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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]

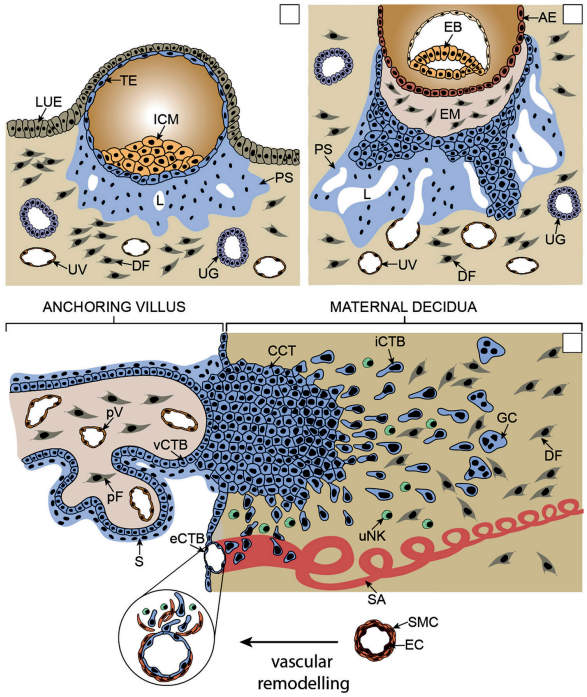

Figure 1. Implantation. CTB: Cytotrophoblast cells; S: Syncytium; uNK: uterine Natural Killer cells. This figure is re-printed with the permission of the publisher and the author and was originally published in Knöfler M, Pollheimer J. (2013). Front. Genet. 4:190. DOI: 10.3389/fgene.2013.00190.

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]

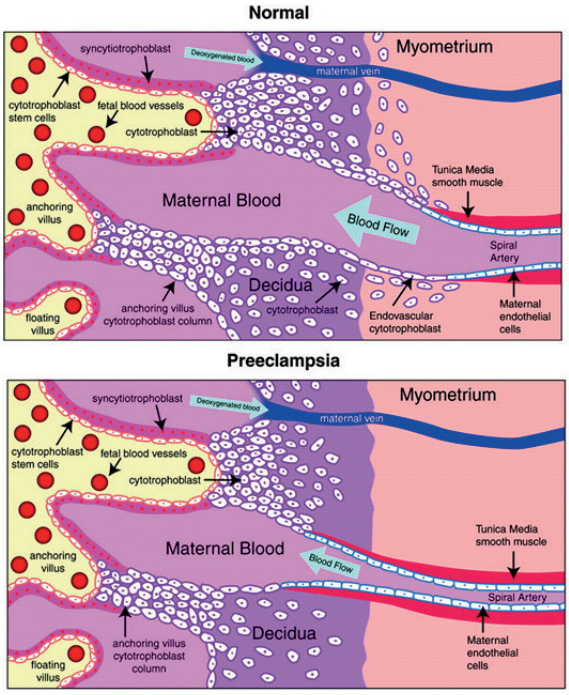

Figure 2. Spiral artery remodeling. This figure is re-printed with the permission of the publisher and the author. It was originally published in Lam C, Lim CH, Karumanchi SA. (2005). Hypertension. 46:5. DOI: 10.1161/01.HYP.0000187899.34379.b0.

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).

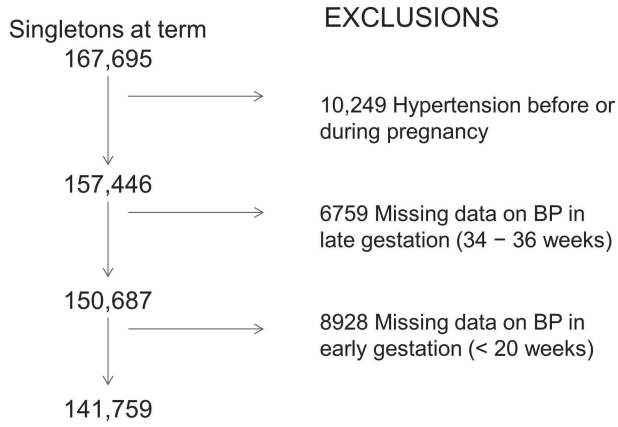

Figure 3: Flow chart of the population in Study IV. Hypertension was defined by a hypertensive medication, blood pressure (BP) > 140/90 mm Hg on two occasions or once > 160/110 mm Hg or hypertensive disorders according to diagnostic codes.

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).

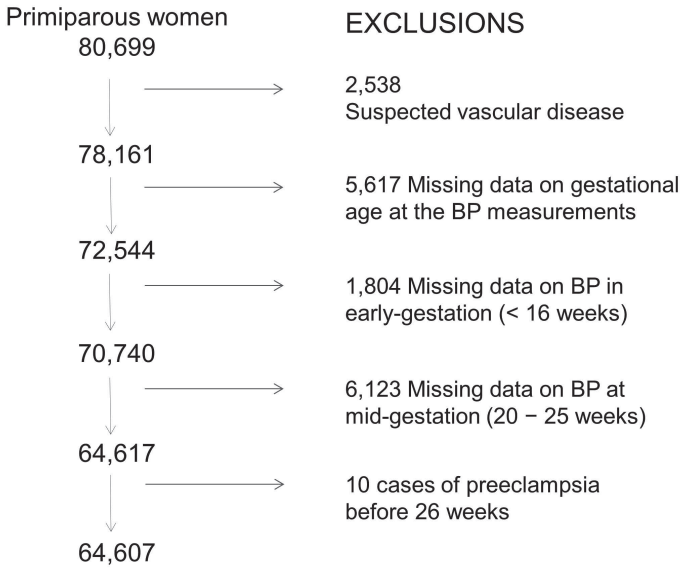

Figure 4. Flow chart of the population in Study V. Suspected vascular disease was defined as: *chronic hypertension* as blood pressure (BP) > 140/90 mm Hg at the first antenatal visit or chronic hypertension according to check-box or a corresponding diagnostic code after delivery; *proteinuria* before 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 $\geq$ 140 mmHg systolic or $\geq$ 90 mmHg diastolic) combined with proteinuria ($\geq$ 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 10th 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).

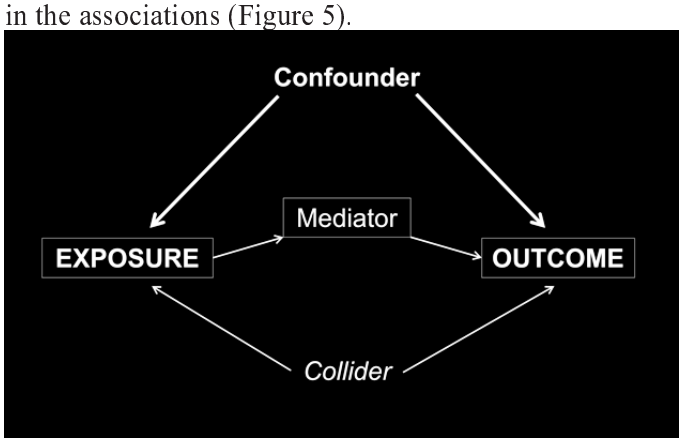

Figure 5. Definition of covariates associated with both exposure and outcomes as confounders, mediators and colliders.

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.

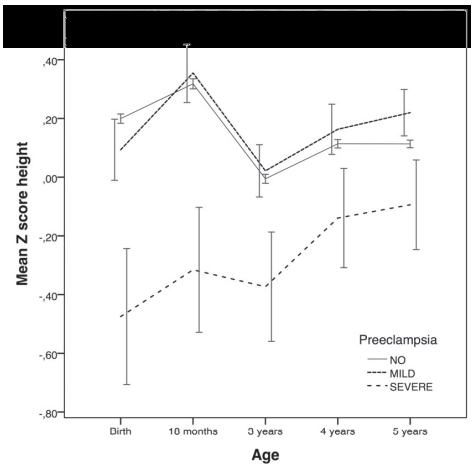

Figure 6. Mean Z-scores of height with 95% confidence intervals at different age in children exposed to severe and mild preeclampsia and unexposed to preeclampsia.

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.

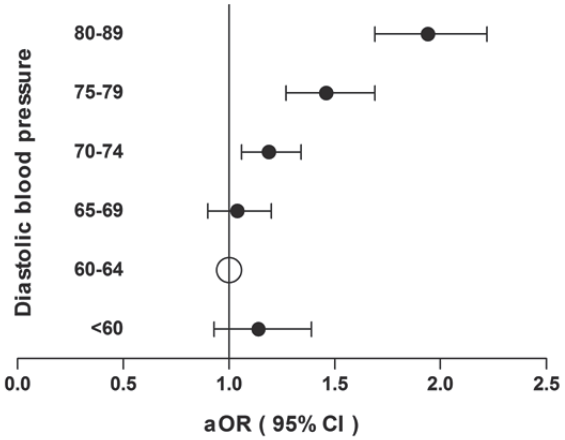

Figure 7. The risk of giving birth to a small-for-gestational-age infant at term by diastolic blood pressure (mm Hg) in late gestation. Odds ratios were adjusted (aOR) for parity, maternal age, height, body mass index, smoking habits, cohabitation with father and diabetes.

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 pregestational 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.

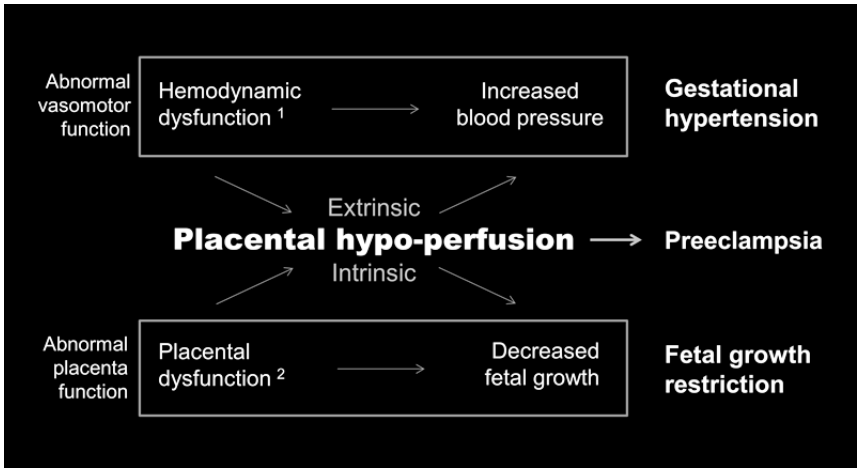

Figure 8. The intrinsic and extrinsic pathway to placental hypo-perfusion. 1) Endothelial dysfunction in early gestation or gestational hemodynamic maladaptation. 2) Early-gestation signs of uterine artery resistance or low placental growth factor. The figure is adapted from the work of Staff, A.C. and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

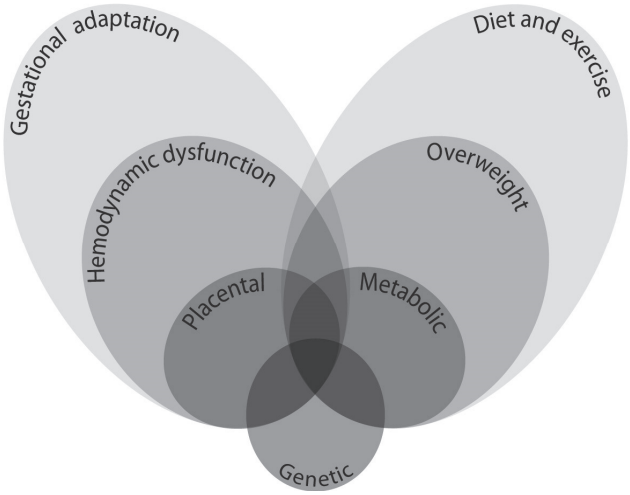

Figure 9. Illustration of an overlap between vascular-related disorders and metabolic diseases.[116, 117] **On the left**: *Large cycle* represents gestational adaptation including hemodynamic changes, *middle cycle* women with endothelial dysfunction or hemodynamic maladaptation during pregnancy, *smallest* 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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Paper I

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The paternal role in pre-eclampsia and giving birth to a small for gestational age infant; a population-based cohort study

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ABSTRACT

Objective: To estimate the effect of partner change on risks of pre-eclampsia and giving birth to a small for gestational age infant.

Design: Prospective population study.

Setting: Sweden.

Participants: Women with their first and second successive singleton births in Sweden between 1990 and 2006 without pregestational diabetes and/or hypertension (n=446 459).

Outcome measures: Preterm (<37 weeks) and term (≥37 weeks) pre-eclampsia, and giving birth to a small for gestational age (SGA) infant. Risks were adjusted for interpregnancy interval, maternal age, body mass index, height and smoking habits in second pregnancy, years of involuntary childlessness before second pregnancy, mother's country of birth, years of formal education and year of birth. Further, when we calculated risks of SGA we restricted the study population to women with non-pre-eclamptic pregnancies.

Results: In women who had a preterm pre-eclampsia in first pregnancy, partner change was associated with a strong protective effect for preterm pre-eclampsia recurrence (OR 0.24; 95% CI 0.07 to 0.88). Similarly, partner change was also associated with a protective effect of recurrence of SGA birth (OR 0.75; 95% CI 0.67 to 0.84). In contrast, among women without SGA in first birth, partner change was associated with an increased risk of SGA in second pregnancy. Risks of term pre-eclampsia were not affected by partner change.

Conclusions: There is a paternal effect on risks of preterm pre-eclampsia and giving birth to an SGA infant.

ARTICLE SUMMARY

Article focus

- Preterm pre-eclampsia and giving birth to a small for gestational age (SGA) are pregnancy disorders associated with abnormal placentation.
- The paternal role in placentation is debated and the focus of this article was therefore to estimate effect of partner change on risks of term and preterm pre-eclampsia and birth of an SGA infant in women with or without corresponding complication in prior pregnancy.

Key messages

- Partner change decreases recurrence risks of preterm pre-eclampsia and giving birth to an SGA infant in second pregnancy.
- In women who have not given birth to an SGA infant in their first delivery, partner change increase the risk of an SGA birth in the subsequent delivery.
- There is a paternal influence on placentation, where some partners seem less favourable for successful placentation.

Strengths and limitations of this study

- A major strength of the present study is the nationwide population-based design with a very small proportion of unidentified fathers (around 1%), although some misclassification of paternity, as in all studies based on self-reported information of fatherhood, is expected. The prospective data collection precludes recall bias. The size of the study population enabled us to separate preterm from term pre-eclampsia and to analyse risk of SGA after excluding pre-eclamptic pregnancies. Although we had the opportunity to account for several important possible confounders that were not controlled for in earlier studies, we were not able to control for previous semen exposure, abortions and miscarriages or paternal characteristics.

INTRODUCTION

Abnormal placentation is associated with pre-eclampsia, especially pre-eclampsia with an early onset, and with intrauterine growth restriction.[1–3] In abnormal placentation, the trophoblast invasion of the decidua and myometrium is restricted. For successful placentation, tolerance against partner alloantigens is necessary and trophoblast invasion appears to be primarily controlled by immune mechanisms.[4] Results from epidemiological studies suggest that some

partners could be less favourable when it comes to successful placentation.[5–7]

On the basis of the partner-specific hypothesis, a change of partner could be protective for a recurrence of pregnancy disorders associated with abnormal placentation. Women with previously normal pregnancy could on the contrary increase their risk of a placental dysfunction disorder with partner change in the next pregnancy. Results from previous studies suggest that pre-eclampsia and fetal growth restriction have a fetal genetic component, and thus can be inherited on the paternal side.[7–9] Thus, both immunological and genetic factors contributed by the father may be of importance for abnormal placentation.

Previous studies have failed to show a protective effect of partner change for recurrence of pre-eclampsia.[10–12] Studies on the effect of partner change on risks of pre-eclampsia and intrauterine growth restriction in women without prior corresponding complication have yielded diverging results.[10–18] Reasons for this could be failure to separate out diseases associated with abnormal placentation, and that most earlier studies in this field lack control of important confounders.[10–12 14–18]

We conducted a nationwide Swedish study and included a cohort of 446 000 women with their first and second births during the years 1990–2006 with available information on important factors influencing pregnancy outcomes. We estimated the effect of partner change on risks of term (≥37 weeks) and preterm (<37 weeks) pre-eclampsia in the second pregnancy as well as giving birth to an infant small for gestational age, in women with or without corresponding complication in their first pregnancy.

MATERIAL AND METHOD

The Swedish Medical Birth Register, held by the Swedish National Board of Health and Welfare, contains data on more than 98% of all births in Sweden since 1973, including demographic data, information on reproductive history and complications during pregnancy, delivery and the neonatal period.[19] In Sweden antenatal care is standardised and free of charge. During the first antenatal visit, usually taking place at the end of the first trimester,[20] the mother is interviewed about her medical and obstetric history, including height, weight, smoking habits and years of involuntary childlessness before current pregnancy. Complications during pregnancy and delivery are classified according to the International Classification of Diseases (ICD) as noted by the responsible doctor at discharge from hospital. Information on each pregnancy and delivery is forwarded to the Birth Register through copies of standardised antenatal, obstetric and paediatric records. Individual record linkage between the Birth Register and other registers was possible through each individual's unique personal registration number, assigned to each Swedish resident.[21] Information on the infant's father from the first and second live births was collected through linkage to the Multigeneration Register, and information about fathers to stillbirths was (when available) collected through the Stillbirth Register, also held by Statistics Sweden. Information on the mothers' country of birth and highest level of formal education was obtained by individual linkage with the Register of Total Population and the Education Register (31 December 2005).

Study population

During the years 1990–2006, there were approximately 1.6 million births recorded in the Birth Register. During this period, there were in all 452 256 women with their first and second consecutive singleton pregnancies resulting in a birth at 22 weeks gestation or later. We excluded 5797 women with essential hypertension or pre-pregnancy diabetes mellitus as noted in first or second pregnancy. These women were identified at the first antenatal visit (using check-boxes) and/or at the discharge from hospital after the delivery (using diagnostic codes for essential hypertension (ICD-9 codes 642A-C; ICD-10 codes O10-11 and I10-15). Thereafter, the study population included 446 459 women (table 1). We further excluded pregnancies with missing information on the father in first pregnancies (n=4206; 0.9%) or second pregnancies (n=1931; 0.4%) and the final study population included 440 322 women.

Main exposure variable

Our main exposure variable was change of partner between pregnancies. The personal registration number of the first infant's father was compared with that of the second infant's father. Paternity was categorised into same partner in the two pregnancies and changed partner between the two pregnancies.

