Arch Gynecol Obstet
DOI 10.1007/s00404-010-1834-1

MATERNO-FETAL MEDICINE

Factor V Leiden and prothrombin G20210A in Portuguese women with recurrent miscarriage: is it worthwhile to investigate?

Fátima Serrano · Maria Luísa Lima · Cristina Lopes · João Paulo Almeida · Jorge Branco

Received: 17 August 2010 / Accepted: 31 December 2010

Abstract
Objective To compare the prevalence of factor V Leiden (FVL) and prothrombin (PT) G20210A mutations in Portuguese women with unexplained recurrent miscarriage (RM) and a control group of parous women.
Materials and methods FVL and PT G20210A analysis were carried out in 100 women with three or more consecutive miscarriages and 100 controls with no history of pregnancy losses. Secondary analysis was made regarding gestational age at miscarriage (embryonic and fetal losses).
Results Overall, the prevalence of FVL and PT G20210A was similar in women with RM (5 and 3%) compared with controls (5 and 1%) OR 1.36 (CI 95% 0.45–4.08). In RM embryonic subgroup, PT G20210A was observed in 1.3% of women and FVL prevalence (2.6%) was inclusively lesser than that of controls. Both polymorphisms were more prevalent in women with fetal losses than in controls, although statistical significance was not reached due to the small size of the >10 weeks' subgroup.
Conclusion These data indicate that neither FVL nor PT G20210A is associated with RM prior to 10 weeks of gestation. Therefore, its screening is not indicated as an initial approach in Portuguese women with embryonic RM and negative personal thromboembolic history.

Keywords Factor V Leiden · Prothrombin G20210A · Recurrent miscarriage

F. Serrano · J. Branco
Department of Obstetrics, Maternity Dr. Alfredo da Costa, Lisbon, Portugal

F. Serrano · J. Branco
Universitary Clinic of Obstetrics and Gynecology, Faculdade Ciências Médicas, Universidade Nova de Lisboa, Lisbon, Portugal

M. L. Lima
Department of Social and Organizational Psychology, ISCTE–Lisbon University Institute, Lisbon, Portugal

C. Lopes
Department of Clinical Pathology, Central Lisbon Hospitalar Center, Lisbon, Portugal

J. P. Almeida
Department of Clinical Pathology, Maternity Dr. Alfredo da Costa, Lisbon, Portugal

F. Serrano (✉)
Rua Joaquim Paço D'Arcos n°2, 3° F, 1500-366 Lisbon, Portugal
e-mail: fatima_serrano@hotmail.com

Introduction

One per cent of women in the reproductive age group experience recurrent miscarriage (RM), three or more clinically recognized pregnancy losses before 22nd gestational week [1–3]. RM is one of the most disturbing women's health issues and several medical factors (chromosomal, anatomic, autoimmune, and metabolic disorders) have been reported as possible causes [4–8]. However, after standard investigations, up to 50% of these cases remain unexplained [2, 9, 10].

Thrombophilia is the main risk factor for maternal thromboembolism. Data accumulated over the past two decades have established a clear association between antiphospholipid syndrome (APS), an acquired thrombophilic state, and RM [11–15]. Recent investigations have focused on a higher prevalence of certain inherited thrombophilias, such as factor V Leiden (FVL) and prothrombin (PT) G20210A mutations, in women with unexplained recurrent

Published online: 23 January 2011

pregnancy losses [16–21]. Nevertheless, these reports have produced conflicting results [22–25] and this heterogeneity is reflected in existing meta-analyses [17, 20, 26, 27].

The relative preponderance of particular type of thrombophilic gene may depend on the patient's ethnic origin, altering the relative importance of thrombophilic marker as a cause of RM [28]. In 1994, it was first described that FVL is the genetic risk factor for thrombosis more prevalent in humans [29]. This polymorphism is relatively common among the Caucasian population, ranging from 1 to 10% in different geographic regions [26–30]. PT G20210A, the second most frequently inherited thrombophilia, is present in 1 to 3% of the Europeans [31]. In Mediterranean countries, prevalence of 5 and 2%, respectively for these mutations were described [32].

