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Thrombotic risk associated with contraceptive choices in women with thrombophilia. A review of the literature

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ABSTRACT

Inherited thrombophilia is related to an increased risk of venous thromboembolism. The Factor V Leiden mutation is usually the genetic cause and can be detected using relatively straightforward genetic tests. Using hormonal contraceptives further elevates the risk of thrombosis. Genetic testing could support the personalization of contraceptive therapy by finding women at high risk. Preparing this review, we based it on a targeted literature search on inherited thrombophilia caused by Factor V Leiden and its impact on contraceptive use. We examined data from twenty-two studies published between January 2000 and May 2025 in PubMed and Google Scholar, with a focus on the last decade. The search terms included contraception, venous thromboembolism, thrombophilia, and Factor V Leiden. We included original research, systematic reviews, official guidelines, and case reports. We focused on risk assessment, contraceptive recommendations, and genetic testing. We wanted to draw attention to the problem of thromboembolic disease in women using contraception. It considers the utility of genetic testing in guiding safer clinical decisions. We discussed the role of contraceptives in thrombosis. The prothrombotic effect of oral contraceptive ingredients is well documented. We have presented alternative contraceptive methods, such as non-hormonal options. The decision on choosing the best treatment should take into account the potential risk of thrombosis. It depends on a thorough family history and patient education. Adding genetic screening to clinical practice could be beneficial. However, further studies on the cost-effectiveness and the development of clear guidelines are necessary.

Keywords: inherited thrombophilia, Factor V Leiden, genetic screening, contraception.

1. INTRODUCTION

In our time, cardiovascular diseases continue to be a significant focus of modern medicine. Hereditary thrombophilia is a relatively common condition. People who carry the thrombophilia gene have an increased risk of venous thromboembolism

(VTE). The risk of pulmonary embolism (PE) and obstetric complications increases, too. The mutation of factor V Leiden (FVL) is the most common genetic cause of VTE. This FVL gene point mutation can be detected using simple genetic tests (Nguyen et al., 2024; Heikinheimo et al., 2022). The scientific literature shows that the risk of VTE increases significantly after starting hormonal contraception.

Thrombophilia is a hematological disorder characterized by the development of blood clots. Genetic mutations impair the function of natural anticoagulants, leading to the overactivation of procoagulants. One of the most common and well-characterized causes is a mutation in the factor V gene (F5 G1691A), known as Factor V Leiden (FVL). The defect in the F5 gene disrupts the proteolytic site of factor V, which is activated by protein C (APC). It often happens that factor V is resistant to inactivation. As a result, factor Va remains active longer, leading to excessive thrombin production.

Thrombophilia can also be linked to recurrent miscarriages and preeclampsia (Undas et al., 2022; Zawilska, 2015). Clinical expression of thrombophilia depends on multiple risk factors. Chronic diseases and prolonged immobilization increase thrombotic risk because of slower blood flow and vascular injury. Pregnancy, hormonal therapy, obesity, diabetes mellitus, and polycystic ovary syndrome can further intensify blood clotting. What is essential is that various individual and environmental causes and lifestyle factors, like smoking and hypertension, modulate both the risk and severity of thrombotic events (Zawilska, 2015).

Deep vein thrombosis (DVT) can affect the deep veins of the lower limbs and pulmonary vessels (thromboembolism). In the lower limbs, it is manifested by pain, swelling, and redness. The symptoms of pulmonary embolism are more acute. Patients report difficulty breathing, chest pain, and weakness. Thrombosis can develop in atypical locations, such as the veins of the brain, liver, or kidneys.

