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MATERNAL AND PATERNAL DETERMINANTS OF PRE-ECLAMPSIA AND ECLAMPSIA

Noora Jaatinen

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SARJA – SER. D OSA – TOM. 1794 | MEDICA – ODONTOLOGICA | TURKU 2024

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To all mothers

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ABSTRACT

Pre-eclampsia is a complex vascular disorder in pregnancy, characterised by new-onset hypertension after 20 weeks of gestation and proteinuria or new-onset signs of other maternal end-organ dysfunction. It affects 3–5 % of pregnancies. One of the most severe complications is eclampsia, which is a seizure occurring in association with pre-eclampsia. The aetiology of pre-eclampsia remains poorly understood, making strategies for its prevention challenging. Therefore, it is important to better understand the factors involved in its aetiology. The aim of this thesis was to evaluate the impact of several maternal and paternal background factors on the risk for pre-eclampsia and to investigate the incidence and outcomes of eclampsia in Finland.

In the first three substudies of this thesis the FINNPEC cohort (Finnish Genetics of Pre-eclampsia Consortium), collected from five Finnish university hospitals between 2008–2011 was studied. The participating women and men completed a questionnaire on their background information and serum samples were collected from a subset of women. For the fourth study, eclampsia diagnoses from 2006 to 2010 were retrieved from the national Medical Birth Register and the Care Register for Health Care.

In this thesis earlier age at menarche, subfertility, depression and non-communicable diseases were associated with increased risk of pre-eclampsia. Moreover, a family history of hypertension, stroke, diabetes and depression were risk factors. Socioeconomic status and physical activity during pregnancy were not related to pre-eclampsia. Physical activity of pre-eclamptic women and controls was not associated with the maternal serum concentrations of angiogenic factors. The phenotype and lifestyle of the partners did not play a significant role in pre-eclampsia susceptibility of parturients. The incidence of eclampsia in Finland was low, 1.5/10 000 deliveries, and it has decreased from the 1990s to the 2000s. Increased use of magnesium sulphate probably contributed to the low incidence as well as to the low number of recurrent seizures and prolonged complications.

KEYWORDS: pre-eclampsia, eclampsia, pregnancy, pregnancy complication, risk factor, paternal, lifestyle, angiogenic factors, physical activity

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Kliininen laitos
Synnytys- ja naistentautioppi
NOORA JAATINEN: Äitiin ja isään liittyvät tekijät pre-eklampsian ja eklampsian taustalla
Väitöskirja, 158 s.
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TIIVISTELMÄ

Pre-eklampsia on raskaudenaikainen verisuonisairaus, jossa 20. raskausviikon jälkeen verenpaine nousee ja ilmaantuu proteinuriaa tai löydöksiä muista elinjärjestelmistä. Raskaana olevista 3–5 % sairastuu pre-eklampsiaan. Yksi vakavimmista komplikaatioista on eklampsia, joka tarkoittaa pre-eklampsiaan liittyvää kouristuskohtausta. Pre-eklampsian etiologia tunnetaan huonosti, mikä vaikeuttaa kehitystyötä sairauden ennaltaehkäisemiseksi. Siksi olisi tärkeää ymmärtää paremmin pre-eklampsian kehittymiseen vaikuttavia taustatekijöitä. Väitöskirjan tavoitteena oli tutkia synnyttäjän ja hänen partnerinsa taustatekijöiden vaikutusta pre-eklampsiariskiin, sekä selvittää eklampsian esiintyvyyttä ja vaikutuksia Suomessa.

Väitöskirjan kolmessa ensimmäisessä osatyössä tutkittiin vuosina 2008–2011 Suomen yliopistosairaaloissa kerättyä FINNPEC (Finnish Genetics of Pre-eclampsia Consortium) -kohorttia. Tutkimukseen osallistuneet naiset ja heidän partnerinsa täyttivät kyselylomakkeen taustatiedoista, ja laskimoverinäytteet kerättiin osalta naisista. Neljännen osatyön aineisto koottiin Terveyden ja hyvinvoinnin laitoksen (THL) syntyneiden lasten rekisterin sekä Terveydenhuollon hoitoilmoitusrekisterin tiedoista eklampsiadiagnoosin saaneista potilaista vuosilta 2006–2010.

Väitöstutkimuksessa havaittiin, että aikainen menarke, subfertiliteetti, masennus ja muut taustasairaudet liittyivät suurentuneeseen riskiin sairastua pre-eklampsiaan. Lisäksi suvussa esiintyvä verenpainetauti, aivoverisuonisairaudet, diabetes ja masennus olivat riskitekijöitä. Sosioekonominen asema ja liikunta raskauden aikana eivät olleet yhteydessä pre-eklampsiaan. Raskaudenaikainen liikunta ei ollut yhteydessä pre-eklampsiaan sairastuneiden ja verrokkien laskimoverinäytteiden angiogeenisten tekijöiden tasoihin. Partnerien ilmiasuun liittyvät tekijät ja elintavat eivät vaikuttaneet merkitsevästi synnyttäjän alttiuteen sairastua pre-eklampsiaan. Eklampsian ilmaantuvuus Suomessa oli matala, 1.5/10 000 synnytystä, ja se on laskenut 1990-luvulta 2000-luvulle. Lisääntynyt magnesiumsulfaatin käyttö liittyy todennäköisesti eklampsian matalaan ilmaantuvuuteen, sekä uusiutuneiden kouristusten ja vakavien pitkittyneiden komplikaatioiden pieneen määrään.

AVAINSANAT: pre-eklampsia, eklampsia, raskaus, raskauskomplikaatio, riskitekijä, isään liittyvä, angiogeeniset tekijät, liikunta

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Abbreviations

ACOG	The American College of Obstetricians and Gynecologists
ACR	Urine albumin to creatinine ratio
ART	Assisted reproductive technology
BMI	Body mass index
CI	Confidence interval
CVD	Cardiovascular disease
FGR	Fetal growth restriction
FMF	The Fetal Medicine Foundation
FINNPEC	The Finnish Genetics of Pre-eclampsia Consortium
FIGO	The International Federation of Gynecology and Obstetrics
EOPE	Early-onset pre-eclampsia
GDM	Gestational diabetes
gwks	Gestational weeks
HDP	Hypertensive disorders of pregnancy
ICD-9	International Classification of Diseases, 9th Revision
ICSI	Intracytoplasmic sperm injection
IVF	In vitro fertilization
ISSHP	The International Society for the Study of Hypertension in Pregnancy
LOPE	Late-onset pre-eclampsia
NICE	National Institute for Health and Care Excellence
OR	Odds ratio
PAF	Population attributable fraction
PE	Pre-eclampsia
PlGF	Placental growth factor
PrCr	Protein to creatinine ratio
RCT	Randomised controlled trial
RR	Relative risk
sEng	Soluble endoglin
sFlt-1	Soluble fms-like tyrosine kinase 1
SSRI	Selective serotonin reuptake inhibitor
SD	Standard deviation

UK	United Kingdom
U.S.	United States
VEGF	Vascular endothelial growth factor

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Jaatinen N, Jääskeläinen T, FINNPEC, Laivuori H, Ekholm E. The non-traditional and familial risk factors for preeclampsia in the FINNPEC cohort. *Pregnancy Hypertens*, 2021; 23: 48–55.

II Jaatinen N, Ekholm E, FINNPEC, Laivuori H, Jääskeläinen T. Impact of physical activity on preeclampsia and angiogenic markers in the Finnish Genetics of Pre-eclampsia Consortium (FINNPEC) cohort. *Annals of Medicine*, 2024; 56:1:2325480. (Published online 11.3.2024)

III Jaatinen N, Jääskeläinen T, Ekholm E, Laivuori H, for FINNPEC. Searching for a paternal phenotype for preeclampsia. *Acta Obstet Gynecol Scand*, 2022; 101: 862–870.

IV Jaatinen N, Ekholm E. Eclampsia in Finland; 2006 to 2010. *Acta Obstet Gynecol Scand*, 2016; 95:7: 787–92.

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1 Introduction

Pre-eclampsia (PE) is a multi-systemic pregnancy-specific disorder, affecting 3–5% of all pregnancies globally.[1] It is one of the main causes of maternal, foetal and neonatal morbidity and mortality, causing approximately 42 000 maternal and 500 000 foetal and neonatal deaths each year.[1–4] Moreover, PE predisposes affected women and their children to long-term morbidity including increased risk for hypertension and cardiovascular disease (CVD) later in life.[5,6] The clinical presentation of PE varies, but it is characterised by hypertension occurring after 20 weeks of gestation in association with proteinuria and/or new-onset signs of other maternal end-organ dysfunction or uteroplacental dysfunction.[3] Eclampsia, which is a seizure occurring in association with PE, can also be the first sign of PE and is a severe manifestation of the disease.[7,8]

The aetiology of PE is not well understood, but placental malperfusion with release of soluble factors into the circulation and subsequent maternal vascular endothelial injury leading to hypertension and multi-organ injury are considered as central features in the pathogenesis.[1,9] A disturbance in the balance of anti-angiogenic and pro-angiogenic factors, with decreased maternal serum levels of placental growth factor (PlGF) and increased levels of soluble fms-like tyrosine kinase 1 (sFlt-1), soluble endoglin (sEng) and sFlt-1/PlGF ratio, is characteristic of PE. [10–12] While PE is commonly considered a maternal disease, it can also be seen as a maternal and paternal disease with both foetal and maternal manifestations. The foetal genotype is a combination of maternal and paternal components and immunogenetic maternal-paternal relationship has been proposed to contribute to the development of PE.[13,14]

Since the aetiology of PE remains unclear, investigation and identification of risk factors is important for identifying pregnant women at high risk for initiating prevention strategies and for more intensive observation and care. Clinical risk factors for PE are used to identify women at high risk for PE and to give them low-dose aspirin prophylaxis, which can reduce the risk of PE if initiated at the end of the first trimester.[15] In cases, where PE has already been diagnosed delivery is the only effective treatment.[1] Magnesium sulphate is the most effective pharmacological

intervention in preventing eclampsia in women who have PE with severe features and to reduce the rate of recurrent seizures in women with eclampsia.[16–20]

There are many well-established maternal and pregnancy related risk factors for PE, including prior PE, chronic hypertension, nulliparity, obesity, pregestational diabetes and advanced maternal age.[21] Nevertheless, the well-acknowledged risk factors have been shown to detect only 34–41% of PE.[22] There are, however other maternal and paternal risk factors that have been less studied or presented conflicting results with respect to PE.

The aims of this thesis were to investigate maternal and paternal determinants of PE and eclampsia and the incidence and outcomes of eclampsia in Finland. The associations of several maternal and paternal background factors with PE were evaluated in a large nationwide Finnish Genetics of Pre-eclampsia Consortium (FINNPEC) study (Studies I–III). The focus was on less explored risk factors: socioeconomic factors, factors related to fertility, health history including family medical history, physical activity and paternal phenotypic and lifestyle factors (Studies I–III). We also evaluated whether exercise in pregnant women with and without PE associate with maternal serum concentrations of angiogenic factors sFlt-1, PlGF and sEng and sFlt-1/PlGF ratio (Study II). The incidence and outcome of eclampsia were assessed after magnesium sulphate became widely used as a drug to treat and prevent eclampsia (Study IV).

2 Review of the Literature

2.1 Incidence of pre-eclampsia

The incidence of PE was 4.2% in Finland during the years 2006–2011. The yearly incidence of PE in Finland between 2006 and 2022 is represented in *Figure 1*.[23] Globally, the incidence of PE was estimated to be approximately 4.6% (95% uncertainty range 2.7–8.2) between 2002 and 2010, with wide variation across different regions.[24]

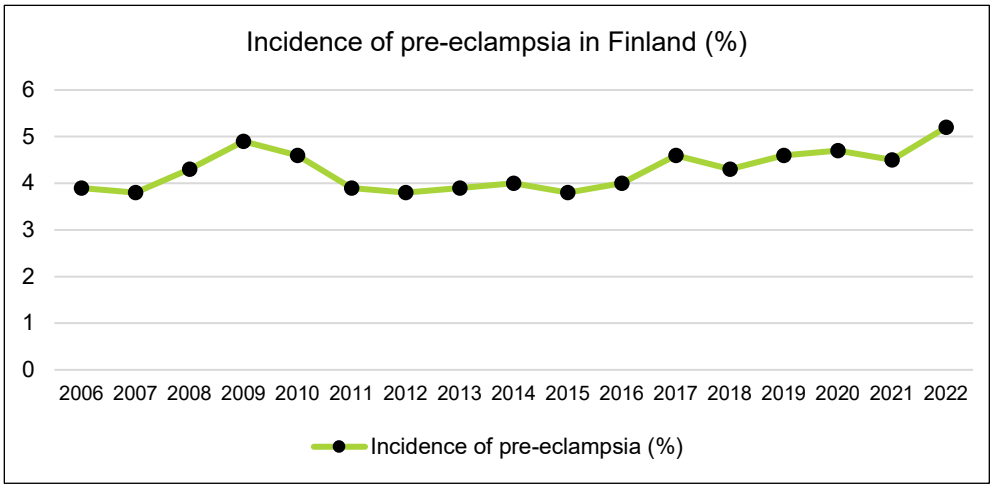

Figure 1. The yearly incidence of pre-eclampsia in Finland between 2006 and 2022.[23]

2.2 Definitions and classifications of hypertensive disorders of pregnancy

Defining PE is challenging because it is a progressive disease involving multiple organ systems and resulting in various clinical features. Improved understanding of the pathophysiology has led to evolvement of the clinical definition of PE. Until recently, PE was defined as new onset hypertension and proteinuria developing ≥ 20 gestational weeks (gwks). Currently the definition of PE includes maternal and uteroplacental organ dysfunctions besides proteinuria.[1,3,9] Major national and

international guidelines (The International Society for the Study of Hypertension in Pregnancy [ISSHP][3], National Institute for Health and Care Excellence [NICE][25], American College of Obstetricians and Gynecologists [ACOG][7]) and the national Finnish Current Care Guideline[26] agree that PE can be defined as new onset hypertension (systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg) with proteinuria, or end organ dysfunction after 20 gwks. There is some variation on the definitions of end-organ dysfunction for the diagnosis of PE in the different guidelines. The definitions of PE and other hypertensive disorders in pregnancy are presented in *Table 1*.[3,7,25,26]

A study from 2016 examined how the new classifications of PE affected PE diagnoses in the FINNPEC cohort. Only minor changes were observed in the number of PE women when comparing ACOG 2002 classification with ACOG 2013 and ISSHP 2014 classifications, in which proteinuria is not necessary for diagnosis when specific symptoms are present.[27]

Subclassifications of pre-eclampsia

PE can be divided into subtypes based on the timing of delivery or diagnosis. PE is commonly defined early-onset (EOPE) if the diagnosis or delivery is before 34^{+0} gwks and late-onset (LOPE) if the diagnosis or delivery is $\geq 34^{+0}$ gwks.[4,28] In preterm PE delivery occurs $< 37^{+0}$ gwks and in term PE $\geq 37^{+0}$ gwks.[4]

Both ISSHP and ACOG do not recommend classifying PE as severe or non-severe, as it can deteriorate unpredictably in any clinical case.[3,7] Instead, the expression PE with or without severe features can be used.[7]

Eclampsia is a severe manifestation of hypertensive disorders of pregnancy (HDP). It is defined by new-onset tonic-clonic, focal, or multifocal seizures in a pregnant/postpartum woman in the absence of other causative conditions.[7]

Table 1. Classification of hypertensive disorders of pregnancy according to ISSHP 2021 Guideline[3] and definition of pre-eclampsia according to ISSHP 2021[3], NICE 2019[25], ACOG 2020[7] and the Finnish Current Care Guideline 2021[26].

Type of hypertensive disorder	Definition
Chronic hypertension	Systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg detected pre-pregnancy or < 20 gwks
Gestational hypertension	Systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg occurring ≥ 20 gwks without proteinuria or other findings suggestive of PE in a woman with previously normal BP
Pre-eclampsia	**According to ISSHP** Gestational hypertension together with ≥ 1 of the following new-onset conditions at ≥ 20 gwks:

	1. Proteinuria* 2. Other maternal end-organ dysfunction, including: - Neurological complications (e.g., eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, or persistent visual scotomata) - Pulmonary edema - Hematological complications (e.g., platelet count < 150,000/µL, DIC, haemolysis) - Acute kidney injury (such as creatinine ≥ 90 µmol/L or 1 mg/dL) - Liver involvement (e.g., elevated transaminases such as ALT or AST > 40 IU/L) with or without right upper quadrant or epigastric abdominal pain) 3. Uteroplacental dysfunction (e.g., placental abruption, angiogenic imbalance, fetal growth restriction, abnormal umbilical artery Doppler waveform analysis, or intrauterine fetal death)
	According to NICE Similar to ISSHP (above), except for the following differences: - Pulmonary edema not included in maternal end-organ dysfunction - Placental abruption and angiogenic imbalance not mentioned in uteroplacental dysfunction
	According to ACOG Systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg occurring ≥ 20 gwks together with proteinuria, or in the absence of proteinuria the new-onset of any of the following: - Platelet count < 100 000 x 10^9/L - Renal insufficiency** - Elevated blood concentrations of liver transaminases to twice normal concentration - Pulmonary edema - New-onset headache unresponsive to medication and not accounted for by alternative diagnoses or visual symptoms
	According to the Finnish Current Care Guideline Systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg occurring ≥ 20 gwks and proteinuria, or in the absence of proteinuria the new-onset of any of the following: - Thrombocytopenia - Elevated blood concentrations of liver transaminases - Increased serum creatinine concentrations - Neurological symptoms (e.g. headache, visual symptoms) - Fetal growth restriction
Superimposed pre-eclampsia on chronic hypertension	In a woman with chronic hypertension, development of new proteinuria and/or another organ dysfunction(s) or uteroplacental dysfunction(s) (as listed above).

* Protein to creatinine ratio (PrCr) of ≥30 mg/mmol (0.3 mg/mg) or Urine albumin to creatinine ratio (ACR) ≥ 8 mg/mmol (71 mg/g) or dipstick proteinuria of ≥ +2 (>1g/l) or or ≥ 0.3 g/d in a complete 24-hour urine collection

** Serum creatinine concentrations greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease

Abbreviations: The American College of Obstetricians and Gynecologists (ACOG), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Blood pressure (BP), Disseminated intravascular coagulation (DIC), gestational weeks (gwks), International Society for the Study of Hypertension in Pregnancy (ISSHP), National Institute for Health and Care Excellence (NICE), pre-eclampsia (PE)

2.3 Diagnostics of pre-eclampsia

The diagnosis of PE is complicated, as the clinical presentation is heterogeneous and often atypical. The diagnostic criteria for PE and HDP are presented in *Table 1*. The diagnosis of PE requires hypertension together with proteinuria and/or other maternal end-organ dysfunction or uteroplacental dysfunction.

2.3.1 Hypertension

Hypertension in pregnancy is defined as at least two readings of clinic systolic BP ≥ 140 mmHg and/or a diastolic BP ≥ 90 mmHg.[3] Among hypertensive pregnant women, self-monitored BP is usually lower than in the clinic setting. There is no consensus about whether self-monitored BP target should be lower than the diagnostic BP threshold in the clinic setting.[3,29] Hypertension in pregnancy is considered severe when systolic BP ≥ 160 mmHg or the diastolic BP ≥ 110 mmHg, or both.[3,7]

2.3.2 Proteinuria

Proteinuria can be detected by urinary dipstick testing (manual or automated), by Protein to creatinine ratio (PrCr), Urine albumin to creatinine ratio (ACR), or 24-hour urine collection.[3] Major national and international guidelines agree that PrCr of ≥30 mg/mmol (0.3 mg/mg) and/or ACR ≥ 8 mg/mmol (71 mg/g) are the preferred tests in diagnosing proteinuria.[3,7,25] Both tests have a high specificity and high sensitivity in detecting proteinuria, and therefore either can be recommended depending on availability.[25]

Dipstick testing for proteinuria has high false-positive and false-negative accuracy at the +1 level.[3,7] The urinary dipstick test is usually recommended to be used as a screening tool for proteinuria.[25] It can be used as a diagnostic test if it is the only available method of assessing proteinuria, taking into account that overall accuracy is better using +2 as the discriminant value.[7,30] The Finnish Current Care Guideline recommend dipstick proteinuria of ≥ +1 to be assured with PrCr or ACR.[26]

A 24-hour urine collection, with proteinuria defined as ≥ 0.3 g/d, usually offers no advantage over other tests, but could delay identification of proteinuria, and it is inconvenient for women. Urinary PrCr and ACR have been shown to correlate with 24-hour urine collection, but the correlation has been found to be lower when the protein excretion is > 1−2 g/24 hours.[31,32]

2.3.3 Other manifestations of pre-eclampsia

PE affects many organs causing various symptoms and clinical findings (*Table 2*).[1,33]

Table 2. Symptoms and signs of pre-eclampsia.

