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The Impact of Inherited Thrombophilia Types and Low Molecular Weight Heparin Treatment on Pregnancy Complications in Women with Previous Adverse Outcome

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Purpose: To assess the distribution of births and spontaneous abortions, first-trimester abortion (FTA) and mid-trimester abortion (MTA), in untreated (n=128) and low molecular weight heparin (LMWH) treated pregnancies (n=50) of the same women with inherited thrombophilias and adverse pregnancy outcome (APO) in previous pregnancies. We particularly investigated the impact of LMWH on reducing the pregnancy complications in two thrombophilia types, "Conventional" and "Novel".

Materials and Methods: 50 women with inherited thrombophilia (26 Conventional and 24 Novel) and APO in previous pregnancies were included in the study. Conventional group included factor V Leiden (FVL), prothrombin G20210A (PT) mutations and antithrombin (AT), protein S (PS), and protein C (PC) deficiency, while the Novel group included methylentetrahydrofolate-reductase (MTHFR), plasminogen activator inhibitor-1 (PAI-1), and angiotensin converting enzyme (ACE) polymorphism. APO was defined as one of the following: preterm birth (PTB), fetal growth restriction (FGR), preeclampsia (PE), intrauterine fetal death (IUFD), placental abruption (PA) and deep venous thrombosis (DVT).

Results: There was no difference in distribution of births and spontaneous abortions between Conventional and Novel thrombophilia in untreated pregnancies (χ^2=2.7; p=0.100) and LMWH treated pregnancies (χ^2=0.442; p=0.506). In untreaed pregnancies thrombophilia type did not have any impact on the frequency of FTA and MTA (χ^2=0.14; p=0.711). In birth-ended pregnancies LMWH treatement reduced the incidence of IUFD (p=0.011) in Conventional and FGR, IUFD, and PTB in Novel thrombophilia group.

Conclusion: The equal impact of two thrombophilia types on the pregnancy outcomes and a more favorable effect of LMWH therapy on pregnancy complications in Novel thrombophilia group point the need for Novel thrombophilias screening and the future studies on this issue should be recommended.

Key Words: Thrombophilia, pregnancy outcome, LMWH

INTRODUCTION

Adverse pregnancy outcomes (APO) have recently been linked to inherited thrombophilias through extensive studies. However, conclusions regarding their association still remain inconsistent. Normal pregnancy is related with an acquired hypercoagulable state due to increased levels of coagulation factors, decreased levels of anticoagulants and decreased fibrinolytic activity.[1] This hypercoagulability may be exacerbated in women with heritable predisposition to thrombosis, known as thrombophilia, and may contribute to various pregnancy complica-

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tions such as venous thromboembolism (VTE), deep venous thrombosis (DVT), first trimester abortion (FTA), mid-trimester abortion (MTA), intrauterine fetal death (IUFD), preeclampsia (PE), placental abruption (PA), and fetal growth restriction (FGR).[2-6] The most common types of inherited thrombophilias are the following: factor V Leiden (FVL) mutation, prothrombin G20210A (PT) mutation, deficiency of protein C (PC), deficiency of protein S (PS) and the most thrombogenic, antithrombin (AT) deficiency. These conventional inherited thrombophilias can be identified in up to 50% of individuals with VTE, their impact on APO has been well explored and they are included in the routine thrombophilia screening.[7-10] The Novel inherited thrombophilias include methylentetrahydrofolate-reductase (MTHFR) gene C677T polymorphism,[11-14] polymorphisms of plasminogen activator inhibitor-1 (PAI-1)[15-18] and angiotensin converting enzyme (ACE)[16,19,20] polymorphism. Although they are not rarely encountered, their impact on APO is still controversial, available literature addressing this issue is limited and they are not routinely included in thrombophilia screening.

Due to available data indicating association between thrombophilias and APO, women with a history of pregnancy complications and inherited thrombophilias are often offered an anticoagulant therapy with low molecular weight heparins (LMWH), since they are most common, because of its safety, easy administration and a very low incidence of complications.[21-25]

In the current study the primary objective was to evaluate the distribution of births and spontaneous abortions, FTA and MTA, in all untreated and in the last LMWH treated pregnancies with regard to the Conventional and Novel thrombophilia types, in women with APO in previous untreated pregnancies. The secondary objective was to evaluate the impact of LMWH treatment in reducing the incidence of pregnancy complications in pregnancies ending in birth with regard to specific types of thrombophilia.

