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Stillbirth and factor V Leiden - A regional based prospective evaluation

Ida Björk[a], Karin Pettersson[b,c], Pelle G. Lindqvist[d,e,*]

[a] Departments Obstetrics and Gynecology, Sodertalje Hospital, Sodertalje, Sweden
[b] Karolinska University hospital, Huddinge, Sweden
[c] Clintec, Karolinska Institutet, Huddinge, Sweden
[d] Sodersjukhuset, Stockholm, Sweden
[e] Clinical Sciences and Education, Sodersjukhuset, Stockholm, Sweden

ABSTRACT

Background: Approximately 10% of Swedes are carriers of coagulation factor V Leiden (FVL). It has been suggested that carriers are at an increased risk of stillbirth. We aimed to assess the risk of stillbirth in carriers of FVL as compared to non-carriers.

Methods: A consecutive registration of all stillbirths from 2001 to 2015 in the whole Stockholm region has been performed. A FVL blood sample, an autopsy and histopathological examination of the placenta was scheduled to be offered all women with stillbirth. Main outcome was the difference in carriership of FVL between cases with live- vs. stillbirth. The primary cause of death was determined according to the Stockholm hierarchical classification of stillbirth.

Results: The incidence of stillbirth was 3.6‰. Out of the 1392 cases of stillbirth occurring during the study period, FVL status was determined in 963 women. Of these 74 (7.7%) were carriers of FVL as compared to 8.1% in the control group ($p = 0.6$). A primary cause of death due to infection was twice as common among non-carriers compared to carriers of FVL (odds ratio [OR] = 2.3, 95% CI 1.08–4.8). In the whole study group, the prevalence of SGA was 14–fold increased among stillbirths as compared to live births (OR = 13.9, 95% CI 12.4–15.6).

Conclusion: Maternal FVL carriership was not related to an increased risk of stillbirth. However, a diagnosis of primary cause of death due to infection was less likely among FVL carriers.

1. Introduction

In West European countries the incidence of stillbirth varies between 1‰ to 9‰, while incidences as high as 25‰ to 32‰ is reported from developing countries [1,2]. Stillbirth is defined as fetal death after 22 pregnancy weeks, i.e. a newborn without signs of life [2]. Stillbirth is traumatic for the pregnant woman and her family and is regarded as a quality indicator of prenatal care [1,3]. Maternal characteristics related to an increased risk for stillbirth are, high maternal age, nulliparity, smoking, overweight, low social economic status, and previous stillbirth [2]. The main obstetric condition related to an increased risk of stillbirth in Sweden is small-for-gestational age (SGA), especially those unidentified antepartum, and placental abruption [4]. In addition, infection, umbilical cord complications, congenital malformations, and preeclampsia are major causes [4,5].

Activated protein C (APC) resistance was discovered 1993 and is caused by a point mutation in the gene for coagulation factor V Leiden (FVL) [6,7]. Carriers of the mutation have lower ability to inactivate activated coagulation factors V and VIII and this will lead to a lifelong increased risk of venous thrombosis. The prevalence of FVL is high among Caucasians, 2%–15% in Western countries [8,9]. The mutation does not exist or is rare in Africa, South America and Southeast Asia [8].

Reviews of retrospective studies have suggested an association between FVL and stillbirth [10,11]. A systematic review and meta-analysis of fetal loss (spontaneous miscarriage or stillbirth) of prospective studies showed a 50% increased risk of fetal loss among maternal carriers of FVL (odds ratio (OR) 1.52, 95% confidence interval (CI) 1.06–2.19) and a non-significantly difference in risk of placental abruption among FVL carriers (1.85, 95% CI 0.92–3.70) [12]. Thus, the relationship between FVL and stillbirth is still unclear and we do not have a plausible explanation.

In this study we aimed to assess the risk of singleton pregnancy stillbirths among FVL carriers in a large prospectively collected cohort in the Stockholm area during 2001–2015.

2. Material and methods

Between 2001 and 2015 there were 390,670 singleton births in the Stockholm area and all stillbirths from gestational week 22 + 0 in Stockholm were registered in an internet database in which information considering the woman and the child are collected. Every stillbirth was reviewed in a perinatal audit consisting of obstetricians, representing

* Corresponding author at: Sjukhusbacken 10, plan 9, Sodersjukhuset, 11883 Stockholm, Sweden.
E-mail address: pelle.lindqvist@ki.se (P.G. Lindqvist).

