Thrombosis Research 134 (2014) 837–845

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Regular Article

Increased activation of blood coagulation in pregnant women with the Factor V Leiden mutation ☆

Ulla Kjellberg [a,b,*], Marianne van Rooijen [c,d], Katarina Bremme [c,d], Margareta Hellgren [a,b,e]

[a] Department of Obstetrics, Sahlgrenska University Hospital, Gothenburg, Sweden
[b] Section for the Health of Women and Children, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Sweden
[c] Department of Obstetrics and Gynaecology, Karolinska University Hospital, Stockholm, Sweden
[d] Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden
[e] Department of Antenatal Care, Närhälsan Primary Care, Västra Götaland, Sweden

ARTICLE INFO

Article history:
Received 13 December 2013
Received in revised form 9 July 2014
Accepted 31 July 2014
Available online 9 August 2014

Keywords:
D-dimer
Factor V Leiden
Pregnancy
Prothrombin fragments 1 + 2
Soluble fibrin

ABSTRACT

Background: The risk of venous thromboembolism is enhanced in pregnant carriers of the Factor V Leiden mutation. The primary aim of the study was to compare prothrombin fragments 1 + 2, soluble fibrin and D-dimer levels in pregnant Factor V Leiden mutation carriers with those in non-carriers. Secondary aims were to evaluate whether these biomarkers could predict placenta-mediated complications or venous thromboembolism, and to study blood coagulation after caesarean section with thromboprophylaxis and after vaginal delivery without thromboprophylaxis.
Material/Methods: Prothrombin fragments 1 + 2, soluble fibrin and D-dimer levels were studied longitudinally in 476 carriers with singleton pregnancies from gestational weeks 23–25 until 8–10 weeks postpartum.
Results: Prothrombin fragments 1 + 2 and D-dimer levels gradually increased during pregnancy. D-dimer levels were higher in carriers, both during pregnancy and puerperium, compared to non-carriers. D-dimer levels above 0.5 mg/l were found in about 30% and 20% of the heterozygous carriers at 4–5 and 8–10 weeks postpartum, respectively. Soluble fibrin levels were mainly unchanged during pregnancy, with no difference between carriers and non-carriers. Biomarker levels were similar in carriers with uncomplicated and complicated pregnancies.
Conclusion: Higher D-dimer levels indicate increased blood coagulation and fibrinolysis activity in carriers. The high proportion of carriers with D-dimer levels exceeding 0.5 mg/l postpartum must be considered when assessing the probability of venous thromboembolism. Large overlaps in biomarker levels in normal and complicated pregnancies suggest that these biomarkers cannot be used as predictors. Thromboprophylaxis following caesarean section may prevent increased activation of blood coagulation.

Introduction

During pregnancy and postpartum, the haemostatic system changes into a state of hypercoagulability. The fibrinolytic system remains active and compensates for increased fibrin formation, although plasminogen activator inhibitor 1 and 2 levels are increased and basal tissue-type plasminogen activator activity is decreased [1–3]. The most common thrombophilia among Caucasians is hereditary activated protein C (APC) resistance, caused by the Factor V Leiden (FVL) mutation [4,5]. The related increased risk of venous thromboembolism (VTE) during pregnancy and puerperium in FVL carriers, compared to non-carriers, is well known [6,7]. However, the influence of the FVL mutation on placenta-mediated complications, including preeclampsia, small for gestational age (SGA) and placental abruption, is still controversial.

In order to study the activity of the blood coagulation and fibrinolysis systems, different biomarkers of blood coagulation activation, fibrin formation and fibrin degradation, such as prothrombin fragments 1 + 2 (F1 + 2), soluble fibrin (SF) complexes and D-dimers, can be analysed in plasma [8–10]. Only two longitudinal studies concerning F1 + 2 and D-dimer in FVL carriers with normal pregnancies, and none concerning SF [11,12], have been published.

The primary aim of this study was to determine F1 + 2, SF and D-dimer levels in pregnant FVL carriers, as well as to evaluate differences

Abbreviations: APC, activated protein C; c.s, caesarean section; CV, coefficient of variation; DIC, disseminated intravascular coagulation; DVT, deep vein thrombosis; ELISA, enzyme-linked immunosorbent assay; FVL, Factor V Leiden; F1 + 2, prothrombin fragments 1 + 2; IUFD, intrauterine fetal death; LMHW, low molecular weight heparin; r, Pearson's correlation coefficient; SD, standard deviation; SGA, small for gestational age; SF, soluble fibrin; VTE, venous thromboembolism.

☆ Authors' contributions: All authors researched the literature, planned the study, developed the protocol and recruited participants. MH and UK applied for ethical approval. UK undertook the data analysis and wrote the first draft of the manuscript. All authors contributed to data analysis, reviewed and edited the manuscript and approved the final version.

* Corresponding author at: Department of Obstetrics and Gynaecology, SU/Östra, S-416 85 Göteborg, Sweden. Tel.: +46 31 3434129.
E-mail address: ulla.kjellberg@hotmail.se (U. Kjellberg).

http://dx.doi.org/10.1016/j.thromres.2014.07.037
0049-3848/

between carriers and non-carriers. Secondary aims were to evaluate whether these biomarkers could serve as predictors for placenta-mediated complications or VTE during pregnancy and whether there was any difference among heterozygous carriers in activation of blood coagulation and fibrinolysis following caesarean section (c.s.) with thromboprophylaxis, compared to vaginal delivery without thromboprophylaxis. Prophylactic anticoagulant regimes might be of interest if increased activation of blood coagulation is found in women with the FVL mutation.

