doi: 10.5505/abantmedj.2016.94803

Abant Medical Journal

Derleme / *Review*

Volume Cilt 5 *Issue* Sayı 1 *Year* Yıl 2016

Gebelikte kalıtsal trombofili ve tromboprofilaksi

Hereditary thrombophilia and thromboprophylaxis in pregnancy

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Özet

Amaç: Kalıtsal trombofilik defekti olan gebelerde yaygın olarak kullanılan antikoagulan tedavilerin maternal venöz tromboembolizm ve olumsuz gebelik sonuçlarına etkisini araştırmaktır.

Gereç ve Yöntemler: "Kalıtsal trombofili", "tromboprofilaksi", "antikoagulan tedavi", "gebelik", "venöz tromboembolizm" anahtar kelimeleri ile literatür taraması yapıldı.

Bulgular: Trombofili daha çok venöz olmak üzere arterio venöz trombotik olaylara genetik yatkınlık olmasıdır ve gebelikte risk artar. Gebelikte en sık görülen kalıtsal trombofili nedenleri faktör V Leiden, protrombin ve metilentetrahidrofolat redüktaz gen mutasyonlarıdır. Geçirilmiş venöz tromboemboli öyküsü, antitrombin eksikliği, kombine defekt, homozigot veya birleşik heterozigot faktör V Leiden ve protrombin gen mutasyonları olanlar yüksek riskli hastalardır. Bu hastalarda, antikoagulan tedavi venöz tromboembolizmin önlenmesinde ve tedavisinde endikedir. Trombofili ile tekrarlayan gebelik kaybı, preeklampsi, fetal büyüme kısıtlılığı ve ablasyo plasenta gibi olumsuz gebelik sonuçları arasında nedensel bir ilişki olup olmadığı tartışmalıdır. Retrospektif, vaka-kontrol çalışmalar ılımlı bir ilişki ortaya koyar iken, prospektif kohort çalışmalar ile bu ilişki kanıtlanmamıştır.

Sonuç: Kalıtsal trombofilide, VTE öyküsü olanlarda ve yüksek riskli gruplarda uygulanan tromboprofilaksinin özellikle tekrarlayan gebelik kayıpları gibi olumsuz gebelik sonuçlarına etkisini ortaya koymak için kalıtsal trombofilinin düşük riskli subgruplarına yönelik daha geniş hasta gruplarında, prospektif, çift-kör, randomize çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: trombofili, tromboprofilaksi, antikoagulan tedavi, gebelik, venöz tromboembolizm

Abstract

Objective: To investigate the effect on maternal venous thromboembolism and negative pregnancy outcomes of widely-used anticoagulant treatments in pregnancies with hereditary thrombophilic defect.

Material and Methods: A scan of literature was made using the key words of 'thrombophilia', 'thromboprophylaxis', 'anticoagulant treatment', 'pregnancy', and 'venous thromboembolism'.

Results: Thrombophilia is a genetic tendency to arterio-venous thrombotic events, primarily venous and in pregnancy the risk is increased. The causes of hereditary thrombophilia, which is most often seen in pregnancy, are factor V Leiden, prothrombin and methylentetrahydrofolate reductase gene mutations. High risk patients are those with a history of venous thromboemboli, antithrombin deficiency, combined defect, homozygote or combined heterozygote factor V Leiden and prothrombin gene mutations. In these patients, anti-coagulant treatment is indicated in the prevention and treatment of venous thromboembolism. It is a matter of debate as to whether or not there is a causal relationship between thrombophilia and negative outcomes of pregnancy such as recurrent miscarriages, pre-eclampsia, fetal growth restriction and placental abruption. While retrospective, case-control studies have determined a moderate relationship, prospective cohort studies have not provided evidence of this relationship.

Conclusion: To determine the effect of thromboprophylaxis applied for hereditary thrombophilia in those with a history of VTE or high risk groups, on negative pregnancy outcomes such as recurrent miscarriages in particular, there is a need for prospective, double-blind randomised studies on larger patient groups with sub-groups of low-risk hereditary thrombophilia.