Outcomes in second pregnancy

Pre-eclampsia was defined through ICD-9 and ICD-10 codes 642E-G and O14-15, respectively. Pre-eclampsia was categorised into term (gestational age 37 weeks or more at birth) and preterm (gestational age less than 37 weeks at birth). In Sweden, gestational age is assessed by ultrasound scans in 97% of women, usually around the 17th week of gestation.[22] If no early second trimester ultrasound scan was available, the last menstrual period was used to calculate gestational age at delivery. The clinical definition of pre-eclampsia during these years was a rise in blood pressure (≥140/90) combined with proteinuria (≥0.3 g/24 h). The quality of the diagnosis of pre-eclampsia has been validated previously: of 148 pregnancies coded as pre-eclampsia in the Birth Register, 137 (93%) had the disease according to the individual records.[23] When calculating risks of pre-eclampsia we included stillbirths, since stillbirth can be a degree of severity of the pre-eclampsia disease. During these years, stillbirth was defined as fetal death at 28 weeks of gestation or later. However, there is a poor reporting of fathers to stillbirths: information on fathers

Table 1 Rates of pregnancy complications in second pregnancy by maternal characteristics

	Adverse outcomes second pregnancy						
		Pre-eclampsia					
		Term (<37 weeks)		Preterm (<37 weeks)		Small for gestational age *	
Maternal characteristics	Total number	Number	Rate (%)	Number	Rate (%)	Number	Rate (%)
Partner							
Same	409922	4779	1.17	958	0.23	22984	5.9
Different	30400	417	1.37	133	0.44	2348	8.2
Data missing	6137	105	1.71	33	0.54	389	9.3
Year of first birth							
1990–1994	187733	2224	1.18	384	0.20	11869	6.7
1995–1999	137445	1760	1.28	438	0.32	7904	6.2
2000–2006	121281	1317	1.09	302	0.25	5948	5.2
Interpregnancy interval (years)							
<1	84268	753	0.89	110	0.13	4914	6.2
1–3.9	305769	3614	1.18	698	0.23	16799	5.8
4–6.9	41681	675	1.62	207	0.50	2837	7.3
7–9.9	10773	166	1.54	77	0.71	821	8.1
≥10	3727	87	2.33	30	0.80	325	9.3
Data missing	241	6	2.49	2	0.83	25	14.0
Age second pregnancy (years)							
<25	60195	585	0.97	109	0.18	4342	7.7
25–29.9	165336	1872	1.13	332	0.20	9152	5.9
30–34.9	160041	1942	1.21	457	0.29	8601	5.7
≥35	60887	902	1.48	226	0.37	3626	6.4
Body mass index second pregnancy (kg/m^2)							
<18.5	9655	48	0.50	18	0.19	1284	13.9
18.5–24.9	242986	1915	0.79	476	0.20	15032	6.5
≥25	125646	2569	2.04	444	0.35	5354	4.6
Data missing	68172	767	1.13	186	0.27	4051	6.3
Height (cm)							
<162	88848	1134	1.28	301	0.34	8184	9.9
162–171	253815	3003	1.18	615	0.24	13653	5.7
≥172	94122	1063	1.13	186	0.20	3213	3.6
Data missing	9674	101	1.10	22	0.23	671	7.3
Smoking habits second pregnancy							
Non-smoker	375372	4646	1.24	924	0.25	18766	5.3
Smoker	45091	354	0.79	77	0.17	5491	12.8
Data missing	25996	301	1.16	123	0.47	1464	6.0
Involuntary childlessness second pregnancy (years)							
<1	427908	4958	1.16	1025	0.24	24615	6.1
1–2	12080	209	1.73	48	0.40	728	6.5
≥3	5441	121	2.22	38	0.70	378	7.6
Data missing	1030	13	1.26	13	1.26	0	
Mother's country of birth							
Nordic	394349	4903	1.24	981	0.25	20875	5.6
Non-Nordic	48097	370	0.77	129	0.27	4442	9.7
Data missing	4013	28	0.70	14	0.35	404	10.5
Education (years)							
<13	130901	1809	1.38	342	0.26	8951	7.3
13–14	177302	2171	1.22	449	0.25	8903	5.4
≥15	102759	1064	1.04	237	0.23	4577	4.7
Data missing	35497	257	0.72	96	0.27	3290	9.8
Total	446459	5301	1.19	1124	0.25	25721	6.1

was available in 574 of 1698 (34%) stillbirths in first pregnancy and in 467 of 1030 (45%) of stillbirths in second pregnancy.

Being born small for gestational age (SGA) was used as a proxy for intrauterine growth restriction and was defined as a birth weight at or below the 10th percentile for the

mean birth weight for gestational age according to the sex-specific Swedish fetal growth curve.[24] When analysing risks of SGA infant we only included live births. Giving birth to an SGA infant is associated with pre-eclampsia, and in the analyses of SGA we therefore excluded women with pre-eclampsia in first or second pregnancy. We further excluded 4655 pregnancies with missing information on infant's birth weight at first or second birth. The total population when calculating risks of SGA at second delivery included 420 089 women (table 1), among whom information on partners from both childbirths was available in 415 922 women (table 2).

Covariates

We calculated interpregnancy interval as the number of completed years between birth of the first infant and the estimated date of conception of the second infant. Information on maternal body mass index (BMI), height, smoking habits and years of involuntary childlessness before the pregnancy was collected from the first antenatal visit in second pregnancy, and data on maternal age were collected at second birth. Categorisations were made according to table 1.

Mother's country of birth was categorised into born in a Nordic country (Sweden, Norway, Denmark, Finland or Iceland) and born in a non-Nordic country, and years of formal education were categorised into three levels according to table 1.

Statistics

The effects of partner change of risks of term and preterm pre-eclampsia 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. OR with 95% CI were estimated by unconditional logistic regression analysis after adjustments for maternal characteristics. When we calculated risks of SGA infant in second pregnancy we only included live births and pregnancies with pre-eclampsia were excluded. Adjustments were made for maternal factors associated with risks of pre-eclampsia and SGA, including interpregnancy interval, maternal age, BMI, height and smoking habits in second pregnancy, years of involuntary childlessness before second pregnancy, maternal country of birth and years of formal education. Further, we adjusted for year of second birth, categorised into before 1997 and 1997 or later.

We hypothesised that the impact of partner change on risk of disorders associated with abnormal placentation may depend on the presence of corresponding complication in prior pregnancy. We therefore performed interaction analyses between pre-eclampsia in first pregnancy (in three categories: no pre-eclampsia/term pre-eclampsia/preterm pre-eclampsia) and partner change (same vs different partner) on risks of term and preterm pre-eclampsia in the second pregnancy. Further, we performed an interaction analysis between SGA in first pregnancy (no/yes) and partner change on risk of SGA in a second pregnancy. All analyses were performed using the Statistical Analysis Software V.9.1 (SAS Institute Inc, Cary, North Carolina, USA).

Ethics committee approval

The study was approved by one of the Regional Ethical Review Boards in Stockholm, Sweden. Reference number: 2011/2:2. Date of approval: 3 March 2011. The board did not require the women to provide informed consent.

RESULTS

The overall rates of term (≥37 weeks) and preterm (<37 weeks) pre-eclampsia in first pregnancy were 2.8% and 0.47%, respectively, whereas 12.1% gave birth to an SGA infant. The corresponding rates in second pregnancy were about half as large as in first pregnancy (term pre-eclampsia 1.2%, preterm pre-eclampsia 0.25% and SGA 6.1%).

In table 1 we notice that rates of pre-eclampsia and SGA in second pregnancy were affected by maternal characteristics. The rates of pre-eclampsia in second pregnancy increased with interpregnancy interval, maternal age, BMI and years of involuntary childlessness before second pregnancy. Smoking was associated with reduced rates of pre-eclampsia, and women born in non-Nordic countries had a lower rate of term pre-eclampsia, compared to those born in Nordic countries. The rates of SGA in second pregnancy were inversely related to maternal height and BMI. Smokers had higher SGA rates than non-smokers, and the rates of SGA increased with years of involuntary childlessness before second pregnancy, longer interpregnancy interval and lower education.

Table 2 displays rates of pregnancy complications in second pregnancy and maternal characteristics by partner change between pregnancies. Compared to women who did not change partners, women who changed partners had higher rates of term and preterm pre-eclampsia and of SGA. Further, women who changed partners had longer interpregnancy intervals, were more often smokers, younger than 25 years or older than 35 years and they were slightly more often overweight (BMI≥25). Finally, compared to women who did not change partners, women who changed partner had slightly more often at least 1 year of involuntary childlessness before pregnancy, were lower educated (less than 13 years) and were less often born in a non-Nordic country.

As previous Scandinavian studies have reported a decreased risk of pre-eclampsia (term and preterm) after partner change in second pregnancy in women without pre-eclampsia in first pregnancy,[10 12 17] we reanalysed our dataset and controlled only for the same categorised variables as previous studies (interpregnancy interval, maternal age and year of birth).[12 17] In this analysis, we also found a reduced risk of pre-eclampsia after partner change (OR 0.85; 95% CI 0.76 to 0.96). To investigate whether this reduction in risk could be

Table 2 Partner change between pregnancies by second pregnancy complications and maternal characteristics

		Partner	
	Number	Same Rate (%)	Different Rate (%)
Second pregnancy complications			
Term (>37 weeks) pre-eclampsia	5196	1.17	1.37
Preterm (<37 weeks) pre-eclampsia	1091	0.23	0.44
SGA†	25322	5.9	8.2
Maternal characteristics			
Year of first birth			
1990–94	184949	40.9	57.1
1995–99	135594	30.7	32.5
2000–06	119779	28.4	10.4
Interpregnancy interval (years)*			
<1	82500	20	2.3
1–3.9	302760	71.6	31
4–6.9	40848	7.2	37
7–9.9	10453	1	20.5
>10	3567	0.2	9.2
Data missing	194		
Age second delivery (years)*			
<25	58938	12.9	19.7
25–29.9	163269	37.2	35.8
30–34.9	158168	36.4	29.4
>35	59947	13.5	15
Body mass index second pregnancy*			
<18.5	9519	2.2	2.2
18.5–24.9	240089	54.7	52.4
>25	123731	27.9	30.8
Data missing	66983	15.3	14.6
Height (cm)*			
<162	87443	19.7	21.6
162–171	250495	56.9	57.2
>172	92890	21.1	19.4
Data missing	9494	2.2	1.8
Smoking habits second pregnancy*			
Non-smoker	370797	85.6	65.7
Smoker	43965	8.6	28.2
Data missing	25560	5.8	6.1
Involuntary childlessness second pregnancy (years)*			
<1	422561	96	94.9
1–2	11943	2.7	3.4
>3	5351	1.2	1.7
Data missing	467	0	0
Mother's country of birth*			
Nordic	389279	88.2	91.8
Non-Nordic	47213	10.9	7.7
Data missing	3830	0.9	0.5
Education (years)*			
<13	128533	27.5	52.5
13–14	175222	40.2	33.8
>15	101778	24.1	10.1
Data missing	34789	8.2	3.6
Total	440322	409922 (93.1%)	30400 (6.9%)

Pregnancies with unknown information on partner change (n=6137) are excluded from this table.
The total population when calculating rates of small for gestational age (SGA) was 415 922 since the population was restricted to live births and pregnancies with pre-eclampsia or missing information on the infant's weight were excluded.
*p<0.0001.
†SGA, small for gestational age, was defined as a birth weight at or below the *10th percentile* for the mean birth weight for gestational age according to the sex specific Swedish fetal growth curve.[24]

Table 3 Risks of term (≥37 weeks) and preterm (<37 weeks) pre-eclampsia in a second pregnancy by change of partner between pregnancies

	Pre-eclampsia in second pregnancy				
			OR (95% CI)		
Pre-eclampsia in first pregnancy	Number	Rates (%)	Crude	Adjusted*	Fully adjusted†
Term					
No					
Same partner	3362	0.85	Reference	Reference	Reference
Different partner	340	1.15	1.36 (1.22 to 1.52)	0.86 (0.75–0.98)	0.97 (0.84–1.14)
Term					
Same partner	1142	9.89	Reference	Reference	Reference
Different partner	67	9.19	0.92 (0.71–1.20)	0.98 (0.73–1.31)	1.03 (0.74–1.44)
Preterm					
Same partner	275	14.20	Reference	Reference	Reference
Different partner	10	8.26	0.54 (0.28–1.05)	0.72 (0.36–1.47)	0.82 (0.37–1.80)
Preterm					
No					
Same partner	669	0.17	Reference	Reference	Reference
Different partner	113	0.38	2.27 (1.86–2.77)	0.97 (0.76–1.24)	1.21 (0.90–1.63)
Term					
Same partner	149	1.29	Reference	Reference	Reference
Different partner	14	1.92	1.50 (0.86–2.61)	0.80 (0.42–1.53)	0.92 (0.43–1.96)
Preterm					
Same partner	140	7.23	Reference	Reference	Reference
Different partner	6	4.96	0.67 (0.29–1.55)	0.42 (0.16–1.06)	0.24 (0.07–0.88)

*Adjusted for interpregnancy interval.
†Fully adjusted model. Adjustments were made for interpregnancy interval, maternal age, early pregnancy body mass index, height and smoking habits in second pregnancy, years of involuntary childlessness before second pregnancy, mother's country of birth and years of formal education, and the year of second birth.

attributable to other factors that differed between women who changed and did not change partners, other variables were added to this model. When we only added smoking or BMI, corresponding ORs were no longer significantly reduced (OR 0.93; 95% CI 0.82 to 1.05; and OR 0.95; 95% CI 0.83 to 1.08, respectively). Finally, when we controlled for all confounders (BMI, height, smoking habits, year of involuntary childlessness, maternal country of birth and years of formal education), we found no effect of partner change on risk of pre-eclampsia (OR 0.97; 95% CI 0.85 to 1.11; results not shown in table).

We found significant interactions between history of pre-eclampsia and partner change on risks of preterm and term pre-eclampsia in a second pregnancy ($p<0.001$, respectively). Further, we also found significant interactions between history of SGA and partner change on risk of SGA in a second pregnancy ($p<0.001$). Analyses of the effects of partner change on risks of pre-eclampsia (term and preterm) and SGA in second pregnancy were therefore stratified by presence or absence of corresponding complication in first pregnancy.

Table 3 displays rates and risks of term and preterm pre-eclampsia in second pregnancy in women with or without corresponding complication in first pregnancy by partner change between pregnancies. In women without pre-eclampsia in first pregnancy, unadjusted risks of term and preterm pre-eclampsia in second pregnancy were higher in women who changed partner between pregnancies than in women who did not. In adjusted analyses, partner change did not increase the risk of term pre-eclampsia, but there was a weak tendency of increased risk of preterm pre-eclampsia in the fully adjusted model.

In women who had a term pre-eclampsia in first pregnancy, partner change did not influence risks of term or preterm pre-eclampsia (table 3). However, in women who had preterm pre-eclampsia in first pregnancy, partner change was strongly protective for recurrence of preterm pre-eclampsia, but there was no significant protective effect of partner change on risk of term pre-eclampsia.

Table 4 displays risks of giving birth to an SGA infant in a second non-pre-eclamptic pregnancy by partner change between pregnancies. Among women who did not give birth to an SGA infant in first pregnancy, partner change was associated with a slightly increased risk of SGA infant in second pregnancy also in the fully adjusted model. In women whose first birth was a SGA birth, partner change was protective for a second SGA birth.

DISCUSSION

The findings in this study support a paternal influence on placentation. Women who in their first pregnancy had preterm pre-eclampsia or an SGA infant decreased their risks for recurrence of the disorder if they changed

Table 4 Risks of giving birth to an infant small for gestational age (SGA) infant in second pregnancy by change of partner between pregnancies, when excluding first and second pregnancies with pre-eclampsia

	SGA in second pregnancy				
			OR (95% CI)		
SGA in first pregnancy	Number	Rates (%)	Crude	Adjusted*	Fully adjusted†
No					
Same partner	13556	4	Reference	Reference	Reference
Different partner	1539	6.2	1.60 (1.52 to 1.69)	1.44 (1.35 to 1.54)	1.15 (1.07 to 1.24)
Yes					
Same partner	9428	20.4	Reference	Reference	Reference
Different partner	809	20.1	0.98 (0.91 to 1.06)	0.89 (0.81 to 0.98)	0.75 (0.67 to 0.84)

*Adjusted for interpregnancy interval.
†Fully adjusted model. Adjustments were made for interpregnancy interval, maternal age, early pregnancy body mass index, height and smoking habits in second pregnancy, years of involuntary childlessness before second pregnancy, mother's country of birth and years of formal education and the year of second birth.

partner. Further, women who did not give birth to an SGA infant at their first delivery slightly increased their risk of an SGA birth at their second delivery if they changed partner between pregnancies.

A major strength of the present study is the nationwide population-based design with a very small proportion of unidentified fathers (around 1%), although some misclassification of paternity, as in all studies based on self-reported information of fatherhood, is expected. The prospective data collection precludes recall bias. The size of the study population enabled us to separate preterm from term pre-eclampsia and to analyse risk of SGA after excluding pre-eclamptic pregnancies. As information on BMI was available from 1992 onwards, we choose to restrict our study population to women with their two first single births between 1990 and 2006. This restriction resulted in a low number of recurrent preterm pre-eclampsia, especially in the group of women who changed partners between pregnancies. However, the same restriction also resulted in that we only used ICD-9 and ICD-10 codes when defining pre-eclampsia, which is a strength compared to earlier Scandinavian studies.[10 12 17] Although we had the opportunity to account for several important possible confounders that were not controlled for in earlier studies, we cannot exclude that our findings partly are results of unmeasured confounding. We were not able to control for previous semen exposure, abortions and miscarriages, although this might be partially controlled for with interpregnancy interval and involuntary childlessness. Another limitation is that we did not have information on paternal characteristics, such as birth weight, height and BMI which could confound at least the SGA results.[25]

Results from several epidemiological studies suggest that some fathers might be less genetically favourable when it comes to successful placentation, sometimes referred to as the dangerous father hypothesis.[26] The risk of pre-eclampsia has been shown to be higher in pregnancies fathered by men who themselves are born in a pre-eclamptic pregnancy[5 7] or who previously fathered a pre-eclamptic pregnancy in another woman.[6] Other studies suggest that priming against partner-specific antigens is important for tolerance induction, the primipaternity hypothesis.[4 26] There are reports of increased pre-eclampsia and SGA risks in primigravidas with short duration of sperm exposure from her partner before pregnancy,[27 28] an increased risk of pre-eclampsia in pregnancies conceived via donator insemination[29] and a partner-specific protection from pre-eclampsia after abortion.[14] Further, most of the early studies on pre-eclampsia risk in multiparas report an increased risk of the disorder after partner change.[11 15 16] However, women who change partners between pregnancies generally have longer interpregnancy intervals than women who do not change partners and risk of pre-eclampsia increases with length of interpregnancy interval. Three large Scandinavian cohort studies report, after controlling for interpregnancy interval (maternal age and year of birth), a decreased risk of pre-eclampsia after partner change in women without prior pre-eclampsia.[10 12 17] Results from our study confirm and extend on these findings. When we controlled for the same variables as previous studies,[12 17] we found a reduced risk of pre-eclampsia after partner change. Interpregnancy interval may reflect different underlying factors in women with and without partner change. For example, among women who do not change partners, long interpregnancy intervals are more common among women with chronic diseases and subfertile women.[30] In our investigation, we found that women who changed partners differed from women who did not change partners with respect to all studied risk factors, including maternal education, BMI and notably smoking. When we adjusted for such variables, we found no association between partner change and risk of pre-eclampsia in women without prior pre-eclampsia, suggesting that previous studies suffer from residual confounding.

