

Thrombophilia and its impact on pregnancy

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Keywords

Thrombophilia, pregnancy, fetal loss, abortion, pre-eclampsia, stillbirth

Summary

In recent years thrombophilia has gained much attention as a risk factor for pregnancy complications. Whereas there is an established correlation between antiphospholipid-antibodies and pregnancy loss, data for other risk factors of thrombosis are less well established. Data suggest associations with antithrombin deficiency, hyperhomocysteinemia and also with factor V Leiden, prothrombin G20210A variation and protein S-deficiency. The association of thrombophilia with pre-eclampsia is still under discussion. A limited number of prospective studies did not reveal an increased risk for pregnancy complications in unselected women with thrombosis risk factors. In a single study low molecular weight heparin seemed to have a positive effect on pregnancy outcome after previous single or recurrent abortions. Experience in prevention of pre-eclampsia by administration of prophylactic heparin is very limited. Data on pregnancy complications in women with known heritable thrombophilia or a history of thrombosis are inconsistent as well. These women usually have a favourable pregnancy outcome. **Conclusion:** Thrombophilia screening might be justified in women with pregnancy loss. Treatment with low molecular weight heparin might be considered for those with pregnancy loss and thrombophilia. Further prospective studies and controlled interventional trials are urgently needed.

Schlüsselwörter

Thrombophilie, Schwangerschaft, Fehlgeburt, Präeklampsie, Totgeburt

Zusammenfassung

In den vergangenen Jahren hat die Thrombophilie als Risikofaktor für Schwangerschaftskomplikationen große Beachtung gefunden. Während der Zusammenhang mit Antiphospholipid-Antikörpern und Aborten als gesichert gilt, ist dies für andere Thromboserisikofaktoren noch in Diskussion. Daten über Antithrombinmangel, Hyperhomocysteinämie, Faktor-V-Leiden-Mutation und Prothrombin-G20210A-Variation sowie Protein-S-Mangel in Zusammenhang mit Aborten liegen vor, die Assoziation mit der Präeklampsie wird diskutiert. Eine limitierte Anzahl von prospektiven Studien konnte das erhöhte Risiko zwischen Thrombophilie und Schwangerschaftskomplikationen nicht schlüssig nachweisen. Eine einzige randomisierte Interventionsstudie mit niedermolekularem Heparin bei Spätaborten ergab ein sehr positives Ergebnis hinsichtlich der Verabreichung von Enoxaparin. Daten über Schwangerschaftskomplikationen bei Frauen mit bereits bekannter Thrombophilie oder einer Vorgeschichte von Thrombosen sind ebenfalls nicht übereinstimmend hinsichtlich des Risikos für Aborte und Präeklampsie. Bei diesen Frauen ist jedoch im Allgemeinen mit einem positiven Schwangerschaftsergebnis zu rechnen. **Schlussfolgerung:** Primäres Thrombophilie-Screening bei Schwangeren ist zurzeit nicht indiziert. Die Prophylaxe mit niedermolekularem Heparin bei rezidivierenden Spätaborten (nach der 10. Schwangerschaftswoche) und vorhandener Thrombophilie soll in Erwägung gezogen werden. Weitere prospektive oder Interventionsstudien sind dringend notwendig.

related deep vein thrombosis and pulmonary embolism. Thrombotic processes may also be involved in other serious obstetric complications, such as recurrent pregnancy loss, pre-eclampsia, intrauterine growth retardation (IUGR) and placental abruption by impairment of placental perfusion.

Pregnancy itself induces a physiological hypercoagulable state (2–6) that might be aggravated by inherited or acquired thrombophilia. Results of studies on pregnancy complications in women with thrombophilia have been conflicting. Interventional trials on the use of anticoagulants for the prevention of pregnancy complications have shown promising results.

Pregnancy loss

Abortion/miscarriage is defined as pregnancy loss before the 20th week of gestation (calculated by sonography or on basis of the first day of the last period) or when the fetus' weight is less than 500 g (7). Systematic studies have revealed that approximately 50% of pregnancies are lost after implantation, but only a minority of these are clinically diagnosed. Sixty percent of first-trimester spontaneous abortions are associated with an abnormal karyotype of the fetal tissue, in contrast to only about 30% of second-trimester abortions and 3% of stillbirths.

Systemic illnesses have not been clearly associated with an increased risk of abortion, but infections and chemotherapeutic agents can cause abortion especially during early gestation. Certain environmental factors are associated with a higher risk of abortion, e. g. cigarette smoking, alcohol and heavy coffee consumption.

