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Summary
Venous thromboembolism is the leading cause of pregnancy-associated morbidity and mortality. Women with thrombophilia have an increased risk of VTE in pregnancy and the puerperium. In individuals with hereditary thrombosis risk factors, a relative risk of pregnancy-associated VTE ranging from 3.4 to 15.2 has been found. Women with previous VTE have an approximately 3.5-fold increased risk of recurrent VTE during pregnancy compared to non-pregnant periods.

Data on the association of thrombophilia and pregnancy loss and pre-eclampsia are conflicting. Besides an established association with antiphospholipid antibodies, available data suggest associations for antithrombin deficiency, hyperhomocysteinemia, factor V Leiden, prothrombin G20210A variation and protein S-deficiency. A contribution of thrombophilia to the risk of pre-eclampsia is less well established. A limited number of prospective studies did not reveal an increased risk of pregnancy complications in unselected women with thrombosis risk factors. Data of only one controlled trial on the prevention of pregnancy loss with low molecular weight heparin (LMWH) are available, which revealed a strikingly positive effect. Thrombophilia screening might be justified in women with pregnancy loss and treatment with LMWH might be considered in those with pregnancy loss and thrombophilia. Further prospective studies and controlled interventional trials are urgently needed.

Risk of pregnancy-associated venous thromboembolism

The risk of pregnancy-associated VTE has been estimated to vary from 1:2000 to 1:1000 in the general population (23). The risk of VTE is five times higher in a pregnant woman than in a non-pregnant woman of similar age. Postpartum VTE is more common than antepartum VTE.

Women with congenital thrombophilia or persistent presence of anti-phospholipid antibodies have an increased risk of VTE during pregnancy and the puerperium (18). In individuals with established hereditary thrombosis risk factors, such as factor V Leiden, prothrombin G20210A variation, antithrombin-deficiency or protein C-deficiency, relative risks of pregnancy-associated VTE ranging from 3.4 to 15.2 have been reported (5). In women with factor V Leiden a thrombosis risk of approximately 1:450 has been found (12). In women with a combination of heterozygous prothrombin G20210A variation and factor V Leiden the risk is disproportionately higher than in those with one mutation only (5). In homozygous carriers of the factor V Leiden mutation the thrombosis risk is most probably close to 5% during pregnancy (17).

Limited data exist on the pregnancy-associated VTE risk in women with a history of VTE. In a recently published prospective study in 125 pregnant women with a history of VTE who did not receive prophylaxis an antepartum recurrence rate of only 2.4%...
Pregnancy loss

Abortion and miscarriage are defined as pregnancy loss before the 20th week of gestation (calculated by ultrasonography or on basis of the first day of the last period) or loss of a fetus that weighs less than 500 g. Habitual or recurrent (repetitive) pregnancy loss is defined as three consecutive losses before the 20th week of gestation. Since long time antiphospholipid antibodies are established risk factors for pregnancy loss (4). Numerous case-control studies investigated the impact of thrombophilia on pregnancy loss (9, 25). In most of these studies factor V Leiden, prothrombin G20210A variation and the methylene tetrahydrofolate reductase (MTHFR) gene 677 C/T variation were determined. Some studies also included other classical markers of thrombophilia, such as antithrombin-, protein C- and S-deficiency and anti-phospholipid antibodies (9). The largest study was performed by Rai et al. (21), who investigated the association between factor V Leiden and recurrent pregnancy loss in 1111 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.

Several meta-analysis have summarised and analysed data on pregnancy loss and thrombophilia. They all reported increased odds ratios (OR) of approximately 2 or more for recurrent fetal loss in carriers of factor V Leiden. Key et al. 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 (22). Homozygous MTHFR variation was not confirmed as a risk factor in meta-analysis (22).

Currently data of two population-based prospective cohort studies with a large number of participating women are available (11; 13). Factor V Leiden was detected in 283 of 3020 women (9.4 %). Besides MTHFR mutation in the study of Murphy and colleagues no other risk markers of thrombophilia were analysed. 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 (Tab. 2).

Data of one randomised controlled trial have been published (6). 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, were included. Eighty women received 40 mg of enoxaparin and the same number of women (controls) received 100 mg of aspirin once daily. Eighty-six percent of pregnancies of women treated with heparin were successful in comparison to only 29% of pregnancies of women treated with aspirin (OR of 16; 95% CI 7-34). The observed rate of successful pregnancies of women treated with aspirin, who had mild thrombophilia (factor V Leiden or prothrombin variation) and a history of a single abortion, is much lower than it would have been expected from other studies: A rate of 65% successful pregnancies was described in women from the general population with a history of recurrent pregnancy loss.

It remains to be elucidated whether thrombophilia definitely increases the risk for pregnancy loss. The positive effect of heparin should be confirmed by further studies before it can be recommended in women with and without thrombophilia and pregnancy loss.

Pre-eclampsia

Pre-eclampsia is a serious pregnancy complication characterised by hypertension and proteinuria. Pre-eclampsia may lead to a widespread organ damage of kidneys, brain and placenta. Hypertension of pregnancy and pre-eclampsia have been considered to have a strong genetic background.

