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Inherited thrombophilia and thromboprophylaxis: a retrospective analysis of pregnancy outcomes in 106 patients

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Summary

Objective: Low-molecular-weight heparin (LMWH) and low-dose aspirin (LDA) given in combination were evaluated in females with five commonly inherited thrombophilia polymorphisms to address unexplained recurrent pregnancy loss (RPL). *Materials and Methods:* After excluding other causes of RPL, 106 of 183 females suffering RPL and diagnosed with inherited thrombophilia were studied along with 62 healthy, age-matched control subjects carrying one or more pregnancies successfully (no gestational complications or abortion). Test patients were given a combination of LMWH and LDA. All participants were screened for five thrombophilic mutations: factor V Leiden G1691A, prothrombin (FII) A20210G, PAI-1 4G/5G insertion/deletion, and two methylenetetrahydrofolate reductase (MTHFR) polymorphisms (C677T and A1298C). *Results:* With thromboprophylaxis, 73 of 84 (86.9%) pregnancies succeeded, representing a significant increase in the rate of live births (*vs*. 232 prior losses). Of the five test panel mutations, three or more (homozygous and/or heterozygous) were observed in 48 test patients (45.3%), whereas only three control subjects (4.8%) were similarly affected ($p < 0.05$). Frequencies of all five mutations were significantly higher in test patients (*vs*. controls), with PAI-1 4G/5G and MTHFR (C677T and A1298C) identified via binary logistic regression as independent correlates of habitual abortion. *Conclusion:* The risk of RPL increases with three or more homozygous or heterozygous genotypes in inherited thrombophilia, especially with PAI-1 4G/5G and MTHFR (C677T and A1298C). As in acquired thrombophilia, LMWH/LDA combination treatment may increase live birth rates in patients with inherited thrombophilia.

Key words: Inherited thrombophilia; Thromboprophylaxis; Recurrent pregnancy loss; Low-molecular-weight heparin; Low-dose aspirin.

Introduction

Recurrent pregnancy loss (RPL), defined as at least three or more (two in some studies) consecutive pregnancy losses (usually in the first trimester), is among the most common causes of female infertility, affecting 1–2% of women of reproductive age [1]. Because the etiologies of RPL vary widely, clinical investigations may be extensive and costly. Given that the study of the fetus/embryo is not feasible in this context, studies are limited to parental analysis. Once endocrine disorders (i.e., ovarian dysfunction, thyroid dysfunction, hypopituitarism, and diabetes), uterine malformations, chromosomal abnormalities, inflammatory diseases (especially systemic lupus erythematosus), and infectious diseases are excluded, one of the most common factors is inherited thrombophilia [2]. In fact, 50–65% of women with a history of unexplained pregnancy loss suffer from inherited or acquired thrombophilia and may benefit from thromboprophylaxis [3, 4].

Pathophysiologic mechanisms in thrombophilia involve placental microcirculatory thrombosis with a heightened hypercoagulable state during pregnancy [5]. As a result, venous thromboembolism, preeclampsia, intrauterine growth retardation, and fetal loss are apt to occur more frequently in patients with inherited thrombophilia. The latter is attributable to a distinct group of genetic mutations, most of which are inherited as autosomal dominant traits and lead to hypercoagulable states, namely factor V Leiden (FVL) G1691A, prothrombin (FII) G20210A, plasminogen activator inhibitor type 1 (PAI-1) 4G/5G insertion/deletion polymorphism, and hyperhomocysteinemia with methylenetetrahydrofolate reductase (MTHFR) C677T and A1298C mutations. Protein S, protein C, and antithrombin deficiencies may also result in hypercoagulable states. As acquired thrombophilic defects, antiphospholipid antibodies [lupus anticoagulant (LA), antiβ2 glycoprotein-1 antibodies (antiβ2GP1 Abs), and anticardiolipin antibodies (aCL)] are now regarded as important, treatable causes of RPL. In such instances, antithrombotic therapies have helped to promote successful pregnancies [6, 7].

