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ORIGINAL ARTICLE

Activated protein C resistance – in the absence of factor V Leiden – and pregnancy

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Summary. *Background:* Activated protein C (APC) resistance with or without factor V Leiden (FVL) is a major risk factor for venous thromboembolism. Many previous pregnancy studies have been focused on APC resistance caused by FVL. Very few have investigated APC resistance in the absence of FVL ($APCR^{FVL-}$). *Material and methods:* In a prospective study of 2480 unselected gravidae, blood was drawn in early pregnancy (mean = 12 weeks of gestation). APC resistance was analyzed by an APTT-based method (Coatest®APC-resistance) and the presence of FVL was determined by PCR. The $APCR^{FVL-}$ group had similar mean APC resistance ratio as the heterozygous carriers of FVL. The analyses were carried out no earlier than 3 months after delivery when all data were recorded. Small-for-gestational age (SGA) was used as a proxy for intrauterine growth restriction. *Results:* When compared with the control group, women with $APCR^{FVL-}$ had no increased risk of SGA, pre-eclampsia, first trimester fetal loss or venous thromboembolism. However, they had an increased risk of second trimester fetal loss (7.3% vs. 2.7%, $P = 0.01$), and a tendency of being overweight (17.3% vs. 12.6%, $P = 0.19$) and of delivering extremely preterm (2.8% vs. 1.0%, $P = 0.11$). *Conclusion:* Women with APC resistance not caused by FVL were not at increased risk for SGA, pre-eclampsia, first trimester fetal loss, or abnormal blood loss. However, they showed an increased prevalence of second trimester fetal loss.

Keywords: APC resistance, fetal loss, growth restriction, Leiden, preeclampsia, pregnancy complications.

Introduction

Activated protein C (APC) resistance was described from Malmö in 1993 as a novel risk factor of venous thrombosis [1]. In most cases, APC resistance is caused by a single gene mutation in coagulation factor V (FV), which results in the replacement of arginine (R) at position 506 with a glutamine (Q) [FV Q506, FV Leiden (FVL)] [2]. This replacement eliminates one of the cleavage sites for APC in FV and causes impaired anticoagulation. The resulting hypercoagulable state is a life-long risk factor for venous thrombosis. However, around 30% of APC-resistant pregnant women have been reported not to be carriers of FVL (here denoted $APCR^{FVL-}$) [3]. $APCR^{FVL-}$ has been found to be an independent risk factor for venous thrombosis [4]. This increased thrombosis risk is partly dependent on elevated coagulation FVIII levels. However, even after adjustment for FVIII, $APCR^{FVL-}$ remains to be an independent risk factor [4,5].

A successful pregnancy outcome is dependent upon adequate uteroplacental circulation, which resembles the venous circulation in terms of its low pressure and low flow velocity. The placental circulation may therefore be particularly susceptible to thrombotic complications in thrombophilic women. Thrombotic complications at the feto-maternal border may predispose to pregnancy complications such as fetal loss, pre-eclampsia, small-for-gestational age (SGA), abruptio placentae, and preterm delivery.

An association has been suggested between the fetal loss and thrombophilias, caused by protein C, protein S, or antithrombin deficiencies [6,7]. In addition, a connection between FVL and the occurrence of adverse pregnancy outcomes has been described [8]. Furthermore, carriership of FVL in women has also been associated with a lower volume of blood loss and with lower prevalence of profuse bleeding during delivery, with higher hemoglobin (Hb) values, and with higher ferritin values [9–11].

The effect of $APCR^{FVL-}$ on pregnancy outcomes is not well characterized. In addition, there are no studies reporting on $APCR^{FVL-}$ individuals and delivery-associated blood loss. The purpose of this prospective study was to profile women with $APCR^{FVL-}$ in relation to pregnancy complications and blood loss measurements.