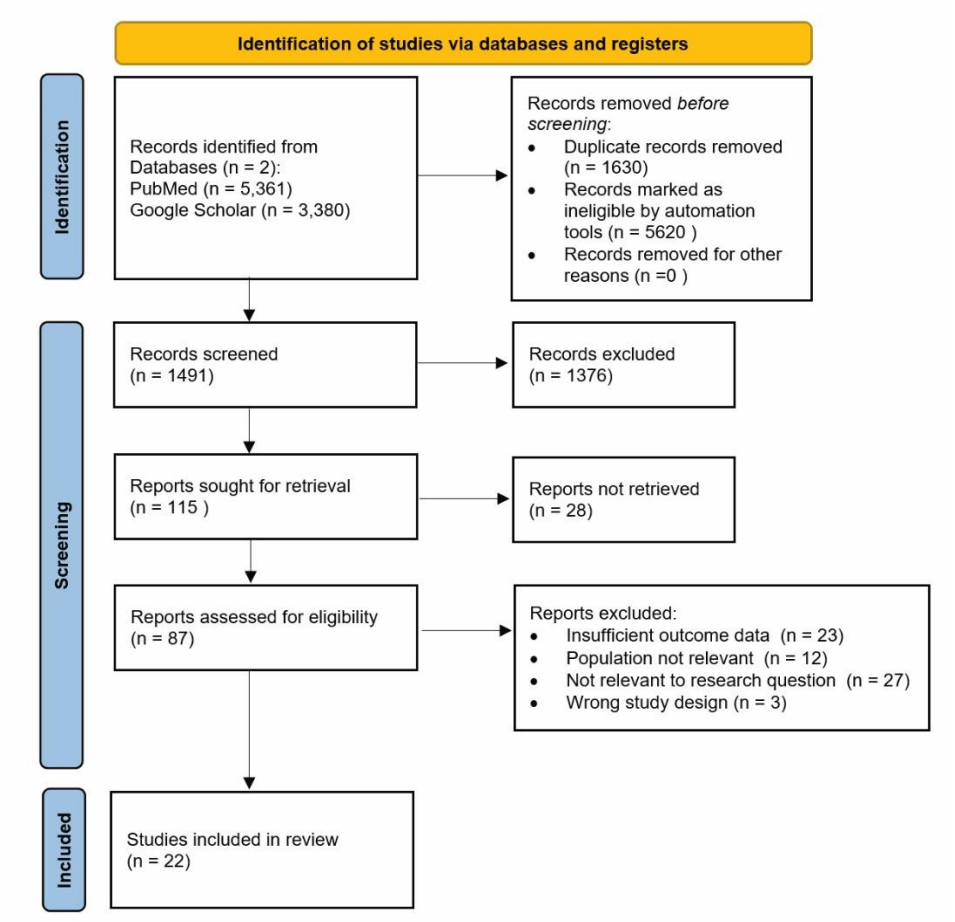

Figure 1: PRISMA flow diagram.

2. REVIEW METHODS

We performed this review as a targeted literature search aiming to analyze current evidence about inherited thrombophilia caused by FVL and its implications for contraceptive use. To achieve the stated aim of this study, a systematic literature review was conducted

using the PubMed and Google Scholar databases, based on articles published between January 2000 and May 2025. Boolean operators AND and OR were used to refine the results. Search terms included: contraception, venous thromboembolism, thrombophilia, and Factor V Leiden. Inclusion criteria included: original research, systematic reviews, official guidelines, and case reports. We included the studies involving women with hereditary thrombophilia who used hormonal contraceptives during that period. Articles had to report on thrombotic risk, contraceptive choice, or genetic screening. Exclusion criteria considered the articles in languages other than Polish or English and studies unrelated to contraception or thrombophilia. The article screening process adhered to the PRISMA guidelines (Figure 1).

3. RESULTS & DISCUSSION

Oral contraceptives as a potential cause of venous thromboembolism

A recent study investigated the impact of oral contraceptive (OC) use on the chance of venous thromboembolism, taking genetic predisposition into account. The results of the study showed that high polygenic tendency correlates with a notably elevated likelihood of the development of VTE within the first two years of OC use (Lo Faro et al., 2024).

We analyzed the case report of a 34-year-old woman with a thrombotic incident. The patient was admitted to the emergency department and reported shortness of breath. Diagnostic tests identified a massive pulmonary embolism. The results of computed tomography angiography confirmed the diagnosis. The medical history of the patient included a previously diagnosed FVL mutation and a positive family history of thrombophilia. She had been taking oral contraceptive pills for the preceding four months. Aside from these factors, the patient denied any other significant thrombosis causative factors, such as immobilization, recent surgery, or malignancy. This case highlights the joint effect of genetic predisposition and exogenous hormonal exposure in the pathogenesis of VTE (Rayamajhi et al., 2024).