Habitual or recurrent (repetitive) pregnancy loss is defined as three consecutive pregnancy losses before the 20th week of

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Thrombophilie und Schwangerschaft

Venous thromboembolism, pre-eclampsia and pregnancy loss are nowadays the most frequent pregnancy complications. Heritable prothrombotic factors lead to an increased risk of thromboembolism and are also under discussion to

- significantly impair the outcome of pregnancy and
- to play a considerable role in the pathogenesis of spontaneous abortions.

Recurrent abortion involves more than 500 000 women in the United States of America per year (1). Within the past ten years interest in correlations between thrombophilia and complications of pregnancy has remarkably increased. Thrombophilia is present in at least 15% of the Western population and is found in up to 50% of individuals with venous thromboembolism. It apparently plays a critical role in the development of pregnancy-

gestation (7). Since the probability of one clinically evident spontaneous abortion is normally about 20%, that of two consecutive losses is about 4% and that of three consecutive losses about 0.8%. Thus, recurrent abortion in normal women is a rare finding. Common gynaecological causes of recurrent first-trimester abortions are a luteal phase defect or uterine abnormalities.

Antiphospholipid antibodies are widely accepted as established risk factors for pregnancy loss in general and have convincingly been established as major risk factors especially for second-trimester pregnancy loss and stillbirth. In 1996, the first reports on an association between other forms of thrombophilia and recurrent pregnancy loss were published (8–10). Since then numerous case/control studies investigating the impact of thrombophilia on pregnancy loss have been conducted (11–18). In most of these studies

- factor V Leiden (factor V 16691 G/A),
- prothrombin 20210 A/G and
- the methylene tetrahydrofolate gene 677 C/T variation were determined.

Some studies also included other classical markers of thrombophilia, such as deficiencies (11, 19) in

- antithrombin,
- protein C,
- protein S and
- the presence of antiphospholipid antibodies.

The largest study was performed by Rai et al. (20), who investigated the association between factor V Leiden and recurrent pregnancy loss in more than 1000 consecutive Caucasian women. This study did not demonstrate an association of recurrent miscarriage with factor V Leiden, but found a significantly higher number of women with acquired APC-resistance in the group with recurrent miscarriage in comparison to control women. Neither could Carp et al. confirm an increased risk for pregnancy loss in women with thrombophilia (21).

In metaanalysis data on pregnancy loss and thrombophilia are summarized (22–24). They all report increased odds ratios (OR) of approximately 2 or more for recurrent fetal loss in carriers of factor V Leiden. Rey

Tab. 1
Pregnancy loss in women with thrombophilia and controls

reference	patients controls	women n	pregnancies n	fetal loss	
				n	%
Preston et al. (8)	AT	108	260	50	19.2
	PC	162	430	73	17.0
	PS	145	378	62	16.4
	factor V Leiden* controls	141	410	48	11.7
		395	1019	124	12.2
Meinardi et al. (50)	factor V Leiden†	228	654	107	16.4
	controls (relatives)	121	352	32	9.1
Pabinger et al. (46)	factor V Leiden	64	212	32	15
	(all homozygous) controls	52	118	14	12
Tormene et al. (51)	factor V Leiden	65	191	31	16.2
	controls (relatives)	44	121	13	10.7
Sanson et al. (10)	AT, PC, PS	60	188	42	22.3
	controls (relatives)	69	202	23	11.4

AT: antithrombin deficiency; PC: protein C-deficiency; PS: protein S-deficiency;
* number of homozygous individuals not given; †15 homozygous

et al. (24) separately analysed women with early recurrent fetal loss (OR = 2.0), non-recurrent fetal loss (OR = 1.7) and fetal loss after 19 weeks of gestation (OR = 3.3). Similarly high odds ratios were calculated for carriers of prothrombin 20210 G/A variation (OR = 2.0 for recurrent fetal loss). Homozygous MTHFR variation was not confirmed as a risk factor in metaanalysis. The highest OR (7.3) was calculated for protein S-deficiency, however, data of only three studies were analysed. A small number of studies was performed in women from populations in whom the factor V Leiden mutation is rare or not even existing. As expected, factor V Leiden was neither identified as a risk factor in women with recurrent fetal loss, nor in the controls (25). The results of a systematic review covering 25 studies with a total of 7167 women confirmed the results outlined (26).

Data of two population-based prospective cohort studies with a large number of participating women are available (27, 28). In these studies 3020 women were included. Factor V Leiden was detected in 283 women. Neither the proportion of second-trimester abortion nor pre-eclampsia or intrauterine growth restriction (IUGR) was significantly higher in carriers of factor V Leiden than in controls.