Material and methods

The study design was approved by the Ethics Committee of Lund University, and informed written consent was obtained from all participants. Between February 1994 and June 1995,

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all pregnant women in Malmö were invited to participate in the study. At their first routine visit to one of the community or private antenatal care clinics in Malmö during pregnancy, the 2496 women enrolled in the study were interviewed by midwives and were given a detailed written questionnaire (including medical history focusing on previous thrombosis, fetal loss and family history of thrombosis). Sixteen women were excluded from the analysis; three delivered at home, 11 delivered abroad, one could not be identified from the interview form because her reference number was inadvertently omitted, and one died of meningococcal septicemia during pregnancy. Of the remaining 2480 gravidae, 1899 delivered at Malmö University Hospital, 485 at other Swedish hospitals (i.e. 2384 parturients, of whom 106 belonged to the $APCR^{FVL-}$ group and 2021 to the control group), and 96 women had abortions [63 had first trimester fetal loss (before 13 weeks of gestation), 19 had second trimester fetal loss (at 13–27 weeks), and 14 underwent induced abortion (in eight cases because of fetal indications: three cases of chromosomal aberrations, two of central nervous system defects, and three of structural anomalies)]. No one in the $APCR^{FVL-}$ group and nine women in the control group received low-molecular weight heparin prophylaxis; 16 and 182 women in $APCR^{FVL-}$ and control groups, respectively, had cesarean delivery. Thus, 90 and 1830 women in respective group were included in analysis of blood loss measurements. In cases of immigrants with language problems, an interpreter was provided. On their initial visit to the clinic, blood was drawn for APC resistance testing. The blood was prepared and stored at −70 °C until analysis, which was not performed until at least 3 months after all women had delivered and all data were noted. Thus, as the study was blind, no action was taken because of the APC resistance status.

The $APCR^{FVL-}$ women were defined as those who had the lowest 5% of functional APC resistance, as determined by the Coatest® APC resistance test (Chromogenix, Mölndal, Sweden) and no FVL (Fig. 1). The consequences of FVL carriership in the investigated study population have previously been published [10]. The mean APC ratio in the $APCR^{FVL-}$ group was similar to that observed in the group with heterozygous FVL. Carriership of FVL was determined with PCR-based analysis, as previously described in detail [10,12].

First trimester fetal loss was defined as fetal loss before 13 weeks of gestation. Second trimester fetal loss occurred between 13 and 27 weeks of gestation and third trimester fetal loss as thereafter. A history of fetal loss was determined, both by the interview and by scrutinizing the patient's medical records. Repeated fetal loss was defined as the presence of at least three first trimester fetal losses or two second trimester fetal losses.

A venous thromboembolic event (VTE) was defined as deep venous thrombosis or pulmonary embolism occurring during pregnancy or the first 3 months postpartum. Familial VTE was defined as one or more VTEs in first-degree relatives (father, mother, or siblings), occurring before the age of 60 years.

The delivering midwife estimated intrapartum blood loss by measuring the volume of free blood approximating the amount

