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Cohort profile: the Finnish Genetics of Pre-eclampsia Consortium (FINNPEC)

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ABSTRACT

Purpose: The Finnish Genetics of Pre-eclampsia Consortium (FINNPEC) Study was established to set up a nationwide clinical and DNA database on women with and without pre-eclampsia (PE), including their partners and infants, in order to identify genetic risk factors for PE.

Participants: FINNPEC is a cross-sectional case–control cohort collected from 5 university hospitals in Finland during 2008–2011. A total of 1450 patients with PE and 1065 pregnant control women without PE (aged 18–47 years) were recruited. Altogether, there were 1377 full triads (625 PE and 752 control triads).

Findings to date: The established cohort holds both clinical and genetic information of mother–infant–father triads representing a valuable resource for studying the pathogenesis of the disease. Furthermore, maternal biological samples (first and third trimester serum and placenta) will provide additional information for PE research. Until now, research has encompassed studies on candidate genes, Sanger and next-generation sequencing, and various studies on the placenta. FINNPEC has also participated in the InterPregGen study, which is the largest investigation on maternal and fetal genetic factors underlying PE until now.

Future plans: Ongoing studies focus on elucidating the role of immunogenetic and metabolic factors in PE. Data on morbidity and mortality will be collected from mothers and fathers through links to the nationwide health registers.

Strengths and limitations of this study

- The established cohort holds both clinical and genetic information of mother–infant–father triads representing a resource for studying the pathogenesis of pre-eclampsia (PE).
- Maternal biological samples (first and third trimester serum and placenta) provide a possibility for further PE research.
- A major strength of this study is its large multi-centre prospective design with opportunities for follow-up through linking to the national data sources as well as the recalling of participants for future studies.
- The Finnish Genetics of Pre-eclampsia Consortium (FINNPEC) cohort also includes valuable information on socioeconomic position such as educational attainment and occupational status.
- Women with PE in this cohort have been referred to university hospitals, and thus may represent the more severe end of the disease.

INTRODUCTION

Pre-eclampsia (PE) is a complex vascular pregnancy disorder. PE begins with a placental trigger followed by a maternal systemic response. The condition is heterogeneous in origin, which results in considerable variation in the clinical presentation.[1] Its classical clinical features are maternal hypertension and proteinuria developing after the 20th week of gestation. The rest of the systemic features can vary from mild cases with little systemic involvement to multiorgan failure.[2] This has often led to inconsistent results in attempts to understand PE on the basis of a single pathogenetic hypothesis.

PE is the leading cause of maternal and neonatal morbidity and mortality and affects 2–8% of pregnancies worldwide, with a higher prevalence in developing countries.[3 4] The aetiology of PE remains largely unknown, but immunological and angiogenic factors are known to play a role in the development of the disease.[5 6] Placentation in early pregnancy appears to involve specific maternal immune responses to fetal alloantigens.[7] In addition, an imbalance of proangiogenic and antiangiogenic factors has been demonstrated, specifically increased levels of the antiangiogenic soluble fms-like tyrosine kinase 1, and reduced levels of proangiogenic placental growth factor.[8] These changes appear in the circulation before clinical signs are apparent; thus, measuring circulating angiogenic proteins may serve as a diagnostic and screening tool for PE.

Epidemiological studies over the past five decades have provided robust and consistent support for the clinical observation that PE

runs in families.[9–11] Deciphering the genetic involvement in PE is challenging, not least because the phenotype is expressed only in pregnant women.[12] Moreover, it is necessary to consider two genotypes, that of the mother and that of the fetus which includes genes inherited from the mother and father. After almost two decades of molecular research, no genetic variants have been reproducibly associated with PE. Genome-wide linkage studies of PE have revealed a number of maternal susceptibility loci; however, they have not been independently replicated.[13 14] Moreover, a large number of candidate genes have been tested addressing mainly the maternal genotype and the susceptibility loci therein but, in common with the experience in other complex disorders, these have generated inconsistent results.[13 15 16] The identification of genetic variants demands large DNA collections from affected mothers and babies, and also controls with reliable supporting phenotypic data.[11]

