Original article

Retrospective Analysis of Hereditary Thrombophilias Outcomes in Pregnancy – Single Institution Experience

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Abstract

Background: Hereditary thrombophilia introduces a layer of complexity to pregnancy, increasing the risk of serious complications and representing diagnostical and therapeutical challenge.

Methods: Retrospective analysis of medical databases from Department of Gynecology and Obstetrics, Institute of Transfusion Medicine and Clinical Department of Pathology and Forensic Medicine, University Hospital Center Osijek consisting of 92 pregnancy cases. Initiation of theraphy with low-molecular-weight heparine started according to evaluation of medical history and genetic risk in I.,II. and III. trimester of pregnancy (33%, 26% and 41%). Data were made from classification of analysed sample (0- as normal value, 1- as unfavorable value, 2- as extremely unfavorable value).

Results: According to listed classification in observed sample 75% had normal outcome, 23% had unfavorable outcome and 2% had extremely unfavorable outcome. Analysed placenta was normal in 68%, unfavorable in 21% and extremely unfavorable in 11% of pregnancies.
The indication for genetic testing based on positive family history of thromboembolic incidents was set to 31.28% and obstetric history was significant in 58.28% of pregnant women. In 62.42% of pregnant women resulting in normal outcome, 18.49% adverse outcome while 10.98% resulted in miscarriage or fetal death. The likelihood of adverse outcomes of pregnancy is almost the same in the group of pregnant women who received LMWH during pregnancy as in the group without therapy (OR = 1.16, 95% CI 0.59-2.30, P = 0.65).

Conclusion: With careful risk assessment, individualized management plans, and close monitoring, the majority of women with these conditions can achieve a successful pregnancy outcome.

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Introduction

Hereditary thrombophilia is a group of inherited disorders that increase the risk of venous thromboembolism (VTE) due to a genetically determined hypercoagulable state. The most clinically significant hereditary thrombophilias include deficiencies of the natural anticoagulants antithrombin, protein C, and protein S, as well as gain-of-function mutations such as factor V Leiden and the prothrombin G20210A variant. These conditions are typically transmitted in an autosomal dominant fashion and predispose affected individuals to VTE, especially in the presence of additional acquired risk factors such as surgery, trauma, pregnancy, or malignancy.(1-8)

The European Venous Forum, International Union of Angiology, North American Thrombosis Forum, Cardiovascular Disease Educational and Research Trust, and International Union of Phlebology highlight that hereditary thrombophilia most commonly manifests as deep vein thrombosis or pulmonary embolism, but can also present in unusual sites such as splanchnic or cerebral veins. The risk of VTE is significantly increased in individuals with these genetic defects, particularly when multiple defects coexist or when there is a family history of VTE.(4)

Routine testing for hereditary thrombophilia is generally reserved for cases where results will impact clinical management, such as in young patients with unprovoked VTE, recurrent events, thrombosis in unusual locations, or a strong family history.(1,2,5)

Hereditary thrombophilia during pregnancy increases the risk of venous thromboembolism (VTE), particularly in women with high-risk defects such as antithrombin deficiency, protein C or S deficiency, or homozygous/compound heterozygous factor V Leiden or prothrombin G20210A mutations. The risk is highest in the postpartum period but is elevated throughout gestation. In addition to VTE, there is a modestly increased risk of adverse pregnancy outcomes, including recurrent miscarriage, late fetal loss, and possibly preeclampsia, though the absolute risk for these complications remains low for most thrombophilias.(9,10)

Management is risk-stratified. The American College of Chest Physicians recommends that women with high-risk thrombophilias (antithrombin deficiency, homozygous or compound heterozygous factor V Leiden/prothrombin G20210A) be considered for antepartum and postpartum thromboprophylaxis, regardless of family history.(11) Low-molecular-weight heparin (LMWH) is the preferred agent; direct oral anticoagulants are contraindicated in pregnancy.(3,4) For women with lower-risk thrombophilias (heterozygous factor V Leiden or prothrombin G20210A) and no personal or family history of VTE, routine prophylaxis is generally not recommended.(9,11)

Testing for hereditary thrombophilia is indicated only if results will alter management, such as in women with a personal or strong family history of VTE or recurrent pregnancy loss. (12,13) Warfarin is contraindicated during pregnancy due to teratogenicity, but may be used postpartum if breastfeeding is not contraindicated.(10-13)

All management decisions should be individualized, considering the type of thrombophilia, personal and family history, and additional risk factors such as obesity, immobility, or cesarean delivery (13,14).

