Chronic Hypertension and Pregnancy

Epidemiological Aspects on Maternal and Perinatal Complications

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Dissertation presented at Uppsala University to be publicly examined in Törnvistalen, A-huset, Universitetssjukhuset, Örebro, Friday, April 20, 2007 at 13:15 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in Swedish.

Abstract


These studies were undertaken to investigate risks of maternal and perinatal complications in pregnant women with chronic hypertensive disease, and to investigate future risk of preeclampsia in women born small for gestational age (SGA). Population based cohort studies using the Swedish Medical Birth Register from different years were performed.

The maternal complications mild and severe preeclampsia, gestational diabetes and abruptio placenta were studied in a population of 681 515 women, with a prevalence of 0.5% for chronic hypertension. Risk estimates were adjusted for differences in maternal characteristics as age, parity, BMI, ethnicity and smoking habits. Chronic hypertensive women were found to have significantly increased risks of all complications.

The perinatal complication SGA was studied in a population of 560 188, with a prevalence of 0.5% for chronic hypertension. Risk estimates were adjusted for differences in maternal characteristics and for the secondary complications mild and severe preeclampsia. Chronic hypertensive women were found to suffer a significantly increased risk of giving birth to an offspring that is SGA.

The perinatal complication fetal/infant mortality was studied in a population of 1 222 952 with a prevalence of 0.6% for chronic hypertension. Risk estimates were adjusted for differences in maternal characteristics and for the complications mild and severe preeclampsia, gestational diabetes, abruptio placenta and offspring being SGA. In the analysis an effect modification by gender was included. Chronic hypertensive women were found to have a significantly increased risk for stillbirth and neonatal death in male, but not in female, offspring. Thus a clear gender difference in mortality was revealed. The risk of mortality of offspring was mediated by severe preeclampsia, abruptio placenta and offspring being SGA. Mild preeclampsia and gestational diabetes did not affect the risk. No increased risk of post neonatal mortality was found.

A generation study was performed in 118 634 girls of which 5.8% were born SGA. Their future risk for mild and severe preeclampsia in first pregnancy was analysed. Risk estimates were adjusted for age, smoking, BMI and for preeclampsia in the mothers while pregnant with the study population. Women who were born SGA were shown to have a significantly increased risk for severe preeclampsia, but not for mild preeclampsia.

Keywords: chronic hypertension, preeclampsia, gestational diabetes, abruptio placenta, SGA, perinatal death, stillbirth, neonatal death, gender, generation

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To all of you who take care of pregnant women
Papers included in the thesis

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

I.

Zetterström K, Lindeberg SN, Haglund B, Hanson U
Maternal complications in women with chronic hypertension: a population-based cohort study.
*Acta Obstet Gynecol Scand 2005 May;84(5):419–24*

II.

Zetterström K, Lindeberg SN, Haglund B, Hanson U
Chronic hypertension as a risk factor for offspring to be born small for gestational age.
*Acta Obstet Gynecol Scand 2006;85(9):1046–50*

III.

Zetterström K, Lindeberg S, Haglund B, Magnuson A, Hanson U
Being born small for gestational age increases the risk of severe preeclampsia.
*BJOG 2007;114:319–324*

IV.

Zetterström K, Lindeberg SN, Haglund B, Hanson U
The effect of chronic hypertension on the risk of perinatal death – including gender aspect.
*Submitted.*
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overview of the papers</td>
<td>24</td>
</tr>
<tr>
<td>Ethics</td>
<td>24</td>
</tr>
<tr>
<td>Results</td>
<td>25</td>
</tr>
<tr>
<td>Study I</td>
<td>25</td>
</tr>
<tr>
<td>Study II</td>
<td>26</td>
</tr>
<tr>
<td>Study III</td>
<td>27</td>
</tr>
<tr>
<td>Study IV</td>
<td>28</td>
</tr>
<tr>
<td>Discussion</td>
<td>31</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>31</td>
</tr>
<tr>
<td>Maternal complications</td>
<td>32</td>
</tr>
<tr>
<td>Perinatal complications</td>
<td>33</td>
</tr>
<tr>
<td>SGA</td>
<td>34</td>
</tr>
<tr>
<td>Perinatal death</td>
<td>35</td>
</tr>
<tr>
<td>Complications across generations</td>
<td>36</td>
</tr>
<tr>
<td>Aims for the future</td>
<td>37</td>
</tr>
<tr>
<td>Conclusions</td>
<td>38</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>39</td>
</tr>
<tr>
<td>References</td>
<td>41</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CHD</td>
<td>Chronic hypertensive disease</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>GD</td>
<td>Gestational diabetes</td>
</tr>
<tr>
<td>ICD</td>
<td>International classification of diseases</td>
</tr>
<tr>
<td>IUFD</td>
<td>Intrauterine fetal death</td>
</tr>
<tr>
<td>MBR</td>
<td>Medical birth register</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PE</td>
<td>Preeclampsia</td>
</tr>
<tr>
<td>SGA</td>
<td>Small for gestational age</td>
</tr>
</tbody>
</table>
Introduction

Most pregnancies are uncomplicated and result in a healthy child and an equally healthy mother who recover well after delivery. That is what we normally expect. But unfortunately it is not always the case; the pregnancy can get seriously complicated, both for the mother and for the child. Sometimes complications are expected, for instance if there is intercurrent disease. The most common intercurrent disease is chronic hypertension, which affects 0.5-5% of pregnant women, depending on which population that is studied and which criteria that are used [1, 2]. The incidence of chronic hypertension during pregnancy is increasing, since there is a tendency for women to postpone their childbearing towards higher ages, and since there is a worldwide trend for increased body mass index (BMI). Therefore it is important to be aware of the magnitude of risks for complications associated with chronic hypertension, and whether those risks are affected by maternal characteristics special to the hypertensive woman, or mediated by secondary complications. Such knowledge could improve prepregnancy advice and antenatal care, and help us to achieve best possible obstetric outcome. It is also important from a health economic point of view, to get prognostic tools to focus antenatal surveillance on the group of women where it is most needed.

There are only few population-based studies concerning chronic hypertension in pregnancy, most earlier studies are made at referral hospitals, on selected, presumably more generally, or severely, diseased groups of women. Since chronic hypertension is a disease of low prevalence, there are quite few cohort studies performed on the development of complications during pregnancy. Most of earlier studies are of case-control design. There is also a lack of studies on long-time consequences of complications, as preeclampsia or offspring being born underweight, even though studies are accomplished in this field during the last years.
Background

Chronic hypertension

Hypertension during pregnancy is diagnosed as chronic if present before conception or if it occurs before the 20th week of gestation. It is defined as a systolic blood pressure of at least 140 mmHg and/or a diastolic blood pressure of at least 90 mmHg (WHO – International Society of Hypertension, 2003) measured on two different occasions. In pregnancy, the higher the maternal blood pressure, the greater the perinatal loss [3]. Even though most women with chronic hypertension have uncomplicated pregnancies [1, 4], with fetal outcomes similar to normotensive women, the risk for fetal and maternal morbidity and mortality is increased among these women [4-7].

Concerning the fetus, there is an increased risk for intra uterine death [8, 9] and intra uterine growth restriction [10]. There is an increased risk for perinatal death [5, 10-12], and for the infant there is an increased risk to be born small-for-gestational-age (SGA) [5, 7, 9, 13-16], which in turn is related to increased morbidity and mortality [17, 18]. But results are conflicting as to whether chronic hypertension is only dangerous to the child if there are secondary complications such as preeclampsia, gestational diabetes or placental abruption [4, 7, 11, 13, 14, 19].

