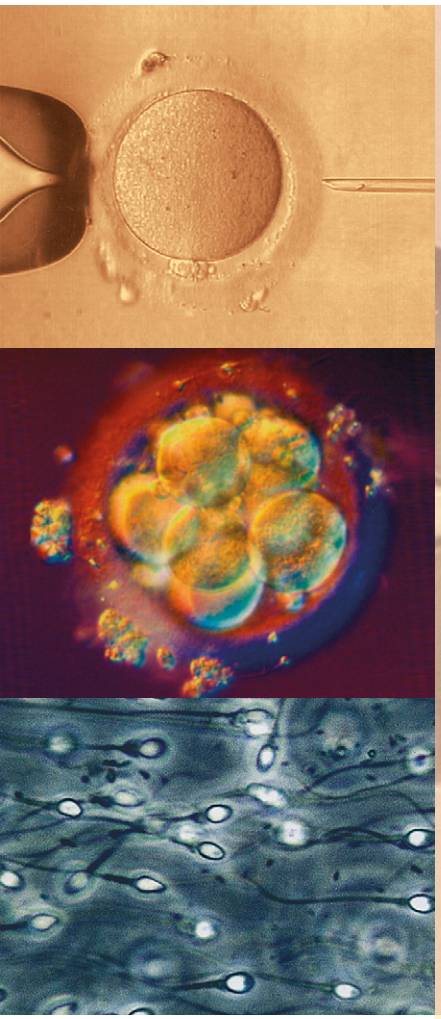
Journal für

Reproduktionsmedizin und Endokrinologie

– Journal of Reproductive Medicine and Endocrinology –

Andrologie • Embryologie & Biologie • Endokrinologie • Ethik & Recht • Genetik
Gynäkologie • Kontrazeption • Psychosomatik • Reproduktionsmedizin • Urologie



Genetic Predispositions to Thrombophilia Associated with Recurrent Pregnancy Loss

Bogdanova N, Markoff A

J. Reproduktionsmed. Endokrinol 2008; 5 (2), 101-105

Offizielles Organ: AGRBM, BRZ, DVR, DGA, DGGEF, DGRM, D·I·R, EFA, OEGRM, SRBM/DGE

Indexed in EMBASE/Excerpta Medica/Scopus

Krause & Pachernegg GmbH, Verlag für Medizin und Wirtschaft, A-3003 Gablitz

Genetic Predispositions to Thrombophilia Associated with Recurrent Pregnancy Loss

N. Bogdanova[1], A. Markoff[2]

This review retraces the current state of knowledge on hereditary hypercoagulation conditions causing thrombophilia-associated recurrent fetal loss. Thrombophilias are a major cause of adverse pregnancy outcome, etiological to up to 40 % of cases worldwide. Hereditary thrombophilic predispositions for recurrent pregnancy wastage include genetic mutations in blood coagulation factors II and V, as well as the factor Va protease protein C and its cofactor protein S. Furthermore MTHFR gene variants conferring higher thrombophilia risk in conjunction with the mentioned mutations and the newly described annexin A5 gene promoter alleles are associated with adverse pregnancy outcome. The review gives a brief description of molecular defects associated with these hereditary genetic changes, roles of these factors in different timing and definition of fetal loss and risk estimates from available studies and meta-analyses. This knowledge is instrumental to the more precise estimate of individual risk for repeated pregnancy loss and should guide the adequate therapeutical measures where relevant. The conclusive advice section summarizes a corollary for the clinical practice. ***J Reproduktionsmed Endokrinol 2008; 5 (2): 101–5.***

Key words: *fetal loss, thrombophilia, genetic predisposition*

Fetal loss is a common and considerable problem during pregnancy. About 20 % of women worldwide have at least one abortion and 5 % have two or more spontaneous pregnancy losses [1]. The most common reason for adverse pregnancy outcome in the first trimester consists in fetal chromosomal abnormalities which are not compatible with survival. However, 30–40 % of recurrent fetal losses remain unexplained after standard gynaecological, hormonal and cytogenetic investigations [1].