	SYMPTOMS	SIGNS
Cardiorespiratory	Breathlessness, chest pain	Elevated blood pressure, tachypnea, decreased oxygen saturation, diastolic dysfunction
Renal		Proteinuria, raised serum creatinine
Neurological	Headache, visual disturbances, seizures	Brisk reflexes
Hematological		Dark brown urine, petechia, low platelets, abnormal clotting tests, haemolysis
Hepatological	Epigastric pain	Right upper quadrant tenderness, elevated serum liver enzymes
Uteroplacental and fetal	Reduced fetal movements	Fetal growth restriction

2.4 Pathophysiology of pre-eclampsia

Despite extensive research, the exact aetiology and pathogenesis of PE are still not fully understood. However, many maternal, foetal and placental causal explanations have been proposed. It is generally agreed that PE is primarily a placental disorder. Indeed, PE can develop even without a foetus[34] and the syndrome eventually resolves only after the delivery of the placenta.[9] Maternal genetic, behavioural and metabolic factors are thought to contribute to the PE phenotype.[35]

2.4.1 The two-stage model

In the classical two-stage model of PE, first proposed in 1993[36], impaired early placental development in the first half of pregnancy leads to maternal disease later in pregnancy.[37] In this model, placental stress is followed by elevated amounts of anti-angiogenic factors that cause dysfunction of maternal peripheral endothelial cells, vascular inflammation and vascular injury.[9,38] These pathological changes lead to the clinical syndrome of PE affecting multiple maternal organs including the central nervous system, cardiorespiratory system, liver, kidney and the coagulation system. Further, metabolic abnormalities including insulin resistance, dyslipidaemia and inflammatory markers are involved in the pathogenesis.[9] The two-stage model was revised in 2019 with the addition of two main placental pathways leading to syncytiotrophoblast stress and the inclusion of maternal risk factors (*Figure 2*).[37]

Physiological transformation with remodelling of uteroplacental spiral arteries is essential to normal placentation and placental function.[39] The exact mechanisms leading to deficient spiral artery remodelling in PE are not well-understood, but immune maladaptation has been proposed as a major contributor.[40] The immune

system plays an essential part in normal and pathological interactions between trophoblast cells of foetal origin and the maternal decidua. A disbalance in immune cell frequencies in the placental bed in early pregnancy might increase the risk of developing PE.[41] The placenta and foetus express both maternal and paternal antigens and together they can be can viewed as a semi-allograft.[42,43] Immune tolerance is required for a healthy pregnancy, as a disturbance in tolerance may lead to maternal anti-foetal rejection, placental defects and possibly PE.[42,44]

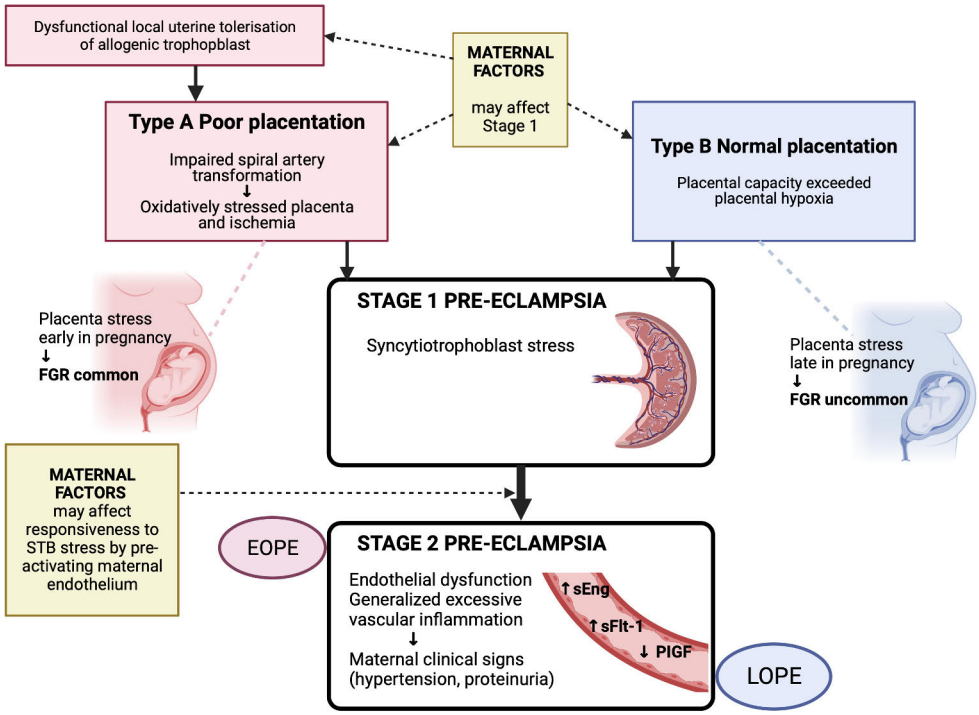

Figure 2. Pathogenesis of pre-eclampsia presented as the two-stage model. Two distinct pathways leading to syncytiotrophoblast stress are shown: Type A depicts impaired placental development, which is associated with EOPE and FGR. Type B describes a process where placental function declines as it outgrows uterine capacity and this is associated with LOPE in which FGR is uncommon. Abbreviations: Early-onset pre-eclampsia (EOPE), Fetal growth restriction (FGR), Late-onset pre-eclampsia (LOPE), placental growth factor (PlGF), soluble fms-like tyrosine kinase 1 (sFlt-1), soluble endoglin (sEng), syncytiotrophoblast (STB). Modified from Staff et. al.[37] Created with Biorender.com

2.4.2 Early- and late-onset pre-eclampsia

The division of PE into two phenotypes EOPE and LOPE, based on gestational age at the onset of the clinical disease, was first presented in 2003.[28] The pathophysiology of the subtypes varies from one to another, as EOPE is generally

linked to poor placentation, whereas LOPE is suggested to focus around interactions between aging of the placenta and maternal genetic predisposition to cardiovascular and metabolic disease. Although, commonly presented as different subtypes, in actuality there is probably individual variation in the balance between placental and maternal causations across the spectrum of gestational age at clinical presentation.[9,37]

The revised two-stage model of PE (*Figure 2*) proposes that both EOPE and LOPE result from placental syncytiotrophoblast stress.[37] While the underlying pathophysiological processes are different, both subtypes express an increased inflammatory response followed by the clinical maternal syndrome.[37,40] The first stage of EOPE is the impaired placental development, and the duration of the stage is long (several months), which is associated with foetal growth restriction (FGR). Whereas, in LOPE the first stage is shorter (several weeks) and involved in a process of compression of the placental terminal villi. As placental growth reaches its limits at term, it leads to intervillous hypoxia and syncytiotrophoblast stress followed by uteroplacental malperfusion.[37,45,46] This process results in foetal hypoxia causing late-onset clinical presentations including stillbirths, late-onset FGR and PE.[46]

2.4.3 Angiogenic factors and endothelial dysfunction

In the second stage of the two-stage model of PE (*Figure 2*), the disordered syncytiotrophoblast secretes an excess of different factors, including proinflammatory cytokines, exosomes, extracellular vesicles and anti-angiogenic molecules, that could contribute to endothelial dysfunction.[1,10]

Angiogenesis is the growth of new blood vessels from existing vasculature, and both pro-angiogenic and anti-angiogenic factors are involved in this complex process.[10] Two major pro-angiogenic molecules are vascular endothelial growth factor (VEGF) and PlGF. The syncytiotrophpblast secretes PlGF and sFlt-1, which is a soluble decoy receptor for VEGF and PlGF. sFlt-1 is a major anti-angiogenic protein that inhibits VEGF and PlGF from binding to endothelial cell surface receptors. In a normally functioning placenta these factors control angiogenesis and maintain normal endothelial structure and function.[10,47,48] The Placenta is not the only source of angiogenic factors, as PlGF and sFlt-1 have also been found to be expressed in vascular endothelial cells.[49]

A disturbance in the balance of anti-angiogenic and pro-angiogenic factors is proposed to be relevant to the pathogenesis of PE (*Figure 3*).[10] Circulating maternal serum levels of s-Flt-1 and sFlt-1/PlGF ratio have been found to be increased and levels of PlGF decreased in PE.[11] These changes are usually present weeks prior to manifestation of PE and are correlated with the severity of the disease.[11] Another extensively studied anti-angiogenic factor released from the syncytiotrophoblast is sEng. It binds and neutralizes transforming growth factor-β (TGF-β), which is a

proangiogenic factor of the syncytiotrophoblast.[50] Raised circulating levels of sEng have been reported in PE women two to three months prior the onset of the clinical disease.[12] These syncytiotrophoblast-derived angiogenic factors have been intensively studied for the ability to use them as biomarkers for prediction and diagnosis of PE.[51,52]

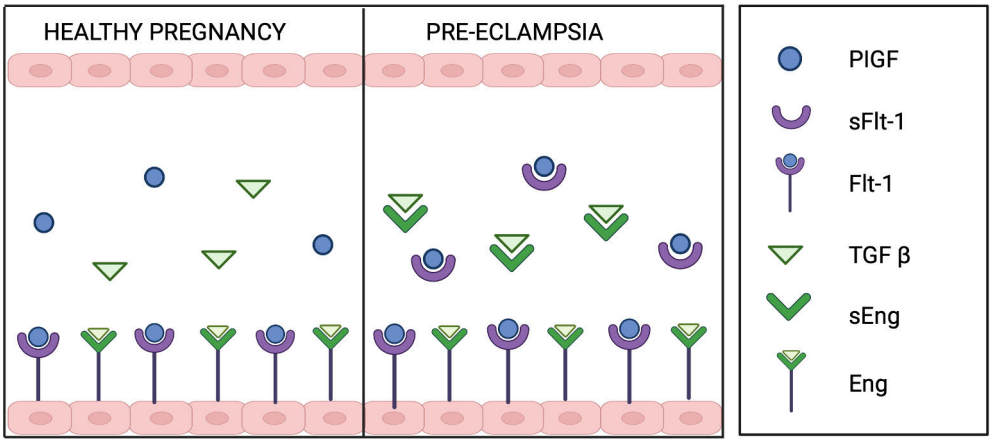

Figure 3. Angiogenic factors in healthy pregnancy and in pre-eclampsia. In healthy pregnancy FMS-like tyrosine kinase 1 (Flt-1) binds to placental growth factor (PlGF) and endoglin (Eng) binds to transforming growth factor β (TGF-β). In pre-eclampsia, soluble Flt-1 (sFlt-1) is cleaved off Flt-1 and competes with Flt-1 to bind to PlGF. Moreover, soluble Eng (sEng) is cleaved off Eng and competes with Eng to bind to TGF-β. Modified from Wu et al.[50] Created with Biorender.com

2.5 Determinants of pre-eclampsia

2.5.1 Well-known risk factors for pre-eclampsia

There are a number of well-established maternal and pregnancy related risk factors for PE (summarized in *Table 3*).[21,53] In a systematic review and meta-analysis PE was shown to affect 7.3% of pregnant women with known clinical risk factors and 2.7% of those without these risk factors.[21] The strongest risk factors are prior PE (an eight-times increase in risk) and chronic hypertension (a five-times increase in risk) if estimated by relative risk (RR). When using the pooled rates, antiphospholipid antibody syndrome had the highest pooled rate of PE (17.3%, 95% confidence interval [CI] 6.8% to 31.4%).[21]

The prioritization of risk factors is different at the individual patient level (based on RR) compared to that at the population level (based on the population attributable fraction [PAF]).[21] PAF means the estimated fraction of all cases that would not have occurred if there had been no exposure.[54] Consequently, the rarely occurring risk

factors are less important in the reduction of risk of PE within the entire population. The systematic review and meta-analysis by Bartsch E. et al. reported PAFs for PE, with nulliparity having the highest PAF, while antiphospholipid antibody syndrome had one of the lowest PAFs (*Table 3*).[21]

Most studies assessing the risk factors for PE are from high-income countries. In low- and middle-income settings, chronic hypertension, body mass index (BMI) ≥ 35 kg/m^2 and severe anaemia increased the risk of PE by three times or more. Other significant risk factors (twice the odds or more) included having cardiac or renal disease, pregestational diabetes, nulliparity and age ≥ 30 years.[55]

Table 3. Well-established risk factors for pre-eclampsia with unadjusted pooled relative risks and population attributable fractions provided from two major systematic reviews (systematic review and meta-analysis by Bartsch et al.[21] and the systematic review by Duckitt et al.[53])

Risk factor	Bartsch et al.[21] RR (95% CI)	Bartsch et al.[21] PAF (95% CI)	Duckitt et al.[53] RR (95% CI)
Previous PE	8.4 (7.1–9.9)	22.8% (19.6–26.3%)	7.19 (5.85–8.83)
Chronic hypertension	5.1 (4.0–6.5)	–	–
Pregestational diabetes	3.7 (3.1–4.3)	–	3.56 (2.54–4.99)
Multifetal pregnancy	2.9 (2.6–3.1)	–	2.93 (2.04–4.21)*
Family history of PE	–	–	2.90 (1.70–4.93)
Antiphospholipid antibody syndrome	2.8 (1.8–4.3)	0.18% (0.08–0.33%)	9.72 (4.34–21.75)
Pre-pregnancy BMI ≥ 30 kg/m^2	2.8 (2.6–3.1)	–	–
Pre-pregnancy BMI > 25 kg/m^2	–	23.8% (22.0–25.6%)	
Systemic lupus erythematosus	2.5 (1.0–6.3)	–	–
Previous stillbirth	2.4 (1.7–3.4)	–	–
Nulliparity	2.1 (1.9–2.4)	32.3% (27.4–37.0%)	2.91 (1.28–6.61)
Previous placental abruption	2.0 (1.4–2.7)	–	–
ART	1.8 (1.6–2.1)	–	–
Chronic kidney disease	1.8 (1.5–2.1)	–	–
Maternal age ≥ 40 years	1.5 (1.2–2.0)	–	1.68 (1.23–2.29)** 1.96 (1.34–2.87)***
Prior FGR	1.4 (0.6–3.0)	–	–

* Twin pregnancy
** Nulliparous women
*** Multiparous women
Abbreviations: Assisted reproductive technology (ART), Body mass index (BMI), Confidence interval (CI), Fetal growth restriction (FRG), Pre-eclampsia (PE), the population attributable fraction (PAF=[$P_{epooled}$ (RR_{pooled}–1)]/[$P_{epooled}$(RR_{pooled}–1)+1]), Relative risk (RR)

Prior pre-eclampsia

A prior PE pregnancy is one of the strongest risk factors. The risk of recurrence was ≈15% after one PE pregnancy and ≈32% after two PE pregnancies in a large cohort study from Sweden with nearly 800 000 pregnancies.[56] Many other studies have also reported recurrence rate of PE ranging from 5.9% to 25%, with a weighted average rate of 14 %.[57] The risk of recurrence has been found to be highest, if the initial case was preterm, EOPE or complicated by eclampsia, HELLP syndrome or FGR.[58,59]

Chronic hypertension and other non-communicable diseases

A systematic review and meta-analysis of 55 studies showed that women with chronic hypertension had high pooled rates of superimposed PE (25.9%, 95% CI 21.0–31.5%).[60] Further, compared with a general pregnancy population from the U.S. the incidence of superimposed PE on average across study populations was nearly eightfold higher compared with PE.[60] Chronic hypertension was more strongly associated with EOPE (HR 11.7, 95% CI 10.1–13.6) than LOPE (HR 5.8, 95% CI 5.4–6.3) in a study from the U.S. with 456 668 singleton deliveries.[61] Moreover, some other non-communicable diseases including pregestational and gestational diabetes[62], chronic kidney disease[63], CVD[64] and hyperlipidemia[65] are associated with higher incidence of PE.

Obesity

Obesity is an increasing issue among pregnant women. A meta-analysis of 22 studies showed that the risk for PE was higher among overweight (OR 1.89, 95% CI 1.74–2.05) and obese (OR 3.57, 95% CI 3.29–3.87) women compared with normal weight women.[66] In a large population-based retrospective study from the United States (U.S.) obese women (BMI ≥ 30 kg/m^2) had a higher risk for PE (OR 2.59, 95% CI 2.87–3.01) compared with normal weight women. The risk for PE increased with increasing BMI, with super-obese women (BMI ≥ 50 kg/m$^{2)}$ having the highest risk (OR 4.71, 95% CI 4.20–5.28). In addition, excessive weight gain during pregnancy increased the risk for PE in a dose-response fashion in both normal weight and obese women.[67]

Obesity causes metabolic abnormalities, such as increased circulating leptin, glucose, insulin, and lipids. These metabolic changes are thought to exaggerate placental ischemia-induced increases in circulating anti-angiogenic factors and pro-inflammatory pathways leading to maternal vascular dysfuntion.[68] Obesity is also associated with other conditions, such as gestational diabetes (GDM) and chronic hypertension, which are known to increase the risk for PE.[66,68]

Nulliparity

The risk of PE is higher in a woman's first pregnancy (≈4%) compared to subsequent pregnancies after a normal first pregnancy (≈2%).[56] In a systematic review and meta-analysis of 26 studies nulliparous women had an increased risk of PE (OR 2.42 [95% CI 2.16, 2.71]) compared to multiparous women.[69] Immune maladaptation has been suggested to be the basis to explain the elevated risk of PE in first pregnancies.[69]

Age

There has been a gradual increase in maternal age during pregnancy over the past few decades in many developed countries.[70] The risk of PE increases with advancing maternal age.[71–73] In a registry-based study from Finland during 1997–2008 PE occurred in 9.4% of women aged ≥ 35 years compared with 6.4% of women aged < 35 years.[71] A retrospective cohort study from the United Kingdom (UK) reported maternal age ≥ 40 years to be associated with higher rates of PE (OR, 1.49, 95% CI 1.22–1.82).[72] One study evaluating the risk separately for EOPE found the risk of LOPE to increase by 4 % with every one-year increase in maternal age above 32 years.[73]

Pregnancy-related risk factors

Several pregnancy-associated factors are also known to increase the risk of PE. These include multifetal pregnancy[74], hydatidifrom mole pregnancy[34] and fetal Trisomy 13[42,75]. The role of maternal infection has also been studied and current knowledge support the association between PE and urinary tract infection[76], periodontal disease[76] and SARS-CoV-2 infection[77] during pregnancy. In addition, there is a higher risk for PE in pregnancies conceived with assisted reproductive technology (ART).[78] Further, both short and long intervals between pregnancies have been associated with PE.[79]

Early- versus late-onset pre-eclampsia

Since there are probably different pathophysiological subtypes of PE, including EOPE and LOPE, the risk factors are not likely to be shared or as strong in all of them. Older maternal age has been linked to both EOPE and LOPE, with stronger association with EOPE in some studies[61,80] and in contrast no association with EOPE in some studies[73]. Obesity is associated with both EOPE and LOPE, with stronger association with LOPE.[67,81] Chronic hypertension[61,73,80,81] and black/African-American race[61,73] appear to be more strongly associated with EOPE. Nulliparity had a stronger association with LOPE than EOPE in some studies.[61,80,81]

2.5.2 Screening for pre-eclampsia

Clinical risk factors can be used in the prediction and prevention of PE, by identifying women at high risk and giving them low-dose aspirin prophylaxis.[51] A cochrane review from 2019 concluded there is high-quality evidence that aspirin 50-150 mg taken daily from the end of the first trimester reduces the risk of developing PE by 18 %.[15] National and international guidelines recommend varying methods for screening of PE. Many of the guidelines rely exclusively on maternal risk factors, while others integrate also additional investigative tools, such as laboratory and ultrasonographic measurements.[3,4,7,25,26] The detection rate of PE with maternal factors alone has been reported to be 39-41% for preterm PE, and 34 % for term PE with false positive rate of ≈10%.[22] While, a screening method proposed by the Fetal Medicine Foundation (FMF), combining maternal risk factors, mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI) and serum PlGF detected 75% of PE < 37 weeks and 43% of PE ≥ 37 weeks, with a 10.0% false positive rate.[22]

NICE, ACOG and the Finnish Current Care guidelines currently screen for PE based on maternal risk factors alone, and recommend aspirin for women with either one high risk factor or at least two moderate risk factors (*Table 4)*.[7,25,26] The ISSHP and The International Federation of Gynecology and Obstetrics (FIGO) advocate screening with FMF algorithm where possible (*Table 4*).[3,4] Concerns about the cost effectiveness, complexity, possible adverse effects and limited external validation of the most effective screening tests are commonly considered obstacles to adopting the use of these tests.[22,26]

Table 4. Clinical risk factors to identify women at risk for pre-eclampsia and recommended criteria for aspirin prophylaxis from five international and national guidelines.

Organization	Risk factors	Criteria for offering aspirin prophylaxis
FIGO 2019[4]	**The FMF first trimester combined test, takes into account the following factors:** Age, weight and height Ethnicity Parity Prior PE Inter-pregnancy interval Gwks at delivery and birth weight of previous pregnancy Family history of PE Method of conception Smoking History of: chronic hypertension, diabetes, SLE, APS	High risk on the FMF first trimester combined test

	High	Moderate	
ISSHP 2021[3]	Prior PE BMI > 30 kg/m^2 ART Chronic hypertension Pregestational diabetes Chronic kidney disease SLE and APS	Nulliparity Age > 40 years Multifetal gestation Prior placental abruption Prior stillbirth Prior fetal growth restriction	≥ 1 high risk factor or ≥ 2 moderate risk factors
ACOG 2020[7]	Prior PE Multifetal gestation Chronic hypertension Pregestational diabetes Renal disease SLE and APS	Nulliparity Age ≥ 30 years BMI ≥ 30 kg/m^2 Family history of PE (mother/sister) Sociodemographic characteristics* Personal history factors**	≥ 1 high risk factor or ≥ 2 moderate risk factors
NICE 2019[25]	Prior HDP Chronic hypertension Pregestational diabetes Chronic kidney disease SLE and APS	Nulliparity Age ≥ 40 years BMI ≥ 35 kg/m^2 Multifetal gestation Family history of PE Pregnancy interval > 10 years	≥ 1 high risk factor or ≥ 2 moderate risk factors
FINLAND 2021[26]	Prior PE Chronic hypertension Pregestational diabetes Renal disease SLE and APS Prior fetal growth restriction*** Prior stillbirth***	Nulliparity Age ≥ 40 years BMI ≥ 30 kg/m^2 Multifetal gestation Oocyte donation Family history of PE (mother/sister) Pregnancy interval > 10 years PAPP-A MoM < 0.4****	≥ 1 high risk factor or ≥ 2 moderate risk factors

* African American race, low socioeconomic status
** Previous adverse pregnancy outcome, low birth weight or small for gestational age, pregnancy interval > 10 years
*** Caused by placental insufficiency
**** In the first trimester screening for chromosomal abnormalities
Abbreviations: The American College of Obstetricians and Gynecologists (ACOG), Antiphospholipid antibody syndrome (APS), Assisted reproductive technology (ART), Body mass index (BMI), the Fetal Medicine Foundation (FMF), The International Federation of Gynecology and Obstetrics (FIGO), gestational weeks (gwks), Hypertensive disorders of pregnancy (HDP), The International Society for the Study of Hypertension in Pregnancy (ISSHP), National Institute for Health and Care Excellence (NICE), pre-eclampsia (PE), systemic lupus erythematosus (SLE)

2.5.3 Socioeconomic status

In general, poorer socioeconomic circumstances lead to poorer health.[82] It is unclear, whether PE is associated with socioeconomic factors or not, as previous studies have reported conflicting results. Various socioeconomic measures have been reported to increase the risk for PE: low maternal education[55,83], low income level[84–86], social deprivation[87,88] and public health insurance status[89] are associated with increased risk

of PE. In contrast, several studies found no link between PE and socioeconomic factors.[61,90–92]

Only a few studies have researched the associations between socioeconomic status in childhood and adulthood and PE.[91,92] Low childhood and adulthood socioeconomic position is known to be associated with CVD. Childhood socioeconomic status is thought to affect future health, because health behaviors are developed during childhood, and the resources of the childhood family can affect educational accomplishments, thereby influencing adulthood socioeconomic position and health.[92] A study from Sweden using education and family social class as indicators of socioeconomic status[92] and a study from the UK using childhood social class based on occupation of study participants' fathers[91] found no association between PE and childhood or adulthood socioeconomic status.

2.5.4 Mental health

Mental health problems are common among pregnant women. The global prevalence of antenatal depression is reported to be 20.7%[93] and in Finland maternal depressive symptoms were reported to be prevalent in 21.4% of pregnant women[93]. Maternal anxiety disorder during pregnancy is estimated to occur in 15.2% of women and self-reported antenatal anxiety symptoms in 22.9% of women.[94] Moreover, stress appears to be common among pregnant women. A study from the U.S. found that 70.2% of postpartum women reported ≥ 1 stressful life event in the year before giving birth.[95]

Prenatal/antenatal depression or depressive symptoms have been associated with PE in most[96–102] but not all studies.[103–107] Two meta-analyses by Hu et al.[96] and Zhang et al.[97] reported an association between PE and depressive symptoms/depression during pregnancy while a meta-analysis by Grigoriadis et al.[103] found no association. Details of these three meta-analyses are presented in *Table 5* and *Table 6* shows details of primary studies assessing the relationship between depression and PE. Previously, in Finland depression in early pregnancy was reported to associate with 2.5-fold increased risk of PE in a study with 652 women.[98]

Table 5. Systematic reviews and meta-analyses assessing the relationships between pre-eclampsia and depression. The table shows the main results of the studies focusing on the association between depression and pre-eclampsia.

Study	Studies* included	Aim	Depression, method assessed	Results	Underlying factors
Hu et al.M Plos One, 2015[96]	3 cohort studies and 2 case-control studies (n=3979)	To investigate the association between depression/depressive symptoms during pregnancy and the risk of an operative delivery or PE	Self-reported screening instruments were used for depression measurement	PE had an association with antenatal depressive symptoms, pooled OR 1.63, 95% CI, 1.32–2.02 After controlling for BMI the risk of PE still existed (OR 1.48, 95% CI 1.04–2.01)	Adjusted for pre-pregnancy BMI
Grigoriadis et al., Journal Of Clinical Psychiatry, 2013[103]	4 studies	To determine whether maternal depression during pregnancy is associated with adverse perinatal and infant outcomes	Measurement of depression at any antenatal time point using validated or unvalidated depression measures	PE was not associated with maternal depression during pregnancy, (OR 1.35, 95% CI 0.95–1.92)	Not examined
Zhang et al., Obstetrical And Gynecological Survey, 2013[97]	12 cohort- and case-control studies	To evaluate the relationships between mental stress and gestational hypertension/PE	Mental stress was defined as psychological feeling of strain or pressure. Anxiety and depression were defined according to classification by standard scales or diagnosis by psychiatrists.	Mental stress was associated with PE, OR 1.49, 95%CI 1.27–1.74 (pooled effect from 12 studies) Depression was associated with PE, OR 1.50, 95% CI 1.10–2.05 (pooled effect from 5 studies) Mood disorders were associated with PE, OR 1.88, 95%CI 1.08–3.25 (pooled effect from 4 studies)	Not examined

*Number of studies reporting data on PE
Abbreviations: Body mass index (BMI), Pre-eclampsia (PE)

Table 6. Primary studies assessing the relationship between pre-eclampsia and depression. The table shows the main results of the studies focusing on the association between depression and pre-eclampsia.