MATERIALS AND METHODS

This prospective cohort study included 50 women with any type of inherited thrombophilia and a history of APO and/or thromboembolic events in previous untreated pregnancies. The study was carried out between July 2008 and September 2012. Participants were recruited at the Department of Obstetrics and Gynecology, University Hospital Split, Croatia, which serves as a tertiary referral hospital with approximately 4500 deliveries per year. Institutional research and ethical approval was obtained before the commencement of the study (No. 003-08/12-03/002) and all included participants have signed an informed consent prior to the inclusion into the study.

APO in previous pregnancies was defined as: 1) three FTA (<12 weeks based on last menstrual period with previously proven fetal viability); 2) two FTA with at least one of the following pregnancy complications in their third pregnancy: (1) MTA defined as pregnancy loss between 12-21+6 weeks; (2) FGR defined by birth weight below the 5th percentile for gestational age and gender according to the criteria adopted for the local population characteristics;[26] (3) severe PE regardless of gestational age, defined as blood pressure >160/110 mm Hg, proteinuria >5 gr/24 hours; (4) HELLP syndrome in pregnancy or puerperium, defined by the presence of hemolysis, elevated serum aminotransferase concentrations and platelet count <100000 per cubic millimeter; (5) IUFD defined as fetal death ≥22 weeks; (6) PA; (7) preterm birth (PTB) defined as delivery before 37 weeks, and (8) thromboembolic event prior or during the pregnancy; 3) MTA; 4) IUFD; 5) pregnancy with some of the following complications: PE and/or HELLP, FGR, AP, and DVT (criteria are described above). Exclusion criteria were: 1) women older than 42 years; 2) presence of an acquired thrombophilia; 3) congenital uterine anomaly; 4) perinatal infections (TORCH); 5) diabetes mellitus, endocrine abnormalities, chronic hypertension, renal impairment or drug abuse; 6) multiple pregnancy; 7) abnormal first-trimester screening test for fetal abnormalities; 8) abnormal karyotype; and 9) fetal malformations.

Having satisfied the inclusive criteria, their subsequent pregnancy was awaited and LMWH was administered. All women were advised to take periconceptional folic acid supplementation. The thromboprophylaxis was initiated between 5th and 9th weeks of pregnancy, after proven fetal viability. Forty seven women were treated with dalteparin 2500 IU/day and three women, who started to receive therapy at another clinical center, with enoxaparin 40 mg/day. Between 25th and 28th weeks of pregnancy, the dosage was doubled; dalteparin 5000 IU/day and enoxaparin 80 mg/day. All women underwent regular antenatal examinations, including ultrasound and blood testing to detect LMWH induced thrombocytopenia. LMWH was continued for 6 weeks postpartum.

Statistics

For the analysis of the quality variables, χ^2 test and Fisher's exact test were used. $p \leq 0.05$ was regarded as significant. The analyses were carried out using statistics package Statistics 10.0 (StaSoft, Tulsa, OK, USA).

RESULTS

In the cohort of 50 women, the FVL mutation (all heterozygous) was identified in 13 (26%), PT mutation (all heterozygous) in 5 (10%), PC deficiency in 6 (12%), and PS deficiency in 6 (12%) women. MTHFR mutation (23 heterozygous and 2 homozygous) was identified in 25 (50%), PAI-1 polymorphism in 33 (66%) and ACE polymorphism in 25 (50%) women. Single mutated gene was found in 7 (14%), two mutated genes in 25 (50%), three mutated genes in 16 (32%), and four mutated genes in 2

(4%) women. Based on the thrombophilia type, the patients were divided into two groups: Conventional thrombophilia group (comprising of women with conventional and combined thrombophilias) including 26 women (52%) and Novel thrombophilia group including 24 women (48%).