Keywords: Thrombophilia, thromboprophylaxis, anticoagulant treatment, pregnancy, venous thromboembolism

Introduction

Thrombophilia is a genetic tendency to arterio-venous thrombotic events, primarily venous. In cases of sinus vein thrombosis or where thrombosis is seen in infrequent areas such as mesenteric veins, in patients with recurring thrombosis attacks or in those where Warfarin-induced skin necrosis (WISN) develops, hereditary thrombophilia should be suspected. Endothelial damage, abnormal blood flow, and hypercoagulability, known as the Virchow classic triad provide a general viewpoint in the etiological explanation of thrombotic events. The most widely-known reason of the

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Geliş tarihi / *Received*: 01.06.2015 **Kabul tarihi / Accepted:** 19.06.2015 **Çıkar Çatışması / Conflict of Interest:** Yok / None

hypercoagulability leg of the triad is hereditary or acquired thrombophilia causing an abnormal coagulation and fibrinolitic system.

Clinically important hereditary thrombophilia (HT) types which cause defects in the physiological anticoagulant pathway are antithrombin (AT), protein C (PC) and protein S (PS) deficiencies. In addition, factor V Leiden (FVL) mutation, activated protein C (APC) with factor Va which can not be inactivated, cause resistance in the physiological anticoagulant pathway. Prothrombin G20210A gene mutation (PGM) results in over-production of procoagulants and is another widespread thrombophilic disorder causing 10% of hereditary thrombophilia. Another subgroup of HT is homozygote and heterozygote methylentetrahydrofolate reductase (MTHFR) gene mutations (MTHFR C677T and A1298C) and although recent studies have reported that hyperhomocysteinemia (fasting level >15micromol/L) is the most common cause, high homocystein levels have been determined as the lowest risk factor for VTE (1). However, there may be a relationship with recurrent miscarriages (2). Increased homocystein can be reduced with the adminstration of folate together with vitamins B12 and B6.

In pregnancy, increased fibrinogen, vWF, Factor II, VII, VIII and X, increased APC resistance in the 2nd and 3rd trimester, decreased PS in addition to increased activity of fibrinolytic inhibitors such as TAFI (thrombin-activated fibrinolytic inhibitor), and plasminogen activator inhibitor types 1 (PAI-1) and 2 (PAI-2) cause an increase in coagulation (3, 4). At the same time, when there is stasis in the lower extremity veins, reduced mobility causing abnormal blood flow and particularly with a caesarean birth this completes the thrombosis triad by forming endothelial damage. As a result, VTE is seen in 0.06% of pregnancies (1:1627 births) (5) and compared to non-pregnant females, there is a 6-fold greater VTE risk in pregnancy (6).

If possible, females with a history of VTE should be screened for hereditary and acquired thrombophilia before pregnancy. The timing of scan testing is important. During an acute thrombotic event, the natural anticoagulant levels are reduced. Heparin reduces AT levels and vitamin K antagonists such as Warfarin lower PC and PS levels. Therefore, scanning of acute thrombosis should not be applied, nor at a time when the patient is taking anticoagulant treatment. Physiologically low levels of PS in pregnancy make it difficult to diagnose PS deficiency.

It is a matter of debate as to whether or not there are benefits to anticoagulant therapy and whether or not there is a causal relationship between HT and negative outcomes of pregnancy, which have been experienced by HT patients such as recurrent miscarriages associated with a history of placental dysfunction, pre-eclampsia, fetal growth restriction and placental abruption. However, anticoagulant therapy is indicated both for prophylaxis and treatment purposes in patients with VTE history and in the prevention of pregnancy complications in patients with antiphospholipid antibody syndrome (AAS) (7, 8). The aim of this review was to discuss the effects on maternal VTE and negative pregnancy outcomes in previous studies conducted on anticoagulant therapy which is widely used in pregnancies with hereditary thrombophilic defect.