In our analyses of risks of SGA, we expanded our analyses on effect of partner change on risks associated with abnormal placentation in second pregnancy. Similar to the findings of pre-eclampsia, we found that partner change reduced the recurrence risk of SGA. In addition, among women with no previous SGA birth, partner

change increased the risk of SGA, supporting the hypothesis that partner change increases the risk of a placental dysfunction disorder in women with a prior normal pregnancy. The non-significant association between partner change and risk of preterm pre-eclampsia in women with a first normal pregnancy could be an effect of the lower prevalence of preterm pre-eclampsia.

In this study we report a novel finding of protection from recurrence of pregnancy disorders associated with abnormal placentation after a change of partner. Women with preterm pre-eclampsia or SGA infant in their first pregnancy decreased their risk of recurrence of the disorder in next pregnancy if they had changed partners. Abnormal placentation has a stronger association to preterm than term pre-eclampsia,[3 31 32] and earlier studies have probably failed to show this association since they have not separated preterm from term pre-eclampsia.[10–17] We have only found one earlier study of SGA recurrence after partner change and this study could not show a protective effect of partner change.[18] This study was of a much smaller sample size than our study and did not control for several important confounders.

We found the highest rates of abnormal placental disorders in parous women who also had the disorder in first pregnancy, independent if they changed partner between pregnancies. This indicates that maternal factors have the major impact on successful placentation. Our findings especially support the 'dangerous father' hypothesis.[26] How the father exerts this effect is unknown, but a genetic effect is likely. Trophoblast cells are shown to express various receptors capable of immune modulation and even spiral artery remodelling.[33] Paternal genetic polymorfism in receptors or transmitters involved in immune regulation or vascular remodelling might be involved in placentation and in adverse pregnancy outcomes associated with abnormal placentation.[26 33–35] Paternal-specific human lymphocyte antigen-C is expressed by trophoblast, interact with maternal uterine natural killer cells, and a mismatch in the couple-specific interaction can lead to a susceptibility to abnormal placentation.[35] There might also be a paternal effect on placentation through variation in composition of the seminal fluid. Seminal fluid might have an immunomodulatory role in the uterus, probably through high levels of transforming growth factor β and probably also other cytokines.[36]

In conclusion, our findings indicate that there is a paternal effect in the development of placental dysfunction disorders.

Contributors A-KW had the original idea to the study. All authors contributed to the design of the study. A-KW performed the analyses and wrote the first draft of the manuscript. All authors made substantial contribution to the interpretation of results and manuscript revision. Further, they had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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Competing interests None.

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The paternal role in pre-eclampsia and giving birth to a small for gestational age infant; a population-based cohort study

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Paper II

OBSTETRICS

Risk of placental dysfunction disorders after prior miscarriages: a population-based study

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OBJECTIVE: The objective of the investigation was to study the association between prior miscarriages and the risks of placental dysfunction disorders, including preeclampsia, stillbirth, birth of a small for gestational age (SGA) infant, placental abruption, and spontaneous preterm birth.

STUDY DESIGN: In a population-based cohort study including 619,587 primiparous women, we estimated risks of placental dysfunction disorders for women with 1 (n = 68,185), 2 (n = 11,410) and 3 or more (n = 3823) self-reported prior miscarriages. Risks were calculated as odds ratios by unconditional logistic regression analysis and adjustments were made for maternal age, early pregnancy body mass index, height, smoking habits, country of birth, years of formal education, in vitro fertilization, chronic hypertension, pregestational diabetes, hypothyroidism, systemic lupus erythematosis, fetal sex, and year of childbirth.

RESULTS: Compared with women with no prior miscarriage, women with 1 prior miscarriage had almost no increased risks. Women with 2 prior miscarriages had increased risks of spontaneous preterm birth, preterm (<37 weeks) SGA infant, and placental abruption. The rates of all disorders were higher for women with 3 or more prior miscarriages compared with women without prior miscarriages: preeclampsia, 5.83% vs 4.27%; stillbirth, 0.69% vs 0.33%, SGA infant, 5.09% vs 3.22%, placental abruption, 0.81% vs 0.41%; and spontaneous preterm birth, 6.45% vs 4.40%. The adjusted odds ratios for preterm (<37 weeks) disorders in women with 3 prior miscarriages were approximately 2.

CONCLUSION: History of 2 or more miscarriages is associated with an increased risk of placental dysfunction disorders and should be regarded as a risk factor in antenatal care.

Key words: intrauterine growth restriction, miscarriage, placental abruption, preeclampsia, spontaneous preterm birth, stillbirth

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Failure of implantation has been suggested to be involved not only in the pathogenesis of miscarriage but also in pregnancy complications associated with placental dysfunction (ie, preeclampsia, stillbirth, intrauterine growth restriction, placental abruption, and spontaneous preterm birth).[1-3] Implantation and placentation can be presented as a continuous process regulated by complex signaling between decidua, immune cells, and fetal tissue.[3]

Vascular adaptation of the uterus, including angiogenesis and spiral artery remodeling, is a key feature in early placental development.[4] Former studies have shown that both miscarriage and placental dysfunction disorders are associated with an imbalance in angiogenic activity, disturbances in uterine blood supply, and placental oxidative stress.[4-7] It has been hypothesized that a complete implantation/placentation failure may result in a miscarriage, whereas a partial failure may result in late pregnancy complications associated with placental dysfunction.[5,8]

Based on the similarities in pathogenesis of miscarriage and placental dysfunction disorders, a history of prior miscarriages might be associated with increased risk of placental dysfunction disorders. This hypothesis is supported by a few previous studies, in which the exposure was either miscarriage or in vitro fertilization (IVF).[9-14] In some of these studies, parity was not controlled for,[10-12] or primiparous women exposed for prior miscarriages were compared with parous women.[13,14] Comparing primiparous women with prior miscarriages with a reference group of parous women might overestimate risks because placental dysfunction disorders are more prevalent in primiparous compared with parous women.[15]

In this study we had the opportunity to obtain data on the number of prior miscarriages and pregnancy complications from more than 600,000

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primiparous women. We hypothesized the following: (1) there is an association between prior miscarriage and the placental dysfunction disorders preeclampsia, stillbirth, intrauterine growth restriction, placental abruption, and spontaneous preterm birth in primiparous women; (2) the strength of the association increases by the number of previous miscarriages; and (3) risks are higher in preterm (<37 weeks) than in term placental dysfunction disorders (≥37 weeks) because preterm disorders are stronger related to placentation failure than term disorders.[16,17]

Materials and Methods

The Swedish Medical Birth Register contains data on more than 98% of all births in Sweden since 1973,[18] including demographic data, information on reproductive history and complications during pregnancy, delivery, and the neonatal period. In Sweden antenatal care is standardized and free of charge. During the first antenatal visit, usually taking place at the end of the first trimester,[19] the mother is interviewed about her medical and obstetric history. Information about maternal characteristics such as weight, height, and smoking habits are also recorded.

After delivery, the responsible doctor records women's diseases and complications during pregnancy and delivery, according to the *International Classification of Diseases* (ICD). Information about pregnancy and delivery is forwarded to the Birth Register through copies of standardized antenatal, obstetric, and pediatric records. Individual record linkage between the Birth Register and other registries is possible through each individual's unique personal registration number, assigned to each Swedish resident.[20]

Study population and exposure variable

Women giving birth to their first singleton infant at 22 weeks of gestation or later during the period 1995-2009 (n = 619,587) were included. Exposure variable was number of self-reported prior miscarriages, recorded by the midwife at the first antenatal visit. Number of miscarriages was categorized into no prior miscarriage (n = 536,169), 1 miscarriage (n = 68,185), 2 miscarriages (n = 11,410), and 3 or more miscarriages (n = 3,823).

Outcomes

Placental dysfunction disorders included preeclampsia, stillbirth, intrauterine growth restriction, placental abruption, and spontaneous preterm birth.

Preeclampsia was defined through the ICD-9 and ICD-10 codes 642E-G and O14-O15. The clinical definition of preeclampsia during the study period was a rise in blood pressure (≥140/90 mm Hg) combined with proteinuria (≥0.3 g/24 hours or +1 or more on dipstick on at least 2 occasions). The quality of the diagnosis of preeclampsia has been validated previously: of 148 pregnancies coded as preeclampsia in the Birth Register, 137 (93%) had the disease according to the individual records.[21] During most of the study period (before July 1, 2008), stillbirth was defined as fetal death at 28 weeks of gestation or later. Analysis of stillbirth was therefore restricted to births at 28 weeks or later. The total population when calculating risk of stillbirth included 617,708 births.

Being born small for gestational age (SGA) was used as a proxy for intrauterine growth restriction. SGA was defined as a birthweight below 2 SD from the mean birthweight for gestational age, according to the sex-specific Swedish fetal growth curve.[22] Only live births were included in this analysis, and pregnancies with missing information on infant's birthweight were excluded (n = 2252). The total population when calculating risk of SGA included 615,130 births. Placental abruption was defined through ICD-9 and ICD-10 codes 641C and O45.

Preeclampsia, stillbirth, birth of an SGA infant, and placental abruption were categorized into preterm (birth before 37 weeks of gestation) and term (birth at 37th week of gestation or later). In Sweden, gestational age is assessed by ultrasound scans in 97% of women, usually around the 17th week of gestation.[23] If no early second-trimester ultrasound scan was available, the last menstrual period was used to calculate gestational age at delivery.

Spontaneous preterm birth was defined as a birth before 37 gestational weeks with a spontaneous onset. At delivery, the responsible midwife records start of labor using the check boxes; spontaneous labor, induced or caesarean section. A total of 6720 births had no information on labor onset and were excluded from this analysis. All births with a diagnosis of preterm premature rupture of the membranes (ICD-9 and ICD-10 codes 658B and O42) were defined as a spontaneous onset in the study. Spontaneous preterm births were categorized into very preterm births (birth before 32 weeks of gestation) and moderately preterm births (birth from 32 to 36 full weeks of gestation). The birth of an SGA infant was excluded from the analysis. The total population when calculating the risk of spontaneous preterm births included 596,659 births.

Covariates

Information about maternal age and fetal sex was collected at delivery, whereas information about body mass index (BMI), height, smoking habits, cohabitation with infant's father, and IVF was collected from the first antenatal visit. The variables were categorized according to Table 1. To achieve information on the mothers' country of birth and highest level of formal education, individual linkages with the Register of Total Population and the Education Register (Dec. 31, 2010) were performed. The mother's country of birth was categorized to Nordic (Denmark, Finland, Iceland, Norway, and Sweden) and non-Nordic countries, and years of formal education were categorized into 3 levels according to Table 1.

Women with chronic hypertension, pregestational diabetes, hypothyroidism, or systemic lupus erythematosis (SLE) were identified with check boxes from the first antenatal visit and/or diagnostic codes from hospital discharge: chronic hypertension (check box; ICD-9 codes 642A-C; ICD-10 codes O10-11 and I10-15), pregestational diabetes (check box; ICD-9 codes 648A and 250; ICD-10 codes E10-E14 and O240-O243),

hypothyroidism (ICD-9 code 244 and ICD-10 code E03), and SLE (check box; ICD-9 code 710A and ICD-10 code M32).

Statistical methods

The associations between 1, 2, and 3 or more prior miscarriages on the risks of preeclampsia, stillbirth, SGA birth, placental abruption, and spontaneous preterm birth were estimated in primiparous women, using women with no prior miscarriage as reference. Odds ratios with 95% confidence intervals were calculated by unconditional logistic regression analysis with adjustments for maternal and infant characteristics. The following variables were initially included in our multiple logistic regression model: maternal age, early pregnancy BMI, height, smoking habits, cohabitation with infant's father, mother's country of birth, years of formal education, IVF, chronic hypertension, pregestational diabetes, hypothyroidism, SLE, fetal sex, and year of birth (categorized into years 1995-1999, 2000-2004, and 2005-2009). Cohabitation with infant's father did not influence any of our outcomes and was therefore excluded from the final model.

Because the causes of miscarriages may vary with maternal age,[24,25] we considered that age might modify the effect of miscarriages on the outcomes. Effect measure modification was investigated by introducing cross-product terms between number of miscarriages and maternal age as categorical variables in the regression models of each outcome; a value of $P < .05$ was considered significant. There was no effect measure modification between the number of prior miscarriages and maternal age concerning the outcomes: preeclampsia, $P = .24$; stillbirth, $P = .41$; SGA, $P = .08$; placental abruption, $P = .12$; or spontaneous preterm birth, $P = .84$. All analyses were performed using the Statistical Analysis Software version 9.2 (SAS Institute, Inc, Cary, NC).

Details of ethics approval

The study was approved by one of the regional ethical review boards in

TABLE 1
Number of prior miscarriages by maternal characteristics

		Prior miscarriages			
Maternal characteristic	**n**	**0, %**	**1, %**	**2, %**	**≥3, %**
Age, y					
<25	159,004	26.6	21.6	16.6	12.8
25-29	230,568	38.0	34.0	29.6	24.6
30-34	168,425	26.8	30.0	32.0	33.7
≥35	60,000	8.7	14.5	21.8	29.0
Data missing	1590				
BMI, kg/m^2					
<18.5	15,843	3.0	2.6	2.5	1.5
18.5-24.9	356,391	66.9	63.8	60.3	59.2
25.0-29.9	119,136	21.9	23.7	25.8	25.6
≥30.0	45,472	8.2	9.9	11.3	13.7
Data missing	82,745				
Height, cm					
<162	120,680	21.0	21.2	21.5	22.7
162-171	325,780	56.9	56.7	57.0	56.0
≥172	126,360	22.1	22.1	21.5	21.3
Data missing	46,767				
Smoking (cigarettes/d)					
0	524,055	90.3	88.3	87.8	86.8
1-9	44,546	7.5	8.9	9.0	8.9
≥10	13,396	2.2	2.8	3.1	4.3
Data missing	37,590				
Mothers' country of birth					
Nordic	518,084	84.8	85.3	85.1	86.1
Non-Nordic	92,103	15.2	14.7	14.9	13.9
Data missing	9400				
Education, y					
≤9	48,601	8.0	8.8	9.4	10.3
10-14	341,539	57.1	58.2	58.1	58.2
≥15	206,798	34.9	33.0	32.5	31.4
Data missing	22,649				
IVF					
No	603,754	97.7	96.0	94.1	92.5
Yes	15,833	2.3	4.0	5.9	7.5
Chronic hypertension					
No	616,243	99.5	99.4	99.2	99.1
Yes	3344	0.5	0.6	0.8	0.9

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TABLE 1
Number of prior miscarriages by maternal characteristics *(continued)*

Maternal characteristic	n	Prior miscarriages 0, %	1, %	2, %	≥3, %
Pregestational diabetes					
No	616,281	99.5	99.4	99.1	99.1
Yes	3306	0.5	0.6	0.9	0.9
Hypothyroidism					
No	617,460	99.7	99.6	99.4	99.0
Yes	2127	0.3	0.4	0.6	1.0
SLE					
No	619,027	99.9	99.9	99.9	99.6
Yes	560	0.1	0.1	0.1	0.4
Fetal sex					
Male	318,748	51.5	51.3	51.0	51.7
Female	300,716	48.5	48.7	49.0	48.3
Missing	123				
Total	619,587	536,169	68,185	11,410	3823

BMI, body mass index; *IVF*, in vitro fertilization; *SLE*, systemic lupus erythematosis.

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Stockholm, Sweden. The reference number was 2012/2088-32.

RESULTS

Compared with women with no prior miscarriage, women with prior miscarriages were older, had a higher BMI, and were more often smokers. Furthermore, women with prior miscarriages were slightly more often born in a Nordic country, had shorter formal education, were more often pregnant after IVF treatment, and were more likely to have chronic hypertension, pregestational diabetes, hypothyroidism, and SLE (Table 1).

Preeclampsia and stillbirth

Compared with women with no prior miscarriage, women with 1 or 2 prior miscarriages did not have increased risks of preeclampsia or stillbirth. The rates of preeclampsia and stillbirth were higher in women with 3 or more prior miscarriages than in women without prior miscarriage: 5.83% vs 4.27% and 0.69% vs 0.33%, respectively. When we divided the outcomes into preterm and term disorders, the associations were significant only between 3 or more miscarriages and preterm disorders (Table 2).

Small for gestational age and placental abruption

Compared with women with no prior miscarriage, women with 1 prior miscarriage did not have increased risks of SGA or placental abruption. Women with 2 prior miscarriages had slightly increased risks of preterm SGA infant and placental abruption. The rates of an SGA infant and placental abruption were higher in women with 3 or more prior miscarriages than in women without prior miscarriage: 5.09% vs 3.22% and 0.81% vs 0.41%, respectively. The adjusted ORs for preterm SGA and placental abruption in women with 3 prior miscarriages were around 2 (Table 3).

Spontaneous preterm births

Compared with women with no prior miscarriage, women with prior miscarriages had an increased risk of spontaneous preterm birth and the risk showed a dose-response pattern. The rates of spontaneous preterm births for women with no prior miscarriage, 1, 2, and 3 or more prior miscarriages were 4.40%, 4.46%, 5.05%, and 6.45%, respectively. The association seemed strongest between 3 or more prior miscarriages and very preterm (birth before 32 weeks) births, with adjusted odds ratio, 2.60 (95% confidence interval, 1.86−3.64) (Table 4).

COMMENT

Main findings

In this large population-based study of primiparous women, we showed that prior miscarriages were associated with increased risks of the placental dysfunction disorders preeclampsia, stillbirth, SGA birth, placental abruption, and spontaneous preterm birth. The associations were strongest for 3 or more prior miscarriages and seemed stronger for preterm placental dysfunction disorders compared with term disorders. The results support the notion that miscarriages and placental dysfunction disorders might partially share the same pathogenesis.