Concerning the mother, she suffers an increased risk for preeclampsia, but the reported risks vary in magnitude [5, 6, 12-14], and we found no studies investigating the risks for mild and severe preeclampsia separately. She probably also suffers an increased risk for gestational diabetes, but only few studies investigating this matter are found [13]. Regarding the chronically hypertensive woman’s increased risk for abruptio placenta, reported risks are varying and results are conflicting as to whether the risk is increased only if the hypertension is complicated by secondary preeclampsia or not [20-25].

All these maternal complications may lead to consequences for the child as well. Apart from those already mentioned, prematurity might be the most serious, both planned iatrogenic prematurity, as can be needed for instance in the case of severe preeclampsia, as well as acute iatrogenic prematurity in the case of an abruptio.
Characteristics of the hypertensive woman

Women with chronic hypertension differ from normotensive women in certain demographic characteristics that could be suspected to affect their risk for some of the complications mentioned. This needs to be taken into consideration in the statistical analysis.

For instance the incidence of chronic hypertension increases with age [9, 10, 13, 14, 26], older mothers are at increased risk for gestational diabetes [27], offspring being born SGA [28] and perinatal death [29]. A natural consequence of the chronically hypertensive mothers being older is that they are of higher parity. Multiparity is associated with a lower incidence of preeclampsia [30] and a higher incidence of stillbirth [29]. Hypertensive mothers have higher BMI [9, 13, 14, 26], obesity is strongly associated with preeclampsia [30, 31], gestational diabetes [27] and stillbirth [29, 32, 33]. The incidence of chronic hypertension and complications differ in different ethnic groups [3, 10, 13, 34].

The widespread habit of smoking is also strongly connected to some of the complications. It increases the risk for SGA births [35, 36], stillbirth [29], perinatal death [35] and abruptio placentae [24, 25, 37] and it seems to “protect” against preeclampsia [30, 35]. Chronically hypertensive women are reported to smoke less than normotensive [9, 13, 14].

Preeclampsia

Preeclampsia is considered to be a disease of multifactorial etiology [38-41]. Two distinct origins have been proposed: placental and maternal. The former, due to primarily reduced placental perfusion caused by abnormal placentation with failure of trophoblast to induce the physiologic dilatation and remodeling of spiral arteries, and the latter due to maternal susceptibility secondary to the insulin resistance syndrome [39].

The disease is commonly divided into mild and severe preeclampsia, depending on the level of blood pressure and/or the level of proteinuria. It can alternatively be divided into early or late preeclampsia depending on time of onset during pregnancy. Preeclampsia of early onset is often comparable to the severe form of the disease, whereas preeclampsia of late onset often remains mild. Most cases of severe, or early onset, preeclampsia are believed to originate from an abnormal placentation whereas mild, or late onset, preeclampsia may be an expression of a more or less insulin resistant body’s reaction to the burden of pregnancy [41].

There are now more and more data supporting the assumption that mild and severe preeclampsia might not be different degrees of the same disease, but might be different diseases with many expressions in common. For instance, there is evidence that the hereditary component is stronger for severe
than for mild preeclampsia [42, 43], and hypertriglyceridemic dyslipidemia before 20 weeks gestation has been shown to be associated with the risk of developing severe, but not mild preeclampsia [44].

Regarding heredity, it is well known that some families have more preeclampsia than others, but the exact pattern of heredity is unknown [45]. Both maternal and combinations of maternal and fetal influence have been discussed [46]. Most studies have focused on transmission of susceptibility for preeclampsia from mother to daughter. A recent study shows a doubled risk for mothers, who were themselves exposed to preeclampsia as fetuses, to have a pregnancy affected by preeclampsia, but also a significantly increased risk for men, who were exposed to preeclampsia as fetuses, to father a preeclamptic pregnancy [42]. This may suggest not only an influence from mother to daughter concerning the risk for preeclampsia, but also that the fetus might affect the mother in some way, making her more prone to develop preeclampsia.

Preeclampsia is one of the most feared complications in pregnancy associated with substantial risks for the fetus including being born SGA [47], prematurity [48] and perinatal death [48]. Concerning the mother it is associated with an increased risk for the pregnancy related complications abruptio placenta, eclampsia and HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome [48] as well as pulmonary oedema, acute renal failure and liver failure [48], pulmonary embolism [49] and stroke [49]. A woman who has had preeclampsia, especially of the severe form, also suffers an increased future risk of ischemic heart disease [50].

Thus, the cause of preeclampsia is unclear and there are no clinically useful screening tests to identify women in whom it will develop. It is therefore important to bear in mind, and to increase, our knowledge about risk factors for the disease. It is also important that further investigations consider the possibility of mild and severe preeclampsia as diseases of different etiologies and study them separately.

Gestational diabetes

Carbohydrate intolerance of varying degrees of severity with onset or first recognition during pregnancy is called gestational diabetes [51]. The incidence increases with maternal age and increasing BMI [52] and it could therefore be associated with the presence of chronic hypertension.

It is a risk factor for preeclampsia [19, 53] but there are differing results concerning the risk of perinatal death [19, 27, 54]. It might lead to a child born large for gestational age [19, 54], which is associated with delivery problems [54].
Abruptio placenta

Cleavage of the decidua, as a result of a dissecting bleeding from ruptured spiral arterioles, will cause a premature separation of the placenta from the uterine wall, a placental abruption. The diagnosis is clinical. The abruption can be either partial or total and is thought to be only small and not symptomatic in many cases, thus under-diagnosed. The reason why the spiral arterioles rupture is unknown.

The incidence of abruptio placenta has been shown to increase with maternal age [20, 55], smoking [25, 37], high parity [55, 56], low BMI [20], and with premature rupture of membranes [23]. Among maternal diseases, chronic hypertension is suggested to increase the incidence [23, 37, 57], though earlier results are conflicting [13, 25, 58]. Preeclampsia is a risk factor [57], and in cases of chronic hypertensive disease superimposed preeclampsia is suggested to further increase the incidence in some studies [21, 59].

A placental abruption can be life threatening to both mother and child. Though the perinatal outcome has not been shown to be significantly different between normotensive and hypertensive women [60].

Small for gestational age

To be born small for gestational age (SGA) is associated with increased perinatal morbidity and mortality [17, 18, 61]. A child can be SGA either for genetic (familial) reasons or for medical reasons [36]. Medical reasons could be preeclampsia or placental insufficiency; in those cases the child is SGA because of undernourishment and growth restriction. But a child can also be SGA because of family reasons, meaning it comes from a family that is small in stature, and might have reached its full, genetic, growth potential but still is small according to population-based standards. Another genetic reason for being born SGA is chromosomal abnormality. The expression SGA is sometimes used as a proxy for growth restriction, or, before birth, intrauterine growth restriction, diagnosed by ultrasound. It is important to be aware of the fact that those two diagnoses are overlapping but not interchangeable. Not all babies who are born SGA are growth restricted, and a child can be growth restricted without fulfilling the criteria for being SGA. And the criteria for SGA is differing between countries; in Sweden we use the definition <2SD below the expected weight for gestational age, while most other countries use <5th or <10th percentile. The two latter ways of definition will include more babies as SGA.

There are studies supporting chronic hypertension as a risk-factor for offspring to be born SGA, but opinions differ on whether the risk is independent of secondary preeclampsia [7, 13-15, 26], since preeclampsia is a strong
risk factor for SGA in itself [11, 36]. Smoking is the strongest environmental risk factor for being born SGA, and it is dose-dependent [62]. Young maternal age is another risk factor [62], as well as low pre-pregnancy maternal weight [63].

There is evidence for a connection between a woman born SGA and her subsequent risk for preeclampsia in a future pregnancy [64-67]. But it is not known whether there is an increased risk for both mild and severe preeclampsia, and little is known about how that risk is influenced if preeclampsia runs in the family.