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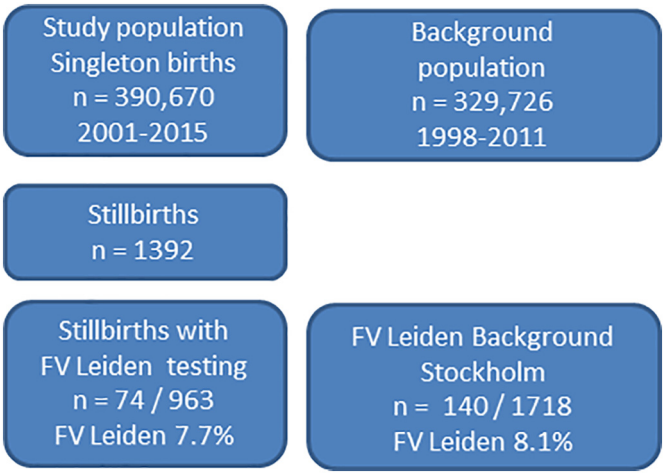

Fig. 1. Flowchart.
Background population for comparison of background characteristics in Table 1.
FV Leiden background for comparison of FVL carriership.

all delivery departments in Stockholm, and perinatal pathologists. The results from the examinations together with relevant family, medical and obstetrical history and all major pregnancy complications during the actual pregnancy are registered in the database. A DNA test for maternal FVL was scheduled to be routinely offered when the stillbirth has occurred. The gestational age is determined from ultrasound in gestational week 11–14 (combined ultrasound and biochemical test) or week 18–20 (routine ultrasound) or calculated from the first day of the last menstrual period when no ultrasound was performed (< 5%). Autopsy of the fetus and histopathological examination of the placenta are routinely offered to all couples with stillbirth. Thus, all stillbirths were included, but testing was optional. Chromosome testing from the amniotic fluid was included in the evaluation setup, but not performed in all cases. The primary cause of death is determined according to the Stockholm hierarchical classification of stillbirth [5,13,14].

In this study, we included all singleton stillbirths from 2001 to 2015 in the Stockholm regions in six delivery units (Karolinska University hospital, Huddinge; Karolinska University Hospital, Solna; Sodersjukhuset; Danderyd Hospital; BB Stockholm, Sodertalje hospital, and from 2014 BB Sophia) (Fig. 1). The total number of singleton deliveries is that reported by the Medical Birth Registry (n = 390,679). For comparison of distribution of selected variables in Table 1 a background population of all singleton deliveries in the Stockholm region 1998 to 2011 (n = 329,726) is given and for comparison of FVL status we used the unselected subgroup of women (n = 1762) recruited in the Stockholm region as part of a large prospective assessment of FVL and pregnancy complications [15]. However, women with prior thromboembolism were not included in the control group [15].

The estimated fetal weight (EFW) was calculated and the FW-deviation from the expected mean was defined as “EFW minus expected FW by gestational age (GA)/expected FW”, and expressed as a percentage. We defined SGA as fetuses being SGA at birth, i.e., the lowest 2.5th centile (≤ −22%) of BW based on a non-customized Swedish birth weight reference [16]. Termination of pregnancy is not permitted after 22 + 0 gestational weeks.

Couples with a stillborn child in Sweden are usually spending time with their stillborn and some couples are even bringing the stillborn home for a while. There is a routine to make a foot-print (Fig. 2) for the memory and to make photos of the stillborn baby.

2.1. Statistics

Descriptive statistics is used with Chi2 test for categorical variables and Students *t*-test or Mann Whitney *U* test as appropriate. Data of primary and associated causes of death, GW at birth and additional demographic data was identified. IBM SPSS 23 (Statistical Package for the Social Sciences [SPSS], Inc., Chicago, IL, USA) was used. Significance of difference was considered when $p < 0.05$. The study was approved by the regional Ethical Committee, 97-440 and 2012/1706-32.

3. Results

We identified 1392 (3.6‰, 1392 out of 390,679) cases of stillbirth in singleton pregnancies during the 15-year study period in Stockholm. Out of all these stillbirths, FVL status was determined in 963 (69%) of the stillbirth cases during the study period. Autopsy of the stillborn was performed in (68%) of the cases and histopathological examination of the placenta in (98%) of the cases. Table 1 shows characteristics of the study population and a background population.

Among the 963 out of 1392 cases with data on FVL status, 7.7% were carriers of FVL (71 [7.4%] were heterozygous and three [0.3%] homozygous), and in the subgroup of the controls with known FVL status from within the same control group the prevalence was 8.1% (140/1718), i.e., odds ratio (OR) = 0.94, 95% CI 0.7–1.3 [15]. Thus, the main result is that maternal carriership of FVL is not associated with an increased risk of stillbirth (Fig. 3).