Together with ethnicity, other confounding factors, such as the specification of the gestational age of pregnancy losses and the inclusion of patients with known causes of RM, have led to heterogeneous results in existing studies, and point to the need for more uniform research before inclusion of these exams in RM etiological investigation. However, two recent studies conducted in the USA and in the UK, exploring practice patterns of obstetricians, showed that a large proportion of clinicians include heritable thrombophilia in RM initial investigation. The majority (70–80%) of the respondents tests patients routinely for FVL and 50% for PT G20210A. About 80% of the women who tests positive start antithrombotic therapy with AAS and/or heparin in subsequent pregnancies [33, 34].

The prevalence of FVL and PT G20210A in Portuguese women with RM has not yet been studied. Therefore, the purpose of this study was to assess the association between these two hereditary thrombophilias and RM in our population.

Materials and methods

Participants

The study population comprised 100 consecutive women with unexplained RM, referred for evaluation at the Recurrent Miscarriage Clinic at Maternidade Dr. Alfredo da Costa, Lisbon, and 100 matched controls.

In the study group, eligibility criteria were the existence of three or more consecutive pregnancy losses before 22nd week, regardless of a previous live birth. Patients were included in the study only if the conventional etiological factors for RM (parental chromosomal abnormalities, uterine structural abnormalities or APS) were found to be normal. Women under the age of 18 or above 40 years were excluded.

The control group consisted of 100 age-matched women with at least one child alive and without history of pregnancy losses or other gestational complication. The control group also matched to the ethnic origin of the patients.

All women with a history of thromboembolic events were excluded from this study (Table 1).

The average number of losses of the RM group was 3.43 per woman (min 3–max 6). The majority (77%) had suffered embryonic losses (<10th gestational weeks) and 23 had at least one fetal loss (11–22 weeks). Sixty-one were nulliparous (primary miscarriage) and the remaining 39 had at least one previous live birth. Controls had an average of 1.6 children (DP = 0.67; min 1–max 3). Ninety-three percent of women in each group were Caucasian. Women with RM were slightly older (M = 32 years) than those of the control group (M = 30.9 years), although this difference was not significant ($t = -1.698$; $df = 198$; $p = 0.091$).

The demographic details and outcome of previous pregnancies of these women are shown in Table 2.

Laboratory procedure

Blood samples were collected in sodium citrate from all women and double centrifuged. Platelet-poor plasma obtained was separated, tested for prothrombin time and partial thromboplastin time and frozen at −20°C. After plasma separation, the resulting cells were stored at −20°C. Screening for FVL was made through the resistance to activated protein C (RPCa), using the kit Hemosil Factor V Leiden (APCTM Resistance V), Instrumentation Laboratory, Italy. A cutoff value of 2.1 was considered, and all samples with higher value were

Table 1 Inclusion and exclusion criteria of patients and controls

	RM women	Controls
Inclusion criteria	≥3 consecutive miscarriages	≥1 living birth without pregnancy losses
Exclusion criteria	<18 >40 years	Previous thromboembolism
	Previous thromboembolism	Previous miscarriage or other gestational complication
	Abnormal parental karyotype	
	Uterine structural abnormalities	
	Antiphospholipid syndrome	

Table 2 Population characteristics

	RM total ($n = 100$)	Embryonic losses ($n = 77$)	Fetal losses ($n = 23$)	Controls ($n = 100$)
Median age (mean ± SD)	32 ± 4.25	31.9 ± 4.27	32 ± 4.23	30.9 ± 5.19
Ethnics				
Caucasian	93	73 (94%)	20 (87%)	93
Black	7	4 (57%)	3 (43%)	7
Nulliparous	61 (61%)	48 (62%)	13 (57%)	–
Miscarriages (mean ± SD)	3.43 ± 0.67	3.40 ± 0.67	3.52 ± 0.66	–

Table 3 Prevalence of FVL and PT G20210A in patients and controls

	Controls	RM total		Embryonic losses		Fetal losses	
	$n = 100$ (%)	$n = 100$ (%)	p	$n = 77$ (%)	p	$n = 23$ (%)	p
Heterozygous FVL	5 (5)	5 (5)	1.0	2 (2.6)	0.406	3 (13)	0.195
Heterozygous PT G20210A	1 (1)	3 (3)	0.302	1 (1.3)	0.853	2 (8.7)	0.065
Total	6 (6)	8 (8)		3 (3.9)		5 (21.7)	

considered negative for the presence of FVL. DNA was extracted and isolated through automatic method of solid phase, according to the manufacturer's instructions (EZ1 200 µl blood DNA Kit used with Biorobot EZ1, both of Qiagen, Germany). Molecular diagnosis of FVL and PT G20210A mutations was performed by reverse hybridization of DNA amplification by PCR products using allele-specific oligonucleotide probes (PTH StripAssay kits and FV StripAssay, ViennaLab Diagnostics GmbH, Austria).

