Pregnancy-related thrombosis and fetal loss in women with thrombophilia

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Introduction

Introduction

Haemostasis is a complex process that maintains the integrity of the vessel wall and the fluidity of blood. Plasma proteins, blood platelets, the vessel wall and blood flow velocity are involved. Vessel wall injury is the physiological trigger of haemostasis. The response is restricted to the site of injury by natural inhibitors of coagulant proteins and platelets. An excess of fibrin is removed by the generation of the proteolytic enzyme plasmin, as soon as it is appropriate. Finally, migration and proliferation of vessel wall cells are induced to repair the vessel wall. Disturbances of this process may result in either bleeding or thrombosis. Pregnancy is a challenge of haemostasis, particularly by the risk of bleeding at time of delivery. It may explain the physiological changes observed during pregnancy.[1] These include increasing plasma levels of procoagulant proteins and adhesion proteins (i.e. fibrinogen and von Willebrand factor), decreasing plasma levels of anticoagulant proteins and a decline of fibrinolytic potency.[1-8] Moreover, stickiness of platelets increases.[1,2] Although these changes protect against maternal bleeding, they will result in a state of hypercoagulability.[9] As a consequence, pregnancy is associated with an increased risk of thrombosis, still an important cause of maternal morbidity and mortality in the Western world.[10]

In pregnant women, the risk of venous thromboembolism is five-to-six fold higher than non-pregnant woman of the same age.[11] The incidence of venous thromboembolism in the general female population ranges from 0.5-1 in 1000 deliveries.[11] Predilection sites of thrombosis during pregnancy are deep leg veins and iliac veins, may be due to venous stasis in addition to hypercoagulability.[12,13] However, venous thrombosis occurs more frequently after delivery than in pregnancy.[14] This is plausible, considering that it takes time before the abovementioned changes of haemostatic compounds have been recovered, while the risk of bleeding has already returned to its baseline level.

It is likely that pregnancy induced hypercoagulability may also result in thrombosis of placenta vessels and thereby contributes to obstetrical complications, like fetal loss.[15,16] Fetal loss occurs frequently. About 20% of conceiving women experience at least one fetal loss, whereas recurrent fetal loss occurs in approximately 5% of these women.[17] Fetal loss is multicausal. Chromosomal abnormalities of either parent(s) or fetus, uterus anomalies, endocrine disorders and infections are known causes.[18] Still, approximately 50% of all fetal losses remain unexplained.[19]

Women with thrombophilia, an inherited or acquired coagulation defect that is associated with an increased risk of venous thrombosis, are more prone to develop thrombotic events related to pregnancy. Women with multiple thrombophilic defects are likely at higher risk than women with a single defect. Therefore, it is plausible that thromboprophylaxis during pregnancy and/or puerperium may particularly be of benefit in women with thrombophilia in order to reduce the risk of venous thrombosis and maybe fetal loss.

Thrombophilia

After Egeberg introduced the term thrombophilia in 1965, many defects of coagulation and fibrinolysis have been recognized as risk factors for thrombosis.[20] Of the established inherited thrombophilic defects, deficiencies of antithrombin, protein C and protein S are the strongest risk factors for venous thromboembolism.[21] Factor V Leiden, prothrombin G20210A, as well as often mixed inherited and acquired elevated levels of factor VIII, factor IX, factor XI, thrombin activated fibrinolysis inhibitor (TAFI) and hyperhomocysteinaemia are mild thrombotic risk factors.[22-34] Elevated levels of factor VIII or TAFI, and hyperhomocysteinaemia have also been associated with an increased risk of arterial thrombosis.[26,28,32] Antiphospholipid antibodies, like lupus anticoagulant and anticardiolipin antibodies, are acquired thrombophilic defects. The clinical entity that consists of these antibodies, venous and/or arterial thrombosis and/or obstetrical complications is known as the antiphospholipid syndrome.[35] Together, thrombophilic defects have been reported in at least 15% of the Western population and in up to 50% of patients with venous thrombosis.[16]

Women with thrombophilia are at higher risk of pregnancy related venous thrombosis. Approximately 50% of these events have been associated with thrombophilic defects.[36] The reported risks for individual thrombophilic defects are summarized in Table 1. Women with combinations of thrombophilic defects may be at higher risk than women with a single defect, but there is hardly data available on this issue.

