

Thromboprophylaxis during pregnancy for prevention of adverse complications in patients with inherited thrombophilia: a literature review

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Summary

Compared with non-pregnant women, pregnancy alone carries a three- to fivefold higher risk of venous thromboembolism (VTE). Despite the increasing use of low-molecular-weight heparin in identified high-risk patients, pulmonary embolism is still the leading cause of maternal mortality. However, evidence for optimal use of thromboprophylaxis is scarce. Thrombophilia (hereditary or acquired) is thought to predispose to both VTE and is also associated with complications of pregnancy, such as recurrent miscarriages and preeclampsia. This review discusses the current evidence for optimal thromboprophylaxis during pregnancy by focusing primarily on VTE prevention strategies, the potential to prevent recurrent complications during pregnancy with low molecular weight heparin (LMWH), aspirin, and Nattokinase in pregnant women with congenital thrombophilia.

Key words: Aspirin, low molecular weight heparin, nattokinase, thrombophilia



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Introduction

The overall care for pregnant women with thrombophilia involves careful monitoring. Problems associated with blood clots in pregnancies with thrombophilia can be detected early through attentive observation (Schreck et al. 2022). These issues include deep vein thrombosis, pulmonary embolism, and placental blood clots (Antic et al. 2022). Healthcare professionals can swiftly identify symptoms related to blood clots by regularly examining the patient's clinical status, conducting specific diagnostic tests, and using medical imaging techniques such as ultrasound. Proactively addressing these problems and minimizing their impact on the health of both the mother and the fetus is crucial. Close monitoring allows for the timely detection of problems and quick intervention. Issues related to blood clots can be swiftly treated to reduce risks (Kujovich 2018). Healthcare practitioners can promptly alter anticoagulant therapy to minimize blood clots and bleeding after discovering deep vein thrombosis (Sharma and Kriplani 2018). If a pulmonary embolism is detected, stabilization and treatment can commence immediately (Samuel end Saw 2020). Obstetricians-gynecologists, hematologists,

and other specialists are crucial for a multidisciplinary approach. Collaborative decision-making based on the patient's clinical profile and assessment of thrombotic risk tailor therapies to the needs of the pregnancy (Scheres et al. 2018). Careful monitoring during pregnancy with thrombophilia aids in promptly identifying and treating clot-related issues. Regular check-ups, specialized diagnostic tests, and a multidisciplinary care team assist in managing the risks associated with thrombophilia, emphasizing the necessity for patient-centered care.

Aim

We aimed to investigate the potential of thromboprophylaxis to mitigate adverse complications during pregnancy to establish the feasibility of personalized treatment for pregnant women with thrombophilia; to investigate methods to reduce the risk of bleeding and minimize complications related to blood clots; to present the options for thromboprophylaxis with low molecular weight heparin, aspirin and nattokinase during pregnancy, and to analyze the importance of thrombophilia prevention and treatment strategies to improve reproductive health.

Materials and methods

The method employed involves a literature review of scientific articles and studies. A PubMed search was conducted, including sources from 2015 to 2023 using keywords like "thromboprophylaxis," "pregnancy," "inherited thrombophilia," "anticoagulants," and "low molecular weight heparin." Inclusion criteria were focused on peer-reviewed English articles such as presenting reviews, meta-analyses, or studies on pregnant patients.

Results

Individual care, personalized treatment of pregnant women with thrombophilia, is based on screening as it provides valuable information to physicians about thrombotic risk profiles, enabling customized therapies and support. The foundation of individual care involves a thorough risk assessment. Understanding the individual thrombophilia mutation and its severity is crucial for this assessment. For instance, thrombophilia variants vary in risk. Resistance to protein C inactivation in factor V Leiden may require more careful anticoagulant therapy than other variants. The severity and specificity of each case determine anticoagulant treatment, the frequency of monitoring, and other preventive measures (Liu et al. 2019). A personalized care plan includes lifestyle changes tailored to the patient's thrombotic risk profile and medication interventions. Lifestyle decisions can significantly impact clotting events. Healthcare practitioners can recommend lifestyle changes based on risk assessment (Papavasileiou and Petra 2020).