Study	Study design, country and years	Study population	Depression, method assessed	Association between depression and PE	Results	Underlying factors
Vollebregt et al., 2008[104]	Prospective cohort, The Netherlands, 2003–2004	n=3679, nulliparous pregnant women with singleton pregnancy, who completed a questionnaire < 24 gwks, and delivered > 24 gwks	Center for Epidemiological Studies Depression Scale	Neutral	Depression in the first half of pregnancy had no effect on the incidence of PE	Adjusted for BMI, chronic hypertension, DM, smoking, previous miscarriage/abortion and haemorrhage
Palmsten et al., 2012[105]	Prospective cohort, Canada, 1997–2006	n=224 827, women with pregnancies ending in a livebirth, and continuous health-care enrollment from 1 year prior to last menstrual period until 2 months after delivery date	ICD-9 codes for depression, Women with ≥ 1 inpatient/outpatient code for depression during the year prior to the last menstrual period until 20 gwks	Neutral	The risk of PE in depressed women not treated with antidepressants (2.4%) was similar to that in women without depression (2.3%)	Not examined
Kurki et al., 2000[98]	Prospective population-based cohort, Finland	n=623, healthy white, pregnant nulliparous women enrolled at first prenatal visit between 8–17 gwks, Women with elevated risk for PE were excluded.	a Finnish modification for of the shortened version of the BDI	Positive	Depression was associated with increased risk for PE (OR 2.5, 95% CI 1.1–5.4)	Not examined
Thombre et al., 2015[106]	Prospective case-control study, 1998–2004, United States	n=1371, women with singleton pregnancy, who provided interview data at enrolment (16–27 gwks) and whose hypertensive disorder status was abstracted from medical records	Maternal history of depression/anxiety symptoms at 4 time points in the life course were ascertained via self-report at enrolment	Neutral	Pre-pregnancy depression or anxiety symptoms were associated with HDP but not independently with PE	Adjusted for maternal race/ethnicity, Medicaid status, smoking history, age, and prepregnancy BMI

Bansil et al., 2010[99]	Retrospective nationwide study, 1998–2005, United States	n=32 156 438, women aged 15–44 with in-hospital delivery	ICD-9 codes for depression	Positive	Depression was associated with increased risk for PE (OR 1.57, 95% CI 1.52–1.62)	Adjusted for age, insurance status, location and region
Packer et al., 2021[100]	Retrospective cohort study, 2007–2011, United States	n=170 572, women with singleton non-anomalous pregnancies diagnosed with GDM in California	Antenatal depression identified by ICD-9 codes in the discharge abstracts	Positive	Women with GDM and depression had higher rates of PE (adjusted OR 1.28, 95% CI 1.11–1.49)	Adjusted for maternal age, education, insurance status, number of prenatal visits, race, ethnicity, parity, BMI, DM and chronic hypertension
Qiu et al., 2009[101]	Prospective cohort, 1996–2004, United States	n=2601, women who initiated prenatal care <20 gwks and were older than 18 years	Maternal pregestational and early pregnancy (< 20 gwks) psychiatric diagnoses were ascertained from medical records	Positive	Women with clinically diagnosed mood or anxiety disorders had increased PE risk (RR 2.12, 95% CI 1.02–4.45)	Adjustment for age, race/ethnicity, and pre-pregnancy BMI
Qiu et al., 2007[102]	Prospective case-control study, 2004–2005, Peru	n=676, cases: women with PE diagnoses identified by daily monitoring of all new admissions to the study hospitals and controls: women with uncomplicated pregnancies	Depression and depressive symptoms during pregnancy were assessed using the Patient Health Questionnaire (PHQ-9)	Positive	Women with moderate depression had increased risk for PE (OR 2.3, 95% CI 1.2–4.4)	Adjusted by maternal age, nulliparity and maternal overweight status
Yedid Sion et al.,, 2016[107]	Retrospective cohort study, 1988–2011, Israel	n=256 312, women with singleton pregnancies	Pre-gestational diagnosis of depression was made by a psychiatrist or family physician	Neutral	No association between antenatal depression and PE	Not examined

Abbreviations: Beck Depression Inventory (BDI), Body mass index (BMI), Diabetes mellitus (DM), Gestational diabetes (GDM), gestational weeks (gwks), Hypertensive disorders of pregnancy (HDP), International Classification of Diseases, 9th Revision (ICD-9), Pre-eclampsia (PE)

The data on the association of antidepressants and PE is inconsistent, and it is unclear whether depression itself or the antidepressive medication independently relate to PE.[108] A systematic review from 2017 reported that half of the included 7 studies showed a moderately increased risk of PE or gestational hypertension with antidepressant use during pregnancy; adjusted RR of PE or gestational hypertension in antidepressant users was 1.28 to 1.53 for any antidepressant, 1.05 to 3.16 for selective serotonin reuptake inhibitors (SSRIs), 1.49 to 1.95 for selective serotonin-norepinephrine reuptake inhibitors, and 0.35 to 3.23 for tricyclic antidepressants.[108] However, the possible contribution of underlying anxiety or depressive disorders was unclear in the included studies.[108] A 2018 meta-analysis of 7 cohort studies reported an increased risk for PE or gestational hypertension in women using SSRIs during pregnancy. The increased risk persisted after adjustment of maternal age, pre-pregnancy BMI, parity, diabetes and smoking, but was no longer significant after adjusting for ethnicity or history of mental disorders.[109] A 2022 meta-analysis of 9 studies showed evidence of increased risk for PE among users of SSRIs (pooled OR 1.43, 95% CI 1.15–1.78), although shared risk factors and other variables were poorly controlled in the included studies.[110]

The possible mechanistic pathways linking PE with depression are not well understood. Shared underlying risk factors along with cardiovascular and metabolic changes, have been suggested to contribute to the relationship between the two conditions (*Figure 4*).[111] Obesity associated with increased risk for both PE[21,66] and antenatal depression[112,113] as well as depression outside pregnancy[113]. A study by Molyneaux et al. reported that every unit increase in pre-pregnancy BMI was associated with 3% higher odds of antenatal depression.[112] CVD has also been connected to both PE[21,61,114,115] and depression[116]. Relationships between inflammation, oxidative stress and vascular function are established in the pathophysiology of PE[9,38] and depression[117–119] as well as in their shared risk factors obesity and CVD.[120] It has been suggested that depression and other distress conditions during pregnancy may lead to PE by increasing cortisol levels.[121] Mental stress activates the hypothalamus-pituitary-adrenal (HPA) axis leading to enhanced cortisol levels and associated changes in cellular immunity. High cortisol levels presented during stress conditions may induce hypertension and endothelial dysfunction[122] and thus result in the development of PE.[121] Additionally, serotonin systems have been found to be abnormal in both PE and mood disorders. Serotonin dysregulation is suggested to be a significant driver of immune dysfunction in PE via metabolic, immune cell and cytokine-based mechanisms.[123]

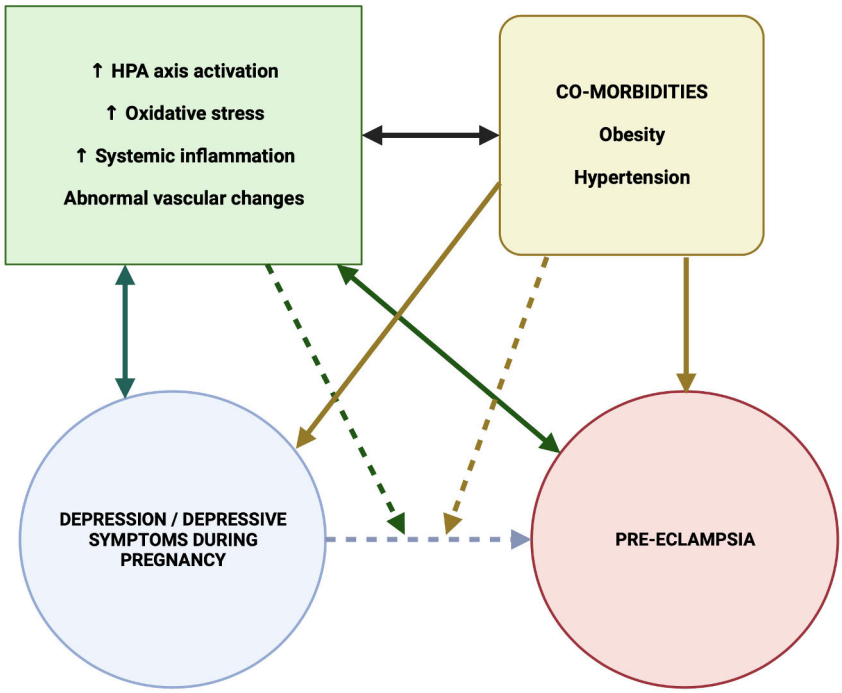

Figure 4. The complex relationships between depression in pregnancy, pre-eclampsia and risk factors – concept map of associations. The solid lines depict known associations and the dashed lines suggested associations. Abbreviations: Hypothalamus-pituitary-adrenal (HPA). Adapted from Yuan et al.[111]. Created with Biorender.com.

Along with depression during pregnancy, postpartum depression[111,124] and other postpartum psychiatric disorders[124] have been linked to PE. Further, maternal anxiety has been reported to increase the risk of PE in some studies[98,101] but other studies have not observed such assocation.[104,106] In a meta-analysis from 2018 exposure to prenatal maternal anxiety was not significantly associated with PE (4 studies, OR 3.30, 95% CI 0.56–19.37), but the included studies showed notable heterogeneity.[125] Mental stress during pregnancy has also been reported to associate with PE in studies, using various stress scales that measured stress in different areas of life.[97,126,127] In contrast, a study assessing the effect of work stress on PE showed no association.[104]

2.5.5 Factors related to fertility

Early age at menarche

Menarche, defined as the first day of menstrual bleeding, is regarded as a late marker of puberty in girls.[128] The age of puberty onset/menarche varies between individuals

and different ethnic populations.[128] In a recent large population-based cohort study from Denmark, menarche occurred at 13.0 (95% CI 13.0–13.1, 95% prediction interval 10.8–15.2) years.[129] A study from the U.S. reported the median age at menarche to be 12.43, with less than 10% starting to menstruate before 11 years and 90 % menstruating by 13.75 years of age.[130] The literature indicates that an early age at menarche is associated with several conditions later in life, including an increased risk of metabolic syndrome, endometrial cancer, type 2 diabetes/impaired glucose tolerance, GDM, breast cancer, obesity, hypertension, endometriosis and ovarian cancer.[131]

The association between PE and early age at menarche is supported in most[132–135] but not all studies[136,137]. A recent large population-based cohort study from China of 209 411 pregnant women found an earlier age at menarche to correlate with PE.[135] For every 1 year decrease in age at menarche the risk of PE was reported to increase by 5%.[135] A study from the U.S. (n=3365 women), defining early age at menarche as ≤ 11 years, reported an inverse association between age at menarche and risk of PE.[132] Similarly, an Indian study with 300 women found an increased risk of PE among women with age of menarche < 12 years (OR 13.17, 95% CI 7.11–24.39).[134] An Ethiopian study of 264 women defined young age at menarche as age 10–15 years, and reported it to be associated with PE (adjusted OR 7.69, 95% CI 3.10–25.29).[133] Contrary, a study from the UK including 250 037 women of white ethnicity found no association between early age at menarche (8–11 years) and PE.[136] Further, Rudra et al. did not find an association between early age at menarche and PE, but they did report PE risk to be lower in women with later age at menarche (≥ 15 years).[137] Petry et al. also found a negative association between age at menarche and subsequent blood pressure in pregnancy, but not independently with the risk of PE.[138]

Genetic factors have a major role in age at menarche with an estimated contribution of 57–82%.[139,140] The most significant contributing non-genetic factors include body weight, high animal protein intake and family stressors such as single parenting.[141] The mechanisms by which menarche timing possibly contributes to development of PE are unknown. However, there are shared risk factors involved in both conditions, including obesity[21,142,143], insulin resistance/diabetes/GDM[21,143–145] and CVD[66,146]. The influence of obesity was recently estimated in a Mendelian randomization study reporting that visceral adipose tissue could accelerate age at menarche contributing to the risk of incident PE.[147] In addition, there may be a common pathophysiology like systemic inflammation linking early age at menarche to metabolic risk factors and PE.[10,138] Indeed, age at menarche has been reported to negatively associate with circulating C-reactive protein concentrations.[148] Increase in inflammatory processes might heighten the risk of PE via endothelial dysfunction and reduced placental perfusion.[9]

Subfertility and infertility

Infertility affects up to 15% of couples.[149] The percentage of newborns conceived through ART in Europe varies between 0.2% and 6.2%, and in Finland 5.8% of babies were born as a result of ART in 2013.[150] ART is usually considered to include any technology involving handling of oocytes or embryos, including in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI).[151] The increased risk of PE following conceiving with ART is well-known.[78,151–153] A meta-analysis from 2019 including 72 cohort studies reported a 10.8% risk of PE followed by ART.[78] In another meta-analysis from 2019 including 48 studies ART treatment was associated with a 1.71-fold increase in PE.[153] Especially frozen embryo transfer and use of donor oocytes or embryos have shown significant associations with PE.[151,152] Suggested mechanisms behind these associations include epigenetic aberrations leading to abnormal placentation, absence of factors (progesterone, estradiol, relaxin, VEGF and more) secreted by the corpus luteum, and immunologic responses to allogenic gametes.[151]

Subfertility implies to any form of reduced fertility with prolonged time of unwanted non-conception.[154] Subfertile women conceiving without ART have been shown to be at increased risk for PE.[155–157] Time to pregnancy is used as a marker of subfertility expressed as the number of cycles a couple tried to conceive before achieving a pregnancy.[157] DoPierala et al. reported that women with subfertility (defined as time to pregnancy > 12 months or having a known condition causing subfertility) had a higher risk of PE (adjusted RR 1.18, 95% CI 1.02–1.37).[155] Jacques et al. defined women as subfertile if they had registered at a clinic for infertility and went on to conceive and give birth to a singleton infant without ART. They found subfertile women to be at increased risk for hypertension or PE (adjusted OR 1.29, 95% CI 1.02–1.61).[156] A study from Denmark with 44 732 live births found PE to occur more often in nulliparous women with time to pregnancy > 2 months and in multiparous women with time to pregnancy > 12 months.[157]

It has been suggested that the increased risk of PE in pregnancies after ART may be related to maternal factors associated with infertility/subfertility rather than ART itself.[151] A recent study comparing ART to naturally conceived pregnancies in the same woman found no association between ART and PE.[158] Many factors associated with subfertility/infertility including nulliparity, older maternal age, comorbidities such as obesity, diabetes and chronic hypertension are also risk factors for PE.[151] Further, diminished ovarian reserve and polycystic ovarian syndrome have been suggested as independent risk factors for PE.[159,160]

2.5.6 Family history and heritability

The familial nature of PE has been recognized for many years.[161] Woman's risk of PE is estimated to be 2–3.4 times higher if her first-degree relative has had PE.[53,162–164] A recent case-control study with 3510 PE cases from Colombia[162] reported that women whose mother or sister was affected with PE had a higher risk for PE (mother: OR 3.38 [95% CI 2.89, 3.96] and sister OR 2.43 95% [CI 2.02, 2.93]). If both the mother and sister of a woman were affected with PE the woman's PE risk was even higher (OR 4.17 [95% CI 2.60, 6.69]).[162]

It has been suggested that more than 50% of the liability to PE is due to genetic factors[165] with a maternal genetic effect of 30–35%, 20 % attributable to foetal genetic effects and 13% to the couple effect.[163,165] Understanding heritability of PE has transpired to be challenging due to the heterogeneous nature of the disease together with combined complex genetic and environmental risk factors and the contribution of both maternal and foetal genomes.[166] Extensive research in genetic susceptibility to PE, including candidate gene studies, linkage analyses and more recently genome wide association studies, have shown limited success. However, the foetal genome has been shown to contain a PE susceptibility locus at FLT1, of which isoform (sFlt-1) of placental origin is implicated in the pathology of PE.[167] The association was strongest in LOPE and when the offspring birthweight exceeded the 10th centile.[167] As to the maternal genome, a large genome wide association study from 2020 identified 5 genetic risk loci which have been previously connected to hypertension.[168] Another recent large genome wide association study found 13 novel PE or HDP associated loci, of which seven are located near genes previously associated with blood pressure traits and others near genes involved in the development of placenta, remodeling of uterine spiral arteries, kidney function and maintenance of proteostasis in pregnancy serum.[169]

Despite advances in genetic studies, no applicable tools have yet been produced for clinical use. Family history studies are still a more accessible way of measuring the inherited component of most diseases. Further, family history represents the overall interaction of genetic factors together with environmental exposures and lifestyle factors.[162,170] In addition to family history of PE, family history of CVD, hypertension and diabetes have been suggested as risk factors of PE.[162,171,172]

Family history of CVD has been shown to increase risk for PE.[162,171–175] Most studies defined family history of CVD as parental myocardial infarction or stroke or coronary artery disease and reported an association with PE with ORs between 1.6 and 1.9.[162,171,172,175] Serrano et al., explored family history of CVD separately for mother and father and reported similar associations with PE for both parents.[162] In a recent register-based cohort study from Denmark including almost 1.3 million parents, PE in daughters was associated with increased parental risk of CVD. The associations were equally strong for both mothers and fathers and increased with an

increasing number of affected daughters especially for parental CVD occurring before 55 years of age.[176]

Family history of hypertension, has also been shown to associate with PE.[127,172–174,177–179] Studies exploring increased risk of PE with family history of hypertension in one first-degree family member reported ORs between 1.5 and 3.8.[127,172,174,177,179] When hypertension in both a parent and a sibling were reported, the risk of PE was higher in those with hypertension occurring in a sibling.[177,179] Similar ORs for the risk of PE were reported for maternal and paternal family history of hypertension in the studies that assessed them separately.[174,179] Hypertension in more than one first-degree relative was associated with a higher risk of PE than hypertension in one first-degree relative alone.[174,177–179]

Studies assessing family history of diabetes and the risk of PE have shown mixed results. Studies that found an association between family history of diabetes and PE reported ORs (adjusted for confounders) between 1.9 and 3.4.[171,172,179,180] Some studies found no association.[127,178,181] Two of these studies reported an association between family history of diabetes and PE before adjusting for confounding factors.[127,181] One study examined family history of diabetes separately for mother and father and reported similar ORs for both.[179] A second study investigating the number of affected first-degree relatives reported no association between family history of diabetes and PE whether one or more relatives were affected.[178]

It has been suggested that PE and CVD probably share common heritable mechanisms along with other possible underlying causal factors.[176] There is substantial evidence on the association between family history of CVD and an individual's risk of CVD in the nonpregnant population.[170] Many studies have also linked PE with increased risk of CVD later in life.[114,115] Hypertension and diabetes are well-known risk factors of CVD[182] and they also increase the risk of developing PE.[21,61] Family history of CVD and hypertension and possibly diabetes are also associated with PE. Together with possible common heritable susceptibility to PE and CVD, the conditions share other underlying factors. These include obesity, metabolic abnormalities, dyslipidemia, insulin resistance, increased inflammatory responses, hypercoagulable states and endothelial dysfunction.[115] Moreover, atherosis, the lipid deposition in the spiral artery walls occurs more often in PE than in healthy pregnancies, and it resembles atherosclerotic lesions in the coronary arteries.[39,42]

2.5.7 Physical activity

Physical activity in pregnancy has several health benefits. Strong evidence shows that it improves or maintains physical fitness[183] reduces the risk of excessive gestational weight gain, GDM and symptoms of postpartum depression[184] Exercise

during pregnancy has also been suggested to lower the risk of PE[185–188], but the data are conflicting[189–191].

The Word Health Organization (WHO)[192] recommends pregnant women to do at least 150 minutes of moderate-intensity aerobic and muscle-strengthening activities throughout the week. Other guidelines including the United Kingdom Chief Medical Officer's Physical Activity Guidelines[193], ACOG[194], The Finnish Current Care Guidelines[195] and the Canadian Guideline for Physical Activity throughout Pregnancy[196] do support similar weekly targets of physical activity. All of the guidelines state that exercising in pregnancy is safe without contraindications (*Table 7)*.