Prime candidates forming molecular basis of fetal loss are various acquired or inherited hypercoagulation disorders promoting thrombosis, collectively termed 'thrombophilias' [2]. Related evidence comes from histological studies reporting microthrombi to be a common finding in the placental vessels amongst women with recurrent miscarriage [3, 4]. Changes in blood coagulation and fibrinolysis during normal pregnancy induce a state of hypercoaculability, which predisposes to development of thrombosis [5, 6]. In combination with the physiological changes during pregnancy, hereditary thrombophilic defects may increase the risk of uteroplacental thrombosis and hence the risk of fetal loss [7].

Up to 70 % of the patients prone to thrombophilia will be found to have one or several of the five major inherited defects listed in Table 1. Two of these genetic defects – the factor V Leiden (FVL) mutation and the prothrombin G20210A mutation (PTm) – found together in more than half of all cases of inherited thrombophilia are well conserved single nucleotide substitutions for which direct DNA-based assays are available.

Table 1. Genetic variations in thrombophilia*

Thrombophilic Defect	Population Prevalence, % (Whites)			Relative thrombotic risk
	Incident VTE	Recurrent VTE	Normal population	
Antithrombin deficiency	1–2	2–5	0.02–0.04	5
Protein C deficiency	2–5	5–10	0.2–0.5	6–10
Protein S deficiency	1–3	5–10	0.1–1	2
Factor V Leiden	20	40–50	3–7	3–7 (heterozygotes) 50–100 (homozygotes)
Prothrombin G20210A	3–8	15–20	1–3	2–8 (heterozygotes)

* VTE indicates for venous thromboembolism

The factor V Leiden mutation results from a guanine substitution for adenine at position 1691 of the gene encoding the coagulation factor V [8–10]. The resulting amino-acid substitution, namely, arginine (R) to glutamine (Q) at amino-acid position 506, occurs precisely at one of the three sites where activated protein C (APC) normally cleaves and inactivates the procoagulant factor Va. Because of this single amino-acid substitution activated factor V Leiden is partially resistant to the anticoagulant action of APC and is inactivated at an approximately ten-fold slower rate than normal, resulting in increased thrombin generation and a prothrombotic state.

Activated protein C resistance not due to factor V Leiden has also been identified as an independent risk factor for deep vein thrombosis [11]. These states may correspond to acquired conditions as reported for pregnancy [12] and oral contraceptive use [13]. Some laboratory phenotypes, such as lupus anticoagulant and high factor VIII levels, are also associated with a reduced sensitivity for APC. It may also be due to other inherited traits. For example, two mutations involving the Arg205 APC cleavage site of factor V were described [14, 15]. One mutation (Arg306Thr, factor V Cambridge) was indeed associated with APC resistance. The other mutation (Arg306Gly) found in a Hong Kong Chinese, was reported not to be associated with APC resistance. In some

Received: February 1, 2008; accepted after revision: June 4, 2008.

From the [1]Institute of Human Genetics, Westfalian-Wilhelms University of Muenster and the [2]Institute of Medical Biochemistry, Westfalian-Wilhelms University of Muenster
Correspondence: Nadja Bogdanova, Institute of Human Genetics, D-48149 Münster, Vesaliusweg 12–14; e-mail: bogdano@uni-muenster.de

patients no obvious reason can be found for the APC-resistant phenotype without the factor V mutation.

The 20210G>A mutation (PTm) in the 3′ untranslated region of the Factor II gene encoding prothrombin causes a gain of function due to increased recognition of the 3′ end cleavage signal and increased 3′ end processing. The net result is accumulation of messenger RNA and increased protein synthesis of prothrombin [16].

Homozygous and heterozygous forms of factor V Leiden and PTm increase the risk of thrombosis (Tab. 1). Factor V Leiden is the most common inherited cause of thrombophilia, being present in heterozygous form in about 12–20 % of the patients with venous thrombosis and in 40–50 % of those with recurrent venous thrombosis. This mutation is very common in the white population: about 3–7 % of the normal white population of northern European or Scandinavian ancestry are heterozygous FVL carriers. Heterozygous carriers of FVL have been shown to have an overall 3- to 7-fold increased risk of venous thrombosis, while homozygous individuals have a 50- to 100-fold increased risk [17–19].