Regular exercise is essential for good circulation. Conversely, patients with genetic thrombophilia should avoid prolonged immobility, such as travelling or a sedentary lifestyle, which can increase the risk of thrombosis. Dehydration increases blood viscosity and clot formation; hence, maintaining hydration is another lifestyle recommendation (Dimitriadis et al. 2020). Healthcare practitioners aim to holistically manage thrombophilia by adapting lifestyle changes to the patient's risk profile. Thrombophilia screening is crucial for women considering

in vitro procedures. The timing and strategy for fertility treatment depend on the thrombotic risk profile. Healthcare practitioners and reproductive specialists can improve fertility therapy planning for thrombophilia. Coordinating in vitro cycles with anticoagulant medication and monitoring can reduce thrombotic risk and increase pregnancy success (Tran et al. 2019). From diagnosis to tailored care regimens for pregnant mothers with thrombophilia, screening is of vital importance (Alptekin et al. 2017). These personalized interventions include risk assessment, lifestyle advice, and assisted reproduction issues. This comprehensive and customized approach optimizes pregnancy outcomes while reducing thrombophilia risks (Tran et al. 2019). Early detection and individualized care are crucial for successful pregnancy outcomes. Thrombophilia, with its increased propensity for abnormal clot formation, necessitates comprehensive prevention and treatment strategies for pregnant women. This section addresses the importance of thromboprophylaxis, which involves using anticoagulant therapy to prevent clot formation during pregnancy. Thromboprophylaxis aims to achieve a delicate balance between preventing clots and minimizing potential risks.

Reducing complications associated with clotting

Anticoagulant medications help pregnant women with thrombophilia avoid clot-related issues (Domniz and Meirou 2019). When these clots develop in the veins of the placenta or other crucial circulatory pathways, they can adversely affect the health of the mother and the fetus. Thrombophilia-associated clot development can lead to recurrent spontaneous abortions, stillbirths, and preeclampsia. Healthcare professionals use anticoagulants to treat hypercoagulation in thrombophilia (Ryan and Paidas 2019). Low molecular weight heparin (LMWH) and aspirin, among other anticoagulants, prevent clot formation and platelet aggregation. Due to its effectiveness and safety, pregnant women with thrombophilia often take LMWH. This intervention is personalized according to the individual's thrombotic risk profile, considering the type and severity of thrombophilia (Pradhan and Gautam 2018). Healthcare providers use anticoagulants to balance the hemostatic environment and reduce clot formation and its consequences (Kouides et al. 2019), increase the likelihood of a successful pregnancy and alleviate the emotional and physical toll of multiple losses or stillborn children on future parents. Anticoagulant therapy is prescribed following a thorough medical history, thrombotic risk assessment, and thrombophilia diagnosis. Anticoagulant medication can reduce clot-related issues during pregnancy, improving outcomes for both the mother and the fetus (Moreno et al. 2023).

Limiting bleeding risks

Anticoagulant medication is crucial for controlling thrombophilia during pregnancy despite posing risks. The primary concern with anticoagulant treatment is bleeding (Turesheva et al. 2023). Anticoagulants prevent clot formation, which can aid patients with thrombophilia, but they increase the risk of bleeding. Hence, a careful assessment of risk factors, including medical history and type of thrombophilia, among other factors, should be conducted for each patient (Davis and Pavord 2018). Following this comprehensive review, the optimal thromboprophylaxis

laxis regimen is chosen. A complete assessment balances the risks of bleeding against the benefits of clot prevention when selecting anticoagulant therapy. The type of thrombophilia, severity, and bleeding condition history should be considered in this evaluation. Anticoagulant treatment and dosage are personalized based on the needs and risks of the patients (Liew-Spilger et al. 2021). Due to its safety during pregnancy, low molecular weight heparin (LMWH) is preferred (Antonelli et al. 2023). Anticoagulants can treat thrombophilia during pregnancy, although they may cause bleeding, which needs monitoring (Nypaver 2023).