Perinatal death

Perinatal death is defined according to WHO (World Health Organization) as death from the 22nd week of gestation until the seventh day of life. But the expression is sometimes extended to include death until the 27th day of life. It is naturally a greater problem in the less developed parts of the world, where common reasons are antepartum hemorrhage, mechanical problems at birth and congenital anomalies [68]. Reasons that we in the more developed countries have greater possibility to anticipate, avoid or handle because of better technical equipment, extensive antenatal care, very few home deliveries and because of the well developed infra structure that allows most women to come under medical attention quick enough. Except for these more or less avoidable reasons maternal hypertension is a common cause, or a contributing cause, to perinatal death [10, 12, 68, 69]. The perinatal mortality rate is tripled in women with mild chronic hypertension compared to normotensive women according to a recent review [22]. But earlier studies are often based on referral hospitals, which makes it important to consider overestimation of risks. Earlier studies are also conflicting on the matter weather the risk for chronic hypertensive women is independent or not of secondary complications such as preeclampsia [5, 11, 13, 14, 21].

Intrauterine death

Intrauterine death is often termed stillbirth. The majority of intrauterine deaths are unexplained, but maternal medical disease increases the risk, and hypertensive disorders and diabetes are the leading contributing maternal illnesses [69]. Hypertension complicated by preeclampsia and abruptio placentae is supposed to carry the highest risk [57]. Obesity and smoking are other strong risk factors for stillbirth [29].
Neonatal death

Neonatal death is subdivided into early and late neonatal death, referring to death before 7 days of life and death from day 7 until day 27. Factors affecting mortality in the neonatal period, and especially in the early neonatal period, are sometimes thought of as being mainly prenatal and natal, or biological, while they are probably more environmental than biological in the postneonatal period [70]. Thus we could expect chronic hypertension to affect neonatal death more than postneonatal death.

Gender aspects on perinatal death

Concerning stillbirth earlier studies show only a weak [71] or no [72] male disadvantage, but there is a well-known male disadvantage in neonatal survival [71]. The more premature the child is, the greater the disadvantage [72]. The reason for this increased risk for boys to die is unknown, but several complications to neonatal life have been shown to be more dangerous to boys, such as infections [73], low birth weight [74], infant respiratory distress syndrome (IRDS) [75] and acidosis [76].

No studies are found concerning the gender aspect on fetal/infant mortality in pregnancies complicated by chronic hypertension. But there is evidence for a male disadvantage in perinatal morbidity concerning diabetes [77]. Both diabetes and chronic hypertension is associated with the insulin resistance syndrome.

Insulin resistance syndrome

Chronic hypertension is often part of the insulin resistance syndrome, also referred to as the metabolic risk syndrome, which includes elevated blood pressure, impaired glucose tolerance, disturbed lipid metabolism, disruption of endothelial function and disturbances of the fibrinolytic system [78, 79]. All pregnancies are accompanied by profound hormonal, metabolic and hemodynamic changes. As a result, a state of insulin resistance develops. The increased blood volume with raised cardiac output and increased renal flow, with demand on glomerular filtration, affects the intricate renin-angiotensin system. A healthy person can handle these changes, but in a person who suffers from insulin resistance syndrome, without yet having overt manifestations of the disease, the pregnancy can unmask the syndrome [80], which is shown in manifestations such as gestational diabetes and preeclampsia [81-83]. Disruption of endothelial function and disturbances of the fibrinolytic system might point at an association with placental abruption.

Studies have also shown that otherwise healthy women who have experienced a preeclamptic pregnancy have increased plasma concentrations of
insulin months to years afterwards [84-88], supporting an underlying or per-
sistent insulin resistance.

The insulin resistance syndrome is closely related to the following hy-
potheses, which are of importance in some aspects of understanding chronic
hypertension, related complications and effects in future generations.

The Barker hypothesis
At the end of the 80s, Barker published his first study, which concluded that
environmental influences that impair growth and development in early life
might be risk factors for ischemic heart disease [89]. He had studied men
and found that those with the lowest weight at birth and at one year of age
had the highest death rates from ischemic heart disease. This was followed
by more studies in the 90s, extending the results to be true also for women,
and to comprise hypertension, stroke and type 2 diabetes, besides ischemic
heart disease [90-92].

The fetal origins hypothesis
The Barker hypothesis has also given rise to the “fetal origins hypothesis”
[93], which suggests that fetal undernourishment “programmes”, or causes,
later cardiovascular disease through persistent metabolic changes, including
reduced insulin sensitivity.

The catch-up-growth hypothesis
It is considered that undernourished children who have a quick weight gain
are at increased risk for developing insulin resistance syndrome [94]. The
hypothesis is that growth retarded children, who have lower concentrations
of insulin and IGF-1 (insulin like growth factor-I) and higher concentrations
of growth hormone compared to appropriately grown children, when these
hormones normalize during the first months of life, may develop insulin
resistance as a metabolic defense mechanism to protect the organism from
hypoglycemia.
Aims of the studies

The overall aim was to analyse the impact of chronic hypertensive disease on maternal and fetal pregnancy outcome. In the papers the specific aims were:

I. First, to analyse if women with chronic hypertension during pregnancy have an increased risk of preeclampsia, gestational diabetes and abruptio placenta independent of their demographic differences from normotensive women. Secondly, to analyse if super-imposed preeclampsia increases the risk for abruptio placenta in this group of women.

II. To analyse if women with chronic hypertension have an increased risk for offspring to be born small for gestational age, independent of their demographic differences from normotensive women, and of secondary mild or severe preeclampsia.

III. To investigate the risk of mild and severe preeclampsia in women born small for gestational age, and to investigate whether preeclampsia in the previous generation modifies the risk.

IV. First, to investigate if there is an increased risk for perinatal mortality, and later mortality within the first year of life, in offspring of women with chronic hypertension. Secondly, to analyse if that risk is mediated by preeclampsia, gestational diabetes, abruptio placenta or offspring being small for gestational age. The intention was also to study the risk for each gender separately.
Material and methods

Data sources

The Swedish Medical Birth Register
This register is held by the National Board of Health and Welfare and contains data on more than 99% of all births in Sweden from 1973 and onwards [95]. Data is collected thorough copies of standardized antenatal, obstetric and pediatric records, which are marked with the mother’s unique national registration number, and sent to the National Board of Health and Welfare. From the first antenatal visit, information is collected prospectively. A midwife, who performs an interview and an examination, records maternal previous reproductive history, smoking habits, height, weight and state of health at a woman’s first visit to the antenatal care center. Since 1991 there are check-boxes for different pre-existing diseases, to be filled in by the midwife. Information about complications during pregnancy and at delivery is collected when the woman is discharged from hospital. The mother’s country of birth is obtained from the Civil Registration held by Statistics Sweden, through linkage of the personal identification number. Complications during pregnancy and delivery are classified according to the Swedish version of the International Classification of Diseases (ICD). Until 1986 the 8th revision is used (ICD-8), from 1987 to 1996 the 9th edition (ICD-9), and from 1997 onwards the 10th edition (ICD-10). A doctor notes the diagnosis at the time of discharge from hospital.

Quality control has been made of the Swedish Medical Birth Register (MBR) [95, 96].

The Cause of Death Register
Information about infant mortality was obtained by linkage to the Cause of Death register. It contains information on all deceased persons recorded as residents in the country at time of death, it comprises all deaths from 1961 and onwards, and is updated annually. Cause of death is generally determined from medical death certificates. Since 1994 the National Board of Health and Welfare holds this register, before it was held by Statistics Sweden.
Definitions of diagnoses

Chronic hypertension
Blood pressure $\geq 140/90$ mmHg at two different occasions at least six hours apart (ICD-9 codes 401 or 642A, ICD-10 codes I10 or O10.0 or hypertension reported in a check-box). Chronic hypertension can be subdivided into primary (idiopathic) or secondary. Secondary chronic hypertension is related to underlying disorders such as diabetes mellitus, chronic renal disease or SLE (systemic lupus erythematosis). 90% of chronic hypertension is primary.