The relationship between acquired thrombophilia and RPL is well established, but studies of RPL developing in inherited thrombophilia report conflicting results with respect to the efficacy of thromboprophylaxis [8]. Hence, the present authors' intent was to examine the effects on live birth rates of low-molecular weight heparin (LMWH) and low-dose aspirin (LDA) given in combination to pa-

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tients with five commonly inherited thrombophilic polymorphisms and RPL. Age-matched healthy subjects with no history of abortions or gestational complications were selected as controls.

Materials and Methods

Patients registering two or more lost pregnancies (early or late miscarriages or stillbirths) for no reason other than thrombophilia qualified for the study. All prior lost pregnancies were verified by positive hCG (urine or serum) plus ultrasound or uterine curettage with histologic confirmation. Pregnancy loss was viewed as early (gestational week 13+6) or late (gestational weeks 14–21+6) miscarriage, whereas stillbirth was equated with pregnancy loss after 22 weeks of gestation. Infant survival beyond the 28-day neonatal period constituted a live birth.

Exclusion criteria were extraneous presumptive etiologies as follows: 1) abnormal blood karyotype in either partner; 2) lethal fetal defect; 3) infectious disease during pregnancy; 4) known erythroblastosis fetalis; 5) autoimmune disease (antiphospholipid antibodies or idiopathic thrombocytopenic purpura); 6) trauma during pregnancy; 7) tobacco consumption (≥ ten cigarettes/day); 8) abnormal uterine anatomy by hysterosalpingography, hysteroscopy, or uterine hydrosonography; 9) endocrine disorder (thyroid dysfunction, hyperprolactinemia, luteal insufficiency, polycystic ovary syndrome, or diabetes mellitus); 10) obesity; 11) single abortion; 12) history of epilepsy; 13) renal or hepatic insufficiency; and 14) thrombocytopenia. In fact, any medical disease with a potential to impact the outcome of pregnancy was grounds for exclusion.

Ultimately, 106 out of 183 females suffering RPL and diagnosed with inherited thrombophilia were recruited in the study. Sixty-two healthy, age-matched women with one or more successful pregnancies, no gestational complications (intrauterine growth restriction, stillbirth, or abruptio placentae), and no abortions were enrolled in the study as control subjects. All participants were seen as outpatients in the Department of Obstetrics and Gynecology at Mevlana University in Turkey, between 2012 and August 30, 2015

Patients in the study group were prescribed a combination of subcutaneous LMWH (enoxaparin sodium 0.4 ml, 4,000 IU, once daily) and oral LDA (100 mg/day). Once starting enoxaparin (early in the fourth week of amenorrhea after positive pregnancy test), patients injected their abdomens or shoulders systematically, and platelets were checked at each weekly visit for heparin-induced thrombocytopenia. All patients were given folic acid tablets (400 mcg) daily until week 13 of gestation. Patients with threatened abortion symptoms such as vaginal bleeding, lower abdominal pain, and subchorionic hematoma at ultrasonography also received oral micronized progesterone (100 mg, twice daily until week 12 of gestation). Physical examinations were carried out during the first visit to determine body mass index (BMI) and blood pressure. Patients were monitored at weeks 6, 8, 11, 14, 18, 24, 28, 32, 36, and 38 of gestation. During antenatal visits, patients underwent routine obstetric ultrasound and laboratory investigations. LDA was abandoned at week 36 of gestation, but enoxaparin was continued until the first signs of labor.