Strengths and limitations

The major strength of our study was the large study population. This enabled us to stratify the exposure by number of miscarriages and also to study rare events like stillbirth and placental abruption and to subdivide these outcomes into preterm and term disorders. Another strength was the population-based design, suggesting that the results from this national study are generalizable to other settings. In contrast to some previous studies,[10,11,13] we were able to control for important confounders such as maternal smoking, BMI, and IVF as well as chronic hypertension, pregestational diabetes, hypothyroidism, and SLE. However, we had no information about other potential confounders, including thrombophilia and polycystic ovarian syndrome.[26,27] Exposure was measured as self-reported miscarriages, which might be both a strength and limitation. Self-reported information made it possible to include miscarriages experienced by the women regardless of a need for specialist care. However, we had no information about their underlying etiology or gestational length at

miscarriage. Another potential limitation is lack of data on prior induced abortions. In a recent review, induced abortions were associated with increased risks of placental abruption and low birthweight but a reduced risk of preeclampsia.[28]

Interpretation

A dose-response relationship was previously shown between prior miscarriages and spontaneous preterm birth, which is in agreement with our finding.[29,30] Regarding other outcomes, there are to our knowledge only 3 previous studies on the association between miscarriages and placental dysfunction disorders, including solely primiparous women in both the exposed and the reference group. Two of these studies investigated the effect of less than three prior miscarriages on preeclampsia or intrauterine growth restriction.[13,14] These results are in agreement with our findings, showing limited effect on the outcomes. The third study investigated the effect of 3 or more miscarriages on preeclampsia.[9] This study could not report a significant increased risk of preeclampsia, which may have been due to lack of power because the sample size of women with 3 or more miscarriages was only 130.

The results in this study are in accordance with the hypothesis that miscarriage and placental dysfunction disorders have a partially common pathogenesis of early placentation failure.[8] Vascularization of the endometrium is of main importance for successful implantation and placentation.[31] Vascular endothelial growth factor (VEGF) is an important proangiogenic factor,[32] and increased expression of VEGF in first-trimester decidua has been associated with both miscarriage and placental dysfunction disorders.[4,33] Increased angiogenic activity and a premature onset of the maternal circulation in early placental development could result in subsequent increase in oxidative stress.

It has been hypothesized that if these disturbances are severe, this may lead to a complete failure of early placentation and miscarriage.[6,33] However, if the failure is partial, the pregnancy might

TABLE 2
Risks of preeclampsia and stillbirth by number of prior miscarriages

Prior miscarriages	Preeclampsia total			Preterm preeclampsia			Term preeclampsia			Stillbirth[b] total			Preterm stillbirth[b]			Term stillbirth[b]		
	n	Rate, %	AOR[a] (95% CI)	n	Rate, %	AOR[a] (95% CI)	n	Rate, %	AOR[a] (95% CI)	n	Rate, %	AOR[a] (95% CI)	n	Rate, %	AOR[a] (95% CI)	n	Rate, %	AOR[a] (95% CI)
No	22,915	4.27	1.00	5095	0.95	1.00	17,820	3.32	1.00	1790	0.33	1.00	773	0.14	1.00	1017	0.19	1.00
Yes																		
1	2989	4.38	0.98 (0.94–1.02)	665	0.98	1.00 (0.92–1.09)	2324	3.41	0.98 (0.94–1.03)	238	0.35	0.96 (0.83–1.12)	97	0.14	0.95 (0.75–1.21)	141	0.21	0.98 (0.80–1.19)
2	501	4.39	0.94 (0.85–1.04)	123	1.08	1.07 (0.88–1.30)	378	3.31	0.92 (0.82–1.03)	41	0.36	1.02 (0.73–1.42)	14	0.12	0.94 (0.54–1.63)	27	0.24	1.08 (0.71–1.64)
≥3	223	5.83	1.23 (1.06–1.42)	67	1.75	1.62 (1.24–2.11)	156	4.08	1.17 (0.98–1.38)	26	0.69	1.62 (1.05–2.51)	14	0.37	2.25 (1.23–4.10)	12	0.32	1.29 (0.69–2.42)

AOR, adjusted odds ratio; *CI*, confidence interval.

[a] Adjustments were made for maternal age, body mass index, height, smoking, country of birth, years of formal education, in vitro fertilization, chronic hypertension, pregestational diabetes, hypothyroidism, systemic lupus erythematosis, fetal sex, and year of birth;

[b] Infants at least 28 weeks of gestation included in the analysis. Total population n = 617,708.

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TABLE 3
Risks of SGA and placental abruption by number of prior miscarriages

	SGA[a] total			Preterm SGA[a]			Term SGA[a]		
Prior miscarriages	n	Rate, %	AOR (95% CI)[b]	n	Rate, %	AOR (95% CI)[b]	n	Rate, %	AOR (95% CI)[b]
No	17,119	3.22	1.00	3468	0.65	1.00	13,651	2.56	1.00
Yes									
1	2241	3.31	0.98 (0.93–1.03)	504	0.74	1.08 (0.97–1.20)	1737	2.57	0.96 (0.91–1.01)
2	424	3.75	1.06 (0.95–1.18)	113	1.00	1.32 (1.07–1.62)	311	2.75	1.01 (0.89–1.14)
≥3	192	5.09	1.38 (1.18–1.62)	68	1.80	2.21 (1.69–2.88)	124	3.29	1.20 (0.99–1.46)
	Placental abruption total			**Preterm placental abruption**			**Term placental abruption**		
Prior miscarriages	n	Rate, %	AOR (95% CI)[b]	n	Rate, %	AOR (95% CI)[b]	n	Rate, %	AOR (95% CI)[b]
No	2225	0.41	1.00	1171	0.22	1.00	1054	0.20	1.00
Yes									
1	295	0.43	1.03 (0.90–1.18)	132	0.19	0.88 (0.72–1.07)	163	0.24	1.19 (1.00–1.42)
2	64	0.56	1.30 (1.00–1.70)	37	0.32	1.45 (1.01–2.08)	27	0.24	1.17 (0.78–1.75)
>3	31	0.81	1.82 (1.25–2.66)	20	0.54	2.23 (1.37–3.62)	11	0.29	1.49 (0.82–2.71)

AOR, adjusted odds ratio; *CI*, confidence interval; *SGA*, small for gestational age.

[a] SGA defined as a live birth infant with a birthweight for gestational age more than 2 SD below the sex-specific Swedish specific growth curve. Total population is 615,130; [b] Adjustments were made for maternal age, BMI, height, smoking, country of birth, years of formal education, in vitro fertilization, chronic hypertension, pregestational diabetes, hypothyroidism, SLE, fetal sex, and year of birth.

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remain viable but with a continued imbalance in angiogenic activity and insufficient vascular remodeling during the remaining placentation process.[4] Although we cannot exclude that the association reported is a result of residual confounding, we speculate that a causal relationship might exist between recurrent miscarriages and placental dysfunction disorders. This possible common pathogenesis might be explained by a genetic variance affecting the endometrial control of implantation or adaptation to pregnancy.[24,34,35] Genetic studies suggest that polymorphisms in the VEGF gene are associated with both recurrent miscarriages and placental dysfunction disorders.[36,37]

Placental dysfunction disorders have a recurrence risk and may predispose to each other (eg, SGA in 1 pregnancy predisposes for preeclampsia in subsequent pregnancy and vice versa).[38,39] This suggests that a failure of implantation/placentation could result in placental dysfunction disorders with different clinical features in successive pregnancies. This might be explained by an interaction between mothers susceptibility to placentation failure and fetal

TABLE 4
Risk of spontaneous preterm birth by number of prior miscarriages

	Spontaneous preterm birth[a]								
	Total (<37 wks)			Very (<32 wks)			Moderate (32-36 wks)		
Prior miscarriages	n	Rate, %	AOR[b] (95% CI)	n	Rate, %	AOR[b] (95% CI)	n	Rate, %	AOR[b] (95% CI)
No	22,738	4.40	1.00	2321	0.45	1.00	20,417	3.95	1.00
Yes									
1	2929	4.46	1.04 (1.00–1.09)	356	0.54	1.28 (1.13–1.45)	2573	3.92	1.02 (0.97–1.06)
2	552	5.05	1.18 (1.08–1.30)	87	0.80	1.84 (1.46–2.33)	465	4.26	1.11 (1.00–1.23)
≥3	232	6.45	1.50 (1.30–1.74)	44	1.22	2.60 (1.86–3.64)	188	5.22	1.38 (1.18–1.62)

AOR, adjusted odds ratio; *CI*, confidence interval.

[a] Spontaneous preterm birth defined as a birth before 37 gestational weeks with a spontaneous onset, including preterm premature rupture of the membranes. Small for gestational age births were excluded. Total population n = 596,659; [b] Adjustments were made for maternal age, body mass index, height, smoking, country of birth, years of formal education, in vitro fertilization, chronic hypertension, pregestational diabetes, hypothyroidism, systemic lupus erythematosis, fetal sex and year of birth.

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genes,[40,41] which are different in subsequent pregnancies.

We speculate that the fetal genotype might also determine the viability of a pregnancy in a mother prone to placentation failure. If the fetus has a gene variation, making it susceptible for implantation failure, this may result in a complete failure of early placentation and a subsequent miscarriage. However, if the gene combination of the fetus is more favorable, the pregnancy stays viable but with risk of later development of placental dysfunction disorder.

In women developing placental dysfunction disorders, the soluble VEGF receptor 1 (sFlt1) has been shown to be increased in the maternal circulation before the onset of symptoms.[41,42] Targeted therapy of preeclampsia aiming to remove or neutralize sFlt1 might become a reality in the future.[43,44] Recently increased sFlt1 levels in serum as well as enhanced sFLt1 expression in chorionic villus were observed in women who suffered from recurrent miscarriages.[45] One might speculate that both miscarriage and preeclampsia might be prevented by sFlt1 removal. Furthermore, women with prior recurrent miscarriages might be prone to high expression of placental sFlt1 during a viable pregnancy but with placentation failure. Therefore, these women might represent a group of patients destined to good response from sFlt1 removal in an attempt to treat or avoid later pregnancy complications such as preeclampsia, stillbirth, SGA birth, or placental abruption.

Conclusion

We report an association between increased risk of placental dysfunction disorders in primiparous women with prior miscarriages. Although the absolute risk increase was largely less than 1%, placental dysfunction disorders are serious complications of pregnancy and we advise that women with prior recurrent miscarriages should be managed as a risk group during antenatal care. Future studies are needed to evaluate the usefulness of increased surveillance during pregnancy and possibly prophylactic treatment, such as low-dose aspirin to prevent or delay the onset of placental dysfunction disorders in women with prior and especially recurrent miscarriages. ■

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Paper III

Prenatal exposure to preeclampsia is associated with accelerated height gain in early childhood

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Short title: Association between prenatal preeclampsia and accelerated childhood height gain

Abstract

Background: Preeclampsia is associated with low birth weight, both because of increased risks of preterm and of small-for-gestational-age births. Low birth weight is associated with accelerated childhood height gain and cardiovascular diseases later in life. The aim was to investigate if prenatal exposure to preeclampsia is associated with accelerated childhood height gain and if the possible association is independent of birth weight.

Methods: In a cohort of children prenatally exposed to preeclampsia (severe n=179, mild preeclampsia n=686) or unexposed (n=22,898) we estimated height gain between birth and five years of age. Linear regression models were used and adjusted for maternal characteristics including socioeconomic factors, height, body mass index (BMI) and diabetes, as well as for infant's breastfeeding and child's BMI at 5 years.

Results: Among term born (≥ 37 weeks) children, those prenatally exposed to preeclampsia were born shorter than unexposed (mean 50.5 *vs*. 51.1 cm; p<0.001), but were taller at five years (mean 112.2 *vs.* 111.6 cm; p<0.001). Further, among term born children the mean height gain was one cm more in exposed than in unexposed, with adjusted estimate 1.0 cm (95% CI 0.6 – 1.3 cm). The difference was even more pronounced when we restricted the exposure to severe preeclampsia, 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.

Conclusion: Prenatal exposure to preeclampsia is associated with accelerated height gain in children born with normal birth weight.

Introduction

Cardiovascular disease is a leading cause of death and imposes a substantial burden on the health care system.[1] According to the Developmental Origins of Health and Disease concept, early life environment induces changes in the development of both a fetus and a child, which may impact future risks of diseases.[2] More than 20 years ago an association between low birth weight and cardiovascular disease was first reported.[3] Recently, the question was raised if also prenatal exposure to preeclampsia is associated with future adverse cardiovascular health in the offspring.[4] Prenatal exposure to preeclampsia is associated with increase the risk of hypertension in young adults, [5] also in offspring born with normal birth weight.[4] Accelerated height gain in children is associated with hypertension in adulthood,[6, 7] and in infants born short, accelerated height gain during childhood is also associated with cardiovascular disease.[8] Accelerated growth in infancy is often seen in children born with low birth weight.[9, 10] Preeclampsia is strongly associated with low birth weight, both because of preterm birth and birth of small-for-gestational-age (SGA) infants.[11, 12] However, it is uncertain if prenatal exposure to preeclampsia is associated with accelerated growth in offspring born with normal birth weight. Regulation of pre- and postnatal growth is complex with various growth factors and hormones involved.[13] Imbalance in growth factor control may be related to both the pathogenesis of preeclampsia [14] and hypertension.[15]

We hypothesized that prenatal exposure to preeclampsia is associated with accelerated height gain during early childhood, and this association may be independent on birth weight. We investigated the association between prenatal exposure to preeclampsia and growth in height during the first five years of life in a population-based cohort of more than 23,000 children.

Methods

Data sources

Uppsala County mother and child database includes children born in Uppsala County during the years 2000-2007 and registered in the Uppsala County Child Health Care. The database was created by linkage between 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 through the personal identity number, uniquely assigned to each Swedish resident at birth or at immigration.

The Swedish Medical Birth Register includes information collected at antenatal visits, during and after delivery until discharge from the hospital. At the first antenatal visit the mother is interviewed about her reproductive history and smoking habits. The mother's weight is measured and recorded, while maternal height is generally self-reported. After delivery, the mother's age and the infant's birth weight, birth length and head circumference are recorded. The responsible doctor records complications during pregnancy and delivery, according to the International Classification of Diseases, tenth revision [ICD-10]. Information about the pregnancy and delivery is forwarded to the Birth Register through copies of standardized antenatal, obstetric and paediatric records.

The Uppsala County Child Health Register includes information collected from visits to child health care units, starting at 1 week of age and ending at six years. Attendance to child health care in Uppsala County is high, where 97% of children have at least six registered visits.[16] Parents are interviewed about breastfeeding of the child at the age of 1 week, 2, 4, 6, 10 and 12 months. Breastfeeding is registered as exclusive, partial and no breastfeeding. The child's height

and weight are measured at 18 months, 3, 4, and 5 years. Anthropometric measurements are not recorded in the Register if the appointments are more than 2 months earlier or later than the planned according to age of the child. Length of newborns and 18 month children (measured in a supine position) will be referred to as height throughout the article.

From the Registers of Total Population and Education, held by Statistics Sweden, we retrieved information on mother's country of birth and years of formal education, respectively.

Study population

The study population was children born in Uppsala County 2000-2007 with registered height at five years of age. During this period 31,951 children were born in Uppsala County. We excluded 445 infants with prenatal exposure to gestational hypertension, since we suspect that there may be some misclassification between preeclampsia and gestational hypertension. Gestational hypertension was defined though the ICD-10 diagnostic code O13, recorded at childbirth and forwarded to the medical birth register. The clinical definitions of gestational hypertension and preeclampsia both include a new onset of hypertension during pregnancy, but during the study period the combination with proteinuria was required for the diagnosis of preeclampsia. The final population included children with a registered height at 5 years, a total of 23,763 children. Electronic registration of height at child health care started in 2005, and children born before 2003 therefore have incomplete series of height measurements at 18 months, 3 and 4 years. (Table 1)

Table 1: Number of children with height registered at different age by year of birth.

Year of birth	2000	2001	2002	2003	2004	2005	2006	2007
18 months	*251	315	*389	*1447	2795	2722	2950	2873
3 years	*263	*355	2479	2615	2835	2818	3005	2892
4 years	*322	2323	2561	2710	2924	2829	3005	2958
5 years	**2544**	**2652**	**2844**	**2986**	**3161**	**3106**	**3313**	**3153**

* The gray cursive numbers represents measurements from before 2005, the year of electronic recording to the Child Health Register. Bold numbers represents our study population in the analysis of height gain.

Exposure

The exposure variable was preeclampsia. Prenatal exposure to preeclampsia was defined through the ICD-10 diagnostic codes O14-O15. 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. According to Swedish guidelines the clinical definition of preeclampsia during the study period was a rise in blood pressure (≥140/90 mm Hg measured on at least two subsequent occasions) combined with significant proteinuria (≥ 0.3 g/24 hours or +1 on at least two subsequent occasions or +2 on dipstick). The quality of the diagnosis of preeclampsia in the Birth Register has been validated previously: of 148 pregnancies coded as preeclampsia according to ICD-9 standards in the Birth Register, 137 (93%) had the disease according to the individual records.[17] Number of children with prenatal exposure to preeclampsia was 865 (3.6 %).

Outcome

The main outcome was height gain (cm) during childhood, defined as the growth in height from birth to five years of age. Height gain was estimated by subtracting height at birth from the height at 5 years of age. We also calculated Z-scores of height and weight at birth, 18 months, 3, 4 and 5 years using population means and standard deviations in each age group according to Swedish standardized growth curves.[18, 19]

Covariates

Maternal parity, age, height, smoking habits in early pregnancy, mothers' country of birth (used as a proxy for ethnicity), level of education, body mass index (BMI) in early pregnancy, diabetes, infant's sex, breastfeeding at 6 months and child's BMI at 5 years were used as covariates. Maternal diabetes was defined as pre-gestational or gestational diabetes and identified through ICD-10 codes (O24.0, O24.1, O24.3, O24.4, O24.9, E10-11 and E13-14). Pre-gestational diabetes was also defined by a check-box in the Birth Register. Breastfeeding included both exclusive and partial breastfeeding.

Statistical analyses

Continuous demographic and clinical variables were compared between pregnancies exposed by severe and mild preeclampsia and unexposed by one-way ANOVA and Tukey post hoc test.