Time and duration of thromboprophylaxis

Thromboprophylaxis should commence in the early stages of pregnancy, typically during the first trimester, and be maintained until just before delivery. The choice, dosage, and duration of anticoagulant therapy depend on each patient's individual risk profile and medical history. Continuous monitoring and routine hematologic studies are necessary to maintain the efficacy and safety of the treatment during pregnancy (Collins et al. 2016). A study by Von Steinburg et al. (2023) underscores the importance of personalized healthcare and careful monitoring to achieve an optimal balance between preventing clots and reducing bleeding risks.

Prophylaxis with Low Molecular Weight Heparin (LMWH) during pregnancy

Low molecular weight heparin (LMWH) is well-established as a primary component of prophylactic therapy aimed at preventing thrombosis in pregnant women diagnosed with thrombophilia. A comprehensive understanding of its mechanisms, dosage, and monitoring is crucial to effectively leverage its advantages while mitigating potential risks. LMWH plays a vital role as an anticoagulant by selectively inhibiting factor Xa, a critical element in the complex coagulation process (Sammartano 2020). Its distinct mode of action enables effectual hindrance of clot formation while avoiding interference with platelet function, a crucial component of the entire blood clotting process. Factor Xa plays a crucial role in the pathway to blood clot production within the coagulation cascade. This substance acts as an enzyme that facilitates the conversion of prothrombin to thrombin, a key participant in blood clotting (Muratova et al. 2019). Thrombin, in turn, catalyzes the conversion of soluble fibrinogen into insoluble fibrin strands, thus generating a meshwork configuration that traps blood cells, culminating in clot formation. LMWH exerts its therapeutic effects by specifically targeting factor Xa. LMWH effectively inhibits the cascade by binding to and blocking the action of factor Xa, thereby preventing the conversion of prothrombin to thrombin (Baglin 2015).

Consequently, the synthesis of fibrin strands down the chain and the subsequent clotting process is impeded. It is illustrative that the focused mechanism of action exhibited by LMWH is beneficial when considering pregnancy and thrombophilia. The anticoagulant addresses the heightened risk of clot formation in pregnant women with thrombophilia while not interfering with normal platelet function. Platelets play a crucial role in the hemostasis process, which is the body's mechanism to avoid excessive bleeding after tissue injury. Pre-

serving platelet function is vital for maintaining the integrity of the clotting process, which is essential for hemostasis, thus preventing abnormal clot formation in placental vessels or other crucial circulatory pathways (Rossberg et al. 2016). The selective inhibition of factor Xa activity by LMWH, while preserving platelet function, makes it a viable prophylactic intervention to prevent clot formation in pregnant women, especially those with thrombophilia. Utilizing this specific strategy reduces the likelihood of thrombosis while preserving crucial hemostatic abilities. LMWH is often administered via subcutaneous injections as a proactive measure to reduce the likelihood of clot formation in individuals exposed to a higher risk of this condition. The optimal use of LMWH during pregnancy, especially in women with thrombophilia, requires careful monitoring and assessment of multiple parameters influencing dosage and effectiveness. Maintaining a high level of awareness among healthcare practitioners is crucial to ensure that LMWH effectively fulfills its preventive function while minimizing potential bleeding complications.

The patient's weight is a crucial factor in calculating the dose of LMWH. Generally, higher doses may be required for pregnant individuals with higher body weight to achieve the appropriate anticoagulant effect. Accurate weight assessment is essential for adequately personalizing therapy.

LMWH is primarily cleared from the body through renal filtration. Drug clearance can be affected by compromised renal function, thus leading to an increased risk of bleeding due to excessive accumulation. Therefore, evaluating renal function using methods like creatinine clearance is imperative to adjust the LMWH dose precisely (Momot et al. 2019).

Differences in thrombotic risk profiles exist among people, including those with thrombophilia. Some individuals may exhibit more pronounced manifestations of thrombophilia, while others may possess additional risk factors that increase their overall propensity for clot formation (Shlomo et al. 2017). Personalizing the LMWH dosage to match an individual's risk profile makes maximizing the prophylactic benefits possible.