PE is also known to have consequences for the long-term health of the mother and her child. In particular, a linkage of the pathophysiology of PE and later cardiometabolic disease has been suggested by large epidemiological studies, but is not well substantiated at a mechanistic level.[17]

The Finnish Genetics of Pre-eclampsia Consortium (FINNPEC) is a cross-sectional case–control cohort collected from the five university hospitals in Finland during 2008–2011. It was established to set up a nationwide clinical and DNA database on women with and without PE, including their partners and infants in order to identify genetic risk factors for PE. The study represents a prospective cohort design with detailed clinical outcome information allowing to characterise accurately the subphenotypes of PE. This study will also provide the opportunity to analyse combined clinical and genetic data. Biobank samples from the first and third trimesters provide a resource for further pregnancy research.

COHORT DESCRIPTION

Altogether, 1450 patients with PE and 1065 pregnant control women without PE were recruited at the five Finnish university hospitals. There were altogether 1377 full triads (625 PE and 752 control triads), the number of available samples and information is presented in table 1.

There are two arms of the study. In the prospectively recruited arm, PE women (n=923) and women with normal pregnancies (n=1009) were identified on admission at all university hospitals in Finland (Helsinki, Kuopio, Oulu, Tampere and Turku). The baby and the spouse of each participant (father of the child) were also enrolled for the study (table 1 and figure 1). After the recruitment of a PE woman, a woman with a non-PE pregnancy attending the same clinic was recruited as a control woman. In the retrospectively recruited arm of the study, all women who had been diagnosed with PE or placental insufficiency during their pregnancies were retrospectively identified based on medical records of the hospitals and invited to participate (from years 2000–2008, except in Kuopio University Hospital which recruited from years 1990–2008). These women were first contacted by letter by a physician in the hospital where they were diagnosed and treated for the disorder. Altogether, 583 women participated in the retrospective study, but 56 of them did not fulfil the diagnostic criteria for PE and were included as controls. All participants provided written informed consent.

Inclusion criteria
Nulliparous or multiparous women with a singleton pregnancy were eligible for the study. PE was defined as hypertension and proteinuria occurring after 20 weeks gestation according to the American College of Obstetricians and Gynecologists (ACOG) 2002 criteria.[18] Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg. Proteinuria was defined as the urinary excretion of