To qualify for the study, other potential etiologic factors were excluded. A total of 168 participants were tested for five thrombophilic mutations: FVL (G1691A), FII (A20210G), PAI-1 4G/5G, and MTHFR (C677T and A1298C). All tests for antiphospholipid antibodies were negative. A blood DNA purification kit was utilized to extract genomic DNA from EDTA-anticoagulated whole blood samples. Real-time polymerase chain reaction (PCR) conducted was used to determine thrombophilic genotypes other than PAI-1. PAI-1 4G/5G I/D was assayed using "allele-specific amplification" PCR (Muetze *et al.*) based on internal control primers specific for the 4G allele (forward: 5'-TGC AGC CAG CCA CGT GAT TGT CTA G-3'; reverse: 5'-AAG CTT TTA CCA TGG TAA CCC CTG GT-34G and 5'- GTC TGG ACA CGT GGG GA-3') and for the 5G allele (forward: 5'-TGC AGC CAG CCA CGT GAT TGT CTA G- 3', reverse: 5'-AAG CTT TTA CCA TGG TAA CCC CTG GT-3', and 5'-GTC TGG ACA CGT GGG GG-3') [9]. As such, females carrying these specific alleles (heterozygous or homozygous) were considered to have inherited thrombophilia.

The primary measure of outcome was live birth rate, defined as survival beyond the 28-day neonatal period. Preeclampsia, abruption placentae, premature delivery (at 24–37 weeks), gestational age at birth (weeks), birth weight (grams), intrauterine growth restriction (birth weight < 2 SD), and adverse effects of therapy, such as bleeding, thrombocytopenia (platelet count < 100,000 / dl), and primary postpartum hemorrhage (> 500 ml blood loss), were assessed as secondary outcomes.

The prevalence of polymorphisms in test patients and control subjects were compared using the two-tailed Fisher's exact test and a Chi-square test; logistic regression was applied to analyze the effects of each polymorphism. The Pearson's chi-square test was instrumental, with significance set at $p < 0.05$. Only one outcome, live birth rate, was investigated. No secondary outcomes were statistically analyzed. Standard software was utilized for all calculations (SPSS v20.0), expressing data as the mean ± SD.

Results

Of 168 participants, 106 had suffered RPL and had inheritable thrombophilia constituted study group; whereas the remaining 62 patients who had successful delivery, without history of abortion constituted the control group. The average age of the subjects was 27.9 ± 5.7 (range, 18–40) years in test patients and 29.4 ± 5.8 (range, 19–39) years in control subjects, which did not differ significantly ($p = 0.1$). In the test group, prior pregnancy losses and live births totalled 232 (mean, 2.8 ± 1.3, range, 2–10) and 38 (single child, 27; two children, eight), respectively. Seventy-one patients (66.9%) had no live children. Outcomes prior to enrollment were poor, with live births in approximately 14% of pregnancies. Although 22 of the test patients were not actually pregnant, thrombophilia panels were run due to habitual abortion. These particular patients were excluded from the live birth rate calculations, because they did not receive thromboprophylaxis. A history or early pregnancy loss was recorded in 104 test patients (98.1%), whereas 12 patients (11.3%) had suffered late pregnancy loss and five patients (4.7%) had experienced stillbirths. With respect to control subjects, 25 were nulliparous and 37 were multiparous. There were no miscarriages, and there were a total of 97 live children.

The first pregnancies following treatment (one twin pregnancy and one with RPL linked to portal vein thrombosis) in 73 of 84 patients (86.9%) with a history of RPL were live births. No stillbirths/neonatal deaths or fetal anomalies were

Table 1. — *Patient characteristics and outcomes of pregnancies at time of referral and after thromboprophylaxis in test females with recurrent pregnancy loss (RPL) and control subjects.*

Characteristic	RPL (n=106)			Controls (n=62)			*p* value
	Mean ± SD	Range	n (%)	Mean ± SD	Range	n (%)	
At time of referral							
Age	27.9±5.7	18–40		29.4±5.8	19–39		0.10
Mean number of EPL[a]	2.6±1.2	2–8	104 (98.1%)	-			
Mean number of LPL[b]	0.1±0.4	0–2	12 (11.3%)	-			
Mean number of stillbirths/ neonatal deaths	0.06±0.3	0–2	5 (4.7%)	-			
Total pregnancy loss[c]	2.8±1.3	2–10		-			
Total live births			38			97	
Live birth rate, unadjusted			38/270 (14%)			97/97 (100%)	
≥ 4 previous losses			24 (22.6%)			-	
≥ 1 previous live birth			35 (33%)			62 (100%)	
After thromboprophylaxis[d]							
Live birth rate, unadjusted			73/84 (86.9%)				
Stillbirth/neonatal death			-				
EPL			11/84 (13.1%)				
LPL			-				
Gestational age (weeks)	38.1±2.5	34–41	82 (97.6%)	38.3±2.7	33–41	61 (98.3%)	0.90
Birth weight (g)	3224±362			3,245±351			0.70