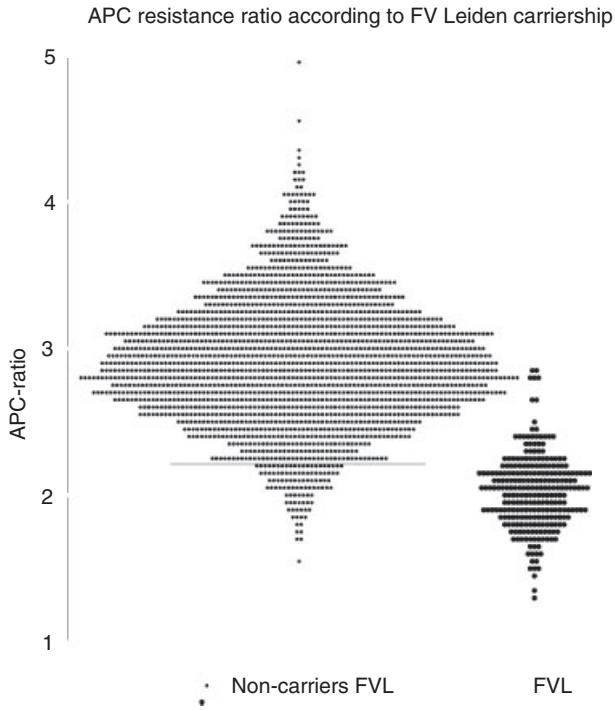

Fig. 1. Distribution of APC resistance ratios among carriers and non-carriers of FVL. The $APCR^{FVL-}$ group is the lowest 5th percentile of non-carriers of FVL (below the line).

of blood in swabs and cloths, and subtracting the amount of amniotic fluid present. This estimated blood loss was noted in the patient's medical record immediately after the delivery. Severe hemorrhage during delivery was defined as blood loss exceeding 600 mL, whereas the profuse blood loss exceeded 1000 mL (according to the International Classification of Diseases, 9th and 10th Rev.) [13]. Only women delivered vaginally and those not treated with heparin were included in the analyses of intrapartum bleeding. Postpartum anemia was defined as an Hb-value < 100 g L^{-1} on the second day postpartum. The Hb-values presented are as follows: Firstly, Hb = the first Hb-value included if taken before 20 weeks of gestation; Hb at 25 weeks = the Hb-value taken closest to 25 weeks included only if taken between 20 and 30 weeks of gestation; last Hb = as the last value taken in pregnancy, included if taken after 30 weeks of gestation. Smoking habits were recorded at the first visit to the antenatal health clinic [mean 12th week of gestation; standard deviation (SD) 3.3 weeks] with the gravidae being classified as non-smokers or smokers. At this visit, maternal weight was also measured. Overweight was defined as a body mass index [BMI (kg m^{-2})] exceeding 27.6, i.e. > 1 SD above the mean for the series.

Pre-eclampsia was defined as pregnancy-induced hypertension and proteinuria > 0.3 g L^{-1} (Albustix®; Boehringer, Mannheim, Germany; ≥1 +). Pregnancy-induced hypertension was defined as a resting diastolic blood pressure > 90 mmHg, measured on two occasions at an interval of at least 5 h, and developing after 20 weeks of gestation in a previously normotensive pregnancy.

Small-for-gestational age was defined in relation to newborn weight deviation [(birthweight minus expected birthweight for gestational age)/expected birthweight for gestational age, and expressed as a percentage] of a term reference population [14]. SGA was defined as a newborn in the lowest 10th percentile in weight deviation and severe SGA as the lowest 3.5th percentile. This corresponds to the cut-off levels of ≤−15% and ≤−22% in weight deviation. Preterm delivery was defined as delivery at < 37 completed weeks of gestation. Extreme prematurity was defined as delivery at < 33 completed weeks of gestation. Gestational age was estimated by ultrasonographic measurements of biparietal diameter and femur length in 98% of cases, and from the date of the last menstrual period in the remaining 2%.

Student's *t*-test was used for the analysis of continuous variables, and the chi-squared test or Fisher's exact test for categorical variables. The odds ratio (OR) for the risk of pregnancy complications or VTE was calculated by cross-tabulation using a 95% confidence interval (CI). Independency of variables influencing the APC ratio was calculated with multivariate linear regression analysis. Adjustment for confounders to SGA was performed with logistic regression analysis with SGA as dependent variable and smoking, fetal gender, parity, maternal height (as a proxy for ethnicity), and $APCR^{FVL-}$ group or FVL group as independent variates. All calculations were performed with SPSS software (Statistical Package for the Social Sciences, SPSS Inc., Chicago, IL, USA) and *P*-values < 0.05 were considered statistically significant.

