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Placental Function

An Epidemiological and Magnetic Resonance Study

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Abstract

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Placental function is central for normal pregnancy and in many of the major pregnancy disorders. We used magnetic resonance imaging techniques to investigate placental function in normal pregnancy, in early and late preeclampsia and in intrauterine growth restriction. We also investigated maternal body mass index and height, as risk factors for preeclampsia.

A high body mass index and a short maternal stature increase the risk of preeclampsia, of all severities. The association seems especially strong between short stature and early preeclampsia, and a high body mass index and late preeclampsia. *(Study I)*

Using diffusion-weighted magnetic resonance imaging, we found that the placental perfusion fraction decreases with increasing gestational age in normal pregnancy. Also, the placental perfusion fraction is smaller in early preeclampsia, and larger in late preeclampsia, compared with normal pregnancies. That these differences are in opposite directions, suggests that there are differences in the underlying pathophysiology of early and late preeclampsia. *(Study II)*

Using magnetic resonance spectroscopy, we found that the phosphodiester spectral intensity fraction and the phosphodiester/phosphomonoester spectral intensity ratio increases with increasing gestational age. Also, we found that the phosphodiester spectral intensity fraction and the phosphodiester/phosphomonoester spectral intensity ratio are higher in early preeclampsia, compared with early normal pregnancy. These findings indicate increased apoptosis with increasing gestational age in normal pregnancy, and increased apoptosis in early preeclampsia. *(Study III)*

The placental perfusion fraction is smaller in intrauterine growth restriction than in normal pregnancy. Fetal growth, Doppler blood flow in maternal and fetal vessels, infant birth weight and plasma markers of placental function are all correlated to the placental perfusion fraction. The placental perfusion fraction examination seems therefore to offer a fast, direct estimate of the degree of placental dysfunction. *(Study IV)*

In conclusion: Our findings in studies I-III all support the hypothesis of partly different pathophysiology between early and late preeclampsia, and suggest a strong link between early preeclampsia and placental dysfunction. Study IV shows that the placental perfusion fraction has potential to contribute to the clinical assessment of placental dysfunction.

Keywords: body height, body mass index, early preeclampsia, late preeclampsia, magnetic resonance imaging, placenta, perfusion, IVIM, risk factors, energy metabolism, magnetic resonance spectroscopy, 31P-MRS

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“Our greatest glory is not in never falling, but in rising every time we fall.”

– Oliver Goldsmith

In memory of Else and Erik Hammerlund

List of Papers

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

I **Sohlberg S**, Stephansson O, Cnattingius S, Wikström AK. Maternal body mass index, height, and risks of preeclampsia. *Am J Hypertension,* 2012 Jan; 25(1):120-5.

II **Sohlberg S**, Mulic-Lutvica A, Lindgren P, Ortiz-Nieto F, Wikström AK, Wikström J. Placental perfusion in normal pregnancy and early and late preeclampsia: a magnetic resonance imaging study. *Placenta,* 2014 May; 35(3):202-6.

III **Sohlberg S**, Wikström AK, Olovsson M, Lindgren P, Axelsson O, Mulic-Lutvica A, Weis J, Wikström J. In vivo ^{31}PMR spectroscopy in normal pregnancy, early and late preeclampsia: a study of placental metabolism. *Placenta,* 2014 Mar; 35(5):318-23.

IV **Sohlberg S**, Mulic-Lutvica A, Olovsson M, Weis J, Axelsson O, Wikström J, Wikström AK. MRI estimated placental perfusion in fetal growth assessment. *Ultrasound in Obstetrics and Gynecology,* in press (Acceptance letter Jan. 7, 2015).

Cover illustration:
The Miraculous Journey, by Damien Hirst
Photographer: Penny Yi Wang

Contents

Abbreviations

AGA	Appropriate for gestational age
AOR	Adjusted odds ratio
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
CRP	C-reactive protein
CTG	Cardiotocography
CVD	Cardiovascular disease
DWI	Diffusion-weighted imaging
ELISA	Sandwich enzyme-linked immunosorbent assay
ISSHP	International Society for the Study of Hypertension in Pregnancy
IUGR	Intrauterine growth restriction
IVIM	Intravoxel incoherent motion
LGA	Large for gestational age
MHz	Megahertz
MR	Magnetic resonance
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
MRSI	Magnetic resonance spectroscopy imaging
NOE	Nuclear Overhauser effect
OR	Odds ratio
PDE	Phosphodiester
PI	Pulsatility index
PlGF	Placental growth factor
PME	Phosphomonoester
PTX-3	Pentraxin-3
SAS	Statistical Analysis Software
SGA	Small for gestational age
SD	Standard deviation
sFlt-1	Soluble Fms-like tyrosine kinase-1
SPSS	Statistical Package for the Social Sciences
TNF-α	Tumor necrosis factor alpha
TNFr1	Tumor necrosis factor receptor-1
TNFr2	Tumor necrosis factor receptor-2

Introduction

Preeclampsia and IUGR are both strongly associated with placental dysfunction (1) and share many risk factors (2). The underlying pathology of different disorders associated with placental dysfunction, such as early and late preeclampsia and IUGR, are difficult to investigate and much remains to be explored. Even the gestational age-related physiological changes in placental function in normal pregnancy are not fully understood. Magnetic resonance offers new *in vivo* techniques for studying placental function during pregnancy.

Preeclampsia

Preeclampsia affects 1.4-4.0% of all pregnancies (3) and is a leading cause of maternal (4-6) and fetal (7-9) morbidity and mortality. Acute maternal complications include eclampsia, stroke, abruptio placentae, disseminated intravasal coagulation, liver hemorrhage/rupture, pulmonary edema, acute renal failure and death (5). Maternal long term risks include increased risk of CVD (10-12), diabetes mellitus (13) and premature death (12). Acute fetal complications include preterm birth, IUGR and stillbirth (14).

Definition of preeclampsia

According to ISSHP the definition of preeclampsia is: de novo hypertension after gestational week 20 and proteinuria $\geq$300 mg/24 hour or a spot urine protein/creatinine ratio of >30 mg/mmol, with subsequent normalisation of blood pressure within 3 months postpartum. Hypertension is defined as a systolic BP of $\geq$140 mmHg and/or diastolic BP $\geq$90 mmHg (15). The ISSHP´s definition of preeclampsia also includes definitions of mild to moderate preeclampsia and severe preeclampsia. Severe preeclampsia is preeclampsia with a systolic blood pressure of >160 mmHg or diastolic blood pressure of >110 mmHg. In their latest statement on the definition of severe preeclampsia the ISSHP concludes that the amount of proteinuria should not be a criterion of severity (16).

Pathophysiology of preeclampsia

In the 1990s a hypothesis that divided the preeclampsia syndrome into two causal origins - placental and maternal preeclampsia - was presented (17). According to current theories, preeclampsia originates from a mixture of both placental and maternal factors, with different proportions in each case (18).

Placental preeclampsia

Placental preeclampsia has been described using a two stage model, where the first stage is defective placentation and the second the clinical syndrome arising from a combination of the defective placentation and maternal factors such as genetics, obesity, diabetes etc. (19). Recently, the placental preeclampsia model has also been expanded into three and even four stages (stage 0-3) (Figure 1) (20).

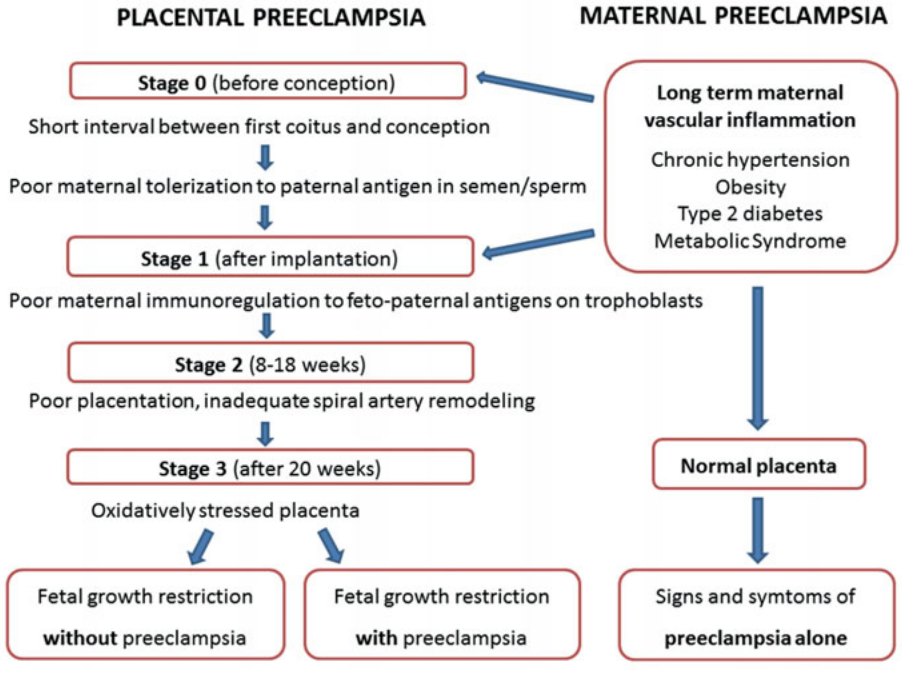

Figure 1. The four stage model of preeclampsia. After Redman, C. *et al*. Pregnancy Hypertension 2011; 1:2-5. With permission from Elsevier.

In the four stage model introduced by Professor Christopher Redman, *the first "zero" step* is pre-conceptual and involves a short interval between first coitus with the father-to-be and conception. This is thought to lead to an increased risk of poor maternal tolerization to paternal antigens in semen/sperm (20).

Stage one, after conception, involves poor maternal immunoregulation to feto-paternal antigens on trophoblasts, leading to abnormal trophoblast growth and differentiation (21, 22). Changes in circulating trophoblast derived factors

associated with preeclampsia can be detected before placentation is completed (23), as early as week 11-13 of gestation.

Stage two, the defective placentation, develops between the eighth and 18th week of gestation. In normal placentation, cytotrophoblast cells cross placental-maternal bridges and invade the maternal decidua and adjacent spiral arteries. They replace the endothelium of the spiral arteries, and remodel the myometrium so that the smooth muscle is lost and the arteries dilate and become unresponsive to vasoconstrictors (24). In placental preeclampsia, the trophoblast invasion is restricted to the peripheral segments of the spiral arteries, leading to shallow placentation and retention of the vasoactive smooth muscles, leading to dysfunctional blood flow (25, 26) (Figure 2). It is hypothesized that, the consequent intermittent hypoxia-reoxygenation and subsequent oxidative stress is harmful to the placenta (25, 27). Hypervelocity perfusion through narrow, undilated spiral arteries is also thought to induce damage to the intervillous space (27).

The extent of the defective placentation is different in each woman, has two major components: the number of spiral arteries with full myometrial remodeling, and whether the remaining spiral arteries display absent or partial remodeling (1).

The third stage of placental preeclampsia, the clinical syndrome, arises when placental stress, due to dysfunctional perfusion of the intervillous space and consequent oxidative and hemodynamic strain, leads to the release of numerous trophoblast-derived placental factors (28, 29), which contribute to the maternal inflammatory response seen in preeclampsia (30); this inflammatory response is thought to give rise to the clinical syndrome (31). Placenta-derived factors that are altered in preeclampsia include: sFlt-1 (32); PlGF (33); sEndoglin (34); Leptin (35); Activin- and Inhibin-A (36); Corticotrophin releasing hormones (37); and trophoblast micro particles (38).