As shown in Table 1, analysis of the pregnancy outcomes with respect to the type of thrombophilia in untreated and LMWH treated pregnancies revealed no significant difference in distribution of births and spontaneous abortions (χ^2=2.7; p=0.100), and even in the frequency of FTA and MTA (χ^2=0.14; p=0.711) in untreated pregnancies (128 untreated pregnancies of the cohort of 50 women before the inclusion in the study). After inclusion into the study, the next pregnancy was treated with LMWH, and 48 out of the 50 treated pregnancies ended in birth and only 2 spontaneous abortions, suggesting significant improvement in pregnancy outcomes by the LMWH treatment. Moreover, in the LMWH treated pregnancies there was no difference in distribution of births and spontaneous abortions with respect to the thrombophilia type (χ^2=0.442; p=0.506).

Analysis of specific pregnancy complications of pregnancies ending in birth in Conventional thrombophilia group (Table 2) revealed that LMWH treatment did not reduce the incidence of PTB (χ^2=1.143; p=0.284), FGR (χ^2=0.119; p=0.729), PE (χ^2=1.988; p= 0.158), PA (p=0.682), and DVT (p=0.432). However, LMWH treatment significantly reduced the incidence of IUFD (p=0.011).

Analysis of the impact of LMWH treatment on specific complications in pregnancies ending in birth in Novel thrombophilias group (Table 3) revealed that LMWH did not reduce the incidence of PE (χ^2=0.016; p=0.899), PA (p=1.0), and DVT

Table 1. Outcomes of Untreated and LMWH Treated Pregnancies Related to the Thrombophilia Type

	Thrombophilia type		*p* value*
	Conventional (n=26), n (%)	Novel (n=24), n (%)	
Total LMWH untreated pregnancies (n=128)			
Births (n=48)	19 (15)	29 (23)	0.100
FTA+MTA (n=80)	45 (35)	35 (27)	
FTA (n=66)	36 (45)	30 (38)	0.711
MTA (n=14)	9 (11)	5 (6)	
LMWH treated pregnancies (n=50)			
Births (n=48)	25 (50)	23 (46)	0.506
FTA and MTA (n=2)	1 (2)	1 (2)	

LMWH, low molecular weight heparin; FTA, first-trimester abortion; MTA, mid-trimester abortion.
*χ^2 test.

Table 2. The Impact of LMWH Treatment on Pregnancy Complications in Pregnancies Ending in Birth in Women with Conventional Thrombophilias

Outcome: BIRTH (n=48)	Conventional thrombophilias		*p* value*†
Pregnancy complications	No LMWH (n=19), n (%)	LMWH (n=25), n (%)	
Preterm birth	10 (52.6)	8 (32)	0.284*
Fetal growth restriction	8 (42.1)	13 (52)	0.729*
Preeclampsia	3 (15.7)	10 (40)	0.158*
Intrauterine fetal death	5 (26.31)	0	0.011†
Placental abruption	3 (15.7)	3 (12)	0.682†
Deep venous thrombosis	1 (5.26)	0	0.432†

LMWH, low molecular weight heparin.
*χ^2 test, †Fisher's exact test.

Table 3. The Impact of LMWH Treatment on Pregnancy Complications in Pregnancies Ending in Birth in Women with Novel Thrombophilias

Outcome: BIRTH (n=48)	Novel thrombophilias		*p* value*†
Pregnancy complications	No LMWH (n=29), n (%)	LMWH (n=23), n (%)	
Preterm birth	12 (41.37)	3 (13.04)	0.053*
Intrauterine growth restriction	16 (55.17)	4 (17.39)	0.012*
Preeclampsia	7 (24.13)	5 (21.73)	0.899*
Intrauterine fetal death	9 (31.03)	0	0.003†
Placental abruption	1 (3.44)	0	1.0†
Deep venous thrombosis	1 (3.44)	1 (4.34)	1.0†

LMWH, low molecular weight heparin.
*χ^2 test, †Fisher's exact test.

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(p=1.0). However, LMWH decreased the frequency of PTB at 95 % level of statistical significance (χ^2=3.73; p=0.053). The LMWH treatment also resulted in 3.2 times decreased incidence of FGR (χ^2=6.221; p=0.012). Lastly, there was no cases of IUFD in the treated pregnancies as opposed to 9 cases in the untreated pregnancies (p=0.003).

DISCUSSION

In the current study, we demonstrated that LMWH treatment significantly improved pregnancy outcomes and decreased the rate of spontaneous abortions irrespective of the type of thrombophilia. Moreover, analysis of the impact of LMWH treatment on the incidence of specific complications during pregnancies that ended in birth revealed that LMWH in Conventional thrombophilia reduced only the incidence of IUFD, while LMWH treatment in Novel thrombophilias reduced the incidence of FGR, IUFD, and PTB.