Table 7. Contraindications to exercise in pregnancy from the Canadian Guideline for Physical Activity throughout pregnancy.[196]

Absolute contraindications	Relative contraindications
Ruptured membranes	Recurrent pregnancy loss
Premature labour	Gestational hypertension
Unexplained persistent vaginal bleeding	A history of spontaneous preterm birth
Placenta previa after 28 gwks	Mild/moderate cardiovascular or respiratory disease
Pre-eclampsia	Symptomatic anemia
Incompetent cervix	Malnutrition
FGR	Eating disorder
High-order multiple pregnancy (e.g., triplets)	Twin pregnancy after 28 gwks
Uncontrolled type 1 diabetes	Other significant medical conditions
Uncontrolled hypertension	
Uncontrolled thyroid disease	
Other serious cardiovascular, respiratory or systemic disorder	

Abbreviations: Fetal growth restriction (FGR), gestational weeks (gwks)

The ISSHP recommends exercise for all pregnant women in the absence of contraindications to reduce the likelihood of PE.[3] To achieve these reductions, women should undertake at least 140 min per week of moderate-intensity exercise (such as brisk walking, stationary cycling with moderate effort and resistance training).[3] Established PE is an absolute contraindication and gestational hypertension a relative contraindication for exercise in pregnancy.[3,196]

The evidence about the effectiveness of physical activity during pregnancy in avoiding the development of PE is not consistent (*Table 8*). Many systematic reviews and meta-analyses support the protective role of physical activity during pregnancy on PE.[185–188] In an umbrella review from 2019, limited evidence suggested an inverse relationship between physical activity and PE.[184] Some studies also investigated physical activity before pregnancy, and reported it to be associated with decreased risk of PE[186–188]. However, several systematic reviews and meta-analyses have shown no association between PE and physical activity during pregnancy.[189–191,197,198] Further, some studies have reported an inverse association between physical activity and HDP, but not independently with PE.[198–200]

Table 8. Recent systematic reviews and meta-analyses assessing the relationship between physical activity during pregnancy and pre-eclampsia. The table shows the main results of the studies focusing on the association between physical activity and pre-eclampsia

Study	Studies included*	Aim	Physical activity, method assessed	Association between PA and PE	Results
DiPietro et al., 2019[184] Umbrella review	9 reviews	To investigate the relationship between PA and various health outcomes during pregnancy and the postpartum period.	Not reported	**Inverse** (limited evidence)	-
Davenport et al., 2018[185] Meta-analysis	16 RCTs (n=3322)	To evaluate the effect of prenatal exercise on the odds of developing GDM, GH and PE.	Subjective or objective measures of frequency, intensity, duration, volume or type of exercise. Exercise was defined as any bodily movement generated by skeletal muscles that resulted in energy expenditure above resting levels.	**Inverse**	OR 0.59, 95% CI 0.37–0.94, Pooled estimate based on 15 studies
Aune et al., 2014[186] Meta-analysis	7 cohort and 4 case-control studies (n=168 602)	To clarify the possible dose–response relationship between PA and PE.	PA in early pregnancy (defined in most studies as PA up to 16–24 gwks or up to first antenatal visit, or the first trimester of pregnancy)	**Inverse**	RR 0.79, 95% CI 0.70–0.91, 11 studies Dose-response analysis: the risk of PE was reduced in a linear manner by 17% for each 1 hour/day increment in PA (RR=0.83; 95% CI 0.72–0.95), 7 studies
Wolf et al., 2014[187] Systematic review	4 case-control studies and 7 cohort studies	To examine the association between LTPA before and/or during pregnancy and the risk of PE.	Self-reported LTPA as main exposure. LTPA included all types of activities one participated in during free time.	**Mixed**	**Inverse**: high intensity LTPA during pregnancy or LTPA more than 4 hours/week may reduce the risk of PE **Neutral**: Light/moderate intensity LTPA was not associated with PE
Kasawara et al., 2012[188] Meta-analysis	6 case-control studies and 10 cohort studies	To evaluate the association between exercise/PA and the development of PE.	PA was considered as any voluntary bodily movement that increased energy expenditure above the basal level. Noted: The studies were of different types, with diverse methodologies, making data analysis more difficult.	**Mixed**	**Inverse**: OR 0.77, 95% CI 0.64–0.91 (6 case-control studies) **Neutral:** OR 0.99, 95% CI 0.93–1.05 (10 cohort studies)

Martínez-Vizcaíno et al., 2023[191] Umbrella review of RCTs and Meta-analysis	5 reviews in Umbrella review 20 RCTs (n=5344) in updated Meta-analysis	To provide a comprehensive overview of the effect of exercise interventions during pregnancy on GDM and HDP.	Exercise programs of all exercise types at any level of intensity were included	**Neutral**	OR 0.81, 95% CI 0.61–1.07, (20 RCTs) Umbrella review: 4 out of 5 studies found no association between PA and PE Inverse association with HDP (8 reviews and 28 RCTs)
Syngelaki et al., 2019[189] Meta-analysis	3 RCTs (387 participants)	To investigate the effect of diet and/or exercise in overweight/obese pregnant women on the risk of PE	Not described	**Neutral**	RR 1.13, 95% CI 0.45–2.86, 3 studies
DaSilva et al., 2017[190] Meta-analysis	3 RCTs (n=1409) 8 cohort studies (n=155 414)	To compare the associations between LTPA in pregnancy on maternal and child health outcomes between RCTs and cohort studies.	Inclusion criteria for RCTs required exposure to a PA structured program. The inclusion criteria for cohort studies required information on LTPA during pregnancy as an exposure.	**Neutral**	RR 0.93, 95% CI 0.55–1.57, 3 RCTs OR, 0.88, 95% CI 0.73–1.06, 8 cohort studies
Magro-Malosso et al., 2017[198] Meta-analysis	6 RCTs (n=2230)	To evaluate the effect of exercise during pregnancy on the risk of gestational hypertensive disorders	Uncomplicated pregnant women assigned before 23 gwks to an aerobic exercise regimen or not, reporting data on gestational hypertensive disorders.	**Neutral**	RR 0.79, 95% CI 0.45–1.38; 6 studies Inverse association with HDP: RR 0.70, 95% CI 0.53–0.83, (7 studies)
Muktabhant et al., 2015[197] Cochrane review	15 RCTs (n=5330)	To evaluate the effectiveness of diet or exercise, or both, interventions for preventing excessive weight gain during pregnancy and associated pregnancy complications.	Any exercise intervention for preventing excessive weight gain in pregnancy. There was considerable variation in the interventions used.	**Neutral** (High quality evidence)	average RR 0.95, 95% CI 0.77–1.16, (15 studies)

*Number of studies reporting data on PE

Abbreviations: Confidence interval (CI), gestational weeks (gwks), Gestational diabetes (GDM), Gestational hypertension (GH), gestational weeks (gwks) Hypertensive disorders of pregnancy (HDP), Leisure time physical activity (LTPA), Odds ratio (OR), Physical activity (PA), Pre-eclampsia (PE), Randomized controlled trial (RCT), Risk ratio (RR)

Effects of physical activity on pre-eclampsia and angiogenic factors

Physical activity is known to provide protection from CVD and improve vascular health in non-pregnant populations.[201] The underlying mechanisms are not well-understood. Exercising improves many established risk factors of CVD including weight, blood pressure, lipid profile and metabolic status, which is thought to partly account for the inverse association of physical activity and CVD.[201,202] It has been suggested that the direct influence of exercise on vascular health might also be a major contributing factor to the protective effect of physical activity on CVD.[203] These same mechanisms probably contribute to the beneficial effects of physical activity in preventing the development of PE. CVD and PE share same risk factors and prenatal exercise is known to prevent from excessive weight gain and improve glucose control.[184]

The effects of physical activity on placental function are ambiguous. A few studies have demonstrated that physical activity in pregnancy improves placental growth, villous vascular volume and functional capacity by increasing the proliferation of terminal villi.[204–206] The proposed mechanisms by which exercise possibly reduces PE are the promotion of placental growth and vascular development, reducing oxidative stress and improving endothelial function as well as immune and inflammatory responses.[207] Further, exercise in pregnancy may promote a pro-angiogenic state.[208–210] The vascular adaptations in response to maternal physical activity and PE are depicted in *Figure 5*.

The data on the association of angiogenic factors and exercise in pregnant women is very limited. Pro-angiogenic changes of higher maternal PIGF and lower s-Flt-1 and sEng concentrations have been reported in regularly exercising pregnant women compared with sedentary women in late gestation.[208] Moreover, higher expression of VEGF and its receptor VEGFR-1 have been detected in endothelial cells of the placenta of physically active women.[210] Increasing expression of VEGF and its receptors promotes angiogenesis, regulates vasodilatation, vascular permeability and endothelial cell survival.[211]

Previously, only rodent studies have explored the association between physical activity and angiogenic factors in PE. Physical activity during pregnancy decreased s-Flt-1 levels in rat[212] and mouse[213] models of PE. In Gilbert et al.'s study exercise before and during pregnancy stimulated a pro-angiogenic state by lowering sFlt-1 and increasing VEGF levels in rats.[212]

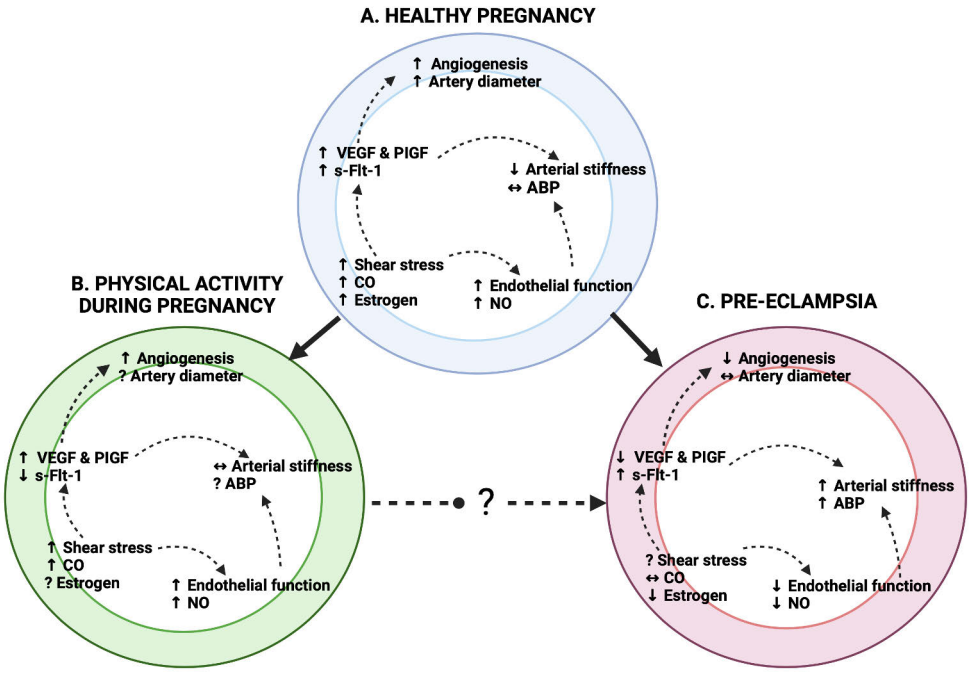

Figure 5. Vascular adaptations during healthy pregnancy (A), in response to maternal physical activity (B) and PE (C). The dashed lines depict proposed mechanisms or pathways. **A.** Vascular changes in healthy pregnancy compared with non-pregnant state. During pregnancy vascular remodeling, mechanics and function are modified in order to support the needs of the growing foetus and maternal hemodynamics. Vascular remodeling is primarily mediated by VEGF, PlGF and sFlt-1, which are increased in pregnancy. Increased levels of estrogen (vasodilator), expanding blood volume, increased CO and increased shear stress are also thought to contribute to the vascular changes in normal pregnancy. Further, shear stress stimulates the release of NO. Together these changes result in a decrease in arterial stiffness and an enhancement in endothelial function (response to NO). **B.** The impact of chronic physical activity on maternal vascular structure and function compared with healthy pregnancy. Increased VEGF and PlGF improve placental vessel formation and the increase in shear stress increases endothelial function. It is not known, whether physical activity alters arterial stiffness. **C.** The vascular implications of PE compared with healthy pregnancy. PE is associated with increased sFlt-1 and decreased PlGF and VEGF, and thus negatively affecting angiogenesis increasing arterial stiffness and reducing endothelial function. The exact mechanisms by which physical activity may reduce incidence of PE are unknown, but changes in angiogenic balance and increased shear stress are proposed to contribute to the prevention of PE by physical activity. Abbreviations: Arterial blood pressure (ABP), Cardiac output (CO), Nitric oxide (NO), Placental growth factor (PlGF), Pre-eclampsia (PE), Soluble fms-like tyrosine kinase 1 (sFlt-1), Vascular endothelial growth factor (VEGF). Adapted from Skow et al.[202] Created with Biorender.com

2.6 Role of the father in pre-eclampsia

PE is commonly considered a maternal disease, but it can also be seen as a maternal and paternal disease with both foetal and maternal manifestations.[14] The placenta is central in the pathophysiology of PE, and it includes important paternal genetic

determinants.[214] The concept of maternal-foetal (paternal) immune maladaptation theory is thought to be central in the causation of PE.[215]

2.6.1 Primipaternity and sperm exposure

Primipaternity has been recognised as a risk factor for PE for decades. The association between change of paternity and PE was first suggested by Need in 1975, when he described a woman who had severe PE in a singleton pregnancy by a new partner after a normotensive twin pregnancy with another man.[216] In their studies from 1980 and 1981 Feeney et al. and Astin et al. suggested a possible role of paternal immunogenetic factors in the pathogenesis of PE.[217,218] Astin et al. reported a case of two women who had become pregnant with the same man, and they both developed severe PE leading to death.[218] In their study Feeney et al. found that changing partners increased susceptibility to PE in 13 multiparous women.[217] A study by Robillard et al. (1993) including 134 women showed that PE was associated with change of partner in multiparous women.[219] Further studies have confirmed the effect of primipaternity on PE, reporting ORs between 1.3 and 5.7.[220–222] However, some studies have reported a long interval between pregnancies to be a confounding factor, and thus possibly explain the higher risk of PE after a change of partner.[223,224]

Men who have already fathered a PE pregnancy have been shown to have an increased risk to father another PE pregnancy with a different woman.[225] The change of partner can also play a protective role depending on the presence or absence of PE in the first pregnancy. In their study, Wikström et al. reported, that in women who had preterm PE with the first pregnancy partner, a change was associated with a strong protective effect for preterm PE recurrence.[226]

The role of the father in the onset of PE has also been demonstrated in men who were born from a pregnancy with PE.[13,227] Esplin et al. showed a 2.1 increase in the odds of PE when the father himself was born from a PE pregnancy.[13] In a study by Skjaerven et al. men born after a pregnancy complicated by PE had a moderately increased risk of fathering a PE pregnancy (OR 1.5, 95% CI 1.3–1.7).[227] They also showed that affected men (born from a PE pregnancy) were more likely to trigger severe PE in a pregnancy they fathered (OR 1.9, 95% CI 1.4–2.5) [227]

Primipaternity has been shown to be important concerning the risk of PE in another way, namely that of a shorter exposure to paternal sperm. In 1977 Marti and Herrman were the first to recognise that repeated prior exposure to paternal sperm reduces the risk of PE in the subsequent pregnancy.[228] Robillard et al. (1994) confirmed that the length of sexual cohabitation before conception was inversely related to pregnancy-induced hypertension including PE.[229] A systematic review of seven studies including 7125 pregnant women showed that paternal sperm exposure before pregnancy is associated with a decreased risk of PE in nulliparous women

(OR 0.63, 95% CI 0.52–0.76). Further, significantly lower rate of PE was found after sexual cohabitation ≥ 12 months (OR 0.73 95% CI 0.59–0.90).[230]

Moreover, the use of barrier contraceptives has been reported to increase the risk of PE.[231,232] In a study by Klonoff-Cohen et al. (1989) the users of contraceptives that prevent exposure to sperm had a 2.37- fold increased risk of PE.[231] A prospective cohort study by Kho et al. (2009) including 2507 women with singleton pregnancies showed that a short duration of sexual relationship is more common among women with PE compared to women with uncomplicated pregnancies (≤ 6 months adjusted OR 1.88, 95% CI 1.05–3.36; ≤3 months adjusted OR 2.32, 95% CI 1.03–5.25; conceived on first intercourse adjusted OR 5.75, 95% CI 1.13–29.3).[232]

The association between shorter exposure to paternal sperm and PE has also been detected in women conceiving with donor sperm.[233,234] A meta-analysis from 2014 including 10 898 women reported that conception using donor sperm was associated with increased risk of PE (OR 1.63, 95% CI 1.36–1.95) compared with using a partner's sperm.[233] Another meta-analysis from 2022 showed an increased risk of PE (adjusted OR 1.77, 95% CI 1.26–2.48) in pregnancies resulting from intrauterine insemination (IUI) with donor sperm compared with IUI with partner sperm.[234] Further, it has been reported that the fewer the number of insemination cycles with donor sperm the higher the risk for PE.[235]

The immune maladaptation theory proposes that rejection of the foetal allograft triggers a maternal alloimmune reaction, that could be prevented through paternal sperm exposure before pregnancy.[215] The protective effect that the longer exposure to paternal sperm has on the occurrence of PE, is thought to be explained by maternal mucosal immune tolerance to paternal antigens.[236,237] Animal and human studies have shown that deposition of semen in the female genital tract triggers a cascade of cellular and molecular events that resembles a classic inflammatory response.[238] Wang et al. showed that the risk of PE was three times higher in women conceiving via ICSI with surgically obtained sperm (from men with complete azoospermia) than in women with standard IVF or ICSI using partner's ejaculated sperm.[239] This further confirms that the antigenic stimulus is likely to be by sperm cells or a factor closely linked by sperm in the ejaculate.[239] Seminal-vesicle-derived transforming growth factor β1 (TGFβ1) seems to be a critical factor in the postcoital inflammatory process of the mother. It initiates a type-2 immune reaction towards paternal antigens, that might inhibit the induction of type-1 immune responses against the semi-allogenic foetus, that are thought to be associated with poor placental development and foetal growth.[215,236]

Other suggested mechanisms, that might contribute to primipaternity increasing the risk of PE, include specific paternal Human Leukocyte Antigen (HLA) characteristics and specific paternal single nucleotide polymorphisms (SNPs), specifically in the paternally expressed genes affecting placentation.[240] Additionally,

microbes in the sperm have been considered as a potential cause of PE. For example cytomegalovirus in the male genital tract has been proposed to change the cytokine levels in seminal fluid affecting adversely the partner-specific mucosal tolerance.[240,241]

2.6.2 Preconceptional paternal health factors

The role of paternal preconceptional health in the development of PE has not received much attention. Most of the evidence on the subject is on paternal age and obesity. Data on morbidity and lifestyle of the fathers is mostly lacking.

Paternal age has been suggested as a risk factor for fathering a PE pregnancy.[242] A study by Harlap et al. including 81 213 deliveries from 1965–1976 in Jerusalem showed that compared with fathers aged 25–34 years, the ORs for PE were 1.24 (95% CI, 1.05–1.46) for ages 35–44 and 1.80 (1.40–2.31) for ages ≥ 45.[242] In a population-based study from Taiwan by Yu et al. with 1 347 672 deliveries advanced paternal age was associated with a higher incidence of gestational hypertension/PE and eclampsia.[243] Conversely, two large studies from the U.S. found no association between paternal age and PE.[244,245] In summary, the few studies conducted have shown conflicting results on the relationship between paternal age and PE.[242–245] If paternal age does increase the occurrence of PE, increased sperm DNA damage has been proposed as a contributing factor.[240,245] With advanced paternal age there is a higher number of male germ cell divisions, more de novo point mutations, more DNA fragmentations and more stress to male germ cells that induce epigenetic changes. Altogether these changes could negatively affect placental and embryonic growth.[245]

Paternal obesity has been reported to associate with SGA infants independently of maternal factors[246], and it has also been suggested to increase the risk for PE. A study by Lin et al.[247] including 7683 Chinese women showed that paternal obesity was associated with increased incidence of PE, with OR 2.13 (95% CI 1.43–3.18) for paternal BMI ≥ 28.[247] In a study by Myklestad et al.[248] comprising of more than 14 000 families, men who had fathered a pregnancy complicated by PE or gestational hypertension had a greater BMI than men who fathered pregnancies without these complications.[248]. Paternal obesity has been shown to have a negative effect on sperm motility, DNA damage and embryos in early developmental stages in murine studies.[249] In human studies, male obesity has been linked to increased sperm DNA fragmentation, infertility and increased absolute risk of pregnancy nonviability.[250] Paternal obesity is thought to both induce pre-conception epigenetic changes to the sperm and influence developmental programming during the gestational period.[249] It is unclear if these changes could contribute to development of PE in partners of obese fathers.

There is little evidence on the relationship between paternal pre-existing medical conditions and PE. In a large study from the U.S. comprising 785 809 deliveries,

Kasman et al.[251] reported an association between paternal comorbidities (including hypertension, hyperlipidemia, diabetes and obesity) and PE (OR 1.31, 95% CI, 1.11–1.56). Murugappan et al.[252] examined preconception paternal health in a retrospective study of 669 256 live births from 2009 through 2016 in the U.S. Preconceptional paternal health was assessed using the number of metabolic syndrome component diagnoses and women with metabolic syndrome components were excluded. The preconception paternal health was reported to independently associate with increased risk of PE in healthy mothers (OR 1.21, 95% CI 1.17−1.26 among women whose partners had ≥2 metabolic syndrome diagnoses).[252] Myklestad et al. studied 14 130 family units in Norway during 1967−1997 and compared paternal cardiovascular risk factors (blood pressure, BMI, waist circumference, serum lipids and glucose) in men who had fathered a pregnancy complicated by PE or gestational hypertension with men who had fathered pregnancies without these complications. They found no association between unfavourable paternal risk factors for CVD and PE.[248]

The evidence regarding the connection between paternal lifestyle factors and PE is mostly lacking. A prospective population-based study including 2264 parents of children born between 2006 and 2007 in the Netherlands investigated the effects of paternal and maternal lifestyle factors on hypertensive pregnancy complications.[253] Paternal lifestyle factors including age, BMI, smoking, alcohol consumption, working hours and physical activity did not have an independent influence on hypertensive pregnancy complications. The Norwegian Mother and Child cohort investigated the role of maternal passive smoking, which probably refers mostly to partner's smoking. In this study passive smoke exposure alone was not associated with PE.[254] Social factors have also been suggested to play a role in the paternal contribution to the risk of PE. Fathers with more morbidities or a less healthy lifestyle may provide less support to their partner during pregnancy, and the male partner is an important source of stress and support to pregnant women.[252]

2.7 Complications of pre-eclampsia

2.7.1 Maternal and perinatal mortality and morbidity

Maternal mortality and morbidity

Hypertensive disorders of pregnancy accounted for 14% (343 000) of maternal deaths worldwide during 2003–09 in a WHO (World Health Organization) systematic review estimating causes of maternal death.[255] Each year about 42 000 maternal deaths are attributed to PE/eclampsia worldwide.[12] The vast majority (99%) of these maternal deaths occur in low-resource settings.[3,256] Lack of prenatal care,

lack of access to hospital care, lack of resources, incorrect diagnosis and management of patients with PE are major causes of the high maternal mortality along with maternal morbidity and perinatal mortality in developing countries.[256] The proportion of maternal deaths attributed to HDP (PE or eclampsia or HELLP) in high-income European countries (Denmark, Finland, France, Italy, the UK, Netherlands, Norway and Slovakia) varied from 0 in Denmark during 2013–2017 to 15% in the Netherlands during 2014–2018.[257] In Finland, HDP accounted for 4.5% (one death) of the maternal mortality during 2008–2012.[257] Maternal mortality and morbidity associated with PE has significantly decreased during the last 100 years in high-income countries.[258] Most of the decline occurred between 1940 and 1970 and was associated with a 90% reduction in the incidence of eclampsia and a 90% reduction in the case fatality rate in women with eclampsia. The probable causes of this decrease were the widespread use of prenatal care with blood pressure and urine protein measurement, and increased access to hospital care for timely induction of labour or caesarean delivery for women with severe PE or eclampsia.[258] The deaths occurring secondary to PE or eclampsia have been reported to be mainly caused by intracerebral haemorrhage. Other reported causes include renal or hepatic failure HELLP syndrome, liver rupture, cerebral edema and cerebral embolus.[259,260]

PE is associated with numerous severe maternal complications, both acute and long-term (*Table 9*)[1,5,256,261,262]. In a large study including approximately 300 000 deliveries during 1988–1997 in the U.S., Zhang et al. showed that women with PE had a 3-fold to 25-fold increased risk of severe complications.[263] Women with PE younger than 20 years or older than 35 years and African American women had the highest risk for morbidity.[263] EOPE has been reported to have higher rates of maternal morbidity and perinatal mortality compared to LOPE.[264]

The HELLP syndrome occurs in 0.5–0.9% of all pregnancies and in 10–20% of cases with severe PE. This serious condition is considered a variant of severe PE or its complication.[265] Diagnosis of the HELLP syndrome requires the presence of haemolysis in association with significant elevation in liver enzymes and a low platelet count after excluding other causes of haemolysis and thrombocytopenia.[266] Right upper quadrant or epigastric pain, nausea and vomiting are the most common symptoms of HELLP, although the clinical presentation varies considerably.[266] In some cases HELLP syndrome can have an atypical onset with lacking either hypertension or proteinuria or both before the onset of the condition.[267]

Women with previous PE are known to have a higher risk of developing CVD later in life.[5,114,115] A meta-analysis by Bellamy et al. showed, that after PE women had increased risk for future hypertension (RR 3.70, 95% CI 2.70–5.05), ischemic heart disease (RR 2.16, 95% CI 1.86–2.52), stroke RR 1.81, 95% CI 1.45–2.27) and venous thromboembolism (RR 1.79, 95% CI 1.37–2.33). Further, the overall mortality after PE was increased (RR 1.49, 95% CI 1.05–2.14).[5]

Table 9. Acute and long-term complications of pre-eclampsia.