Hereditary Thrombophilia and Pregnancy Complications

It is a matter of debate as to whether or not there is a causal relationship between thrombophilia and negative outcomes of

pregnancy such as recurrent miscarriages, preeclampsia, fetal growth restriction and placental abruption. While retrospective, case-control studies have determined a moderate relationship, prospective cohort studies have not provided evidence of this relationship. In a study by Sanson et al of 60 patients determined with HT, of 188 pregnancies, 42 (22.3%) resulted in miscarriage or stillbirth whereas in the control group of 69 patients without HT, only 23 of 202 pregnancies (11.1%) had the same negative outcomes (RR 2.0, 95%CI, 1.2-3.3) (9). Said et al examined 1707 nulliparous women and in a scan for HT, heterozygote mutation was determined for FVL in 5.39% and for PGM in 2.38%. In these patients determined with HT, VTE was not observed. In the same study, the negative outcomes of pregnancy observed in 136 (8%) patients were not determined to be related to HT and it was reported that asymptomatic HT patients could have successful pregnancy outcomes (10).

Fetal Loss

The pregnancy complication most related to HT and the effect on pregnancy outcomes of anticoagulants is early or late fetal loss. After the relationship between fetal loss and thrombophilia was identified in a study by Sanson et al (1996), the use of thromboprophylaxis became more common in these patients (9). In the 2005 LIVE-ENOX study, the live birth rate was determined to have increased at the same rates from 20% to 75-80% with 40mg and 80mg enoxaparin (11). The relationship was examined between fetal loss and thrombophilic disorders in a 2003 meta-analysis which included 31 case-controlled and cross-sectional studies from 1975-2002, and the 95% CI and total odds ratio (OR) results are given below:

After discounting other reasons for fetal loss, FVL was related with early (first 13 weeks) (OR 2.01, 95% CI 1.13-3.58) and late (after 22 weeks) fetal loss, and recurrent miscarriages (OR 7.83, 95% CI 2.83-21.67) and non-recurrent late (after 19 weeks) (OR 3.26, 95% CI 1.8-5.8) fetal losses.

- APC resistance is related with early recurrent miscarriage (OR 3.48, 95% CI 1.58-7.69)
- PGM is related with early recurrent miscarriage (OR 2.56, 95% CI 1.04-.29) and non-recurrent late fetal losses (OR 2.30, 95%CI 1.09-4.87).
- PS deficiency is related with recurrent miscarriage (OR 14.7, 95% CI 0.99-218) and non-recurrent late fetal losses (OR 7.39, CI 1.28-42.63).
- No significant relationship was determined between fetal losses and MTHFR mutation, or PC and AT deficiency (1).

The European Prospective Cohort on Thrombophilia (EPCOT) study published 1 year after that meta-analysis was a prospective study researching the relationship between HT and fetal loss and the effect of thromboprophylaxis on pregnancy outcomes. The study results were as follows:

- A comparison was made of fetal loss and the effect of thromboprophylaxis in 131 patients with FVL or AT, PC, PS deficiency and 60 control subjects
- In patients with thrombophilia who were not using anticoagulants and had no history of fetal loss, there was a slight increase in fetal loss (in comparison with the control group, FVL RR: 1.4, AT deficiency RR: 1.6)
- Thrombophilia is responsible for late fetal losses in particular. The benefit of prophylactic anticoagulants was not significant in 83 HT patients (2).

In both studies, a relationship was determined between HT and miscarriages.

As the EPCOT study could not clarify the effect of prophylactic anticoagulants on pregnancy losses, there is a need for further prospective studies with a greater number of cases of different types of HT and combined defects.

A summary of randomised, controlled, double-blind, multi-centre studies of different anticoagulant regimes in patients with thrombophilia but no history of recurrent miscarriages is shown in Table 1.

researching the relationship between RFG and HT patients with homozygote or heterozygote FVL (12 case –control and 4 cohort studies) or PGM G2021A (11 case-control studies) and homozygote MTHFR C677T (10 case-control and 2 cohort studies) mutations, no evidence-based significant relationship was determined (18)

Table 1. The live birth-rate results of randomised, controlled, double-blind, multi-centre studies odf different anticoagulant regimes in patients with thrombophilia but no history of recurrent miscarriages