Aim of the study

Thrombophilia has became a focus of interest for perinatologists because of it's association with pathological processes in pregnancy. The aim of this study was to analyse course and outcome of the pregnancies with hereditary thrombophilia and assess its impact on perinatal outcome, therapy and asses the role of genetic testing.

Participants and methods

Retrospective analysis of the database of the Clinic of Gynecology and Obstetrics, Clinical Institute of Transfusion Medicine and Pathology and Forensic Medicine, University Hospital Center Osijek.

Results

Retrospective analysis of birth database from Department of Gynecology and Obstetrics, databases from Institute of Transfusion Medicine and databases which contain histopathological diagnosis (HPD) placenta report Clinical Department of Pathology and Forensic Medicine, University Hospital Center Osijek, Croatia. We have analyzed data of 92 pregnancy cases (obstetrics anamnesis, duration of pregnancy and outcome, HPD of placenta and genetic predisposition for thrombophilia). Composite data has been given in Figure 1.

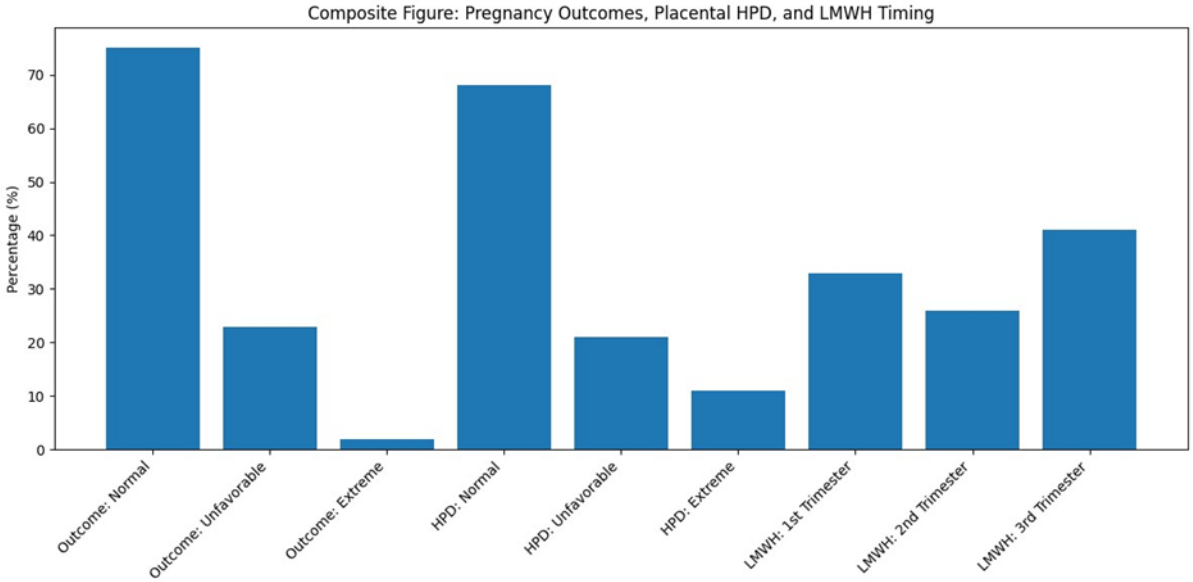

Figure 1. Composite distribution of pregnancy outcomes, placental histopathological diagnosis, and timing of low-molecular-weight heparin initiation in a cohort of 92 pregnancies with hereditary thrombophilia.

Initiation of therapy with low-molecular-weight heparin started after evaluation of pregnancy, anamnesis and genetic risk in I.,II. and III. trimester of pregnancy (33%, 26% and 41%). Data were made from classification of analyzed sample (0- as normal value, 1- as unfavorable value like IUGR etc., 2- as extremely unfavorable value – fetal demise or abortion). According to listed classification in observed sample 75% had normal outcome, 23% had unfavorable outcome and 2% had extremely unfavorable outcome. Analyzed HPD of placenta report was normal in 68%, unfavorable in 21% and extremely unfavorable in 11% of pregnancies. Pregnancy outcomes in correlation with HPD report were moving from extremely unfavorable to unfavorable and normal. Extremely unfavorable HPD of placenta report resulted with unfavorable and extremely unfavorable outcome of pregnancy in 40% of cases. Observed sample had extremely unfavorable genetic predisposition in 42% and unfavorable in 58% of pregnancies. Probability of unfavorable and extremely unfavorable outcome of

pregnancy is nearly 25% in women with genetic predisposition of thrombophilia regardless of classification. During the analysis of pregnancy outcomes with normal, unfavorable and extremely unfavorable obstetrics anamnesis in our datas meaningful correlation wasn't found. Observed pregnancies with unfavorable outcomes had the following factors: in 17% HPD of placenta was extremely unfavorable and in 17% unfavorable, 39% had extremely unfavorable and 61% unfavorable genetic predisposition, 9% of cases had pathological level and increased values of serum D-dimers.