Table 1. Incidence of pregnancy related venous thrombosis in women with thrombophilia

	%
Antithrombin deficiency	3-47 [37-40]
Protein C deficiency	2-19 [37-40]
Protein S deficiency	2-27 [37-40]
Factor V Leiden (heterozygous)	2.1 [41]
Prothrombin G20210A (heterozygous)	2.4 [42]
Elevated factor VIII levels (>150 IU/dL)	1.3 [26]
Mild hyperhomocysteinaemia	0.45 [43]
Elevated TAFI levels	unknown

Since 1996, several studies have been performed, that addressed the association of fetal loss with thrombophilia.[42,44-49] In a number of these studies, early and late fetal loss rates were separately reported, considering that there are differences in pathophysiology between early and late fetal loss. Relative risks of early and late fetal loss in women with various thrombophilic defects compared to controls are presented in Table 2. It should be noted that different definitions of early and late fetal loss were used in these studies. The cut-off gestational age at time of fetal loss ranged from 10 weeks to 28 weeks, whereas fetal loss at gestational age less than 20-22 weeks and

more than 20-22 weeks are classified early and late, respectively, according to the criteria of the World Health Organization.[17] Although one might expect a higher risk of fetal loss in women with multiple thrombophilic defects than in women with a single thrombophilic defect, as shown in one study,[46] this assumption has not been established yet.

Table 2. Relative risk of early and late fetal loss in women with thrombophilia

	Early fetal loss	Late fetal loss
Antithrombin deficiency	1.5-1.7 [44,46]	5.2-7.6 [44,46,48]
Protein C deficiency	1.4 -2.3 [44,46,48]	2.3-3.1 [44,46,48]
Protein S deficiency	1.3-3.6 [44,46,48]	3.3-20.1 [44,46,48]
Factor V Leiden (heterozygous)	1.0-2.0 [45,47,48]	1.4-3.3 [45,47,48]
Prothrombin G20210A (heterozygous)	1.3-2.5 [42,48]	2.3-2.7 [48]
Elevated factor VIII levels (>150 IU/dL)	1.2 [49]	unknown
Hyperhomocysteinaemia	0.8-6.3 [48,49]	1.0-1.3 [48]
Elevated TAFI levels	unknown	unknown
Combined defects	0.8 [46]	14.3 [46]

Thromboprophylaxis

It is still a matter of debate whether thromboprophylaxis should be applied during pregnancy and/or puerperium in women with prior venous thromboembolism, either related to pregnancy or not. Whether thromboprophylaxis during pregnancy and/or puerperium should be considered in women with symptomatic or even asymptomatic thrombophilia is also a controversial issue. Anticoagulant treatment in order to reduce the risk of fetal loss in women with thrombophilia has been suggested, although available evidence is not convincing. The major concerns about the use of anticoagulant drugs during pregnancy are efficacy of the regimes, maternal and fetal risks, and management around the time of delivery.