Organ	Acute complications	Long-term complications
Neurological	Eclampsia, PRES, intracranial haemorrhage, stroke, cortical blindness, retinal detachment	Neurologic deficit, stroke
Renal	Acute kidney injury	Chronic renal failure
Hepatological	Liver dysfunction, hepatic hematoma or rupture, HELLP	
Hematological	Coagulopathy, DIC	Venous thromboembolism
Cardiorespiratory	Pulmonary edema, myocardial ischemia and infarction, adult respiratory distress syndrome	Chronic hypertension, coronary artery disease
Multiorgan dysfunction	HELLP, DIC	
Uteroplacental and foetal	Placental abruption, placental infarction, FGR, intrauterine foetal death, premature birth	

Abbreviations: Disseminated intravascular coagulation (DIC), Foetal growth restriction (FGR), Haemolysis, elevated liver enzymes and low platelet count (HELLP), Posterior reversible encephalopathy syndrome (PRES)

Perinatal mortality and morbidity

PE is associated with substantial perinatal mortality and morbidity, primarily due to uteroplacental insufficiency and the need for premature delivery.[268] Foetal complications associated with PE include FGR, oligohydramnion, intrauterine foetal death, preterm birth, non-reassuring foetal heart rate during delivery, low Apgar score and need for treatment in a neonatal intensive care unit.[4] The impaired placental development of PE leading to oxidative stress, ischemia and endothelial damage can cause FGR and oligohydramnion. Further, the underlying hypoxia probably contributes to the increased incidence of foetal distress before or during delivery in PE pregnancies.[4] Placental insufficiency, FGR, acute and chronic hypoxia and placental abruption are the contributors for intrauterine foetal death in PE.[4] The deprived intrauterine environment in PE contributes to preterm birth, which is often iatrogenic in PE. Preterm birth is the most significant cause of neonatal morbidity and mortality, associating with higher rates of infant respiratory distress syndrome, intraventricular haemorrhage, sepsis, bronchopulmonary dysplasia, necrotizing enterocolitis, retinopathy of prematurity and neurodevelopmental disability in childhood.[4,268] PE is estimated to be the cause of preterm birth in one-fifth of premature deliveries.[262]

In a multicenter prospective study with 30 639 women the prevalence of SGA among PE women was 82% for those who delivered at < 34 gwks, 47% for those

who delivered at 34–37 gwks and 30% in those who delivered at ≥ 37 gwks. Respectively, the frequency of SGA in pregnancies without PE was 44%, 21 % and 8%.[269]

The perinatal mortality rates associated with PE have high variance depending on the population, the health care resources and the severity of the PE. Mortality of the infants is three times higher in low- and middle-income countries than in high-income countries.[262] One-quarter of stillbirths and neonatal deaths have been reported to associate with PE in developing countries.[270] The reported stillbirth rate among women with PE was 4.6% in China and 0.4% in Sweden.[271] The risk of foetal death is significantly higher in women with EOPE, with reported risk of foetal death more than sevenfold higher than in pregnancies without PE at 34 gwks.[272]

2.7.2 Eclampsia

Eclampsia is considered one of the most severe manifestations of PE and causes a high morbidity and mortality to both mother and baby. Eclampsia is defined as the occurrence of new-onset tonic-clonic, focal, or multifocal seizures in a pregnant/postpartum woman with HDP and in the absence of other causative conditions.[7] The pathogenesis of eclampsia is not well understood. Blood-brain barrier disruption with the passage of fluid, ions and plasma protein into the brain parenchyma has been proposed as one possible mechanism.[273] Moreover, permeability of the blood-brain barrier has been suggested to be increased by circulating factors found in the plasma of women with PE, such as VEGF and PlGF.[274]

Globally, the estimated incidence of eclampsia is 0.3–1.4% of all deliveries with a wide variation across different regions.[24,275] There has been a reduction in the rate of eclampsia during the last 60 years[256] in developed countries, with reported incidences between 1.5 per 10 000 deliveries to 8.6 per 10 000 deliveries.[276–284] In developing countries the incidence of eclampsia ranges from 53.6 to 150.6 per 10 000 deliveries (*Figure 6*)[285–287].The incidence of eclampsia in Finland was 2.4/10 000 deliveries in 1990–94[277] and 15–20/10 000 deliveries in 1956[277].

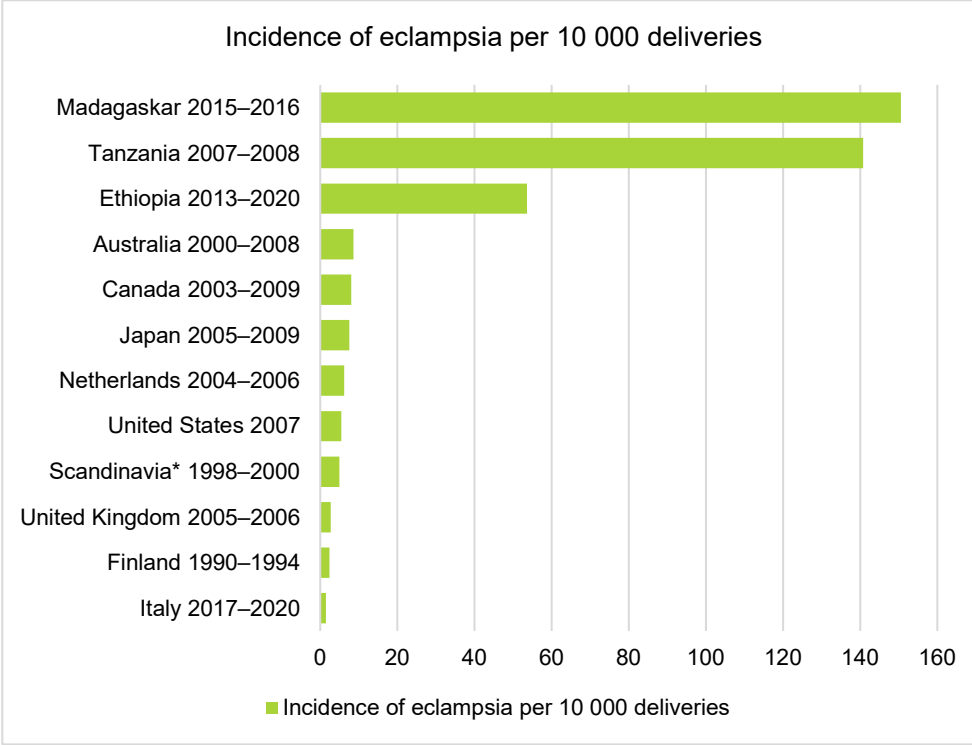

Figure 6. Incidence of eclampsia per 10 000 deliveries in some developed and developing countries around the world. * Sweden, Norway and Denmark.

Eclampsia can occur before, during or after delivery. In the literature, the proportion of antepartum eclampsia has been 52–72%, intrapartum 15–20 % and postpartum 21–33 %.[287–289] Historically eclampsia was believed to occur only < 48 hours from delivery, but late postpartum eclampsia can also occur between > 48 hours and < 6 weeks after delivery.[273,290] Premonitory symptoms may or may not precede eclampsia.[287,288] In a systematic review of published reports on eclampsia 66% of women had headaches, 27% had visual disturbances and 25% had epigastric pain preceding eclampsia, while 25% had no premonitory symptoms.[288] In the same study 25% of 3443 eclamptic women had normal blood pressure when eclampsia occurred.[288] In a retrospective study of 53 women with eclampsia in 60% of cases seizures were the first signs of PE.[8] Further, in a nationwide study from the UK 59% of women with eclampsia had premonitory symptoms and in the same study in 38% of eclamptic cases the seizure occurred before any prior documentation of hypertension or proteinuria in a hospital setting.[291]

Risk factors for eclampsia are similar to those with PE.[273] Few studies have examined the association of various factors specifically with eclampsia[275,280,281,292]. A retrospective cohort study by Esakoff et al. from the U.S. during 2005–2008

included 143 093 pregnancies with PE or gestational hypertension, of which 1719 had eclampsia. Factors that were associated with an increased risk of eclampsia among women with PE/gestational hypertension included nulliparity, black and Hispanic race, maternal age ≤ 20, preterm delivery < 32 gwks and < 5 prenatal care visits, while chronic hypertension, GDM, maternal age ≥ 35 and college education were protective.[292] Three large studies compared women with eclampsia with an unselected population of women and assessed risk factors for eclampsia *(Table 10)*.[275,280,281] These three studies included a study from the U.S. by Fong et al.[280] with 2 770 871 women, of which 1888 had eclampsia (0.07%), a Canadian population-based cohort study by Liu et al.[281] including 1 910 729 women, of which 1530 had eclampsia (0.08%) and a study by Abalos et al.[275] with participants from 29 different countries from Africa, Asia, Latin America and Middle East including 313 010 women, of which 875 had eclampsia (0.28%).

Table 10. Risk factors significantly associated with eclampsia with adjusted odds ratios from three large studies by Liu et al.[281], Abalos et al.[275] and Fong et al.[280]

Risk factor	Reported ORs	Study
Nulliparity	2.3–2.4	Liu et al., Abalos et al.
Multiple pregnancy	2.8–3.3	Fong et al., Abalos et al.
Teen pregnancy	1.7–2.0	Liu et al., Abalos et al.
Obesity	2.3	Fong et al.
Non-Hispanic Black race	1.8	Fong et al.
Low education level	2.7	Abalos et al.
Cardiac disease	4.8–6.8	Fong et al., Liu et al.
Systemic lupus erythematosus	2.9–3.7	Fong et al., Liu et al.
Pregestational diabetes	2.7	Fong et al.
Gestational diabetes	1.5	Fong et al.
Chronic hypertension	2.3–12.1	Liu et al., Abalos et al.
Renal disease	2.4–7.8	Fong et al., Abalos et al.
Asthma	2.2	Fong et al.
Thyroid dysfunction	2.0	Fong et al.
Urinary tract infection	1.5–2.8	Fong et al., Liu et al.
Hepatic disease	4.1	Abalos et al.
Anemia	2.4–4.1	Liu et al., Abalos et al.
Systemic infection/sepsis	5.3	Abalos et al.

Abbreviations: Odds ratio (OR)

Treatment and prevention of eclampsia

Magnesium sulphate has become the drug of choice for treatment and prevention of eclampsia and PE with severe features after the release of The Collaborative Eclampsia Trial[16] in 1995 and The Magpie Trial[17] in 2002. The Collaborative Eclampsia trial was an international multicentre randomised trial including 1680 women with eclampsia, and it indicated that women who received magnesium sulphate for treatment of eclampsia had a 52% and a 67% lower risk of recurrent seizures than women who were treated with diazepam or phenytoin.[16] In the Magpie study, a randomised placebo-controlled trial with 10 110 women from 33 countries, the risk of eclampsia was reduced by 58% with magnesium sulphate treatment.[17] Subsequent studies support these findings.[18–20] In a Cochrane review from 2010, when magnesium sulphate was compared to a placebo it more than halved the risk of eclampsia (RR, 0.41, 95% CI 0.29– 0.58) among women with PE.[19] Another Cochrane review from 2010 compared magnesium sulphate and diazepam for treatment of eclampsia and found that magnesium sulphate was associated with a reduction in recurrent seizures (RR 0.43, 95% CI 0.33–0.55) and maternal mortality (RR 0.59, 95% CI 0.38–0.92) compared to diazepam.[20]

The rate of eclampsia among women who have PE with severe features has been reported to be 2.0% in those not receiving preventative treatment with magnesium sulphate and 0.6% in those receiving magnesium sulphate.[293] It is controversial whether magnesium sulphate should be given as a prophylactic to all women with PE. Currently, major international and national guidelines recommend the use of intravenous magnesium sulphate only to women who have PE with severe features or for women with eclampsia to prevent recurrent seizures.[3,7,25] The use of benzodiazepines and phenytoin in treatment and prevention of eclampsia is considered justified only in the context of antiepileptic treatment or when magnesium sulphate is contraindicated or unavailable.[25]

In addition to treatment with magnesium sulphate, women with ante- or intrapartum eclampsia should be delivered in a timely fashion. Once the patient is stabilised the decision on the mode of delivery should be based on gestational age, foetal condition, presence of delivery and the findings of the cervical examination.[25,273] Prolonged foetal heart rate decelerations and foetal bradycardia are common during eclamptic seizures. Increase in uterine contractility and basal tone may also be present. After a seizure maternal hypoxia and hypercarbia can lead to recurrent decelerations, tachycardia and reduced variability in the foetal heart rate tracing. These changes usually resolve after the termination of seizures and maternal hemodynamic stabilisation.[7,273,294] Therefore in case of eclampsia, the focus should be first on maternal resuscitation and stabilisation with prevention of recurrent seizures, control of maternal blood pressure, prevention of maternal injury and

administration of oxygen. After this a decision should be made regarding the time and mode of delivery.[7,273,294]

Maternal and perinatal morbidity and mortality

Eclampsia is a significant cause of maternal death, especially in developing countries, with reported maternal mortality of 7%.[2] The maternal mortality rates associated with eclampsia are notably lower in developed countries: 0.63% in California[280], 0.34% in Canada[281] and 1.4% in the Netherlands[282]. In Finland there were no reported maternal deaths due to eclampsia between 1990–94.[277] However, in Finland out of two million births (0.7/100 000) between 1972 and 2005 there were 15 maternal deaths due to eclampsia and PE.[295]

Women with eclampsia have an increased risk of several complications, including placental abruption, pulmonary edema, aspiration pneumonia, HELLP, DIC, cardiopulmonary arrest, acute renal failure, adult respiratory distress syndrome and thromboembolisms.[256,281] Higher rates of maternal complications have been reported among women with antepartum eclampsia, particularly among those with preterm eclampsia.[256] Recently, eclampsia was associated with a 12-fold increased risk of acute cardiovascular morbidity, including myocardial infarction, cerebrovascular disease, acute heart failure, cardiomyopathy and cardiac arrest, during the delivery hospitalization.[296] Further, posterior reversible encephalopathy syndrome (PRES) can be seen in neuroimaging following eclampsia in up to 90% of women.[297,298] PRES is a reversible neurologic disorder, manifesting as various neurologic signs and symptoms including headache, impaired visual acuity or visual field deficits, disorders of consciousness, confusion, seizures and focal neurologic deficits.[298] The prognosis of PRES is usually favourable and most will recover within one week.[299] However, PRES can rarely cause severe morbidity and even mortality, which are most often caused by intracranial haemorrhage or posterior fossa edema with brainstem compression or obstructive hydrocephalus.[299] As to potential long-term sequelae, women with eclampsia may have more long-term cognitive difficulties related to memory and concentration.[300,301] Moreover, a large retrospective study showed that a future seizure disorder (a seizure, seizure disorder or epilepsy diagnosed more than 30 days after the index birth discharge date) was more likely after a pregnancy with eclampsia (4.58/10 000) than a pregnancy without HDP (0.72/10 000).[302]

Eclampsia is also a significant cause of perinatal mortality and morbidity. The eclampsia associated perinatal mortality rate was 5% in Finland in 1990–1994. Similar rates have been reported from other developed countries: 5.9% in the UK in 2005–2006[278] and in 2.7% Italy in 2017–2020[276]. In developing countries the perinatal mortality associated with eclampsia is much higher: 25.5% in Nigeria

during 2000–2009[303] and 50% in Madagascar during 2016–2016[285]. Along with increased risk of mortality, newborns of women with eclampsia have an elevated risk of SGA at birth, very preterm birth and respiratory distress syndrome.[281]

3 Aims

The aim of this study was to investigate maternal and paternal determinants of PE and eclampsia and the incidence and outcomes of eclampsia in Finland.

The specific aims of the study were:

1. To study the association of background factors with PE with an emphasis on socioeconomic factors, reproductive factors and health history including the parents of pregnant women in the Finnish Genetics of Pre-eclampsia Consortium (FINNPEC) cohort. (Study I)
2. To study the association between physical activity and PE in a case-control setting and to assess whether exercise in pregnant women with and without PE associate with maternal serum concentrations of sFlt-1, PlGF and sEng and sFlt-1/PlGF ratio in the Finnish Genetics of Pre-eclampsia Consortium (FINNPEC) cohort. (Study II)
3. To study whether paternal phenotype and lifestyle are associated with a risk of PE in the Finnish Genetics of Pre-eclampsia Consortium (FINNPEC) cohort. (Study III)
4. To assess the incidence and outcome of eclampsia in Finland after magnesium sulphate became widely used. (Study IV)

4 Materials and Methods

4.1 Study subjects, study design and methods of Studies I-III

Studies I–III focused on evaluating the association of maternal and paternal background factors with PE in the FINNPEC cohort.

The FINNPEC study

The FINNPEC (Finnish Genetics of Pre-eclampsia Consortium) study is a nationwide cross-sectional case-control cohort consisting of pregnant women with and without PE including their partners and infants. Details of the study design, methods and procedures have been published elsewhere.[304] The FINNPEC was established in order to identify genetic risk factors for PE. The cohort was collected from five Finnish university hospitals during 2008–2011 and it consists of biological samples and clinical data.

The FINNPEC study consists of prospective and retrospective arms. The data for Studies I, II and III came from the prospective arm of the FINNPEC cohort. Pregnant women with and without PE were identified on admission at Finland's university hospitals (Helsinki, Turku, Tampere, Kuopio and Oulu) and enrolled to the study along with their spouses and neonates. After a PE patient was recruited, a non-PE woman attending the same university clinic was recruited as a control. The control group consisted of women with uncomplicated pregnancies and women with pregnancy complications excluding PE.

The inclusion criteria for the FINNPEC study and the formation of data for Studies I–III is presented in *Figure 7*. PE was defined as hypertension and proteinuria occurring after 20 weeks of gestation as based on ACOG 2002 criteria.[305] Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg. Proteinuria was defined as the urinary excretion of ≥ 0.3 g protein in a 24-hour specimen, 0.3g/l or two ≥ 1+ readings on a dipstick in a random urine sample with no evidence of a urinary tract infection. PE was identified as EOPE if diagnosed before 34+0 weeks of gestation and LOPE if diagnosed ≥34+0 weeks

of gestation. Each diagnosis was independently verified from medical records by a research nurse and research physician.

A total of 923 pregnant women with PE and 1009 control women (non-PE) along with 719 men who had fathered a PE pregnancy (PE fathers) and 899 control men who had fathered a non-PE pregnancy were recruited for the study from 2008 to 2011.

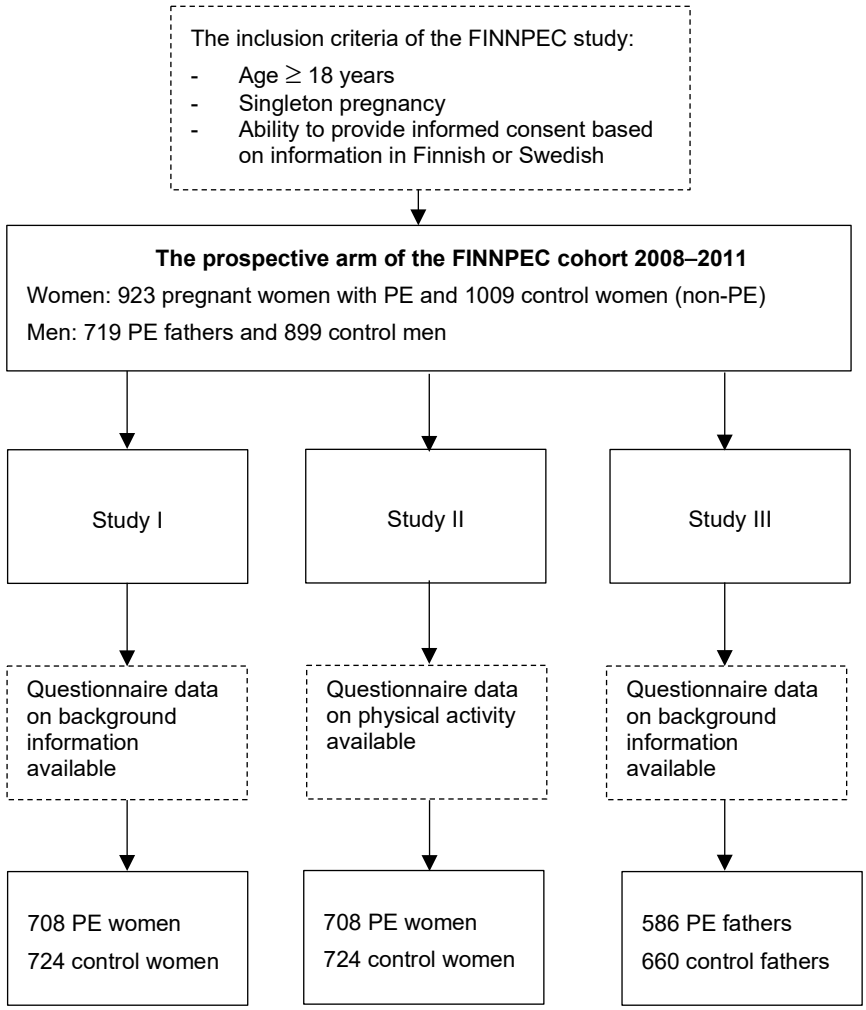

Figure 7. Flow chart of the formation of the data and inclusion criteria in Studies I-III.

Clinical data and questionnaires

The clinical data of the women was obtained from the hospital records and maternity cards and from a detailed questionnaire on background information. The participating women and men completed a questionnaire that included data on personal and family medical history, reproductive history, socioeconomic and lifestyle factors. Information on the women's age, ethnicity, pre-pregnancy weight and height, obstetric history, medical history, pregnancy complications, pregnancy outcome, blood pressure, delivery and newborn were obtained from hospital records and maternity cards. Data on smoking were collected from maternity cards and complemented by the background information questionnaires. Information on the men's previously fathered children and PE in these prior pregnancies was obtained from the questionnaires. The age of the fathers was obtained from the written consent and ethnicities from the hospital records. Each participant completed and returned the questionnaire during the index mother's pregnancy or shortly after delivery.

Study II utilised eight questions about physical activity and exercise habits during pregnancy from the questionnaire (*Table 11*). Two new variables were set in order to divide the women into two categories according to their physical activity: physically active and inactive. A new variable (How often do you exercise?) was established from question 5. (*Table 11*). This variable classified women into categories of physically active (exercise 2–3 times/week or more) and physically inactive (exercise less than 2–3 times/week). Moreover, another variable (Do you exercise ≥ 2–3 times/week, ≥ 30 minutes at a time with at least moderate intensity? [Yes/No]) was created by combining data from three questions (questions 5., 6. and 7. in *Table 11*). These classifications were based on the recommendations of the Finnish Current Care Guidelines for exercise during pregnancy (exercise training at least 150 minutes/week divided among at least 3 days/week).[195]

Table 11. Questions about physical activity and exercise habits during pregnancy from the background questionnaire.

Question	Answer options
1. Do you think your current physical fitness is	1) very good 2) quite good 3) satisfactory 4) quite poor 5) very poor
2. How much time do you spend walking, cycling, running and/or skiing every day to work or where you study?	1) Less than 15 minutes 2) 15 minutes – less than half an hour 3) Half an hour – less than an hour 4) One hour or more 5) I don't work or study
3. How physically strenuous is your work or studies?	1) My job or studies mainly involve sitting and I don't walk much during my working hours 2) I walk quite a lot but don't have to lift or carry heavy objects 3) I have to walk and lift things a lot 4) My work is heavy physical labour: I have to lift or carry heavy objects, dig, shovel or chop/hack, etc 5) I don't work or study
4. How much exercise do you do in your free time?	1) I regularly practise competitive sports several times a week in my free time 2) I do an average of at least 3 hours of fitness exercise a week during my free time 3) I walk, cycle, or otherwise exercise without sweating too much for at least 4 hours a week 4) I don't exercise much
5. How often do you do sports or exercise in your free time?	1) None 2) Less than once a month 3) A couple of times a month 4) About once a week 5) 2–3 times a week 6) 4–5 times a week 7) Approximately every day
6. Is your free-time exercise about as strenuous as	1) walking 2) alternating between walking and light running 3) light running (jogging) 4) brisk running
7. How long does an average free-time exercise session last?	1) Less than half an hour 2) Half an hour – less than an hour 3) An hour – less than two hours 4) Two hours or more
8. How long do you spend doing free-time activities that require other exercise on average per day? (e.g., gardening, repairs, cleaning. do not include incidental exercise that is part of work, business trips and leisure)	1) Less than half an hour 2) Half an hour – less than an hour 3) An hour – less than two hours 4) Two hours or more

Serum samples (Study II)

First and second/third trimester serum samples were collected from a sub-cohort of women who received care in the Hospital District of Helsinki and Uusimaa. First trimester serum samples were obtained from the first trimester biochemical screening for foetal chromosomal abnormalities (range 9–15 weeks of gestation), and serum samples from the second/third trimesters (range 20–42 weeks of gestation) were collected at hospitals according to the study protocol. The samples were collected in 10 ml serum tubes, centrifuged, and the serum was removed and stored at − 80 °C.