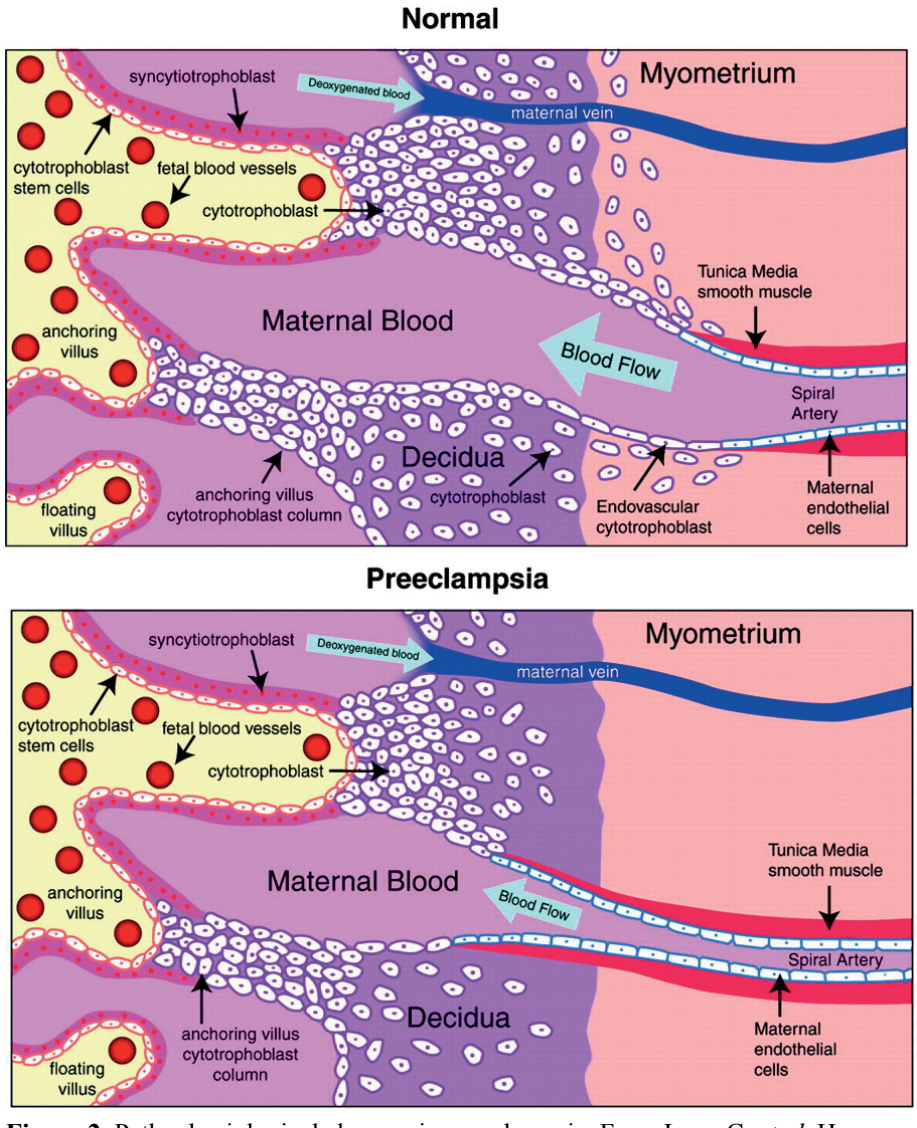

Figure 2. Pathophysiological changes in preeclampsia. From Lam, C. *et al*. Hypertension 2005; 46:1077-1085. Reprinted with permission from AHA Journals.

Maternal preeclampsia

Normal pregnancy is associated with a systemic inflammatory response (39). Maternal preeclampsia is thought to have its origin in an exaggerated maternal inflammatory response.

Maternal background factors such as hypertension (40), obesity (41, 42) and diabetes (43) are strong risk factors for preeclampsia and are known to be states of chronic systemic inflammation (44-46). Maternal preeclampsia is thought to arise when the normal systemic inflammation of pregnancy is com-

bined with such chronic systemic inflammation. Together, the resulting inflammation becomes so excessive, that it gives rise to the clinical syndrome (18) (Figure 1).

Early and late preeclampsia

A well-established way of sub-classifying preeclampsia (47) that has recently been adopted by the ISSHP (16) is to distinguish 'early' and 'late' preeclampsia, defined as having onset before 34+0 weeks gestation and at 34+0 weeks or more, respectively.

Early preeclampsia affects 0.3-0.7% of pregnancies (3) and is believed to have a stronger placental component and thus be more dependent on underlying defective placentation than late preeclampsia (48-50). Late preeclampsia is thought to be a mainly maternal disease, related to maternal metabolic risk factors (17, 51).

Compared with late preeclampsia, early preeclampsia has a higher risk of maternal (6) and fetal (52) mortality, a stronger association with increased-long-term cardiovascular risk in the mother (6), and higher risk of recurrent disease in future pregnancies (53). Early preeclampsia is strongly associated with preterm birth (7). Early preeclampsia also has a strong association with IUGR (54, 55), while most women with late preeclampsia give birth to infants that are AGA (55, 56). In late preeclampsia the association with giving birth to an SGA infant is about as strong as the association with giving birth to an LGA infant (54).

Risk factors for preeclampsia

Risk factors for preeclampsia include nulliparity (57), old maternal age (58), multiple gestation (43), diabetes (43), obesity (41), chronic hypertension (40), previous preeclampsia (53), family history of preeclampsia (59), renal disease (60), >10 years since last pregnancy (61), and the presence of antiphospholipid antibodies (62, 63). CVD and preeclampsia share constitutional risk factors, such as obesity, hyperlipidemia, hypertension and increased blood glucose levels (64).

Overweight and obesity are well known risk factors for preeclampsia (43, 65), both for severe (66) and mild to moderate disease (41). Only a few studies have investigated BMI as a risk factor for early and late preeclampsia separately, and these studies used different definitions of early and late, and had diverging results (42, 67-70).

Few studies have looked at maternal height as a risk factor for preeclampsia (71, 72); neither of them looked at early and late preeclampsia separately, and only one was able to show a correlation between short maternal height and risk of severe preeclampsia (72). Short height in women is associated with an increased risk of CVD (73). Preeclampsia is also associated with an increased risk of CVD (10, 12, 74); this association is especially strong for early preeclampsia (10, 12).

The clinical syndrome of preeclampsia

Clinical preeclampsia is a disease characterized by endothelial dysfunction (31). The disease is a multisystem disorder that affects individual patients differently. Most women have a mild disease that presents late in pregnancy with mild or no symptoms (75). The most typical symptoms associated with preeclampsia are headache, visual disturbances, epigastrial pain and edema. Severe cases of preeclampsia can also have symptoms derived from liver damage, renal insufficiency, pulmonary edema, disseminated intravascular coagulation, intracranial hemorrhage and/or eclampsia.

Hypertension

Multiple mechanisms contribute to the hypertension seen in preeclampsia. These include a rise in sympathetic tone, alterations in the renin-angiotensin system and a shift in vasoconstrictor versus vasodilator balance towards increased vasoconstriction (76). The underlying pathophysiology behind this is only partly known. Endothelial dysfunction leading to altered levels of vasoactive mediators (77, 78) is thought to play an important role.

Proteinuria and renal dysfunction

Women with preeclampsia have proteinuria and hypoperfusion of their kidneys. The proteinuria seen in preeclampsia is thought to, at least in part, depend on loss of size-, and possible charge-, selectivity in the glomeruli due to glomerular dysfunction (79). Compared to women with normal pregnancies, the glomerular filtration rate and the renal plasma flow in women with preeclampsia is reduced by 30-40% (80). The classical renal lesion in preeclampsia is glomerular capillary endotheliosis, which is also seen in gestational hypertension and in some normal pregnancies, but then often in milder forms (81). "Glomerular endotheliosis" represents a specific type of thrombotic microangiopathy that is characterized by glomerular endothelial swelling with loss of endothelial fenestrae and occlusion of the capillary lumens (82).

Neurological symptoms

Headache, blurred vision and temporary loss of vision are known preeclampsia symptoms (76). The underlying pathophysiology is thought to be a combination of endothelial dysfunction (83) and hypertension leading to cerebral edema (76). Women with preeclampsia are at risk of developing eclampsia, generalized seizures, which are often preceded by severe headache and visual symptoms (76).

Edema

Edema, especially of the hands, feet and face, and rapid weight gain are often seen in preeclampsia. The edema appears similar to the "over-fill" edema of

acute glomerulonephritis, in which renal dysfunction leads to sodium and fluid retention (76). The underlying pathophysiology of edema in preeclampsia is not fully known; increased endothelial permeability (84) and hypoalbuminemia (85) probably contribute.

Intrauterine growth restriction

Intrauterine growth restriction is the inability of a fetus to reach its individual genetic growth potential (86). IUGR is a major cause of perinatal mortality and morbidity (87-90) and is also associated with long term consequences including impaired neurological development (91), increased risks of developing CVD (92), and the metabolic syndrome (93). There is no generally accepted definition of IUGR (94).

Pathophysiology of IUGR

The most common underlying cause of IUGR is placental dysfunction (95-97), but it can also be caused by conditions such as chromosomal abnormalities, intrauterine infections or maternal substance abuse (95). Placental dysfunction is a progressive process, that initially leads to subtle compensatory reactions in the fetal circulation, but which can progress to circulatory failure in multiple organ systems and finally to intrauterine death (98). The placental dysfunction seen in IUGR seems to have a similar pathophysiology as placental preeclampsia, involving a defective placentation (25). Some studies have shown partial transformation of the spiral arteries in placentas from normotensive IUGR pregnancies (25, 26) and it has therefore been hypothesized that the defective placentation in normotensive IUGR might be less extensive than in preeclampsia. Interestingly, other pregnancy complications, such as miscarriages, spontaneous preterm labour and abruptio placentae are also associated with defective placentation (1, 99).

Risk factors for IUGR; a comparison with preeclampsia

Many of the risk factors for IUGR are also risk factors for preeclampsia, including nulliparity (57, 100), low socioeconomic status (101, 102), underlying maternal illness such as chronic hypertension (40, 101), renal disease (60, 103), auto-immune disorders (62, 104) and thrombophilia (105, 106). Diabetes is a shared risk factor (43), but in IUGR it seems that the risk increase is limited to women suffering from diabetes with vascular disease (107).

Smoking is considered to be the single most important risk factor for giving birth to an SGA infant in developed countries (108). Paradoxically, smoking reduces the risk of preeclampsia (43). Other risk factors for IUGR, such as low pre-pregnancy weight and low weekly weight gain (100), are not risk factors for preeclampsia. In preeclampsia a high pre-pregnancy BMI and high

pregnancy weight gain increase the disease risk (42), while low pre-pregnancy BMI is associated with a low preeclampsia risk (43).

A history of pregnancy complications, including IUGR (109), preeclampsia (110, 111), placental abruption (111) and miscarriage (112, 113), increases the risk of both IUGR and preeclampsia in a subsequent pregnancy. Also, women who were born SGA have an increased risk not only of SGA, but of several disorders associated with placental dysfunction, including preeclampsia (114). Both the increased risk of IUGR and preeclampsia in women with a history of pregnancy disorders associated with placental dysfunction, and the inter-generational recurrence of disorders associated with placental dysfunction in women born SGA, indicate a common pathophysiological pathway among these disorders (111, 114).

Antenatal management of IUGR

Since there are no effective therapies for IUGR, antenatal management focuses on monitoring the pregnancy and choosing the ideal time for delivery. Doppler velocimetry measurements of fetal and maternal vessels are the gold standard in assessment of placental function in cases of suspected IUGR. By assessing the circulation on both sides of the placenta, this method offers a non-invasive estimate of placental function. Doppler velocimetry measurements can also be used to examine fetal compensatory and circulatory adaptations (115).

Doppler velocimetry measurements are usually recorded as PIs. The PI is a measure of the blood flow resistance in a vessel (PI= (peak systolic velocity-minimum diastolic velocity)/ mean velocity during the cardiac cycle).

Of the Doppler velocimetry measurements used in obstetric practice, the umbilical artery blood flow was the first to be linked to pregnancy outcome (116). The Doppler blood flow in the umbilical artery provides an indirect measure of vascular resistance in the placenta (116). Umbilical artery Doppler velocimetry measurements in cases of suspected IUGR reduce the number of perinatal deaths and also the number of unnecessary obstetric interventions (117).

Other vessels assessed in cases of IUGR include, on the maternal side, the uterine arteries and, on the fetal side, the middle cerebral artery and the ductus venosus (115). When assessing the uterine arteries, both the right and left artery PI and the presence or absence of an end diastolic notch, are determined. The uterine artery measurements can be used to predict preeclampsia and IUGR (118, 119). Their predictive power is stronger for preeclampsia than for IUGR, and stronger for severe preeclampsia than mild preeclampsia (120). The PI in the uterine arteries and the presence or absence of a diastolic notch can be combined to give a uterine artery score, 0-4 points (121). When applied to high risk pregnancies a pathological uterine artery score, >2 points, is strongly related to adverse pregnancy outcomes (121).

