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Regular Article

# Factor V Leiden as risk factor for unexplained stillbirth – a population-based nested case-control study

Leena M. Hiltunen [a,*], Hannele Laivuori [b,c], Anna Rautanen [d,1], Risto Kaaja [e,2], Juha Kere [b,f], Tom Krusius [a], Mikko Paunio [g,h], Vesa Rasi [a]

[a] Department of Hemostasis, Finnish Red Cross Blood Service, Helsinki, Finland
[b] Haartman Institute, Department of Medical Genetics, Biomedicum Helsinki, University of Helsinki, Helsinki, Finland
[c] HUSLAB Department of Clinical Genetics, Helsinki University Central Hospital, Helsinki, Finland
[d] Finnish Genome Center, University of Helsinki, Helsinki, Finland
[e] Department of Obstetrics and Gynaecology, Helsinki University Central Hospital, Helsinki, Finland
[f] Department of Biosciences and Nutrition and Clinical Research Centre, Karolinska Institutet, Huddinge, Sweden
[g] Department of Public Health, University of Helsinki, Helsinki, Finland
[h] Ministry of Social Affairs and Health, Helsinki, Finland

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ABSTRACT

*Introduction:* Stillbirth is a relatively uncommon pregnancy complication in developed countries yet causing strong emotional burden. Thrombophilia has been associated with stillbirth but population-based studies are few. We assessed selected genetic and acquired parameters for the risk of unexplained stillbirth, including FV Leiden.

*Materials and methods:* We performed a population-based nested case-control study of 100,000 consecutive pregnancies in Finland. Cases and controls were identified by combining national registers and accepted according to strict criteria after checking their medical records. Stillbirth was defined as intrauterine fetal death ≥22 weeks of gestation. We excluded stillbirths due to lethal congenital developmental conditions, umbilical cord complications, and infections. We studied 44 cases of unexplained stillbirth and 766 controls.

*Results:* FV Leiden was associated with 3.8-fold (95% CI 1.2-11.6) risk for unexplained stillbirth, 3.9-fold (95% CI 1.1-13.9) risk for unexplained late stillbirth (≥28 weeks of gestation), and 10.8-fold (95% CI 2.1-55.3) risk for unexplained stillbirth with placental lesions. The same figures for singleton pregnancies were 3.1-fold (95% CI 0.9-10.9), 4.3-fold (95% CI 1.2-15.3), and 10.6-fold (95% CI 2.1-54.3). Slightly increased risk associated with blood group O was not statistically significant. We found a trend for increased risk in advanced maternal age and smoking during pregnancy. High pre-pregnancy BMI was not associated with increased risk, nor was low educational level or first pregnancy.

*Conclusions:* Our population-based study from a country with comprehensive prenatal care confirms the association between FV Leiden and unexplained stillbirth.



## Introduction

Stillbirth is a relatively uncommon pregnancy complication in developed countries yet causing strong emotional burden. Classic risk factors for stillbirth include multiple pregnancy and maternal characteristics such as advanced age, pre-pregnancy obesity, smoking, nulliparity, and maternal diseases, as well as low socio-economic status [1–3]. The cause remains unknown in 25-60% of stillbirths [1–3]. Genetic defects causing thrombophilia are also considered to be associated with increased risk for stillbirth [1–3].

The association of thrombophilia with stillbirth has been evaluated in meta-analyses of case-control studies [4,5]. This kind of approach has been necessary because of contradictory results in single studies. In meta-analyses, two common genetic causes of thrombophilia, FV Leiden and FII G20210A mutations, are found to be significantly associated with late fetal loss. Even though an association between inherited thrombophilia and stillbirth has been demonstrated, the exact mechanism is not known and causality has not been proven [6]. Population-based studies are few [7,8].