Anticoagulant therapy during pregnancy can reduce the risk of venous thrombosis.[50] Although this risk is low, venous thrombosis is the second cause of maternal mortality in the Netherlands[51] and can cause serious morbidity due to deep venous insufficiency (i.e. post-thrombotic syndrome).[52] Furthermore, the recurrence rate of venous thromboembolism during pregnancy in women with previous idiopathic venous thrombosis is 2.7%-5.6% and 2.2%-4.5% in women with previous pregnancy related thrombosis.[53, 54] Current guidelines for primary and secondary thromboprophylaxis in pregnant women are mainly based on experts' opinions. Issues to be resolved, apart from efficacy and safety, include the dosage of anticoagulant drugs, the

need for dose adjustments, stratification for risk of venous thrombosis, and start and duration of thromboprophylaxis. An individualized approach may be preferred.[55,56]

Considering uteroplacental thrombosis as a cause of fetal loss, it is rational to use anticoagulant drugs for its prevention. This is already common practice in pregnant women with the antiphospholipid syndrome.[57] Some studies suggested a benefit of thromboprophylaxis in women with thrombophilia and (recurrent) fetal loss, but most of these studies had major methodological limitations. As fetal loss is relatively common, the need for treatment also depends on the prognosis of a successful pregnancy outcome after a first fetal loss in women with thrombophilia. Because available evidence from previous studies is not convincing, it does not justify anticoagulant routine treatment in these women.[58,59,60]

Aim of this thesis

This thesis addresses the absolute risk of pregnancy related venous thromboembolism and fetal loss in women with thrombophilic defects, either single or multiple. The presented studies were performed to assess:

1 The absolute risk of venous thromboembolism during pregnancy and puerperium in women with hereditary deficiencies of antithrombin, protein C or protein S, and the contribution of other concomitant thrombophilic defects to this risk.

2 The absolute risk of fetal loss in women with hereditary deficiencies of either antithrombin, protein C or protein S, and the contribution of other concomitant thrombophilic defects to this risk.

3 The effects of thromboprophylaxis during pregnancy on fetal loss rates in women with hereditary deficiencies of either antithrombin, protein C or protein S.

4 The risk of a second fetal loss in carriers and non-carriers of either factor V Leiden or prothrombin G20210A after a first unexplained fetal loss.

5 The absolute risk of venous and arterial thromboembolism associated with high TAFI levels, and the contribution of other concomitant thrombophilic defects to this risk.

6 The absolute risk of fetal loss in women with high TAFI levels.

References

1 Stirling Y, Woolf L, North WR, Seghatchian MJ, Meade TW. Haemostasis in normal pregnancy. Thromb Haemost 1984; 52: 76-82.

2 Hellgren M, Blomback M. Studies on blood coagulation and fibrinolysis in pregnancy, during delivery and in the puerperium. I. Normal condition. Gynecol Obstet Invest 1981; 12: 141-154.

3 Cordts PR, Gawley TS. Anatomic and physiologic changes in lower extremity venous hemodynamics associated with pregnancy. J Vasc Surg 1996; 24: 763-767.

4 Eichinger S, Weltermann A, Philipp K, Hafner E, Kaider A, Kittl EM, Brenner B, Mannhalter C, Lechner K, Kyrle PA. Prospective evaluation of hemostatic system activation and thrombin potential in healthy pregnant women with and without factor V Leiden. Thromb Haemost 1999; 82: 1232-1236.

5 Kjellberg U, Andersson NE, Rosen S, Tengborn L, Hellgren M. APC resistance and other haemostatic variables during pregnancy and puerperium. Thromb Haemost 1999;81: 527-531.

6 de Moerloose P, Mermillod N, Amiral J, Reber G. Thrombomodulin levels during normal pregnancy, at delivery and in the postpartum: comparison with tissue-type plasminogen activator and plasminogen activator inhibitor-1. Thromb Haemost 1998; 79: 554-556.

7 Nakashima A, Kobayashi T, Terao T. Fibrinolysis during normal pregnancy and severe preeclampsia relationships between plasma levels of plasminogen activators and inhibitors. Gynecol Obstet Invest 1996; 42: 95-101.

8 Chabloz P, Reber G, Boehlen F, Hohlfeld P, de Moerloose P. TAFI antigen and D- dimer levels during normal pregnancy and at delivery. Br J Haematol 2001; 115: 150-152.