In pregnancies with unfavorable outcomes correlation was noticed with pathological HPD of placenta, but not with genetic predisposition for thrombophilia and unfavorable obstetrics anamnesis. Pregnancies with pathological outcomes are result of many local and systematic factors and their activities on which effects of low-molecular-weith heparin theraphy, applied because of hereditary thrombophilia, wasn't found with certainty. Prophylaxis of low-molecular-weight heparin in different genetic predispositions results with constant number of unfavorable outcomes.

The indication for genetic testing based on positive family history of thromboembolic incidents is set to 31.28% and obstetric history was significant in 58.28% of pregnant women. In 62.42% of pregnant women resulting in normal outcome, 18.49% in adverse outcome while 10.98% resulted in miscarriage or fetal death. The likelihood of adverse outcomes of pregnancy is almost the same in the group of pregnant women who received anticoagulant prophylaxis during pregnancy as in the group without therapy (OR = 1.16, 95% CI 0.59-2.30, P = 0.65). In the group who have had an adverse outcome we have not noticed higher appearance of unfavorable histological diagnosis (OR = 2.24, 95% CI 0.81-6.17, P = 0.11) and there was no higher appearance of elevated D-dimers in circulation (OR = 3.43, 95% CI 0.78-14.92, P = 0.10).

The relationship between obstetric history, pregnancy outcome and perinatal outcome was also analyzed.

In the analyzed sample, 52% of patients had a normal pregnancy, 31% had an unfavorable pregnancy outcome, while 17% of patients had an extremely unfavorable pregnancy outcome:

In 52% of patients in the analyzed sample, the obstetric history was normal, in 23% of patients it was unfavorable, while the obstetric history was extremely unfavorable in 25% of patients.

In the group with a normal obstetric history, 22.9% of patients had an extremely unfavorable pregnancy outcome, 39.6% had an unfavorable pregnancy outcome, while 37.5% of patients had a normal pregnancy outcome, of which, in the same group, 22.9% of patients had an unfavorable and extremely unfavorable pregnancy outcome, and 77.1% of patients had a normal pregnancy outcome.

In the group with an unfavorable obstetric history, 9.5% of patients had an extremely unfavorable pregnancy outcome, 28.6% had an unfavorable pregnancy outcome, while 61.9% of patients had a normal pregnancy outcome, of which, in the same group, 14.3% of patients had an unfavorable and extremely unfavorable pregnancy outcome, and 85.7% of patients had a normal pregnancy outcome.

The thrombophilia was classified according to propensity to thromboembolic incident at high-risk (2.45%;) low-risk (23.92%) and thrombophilia undetermined significance (73.61%), according to pregnancy outcomes as 0 normal values, 1 and 2 as unfavorable outcomes. Total number of patients enrolled was 92, 75% have had good perinatal outcome 23% unfavorable (IUGR etc.) and 2% have had extremely unfavorable outcome (fetal demise)

Probability of poor perinatal outcome in our study has been the same for both groups in unfavorable and normal placental histopathological finding has been the same.

Discussion

Despite conflicting data about the connection between hereditary thrombophilia and adverse pregnancy outcome, a significant increase in the number of screenings for thrombophilia is

observed. While in pregnant women with high-risk thrombophilia anticoagulant prophylaxis is carried out during pregnancy is dubious justification therapy in pregnant women with low-risk and undetermined significance thrombophilia. The likelihood of an adverse outcome is almost the same in the group treated with NMH and one that is not, there was no apparent link between adverse outcomes and histological changes in the placenta as well as an adverse outcome in the group with elevated D-dimers in circulation.(15,16)

Hereditary thrombophilia can lead to placental microthrombi and impaired placental perfusion during pregnancy, which may compromise placental function. The proposed mechanism involves increased maternal hypercoagulability leading to thrombosis in the placental vasculature, resulting in placental infarction, reduced oxygen and nutrient delivery, and ultimately uteroplacental insufficiency. This pathophysiology is associated with an increased risk of adverse pregnancy outcomes, including recurrent miscarriage (particularly in the second and third trimesters), late fetal loss, intrauterine growth restriction, preeclampsia, placental abruption, and preterm birth (13,17).