Maternal serum sFlt-1 and PlGF concentrations were measured using sFlt-1 and PlGF electro-chemiluminescence immunoassays (ECLIA; Roche Diagnostics GmbH, Mannheim, Germany) on a cobas e 601 analyzer (Hitachi High Technology Co, Tokyo, Japan). Serum concentration of endoglin (CD105) was measured using a human Quantikine Endoglin ELISA kit (R&D Systems, UK) according to the manufacturer's instructions.

4.2 Study subjects, study design and methods of Study IV

Study IV is a retrospective study evaluating the incidence and outcome of eclampsia in Finland during 2006 to 2010. Eclampsia diagnoses during 2006 to 2010 were retrieved from the national Medical Birth Register and the Care Register for Health Care. Women with International Classification of Diseases 10th revision diagnoses of eclampsia (O15, O15.0, O15.1, O15.2 and O15.9) or with a marking of seizures in the Medical Birth Register were retrieved. Medical records were collected from the treating hospitals and reviewed. The formation of data is depicted in *Figure 8*.

Registers

The Finnish Medical Birth Register and The Care Register for Health Care are controlled by the Finnish Institute for Health and Welfare. The Finnish Medical Birth Register, established in 1987, includes nationwide data on all live and stillbirths from gwks 22 or birth weight of 500 g onward. The Care Register for Health Care, operating since 1994, holds data on the clients treated in hospitals, health centers and other institutions providing inpatient care in Finland.

Basic definitions

Eclampsia was defined as the occurrence of one or more seizures before, during or after delivery in women with signs or symptoms of PE.[16] PE was diagnosed if

systolic blood pressure was repeatedly ≥ 140 mmHg and/or diastolic blood pressure was repeatedly ≥ 90 mmHg after 20 weeks of gestation in association with proteinuria. Proteinuria was defined as the urinary excretion of ≥ 0.3 g protein in a 24-hour specimen or ≥ +1 reading on a dipstick in a random urine sample.[306]

Perinatal mortality was defined as the percentage of stillborn and neonatal deaths during the first week of life. The diagnosis of birth asphyxia was made if the 1-min Apgar score was 0–6 and the umbilical artery blood pH was < 7.16 or if the 1-min Apgar score was > 6 and the umbilical artery blood pH was < 7.00.[307] Small for gestational age was defined as a birthweight < 10th percentile for gestational age according to growth charts by iPana (Intelligent Patient Archives for Neonatal and Antenatal Services; MediWare Oy, Tampere, Finland).

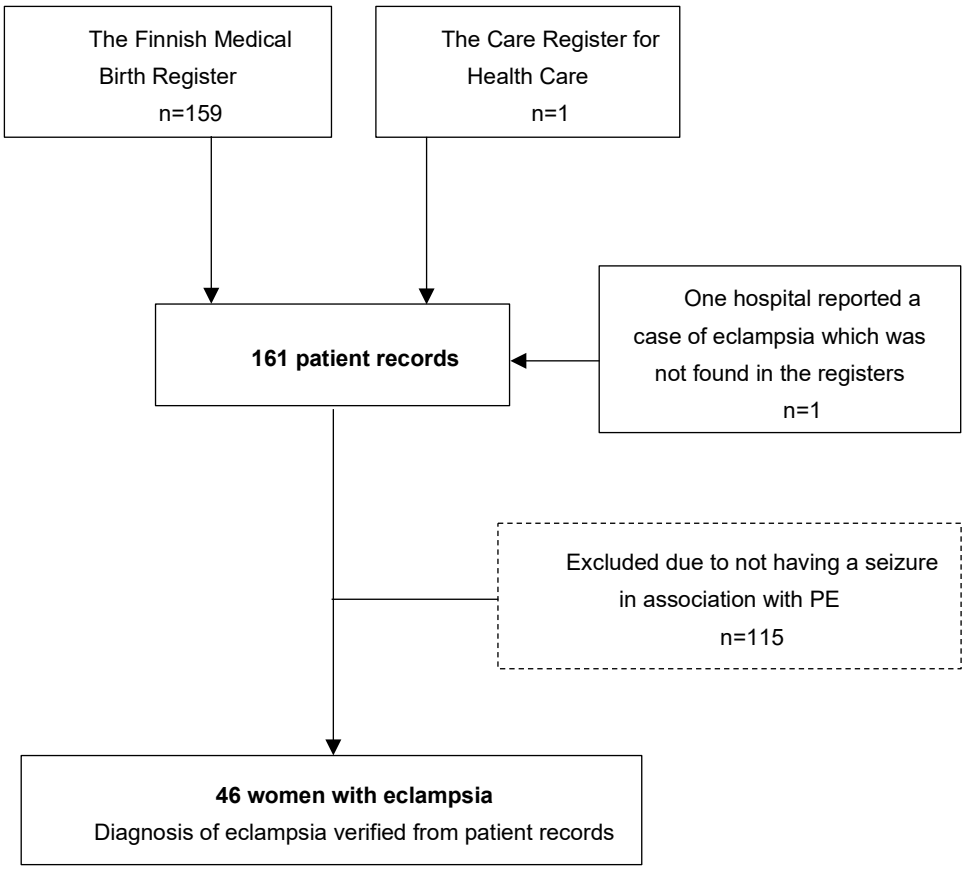

Figure 8. Formation of data in Study IV. The author's own drawing.

4.3 Statistical analyses

All statistical analyses were performed using SPSS Statistics versions 20.0, 23.0 and 25.0 (IBM Corp., Armonk, NY, USA); version 20.0 in study IV, version 23.0 in Study I and version 25.0 in Studies II and III. Categorical variables were presented as frequencies and percentages. Continuous variables were described by means with standard deviations (SDs), or medians with interquartile ranges depending on the skewness of the distributions. The normality of the variable distributions was verified graphically and with a Kolmogorov-Smirnov-test. P-values of < 0.05 were considered statistically significant.

Study I. Background information on PE women with the two control groups were compared separately (PE vs healthy controls and PE vs all controls) since the control groups largely overlap. Further, the comparisons were made between EOPE and LOPE. Statistical analyses of continuous variables were performed using the two-sample t-test for normal and Mann–Whitney U test for skewed distributions. For categorical variables comparisons between the groups were performed with the Chi-square test.

Study II. The physical activity of the PE and non-PE women was compared. The maternal and perinatal characteristics of the PE and non-PE women were compared according to physical activity separately. The statistical analyses of the continuous variables were performed using two-sample t-tests for the normal distributions and Mann–Whitney U-tests for the skewed distributions. The categorical variable comparisons between the groups were performed with Chi-square tests.

The first and second/third trimester serum concentrations of angiogenic markers in PE and non-PE women divided according to physical activity were compared. Logarithmic transformation was used when appropriate. Each biomarker was ln-transformed to correct for right-skewness, and estimated means were back-transformed as mean estimates/model-based means and 95% CIs for purposes of presentation. Comparisons between groups were analyzed with a two-way analysis of variance (ANOVA). Selected co-variables (parity, maternal age, smoking status, BMI) were included in the models as covariates.

Study III. Background information on the PE fathers and the two different control groups were compared separately (PE vs healthy controls and PE vs other controls). Differences between the groups were tested with logistic regression analysis with odds ratios (OR) and 95% CIs or with Fisher's exact test. Multivariable-adjusted logistic regression analyses were conducted to examine which paternal risk factors were independently associated with PE after controlling for known maternal risk factors for PE (index mother's BMI, age at birth, parity and smoking during pregnancy.

Study IV. The distributions of variables were described by number of patients with percentages for categorical variables and by medians with interquartile ranges for continuous but skewed variables.

4.4 Ethics

The FINNPEC study protocol (Studies I, II and III) was approved by the coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa (149/ EO/2007) on October 7, 2007 (updated May 16, 2018). All study participants provided written informed consent.

For Study IV, The National Institute for Health and Welfare approved the use of registry-based data and the review of medical records. According to Finnish law, Ethical review board approval is not required for retrospective registry-based studies.

5 Results

5.1 The non-traditional and familial risk factors for pre-eclampsia (Study I)

Questionnaires on background information were available from 708 women with PE and 724 control women. Two different control groups were established for Study I: one a group of Healthy controls (n=498) that consisted of women with uncomplicated pregnancies and without pregestational diabetes or chronic hypertension and another for All controls (n = 724) that also included women with pregnancy complications besides PE and with pregestational diabetes and chronic hypertension (*Table 12*).

Maternal and perinatal characteristics of the study participants are presented in *Table 12*. PE women were more often nulliparous and had a higher BMI than the women in the two control groups. Their delivery was more often preterm and with a caesarean section. The response rates to the questionnaires were 76.7% for PE women and 71.8% for non-PE women. The PE women who did not complete the questionnaire were more often multiparous, had a higher BMI and delivered earlier and more often with a caesarean section compared to those who completed the questionnaire. The maternal and perinatal characteristics were similar in the respective control groups (data not shown).

Socioeconomic status

The socioeconomic status of the PE and non-PE women was similar when estimated both by education level and income. Higher education was reported in the fathers of women in the control groups than those of PE women ($p < 0.05$ for all), whereas there were no differences in mothers' education level.

Health and factors related to fertility

Information on participants' health and fertility is shown in *Table 13*. PE women suffered more from pre-existing medical conditions (type 1 diabetes, hypercholesterolemia, chronic hypertension and depression) compared to the women

in the control groups. Women with PE reported earlier menarche, and it took them longer to conceive than the women in the control groups. However, the use of ART did not differ between the groups. The use of insulin and antihypertensive medication (including medications used before pregnancy) was more common in PE women than in the women in the two control groups ($p < 0.05$ for all). PE women used more often SSRIs and metformin when compared to the healthy controls ($p < 0.05$ for all).

Medical family history

The medical history of the parents of PE women differed from the parents of non-PE women (*Table 14*). Hypertension occurred more often in both parents of PE women, strokes in fathers and diabetes in mothers. Mental disorders including depression were more prevalent in mothers of PE women compared to both control groups. Moreover, PE women were more often born from a pregnancy complicated by PE than women in the control groups.

There was no difference between the groups in the number of women who had depression themselves and also a mother with a history of depression (nine PE women [29.0%], one in the healthy controls [11.1%, p=0.274] and two in all the controls [18.2%, p=0.287]).

Early- versus late-onset pre-eclampsia

The determinants for *EOPE* (n = 157) and *LOPE* (n = 551) were observed separately. Women with EOPE delivered earlier (at median 33 (24–39) gwks vs 38 gwks (34–42), $p < 0.001$) and more often with a caesarean section (76.9% vs 29.2%, $p < 0.001$). A higher pre-pregnancy BMI was observed in women with EOPE (at median 24.9 kg/m^2 (18.0–45.9) vs 23.9 kg/m^2 (16.2–47.3), $p = 0.049$). The groups were similar in age, parity and smoking. Chronic hypertension was more prevalent in women with EOPE (14.6% vs 6.5%, $p = 0.002$), but there were no other differences between the two groups in pre-existing medical conditions. It took longer to conceive for women with LOPE (at median 3 months (0–120) vs 2 months (0–144), $p = 0.016$). There were no differences in the age at menarche and use of ART between the groups.

Table 12. Basic maternal and perinatal characteristics. Modified with permission from the original publication I Table 1.

	Pre-eclampsia (n=708)		Healthy controls (n=498)			All controls (n=724)		
	N	**% or median (range)**	**N**	**% or median (range)**	***p* value**	**N**	**% or median (range)**	***p* value**
Age at delivery, years	(n=707)	29.9 (5.6) *		29.7 (5.2) [a]	0.596	(n=721)	29.9 (5.1) *	0.887
Ethnicity: finnish	706	99.7	497	99.8	0.779	722	99.7	0.982
Nulliparous	535 (n=707)	75.7	263	52.8	**<0.001**	404 (n=721)	56.0	**<0.001**
BMI, kg/m^2 (self-reported, pre-pregnancy)	(n=707)	24.0 (16.2-47.3)		22.7 (17.0-38.4)	**<0.001**	(n=721)	23.1 (17.0-47.4)	**<0.001**
Smoking before pregnancy	208 (n=696)	29.9	137 (n=487)	28.1	0.514	209 (n=708)	29.5	0.881
Smoking during pregnancy	63 (n=700)	9.0	58 (n=497)	11.7	0.131	85 (n=720)	11.8	0.084
Mode of delivery	(n=707)				**<0.001**	(n=723)		**<0.001**
Vaginal	426	60.3	440	88.4		614	84.9	
Caesarean section	281	39.7	58	11.6		109	15.1	
Gestational weeks at delivery	(n=707)	38 (24-42)		40 (36-43)	**<0.001**	(n=723)	40 (23-43)	**<0.001**
Preterm delivery	213 (n=707)	30.1	5	1.0	**<0.001**	35 (n=723)	4.8	**<0.001**
Pregnancy complications								
SGA	132	18.6	0	0		36	5.0	**<0.001**
Gestational diabetes	114	16.1	0	0		63	8.7	**<0.001**
Gestational hypertension	0	0	0	0		70	9.7	**<0.001**
Placental insufficiency**	67	9.5	0	0		24	3.3	**<0.001**
Foetal death	1	0.1	0	0		1	0.1	0.990
Proteinuria without high blood pressure	0	0	0	0		11	1.5	**<0.001**
Other pregnancy complication	31	4.4	0	0		49	6.8	**0.049**

* mean (SD)
** Umbilical artery pulsatility index > +2 SD or umbilical artery resistance index > +2 SD
Bold text shows p values < 0.05
( ) Number of available information unless from all
Abbreviations: Body mass index (BMI), Small for gestational age infant (SGA), Standard deviation (SD)

Table 13. Health and fertility in PE and non-PE women. Modified with permission from the original publication I Tables 3 and 4.

	Pre-eclampsia (n=708)		Healthy controls (n=498)			All controls (n=724)		
	N	% or median (range)	N	% or median (range)	*p* value	N	% or median (range)	*p* value
HEALTH								
Current state of health	(n=694)		(n=493)		**<0.001**	(n=716)		**<0.001**
Good	541	78.0	455	92.3		636	88.8	
Average	133	19.2	34	6.9		67	9.4	
Poor	20	2.9	4	0.8		13	1.8	
Any pre-existing medical condition	93 (n=694)	13.4	29 (n=497)	5.8	**<0.001**	66 (n=718)	9.2	**0.012**
Type 1 diabetes	19 (n=666)	2.9	0 (n=483)	0	**<0.001**	4 (n=691)	0.6	**0.001**
Type 2 diabetes	5 (n=664)	0.8	0 (n=483)	0	0.056	5 (n=692)	0.7	0.948
Chronic hypertension	55 (n=665)	8.3	0 (n=483)	0	**<0.001**	18 (n=692)	2.6	**<0.001**
Hypercholesterolemia	37 (n=664)	5.6	10 (n=483)	2.1	**0.003**	14 (n=691)	2.0	**0.001**
Asthma	74 (n=664)	11.1	37 (n=480)	7.7	0.053	67 (n=687)	9.8	0.403
Depression	76 (n=668)	11.4	32 (n=483)	6.6	**0.006**	53 (n=693)	7.6	**0.019**
Panic disorder	24 (n=662)	3.6	17 (n=483)	3.5	0.924	23 (n=692)	3.3	0.762
Other mental disorder	16 (n=662)	2.4	6 (n=482)	1.2	0.154	11 (n=690)	1.6	0.280
FERTILITY								
Age at menarche (years)	(n=688)	13.0 (9.0-17.0)	(n=490)	13.0 (10.0-18.0)	**0.001**	(n=708)	13.0 (9.0-18.0)	**0.022**
11–15	650	94.5	464	94.7		669	94.5	
< 11	29	4.2	8	1.6		14	2.0	
> 15	9	1.3	18	3.7		25	3.5	
Time to pregnancy (months)	(n=639)	3 (0-144)	(n=461)	2 (0-144)	**0.013**	(n=670)	2 (0-144)	**0.019**
≤ 3	361	56.5	296	64.2		427	63.7	
> 3–12	171	26.8	108	23.4		157	23.4	
> 12	107	16.7	57	12.4		86	12.8	
ART	84 (n=671)	12.5	46 (n=469)	9.8	0.157	68 (n=680)	10.0	0.143

Bold text shows p values < 0.05
( ) Number of available information unless from all
Abbreviations: Assisted reproductive technology (ART)

Table 14. Medical family history. Modified with permission from the original publication I Table 6.

	Pre-eclampsia (n=708)		Healthy controls (n=498)			All controls (n=724)		
	N	% or median (range)	N	% or median (range)	*p* value	N	% or median (range)	*p* value
Father's medical conditions								
Myocardial infarction	54 (n=659)	8.2	44 (n=472)	9.3	0.506	75 (n=680)	11.0	0.079
stroke	41 (n=664)	6.2	15 (n=476)	3.2	**0.020**	24 (n=684)	3.5	**0.022**
diabetes	81 (n=666)	12.2	58 (n=475)	12.2	0.980	88 (n=683)	12.9	0.689
hypertension	229 (n=663)	34.5	103 (n=470)	21.9	**<0.001**	165 (n=676)	24.4	**<0.001**
mental disorder	36 (n=661)	5.4	22 (n=473)	4.7	0.549	30 (n=679)	4.4	0.385
of which depression	14 (n=661)	2.1	11 (n=473)	2.3	0.814	15 (n=679)	2.2	0.909
Mother's medical conditions								
myocardial infarction	18 (n=686)	2.6	7 (n=484)	1.4	0.170	11 (n=699)	1.6	0.172
stroke	17 (n=686)	2.5	12 (n=484)	2.5	0.999	15 (n=698)	2.1	0.684
diabetes	51 (n=684)	7.5	15 (n=485)	3.1	**0.001**	30 (n=700)	4.3	**0.012**
hypertension	209 (n=678)	30.8	102 (n=483)	21.1	**<0.001**	152 (n=698)	21.8	**<0.001**
mental disorder	49 (n=682)	7.2	18 (n=483)	3.7	**0.013**	27 (n=696)	3.9	**0.007**
depression cases	33 (n=682)	4.8	9 (n=483)	1.9	**0.007**	15 (n=696)	2.2	**0.007**
Pre-eclampsia when pregnant with the study participant	69 (n=633)	10.9	13 (n=473)	2.7	**<0.001**	18 (n=678)	2.7	**<0.001**

Bold text shows p values < 0.05
( ) Number of available information unless from all

5.2 Impact of physical activity on pre-eclampsia and angiogenic markers (Study II)

In Study II, 281 of the PE women (43.4 %) and 290 of the non-PE women (42.4 %) were categorised as physically active (exercising ≥ 2–3 times/week, ≥ 30 minutes at a time with at least moderate intensity). There were no differences in physical activity and exercise habits between the groups, except for PE women spending less time daily doing household work, yard work and/or gardening than the non-PE women (*Table 15*). The physically active women were more often nulliparous and non-smokers and had a lower BMI ($p < 0.05$ for all).

Both first trimester serum samples and the questionnaire data on physical activity were available from 160 PE women and 160 non-PE women, and second/third trimester serum samples and questionnaire data on physical activity were available from 139 PE women and 47 non-PE women. There were no differences in the concentrations of angiogenic markers (sFlt-1, PlGF and sEng and sFlt-1/PlGF ratio) between the groups who exercised more or less than 2–3 times/week. Thus, physical activity was not associated with the concentrations of angiogenic markers. The same analyses were conducted with the variable "Do you exercise ≥ 2–3 times/week, ≥ 30 minutes at a time with at least moderate intensity?" with similar results.

Table 15. Physical activity of the FINNPEC women. Reproduced with permission from the original publication II.

	Pre-eclampsia (n=708)		Non-pre-eclampsia (n=724)		
	N	**%**	**N**	**%**	***p* value**
Physical fitness status, own estimate	695		715		**0.001**
Good	298	42.9	373	52.2	
Average	286	41.2	263	36.8	
Poor	111	16.0	79	11.0	
Time spent physically active* daily when traveling to workplace	571		560		0.169
< 15 minutes	272	47.6	236	42.1	
15–30 minutes	146	25.6	154	27.5	
> 30 minutes	153	26.8	170	30.4	
How physically strenuous is your job?	569		544		0.463
Light (mostly sitting)	276	48.5	264	48.5	
Somewhat light	122	21.4	131	24.1	
Somewhat strenuous or strenuous	171	30.1	149	27.4	
How often do you exercise?	685		709		0.866
1–2 times/month or less	135	19.7	137	19.3	
1 time/week	136	19.9	152	21.4	
2–3 times/week	264	38.5	274	38.6	
4–5 times/week or more	150	21.9	146	20.6	
How strenuous is your exercise?	672		699		0.452
Similar to walking	255	37.9	236	33.8	
Similar to walking and jogging in turns	247	36.8	274	39.2	
Similar to jogging	136	20.2	150	21.5	
Similar to running	34	5.1	39	5.6	

The length of an exercise session	681		701		0.566
< 30 minutes	50	7.3	46	6.6	
30–60 minutes	330	48.5	359	51.2	
> 60 minutes	301	44.2	296	42.2	
Time spent otherwise physically active daily**	691		718		**0.036**
< 30 minutes	181	26.2	195	27.2	
30–60 minutes	304	44.0	278	38.7	
1–2 hours	164	23.7	175	24.4	
≥ 2 hours	42	6.1	70	9.7	
Physically active vs inactive					
How often do you exercise?	685		709		0.648
2–3 times/week or more	414	60.4	420	59.2	
Less than 2–3 times/week	271	39.6	289	40.8	
Do you exercise ≥ 2–3 times/week, ≥ 30 minutes at a time with at least moderate intensity***?	647		684		0.703
Yes	281	43.4	290	42.4	
No	366	56.6	394	57.6	

* Walking, running, cycling or cross-country skiing
** Including household work, yard work and gardening
*** Similar to walking and jogging in turns
Bold text shows *p* values < 0.05
() Number of available information sources if not from all

5.3 Paternal background factors and pre-eclampsia (Study III)

Questionnaires on background information were available from 586 PE fathers and 660 control fathers. Two different control groups were established: one a group of healthy controls (n = 457) that consisted of fathers whose current partners were healthy women with uncomplicated pregnancies and another for other controls (n = 203) that included fathers whose current partners had pregnancy complications other than PE and also including partners with pregestational diabetes and chronic hypertension. The response rates to the questionnaire were 85.1% for PE fathers and 79.4% for control fathers.

The basic characteristics of the participating fathers are presented in *Table 16* and *Table 17.* The PE fathers more often reported PE in a previously fathered pregnancy. The PE and control fathers were similar regarding age, BMI and smoking. There were no differences in pre-existing medical conditions or the socioeconomic background of the groups of fathers. The PE and control fathers comparably often reported having been born from a PE pregnancy (PE fathers: 15 (2.6 %), healthy controls: 12 (5.3 %) and other controls 10 (5.0 %)). However, many of the fathers did not know whether their mother had PE (PE fathers: 99 (17.4 %), healthy controls: 77 (17.2 %) and other controls 38 (19.0 %)).

The parents of the FINNPEC fathers were similar regarding educational background. There were no differences in medical history (history of stroke, myocardial infarction, hypertension, diabetes or mental disorders) of the parents of the fathers, except for mental disorders being more prevalent in the fathers of the healthy control group fathers (PE fathers: 14 (2.6 %) and healthy controls: 21 (4.9 %, p=0.026)).