Preeclampsia
At least two diastolic blood pressures of $\geq 90$ mmHg combined with proteinuria of $\geq 0.3$ gm/day or at least $1+$ on a urine dipstick.

Mild preeclampsia
A diastolic blood pressure from 90 to 109 combined with proteinuria of $< 5$ gm/day (or $1+$ or $2+$) on a urine dipstick (ICD-8 code 637.03, ICD-9 code 642E and ICD-10 code O14.0). (ICD8-codes 637.09 and 637.99, ICD-9 code 642H and ICD-10 code O14.9 representing preeclampsia NUD and toxicosis NUD have also been referred to mild preeclampsia.)

Severe preeclampsia
A diastolic blood pressure of $\geq 110$ or proteinuria of $\geq 5$ gm/day (or $3+$ on a dipstick) or both (ICD-8 code 637.04, ICD-9 code 642F, ICD-10 code O14.1). Severe preeclampsia also includes eclampsia (ICD-8 code 637.10, ICD-9 code 642G, ICD-10 code O15).

Gestational diabetes
There is no consensus nationally or internationally on the diagnostic criteria of gestational diabetes (GD). In Sweden it is defined by the 75-gram oral glucose tolerance test. The diagnostic criteria by most centres is and has been a fasting blood glucose of $\geq 6.7$ mmol/l and/or two hours blood glucose of $\geq 9.0$ mmol/l (ICD-9 code 648W, ICD-10 code O24.4). This does not include diabetes mellitus, when present before pregnancy.

Abruptio placenta
Definition of abruptio placenta is not as strict as the above-mentioned diagnoses, but the meaning is premature separation of the placenta from the uter-
The separation can be partial or total. The diagnosis of a partial separation is clearly subjective and could be both under- and overestimated. The definition according to ICD-9 includes also accidental ante partum haemorrhage (ICD-9 code 641C, ICD-10 code O45).

Small for gestational age
Birth weights less than two standard deviations below the mean for gestational age and sex, are considered small for gestational age (SGA). In Sweden a population-based birth weight standard is currently being used, where the growth curves are based on ultrasonically estimated intrauterine weights [97]. Before that another population-based standard based on real birth weights during different weeks of gestation was used [98]. In the Swedish MBR birth weights for all years are classified as SGA or not according to the present standards.

Perinatal death
Perinatal death includes intrauterine death and neonatal death.

Intrauterine death
According to Swedish standards intrauterine death, or stillbirth, means death of a fetus of at least 28 weeks gestation. A stillbirth before 28 weeks gestation is diagnosed as a miscarriage, and thus is not included in the MBR, and not in the studies.

Neonatal death
Neonatal death can be subdivided into early and late neonatal death. Early neonatal death meaning death within the first seven days of life, late neonatal death meaning death from day eight to 27. In this thesis we refer to neonatal death as death within the first 27 days of life. Every child who is born alive, no matter how prematurely, and later die, is recorded in the Cause of Death Register. Thus a child, who is born alive before the 28th week of gestation and later die, is included in the studies.

Post neonatal death
Death within the first year of life but after the neonatal period, days 28-364, is referred to as post neonatal death.
Validation of the diagnosis chronic hypertension

The accuracy of the diagnostic recording of chronic hypertension in the Medical Birth Register was validated in a randomly selected sample of women who delivered at three different hospitals (Uppsala University hospital, Västerås hospital and Örebro University hospital) during 1992–2004. The diagnosis recorded in the MBR was compared with the diagnosis recorded in the records, both as ICD-code and in check-box. The notes on blood pressure in the records were checked related to gestational week and the notes on proteinuria were also checked, to identify misclassification of gestational hypertension or preeclampsia as chronic hypertension, and to identify misuse of check box.

The intention was to analyze 70 records at each hospital, however six records could not be found. Among 204 women coded in the MBR as chronic hypertension, the diagnosis was correct in 166 cases (81%).

When comparing diagnosis in check-box, set by a midwife at antenatal care centers, with diagnosis according to ICD, set by a doctor at discharge from hospital after delivery, there was some variation in how it was used. Among the 166 cases correctly registered, 123 were correctly diagnosed in check-box and 108 had a correct ICD-code. Only in 62 out of the 166 cases were the diagnoses set correctly in both check-box and by ICD-code. Among the 38 cases who were not correctly registered, 29 were diagnosed in check-box as chronic hypertension, three were ICD-coded as chronic hypertension and six were registered as chronic hypertension without having been diagnosed either way.

Accordingly, the diagnostic criteria are not followed as strictly at the antenatal care centers as at hospitals. But, in a certain amount of cases, the doctor neglect to record correct diagnosis at discharge from hospital.

Design and statistical analyses of the studies

Paper I and II

Population based cohort studies using the Swedish MBR 1992-98. Women age 15-44 with singleton pregnancies were included, women with diabetes mellitus, systemic lupus erythematosus (SLE) and chronic renal disease were excluded. Women with chronic hypertension were compared to normotensive women concerning their risk for the complications preeclampsia, gestational diabetes, abruptio placenta and SGA. Multiple logistic regression analysis was performed and the outcome measures of crude and adjusted odds ratios were presented with 95% confidence intervals (CIs).

Analyses were performed with the statistical package SAS.
Paper III
A population based cohort study using the Swedish MBR 1973-2003. Women registered both as newborns and as mothers during the time period, only first-time mothers and singletons, were included. Women born SGA were compared to the rest concerning their risk for preeclampsia. $\chi^2$-test was used to compare groups. Multiple logistic regression analysis was performed and the outcome measures of crude and adjusted odds ratios were presented with 95% CIs.

The statistical analysis was performed using the SPSS software.

Paper IV
A population based cohort study using the Swedish MBR 1992-2003. Women born in a Nordic country, with singleton pregnancies, were included. Chronically hypertensive women were compared to normotensive women concerning their risk for fetal or infant loss. Multiple logistic regression analysis was performed and the outcome measures of crude and adjusted odds ratios were presented with 95% CIs. An effect modification by gender was included in the model.

The statistical analysis was performed using the SPSS software.

Overview of the papers

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<tr>
<th>Study</th>
<th>Subjects</th>
<th>Outcome measures</th>
<th>Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>681 515 women, including 3 374 with CHD</td>
<td>Mild and severe PE, GD, abruptio</td>
<td>Age, parity, smoking, ethnicity, BMI</td>
</tr>
<tr>
<td>II</td>
<td>560 188 women, including 2 754 with CHD</td>
<td>SGA</td>
<td>Age, parity, smoking, ethnicity, BMI, mild and severe PE</td>
</tr>
<tr>
<td>III</td>
<td>118 634 women, including 6 883 born SGA</td>
<td>Mild and severe PE</td>
<td>Age, smoking, BMI, PE in previous generation</td>
</tr>
<tr>
<td>IV</td>
<td>1 047 785 women, including 5 813 with CHD</td>
<td>Stillbirth, neonatal death, postneonatal death</td>
<td>Age, parity, smoking, BMI, gender, mild and severe PE, GD, SGA, abruptio</td>
</tr>
</tbody>
</table>

CHD=Chronic hypertensive disease, SGA=Small-for-gestational-age, PE=Preeclampsia, GD=Gestational diabetes, BMI=Body Mass Index

Ethics
When needed the studies were approved by the ethics committee of Uppsala University.
Results

Study I

0.5% of the women were diagnosed with chronic hypertensive disease. They were older, of higher parity, less often smokers, more often of Nordic origin and had higher BMI than the normotensive population. Complications were more frequent among chronically hypertensive women (table 1).