First reports on a higher incidence of thrombosis risk factors in women with pre-eclampsia and or HELLP syndrome were published in 1996 and a number of case/control studies followed. A large meta-analysis by Kosmas et al. focused on factor...
V Leiden (7). The meta-analysis 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 studies included in the analysis were very conflicting and statistically significant heterogeneity in the results of different studies was found. Interestingly, no study published since 2000 found a positive association. In a recent meta-analysis Kosmas et al. (8) 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 studies included in the analysis were very conflicting, as before in the analysis of factor V Leiden. Moreover, all studies published between 2001 and 2003 reported no significant association (OR 1.3, 95% CI 0.8 – 2.2). In conclusion, factor V Leiden, MTHFR 677 C/T polymorphism and other hereditary thrombosis risk factors 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 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 in pregnancy outcome was observed under treatment with aspirin compared to placebo in women with a history of pre-eclampsia in two prospective trials. Ongoing prospective studies investigate the recurrence rate of pre-eclampsia in women under LMWH.

### Pregnancy complications in women with thrombophilia

Women with a history of thromboembolism or known thrombophilia have an increased risk for pregnancy associated recurrent thromboembolism (16, 18). Women with anti-phospholipid antibodies have a high risk of thrombosis, pregnancy loss and pre-eclampsia. Only a limited number of studies on pregnancy outcome in women with a history of venous thromboembolism or known thrombophilia have been published. Preston et al. (19) reported on an increased risk of stillbirth (defined as intrauterine death after and including the 28th week of gestation) in women with antithrombin- 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). Data on further case-control studies are conflicting, but mostly support an association between thrombophilia and pregnancy loss. Pregnancy outcome was evaluated in 64 women with homozygous factor V Leiden mutation in comparison to 52 matched control women (17). 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. Numbers were almost equal in homozgyous carriers in comparison to controls regarding miscarriage. The only prospective and controlled observational study specifically addressing hereditary thrombophilia and fetal loss was performed by the EPCOT (European prospective cohort on thrombophilia) study group (24). No significantly increased risk for fetal loss was found in 48 women with anti-thrombin-, protein C- or protein S-deficiency of factor V Leiden in comparison to 60 controls from the general population.

Women with anti-phospholipid antibodies have a high risk of thrombosis, pregnancy loss and pre-eclampsia. The hypothetical pathomechanism includes placental thrombosis and infarction. Rai et al. reported data of a randomised controlled trial, in which pregnancy outcome in women with anti-phospholipid antibodies and previous recurrent fetal loss was markedly improved by combined treatment with 75 mg acetylsalicylic acid (once daily) and 5000 units unfractionated heparin every 12 hours (20). The life birth rate of women treated with aspirin and heparin was 71% and 42% in those treated with acetylsalicylic acid alone. A

### Tab. 2 Pregnancy associated complications in women with and without factor V Leiden according to two prospective studies (15, 16)

<table>
<thead>
<tr>
<th>pregnancy complication</th>
<th>positive (n = 283)</th>
<th>negative (n = 2737)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>late spontaneous abortion*</td>
<td>6 (2.1)</td>
<td>40 (1.5)</td>
<td>1.4 (0.6-3.5)</td>
</tr>
<tr>
<td>pre-eclampsia</td>
<td>5 (1.8)</td>
<td>56 (2.0)</td>
<td>0.9 (0.3-2.2)</td>
</tr>
<tr>
<td>intrauterine growth restriction</td>
<td>9 (3.2)</td>
<td>88 (3.2)</td>
<td>1.0 (0.5-2.0)</td>
</tr>
</tbody>
</table>

*abortion within second or third trimester

### Tab. 3 Randomised trials comparing treatment with heparin or low molecular weight heparin (LMWH) plus acetylsalicylic acid alone in women with recurrent pregnancy loss and anti-phospholipid antibodies

<table>
<thead>
<tr>
<th>first author (reference)</th>
<th>event rate n/n (%)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kutteh (23)</td>
<td>heparin/LMWH + ASS</td>
<td>0.36 (0.15-0.84)</td>
</tr>
<tr>
<td>Rai (22)</td>
<td>ASS</td>
<td>0.50 (0.30-0.84)</td>
</tr>
<tr>
<td>Farquharson (24)</td>
<td>11/51 (22)</td>
<td>0.78 (0.39-1.57)</td>
</tr>
</tbody>
</table>

ASS: acetylsalicylic acid
similar observation was made by Kutter et al. (10) It has to be mentioned that in this study women with lupus anticoagulant were excluded. In contrast to previous studies Farquharson et al. (3) did not confirm a significantly better outcome under treatment with aspirin plus heparin. Life birth rate was 78% in 51 women treated with acetylsalicylic acid plus heparin and 72% in those (n = 47) treated with acetylsalicylic acid alone (Tab. 3)

Since randomised studies came to different conclusions it remains to be established, whether treatment with low molecular weight heparin plus aspirin is superior to aspirin alone regarding pregnancy outcome in women with anti-phospholipid antibodies.

We studied pregnancy outcome in 345 women with a history of objectively confirmed venous thromboembolism and in 313 healthy female controls from the same population without a history of venous thromboembolism (15). Women of the patient group had statistically significantly more often a history of pregnancy-induced hypertension and a non-significant tendency for severe pre-eclampsia. The rate of miscarriage and stillbirth was equally distributed between the two groups. An increased risk according to laboratory diagnosis of thrombophilia was not found.

Data regarding pregnancy outcome in women with thrombophilia are inconsistent. Most of the women with a history of venous thromboembolism without anti-phospholipid antibodies have a favourable pregnancy outcome that might be improved further by thrombosis prophylaxis. However, more prospective data of women with thrombophilia on their pregnancy outcome are needed, since this could have an influence on treatment recommendations.

References