Results

The clinical characteristics of $APCR^{FVL-}$ individuals and the control group are given in Table 1. It is notable that there was a trend toward an increased prevalence of maternal overweight and of first-degree relatives with venous thromboembolism among women in the $APCR^{FVL-}$ group (OR, 1.4; 95% CI, 0.8–2.4, and OR, 1.6; 95% CI, 0.7–3.3, respectively), when compared with controls. There was also a non-significant lower prevalence of women belonging to blood group 0 in the $APCR^{FVL-}$ group, when compared with controls (OR, 0.7; 95% CI, 0.4–1.0). In addition, more $APCR^{FVL-}$ women were delivered by cesarean delivery (OR, 1.8; 95% CI, 1.0–3.1), although this was not because of threatening asphyxia. Among carriers of FVL, the percentage of heredity of thrombosis, overweight, and blood group 0 was 7.0%, 12.2%, and 38.9%, respectively.

The mean APC resistance ratio was 2.1 (±0.1) in the $APCR^{FVL-}$ subgroup, when compared with 3.0 in the control group. The mean APC resistance ratio of heterozygous carriers of FVL was 2.1 ± 0.2, whereas homozygous carriers of FVL had a mean APC resistance ratio of 1.3 (±0.1). We have previously described the consequences of FVL carriership on this study population [10].

The occurrences of fetal loss and pregnancy complications in the subgroups are shown in Table 2. The results regarding fetal loss were divided into both a prospective observational cohort study (current pregnancy) and a retrospective cohort study

Table 1 Clinical characteristics of women with APC resistance without FV Leiden ($APCR^{FVL-}$) and control groups of parturents

	$APCR^{FVL-}$ group ($n = 106$)	Control group ($n = 2021$)	Difference (*P*)
Maternal characteristics			
Age (years)	29.3 (± 4.5)	29 (± 4.9)	0.5
Nulliparae	45 (42.5%)	941 (46.6%)	0.4
Smokers	19 (17.9%)	386 (19.6%)	0.8
Weight (kg)	65.3 (± 10.9)	65.1 (± 12.2)	0.9
APCR ratio	2.1 (± 0.14)	3.0 (± 0.9)	< 0.001
First degree heredity of thrombosis	8 (7.5%)	99 (4.9%)	0.2
Overweight > 27.6 (≥ + 1SD)	19 (17.3%)	265 (12.6%)	0.2
Blood group 0	31 (29.2%)	763 (37.8%)	0.08
Mode of delivery			
Vaginal. spontaneous	84 (79.2%)	1709 (84.6%)	0.1
Vaginal. operative	6 (5.7%)	130 (6.4%)	0.8
Cesarean section	16 (15.1%)	182 (9.0%)	0.04
asphyxia	1 (0.9%)	56 (2.8%)	0.4
Neonates			
Male gender	54 (50.9)	1116 (50.3)	0.9
Gestational age at birth (weeks)	39.2 (± 2.3)	39.4 (± 1.9)	0.4
Birthweight (g)	3516 (± 633)	3516 (± 577)	1.0
Birthweight deviation (%)*	1.9 (± 13.4)	1.0 (± 12.9)	0.5
5-min Apgar score < 7	2 (1.9)	27 (1.3)	0.6
pH umbilical artery**	7.23 ($n = 74$) (± 0.09)	7.23 ($n = 1380$) (± 0.08)	0.9
pH umbilical vein**	7.31 ($n = 84$) (± 0.08)	7.31 ($n = 1471$) (± 0.08)	0.7

Means ± SD or numbers and percentages are given.
$APCR^{FVL-}$ group (non-carriers of FV Leiden with APC ratio < 2.271).
Control group (non-carriers of FV and APC resistance ratio > 2.271).
*Birthweight when compared with a gestational age adjusted reference population [14].
**Not investigated in all cases.