Table 1. Incidence of pregnancy complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>Normotensive (per 1000)</th>
<th>Chronic hypertension (per 1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE, total</td>
<td>27.4</td>
<td>116.5</td>
</tr>
<tr>
<td>PE, mild</td>
<td>19.3</td>
<td>73.2</td>
</tr>
<tr>
<td>PE, severe</td>
<td>8.2</td>
<td>43.3</td>
</tr>
<tr>
<td>GD</td>
<td>7.9</td>
<td>23.4</td>
</tr>
<tr>
<td>Abruptio placenta</td>
<td>4.9</td>
<td>11.3</td>
</tr>
</tbody>
</table>

PE=Preeclampsia, GD=Gestational diabetes

Women with chronic hypertension differed from normotensive women especially concerning their BMI, with 42.0% vs. 23.6% being overweight (BMI≥25), and, of these 17.6% were considered obese (BMI≥30) compared to only 6.0% among the normotensive women. Since this marked diversity was found we counted the risks for complications associated with BMI in the total population (table 2). (Data not presented in the paper.)

Table 2. Complication risk associated with Body Mass Index (BMI)

<table>
<thead>
<tr>
<th>BMI</th>
<th>Mild PE OR (95% CI)</th>
<th>Severe PE OR (95% CI)</th>
<th>GD OR (95% CI)</th>
<th>Abruptio placenta OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>0.8 (0.7–0.8)</td>
<td>0.9 (0.8–1.0)</td>
<td>0.7 (0.6–0.8)</td>
<td>1.2 (1.1–1.4)</td>
</tr>
<tr>
<td>20–25</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>25–30</td>
<td>1.9 (1.8–1.9)</td>
<td>1.5 (1.4–1.7)</td>
<td>2.1 (2.0–2.3)</td>
<td>1.0 (0.9–1.1)</td>
</tr>
<tr>
<td>30–35</td>
<td>3.1 (2.9–3.3)</td>
<td>2.5 (2.3–2.8)</td>
<td>4.9 (4.5–5.3)</td>
<td>1.0 (0.8–1.2)</td>
</tr>
<tr>
<td>35+</td>
<td>4.2 (3.8–4.6)</td>
<td>3.7 (3.2–4.3)</td>
<td>9.5 (8.5–10.7)</td>
<td>1.0 (0.7–1.3)</td>
</tr>
</tbody>
</table>

BMI=body mass index, OR=Odds ratio, CI=Confidence interval

Increasing BMI was strongly associated with enhanced risk for both mild and severe preeclampsia and it was very strongly associated with enhanced risk for gestational diabetes. Increased BMI was not associated with the risk
for abruptio placenta though, which seemed to be slightly enhanced by low BMI.

To calculate the risks for these complications in women with chronic hypertension, we included BMI as well as the other demographic variables mentioned, in a logistic regression analysis (table 3).

Table 3. Odds ratios for chronically hypertensive women compared to normotensive women to develop PE, GD and abruptio placenta

<table>
<thead>
<tr>
<th>Complication</th>
<th>Crude OR</th>
<th>95% CI</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE, mild</td>
<td>4.0</td>
<td>(3.5–4.7)</td>
<td>3.2</td>
<td>(2.7–3.7)</td>
</tr>
<tr>
<td>PE, severe</td>
<td>6.1</td>
<td>(5.1–7.4)</td>
<td>5.2</td>
<td>(4.3–6.3)</td>
</tr>
<tr>
<td>GD</td>
<td>3.1</td>
<td>(2.4–4.0)</td>
<td>1.8</td>
<td>(1.4–2.4)</td>
</tr>
<tr>
<td>Abruptio</td>
<td>2.4</td>
<td>(1.7–3.5)</td>
<td>2.3</td>
<td>(1.6–3.4)</td>
</tr>
</tbody>
</table>

The chronically hypertensive woman was shown to suffer a 5-fold risk for severe preeclampsia, a 3-fold risk for mild preeclampsia, an almost doubled risk for gestational diabetes and a slightly more than doubled risk for abruptio placenta compared to the normotensive woman.

Of the 3374 women with chronic hypertension, there were 38 cases of abruptio placenta, of which three had superimposed preeclampsia. Thus there were too few cases to make calculations for the second aim of the study.

Study II

0.5% of the women had chronic hypertensive disease. Of these 7.0% had offspring that was born SGA, compared to 2.5% in the rest of the population. The incidence of having an offspring born SGA was consistently higher among hypertensive women, also when stratified by demographic data. For both hypertensive and normotensive women the incidence of having an offspring born SGA was higher if the woman was older, primipara, smoker and if she had non-Nordic origin. Concerning BMI, the lowest BMI was associated with the highest incidence of an offspring born SGA, but there was a tendency towards higher incidence of SGA babies also in the very obese group.

The risk for offspring born SGA, in chronically hypertensive women compared to normotensive women (model I), considering confounding from age, parity, smoking habits, ethnicity and BMI (model II) and a mediating effect from mild and severe preeclampsia (model III) was calculated (table 4).
Table 4. Odds ratio for chronically hypertensive women compared to normotensive women to have an offspring that is SGA

<table>
<thead>
<tr>
<th>Model</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>3.0</td>
<td>(2.6–3.5)</td>
</tr>
<tr>
<td>II</td>
<td>3.1</td>
<td>(2.7–3.7)</td>
</tr>
<tr>
<td>III</td>
<td>2.4</td>
<td>(2.1–2.8)</td>
</tr>
</tbody>
</table>

The risk for a chronically hypertensive woman to have an offspring born SGA was highly significant in all three models, and 2.5–3-fold compared to that of a normotensive woman.

Study III

Of the women included in the study, 5.8% were born SGA. They were found to have a higher incidence of severe preeclampsia as well as gestational diabetes and offspring born SGA. See table 5. (Data not presented in the paper.)

Table 5. Incidences (%) of pregnancy complications in women born SGA and women not born SGA

<table>
<thead>
<tr>
<th>Complication</th>
<th>Born SGA</th>
<th>Not born SGA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild PE</td>
<td>3.4</td>
<td>3.2</td>
<td>ns</td>
</tr>
<tr>
<td>Severe PE</td>
<td>2.6</td>
<td>1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>0.8</td>
<td>0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SGA</td>
<td>6.5</td>
<td>2.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

SGA=Small for gestational age

Below the incidences of mild and severe preeclampsia in the study population are shown. The data is stratified by exposition to preeclampsia in uterus or not, whether preeclampsia was present or not in the previous generation while pregnant with the study population (table 6).

Table 6. Incidence (per 1000) of mild and severe preeclampsia in women born SGA, and women not born SGA, with regard to preeclampsia in the previous generation

<table>
<thead>
<tr>
<th>Previous generation</th>
<th>Born SGA</th>
<th>Not born SGA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE</td>
<td>61</td>
<td>45</td>
<td>61</td>
</tr>
<tr>
<td>No PE</td>
<td>34</td>
<td>22</td>
<td>31</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>23</td>
<td>32</td>
</tr>
</tbody>
</table>

The incidences of both mild and severe preeclampsia seemed to be doubled when there was preeclampsia in the previous generation, and that was true both if the woman was born SGA and if she was not. Women who were
themselves born SGA, had a significantly higher incidence of preeclampsia (p<0.001), especially pronounced for the severe form of the disease.

