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Epidemiological Studies of Preeclampsia

Maternal & Offspring Perspectives

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Abstract

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Preeclampsia is a placental-related disorder characterized by generalized endothelial activation. Vascular predisposition is associated with the occurrence of preeclampsia and the recurrence risk is substantial. Onset of preeclampsia is preceded by placental hypo-perfusion, and placental over-production of vasoconstrictive agents might explain symptoms such as hypertension and proteinuria. Preeclampsia is associated with the birth of small-for-gestational-age (SGA) infants. The trajectory of postnatal growth in SGA-born children is described as catch-up, but it is unclear whether prenatal preeclampsia is independently associated with postnatal growth.

The objectives were: firstly, to study the association between partner change and prior miscarriages on the occurrence of preeclampsia and SGA; secondly, to study postnatal growth in children prenatally exposed to preeclampsia; and thirdly, to address the association between blood pressure (BP) changes during pregnancy and risks of preeclampsia and SGA.

Population-based cohort studies were performed with information from the following registers: Swedish Medical Birth Register, Uppsala Mother and Child Database and Stockholm-Gotland Obstetric Database. Associations were estimated with logistic and linear regression analyses, with adjustments for maternal characteristics, including body mass index, pre-gestational diseases and socioeconomic factors.

The results were, firstly, that partner change was associated with preeclampsia and SGA birth in the second pregnancy but depended on the outcome of the first pregnancy, and that a history of recurrent miscarriages was associated with increased risks of preeclampsia and SGA. Secondly, prenatal exposure to preeclampsia was associated with increased offspring growth in height during the first five years. This association was also seen in children born with normal birth weight for gestational age. Thirdly, pre-hypertension in late gestation and elevated diastolic BP from early to mid-gestation were both associated with SGA birth. Further, women with pre-hypertension in early gestation without lowered diastolic BP until mid-gestation seemed to represent a risk group for preeclampsia.

To conclude, the importance of previous pregnancy outcomes in the antenatal risk evaluation was highlighted. Secondly, the results imply that postnatal growth trajectory is related to maternal preeclampsia, in addition to SGA. Thirdly, the association between BP changes within a normal range and SGA may challenge the clinical cut-off for hypertension in pregnancy.

Keywords: Placental dysfunction, blood pressure, small-for-gestational-age, fetal growth restriction, intrauterine, prenatal exposure, postnatal height gain, linear growth

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The Search for the Ultimate Question of Life,
the Universe and Everything!

The Hitchhiker's Guide to the Galaxy
Douglas Adams

To friends and family
for their support and inspiration.

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Wikström, A-K., Gunnarsdottir, J., Cnattingius, S. (2012) The Paternal Role in Preeclampsia and Giving Birth to Small for Gestational Age Infant. A Population-Based Cohort Study. *BMJ open*, 1(2): 3–4

II Gunnarsdottir, J., Stephansson, O., Cnattingius, S., Åkerud, H., Wikström, A-K. (2014) Risk of Placental Dysfunction Disorders after Prior Miscarriages: A Population-Based Study. *AJOG*, 211(1): 34.e1–34.e8.

III Gunnarsdottir, J., Cnattingius, S., Lundgren, M., Selling, K., Högberg, U., Wikström, A-K. Prenatal Exposure of Preeclampsia is Associated with Accelerated Height Gain in Early Childhood. *Submitted manuscript.*

IV Wikström, A-K., Gunnarsdottir, J., Nelander, M., Simic, M., Stephansson, O., Cnattingius, S. (2016) Prehypertension in Pregnancy and Risks of Small for Gestational Age Infant and Stillbirth. *Hypertension,* 67: 640–646.

V Gunnarsdottir, J., Högberg, U., Akhter, T., Cnattingius, S., Wikström, A-K. Elevated Diastolic Blood Pressure until Mid-Gestation is Associated with Preeclampsia and Small for Gestational Age. *Manuscript.*

Contents

Abbreviations and definitions

CVD	Cardiovascular disease
SGA	Small for gestational age
PCOS	Polycystic ovarian syndrome
HLA	Human leucocyte antigens
TGFβ	Transforming growth factor β
NK cell	Natural killer cell
KIR	Killer immunoglobulin-like receptors
VEGF	Vascular endothelial growth factor
sFlt-1s / VEGFR-1	Soluble VEGF receptor 1
RUPP	Reduced uterine perfusion pressure
PlGF	Placental growth factor
BP	Blood pressure
NO	Nitric oxide
sEng	Soluble endoglin
ICD	International Classification of Diseases
DBP	Diastolic blood pressure
HELLP	Hemolysis elevated liver enzymes low platelets
BMI	Body mass index
IVF	In vitro fertilization
SLE	Systemic lupus erythematosus
AGA	Appropriate for gestational age
LGA	Large for gestational age

Parity: Number of live births or stillbirths ≥ 22 gestational weeks.
Parous: Women with one or more previous births.
Primiparous: Women with no previous births (with or without prior miscarriages, legal abortions or extra-uterine pregnancies).
Placental dysfunction disorder: Placenta-related obstetric outcome. Defined as one of the following; preeclampsia, small for gestational age, stillbirth, placental abruption or spontaneous preterm births.
Preterm birth: Birth before 37 weeks of gestation.
Early-onset: Before 34 weeks of gestation.
Partner change: Two consecutive pregnancies with different fathers, according to personal identity numbers of registered fathers.
Self-reported prior miscarriages: Miscarriages that are reported by mothers during interviews with midwives at antenatal care.
Prenatal exposure: Relating to exposure during fetal life, before birth.
Offspring height gain: The gain in height (in cm) from birth to 5 years of age; length at birth subtracted from the height at 5 years.
Z-score: Standard deviation score that can be calculated by:
(Observed value – Mean) / Standard deviation.
Pre-hypertension: Systolic blood pressure 120 – 139 mm Hg and/or diastolic blood pressure 80 – 89 mm Hg.
Pre-gestational: Refers to something before the target pregnancy.
Early gestation: Defined as pregnancy before 20 weeks of gestation (Study IV) or before 16 weeks of gestation (Study V).
Mid-gestation: Defined as the period 20 – 25 gestational weeks.
Late gestation: Defined as the period 34 – 36 gestational weeks.

Introduction

Definition of Preeclampsia

Preeclampsia is a potentially deadly disease that can be described as a pregnancy-specific systematic disorder with symptoms related to a general vascular endothelial activation. The cause is still unknown, but the placenta seems to be a crucial component in the pathophysiology of the disease. Preeclampsia can be defined as a new onset of hypertension (≥140/90 mmHg) after gestational week 20 together with significant proteinuria (300mg/24 hours).[1, 2] The International Society of Hypertension in Pregnancy recently suggested that a clinical diagnosis is made even in the absence of proteinuria if organ-specific signs or symptoms are present with new onset of hypertension.[3] This advice is in line with national recommendations from Australia and New Zealand[4] as well as Canada.[5] However, proteinuria is still a required diagnostic criterion according to the British[6] and Swedish[7] national guidelines.

Organ-specific dysfunction may include:

- Renal insufficiency
- Liver involvement
- Neurological involvement
- Hematological complication
- Placental insufficiency

Risk Factors of Preeclampsia

Parity

Preeclampsia occurs more often in primiparous than in parous women. However, parous women whose previous pregnancies were complicated with preeclampsia are more likely to develop preeclampsia in later pregnancies than women with previously uncomplicated pregnancies. The highest risk of recurrence for preeclampsia is seen in women with severe or early-onset preeclampsia.[8, 9]

Placenta-related factors
Preeclampsia has been reported to occur in molar pregnancies and extra-uterine pregnancies.[10] The risk of preeclampsia is also increased in multiple pregnancies.[8]

Vascular predisposition
Preeclampsia and cardiovascular diseases[11] (CVD) share many risk factors, such as; family history of CVD, being born small for gestational age (SGA), advancing age, low socioeconomic status, obesity, hypertension, diabetes,[8, 12] renal disease,[9] and short adult height.[13] Paradoxically, smoking is protective against preeclampsia, while also increasing the risk of fetal growth restriction and stillbirth.[14] Auto-immune diseases[8, 15] and endocrine diseases such as polycystic ovarian syndrome (PCOS)[16] may also be risk factors for both preeclampsia[17] and CVD, although the evidence is somewhat less established.

Partners and inter-pregnancy interval
A short period of semen exposure before conception and a long interval between pregnancies are associated with increased risk of preeclampsia. Change of partners between pregnancies has also been associated with increased risk of preeclampsia.[18, 19] However, in later studies that account for inter-pregnancy interval, partner change instead seems to be a protective factor.[20, 21]

Key Elements of the Pathophysiology

- **Vascular predisposition:** Cardiovascular disease and preeclampsia share many risk factors, some of which are associated with dysfunction of the endothelium.[22]
- **The presence of a placenta:** The symptoms of preeclampsia are usually resolved soon after delivery and the birth of the placenta is essential for the woman's recovery.[10]
- **Utero-placental perfusion:** Preeclampsia-like symptoms can be induced in animals by decreasing the blood flow through the uterus.[23] Further, increased resistance in uterine arteries in early pregnancy can predict the onset of preeclampsia.[24]
- **Placenta-produced substances**: The preeclampsia disorder is associated with generalized endothelial activation, which seems to be mediated through placental production of toxic substances, hence its previous name, toxemia.[25, 26]

Abnormal Placenta Function

Abnormal implantation followed by incomplete spiral artery remodeling during placentation seems to be associated with preeclampsia. The abnormal placentation is thought to cause a high resistance in spiral arteries with negative effect on the utero-placental perfusion. Ischemia reperfusion may subsequently lead to cellular damage and a release of toxic substances.[27, 28] The maternal vasculature seems to respond to these toxic substances with a general endothelial activation that results in a symptomatic disease.[26, 29] Traditionally, the pathophysiology is described as a two-stage disorder with a preclinical and a clinical phase.[27] More steps have been introduced to this model of pathophysiology by professor Christopher Redman.[30] Five of these steps will be described below; from the preconception period to maternal vascular response.

Five Stages of Preeclampsia

1. **Preconception**

   Tolerance to paternal antigens may be important for successful implantation.[29] Preeclampsia is known to occur more often in first pregnancies, and a short duration of sexual relationship before pregnancy is shown to increase the risk of preeclampsia.[31] Seminal fluid is shown to contain human leucocyte antigens (HLA), as well as high amounts of transforming growth factor β (TGFβ), which may be important for the maternal T cell response to paternal antigens.[19, 29] Priming of seminal fluid may influence the differentiation of T cells towards the regulatory cells that are thought to be important for immune suppression and tolerance.[32, 33] Expansion of the pool of T regulatory cells before implantation may be crucial to avoid rejection of semi-allogeneic fetal tissue.[32] The amount of T regulatory cells present in the circulatory system is shown to be lower in preeclampsia, which could reflect a lack of immunological tolerance.[33]

2. **Implantation**

   During implantation, the conceptus penetrates the uterine epithelium and becomes embedded in the decidua.[34] As early as one week after fertilization, the edge of the conceptus consists of two populations of trophoblast cells, one which forms the syncytiotrohpoblast, and the other the cytotrophoblast (Figure 1).[34, 35] The syncytiotrophoblast successively loses its invasive capacity and forms a multinucleated syncytium that seems to have a secretory phenotype.[34] The cytotrophoblast further differentiates and invades through the de-

cidua.[35] A cross-talk between trophoblast and maternal cells (immune cells and decidua) seems to be important for trophoblast differentiation and angiogenesis.[34, 35] The principal ligands for T cell receptors, HLA-A and B, are not expressed in trophoblast cells, but this allows the semi-allogeneic fetal tissue to avoid cytotoxic attack by maternal T cells.[29] However, cytotrophoblast cells do express HLA-C and HLA-G, which is bound by natural killer cells (NK cells), the most abundant maternal immune cells in the decidua.[36] The killer immunoglobulin-like receptors (KIR) on NK cells bind to HLA-C on the trophoblast, but both molecules are polymorphic. The haplotype combination of maternal KIR and fetal HLA-C may be important to promote trophoblast invasion and angiogenesis. Maternal KIR AA genotype, together with a fetal HLA-C2 genotype, seems to be associated with preeclampsia.[18, 19, 29] The invasion and differentiation of the trophoblast is further influenced by a complex signaling network that involves both hormones, such as estrogen, as well as locally produced mediators, such as TGFβ, hypoxia-inducible factor (HIF-1α), leptin, and vascular endothelial growth factor (VEGF).[37, 38]

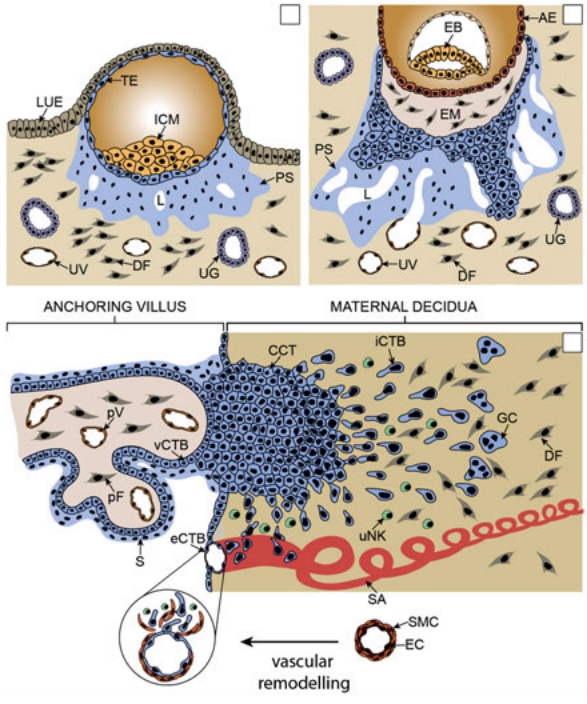

Figure 1. Implantation. CTB: Cytotrophoblast cells; S: Syncytium; uNK: uterine Natural Killer cells. This figure is re-printed with the permission of the publisher and the author and was originally published in Knöfler M, Pollheimer J. (2013). Front. Genet. 4:190. DOI: 10.3389/fgene.2013.00190.