Prevention of recurrent pregnancy loss by treatment with anticoagulants has been

evaluated in a number of studies. Usually heparin was administered; in some women additionally aspirin was given (15, 29–32). A better outcome in comparison to historical controls or the previous pregnancy was noted in all studies. Data of one randomized controlled trial have been published (33). In this trial women with either factor V Leiden, the prothrombin 20210 G/A variation or protein S deficiency with a single pregnancy loss after the 9th week of gestation, with no unexplained loss before the 10th week of gestation and no explained pregnancy losses after the 10th week of gestation were included. Eighty women received 40 mg of enoxaparin subcutaneously and the same number of women (controls) received 100 mg of aspirin once daily. Eighty-six percent of women treated with heparin had a successful pregnancy outcome in comparison to only 29% of those treated with aspirin. It has to be mentioned that the rate of successful pregnancies even after recurrent abortion is higher than 50%.

Further randomized controlled (blinded) trials are urgently needed to prove a positive effect of heparin on the outcome of pregnancies in women with previous pregnancy loss with and without known thrombophilia. Until stronger evidence is available it is difficult to decide whether treatment with heparin should be recommended for women with previous pregnancy loss. Prophylactic

Tab. 2 Randomized studies comparing prophylaxis with heparin or LMWH plus aspirin versus aspirin alone in women with recurrent pregnancy loss and antiphospholipid antibodies

reference	event rate under		
	heparin/ LMWH plus aspirin, n/n (%)	aspirin, n/n (%)	relative risk (95% CI)
Kutteh (55)	5/25 (20)	14/25 (56)	0.36 (0.15–0.84)
Rai et al. (54)	13/45 (29)	26/45 (58)	0.50 (0.30–0.84)
Farquharson et al. (56)	11/51 (22)	13/47 (28)	0.78 (0.39–1.57)

Kutteh and Rai et al. administered unfractionated heparin 5000 units twice daily, whereas Farquharson et al. dalteparin 5000 units once daily.
LMWH: low-molecular weight heparin; CI: confidence interval

doses usually do not harm mother or fetus. Heparin significantly reduces the risk of thromboembolic events during pregnancy, which is particularly important for thrombophilic women as long as treatment alternatives with proven efficacy are not available.

Pre-eclampsia

The incidence of pre-eclampsia is approximately 5% in a Caucasian population (34). The term severe pre-eclampsia is used when a blood pressure above 160/110 mmHg in two measurements at least six hours apart and proteinuria of more than five gram during 24 hours occur. HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome is considered to be an atypical form of pre-eclampsia.

First reports on a higher incidence of thrombosis risk factors in women with pre-eclampsia and/or HELLP syndrome were published in 1996 (35, 36). Since then numerous studies mostly with a case-control design have been published, e. g. van Pampus et al. (37) found a very high prevalence of thrombophilia (40%) in women with a history of severe pre-eclampsia. In this study tests for thrombophilia included not only genetic polymorphisms but also APC-resistance, hyperhomocysteinemia and anti-

cardiolipin antibodies.

Metaanalyses (38–40) were performed to analyse an association between thrombophilia and pre-eclampsia. A large meta-analysis by Kosmas et al. (38) focused on factor V Leiden. It included data of almost 3000 women with pregnancy-associated hypertension and normotensive controls and an odds ratio of 2.3 (95% CI: 1.5–3.4) was calculated. However, results of the studies included in the analysis were very conflicting and statistically significant heterogeneity in the results of different studies was found (38). Of three of four large studies including more than 200 women with pre-eclampsia none could find an association with factor V Leiden, whereas only one did.

In a metaanalysis Kosmas et al. (39) specifically addressed whether the C677T polymorphism in the MTHFR gene had an impact on the development of pre-eclampsia. A moderately increased risk in carriers of the T allele (MTHFR 667 CT and TT) in comparison to homozygous carriers of the C allele (MTHFR 667 CC) was found (OR 1.3, 95% CI: 1.0–1.4). However, data of the studies included in the analysis again were very conflicting, as described above for the analysis of factor V Leiden. Hyperhomocysteinaemia determined in early second trimester predicted neither the development of pre-eclampsia nor intrauterine growth restriction in a recently published prospective study including 1874 women.

In conclusion, factor V Leiden and MTHFR 677 C/T polymorphism and other hereditary forms of thrombophilia may moderately increase the risk of pre-eclampsia during pregnancy, however, the evidence linking thrombophilia to pre-eclampsia is weak and routine screening of pregnant women for thrombophilia is not recommended.

While large interventional trials studied the effect of aspirin on the recurrence rate of pre-eclampsia, only limited data are available regarding low molecular weight heparin (LMWH). No benefit for pregnancy outcome was observed under treatment with aspirin compared to placebo in women with a history of pre-eclampsia (41). Ongoing prospective studies investigate the recurrence rate of pre-eclampsia in women under LMWH.