The prevalence of the prothrombin mutation in Europe is about 2 % overall, with a range of 1–3 %. The highest prevalence appears to be in southern European regions (approximately 3 %) and the lowest prevalence in the northern parts of the continent (approximately 1.7 %). Heterozygous carriers of the 20210A allele have a 2- to 8-fold increased risk for venous thrombosis [20]. There are very few cases of homozygosity for this mutation. Although more severe thrombotic risk may be expected in the homozygous state, there is a broad clinical spectrum with striking heterogeneity, because of the very small number of cases [21].

Patients carrying both the FVL and prothrombin G20210A mutations have an odds ratio for venous thrombosis of 20, i.e. higher risk as compared to heterozygous for FVL or prothrombin G20210A only. Analysis for both mutations is therefore recommended in patients with personal or family history of thrombosis [22, 23]. Hereditary deficiencies of the anticoagulant proteins antithrombin, protein C and protein S are heterogeneous in nature and caused by several different genetic mutations [24]. Although these deficiencies have been more frequent targets for clinical thrombophilia research, together they are found in less than 10 % of the patients with thrombophilia [25].

Table 2. Relative risks for fetal loss based on the results of the meta-analysis [43]

Thrombophilic effect	Recurrent pregnancy loss before 13 weeks	Non-recurrent pregnancy loss	Non-recurrent pregnancy loss after 19 weeks
Antithrombin deficiency	0.88	1.54	Not analysed
Protein C deficiency	1.57	1.41	Not analysed
Protein S deficiency	14.72	7.39	Not analysed
Factor V Leiden	2.01	1.73	3.26
Prothrombin G20210A	2.05	2.32	2.30

It has been suggested that elevated total plasma homocysteine level (hyperhomocysteinemia) could predispose to thrombophilia. Homocysteine is a non-protein-forming sulfhydryl amino-acid formed from the intracellular demethylation of methionine. In hepatocytes, homocysteine is remethylated to methionine by donation of a methyl group from methyltetrahydrofolate, derived in a reaction catalyzed by methylenetetrahydrofolate reductase (MTHFR). A quite common variant in the MTHFR gene, a C to T substitution at cDNA position 677 leading to a change from alanine to valine, may lead to an increased level of plasma homocysteine. This variant demonstrates reduced activity at 37 °C and increased thermolability at 46 °C. About 12 % of the white population is homozygous for this mutation, and moderate hyperhomocysteinemia is typically manifest when folic levels are in the lower end of the normal range [26]. Although initial studies have suggested an association between homozygosity for MTHFR C677T and venous thrombosis, prospective studies could not confirm such an association [27, 28]. However, the risk for thrombosis may be more closely linked to a combined defect of homozygosity for MTHFR C677T and for another unequivocal risk factor such as factor V Leiden [19, 29, 30].

A second common polymorphism in the MTHFR gene, A1298C, has been described by van der Put [31]. The prevalence of individuals homozygous for this variant in the white population is approximately 10 % and 23 % are combined heterozygous for C677T and A1298C [32]. It has been shown that combined heterozygosity for C677T and A1298C, but not homozygosity for A1298C, is associated with increased fasting and post-methionine load homocysteine plasma levels [32].

In the last years a large number of studies on the association between inherited thrombophilia and pregnancy loss has been published [33–42]. Because of the conflicting results of these studies regarding the presence and magnitude of the associations, and because of the increasingly widespread availability of screening tests for thrombophilia, a meta-analysis on 31 association studies published in literature has been put together [43] in order to estimate the strength and precision of the association between individual inherited thrombophilia and fetal loss and to examine whether these associations vary according to the timing or definition of fetal loss (Tab. 2). From this analysis factor V Leiden is associated with early and late recurrent fetal loss (OR 2.01; 95 % CI: 1.13–3.58) and late non-recurrent fetal loss (7.83; 2.83–21.67). Exclusion of women with other pathologies that could explain fetal loss strengthened the association between factor V Leiden and recurrent abortions. Furthermore, there is a significant association between PTm and recurrent abortions before 13 weeks of pregnancy (2.56; 1.04–6.29) as well as non-recurrent fetal loss after 20 weeks. While protein S deficiency is related to non-recurrent pregnancy loss occurring after 22 weeks, activated protein C resistance not due to factor V Leiden is associated with recurrent early pregnancy loss. In contrast, there is no signifi-

cant association between protein C and antithrombin deficiency and recurrent or non-recurrent fetal loss.