Ethics

The study was approved by the Ethical Committee of the Hospital. Informed consent was obtained from each woman.

Statistical analysis

Data were expressed in the form of mean ± SD and percentages as appropriate. To compare the groups on categorical variables, Chi square test (χ^2) was used and, when the expected frequencies were lesser than five, it was replaced by the likelihood ratio Chi square test (G test), as recommended by Agresti [35] and Özdemir and Eyduran [36]. For comparison between the two means, an independent Student's t test was performed. The magnitude of association odds ratio (OR) and their confidence intervals (CI) to 95% were calculated by logistic regression. The statistical analysis was carried out in the program SPSS version 15 (Inc., Chicago, IL), considering a significance level of 5%.

Results

An abnormal thrombophilic genotype was found in a similar percentage (8% vs. 6%) among women with RM and healthy controls (Table 3). However, the prevalence of FVL was equal among patients and controls (5%); PT G20210A was more frequent in RM women, although this difference was not significant (3% vs. 1%) OR 3.06 (CI 95% 0.31–29.94). There was no detected double carriage of the mutations in our investigated group of women. All heterozygous for FVL occurred in the Caucasian women.

When analyzed separately, carriage of these mutations was found in 3 of 77 women (3.9%) with embryonic losses and in 6% of the controls OR 0.64 (CI 95% 0.15–2.63; $p > 0.05$). In this group of women, the prevalence of FVL was inclusively inferior in patients (2.6%) compared to controls (5%) (Table 3).

In 5 out of the 23 the women with fetal losses (21.7%) a polymorphism was identified (Table 3). The prevalence of both FVL (13%) and PT G20210A (8.7%) in this subgroup of women was much more pronounced than in the control group (5 and 1%, respectively).

Ethnicity or parity did not influence our results in either embryonic or fetal losses subgroups.

Discussion

In our study, no difference was found in the prevalence of these two polymorphisms among women with RM and a control group of healthy parous women. Similar results have been reported by Dilley et al. [23] in a controlled

study conducted in 60 women with RM and 92 parous controls. Two prospective multicenter studies, involving each over 4,000 first trimester pregnant women, did not find an increased miscarriage rate in carriers of these mutations [37, 38]. A European prospective research, conducted in women with a previous miscarriage, has also found a similar outcome between subsequent pregnancies of FVL and PT G20210A carriers and noncarriers [22]. However, other studies revealed discordant results and clinicians continue to incorporate these tests in RM investigation protocol [17, 21, 26, 33, 34].

Some methodological aspects such as inclusion in studies of participants with other potential underlying causes of RM, the lack of stratification of cases by women's ethnicity and gestational age of losses, may have impaired the quality of the available data [26].

RM is a multifactorial entity and the great variation in the strength of this association found in most studies may indicate the presence of additional risk factors. To diminish this type of potential biases, in our research, only cases of unexplained RM were considered.

Gestational age of the losses may also influence the strength of this association. Clinical miscarriage is an entity that covers a wide period of time which extends from the biochemical identification of pregnancy until the 22nd week, and different pathophysiological mechanisms may be responsible for pregnancy loss. For this reason, many authors have chosen to examine separately the impact of hereditary thrombophilia on each trimester of pregnancy. Controlled studies conducted in the European Caucasian women with a history of unexplained RM failed to demonstrate an association between these two polymorphisms and 1st trimester RM [19, 39]. The meta-analyses that have adopted this methodology has also revealed a higher ratio of FLV related losses after the 14th week (OR 2.28) compared with 1st trimester RM (OR 1.6–1.91) [20, 26, 27, 40].

Factor V plays an important role in cell adhesion, proliferation of smooth muscle and vasculogenesis during embryonic development, and a possible beneficial effect of FVL, due to facilitation in embryonic implantation, had already been suggested by Majerus and Roque et al. [41–43]. According to this hypothesis, an increase in implantation rate has been reported in pregnancies resulting from intracytoplasmatic sperm injection, in situations where the mother and/or fetus were carriers of FVL [44]. A recent study, conducted by Ivanov et al. [45] in the Caucasian women with unexplained RM, has consolidated these results. These authors found a similar prevalence of FVL (9.6 vs. 7%) in women with embryonic losses and controls OR 1.41 (CI 95% 0.45–4.41). On contrary, in the group of women who suffered losses between 10 and 14 weeks of gestation, the prevalence of FVL (18.6%) was much more pronounced OR 3.05 (CI 95% 1.01–9.38, $P = 0.047$). Our results are also in line with those of this study, and while among women with embryonic losses FVL prevalence (2.6%) was even lesser than that of controls (5%) OR 0.50 (CI 95% 0.09–2.68), in women with fetal losses this prevalence (13%), though not significant, was substantially higher OR 2.85 (0.63–12.9).