Pregnancy outcome in women with thrombophilia

Women with a history of thromboembolism or known thrombophilia have an increased risk for pregnancy-associated recurrent thromboembolism (42–45). Retrospective and prospective studies have revealed a relatively favourable outcome of pregnancies in women with a history of venous thrombosis regardless of heparin prophylaxis during pregnancy (46–48). Women with antiphospholipid-antibodies are an important exception. They have a high risk of thrombosis, pregnancy loss and pre-eclampsia (49). Only a limited number of studies on pregnancy outcome in women with a history of venous thromboembolism or known thrombophilia has been published. Preston et al. (8) reported on an increased risk of stillbirth (defined as intrauterine death after and including the 28th week of gestation) in women with anti-thrombin- and protein S-deficiency and combined defects, whereas the risk was not significantly increased in women with protein C-deficiency and factor V Leiden.

There was no significant increase in the risk of miscarriage (fetal loss up to and including the 27th week of gestation) for various deficiency states except a borderline increased risk in antithrombin-deficient women (OR 1.7, 95%-CI 1.0–2.8). Meinardi et al. (50) found an increased frequency of fetal loss, especially miscarriage, in women carrying the factor V Leiden mutation in comparison to non-carrier relatives, whereas Tormene et al. (51) described an increased risk of stillbirth but not miscarriage in women with factor V Leiden in comparison to non-carrier relatives.

In a multicenter study (46) we retrospectively evaluated pregnancy outcome in 64 women with homozygous factor V Leiden mutation in comparison to 52 age-matched control women. The proportion of pregnancies ending with stillbirth was higher in the patient group (3.3%) than in controls (1.7%). However, the difference was not statistically significant. Results regarding miscarriage were almost equal in homozygous carriers in comparison to controls. In a case control study the frequency of fetal

loss and pre-eclampsia was studied in women with and without a history of VTE (52). Whereas fetal loss was no more frequent in women with previous VTE, pregnancy-induced hypertension was more prevalent in cases than in controls.

The only prospective and controlled study specifically addressing hereditary thrombophilia and fetal loss was performed by the EPCOT (European prospective cohort on thrombophilia) study group (53). No significantly increased risk for fetal loss was found in 48 women with thrombophilia in comparison to 60 controls from the general population.

The most compelling association between thrombophilia and pregnancy loss is with

- antiphospholipid antibodies,
- lupus anticoagulant, and
- cardiolipin antibodies.

Women with antiphospholipid-antibodies have a high risk for thrombosis, pregnancy loss and preeclampsia (49). Rai et al. (54) reported data of a randomized controlled trial in which the outcome of pregnancies of women with antiphospholipid antibodies and previous recurrent fetal loss was markedly improved by combined treatment with 75 mg of aspirin and unfractionated heparin 5000 Units 12 hourly. The rate of life births was 71% in women treated with aspirin and heparin and 42% with aspirin alone. A similar observation was made by Kutteh et al. (55), while it has to be mentioned that in this study women with lupus anticoagulant were excluded.

In contrast to the previous studies Farquharson et al. (56) did not confirm an improvement by adding heparin: He found a comparable life birth rate of 78% in the group of 51 women treated with aspirin and heparin and of 72% in the 47 women treated with aspirin alone. Since the randomized studies arrived at different conclusions it remains unclear whether adding low molecular weight heparin definitely improves pregnancy outcome in women with antiphospholipid antibodies. From clinical experience the author of this review is in favour of using combined LMWH and aspirin in women with antiphospholipid antibodies.

Published data are inconsistent regarding pregnancy outcome in women with

thrombophilia. Nowadays, it has been widely accepted that women with a history of venous thromboembolism without antiphospholipid antibodies have usually a favourable pregnancy outcome. Data of one prospective study are available, in which women with a history of venous thromboembolism did not receive heparin prophylaxis (47). The investigators found a low risk of recurrent thrombosis (around 3%), but unfortunately did not give any information on other pregnancy complications.

A study on women with an increased risk for VTE was recently published (57). Women were stratified into three different risk groups and received either no prophylaxis or dalteparin in two dosage regimens (50–100 U/kg/day and 100–200 U/kg/day). The overall outcome was favourable with a low risk of VTE and an acceptable risk for adverse pregnancy outcome (4.9% of miscarriage, 16% premature births). A large review (58) confirms the safety of LMWH during pregnancy. Randomized trials are urgently needed in order to base treatment decisions in pregnant women with thrombophilia on improved evidence.

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