Doppler velocimetry measurements in the middle cerebral artery are performed in cases of suspected IUGR (115). A decrease in the middle cerebral artery PI is known as "brain sparing", and is a compensatory measure that usually occurs early in the hypoxic process (122).

Blood flow in the ductus venosus is also examined in cases of suspected IUGR, especially preterm (115). Changes in ductus venosus blood flow are seen during atrial contraction, where the flow velocity can be reduced, or in cases of severe hemodynamic compromise, even be reversed (123). These changes occur late in the hypoxic process (124) and when minimum ductus venosus blood flow reaches baseline or becomes negative heart failure is imminent (123).

Methods to estimate optimal time of delivery

Managing IUGR in preterm pregnancy is a delicate balance between fetal and neonatal risks. In second trimester IUGR the benefits of prolonged gestation are extensive and the hypoxic process is therefore allowed to proceed further before the decision to deliver is made. Also, the duration between the occurrence of pathological Doppler findings in the umbilical artery and the development of a pathological CTG, with late decelerations (125) or pathological short-term variability (126), is inversely correlated to the gestational age of the fetus, indicating that the premature IUGR fetuses tolerate the hypoxia process better than term IUGR fetuses. In cases of second trimester IUGR, ductus venosus blood flow (115) and/or short-term heart rate variability (126) can be used to determine the optimal time of delivery. In third trimester IUGR, the potential benefits of prolonged gestation are smaller and the hypoxic process is not allowed to proceed as far. In the third trimester, umbilical artery blood flow is often used to determine optimal time of delivery (115).

There are presently no clinically available methods to directly estimate placental function *in vivo*. For IUGR there is a need for new techniques to diagnose and estimate the severity of placental dysfunction.

Circulatory markers of placental function

Multiple studies have shown that both IUGR (127) and preeclampsia (128) are associated with an imbalance between angiogenic and anti-angiogenic placenta-derived factors such as PlGF, sFlt-1 and sEndoglin (32, 129, 130). In preeclampsia this imbalance is less dramatic in the late than in the early disease (130, 131). Some of the most extensively studied markers are PlGF and sFlt-1 (132), where PlGF is reduced and sFlt-1 increased in preeclampsia compared with normal pregnancy (131).

Both IUGR (133) and preeclampsia (37) are also characterized by an exaggerated inflammatory response and are associated with increased levels of inflammatory markers such as CRP, TNF-α, and PTX-3 (134-139). In studies of preeclampsia some inflammatory markers are more associated with late than early preeclampsia (140). Inflammatory marker levels are also higher in severe than in mild preeclampsia, and higher in preeclampsia with IUGR than in preeclampsia without IUGR (141, 142). Placental protein 13 is another promising marker for preeclampsia and IUGR (143, 144).

Circulating markers of placental function are used in studies investigating the pathophysiology of diseases involving placental dysfunction (128, 134), prediction models for placental disease (143, 144) and, in some cases, to distinguish subtypes of disease that involve placental dysfunction from those with normal placental function (145).

Magnetic resonance

The nuclear magnetic resonance phenomenon was discovered in 1940 by Isidor Isaac Rabi (146), who was subsequently awarded The Nobel Prize in Physics 1944 *"for his resonance method for recording the magnetic properties of atomic nuclei"*. MR can be used in MRI to produce anatomical images and in MRS to produce spectra of metabolites present in the scanned tissue. When MRI and MRS are combined in MRSI, spatially localized spectra from all parts of the examined tissue can be obtained (147).

Basic principles of magnetic resonance

The basis of Rabi's discovery is the resonance phenomenon, the constructive coherence of waves of the same frequency and phase, leading to an increase in amplitude. This phenomenon only occurs at the resonance frequency, which is unique to each atom and proportional to the magnetic field strength (147).

The MR technique involves placing the study subject in a static magnetic field, thereby achieving a steady state among the magnetic dipole moments in the atom nuclei of the study subject. By then applying external magnetic field gradients at the resonance frequency, the magnetic dipole moments can be manipulated. In response to the manipulations the nuclei emit radio signals, which are recorded and analyzed (147). The recorded signal depends on the properties of the examined object, e.g. the number of protons in the studied tissue, but also on the molecular environment of the protons. By applying magnetic field gradients in three dimensions and then performing mathematical transformations on the recorded radio signal, the signal contribution from different parts of the studied object can be deduced, and cross-sectional images in arbitrary planes can be created (148).

Important advantages of the MR technique are that it does not involve any ionizing radiation and that it is non-invasive.

Safety aspects of magnetic resonance in pregnancy

The use of MR in pregnancy has no known risks to the mother or the fetus. There are however recommendations to avoid exposure over 1.5 Tesla and to avoid MR during the organogenesis, which takes place in the first trimester (149).

Different aspects of MR safety during pregnancy have been studied. A three-year follow up of children imaged in utero using MRI showed no increased disease or disability occurrence (150). Studies using fetal CTG during MRI examinations at 1.5 Tesla showed no effects on the heart rate or movement incidence (151, 152). Animal studies on chick embryos have shown no negative effects on cell proliferation and migration of chick motor neurons after 6 hours exposure to a static magnetic field of 1.5 Tesla and 4 hours exposure to a 64-MHz radio-frequency field (153).

Perfusion estimation using DWI and the IVIM method

Diffusion-weighted imaging is an MRI technique where the image contrast is based on the random molecular motion of water in different tissues (154). This technique is mostly used in ischemic stroke (155, 156), but also in the study of other diseases such as cancer (157) and multiple sclerosis (158).

The DWI technique is used in the IVIM method, which was developed by Denis Le Bihan (159). IVIM is based on the acquisition of a diffusion-weighted sequence with multiple degrees of diffusion weighting (b-values). With IVIM, both the slow movement of water particles, diffusion, and the fast movement of blood in the capillary network, perfusion, can be calculated. The differences in motion speed enable the perfusion component to be separated from the diffusion component. This is done mathematically by calculations based on differences in the signal intensity at the different b-values (160). One of the measures of perfusion that can be calculated using IVIM is the perfusion fraction, which is an estimate of the volume fraction of capillary perfused tissue (156, 161, 162). In previous studies, the perfusion fraction has been shown to correlate with established, contrast agent-based measurements of perfusion (163).

Magnetic resonance spectroscopy

Magnetic resonance spectroscopy enables noninvasive *in vivo* quantification of the relative concentrations of target metabolites within a tissue. The amount of the examined nuclei determines the strength of the signal, while the frequency depends on the molecule in which it is located. The same nuclei, in

different molecules, display slightly different net magnetic dipole moments and resonate at slightly different frequencies, depending on the shielding effects from the surrounding electronic clouds (147). These small differences in resonant frequencies cause a phenomenon called chemical shift, from which a chemical shift frequency spectrum of metabolites can be obtained with the help of complex mathematical transformations (147).

The MRS technique has been used mainly to study the three nuclei ^{1}H , ^{31}P or ^{13}C, because they are abundant in human tissue and are small enough to produce a sharp resonance (164).

^{31}P-MRS can be used to visualize important metabolites linked to bioenergetics, and the turnover of phospholipids and membranes (164). For over 20 years the ^{31}P-MRS technique has been used to study human tissues, such as muscle (165), brain (166), liver (167) and heart (168). Only a few studies have used ^{31}P- MRS to study human placenta and, with few exceptions (169), these studies have been performed either *in vitro* (170, 171) or *ex vivo* in perfused placental models (172).

Aims

The overall purpose of this thesis was to investigate maternal habitus as a risk factor for early and late preeclampsia, and to study placental function in normal pregnancy, early and late preeclampsia and intrauterine growth restriction using MR techniques.

I To assess if high BMI and short stature have similar associations with early and late preeclampsia.

II To assess if and how placental perfusion and energy metabolism in normal pregnancy change with increased gestational length.

III To assess if placental perfusion and energy metabolism are different in women with early and late preeclampsia, compared to women with normal pregnancy at corresponding gestational lengths.

IV To assess placental perfusion estimated by magnetic resonance as a direct measure of placental function.

Material and Methods

Study populations and study designs

Study I

This population-based cohort study of 503179 nulliparous women is based on information from the Swedish Medical Birth Register. Primiparous women born in the Nordic countries (Sweden, Norway, Denmark, Finland or Iceland) who delivered a singleton infant in gestational week 22 or later, without congenital malformations, during the years 1992 to 2006, were included. Women with gestational hypertension were excluded (n=6182). The Birth Register contains data on more than 98% of all births in Sweden (173) and includes prospectively collected demographic data, and information on reproductive history and complications that occur during pregnancy, delivery, and the neonatal period.

Studies II-IV

These studies are based on one original study cohort of 53 women recruited at Uppsala University Hospital during 2008-2013 (Figure 3). Only women with singleton pregnancies, with a living fetus and a gestational age between 22+0 and 41+6 weeks, were eligible to participate. Women with chronic hypertension, pre-existing renal disease, diabetes mellitus or severe claustrophobia were not included. For technical reasons related to the MRS examination (study III), only women with an anterior placenta and a BMI of 36 or less were included.

Studies II-III

Studies II and III are cross-sectional studies. In these studies preeclampsia was defined as hypertension of $\geq$140/90 mmHg at two separate occasions $\geq$4 hours apart, and proteinuria ($\geq$2+ on a dipstick or a urine collection showing $\geq$300 mg /24 hours) and normal pregnancy was defined as a healthy, single pregnancy with term birth ($\geq$37 weeks of gestation) to a child with a birth weight appropriate for the gestational age (within ±2 SDs of the Swedish reference standard for new-borns (174). Both women with preeclampsia and normal

pregnancy were sub-grouped into early (<34 weeks) and late (≥34 weeks), depending on completed gestational weeks at examination.

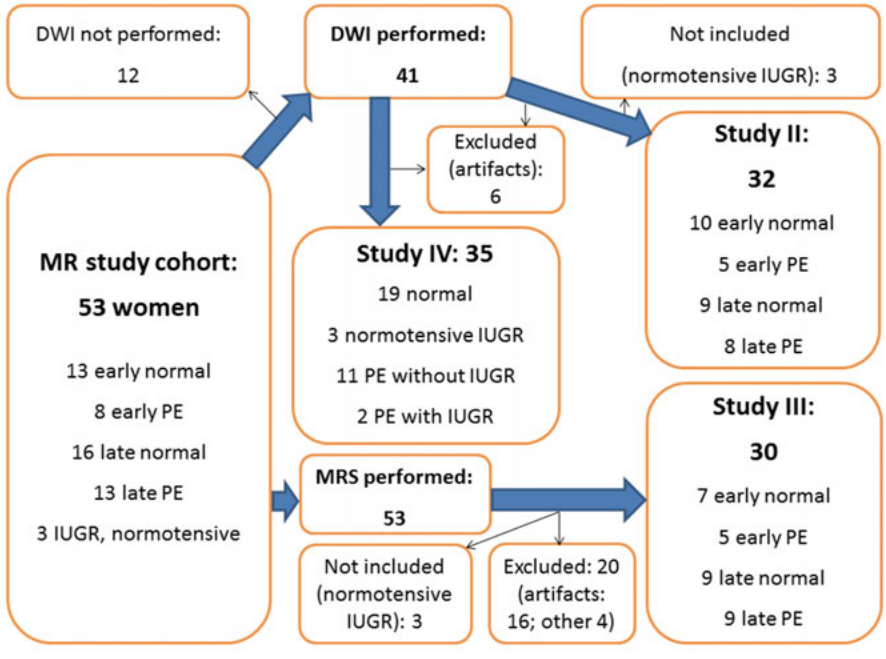

Figure 3. Flow-chart of the MR study cohort.

Study II included thirteen women with preeclampsia (five with early and eight with late preeclampsia), and nineteen women with normal pregnancy (ten with early and nine with late pregnancy).

Study III included fourteen women with preeclampsia (five with early and nine with late preeclampsia), and sixteen women with normal pregnancy (seven with early and nine with late pregnancy).

Study IV

This cross-sectional study included thirty-five women, five of whom had IUGR (three normotensive IUGR and two preeclampsia with IUGR), and thirteen preeclampsia IUGR (Figure 3). IUGR was defined as an estimated fetal weight less than -22% from the mean gestational-age related Swedish reference curve (175), and a pathological umbilical artery or ductus venosus PI. Preeclampsia was defined as previously described (studies II-III).