Primary objective

In the present study, we found that the type of thrombophilias (Conventional vs. Novel) did not influence the distribution of births and spontaneous abortions in the overall number of untreated pregnancies (n=128). Moreover, the distribution of FTA and MTA did not differ with regard to the thrombophilia type. We also found that LMWH treatment significantly improved the perinatal outcome (48 births and 2 spontaneous abortion), confirming our previous results.[27] We compared two groups of thrombophilias in LMWH treated pregnancies (n=50) and found no difference in distribution of births and spontaneous abortions.

In the current study, therefore, we rather unexpectedly found that Conventional and Novel thrombophilias have equal adverse impact on pregnancy outcome in women with APO in previous pregnancies. This is a rather novel finding, since there have been no studies on the analysis of the division of eight inherited thrombophilias into two groups. Also, a small number of similar studies presented conflicting results about the impact of Novel thrombophilias on APO.[11-20]

The pathophysiological link between thrombophilias in general and pregnancy complications was not unexpected. Processes of impaired implantation caused by deficient trophoblast invasiveness during angiogenesis of the placental blood vessels, enhanced trophoblast apoptosis and coagulation in the intervillous space develop independently of the thrombophilia type. Therefore, various types of thrombophilia should develop the same pattern of the disease. However, it still remains unexplained why some women with certain type of thrombophilia experience pregnancy complications, whereas the other women with the same thrombophilia type do not. Also, the reason remains unknown why the same woman may have regular and pathological pregnancies. There are two possible explanations for these questions: the existence of a still unidentified predisposition for development of disease that is only enhanced by the thrombophilias and co-existence of an additional, still unidentified thrombophilias (together with the known thrombophilias) that might enhance the impact of the existing ones. The fact that pregnancy complications occur earlier and more intensively in women with multiple thrombophilias supports the latter hypothesis.[28]

The equal distribution of FTA and MTA in both thrombophilia types can be explained by the fact that the placentation occurs in two phases, between the 8th and 12th and the 16th and 18th week of the pregnancy, and that the thrombophilia type does not have an impact on the time of the occurrence of miscarriage. These results support the hypothesis that the etiogenesis of the pregnancy loss results from poor implantation and placentation, regardless of the duration of pregnancy.

Secondary objective

Analysis of the impact of LMWH treatment on pregnancy complications in pregnancies ending in birth revealed that LMWH treatment in Conventional thrombophilias reduced the incidence of IUFD only, whereas LMWH treatment in Novel thrombophilias reduced the incidence of FGR, IUFD, and PTB.

Our present findings of the lack of a favorable impact of LMWH on the incidence of PE and FGR in women with Conventional thrombophilia are different from the results of previous small, non-randomized studies[21-23] as well as one multicentre randomized controlled study (RCS) which demonstrated small, but statistically significant reduction of PE and FGR in LMWH treated pregnancies in women with inherited thrombophilia and history of APO.[24] A possible explanation for such conflicting results might be found in different definitions of the pregnancy complications, different ethnical background and creation of an unrepresentative sample as a consequence. The small case control studies often include women with milder forms and later onset of disease, consequently observing reduced incidence of PE and FGR in subsequent LMWH treated pregnancies.[22,23] The principal strength of the only available RCS which demonstrated reduction of PE and FGR in LMWH treated pregnancies is the fact that the study examined only severe and early onset of PE and FGR.[24]

The results of previous studies on influence of LMWH treatment on pregnancy complications in Novel thrombophilias are very sparse and conflicting. A limited number of studies showed an association of Novel thrombophilias with mostly PE[13,19] and RPL,[14-16,20] with conflicting conclusions. Furthermore, the last published study with the largest sample number of nulliparous excluded the impact of PAI-1 polymorphism on APO.[17] Finally, there is only a single study analysing the impact of LMWH in women with ACE polymorphism and concluded that it reduces the incidence of PE.[25] Therefore, our present finding that LMWH treatment reduces the incidence of FGR, IUFD, and PTB in women with Novel thrombophilias constitutes

some novel data.