SGA was a major fetal risk factor for stillbirth as compared to background population (475/1392 (34.1%) vs. 11,814/328,901 (3.6%), OR = 13.9, 95% CI 12.4–15.6) (Table 1). Infection as the primary cause of death was twice as frequent in the non-FVL subgroup as compared to the FVL group (21.9% vs. 10.8%, OR = 2.3, 95% CI 1.1–4.8) (Table 2). In addition, FVL carriers had placental abruption as the primary cause of death in 13.5% as compared to the non-FVL subgroup 8.1% (OR = 1.8, 95% CI 0.9–3.7).

There are different definitions of stillbirth such as > 22, > 24, > 28 gestational weeks and > 1000 g. For comparative reason we present them all. The respective number of stillbirths without chromosomal aberrations or major malformations ≥22 weeks and > 24 weeks are given in Table 1. The respective number of cases 28 to < 37 weeks and 37 to < 42 weeks were 398 and 489.

We give the percentage of primary cause of stillbirth divided into three time-periods (2001–2005, 2006–2010, 2011–2015) among those included in Table 2. The percentage of IUGR/placental insufficiency were (22.2%, 28.9%, and 32.1%), infection (24.0%, 19.2%, and 18.2%) and placental abruption (10.5%, 9.5%, and 8.0%). The respective, percentages defined as SGA were 34.2%, 36.5%, and 33.2%.

We assessed if FVL testing differed depending on primary cause of death and in three groups it differed significantly. It was assessed significantly more often in relation to preeclampsia (5.8% vs. 2.8%, $p = 0.02$), and IUGR/placental insufficiency (31.1% vs. 21.8%, $p < 0.001$).

4. Discussion

4.1. Main results

In this study we found that maternal FVL status did not differ in stillbirths as compared to live births, i.e., we did not find carriership of FVL a risk factor for stillbirth in singleton pregnancies (7.7% VS. 8.1%, OR = 0.94, 95% CI 0.7–1.3). Since approximately 0.3% of our population can be estimated to have a prior VTE [17], approximately half can be expected to be FVL carriers [18]. Thus, the 8.1% FVL prevalence in the FVL control group is probably a small (≈0.15%) underestimation of the true prevalence of FVL in the Stockholm pregnant population. In line with prior research, we found SGA newborn to be a major risk factor for stillbirth [4]. In comparison of stillbirths ≥24 gestational weeks without chromosomal aberrations or major malformations (n = 1112 in this cohort), there was no difference in incidence of

Table 1
Background variables of pregnancies with stillbirth and in background population.

	Stillbirth		Background population		Significance of difference (*p*)
Number (proportion)	1392	3.6‰[a]	328,901		
Maternal characteristics					
Maternal age (years)	31.5	5.4%	31.1	5.0%	0.001
BMI (kg/m^2)	24.9	4.8%	23.9	4.1	< 0.001
Previous stillbirth (n)	26	2.6%	na		
≥3 prior miscarriages	30	1.9%	na		
Gestational length (weeks)					< 0.001
22– < 24 gestational weeks	150	10.8%	82	0.03%	
24– < 28 gestational weeks	226	16.2%	623	0.2%	
28– < 37 gestational weeks	474	34.1%	14,229	4.4%	
37– < 42 gestational weeks	525	37.7%	290,816	88.4%	
≥42 gestational weeks	17	1.2%	22,569	6.9%	
Missing			582	0.2%	
≥22 w, wo malform/chrom	1251	3.2‰[a]			
≥24 w, wo malform/chrom	1112	2.8‰[a]	na		
Maternal complications					
Diabetes	33	2.4%	1322	0.4%	< 0.001
Abruptio placenta	233	16.7%	1136	0.3%	< 0.001
Preeclampsia/hypertension	94	6.8%	12,232	3.7%	< 0.001
Mode of delivery					
Vaginal delivery	1361	92.4%	246,694	75.0%	< 0.001
Newborn characteristics					
Male fetal gender	704	50.6%	168,824	51.4%	1.0
Newborn weight (grams)	2324	1274	3540	551	< 0.001
Weight deviation (%)	−12.9%	22.7	−0.3%	13.8	< 0.001
Newborn weight < 1000 g	411	24.9%	701	0.2%	< 0.001
SGA (n)	475	34.1%	11,814	3.6%	< 0.001

SGA = small-for-gestational age, smallest 2.5th percentile by gestational age, Preterm delivery = < 259 days or 37 + 0 weeks, na = not accessed, background population of Stockholm 1998–2011, singleton and no stillbirth, ≥24 w, wo malform/chrom = ≥ 24 gestational weeks, no chromosomal or major malformations.
[a] As compared to the total number of singleton deliveries (n = 390,679) during study interval (2001–2015) in the Stockholm area.