Methods

Study I

All information was collected from the Swedish Medical Birth Register, the Education Register and the Register of Total Population. The exposures were BMI and height. Covariates were maternal age, years of formal education, smoking habits, diabetes mellitus (gestational or pre-gestational), and the presence of chronic hypertension, chronic renal disease or systemic lupus erythematosus. Outcomes were preeclampsia, classified either according to gestational age at delivery [as early (<32 weeks), moderately early (32-36 weeks), and late (≥37 weeks)], or according to severity (mild to moderate and severe preeclampsia, as defined by diagnostic codes).

Studies II-IV

All study participants underwent blood pressure measurement, urine sampling, and ultrasound and MR examinations within less than 24 hours. The MR examinations were performed on a 1.5 Tesla Gyroscan Achieva MR scanner (Philips, Best, the Netherlands).

The ultrasound examinations were performed with Voluson E8 ultrasound equipment (GE Healthcare, Kretz Ultrasound, Zipf, Austria) using a 4-5 MHz transabdominal transducer. The mechanical index was below 1.1 and the thermal index below 0.9. Physicians specialized in fetal medicine performed the ultrasound examinations, which included an estimation of fetal weight, measurements of amniotic fluid index and assessment of blood flow parameters. Fetal growth was categorized into: 1) AGA (-22% to +22%); 2) LGA (>22%); 3) SGA (<-22% and a normal umbilical artery pulsatility index) and 4) IUGR (<-22% and pathological umbilical artery or ductus venosus PI). Oligohydramnios was defined as amniotic fluid index less than 5 cm.

Studies II and IV

MR imaging was performed using the integrated body coil. An echo-planar imaging, diffusion-weighted sequence with five different b-values (0, 200, 400, 600, and 800 s/mm^2) was obtained perpendicular to the placenta. Depending on the size of the placenta, three to seven slices of six mm thickness were collected. Imaging time for the diffusion-weighted sequence was typically 3 minutes and 45 seconds.

Measurements, on which to base calculations of the perfusion fraction, were performed using research software (Philips Medical Systems, Best, the Netherlands). In each slice from the diffusion-weighted sequence, regions-of-interest were placed to include as much of the placenta as possible, excluding

areas with artefactual signal loss. Estimates of the perfusion fraction were obtained using a monoexponential fit for the signal intensities at b values of 200-800 s/mm^2. Only estimates with a goodness of fit (R^2) of 0.9 or more were accepted for further analysis. The mean perfusion fraction from the different slices was calculated.

Study III

The whole body coil was used for MR imaging. Axial, coronal and sagittal T_2-weighted, single-shot turbo spin echo images were used to guide the positioning of the spectroscopic volume of interest, the so called voxel (Figure 4). The in-plane spatial resolution was 1.8×2.5 mm^2 and slice thickness 8 mm. Acquisition of ~20-40 slices required ~20-40 seconds. A single-voxel ^{31}P spectrum was measured by a transmit-receiver surface coil (diameter 14 cm). An image-selected in vivo spectroscopy localization sequence (176) was combined with broad band proton decoupling (WALTZ-4 modulation) (177) and nuclear Overhauser effect enhancement (178). A whole body coil was used for both decoupling and NOE enhancement. The main measurement parameters were as follows: spectral bandwidth, 1500 Hz; repetition time, 2500 ms; 512 points; NOE mixing time, 2000 ms; 512 acquisitions. Typical voxel size was 80×90×20 mm^3 (Figure 4). The net acquisition time was 21.3 minutes. However, the total examination time was approximately 45 minutes.

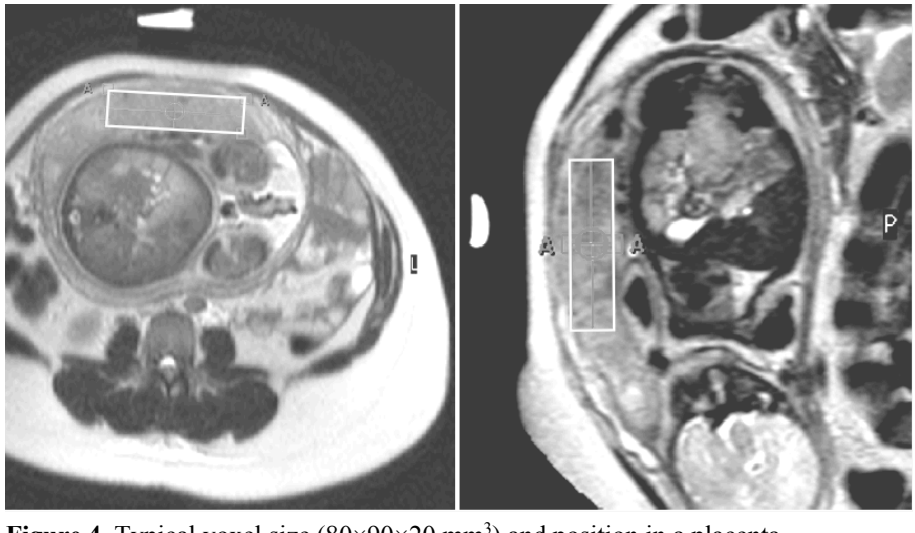

Figure 4. Typical voxel size (80×90×20 mm^3) and position in a placenta.

Spectra were fitted by the AMARES algorithm (179), which is a part of the jMRUI software package (180). Spectra were fitted as measured, i.e. without previous apodization of the free induction decays, to improve the signal-to-noise ratio. However, for presentation purposes (Figure 5), an exponential

apodization function corresponding to 10 Hz line broadening was applied. Spectral intensities of the following metabolites were evaluated: phosphomonoester (PME = phosphoethanolamine (PE) + phosphocholine (PC)); inorganic phosphate (Pi); phosphodiester (PDE = glycerophosphoethanolamine (GPE) + glycerophosphocholine (GPC)); phosphocreatine (PCr); and adenosine triphosphate (ATP). The PCr line was placed to 0 ppm and 13 spectral lines were fitted by Lorentzians (Figure 5). Spectral intensities of metabolites were quantified as a fraction of the total phosphorus signal (total spectral intensity) (ALL) (169). The following spectral intensities fractions were considered: PME/ALL, Pi/ALL, PDE/ALL, PCr/ALL and ATP/ALL. The PDE/PME spectral intensity ratio was also quantified.

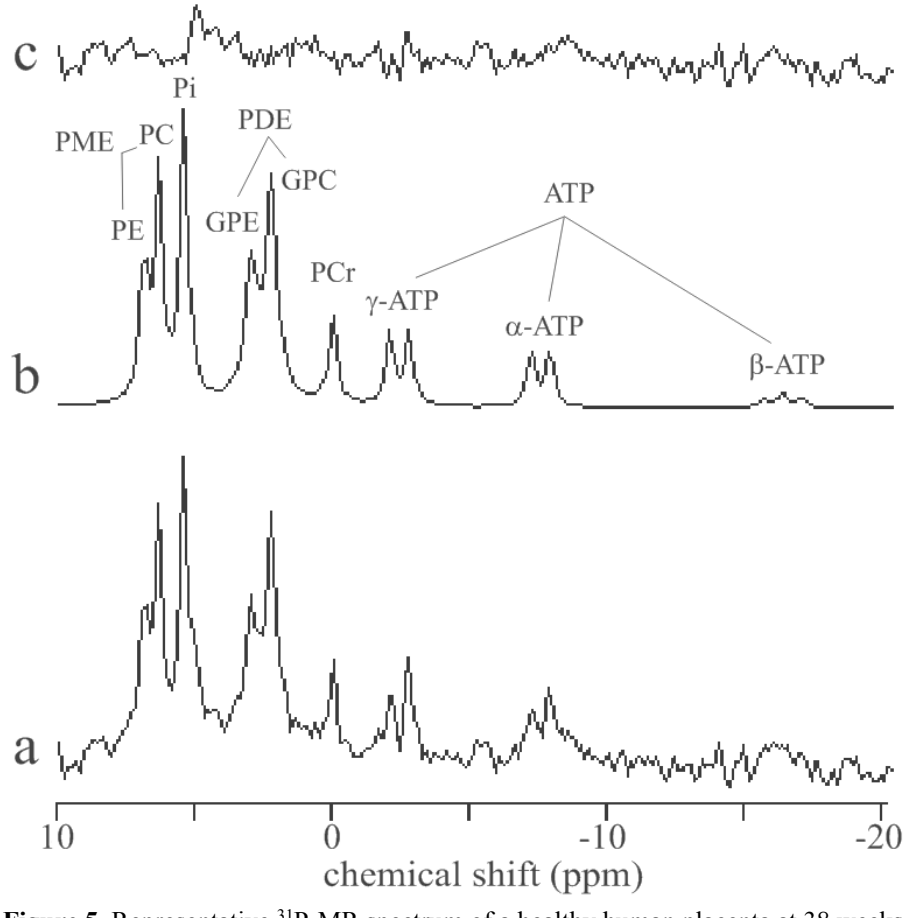

Figure 5. Representative ^{31}P-MR spectrum of a healthy human placenta at 38 weeks gestation (a), fitted spectrum (b), and residue (c).

Study IV

Color and pulsed Doppler ultrasound were used to record the waveforms from maternal and fetal vessels. Both uterine arteries were identified by color Doppler, with the transducer directed to the lateral wall of the uterus in the region of the lower uterine segment. The measurements were performed at the point where the uterine artery crosses the external iliac artery. The mean of the right and left uterine artery PI was calculated and the presence of an early diastolic notch was noted. The umbilical artery was assessed in a free loop of the umbilical cord. PI was measured and absence of diastolic flow recorded. The middle cerebral artery was visualized using color Doppler in a transverse section of the brain and the measurements were done in the proximal section at the level of the circle of Willis. The ductus venosus was assessed either in a mid-sagittal longitudinal plane of the fetal trunk or in an oblique transverse plane through the upper abdomen. The sample volume was positioned at its origin from the umbilical vein, where color Doppler indicated the highest velocities. All Doppler waveforms were traced and the PI was automatically calculated.

Venous blood samples were collected from each woman, at the time of the examinations. The samples were immediately put into a refrigerator where they were kept for 20 minutes to 2 hours before being centrifuged for 10 minutes at 1,500 g. Plasma samples were stored at -70°C until analysed. Levels of PTX-3, PlGF, sFlt-1, TNFr1 and TNFr2 were analyzed using commercial ELISAs (DY1826, DY264, DY321B, DY225 and DY726, R&D Systems, Minneapolis, MN, USA), according to the recommendations from the manufacturer. The total coefficients of variation for the assays were 5-7%.

Statistical analysis

Study I

We estimated risks of preeclampsia in underweight (BMI $\leq$18.4 kg/m^2), overweight (BMI 25.0-29.9 kg/m^2), obese class I (BMI 30.0-34.9 kg/m^2) and obese class II-III (BMI $\geq$35.0 kg/m^2) women, as well in short (<164 cm) and tall ($\geq$172 cm) women. OR with 95 percent CI were estimated using multiple logistic regression, and women of normal weight (BMI 18.5-24.9) and normal height (164-171 cm) were used as reference. We adjusted the analysis for available covariates (maternal age, BMI, height, years of formal education, smoking habits, diabetes mellitus (gestational or pre-gestational), and the presence of chronic hypertension, chronic renal disease or systemic lupus erythematosus). When calculating effect of maternal BMI, we adjusted for maternal height and vice versa. All analyses were performed using the Statistical Analysis Software version 9.2 (SAS Institute, Inc., Cary, NC).

Studies II-III

In studies II and III differences in maternal characteristics between early preeclampsia and early normal pregnancy, and late preeclampsia and late normal pregnancy, were assessed with the Mann Whitney U test or Fisher´s exact test. Further, the correlations in normal pregnancy between gestational length and perfusion fraction and phosphorous metabolites, respectively, were estimated using simple linear regression. In study II differences in perfusion fraction between early preeclampsia and early normal pregnancy, and late preeclampsia and late normal pregnancy, were assessed with the Mann Whitney U test. In study III differences in spectral intensity fractions and spectral intensity ratios between early preeclampsia and early normal pregnancy, and late preeclampsia and late normal pregnancy, were assessed with the Mann Whitney U test. P-values <0.05 were considered statistically significant and all analyses were performed using IBM SPSS Statistics 20 (IBM SPSS, Inc., Chicago, IL).