The influence of hormones on homeostatic balance is the basis of the blood coagulation mechanism. Virchow's triad consists of endothelial damage, slowed blood flow, and hypercoagulability (Undas et al., 2022). Estrogens elevate the levels of hemostatic agents, including factors II, VII, VIII, IX, X, as well as fibrinogen. Concurrently, it reduces the activity of natural anticoagulants, primarily protein S and APC (Heikinheimo et al., 2022).

OCs users commonly develop acquired resistance to activated protein C (APC-R). It impairs the degradation of activated factor V and accelerates blood clotting (Sandset, 2013; Tchaikovski and Rosing, 2010). The concentration of sex hormone-binding globulin rises proportionally to estrogen levels; therefore, it serves as a biomarker evaluating the risk of thrombosis (Raps et al., 2012). Figure 2 shows the mechanism of APC-R formation.

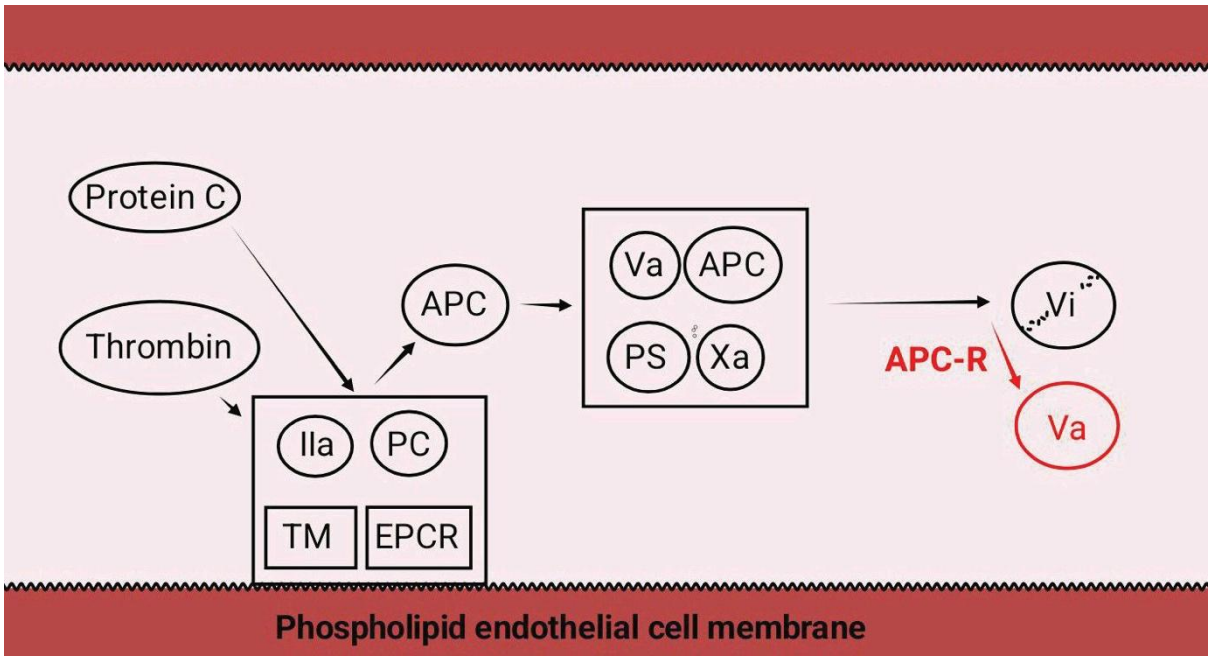

Figure 2: Protein C action leads to APC activation and APC-R formation.

Thrombosis risk according to the type of contraceptive used

Researchers investigated the joint impact of over-the-counter drugs (OTCs) usage and the presence of genetic variants predisposing to venous thromboembolism. The usage of contraceptives containing levonorgestrel showed the lowest odds ratios (ORs). It depended on the specific combination of genetic variants. Gestrodene, desogestrel, and cyproterone acetate-containing formulations showed higher ORs than levonorgestrel. It may indicate that contraceptives containing levonorgestrel might carry a relatively lower risk of VTE in patients with hereditary thrombophilia.