9 Kierkegaard A. Incidence and diagnosis of deep vein thrombosis associated with pregnancy. Acta Obstet Gynecol Scand 1983; 62: 239-243.

10 Rochat RW, Koonin LM, Atrash HK, Jewett JF. Maternal mortality in the United States: report from the Maternal Mortality Collaborative. Obstet Gynecol 1988; 72: 91-97.

11 Toglia MR, Weg JG. Venous thromboembolism during pregnancy. N Engl J Med 1996; 335: 108-114.

12 McColl MD, Ramsay JE, Tait RC, Walker ID, McCall F, Conkie JA, Carty MJ, Greer IA. Risk factors for pregnancy associated venous thromboembolism. Thromb Haemost 1997; 78: 1183-1188.

13 Ginsberg JS, Brill-Edwards P, Burrows RF, Bona R, Prandoni P, Buller HR, Lensing A. Venous thrombosis during pregnancy: leg and trimester presentation. Thromb Haemost 1992; 67: 519-520.

14 Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton LJ 3rd. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. Ann Intern Med 2005; 143: 697-706.

15 Rai RS, Regan L, Chitolie A, Donald JG, Cohen H. Placental thrombosis and second trimester miscarriage in association with activated protein C resistance. Br J Obst Gynaecol 1996; 103: 842-844.

16 Pabinger I, Vormittag R. Thrombophilia and pregnancy outcomes. J Thromb Haemost 2005; 3: 1603-1610.

17 Stirrat G.M. Recurrent miscarriage. Lancet 1990; 336: 673-675.

18 Rai R, Regan L. Recurrent miscarriage. Lancet 2006; 368:601-611.

19 Branch DW, Silver RM, Blackwell JL, Reading JC, Scott JR. Outcome of treated pregnancies in women with antiphospholipid syndrome: an update of the Utah experience. Obstet Gynaecol 1992; 80: 614-620.

20 Egeberg O. Inherited Antithrombin deficiency causing thrombophilia. Thromb Diath Haemorrh 1965; 13: 516-530.
21 Sanson BJ, Simioni P, Tormene D, Moia M, Friederich PW, Huisman MV, Prandoni P, Bura A, Rejto L, Wells P, Mannucci PM, Girolami A, Buller 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: 3702-3706.
22 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: 64-67.
23 Koster T, Rosendaal FR, de Ronde H, Briet E, Vandenbroucke JP, Bertina RM. Venous thrombosis due to poor anticoagulant response to activated protein C: Leiden Thrombophilia Study. Lancet 1993; 34: 1503-1506.
24 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: 3698-3703.
25 Koster T, Blann AD, Briet E, Vandenbroucke JP, Rosendaal FR. Role of clotting factor VIII in effect of von Willebrand factor on occurrence of deep-vein thrombosis. Lancet 1995; 345: 152-155.
26 Bank I, Libourel EJ, Middeldorp S, Hamulyak K, van Pampus EC, Koopman MM, Prins MH, van der Meer J, Buller HR. Elevated levels of FVIII:C within families are associated with an increased risk for venous and arterial thrombosis. J Thromb Haemost 2005; 3: 79-84.
27 Den Heijer M, Koster T, Blom HJ, Bos GM, Briet E, Reitsma PH, Vandenbroucke JP, Rosendaal FR. Hyperhomocysteinemia as a risk factor for deep-vein thrombosis. N Engl J Med 1996; 344: 759-761.
28 Lijfering WM, Coppens M, van de Poel MHW, Middeldorp S, Hamulyak K, Bank I, Veeger NJ, Prins MH, Buller HR, van der Meer J. The risk of venous and arterial thrombosis in hyperhomocysteinemia is low and mainly depends on concomitant thrombophilic defects. Thromb Haemost 2007; 98: 457-463.
29 Martinelli I, Bucciarelli P, Zighetti ML, Cafro A, Mannucci PM. Low risk of thrombosis in family members of patients with hyperhomocysteinaemia. Br J Haematol 2002; 117: 709-711.
30 Bajzar L, Manuel R, Nesheim ME. Purification and characterization of TAFI, a thrombin-activatable fibrinolysis inhibitor. J Biol Chem 1995; 270: 14477-14484.
31 Henry M, Aubert H, Morange PE, Nanni I, Alessi MC, Tiret L, Juhan-Vague I. Identification of polymorphisms in the promoter and the 3' region of the TAFI gene: evidence that plasma TAFI antigen levels are strongly genetically controlled. Blood 2001; 97: 2053-2058.
32 Juhan-Vague I, Renucci JF, Grimaux M, Morange PE, Gouvernet J, Gourmelin Y, Alessi MC. Thrombin-activatable fibrinolysis inhibitor antigen levels and cardiovascular risk factors. Arterioscler Thromb Vasc Biol 2000; 20: 2156-2161.
33 van Tilburg NH, Rosendaal FR, Bertina RM. Thrombin activatable fibrinolysis inhibitor and the risk for deep vein thrombosis. Blood 2000; 95: 2855-2859.
34 Libourel EJ, Bank I, Meinardi JR, Balje -Volkers CP, Hamulyak K, Middeldorp S, Koopman MM, van Pampus EC, Prins MH, Buller HR, van der Meer J. Co-segregation of thrombophilic disorders infactor V Leiden carriers; the contributions of factor VIII, factor XI, thrombin activatable fibrinolysis inhibitor and lipoprotein(a) to the absolute risk of venous thromboembolism. Haematologica 2002; 87: 1068-1073.