Most of the scientific evidence that associates PT G20210A mutation to pregnancy failure originates in case–control studies [24, 25, 46]. These studies, as those carried out on the FLV, are subject to bias and may overstate its impact on obstetric outcome [38]. Nevertheless, in most investigations, this relationship is consistent and, as described for FLV, is weaker with 1st trimester compared with 2nd trimester RM [17, 20, 27]. In the study of Ivanov et al. [45], the prevalence of PT20210A was higher in women with both embryonic (17%) and fetal (16.9%) losses compared with controls (3%). Our results also showed an increased prevalence of this polymorphism in RM women, particularly patent in those with fetal miscarriages. However, the reduced size of this subgroup of patients ($n = 23$) does not allow us to establish any secure association.

The main limitation of our investigation relates to the dimension of our population and a larger study might clarify some interpretations.

Conclusions

The impact of heritable thrombophilia on RM remains a controversial issue and recent investigations have sparked the uncertainty about the existence of a causal relationship between these two entities [47–51]. Our data reinforce the results of previous research and indicate that FVL and PTG20210 are not associated with pregnancy wastage prior to 10 weeks of gestation. Although these polymorphisms were more prevalent in women with fetal losses, overall, our results do not support their screening as an initial approach in the Portuguese women with RM and a negative personal history of thromboembolism.

Acknowledgments We are especially grateful to the colleagues that collaborated in the recruitment of women of group control and to the staff of the laboratory of Maternity Dr. Alfredo da Costa, especially to laboratory technician Fatima Covas, for the valuable contribution in blood samples preparation.

Conflict of interest The authors declare that they do not have any conflict of interest, whether financial or personal.