The initial observations that homozygosity for MTHFR C677T could be related to pregnancy loss [44, 45], supported by some recent studies [46, 47], have not been confirmed by Foka et al [38] and by a meta-analysis [43]. However, when additional thrombophilic factors were considered in combination, this MTHFR variant seemed to significantly increase the risk of pregnancy wastage [48–50]. The A1298C MTHFR variant showed no significant association with recurrent pregnancy when analysed separately, but a significant correlation was confirmed when analysed cumulatively [46, 47].

It is important to note that women who are homozygous for C677T or compound heterozygous for C677T and A1298C are prone to hyperhomocysteinaemia under folate deficiency, which means that the serum homocysteine levels will not be abnormal when folic acid is in the normal range. Thus such a predisposition could be missed when no genetic testing has been performed. Hyperhomocysteinaemia is a risk factor for placenta-mediated diseases such as pre-eclampsia and placenta abruption as well as for fetal neural-tube defects [31, 45]. Therefore the regular folate intake is essential especially for carriers of a predisposing MTHFR genotype.

Another major risk factor for recurrent pregnancy loss (RPL) is the presence of circulating maternal antiphosholipid antibodies (aPL). A higher incidence of RPL has been documented in both low-risk and high-risk pregnancies when aPL were present [47, 51]. Antiphospholipid antibodies are thought to lead to fetal loss by causing thrombosis of the placental vessels, although the observed variability in placental pathology somehow argues against such a direct involvement [52, 53]. Annexin A5 (placental anticoagulant protein) occurs in normal placental villi and appears to be reduced in the presence of aPL [54]. Reduced annexin A5 expression in placental trophoblasts has also been documented immunohistochemically in patients with preeclampsia [55]. Based upon these observations and the reported anticoagulation activity of annexin A5 [56], it has been suggested that annexin A5 molecules form an antithrombotic shield on the apical surface of placental syncytiotrophoblasts, which may then be disrupted by antiphospholipid antibodies [57]. This hypothesis has recently received additional support from in vitro studies employing atomic force microscopy and functional assays [58].

Recently, we found that a sequence variation in the promoter of the placental anticoagulant protein annexin A5 (*ANXA5*) gene represents a risk factor for recurrent pregnancy loss [59]. Sequence analysis of 70 German RPL patients, all known to carry neither factor V Leiden nor a prothrombin mutation, revealed four consecutive nucleotide substitutions in the *ANXA5* promoter that were transmitted as a joint haplotype (*M2*). Reporter gene assays revealed that *M2* reduces the in vitro activity of the *ANXA5* promoter to 37–42 % of the normal level. The possible relationship between *M2* and RPL was evaluated by comparing RPL patients (n = 70) with two independent control groups recruited from the registry of the Institute of Human Genetics in Münster (n = 500) and the PopGen biobank in Kiel (n = 500), respectively. Carriers of *M2* were found to exhibit a more than two-fold higher RPL risk than non-carriers (OR 2.42; 95 % CI: 1.27–4.58) when using unselected controls (PopGen), and an almost four-fold higher risk when using the Münster 'super-controls', i.e. women with successful pregnancies and no previous history of pregnancy losses (OR 3.88; 95 % CI: 1.98–7.54).

However, the distribution of *ANXA5* promoter haplotypes in other populations and their impact on RPL and other prothrombotic pathological conditions requires further evaluation. Analyses of the presence of RPL-associated aPL in conjunction with *ANXA5* promoter haplotypes is also an important subject for future investigation. Another interesting avenue of further studies would be to clarify the possibility of interaction of the *M2* haplotype with the other known RPL genetic factors. All these issues will be addressed in a research project planned to start in the next future. Nevertheless, the *ANXA5* promoter *M2* haplotype is a strong candidate for predisposition to fetal loss and will be probably included in the analytical panel in the near future after the results of this initial study are proved in large patient groups from different populations. This should facilitate the development of improved prognostic algorithms for RPL, involving a more precise assessment of individual disease risks, and provide a guide to offering adequate therapies where relevant.