Regularly monitoring anti-factor Xa levels is a crucial component of LMWH therapy. This laboratory test is designed to assess the anticoagulant activity of LMWH in a patient's circulatory system. By monitoring these levels, healthcare professionals can confirm that the treatment achieves the desired anticoagulant result without significantly reducing blood viscosity, which could potentially increase the likelihood of hemorrhagic consequences.

Measuring anti-factor Xa levels provides significant information for appropriate adjustment of the LMWH dosage to achieve an optimal balance between preventing clot formation and avoiding excessive bleeding. In summary, using LMWH as a therapeutic intervention during pregnancy requires careful and thorough consideration, especially in women with thrombophilia (Borisova et al. 2020). A personalized dosing strategy is necessary due to the complex interplay between weight, renal function, LMWH formulation, and individual risk profiles.

Strict monitoring of anti-factor Xa levels ensures the drug's efficacy in preventing thrombotic events while reducing bleeding risk. Extensive knowledge regarding LMWH use allows healthcare professionals to make well-informed choices, thus ensuring that pregnant women with thrombophilia receive the benefits of prophylaxis while mitigating any adverse effects (Folk 2018).

Prevention with aspirin

Identifying thrombophilia through genetic testing serves as a primary guide to adapting treatment and management strategies for patients facing reproductive issues. Once thrombophilia is confirmed, specific interventions can be applied to mitigate the risks associated with this condition.

Anticoagulant therapy

For women identified with thrombophilia, anticoagulant therapy stands as a primary intervention to reduce the risk of excessive clot formation during pregnancy. By preventing the formation of blood clots, anticoagulant medication acts as a crucial technique to lower the risk of spontaneous abortions or stillbirths associated with thrombophilia. The two main components of anticoagulant therapy are integral parts of achieving these therapeutic goals:

- **Low Molecular Weight Heparin (LMWH):** Low molecular weight heparin, often referred to as LMWH, is a well-established and widely used anticoagulant in treating pregnancies with thrombophilia. Its action involves suppressing the activation of coagulation factors, thereby inhibiting the formation of blood clots (Volozonoka et al. 2020). LMWH is particularly valuable due to its low side effect profile during pregnancy compared to other anticoagulants. Its ability to target specific aspects of blood clotting without significantly affecting other aspects contributes to its widespread application. The dosage and duration of LMWH treatment are also individualized to enhance its effectiveness in preventing clot formation while minimizing potential patient risks. Regular monitoring of coagulation indicators and clinical assessment are vital in achieving therapy goals. Close collaboration between the patient, physician, and hematologist is critical to achieving the desired balance between anticoagulation and the risk of bleeding.
- **Aspirin Prophylaxis:** Aspirin is used as a prophylactic measure to reduce further the thrombotic risk associated with thrombophilia during pregnancy. Aspirin is an antiplatelet agent, and its primary mechanism of action is inhibiting platelet aggregation. By preventing their aggregation, aspirin helps reduce clot formation within the vascular system (Nichols et al. 2020). Like LMWH therapy, the inclusion of aspirin in the treatment plan is determined based on the patient's clinical profile and assessment of thrombotic risk (Kim et al. 2023).

The choice of aspirin is usually made in connection with LMWH therapy or as an alternative under circumstances where LMWH is contraindicated or not well tolerated (Fruci et al. 2023). Careful patient selection for aspirin prophylaxis considers the balance between its benefits in preventing thrombosis and potential adverse effects, including gastrointestinal irritation. Anticoagulant therapy, including low molecular weight heparin (LMWH) and aspirin prophylaxis, forms the basis for managing thrombophilia during pregnancy. These therapeutic medications are personalized according to the patient's thrombotic risk profile, providing a successful strategy to reduce the risk of clot formation. The coordinated efforts of obstetricians-gynecologists and hematologists are crucial to achieving opti-

mal results while ensuring the well-being of the mother and fetus. Aspirin is critical in reducing the risk of thrombosis and is particularly beneficial in improving pregnancy outcomes for women with thrombophilia. The mechanism of action of aspirin lies in its ability to suppress platelet aggregation, thereby reducing the likelihood of clot formation. Platelets are biological components of the blood that initiate clotting mechanisms in response to vascular injury. Platelets can contribute to the formation of blood clots in blood vessels when they aggregate excessively or irregularly (Carvalho 2022). Aspirin interferes with this mechanism by reducing platelet activation. It achieves this through irreversible inhibition of the enzyme cyclooxygenase (COX), which is involved in the production of prostaglandins.