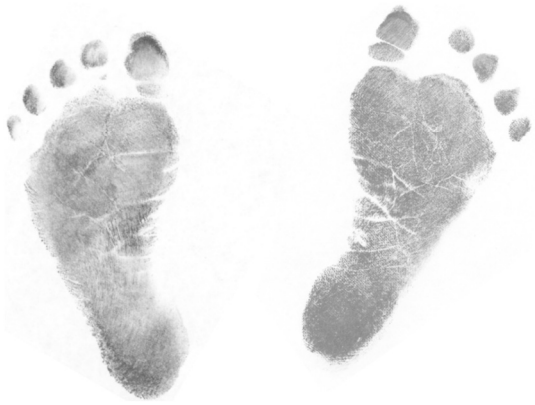

Fig. 2. Foot print to take home as a memory of stillborn.

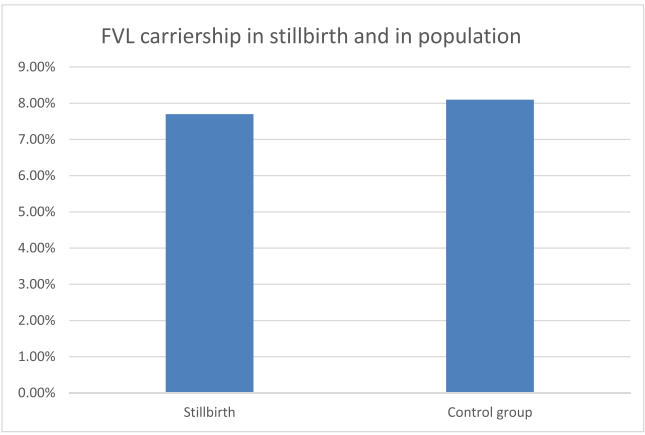

Fig. 3. Proportion of factor V Leiden (FVL) carriership among cases and control group.

stillbirth compared to our prior Malmö cohort (including 32 week ultrasound screening in combination with a strict surveillance program) from the 1990[ies], 2.8‰, vs. 2.9‰ (OR 0.97, 95% CI 0.8–1.2) [4,19].

We have previously reported that fetal, but not maternal, FVL carriership was related to a 7-fold increased risk of ischemic placental lesions and 8-fold increased risk of abnormal umbilical artery (UA) Doppler measurements [20]. Both smallness of the fetus and increasing UA blood flow classes (BFC) are major determinant of stillbirth [4]. Thus, even if there is no direct relation between maternal FVL and placental mediated pregnancy complications, there might be a causal relation with fetal FVL carriership.

There seem to be a bias of FVL testing due to indication of primary cause of death. When preeclampsia or IUGR/placental insufficiency was primary cause of death, FVL testing was significantly more often performed. This was supposedly due to the ongoing academic discussions regarding activated protein C/FVL and pregnancy complications. Two publications with entirely different results regarding FVL and pregnancy complications were published in 1999 [21,22]. A case control study from Israel reported a five-fold increased risk carriers of FVL for severe preeclampsia, abruptio placenta, and stillbirth and a doubled risk of growth restriction. A Swedish prospective unselected pregnant cohort comprising almost 2480 gravidae showed no significantly negative effects regarding growth restriction or preeclampsia, but an increased risk of thromboembolism [22]. The discussion regarding preeclampsia and growth restriction was ended in 2010, with a systematic review and meta-analysis of prospective studies. It did not find an increased risk of preeclampsia or IUGR with carriership of FVL [12]. However, they reported an 85% non-significantly increased risk (OR = 1.85, 95% CI 0.92–3.70) of placental abruption among carriers of FVL as compared to non-carriers. This is almost identical to our finding of abruptio placenta as primary cause of stillbirth (OR = 1.8, 95% CI 0.9–3.6) and similar to other large retrospective reports (ORs between 1.5 and 3.0) [12,23,24]. In our study abruptio placenta was

Table 2
Primary cause of death and selected pregnancy variables in stillbirths by carriership of FVL.