[a]Early pregnancy losses (EPL), [b]Late pregnancy losses (LPL), [c]All pregnancy losses, [d]22 non-pregnant patients with a history of habitual abortions were excluded.

identified in any of the test patients given thromboprophylaxis. First-trimester abortions recurred in 11 patients (13.1%), and one pregnancy was terminated due to cystic hygroma. Karyotyping of products of conception was performed in seven of 12 miscarriages [normal, four; abnormal, one (48 XY, +13, +15); failed cultures, two]. No significant differences were observed between birth weights registered for test patients and controls (3224 ± 362.8 and 3245 ± 351.8 grams, respectively; $p = 0.7$). The details of demographics and outcomes of prior pregnancies are summarized in Table 1.

Analysis of DNA, isolated from peripheral blood samples collected in EDTA and carried out specifically for identifying FVL (G1691A), FII (G20210A), MTHFR (C677T and A1298C), and PAI-1 4G/5G I/D polymorphisms, is provided for all study participants (Table 2).

In binary comparisons, FVL (G1691A), FII (G20210A), PAI-1 4G/5G, and MTHFR (C677T and A1298C) differed significantly in test patients (*vs*. controls). Binary logistic regression analysis identified PAI-1 4G/5G and MTHFR (C677T and A1298C) as independent correlates of habitual abortion.

Homozygous and/or heterozygous mutations were observed in all 102 test patients (54 homozygous mutations in one or two thrombophilia panels) and in 58 of 62 control subjects (23 homozygous mutations in one or two thrombophilia panels). However, three or more homozygous and/or heterozygous mutations (in panel of five) were observed in 48 test patients (45.3%), but in only three control subjects (4.8%) ($p < 0.05$), constituting a significant difference. Coexistence of mutations in the 11 test patients, for whom thromboprophylaxis failed and in the other 73 patients who had live births, did not differ significantly ($p > 0.05$) (Table 3).

Table 2. — *Frequencies of genotypic polymorphisms in patients with recurrent pregnancy loss (RPL) and control subjects.*

Gene	RPL (n=106)	Controls (n=62)	*p* value*
FVL (G1691A)			
Normal homozygous G/G	80 (75.4%)	56 (90.3%)	0.018
Heterozygous G/A	23 (21.6%)	4 (6.5%)	
Mutant homozygous A/A	3 (2.8%)	2 (3.2%)	
FII (G20210A) (prothrombin)			
Normal homozygous G/G	93 (87.7%)	60 (96.8%)	0.047
Heterozygous G/A	13 (12.3%)	2 (3.2%)	
Mutant homozygous A/A	0	0	
MTHFR (C677T)			
Normal homozygous C/C	49 (46.2%)	37 (59.7%)	0.092
Heterozygous C/T	43 (40.5%)	20 (32.3%)	
Mutant Homozygous T/T	14 (13.2%)	5 (8.1%)	
MTHFR (A1298C)			
Normal homozygous A/A	26 (24.5%)	38 (61.3%)	0.000
Heterozygous A/C	65 (61.3%)	17 (27.4%)	
Mutant Homozygous C/C	15 (14.1%)	7 (11.3%)	
PAI-1 4G/5G I/D polymorphism			
Normal 5G/5G	21 (19.8%)	30 (48.4%)	0.000
Heterozygous 4G/5G	57 (53.7%)	21 (33.9%)	
Mutant Homozygous 4G/4G	28 (26.4%)	11 (17.7%)	

*Homozygous and heterozygous groups analyzed together.