Advice for the Clinical Practice

Based on the present knowledge some forms of hereditary thrombophilia are associated with recurrent fetal loss. Genetic testing for the factor V Leiden mutation and for the Prothrombin G20210A variation is indicated in women with recurrent fetal loss (two or more miscarriages) as well as non-recurrent late miscarriage. Since homozygosity for the MTHFR C677T variant combined with another thrombophilic factor increases the risk for pregnancy wastage, it is advisable to include this variant in the analytical panel. Optionally the MTHFR A1298C variant could be also tested, but the interpretation of its' relevance should be done with precautions and exclusively in conjunction with C677T. Evaluation of the activated protein C resistance not due to factor V Leiden and protein S deficiency using plasma-based functional assays is indicated in women with early recurrent abortions, whereas women with late miscarriage should be tested for protein S deficiency only.

It is advisable to refer women, tested positive for one or more mutations, to a specialised centre for monitoring a future pregnancy and for eventually considering heparin or aspirin prophylaxis during and/or after pregnancy. Women who are homozygous for MTHFR C677T or are C677T/A1298C combined heterozygous should be strongly advised to ensure the regular folate intake before a pregnancy has occurred.

References:

1. Branch DW, Silver RM, Blackwell JL, Reading JC, Scott JR. Outcome of treated pregnancies in women with antiphospholipid syndrome: um update of the Utah experience. Obstet Gynecol 1992; 80: 614–20.