Study IV

Maternal and fetal characteristics are presented as means ±SD or numbers (%). Correlations between placental perfusion fraction and estimated fetal weight, amniotic fluid index, Doppler velocity measurements, infant birth weight and plasma markers were estimated by multiple linear regression. Compared to normal pregnancy, perfusion fraction is affected in preeclampsia with a smaller perfusion in early preeclampsia ($\leq$34 weeks) and a larger perfusion in late preeclampsia (>34 weeks) (181). We therefore investigated a possible effect measure modification by presence of preeclampsia. We introduced a cross product for presence of preeclampsia (yes/no) and the explanatory variable when estimating the associations, and we found significant interactions ($p<0.05$). Therefore, we included the cross product as an interaction term in the models. In normal pregnancy placental perfusion fraction decreases with increasing gestational age (181), and for that reason we adjusted for gestational age at examination in the models. However, gestational age and estimated fetal weight at examination were highly correlated; accordingly, either gestational age or estimated fetal weight was used in the models. Some of the plasma marker levels had a skewed distribution. All regression models were validated using residual plots, and variables were log-transformed prior to statistical analyses unless the residuals of the model were normally distributed. PlGF levels were not normally distributed, even after log-transformation, probably due to the fact that more than one third of the women (all women with preeclampsia) had a PlGF value lower than the detection limit. Therefore, PlGF-levels were not included in the models. P-values <0.05 were considered

statistically significant. All analyses were performed using IBM SPSS Statistics 20 (IBM SPSS, Inc., Chicago, IL) or RStudio version 0.98.1062 (2009-2013 RStudio, Inc.).

Results

Study I: Maternal BMI, height and risks of different types of preeclampsia

In our nulliparous cohort, 4.8% developed preeclampsia; this percentage comprised 3.7% term preeclampsia, 0.9% moderate early preeclampsia, and 0.2% early preeclampsia.

The risk of all preeclampsia types increased with BMI, but seemed higher, for term than for early preeclampsia (Table 1), and also seemed higher, for mild to moderate than for severe preeclampsia.

Compared with a normal BMI, a BMI $\geq$35 was associated with a fourfold increased risk of term preeclampsia (AOR 4.0; 95% CI 3.8-4.4) or mild to moderate preeclampsia (AOR 4.0; 95% CI 3.7-4.4).

The risk of all preeclampsia types was higher in short women, and lower in tall women, compared with women of normal height (Table 1 and 2). The association seemed stronger between short maternal height and early preeclampsia (AOR 1.3; 95% CI 1.2-1.6), than term preeclampsia (AOR 1.1; 95% CI 1.1-1.2). The association also seemed slightly stronger between short maternal height and severe (AOR 1.2; 95% CI 1.2-1.3) rather than mild to moderate preeclampsia (AOR 1.1; 95% CI 1.0-1.1).

Table 1. Risks of term (≥37 weeks), moderate early (32-36 weeks) and early preeclampsia (<32 weeks) based on early pregnancy BMI or maternal height.

	Term Preeclampsia (N=15,894)	**Moderate Early Preeclampsia** (N=3598)	**Early Preeclampsia** (N=962)
	AOR* (95% CI)	AOR* (95% CI)	AOR* (95% CI)
BMI (kg/m^2)			
≤18.4	0.8 (0.7-0.9)	1.1 (0.8-1.4)	0.6 (0.4-1.1)
18.5-24.9	Reference	Reference	Reference
25.0-29.9	1.8 (1.7–1.9)	1.4 (1.3–1.5)	1.5 (1.3–1.7)
30.0-34.9	2.7 (2.6–2.9)	2.1 (1.9–2.3)	2.4 (1.9–3.0)
≥35.0	4.0 (3.8-4.4)	3.0 (2.6-3.5)	3.4 (2.6-4.5)
Height (cm)			
<163	1.1 (1.1–1.2)	1.2 (1.1–1.3)	1.3 (1.2–1.6)
164-171	Reference	Reference	Reference
≥172	0.9 (0.88-0.96)	0.8 (0.7-0.9)	0.7 (0.6-0.8)

**Adjustments for BMI, height, maternal age, years of formal education, smoking habits, diabetes mellitus (pre-gestational or gestational), and presence of chronic hypertension, chronic renal disease, systemic lupus erythematosus.*

Study II: Placental perfusion in normal pregnancy, and in early and late preeclampsia

There were no significant differences in maternal age, early pregnancy BMI or gestational age at examination between women with early preeclampsia or late preeclampsia, compared with women with normal pregnancies at corresponding gestational ages.

Women with early preeclampsia had a median fetal weight deviation, from the mean gestational-age related reference curve (175) of -18%, and women with early normal pregnancy ±0% (p=0.001). There was no statistically significant difference in the estimated fetal weight deviation between women with late preeclampsia and women with late normal pregnancy. Women with early preeclampsia had a median uterine artery PI of 1.2, and women with early normal pregnancy 0.8 (p=0.04). There was no statistically significant

difference in uterine artery PI between women with late preeclampsia and women with late normal pregnancy.

In normal pregnancy of all gestational ages the median perfusion fraction was 29% (range 21-43%). In normal pregnancy the placental perfusion fraction decreased with gestational age (p=0.001; R^2 linear 0.514) (Figure 6). The decrease was 0.7% per gestational week.

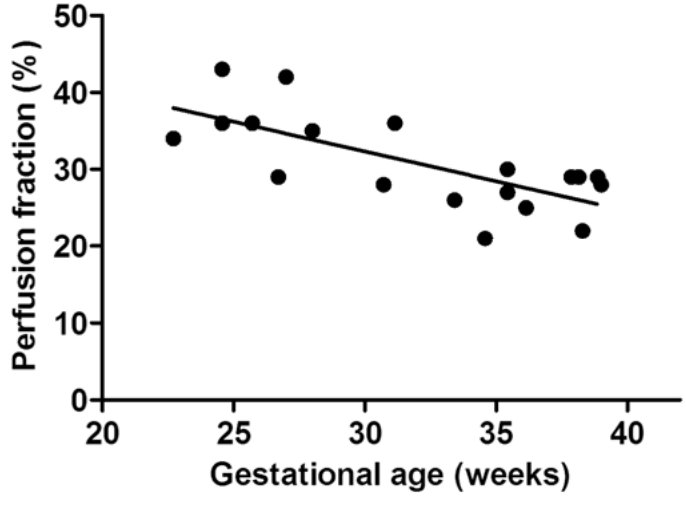

Figure 6. Scatter plot showing the perfusion fraction in relation to gestational age in normal pregnancies (p=0.001). The estimated regression line is shown in the scatter plot (R^2 linear=0.514).

The women with early preeclampsia had a median perfusion fraction of 19% (range 11-23%), while the women with early normal pregnancy had a median perfusion fraction of 36% (range 26-43%) (p=0.001) (Figure 7).

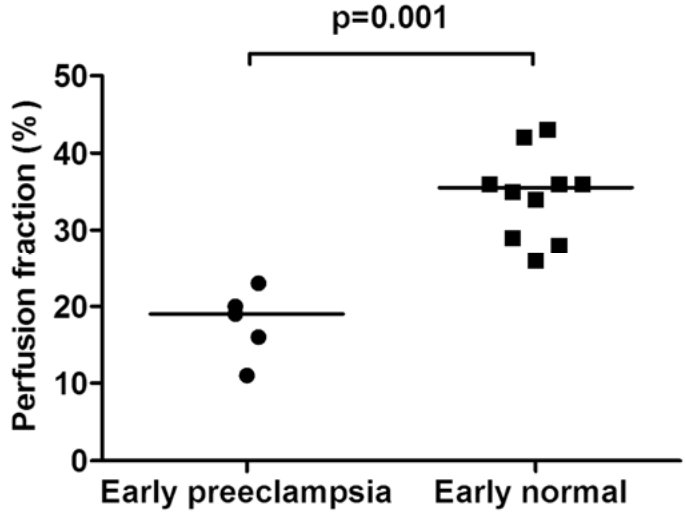

Figure 7. Scatter plot showing the perfusion fraction in early preeclampsia and in early normal pregnancy. Early defined as <34 completed weeks of gestation at the time of the MRI examination. Medians are marked with horizontal lines.

The women with late preeclampsia had a median perfusion fraction of 35% (range 25-44%), while the women with late normal pregnancy had a median perfusion fraction of 28% (range 21-30%) (p=0.01) (Figure 8).

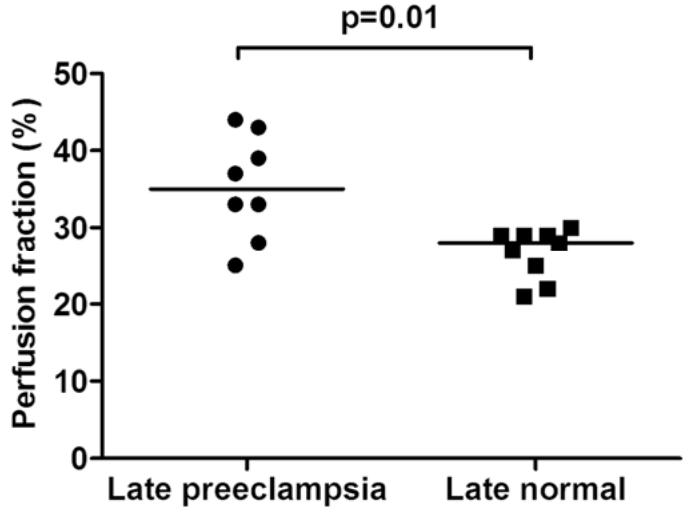

Figure 8. Scatter plot showing the perfusion fraction in late preeclampsia and in late normal pregnancy. Late defined as ≥34 weeks of gestation at the time of the MRI examination. Medians are marked with horizontal lines.

Study III: Placental metabolism in normal pregnancy, and in early and late preeclampsia

There were no significant differences in maternal age, early pregnancy BMI or gestational age at examination between women with early preeclampsia or late preeclampsia, compared with women with normal pregnancies at corresponding gestational ages.

Women with early preeclampsia had a median fetal weight deviation, from the mean gestational-age related reference curve (175), of -16% and women with early normal pregnancy ±0% (p=0.003). Women with late preeclampsia had a median fetal weight deviation of 3%, and women with late normal pregnancy 9% (p=0.02). Women with early preeclampsia had a median uterine artery PI of 1.1, and women with early normal pregnancy 0.7 (p=0.02). There was no statistically significant difference in uterine artery PI between women with late preeclampsia and women with late normal pregnancy.

The PDE spectral intensity fraction in women with normal pregnancies increased with increased gestational age (p=0.006; R^2 linear=0.434). The PDE/PME spectral intensity ratio in women with normal pregnancies also increased with increased gestational age (p=0.001; R^2 linear=0.536) (Figure 9).

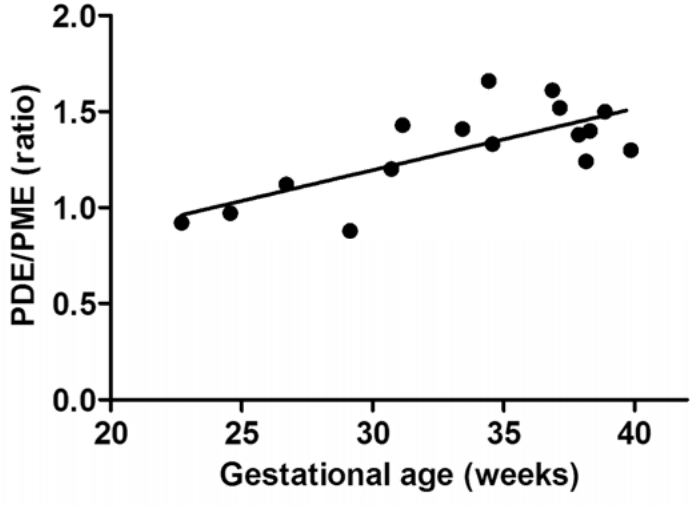

Figure 9. Scatter plot showing the PDE/PME spectral intensity ratio in relation to gestational age in normal pregnancies (p=0.001). The estimated regression line is shown in the scatter plot (R^2 linear=0.536).