It should be emphasized that not a single case of IUFD was recorded in LMWH treated pregnancies regardless of the thrombophilia type: in untreated pregnancies, there were 5 cases of IUFD in Conventional group and even 9 cases of IUFD in Novel thrombophilia group. Improved outcome and reduced pregnancy complication may partially be due to intensive prenatal care in LMWH treated pregnancies.

The strengths of the current study include: 1) analysis of eight inherited thrombophilias in relation to APO; 2) thrombophilia division in two groups and its relation to APO; 3) very strict inclusive criteria; 4) clearly distinguished FTA and MTA; and 5) exclusion of women with acquired thrombophilia. The main limitations of the study are lack of control, untreated group of pregnant women and small sample size. The first limitation is common to all studies dealing with this topic, since it would be unethical to recruit participants and offer them placebo after devastating failures in previous pregnancies. The second limitation is understandable, because of overall incidence of inherited thrombophilias and very strict inclusive criteria of the study.

In conclusion, our results suggest that distribution of births and spontaneous abortions is equal in Conventional and Novel thrombophilia type in women with severe APO in previous pregnancies. Therefore, we recommend that the screening for thrombophilias should also include Novel thrombophilias in addition to Conventional thrombophilias. The study also suggests that LMWH treatment is more effective in reducing APO in Novel thrombophilias. This is an additional reason why future studies of Novel thrombophilias should be encouraged. Regardless of the limitations of the current study, we believe that the results emphasize the relevance of the topic of Novel thrombophilias in pregnancy and point the need for further research.