2. Kupferminc MJ, Eldor A, Steinman N, Many A, Bar-Am A, Jaffa A, Fait G, Lessing JB. Increased frequency of genetic thrombophilia in women with complications of pregnancy. N Engl J Med 1999; 340: 50–2.
3. Out HJ, Kooijman CD, Bruinse HW, Derksen RH. Histopathological findings in placentae from patients with intra-uterine fetal death and anti-phospholipid antibodies. Eur J Obstet Gynecol Reprod Biol 1991; 41: 179–86.
4. Rai R, Regan L, Hadley E, Dave M, Cohen H. Second-trimester pregnancy loss is associated with activated protein C resistance. Br J Haematol 1996; 92: 489–90.
5. Sanson BJ, Simioni P, Tormene D, Moia M, Friederich PW, Huisman MV, Prandoni P, Bura A, Rejto L, Wells P, Mannucci PM, Girolami A, Büller HR, Prins MH. The incidence of venous thromboembolism in asymptomatic carriers of a deficiency of antithrombin, protein C, or protein S: a prospective cohort study. Blood 1999; 94: 3702–6.
6. Simioni P, Sanson BJ, Prandoni P, Tormene D, Friederich PW, Girolami B, Gavasso S, Huisman MV, Büller HR, Wouter ten Cate J, Girolami A, Prins MH. Incidence of venous thromboembolism in families with inherited thrombophilia. Thromb Haemost 1999; 81: 198–202.
7. Kupferminc MJ. Thrombophilia and pregnancy. Reprod Biol Endocrinol 2003; 1: 111.
8. Bertina RM, Koeleman BP, Koster T, Rosendaal FR, Dirven RJ, de Ronde H, van der Velden PA, Reitsma PH. Mutation in blood coagulation factor V associated with resistance to activated protein C. Nature 1994; 369: 64–7.
9. Voorberg J, Roelse J, Koopman R, Büller H, Berends F, ten Cate JW, Mertens K, van Mourik JA. Association of idiopathic venous thromboembolism with single point-mutation at Arg506 of factor V. Lancet 1994; 343: 1535–6.
10. Greengard JS, Sun X, Xu X, Fernandez JA, Griffin JH, Evatt B. Activated protein C resistance caused by Arg506Gln mutation in factor Va. Lancet 1994; 343: 1361–2.
11. de Visser MC, Rosendaal FR, Bertina RM. A reduced sensitivity for activated protein C in the absence of factor V Leiden increases the risk of venous thrombosis. Blood 1999; 15: 1271–6.
12. Cumming AM, Tait RC, Fildes S, Yoong A, Keeney S, Hay CR. Development of resistance to activated protein C during pregnancy. Br J Haematol 1995; 90: 725–7.
13. Olivieri O, Friso S, Manzato F, Guella A, Bernardi F, Lunghi B, Girelli D, Azzini M, Brocco G, Russo C, Corrocher R. Resistance to activated protein C in healthy women taking oral contraceptives. Br J Haematol 1995; 91: 465–70.
14. Chan WP, Lee CK, Kwong YL, Lam CK, Liang R. A novel mutation of Arg 506 of factor V genein Hong Kong Chinese. Blood 1998; 91: 1135.
15. Williamson D, Brown K, Luddington R, Baglin C, Baglin T. Factor V Cambridge: A new mutation (Arg^{506}→Thr) associated with resistance to activated protein C. Blood 1998; 91: 1140.
16. Gehring NH, Frede U, Neu-Yilik G, Hundsdoerfer P, Vetter B, Hentze MW, Kulozik AE. Increased efficiency of mRNA 3' end formation: a new genetic mechanism contributing to hereditary thrombophilia. Nat Genet 2001; 28: 389–92.
17. Koster T, Rosendaal FR, de Ronde H, Briet E, Vandenvroucke JP, Bertina RM. Venous thrombosis due to poor anticoagulant response to activated protein C: Leiden thrombophilia study. Lancet 1993; 342: 1503–6.
18. Griffin JH, Evatt B, Wideman C, Fernández JA. Anticoagulant protein C pathway defective in majority of thrombophilic patients. Blood 1993; 82: 1989–93.
19. Ridker PM, Hennekens CH, Selhub J, Miletich JP, Malinow MR, Stampfer MJ. Interrelation of hyperhomocyst(e)inemia, factor V Leiden, and risk of future venous thromboembolism. Circulation 1997; 95: 1777–82.
20. Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. Blood 1996; 88: 3698–703.
21. Bosler D, Mattson J, Crisan D. Phenotypic heterogeneity in patients with homozygous Prothrombin 20210AA genotype. J Mol Diagn 2006; 4: 420–5.
22. Press RD, Bauer KA, Kujovich JL, Heit JA. Clinical utility of factor V leiden (R506Q) testing for the diagnosis and management of thromboembolic disorders. Arch Pathol Lab Med 2002; 126: 1304–18.
23. McGlennen RC, Key NS. Clinical and laboratory management of the prothrombin G20210A mutation. Arch Pathol Lab Med 2002; 126: 1319–25.
24. Seligsohn U, Lubetsky A. Genetic susceptibility to venous thrombosis. N Engl J Med 2001; 344: 1222–31.
