure statement

The authors declare no conflict of interest.

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