3. Placentation

Implantation and placentation can be seen as a continuous process, but, traditionally, placentation has been described as the formation of an organ capable of transferring oxygen and nutrients between mother and fetus. During early placentation, the cytotrophoblast cells invade through the decidua and differentiate to form cells that can replace maternal endothelium in spiral arteries. Vascular remodeling of the spiral arteries then occurs, which transforms the vessels from being high resistance to low resistance vessels, rendering them capable of more blood flow (Figure 2).[10] The circulation and oxygen tension in the placenta gradually increases from gestational week eight,[28, 39] and the survival of the fetus is thought to depend on its protection against oxidative stress.[29] It has been hypothesized that severe disturbances of implantation may lead to a complete failure of early placentation and miscarriage.[39, 40] However, if the placentation failure is partial, the pregnancy might remain viable, but with an imbalance in angiogenic activity and an insufficient vascular remodeling.[28, 38]

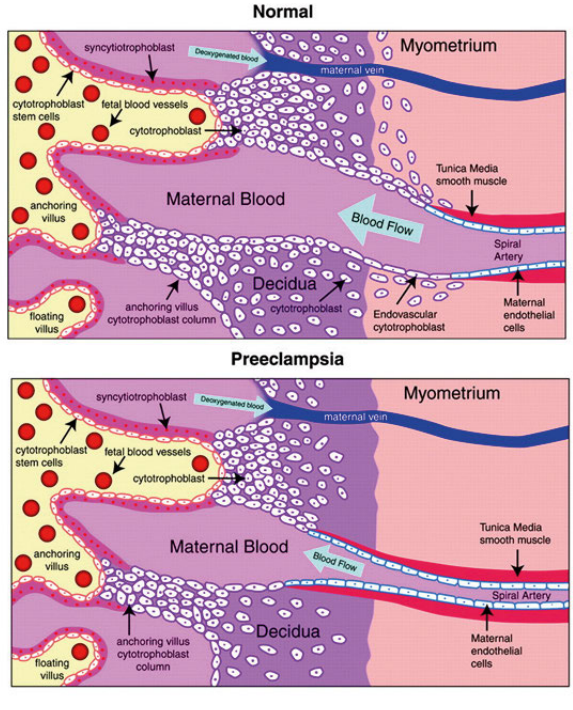

Figure 2. Spiral artery remodeling. This figure is re-printed with the permission of the publisher and the author. It was originally published in Lam C, Lim CH, Karumanchi SA. (2005). Hypertension. 46:5. DOI: 10.1161/01.HYP.0000187899.34379.b0.

4. **Placental damage**

   Partial failure of placentation with incomplete remodeling of the spiral arteries is thought to lead to ischemia re-perfusion injury in the placenta.[27] The oxidative stress that follows is accompanied by inflammatory response as well as cellular damage, which mainly affects the syncytium.[27, 29] An increase or decrease in placental production of various mediators, such as anti-angiogenic factors, may be the cellular response to this stress. The anti-angiogenic factor soluble VEGF receptor 1 (or sFlt-1) is shown to be higher in the serum of pregnant women who later develop preeclampsia compared with women who have uncomplicated pregnancies.[27] In a rat preeclampsia model, production of sFlt-1 is shown to be increased as a result of surgical reduction of uterine perfusion pressure (RUPP).[23, 41] The RUPP procedure (the clipping of the aorta and ovarian arteries) results in enough uterine perfusion for the survival of the pups, but their growth becomes restricted and maternal preeclampsia-like symptoms develop.[41] Although sFlt-1 expression is increased in response to hypoxia in the placenta, other stressors may also be involved.[27]

5. **Endothelial activation**

   Imbalance in pro- and anti-angiogenic factors is probably involved in the pathogenesis of preeclampsia before the onset of a clinical disorder.[10, 26, 42] VEGF has a vasodilatory effect and is thought to be important for maintaining the stability of endothelial function, particularly in the kidneys.[10] It is known that sFlt-1 binds to VEGF as well as placental growth factor (PlGF) in the circulation and blocks its effect on maternal endothelium. The angiogenic imbalance is thought to activate the endothelium and increase the vascular tonus, resulting in the clinical disorder, preeclampsia, which is characterized by hypertension and proteinuria.[10, 23, 26, 42] Although sFlt-1 provides a link between reduced utero-placental perfusion and later onset of symptomatic disorder, it should be noted that cellular damage in the placenta can also result in an increase in many other toxic substances.[10, 17, 27] Examples of such substances may include microvesicles[29] and fetal hemoglobin.[43]

Placental Dysfunction

The histologic evidence of abnormal placentation is central in the above hypothesis. In placental tissue taken from women whose pregnancies were complicated by preeclampsia, remodeling is seen in fewer spiral arteries compared with placentas from uncomplicated pregnancies.[44, 45]

Further, incomplete spiral artery remodeling may be more strongly associated with early- rather than late-onset preeclampsia.[46] It seems that the presence of trophoblast cells around and inside the spiral arteries is necessary for the remodeling of the vessels, because the muscular layer is thicker in spiral arteries without endovascular cytotrophoblast. Further, the presence of cytotrophoblast in the myometrium is seen to a lesser extent in preeclampsia, suggesting a shallower invasion.[47] Although this evidence is gathered after delivery, other studies suggest that remodeling of the spiral arteries already occurs early in pregnancy.[34, 48, 49] Therefore, it is concluded that a lack of cytotrophoblast invasion into the spiral arteries and myometrium may cause preeclampsia.[44] However, evidence of incomplete remodeling of the spiral arteries is also associated with other pregnancy complications, that is to say, fetal growth restriction, stillbirth, placental abruption, spontaneous preterm birth and miscarriages.[44, 45] These pregnancy complications are sometimes called placental dysfunction disorders, but other terms have also been used (e.g. the great obstetrical syndromes, disorders of deep placentation,[44] and placenta bed disorders[45]).

Utero-Placental Perfusion

Hypo-perfusion is the term used to describe a perfusion capacity that does not meet an organ's demand. The placenta provides oxygen and nutrients to a growing fetus and therefore fetal growth has been thought to reflect the placenta's function. Compared with uncomplicated pregnancies, preeclampsia is associated with fetal growth restriction and reduced utero-placental blood flow, which is estimated with Doppler ultrasound.[50] Women with increased uterine artery resistance in the first and second trimester have an increased risk of preeclampsia, especially early-onset (< 34 weeks)[24] or preterm (< 37 weeks) preeclampsia.[51, 52] Interestingly, the predictive value of uterine artery Doppler measurements is shown to be increased if it is combined with angiogenic markers.[24, 51, 52] With a 5% false-positive rate, the combination of uterine artery Doppler with mean arterial pressure and PlGF detects 65% of preterm (< 37 weeks) preeclampsia cases.[52] In conclusion, there is compelling evidence of abnormal placental function in preeclampsia, and placental hypo-perfusion may initiate a chain of events leading to a general endothelial activation.

Abnormal Vasomotor Function

Gestational Hemodynamic Adaptation

In normal pregnancy, the cardiovascular system undergoes adaptive hemodynamic changes that might facilitate utero-placental perfusion.[53] The plasma volume and cardiac output increases early in pregnancy, while the total peripheral resistance decreases.[54,53] Higher total peripheral resistance and reduced cardiac output in early pregnancy are seen in normotensive pregnancies with fetal growth restriction, compared with those without fetal growth restriction.[55] This is also seen in pregnancies with early-onset preeclampsia, but the insufficiency of hemodynamic adaptation may be more severe in preeclampsia than in normotensive pregnancies complicated with fetal growth restriction.[56, 57] During normal pregnancy, the blood pressure (BP) is known to decrease from early to mid-gestation (mid-gestational BP drop), and thereafter progressively increases to pre-gestational levels in late gestation.[58, 59] In women who later develop preeclampsia, the BP is higher from early pregnancy and increases faster than in women with uncomplicated pregnancies.[59, 60] In normotensive pregnancies, an increase in diastolic BP between gestational weeks 18 and 30 is also negatively associated with fetal growth.[61] The severity of placental dysfunction may therefore be related to the amount of change in vascular resistance and BP with increasing gestational age.

Dysfunctional Endothelium

Blood pressure and vascular resistance is mainly regulated though changes in the vessel diameter, which is accomplished by vasoconstriction or vasodilation. This vasomotor function is strongly dependent on the endothelium, because one important mediator of vasodilation, nitric oxide (NO), is produced in endothelial cells.[62] Endothelial dysfunction is a term for imbalance in endothelial-dependent vasomotor function. It can be measured by flow-mediated dilation, which is the change in vessel diameter in response to temporary occlusion of the brachial artery.[63, 64] Compared with uncomplicated pregnancies, preeclampsia seems to be associated with lower flow-mediated dilation from mid-gestation up to three years after delivery.[64-66] VEGF and hypoxia are examples of factors that can induce endothelium-dependent vasodilation through increased NO production in the endothelium. The stability of the endothelium may depend on VEGF and perhaps TGFβ.[66] During pregnancy, the production of sFlt-1 and endoglin (sEng) is increased, but, in women who later develop preeclampsia, the increase is

more pronounced and starts earlier.[63] VEGF-mediated vasodilation is blocked by sFlt-1, whereas sEng blocks the function of TGFβ, resulting in vasoconstriction and proteinuria.[66] However, sFlt-1 and sEng may not be the sole explanation for the disrupted endothelial and vasomotor function seen in preeclampsia. Preeclampsia-like disorder can also be induced in animals by chronic inhibition of NO[53] and by angiotensin receptor-activating antibodies.[66] Further, endothelium-dependent vasodilation, together with the renin-angiotensin-aldosterone pathway, may be involved in the physiological plasma volume expansion seen in early pregnancy.[53, 66] It is currently unknown whether endothelial dysfunction before conception can predict the onset of preeclampsia. However, risk factors related to preeclampsia, such as diabetes, are known to be associated with endothelial dysfunction.[22]

Association with Cardiovascular Diseases

Preeclampsia is associated with a later development of CVD,[67, 68] and family history of CVD is a recognized risk factor of preeclampsia.[12] Women who give birth to preterm or SGA infants are at increased risk of developing CVD later in life.[69] Recurrent miscarriages or stillbirths have also been linked to CVD in women later in life.[70] Thus, placental dysfunction disorders during pregnancy seem to be associated with increased risk of CVD in women later in life. Some possible explanations for this association are; a) shared risk factors, b) a subclinical vascular disease before conception that temporarily becomes symptomatic in relation to the hemodynamic stress of pregnancy, and c) permanent damage of endothelium or cardiovascular remodeling as a result of placental dysfunction.[71]

Prenatal Exposure

Developmental Origins of Health and Diseases (DOHaD)

The DOHaD concept describes how the early-life environment induces changes in the development of both a fetus and a child, which may have an impact on their future risk of diseases.[72] More than 20 years ago, Barker and colleagues reported an association between low birth weight and cardiovascular-related deaths.[73] Later studies from the same group suggest that childhood growth trajectory may modify the association between birth weight and CVD.[74, 75] It is proposed that undernutrition during critical periods of development may induce permanent physiological or metabolic changes, that later have an unfavorable effect upon

a mismatch in the nutritional environment.[76, 77] However, in a twin study, the association between birth weight and CVD was only found in dizygotic twin pairs but not monozygotic, suggesting that genetic factors may explain the association.[78] Recently, prenatal exposure to preeclampsia is shown to be associated with an increased risk of hypertension in young adults and is seen in children of all sizes at birth.[79] The risk of obesity also seems to be increased in offspring with prenatal exposure to preeclampsia, but this may be restricted to children of obese mothers.[79, 80]

Catch-up Growth

The growth of both fetuses and children can reflect the amount of nutrients they receive, but a failure to thrive may also be associated with maternal or childhood diseases. Accelerated growth during the first two years of life is usual in children who are born SGA. The majority of children born SGA, catch up in size with peers of the same age.[81] Children who do not catch up during the first two years often fail to reach their adult target height (determined by the parental height) and become short as adults.[82,83] The growth in height and weight during the first few years of life is highly correlated,[84] and although catch-up growth is traditionally defined by the change in height, the pattern of weight gain has also been studied.[85] Catch-up growth is usually defined by an increase in the standard deviation score (or Z-score) between two time points, but both the duration of the timespan and amount of change differs between studies.[86]

Postnatal Growth and Children's Health

Children's growth trajectories are studied in relation to their future cognitive function,[87] obesity[81, 86] and hypertension.[74, 88, 89] Although postnatal growth of children who are born SGA is intensively studied, the optimal growth trajectory seems hard to identify.[81, 88] An intermediate trajectory may be the most favorable pattern of growth, as growth that is too slow seems to be associated with lower cognitive function,[90] whereas growth that is too fast is associated with hypertension and being overweight.[81, 88] Accelerated weight gain before the age of 2 years seems to increase the risk of obesity in all birth-weight groups.[81, 86] Accelerated height gain in children between 8 and 13 years of age is associated with hypertension, independent of birth weight.[89] Therefore, both preeclampsia and an accelerated childhood growth trajectory may be associated with cardio-metabolic risks, irrespective of birth-weight group.