The risks of mild and severe preeclampsia in women born SGA were calculated separately. Since women born SGA were slightly younger, more often smokers and had a lower BMI than the rest of the population, we had to control for confounding from this (model II) as well as for exposition to preeclampsia in uterus (model III). See table 7.

Table 7. Odds ratios for women born SGA to get preeclampsia, compared to women not born SGA

<table>
<thead>
<tr>
<th>Model</th>
<th>Mild PE</th>
<th>Severe PE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>I</td>
<td>1.13</td>
<td>(0.98–1.31)</td>
</tr>
<tr>
<td>II</td>
<td>1.19</td>
<td>(1.03–1.38)</td>
</tr>
<tr>
<td>III</td>
<td>1.16</td>
<td>(1.00–1.35)</td>
</tr>
</tbody>
</table>

There was a clearly significant risk increase for severe, but not for mild, preeclampsia in all steps of the analysis.

Finally we analyzed, whether the effect of having been born SGA, on the risk for severe preeclampsia, was modified by the presence of preeclampsia in the previous generation, during the woman’s own fetal period. The point estimate of the effect modification was 1.25, however non-significant (95% CI 0.68-2.31).

Study IV

0.6% of the women had chronic hypertension, compared to 0.5% in studies I and II. Study IV was performed on a population including that of the former studies (I and II) with mothers of five more recent years added. Compared to the former studies there had also been a slight change in the incidence of complications (table 8).

Table 8. Incidence of pregnancy complications.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Normotensive (per 1000)</th>
<th>Chronic hypertension (per 1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE, mild</td>
<td>20.6</td>
<td>81.5</td>
</tr>
<tr>
<td>PE, severe</td>
<td>9.0</td>
<td>54.0</td>
</tr>
<tr>
<td>GD</td>
<td>7.2</td>
<td>24.8</td>
</tr>
<tr>
<td>Abruptio placenta</td>
<td>4.7</td>
<td>10.3</td>
</tr>
<tr>
<td>SGA</td>
<td>20.6</td>
<td>72.5</td>
</tr>
</tbody>
</table>

Among normotensive women 0.6% lost their child either as a stillbirth or before one year of age while the corresponding number among hypertensive mothers was 1.5%. There was no obvious gender difference in stillbirth rate
among offspring of normotensive women and only a slight gender difference concerning infant death, but there seemed to be a doubled death rate in male offspring of hypertensive women compared to their female offspring, both intrauterine and neonatally.

The incidence of stillbirth, neonatal death and post neonatal death, in the total population, was studied in relation to chronic hypertensive disease, mild and severe preeclampsia, gestational diabetes, abruptio placenta and SGA. The mortality was increased, both as stillbirth and in the neonatal period, regarding chronic hypertension. There was an increased mortality associated with severe preeclampsia, abruptio placenta and SGA, both as stillbirth and within the first year of life. No such association was found for mild preeclampsia or gestational diabetes (table 9).

Table 9. Incidence (per 1000) of fetal/infant mortality related to certain pregnancy complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>IUFD</th>
<th>Neonatal death</th>
<th>Post neonatal death</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>8.4</td>
<td>5.7</td>
<td>1.4</td>
</tr>
<tr>
<td>Mild PE</td>
<td>2.2</td>
<td>2.3</td>
<td>1.8</td>
</tr>
<tr>
<td>Severe PE</td>
<td>6.9</td>
<td>13.3</td>
<td>4.1</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>3.7</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>SGA</td>
<td>33.0</td>
<td>20.1</td>
<td>7.9</td>
</tr>
<tr>
<td>Abruptio placenta</td>
<td>67.9</td>
<td>34.0</td>
<td>7.2</td>
</tr>
<tr>
<td>TOTAL</td>
<td>3.2</td>
<td>2.1</td>
<td>1.1</td>
</tr>
</tbody>
</table>

IUFD=intrauterine fetal death=stillbirth, CHD=Chronic hypertensive disease

A strong and significantly increased risk for hypertensive mothers, compared to normotensive mothers, to lose their child either intrauterine or in the neonatal period was found, but no significant difference in risk for post neonatal death could be shown.

To study the risk for fetal/infant death, divided by gender, for chronically hypertensive mothers compared to normotensive mothers, a regression analysis was performed (table 10).

Table 10. Risk for mortality of offspring in chronically hypertensive mothers compared to normotensive mothers

<table>
<thead>
<tr>
<th>Model</th>
<th>Gender</th>
<th>IUFD (95%CI)</th>
<th>Neonatal death (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td></td>
<td>OR</td>
</tr>
<tr>
<td>I</td>
<td>M+F</td>
<td>2.70 (1.96–3.73)</td>
<td>2.89 (1.95–4.30)</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>4.12 (2.84–5.96)</td>
<td>3.45 (2.13–5.59)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>1.29 (0.67–2.48)</td>
<td>2.17 (1.08–4.35)</td>
</tr>
<tr>
<td></td>
<td>M+F</td>
<td>2.04 (1.47–2.82)</td>
<td>2.51 (1.69–3.74)</td>
</tr>
<tr>
<td>II</td>
<td>M</td>
<td>3.07 (2.12–4.46)</td>
<td>2.99 (1.84–4.85)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>0.98 (0.51–1.89)</td>
<td>1.88 (0.93–3.79)</td>
</tr>
</tbody>
</table>

M=male, F=female, Model I: crude, Model II: adjusted for age, parity, smoking and BMI
When the risks were studied for each gender separately, it was revealed that the over risk compared to normotensive mothers was only applicable to boys, who had a 3-fold risk for intrauterine and neonatal death.

A third step of the regression analysis was performed, adjusting for the mediating effect of complications. Severe preeclampsia and having been born SGA were shown to have a strong mediating effect on neonatal death, as had abruptio, though weaker. All three complications had mediating effects on stillbirth as well, SGA had the strongest mediating effect while the mediating effect from severe preeclampsia was only weak.

Since both severe preeclampsia and being SGA were mediators of risk for death in offspring of hypertensive mothers, it was investigated if there was any gender difference in death rates in the total population according to these complications (table 11).

Table 11. Fetal/infant death (per 1000), in the total population, related to chronic hypertensive disease, severe preeclampsia and SGA.

<table>
<thead>
<tr>
<th>Gender</th>
<th>No CHD</th>
<th>CHD</th>
<th>No severe PE</th>
<th>Severe PE</th>
<th>No SGA</th>
<th>SGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>IUDF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>3</td>
<td>12</td>
<td>3</td>
<td>7</td>
<td>2</td>
<td>33</td>
</tr>
<tr>
<td>F</td>
<td>3</td>
<td>5</td>
<td>3</td>
<td>7</td>
<td>2</td>
<td>32</td>
</tr>
<tr>
<td>Neonatal death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>2</td>
<td>8</td>
<td>2</td>
<td>13</td>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td>F</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>14</td>
<td>1</td>
<td>19</td>
</tr>
</tbody>
</table>

There was no such gender difference. (Data not presented in the paper.)
Discussion

Chronic hypertension

This thesis focuses on risks for women with chronic hypertension in pregnancy. It is an important matter since chronic hypertension, though not commonly occurring in pregnancy, is associated with considerable risks both maternally and perinatally, as well as in the future generation. The incidence of chronic hypertension in pregnancy is increasing, as shown; it was 0.5% in 1992-98 but increased to 0.6% when the studied population was extended five more years. That is an increase in about 20% over quite few years. It is also pointed out that there is a clear tendency for a larger part of pregnant women being obese (comparing tables I of paper I and IV). Obesity is associated with a strong risk increase for preeclampsia, little more pronounced for mild preeclampsia than for severe, and with a pronounced risk increase for gestational diabetes. We can also point at an established increase in the incidence of preeclampsia, more pronounced in chronically hypertensive women than in normotensive women, during the same time period. Concerning gestational diabetes and abruptio placenta there is no uniform tendency. These changes over time should gain interest in knowledge about how to anticipate risks for pregnant women with chronic hypertension.