Height gain (cm) during the first five years of life was calculated for children prenatally exposed and unexposed to preeclampsia. The difference in mean height gain between exposed and unexposed was estimated using t-test. In an attempt to separate the possible effect of

preeclampsia on height gain from preterm birth and SGA, we performed analyses on height gain separately in children born preterm (before 37 weeks of gestation) and at term (37 weeks or later). The analysis on term born children was further stratified by birth weight for gestational age, where small, appropriate, and large for gestational age infants were defined by the 10^{th} and 90^{th} percentiles according to the Swedish sex-specific fetal growth curve.[18] In each of these birth weight strata, means of height gain were calculated for term born children exposed and unexposed to preeclampsia. We performed similar stratified analyses using groups of birth length defined by 10^{th} and 90^{th} percentiles according to the same population standard.[18]

Adjusted analyses were performed using multiple linear regressions, estimating the difference in mean height gain between exposed and unexposed. This analysis was performed for children exposed to severe and mild preeclampsia both combined and as separate exposures. Adjustments were made in two steps. Step one (model 1) included parity, maternal age, height, smoking habit in early pregnancy, mothers' country of birth, level of education and infant's sex. Maternal predisposition to metabolic syndrome or insulin resistance[20] and the associated disorders obesity, diabetes[21] and polycystic ovarian syndrome[22] are all associated with risk of preeclampsia. Further, metabolic syndrome may be associated with shorter duration of breastfeeding[23]. Formula fed children may grow faster compared with breastfeed infants[24] and accelerated post-natal growth is associated with insulin resistance[25] and childhood obesity[26]. In step two (model 2) we therefore added maternal BMI, maternal diabetes, breastfeeding at 6 months, and child's BMI at 5 years to account for possible genetic confounding of the metabolic syndrome. Maternal BMI and height as well as child's BMI were used as continuous variables whereas other variables were categorized according to Table 1 and supplementary Table 1S. Sensitivity analysis was done by restricting the analysis to term born

children. We repeated the analysis of term born children stratified by birth weight groups in the adjusted models. To have the opportunity to detect a possible effect modification by sex, we also repeated the analysis stratified by children's sex instead of adjusting for the sex.

Lastly, to compare exposed and unexposed children's pattern of height gain longitudinally, measurements at birth, 18 months, 3, 4 and 5 years were standardized to population growth curves. Z scores at different ages were calculated from population standards in boys and girls separately.[18, 19] Population mean in each age group was subtracted from the observed value, which was then divided by the population standard deviation. The Z score at birth was further standardized by gestational age in weeks. Mean Z-scores of height with 95% CI were calculated at each time point in children exposed to preeclampsia (severe and mild as separate groups) and unexposed to create line graph. Because of the partly missing data at 18 months, 3 and 4 years of age in children born 2000-2003 we re-analyzed the z scores in a population of children born 2003-2007.

SPSS software (version 22) was used for the analysis.

The study was approved by the Regional Ethical Review Board in Uppsala (2013-351).

Results

In pregnancies complicated with preeclampsia (severe and mild), mothers seemed slightly younger and had higher mean BMI than in pregnancies without preeclampsia (Table 2). Maternal height was similar in women with and without preeclampsia. Further, mothers with mild preeclampsia seemed more often born in Nordic countries and had slightly shorter education than

those without preeclampsia. Lastly, mothers with severe and mild preeclampsia had more often pre-gestational or gestational diabetes than mothers without preeclampsia.

Table 2: Maternal characteristics in pregnancies complicated with severe and mild preeclampsia and women without preeclampsia.

	Severe preeclampsia		**Mild preeclampsia**		**No preeclampsia**	
	(N = 179)		(N = 686)		(N = 22,898)	
Age (years)						
< 25 years	21	11.7 %	85	12.4 %	2737	12.0 %
25 - 29 years	57	37.4 %	235	34.3%	6954	30.4 %
30 - 34 years	56	31.3 %	227	33.1 %	8475	37.0 %
≥ 35 years	35	19.6%	139	20.3 %	4732	20.7 %
BMI in early pregnancy						
Mean (kg/m^2)	151	26.0 (4.9)[a]	583	26.8 (5.5)[a]	19,501	24.5 (4.3)
Missing	28	15.6 %	103	15.0 %	3397	14.8 %
Height						
Mean (cm)	174	166.0 (5.8)[c]	659	166.6 (6.3)[c]	22,120	166.7 (6.3)
Missing	5	2.8 %	27	3.9 %	778	3.4 %
Mothers country of birth						
Nordic counties	155	86.6 %	635	92.6 %	19,985	87.3 %
European other	7	3.9 %	14	2.0 %	768	3.4 %
Asian countries	9	5.0 %	23	3.4 %	1521	6.6 %
Other	8	4.5 %	14	2.0 %	623	2.7 %
Early pregnancy smoker						
Daily smoking	10	5.6 %	51	7.4 %	1594	7.0 %

Missing	9	5.0 %	25	3.6 %	725	3.2 %
Education (years)						
≤9	24	13.4 %	102	14.9 %	3594	15.7 %
10-14	120	67.0 %	480	70.0 %	14,351	62.7 %
≥15	30	16.8 %	86	12.5 %	4032	17.6 %
Missing	5	2.8 %	18	2.6 %	921	4.0 %
Diabetes [†]	12	6.7 %	32	4.7 %	311	1.4 %

P values calculated with one-way ANOVA and Tukey post hoc test. [a] $p < 0.001$ compared to unexposed, [b] $p < 0.05$ compared to unexposed [c] $p>0.05$ compared to unexposed. [†] Pre-gestational or gestational diabetes.

Children prenatally exposed to preeclampsia were more often their mother's first born child and seemed less often breastfed at the age of six months than unexposed. (Table 3) 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 (45.6 cm) than unexposed (50.8 cm) children. Although children exposed to severe preeclampsia grew more than unexposed from birth to 5 years, they were on average shorter than unexposed at the age of 5. Among children exposed to mild preeclampsia, only 12.1% were born preterm and they were only slightly shorter at birth than unexposed. However, children exposed to mild preeclampsia were taller than unexposed at the age of five. The BMI at the age of 5 did not differ between groups. The scheduled 5 year measurements were on average about 2 weeks after children's fifth birthday in both groups. (Not shown in table)

Table 3: Characteristics of children exposed to mild and severe preeclampsia and unexposed to preeclampsia.

	Severe preeclampsia (N = 179)		Mild preeclampsia (N = 686)		No preeclampsia (N = 22,898)	
Child characteristics	N	% or mean (SD)	N	% or mean (SD)	N	% or mean (SD)
Firstborn	122	68.2 %	445	64.9 %	9731	42.5 %
Girl	94	52.5 %	350	51.0 %	11,093	48.4 %
Breastfed at 6 months *						
Yes	96	53.6 %	452	65.9 %	15,730	68.7 %
No	63	35.2 %	199	29.0 %	5069	22.1 %
Missing	20	11.2 %	35	5.1 %	2099	9.2 %
Birth weight						
Mean (grams)	179	2372 (920)[a]	686	3318 (674)[a]	22,890	3567 (561)
SGA †	65	36.3 %	137	20.0 %	2228	9.7 %
AGA †	98	54.7 %	484	70.6 %	18,244	79.7 %
LGA †	16	8.9 %	64	9.3 %	2330	10.2 %
Gestational age at birth						
Mean (weeks)	179	34.6 (3.6)[a]	686	38.5 (2.0)[a]	22,880	39.3 (1.8)
Preterm (< 37 weeks)	113	63.1 %	83	12.1 %	1212	5.3 %
Height (cm)						
Birth (length)	167	45.6 (4.9)[a]	682	50.0 (2.9)[a]	22,788	50.8 (2.5)
At 5 years	179	110.6 (4.6)[b]	686	112.0 (4.8)[b]	22,894	111.5 (4.5)
Height gain §	167	65.1 (5.2)[a]	682	62.0 (4.4)[a]	22,785	60.7 (4.3)
BMI at 5 year	179	15.8 (1.7)[c]	680	16.0 (1.6)[c]	22,763	16.0 (1.5)

P values calculated with one-way ANOVA and Tukey post hoc test. [a] $p < 0.001$ compared to unexposed, [b] $p < 0.05$ compared to unexposed [c] $p>0.05$ compared to unexposed. [*] Exclusively or partially breastfed. [†] Small for gestational age (SGA) defined by standardized birthweight for gestational age less than 10th percentile, appropriate for gestational age (AGA) 10th – 90th percentile and large for gestational age (LGA) more than 90th percentile, according to the Swedish sex-specific fetal growth curve.[18] § Height gain defined as length at birth subtracted from the height at 5 years of age.

When term born children exposed to preeclampsia were compared with term born unexposed children, they were born shorter than unexposed (mean length 50.5 cm *vs*. 51.1 cm, $p<0.001$) but were taller at the age of five (mean height 112.2 cm *vs*. 111.6 cm, $p<0.001$) (not shown in table). The average height gain from birth to five years of age was 1.9 cm (95% CI 1.6 – 2.1 cm) larger in children prenatally exposed to preeclampsia than in unexposed children (Table 4). The pattern of accelerated height gain in children exposed to preeclampsia persisted when the analysis was carried out in preterm and term born children separately, but the estimates were attenuated. When we further stratified the term born children in groups based on standardized birth weight, exposed children in all birth weight groups had increased height gain compared with unexposed. Among children born at term with appropriate birth weight for gestational age, exposed children grew on average 1.1 cm (95% CI 0.7 – 1.5 cm) more than unexposed children during the first five years of life. When we restricted the study population to children born at term with normal birth length (birth length between 10th – 90th percentiles for gestational age), a similar difference was seen in height gain between children prenatally exposed and unexposed to preeclampsia (1.2 cm 95% CI 0.8 – 1.6 cm, data not shown in a table).

Table 4: Mean height gain from birth to 5 year in exposed and unexposed children.

	PREECLAMPSIA				
	YES		NO		Mean difference
	Number	Height gain	Number	Height gain	cm with 95% CI
All children	849	62.6	22,785	60.7	1.9 (1.6 – 2.1)
Restriction to children born preterm (< 37 weeks)					
All birth weights	182	65.9	1175	64.6	1.3 (0.5 – 2.0)
Restriction to children born at term (≥ 37 weeks)					
All birth weights	667	61.7	21,592	60.5	1.2 (0.9 – 1.5)
SGA born *	117	62.1	2067	60.6	1.5 (0.7 – 2.3)
AGA born *	482	61.5	17,292	60.5	1.1 (0.7 – 1.5)
LGA born *	67	62.2	2168	60.5	1.7 (0.7 – 2.7)

Height gain defined as length at birth subtracted from the height at 5 years of age.* Small for gestational age (SGA) defined by standardized birthweight for gestational age less than 10^{th} percentile, appropriate for gestational age (AGA) 10^{th} – 90^{th} percentile and large for gestational age (LGA) more than 90^{th} percentile, according to the Swedish sex-specific fetal growth curve.[18]

After adjustments for maternal parity, age, height, country of birth, smoking in early pregnancy, level of education and infants sex, the difference in mean height gain between exposed and unexposed was slightly attenuated from 1.9 cm (95% CI 1.6 – 2.1 cm) to 1.8 cm (95% CI 1.5 –

2.0 cm) (Table 5). With further adjustments for covariates associated with the metabolic syndrome (maternal BMI, maternal diabetes, breastfeeding at six months and children's BMI at 5 years) the estimate was reduced to 1.7 cm (95% 1.4 – 2.0 cm). In analysis restricted to term born children, the difference in mean height gain between children exposed to severe preeclampsia and unexposed in the fully adjusted model was 1.5 cm (95% CI 0.4 – 2.7), but for mild preeclampsia the difference was 0.9 cm (95% CI 0.6 – 1.3).

Table 5: The mean difference in height gain between children exposed and unexposed to preeclampsia (severe and mild combined, and below as separate groups vs. unexposed).

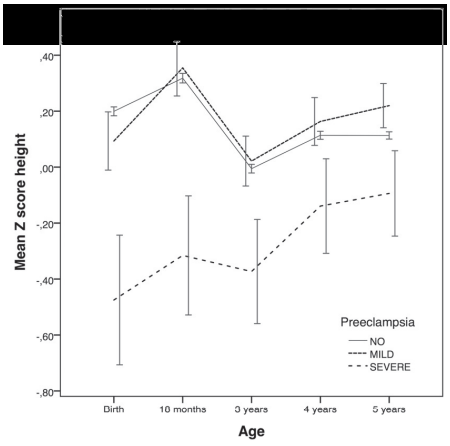
	Mean difference in height gain in cm (95% CI)		
	Crude estimate	Adjusted model 1*	Adjusted model 2†
All children	1.9 (1.6 – 2.1)	1.8 (1.5 – 2.0)	1.7 (1.4 – 2.0)
Mild preeclampsia	1.3 (1.0 – 1.6)	1.1 (0.8 – 1.4)	1.1 (0.7 – 1.4)
Severe preeclampsia	4.4 (3.7 – 5.0)	4.6 (3.9 – 5.2)	4.5 (3.8 – 5.3)
Restriction to children born at term (≥ 37 weeks)			
All term born	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)

* Model 1: Adjusted for maternal parity, age, height, country of birth, smoking in early pregnancy, level of education and child's sex. † Model 2: Adjusted for covariates as in model 1, together with maternal BMI, diabetes, infant's breastfeeding at 6 months and child's BMI at 5 years of age.

In adjusted analysis stratified on birth weight group, the crude estimates (seen in table 4) of increased height gain in children exposed to preeclampsia (severe and mild combined) were only slightly attenuated (not shown in a table). Further, in analysis stratified by sex, the association between prenatal preeclampsia and height gain seemed similar in boys and girls (not shown in a table).

In children exposed to severe preeclampsia height Z-scores increase the first 5 years, but their average height was still below the population mean at the age of five. (Figure 1) In children exposed to mild preeclampsia, the mean Z-score of height at the age of 5 was higher than in unexposed children. There was a non-significant difference in the Z-score of height at birth between children exposed to mild preeclampsia and unexposed, but the graph shows an overall trend of crossing lines. Re-analysis in a population of children born 2003-2007 that have more completed anthropometric follow-up at all ages did not change the results (data not shown).

Figure 1: Mean Z scores of height with 95% confidence intervals at different ages in children exposed to mild and severe preeclampsia and unexposed to preeclampsia.



Discussion

In this population-based prospective study we could show that prenatal exposure to preeclampsia is associated with accelerated height gain during early childhood, and the association seemed independent of birth weight for gestational age. Both children prenatally exposed to preeclampsia [4] and children with accelerated height gain in childhood have increased risks of hypertension in adulthood.[7] Thus, accelerated height gain may be an intermediate marker in the association between prenatal exposure of preeclampsia and hypertension in adulthood.

Strengths and limitations

The major strength of the study was the large number of included children that made it possible to estimate the association between preeclampsia and childhood height gain. Further, we could perform stratified analysis in birth weight groups and show that the association with accelerated growth applies to all birth weight groups. The exposure data was collected before measurement of the outcome which precludes recall bias, and the population-based design makes the results generalizable. Further, we had available information on many possible confounding factors, including maternal parity, height and smoking.[24] Information was also available on several covariates related to the metabolic syndrome, including maternal BMI, maternal diabetes,[21] breastfeeding,[24] and children's obesity.[25] However, we lacked information on maternal gestational weight gain and the family diet, factors that may have affected the association.[24] Further, we lack information on paternal height that seems to be associated with children´s height gain, especially between the age of two and five years.[27]

Comparisons to earlier studies

A pattern of accelerated post-natal growth (height and weight gain) is previously described in children born SGA.[9, 10] The majority of children born SGA catch-up in size with their same age peers within the first two years of life, but those who do not catch-up have increased risk of short adult stature.[9] Further, the post-natal growth in children born to mothers with preeclampsia is previously described in a cohort of 135 premature born SGA infants.[28] Our results of increasing Z-scores in children exposed to severe preeclampsia indicates a pattern of catch-up growth, and one third of those children were born SGA and more than half of them were born preterm. Therefore, our results seem in concert with previous findings of catch-up growth in children born SGA.[29] However, our results also extend on this in two aspects. Firstly, accelerated height gain was also seen in term born children exposed to preeclampsia, and those children were taller than unexposed children at the age of five. Secondly, in our study we showed an association with accelerated height gain during the first five years in children of all sizes at birth, which suggest an effect that is independent of SGA. It is of note that the final height of children prenatally exposed to preeclampsia has in a previous study not shown to differ from unexposed,[30] whereas gestational age at birth is associated with the final height.[31]

Potential explanation of the association

More than 20 years ago Barker hypothesized that an intrauterine environment of restricted nutrition might alter the physiology or metabolism in the fetal tissue to optimize the growth of key organs.[32] Further, this adaptation could become unfavorable in a high nutritional post-natal environment.[25, 33] Our results indicate that not only children born growth restricted but also those exposed to preeclampsia, may have different physiology or metabolism compared with unexposed children. A common imbalance in growth factor signaling may explain the shown association between prenatal exposure to preeclampsia and childhood height gain.[13, 14]

Insulin-like growth factors (IGFs) are found to correlate with both intrauterine [14] and post-natal growth[13], but the evidence that prenatal preeclampsia induces epigenetic changes in IGFs is limited to small case-control studies at present time.[34, 35]

Alternatively, the shown association may be related to a maternal inheritable trait (genetic or environmental) that predisposes the mother to preeclampsia and the child to an accelerated growth pattern. The metabolic syndrome may be a predisposing trait that confounds the association between prenatal preeclampsia and childhood height gain.[20, 25, 36] Adjustments for factors associated with the metabolic syndrome as well as childhood obesity only had a minor impact on the association in our study. Therefore we conclude that confounding by the metabolic syndrome may not explain the accelerated height gain in childhood seen after prenatal exposure to preeclampsia. However, unknown genetic confounding may explain the association, i.e. that the same sets of genes influence preeclampsia development in mothers and growth in height of their children.

Conclusion

Our data implies that early childhood growth trajectories are associated not only with intrauterine growth restriction, but also with prenatal exposure to preeclampsia. The association was seen in children born with normal birth weight, although the effect seemed stronger in children born prematurely. Restriction of cohorts based on birth weight for gestational age should be avoided in future investigations regarding prenatal exposures and later development of hypertension. We warrant future research on accelerated height gain in early childhood and cardio-metabolic outcome later in life, especially in children prenatally exposed to preeclampsia.