Aim

The objective was to increase the epidemiological knowledge regarding the occurrence of preeclampsia, and address the associations between blood pressure changes during pregnancy and fetal or postnatal growth.

The specific aims of the separate studies were as follows:

I To estimate associations between partner change and risks of preeclampsia and giving birth to an SGA infant.

II To study the association between number of prior miscarriages and risks of placental dysfunction disorders, including preeclampsia, stillbirth, birth of an SGA infant, placental abruption and spontaneous preterm birth.

III To study the association between prenatal exposure of preeclampsia and offspring's gain in height from birth until five years of age.

IV To estimate associations between pre-hypertension in late gestation and risks of SGA birth and stillbirth.

V To study the association between changes in diastolic blood pressure from early to mid-gestation and risks of preeclampsia as well as SGA birth.

Material and Methods

The studies were all designed as population-based cohort studies, with information sourced from large registers. The data collection was mainly prospective during antenatal care, at delivery and in child health care. Some of the variables were based on diagnostic codes according to the International Classification of Diseases [ICD], versions 9 (used during the period 1987–2010) and 10 (from the year 2011 and onwards).

Overview of the Studies

Table 1. *Population, exposure and outcome measures of the studies.*

Study		**Population**		**Exposure**		**Outcome**
No.	Data	Period	Total *N* [a]	Definition	*N* [b]	Definition
I	A	1990 − 2006	440,322	Partner change	30,400	Preeclampsia and SGA [c]
II	A	1995 − 2009	619,587	Self-reported miscarriages	83,418	Placental dysfunction [d]
III	B	2000 − 2007	23,763	Prenatal preeclampsia	865	Offspring height gain
IV	C	2008 − 2014	150,687	Pre-hypertension in late gestation	16,864	SGA and stillbirth
IV	C	2008 − 2014	64,607	Elevated BP from early to mid-gestation	18,056	Preeclampsia and SGA

[a] Number of women or children in the total population and [b] number of exposed.
[c] SGA: Small for gestational age. [d] Placental dysfunction disorders including preeclampsia, stillbirth, SGA, placental abruption and spontaneous preterm birth.
A) Swedish Medical Birth Register
B) Uppsala Mother and Child Database
C) Stockholm - Gotland Obstetric Database

Data sources

Swedish Medical Birth Register

The Swedish Medical Birth Register contains data on more than 98% of all births in Sweden since 1973. These include data on maternal demographics, reproductive history, and complications during pregnancy, delivery and the neonatal period. In Sweden, antenatal care is standardized, free of charge and home deliveries are rare. Information on the maternal medical and obstetric history is collected with an interview during the first antenatal visit, which usually takes place at the end of the first trimester. Maternal characteristics, such as weight, height and smoking habits, are also recorded. After delivery, the responsible doctor records each woman's diseases and complications during pregnancy and delivery, according to the appropriate ICD codes. Standardized information about the pregnancy and delivery is thereafter forwarded to the Birth Register. Individual record linkage between the Birth Register and Registers of Total Population and Education was made possible by matching personal identity numbers, which are uniquely assigned to each Swedish resident at birth or at immigration.[91]

Uppsala Mother and Child Database

The Uppsala County mother and child database includes children who were born during the years 2000–2007 and who were registered in Child Health Care in Uppsala County. The Uppsala County Child Health Register includes information collected from visits to child health care units, starting at one week of age and ending at six years. Attendance at child health care services in Uppsala County is high, where 97% of children have at least six registered visits.[92] Parents are interviewed about the breastfeeding of the child. The child's height and weight are measured at 18 months, and 3, 4, and 5 years. The database was created by linking the Swedish Medical Birth Register, the Uppsala County Child Health Register, the Register of Total Population and the Register of Education. Individual record linkage was enabled by matching each personal identity number.[91]

Stockholm-Gotland Obstetric Database

The Stockholm-Gotland database includes information, from 2008 onwards, which is forwarded daily from the medical record system used in the Stockholm-Gotland region for all antenatal, delivery and postnatal care units. During the first antenatal visit the mother is interviewed

about her medical and reproductive history and smoking habits. The mother's BP and weight are measured and recorded, while information on maternal height is self-reported. BP is thereafter re-measured and recorded at each antenatal visit. The antenatal visits are standardized to around gestational weeks 10 (first visit), 25 (second visit), and thereafter every second week in primiparous women, and every third week in parous women, until delivery. The database includes BP measurements from both outpatient and hospital care.

Study Populations and Exposures

Study I

The study included women in Sweden with two consecutive singleton pregnancies, during the period 1990–2006, that resulted in live births at 22 weeks of gestation or later. Women with chronic hypertension or pre-gestational diabetes in either pregnancy (*n*=5797) were excluded. The exposure variable was defined as a change of partners between pregnancies, identified by making a comparison of the fathers' personal identity numbers. Pregnancies with missing data on fathers were excluded (first pregnancies *n*=4206 and second pregnancies *n*=1931). The final number of women in the population was 440,322. The number of women who had a different partner in their second pregnancy was 30,400 (6.9%).

Study II

The study included women in Sweden who gave birth to their first singleton infant at 22 weeks of gestation or later during the period 1995–2009. The exposure variable was defined as the number of self-reported prior miscarriages, recorded by the midwife at the first antenatal visit. The number of miscarriages was categorized into no prior miscarriage (*n*=536,169), one miscarriage (*n*=68,185), two miscarriages (*n*=11,410), and three or more miscarriages (*n*=3,823). The number of women in the population was 619,587 and the total number of exposed women was 83,418 (13.5%).

Study III

The study population included children born in Uppsala County during the period 2000–2007 who had a registered height at five years of age. The exposure variable was defined as prenatal exposure to preeclampsia

that had been identified through maternal ICD codes (see definition below). Because some misclassification between preeclampsia and gestational hypertension was suspected, infants with prenatal exposure of gestational hypertension were excluded (*n*=445). The final number of children in the population was 23,763. The number of children exposed to prenatal preeclampsia was 865 (3.6%). Of those 865 children, 179 were exposed to severe preeclampsia and 686 to mild preeclampsia.

Study IV

The study included women without hypertensive disorders (before or during pregnancy) in Stockholm or Gotland who gave birth to a singleton at 37 completed gestational weeks or later, during the period 2008–2014 (*n*=157,446). The main exposure variable was pre-hypertension in late gestation, defined as a diastolic blood pressure (DBP) of 80–89 mm Hg at the last recorded measurement before 37 weeks (gestational weeks 34 to 36). Consequently, DBP below 80 mm Hg was defined as normotension. Pre-hypertension was also investigated in relation to BP changes from early gestation (before 20 weeks of gestation) to late gestation. Women were categorized into: 1) normotensive in late-gestation and less than 15 mm Hg rise in DBP between early and late gestation; 2) normotensive and at least 15 mmHg rise; 3) pre-hypertensive and less than a 15 mm Hg rise; and 4) pre-hypertensive and at least 15 mm Hg rise. The population and missing data are described in a flow chart (Figure 3).

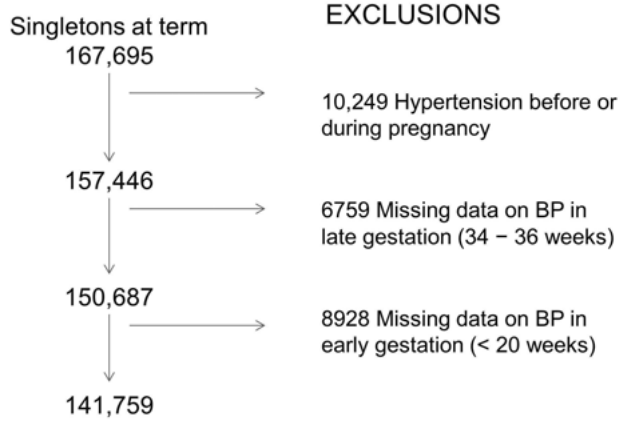

Figure 3: Flow chart of the population in Study IV. Hypertension was defined by a hypertensive medication, blood pressure (BP) > 140/90 mm Hg on two occasions or once > 160/110 mm Hg or hypertensive disorders according to diagnostic codes.

Study V

The population was defined as healthy women who gave birth to their first infant during the period 2008–2014 in Stockholm or Gotland counties. Women with suspected vascular disease (*n*=2,538), defined as chronic hypertension or proteinuria before 20 weeks of gestation or pre-gestational diabetes, were excluded (Figure 4). Ten women who developed preeclampsia before 26 weeks of gestation were also excluded. The main exposure was the change in DBP from early gestation (before gestational week 16) until mid-gestation (from gestational weeks 20 and 25). The change in DBP was categorized into; 1) lowered DBP (change < -2 mm Hg), 2) unchanged DBP (change -2 to +2 mm Hg), and 3) elevated DBP (> 2 mm Hg). The final number of women in the population was 64,607 (Figure 4).

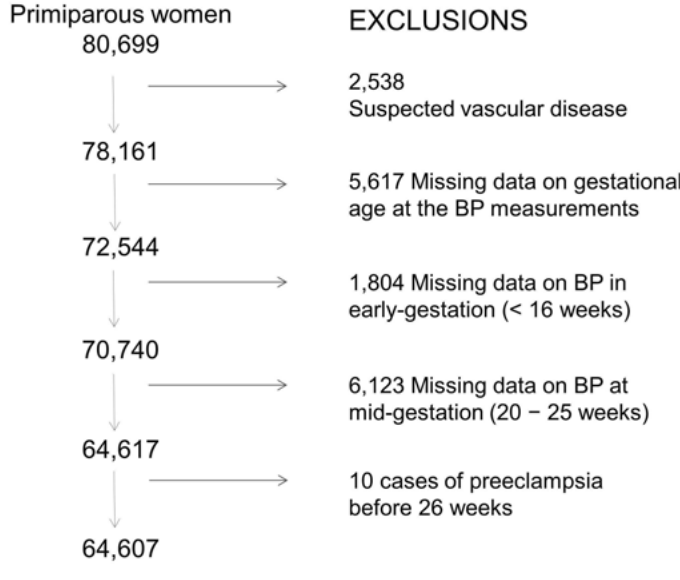

Figure 4. Flow chart of the population in Study V. Suspected vascular disease was defined as: *chronic hypertension* as blood pressure (BP) > 140/90 mm Hg at the first antenatal visit or chronic hypertension according to check-box or a corresponding diagnostic code after delivery; *proteinuria* before 20 gestational weeks (2+ on dipstick or 1+ on two consecutive occasions); or *pre-gestational diabetes* as registered in check-box or a corresponding diagnostic code.