Table 1	Number of available samples (November 2015)					
	Pre-eclampsia (n=1450)			Control (n=1065)		
	Mother	Father	Baby	Mother	Father	Baby
Serum 1 Trimester	267			282		
Serum 3 Trimester	277			243		
Antepartum	150			42		
At delivery	35			24		
Postpartum	92			177		
DNA	P: 879	P: 677	P: 859	P: 922	771	972
	R: 525			R: 55		
Cord blood			805			878
Cord plasma			486			526
Placental tissue, 9-site	101			78		
Background information	P: 749	P: 616		P: 780	P: 701	
	R: 494			R: 52		
P, prospective study arm; R, retrospective study arm (only maternal DNA was collected).						
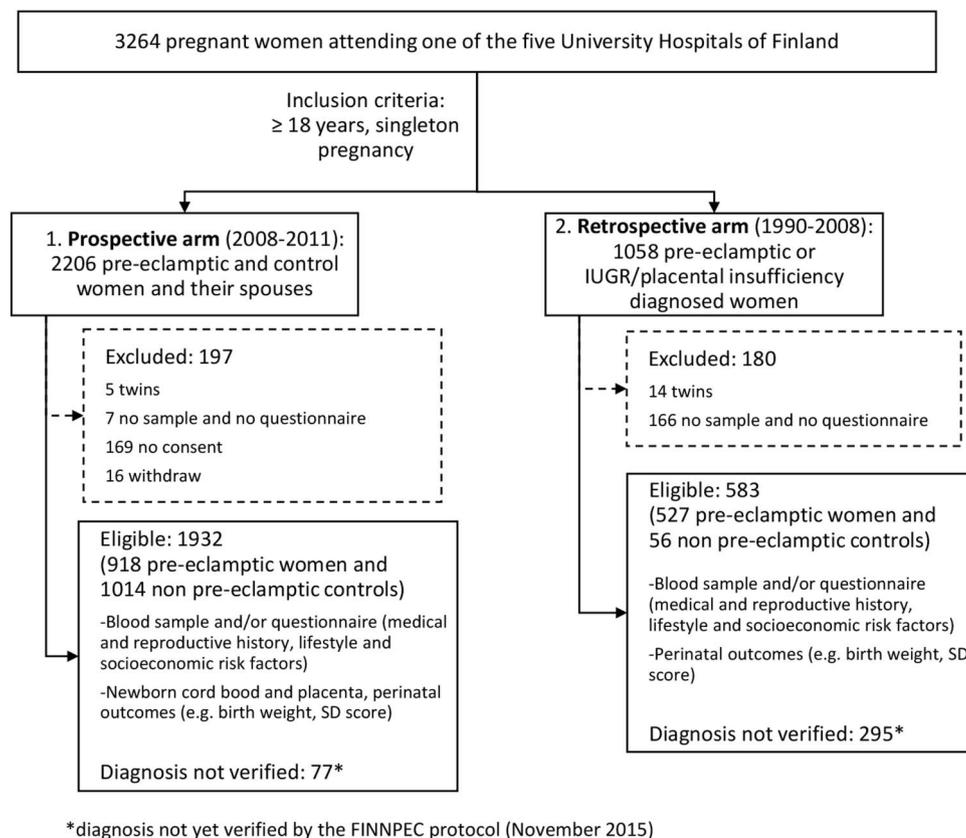
Figure 1 Flow chart of the FINNPEC Study. FINNPEC, Finnish Genetics of Pre-eclampsia Consortium. IUGR, intrauterine growth restriction.

≥0.3 g protein in a 24-hour specimen, or 0.3 g/L, or two ≥1+ readings on a dipstick in a random urine determination with no evidence of a urinary tract infection. The control group included pregnant women who suffered from proteinuria without hypertension (n=19) and women who suffered from gestational hypertension but did not meet the criteria for PE (n=111 and n=28 for the prospective and retrospective arms, respectively). Haemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome was diagnosed when at least two of the following criteria were met: lactate dehydrogenase ≥235 U/L, alanine aminotransferase ≥70 U/L, aspartate aminotransferase ≥70 U/L, thrombocytes ≤100 E9/L. Each diagnosis was ascertained based on hospital records and confirmed independently by a research nurse and a study physician.

Exclusion criteria

Exclusion criteria were multiple pregnancy, maternal age <18 years and the inability to provide an informed consent based on information in Finnish or Swedish.

Background, obstetric and perinatal data

Extensive information on medical history, family history, obstetric history, pregnancy complications, pregnancy outcome, proteinuria, blood pressure, laboratory measurements, delivery and newborn was obtained from the hospital records (~500 variables).

The participating mother and father were also asked to fill in a detailed questionnaire on background information. The questionnaire included data on pre-pregnancy weight and height, pregnancy history including previous PE and family history of PE, personal medical history, family medical history and lifestyle factors (physical activity, smoking and diet). Data on pre-pregnancy weight, height, diastolic and systolic blood pressure at first antenatal visit, and smoking status were also obtained from primary care maternity records. A woman was considered as a pre-pregnancy smoker if she still smoked 6 months before conception.

PE was defined as early onset when delivery occurred before 34+0 weeks of gestation and late onset when at 34+0 weeks of gestation or later. Preterm delivery was defined as delivery occurring before 37 weeks of gestation. Birth weights below −2.0 SD units were classified as small-for-gestational age (SGA) according to Finnish standards.[19]

Socioeconomic factors

The participating mother and father were asked to fill in a detailed questionnaire on socioeconomic factors including education, occupation and marital status.