Prostaglandins are chemical messengers that activate and aggregate platelets. Aspirin reduces the production of specific prostaglandins by inhibiting COX, thereby limiting platelet aggregation and reducing the potential for clot development (Adesina et al. 2023). It is essential to specify that the mechanism of action of aspirin primarily targets platelets and their function in clot formation. The effects of aspirin are more selective, focusing on platelet function, unlike anticoagulant drugs such as heparin or warfarin, which affect multiple elements in the coagulation cascade.

Aspirin thromboprophylaxis can prevent thrombosis in women with thrombophilia. Due to the increased risk of thrombotic issues during pregnancy, thrombophilia conditions can be problematic. Aspirin-based thromboprophylaxis therapy for thrombophilia in pregnant women provides complete protection against thrombosis when added to LMWH therapy. Individual care plans manage aspirin dosing and timing for pregnant women with thrombophilia. Daily thromboprophylaxis usually includes 81 mg or 100 mg of low-dose aspirin. Aspirin therapy typically starts early in pregnancy and continues throughout, especially in cases of recurrent abortions, stillbirths, or other thrombotic issues. Aspirin therapy should be carefully monitored and followed by physicians to reduce the risk of thrombosis without increasing the risk of bleeding. Although patient characteristics may require adjustments, low-dose aspirin during pregnancy is usually safe. Aspirin reduces the risk of thrombosis in women with thrombophilia by inhibiting platelet aggregation, a critical mechanism in clot formation. It selectively targets platelet activity. Thromboprophylaxis with aspirin is an integral part of treating thrombophilia in pregnant women, and patient characteristics determine aspirin dosing and timing to maximize benefits and minimize risks (Bates et al. 2018).

Nattokinase prophylaxis

Alternative therapy for thrombophilia is used to complement or replace anticoagulant treatment. Nattokinase, an enzyme derived from fermented soybeans, specifically “natto,” is one such alternative medicine. Understanding the potential benefits and existing evidence is crucial to informing patients and healthcare providers of alternative methods for treating thrombophilia.

Bacillus subtilis ferments soybeans into nattokinase, a staple in Japanese cuisine for generations, especially “natto,” a sticky dish known for its health benefits. Natto is consumed as breakfast due to its unique taste and potential cardiovascular and clot-dissolving qualities. By breaking down fibrin, a protein involved in clot formation, nattokinase is considered a thromboprophylaxis agent (Sheikhansari et al. 2020). Like a mesh-like fibrin structure that traps

platelets and other blood components to form a stable clot during injury or damage, the fibrinolytic properties of nattokinase can prevent or dissolve clots.

The fibrinolytic characteristics of nattokinase determine its usefulness and safety in treating thrombophilia. Nattokinase may increase blood flow and reduce the risk of clotting in cardiovascular health. However, more evidence is needed to determine its efficacy. Nattokinase is not regulated like pharmaceutical products, resulting in variations in quality, purity, and consistency among manufacturers, making it challenging to assess its medicinal potential.