Definition of Outcomes

Preeclampsia

Preeclampsia was defined through the following diagnostic codes: ICD-9 codes 642E–G; and ICD-10 codes O14–O15. Further, severe preeclampsia was defined by O14.1 (severe preeclampsia), O14.2 (HELLP-syndrome), or O15 (eclampsia), whereas mild preeclampsia was defined by O14.0 and O14.9. During the study period the clinical definition of preeclampsia was hypertension (BP ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic) combined with proteinuria (≥ 0.3 g/24 hours or +1 or more on dipstick on at least two occasions) after 20 gestational weeks. The clinical definition of HELLP was elevated transaminases and platelets below 100 $x10^9$ L accompanied by evidence of hemolysis. Eclampsia was defined by generalized convulsions during pregnancy, delivery or the early post-partum period. According to the Swedish national guidelines on preeclampsia, proteinuria is a recommended criterion for clinical diagnosis. However, HELLP and eclampsia are regarded as uncommon and serious complications of preeclampsia, and proteinuria is not obligatory for diagnosis.[7] When the criteria for preeclampsia above are used as a golden standard and patient data are reviewed retrospectively, the positive predictive value of preeclampsia diagnosis in Nordic Birth Registers is found to be 80–90%.[93-95]

Small for Gestational Age

Being born SGA can be used as a proxy for fetal growth restriction. Birth weight was standardized to gestational age, to account for the effect of gestational age on birth weight. Gestational age was generally determined by an early-second-trimester ultrasound. In Sweden, SGA is usually defined as a birth weight that is more than two standard deviations below the population mean weight for gestational age. This definition was used in Studies II and IV–V, and the fetal growth curve reference used was produced from repeated estimates of fetal growth by ultrasound.[96] Internationally, SGA is often defined as a birth weight for gestational age below the 10^{th} percentile according to population standards. This definition was used in Studies I and III. The population standard used in Study III was a reference growth curve produced from measurements of birth weights for gestational age and postnatal growth.[97]

Preterm Preeclampsia and SGA

If preeclampsia or SGA were present in combination with a birth before 37 weeks of gestation, these outcomes were defined as preterm.

Stillbirth

Before July 1st 2008, stillbirth was defined as antepartal or intrapartal deaths at 28 weeks of gestation or later, but from July 1st 2008 and onwards the definition of stillbirth included deaths from 22 gestational weeks and later. The first definition was applied in Study II, whereas the latter was applied in Study IV.

Placental Abruption

Placental abruption was defined through the following diagnostic codes: ICD-9 code 641C; and ICD-10 code O45.

Spontaneous Preterm Birth

Spontaneous preterm birth was defined as a birth before 37 gestational weeks with a spontaneous onset. The responsible midwife recorded the type of delivery using one of the following check-boxes; spontaneous labour, induced labour, or caesarean section. All deliveries with a diagnostic code of preterm premature rupture of the membranes (ICD-9 code 658B; and ICD-10 code O42) were also defined as a spontaneous onset. Spontaneous preterm births were categorized into very preterm births (before 32 weeks of gestation) and moderately preterm births (from 32 to 36 full weeks of gestation).

Height Gain in Early Childhood

Height gain (cm) during early childhood was defined as the growth in height from birth to five years of age. Height gain was estimated by subtracting length at birth from the height at 5 years of age. Children's growth was further described by comparing Z-scores of height at birth, 18 months, and 3, 4 and 5 years, calculated with population means and standard deviations in each age group according to Swedish standardized growth curves.[97, 98]

Covariates

The other covariates that were used in the studies are listed below and defined briefly. These covariates were considered possible confounders in the associations (Figure 5).

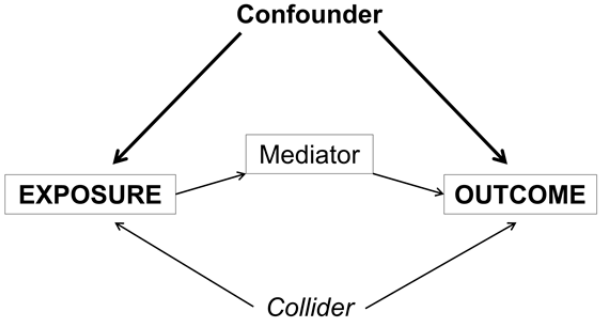

Figure 5. Definition of covariates associated with both exposure and outcomes as confounders, mediators and colliders.

Maternal covariates used in all the studies:

- **Age:** Registered at the delivery.
- **Height:** Usually self-reported at antenatal care.
- **Body mass index (BMI):** Weight (kg) / height^2 (m), according to the weight measured at the first antenatal visit (early-pregnancy). Categorized as underweight <18.5, normal weight 18.5–24.9, overweight 25.0–29.9, and obese ≥30.0.
- **Smoking habits:** Information on smoking in early pregnancy was collected at the first antenatal visit, registered in the following categories; no smoking, 0–10 cigarettes, and >10 cigarettes per day.

Studies II and V were restricted to primiparous, whereas the parity was adjusted for in Studies III and IV. Maternal diseases were defined by midwives' recordings at the first antenatal visit (by marking ticks in pre-defined check-boxes) or doctors' diagnostic codes at delivery (ICD). Adjustments for maternal diseases and the number of socioeconomic covariates used were defined slightly differently between studies.

Definition of maternal diseases

- **Chronic hypertension:** History of hypertension before pregnancy check-box ticked; or ICD-9 codes 642A–C and ICD-10 codes I10–15 (Studies I–II) and O10–11 (Studies I–V); or ongoing BP medication at the first ante-natal visit (Study IV); or blood pressure >140/90 before gestational week 20 (Studies IV–V).

- **Gestational hypertension:** New onset of hypertension after 20 gestational weeks without significant proteinuria, defined by the ICD-code O13 (Study III).
- **Pre-gestational diabetes:** Diabetes mellitus before pregnancy check-box ticked (Study I); or ICD-9 codes 648A and 250 (Study II) and ICD-10 codes E10–E14 and O240–O243 (Studies II–III); or less stringent with check-box ticked; or ICD-10 codes O240 and O243 (Studies IV–V).
- **Gestational diabetes:** Diabetes during pregnancy ICD-10 code O244 (Studies III–IV) and O249 (Study III).
- **Involuntary childlessness:** Self-reported at antenatal care as years of involuntary childlessness (Study I).
- **In vitro fertilization (IVF):** Self-reported at antenatal care defined as assisted reproduction and registered in a check-box (Study II).
- **Hypothyroidism:** ICD-9 code 244; ICD-10 code E03 (Study II).
- **Systemic lupus erythematosus (SLE):** Check-box ticked; or ICD-9 code 710A and ICD-10 code M32 (Study II).

Socioeconomic covariates

- **Country of birth:** Information from the Register of Total Population (Studies I–III and Study V).
- **Level of education:** Information on the number of years of formal education from the Register of Education (Studies I–III).
- **Cohabitation with partner:** Self-reported at antenatal care to define whether women were living with partners (Studies IV–V).

Other covariates

- **Inter-pregnancy interva**l: Number of whole years from the birth of the first infant to the estimated conception of the second infant (Study I).
- **Fetal sex:** Registered at delivery as girls and boys (Studies I–III).
- **Year of birth:** Registered year at delivery (Studies I–II).
- **Breastfeeding:** Exclusive or partial breastfeeding at 6 months of age. Information collected at child health care (Study III).

The methods used to choose covariates for the final models also differed between studies. Previous studies were used as a framework for the choice of covariates in Studies I and IV, with some adjustments related to the availability of information. Possible confounders were listed in Study II and backwards elimination (manual) was used. A directed acyclic graph (DAG) was built in Studies III and V, and used as a framework for choosing covariates.

Statistical Methods

Study I

The effects of partner change on risks of term and preterm preeclampsia and giving birth to an SGA infant in a second pregnancy were calculated for both women with and without corresponding pregnancy complication in a first pregnancy. When the risk of SGA infant in second pregnancy was calculated, only live births and pregnancies without preeclampsia were included. Odds ratios (OR) with 95% confidence intervals (CI) were estimated by multiple logistic regression analysis after adjustments were made for maternal characteristics at the second pregnancy. Adjustments were made for inter-pregnancy interval, maternal age, height, early-pregnancy BMI, smoking habits, years of involuntary childlessness, country of birth, and level of education. Further, adjustments were made for the year of second birth (categorized into before 1997 and 1997 or later). The impact of partner change on the risk of preeclampsia and SGA was hypothesized to depend on the presence of the corresponding complication in prior pregnancy. Therefore, an interaction analysis was performed between preeclampsia in the first pregnancy (in three categories: no preeclampsia; term preeclampsia; and preterm preeclampsia) and partner change (same versus different partner) on risks of term and preterm preeclampsia in the second pregnancy. Further, an interaction analysis was performed between SGA in the first pregnancy (no/yes) and partner change on risk of SGA in second pregnancy. The analysis was performed using the Statistical Analysis Software package, V.9.1 (SAS Institute Inc., Cary, North Carolina, USA).

Study II

The associations between one, two, and three or more prior miscarriages and the risks of preeclampsia, stillbirth, SGA, placental abruption and spontaneous preterm birth (placental dysfunction disorders) were estimated, using women with no prior miscarriage as reference. ORs with 95% CI were estimated by logistic regression analysis with adjustments for maternal age, early-pregnancy BMI, height, smoking habits, chronic hypertension, pre-gestational diabetes, in vitro fertilization, hypothyroidism, systemic lupus erythematosus, country of birth, level of education, fetal sex, and year of birth (categorized into years 1995–1999, 2000–2004 and 2005–2009). As the causes of miscarriages may vary with maternal age, the maternal age was considered as an effect-modifier in the association between miscarriages and outcomes. Therefore, cross-product terms between age and miscarriages as categorical

variables were introduced into the regression models. This showed no effect modification relating to the outcomes. All analyses were performed using the Statistical Analysis Software package, version 9.2 (SAS Institute, Inc., Cary, NC).

Study III

Mean height gain (cm) in the first five years of life was calculated for children prenatally exposed and unexposed to preeclampsia, and the difference in means between groups was estimated by *t*-test. The association between preeclampsia and height gain was also estimated in a stratified analysis by birth weight for gestational age in three groups, defined by the 10^{th} and 90^{th} percentiles; SGA, appropriate for gestational age (AGA), and large for gestational age (LGA). In each stratum, mean height gain was calculated for term-born children who were exposed and unexposed to preeclampsia. Adjusted analyses on height gain were performed using multiple linear regressions with adjustments in two steps. Model 1 included; parity, maternal age, height, smoking habits, country of birth, level of education, and infant's sex. To account for possible genetic confounding of the metabolic syndrome the following covariates were added in a second model; maternal early-pregnancy BMI and diabetes, breastfeeding at 6 months, and child's BMI at 5 years. This analysis was also repeated for children exposed to severe and mild preeclampsia separately. Sensitivity analysis was completed by restricting the analysis to term-born children. Z-scores were used to visualize children's height gain from birth to five years of age. Z-scores at different ages were calculated using population means and standard deviations in boys and girls separately, and, at birth, the Z-scores were further standardized to gestational week at birth. Mean Z-scores of height with 95% CI were calculated at each time point in children exposed to severe and mild preeclampsia and in unexposed children and line graphs were created. SPSS software (version 22, IBM Corp., Armonk, NY) was used for the analysis.

Study IV

The associations were estimated between DBP in late gestation and risks of an SGA birth or a stillbirth at 37 completed gestational weeks or later. ORs with 95% CIs were calculated, using SAS PROC GENMOD. Adjustments were made for maternal parity, age, height, early-pregnancy BMI, smoking habits, pre-gestational or gestational diabetes, and cohabitation with partner. To estimate risks of SGA birth and stillbirth by DBP in late gestation, DBP values were dichotomized into normo- and pre-hypertension, using normotension as reference

group. DBP values were also categorized into 6 groups (as in Figure 7) and 60–64 mm Hg was used as reference group. To estimate the association between rise in DBP from early to late gestation and SGA birth and stillbirth, the risk increase associated with the change in DBP as a continuous variable was analyzed. Further, normotensive and pre-hypertensive women were stratified into 2 groups each, depending on the rise in DBP from early to late gestation of less than or at least 15 mm Hg. The reference group used in this analysis was normotensive women with a less than 15 mm Hg rise in DBP. All analysis was performed using Statistical Analysis Software version 9.4 (SAS Institute Inc., Cary, NC).

Study V

The risks of preeclampsia and SGA were calculated for women with unchanged DBP (change -2 to +2 mm Hg) and elevated DBP (> 2 mm Hg) between early and mid-gestation, with lowered DBP (change < -2 mm Hg) as the reference category. ORs with 95% CIs were calculated using logistic regression analysis. Adjustments were made for maternal age, height, early-pregnancy BMI, smoking habits, country of birth, and cohabitation with partner. The analysis was repeated for SGA without women who developed preeclampsia. Further, the risk of preterm (< 37 weeks at delivery) preeclampsia and SGA was estimated in a separate analysis. Interactions between early-gestation DBP and change in DBP from early to mid-gestation on the outcomes were investigated by introducing a cross-product term between these categorical variables in the regression model, where early-gestation DBP was categorized into low (<70 mm Hg; reference category), intermediate (70–79 mm Hg) and pre-hypertensive (80–89 mm Hg). Stratified analyses were performed on the change in DBP from early to mid-gestation by strata of early-gestation DBP. The risks of preeclampsia and SGA were calculated in each stratum of early-gestation DBP (low, intermediate and pre-hypertensive) for women with unchanged and elevated diastolic BP from early to mid-gestation, with lowered diastolic BP as the reference category with the same adjustments as previously described. All analysis was performed using Statistical Analysis Software version 9.3 (SAS Institute, Inc., Cary, NC).