Table 2 Fetal loss and pregnancy complications

	APCR $^{FVL-}$ ($n = 110$)	Controls ($n = 2100$*)	FV Leiden ($n = 270$)
Women with fetal loss in present pregnancy			
First trimester fetal loss	2 (1.8%)	52 (2.5%)	9 (3.3%**)
Second trimester fetal loss	2 (1.8%)	14 (0.7%)	3 (1.1%**)
Third trimester fetal loss	0 (0.0%)	3 (0.1%)	1 (0.4%)
Women with fetal loss in previous pregnancies			
First trimester fetal loss	19 (17.3%)	390 (18.6%)	51 (18.9%**)
Second trimester fetal loss	6 (5.5%*)	44 (2.1%)	3 (1.1%**)
Third trimester fetal loss	0 (0.0%)	4 (0.2%)	2 (0.7%)
Women with fetal loss in previous or present pregnancies			
First trimester fetal loss	21 (19.1%)	438 (20.9%)	60 (22.0%)
Second trimester fetal loss	8 (7.3%*)	57 (2.7%)	5 (1.9%)
Third trimester fetal loss	0 (0.0%)	7 (0.3%)	3 (1.1%)
Women with prior repeated fetal loss			
Repeated fetal loss	4 (3.6%)	28 (1.3%)	5 (1.9%)
Pregnancy complications	$n = 106$	$n = 2021$	$n = 257$
Pre-eclampsia	2 (1.9%)	32 (1.6%)	5 (1.9%**)
SGA	8 (7.5%)	213 (10.5%)	23 (8.9%)
Severe SGA	6 (5.7%)	73 (3.6%)	9 (3.5%**)
Abruptio placentae	0 (0.0%)	11 (0.5%)	2 (0.8%**)
Premature delivery	9 (8.5%)	109 (5.4%)	15 (5.8%**)
< 33 weeks of gestation	3 (2.8%)	21 (1.0%)	4 (1.6%)
Glucose metabolism			
Diabetes type 1	0 (0.0%)	12 (0.6%)	1 (0.4%)
Gestational diabetes	0 (0.0%)	31 (1.5%)	4 (1.6%)
Venous thromboembolism			
Previous or presently	0 (0.0%)	9 (0.4%)	5 (1.9%**)

First trimester fetal loss < 13 weeks of gestation, second trimester fetal loss ≥13 but ≤ 27 weeks of gestation. Intrauterine death = fetal death > 27 gestational weeks.
SGA = small-for-gestational age.
*Values differ significantly from control group.
**Results previously presented [10], but included as reference.

(prior history). The APCR^{FVL-}-group did not differ from the control group in the prevalence of first trimester fetal loss during prior pregnancies (OR, 0.9; 95% CI, 0.6–1.5). The risk of second trimester fetal loss in the APCR^{FVL-} group in this prospective study was increased almost threefold (OR, 2.8; 95% CI, 0.6–12.3), when compared with controls, but the difference did not reach statistical significance. However, in previous pregnancies, second trimester fetal loss (OR, 2.7; 95% CI, 1.1–6.5) was more prevalent in the APCR^{FVL-} group than among controls. The risk of second trimester fetal loss in all pregnancies, i.e. when previous and present pregnancies were combined, was significantly increased (OR, 2.8; 95% CI, 1.3–6.1). There was a non-significant increased risk of repeated pregnancy loss in the APCR^{FVL-} group, when compared with controls (OR, 1.6; 95% CI, 0.8–3.3). There was no increased prevalence of SGA in the APCR^{FVL-} (OR, 0.7; 95% CI, 0.3–1.4). Adjustments for possible confounders (parity, smoking, gender and maternal height) did not change the estimate considerable (OR, 0.7; 95% CI, 0.3–1.4). There was no difference in frequency of severe SGA between the APCR^{FVL-} and control groups (OR, 1.6; 95% CI, 0.7–3.8). In addition, both fetal weight and fetal weight deviation were similar among APCR^{FVL-} and controls. There were no SGA or severe SGA cases of fetal malformations in the APCR^{FVL-} group. The respective number of cases in the control group and FVL group were four and three, and one and nil, respectively. There was a slight, but non-significant, higher proportion of premature deliveries in the APCR^{FVL-} group, when compared with the control group (8.5% vs. 5.4%) (OR, 1.6; 95% CI, 0.7–3.3). This trend was even more pronounced, but still not significant, when extreme prematurity was regarded (2.8% vs. 1.0%) (OR, 2.8; 95% CI, 0.8–9.4). No VTE occurred in the APCR^{FVL-} group. In the whole cohort, the prevalence of VTE in the current pregnancy was 0.24% (6/2480), of which three occurred in the control group and three in the FVL group.