Compared to earlier studies in chronic hypertension, this thesis is based on population-based studies, which should strengthen its relevance in comparison to studies based on selected groups of patients in referral hospitals, where we must suspect risks to be overestimated. The study populations are gathered from the Swedish MBR, which is a register of high validity [95, 96]. Almost no women in Sweden deliver at home, so suspicion of losses to follow up, or selection bias, can be ignored. All data in the register is prospectively gathered, whereby recall bias can be disregarded.

A separate validation of the registration of the diagnosis chronic hypertension in the MBR was made. The positive predictive value was 81%. Some women may have escaped diagnosis, for instance if they have begun attending antenatal care in the middle of pregnancy, when blood pressure is physiologically lowered. Since the prevalence of chronic hypertension is low, and the studied populations are large, this should not have affected the incidences of complications among normotensives. Some women were diagnosed with chronic hypertension without fulfilling the criteria. In nine cases, those were misclassified preeclampsia cases, registered in check-box as
chronic hypertension and later given an ICD-code agreeing with preeclampsia. Thus the complication preeclampsia might be a little overestimated, since these women were incorrectly classified. Only one of these cases represented severe preeclampsia though. In some cases the women were falsely registered in check box as an expression for heredity for hypertension. These women are probably at risk of later developing chronic hypertensive disease and can be suspected to be at increased risk for related complications, compared to purely normotensive women. Theoretically they may then have contributed to an overestimation of risks, but since they were very few they can be neglected. Then there were seven cases of gestational hypertension, either in check-box or as ICD code, and as many registered in check-box because of hypertension in former pregnancy. These might also have contributed to overestimation of complications.

It may be a weakness that we have not considered the influence of anti-hypertensive medication during pregnancy, on maternal and perinatal outcome. Detailed information about medication is not possible to obtain from the register. Two recent reviews [2, 48] conclude, however, that there is none or little evidence for a difference in the risk of severe preeclampsia and no significant effect on the risk of perinatal death, preterm birth or small for gestational age babies when hypertension is medically treated. However, atenolol, a selective β-blocker, has been associated with a significantly increased risk for SGA when taken from early pregnancy, not when treatment was begun in the third trimester [99]. When the validation of the diagnostic recording of chronic hypertension in the MBR was made, the personal records were also checked for medication. Medication was in most cases commenced in the last trimester, and labetalol, a combined α- and β-blocker, was the most commonly used drug.

Maternal complications

We have found that chronic hypertension is a strong risk factor for mild and severe preeclampsia, gestational diabetes and abruptio placenta, independent of age, parity, BMI, ethnicity and smoking. The increased risks for all of these complications might be explained by all of them being associated to the insulin resistance syndrome. The risks found for preeclampsia and gestational diabetes are lower than in earlier studies [7, 8, 13, 14], but those were not population based. It is also important to be aware that diagnostic criteria are not always strictly the same, so risks should be interpreted with care. The risk found for abruptio placenta is in accordance with an earlier meta-analysis [23] and a more recent review [22]. Despite the size of our study population, the incidence of abruptio placenta in chronic hypertensive moth-
ers was too low to make any statement on whether the risk is independent of superimposed preeclampsia.

We also point out, that when a woman with chronic hypertension gets preeclampsia, the disease turns out to be severe in proportionally more cases than in normotensive women. This is not earlier revealed and should be considered in antenatal care of chronically hypertensive women, since the severe form of the disease is associated with much worse outcome for the fetus as shown in this thesis. We speculate that this tendency towards severe preeclampsia might reflect an association with the insulin resistance syndrome. Maybe women with an underlying insulin resistance syndrome, who experience an abnormal placentation, are more prone to develop severe preeclampsia. Whereas women with an underlying insulin resistance syndrome, with a normal placentation, develop preeclampsia of milder degree, when the metabolic burden of the pregnancy increases towards the later stage of pregnancy. It is thus hypothesized that the consequences of an abnormal placentation strikes harder in a woman affected by the insulin resistance syndrome. That is supported by the fact that women with gestational diabetes have an increased risk of preeclampsia independent of risk factors such as increased BMI and first parity [52]. The hypothesis is also possible to combine with another recently published hypothesis by Ness & Sibai [100], that preeclampsia develops when an abnormal placentation interacts with the insulin resistance syndrome, whereas an abnormal placentation in a woman not suffering from that syndrome may lead to intrauterine growth restriction without preeclampsia. We suggest their hypothesis is true for the severe form of preeclampsia, often accompanied by growth restriction.

There are earlier studies pointing at mild and severe preeclampsia as diseases of at least partly different origin. As examples there is evidence that severe preeclampsia is associated with stronger heredity [42, 43], a different lipid profile in early pregnancy [44] and a higher risk for future ischemic heart disease [50] compared to mild. In this thesis we can also show that severe preeclampsia is associated with perinatal death whereas mild preeclampsia is not, and that women born SGA have an increased risk for severe, but not mild, preeclampsia. These findings are new and may support the concept that that mild and severe preeclampsia do not have all etiology in common.

Perinatal complications

We show that chronic hypertension is a strong risk factor for offspring to be born small for gestational age, independent of secondary preeclampsia, though secondary preeclampsia, both mild and severe, increases the risk. It is also a strong risk factor for intrauterine and neonatal death, independent of secondary preeclampsia, gestational diabetes, abruptio placenta and off-
spring being born small for gestational age. If the pregnancy is complicated by severe preeclampsia or abruptio placenta, or if the baby is small for gestational age, the risk for perinatal death is increased, while mild preeclampsia or gestational diabetes do not enhance the risk for perinatal death. Chronic hypertension is shown not to be a risk factor for post neonatal death.

SGA

The proved incidence of a chronically hypertensive woman giving birth to an SGA baby is a little lower than in earlier, hospital based, studies [7, 11, 13, 14], but in line with a recent population based study [9].

The risk for a chronically hypertensive mother to have an SGA baby is more than doubled compared to normotensive women. It is interesting, that even though chronically hypertensive mothers are more multiparous, have higher BMI, smoke less and more often are of Nordic ethnicity, all characteristics which are associated with offspring not being growth restricted, they still have an increased rate of SGA babies. Since these babies fail to reach their proper weight according to gestational age and sex, in spite of maternal characteristics that should favor appropriate growth, it could be questioned whether SGA babies to chronically hypertensive mothers have a higher mortality than SGA babies to normotensive mothers. We therefore analyzed the incidence of stillbirth in SGA babies in both groups and there was no significant difference. The incidence of neonatal death in SGA babies of both groups was also analyzed, and there was almost a significant difference (p=0.06), with SGA babies of chronically hypertensive mothers having a little higher incidence of neonatal death. No inference can be drawn from this, but it is important to further study perinatal mortality in this group of women.

This finding also makes it interesting to speculate if individual birth weight standards could be useful in this group of women. In the 1990s Gardosi et al presented studies on so called customized birth weight standards, taking into account not only gestational age and sex but also maternal characteristics as height, weight, parity and ethnicity [101, 102]. Identifying babies that are SGA by that method has been shown to better relate to pregnancies at increased risk for adverse perinatal outcome [18, 103-107].

Chronic hypertension is a risk factor for offspring being SGA independent of superimposed preeclampsia, that is contradictory to some earlier studies [6, 7, 16]. It is important to be aware of this increased risk for growth restriction, even before preeclampsia is present, in antenatal care, especially if these SGA babies would have a higher neonatal mortality, something that needs further investigation.
Perinatal death

The increased risk for perinatal death in chronically hypertensive mothers independent of secondary complications is in accordance with some earlier studies [10, 12, 21, 108], whereas others have suggested an increased perinatal mortality only when secondary preeclampsia is present [4, 6]. Those studies were however quite small to analyze such a rare complication.