Ethical Considerations

In each Register database the personal identity numbers were re-coded to serial numbers to protect the identity of the women and children during the analysis. Applications for Register linkages were sent to the relevant Swedish authorities but researchers did not at any time have direct access to the personal identity numbers. Therefore, informed consent by each person involved was not needed. However, the aims and designs of each study were approved by the respective Regional Ethical Review Boards.

Results

Study I

Women who changed partners had longer inter-pregnancy intervals than women who did not. Compared with women who did not change partners, women who changed partner were more often younger than 25 years or older than 35 years and slightly more often had a BMI of over 25. Further, women who changed partners were more often smokers or born in a Nordic country and they had slightly lower education levels than women who did not change partners. Finally, in women who changed partners, involuntary childlessness for at least one year was more frequent than in women who did not.

The rates of term and preterm preeclampsia in the second pregnancy were 1.4% and 0.4% in women who changed partners, whereas the corresponding rates in women who did not change partners were lower, at 1.2% and 0.2%, respectively. The rate of SGA in the second pregnancy was 8.2% in women who changed partners, but 5.9% in women who did not. However, when years of inter-pregnancy interval were accounted for, no risk increase of preeclampsia in the second pregnancy was seen with change of partner between pregnancies. Preeclampsia and SGA in the first pregnancy modified the effect of partner change on the risks of preeclampsia and SGA in the second pregnancy. Among women with preterm preeclampsia in the first pregnancy, partner change was associated with a protective effect for recurrence of preterm preeclampsia (Table 2). Partner change was also associated with a protective effect of recurrence of SGA birth (Table 3). In contrast, in women without SGA in the first birth, partner change was associated with an increased risk of SGA in the second pregnancy.

Table 2. *Risks of term (≥ 37 weeks) and preterm (< 37 weeks) pre-eclampsia in a second pregnancy by change of partner between pregnancies.*

Preeclampsia		**Term preeclampsia in second pregnancy**			
1st pregnancy	Partner	*n*	%	Crude OR	Adjusted OR
No	Same	3362	0.9	Reference	Reference
	Different	340	1.2	1.4 (1.2 – 1.5)	1.0 (0.8 – 1.1)
Term	Same	1142	9.9	Reference	Reference
	Different	67	9.2	0.9 (0.7 – 1.2)	1.0 (0.7 – 1.4)
Preterm	Same	275	14.2	Reference	Reference
	Different	10	8.3	0.5 (0.3 – 1.1)	0.8 (0.4 – 1.8)
Preeclampsia					
1st pregnancy		**Preterm preeclampsia in second pregnancy**			
No	Same	669	0.2	Reference	Reference
	Different	113	0.4	2.3 (1.9 – 2.8)	1.2 (0.9 – 1.6)
Term	Same	149	1.3	Reference	Reference
	Different	14	1.9	1.5 (0.9 – 2.6)	0.9 (0.4 – 2.0)
Preterm	Same	140	7.2	Reference	Reference
	Different	6	5.0	0.7 (0.3 – 1.6)	0.2 (0.1 – 0.9)

OR, Odds ratios calculated with 95% Confidence intervals. Adjustments were made for inter-pregnancy interval, maternal age, height, body mass index and smoking habits early in second pregnancy, years of involuntary childlessness before second pregnancy, country of birth and level of formal education, and year of second birth.

Table 3. *Risk of giving birth to small-for-gestational-age (SGA) infants in second pregnancy by change of partner between pregnancies, when excluding first and second pregnancies with preeclampsia.*

SGA		**SGA in second pregnancy**			
1st pregnancy	Partner	*n*	%	Crude OR	Adjusted OR
NO	Same	13,556	4.0	Reference	Reference
	Different	1539	6.2	1.6 (1.5 – 1.7)	1.2 (1.1 – 1.2)
YES	Same	9428	20.4	Reference	Reference
	Different	809	20.1	1.0 (0.9 – 1.1)	0.8 (0.7 – 0.8)

OR, Odds ratios calculated with 95% Confidence intervals. Adjustments were made for inter-pregnancy interval, maternal age, height, body mass index and smoking habits early in second pregnancy, years of involuntary childlessness before second pregnancy, country of birth and level of formal education, and year of second birth.

Study II

Compared to women with no prior miscarriage, women with prior miscarriages were older, had a higher BMI and were more often smokers. Further, women with prior miscarriages were slightly more often born in a Nordic country and had shorter duration of education than women with no prior miscarriages. Finally, women with prior miscarriages were more often pregnant after IVF treatment, and were more likely than women with no prior miscarriages to have chronic hypertension, pre-gestational diabetes, hypothyroidism and SLE.

Compared to women with no prior miscarriage, women with one prior miscarriage had almost no increased risks of preeclampsia, stillbirth or birth of SGA infants, placental abruption or spontaneous preterm births. Women with two prior miscarriages had increased risks of spontaneous preterm birth, birth of preterm (< 37 weeks) SGA infants, and placental abruption. The rates of all placental dysfunction disorders were higher in women with three or more prior miscarriages than in women without prior miscarriages: preeclampsia, 5.8% versus 4.3%; stillbirth, 0.7% versus 0.3%; SGA infant, 5.1% versus 3.2%; placental abruption, 0.8% versus 0.4%; and spontaneous preterm birth, 6.5% versus 4.4%. In women with three or more prior miscarriages, the risk of preterm preeclampsia and SGA was increased, compared to women without prior miscarriages (Table 4). In women with three or more prior miscarriages, the risk for preterm stillbirth and placental abruption was also increased, with an adjusted odds ratio (AOR) of 2.3 (95% CI: 1.2 – 4.1) for preterm stillbirth and 2.2 (95% CI: 1.4 – 3.6) for preterm abruption (results not shown in a table). The risk of spontaneous preterm birth increased with number of miscarriages in a dose-response pattern. The rates of spontaneous preterm births in women with no prior miscarriage, and one, two and three or more prior miscarriages, was 4.4%, 4.5%, 5.1%, and 6.5%, respectively. The association seemed strongest between three or more prior miscarriages and very preterm (birth before 32 weeks) birth (Table 5).

Table 4. *Risks of preeclampsia and SGA, subdivided into preterm (< 37 weeks) and (≥ 37weeks), by number of prior miscarriages.*

Prior miscarriages	Preterm preeclampsia			Term preeclampsia		
	n	%	aOR (95% CI)	*n*	%	aOR (95% CI)
No	5095	1.0	Reference	17,820	3.3	Reference
Yes						
1	665	1.0	1.0 (0.9 – 1.1)	2324	3.4	1.0 (0.9 – 1.0)
2	123	1.1	1.1 (0.9 – 1.3)	378	3.3	0.9 (0.8 – 1.0)
≥3	67	1.8	1.6 (1.2 – 2.1)	156	4.1	1.2 (1.0 – 1.4)
Prior miscarriages	**Preterm SGA**[a]			**Term SGA**[a]		
	n	%	aOR (95% CI)	*n*	%	aOR (95% CI)
No	3468	0.7	Reference	13,651	2.6	Reference
Yes						
1	504	0.7	1.1 (1.0 – 1.2)	1,737	2.6	1.0 (0.9 – 1.0)
2	113	1.0	1.3 (1.1 – 1.6)	311	2.8	1.0 (0.9 – 1.1)
≥3	68	1.8	2.2 (1.7 – 2.9)	124	3.3	1.2 (1.0 – 1.5)

aOR, Adjusted odds ratio, CI, Confidence Interval. [a] SGA defined as a live birth infant with a birth weight for gestational age >2 SD below the sex-specific Swedish-specific growth curve (total population when calculating risks of SGA was 615,130).
Adjustments were made for maternal age, height, body mass index, smoking habits, chronic hypertension, pre-gestational diabetes, in vitro fertilization, hypothyroidism, and systemic lupus erythematosis, country of birth and level of education, and fetal sex and year of birth.

Table 5. *Risk of spontaneous preterm birth, subdivided into very preterm (< 32 weeks) and moderately preterm (32–36 weeks), by number of prior miscarriages.*

Prior miscarriages	Very preterm (< 32 weeks)			Moderately preterm (32 – 36 weeks)		
	n	%	aOR (95% CI)	*n*	%	aOR (95% CI)
No	2321	0.5	Reference	20,417	4.0	Reference
Yes						
1	356	0.5	1.3 (1.1 – 1.5)	2573	3.9	1.0 (1.0 – 1.1)
2	87	0.8	1.8 (1.5 – 2.3)	465	4.3	1.1 (1.0 – 1.2)
≥3	44	1.2	2.6 (1.9 – 3.6)	188	5.2	1.4 (1.2 – 1.6)

aOR, Adjusted odds ratio, CI, Confidence Interval. Spontaneous preterm birth defined as a birth before 37 gestational weeks with a spontaneous onset, including preterm premature rupture of the membranes. SGA births were excluded (total population when calculating risks of spontaneous preterm births was 596,659).
Adjustments were made for maternal age, height, body mass index, smoking habits, chronic hypertension, pre-gestational diabetes, in vitro fertilization, hypothyroidism, and systemic lupus erythematosis, country of birth and level of education, fetal sex and year of birth.

Study III

In pregnancies complicated with preeclampsia, the mothers were more often primiparous and the maternal BMI was higher than in pregnancies without preeclampsia, whereas maternal height was similar. Maternal pre-gestational and gestational diabetes was more common in pregnancies complicated with preeclampsia than in those without preeclampsia.

Children prenatally exposed to preeclampsia seemed less often breastfed at the age of six months than unexposed children. Further, children exposed to preeclampsia were more often born SGA than unexposed, especially those exposed to severe preeclampsia. Among children exposed to severe preeclampsia, 63.1% were born preterm and they were, on average, shorter at birth than unexposed children. Among children exposed to mild preeclampsia, only 12.1% were born preterm and they were only slightly shorter at birth than unexposed. The BMI at the age of 5 did not differ between groups.

Among term-born (≥ 37 weeks) children, those prenatally exposed to preeclampsia were born shorter, but were taller at five years (Table 6). Further, among term-born children, the mean height gain was 1 cm more in exposed than in unexposed, with an adjusted estimate of 1.0 cm (95% CI 0.6 – 1.3 cm) (Table 7). The difference was even more pronounced when the exposure was restricted to severe preeclampsia, at 1.5 cm (0.4 – 2.7 cm). In stratified analyses, preeclampsia was associated with accelerated height gain during the first five years in term-born children of all birth weights for gestational age (Table 6).

Table 6. *Height and height gain in children born at term (> 37 weeks) exposed and unexposed to preeclampsia.*

	Preeclampsia				
	YES		**NO**		**Mean difference**
	n	Mean cm	*n*	Mean cm	cm with 95% CI
Length at birth	667	50.5	21,595	51.5	-0.6 (-0.8 – -0.5)
Height at 5 year	669	112.2	21,663	111.6	0.6 (0.3 – 0.9)
Height gain	667	61.7	21,592	60.5	1.2 (0.9 – 1.5)
Height gain - *stratified on birth weight for gestational age*					
SGA [a]	117	62.1	2067	60.6	1.5 (0.7 – 2.3)
AGA [a]	482	61.5	17,292	60.5	1.1 (0.7 – 1.5)
LGA [a]	67	62.2	2168	60.5	1.7 (0.7 – 2.7)

CI; Confidence interval. [a] Small for gestational age (SGA) defined by standardized birthweight for gestational age lower than the 10th percentile, appropriate for gestational age (AGA) at the 10th – 90th percentile, and large for gestational age (LGA) higher than 90th percentile, according to the Swedish sex-specific fetal growth curve.

Table 7. *The mean difference in height gain between children exposed and unexposed to preeclampsia (severe and mild combined, and below as separate groups vs. unexposed).*

	Difference in height gain in cm (95% CI)		
	Crude estimate	Adjusted model 1 [a]	Adjusted model 2 [b]
All children	1.9 (1.6 – 2.1)	1.8 (1.5 – 2.0)	1.7 (1.4 – 2.0)
Mild preeclampsia	1.3 (1.0 – 1.6)	1.1 (0.8 – 1.4)	1.1 (0.7 – 1.4)
Severe preeclampsia	4.4 (3.7 – 5.0)	4.6 (3.9 – 5.2)	4.5 (3.8 – 5.3)
Term-born children [c]	1.2 (0.9 – 1.5)	1.0 (0.7 – 1.3)	1.0 (0.6 – 1.3)
Mild preeclampsia	1.2 (0.8 – 1.5)	0.9 (0.6 – 1.3)	0.9 (0.6 – 1.3)
Severe preeclampsia	1.9 (0.9 – 2.9)	1.8 (0.8 – 2.8)	1.5 (0.4 – 2.7)

[a] Model 1: Adjusted for maternal parity, age, height, smoking habits, country of birth, level of education and child's sex. [b] Model 2: Adjusted for covariates as in model 1 and maternal body mass index (BMI), diabetes, infant's breastfeeding at 6 months and child's BMI at 5 years. [c] Term: Born at gestational age 37 weeks or later.