The strength of these associations varies by the specific thrombophilia. For example, factor V Leiden, prothrombin G20210A mutation, and protein S deficiency are most consistently linked to recurrent pregnancy loss, while the evidence for other complications such as preeclampsia and fetal growth restriction is less robust and sometimes inconsistent. (13-17) Notably, the absolute risk for these complications remains low for most women with hereditary thrombophilia, and the majority will have normal pregnancies (18,19).

In summary, hereditary thrombophilia may impair placental function by promoting placental thrombosis, which can result in pregnancy loss and other placenta-mediated complications, but the magnitude of risk depends on the specific defect and the presence of additional risk factors.(13,19,20)

Conclusion

Monitoring of pregnancy with an underlying hereditary thrombophilia requires an individualized approach to the assessment of associated risk factors. The causes of adverse outcomes of pregnancy are multi factorial and the result of the actions of many affiliated local and systemic factors whose mechanism of action still remains clinically unrecognized.

In pregnancies with unfavorable outcomes correlation was noticed with pathological HPD of placenta, but not with genetic predisposition for thrombophilia and unfavorable obstetrics anamnesis. Pregnancies with pathological outcomes are result of many local and systematic factors and their activities on which effects of low-molecular-weight heparin therapy, applied because of hereditary thrombophilia, wasn't found with certainty. Prophylaxis with LMWH in different genetic predispositions results with constant number of unfavorable outcomes. Hereditary thrombophilia introduces a layer of complexity to pregnancy, increasing the risk of serious complications. However, with careful risk assessment, individualized management plans, and close monitoring, the majority of women with these conditions can achieve a successful pregnancy outcome. The decision-making process regarding screening and treatment should be a collaborative effort between the patient and her healthcare provider, taking into account the specific type of thrombophilia, personal and family medical history, and the current evidence-based guidelines. Ongoing research continues to refine our understanding of the intricate relationship between hereditary thrombophilia and pregnancy, paving the way for even more targeted and effective management strategies in the future.

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References

1. Chopard R, Albertsen IE, Piazza G. Diagnosis and Treatment of Lower Extremity Venous Thromboembolism: A Review. JAMA 2020;324(17):1765-1776. doi:10.1001/jama.2020.17272.

2. Connors JM. Thrombophilia Testing and Venous Thrombosis. The New England Journal of Medicine. 2017;377(12):1177-1187. doi:10.1056/NEJMra1700365.

3. Mannucci PM, Franchini M. Classic Thrombophilic Gene Variants. Thrombosis and Haemostasis. 2015;114(5):885-9. doi:10.1160/TH15-02-0141.

4. Nicolaides A, Hull RD, Fareed J. Thrombophilia. Clinical and Applied Thrombosis/Hemostasis. 2013;19(2):177-87. doi:10.1177/1076029612474840m.

5. Vrotniakaite-Bajerciene K, Angelillo-Scherrer A, Castellucci LA. Thrombophilia Testing in Venous Thromboembolism. The Medical Clinics of North America. 2025;109(4):907-921. doi:10.1016/j.mcna.2025.01.008.

6. Khider L, Gendron N, Mauge L. Inherited Thrombophilia in the Era of Direct Oral AnticoagulantsInternational Journal of Molecular Sciences. 2022;23(3):1821. doi:10.3390/ijms23031821.

7. Rao AK, Kaplan R, Sheth S. Inherited Thrombophilic States. Seminars in Thrombosis and Hemostasis. 1998;24 Suppl 1:3-12.

8. Zöller B, García de Frutos P, Hillarp A, Dahlbäck B. Thrombophilia as a Multigenic Disease. Haematologica. 1999;84(1):59-70.

9. Croles FN, Nasserinejad K, Duvekot JJ, et al. Pregnancy, Thrombophilia, and the Risk of a First Venous Thrombosis: Systematic Review and Bayesian Meta-Analysis. BMJ (Clinical Research Ed.). 2017;359:j4452. doi:10.1136/bmj.j4452.

10. Gerhardt A, Scharf RE, Greer IA, Zotz RB. Hereditary Risk Factors for Thrombophilia and Probability of Venous Thromboembolism During Pregnancy and the Puerperium. Blood. 2016;128(19):2343-2349. doi:10.1182/blood-2016-03-703728.

11. Bates SM, Greer IA, Middeldorp S, et al. VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th Ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e691S-e736S. doi:10.1378/chest.11-2300.

12. Trasca LF, Patrascu N, Bruja R, et al Therapeutic Implications of Inherited Thrombophilia in Pregnancy. American Journal of Therapeutics. 2019 May/Jun;26(3):e364-e374. doi:10.1097/MJT.0000000000000985.