25. Florell SR, Rodgers GM 3rd. Utilization of testing for activated protein C resistance in a reference laboratory. Am J Clin Pathol 1996; 106: 248–52.
26. Hanson NQ, Aras O, Yang F, Tsai MY. C677T and A1298C polymorphisms of the methylenetetrahydrofolate reductase gene: incidence and effect of combined genotypes on plasma fasting and post-methionine load homocysteine in vascular disease. Clin Chem 2001; 47: 661–6.
27. Tsai AW, Cushman M, Tsai MY. Serum homocysteine, MTHFR C677T genotype and risk of venous thromboembolism: the LITE study. Thromb Haemost 2001; 85 (Suppl): 324a.
28. Cattaneo M. Hyperhomocysteinemia, atherosclerosis and thrombosis. Thromb Haemost 1999; 81: 165–76.
29. Cattaneo M, Tsai MY, Bucciarelli P, Taioli E, Zighetti ML, Bignell M, Mannucci PM. A common mutation in the methylenetetrahydrofolate reductase gene (C677T) increases the risk for deep-vein thrombosis in patients with mutant factor V (factor V:Q506). Arterioscler Thromb Vasc Biol 1997; 17: 1662–6.
30. Eldibany MM, Caprini JA. Hyperhomocysteinemia and thrombosis: an overview. Arch Pathol Lab Med 2007; 131: 872–84.
31. van der Put NML, Gabreels F, Stevens EMB, Smetink JA, Trijbels FJ, Eskes TK, van den Heuvel LP, Blom HJ. A second common mutation in the methylentetrahydrofolate reductase gene: an additional risk factor for neural-tube defects? Am J Hum Genet 1998; 62: 1044–51.
32. Hanson NQ, Aras O, Yang F, Tsai MY. C677T and A1298C polymorphisms of the methylentetrahydrofolate reductase gene: incidence and effect of combined genotypes on plasma fasting and post-methionine load homocysteine in vascular disease. Clin Chem 2001; 47: 661–6.
33. Brenner B, Sarig G, Weiner Z, Younis J, Blumenfeld Z, Lanir N. Thrombophilic Polymorphisms are common in women with fetal loss without apparent cause. Thromb Haemost 1999; 82: 6–9.
34. Ridker PM, Miletich JP, Buring JE, Ariyo AA, Price DT, Manson JE, Hill JA. Factor V Leiden mutation as a risk factor for recurrent pregnancy loss. Ann Intern Med 1998; 128 (12 Pt 1): 1000–3.
35. Younis JS, Brenner B, Ohel G, Tal J, Lanir N, Ben-Ami M. Activated protein C resistance and factor V Leiden mutation can be associated with first-as well as second-trimester recurrent pregnancy loss. Am J Reprod Immunol 2000; 43: 31–5.
36. Sarig G, Younis JS, Hoffman R, Lanir N, Blumenfeld Z, Brenner B. Thrombophilia is common in women with idiopathic pregnancy loss and is associated with late pregnancy wastage. Fertil Steril 2002; 77: 342–7.
37. Finan RR, Tamim H, Ameen G, Sharida HE, Rashid M, Almawi WY. Prevalence of factor V G1691A (factor V-Leiden) and prothrombin G20210A gene mutations in a recurrent miscarriage population. Am J Hematol 2002; 71: 300–5.
38. Foka ZJ, Lambropoulos AF, Saravelos H, Karas GB, Karavida A, Agorastos T, Zournatzi V, Makris PE, Bontis J, Kotsis A. Factor V leiden and prothrombin G20210A mutations, but not methylenetetrahydrofolate reductase C677T, are associated with recurrent miscarriages. Hum Reprod 2000; 15: 458–62.
39. Reznikoff-Etiévan MF, Cayol V, Carbonne B, Robert A, Coulet F, Milliez J. Factor V Leiden and G20210A prothrombin mutations are risk factors for very early recurrent miscarriage. Br J Obstet Gyecol 2001; 108: 1251–4.
40. Kovalevsky G, Gracia CR, Berlin JA, Sammel MD, Barnhart KT. Evaluation of the association between hereditary thrombophilias and recurrent pregnancy loss: a meta-analysis. Arch Intern Med 2004; 164: 558–63.
41. Pihusch R, Buchholz T, Lohse P, Rübsamen H, Rogenhofer N, Hasbargen U, Hiller E, Thaler CJ. Thrombophilic gene mutations and recurrent spontaneous abortion: prothrombin mutation increases the risk in the first trimester. Am J Reprod Immunol 2001; 46: 124–31.
42. Wramsby ML, Sten-Linder M, Bremme K. Primary habitual abortions are associated with high frequency of factor V Leiden mutation. Fertil Steril 2000; 74: 987–91.
43. Rey E, Kahn SR, David M, Shrier I. Thrombophilic disorders and fetal loss: a meta-analysis. Lancet 2003; 361: 901–8.
44. Nelen WL, Blom HJ, Steegers EA, den Heijer M, Eskes TK. Hyperhomocysteinemia and recurrent early pregnancy loss: a meta-analysis. Fertil Steril 2000; 74: 1196–9.
45. van der Molen EF, Arends GE, Nelen WL, van der Put NJ, Heil SG, Eskes TK, Blom