	Non-FVL		FVL		Significance of difference *p*
	n = 889	%	n = 74	7.7%	
Primary cause of death[a]					
Malformation/chromosomal abnormalities	71	8.0%	6	8.1%	1.0
Infection	193	21.7%	8	10.8%	0.03
Immunization	2	0.2%	0	0.0%	1.0
Birth asphyxia	5	0.6%	0	0.0%	0.5
Feto-maternal transfusion	23	2.6%	1	1.4%	0.5
IUGR/placental insufficiency	271	30.4%	26	35.1%	0.4
Umbilical cord complication	53	6.0%	3	4.1%	0.5
Placental abruption	72	8.1%	10	13.5%	0.1
Preeclampsia/hypertension	50	5.6%	6	8.1%	0.4
Uterine complication	1	0.1%	1	1.4%	1.0
Diabetes mellitus	15	1.7%	0	0.0%	0.3
Intrahepatic cholestasis of pregnancy	5	0.6%	0	0.0%	0.5
Coagulation disorders	5	0.6%	1	1.4%	0.4
Other/missing/unexplained	123	13.8%	12	16.3%	0.3
Selected pregnancy variables					
Weight deviation (mean %)	−15.6%	23	−20.3%	20	0.09
Gestational length (weeks)					0.5
22– < 24 gestational weeks	89	10.0%	5	6.8%	
24– < 28 gestational weeks	157	17.6%	10	13.5%	
28– < 37 gestational weeks	301	33.8%	30	40.5%	
37– < 42 gestational weeks	330	37.1%	29	39.2%	
≥42 gestational weeks	12	1.3%	0	0.0%	
Small-for-gestational age	300	33.7%	33	44.6%	0.06

Number and percentage is given or percentage and standard deviation. Coagulation factor V Leiden = FVL.
[a] According to the Stockholm classification.

the primary cause of stillbirth in 8.5% of cases. Risk factors for placental abruption have been reported similar as those for venous thrombosis [25]. For example repeated fetal loss, late fetal loss, thrombophilias, familial history of venous thromboembolism, preeclampsia, fetal growth restriction, high maternal age, and cigarette smoking are risk factors for both venous thromboembolism and placental abruption [25]. This indicates that placental abruption might be a thrombotic complication. In line with this, abruptio placenta is included as a major risk factor for thromboembolism in the Swedish thromboprophylaxis guidelines [26,27].

The halved risk of infection as the cause of death among those carrying FVL is interesting, and the possible effect of carriership of FVL on inflammation/infection has attracted a lot of attention. FVL carriers with prior VTE have higher APC-protein C complex levels compared to non-carriers of FVL [28]. APC-protein C inhibitor complex is the prime inhibitor of APC in plasma and is present in a 10,000-fold higher concentration than APC. Thus, the APC-protein C inhibitor complex is supposed to reflect the APC concentration [29]. In a study baboons were injected with APC and lethal concentrations of *E. coli* organisms and the results showed that low APC levels were related to poor prognosis of survival in sepsis [30]. In a randomized controlled trial (RCT), patients with systemic inflammation and organ failure due to acute infection were enrolled and assigned to receive an intravenous infusion of either placebo or recombinant human APC. It was found that treatment with recombinant human APC significantly reduced mortality in patients with severe sepsis [31]. Despite several additional human and animal RCTs, these findings could not be reproduced and in two studies, FVL-carriers had worse outcome [9]. These findings resulted in withdrawal of the drug from the market in 2011 [32,33].

It has recently been reported that APC have cyto-protective and anti-inflammatory effect. It was found that APC cleaves and detoxifies extracellular histones, a major component of neutrophil extracellular traps (NETs) [34]. NETs promote pathogen clearance, but can also lead to thrombosis [34]. In a primate model of *E. coli*-induced sepsis, pretreatment with APC inhibited the release of myeloperoxidase from neutrophils, a marker of neutrophil activation [34]. It has been reported cyto-protective by APC with reduced damage due to ischemia and sepsis [35]. In this context, our finding that infection as primary cause of death, is half as common in stillbirths in FVL-carriers than in non-FVL-carriers is an observation that give some support to the above mechanism.

4.2. Strengths and limitations

The large prospective cohort of stillbirths with stringent pre-determined diagnosis of primary cause of stillbirth is a strength. A limitation is that FVL status was assessed in only 69% of the cases and autopsy of the stillborn was performed in 68%, but placental examination was performed in 98%. In cases with preeclampsia or growth restriction as a primary cause of stillbirth, FVL testing was performed more often. We acknowledge a small underestimation in our FVL control group due to exclusion of women with prior thromboembolism, but we have no indication that the FVL status was biased in any other way. In addition, it is a strength that we within our geographical population had a random sample of women where FVL was taken as part of a prospective study. We also acknowledge it as a limitation that we did not have access to other thrombophilia's.

We conclude that maternal FVL carriership was not a risk factor for stillbirth in our large cohort. The risk of stillbirth due to infection was lower among carriers of FVL as compared to non-carriers.

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Conflict of interest

The authors report no conflicts of interest.

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