Biological samples

A venous blood sample was drawn from mothers and fathers (table 1). Genomic DNA was extracted from

whole blood using the NucleoSpin Blood XL DNA extraction kit (Macherey-Nagel GmbH and Co) or Chemagic Magnetic Separation Module I-machine (Chemagen) and subsequently stored at −20°C.

First and third trimester serum samples were collected from a subcohort from the Hospital District of Helsinki and Uusimaa only. First trimester serum samples were obtained via first trimester biochemical screening for fetal chromosome abnormalities (range 9–15 weeks of gestation), and third trimester (range 20–42 weeks of gestation) serum samples were collected at hospitals at recruitment. Table 1 shows the number of antepartum, at delivery and postpartum samples for the third trimester. All samples drawn before contractions were regarded as antepartum samples.

Cord blood, cord plasma and placental samples were collected after delivery from a subcohort. The placental samples were collected according to a nine-site protocol where the placenta is divided into nine sections and a biopsy sample is harvested from each of these sections. The samples were obtained shortly after detachment of the placenta: 70% of the samples were collected within half an hour, 92.5% within an hour and the remaining three samples within 80 min of placental detachment. The samples were subsequently stored in an RNA later solution at −80°C.

Basic characteristics

PE women were older and suffered more from obesity and pre-existing medical conditions (eg, chronic hypertension, type 1 diabetes and gestational diabetes) compared with control women (table 2). The proportion of primiparous women was also higher in the PE group (table 2). In women who later developed PE, both diastolic and systolic blood pressure were already increased at the first antenatal visit occurring on average at 8.6 ±1.5 weeks of gestation. In women suffering from PE, proteinuria occurred on average at 34.7±3.9 weeks of gestation. Proteinuria was also observed in some controls but they did not meet the diagnostic criteria for PE.

There were no differences in age, body mass index (BMI) or self-reported chronic hypertension between the fathers in the PE and control groups (table 2).

Altogether, 262 of the 1450 PE pregnancies (18.1%) were early onset (delivery before 34+0 weeks of gestation). The women in the early-onset group were older and they had had more pregnancies and deliveries than mothers in the late-onset group (table 3). Furthermore, they had more proteinuria and higher diastolic blood pressure already at the first antenatal visit. They also suffered more frequently from chronic hypertension. There were no differences in smoking before or during pregnancy. These findings support the view that classifying PE into early-onset and late-onset disease differentiates two distinct clinical forms with pathophysiologically specific features.

Women with PE more often reported a history of PE (14.8% in women with PE vs 1.7% in controls). These data were based on hospital records and/or questionnaires. The possibility for recall bias must be acknowledged. More detailed information will be published in the near future after information on PE history has been verified solely from the hospital records.

In the FINNPEC Study, controls were more often smokers before and during pregnancy than women with PE. We also detected a trend for greater proportion of SGA babies for those women with PE who smoked during pregnancy (data not shown).

FINDINGS UNTIL NOW

The established cohort holds both clinical and genetic information of mother–infant–father triads representing a resource for studying the pathogenesis of the disease as well as later implications in the mother, father and the offspring. Furthermore, placental samples collected will provide an important addition for future research.

The research so far from the FINNPEC has encompassed studies on candidate genes (heme oxygenase-1 promoter and CYP subfamily 2J polypeptide 2),[20] [21] Sanger and next-generation sequencing[22] [23] and various studies on the placenta.[24] [25] FINNPEC has also served as a replication cohort in various collaborative efforts to identify genetic risk factors for PE.[15] [26]

Ongoing studies focus on elucidating the role of immunogenetic and metabolic factors in PE. Metabolomic studies on serum samples collected at the first and third pregnancy trimesters, respectively, and on fetal cord plasma will be performed in collaboration with researchers from the University of Eastern Finland.

Family study

The Finnish Pre-eclampsia Family Study[14] [27] will be expanded by families with PE recruited from the FINNPEC cohort. Those participants who have reported in the background information questionnaire having first-degree relatives with a history of PE will be requested to contact their relatives and provide them with oral or written information about the FINNPEC Study and the research group's contact information with the support of an information letter. First-degree and second-degree relatives (parents, siblings, grandparents, uncles, aunts and cousins) of the study participants will be recruited. The protocol for collecting the families with PE has already been approved by the Ethics Committee.