35 Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, Derksen RH, de Groot PG, Koike T, Meroni PL, Reber G, Shoenfeld Y, Tincani A, Vlachoyiannopoulos PG, Krilis SA. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006; 4: 295-306.

36 Greer IA. Inherited thrombophilia and venous thromboembolism. Best Pract Res Clin Obstet Gynaecol 2003; 17: 413-425.

37 Friederich, P.W., Sanson, B.J., Simioni, P., Zanardi, S., Huisman, M.V., Kindt, I., Prandoni, P., Buller, H.R., Girolami, A. & Prins, MH.(1996) Frequency of pregnancy-related venous thromboembolism in anticoagulant factor- deficient women: implications for prophylaxis. Annals of Internal Medicine, 125, 955-960.

38 Conard J, Horellou MH, Van Dreden P, Lecompte T, Samama M. Thrombosis and pregnancy in congenital deficiencies in AT III, protein C or protein S: study of 78 women. Thromb Haemost 1990; 63: 319-320.

39 De Stefano V, Leone G, Mastrangelo S, Tripodi A, Rodeghiero F, Castaman G, Barbui T, Finazzi G, Bizzi B, Mannucci PM. Thrombosis during pregnancy and surgery in patients with congenital deficiency of antithrombin III, protein C, protein S. Thromb Haemost 1994; 71: 799-800.

40 Pabinger I, Schneider B. Thrombotic risk in hereditary antithrombin III, protein C, or protein S deficiency. A cooperative, retrospective study. Gesellschaft fur Thrombose- und Hamostaseforschung (GTH) Study Group on Natural Inhibitors. Arterioscler Thromb Vasc Biol 1996; 16: 742-748.

41 Middeldorp S, Henkens CMA, Koopman MMW, van Pampus ECM, Hamulyák K, van der Meer J, Prins MH, Buller HR. The incidence of venous thromboembolism in family members of patients with factor V Leiden mutation and venous thrombosis. Ann Intern Med 1998; 128: 15-20.

42 Bank I, Libourel EJ, Middeldorp S, van Pampus ECM, Koopman MMW, Hamulyák K, Prins MH, van der Meer J, Büller HR. Prothrombin G20210A mutation: a mild risk factor for venous thromboembolism but not for arterial thrombotic disease and pregnancy-related complications in a family study. Arch Intern Med 2004; 164: 1932-1937.