In children exposed to severe preeclampsia, the Z-scores of height increased for the first 5 years, but their average height was still below the population mean at five years (Figure 6). In children exposed to mild preeclampsia, the Z-score of heights in the exposed group showed an overall trend of crossing the height–growth trajectory of those who were unexposed.

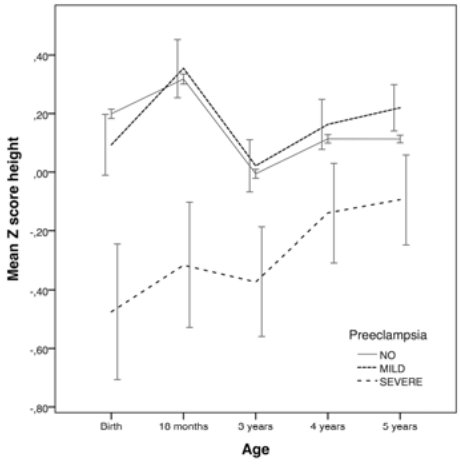

Figure 6. Mean Z-scores of height with 95% confidence intervals at different age in children exposed to severe and mild preeclampsia and unexposed to preeclampsia.

Study IV

Pre-hypertension in late gestation occurred in 11% of the study population. Pre-hypertension in late gestation was more common in primiparous than parous women. The risk of pre-hypertension in late gestation increased with maternal DBP in early gestation, maternal BMI and height. Pre-hypertension was more common in women who were living with their partner than those who did not, and in women with diabetes mellitus than those without diabetes.

Pre-hypertension in late gestation was associated with increased risks of both SGA birth and stillbirth (AORs (95% CI) 1.7 (1.5 – 1.9) and 1.7 (1.2 – 2.5), respectively). In women with DBP of 60–64 mm Hg in late gestation, the rate of term SGA birth was 1.4%, whereas the rate was 2.4% in women with pre-hypertension in late gestation. Figure 7 illustrates the increasing risk estimates for SGA by the DBP in late gestation. The risk of SGA birth increased by 2.0% (95% CI 1.5 – 2.8%) per each mm Hg rise in DBP from early to late gestation, while the risk of stillbirth was not affected by rise in DBP during pregnancy. Table 8 illustrates risks of SGA birth and stillbirth in normotensive and pre-hypertensive women in late gestation, stratified by blood pressure increase from early to late gestation.

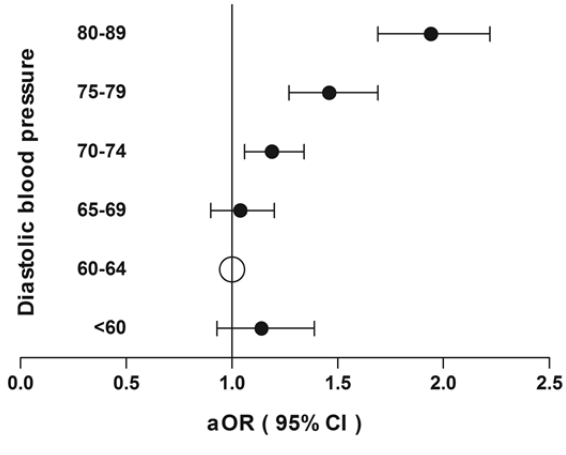

Figure 7. The risk of giving birth to a small-for-gestational-age infant at term by diastolic blood pressure (mm Hg) in late gestation. Odds ratios were adjusted (aOR) for parity, maternal age, height, body mass index, smoking habits, cohabitation with father and diabetes.

Table 8. *Normotensive and pre-hypertensive women in late gestation, stratified by increase in diastolic blood pressure (DBP) of at least 15 mm Hg from early to late gestation, and associated risks of small-for-gestational-age (SGA) birth or a stillbirth.*

	SGA			Stillbirth		
DBP	*n*	%	aOR (95% CI)	*n*	%	aOR (95% CI)
< 80 mm Hg *with increase from early to late gestation*						
<15mm Hg	1684	1.4	Reference	134	0.1	Reference
≥15mm Hg	134	2.2	1.4 (1.2 – 1.7)	6	0.1	0.6 (0.2 – 1.7)
80 – 89 mm Hg *with increase from early to late gestation*						
<15mm Hg	212	1.9	1.5 (1.3 – 1.7)	30	0.3	2.2 (1.4 – 3.3)
≥15mm Hg	164	3.6	2.4 (2.0 – 2.8)	4	0.1	0.8 (0.3 – 2.1)

Odds Ratios were adjusted (aOR) for maternal parity, age, height, body mass index, smoking habits, cohabitation with father and diabetes.

Study V

In the cohort of primiparous women without suspected vascular disease in early pregnancy, preeclampsia was diagnosed in 3.4% of women. In women with pre-hypertensive early-gestation DBP and in obese women (BMI ≥ 30) the rate of preeclampsia was above 7%. Women aged 35 years or more were more likely to be diagnosed with preeclampsia than younger women and preeclampsia occurred more often in short (< 164 cm) women than in tall (≥ 172 cm) women.

Three percent of the women in the cohort gave birth to SGA infants. There was only a slight difference in SGA rates between women with low and pre-hypertensive early-gestation DBP. Birth of an SGA infant was more likely in underweight (BMI < 18.5) than normal-weight women. Women aged 35 years or more were more likely to give birth to an SGA infant than younger women. The SGA rate was 4.6% in short women and 1.7% in tall women.

The risk of preeclampsia and SGA birth increased with elevation of DBP from early to mid-gestation. Compared to women with lowered DBP, women with elevated DBP had 20–30% higher risks of preeclampsia and SGA. The risks for preterm (< 37 weeks) disorders in women with elevated DBP was higher, with AORs at 1.6 (95% CI 1.2 – 2.0) for preeclampsia and 1.7 (95% CI 1.3 – 2.3) for SGA. There was an interaction between early-gestation DBP and change in DBP until mid-gestation concerning risks of preeclampsia and SGA birth

(both $p < 0.05$). The risk effects of elevated DBP seemed stronger in women with pre-hypertensive than low early-gestation DBP (Table 9). The rate of preeclampsia in women with low early-gestation DBP and further lowered DBP until mid-gestation was 1.6%, compared to 15.8% in those with pre-hypertensive early-gestation DBP and elevated DBP until mid-gestation (Table 9. a).

Table 9. a) *Risk of preeclampsia by diastolic blood pressure (BP) in early gestation and the change in diastolic BP from early to mid-gestation.*

Any preeclampsia						
Early-gestation DBP mm Hg	**Change in DBP**					
	Lowered		**Unchanged**		**Elevated**	
	%	aOR (95% CI)	%	aOR (95% CI)	%	aOR (95% CI)
< 70	1.6	Reference	1.9	1.1 (0.9 – 1.4)	3.2	1.8 (1.4 – 2.2)
70 – 79	3.3	Reference	4.2	1.2 (1.0 – 1.4)	8.1	2.4 (2.0 – 2.8)
80 – 89	6.1	Reference	11.0	1.8 (1.4 – 2.3)	15.8	2.7 (1.7 – 4.2)
Preterm preeclampsia						
< 70	0.3	Reference	0.4	1.3 (0.8 – 2.3)	0.6	2.1 (1.3 – 3.6)
70 – 79	0.5	Reference	0.8	1.3 (0.9 – 1.9)	1.9	3.7 (2.6 – 5.5)
80 – 89	1.3	Reference	1.7	1.2 (0.6 – 2.2)	5.4	4.1 (2.0 – 8.6)

Table 9. *b) Risk of giving birth to a small-for-gestational-age (SGA) infant by diastolic blood pressure (BP) in early gestation and the change in diastolic BP from early to mid-gestation.*

Any SGA						
Early-gestation DBP mm Hg	**Change in DBP**					
	Lowered		**Unchanged**		**Elevated**	
	%	aOR (95% CI)	%	aOR (95% CI)	%	aOR (95% CI)
< 70	2.7	Reference	2.7	1.0 (0.8 – 1.2)	3.3	1.3 (1.0 – 1.5)
70 – 79	2.7	Reference	3.1	1.2 (1.0 – 1.4)	4.1	1.5 (1.2 – 1.9)
80 – 89	3.0	Reference	4.1	1.7 (1.1 – 2.4)	6.3	2.5 (1.3 – 4.8)
Preterm SGA						
< 70	0.4	Reference	0.4	1.0 (0.6 – 1.7)	0.7	2.3 (1.3 – 3.8)
70 – 79	0.5	Reference	0.6	1.3 (0.8 – 2.0)	1.3	2.8 (1.7 – 4.4)
80 – 89	0.8	Reference	0.8	0.8 (0.3 – 2.0)	2.7	3.9 (1.4 – 10.7)

CI, confidence interval. Odds ratios are adjusted (aOR) for maternal age, height, body mass index, smoking habits, country of birth and cohabitation with partner. Preterm: defined as preeclampsia or SGA in women who deliver before 37 gestational weeks.

Discussion

Main Findings

Brief summary of the principal findings in each study:

I Partner change was associated with preeclampsia and birth of an SGA infant in second pregnancy, but the effect seemed to depend on the outcome of the first pregnancy.

II Recurrent prior miscarriages were associated with increased risks of placental dysfunction disorders, including preeclampsia, stillbirth, birth of an SGA infant, placental abruption and spontaneous preterm birth.

III Prenatal exposure of preeclampsia was associated with accelerated height gain in offspring from birth until five years of age.

IV Pre-hypertension in late gestation was associated with increased risks of SGA birth and stillbirth at term.

V Elevated diastolic blood pressure from early to mid-gestation was associated with increased risks of preeclampsia as well as SGA birth.

Methodological Considerations

In these register-based cohort studies, associations between pre-defined exposures and the subsequent outcomes were estimated. The specific study questions were designed to test some hypotheses related to the pathophysiology of preeclampsia and other placental dysfunction disorders. However, observational data need to be interpreted with caution and estimates of associations do not include any information on the direction of a possible effect. Further, the findings of cohort studies may be subject to bias related to the information used and the selection of covariates that are associated with our measures of exposures and outcomes (confounders, mediators and collider).[99] Regardless of the general limitation of epidemiology, such studies are platforms on which to build models of plausible causal pathways. Later, a possible causation should be tested in an experimental setting or randomized trials.

The general strengths

- Mostly prospective data collection that precludes recall bias.
- The population-based design may decrease the likelihood of selection bias.
- The setting was in a country with free antenatal, delivery and child health care, minimizing the impact of socioeconomic bias.
- The large size of the study populations enables risk estimates of rare outcomes and allows stratified analysis.
- Information was available on important covariates such as maternal BMI in early pregnancy, smoking habits, and pre-gestational diseases.

The general limitations

- Register-based studies may suffer from an inaccurate exposure measure, such as self-reported information on paternity or prior miscarriages, and incorrect BP measurements or registrations.
- Most outcomes were defined by diagnostic codes, but the criteria for diagnosis can differ by country and change over time.
- The outcome of SGA is an imprecise proxy for fetal growth restriction, because SGA does represent a heterogeneous group of children who are growth restricted, congenitally abnormal or just constitutionally small.
- The information on maternal diseases is limited because the coding of a diagnosis may be more frequent after a complicated rather than a normal pregnancy or delivery.
- Country of birth is an imprecise proxy for ethnicity and can be partially seen as a socioeconomic covariate.
- Large amount of missing information on gestational weight gain.
- Lack of information on paternal covariates (such as height and BMI) and dietary habits in the families.
- Lack of information on legal abortions, contraceptive use and semen exposure before the index pregnancy.

Study design and bias

Possible sources of bias in each study:

I Adjustment of inter-pregnancy interval may be inappropriate if this is a collider rather than a confounder in the association.

II Lack of information on thrombophilia or PCOS may have resulted in residual confounding. The use of gestational age to define the severity of placenta dysfunction disorders.

III Residual confounding by paternal height or dietary habits in the families (over-nutrition). Possibly genetic confounding.
IV Lack of adjustment for ethnicity and maternal weight gain.
V Limited adjustment of socioeconomic variables. The exposure variable, elevated BP, is related to the diagnostic criteria of the outcome of preeclampsia.