Women with early preeclampsia had a higher median PDE spectral intensity fraction than women with early normal pregnancy (median 32.9, range 28.2-37.5 vs. median 28.7, range 23.2-30.0; p=0.03). Further, women with early preeclampsia had a higher PDE/PME spectral intensity ratio than the women

with early normal pregnancy (median 1.4, range 1.3-2.5 vs. median 1.1, range 0.9-1.4; p=0.02). There were no significant differences in spectral intensity fractions of phosphorous metabolites or PDE/PME spectral intensity ratio between women with late preeclampsia and late normal pregnancy.

Study IV: Placental perfusion in fetal growth assessment

The placental perfusion fraction was smaller in women with IUGR than in women without IUGR (median perfusion 21% vs. 32%; p=0.005 after adjusting for presence of preeclampsia) (Figure 10). The women were matched for gestational age and all were examined before 34 weeks.

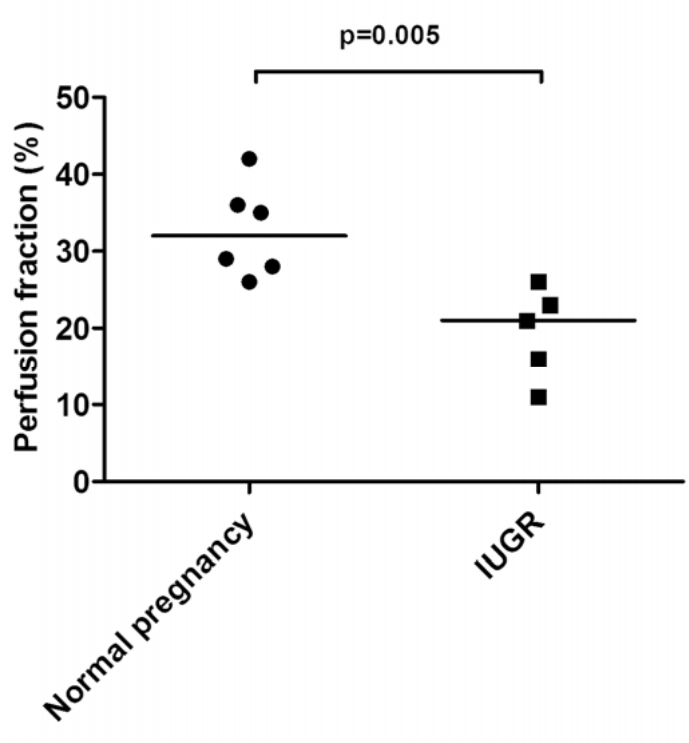

Figure 10. Scatter plot showing the perfusion fraction in normal pregnancy and IUGR. All pregnancies were examined before 34 weeks. Medians are marked with horizontal lines.

The women with IUGR were thereafter subdivided, into normotensive IUGR and preeclampsia with IUGR, and we also added gestational age matched women with preeclampsia but without IUGR (Figure 11). The median placental perfusion fractions in normal pregnancies, normotensive IUGR,

preeclampsia without IUGR and preeclampsia with IUGR were, respectively, 32% (range 26-42%), 23% (range 21-26%), 20% (range 19-23%) and 14% (range 11-16%). Compared to normal pregnancy, both normotensive IUGR and preeclampsia without IUGR had smaller perfusion fraction (p=0.02 for both), while preeclampsia with IUGR had a borderline significant reduced perfusion fraction (p=0.07).

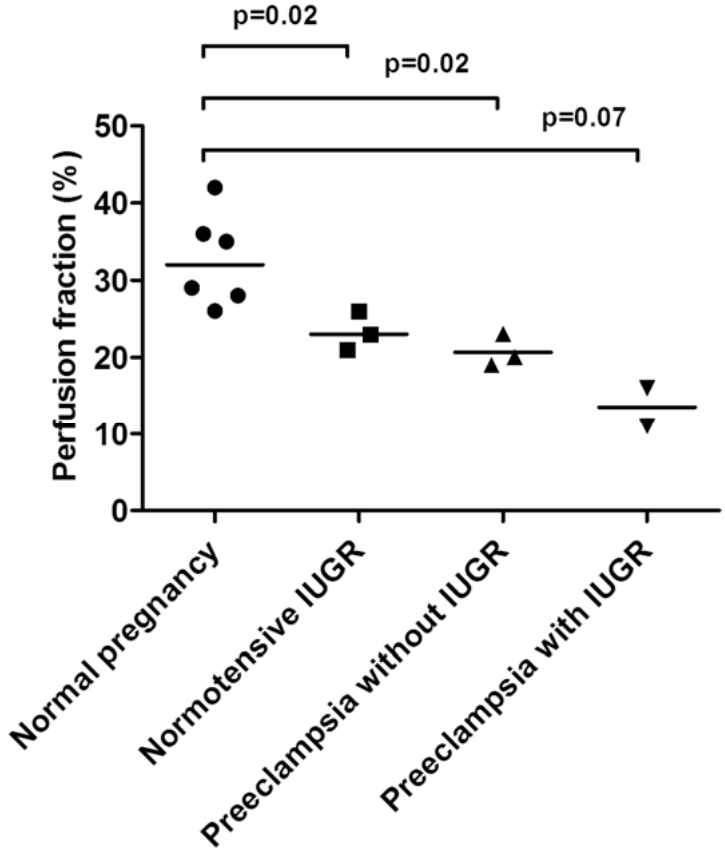

Figure 11. Scatter plot showing the perfusion fraction in normal pregnancy and normotensive IUGR, preeclampsia without IUGR and preeclampsia with IUGR. All pregnancies were examined before 34 weeks. Medians are marked with horizontal lines.

We explored different models of explanatory variables to the placental perfusion and illustrated them with calculated coefficients of determination (R^2) (Table 2). All models include presence of preeclampsia, and gestational age or estimated weight at examination. When the ultrasound estimates were added to the model, one at a time, the R^2-value increased. The highest R^2-value was found when PI in the ductus venosus was added to the model

R^2=0.54. We explored adding plasma markers, also one at a time, into the model and found that both sFlt-1 and PTX-3 increased the R^2-values.

Table 2. Different explanatory models for placental perfusion

Explanatory variables in the model	**Adjusted* R^2**	**p-value**
Estimated weight at examination	0.39	0.0004
Gestational age at examination	0.36	0.0007
Gestational age at examination and		
Amniotic fluid index	0.41	0.0010
Uterine artery PI (mean)	0.40	0.0007
Umbilical artery PI	0.46	0.0001
Middle cerebral artery PI	0.42	0.0020
Ductus venosus PI	0.54	0.0002
Infant birth weight	0.47	0.0001
Plasma level of		
Soluble Fms-like tyrosine kinase-1	0.43	0.0006
Pentraxin-3	0.42	0.0004
Tumor necrosis factor receptor-1	0.38	0.0010
Tumor necrosis factor receptor-2	0.36	0.0010

**Adjusted for presence of preeclampsia (yes/no) and the models include an interaction term between preeclampsia and estimated weight or gestational age at examination.*

When using the same model, but adding one ultrasound marker and one plasma marker, the best R^2-value we found was 0.56. This model included: presence of preeclampsia, gestational age at examination, PI in the ductus venosus, and the mean level of either sFlt-1 or PTX-3.

Discussion

Study I

In study I we investigated BMI and maternal height as risk factors for different subtypes of preeclampsia, including early, moderate early and late, and mild to moderate and severe. We found that a high BMI and a short maternal height increase the risk of preeclampsia of all severities in a dose-dependent pattern in nulliparous women. The risks associated with a high BMI seemed slightly higher for late preeclampsia, while the risks associated with a short maternal height seemed slightly higher for early preeclampsia.

It is well known that a high BMI is associated with an increased risk of preeclampsia (41, 43). The association is hypothesized to be related to the state of chronic low-grade inflammation, insulin resistance and increased oxidative stress that is associated with overweight and obesity (182). Even though many studies have investigated BMI as a risk factor for preeclampsia, only a few previous studies have investigated the effect of maternal BMI on the risk of early and/or late preeclampsia separately and those studies showed diverging results (42, 67-69). One recent, large study showed a similar result to ours: that a high BMI is associated with preeclampsia of all severities, and the association seemed stronger for milder forms of the disease (42). Another study found that a high BMI is associated with an increased risk of both early and severe preeclampsia, but did not investigate risks of late or mild preeclampsia (69), while two smaller studies showed that a high BMI is a risk factor for mild preeclampsia, but not for severe preeclampsia (68), and that a high BMI is associated with late but not early preeclampsia (67).

Short height is associated with an increased risk of CVD (73). Preeclampsia is similarly associated with an increased risk of future CVD (10-12, 183). Further, there is an association between being born SGA and short final stature (184) and also an association between being born SGA and an increased risk of future obstetric disorders associated with placental dysfunction, including preeclampsia (114). These findings raise the issue of a possible association between short maternal stature and an increased risk of placental dysfunction in general and, specifically, the risk of preeclampsia. Few previous studies have investigated maternal height as a potential risk factor for preeclampsia (71, 72), and only one of these studies found a correlation: an increased risk of severe preeclampsia in short, compared to tall, multiparous women (72). The authors could not find a significant increased risk of preeclampsia in

short, nulliparous women, compared with women of normal height; however, they did show a trend similar to our results.

Preeclampsia is hypothesized to have two main causal origins: placental or maternal. Placental preeclampsia is thought to be predominantly caused by abnormal placentation, while maternal preeclampsia is thought to have more of a metabolic origin (17). Similarly, early preeclampsia is thought to be a predominantly placental disorder, and late preeclampsia to have a stronger maternal, metabolic origin (48, 49, 51, 185).

In this study we found that a high BMI and a short maternal stature, are both associated with an increased risk of all types of preeclampsia, compared with women of normal weight or height. The associations seem to be stronger between a high maternal BMI and milder forms of preeclampsia, and between short maternal stature and more severe types of preeclampsia. Our findings correspond well to the hypothesis of two subsets of preeclampsia: the early-onset disease, with a strong placental component, and the late-onset disease, with a stronger metabolic component.

Study II

In study II we found that the placental perfusion fraction decreases with gestational age in normal pregnancies. We also found that the placental perfusion fraction is smaller in early preeclampsia than in early normal pregnancy and larger in late preeclampsia, than in late normal pregnancy.

Our study is the first to show a correlation between the perfusion fraction and gestational age. It is, to date, the largest study of the perfusion fraction in normal pregnancy (n=19) and it covers pregnancies from 22 to 39 weeks. Three previous studies have investigated the perfusion fraction in normal pregnancy (186-188). However, one of these studies only covered pregnancies from 24 to 29 gestational weeks (186), and another estimated the placental perfusion fraction solely in the basal plate (187). Similar to our finding of a 0.7% decrease in perfusion fraction per gestation week, Moore et al. found a 0.6% decrease per week in perfusion fraction, although this was only borderline significant, probably due to a small study population (n=11) (188). Further, our finding is in line with a previous histological study, that showed a decreasing volume fraction of intervillous space with increasing gestational age in normal pregnancies (189).

Reduced placental perfusion in preeclampsia, compared with normal pregnancy, and in severe preeclampsia compared with mild preeclampsia, has been previously shown in *in vivo* gamma scintigraphy studies (190, 191). Such studies are no longer performed, due to the risks associated with radiation exposure. Histological studies have indicated that placental hypoxia is an im-

portant factor in preeclampsia, especially early preeclampsia (48, 49), and animal models (192, 193) and Doppler blood flow (119) studies have suggested reduced placental perfusion in preeclampsia.

Our study was the first to investigate the placental perfusion fraction in early and late preeclampsia separately. Previous studies of the placental perfusion fraction have shown a smaller placental perfusion in IUGR, with or without preeclampsia, compared with normal pregnancy (186), and a smaller perfusion fraction in the basal plate of placenta in preeclampsia, with and without IUGR, compared with normal pregnancy (187).

Studies of maternal hemodynamics have shown that late preeclampsia is related to general hyperperfusion (194) and early preeclampsia to hypoperfusion (51). In late preeclampsia an increased cardiac output and decreased peripheral resistance have been shown, while in early preeclampsia the opposite results have been found, with a decrease in cardiac output and an increase in peripheral resistance (51, 194). These findings correspond well to the results of our study.