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Paper IV

Prehypertension in Pregnancy and Risks of Small for Gestational Age Infant and Stillbirth

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See Editorial Commentary, pp 499–500

Abstract—It is not fully known whether maternal prehypertension is associated with increased risk of adverse fetal outcomes, and it is debated whether increases in blood pressure during pregnancy influence adverse fetal outcomes. We performed a population-based cohort study in nonhypertensive women with term (≥37 weeks) singleton births (n=157 446). Using normotensive (diastolic blood pressure [DBP] <80 mm Hg) women as reference, we calculated adjusted odds ratios with 95% confidence intervals between prehypertension (DBP 80–89 mm Hg) at 36 gestational weeks (late pregnancy) and risks of a small-for-gestational-age (SGA) birth or stillbirth. We further estimated whether an increase in DBP from early to late pregnancy affected these risks. We found that 11% of the study population had prehypertension in late pregnancy. Prehypertension was associated with increased risks of both SGA birth and stillbirth; adjusted odds ratios (95% confidence intervals) were 1.69 (1.51–1.90) and 1.70 (1.16–2.49), respectively. Risks of SGA birth in term pregnancy increased by 2.0% (95% confidence intervals 1.5–2.8) per each mm Hg rise in DBP from early to late pregnancy, whereas risk of stillbirth was not affected by rise in DBP during pregnancy. We conclude that prehypertension in late pregnancy is associated with increased risks of SGA birth and stillbirth. Risk of SGA birth was also affected by rise in DBT during pregnancy. Our findings provide new insight to the relationship between maternal blood pressure and fetal well-being and suggest that impaired maternal perfusion of the placenta contribute to SGA birth and stillbirth. (***Hypertension*. 2016;67:640-646. DOI: 10.1161/HYPERTENSIONAHA.115.06752.) • Online Data Supplement**

Key Words: blood pressure ■ fetal death ■ fetal growth retardation ■ prehypertension ■ stillbirth

Gestational hypertension and preeclampsia are associated with increased risks of intrauterine growth restriction and stillbirth.[1,2] In these pregnancy hypertensive disorders, maternal blood pressure is elevated to or above the threshold of systolic blood pressure 140 mm Hg or diastolic blood pressure (DBP) of 90 mm Hg.[3] Prehypertension is defined as a systolic blood pressure of 120 to 139 mm Hg or a DBP of 80 to 89 mm Hg.[4] In nonpregnant adults, prehypertension has an association with cardiovascular mortality, especially deaths caused by stroke.[5] We are only aware of one study on prehypertension in pregnancy and risks of adverse fetal outcomes. This study was small, but the results indicate that prehypertension at 32 gestational weeks is associated with a slightly increased risk of a small-for-gestational-age (SGA) birth.[6]

During normal pregnancy, blood pressure generally decreases from the first trimester to around 20 gestational weeks and thereafter increase until delivery.[7] Larger increases in blood pressures from the early second to the third trimester are related to reduced fetal growth[8–11] and increased risk of pregnancy hypertensive disorders.[12] The influence of changes in blood pressure during pregnancy on fetal outcomes in nonhypertensive women is not fully known. One study reports reduced fetal growth with increasing blood pressure during pregnancy,[8] whereas other studies report no association between increasing blood pressure and adverse fetal outcome in nonhypertensive women.[13,14] We hypothesized that prehypertension in late pregnancy is associated with increased risks of adverse fetal outcomes and that these risks vary by change in blood pressure during pregnancy.

In a population-based cohort of >150 000 singleton term pregnancies, we estimated associations between prehypertension in late pregnancy and risks of SGA birth and stillbirth. Further, we estimated how change in blood pressure between early and late pregnancy influenced these risks.

Methods

Data Sources

Data on maternal, delivery, and infant characteristics were obtained from the Swedish population-based Stockholm-Gotland Obstetric

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Database,[15] based on the medical record system used in the region for all antenatal, delivery, and postnatal care units. Data from the medical record system is daily forwarded to the database, which contains information from 2008 and onwards.

In Sweden, antenatal and delivery care is standardized and free of charge. Home deliveries are rare. During the first antenatal visit, the mother is interviewed about her medical and reproductive history and smoking habits. The mother's blood pressure and weight are measured and recorded, whereas information on maternal height is self-reported. Blood pressure is thereafter remeasured and recorded at each antenatal visit, standardized to around gestational week 10 (first antenatal visit), 25, and thereafter every second week in primiparous women and every third week in parous women until delivery. The database includes blood pressure measures from both outpatient and hospital care.

Study Population

From January 1, 2008, to October 22, 2014, the database included information on 167 695 singleton births at 37 completed gestational weeks or later (Figure 1). We excluded 10 249 pregnancies with hypertensive disorders (definitions of hypertensive disorders are provided in web appendix in the online-only Data Supplement).

Of 157 446 women without pregnancy hypertensive disorders, we excluded 6759 (4.3%) women with missing data on blood pressure value between 34 and 36 gestational weeks (late pregnancy). Seventy-threethousand ninety-four (49%) of the blood pressure measurements were included from 36 gestational weeks, and the corresponding numbers from gestational weeks 35 and 34 were 61 666 (41%) and 15 927 (11%), respectively. In analyses of changes in blood pressure during pregnancy and fetal outcomes, we also excluded 8928 (5.7%) women with missing data on blood pressure value before 20 gestational weeks (early pregnancy).

Exposure

The main exposure was DBP at 36 completed gestational weeks (late pregnancy). We selected the last recorded measurement before term (37 gestational weeks). If the woman had no recorded blood pressure measure at 36 gestational weeks, we used the most recent value. DBP measure was first categorized into 6 groups according to Table 1 and thereafter recategorized into presence of prehypertension (prehypertension group) or not (normotension group). Prehypertension was defined as a DBP 80 to 89 mm Hg.[4] Consequently, the normotension group included women with a DBP below 80 mm Hg.

We also wanted to investigate how blood pressure changes from early (first antenatal visit) to late pregnancy affected outcomes. Women were, therefore, categorized into (1) normotensive in late

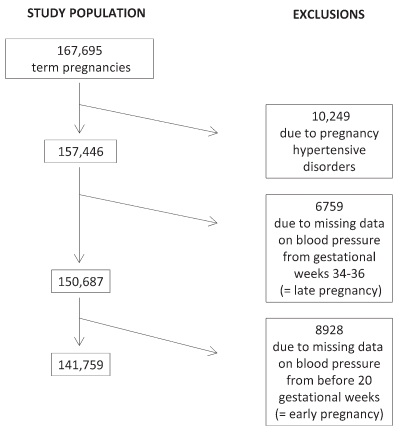

Figure 1. Flow chart of the study population.

Table 1. Maternal Characteristics for Women Giving Birth to Term Singleton Small-for-Gestational-Age (SGA) Infants or Stillbirths

		SGA*		Stillbirth	
Maternal Characteristics	Total	n	%	n	%
Diastolic blood pressure at gestational week 36					
–60	8287	137	1.66	10	0.12
60–64	40 943	561	1.37	44	0.11
65–69	23 147	313	1.36	32	0.14
70–74	43 165	656	1.52	49	0.11
75–79	18 281	343	1.88	23	0.13
80–89	16 864	406	2.41	36	0.21
Missing	6759	179	2.60	12	0.18
Maternal age					
10–24	15 205	381	2.51	17	0.11
25–29	38 708	664	1.72	46	0.12
30–34	59 316	871	1.47	78	0.13
35–	44 136	678	1.54	65	0.15
Missing	81	1	0.41	0	
Parity					
Primiparous	70 233	1717	2.45	101	0.14
Parous	87 211	876	1.01	105	0.12
Missing	2	0		0	
BMI in early pregnancy					
10.0–18.4	4097	143	3.50	7	0.17
18.5–24.9	100 587	1663	1.66	99	0.10
25.0–29.9	32 586	472	1.45	61	0.19
30.0–	12 527	181	1.45	26	0.22
Missing	7649	136	1.74	11	0.14
Maternal height					
–163	52 470	1367	2.61	81	0.15
164–171	69 735	926	1.33	83	0.12
172–	33 757	263	0.78	39	0.12
Missing	1484	39	2.38	3	0.20
Daily smoker in early pregnancy					
Yes	6618	234	3.55	15	0.23
No	149 519	2338	1.57	189	0.13
Missing	1309	23	1.57	2	0.15
Living with partner					
Yes	145 832	2299	1.58	185	0.13
No	9816	261	2.67	17	0.17
Missing	1798	35	1.79	4	0.22
Diabetes mellitus					
Pregestational	692	5	0.74	4	0.58
Gestational	742	10	1.37	3	0.40
None	156 012	2580	1.66	199	0.13
Total	157 446	2595	1.65	206	0.13

Women with chronic hypertension, gestational hypertension, or preeclampsia were excluded. BMI indicates body mass index.

*Defined as a birth weight of >2 standard deviations below the mean weight for gestational age, according to the Swedish sex-specific fetal growth curve. Only live births were included and 163 pregnancies were excluded because of missing information on birth weight and gestational age.

pregnancy and <15 mm Hg rise in DBP between early and late pregnancy; (2) normotensive and at least 15 mm Hg rise; (3) prehypertensive and <15 mm Hg rise; and (4) prehypertensive and at least 15 mm Hg rise. If a woman had several blood pressure measurements before 20 gestational weeks, we used the first recorded measurement.

Blood pressure was measured in the supine position on the right upper arm using manual blood pressure equipment with a cuff size appropriate for arm circumference. Korotkoff V was used for DBP.

Outcomes

Outcomes were giving birth to a live-born SGA infant or a stillbirth at 37 completed gestational weeks or later. SGA was defined as a birth weight of >2 standard deviations below the mean weight for gestational age according to the Swedish sex-specific fetal growth curve.[16] Gestational age was determined using the following hierarchy: (1) date of embryo transfer (3.0%); (2) early second trimester ultrasound (95.2%); (3) date of last menstrual period (1.8%); and (4) from a postnatal assessment (<1%). In SGA analyses, we only included live births, and 163 pregnancies were excluded because of missing information on birth weight or gestational age. Stillbirths include both antepartal and intrapartal deaths from 22 gestational weeks and onwards.

Covariates

Covariates were maternal age at delivery, parity, early pregnancy body mass index (BMI), maternal height, smoking habit in early pregnancy, living with a partner, and presence of pregestational or gestational diabetes mellitus. Pregestational and gestational diabetes mellitus were defined by corresponding codes provided in the International Classification of Diseases, tenth revision, provided by the responsible doctor at discharge from the hospital after delivery (International Classification of Diseases codes are provided in web appendix in the online-only Data Supplement). The covariates were categorized as in Table 1.

Statistical Analyses

We calculated associations between DBP in late pregnancy and risks of an SGA birth or a stillbirth at 37 completed gestational weeks or later. Odds ratios with 95% confidence intervals (CIs) were calculated, using SAS PROC GENMOD in Statistical Analysis Software version 9.4 (SAS Institute Inc, Cary, NC). Adjusted odds ratios (aOR) were calculated after accounting for possible influence of maternal age, parity, BMI, height, smoking habit, living with a partner, and presence of diabetes mellitus. To estimate risks of SGA birth and stillbirth by DBP in late pregnancy, we first analyzed DBP as a continuous variable. Thereafter, DBP values were categorized into 6 groups using 60 to 64 mm Hg as reference group (Table 1), and finally we dichotomized DBP values into normo- and prehypertension using normotension as reference group. To estimate the association between rise in DBP from early to late pregnancy and risks of SGA birth and stillbirth, we analyzed change in blood pressure as a continuous variable. Finally, we stratified normotensive and prehypertensive women in late pregnancy into 2 groups each depending on if the rise in DBP from early to late pregnancy was less than or at least 15 mm Hg. We used women with normotension and a rise in DBP of <15 mm Hg as the reference group.

Effect measure modification was investigated by introducing cross product terms between prehypertension and early pregnancy BMI and parity as categorical variables in the regression models of each outcome; a value of $P<0.05$ was considered significant.

Results

Maternal characteristics and rates and risks of prehypertension at 36 gestational weeks are presented in Table S1 in the online-only Data Supplement. Prehypertension was present in 16 864 women (11.2%) at 36 gestational weeks. Rates and risks of prehypertension in late pregnancy increased rapidly with maternal DBP in early pregnancy, moderately with early pregnancy BMI, and slightly with maternal height. Prehypertension was more common in primiparous versus parous women, in women who were living with their partner versus those who did not, and in women with diabetes mellitus versus those without diabetes mellitus. Maternal age and smoking habits did not influence prehypertension risk.

Table 1 illustrates rates of SGA and stillbirth by maternal characteristics. Rates of SGA birth had a J-shaped association with DBP, a U-shaped association with maternal age, and increased with decreasing maternal BMI and height. The rate of stillbirth was doubled in women with prehypertension compared with the other blood pressure groups, increased with increasing maternal age and decreasing maternal height, and had a J-shaped association with maternal BMI. Rates of SGA and stillbirth were higher in nulliparous than in parous women, in smokers than in nonsmokers, and in women not living with a partner compared with their cohabiting counterparts. Diabetic mellitus during pregnancy was associated with reduced rates of SGA birth and increased rates of stillbirth.

The risks of SGA birth increased by 2.5% (95% CI 1.8–3.0) per mm Hg in DBP at 36 gestational weeks, whereas corresponding stillbirth risk was not significantly increased (1.5% [95% CI −0.5 to 3.6]; data not shown in table or figure).

Figure 2 illustrates aOR for SGA birth by DBP at 36 gestational weeks. Compared with women with a DBP between 60 and 64 mm Hg, risk of SGA increased with DBP from a DBP of at least 70 mm Hg. Specifically, the aORs (95% CI) of an SGA birth were 1.19 (1.06–1.34) among women with 70 to 74 mm Hg and 1.46 (1.27–1.68) among women with 75 to 79 mm Hg, and among women with 80 to 89 mm Hg (prehypertension), there was almost a doubled risk (aOR 1.94; 95% CI 1.69–2.22).

Compared with normotensive women (DBP <80 mm Hg) at 36 gestational weeks, women with prehypertension (DBP 80–89 mm Hg) had a 70% increased risk of both SGA birth and stillbirth (Table 2). There was no interaction between prehypertension and early pregnancy BMI or parity concerning the risk of SGA (P=0.40 and P=0.46, respectively) or stillbirth (P=0.20 and 0.52, respectively). Intrauterine growth

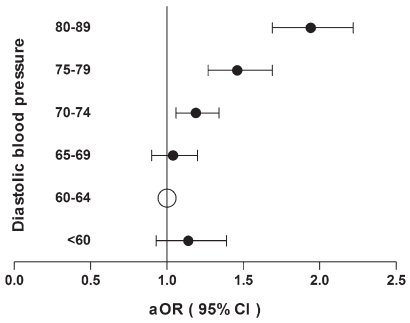

Figure 2. Diastolic blood pressure at 36 gestational weeks and adjusted odds ratios (aOR) of giving birth to a live small-for-gestational-age infant in term nonhypertensive pregnancies. Risks were adjusted for maternal age, parity, early pregnancy body mass index, maternal height, smoking habit in early pregnancy, living with partner or not, and presence of pregestational or gestational diabetes mellitus.

Table 2. Prehypertension at Gestational Week 36 and Risks of Small-for-Gestational-Age Birth (SGA) or a Stillbirth in Singleton-Term Pregnancies

	SGA*				Stillbirth			
Blood Pressure at 36 wk	n	%	aOR†	95% CI	n	%	aOR†	95% CI
Normotension (<80 mm Hg)	2010	1.51		Reference	158	0.12		Reference
Prehypertension (80–89 mm Hg)	406	2.41	1.69	1.51–1.90	36	0.21	1.70	1.16–2.49

Women with chronic hypertension, gestational hypertension, or preeclampsia are excluded. aOR indicates adjusted odds ratios; and CI, confidence interval.

*Defined as a birth weight of >2 standard deviations below the mean weight for gestational age, according to the Swedish sex-specific fetal growth curve. In analysis of SGA, only live births were included and 163 pregnancies were excluded because of missing information on birth weight and gestational age.

†Adjusted for maternal age, parity, early pregnancy body mass index (BMI), maternal height, smoking habit in early pregnancy, living with partner or not, and presence of pregestational or gestational diabetes mellitus.

restriction is a common cause of stillbirth.[2] When we reanalyzed the risk of stillbirth in women with prehypertension after excluding pregnancies complicated by SGA, the risk was slightly attenuated; the aOR (95% CI) was 1.62 (1.07–2.45; not shown in table).

Risk of SGA birth in term pregnancy increased by 2.0% (95% CI 1.5–2.8) per each mm Hg rise in DBP from early to late pregnancy. However, risk of stillbirth was not affected by rise in DBP during pregnancy (0.0%; 95% CI −1.4 to 1.7).

Next, normotensive and prehypertensive women at 36 gestational weeks were stratified by increase in DBP since early pregnancy (less or at least 15 mm Hg, respectively). Compared with normotensive women with an increase in DBP of <15 mm Hg, all other exposure groups had increased risks of SGA birth (Table 3). Prehypertensive women in late pregnancy whose DBP had increased at least 15 mm Hg from early pregnancy had the highest rate (3.6%) and risk (aOR 2.39; 95% CI 2.01–2.84). The increased stillbirth risk was restricted to prehypertensive women who had an increase of <15 mm Hg in DBP since early pregnancy.

Discussion

In this large population-based study including nonhypertensive pregnant women with term births, we showed that prehypertension in late pregnancy was associated with a 70% increased risk of both SGA birth and stillbirth. These findings are of major importance because prehypertension in late pregnancy is common, with an incidence of 11% in our study population. Further, we showed that an increase in DBP of at least 15 mm Hg from early to late pregnancy increased the risk of SGA birth also in pregnancies that had not reached the level of prehypertension in late pregnancy.

Comparisons to Earlier Studies

We found a dose–response association between high DBP in late pregnancy and risk of SGA birth in nonhypertensive pregnancies, with the highest risk seen in women with prehypertension. We are only aware of 2 earlier studies on the effect of level of blood pressure in nonhypertensive pregnancies on fetal growth,[6,9] and both studies report results in accordance with ours. One small Japanese study found that women with prehypertension at 32 gestational weeks had a slightly increased risk of SGA birth (odds ratio 1.09; 95% CI 1.01–1.17) compared with normotensive women.[6] The study only included 71 women with prehypertension, and adjustments were solely made for maternal BMI. The second study reports the highest birth weights in pregnancies where the highest recorded DBP during pregnancy was 80 mm Hg (at higher blood pressure levels, the birth weights decreased).[9] Our results are further supported by a recent study of normotensive women, reporting a higher blood pressure in women carrying a growth-restricted compared with a normal sized fetus.[17]

We could not confirm previous findings of associations between hypotension and increased risks of both SGA birth[10] and stillbirth.[9,18,19] The divergent findings might be explained by differences in study design. We used information about blood pressure at 36 weeks, whereas earlier studies used information of the highest measured blood pressure during pregnancy. Our study was restricted to term deliveries, whereas preterm deliveries were also included in earlier studies. Further, one of the former studies[9] included total perinatal mortality.

Before the millennium shift, a rise of at least 15 mm Hg in DBP during pregnancy was diagnosed as hypertension in national and international guidelines even if the threshold of 90 mm Hg was not reached.[13] This definition was omitted because of data that did not support any adverse maternal or fetal outcomes in these women,[20,21] and that a large proportion of women demonstrate such increase in blood pressure.[7,20] However, the results of our study reintroduce that we should have an alertness of pregnancies where the DBP increases at least 15 mm Hg during the pregnancy. Special attention to an increase in blood pressure should be considered in women with prehypertension in late pregnancy because our findings indicate an association with 2.4-fold increased risk of SGA birth in these pregnancies. This finding is in accordance with a recent report from the Avon Longitudinal Study of Parents and Children (ALSPAC),[8] reporting an association between increasing maternal blood pressure levels during pregnancy and reduced fetal growth also in women whose blood pressure does not cross the threshold for pregnancy hypertensive disorders.