43 McColl MD, Ellison J, Reid F, Tait RC, Walker ID, Greer IA. Prothrombin 20210 G-->A, MTHFR C677T mutations in women with venous thromboembolism associated with pregnancy. BJOG 2000; 107: 565-569.

44 Sanson BJ, Friederich PW, Simioni P, Zanardi S, Hilsman MV, Girolami A, ten Cate JW, Prins MH. The risk of abortion and stillbirth in antithrombin-, protein C-, and protein S-deficient women. Thromb Haemost 1996; 75: 387-388.

45 Meinardi JR, Middeldorp S, de Kam PJ, Koopman MM, van Pampus ECM, Hamulyák K, Prins MH, Büller HR, van der Meer J. Increased risk for fetal loss in carriers of the factor V Leiden mutation. Ann Intern Med 1999; 130: 736-739.

46 Preston FE, Rosendaal FR, walker ID, Briet E, Berntorp E, Conard J, Fontcuberta J, Makris M, Mariani G, Noteboom W, Pabinger I, Legnani C, Scharrer I, Schulman S, van der Meer FJM. Increased fetal loss in women with heritable thrombophilia. Lancet 1996; 348: 913-916.

47 Rey E, Kahn SR, David M, Shrier I. Thrombophilic disorders and fetal loss: a meta-analysis. Lancet 2003; 361: 901-908.

48 Robertson L, Wu O, Langhorne P, Twaddle S, Clark P, Lowe GDO, Walker ID, Greaves M, Brenkel I, Regan L, Greer IA. Thrombophilia in pregnancy: a systematic review. Br J Haematol 2006; 132: 171-196.
49 Middeldorp S, van der Poel MH, Bank I, Hamulyák K, Libourel EJ, Koopman MMW, Prins MH, van der Meer J, Buller HR. Unselected women with elevated levels of factor VIII:c or homocysteine are not at increased risk for obstetric complications. Thromb Haemost 2004; 92: 787-790.
50 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: 401-407.
51 Schuitemaker NW, Gravenhorst JB, Van Geijn HP, Dekker GA, Van Dongen PW. Maternal mortality and its prevention. Eur J Obstet Gynecol Reprod Biol 1991; 42: S31-S35.
52 McColl M, Ellison J, Greer IA, Tait RC, Walker ID. Prevalence of the post-thrombotic syndrome in young women with previous venous thromboembolism. Br J Haemotol 2000; 108: 272-274.
53 Brill-Edwards P, Ginserg JS. Safety of withholding antepartum heparin in women with a previous episode of venous thromboembolism. N Engl J Med 2000; 343: 1439-1444.
54 White RH, Chan WS, Zhou H, Ginsberg JS. Recurrent venous thromboembolism after pregnancy-associated versus unprovoked thromboembolis. Thromb Haemos 2008; 2: 246-252.
55 Bates SM, Greer IA, Pabinger I, Sofaer S, Hirsh J. Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133: 844S-886S.
56 NVOG. Diepveneuze trombose, longembolie en zwangerschap. Richtlijn 2003.
57 Bates SM, Greer IA, Pabinger I, Sofaer S, Hirsh J. Venous thromboembolism, thrombophilia, anti-thrombotic therapy, and pregnancy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133: 844S-886S.
58 Rai R, Backos M, Elgaddal S, Shlebak A, Regan L. Factor V Leiden and recurrent miscarriage-prospective outcome of untreated pregnancies. Hum Reprod 2002; 17: 442-445.
59 Lindqvist PG, Merlo J. The natural course of women with recurrent fetal loss. J Thromb Haemost 2006; 4: 896-897
60 Frias AE Jr, Luikenaar RA, Sullivan AE, Lee RM, Porter TF, Branch DW, Silver RM. Poor obstetric outcome in subsequent pregnancies in women with prior fetal death. Obstet Gynecol 2004; 104: 521-526.