Materials and Methods

Participants

Random screening of 6000 pregnant women for APC resistance was performed in connection with the routine ultrasound at gestational week 17–18 in Gothenburg and Stockholm. 484 healthy carriers of the FVL mutation with no history of VTE and with singleton pregnancies were identified, and 476 agreed to participate in the study (Fig. 1).

The prothrombin gene (Factor II) mutation was routinely analysed in women with APC resistance in one of the study regions (n = 300), while it was analysed in the other study region only if there was heredity for VTE or if a complication occurred (n = 133.) The women were followed longitudinally, as previously described [10]. Short-term low molecular weight heparin (LMHW) was administered, according to routine, to women at transient increased risk of VTE during pregnancy. Thromboprophylaxis with LMHW was also given for six weeks postpartum to homozygous women and to women with additional thrombophilia and for one week postpartum to all carriers delivered by c.s.. Women who contracted VTE or superficial thrombophlebitis were treated with LMWH in therapeutic doses.

The local Ethics Committee for Medical Research at the University of Gothenburg approved the study.

Blood Sampling

Blood samples were taken, through careful venipuncture of a cubital vein following a 20-minute rest, between 7.30 and 10.00 a.m. at 23–25, 32–34 and 38–40 gestational weeks and at one day, 4–5 weeks and 8–10 weeks postpartum. Blood was collected in Vacutainer tubes containing 0.5 ml trisodium citrate (0.13 mol/l) (Venoject®, Terumo, Leuven, Belgium). The blood was handled as previously described and stored at −70 °C until analysed [3].

Samples taken during treatment with low-dose aspirin, dextran or LMWH were excluded from the statistical analyses, except from the comparison between women delivered with c.s. and those delivered vaginally.

Criteria for Diagnosis of Complications

Blood pressure was measured in the sitting subject's left arm at heart level after a 20-minute rest.

Gestational hypertension: ≥90 mm Hg diastolic blood pressure on two occasions, at minimum six-hour interval, after gestational week 20

Mild preeclampsia: ≥90 mm Hg diastolic blood pressure on two occasions and proteinuria (≥1 + reading on dipstick) on two occasions, at minimum six-hour interval, and negative urine culture

Severe preeclampsia: as mild preeclampsia but with one of the following additional findings:

- ≥120 mm Hg diastolic blood pressure once or ≥ 110 mm Hg diastolic blood pressure on two occasions, at minimum six-hour interval
- proteinuria ≥ 3 g per 24 hours
- symptoms/signs of organ dysfunction, such as renal insufficiency, pulmonary edema, eclampsia, visual disturbances, IUGR or platelet count $<100x10^9$/L

Small for gestational age (SGA): birth weight below two standard deviations (SD)

Placental abruption: abdominal pain, uterine tenderness, frequent small contractions and elevated uterine tone, together with vaginal bleeding or a retroplacental clot, i.e. a condition leading to immediate delivery

VTE: deep vein thrombosis (DVT) was diagnosed by triplex ultrasonography (combination of venous compression, color Doppler and pulsed Doppler ultrasonography), magnetic resonance venography or phlebography. Pulmonary embolism was diagnosed by spiral computed tomography or ventilation-perfusion lung scintigraphy according to Biello.

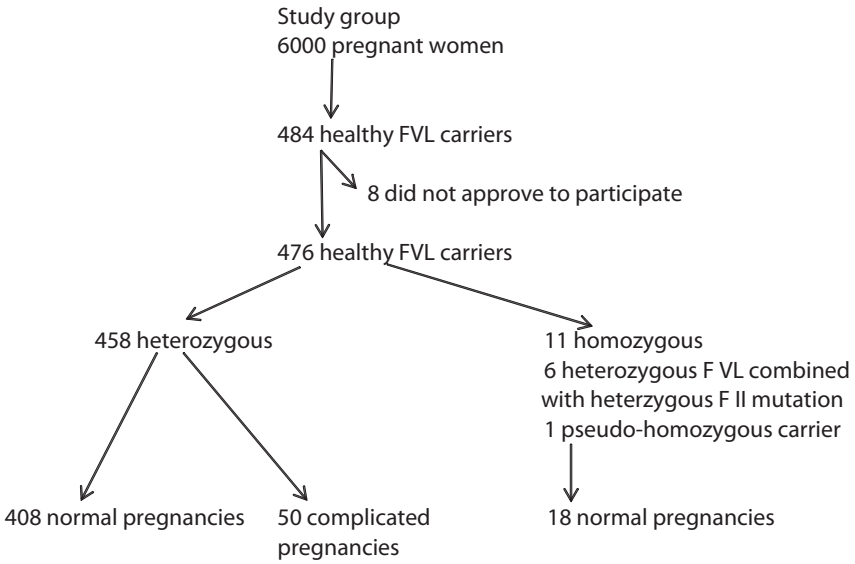

Fig. 1. Flow chart of Factor V Leiden carriers. FVL: Factor V Leiden, FII: Factor II.