Long-term follow-up

PE is known to have consequences for the long-term health of the mother and child.[17] There are very little long-term data on the morbidity and mortality of fathers. Thus, data on morbidity and mortality (focusing on cardiometabolic disease) will be collected from mothers and fathers through links to the nationwide health registers including the Hospital Discharge Register with data on hospital inpatient and outpatient

Table 2 Maternal, perinatal and paternal characteristics of pre-eclamptic and control groups in FINNPEC

Maternal or perinatal characteristics	Pre-eclampsia (n=1450)	Control (n=1065)	p Value*	p Value†
Age at delivery, year	30.3±5.5 (1449)	29.8±5.2	0.015	
Gravity	1.9±1.6	2.3±1.7	**<0.001**	
Parity	0.5±1.1	0.8±1.3	**<0.001**	
Primiparous	1065 (73.5%)	596 (56.0%)	**<0.001**	
Weight, kg (self-reported, pre-pregnancy)	68.8±15.1 (1447)	66.3±13.0 (1064)	**<0.001**	**<0.001‡**
Height, m	1.65±0.06 (1449)	1.66±0.06 (1064)	**0.001**	
BMI, kg/m^2 (self-reported, pre-pregnancy)§	25.3±5.2 (1447)	24.1±4.4 (1063)	**<0.001**	**<0.001‡**
Systolic blood pressure at first antenatal visit, mm Hg	125±13 (1407)	119±13 (1023)	**<0.001**	**<0.001¶**
Diastolic blood pressure at first antenatal visit, mm Hg	78±10 (1407)	73±10 (1023)	**<0.001**	**<0.001¶**
Highest systolic blood pressure, mm Hg**	167±19	131±17 (1063)	**<0.001**	**<0.001¶**
Highest diastolic blood pressure, mm Hg	110±9	87±11 (1063)	**<0.001**	**<0.001¶**
Proteinuria (maximum), g/24 hour	4.2±4.1 (1283)		–	
Smoking before pregnancy	313 (22.2%) (1396)	288 (27.4%) (1037)	**0.003**	
Smoking during pregnancy	108 (7.6%) (1404)	121 (11.5%) (1052)	**0.005**	
Chronic hypertension††	259 (17.9%)	65 (6.1%)	**<0.001**	
Gestational hypertension‡‡	–	139 (13.1%)	–	
Gestational diabetes mellitus	207 (14.3%)	89 (8.4%)	**<0.001**	
Pregestational diabetes mellitus	47 (3.2%)	9 (0.8%)	**<0.001**	
Type 1 diabetes	38 (2.6%)	6 (0.6%)	**<0.001**	
Type 2 diabetes	9 (0.6%)	3 (0.3%)	0.223	
Mode of delivery				
Vaginal	757 (52.3%)	889 (83.5%)		
Caesarean section	693 (47.8%)	175 (16.4%)		
Birth weight, g	2692±897	3455±687	**<0.001**	**<0.001§§**
Relative birth weight, SD	−1.0±1.3 (1449)	−0.2±1.1	**<0.001**	**<0.001§§**
SGA	306 (21.1%)	71 (6.7%)	**<0.001**	
Gestational weeks	36.4±3.5	39.3±2.3	**<0.001**	**<0.001‡**
Paternal characteristics				
Age, years	32.5±6.3 (699)	32.3±5.9 (854)	0.478	
BMI, kg/m^2 (self-reported)	26.2±3.9 (548)	26.1±3.5 (611)	0.568	
Chronic hypertension (requiring medication, self-reported)	14 (2.6%) (545)	9 (1.5%) (616)	0.176	