Table 16. Basic characteristics of the PE fathers and Healthy controls. Reproduced with permission from the original publication III.

	Pre-eclampsia (n = 586)		Healthy controls (n = 457)							
	N	**% or median (range) or mean (SD)**	**N**	**% or median (range) or mean (SD)**	**OR**	**95 % CI**	***p* value**	**OR adj [a]**	**95 % CI adj [a]**	***p* value adj[a]**
Age at enrollment, years		31.8 (6.2) [b]		31.5 (5.8)	1.01	0.99–1.03	0.522	0.99	0.953–1.03	0.589
Ethnicity: Caucasian (ref.=other)	577	98.5	449	98.2	1.14	0.44–2.98	0.786	1.21	0.43–3.47	0.718
Any children fathered before index pregnancy	171	30.3	215	49.3	0.45	0.35–0.58	**< 0.001**	0.84	0.50–1.40	0.497
Previous children fathered with index mother [b]	129 (n = 170)	75.9	196 (n = 214)	91.6	0.29	0.16–0.53	**< 0.001**	1.06	0.29–3.86	0.934
Previous children fathered with different mother than index mother [b]	50 (n = 164)	30.5	31 (n = 209)	14.8	2.52	1.52–4.18	**< 0.001**	0.82	0.35–1.94	0.654
PE in previously fathered pregnancy with index mother [b]	55 (n = 170)	32.4	3 (n = 215)	1.4	33.80	10.34–110.43	**< 0.001**	42.33	12.49–143.41	**< 0.001**
PE in previously fathered pregnancy with mother different than index mother [b]	1 (n = 170)	0.6	0 (n = 215)	0			0.442 [c]			
BMI, kg/m^2		25.7 (14.8–46.9)		25.4 (18.6–39.7)	1.03	0.99–1.06	0.161	0.98	0.95–1.02	0.405
Smoking before index mother's pregnancy	203	35.1	161	35.9	0.97	0.75–1.25	0.791	1.13	0.84–1.52	0.409
Smoking during index mother's pregnancy	186	32.0	145	32.1	1.00	0.77–1.30	0.982	1.10	0.82–1.48	0.533

Differences between PE and control women were determined using logistic regression analysis with odds ratios (OR) and 95% confidence intervals (CI). No mathematical correction was made for multiple comparisons.

[a] Logistic regression adjusted for index mother's BMI, age at birth, parity and smoking during pregnancy

[b] of those who had had had children before

[c] Fisher's exact test

Bold text shows *p* values < 0.05

() Number of unknown data were shown if the number of unknown data was over 10%.

Abbreviations: Body mass index (BMI), Confidence interval (CI), Odds ratio (OR), Pre-eclampsia (PE), Standard deviation (SD)

Table 17. Basic characteristics of the PE fathers and Other controls. Reproduced with permission from the original publication III.

	Pre-eclampsia (n = 586)		Other controls (n = 203)							
	N	% or median (range) or mean (SD)	N	% or median (range) or mean (SD)	OR	95 % CI	*p* value	OR adj [a]	95 % CI adj [a]	*p* value adj [a]
Age at enrollment, years		31.8 (6.2) [b]		32.3 (5.5)	0.99	0.96–1.01	0.297	0.99	0.95–1.04	0.708
Ethnicity: Caucasian (ref.=other)	577	98.5	200	99.5	0.32	0.04–2.55	0.282	0.38	0.05–3.04	0.360
Any children fathered before index pregnancy	171	30.3	81	42.0	0.60	0.43–0.84	**0.003**	1.07	0.59–1.92	0.831
Previous children fathered with index mother [b]	129 (n = 170)	75.9	69 (n = 81)	85.2	0.55	0.27–1.11	0.094	1.14	0.29–4.58	0.852
Previous children fathered with different mother than index mother [b]	50 (n = 164)	30.5	15 (n = 80)	18.8	1.90	0.99–3.65	0.054	1.16	0.40–3.38	0.786
PE in previously fathered pregnancy with index mother [b]	55 (n = 170)	32.4	8 (n = 81)	9.9	4.36	1.97–9.69	**< 0.001**	6.86	2.75–17.13	**< 0.001**
PE in previously fathered pregnancy with mother different than index mother [b]	1 (n = 170)	0.6	1 (n = 81)	1.2			0.542 [c]			
BMI, kg/m^2		25.7 (14.8–46.9)		25.9 (14.8–46.9)	0.98	0.94–1.03	0.447	0.98	0.93–1.02	0.341
Smoking before index mother's pregnancy	203	35.1	81	40.1	0.81	0.58–1.12	0.200	0.83	0.58–1.19	0.310
Smoking during index mother's pregnancy	186	32.0	71	35.7	0.85	0.61–1.19	0.343	0.85	0.59–1.23	0.389

Differences between PE and control women were determined using logistic regression analysis with odds ratios (OR) and 95% confidence intervals (CI). No mathematical correction was made for multiple comparisons.

[a] Logistic regression adjusted for index mother's BMI, age at birth, parity and smoking during pregnancy

[b] of those who had had had children before

[c] Fisher's exact test

Bold text shows *p* values < 0.05

() Number of unknown data were shown if the number of unknown data was over 10%.

Abbreviations: Body mass index (BMI), Confidence interval (CI), Odds ratio (OR), Pre-eclampsia (PE), Standard deviation (SD)

5.4 Eclampsia in Finland; 2006 to 2010 (Study IV)

5.4.1 Incidence of eclampsia

Between 2006 and 2010, 295 447 deliveries were registered in Finland and 46 women with eclampsia were identified. Thus, the incidence of eclampsia was 1.5 per 10 000 deliveries (annual range 1.3–1.8/10 000 deliveries). The women with eclampsia were treated in 19 different hospitals: 48% in university hospitals, 39% in central hospitals and 13% in regional hospitals.

5.4.2 Determinants of eclampsia

The clinical characteristics of the 46 women with eclampsia are shown in *Table 18*. Blood pressure levels during pregnancy were repeatedly higher than 140 / 90 mmHg in 42 women (91%). The high blood pressure was observed for the first time at gestational week 36 (26–42). Proteinuria occurred in 43 women (96%), and in two of them it was observed after eclampsia. Premonitory symptoms appeared in 43 (98%) women (*Table 19*).

The median gestational age at the time of eclampsia was 38 gwks (26–42 gwks). The median number of seizures was one (1–3), but 10 women (22%) had more than one seizure. Eclampsia occurred before labor in 14 women (30 %), during labor in 18 women (39 %) and after labor in 14 women (30 %).

Six women (13 %) were at home at the onset of eclampsia. All of them had premonitory symptoms. Three of these women attended a hospital outpatient clinic because of symptoms of PE, high blood pressure or proteinuria and one was hospitalised for PE but later discharged. One of the six women was unaware of her pregnancy and had not attended any antenatal examination. Eight of the 14 women with antepartum eclampsia were at the hospital when the first seizure occurred.

Table 18. Clinical characteristics of 46 women with eclampsia, Finland 2006 to 2010. Modified with permission from the original publication IV Tables 1 and 4.

Maternal characteristics	**Cases (%) or Median (range)**
Maternal age (years)	23 (17–48)
Nulliparous	42 (91)
Previous history of eclampsia / pre-eclampsia	0 (0)
BMI, kg/m^2	22 (18–35)*
BMI > 30, kg/m^2	4 (7)*
Co-morbidity**	13 (28)
Chronic hypertension	1 (2)
Type 1 diabetes	2 (4)
Gestational diabetes	4 (9)
Smoking during pregnancy	8 (19)***
Smoking after the first trimester of pregnancy	4 (9)***
Multiple pregnancy	4 (9)
Infertility treatment	4 (9)
Bleeding in pregnancy	2 (4)
Mode of delivery	
CS	35 (76)
Planned CS	4 (9)
Emergency CS	10 (22)
Crash emergency CS	21 (46)
Eclampsia as the indication of CS	27 (77)
PE as the indication of CS	2 (6)
Vaginal delivery	11 (24)
Induced labor	21 (46)
Induced labor because of PE	19 (90)

* n=44
** The most common co-morbidities were hypothyroidism, type 1 diabetes, depression and asthma.
***n=43
Abbreviations: Body mass index (BMI), Caesarean section (CS), Pre-eclampsia (PE)

Table 19. Premonitory symptoms within a week before eclampsia in 46 eclampsia patients, Finland 2006 to 2010. Modified with permission from the original publication IV Table 2.

Symptom	**Cases**	**%**
Headache	33 (44)	75
Visual disturbances	14 (43)	33
Nausea	11 (43)	26
Vomiting	7 (43)	16
Upper epigastric pain	16 (44)	36
Dyspnea	3 (42)	7

() Number of women with available information if not from all

5.4.3 Outcome of eclampsia

Altogether 21 women (46 %) had severe complications from eclampsia (*Table 20)*. All recovered with no remaining symptoms. There were no maternal deaths due to eclampsia. The median duration of intensive care admission was two days (1–8 days) and the mean stay in hospital was 11 days (4–20) days.

Thirty-nine women (87 %) received magnesium sulphate for treatment and three (7 %) for prevention of eclampsia. Information about medication before the seizure was available for 45 women and after the seizure for 44 women.

The perinatal outcome of the children of the women with eclampsia is presented in *Table 21.* The perinatal mortality rate was 8 %, but excluding one death unrelated to eclampsia or PE the perinatal mortality rate was 6 %. In these cases, leading to neonatal death, two women were at home at the onset of eclampsia.

Table 20. Maternal complications due to eclampsia in 46 eclampsia patients, Finland 2006 to 2010. Modified with permission from the original publication IV Table 5.

Complication	Cases	%
HELLP-syndrome	10	22
PRES in TT/MRI	10 (24)*	42
Neurological symptoms**	9 (36)	25
Placental abruption	1	2
Uterine rupture	1	2
Deep vein thrombosis	1	2
Metabolic acidosis	3	7
Aspiration pneumonia	1	2
Pulmonary edema and pleural effusion	1	2
DIC, acute renal failure and paralytic ileus	1	2
Treatment in intensive care unit	27 (41)	66

() Number of women with available information if not from all
* Number of women who underwent imaging with CT or MRI
** Hypesthesia, disorientation and transient visual symptoms such as blindness or visual field loss
One woman may have had more than one complication.
Abbreviations: Haemolysis, elevated liver enzymes and low platelet count (HELLP), Posterior reversible encephalopathy syndrome (PRES), Computed tomography (CT), Magnetic resonance imaging (MRI), Disseminated intravascular coagulation (DIC)

Table 21. Perinatal outcome of the children from the 46 eclampsia patients, Finland 2006 to 2010; including four sets of twins, total number n=50. Modified with permission from the original publication IV Table 6.

Complication	Cases (%) or Median (range)
Perinatal death	4 (8)*
Birthweight, g	2905 (610–4540)
Umblilical cord arterial pH	7.20 (6.80-7.33)**
Apgar score at 1 min	8 (0–10)***
Apgar score at 1 min < 6	20 (41)***
Preterm	17 (34)
Small for gestational age	5 (12)****
Birth asphyxia	14 (28)
Seizure	1 (2)
Treatment in a neonatal intensive care unit	26 (52)
Respirator treatment	5 (10)
Cardiopulmonary resuscitaion	6 (12)

* One of the deaths was unrelated to eclampsia or pre-eclampsia.
** n=39
*** n=49
**** n=Twins were excluded, n=42

6 Discussion

6.1 Determinants of pre-eclampsia (Study I and II)

6.1.1 Socioeconomic status

In the present study the socioeconomic status of the PE and non-PE women was similar. This is in line with some previous studies[61,90–92], but in contrast several other studies have reported an association between low socioeconomic status and PE[55,83–89]. Most of the previous studies that found no association were based on small samples of PE (one to three hundred cases)[90–92], while most of the studies reporting an association had notably larger samples of PE (from over a thousand to over ten thousands cases)[55,86,88,89]. The number of PE women also in the present study was smaller compared to the largest studies, which reported low socioeconomic status to be associated with PE. The smaller sample size of PE women might not have had sufficient power to detect associations.

Differences in measuring socioeconomic status might partly contribute to the conflicting results. In the studies that reported an association between low socioeconomic status and PE, low maternal education[55,83], low income level[84–86], social deprivation[87,88] and public health insurance status[89] were used as measures. The present study used both education and income level.

The majority of studies have explored socioeconomic status and race/ethnicity as separate risk factors of PE, but in many settings they are likely to be conflated. PE is more common in black[88,89,308,309] and South Asian[310] women compared with white women. Most studies are from high-income countries, and there women from minority groups more often live in areas of deprivation compared to white women.[88] In the U.S. black women are more likely to be of lower socioeconomic status compared to white women.[89] Higher socioeconomic status has been reported to attenuate the risk of PE in white women, but not in black women.[88,89] In the present study 99.7% of the participants were of Finnish ancestry, thus ethnicity could not affect the results.

It is possible, that the association between PE and low socioeconomic status found in many but not all studies might be attributed to inadequate prenatal care rather than to low socioeconomic status itself. Women with low socioeconomic

status are less likely to receive adequate prenatal care, and inadequate prenatal care has been linked to PE.[84] In Finland, inadequate prenatal care is not likely to be an intermediating factor, since services at maternity clinics are free of charge, of high-quality and used by more than 90% of pregnant women. In addition, free university level education and rather small differences between social classes in the Finnish population might have contributed to the lack of association in our cohort. However, PE was associated with low socioeconomic status in other universal, government-funded health care settings in Korea and Sweden.[84,86] A study from an ethnically diverse area in southern Sweden, with 46 618 pregnancies from 1999 to 2009, found an increased risk for PE in women with lower socioeconomic positions, and the relationship was not explained by ethnicity.[86] On the other hand, another Swedish study found PE to be more common in women living in better socioeconomic areas.[311] In this study from the city of Malmö in southern Sweden, with 7056 pregnancies from 1990 to 1992, the higher parity among women living in lower socioeconomic areas was thought to contribute to the lower incidence of PE among them.[311] In summary, comparing the effect of socioeconomic status on the risk of PE is difficult, due to variation in measuring socioeconomic status, diverse study populations and different health care systems.

A few studies, that have investigated the association between socioeconomic status in childhood and PE reported no associations[91,92]. In the present study fathers of the PE women had a lower education than fathers of the non-PE women. The results are not completely comparable with previous studies, because of different measures of socioeconomic status. The study from Sweden used education and family social class[92], whereas the study from the UK used childhood social class based on the occupation of the study participants' fathers[91].

6.1.2 Mental health

The current study showed higher rates of depression among women with PE. Similarly, several previous studies have found an association between pregestational/antenatal depression or depressive symptoms and PE[96–102] but some studies have found no association[103–107].

The heterogeneity of the studies probably contributes to the confounding results. The methods to assess depression vary considerably among studies. Moreover, the timing of symptoms or diagnosis of depression in relation to pregnancy has wide variance. The current study used self-reported depression (physician-diagnosed or -treated), but we do not know the status of depression during the index pregnancy. Previously in Finland, depression was associated with increased risk of PE in a study that assessed depression with a modification of the Beck Depression Inventory.[98] Other previous studies reporting an association between depression and PE have

used pregestational or early pregnancy diagnoses of depression[101], International Classification of Diseases, 9th Revision (ICD-9) codes for depression[100,109] and the Patient Health Questionnaire during pregnancy[102] to assess depression. Whereas studies reporting no association between PE and depression used pregestational physician-diagnosed depression[107], self-reported history of depression symptoms[106], ICD-9 codes for depression[105] and Center for Epidemiological Studies Depression Scale[104]. Moreover, most studies, including ours, did not adjust for relevant confounding factors. Only a few studies adjusted for both obesity/BMI and chronic hypertension.[100,104], which are shared risk factors for depression and PE.[60,66,111–113]

In a case-control study with 676 women from Peru, no increased risk of PE was detected among women with mild depression as compared to the control group, but those with moderate depression had a 2.3-fold increased risk of PE, while moderate-severe depression was associated with a 3.2-fold increased risk of PE.[102] Most other studies, including ours, have not evaluated the severity of depression. This might have led to some studies finding no association between depression and PE.

The present study evaluated the use of SSRIs during the last 12 months. PE women used SSRIs more often when compared to healthy controls, but there was no difference when compared to all controls. From our data it was not possible to separate whether the women used SSRIs solely before pregnancy or during pregnancy or both. Previous data on the relationship between antidepressant use and PE is conflicting.[108–110] Most studies, including ours, did not account for the severity of depression or other psychiatric disease, that the antidepressants were used for.[108–110] More severe maternal depression is associated with increased use of antidepressants.[110] Thus, it is possible that women using antidepressants during pregnancy may have higher rates of PE simply because they have more severe depression.

The underlying mechanisms connecting depression and PE are unclear. Increased inflammation and oxidative stress and decreased vascular and endothelial function are associated with both depression and PE, as well as with their shared risk factors obesity and CVD.[9,38,117–120] The association between depression and CVD has been thought to be partly mediated by poor adherence to risk-reducing health behaviours.[116] Behavioral factors such as reduced physical activity and associated excessive weight gain in depressed pregnant women may possibly also contribute to the increased risk of PE.

6.1.3 Factors related to fertility

Early age at menarche

Earlier age at menarche was associated with the risk of PE in the current study. Only a few other studies have investigated the relationship between age at menarche and PE. Most of the studies support the association between early age at menarche and PE[132–135] but not all[136,137].

Several factors may have contributed to the conflicting results of the few studies conducted[132–137]. All of the studies, including the present study, used self-reported age at menarche, and the validity of self-reported age at menarche decades later has been estimated to be of only moderate accuracy.[312] Most of the studies had limited samples of PE (from 80 to 286 cases).[132–134,137] However, two large studies also showed opposite results: A study from China with 209 411 pregnant women found an association between earlier age at menarche and PE[135], while a study from the UK including 250 037 women did not.[136] The limitation in our study was that it did not adjust for confounding factors. However, most other studies have included confounding factors (most often BMI/adiposity, ethnicity, parity and maternal age).[132,135–137] There was also inconsistency in defining early age at menarche among studies, which makes comparisons between studies difficult.

Mendelian randomisation studies have been conducted to try to overcome the limitations of epidemiological/observational studies. This study type utilises genetic variants related to the exposures of interest to examine true causal relationship of exposure on the outcome.[147] A recent Mendelian randomisation study using data from the FinnGen consortium with 3903 cases and 114 735 controls found weak evidence of later age at menarche to associate with decreased risk of PE.[313]

In line with most studies[132–135,147], our findings support a negative relationship between age at menarche and PE. In the present study women with PE had more often risk factors for metabolic syndrome, such as a higher BMI and pregestational and gestational diabetes, which are also associated with earlier menarche.[142–145] Systemic inflammation has been suggested as common pathophysiology to both early age at menarche, PE and also their shared metabolic risk factors.[138]

Subfertility and infertility

The use of ART did not differ between PE and non-PE women. Contrary to our results, there is substantial evidence of the association between conceiving with ART and increased risk of PE.[78,151–153] The contradictory results may be due to a small number of women conceiving with ART in the present study.

Despite extensive research regarding the relationship between PE and ART, the association between subfertility and PE has been much less studied. In Study I we found that conceiving took more time for PE women than non-PE women. Most of the few studies conducted support our findings of subfertile women having higher rates of PE.[155–157] A study from Denmark reported that time to pregnancy ≥ 12 months was associated with PE (RR 1.76, 95% CI 1.00–3.12), but after adjusting for confounding factors (maternal and paternal age, maternal smoking, BMI, parity and education) the association was no longer significant (RR 1.45, 95% CI 0.79–2.65).[314] Our study did not control for confounding factors, but the other studies supporting an association between subfertility and PE did (most often adjusted for maternal age, parity, BMI and smoking)[155–157].

The association between subfertility and PE suggests, that the increased risk of PE in pregnancies following ART may, at least in part, be related to maternal factors related to infertility/subfertility.[151] There is significant overlap in the characteristics of women seeking fertility treatment and the risk factors for PE: Nulliparity, older maternal age and comorbidities such as obesity, diabetes and chronic hypertension, diminished ovarian reserve and polycystic ovary syndrome are associated with both conditions.[151]

6.1.4 Family history

We demonstrated that PE women were more often born from a pregnancy complicated by PE than women in the control groups, which is in line with previous studies.[53,162–164] Family history of PE (in sister or mother) is included in FIGO[4], NICE[25] and ACOG[7] guidelines and the Finnish Current Care Guideline[26] as one of the clinical risk factors to identify women at risk for PE.

In the present study the parents of PE women had more morbidity: Hypertension occurred more often in both parents of PE women, strokes in fathers and diabetes in mothers. In accordance with our results, previous studies have shown, that family history of hypertension[127,172–174,177–179] and CVD (including stroke)[162,171–175] increase risk for PE. Previous data on family history of diabetes is inconsistent, as several studies have found an association between family history of diabetes and PE[171,172,179,180], but some studies have not[127,178,181]. The few studies that assessed maternal and paternal family history of hypertension[174,179], CVD (myocardial infarction or stroke)[162] or diabetes[179] separately reported similar associations with PE for both parents. It should be taken into account, that hypertension, CVD and PE are all linked to advanced age, meaning that family history is more likely to be positive in older women or in women born to parents of advanced age.[315] Our study did not adjust for maternal age, which might have influenced the results. Most of the previous studies adjusted their results for maternal age supporting family history of

hypertension or CVD as independent risk factors for PE. In addition, our study, as well as most of the previous studies, used self-reported definitions of family history based on patient knowledge and recollection, which might have led to a misclassification of some study participants.

PE and CVD have been suggested to share common heritable mechanisms[176] and hypertension and diabetes are known risk factors for both PE and CVD[21,61,182]. Family history of PE, CVD, hypertension and possibly diabetes has the potential to capture both genetic and environmental as well as lifestyle factors that predispose women to PE.[162,170]

The present study found mental disorders including depression to be more prevalent in mothers of PE women. To our knowledge, there are no other studies looking at the relationship between family history of depression and PE. Depression was reported to associate with higher rates of PE in the participants of the current study as well as in previous literature.[96–102] Our study did not adjust for confounding factors. As both PE and depression are linked to obesity and chronic hypertension/CVD, the contribution of these factors to the higher prevalence of depression in mothers of PE women can not be ruled out.[21,61,66,113–116]

It is well known that there is an increased risk of psychiatric disorders/depression in the offspring of depressed parents.[315] The estimated heritability of major depressive disorders is 30–40 %, but the genetic factors behind depression are still not well known. There is mixed evidence for a stronger genetic risk for women than for men.[315] In the present study, there was no difference between the study groups in the number of women who themselves had depression and also had a mother with a history of depression. However, the sample sizes of women with depression were small, possibly leading to insufficient power to detect associations.

In the current study we knew that the mothers of the participants had a history of depression, but not the time of the depressive episodes. According to the Developmental Origins of Health and Disease hypothesis, maternal depression during and after pregnancy could possibly affect child through developmental programming, permanently changing the structure and functioning of organs and body's biological feedback systems.[316,317] Accordingly, maternal depression during pregnancy, postpartum and in early childhood have been associated with structural brain changes and neurodevelopmental disadvantages in children.[317] PE has also been associated with offspring neurodevelopmental disorders, and systemic chronic inflammation is thought to be an underlying factor in both PE and depression and the consequences in their children.[318] Parental systemic chronic inflammation has been suggested to be transmitted to their offspring through epigenetic alterations during intrauterine life or before conception. This potentially results in an increased risk of inflammation-related health problems, including obesity, CVD, depression and PE in the next generation.[318,319]

6.1.5 Impact of physical activity on pre-eclampsia and angiogenic factors

In the study population, 43.4 % of PE women and 42.4 % of non-PE women were classified as physically active. There were no differences in the physical activity and exercise habits in pregnancy between the study groups. Previous studies have shown conflicting results. Contrary to our results an umbrella review from 2019 concluded that physical activity possibly reduces the risk of PE, but considered the evidence to be limited.[184] Davenport, et al. showed in their systematic review and meta-analysis with 16 randomized controlled trials (RCTs), that prenatal exercise interventions reduced the odds of developing PE by 41%.[185] Some earlier systematic reviews and meta-analyses have reported similar findings.[186–188] The systematic reviews by Kasawara, et al.[188] and Wolf, et al.[187] both showed mixed results.