References

1. Stirrat GM (2009) Recurrent miscarriage: definition and epidemiology. Lancet 336:673–675

2. Clifford K, Rai R, Regan L (1997) Future pregnancy outcome in unexplained recurrent first trimester miscarriage. Hum Reprod 12:387–389
3. Maconochie N, Doyle P, Prior S (2004) The national women's health study: assembly and description of a population-base reproductive cohort. BMC Public Health 4:35
4. Stephenson MD (1996) Frequency of factors associated with habitual abortion in 197 couples. Fertil Steril 66(1):24–29
5. Makino T, Tabuchi T, Nakada K, Iwasaki K, Tamura S, Iizuka R (1990) Chromosomal analysis in Japanese couples with repeated spontaneous abortions. Int J Fertil 35:266–270
6. Rai R, Regan L (1997) Antiphospholipid antibodies, infertility and recurrent miscarriage. Curr Opin Obstet Gynecol 9:279–282
7. Lashen H, Fear K, Sturdee DW (2004) Obesity is associated with increased risk of first trimester and recurrent miscarriage: matched case–control study. Hum Reprod 19:1644–1646
8. Salim R, Regan L, Woelfer B, Backos M, Jurkovic D (2003) A comparative study of the morphology of congenital uterine anomalies in women with and without a history of recurrent first trimester miscarriage. Hum Reprod 28:162–166
9. Jauniaux E, Farquharson RG, Christiansen OB, Exalto N (2006) Evidence-based guidelines for the investigation and medical treatment of recurrent miscarriage. Hum Reprod 21:2216–2222
10. Yang C, Stone P, Stewart AW (2006) The epidemiology of recurrent miscarriage: a descriptive study of 1214 prepregnant women with recurrent miscarriage. Aust NZ J Obstet Gynaecol 46:316–322
11. Rai R, Regan L (2006) Recurrent miscarriage. Lancet 368:601–611
12. Kutteh WH (1996) Antiphospholipid antibody-associated recurrent pregnancy loss: treatment with heparin and low-dose aspirin is superior to low-dose aspirin alone. Am J Obstet Gynecol 174:1584–1589
13. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, Derksen RH, de Groot PG, Koike T, Meroni PL et al (2006) International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 4:295–306
14. Rai RS, Regan L, Clifford K, Pickering W, Dave M, Mackie I, McNally T, Cohen H (1995) Antiphospholipid antibodies and beta2-glycoprotein-I in 500 women with recurrent miscarriage: results of a comprehensive screening approach. Hum Reprod 10:2001–2005
15. Serrano F, Nogueira I, Borges A, Branco J (2009) Primary antiphospholipid syndrome: pregnancy outcome in a Portuguese population. Acta Reumatol Port 34(3):492–497
16. Kupferminc MJ, Eldor A, Steinman N, Many A, Bar-Am A, Jaffa A et al (1999) Increased frequency of genetic thrombophilia in women with complications of pregnancy. N Engl J Med 340:9–13
17. Rey E, Kahn SR, David M, Shrier I (2003) Thrombophilic disorders and fetal loss: a meta-analysis. Lancet 361(9361):901–908
18. Roque H, Paidas MJ, Funai EF, Kuczynski E, Lockwood CJ (2004) Maternal thrombophilias are not associated with early pregnancy loss. Thromb Haemost 91:290–295
19. Jivraj S, Rai R, Underwood J, Regan (2006) Genetic thrombophilic mutations among couples with recurrent miscarriage. Hum Reprod 21(5):1161–1165
20. Robertson L, Wu O, Langhorne P, Twaddle S, Clark P, Lowe GD, Walker ID, Greaves M, Brenkel I, Regan L, Greer IA (2006) Thrombophilia in pregnancy: a systematic review. Thrombosis: risk and economic assessment of thrombophilia screening (TREATS) Study. Br J Haematol 132(2):171–196
21. Glueck CJ, Gogenini S, Munjal J, Tracy T, Pranikoff J, Wang P (2008) Factor V Leiden mutation: a treatable etiology for sporadic and recurrent pregnancy loss. Fertil Steril 89:410–416
22. Coppens M, Folkeringa N, Teune MJ, Hamulyák K, van der Meer J, Prins MH, Büller HR, Middeldorp S (2007) Outcome of the subsequent pregnancy after a first loss in women with the factor V Leiden or prothrombin 20210A mutations. J Thromb Haemost 5(7):1444–1448
23. Dilley A, Benito C, Hooper WC, Austin H, Miller C, El-Jamil M, Cottrell S, Benson J, Evatt BL, Patterson-Bamett A, Eller D, Philipp C (2002) Mutations in the factor V, prothrombin and MTHFR genes are not risk factors for recurrent fetal loss. J Matern Fetal Neonatal Med 11(3):176–182
24. Finan RR, Tamim H, Ameen G, Sharida HE, Rashid M, Almawi WY (2002) Prevalence of factor V G1691A (factor V Leiden) and prothrombin G20210A gene mutations in a recurrent miscarriage population. Am J Hematol 71:300–305
25. Foka ZJ, Lambropoulos AF, Saravelos H, Karas GB, Karavida A, Agorastos T, Zournatzi V, Makris PE, Bontis J, Kotsis A (2000) Factor V Leiden and prothrombin G20210A mutations, but not methylenetetrahydrofolate reductase C677T, are associated with recurrent miscarriages. Hum Reprod 15:458–462
26. Kist WJ, Janssen NG, Kalk JJ, Hague WM, Dekker GA, de Vries JI (2008) Thrombophilas and adverse pregnancy outcome: a confounded problem. Thromb Haemost 99(1):77–85
27. Kovalevsky G, Gracia CR, Berlin JA, Sammel MD, Barnhart KT (2004) Evaluation of the association between hereditary thrombophilias and recurrent pregnancy loss: a meta-analysis. Arch Intern Med 164(5):558–563
28. Ghosh K, Vora S, Shetty S (2006) Thrombophilia and pregnancy loss–picking up a needle from the haystack. Am J Obstet Gynecol 194(3):900–901
29. Bertina RM, Koeleman BP, Koster T, Rosendaal FR, Dirven RJ, de Ronde H, van der Velden PA, Reitsma PH (1994) Mutation in blood coagulation factor V associated with resistance to activated protein C. Nature 369(6475):64–67
30. Stella CL, How HY, Sibai BM (2006) Thrombophilia and adverse maternal–perinatal outcome: controversies in screening and management. Am J Perinatol 23:499–506
31. Rosendaal FR, Doggen CJ, Zivelin A, Arruda VR, Aiach M, Siscovick DS, Hillarp A, Watzke HH, Bernardi F, Cumming AM, Preston FE, Reitsma PH (1998) Geographic distribution of the 20210 G to A prothrombin variant. Thromb Haemost 79(4):706–708
32. Turri D, Rosselli M, Simioni P, Tormene D, Grimaudo S, Martorana G, Siragusa S, Mariani G, Cottone M (2001) Factor V Leiden and prothrombin gene mutation in inflammatory bowel disease in a Mediterranean area. Dig Liver Dis 33(7):559–562
33. Cleary-Goldman J, Bettes B, Robinson JN, Norwitz E, Schulkin J (2007) Thrombophilia and the obstetric patient. Obstet Gynecol 110(3):669–674
34. Norrie G, Farquharson RG, Greaves M (2009) Screening and treatment for heritable thrombophilia in pregnancy failure: inconsistencies among UK early pregnancy units. Br J Haematol 144(2):241–244
35. Agresti A (2002) Categorical data analysis, 2nd edn. Wiley, New York
36. Özdemir T, Eyduran E (2005) Comparison of Chi-square and likelihood ratio Chi-square tests: power of tests. J Appl Sci Res 1:242–244
37. Dizon-Townson D, Miller C, Sibai B, Spong CY, Thom E, Wendel G Jr et al (2005) The relationship of the factor V Leiden mutation and pregnancy outcomes for mother and fetus. Obstet Gynecol 106:517–524
38. Silver RM, Zhao Y, Spong CY, Sibai B, Wendel G Jr, Wenstrom K, Samuels P, Caritis SN, Sorokin Y, Miodovnik M, O'Sullivan MJ, Conway D, Wapner RJ (2010) Prothrombin gene G20210A mutation and obstetric complications. Obstet Gynecol 115(1): 14–20
39. Altintas A, Pasa S, Akdeniz N, Cil T, Yurt M, Ayyildiz O, Batun S, Isi H (2007) Factor V Leiden and G20210A prothrombin