Potential Explanations for the Associations Between Prehypertension and SGA Birth and Stillbirth

During pregnancy, the mother undergoes physiological adaptation with increases in plasma volume and cardiac output and

Table 3. Normotensive and Prehypertensive Women in Late Pregnancy, Stratified by Increase in Diastolic Blood Pressure (BP) of At Least 15 mm Hg Since Early Pregnancy and Associated Risks of Small-for-Gestational-Age (SGA) Birth or a Stillbirth

	SGA*				Stillbirth			
Blood Pressure	n	%	aOR†	95% CI	n	%	aOR†	95% CI
Normotension (<80 mm Hg)								
≥15 mm Hg increase in diastolic BP since early pregnancy								
No (n=119 725)	1684	1.41	Reference		134	0.11	Reference	
Yes (n=6147)	134	2.18	1.41	1.17–1.70	6	0.10	0.63	0.23–1.71
Prehypertension (80–89 mm Hg)								
≥15 mm Hg increase in diastolic BP since early pregnancy								
No (n=11 287)	212	1.89	1.46	1.25–1.69	30	0.27	2.17	1.42–3.32
Yes (n=4600)	164	3.57	2.39	2.01–2.84	4	0.09	0.78	0.29–2.10

Women with chronic hypertension, gestational hypertension, or preeclampsia are excluded. AOR indicates adjusted odds ratio; and CI, confidence interval.

*Defined as a birth weight of >2 standard deviations below the mean weight for gestational age, according to the Swedish sex-specific fetal growth curve. Only live births were included and 163 pregnancies were excluded because of missing information on birth weight and gestational age.

†Adjusted for maternal age, parity, early pregnancy body mass index (BMI), maternal height, smoking habit in early pregnancy, living with partner or not, and presence of pregestational or gestational diabetes mellitus.

a decrease in total peripheral resistance.[22,23] These changes might facilitate uteroplacental perfusion and thereby fetal oxygenation and nutrition. Normotensive pregnancies with fetal growth restriction have, compared with those without fetal growth restriction, a higher total peripheral resistance and reduced cardiac output already in early pregnancy.[24] Similar but even more severe insufficient maternal physiological adaptation has been shown in pregnancies complicated with preeclampsia.[17,25] Intrauterine growth restriction and preeclampsia are closely linked with abnormal placentation.[26,27] Reduced uteroplacental perfusion has been shown to induce a rise in maternal blood pressure through increased production of vasoconstrictive agents.[28–30] We speculate that differences in efficiency of maternal cardiovascular adaptation might explain why some women with fetal growth restriction (and reduced uteroplacental perfusion) increase their blood pressure beyond the threshold of pregnancy hypertensive disorder, whereas others do not. Probably, some women with blood pressure levels below the hypertension threshold would have passed this threshold later in pregnancy if not birth had intervened.

We could only show an association between prehypertension in late pregnancy and stillbirth in pregnancies with <15 mm Hg increase since early pregnancy, indicating that a blood pressure in the higher normal range during the entire pregnancy may be harmful for the fetus. When we excluded pregnancies with SGA births, the association between prehypertension and stillbirth was only slightly attenuated. This might question that fetal growth restriction is in the causal pathway between prehypertension and stillbirth risk. Still, recent reports suggest that placental insufficiency and fetal growth restriction may also be present in term pregnancies with fetuses of normal size.[31,32] Prehypertension in nonpregnant populations is associated with micro- and macrovascular pathology,[33,34] enhanced oxidative stress,[35] increased levels of inflammatory markers,[36] and microalbuminuria (a marker of endothelial dysfunction).[37] These characteristics are also seen in pregnancies complicated with placental insuffiency,[38] which give us further support for an association between prehypertension and placental disorders.

Strengths and Limitations

The main strengths of this investigation are the population-based study design, the prospectively recorded information of blood pressure levels during pregnancy, and the large cohort size. The population had antenatal and obstetric care that was free of charge, and management routines were standardized. Such factors should minimize the potential for confounding by unmeasured sociodemographic factors or differences in management. In our study, we had the ability to adjust for several important confounders, such as maternal age, smoking, early pregnancy BMI, and diabetes mellitus.[39,40] However, we did not have data on weight gain during pregnancy, which can affect blood pressure trajectories during pregnancy[39] and also the association with SGA.[41] Nor we had data on maternal ethnicity, which can affect both blood pressure trajectories during pregnancy and our outcomes.[39,42,43] Blood pressure measurements were collected during routine antenatal appointments by midwifes, and the measurements can, therefore, have inherent and interobserver variability. This would, however, only expect to introduce random rather than systemic error.

Perspectives

Maternal prehypertension in late pregnancy is associated with increased risks of SGA birth and stillbirth. Further, risk of SGA birth increased by 2% per mm Hg increase in DBP from early to late pregnancy. Still, we do not suggest blood pressure medication in these women because earlier studies have failed to show improved fetal outcome when lowering blood pressures below a prehypertensive level.[44] The greatest impact of our findings is probably the improved insight to the relationship between maternal blood pressure, placental function, and fetal well-being. Our data implies that both impaired maternal perfusion of

the placenta (an extrinsic defect) and impaired placental development (an intrinsic defect) may lead to SGA and stillbirth.

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Disclosures

None.

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Novelty and Significance

What Is New?

- The large sample size of nonhypertensive pregnancies allowed us to investigate the association between diastolic blood pressure in late pregnancy and risks of small-for-gestational-age (SGA) infant birth and stillbirth. We also investigated whether change in blood pressure from early to late pregnancy influenced risks.
- The risk of SGA birth increased by 2.5% (95% confidence interval 1.8–3.0) per mm Hg diastolic blood pressure measured in late pregnancy and by 2.0% (95% confidence interval 1.5–2.8) per each mm Hg rise in diastolic blood pressure from early to late pregnancy.
- Risk of stillbirth was associated with a 70% increased risk of stillbirth in women with prehypertension (80–89 mm Hg) in late pregnancy compared with normotensive women (<80 mm Hg). However, risk of stillbirth was not affected by rise in diastolic blood pressure from early to late pregnancy.

What Is Relevant?

- Our findings improve the knowledge of the relationship between maternal blood pressure, placental function, and fetal growth.

Summary

Both SGA birth and stillbirth are associated with prehypertension in late pregnancy. SGA birth is further associated with blood pressure elevation from early to late pregnancy. The findings suggest that impaired maternal perfusion of the placenta contribute to SGA birth and stillbirth.

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Prehypertension in Pregnancy and Risks of Small for Gestational Age Infant and Stillbirth

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Supplemental material

PREHYPERTENSION IN PREGNANCY AND RISKS OF SMALL FOR GESTATIONAL AGE INFANT AND STILLBIRTH

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Table S1. Maternal characteristics and rates and risks of prehypertension (diastolic blood pressure 80-89 mmHg) at 36 gestational weeks in singleton term births

	Prehypertension at 36 gestational weeks			
Maternal characteristics	n	%	aOR*	95% CI
Diastolic blood pressure in early pregnancy				
-60	287	2.5		Reference
60-64	2524	5.3	2.07	1.82-2.35
65-69	1688	7.8	3.13	2.75-3.57
70-74	4758	13.0	5.23	4.61-5.92
75-79	2571	20.8	8.96	7.87-10.20
80-89	4059	34.4	17.36	15.27-19.74
Missing	977	6.2		
Maternal age				
10-24	1447	10.0	0.91	0.85-0.98
25-29	4221	11.4		Reference
30-34	6413	11.2	1.01	0.97-1.06
35-	4776	11.4	0.99	0.94-1.04
Missing	7	0.10		
Parity				
0	8996	13.1	1.52	1.47-1.58
1	78868	9.6		Reference
Missing	0			
BMI in early pregnancy				
10.0-18.4	250	6.4	0.76	0.66-0.87
18.5-24.9	8985	9.3		Reference

25.0-29.9	4395	14.2	1.38	1.32-1.44
30.0-	2371	20.3	1.70	1.61-1.80
Missing	863	6.2		
Maternal height				
-163	4941	9.9	0.87	0.83-0.91
164-171	7729	11.5		Reference
172-	4042	12.5	1.07	1.02-1.12
Missing	152	1.9		
Daily smoker in early pregnancy				
Yes	681	10.9	1.01	0.92-1.11
No	16,038	11.2		Reference
Missing	145	1.8		
Living with partner				
Yes	15,669	11.2	1.12	1.04-1.22
No	991	10.8		Reference
Missing	204	2.4		
Diabetes Mellitus				
Pre-gestational	99	15.9	1.62	1.28-2.05
Gestational	94	17.7	1.28	1.00-1.65
None	16,671	11.2		Reference
Total	16,864	11.2		

Women with chronic hypertension, gestational hypertension or preeclampsia are excluded.

*aOR; adjusted Odds Ratio, adjustments for all other variables in the Table.

Web appendix

Hypertensive disorders during pregnancy were identified by:

a) Presence of ongoing medication for hypertension at the first antenatal visit.

b) Hypertensive blood pressure measurement during pregnancy (defined as 140/90 mmHg or higher at two consecutive measurements with at least 6 hours a part, or 160/110 mmHg or higher recorded at one occasion).

c) Diagnosis of chronic hypertension (ICD-10: O10, O11), gestational hypertension (ICD-10: O139) or preeclampsia (ICD-10: O141, O142, O149, O15) at discharge from the delivery hospital.

Pre-gestational diabetes was identified by ICD-10 codes O240 and O243.

Gestational diabetes was identified by ICD-10 code O24.

Paper V

ELEVATED DIASTOLIC BLOOD PRESSURE UNTIL MID-GESTATION IS ASSOCIATED WITH PREECLAMPSIA AND SMALL FOR GESTATIONAL AGE

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Short title: Diastolic blood pressure until mid-gestation

Abstract

Gestational hemodynamic adaptations, including lowered blood pressure until mid-gestation, might benefit placental function. We hypothesized that elevation in diastolic blood pressure (DBP) from early to mid-gestation increases risks of preeclampsia and small-for-gestational-age birth (SGA), and those risks may differ by level of early-gestation DBP. In 64,607 healthy primiparous women, we estimated risks of preeclampsia and SGA birth depending on the change in DBP from early to mid-gestation, categorized into lowered, unchanged (- 2 to +2 mm Hg change) and elevated DBP. Risks were estimated by logistic regression, presented with adjusted odds ratio (AOR) and 95% confidence intervals (CI). Further, the analyses of change in DBP was stratified by level of early-gestation DBP, categorized into low (< 70 mm Hg), intermediate (70 – 79 mm Hg) and pre-hypertensive (80 – 89 mm Hg) DBP levels. The risk of preeclampsia and SGA birth increased with elevated DBP from early to mid-gestation. Compared to women with lowered DBP, women with elevated DBP had 60% increased risk of preterm (< 37 weeks) preeclampsia and 70% increased risk of preterm SGA. The risk effects of elevated DBP seemed stronger in women with pre-hypertensive than low early-gestation DBP. The rate of preeclampsia in women with low early-gestation DBP that decreased until mid-gestation was 1.6%, compared to 15.8% in those with pre-hypertensive early-gestation DBP that elevated until mid-gestation. The results indicate that DBP may start to increase already around mid-gestation in women later developing placental dysfunction disorders, and that this increase may influence risks of preeclampsia and SGA birth more in women with high early-gestation DBP.

Introduction

Normal pregnancy is associated with gestational hemodynamic adaptations that include blood pressure (BP) changes,[1-4] which might benefit placental perfusion.[5] During normal pregnancy, the BP is established to decrease from early to mid-gestation ("mid-gestational BP drop"), and thereafter progressively increase to pre-pregnancy levels in late gestation.[1-3] In women who develop placental dysfunction disorders (i.e. preeclampsia and fetal growth restriction), the BP may start to increase before mid-gestation and increases faster than normal.[6-8] Preeclampsia has also been associated with absence of mid-gestational BP drop.[1, 6, 7] It is unknown if fetal growth restriction has such association.

Women who develop preeclampsia and fetal growth restriction have generally higher BP in early gestation than women who do not develop these complications. [9-11] High early-gestation BP may be associated with an incapacity for gestational hemodynamic adaptation, perhaps because of a predisposition for endothelial dysfunction.[12-14] Level of early-gestation BP may therefore influence the effect of BP change before mid-gestation on the development of preeclampsia and intrauterine growth restriction. Further, the risks associated with increase in BP before mid-gestation may be higher for preterm preeclampsia and fetal growth restriction, because these conditions are more strongly related to placental dysfunction than term preeclampsia and fetal growth restriction.[9]

In this population-based cohort study including 64,607 healthy primiparous women, we estimated the association between the change in diastolic blood pressure (DBP) from early to mid-gestation and risks of preeclampsia and birth of small-for-gestational-age (SGA) infant. We hypothesized that the risks of preeclampsia and SGA birth increased with elevated BP from early to mid-gestation, and that these associations were especially strong in preterm (< 37 weeks)

preeclampsia and in preterm SGA births. We also hypothesized that these risks may differ depending on early-gestation DBP level.

Methods

Data sources

Data was obtained from the Swedish population-based Stockholm-Gotland Obstetric Database,[15] which is based on the medical record system used in the region for all antenatal-, delivery- and postnatal care units. Data from the medical record system is daily forwarded to the database, which contains information from 2008 and onwards.

In Sweden, antenatal and delivery care is standardized and free of charge. Home deliveries are rare. During the first antenatal visit, standardized to take place around gestational week 10, the mother is interviewed about her medical and reproductive history and smoking habits. Information on pre-gestational hypertension or diabetes is registered in check-boxes. The mother's height is generally self-reported, while weight and BP are measured and recorded in the database. A urine test is acquired for a dipstick test of proteinuria. In cases of a positive dipstick, another dipstick test is taken on a separate occasion within a short time. The BP is re-measured at each antenatal visit. The second visit is standardized to occur at 20 – 25 gestational weeks, but occurs earlier if considered necessary. BP is measured on the right upper arm, using manual BP equipment with a cuff size appropriate for arm circumference. Korotkoff V is used to measure the diastolic BP. At discharge from the hospital after delivery, the responsible doctor records complications during pregnancy and delivery, according to the International Classification of Diseases, tenth revision [ICD-10].

Study Population

The population was defined as women without suspected vascular disease in early pregnancy that gave birth to their first infant from 2008 to 2014 in Stockholm or Gotland counties (Figure 1). We excluded women with suspected vascular disease defined as chronic hypertension, early-pregnancy proteinuria or pre-gestational diabetes (n = 2,538). Chronic hypertension was defined as systolic BP ≥ 140 or DBP ≥ 90 at the first antenatal visit, registration in a check-box at first antenatal visit by the midwife or by ICD-10 codes O10 and O11 at discharge from the hospital after delivery. Early-pregnancy proteinuria was defined as 2+ on dipstick or 1+ on two separate occasions (more than 4 hours apart) within the first 20 weeks of gestation. Women with pre-gestational diabetes were identified by a check-box, as well by ICD-10 codes O24.0 and O24.3. The study population was further confined to women with a first registered BP measurement before gestational week 16 ("early gestation") and a BP measurement between gestational weeks 20 and 25 ("mid-gestation"). The mean gestational age at the BP measurements was 10 weeks in early gestation and 22 weeks at mid-gestation. Finally, we excluded 10 women who developed preeclampsia before 26 weeks of gestation, because this was within the period of defined exposure variable (see below). The final study population included 64,607 women (Figure 1).

Exposure

The main exposure was the change in DBP from early to mid-gestation, which was calculated by subtracting the mid-gestation DBP from the early-gestation DBP. The median of this change in DBP was 0 mm Hg with interquartile range (-5 to +4). The change was categorized into; 1) lowered DBP: change < -2 mm Hg (n = 25,291 and 39.2 %), 2) unchanged DBP: change -2 to +2 mm Hg (n = 22,497 and 34.8 %), 3) Elevated DBP (> 2 mm Hg, n = 16,811 and 26.2 %) from early to mid-gestation.

Outcomes

Outcomes were preeclampsia and birth of a small for gestational age (SGA) infant, where the latter was used as a proxy for fetal growth restriction. Preeclampsia was defined through the ICD-10 codes O14-O15. The clinical definition of preeclampsia during the study period was a BP ≥ 140 systolic or ≥ 90 mm Hg diastolic measured at two subsequent occasions, combined with proteinuria (≥ 0.3 g/24 hours or +1 or more on dipstick on at least two subsequent occasions). Preeclampsia diagnosis registered in the Nordic countries is previously retrospectively validated with the above definition as a golden standard, suggesting a positive predictive value around 80%.[16, 17] SGA infant was defined as a live born infant with birth weight of more than two standard deviations below the mean weight for gestational age, according to the Swedish sex-specific fetal growth curve.[18] Gestational age was determined using the following hierarchy: a) date of embryo transfer (3.0%), b) early second trimester ultrasound (95.2%), c) date of last menstrual period (1.8%) and d) from a postnatal assessment (< 1%). If preeclampsia or SGA was present in combination of preterm birth (< 37 completed weeks of gestation), the outcomes were defined as preterm. In the final cohort 2,246 women developed preeclampsia and 1,945 women gave birth to an SGA infant.

Covariates

Covariates were maternal early-gestation DBP, body mass index (BMI) in early pregnancy, age at delivery, height, cohabitation status with partner, smoking in early pregnancy, and country of birth. The covariates were categorized as in Table 1.

Statistical analysis

The risks of preeclampsia and SGA were calculated for women with unchanged and elevated DBP from early to mid-gestation, with lowered DBP as the reference category. Odds ratios (ORs) with 95% confidence intervals (CI) were calculated using unconditional logistic regression analysis. Adjustments were made for maternal BMI, age, height, cohabitation status, smoking, and country of birth. The analysis was repeated for preterm preeclampsia and preterm SGA. Further, to investigate if an association between the change in DBP from early to mid-gestation and SGA was only explained by the association between SGA and preeclampsia, we repeated the analysis of SGA in women who did not developed preeclampsia.

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. Early-gestation DBP was categorized into low (< 70 mm Hg, intermediate (70 – 79 mm Hg) and pre-hypertensive (80 – 89 mm Hg) levels. Change in DBP was categorized into lowered (< -2 mm Hg), unchanged (-2 to +2 mm Hg), and elevated DBP (> 2 mm Hg) from early to mid-gestation.

We thereafter performed analyses of change in DBP from early to mid-gestation stratified by early-gestation DBP. The risks of preeclampsia and SGA were calculated in each stratum of early-gestation DBP (low, intermediate, pre-hypertensive levels) for women with unchanged and elevated DBP, with lowered DBP as the reference category and the same adjustments as previously described.