In conclusion: in our study both early and late preeclampsia differ in placental perfusion from normal pregnancy at corresponding gestational age. These differences are, however, in opposite directions. Again, our findings correspond well to the hypothesis of partly different pathophysiology in early and late preeclampsia.

Study III

In study III we found that the PDE spectral intensity fraction and the PDE/PME spectral intensity ratio increase with gestational age in normal pregnancy. We also found that the PDE spectral intensity fraction and the PDE/PME spectral intensity ratio are higher in early preeclampsia than in early normal pregnancy. There were no differences in the PDE spectral intensity fraction and the PDE/PME spectral intensity ratio in late preeclampsia, compared with late normal pregnancy.

The PDE signal in the ^{31}P-spectra is made up of glycerophosphorylethanolamine and glycerophosphorylcholine, which are degradation products of phospholipids (195), and an increased PDE spectral intensity ratio is considered to represent increased cell degradation (196, 197). The PME signal is made up of phosphoetanolamine and glycerophosphorylcholine which are intermediates in phospholipid biosynthesis (198), and PME is considered a cell membrane precursor (197-199).

Our findings of an increasing PDE spectral intensity fraction and PDE/PME ratio with gestational age, could be explained by an increasing degree of placental apoptosis throughout pregnancy. These findings are supported by earlier studies, which have suggested that placental apoptosis is part of the normal placental development and aging process (200). Two previous

histological studies have shown increased placental apoptosis between the first and the third trimester (200), and between mid-term and full-term (201). Increased apoptosis has also been shown in post-term placentas compared with term placentas (202). Further, with increasing gestational age, trophoblast cell proliferation in the placenta has been shown to decrease (201, 203).

Our findings that the PDE spectral intensity fraction and the PDE/PME intensity ratio are higher in early preeclampsia, compared with normal pregnancy, could be explained by increased apoptosis, due to hypoxia and oxidative stress, in early preeclampsia. These findings are supported by earlier histological studies, which have also shown increased placental apoptosis in preeclampsia (204, 205) compared with normal pregnancy, especially in preterm or severe preeclampsia. It has been speculated that the increased apoptosis in preeclampsia is a result of altered placental oxygenation in these pregnancies (204). Both hypoxia and oxidative stress, processes associated with early preeclampsia placentas (50, 206, 207), have been shown to induce apoptosis in trophoblast cells (208, 209).

Our findings correspond well with the hypothesis of partly different pathophysiology in early and late preeclampsia; according to which early preeclampsia is believed to be a predominantly placental disease (185).

Study IV

In study IV we found that the placental perfusion fraction is smaller in pregnancies with IUGR than in normal pregnancy. We also found that the perfusion fraction is correlated to fetal growth, Doppler blood flow in fetal and maternal vessels, infant birth weight, and plasma markers of placental function.

That the placental perfusion is reduced in pregnancies affected by IUGR, has been shown in earlier *in vivo* scintigraphy studies (210), by Doppler technique (124), and histology (211). In a recent study, by Brunelli et al, placental perfusion was investigated using contrast-enhanced MRI (212). They found that the placental perfusion fraction was smaller in normotensive IUGR compared with normal pregnancy. They also found that the placental perfusion was smaller in normotensive IUGR, with pathological PI in ductus venosus, compared with IUGR that had normal PI in ductus venosus. In our study, we found the highest correlation, among the ultrasound estimates, between the Doppler blood flow in the ductus venosus and the placental perfusion fraction. Hence, both in our study and in the study by Brunelli, a strong association between Doppler blood flow in the ductus venosus and the placental perfusion was seen.

Histological studies have indicated that there is an increasing degree of compromised vascular remodeling and obstructive occlusions in the spiral arteries in pregnancies with normotensive IUGR, preeclampsia without IUGR,

and preeclampsia with IUGR (1). In our study, we found indications of similar differences in the degree of compromise to the placental perfusion in normotensive IUGR, preeclampsia without IUGR, and preeclampsia with IUGR (Figure 11).

Also, earlier scintigraphy studies have shown reduced placental perfusion in IUGR (213) as well as in preeclampsia (191), compared with normal pregnancies. However, we have not found any scintigraphy study that has compared placental perfusion in normotensive IUGR and preeclampsia with IUGR.

We have only found one previous study that has investigated possible correlations between placental perfusion fraction and Doppler blood flow in the uterine artery and infant birth weight (186). Their results correspond well to ours, with correlations between the placental perfusion fraction and infant birth weight percentile (R=0.40) and the mean uterine artery PI (R=0.48). However, the focus of their study was different from ours: they investigated the correlation between the perfusion fraction at 24-29 gestational weeks and the risk of giving birth to an SGA infant.

Deciding the optimal time of delivery in preterm IUGR, is one of the big conundrums in modern obstetrics. Several studies have investigated which techniques to use and at what signs the IUGR fetus should be delivered, to achieve the best short-term outcome (126, 214, 215). More recent studies also include long-term neurological development in the outcome assessment (216).

However, it is possible that the optimal time of delivery could be achieved by using not only one measure of fetal wellbeing, placental function etc., but by combining several of these, as is done in the CUB-test for chromosomal abnormalities (217). Our findings indicate an effect on placental perfusion by the presence of preeclampsia, which could have both short- and long-term effects on the fetus. We suggest, therefore, that presence of preeclampsia should be included in such a combined model. Also, a direct measurement of placental function, such as the placental perfusion fraction used in this study, could be part of such a test for optimal time of delivery in preterm IUGR.

In conclusion, this study shows that the placental perfusion fraction has potential to contribute to the clinical assessment in cases of placental dysfunction.

Methodological considerations

The main strengths and weaknesses of study I, lie in the registry-based design. The study cohort is large and the data was collected relatively recently. The Swedish public health system, where almost all women have their pregnancies dated by routine ultrasound early in the second trimester and go on to give birth in public hospitals, is a strong foundation for good obstetrical register

studies. In the Swedish Birth Register, from which we have collected our obstetrical data, the preeclampsia diagnosis has been validated and shown to have high accuracy (173): however, the diagnoses of mild to moderate or severe preeclampsia have not been validated. In study I we adjusted for smoking and years of education; however, in a registry-based study the number of possible confounders, for which data are available, are limited, and an effect of unknown factors cannot be excluded.

Our definition of early preeclampsia in studies II and III, <34 weeks gestational age at examination, can be discussed. The ISSHP bases their definition on gestational age at onset (16). Implementing their definition to our cohort would not alter the groups. Another quite common definition of early and late preeclampsia, especially in epidemiological studies, is gestational age at delivery. Using this definition in study II, two of the women with early preeclampsia would have been redefined, from early to late preeclampsia, since they were delivered at 34+1 weeks and 34+2 weeks. If we transfer these two cases to the late preeclampsia group, the perfusion fraction remains smaller in early preeclampsia, compared with normal early pregnancy ($p=0.007$). However, the difference between late preeclampsia and late normal pregnancy would no longer be significant.

Figure 12 illustrates the perfusion fraction in relation to gestational age in preeclampsia. The two women who were redefined from early to late preeclampsia are marked with +. The estimated fetal sizes in the redefined cases were -15% and -18% compared to the reference curve (175), to be compared with the average estimated fetal size in the original late preeclampsia group of 0.5%. This indicates that our original definition of early and late preeclampsia, by onset of disease or time point of examination, is more suitable for our study population.

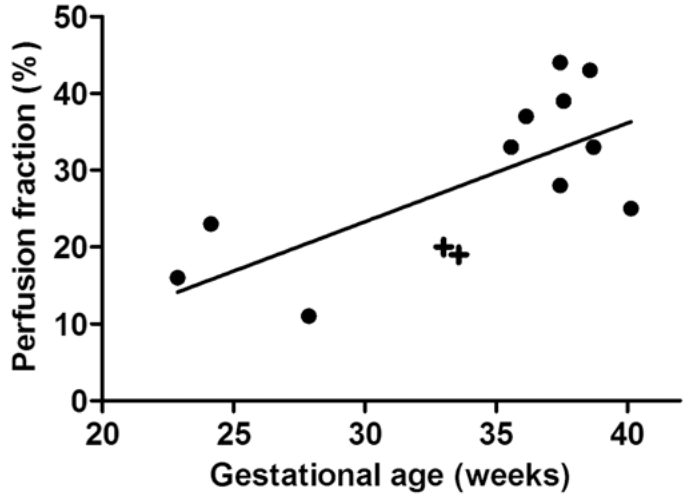

Figure 12. Placental perfusion fraction in relation to gestational age in preeclampsia. The two women who delivered at 34 weeks are marked with +.

Using the gestational age at delivery definition in study III, the same two women would be transferred from the early to the late preeclampsia group. Here too, the significant differences in early pregnancy would remain. The PDE spectral intensity fraction and the PDE/PME spectral intensity ratio were both higher in early preeclampsia than in early normal pregnancy ($p=0.02$ and $p=0.03$, respectively). There were still no significant differences between late preeclampsia and late normal pregnancy.

The number of participants in the MR studies (studies II-IV) is relatively small. It is possible that observed differences seen in studies II and III are not associated with preeclampsia, but may be due to confounding factors. In study IV the small sample size will have increased the risk of random bias.

In the MR studies, it was our ambition to collect the placentas from all participating women and have them histologically examined. However, since not all placentas were collected postpartum, the MR-based findings of studies II, III and IV, could not be correlated to placental histopathological examinations.

The DWI technique used in studies II and IV has technical advantages and limitations. An important advantage is that it is a relatively simple examination to perform, which takes less than four minutes. The examination is also independent of maternal obesity, even though we only included women with a BMI of $\leq$36, due to, technical reasons related to the MRS-examination. The most important limitation of the DWI technique is that it is sensitive to motion, which can lead to artifacts. In studies II and IV motion related artifacts resulted in the exclusion of six of the originally included women.

The main strengths of study III are that it is the largest *in vivo* ^{31}P-MRS study of placental function and the first ^{31}P-MRS study to investigate placental function in women with preeclampsia. The cohort size was large enough to allow separate comparisons of early and late preeclampsia with normal pregnancy. The main weaknesses of study III are technical. Because acceptable receiver coil sensitivity was limited to 4-6 cm, only women with an anterior placenta and a limited amount of subcutaneous abdominal fat could be included. Further, the MRS-examination is relatively time consuming and sensitive to motion. This resulted in the exclusion of sixteen of the measured spectra.

The main strength of study IV is that we were able to correlate the perfusion fraction to different measures of placental function, including ultrasound based measures, birth weight, and plasma markers of placental function. Within this strength lies, at the same time, the main weakness of the study. In our study we tried to evaluate the perfusion fraction, as a direct measure of placental insufficiency, by relating it to established indirect measures of placental function. Before considering implementing the placental perfusion fraction in a clinical setting, larger studies, including fetal short- and preferably also long-term outcome data, would be required.

General discussion

The hypothesis that there are two causal origins of preeclampsia, placental and maternal, was presented almost 20 years ago (17) and has had a great impact on how we view the disorder. Our knowledge and understanding of the underlying pathophysiology in preeclampsia has increased and evolved during the past two decades (1, 12, 48, 51, 54). According to current theories, preeclampsia originates from a mixture of both placental and maternal factors, with different proportions in each case (18).

Understanding of the placental factor in the pathophysiology, not only of preeclampsia, but also of many other major pregnancy disorders, has improved (1, 218, 219). Preeclampsia, especially early preeclampsia or preeclampsia with IUGR (48-50), normotensive IUGR (219, 220), abruptio placentae (99), preterm labor (221, 222) and late miscarriages (223) all seem to be associated with placental dysfunction. Recurrence risks among many of these disorders indicate a common pathophysiological pathway, both in subsequent pregnancies and across generations (111, 114). Early-onset placental dysfunction disorders tend have a higher risk of recurrence than late-onset subtypes (110).

Findings regarding early and late preeclampsia

- Early preeclampsia seems to be more strongly associated with short maternal height, and late preeclampsia with a high maternal BMI.

- In early preeclampsia the placental perfusion fraction is smaller, and in late preeclampsia larger, than in normal pregnancy.
- In early preeclampsia placental apoptosis seems to be increased compared with normal pregnancy.

Our findings regarding early and late preeclampsia, correspond well with the hypothesis of two causal origins in preeclampsia. According to this: early preeclampsia is mainly a placental disorder, whereas late preeclampsia has more of a maternal, metabolic origin (48, 50).