mutations in patients with recurrent pregnancy loss: data from the southeast of Turkey. Ann Hematol 86(10):727–731
40. Krabbendam I, Franx A, Bots ML, Fijnheer R, Bruinse HW (2005) Thrombophilias and recurrent pregnancy loss: a critical appraisal of the literature. Eur J Obstet Gynecol Reprod Biol 118(2):143–153
41. Sood R (2009) Thrombophilia and fetal loss: lessons from gene targeting in mice. Thromb Res 123(Suppl 2):S79–S84
42. Majerus PW (1994) Human genetics. Bad blood by mutation. Nature 369:14–15
43. Roqué H, Paidas MJ, Funai EF, Kuczynski E, Lockwood CJ (2004) Maternal thrombophilias are not associated with early pregnancy loss. Thromb Haemost 91(2):290–295
44. Göpel W, Ludwig M, Junge AK, Kohlmann T, Diedrich K, Moller J (2001) Selection pressure for the factor-V-Leiden mutation and embryo implantation. Lancet 358:1238–1239
45. Ivanov PD, Komsa-Penkova RS, Konova EI, Kovacheva KS, Simeonova MN, Popov JD (2009) Association of inherited thrombophilia with embryonic and postembryonic recurrent pregnancy loss. Blood Coagul Fibrinolysis 20(2):134–140
46. Reznikoff-Etievan MF, Cayol V, Carbonne B, Robert A, Coulet F, Millez J (2001) Factor V Leiden and G20210A prothrombin mutations are risk factors for very early recurrent miscarriage. BJOG 108:1251–1254
47. Bates SM, Greer IA, Pabinger I, Sofaer S, Hirsh J, American College of Chest Physicians (2008) Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). Chest 133(6 Suppl):844S–886S
48. Branch DW (2010) The truth about inherited thrombophilias and pregnancy. Obstet Gynecol 15(1):2–4
49. Gris JC (2009) Thrombophilia and pregnancy loss: cause or association. Thromb Res 123(Suppl 2):105–110
50. Middeldorp S (2007) Thrombophilia and pregnancy complications: cause or association? J Thromb Haemost 5(Suppl 1):276–282
51. Rodger MA, Paidas M, McLintock C, Middeldorp S, Kahn S, Martinelli I, Hague W, Rosene Montella K, Greer I (2008) Inherited thrombophilia and pregnancy complications revisited. Obstet Gynecol 112(2 Pt 1):320–324