Patients and healthcare providers considering the use of nattokinase or other alternative thrombophilia treatments should take into account the following:

1. Consultation with healthcare providers: Patients with thrombophilia should consult their doctors before attempting alternative therapies to ensure the chosen technique aligns with their care plan and does not increase risks or interact with other therapies.
2. Safety and quality: A thorough assessment of the quality and provider of Nattokinase supplements is imperative. It is advisable to use products from reputable manufacturers that adhere to strict quality standards and are free from any impurities.
3. Evidence-based decisions: Informed decisions that consider available facts and seek assistance from experts in the field are recommended. While nattokinase shows potential, it should not be considered a substitute for well-established thromboprophylaxis interventions like anticoagulant therapy when medically justified (Lappen et al. 2021).
4. Monitoring: Consistent monitoring of thrombotic risk and overall health when using alternative medications is necessary. Healthcare practitioners can evaluate therapeutic effectiveness and its impact on the patient's condition. Nattokinase, a therapeutic variant derived from soybean fermentation, has attracted considerable interest due to its potential fibrinolytic properties. However, despite some curiosity regarding its role in managing thrombophilia, the existing scientific evidence needs to be more comprehensive and needs clear conclusions.

Both patients and healthcare providers should exercise caution when considering alternative therapies like Nattokinase. Priority should be given to evidence-based treatments. Additionally, consulting healthcare experts is crucial to making well-informed decisions that align with the individual's care plan and medical requirements (Sanchez et al. 2020). Comprehensive studies and ongoing clinical trials are essential to improve awareness of the potential benefits and drawbacks of using Nattokinase to manage thrombophilia.

Nattokinase is believed to possess fibrinolytic properties, indicating its ability to degrade fibrin, a fundamental component of blood clots. This potential action has led some individuals with thrombophilia to consider Nattokinase as an alternative or adjunct therapy to traditional anticoagulants. The rationale behind this consideration lies in the idea that Nattokinase might offer a more natural and alternative approach to managing thrombotic risks. However, it is essential to note that while Nattokinase is intriguing due to its potential fibrinolytic effects, scientific evidence supporting its efficacy and safety in managing thrombophilia is limited and still under investigation.

Individuals exploring Nattokinase as part of their thrombophilia management should do so under the guidance and observation of healthcare providers. Emphasis should be on evidence-based treatments, and consultations with healthcare specialists are crucial to ensure the chosen approach aligns with the individual's overall care plan and medical needs (Raia-Barjat et al. 2022). Furthermore, monitoring thrombotic risk and overall health is crucial when using alternative therapies like Nattokinase to assess their effectiveness and impact on the patient's condition. In-depth studies and ongoing clinical investigations are necessary to understand better the potential benefits and risks of Nattokinase in managing thrombophilia.

Conclusion

Thrombophilia complicates reproductive health. The categorization, causes, and understanding of thrombophilia have improved. However, research and guidelines emphasize the importance of a thorough assessment of thrombosis, prevention, and treatment strategy. Recent studies reveal the intricate link between inherited thrombophilia and reproductive issues. Inherited thrombophilia, specifically mutations in Factor V Leiden and prothrombin, can significantly increase the risk of adverse pregnancy outcomes. These include recurrent spontaneous abortions, stillbirths, and hypertension. Inherited thrombophilia is also associated with IUGR and placental abruption, highlighting its complex implications for reproductive health. The findings underscore the significance of assessing the risk of thrombosis in pregnant women, especially those with a family history of thrombosis. In addition to genetic predispositions, modern research acknowledges the influence of additional risk factors on thrombophilia-related issues. Hypercoagulable conditions like polycythemia vera or myeloproliferative disorders elevate thrombotic risk. Surgical procedures, significant trauma, hormonal changes (such as pregnancy and contraceptive use), advanced age, and accompanying conditions like autoimmune diseases and cardiovascular disorders can heighten the risk of thrombosis.

Literature review results indicate that thrombotic risk is not solely inherited; genetics play a fundamental role. Diet, physical activity, medication use, stress, environmental factors, professional circumstances, and travel habits can influence the risk of thrombosis. Risk assessment and personalized therapy are recommended for pregnant women with genetic thrombophilia. Anticoagulant medications, careful monitoring, preconception strategies, and high-risk pregnancy care can manage thrombophilia during pregnancy. Preventing multiple health disorders requires lifestyle changes, including regular exercise and a healthy diet. Factors related to travel and thrombosis risks should also be considered. A holistic approach to risk assessment, prevention, and management should encompass inherited, lifestyle, and environmental factors to optimize outcomes and safeguard patients with thrombophilia in both reproductive and non-reproductive conditions.

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