Early and late preeclampsia share the same risk factors, but some of these risk factors seem to be more strongly associated with one or the other subtype (42, 52), as indicated by the findings of our first study. The hypothesis of Developmental Origins of Health and Disease could explain why a person born as an SGA infant, who has an increased risk of a short final stature (184), also stands an increased risk of having developed a phenotype prone to CVD and the metabolic syndrome (224, 225).

Both obesity and short height are associated with an increased risk of CVD. Recently, a hypothesis has been presented, suggesting that the common denominator in preeclampsia and in CVD is a tendency in these women to develop acute atherosis (226). The authors speculate that the stress of pregnancy reveals a group of women with this tendency, and that many of them develop preeclampsia, some develop normotensive IUGR, but some remain healthy - depending on underlying maternal factors, such as obesity.

The future risk of CVD is higher in women who have had early preeclampsia than in those who have had late preeclampsia (227). Studies of hemodynamics in pregnant women who later develop early and late preeclampsia, have shown decreased cardiac output and increased peripheral resistance in women who develop early preeclampsia (51), and increased cardiac output and decreased peripheral resistance in women who develop late preeclampsia (51, 194). Similar results, with decreased cardiac output and increased peripheral resistance, have been found in preterm normotensive IUGR and preterm preeclampsia with IUGR, with seemingly more pronounced impairment in preterm preeclampsia with IUGR, than in preterm normotensive IUGR (228).

Recently, a new hypothesis has been presented that separates late preeclampsia into two types with different etiology: late preeclampsia with SGA, which shares its etiology with early preeclampsia; and late preeclampsia associated with LGA (229). Unfortunately, our study cohort did not include any pregnancies with late preeclampsia and an SGA infant, and we could therefore not investigate if placental perfusion fraction and degree of apoptosis differ in late preeclampsia depending on whether the fetus is SGA or not.

Findings regarding placental function in normal pregnancy

- The placental perfusion fraction decreases with increased gestational length in normal pregnancy.

- Placental apoptosis seems to increase with increased gestational length in normal pregnancy.

Normal pregnancy is associated with a systemic inflammatory response, which increases with gestational length (39). Preeclampsia is hypothesised to represent the extreme end of such an inflammatory continuum (230). According to professor Redman, all pregnancies would eventually end in preeclampsia (230). Both reduced placental perfusion and increased placental apoptosis lead to secretion of pro-inflammatory factors from the placenta (38, 208, 231). The findings of this thesis are therefore in agreement with the statement by professor Redman: that all pregnancies would eventually end in preeclampsia, if delivery did not interrupt the process.

Findings regarding placental function in IUGR, and the DWI method in assessment of placental function

- The placental perfusion fraction is smaller in IUGR than in normal pregnancy.
- The placental perfusion fraction is strongly associated with ultrasound markers of fetal growth and placental function.

Findings in this thesis indicate that there is an increasing degree of placental dysfunction, ranging from normal pregnancy, through normotensive IUGR and early preeclampsia, and ending with early preeclampsia with IUGR as most affected. Histological studies have found similar results (1, 218). The extent of the insufficient spiral artery remodeling in disorders of placental dysfunction varies (1). In these pregnancies, the placenta becomes increasingly dysfunctional (and hypoxic) with increased gestational length. The larger the extent of the insufficient spiral artery remodeling, the sooner this hypoxic process begins (232, 233). The hypoxic placenta secrets substances that induce the endothelial dysfunction associated with preeclampsia (31). Maternal factors probably interact with these substances, making some women more prone to develop preeclampsia (39). Our findings indicate that cases of early preeclampsia with IUGR have the highest degree of defective spiral artery remodeling (= lowest perfusion fraction). These placentas probably secrete large amounts of substances, due to severe hypoxia. These inflammatory substances might trigger the preeclampsia process, even in mothers with a low to moderate degree of maternal factors.

The highly significant correlations that we found between the placental perfusion fraction and ultrasound markers of fetal growth and placental function, indicate that the placental perfusion fraction has potential to contribute to the clinical assessment of placental dysfunction in IUGR. The findings support the hypothesis that placental perfusion is affected in both early preeclampsia and in normotensive IUGR.

The MR method has opened up new possibilities for *in vivo* studies of placental function, both in pathophysiology studies, and in clinical practice, to estimate the degree of placental dysfunction. DWI for calculation of the placental perfusion fraction is especially promising in clinical practice, since it is quite easy to perform and has a short examination time. With rapid technical advances in MR, leading to improvements in aspects such as susceptibility to motion and further reductions in examination times, these possibilities seem likely to increase even further.

Conclusions

- High maternal BMI increases the risk of preeclampsia of all severities. The association seems especially strong between a high BMI and late preeclampsia. **(Paper I)**

- Short maternal stature increases the risk of preeclampsia of all severities. The association seems especially strong between short stature and early preeclampsia. **(Paper I)**

- The perfusion fraction in normal pregnancy decreases with increased gestational length. **(Paper II)**

- In normal pregnancies the PDE spectral intensity fraction and the PDE/PME spectral intensity ratio increase with increasing gestational length. **(Paper III)**

- The perfusion fraction is smaller in early preeclampsia than in early normal pregnancy and larger in late preeclampsia than in late normal pregnancy. **(Paper II)**

- The median PDE spectral intensity fraction and the median PDE/PME spectral intensity ratio are both higher in early preeclampsia than in early normal pregnancy; these differences are not seen when late preeclampsia is compared to late normal pregnancy. **(Paper III)**

- The placental perfusion fraction has potential to contribute to clinical assessment in cases with IUGR, by offering a direct measurement of placental function. **(Paper IV)**

Future work

At the same time as the MR examinations that we based papers II, III and IV on, a blood oxygen level dependent MRI examination was performed. These data remain to be analyzed, but should yield the oxygen saturation levels in the placental blood of the examined women. From these data we hope to be able to investigate whether, placental oxygen saturation in normal pregnancy is related to gestational length. We also plan to investigate differences in placental oxygen saturation in early preeclampsia compared to early normal pregnancy, and in late preeclampsia compared to late normal pregnancy.

Placental function is key to understanding both preeclampsia and IUGR. MR-techniques and the rapid technical improvements in this field in recent years, open many new possibilities regarding *in vivo* studies of placental function.

Summary in Swedish – sammanfattning på svenska

Preeklampsi, så kallad ”havandeskapsförgiftning”, drabbar 1,4–4,0 % av alla gravida och är en av de vanligaste orsakerna till sjukdom och död hos nyfödda barn och deras mammor. Diagnosen preeklampsi sätts då en kvinna, efter graviditetsvecka 20, utvecklar förhöjt blodtryck och proteinläckage i urinen. Det är oftast farligare att få preeklampsi tidigt i graviditeten än i slutet, framförallt för barnet. Det är vanligt att kvinnor med tidig preeklampsi måste förlösas innan, ibland långt innan, graviditeten är fullgången.

Vi vet inte vad som orsakar preeklampsi, men moderkakan spelar sannolikt en central roll. Det enda sättet att bli botad från preeklampsi är att moderkakan avlägsnas, det vill säga att kvinnan blir förlöst. På senare år har man funnit att tidigt debuterande preeklampsi i större utsträckning beror på en dåligt fungerande moderkaka, medan den sent debuterande preeklampsin beror mer på metabola riskfaktorer hos den blivande mamman.

Intrauterin tillväxthämning förekommer både hos kvinnor med preeklampsi och normalt blodtryck. Intrauterin tillväxthämning är en vanlig orsak till att foster dör i magen eller att barnet förlöses i förtid. Det är också en vanlig orsak till sjukdom och död hos nyfödda barn. Intrauterin tillväxthämning orsakas oftast av att moderkakan fungerar dåligt. Tyvärr finns det få möjligheter att behandla eller förebygga preeklampsi och tillväxthämning. Det finns också få metoder för att undersöka moderkakans funktion under pågående graviditet.

Målet med det här avhandlingsarbetet har varit att undersöka riskfaktorer för olika sorters preeklampsi och även att undersöka moderkakans funktion i normal graviditet, i tidig och sen preeklampsi och vid tillväxthämning, med hjälp av olika magnetkamerametoder.

Studie I

I en registerstudie undersökte vi sambandet mellan den blivande mammans vikt (BMI) och hennes risk att utveckla tidig, måttligt tidig och sen preeklampsi. Vi fann att ett högt BMI ökar risken för alla sorters preeklampsi, men framför allt för sen preeklampsi.

Sambandet mellan den blivande mammans längd och risk att utveckla olika sorters preeklampsi undersöktes också. Vi fann att en kort längd ökar risken för alla sorters preeklampsi, men framför allt för tidig preeklampsi.

Studie II

Med hjälp av en magnetkameraundersökning kunde perfusionen (genomblödningen) i moderkakan beräknas.

Syftet med den här studien var att undersöka perfusionen i moderkakan i normala graviditeter av olika graviditetslängder. Vi fann att perfusionen i moderkakan är lägre ju längre graviditeten framskridit.

Syftet var också att jämföra perfusionen i moderkakan mellan kvinnor med tidig preeklampsi och tidig normal graviditet och mellan kvinnor med sen preeklampsi och sen normal graviditet. Vi fann att perfusionen i moderkakan hos kvinnor med tidig preeklampsi är lägre än hos kvinnor med normala tidiga graviditeter och att perfusionen i moderkakan är högre vid sen preeklampsi än hos kvinnor med normala sena graviditeter.

Studie III

Med hjälp av en tekniskt avancerad magnetkameraundersökning, så kallad magnetisk resonans-spektroskopi, undersökte vi energi- och cellmembranomsättningen i moderkakan.

Syftet med den här studien var att undersöka energi- och cellmembranomsättning i moderkakan vid normala graviditeter av olika graviditetslängder. Vi fann att andelen fosfodiester och fosfodiester/fosfomonoester-kvoten ökar med ökande graviditetslängd. Mängden fosfodiester tros bero på cellmembrannedbrytning, medan mängden fosfomonoester beror på cellmembrannybildning. Våra fynd talar således för ökad cellnedbrytning (s.k. apoptos) i moderkakan med ökande graviditetslängd.

Syftet var också att jämföra energi- och cellmembranomsättningen i moderkakan mellan kvinnor med tidig preeklampsi och tidig normal graviditet och mellan kvinnor med sen preeklampsi och sen normal graviditet. Vi fann att kvinnor med tidig preeklampsi hade en högre andel fosfodiester och en högre fosfodiester/fosfomonoester-kvot än kvinnor med tidig normal graviditet. Vi fann inga skillnader i mängden av dessa ämnen mellan kvinnor med sen preeklampsi och sena normala graviditeter. Fynden talar således för ökad cellnedbrytning i moderkakan vid tidig, men inte sen preeklampsi.

Studie IV

Syftet med den här studien var att undersöka om det mått på perfusionen i moderkakan som vi även använde i delstudie II, har förutsättningar att kunna användas som ett mått på moderkakans funktion, framförallt vid misstänkt intrauterin tillväxthämning. Vid misstanke om intrauterin tillväxthämning bedöms idag fostrets vikt och blodflöden i kärl till moderkakan och hos fostret med hjälp av ultraljud. Vi undersökte sambanden mellan perfusionen i moderkakan och dessa ultraljudsmätningar, samt även med blodmarkörer för moderkaksfunktion. Vi fann tydliga samband och våra resultat talar för att perfusionen i moderkakan, baserad på magnetkameraundersökning, skulle kunna vara till hjälp vid bedömning av foster med misstänkt tillväxthämning. Dock är vår studie liten och det skulle krävas fler och större studier, innan metoden eventuellt kan användas i den kliniska bedömningen av patienter.

Sammanfattningsvis visar studie I, att övervikt och fetma är en viktig riskfaktor för alla sorters preeklampsi. Sambandet som vi visar i samma studie, mellan mammans längd och preeklampsi, får betraktas som en intressant ledtråd till mekanismerna bakom uppkomsten av preeklampsi. I studie II och III fann vi, att endast vid tidig preeklampsi, visar moderkakan tecken på nedsatt perfusion och ökad cellnedbrytning. Fynden stämmer väl med hypotesen att tidig preeklampsi har en starkare koppling till dålig placentation än sen preeklampsi. Slutligen visar vi i studie IV, att placentaperfusionen mätt med MR teknik är en lovande metod för bedömning av moderkakans funktion under pågående graviditet.

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