HJ. A common mutation in the 5,10-methylenetetrahydrofolate reductase gene as a new risk factor for placental vasculopathy. Am J Obstet Gynecol 2000; 182: 1258–63.

46. Goodman CS, Coulam CB, Jeyendran RS, Acosta VA, Roussev R. Which thrombophilic gene mutations are risk factors for recurrent pregnancy loss? Am J Reprod Immun 2006; 56: 230–6.
47. Subrt I, Ulvova-Gallova Z, Bibkova K, Micanova Z, Hejnalova M, Cerna M, Hradecky L, Novotny Z. Recurrent pregnancy loss and frequency of eight antiphospholipid antibodies and genetic thrombophilic factors in Czech women. Am J Reprod Immun 2008; 59: 193–200.
48. 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.
49. Kupferminc MJ, Eldor A, Steinman N, Many A, Bar-Am A, Jaffa A, Fait G, Lessing JB. Increased frequency of genetic thrombophilia in women with complications of pregnancy. N Engl J Med 1999; 340: 9–13.
50. Tranquilli AL, Giannubilo SR, Dell'Uomo B, Grandone E. Adverse pregnancy outcomes are associated with multiple maternal thrombophilic factors. Eur J Obstet Gynecol Reprod Biol 2004; 117: 144–7.
51. Empson M, Lassere M, Craig JC, Scott JR. Recurrent pregnancy loss with antiphospholipid antibody: A systematic review of therapeutic trials. Obstet Gynecol 2002; 99: 135–44.
52. Nilsson I, Astedt B, Hedner U, Berezin D. Intrauterine death and circulating anticoagulant ("antithromboplastin"). Acta Med Scand 1975; 197: 153–9.
53. Salafia CM, Cowchock FS. Placental pathology and antiphospholipid antibodies: A descriptive study. Am J Perinat 1997; 14: 435–41.
54. Rand JH, Wu XX, Guller S, Gil J, Guha A, Scher J, Lockwood CJ. Reduction of annexin-V (placental anticoagulant protein-I) on placental villi of women with antiphospholipid antibodies and recurrent spontaneous abortion. Am J Obstet Gynecol 1994; 171: 1566–72.
55. Shu F, Sugimura M, Kanayama N, Kobayashi H, Kobayashi T, Terao T. Immunohistochemical study of annexin V expression in placentae of preeclampsia. Gynecol Obstet Invest 2000; 49: 17–23.
56. Romisch J, Seiffge D, Reiner G, Paques EP, Heimburger N. In-vivo antithrombotic potency of placenta protein 4 (annexin V). Thromb Res 1991; 61: 93–104.
57. Rand JH, Wu XX. Antibody-mediated disruption of the annexin-V antithrombotic shield: a new mechanism for thrombosis in the antiphospholipid syndrome. Thromb Haemost 1999; 82: 649–55.
58. Rand JH, Wu XX, Quinn AS, Chen PP, McCrae KR, Bovill EG, Taatjes DJ. Human monoclonal antiphospholipid antibodies disrupt the annexin A5 anticoagulant crystal shield on phospholipid bilayers: evidence from atomic force microscopy and functional assay. Am J Pathol 2003; 163: 1193–2000.
59. Bogdanova N, Horst J, Chlystun M, Croucher PJ, Nebel A, Bohring A, Todorova A, Schreiber S, Gerke V, Krawczak M, Markoff A. A common haplotype of the annexin A5 (ANXA5) gene promoter is associated with recurrent pregnancy loss. Hum Mol Genet 2007; 16: 573–8.

Mitteilungen aus der Redaktion

Besuchen Sie unsere Rubrik

☑ Medizintechnik-Produkte

Neues CRT-D Implantat
Intica 7 HF-T QP von Biotronik

Artis pheno
Siemens Healthcare Diagnostics GmbH

Philips Azurion:
Innovative Bildgebungslösung

Aspirator 3
Labotect GmbH

InControl 1050
Labotect GmbH

e-Journal-Abo

Beziehen Sie die elektronischen Ausgaben dieser Zeitschrift hier.

Die Lieferung umfasst 4–5 Ausgaben pro Jahr zzgl. allfälliger Sonderhefte.

Unsere e-Journale stehen als PDF-Datei zur Verfügung und sind auf den meisten der marktüblichen e-Book-Readern, Tablets sowie auf iPad funktionsfähig.

☑ Bestellung e-Journal-Abo