13. Arachchillage DRJ, Makris M. Inherited Thrombophilia and Pregnancy Complications: Should We Test? Seminars in Thrombosis and Hemostasis. 2019;45(1):50-60. doi:10.1055/s-0038-1657782.

14. Bonnar J, Green R, Norris L. Perinatal Aspects of Inherited Thrombophilia. Seminars in Thrombosis and Hemostasis. 1999;25(5):481-5. doi:10.1055/s-2007-994954.

15. Trasca LF, Patrascu N, Bruja R, et al.Therapeutic Implications of Inherited Thrombophilia in Pregnancy. American Journal of Therapeutics. 2019;26(3):e364-e374. doi:10.1097/MJT.0000000000000985.

16. Liu X, Chen Y, Ye C, et al. Hereditary Thrombophilia and Recurrent Pregnancy Loss: A Systematic Review and Meta-Analysis. Human Reproduction (Oxford, England). 2021;36(5):1213-1229. doi:10.1093/humrep/deab010.

17. Simcox LE, Ormesher L, Tower C, Greer IA. Thrombophilia and Pregnancy Complications. International Journal of Molecular Sciences. 2015;16(12):28418-28. doi:10.3390/ijms161226104.

18.Thrombophilia and Pregnancy Complications: Cause or Association?.Middeldorp S.

Journal of Thrombosis and Haemostasis : JTH. 2007;5 Suppl 1:276-82. doi:10.1111/j.1538-7836.2007.02501.x.

19. Kujovich JL.Thrombophilia and Pregnancy Complications. American Journal of Obstetrics and Gynecology. 2004;191(2):412-24. doi:10.1016/j.ajog.2004.03.001.

20. Rodger MA, Walker MC, Smith GN, et al.Is Thrombophilia Associated With Placenta-Mediated Pregnancy Complications? A Prospective Cohort Study. Journal of Thrombosis and Haemostasis : JTH. 2014;12(4):469-78. doi:10.1111/jth.12509..

Author contribution.

Acquisition of data: AM, DŠ, MV, DV
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Analysis and interpretation of the data: AM, DŠ, MV, DV
Conception and design: AM, DŠ, MV, DV
Critical revision of the article for important intellectual content: AM, DŠ, MV, DV
Drafting of the article: AM, DŠ, MV, DV
Final approval of the article: AM, DŠ, MV, DV
Guarantor of the study: AM, DŠ, MV, DV
Provision of study materials or patients: AM, DŠ, MV, DV

Retrospektivna analiza ishoda nasljednih trombofilija u trudnoći – iskustva jedne institucije

Sažetak

Cilj: Nasljedna trombofilija unosi sloj složenosti u trudnoću, povećavajući rizik od ozbiljnih komplikacija i predstavljajući dijagnostički i terapijski izazov.

Materijali i metode: Retrospektivna analiza medicinske dokumentacije Klinike za ginekologiju i opstetriciju, Zavoda za transfuzijsku medicinu i Zavoda za patologiju i sudsku medicinu, Kliničkog bolničkog centra Osijek, koja se sastoji od 92 trudnoća. Terapija heparinom niske molekularne težine započela je prema anamnezi i genetskom riziku u I., II. i III. tromjesečju trudnoće (33%, 26% i 41%). Podaci su dobiveni klasifikacijom analiziranog uzorka (0 - kao normalna vrijednost, 1 - kao nepovoljna vrijednost, 2 - kao izrazito nepovoljna vrijednost).

Rezultati: Prema navedenoj klasifikaciji u promatranom uzorku, 75% imalo je normalan ishod, 23% nepovoljan ishod, a 2% izrazito nepovoljan ishod. Analizirane posteljice su bile normalne u 68%, nepovoljne u 21% i izrazito nepovoljne u 11% trudnoća.

Indikacija za genetsko testiranje na temelju pozitivne obiteljske anamneze tromboembolijskih incidenata postavljena je na 31,28%, a opstetrička anamneza bila je značajna kod 58,28% trudnica. Kod 62,42% trudnica ishod je bio normalan, kod 18,49% nepovoljan, dok je 10,98% rezultiralo pobačajem ili smrću fetusa. Vjerojatnost nepovoljnih ishoda trudnoće gotovo je ista u skupini trudnica koje su primale niskomolekularni heparin tijekom trudnoće kao i u skupini bez terapije (OR = 1,16, 95% CI 0,59-2,30, P = 0,65).

Zaključak: Uz pažljivu procjenu rizika, individualizirane planove liječenja i pažljivo praćenje, većina žena s ovim stanjima može postići uspješan ishod trudnoće.

Ključne riječi: trombofilija, trudnoća, heparin niske molekularne težine