However, several systematic reviews and meta-analyses support our findings of no association between PE and physical activity during pregnancy.[189–191,197,198] Umbrella review of RCTs and updated meta-analysis from 2023 found no association between physical activity and PE, but reported that exercise interventions reduced the risk of HDP overall.[191] Other studies have also reported an inverse association between physical activity and HDP, but not independently with PE.[198–200]

The inconsistency of the results may be due to the substantial heterogeneity of the studies in terms of different methods used to assess physical activity, differences in defining who is physically active and who is inactive and varying definitions of PE. Further, differences in the characteristics of pregnant women and insufficient statistical powers have been suspected to contribute to the mixed results.[191,198] The present study used self-reported physical activity, which may be partly inaccurate due to possible recall bias. Many other studies have also used self-reported information on physical activity, but others have used various supervised exercise regimens or accelerometry.[186,187,190,198]

A meta-analysis by Aune et al. showed that physical activity in early pregnancy (up to 16–24 gwks or up to first antenatal visit, or the first trimester of pregnancy) reduced the risk of PE.[186] In addition, physical activity before pregnancy has been reported to associate with decreased risk of PE.[186–188] In the present study women reported on their average exercise habits during pregnancy. The frequency and intensity of physical activity may have varied between the trimesters and from exercise habits before pregnancy, and this might have influenced our results. Indeed, previous studies have shown that pregnant women tend to reduce physical activity throughout pregnancy and the prevalence of physical activity during pregnancy is lower compared to pre-pregnancy period.[320,321] As both pregnancy and exercise can be major physiological stressors, pre-pregnancy exercise status might contribute to

whether or not exercise during pregnancy is effective and safe as a preventive measure for increased blood pressure.[212]

A meta-analysis of 16 RCTs by Davenport et al. showed that to achieve at least a 25% reduction in the odds of developing PE, pregnant women should accumulate at least 140 minutes of moderate-intensity exercise (brisk walking, water aerobics, stationary cycling or resistance training)/week. A systematic review by Wolf et al. reported, that light or moderate intensity leisure time physical activity during pregnancy was not associated with reduced risk of PE, but leisure time physical activity of high intensity or performed more than 4 hours/week might reduce the risk of PE. Our questionnaire data on physical activity did not allow us to make a comparative evaluation of the amount or intensity of weekly exercise.

The underlying mechanisms of physical activity possibly lowering the risk of PE are unclear. It is well-known that prenatal exercise prevents excessive weight gain and improves glucose control.[184] This might contribute to physical activity reducing the risk of PE, as obesity/excessive weight and pregestational/gestational diabetes are associated with increased risk of PE.[62,66,67] Physical activity in pregnancy has been suggested to promote placental growth and vascular development, reduce oxidative stress and improve endothelial function as well as immune and inflammatory responses.[207] In addition, exercise in pregnancy may promote a pro-angiogenic state.[208–210]

Impact of physical activity on angiogenic factors in women with and without pre-eclampsia

To the best of our knowledge, this is the first study to investigate the association between physical activity in pregnancy and concentrations of angiogenic factors comparing pregnant PE women with non-PE women. In this study, physical activity did not affect the concentrations of angiogenic markers (sFlt-1, PlGF and sEng and sFlt-1/PlGF ratio) in either PE or non-PE women. Contrary to humans, physical activity in pregnancy has been shown to decrease sFlt-1 levels in rat[212] and mouse[213] models of PE. Along with decreasing s-Flt-1 levels, exercise training before and during pregnancy increased VEGF levels stimulating a pro-angiogenic state in rats.[212] This rat study by Gilbert et al. reported that it was unclear, whether regular exercise training prior to pregnancy was important to their observations.[212] The present study did not include data on physical activity before pregnancy, which might have influenced the results. Further, the sample sizes of women with available serum samples were small, which might have led to insufficient power to detect associations. Moreover, this study used self-reported physical activity, which is prone to recall bias.

One previous study by Weissgerber et al. examined the association of circulating angiogenic factors and exercise in pregnant women without PE. Contrary to our results, this cross-sectional study including 25 pregnant women reported higher serum PIGF and lower sFlt-1 and sEng concentrations in the third trimester in physically active pregnant women compared with inactive pregnant women.[208] Both the present and Weissgerber et al. study used self-reported questionnaires to define the exercise habits of pregnant women. However, the definitions of physically active differed: ours was exercising 2–3 times/week or more or exercising ≥ 2–3 times/week, ≥ 30 minutes at a time with at least moderate intensity, whereas Weissgerber et al. defined physically active as "exercising for at least 3 hours/week at an intensity that is sufficient to cause sweating". Further, the sample size in the Weissgerber et al. study was small compared to the present study and they did not adjust for possible confounding factors.

The few studies conducted with nonpregnant people have shown contrary results on the effect of physical activity on angiogenic factors. Regular exercise in nonpregnant women was not associated with sFlt-1, sEng, PlGF or vascular endothelial growth factor (VEGF) concentrations in one study.[208] Increased plasma sFlt-1 levels were reported after acute exercise in nonpregnant women[208,322] and in men[323,324].

6.2 The role of paternal factors in pre-eclampsia (Study III)

In the present study the number of first-time fathers was higher among PE fathers, but there was no longer a difference after adjusting for the index mother's BMI, age at birth, parity and smoking during pregnancy. Several previous studies have shown primipaternity, defined as a woman's first pregnancy with a new partner, to increase risk for PE.[219–222] Due to our study design we could not evaluate the rate of primipaternity in the FINNPEC cohort. The role of primipaternity as a risk factor for PE has been thought to relate to shorter exposure to paternal sperm.[228–230] The use of barrier contraceptives[231,232], conceiving with donor sperm[233,234] and conceiving via ICSI with surgically obtained sperm[239] have been associated with increased risk for PE, supporting the theory of limited paternal sperm exposure.

Men who themselves were born from pregnancies with PE have been shown to have an increased risk to father a PE pregnancy, suggesting a role of paternal genes in the increased risk of PE through the foetal genome.[13,227] In the present study PE and non-PE fathers reported comparably often being born from PE and normal pregnancies. However, a large number of fathers did not know whether their mother had PE (17.4 % of PE fathers, 17.2 % of healthy controls and 19.0 % of other controls).

In the present study the occurrence of PE in a previously fathered pregnancy was more common among the men who fathered a current PE pregnancy. Similarly, a large Norwegian population-based study showed that women who were pregnant by a partner who fathered a PE pregnancy with another woman had nearly twice the risk in their own pregnancy.[225] This phenomenon supports the role of paternal genes in development of PE. Contrary to the Norwegian study, in our study almost all previous cases of PE were with the index mother. As prior PE is a well-known risk factor for PE in a woman's current pregnancy[57], the father's contribution is unclear in our study.

Considering paternal phenotypic and lifestyle characteristics, the PE and non-PE fathers were similar in age, BMI, smoking and pre-existing medical conditions. There were no differences in socioeconomic background or health history of the fathers or their parents.

Previous studies investigating the relationship between paternal age and PE have shown mixed results.[242–245] A study by Harlap et al. including 81 213 deliveries from 1965–1976 in Jerusalem reported higher rates of PE in pregnancies fathered by older men.[242] In a population-based study from Taiwan by Yu et al. with 1 347 672 deliveries advanced paternal age was associated with a higher incidence of gestational hypertension/PE and eclampsia, but the study did not examine independent association with PE.[243] Neither of the studies by Harlap et al. and Yu et al. accounted for paternal/maternal BMI, which can be considered a limitation.[242,243] In line with our results, recent large studies from the U.S. found no association between paternal age and PE.[244,245] Hurley et al. examined more than 1 million deliveries from 2006 to 2012, and found that after accounting for maternal age, advanced paternal age was not associated with PE.[244] Similarly, in a study including more than 40 million deliveries from 2007 to 2016 by Khandwala et al. no significant association was detected between paternal age and PE.[245]

The studies evaluating the effect of paternal obesity/BMI on the risk of PE are scarce and their results are unclear.[247,248] Contrary to our results, a study from China including 7683 women reported that paternal obesity increased the risk of PE. The limitation in this study was that it did not adjust the results for any confounding paternal or maternal factors.[247] A Norwegian study including more than 14 000 families showed that a higher BMI in men was associated with fathering a pregnancy complicated by HDP.[248] However, after accounting for confounding paternal and maternal factors (including paternal smoking, paternal BMI, paternal education, parity, maternal age at delivery, maternal education, maternal smoking and maternal BMI, maternal blood pressure) there was no longer an association. In addition, the association was not estimated independently for PE.[248]

The evidence on the relationship between paternal health/pre-existing medical conditions and PE is very limited. In the present study the health of the fathers was

similar, estimated by pre-existing medical conditions, number of sick days during the previous 12 months and subjective health status. Comparing our results with previous studies is difficult due to different methods used to assess paternal preconceptional health. In contrast to our results, a study by Kasman et al. reported an association between paternal comorbidities (including hypertension, hyperlipidemia, diabetes and obesity) and PE.[251] Moreover, in another study by Murugappan et al., preconceptional paternal health, assessed as the number of metabolic syndrome component diagnoses, was associated with increased risk of PE.[252] Conversely, a study by Myklestad et al. found no association between PE and cardiovascular risk factors (blood pressure, BMI, waist circumference, serum lipids and glucose).[248]

The role of paternal smoking/maternal passive smoking has been previously studied in The Norwegian Mother and Child cohort, showing no association with PE.[254] This is in line with our findings. In addition, a population-based study from the Netherlands reported that paternal smoking was not associated with hypertensive pregnancy complications, but the association independently with PE was not evaluated.[253]

The present study also reported on paternal socioeconomic factors and health history of the parents of the father. One previous study reported that paternal working hours did not have an influence on hypertensive complications, which is in line with our results.[253] To our knowledge there are no other studies on the relationship between PE and paternal socioeconomic factors as well as medical and socioeconomic background of the parents of the father to a PE pregnancy.

6.3 Incidence and outcome of eclampsia (Study IV)

The incidence of eclampsia in Finland was 1.5 per 10 000 between 2006 and 2010. The incidence has decreased from 15–20/10 000 deliveries in 1956[277] and 2.4/10 000 deliveries in 1990–94[277]. The incidence of 1.5/10 000 is low compared to other developed countries (*Figure 6*). The global rates of eclampsia are highly variable with the highest rates reported from developing countries. The differences in incidences are probably related to the quality of antenatal and intrapartum care.[256]

Almost all (91%) of the women with eclampsia were nulliparous, corresponding to previous studies reporting nulliparity as a risk factor for eclampsia.[275,281,292] The median age of women with eclampsia was 23 (mean 25.4), which is lower than the mean age of parturients (30.1 years) in Finland during the years 2006 to 2010.[325] Previous studies have shown that a younger maternal age, in terms of maternal age ≤ 20[292] or teen pregnancy[275,281] increases the risk for eclampsia. In addition older maternal age ≥ 35 has been reported to be protective of eclampsia.[292]

In the present study, 98% of the women had premonitory symptoms. In the previous literature a much greater proportion of women was indicated who had no reported premonitory symptoms; the percentage varying from 25% to 60%.[8,288,291] This may be due to missing data of the symptoms in the medical records in these retrospective studies.

Magnesium sulphate has been shown to be the most effective pharmacological intervention to prevent eclampsia in women with PE with severe features and to reduce the rate of recurrent seizures.[16–20] Since the release of The Collaborative Eclampsia Trial[16] in 1995 and The Magpie Trial[17] in 2002 the use of magnesium sulphate in clinical practice has increased. In the current study 87% of women received magnesium sulphate for treatment of an eclamptic seizure, compared to none in the Finnish study from 1990 to 1994.[277] Nevertheless, the use of magnesium sulphate in Finland was lower than in the Netherlands (95%) between 2004 and 2006 and in the UK (99%) between 2005 and 2006.[326] In Italy the rate of women treated with magnesium sulphate to reduce recurrent seizures was 89% during the years 2017–2020.[276]

In our study only three (7%) of the women who developed eclampsia were given prophylactic magnesium sulphate. This is in accordance with 10% reported from the Netherlands and 6% in the UK in the mid-2000s.[326] In Scandinavia from 1998 to 2000 only two out of 211 women (0.9%) were reported to have received prophylactic magnesium sulphate.[279] Compared to the Scandinavian study, the use of magnesium sulphate has increased, and probably contributes to the decreased incidence of eclampsia. Recently, during 2017 to 2020 in Italy, magnesium sulphate was used as prophylaxis in almost 30% of women with PE who developed eclampsia.[276] Our study did not investigate how many women with PE were treated with magnesium sulphate and subsequently did not develop eclampsia, and thus this study's ability to estimate the efficacy of magnesium sulphate prophylaxis is limited.

In Finland the incidence of eclampsia was reduced by approximately one-third after the initiation of magnesium sulphate prophylaxis and treatment. Increased use of antenatal corticosteroids and improvement of neonatal intensive care possibly also contributed to the decreased incidence by enabling earlier deliveries in women with PE. A study from the UK in 2005 reported that both the incidence of eclampsia and recurrent seizures had halved since the increased use of magnesium sulphate.[278] In Finland the median number of seizures was one, both in the current study and between 1990–94, but the range of the seizures decreased from 1–9 to 1–3.[277] More than one seizure occurred in 22% of the women, in accordance with 24% reported from the Netherlands and 26% from the UK.[326]

Eclampsia causes significant maternal and perinatal mortality and morbidity especially in developed countries.[2,285,303] No maternal deaths due to eclampsia were reported in the current study or between 1990–94 in Finland.[277] During the years

1972–2005 in Finland the maternal mortality rate associated with PE and eclampsia was 0.7/100 000.[295] In the UK maternal mortality associated with PE/eclampsia decreased from 19/100 000 to 9/100 000 deliveries between 2006–2008 and 2010–2012.[327]

In the present study, severe maternal complications occurred in 46% of the pregnancies, but all the women recovered without remaining symptoms. None of the women had prolonged neurological symptoms in the present study compared with 9% between 1990 and 1994[277] or 1.9% in Scandinavia between 1998 and 2000[279] In the UK the incidence of severe morbidity associated with eclampsia decreased from 35% to 10% after increased use of magnesium sulphate.[278] Severe complications were reported in 33% both in Scandinavia during the period 1998–2000[279] and in Italy during the period 2017–2020.[276] Compared to these other studies a relatively high proportion of women had severe complications in our study. This is probably due to differences in what was included as severe complications. For instance, there was a high incidence of PRES in the present study (10 women out of 24 women who underwent brain imaging [42%]), whereas brain imaging was not reported in the studies from the UK[278] and Scandinavia[279]. PRES was first introduced in 1996[328], and therefore in Finland during the years 1990–1994 this condition could not be evaluated.[277] In Italy between 2017 and 2020 PRES was reported only in 13.8% of women, but the number of women who underwent brain imaging was not reported.[276] High incidences of PRES in women with eclampsia were found in two retrospective cohort studies: 92.3% in Japan between 2007–2015[297] and 97.9% in the U.S. between 2001–2010[329]. The high rates of PRES were possibly due to patient selection of women with severe neurological symptoms to undergo neuroimaging.[297,329]

The perinatal mortality rate in the present study was 8%, but after excluding one death not associated with eclampsia the perinatal mortality rate was 6%. Comparable rates of eclampsia-associated perinatal mortality have been reported: 5% in Finland between 1990–1994[277] and 5.9% in the UK between 2005–2006[278]. A lower perinatal mortality rate of 2.7% was reported in Italy in the years between 2017–2020.[276] The number of SGA newborns was lower (12%) in the current study compared with 35% between 1990–1994.[277] This might be due to a more active approach in delivering women with PE.

6.4 Strengths and limitations of the study

The main strength of Studies I–III is that they use a nationwide population-based cohort with detailed clinical information from medical records. Moreover, background information on the PE women and their partners was collected on a wide basis comprising health, lifestyle and family health history. The response rates to the questionnaires were good (PE women 76.7%, non-PE women 71.8%, PE fathers

85.1% and non-PE fathers 79.4%), considering that a response rate of 60% has face validity as a measure of survey quality.[330] However, the PE women who did not respond to the questionnaire differed somewhat from the PE respondents, which may have biased some results of the study.

The FINNPEC cohort (Studies I–III) was ethnically homogeneous, as more than 98% of the participants were of Finnish ancestry, which can be seen as a strength or a weakness. The findings may not be applied to other populations. Further, self-reported information gained through questionnaires is prone to recall bias. The completeness and accuracy of the family history information may especially vary from case to case. Multiple hypothesis testing can be also considered a weakness in Studies I and III. The *p*-values reported in the tables have not been Bonferroni-corrected. However, over adjustment for multiple comparisons may increase a type II error, which reduces the power to detect significant differences.

Potential confounding factors were considered in the analyses of Studies II and III, but not in Study I, which can be considered a limitation. Moreover, in Study I we only evaluated whether there was an association between PE and various background factors, but not the strength of the association.

In Study II the questionnaire collected data on the women's average exercise habits during the whole pregnancy. It would have been useful to have information on the women's physical activity during early pregnancy and before pregnancy. Further, in Study II the inter-individual variations in the serum concentrations of the angiogenic markers were relatively large and the sample size was small. In addition, there was a much smaller number of second/third trimester serum samples available from the non-PE women (n=47) compared with the PE women (n=139), which might have influenced the results.

In Study III we did not know the number of possible cases, in which men who believed to be biological fathers were in fact not. A median paternal discrepancy of 3.7% (2.0–9.6%) has been reported for studies based on populations chosen for reasons other than disputed paternity.[331] The study design in Study III did not allow us to evaluate the relationship between primipaternity and PE or the risk of PE in women who were pregnant by men who had fathered PE pregnancies with other women. This would have provided better understanding of the father's contribution to PE. Regarding the questionnaire, it is likely that the fathers were not aware of all details of the obstetric history concerning their partners' pregnancies.

In Study IV, the data were retrieved from national registers and data from the National Birth Register is considered reliable.[332] Almost all (98%) of the eclampsia cases were identified from the National Birth Register. One hospital reported an additional case of eclampsia outside the registers. However, the validity of the eclampsia diagnoses in the registers was low, as 115 of the 160 women found in the registers did not have eclampsia according to review of the medical records. The

retrospective nature of Study IV can be considered a limitation. The completeness and accuracy of the medical records may vary from case to case. Particularly the results on premonitory symptoms of eclampsia are only suggestive.

Finally, Studies I–IV used the previously accepted definition of PE (defined as new onset hypertension and proteinuria developing ≥ 20 gwks). Since the commencement of this study major international and national guidelines have changed their definition of PE to include maternal and uteroplacental organ dysfunctions besides proteinuria.[3,7,25,26] However, the old and new classifications of PE were studied in the FINNPEC cohort in 2016, and only minor changes were observed in the number of PE women.[27]

6.5 Future prospects and clinical implications

The identification of women at high risk for PE/eclampsia is mainly based on clinical risk factors. However, the detection rate of PE with traditional maternal risk factors has been reported to be 39–41% for preterm PE, and 34 % for term PE.[22] Further, PE was shown to affect 2.7% of pregnant women without traditional clinical risk factors (in a systematic review and meta-analysis).[21] Future studies are needed to better understand the factors involved in the aetiology of PE and to improve early recognition of women at high risk for the disease.

The results of this thesis suggest additional non-traditional risk factors that could be considered when evaluating a woman's risk for PE in antenatal health care. The non-traditional and traditional risk factors are to some extent connected, and therefore it is important to evaluate the woman and her risk as a whole.

The present study confirms the association between depression and increased risk for PE reported in several previous studies.[96–102] Therefore, more attention should be paid to depression/depressive symptoms in antenatal care. The family history of hypertension and CVD are associated with increased risk of PE based on this study and previous literature.[127,162,171–175,177–179] Considering family history as a risk factor might be useful, especially in primiparous women with no prior pregnancy history. Moreover, there was an association between a family history of depression in mothers and an increased risk for PE in daughters. To the best knowledge of the author, this is the first study to investigate the association between PE and family history of mental disorders. Future studies with larger sample sizes, documentation of the time of depressive episodes and controlling for confounding factors could improve understanding of the relationship between family history of depression/mental disorders and PE.

Our findings that early age at menarche and subfertility have an association with PE, add to the awareness of the limited literature on the subject. More studies with

adjustment for relevant confounding factors (BMI, age, parity, diabetes) are needed to confirm the associations.

In the present study, physical activity during pregnancy was not associated with PE. Overall, based on previous literature physical activity probably reduces the risk of PE in some settings.[184–188] Future studies are needed to clarify the impact of weekly amounts, intensities, and timing of physical activity. Further, more objective measuring tools, such as pedometers or activity trackers, would be useful.

This is the first study to investigate the association of physical activity in pregnancy with concentrations of angiogenic factors while comparing pregnant women with and without PE. No association was found between physical activity and concentrations of sFlt-1, PlGF and sEng and sFlt-1/PlGF ratio in pregnant women with or without PE. Previously rodent studies have reported opposing results.[212,213] Further human studies with larger sample sizes and more objective measuring tools of physical activity are needed to better understand the relationship of angiogenic factors and physical activity in the development of PE.

The current study showed no association between paternal phenotypic and lifestyle factors and risk for PE. Previous studies on the subject are few in number and report mixed results. Future studies are needed to confirm or oppose our results. Further, studies addressing genetic and epigenetic mechanisms are needed to better understand the role of the father in the risk of PE. Although the phenotype and lifestyle of the fathers was not an independent factor in their partners' susceptibility to PE, fathers might have an effect on the lifestyle of their partner. It would be useful to estimate the correlation of maternal and paternal lifestyle factors in PE susceptibility in the future, as a previous study showed them to be positively correlated.[253]

Although, in Finland, the incidence of eclampsia between 2006–2010 was low and the affected women recovered without prolonged complications, eclampsia is still a severe disease threatening the life and well-being of both the mother and the foetus.

Based on our study, the Finnish health care system detects most of the women at risk for eclampsia and refers them for appropriate treatment. However, some women at risk for eclampsia remained undetected and untreated. It is important that both health care personnel and pregnant women recognise the signs and symptoms of PE in order to initiate appropriate treatment before the development of eclampsia. Only seven percent of women with eclampsia had received prophylactic magnesium sulphate. An increase in prophylactic magnesium sulphate administration might further reduce the incidence of eclampsia. Nevertheless, this study did not examine how many PE women receiving magnesium sulphate prophylaxis did not develop eclampsia. It would be of interest to evaluate the efficacy of magnesium sulphate prophylaxis in PE women in Finland in the future.

7 Conclusions

Based on the results of the present study, the following conclusions can be made:

1. In the FINNPEC cohort earlier age at menarche, subfertility, non-communicable diseases and depression were associated with increased risk of PE. Socioeconomic status was not related to PE. Family history of hypertension in both parents, stroke in fathers and diabetes and mental disorders including depression in mothers were associated with higher rates of PE.

2. There was no association between physical activity during pregnancy and PE. Physical activity of pregnant women with or without PE was not associated with the maternal serum concentrations of angiogenic factors sFlt-1, PlGF and sEng and sFlt-1/PlGF ratio.

3. The occurrence of PE in a previously fathered pregnancy was more common among men who fathered a PE pregnancy. The phenotype and lifestyle of the fathers did not play a significant role in PE susceptibility of their partners.

4. The incidence of eclampsia in Finland was very low. Increased use of magnesium sulphate probably contributed to the low incidence as well as to the low number of recurrent seizures and prolonged complications. However, eclampsia caused serious complications and long hospital stays to the majority of affected women.

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