Studies imply that combined oral contraceptives (COCs) that contain desogestrel induce more pronounced alterations in the anticoagulant system, compared to contraceptives containing levonorgestrel. The previously mentioned finding is particularly evident in the protein C pathway. Ethinylestradiol is the main estrogenic compound of COCs. It promotes a prothrombotic shift in the organism via modulation of the balance between procoagulant and anticoagulant factors. The magnitude of prothrombotic shift promotion depends on the specific type of progesterone used. Levonorgestrel, used as a progesterone, exhibits more vigorous androgenic activity. Levonorgestrel might lead to a reduction in ethinylestradiol's prothrombotic effect. Its ability to offset estrogen-mediated procoagulant effects is limited. It results in an enhanced resistance to APC (Kemmeren et al., 2004). Levonorgestrel concentrations across five different COC formulations inversely correlate with the degree of APC resistance. Higher doses of levonorgestrel may effectively mitigate the APC-resistance (van Hylckama Vlieg et al., 2009).

FVL mutation and the administration of OCs exert an additional prothrombotic effect on hemostasis. Both factors impair the APC function, which promotes blood clotting.

Diagnostic evaluation of thrombophilia

The diagnosis of thrombophilia, including the detection of the FVL mutation, is currently relatively easy to perform and available in most specialized laboratories. The primary molecular method used to identify point mutations such as F5 Leiden (G1691A) is polymerase chain reaction (PCR) combined with restriction fragment length polymorphism (RFLP) analysis. This method allows not only confirmation of the mutation's presence, but also differentiation between heterozygous and homozygous variants. The process mentioned above is clinically significant because of the correlation between VTE risk and patient genotypes (Zawilska, 2015; Kujovich, 2011).

In actual clinical use, initial screening tests often include functional assays indicating APC-R. The results of these tests are helpful because they are rapid and relatively inexpensive. However, they do not enable precise genotyping, and therefore, positive results are always confirmed using PCR (Tepper et al., 2025). It is essential to mention the concept of so-called "pseudohomozygotes". It refers to compound heterozygotes for the mutation and deficiency of factor V. Despite their heterozygous status, they exhibit a very low APC resistance index, which can complicate the interpretation of the results without genetic analysis (Brugge et al., 2005).

The costs of thrombophilia diagnostics depend on the geographic region and the extent of testing performed. Despite ongoing controversies on the clinical indications for genetic testing, molecular diagnostics of thrombophilia have gained increasing relevance due to advancements in laboratory methodologies. Nowadays, it is possible to combine DNA extraction techniques with PCR assays. It gives us a fast, simple, and relatively cost-effective method to detect the most prevalent mutations associated with VTE. It includes FVL and the prothrombin mutation. Consequently, this enables effective and affordable screening of patients within selected risk populations.

In response to the growing demand for personalized prevention and treatment, molecular testing has become an essential part of diagnostic strategies (Angelini et al., 2003). Present expert recommendations focus on screening for five genetically determined abnormalities that have a documented impact on the risk of VTE. The most significant mutations occur in the genes encoding FVL, prothrombin (G20210A), protein C, protein S, and antithrombin. Those mutations contribute to their encoded protein deficiencies (Undas et al., 2022).

Despite being relatively inexpensive and available, genetic testing faces barriers. It involves a financial burden associated with large-scale implementation, limited access in some regions, and the requirement for genetic counseling. Each of those aspects restricts its routine use.

Personalized VTE Risk in Hormonal Contraception

Evaluating VTE risk in women planning to use combined hormonal contraceptives is a crucial aspect of ensuring therapeutic safety. Implementation of the Pill Protect tool in clinical practice enables a more effective. These results have been confirmed in simulation

studies conducted in Switzerland. The Pill Protect test combines genetic profiling of key mutations associated with thrombophilia with relevant clinical variables and the medical history of the patient (Sutherland et al., 2019). Medical Eligibility Criteria recommend avoiding combined hormonal contraceptives (CHCs) in women with known thrombophilia (Nguyen et al., 2024). It encourages the use of risk assessment tools, such as Pill Protect.

Screening for genetic thrombophilia is generally recommended in cases of venous thrombosis or PE occurring without an apparent cause before age 50. Screening may also be valuable when thrombosis is present in a family history or when thrombosis develops in atypical vascular sites. Testing is often indicated for recurrent miscarriage or preeclampsia. Clinicians should also evaluate thrombophilia after VTE episodes that appear during CHC use or menopausal hormone therapy. While routine screening before starting estrogen-containing contraceptives is not standard practice nowadays, it is suggested in women presenting with a marked family history (Undas et al., 2022).