REFERENCES

1. Bremme KA. Haemostatic changes in pregnancy. Best Pract Res Clin Haematol 2003;16:153-68.
2. Cerneca F, Ricci G, Simeone R, Malisano M, Alberico S, Guaschino S. Coagulation and fibrinolysis changes in normal pregnancy. Increased levels of procoagulants and reduced levels of inhibitors during pregnancy induce a hypercoagulable state, combined with a reactive fibrinolysis. Eur J Obstet Gynecol Reprod Biol 1997;73:31-6.
3. Robertson L, Wu O, Langhorne P, Twaddle S, Clark P, Lowe GD, et al. Thrombophilia in pregnancy: a systematic review. Br J Haematol 2006;132:171-96.
4. Pabinger I. Thrombophilia and its impact on pregnancy. Thromb Res 2009;123 Suppl 3:S16-21.
5. Alfirevic Z, Roberts D, Martlew V. How strong is the association between maternal thrombophilia and adverse pregnancy outcome? A systematic review. Eur J Obstet Gynecol Reprod Biol 2002;101:6-14.
6. Middeldorp S. Thrombophilia and pregnancy complications: cause or association? J Thromb Haemost 2007;5 Suppl 1:276-82.
7. Paidas MJ, Ku DH, Arkel YS. Screening and management of inherited thrombophilias in the setting of adverse pregnancy outcome. Clin Perinatol 2004;31:783-805, vii.
8. Pabinger I, Nemes L, Rintelen C, Koder S, Lechler E, Loreth RM, et al. Pregnancy-associated risk for venous thromboembolism and pregnancy outcome in women homozygous for factor V Leiden. Hematol J 2000;1:37-41.
9. Facchinetti F, Marozio L, Frusca T, Grandone E, Venturini P, Tiscia GL, et al. Maternal thrombophilia and the risk of recurrence of preeclampsia. Am J Obstet Gynecol 2009;200:46.e1-5.
10. Facco F, You W, Grobman W. Genetic thrombophilias and intrauterine growth restriction: a meta-analysis. Obstet Gynecol 2009; 113:1206-16.
11. Bezemer ID, Doggen CJ, Vos HL, Rosendaal FR. No association between the common MTHFR 677C->T polymorphism and venous thrombosis: results from the MEGA study. Arch Intern Med 2007;167:497-501.
12. Foka ZJ, Lambropoulos AF, Saravelos H, Karas GB, Karavida A, Agorastos T, et al. Factor V leiden and prothrombin G20210A mutations, but not methylenetetrahydrofolate reductase C677T, are associated with recurrent miscarriages. Hum Reprod 2000;15:458-62.
13. Kosmas IP, Tatsioni A, Ioannidis JP. Association of C677T polymorphism in the methylenetetrahydrofolate reductase gene with hypertension in pregnancy and pre-eclampsia: a meta-analysis. J Hypertens 2004;22:1655-62.
14. Chen Z, Xu F, Wei Y, Liu F, Qi H. Angiotensin converting enzyme insertion/deletion polymorphism and risk of pregnancy hypertensive disorders: a meta-analysis. J Renin Angiotensin Aldosterone Syst 2012;13:184-95.
15. Wu X, Zhao L, Zhu H, He D, Tang W, Luo Y. Association between the MTHFR C677T polymorphism and recurrent pregnancy loss: a meta-analysis. Genet Test Mol Biomarkers 2012;16:806-11.
16. Subrt I, Ulcova-Gallova Z, Cerna M, Hejnalova M, Slovanova J, Bibkova K, et al. Recurrent pregnancy loss, plasminogen activator inhibitor-1 (-675) 4G/5G polymorphism and antiphospholipid antibodies in Czech women. Am J Reprod Immunol 2013;70:54-8.
17. Buchholz T, Lohse P, Rogenhofer N, Kosian E, Pihusch R, Thaler CJ. Polymorphisms in the ACE and PAI-1 genes are associated with recurrent spontaneous miscarriages. Hum Reprod 2003;18:2473-7.
18. Fatini C, Gensini F, Battaglini B, Prisco D, Cellai AP, Fedi S, et al. Angiotensin-converting enzyme DD genotype, angiotensin type 1 receptor CC genotype, and hyperhomocysteinemia increase first-trimester fetal-loss susceptibility. Blood Coagul Fibrinolysis 2000;11:657-62.
19. Yang C, Fangfang W, Jie L, Yanlong Y, Jie W, Xuefei L, et al. Angiotensin-converting enzyme insertion/deletion (I/D) polymorphisms and recurrent pregnancy loss: a meta-analysis. J Assist Reprod Genet 2012;29:1167-73.
20. Said JM, Tsui R, Borg AJ, Higgins JR, Moses EK, Walker SP, et al. The PAI-1 4G/5G polymorphism is not associated with an increased risk of adverse pregnancy outcome in asymptomatic nulliparous women. J Thromb Haemost 2012;10:881-6.
21. Greer IA, Nelson-Piercy C. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. Blood 2005;106:401-7.
22. Leduc L, Dubois E, Takser L, Rey E, David M. Dalteparin and low-dose aspirin in the prevention of adverse obstetric outcomes in women with inherited thrombophilia. J Obstet Gynaecol Can 2007; 29:787-93.
23. Kupferminc MJ, Rimon E, Many A, Sharon M, Lessing JB, Gamzu R. Low molecular weight heparin treatment during subsequent pregnancies of women with inherited thrombophilia and previous severe pregnancy complications. J Matern Fetal Neonatal Med 2011;24:1042-5.
24. de Vries JI, van Pampus MG, Hague WM, Bezemer PD, Joosten JH;

http://dx.doi.org/10.3349/ymj.2016.57.5.1230

FRUIT Investigators. Low-molecular-weight heparin added to aspirin in the prevention of recurrent early-onset pre-eclampsia in women with inheritable thrombophilia: the FRUIT-RCT. J Thromb Haemost 2012;10:64-72.
25. Mello G, Parretti E, Fatini C, Riviello C, Gensini F, Marchionni M, et al. Low-molecular-weight heparin lowers the recurrence rate of preeclampsia and restores the physiological vascular changes in angiotensin-converting enzyme DD women. Hypertension 2005; 45:86-91.
26. Roje D, Tadin I, Marušić J, Vulić M, Aračić N, Vučinović M, et al. Porodne težine i duljine novorođenčadi u Splitu, opravdanost razvijanja vlastitih referentnih vrijednosti za ocjenjivanje fetalnog rasta. Gynecol Perinatol 2005;14:66-74.
27. Aracic N, Roje D, Drmic Hofman I, Capkun V, Stefanovic V. Low molecular weight heparin treatment and impact of inherited thrombophilia type in pregnancies with previous adverse outcome. J Matern Fetal Neonatal Med 2015;28:306-10.
28. Coulam CB, Jeyendran RS, Fishel LA, Roussev R. Multiple thrombophilic gene mutations rather than specific gene mutations are risk factors for recurrent miscarriage. Am J Reprod Immunol 2006; 55:360-8.