The APCR^{FVL-} subgroup did not differ significantly from the control group with regard to volume of blood loss during delivery, profuse blood loss during delivery, or postpartum anemia. In addition, Hb measurements were almost identical between the APCR^{FVL-} and the control groups, and the subjective estimation of menstrual blood loss did not differ (Table 3).

Smokers, when compared with non-smokers, were found to have a higher APC-ratio (2.89 vs. 2.81, $P = 0.004$) and women with blood group 0 were found to have a higher APC-ratio, when compared with those in other blood groups (APC-ratio 2.88 vs. 2.78, $P < 0.001$). There was a significant negative correlation between APC-ratio and BMI (Spearman's $\rho = -0.07$, $P < 0.001$), but no correlation was found between APC-ratio and maternal age (Spearman's $\rho = -0.01$,

Table 3 Blood loss measurements*

	$APCR^{FVL-}$ group ($n = 90$)	Control group ($n = 1,830$)
Measurements of blood loss during delivery*		
Blood loss > 600 mL (*n*)	5 (5.6%)	147 (8.0%)
Blood loss > 1000 mL (*n*)	2 (2.2%)	58 (3.2%)
Postpartum anemia (< 100)*(*n*)	5 (5.6%)	126 (6.9%)
Blood loss during delivery		
Geometric mean ± SD (mL)**	355 (240–524)	361 (231–563)
Hemoglobin values***		
Initial Hb (g L^{-1})	125.7 (11.2)	125.7 (10.4)
Hb at 25 weeks (g L^{-1})	114.7 (9.8)	115.7 (9.9)
Last Hb (g L^{-1})	121.6 (9.6)	121.6 (9.7)
Menstruation****	($n = 69$)	($n = 1,443$)
Small	10 (14.5%)	269 (18.6%)
Moderate	43 (62.3%)	831 (57.6%)
Large	13 (18.8%)	283 (19.6%)
Profuse	3 (4.3%)	60 (4.2%)

*Only vaginally delivered non-heparin-treated women were included.
**Blood loss value was converted to its natural logarithm to normalize a skewed distribution.
***Initial Hb = first Hb in pregnancy, last Hb = last Hb-value in pregnancy.
****A subjective classification by each woman on the size of her menstruations [11].

$P = 0.7$). In multivariate linear regression analysis, smoking, blood group O, and maternal BMI were all independently related to the APC-ratio ($t = 3.2$, $P = 0.001$, $t = 4.4$, $P < 0.001$, $t = -2.9$, $P = 0.004$, respectively).

Discussion

We found solid evidence that neither SGA nor first trimester fetal loss was associated with $APCR^{FVL-}$ in this large prospective cohort study. Also, we found similar birth weights and birth weight deviation in both the $APCR^{FVL-}$ and the control group (Table 1), which adds to the conclusion of no association between $APCR^{FVL-}$ and SGA. Regarding SGA, our results are in agreement with those of Clark *et al*., even though they reported a slight inverse relationship between APC ratio and birthweight [15]. Moreover, we found no increased risk of pre-eclampsia among women with $APCR^{FVL-}$ in contrast to what Clark *et al.* reported [15]. We have no explanation for this. However, smokers, when compared with non-smokers, have a higher APC resistance ratio and they have a lower prevalence of both term and preterm pre-eclampsia [16]. Thus, a difference in the prevalence of smokers might affect the results. In addition, Clark *et al*. found an inverse relationship between APC resistance ratio and diastolic blood pressure and cholesterol already in early pregnancy [15]. Thus, a low APC resistance ratio might be a marker of pre-existing hypertensitive disease and not of pre-eclampsia.