*Abbreviations:* BMI, body mass index; CI, confidence interval; FV Leiden, factor V Leiden; ICD, International Classification of Diseases; IUGR, intrauterine growth restriction; MTHFR, methylenetetrahydrofolate reductase; OR, odds ratio; *P*-value, probability value; PROC, protein C; SD, standard deviation; TFPI, tissue factor pathway inhibitor.

* Corresponding author. Department of Hemostasis, Finnish Red Cross Blood Service, Kivihaantie 7, FIN-00310 Helsinki, Finland. Tel.: +358 9 5801 362; fax: +358 9 5801 484.
*E-mail address:* leena.hiltunen@bts.redcross.fi (L.M. Hiltunen).
[1] Present address: Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK.
[2] Present address: Satakunta Central Hospital, University of Turku, Turku, Finland.

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We performed a population-based nested case-control study of 100,000 consecutive pregnancies to evaluate selected inherited and acquired variables as risk factors for unexplained stillbirth at or after 22 weeks of gestation. The variables included demographic parameters, seven polymorphisms that have been associated with thrombophilia, and ABO blood group. We gathered exact clinical data by checking medical records and were able to analyze unexplained stillbirth by excluding obvious causes of fetal death. Late stillbirths, at or after 28 weeks of gestation, were analyzed separately. As twin pregnancy is a major risk factor for stillbirth, the main results are presented also for singleton pregnancies. In Finland, like in all Nordic countries, the stillbirth rate is among the smallest in the world [9].

## Materials and methods

### *Subjects*

Finland has a predominantly Caucasian population of 5.3 million people with about 56,000 births per year. Practically all pregnant women attend antenatal care, a precondition for benefits given by The Social Insurance Institution. The first contact to the local Maternity Welfare Clinic is usually in the 8th to 12th week of pregnancy. Samples are then taken for blood group serology tests, which are performed in the Finnish Red Cross Blood Service at the Department of antenatal serology. The department maintains The National Register of Blood Group and Blood Group Antibodies of Pregnant Women from which data for 100,000 consecutive pregnancies were obtained. Of each woman, only the first pregnancy after 1 January 1997 (index pregnancy) was included in the cohort.

The National Institution for Health and Welfare (HTL) maintains the National Hospital Discharge Register with diagnoses classified according to International Classification of Diseases (ICD-10 since 1996). The two registers were linked by unique ID numbers. Stillbirth was defined as intrauterine fetal death at 22 weeks of gestation or later.

Fig. 1 shows the recruitment of cases and controls. In the cohort of 100,000 pregnancies, 224 women had an ICD-10 code for stillbirth (O36.4). Of those, 222 fulfilled the invitation criteria (alive, mother tongue Finnish or Swedish, residence in Finland) and 120 participated (54%). Checking their medical records revealed that 22 intrauterine fetal deaths occurred before gestational week 22 and were therefore excluded. In two women the diagnosis was wrong and information was missing in two, leaving 94 stillbirths to be evaluated. Of them, we further excluded stillbirths due to lethal congenital developmental conditions (chromosome anomalies, malformations) (16), umbilical cord complications (for example prolapse, true knot, strangulation) (23), and infections (for example chorionamnionitis, cytomegalovirus, parvovirus, *Listeria monocytogenes*) (14). These numbers are partially overlapping as three had both infection and umbilical cord complication. There were no birth injuries, isoimmunizations, or advanced stage twin-twin transfusion syndromes, leaving 44 women with unexplained stillbirth (cases). We did not exclude placental infarction (11) and placental abruption (7) as they could be etiologically related to the exposure and outcome. Twin-pregnancies (6) were not excluded, but main findings are presented also for singleton pregnancies. Late stillbirth was defined as intrauterine fetal death at 28 weeks of gestation or later.