The specificity of the research question and the study design can be vital regarding inference. Further, the choice of covariates adjusted for in the models is complicated and there is no consensus about an optimal method. In Study I, the inter-pregnancy interval was adjusted for, but it is unclear whether this was a confounder or a collider in the association between partner change and preeclampsia.[100] The direction of an association between partner change and inter-pregnancy interval is currently unclear. Therefore, the use of directed acyclic graphs (DAGs) would not have solved this problem. However, it would be informative to study the outcomes in relation to other covariates that may explain longer inter-pregnancy intervals, such as; duration of breastfeeding after the first pregnancy, contraceptive use and frequency of coitus, legal abortions, miscarriages, and infertility. In Study II, the association between prior miscarriages and obstetric complications, including spontaneous preterm births, was estimated. There seemed to be a dose-response association between prior miscarriages and preterm births. A dose-response pattern is generally considered to strengthen the possibility of causal relationships (Hill's criterion).[101] However, the exposure of miscarriages before the first birth may introduce a bias related to the fecundity. Further, a distinction cannot be made between the possible effect of miscarriages and the following treatment for miscarriages in this study design. It may be interesting to study maternal diseases (such as those adjusted for in Study II) in relation to the time to a viable pregnancy or preeclampsia diagnosis (with analysis of time to event, instead of the outcome of preterm preeclampsia and SGA). In Study III there is a possible source of genetic confounding, which cannot be detected in the study design used. Some suggestions about an inherited component could be detected in a study comparing siblings, although the effect of the environment and genes could not be separated. The other possibility would be to use methods of genome-wide association studies. In Studies IV and V, the exposure is very close in time to the outcome, which complicated the interpretation of the data. The temporal relationship of the exposure and the outcome is important regarding inference (according to one Hill's criterion). In Studies IV and V, it is difficult to identify the most likely explanation of the associations between BP and fetal growth; it may be confounded by a common unknown covariate, inverse relationship (placental dysfunction increases BP), or high BP that

affected fetal growth. In an optimal study, the exposure measure would be a more sensitive and specific estimate of vasomotor function (such as hemodynamic measurements or serologic markers), preferably measured before pregnancy or during the implantation in pregnancy.

Studies I & II

In Study I, partner change between pregnancies seemed to decrease the risk of recurrence of preterm preeclampsia or giving birth to a preterm SGA infant. Further, women who did not give birth to an SGA infant at their first delivery had a slightly increased risk of an SGA birth at their second delivery if they changed partner between pregnancies. These findings may indicate a paternal influence on placentation.

In Study II, two or more prior miscarriages were associated with increased risks of the placental dysfunction disorders; preeclampsia, stillbirth, SGA birth, placental abruption, and spontaneous preterm births. The associations were strongest for three or more prior miscarriages, and seemed stronger for preterm than term placental dysfunction disorders. The results may imply a common pathogenesis of recurrent miscarriages and placental dysfunction disorders.

The rate of preeclampsia in the first pregnancy (in Study II) was 3–4%. In the second pregnancy (Study I), the rate of preeclampsia in women with uncomplicated first pregnancy was around 1%, both in women who had the same partners and in those who changed partners between pregnancies. However, the recurrence rate of preeclampsia in the second pregnancy in women with previous preeclampsia was 8–14%, and seemed to depend on the severity of the disorder in the first pregnancy. This is in consonance with previous findings of higher incidence of preeclampsia in primiparous women than parous women with previously uncomplicated pregnancies.[8] More importantly, the results highlight that women with previous preeclampsia are more likely than other parous women to suffer from the disorder again in later pregnancies.[9] Partner-specific tolerance induction has been suggested to explain the observed protective effect of a previous uncomplicated pregnancy. Further, it has been suggested that such partner-specific tolerance is lost if a woman changes partner between pregnancies (primipaternity hypothesis).[19, 29] The findings in Study I do not support this obsolete hypothesis because the rate of preeclampsia in parous women with previous uncomplicated pregnancies who change partners is very similar to the rate in parous women with the same partner (and at least two times lower than the rate observed in primiparous women). However, the findings

may indicate a partner-specific effect that depends on the pregnancy outcome in the first pregnancy. The aim of Study II was to estimate the association between prior miscarriages and the outcome of placental dysfunction disorder. The study design was complicated because the exposed and reference groups cannot at the same time have an equal number of pregnancies (gravidity) and births (parity).[102, 103] In theory, the tolerance to paternal antigens may be affected by any gestation (including legal abortions and miscarriages) but the probability of the outcome of placental dysfunction disorder is known to be higher in primiparous than parous women. To avoid comparison of primiparous and parous women, only primiparous were included in the study. The results of Study II indicate a relationship between two or more prior miscarriages (recurrent miscarriages) and the risk of different placental dysfunction disorders, including preeclampsia. Unlike the study of Trogstad *et al.*,[104] the possible confounding by maternal diseases (e.g. chronic hypertension and diabetes) was accounted for. The results strengthen previous evidence of an association between prior recurrent miscarriages and preeclampsia. In the future, it may be important to investigate the association between an adverse outcome in the first pregnancy (such as preeclampsia, stillbirths, fetal growth restriction and preterm birth) and the probability of another viable pregnancy during the fertile period of a woman's life. One possible explanation of the protective effect of previous pregnancies (primiparity effect) is that multiparous women represent a selection of women who manage to become repeatedly pregnant, which relates to their fertility, fecundity and perhaps their lifestyle in general (related to, e.g., BMI and weight gain).

Studies III, IV & V

In Study III, prenatal exposure to preeclampsia was associated with accelerated height gain during early childhood, and the association seems independent of birth weight for gestational age. However, the pattern of accelerated height gain was more pronounced in children exposed to severe preeclampsia than mild preeclampsia.

In Study IV, pre-hypertension in late gestation was associated with a 70% increased risk of both SGA birth and stillbirth at term. Further, an increase in DBP at least 15 mmHg from early to late gestation increased the risk of SGA birth, and also in pregnancies that had not reached the level of pre-hypertension in late gestation.

In Study V, elevated DBP from early to mid-gestation was associated with increased risks of preeclampsia and SGA births, and the association was stronger for preterm outcomes. Further, the results indicated that early-gestation DBP and change in DBP until mid-gestation interact regarding the risks of preeclampsia and SGA birth.

Studies III–V combined show that increased BP or preeclampsia during pregnancy is associated with fetal and postnatal growth. It has previously been well decribed that preeclampsia is associated with fetal growth restriction.[105] Further, children who are born growth-restricted (SGA) seem to grow with an accelerated pattern after birth and catch up with children born in the normal range of birth weight.[82] In Study III, an association between prenatal exposure to preeclampsia and accelerated postnatal growth was shown. The children exposed to severe preeclampsia were more often born preterm and SGA than those who were unexposed, and indeed they had a pattern of postnatal catch-up growth. However, an accelerated growth pattern was also seen in children exposed to preeclampsia born at term and with normal birth weight, and, interestingly, these children were taller on average than those who were unexposed at the age of five. The results suggest an assocation between preeclampsia and postnatal growth that may be independent of birth weight for gestational age. In Studies IV and V, an association between BP increase during pregnancy and birth of SGA infants was shown. In one previous study, BP increase in pregnancy was shown to be negatively associated with birth weight for gestational age.[61] The results remained when women with hypertension were excluded, which may imply an association thoughout the normal range of BP. In Study IV, only women without hypertension before or during pregnancy were included. Pre-hypertension in late gestation was associated with birth of an SGA infant and stillbirth at term. Further, increase in BP from early to late gestation was associated with SGA, and also in women who did no reach the level of pre-hypertension in late gestation. The results in Study V suggest an association between increase in BP from early to mid-gestation and SGA as well as with preeclampsia, and the effect seemed to depend on the level of BP in early gestation. The results in Studies IV and V may indicate that both the level of BP throughout the pregnancy as well as the amount of increase in BP during pregnancy may be relevant to the physiology of fetal growth and the development of preeclampsia. The results of Study V may also support the notion that a mid-gestation lowering of DBP may reflect a beneficial hemodynamic adaptation induced by the pregnancy status.

To conclude, not only preeclampsia but also BP increase during pregnancy within a normal range is associated with SGA birth. Further, not only SGA but also preeclampsia is associated with accelerated postnatal growth. The results may imply a common physiological component behind vasomotor function and growth.

Possible Pathophysiological Implications

The results of Study I suggest that partner change is protective of recurrent placenta dysfunction disorders. The findings indicate a paternal effect in the pathophysiology of placental dysfunction. It may be speculated that a fetal genetic component is relevant in the pathophysiology of placental dysfunction disorder,[106, 107] non-specific to preeclampsia. The results of Study II suggest that recurrent miscarriages are associated with increased risk of several different placental dysfunction disorders. A previous hypothesis describes that a miscarriage may be explained by a complete implantation failure while pregnancies with partial failure of implantation may be viable but suffer from placenta dysfunction.[28] Further, there are some studies that imply that specific haplotype combinations of maternal and fetal genes may be associated with preclampsia.[29, 108] The maternal-fetal haplotype combination could theoretically affect the cross-talk between maternal cells and thropoblast during the implantation. The observations in Studies I and II combined may indicate that a fetal component is involved in the implantation and early placentation process. Hypothetically, in women who lack a favourable fetal component in their first pregnancy, a protective effect would be expected from partner change before the next pregnancy. Further, the presence of a favourable fetal component might determine the viability of a pregnancy, especially in a mother who is prone to a placentation failure.

The results from Study III imply that the early-childhood growth trajectory is associated not only with fetal growth restriction, but also with prenatal exposure to preeclampsia. This observation could be of clinical interest because both prenatal exposure to preeclampsia[79] and accelerated height gain in childhood[89] have been associated with increased risks of hypertension in adulthood. If prenatal exposure to preeclampsia induces fetal changes (epigenetic) that affect the growth trajectory, accelerated height gain could be a mediator in the association between prenatal exposure of preeclampsia and hypertension in adulthood. However, it is more likely that the association between prenatal preeclampsia and accelerated height gain can be explained by unadjusted environmental components such as dietary habits in families (over-nutrition) or by

genetic components that increase the risk of preelampsia and also the offspring's height gain (genetic confounding). A recent study that investigates the association between prenatal exposures of preeclampsia and cardio-metabolic outcome in early adulthood indeed suggests the involvement of an inherited component (genetic or environmental), because a similar association was seen in siblings from later normotensive pregnancies.[109] Further, in a twin study of birth weight and the associated increased risk of CVD, the association only seems to exist in dizygotic twin pairs but not in monozygotic.[78]

In Study IV, pre-hypertension in late gestation is associated with both SGA births and stillbirths and large changes in DBP during pregnancy increase the risk of SGA, irrespective of the presence or absence of pre-hypertension in late gestation. In Study V, an increase in DBP from early to mid-gestation was associated with both preeclampsia and birth of SGA infants, and this effect seemed to depend on the level of early-gestation DBP. An increase in BP during pregnancy is thought to be related to hypo-perfusion of the placenta, which results in the production of vasoconstrictive substances in the placenta.[23, 41] The results in Study V may suggest that hypo-perfusion indeed resulted in increased vasoconstriction in as early as mid-gestation and a rise in DBP before the gestation week of 25. However, not all women with hypo-perfusion of the placenta and later growth restricted fetuses develop hypertension or preeclampsia. Results in Studies IV and V indicate a possible biological interaction between the the early-gestation level of BP and the later increase in BP on the development of SGA. Further, the results in Study V strengthen the notion that a mid-gestation lowering of DBP may reflect a beneficial hemodynamic adaptation induced by the pregnancy status. It may be plausible that, in pregnancies complicated with placental hypo-perfusion, gestational hemodynamic maladaptation or vascular predisposition may differentiate between those women who develop hypertensive disorder during pregnancy and those who do not.

Future Perspectives

Final hypothetical models

Hypo-perfusion of the placenta is most probably central in the development of preeclampsia, meaning that the level of perfusion is less than required. With increasing gestational length and fetal size, the perfusion of the placenta is increased. A state of placental hypo-perfusion seems to cause an increase in vasoconstrictive agents such as sFlt-1 (evidence from RUPP animal models) and may mediate the BP increase and other symptoms of preeclampsia.[23] With progressing gestation, sFlt-1 increases in all pregnancies, but in women who develop preeclampsia, the increase is larger. There is an inverse correlation between PlGF and fetal growth during pregnancy, and PlGF is usually low in pregnancies complicated with preterm preeclampsia or growth restriction.[110] Interestingly, the ratio of sFlt-1/PlGF predicts preterm birth, and not only in women who develop preeclampsia.[111] Although the imbalance in angiogenic factors seems to mediate the symptoms of preeclampsia, the cause of placental hypo-perfusion continues to be debated. The evidence is rather convincing that a lack of cytotrophoblast invasion into the myometrial spiral arteries may be involved in abnormal placental function, but causality is not proven.[112] Further, abnormal cytotrophoblast invasion may explain preterm preeclampsia and growth restriction but not term preeclampsia (sometimes referred to as maternal preeclampsia).[113] Recently, it has been proposed that preeclamspia should be re-defined by the combination of low PlGF and pre-gestational endothelial dysfunction.[110] Further, the general importance of cardiac function in organ perfusion has been brought to attention, because the placenta is a highly perfusion-dependent organ.[114] These ideas are the basis for the hypothetical model illustrated below (Figure 8). Two pathways to hypo-perfusion of the placenta are proposed; maternal hemodynamic dysfunction (extrinsic), and placental dysfunction (intrinsic).[110, 114] This model assumes that the hemodynamic function before or during pregnancy mainly determines the maternal outcome, whereas the placental development and function mainly determines the outcome of the fetus.