We found an almost threefold increased risk of second trimester fetal loss in the $APCR^{FVL-}$ subgroup, when compared with controls, which is in agreement with the large study of Rai *et al*., who reported almost identical OR (OR, 2.8; 95% CI, 1.0–7.6) for second trimester fetal loss in the $APCR^{FVL-}$ group [3]. Clark *et al*. reported no difference in the prevalence of fetal loss before 24 weeks of gestation [15], that is, a combination of first and second trimester fetal loss. Paradoxically, smokers, a group known to have a higher risk of VTE during pregnancy [17], were less APC-resistant than non-smokers. This is in agreement with Clark *et al.* who reported smokers to be less APC-resistant [15]. The negative correlation between BMI and APC-ratio may, at least in part, contribute the increased risk of VTE in overweight women [10]. As women gain some 12–15 kg in weight during pregnancy, the inverse relation between BMI and APC-ratio may also explain some of the 'induced' APC resistance known to exist during pregnancy [18]. Women with blood group O were found to have higher APC-ratio than women with other blood groups. In this context, it is interesting that the prevalence of VTE is lower among individuals in blood group O [19]. Erhard *et al*. reported an increased prevalence of prematurity among women with FVL [20]. Regarding this question, our material is scant, but both the FVL group and the $APCR^{FVL-}$ group were at a non-significant 1.6- and 2.8-fold increased risk of prematurity and extreme prematurity, when compared with controls.

The $APCR^{FVL-}$ is regarded as a risk factor for VTE of the same magnitude as heterozygous FVL or FII mutation [4]. The absolute risk of thromboembolism, however, is still low. Therefore, we were not surprised that no cases of thromboembolism appeared in our population of $APCR^{FVL-}$ women because of the study size.

Strengths and weaknesses of the study

The major strength of this study is that it is based on a large prospective cohort of unselected gravidae, and that it was blind. Although the study was large, some complications are rare, which limit analysis. Regarding first trimester fetal loss and SGA, the study is statistically rather strong; that is with 5% significance level and the given number of women, it has an 87% and 74% resulting power, respectively, to detect a doubled prevalence in the $APCR^{FVL-}$ group, when compared with the control group. Another strength is that almost all the women in the study (98%) were dated by ultrasound in their second trimester, which is essential for the analysis of SGA and prematurity. The cut-off level of APC-ratio was arbitrary, but the mean of the APC-ratio in the $APCR^{FVL-}$ and heterozygous FVL carriers was similar, and also approximately similar to that used in other studies [3]. It should be pointed out that the APC resistance test used in our study was not designed to be specific for FVL identification, but rather was meant as a screening test for APC resistance. Because of the design of the study, with inclusion at a mean of 12 weeks of gestation, the prevalence of first trimester fetal loss in the current pregnancy was presumably underestimated. One might question the use of retrospective data of fetal loss in a primarily prospective study. The study included only women who were pregnant, which might introduce some selection bias. However, the study population was collected without selection for fetal loss. The

odds ratio for second trimester fetal loss was similar in the index and prior pregnancies. The prospective part of the study was underpowered to answer the question regarding the second trimester fetal loss. Adding to the validity of our results are the similar results of the large study by Rai *et al*. [3]. A drawback of the study is that we did not test for antiphospholipid antibodies, which may be of relevance for second trimester fetal loss. However, even with this limitation in mind, the resultant data might be of interest for clinicians, as it reflects the way unselected pregnant women can present.

Conclusions

In this prospective cohort study of 2480 pregnant women, those with $APCR^{FVL-}$ were not at increased risk for pre-eclampsia, SGA, first trimester fetal loss, or abnormal blood loss. However, the women with $APCR^{FVL-}$ were characterized by an increased risk of second trimester fetal loss and a non-significant trend toward maternal overweight, and extreme prematurity.

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