()Number of available information/samples unless from all.
Data are presented as mean±SD or percentages.
Bold text shows p values <0.05.
*Unadjusted.
†Adjusted.
‡Adjusted for parity, mother's age at birth.
§Based on weight and height before pregnancy, self-reported at first antenatal visit.
¶Adjusted for parity, mother's age at birth, pre-pregnancy BMI.
**When highest diastolic value recorded.
††Systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg detected before 20 weeks of gestation.
‡‡Blood pressure ≥140/90, no proteinuria.
§§Adjusted for parity, mother's age at birth, gestation weeks, pre-pregnancy BMI, chronic hypertension, gestational diabetes, pregestational diabetes mellitus.
BMI, body mass index; FINNPEC, Finnish Genetics of Pre-eclampsia Consortium; SGA, small-for-gestational age.

care and Cause-of-Death Register in collaboration with the National Institute for Health and Welfare (THL) and Statistics Finland. Furthermore, data on familial PE history data will be collected through linkage to these registers. Linkage to health registers is possible through the Finnish personal identification numbers.

International collaboration
FINNPEC has participated in the genetic studies of PE in Central Asian and European populations (InterPregGen), which was the largest investigation on the maternal and fetal genetic factors underlying PE until now (http://www.interpreggen.org).[28] It was funded by the European Community's Seventh Framework Programme. Six hundred PE women, 600 affected fetuses and 600 healthy pregnant control women from the FINNPEC cohort were included in the follow-up genotyping after the genome-wide association screening was performed in the discovery cohorts. FINNPEC also participates in the Global Pregnancy

Table 3 Early-onset (delivery before 34 +0 weeks of gestation) versus late-onset pre-eclampsia

Maternal or perinatal characteristics	Pre-eclampsia Early vs late onset (n=262) (n=1188)		Control (n=1065)	p Value early vs late	p Value early vs control	p Value late vs control
Age, year	31.5±6.1 (261)	30.0±5.3	29.8±5.2	**<0.001**	**<0.001**	0.239
Gravity	2.3±2.0	1.9±1.5	2.3±1.7	**0.014**	0.934	**<0.001**
Primiparous	176 (67.2%)	889 (74.8%) (1187)	596 (56.0%)	**0.013**	**0.001**	**<0.001**
Weight, kg (self-reported, pre-pregnancy)	68.9±14.6 (261)	68.8±15.2 (1186)	66.3±13.0 (1064)	0.713*	**0.006***	**<0.001***
BMI, kg/m^2 (self-reported, pre-pregnancy)	25.6±5.1 (261)	25.2±5.3 (1186)	24.1±4.4 (1063)	0.542*	**<0.001***	**<0.001***
Systolic blood pressure at first antenatal visit, mm Hg	126±14 (256)	124±13 (1151)	119±13 (1023)	0.160†	**<0.001†**	**<0.001†**
Diastolic blood pressure at first antenatal visit, mm Hg	80±10 (256)	77±10 (1151)	73±10 (1023)	**0.001†**	**<0.001†**	**<0.001†**
Highest systolic blood pressure, mm Hg	177±19	165±18	131±17 (1063)	**<0.001†**	**<0.001†**	**<0.001†**
Highest diastolic blood pressure, mm Hg	115±10	109±9	87±11 (1063)	**<0.001†**	**<0.001†**	**<0.001†**
Proteinuria (maximum), g/24 hours	6.7±5.4 (254)	3.6±3.4 (1029)		**<0.001†**		
Smoking before pregnancy	43 (17.1%) (251)	270 (23.4%) (1145)	288 (27.4%) (1037)	0.058	**0.001**	0.041
Smoking during pregnancy	26 (10.3%) (251)	82 (7.1%) (1153)	121 (11.5%) (1052)	0.200	0.875	**0.001**
Chronic hypertension	71 (27.1%)	188 (15.8%)	65 (6.1%)	**<0.001**	**<0.001**	**<0.001**
Gestational diabetes mellitus (diet and/or insulin treated)	29 (11.1%)	178 (15.0%)	89 (8.4%)	0.096	0.173	**<0.001**
Pregestational diabetes mellitus	5 (1.9%)	42 (3.5%)	9 (0.8%)	0.175	0.133	**<0.001**
Birth weight, g	1307±423	2997±652	3455±687	**<0.001‡**	**<0.001‡**	**<0.001‡**
SGA	135 (51.3%)	171 (14.4%) (1185)	71 (6.7%)	**<0.001**	**<0.001**	**<0.001**
Relative birth weight (SD)	−2.0±1.0	−0.8±1.2	−0.2±1.1	**<0.001‡**	**<0.001‡**	**<0.001‡**
Gestation weeks	30.3±2.4	37.7±1.9	39.3±2.3	**<0.001***	**<0.001***	**<0.001***