No heparin-induced thrombocytopenia or allergies were seen or recorded during the trial. Test patients experienced

Table 3. — *Zygosity of factor V Leiden (G1691A), FII (G20210A), PAI-1 4G/5G, and MTHFR (C677T and A1298C) in patients with recurrent pregnancy loss (RPL) and control subjects.*

	RPL (n=106)	Controls (n=62)	*p* value
Homozygosity (mutant)			
None	52/106 (49.1%)	39/62 (62.9%)	0.211
1	48/106 (45.3%)	21/62 (33.9%)	
2	6/106 (5.7%)	2/62 (3.2%)	
Homozygosity and/or heterozygosity			
None	-	4/62 (6.5%)	0.000
1	17/106 (16%)	30/62 (48.4%)	
2	41/106 (38.7%)	25/62 (40.3%)	
3	32/106 (30.2%)	3/62 (4.8%)	
4	12/106 (11.3%)	-	
5	4/106 (3.8%)	-	

minor vaginal bleeding during first, second, and third trimesters, although such bleeding was largely a first trimester event and was mild (11.3%), without any need for blood transfusion. Subsequently, LMWH was discontinued until bleeding ceased completely. Any skin reactions, bruising, and itching at injection sites were resolved by switching sites. None of the neonates suffered hemorrhagic disease, intracranial hemorrhage, or thrombocytopenia.

Discussion

Acquired thrombophilia is a feature of antiphospholipid syndrome (APS), which occurs as a primary or secondary event in systemic lupus erythematosus. Diagnosis of APS is based on the presence of LA, antiβ2GP1, and aCL antibodies, and the use of LMWH/LDA together in this context usually enhances both fetal and mother outcomes [10]. Although the pathogenic mechanisms of antiphospholipid antibodies have been described [11], there is no real consensus on the pathophysiology or treatment of inherited thrombophilia. Once Dahlback *et al.* defined activated protein C (APC) resistance, Bertina *et al.* found that a single mutation in the factor V gene (known as factor V Leiden) was responsible. FVL is an autosomal-dominant mutation, with 12–15% prevalence in various populations [12, 13]. The risk of thrombosis is three- to eight-fold higher with heterozygous FVL status, increasing to 80-fold in homozygous states [13, 14]. APC resistance accounts for almost 50% of patients with inherited thrombophilia [12].

In a study conducted by Ivanov *et al.*, the prevalence of 4G/5G I/D was substantially higher in females with RPL (41.8%) *vs*. controls (26.8%) (OR=1.96, 95% CI: 1.05–3.69; $p = 0.034$) [15]. Subrt *et al.* also showed that the PAI-1 4G/4G homozygous genotype increases the risk of RPL, independent of a positive antiphospholipid antibody test [16]. The present study similarly identified MTHFR (C677T and A1298C) and PAI-1 4G/5G mutations as independent correlates of RPL (OR = 2.41, 95% CI: 1.13–5.12; $p = 0.022$; OR = 7.81, 95% CI: 3.49–17.4; $p = 0.000$, and OR = 6.67, 95% CI: 2.88–15.41; $p = 0.000$, respectively). According to Habibovic *et al.*, FVL (G1691A), FII (G20210A), MTHFR (C677T) mutations, and RPL share no associations, but the combined mutations may be linked to recurrent miscarriages [17].

The number of approaches for treating pregnant women with known thrombophilia has evolved over the years with varying success, including immunoglobulins, aspirin, and glucocorticoids. Unfortunately, none of these treatments have been very effective. Greer and Nelson-Piercy proved that LMWH does not cross the placenta, which makes it a safe and effective means of venous thromboembolic prophylaxis/treatment during all stages of pregnancy [18]. Low-level LMWH as antithrombotic therapy was endorsed at the Seventh American College of Chest Physicians (ACCP) Conference on Antithrombotic and Thrombolytic Therapy [19]. Without therapeutic intervention, the percentage of pregnancies resulting in live births is only 20–28% [20]. No maternal and fetal serious side effects related to combined LMWH/LDA were observed during the course of the present study, and a live birth rate of 86.9% was achieved. Prior to this trial, only 38 live births in 270 pregnancies (14%) were accrued in our test patients.