Study	No of patients	Miscarriage n (%)	Treatment groups	Live birth rates (%)	P value
HepASA (2009)	88	2 (100)	LMWH + LDA LDA	77.8 79.2	0.75
ALIFE (2010)	299	2 (40.1) ≥3 (59.9)	LMWH + LDA LDA Placebo	69 62 67	0.63
SPIN (2010)	294	2 (57.1) ≥3 (42.9)	LMWH + LDA Placebo	78 80	0.85
HABENOX (2011)	207	2 (1.0) ≥3 (99.0)	LMWH + LDA LDA LMWH	65 61 71	0.45

HepASA (14): Heparin and Aspirin, ALIFE (15): Anticoagulants for Living Fetuses, SPIN (16): Scottish Pregnancy Intervention, HABENOX (17): Low Molecular Weight Heparin and Prevention of Habitual Abortion, LMWH: Low-molecular-weight heparin, LDA: Low dose aspirin

In the ALIFE study, Kaandrop et al randomised pregnant patients with unexplained recurrent miscarriages into 3 groups (Nadroparin 2850 IU+ low dose aspirin (LDA); LDA; Placebo) of 13, 17 and 17 HT patients. Live birth rates were reported as 62-69% (15). The SPIN study comprised only 10 HT pregnant patients with a history of 2 or more miscarriages [8 FVL (5 treatment, 3 control), 2 PGM (1 treatment, 1 control)]. Pregnancy losses were reported at 22% in the treatment group and 20% in the control group (16). However, in both studies the number of HT patients was insufficient to be able to evaluate the effect of thromboprophylaxis and recurrent miscarriages on HT.

Fetal growth restriction (FGR)

The relationship between thrombophilia and RFG is not clear. In a meta–analysis

Preeclampsia

Although some clinical studies have determined a relationship between pre-eclampsia and FVL mutation, several case-controlled studies have not shown this relationship (19).

Placenta Ablatio

There is no consistent relationship between HT and placental abruption (3).

Hereditary Thrombophilia and Maternal Venous Thromboembolism

The VTE risk in patients increases when there is a personal or family history of VTE, in pregnancy, in hereditary or acquired thrombophilia, with immobilisation, obesity, varicose veins, cigarette smoking and in general medical events such as surgery and some haematological diseases (20). The most

significant risk factor is a history of VTE in the patient or a first-degree relative (21). Of VTE cases in pregnancy, 50% are

hereditary or acquired thrombophilia (22). While patients with natural anticoagulant deficiencies, homozygote FVL mutation, combined thrombophilic defects and a positive family history of VTE have earlier onset and recurring attacks of VTE, in the more frequently seen HT types such as heterozygote FVL or PGM, the VTE risk is lower (23).

To define the VTE risk in pregnancy according to specific thrombophilic type with personal and family history, the British Committee for Standards in Haematology (BCSH), separated HT patients into 3 categories (20). Treatment choices and durations are defined by the patient risk category. These risk groups and recommended treatments are summarised in Table 2.

antithrombin effect, UFH rapidly inhibits thrombin and all the series protease clotting factors apart from activated factor X (X_a) and factor VII_a (24). UFH haas been used for many years as prophylaxis and treatment for VTE in non-pregnant patients. High-molecular weight (mean 15000 dalton), can not pass into the placenta (25) and can be used in pregnancy. Rapid effects in the treatment of massive pulmonary embolism and that application can be made by intravenous infusion following bolus dose are reasons for primary selection. However, as treatment with LMWH does not require as much monitorisation as UFH, it can be administered to outpatients.

In addition lower rates of complications such as heparin-induced thrombocytopenia (HIT), osteopenia, or haemorrhage are significant advantages of LMWH (26, 27). In patients who develop HIT, heparin is terminated and then

Table 2. Recommended thromboprophylaxis and treatment regimes in pregnancy according to the VTE history and thrombophilia type