Contraception in Carriers of Thrombophilia

Diagnosis of FVL does not preclude the use of contraception altogether. It is important to remember that both the use of OCs and pregnancy are significant risk factors for the development of VTE. Therefore, selecting contraceptive methods that are effective and minimize the risk is very important (Khialani et al., 2020). First-line contraceptive options include intrauterine devices (IUDs). They can be non-hormonal copper-bearing (Cu-IUD) and hormonal types releasing levonorgestrel (LNG-IUD). These options are widely regarded as safe and effective (Tepper et al., 2025).

In women with confirmed thrombophilia, CHCs with estrogen are generally avoided. In women suffering from thrombophilia, CHC containing estrogen may cause side effects such as thrombosis. Therefore, progestin-only contraceptives in the form of tablets, subdermal implants, and intrauterine devices are safer (Kujovich, 2011; ACOG, 2021). They have a less pronounced impact on coagulation parameters compared to oral OTCs that contain estrogen. Furthermore, they can even reduce the likelihood of VTE (Dinger et al., 2007; Vandenbroucke et al., 2001). Table 1 summarizes the contraceptive methods, their correlation with thrombosis risk, and clinical recommendations.

Table 1: Contraceptive methods, their correlation with thrombosis risk, and clinical recommendations.

Contraceptive Method	Hormonal Component	Relative Risk of VTE	Pathophysiological Considerations	Clinical Significance
Antiandrogenic COC	Cyproterone acetate + EE	Very high	Strong estrogenic and antiandrogenic effects exacerbate APC resistance and disturb coagulation balance	Contraindicated in women with inherited thrombophilia due to markedly increased thrombotic risk.
Third-generation COC	Desogestrel / Gestodene + EE	High	Low androgenicity fails to oppose estrogen-induced procoagulant effects; increases APC resistance	Not recommended in thrombophilic women; associated with enhanced thrombotic potential.
Second-generation COC	Levonorgestrel + EE	Moderately elevated	Higher androgenic activity mitigates estrogenic effects on coagulation; partially reduces APC resistance	Lower relative risk among COCs, but still elevated; may be cautiously considered only after specialist evaluation.
Progestin-only pill (POP)	Desogestrel or norethindrone	Minimal or no increase	No estrogenic component; minimal systemic effect on coagulation	Preferred hormonal option in women with thrombophilia; safe for long-term use.
Subdermal implant	Etonogestrel	No confirmed increase	Progestin-only mechanism; minimal impact on hemostasis	Long-acting and safe in high-risk patients; requires minimal maintenance.

LNG-releasing IUS (LNG-IUD)	Levonorgestrel	Minimal	Local hormone release with minimal systemic exposure	High safety profile in thrombophilic women; effective and well-tolerated.
Copper IUD (Cu-IUD)	None (non-hormonal)	Not associated with thrombotic risk	No influence on hormonal or coagulation pathways	First-line recommendation for patients at high thrombotic risk or with contraindications to hormonal methods.

4. CONCLUSION

Hereditary thrombophilia notably increases the chance of VTE in women. Combining the FVL mutation with inappropriately selected hormonal therapy may result in serious complications. Screening for the FVL mutation can be a helpful tool in assessing individual risk before starting contraceptive use. By considering the genetic background of patients, clinicians can select safer contraceptive options, which later reduces the chance of thrombotic events. The research suggests that using progestin-only methods or intrauterine devices lowers the risk of thrombosis. CHCs containing estrogens should be prescribed cautiously or even avoided in patients with confirmed FVL mutation.

When choosing a contraceptive method, it should be preceded by a thorough medical analysis. The researchers considered the condition of the patient, lifestyle, age, weight, and other health issues in a comprehensive analysis. The purpose of contraception is well known, but the health and safety of the patient come first. More research is needed, especially describing the effects of new contraceptive methods on women's health.

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Informed consent

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Ethical approval

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Conflict of interest

The authors declare that there is no conflict of interest.

Data and materials availability

All data associated with this work are present in the paper.

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