Mitic *et al.* achieved success in 29 of 38 pregnancies through thromboprophylaxis, reflecting significant improvement (76%) over 81 prior pregnancy losses [21]. In addition, Giancotti *et al.* reported that LMWH or LMWF plus aspirin increased the rate of live births effectively in patients with RPL and positive thrombophilic scans [22]. Taken together with the present results (i.e., 86.9% live birth rate) in a broader group of patients, it appears that the combination treatment of LMWH/LDA is a promising therapeutic approach for women with inherited thrombophilia and RPL.

In the Live-Enox study, pregnancy outcomes and drug safety were assessed in females with thrombophilia and histories of RPL who were given enoxaparin (40 mg and 80 mg daily doses). Regardless of dose, outcomes and safety proved equivalent, culminating in live birth rates of 84% and 78%, respectively [20]. Use of LMWH early as thromboprophylaxis also brought success in reducing early and late spontaneous abortions for at least 50% of patients in another study [23]. Likewise, the rate of live births increased significantly (by 9.76-fold) in females given LMWH compared with placebo in the Qublan *et al.* study (RR = 9.76, 95% CI: 1.31–72.86; $p = 0.03$) [24]. Finally, when patients given aspirin only were compared with others taking LMWH, a statistically significant increase in live birth rate was documented by Gris *et al.* (RR = 3.0, 95% CI: 2.10–4.28; $p < 0.00001$) [25]. In all these trials, the use of LMWH in pregnant women with inherited thrombophilia proved superior to control interventions (placebo and aspirin) in terms live birth rates achieved.

When Laskin *et al.* compared female patients given LMWH and aspirin with other patients given aspirin alone, they found no significant differences in live birth rates (RR = 1.01, 95% CI: 0.8–1.26; $p = 0.95$) [26]. Their findings were consistent with two other studies by Tan *et al.* [27] and Kovalevsky *et al.* [28], neither of which reported significant differences in treatment efficacies. In the present test patients, however, thromboprophylaxis increased the live birth rate significantly. Furthermore, three or more mutations (homozygous and/or heterozygous) out of five in a thrombophilia test panel coexisted at a significantly higher rate in patients with RPL than in control subjects. PAI-1 4G/5G and MTHFR (C677T and A1298C) mutations in particular were identified as independent variables, correlating with habitual abortion. In patients with a history of RPL, DNA screening for thrombophilia is therefore advisable. Infarction and impairment of chorionic villous vascularization are putative risk factors in inherited thrombophilia [29]. By initiating thromboprophylaxis at the earliest opportunity, the chances of a healthy pregnancy may increase. Indeed, the conflicting outcomes of these studies are perhaps due to discrepancies in the onset of treatment.

The benefit of thromboprophylaxis in this setting is best evaluated using a control group where treatment is withheld. For ethical reasons, however, this scenario is unacceptable but nevertheless detracted from the present study. On the same basis, it is impossible to avoid folic acid and progesterone in patients with threatened abortion co-therapies that are routinely used for antenatal care. Hence, some participants were exposed to a multiplicity of therapies, in addition to anticoagulants, clouding final therapeutic assessment. Still, the present comparison of live birth rates determined both before and after thromboprophylaxis does provide some index of treatment efficacy.

In conclusion, the data herein indicate that with three or more mutations (homozygous or heterozygous) out of the five that are frequently seen in inherited thrombophilia, especially PAI-1 4G/5G and MTHFR (C677T and A1298C), the risk of RPL is heightened. As in acquired thrombophilia, LMWH/LDA given in combination to patients with RPL and inherited thrombophilia may increase live birth rates. A multicenter collaboration (i.e., randomized, placebo-controlled study) is needed to corroborate the present findings and establish an evidence-based treatment protocol.

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