Risk	VTE history and thrombophilia scan	Prophylaxis and treatment	Dose
High risk	VTE in current pregnancy History of recurrent VTE Previous AAS and thrombosis (arterial or venous) or recurrent miscarriages VTE history and high risk thrombogenic thrombophilia (AT deficiency, combined defect, homozygote or combined heterozygote FVL and PT mutations)	Antenatal and postnatal 6 -week **therapeutic dose** LMWH	Enoxaparin(100$_{unit/mg}$): 40 mg at 12-hr intervals or 1 mg/kg at 12-hr intervals with Deltaparin: 5000 units at 12-hr intervals or 90 units/kg at 12-hr intervals
Moderate risk	VTE history and low-risk thrombophilia (PC and PS deficiency, heterozygote FVL or PT mutations) Asymptomatic high-risk thrombogenic thrombophilia	Antenatal and postnatal 6 -week **prophylactic dose** LMWH	Enoxaparin(100$_{unit/mg}$): 40 mg at 24-hr intervals with Deltaparin: 5000 units at 12-hr intervals
Low risk	Recoverable risk factor (OKS, surgery etc) together with 1 incidence of VTE Asymptomatic low-risk thrombogenic thrombophilia	Postnatal 6-week **prophylactic dose** LMWH	Enoxaparin(100$_{unit/mg}$): 40 mg at 24-hr intervals with Deltaparin: 5000 units at 12-hr intervals

VTE: Venous thromboembolism, AT: Antithrombin, FVL: Factor V Leiden, PC: Protein C, PS: Protein S, AAS: Antiphospholipid antibody syndrome,

Antcoagulant Treatment Choices

The number of potential therapeutic anticoagulants is increasing. However, not all of these are safe for use in pregnancy. Clinical experience has shown that there are advantages to low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH). By increasing the

danaparoid and r-hirudin can be used as anticoagulants. Danaparoid should be the primary choice as r-hirudin passes into the placenta in pregnant patients (28, 29). If bleeding develops with the treatment doses of UFH or LWMH, treatment is halted and antagonising effects can be

made with protamin sulfate (1 mg/100$_{unit}$, maximum 50 mg) (30).

Warfarin is a vitamin K antagonist oral anticoagulant. Warfarin-induced skin necrosis (WISN) may be caused by inhibition of the natural anticoagulants PC and PS besides vitamin K-associated factors II, VII, IX and X. As Warfarin passes into the placenta causing embryopathy characterised by central nervous system abnormalities, nasal hypoplasia and epiphyseal effects, it should not be used in pregnancy. Chan et al reported congenital defects at the rate of 6.4% in patients using Warfarin throughout pregnancy because of mechanical heart valve (MHV) disease (31). The risk of warfarin-associated embryopathy is markedly reduced if warfarins is used after the first trimester, and lower among patients whose warfarin doses do not exceed 5 mg per day (32). In another prospective cohort study of 250 pregnant patients with MHVs, 150 patients continued warfarin throughout their pregnancies; there were no incidences of valve thrombosis or Warfarin-induced fetal malformations among this group in comparison to those receiving UFH (33).

Post-partum thromboprophylaxis

Post-partum treatment is just as important as antepartum treatment. Patients who are diagnosed with VTE while pregnant should continue for at least 6 months after diagnosis and those taking a prophylactic dose of LMWH should continue anticoagulation with Warfarin or LMWH for 6 weeks postpartum. LMWH, UFH and Warfarin can be used safely by breast-feeding mothers (19).

Conclusions

- Hereditary thrombophilia in pregnancy increases thromboembolic complications, especially in high-risk patients.
- Anticoagulants should be administered antepartum and postpartum to patients with a history of VTE secondary to thrombophilia.
- As pregnancy is an independent acquired risk factor for VTE, in patients with a history of hereditary thrombophilia, or even if there is no previous history, anticoagulation is potentially beneficial in respect of at least protecting against pulmonary embolism.
- Personal and family history is important in VTE.
- As there is insufficient evidence of the relationship between MTHFR mutation and fasting homocystein level and negative pregnancy outcomes, scanning is not recommended.
- In patients determined with early recurrent or late non-recurring fetal loss and hereditary thrombophilia, there is insufficient evidence of improvements in pregnancy outcomes for the routine use of LMWH.
- The reliability of studies is reduced when numbers are low, and studies are observational, non-randomised and with no appropriate control groups.
- Postpartum prophylaxis is at least as important as antepartum prophylaxis to protect against VTE coplications of hereditary thrombophilia.
- There is a need for further prospective, double-blind, randomised studies with larger patient groups, especially to examine subgroups of thrombophilia.

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