All analysis was performed using Statistical Analysis Software version 9.3 (SAS institute, Inc, Cary, NC). The study was approved by a regional ethical board in Stockholm. Reference numbers 2009/275-31, 2012/365-32 and 2014/962-32.

Results

In the final cohort of primiparous women without suspected vascular disease in early pregnancy, 3.4% were diagnosed with preeclampsia. In women with pre-hypertensive early-gestation DBP and in obese women (BMI $\geq$ 30), the rate of preeclampsia was above 7% (Table 1). Women above 35 years old were more likely to be diagnosed with preeclampsia than younger women and preeclampsia occurred more often in short (< 164 cm) women than in tall ($\geq$ 172 cm) women.

Three percent of the women gave birth to SGA infants. Preeclampsia coincided with SGA in 290 of 1,945 women that 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 above 35 years old were more likely to give birth to SGA infants than younger women. SGA rate was 4.6% in short women and 1.7% in tall women.

In the excluded group of women with suspected vascular disease, 12.7% developed preeclampsia and 4.4% gave birth to an SGA infant.

Among women with a lowered DBP from early to mid-gestation, 3.3% were later diagnosed with preeclampsia (Table 2). In women with elevated DBP, the corresponding rate was 4.2%. Similarly, the rate of SGA infants was 2.8% in women with lowered DBP and 3.5% in women with elevated DBP. Compared with women with lowered DBP, women with elevated DBP were at increased risks of both preeclampsia and SGA. The adjusted ORs (95% CI) for preterm preeclampsia was 1.6 (1.2 – 2.0) and for preterm SGA 1.7 (1.3 – 2.3). When the analysis of SGA was repeated with exclusion of women who developed preeclampsia, the association between

elevated DBP from early to mid-gestation and SGA remained (adjusted ORs [95% CI]: SGA 1.2 [1.0 – 1.4] and preterm SGA 1.9 [1.2 – 2.8]; data not shown in table).

There were significant interactions between early-gestation DBP and change in DBP from early to mid-gestation regarding both outcomes (preeclampsia $p = 0.005$ and SGA $p = 0.014$).

In stratified analyses, the associations between elevated DBP from early to mid-gestation and risks of preeclampsia were more pronounced in women with pre-hypertensive (80 – 89 mm Hg) early-gestation DBP than in women with low (< 70 mm Hg) DBP (Table 3). The rate of preeclampsia in women with low early-gestation DBP and further lowered DBP until mid-gestation was 1.6%. In contrast, the rate of preeclampsia was 15.8% among women with a pre-hypertensive early-gestation DBP which was further elevated DBP until mid-gestation.

In stratified analyses by early-gestation DBP on risks of SGA birth, the effect of change in DBP from early to mid-gestation had a similar pattern as in analyses of preeclampsia (Table 4). In women with pre-hypertensive early-gestation DBP, the risk of SGA birth was more than doubled in women with elevated DBP from early to mid-gestation, whereas corresponding risk in women with low early-gestation DBP was only increased by 30%. In women with low early-gestation DBP and further lowered DBP until mid-gestation, birth of SGA infants occurred in 2.7%. Rate of SGA birth was more than 6.3% in women with pre-hypertensive early-gestation DBP which was further elevated DBP until mid-gestation.

Discussion

In this study we found that elevated DBP from early to mid-gestation was associated with increased risks of preeclampsia and SGA births. The associations seemed stronger for preterm

preeclampsia and preterm SGA than for term preeclampsia and SGA. Further, the association between change in DBP from early to mid-gestation and risks of preeclampsia and SGA differed across levels of the early-gestation DBP. Women with early-gestation DBP in a pre-hypertensive range (80 – 89 mm Hg) that failed to lower from early to mid-gestation may represent a clinically relevant risk group for placental dysfunction disorders with preeclampsia and SGA rates of 11% and more than 4%, respectively.

A major strength of the study was the large amount of detailed information that enabled us to detect a small effect size and to stratify by early-gestation DBP. The possibilities to define and exclude a risk group of women with suspected vascular disease in early pregnancy[9-11] made it possible to study effects of DBP within a cohort of seemingly cardiovascular healthy women. Information was available on important covariates that may confound the association, as early pregnancy BMI.[19] Socioeconomic factors may be important confounders for the associations between BP changes during pregnancy and preeclampsia and SGA birth.[20] We did not have information on maternal education level or income, but this may have been partly adjusted for by the other socioeconomic related factors, including cohabitation status, country of birth, maternal age, BMI, and smoking. The mean gestational age at the mid-gestation BP measurement in this study was 22 gestational weeks, while the nadir of BP is considered to be around 20 weeks.[2] Therefore, we cannot exclude a BP drop before the time-point of measurement in some women categorized with unchanged or elevated BP from early to mid-gestation in this study.

BP measurements are generally affected by a large inter- and intra-observational variance which is expected to introduce mostly random error. Our exposure of the change in DBP includes information from measurements at two separate occasions. Repeated occasions of BP measurements are expected to identify the true BP values more accurately than measurement only

at one occasion.[21] The combination of early-gestation DBP and the change in DBP could therefore more accurately identify women with truly pre-hypertensive BP than one measurement occasion in early gestation (by increasing the sensitivity and specificity). Therefore we cannot exclude that the association found between elevated BP and the outcome may be partially explained by the association between the true BP level in early gestation, rather than a true change in BP. However, until a more sensitive and specific method to estimate vascular resistance has been standardized in pregnancy the findings may be clinically useful.

In this study we found increased risks of preeclampsia and SGA in women with elevated DBP from early gestation (mean gestational age 10 weeks) to mid-gestation (mean 22 weeks). Macdonald-Wallis et al found that the risk of preeclampsia increased with increasing BP from gestational week 18 to 30.[7] However, the relationship between BP changes during pregnancy and birth weight seems complex. Results from another Macdonald-Wallis et al study suggest that a BP increase from gestational week 18 to 30 is negatively associated with birth weight, but an opposite positive association was seen between the change in systolic BP from gestational weeks 8 to 18 and birth weight.[8] Women who develop preeclampsia have increased risks of giving birth both to small- and large- for gestational-age infants, which suggests a U-formed relationship between BP changes during pregnancy and birth weight.[22] Thus, our results may not contradict previous findings.

Interestingly, our results showed that the rates of placental dysfunction disorders were comparable in women with early-gestation DBP in a pre-hypertensive range that failed to lower towards mid-gestation (preeclampsia $\geq$ 11%; SGA > 4%) and in the excluded group of women with suspected vascular disease in early gestation (preeclampsia: 13%; SGA: 4%). The latter group includes women with pre-gestational diabetes and chronic hypertension[11] which are well-

recognized risk factors of preeclampsia, perhaps because of a predisposition to endothelial dysfunction.[23, 24] Recently, it was shown that hemodynamic measurements around gestational week 13 can, in combination with maternal anthropometrics, predict SGA in women with chronic hypertension or a previous hypertensive disorder in pregnancy.[25] Therefore, both pre-gestational endothelial dysfunction and gestational hemodynamic adaptation may affect the placental function.

The gestational hemodynamic adaptations before mid-gestation include decreased BP[2, 3] and total vascular resistance.[4] These adaptive changes might benefit placental perfusion[5] and may be explained by the induction of several vasodilatory systems in early-gestation.[26] From mid-gestation and onward, the BP normally increases. This BP increase may reflect an increasing production of placental agents that interfere with vasodilation. One such agent is soluble vascular endothelial growth factor (VEGF) receptor-1 or sFlt-1, which interferes with the function of VEGF and placental growth factor.[27, 28] Further, this production seems especially high in women with placental dysfunction.[29] The shown association between elevated DBP from early to mid-gestation and preterm preeclampsia and SGA may suggest that placental dysfunction indeed resulted in increased vasoconstriction as early as mid-gestation and a rise in DBP before the gestation week of 25. Alternatively, a gestational hemodynamic maladaptation may decrease the perfusion capacity to the utero-placental unit already in early-gestation.[12, 30, 31] Further, we speculate that women with early-gestation DBP in a pre-hypertensive range may be less responsive to gestational adaptive vasodilation because of a tendency to endothelial dysfunction.[12, 32] However, the pathophysiological inference of this study is limited by the lack of pre-gestational hemodynamic measurements and information on adaptive changes before gestational week 20.

Conclusion and future perspectives

Our study indicates that the DBP may start to increase before 25 weeks of gestation in women who develop placental dysfunction disorders, especially in women who deliver preterm. An elevated DBP until mid-gestation should alert midwifes and obstetricians to look for other risk factors and signs of placental dysfunction during pregnancy. Women who have a pre-hypertensive DBP in early-gestation that fails to lower from early to mid-gestation should be regarded as a risk group for placental dysfunction. The results could imply that gestational hemodynamic adaptations are beneficial to placental function. We speculate that early-gestation adaptive vasodilation may interact with the pre-gestational endothelial function towards increasing placental perfusion.

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Conflict of Interest

All authors address no conflict of interest.

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Novelty and Significance

What Is New?

- Compared with lowered diastolic blood pressure (DBP) from early to mid-gestation, elevated DBP was associated with the placental dysfunction disorders preeclampsia and birth of small-for-gestational-age infants (SGA).
- This may indicate that DBP started to elevate before 25 gestational weeks in women that later developed placental dysfunction disorders.
- The risk effects of elevated DBP seemed stronger in women with pre-hypertensive (80 – 89 mm Hg) than low (< 70 mm Hg) early-gestation DBP.

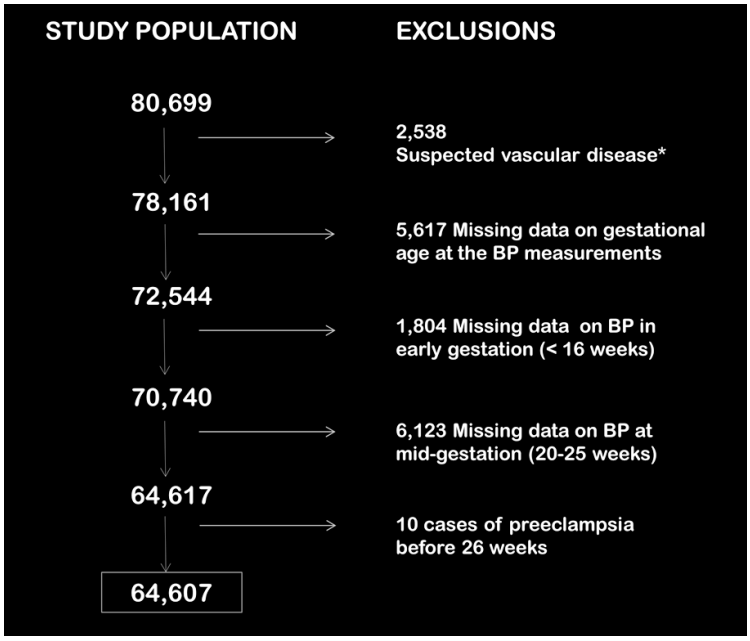
What Is Relevant?

- Women with DBP in a pre-hypertensive range in early-gestation that failed to lower until mid-gestation seemed to represent a clinically relevant risk group of placental dysfunction disorders (rates of preeclampsia ≥ 11% and SGA > 4%).
- Women with low DBP that was unchanged or further lowered until mid-gestation seem to have low risk of placental dysfunction disorders (rates of preeclampsia < 2% and SGA < 3%).

Summary

Elevated DBP from early to mid-gestation was associated with the occurrence of preeclampsia and birth of SGA infants and these risks differed depending on early-gestation DBP level.

Figure 1: Flow chart of the study population that includes primiparous women without suspected vascular disease in early pregnancy.



* Defined as: *chronic hypertension* identified as systole ≥ 140 or diastole ≥ 90 at the first antenatal visit, registration of chronic hypertension by checkbox at first antenatal visit 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* identified registration in checkbox at first antenatal visit or a corresponding diagnostic code after delivery.

Table 1: The rate of preeclampsia and giving birth to small-for-gestational-age infant by maternal characteristics.

Maternal characteristics	Numbers	Preeclampsia		Small-for-gestational-age	
		Any	Preterm*	Any	Preterm*
DBP in early gestation†					
< 70 mm Hg	35,205	2.3	0.5	3.0	0.5
70 – 79	23,490	4.2	0.8	3.0	0.7
80 – 89	5,910	7.4	1.6	3.3	0.9
BMI ‡ in early gestation†					
< 18.5	1,999	2.6	0.6	4.8	0.7
18.5 – 24.9	44,095	2.9	0.6	3.0	0.6
25 – 29.9	11,499	4.5	0.8	2.8	0.7
≥ 30	4,034	7.1	1.1	3.3	0.8
Missing	2,980	3.3	0.5	2.9	0.5
Age					
< 25 years	9,158	3.3	0.7	3.0	0.6
25 – 29	20,396	3.4	0.6	2.7	0.6
30 – 34	23,808	3.2	0.6	2.9	0.5
≥ 35	11,229	4.4	0.9	3.8	0.8
Missing	16	6.3	-	6.3	-
Height					
< 164 cm	20,647	3.8	0.8	4.6	0.8
164 – 171	28,960	3.5	0.7	2.6	0.6
≥ 172	14,516	3.0	0.4	1.7	0.4
Missing	489	2.9	-	3.5	-
Cohabitation status					
Living with partner	59,095	3.5	0.7	3.0	0.6
Not living with partner	4,826	3.5	0.8	3.6	0.7

Missing	686	3.6	0.6	3.4	0.3
Smoking [§]					
Yes	2,630	2.7	0.5	5.2	1.1
No	61,443	3.5	0.7	2.9	0.6
Missing	534	3.6	0.2	2.6	0.6
Country of birth					
Sweden	41,482	3.7	0.7	2.6	0.6
Other Nordic countries	878	3.9	0.6	3.0	0.3
Outside Nordic region	12,558	2.8	0.7	4.3	0.7
Missing	9,689	3.4	0.6	3.4	-

[*]Preterm; defined as the combination of the outcome and delivery before 37 gestational weeks. [†] DBP: Diastolic blood pressure, Early gestation: Before 16 weeks of gestation, [‡] BMI: Body mass index, [§]Daily smoking in early gestation.

Table 2: The risk of preeclampsia (PE) and small-for-gestational-age (SGA) depending on the change in diastolic blood pressure from early to mid-gestation.

	Change in diastolic blood pressure								
	Lowered (< -2 mm Hg)			**Unchanged (-2 to +2 mm Hg)**			**Elevated (> 2 mm Hg)**		
	n	rate (%)		*n*	rate (%)	Adjusted OR (95% CI)*	*n*	rate (%)	Adjusted OR (95% CI)*
Any:									
PE	841	3.3	*Ref*	692	3.1	0.9 (0.8 – 1.0)	713	4.2	1.3 (1.1 – 1.4)
SGA	696	2.8	*Ref*	659	2.9	1.0 (0.9 – 1.2)	590	3.5	1.2 (1.1 – 1.4)
Preterm†:									
PE	147	0.6	*Ref*	127	0.6	0.9 (0.7 – 1.2)	158	0.9	1.6 (1.2 – 2.0)
SGA	126	0.5	*Ref*	107	0.5	0.9 (0.6 – 1.2)	140	0.8	1.7 (1.3 – 2.3)

* OR, odds ratio. CI, Confidence Interval. Odds ratios are adjusted for maternal early-gestation BMI, age, height, family situation, daily smoking in early gestation and country of birth. †Preterm: Defined as the combination of the outcome and delivery before 37 gestational weeks.

Table 3: 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	**Change in diastolic blood pressure (DBP)**								
	Lowered (< -2 mm Hg)			**Unchanged (-2 to +2 mm Hg)**			**Elevated (> 2 mm Hg)**		
mm Hg	*n*	rate (%)		*n*	rate (%)	Adjusted OR (95%CI)*	*n*	rate (%)	Adjusted OR (95%CI)*
< 70	121	1.6	*Ref*	268	1.9	1.1 (0.9 – 1.4)	429	3.2	1.8 (1.4 – 2.2)
70 – 79	443	3.3	*Ref*	298	4.2	1.2 (1.0 – 1.4)	249	8.1	2.4 (2.0 – 2.8)
80 – 89	277	6.1	*Ref*	126	11.0	1.8 (1.4 – 2.3)	35	15.8	2.7 (1.7 – 4.2)
	PRETERM PREECLAMPSIA†								
< 70	19	0.3	*Ref*	52	0.4	1.3 (0.8 – 2.3)	87	0.6	2.1 (1.3 – 3.6)
70 – 79	68	0.5	*Ref*	55	0.8	1.3 (0.9 – 1.9)	59	1.9	3.7 (2.6 – 5.5)
80 – 89	60	1.3	*Ref*	20	1.7	1.2 (0.6 – 2.2)	12	5.4	4.1 (2.0 – 8.6)

* OR, odds ratio. CI, Confidence Interval. Odds ratios are adjusted for maternal early-gestation BMI, age, height, family situation, daily smoking in early gestation and country of birth. † Preterm: Defined as the combination of the outcome and delivery before 37 gestational weeks.

Table 4: Risk of giving birth to a small-for-gestational-age (SGA) infant by diastolic blood pressure (BP) in early gestation and change in diastolic BP from early to mid-gestation.

	ANY SGA								
Early-gestation DBP	**Change in diastolic blood pressure (DBP)**								
	Lowered (< -2 mm Hg)			**Unchanged (-2 to +2 mm Hg)**			**Elevated (> 2 mm Hg)**		
mm Hg	*n*	rate (%)		*n*	rate (%)	Adjusted OR (95%CI)*	*n*	rate (%)	Adjusted OR (95%CI)*
< 70	201	2.7	*Ref*	390	2.7	1.0 (0.8 – 1.2)	450	3.3	1.3 (1.0 – 1.5)
70 – 79	361	2.7	*Ref*	222	3.1	1.2 (1.0 – 1.4)	126	4.1	1.5 (1.2 – 1.9)
80 – 89	134	3.0	*Ref*	47	4.1	1.7 (1.1 – 2.4)	14	6.3	2.5 (1.3 – 4.8)
	PRETERM SGA†								
< 70	26	0.4	*Ref*	55	0.4	1.0 (0.6 – 1.7)	93	0.7	2.3 (1.3 – 3.8)
70 – 79	63	0.5	*Ref*	43	0.6	1.3 (0.8 – 2.0)	41	1.3	2.8 (1.7 – 4.4)
80 – 89	37	0.8	*Ref*	9	0.8	0.8 (0.3 – 2.0)	6	2.7	3.9 (1.4 – 10.7)

* OR, odds ratio. CI, Confidence Interval. Odds ratios are adjusted for maternal early-gestation BMI, age, height, family situation, daily smoking in early gestation and country of birth. † Preterm: Defined as the combination of the outcome and delivery before 37 gestational weeks.