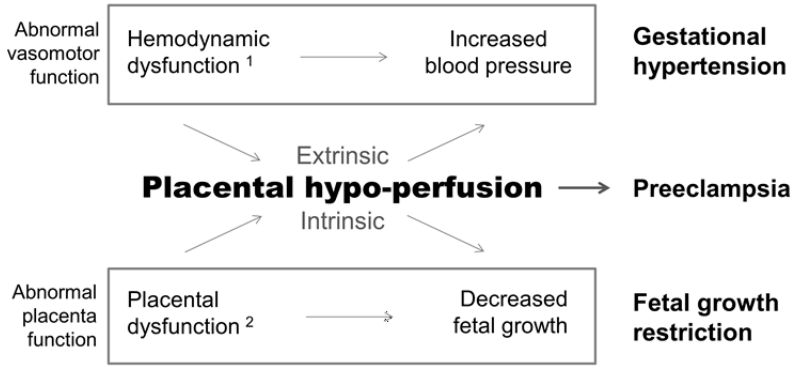

Figure 8. The intrinsic and extrinsic pathway to placental hypo-perfusion. 1) Endothelial dysfunction in early gestation or gestational hemodynamic maladaptation. 2) Early-gestation signs of uterine artery resistance or low placental growth factor. The figure is adapted from the work of Staff, A.C. and Thilaganathan, B.[110, 115]

Placental dysfunction in this model could involve abnormal implantation and placentation and may be reflected in low levels of PlGF and abnormal Doppler flows. However, it is quite unclear what could represent the hemodynamic dysfunction in this hypothetical model, but it may involve pre-gestational endothelial dysfunction,[63, 64] gestational hemodynamic maladaptation,[114] or vascular predisposition because of a metabolic disease.[116, 117] Both pathways may contribute to hypo-perfusion of the placenta and perhaps interact in the development of the disorder of preeclampsia.[63, 64] An overlap between vascular disorders and metabolic diseases may also explain the observed association between BP and growth.[117] In the model illustrated in Figure 9 it is assumed that placental dysfunction is a severe form of hemodynamic dysfunction during pregnancy. In contrast to the interaction between intrinsic and extrinsic pathways suggested in Figure 8, it is suggested that an overlap of hemodynamic and placental dysfunction with metabolic diseases may explain the diversity of the preeclampsia disorder.

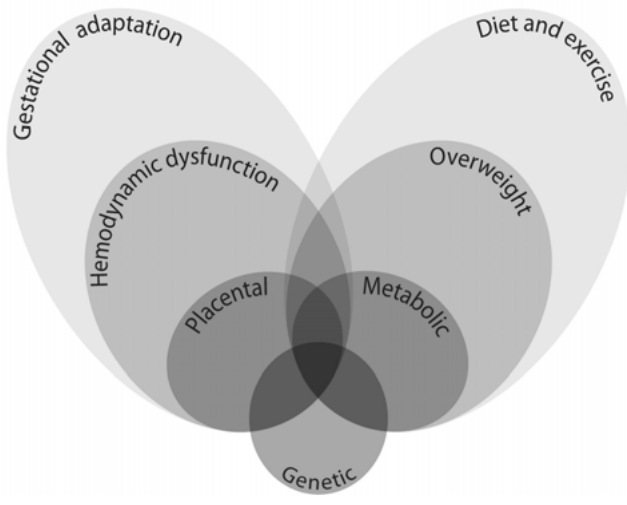

Figure 9. Illustration of an overlap between vascular-related disorders and metabolic diseases.[116, 117] **On the left**: *Large cycle* represents gestational adaptation including hemodynamic changes, *middle cycle* women with endothelial dysfunction or hemodynamic maladaptation during pregnancy, *smallest* cycle is the women with placental dysfunction with a possible genetic component. **On the right**: *Large cycle* represents the behavioral habits of women regarding their diet and exercise, *middle cycle* women who are overweight or obese and *smallest cycle* the women with diabetes or metabolic syndrome.

Abnormal placental function

The intrinsic pathway to placental hypo-perfusion described above may be referred to as placental dysfunction. It is probably not specific to preeclampsia, but is rather associated with other obstetric complications that can be referred to as placental dysfunction disorders. It has been speculated that placental dysfunction disorders are inherited, possibly with a fetal genetic component. The diversity of the preeclampsia disorder could mean that genome-wide studies on the phenotype of preeclampsia may be difficult to perform, and it might be better to study the phenotype of increased resistance in uterine arteries in early gestation. Another approach in genetic studies could be to study the phenotype of preterm growth restriction regardless of the mother's BP changes during the pregnancy or the phenotype of accelerated height gain in childhood, irrespective of birth weight.

Abnormal vasomotor function

Ongoing prospective studies on gestational hemodynamic function will soon identify the value of maternal hemodynamic measurments such as cardiac index in predicting preeclampsia, and whether this adds to the predictive value of angiogenic factors and uterine artery Doppler. Interestingly, there are previous, ongoing, and will be future,

randomized trials that test the benefit of well-known cardiovascular medications in the treatment or prevention of preeclampsia/fetal growth restriction (aspirin[17], sildenafil[118] and statins[119]). However, in order to reveal a possible causal involvment of the cardiovascular system in preeclampsia, the association between the pre-gestational hemodynamic function on the development of preeclampsia needs to be estimated. Further, a long-term follow-up on such cohorts could answer the question of whether the association between preeclampsia and CVD can be explained by; A) confounding by common risk factors, B) undiagnosed endothelial dysfunction, or C) preeclampsia-induced damage of vessels or the cardiac muscle. Further, a gestational register that includes a prospective registry of all pregnancies, including legal abortions, miscarriages and extra-uterine pregnancies, should replace birth registers. It may be advisable to register outcomes in a way that allows analysis of time to event (such as dates of preeclampsia diagnosis).

Prenatal exposure

Estimates of the effect of prenatal exposure (such as fetal growth restriction) on the offspring's risk of having a future disease may be confounded by inherited components. In the prediction of the offspring's health, pregnancy complications (such as preeclampsia and gestational diabetes) and family habits (regarding diet or exercise) may be more relevant than the birth weight for gestational age.[120] Further, an estimate of dietary and exercise habits in addition to the BMI may identify individuals at risk of vascular-related outcomes (including preeclampsia) more effectively than BMI as a single estimate of being overweight (Figure 9).

Conclusions

First, the importance of the outcomes in previous pregnancies (obstetric outcomes or prior miscarriages) in the antenatal risk evaluation was highlighted (Studies I and II). Second, the association between inter-pregnancy intervals as well as parity, and preeclampsia should be further investigated. Third, the results indicate that the postnatal growth trajectory may be related to a maternal disease in addition to gestational length and fetal growth restriction (Study III). Fourth, the results imply an association between BP changes during pregnancy, within the normal range and fetal growth, which perhaps reflect the low predictive value of BP and may challenge the clinical cut-off for hypertension (Studies IV and V).

Clinical conclusion of specific studies

I Partner change slightly increased the rate of preeclampsia and SGA births in women without the disorders in first pregnancy, but no association was found between partner change and preeclampsia when inter-pregnancy interval was accounted for. In the clinical risk evaluation of parous women, the outcome of previous pregnancies seems more relevant than partner change between pregnancies.

II Primiparous women with recurrent miscarriages seem to have an increased risk of placental dysfunction disorders. Although the absolute risk increase is small, the information may be used to clinically evaluate the risk of pregnancy complications related to dysfunction of the placenta.

III The clinical importance of the accelerated height gain in children with prenatal exposure to preeclampsia is unclear. This accelerated height gain seems to be independent of birth weight for gestational age. Therefore, future cohorts should not be selected based on birth weight if the aim is to assess the role of prenatal exposures in the development of hypertension.

IV Pre-hypertension in late gestation is associated with increased risk of SGA birth and stillbirth at term. These findings are important because pre-hypertension in late gestation is common (11% in our study population), but BP medication for pre-hypertension is not suggested. Further studies are needed to evaluate the usefulness of Doppler measurements to predict stillbirth in women with pre-hypertension in late gestation.

V Elevated DBP from early to mid-gestation (20–25 weeks) was associated with increased risks of preeclampsia and SGA births. This may indicate that DBP starts to elevate before 25 weeks in some women who develop placental dysfunction disorders. A second dipstick test seems reasonable for women with elevated DBP until mid-gestation. In the presence of other risk factors, a clinical evaluation by an obstetrician is recommended.

Swedish summary

Sammanfattning på Svenska

Havandeskapsförgiftning (preeklampsi) är en potentiellt livsfarlig placentarelaterad graviditetskomplikation som kan definieras som nytillkommet högt blodtryck och läckage av protein i urinen hos den blivande mamman. Sjukdomen drabbar alla organ i mammans kropp och kännetecknas av en generellt ökad kärlspänning med onormal endotelfunktion. Anlag för kärlsjukdom har samband med ökad förekomst av havandeskapsförgiftning och återupprepningsrisken i senare graviditeter är betydande. Dålig genomblödning av moderkakan föregår sannolikt uppkomsten av havandeskapsförgiftning. Den dåliga genomblödningen kan uppkomma på grund av dålig anläggning av moderkakan, men på senare tid har också föreslagits att den kan bero på att den gravida kvinnan inte klarar den anpassning av hjärtkärlsystemet som en normal graviditet kräver. En förändring som kan vara en del av den normala anpassningen är en sänkning av blodtrycket under graviditetens första halva, vilket anses förbättra moderkakans genomblödning. Om moderkakan utsätts för syrebrist utsöndras kärlsammandragande ämnen från moderkakan till den blivande mammans cirkulation och den generella kärlspänningen uppkommer. Havandeskapsförgiftning är starkt förknippat med dålig fostertillväxt, vilket ofta kännetecknas av att barnen föds lätta för tiden (small for gestational age; SGA). Barn som är födda lätta för tiden växer ofta snabbare efter födelsen än barn som är födda normalstora. Det är oklart om havandeskapsförgiftning är associerat med snabbare barntillväxt även då barnet fötts normalstort.

Avhandlingens delstudier hade följande mål: för det första att studera sambanden mellan partnerbyte och tidigare missfall och förekomsten av havandeskapsförgiftning samt att föda ett barn lätt för tiden, för det andra att studera tillväxten efter födelsen hos foster som exponerats för havandeskapsförgiftning och för det tredje att studera samband mellan blodtrycksförändringar under graviditet och förekomst av havandeskapsförgiftning samt att föda ett barn lätt för tiden.

Befolkningsbaserade kohortstudier utfördes med information från följande register: Medicinska Födelseregistret, Uppsala Mor-Barn databas och Stockholm-Gotland Graviditetsdatabasen. Associationer beräknades med logistiska och linjära regressioner med justeringar för följande egenskaper hos modern, ålder, längd, kroppsmasseindex (BMI), rökning i tidig graviditet, sjukdomar innan graviditet och socioekonomiska faktorer.

Partnerbyte mellan den första och andra graviditeten var associerat med havandeskapsförgiftning och att föda ett barn lätt för tiden i andra graviditeten, men associationen var beroende av utfallet i första graviditeten. Upprepade missfall innan den första födseln var associerat med ökade risker för havandeskapsförgiftning samt att föda ett barn lätt för tiden. Exponering för havandeskapsförgiftning var associerat med ökad längdtillväxt hos barnet under de första fem åren, även hos barn med födelsevikt som var normal för tiden. Stegrat blodtryck från tidig graviditet till mitten av graviditeten och ett gränsblodtryck i sen graviditet var båda associerade med födsel av ett barn lätt för tiden. Kvinnor som hade ett gränsblodtryck i tidig graviditet som inte sjönk till mitten av graviditeten utgjorde en uttalad riskgrupp för havandeskapsförgiftning. Risken för att föda ett barn lätt för tiden var också ökad.

Avhandlingens resultat betonar betydelsen av utfall i tidigare graviditeter när det gäller riskbedömning av graviditet. Havandeskapsförgiftning är associerat med ökad längdtillväxt hos barn, även om barnet är fött normalstort. Studieresultaten tyder vidare på ett samband mellan blodtrycksförändringar inom det normala intervallet och att föda ett barn lätt för tiden. Resultaten belyser att det kan finns ett samband mellan kvinnans anpassning av hjärtkärlsystemet under graviditet och fostertillväxt, men ifrågasätter också den sedvanliga kliniska gränsen för högt blodtryck under graviditet.

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