Bold text shows p values <0.05.
*Adjusted for parity, mother's age at birth.
†Adjusted for parity, mother's age at birth, pre-pregnancy BMI.
‡Adjusted for parity, mother's age at birth, pre-pregnancy BMI, chronic hypertension, gestational diabetes, pregestational diabetes mellitus.
BMI, body mass index; SGA, small-for-gestational age.

Collaboration (CoLab), a major Bill and Melinda Gates Foundation supported initiative focused on adverse pregnancy outcomes and achieving a better understanding of their causes.[29] CoLab is the largest international initiative until now to understand major pregnancy disorders in a global setting.

STRENGTHS AND LIMITATIONS

A major strength of this study is its large multicentre prospective design with opportunities for follow-ups as well as the recalling of participants for future studies. The established cohort holds both clinical and genetic information of mother–infant–father triads representing a resource for studying the pathogenesis of PE. Furthermore, maternal biological samples (first and third trimester serum and placenta) will provide additional information for PE research.

In addition, one of the strengths of the current study is the ascertainment of the outcome: each diagnosis was ascertained based on hospital records and confirmed independently by a research nurse and a study physician. When rediagnosed carefully using this protocol, not all recruited cases meet the criteria for PE. Most of these women suffered from gestational hypertension without proteinuria.

The majority of genetic studies of PE have until now focused on maternal genetic contribution. However, owing to the placental origin of PE, it is likely that fetal and/or paternal genetic factors play a central role in the pathogenesis. Evidence supports the idea that paternal and/or fetal genetic factors might contribute to the risk of PE.[30] [31] It has been shown that men born to a PE pregnancy are twice as likely to father a PE pregnancy.[30] In addition, men who have fathered a PE pregnancy are nearly twice as likely to father a PE pregnancy with a different woman.[31] Thus, it is important to include the father and the offspring in genetic studies of PE. The study design at FINNPEC opens up this possibility for detecting maternal, paternal and fetal genes and their interactions.

Association between PE and the development of maternal cardiovascular diseases (CVDs) later in life has been well established through epidemiological research.[17] Follow-up studies that will be carried out in FINNPEC through linkage of the national data sources may help identify prognostic subgroups of mothers, fathers and infants that have a linkage between PE and later life CVD and other non-communicable diseases. In future, this may provide tools for early screening and targeted postpartum preventive strategies.

The FINNPEC cohort also includes information on socioeconomic position such as educational attainment and occupational status, which are currently being analysed. This is important because the role of socioeconomic position as a risk factor of PE has been little studied.

It must be acknowledged that a large unselected material would have had more epidemiological advantages. This cohort is not directly generalisable to the general population since the participants represented a Finnish population of women with PE who were referred to university hospitals and thus may represent a more severe end of the disease. However, apart from serving as a tertiary centre of a larger catchment area, all these hospitals serve as primary delivery hospitals for a smaller catchment area. The incidence of early-onset disease (18.1%) was comparable to reports in population-based studies,[32] whereas the incidence of HELLP (7.4%) was quite high. However, the most severe cases are missing as deliveries had taken place immediately before recruitment could take place.

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Competing interests None declared.

Ethics approval The FINNPEC Study protocol was approved by the coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa (149/EO/2007).

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Data sharing statement The authors confirm that some access restrictions apply to the data. The researchers interested in using the data must obtain approval from the FINNPEC Board (steering committee). The researchers using the data are required to follow the terms of a number of clauses designed to ensure the protection of privacy and compliance with relevant Finnish laws. Data requests may be subject to further review by the Ethics Committee and may also be subject to individual participant consent.

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