We found, that the increased risk for stillbirth only affects male fetuses, a fact that is not earlier revealed. Also concerning neonatal death there is an increased risk for boys compared to girls. Regarding neonatal death there was a non-significantly increased risk for girls after logistic regression analysis and a significantly increased risk for boys, but the point estimates for boys and girls were not significantly separated. So, the gender difference was more distinct prenatally. An excessive risk for perinatal death in boys compared to girls was shown several years ago, although the difference was not as pronounced for stillbirth as for neonatal death [71]. In a Norwegian study, they found a non-significant increase in male stillbirth compared to female [29]. A recent Swedish study found a similar stillbirth rate between male and female fetuses, but there was a >50% increase in the number of male infants dying neonatally or within their first year of life [72]. In this study on chronically hypertensive women, we found a gender difference in stillbirth as well as in neonatal death and no increased incidence of post neonatal death within the first year of life.

The reason for this gender difference is unknown. Concerning neonatal death, boys have been shown to be more vulnerable to many diseases complicating neonatal life [73, 75] [76]. Low birth weight [74] is shown to be associated with a higher death rate in boys whereas, a little contradictory, no gender difference is shown concerning adverse outcome in intrauterine growth restriction [109]. Boys are also generally more vulnerable than girls when born prematurely [72]. As the present study shows, some of the neonatal death is mediated by severe preeclampsia and SGA, complications that may cause prematurity. It could be regarded as a weakness in our study that we did not analyze mortality according to gestational week. Prematurity cannot be the only reason though, since increased perinatal mortality has been found in a study investigating only full-term pregnancies in chronically hypertensive women [10].

Since some of the perinatal deaths were mediated by severe preeclampsia and SGA we examined if there was a gender difference in death rates associated with these diagnoses in the total population. On the contrary to chronic hypertension, there was no general gender difference associated with these diagnoses.

The gender difference in mortality, especially prenatally, makes it tempting to speculate that there is a male disadvantage associated with the fact that the fetus is exposed to maternal chronic hypertension in uterus. Chronic hy-
pertension can be an expression of the insulin resistance syndrome, another expression of that syndrome is diabetes, which has been reported to be associated with increased perinatal morbidity in male infants [77]. We can only speculate that there could be reasons in common.

Complications across generations

As we have stated above, chronic hypertension is a strong risk factor for offspring to be born SGA. Concerning future risks we have found, that a girl that has been born SGA suffers an increased risk for severe, but not for mild, preeclampsia when she becomes pregnant. The increased risk for the severe form of preeclampsia is not earlier revealed. In addition, she has an increased risk of gestational diabetes, and of giving birth to an offspring that is small for its gestational age. That supports the results of a few earlier studies [110-112] but is not further investigated in this thesis.

It could be argued, that since a quite common reason for being born SGA is that the mother had preeclampsia during pregnancy [36], the risk for severe preeclampsia in a woman born SGA is not surprising, but merely an expression of heredity for preeclampsia. For that reason, we analyzed if the increased risk for severe preeclampsia, in a woman born SGA, was independent of preeclampsia in the previous generation, and it was.

The increased risk for a woman born SGA, or with low birth weight, to develop preeclampsia is supported by a few earlier studies [64-67]. However, two of the studies focus on pregnancy induced hypertension both with and without proteinuria [64, 66], not purely on preeclampsia, and in none of the studies has preeclampsia been separated into mild and severe forms. Two of the cited studies have adjusted for both maternal preeclampsia and BMI [64, 66], which is important since both are risk factors for preeclampsia [30, 42]. According to the catch-up-growth hypothesis [94], that children born growth restricted who have a quick weight gain or end up overweight, are at increased risk to develop insulin resistance syndrome, and since preeclampsia can be an expression of that syndrome [82], it is important to adjust for adult BMI when the association between SGA and preeclampsia is studied. In our study we have adjusted for that, as well as for smoking and maternal age.

Maternal preeclampsia, i.e. exposition to preeclampsia in uterus, approximately doubled the incidence of both mild and severe preeclampsia in daughters, irrespective of whether they were born SGA or not. This doubled incidence is most commonly supposed to be caused by heredity. But referring to the fetal origins hypothesis, we could speculate that it is caused by metabolic or endocrine changes in the intrauterine milieu in a pregnancy affected by preeclampsia, that makes the daughters more vulnerable to preeclampsia themselves when they get pregnant. Risks of equal magnitude have
been found in other population-based Scandinavian studies [42, 113] and even higher risk was found in a smaller Australian study [43]. Two of the studies suggested a stronger familial association for the severe than for the mild form of the disease [42, 43]. In none of them was the influence of birth weight or adult BMI on the risk for preeclampsia considered, since they were aiming at analyzing heredity patterns. We show, that there is an equally increased risk of mild and severe preeclampsia when there is a positive family history, and a further increased risk of severe, but not of mild disease, when the family history is combined with SGA. Because of this tendency, a positive family history may be more strongly related to severe preeclampsia and to those cases where the maternal preeclampsia has caused growth restriction. According to the Barker hypothesis [89, 114], and to the fetal origins hypothesis [93], we may suspect that women born growth restricted are more susceptible to preeclampsia. We thus expected some effect modification from maternal preeclampsia on the risk for a woman born SGA to develop preeclampsia, but we were unable to prove any significance.

A weakness of this study could be that we only included primiparas, and since primiparity is associated with a higher incidence of preeclampsia [30] the risks could be overestimated when applied to a general population. Also, we have only included women up to the age of 30 years, which precludes generalization to all women, but since the register started in 1973 and we had to include three generations, we could not accomplish more.

Aims for the future

It would be interesting to further investigate the increased risk, in women born small for gestational age, to have a pregnancy complicated by gestational diabetes. Studies should aim at analyzing how that risk is affected by known risk factors for gestational diabetes such as high body mass index, and a family history of diabetes.

Since chronically hypertensive women differ from normotensive women in many demographic variables, and because there are now many studies in the field of using customized birth weight standards instead of population based birth weight standards, it would be interesting to find a way to apply such a standard on this group of women to investigate if we can find a more appropriate way of identifying the babies at risk for morbidity and mortality.

Certainly, there is a demand for more knowledge on how the fetus is affected in uterus if the mother is suffering from the insulin resistance syndrome.
Conclusions

- Chronic hypertension is a strong risk factor for mild and severe preeclampsia, gestational diabetes, abruptio placenta and small for gestational age births.

- Preeclampsia in a woman with chronic hypertension is more often of the severe form compared to preeclampsia in a normotensive woman.

- Whether superimposed preeclampsia in chronically hypertensive women enhances the risk for abruptio placenta is still in doubt.

- Superimposed preeclampsia enhances the risk for offspring of chronically hypertensive mothers to be born small for gestational age.

- A woman who has been born small for gestational age has an increased risk for severe, but not for mild, preeclampsia.

- Preeclampsia in the previous generation does not significantly modify the effect of being born small for gestational age on a woman’s risk for severe preeclampsia.

- Chronic hypertension is a strong risk factor for perinatal death in male, but not in female, offspring.

- The risk for perinatal death in offspring of chronically hypertensive women is independent of the maternal complications preeclampsia, gestational diabetes and abruptio placenta, though it is enhanced by severe preeclampsia and abruptio placenta.

- The risk for perinatal death in offspring of chronically hypertensive women is independent on if the offspring is small for gestational age, though being small for gestational age enhances the risk.
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