Intrauterine growth restriction (IUGR) was defined as the birth weight of fetus being minus two standard deviations for gestational age

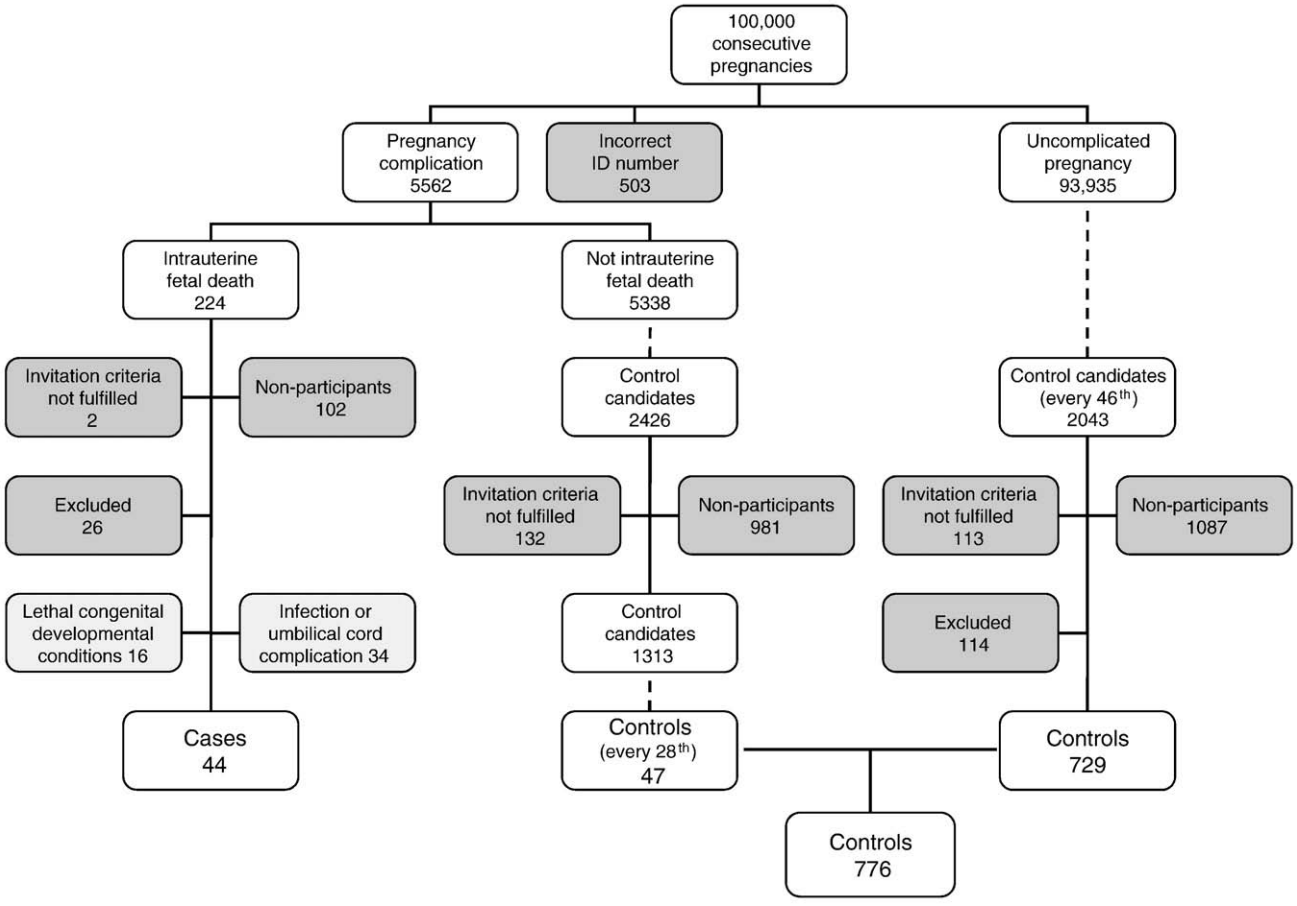


**Fig. 1.** Flow-chart shows the recruitment of cases and controls. For more information, see text. The control group comprised two subgroups to ascertain that the proportion of women with pregnancy complications other than stillbirth would be the same as in the population.