Hypertensive disorders in pre-term pregnancy: management and long-term consequences

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Chapter 10

Summary and discussion
Summary

This thesis explores questions concerning hypertensive disorders during pregnancy and covers three main questions; first, what are the long-term health consequences for neonates born after a pregnancy with a compromised uterine environment? Second, what are the rates of recurrence of a hypertensive disorder in subsequent pregnancies? And third, what is the best management strategy, when hypertensive disorders arise in the late pre-term period (between 34 and 37 weeks’ gestation)?

The presentation of the studies in this thesis follows the timeline of the execution of the studies. The basis of this thesis was laid in 2004 - 2005 at the University of Texas Medical Branch, with a “basic science” program on vascular function, exploring the underlying pathophysiological mechanism of the association between an impaired uterine environment and the long-term health consequences for the offspring. On return in the Netherlands, studies were initiated on recurrence rates. In 2008 preparation started for the multicentre trial, HYPITAT-II. After development of the protocol, the case record form, gaining ethical approval and applying for a Grant, this study had its start in 2009.

Part I: Fundamental research

Stimuli or insults to the fetus during the critical period of intrauterine development lead to “fetal programming” and produce adaptive changes in fetal anatomy, physiology, and metabolism that have long-term consequences. For example, being born small for gestational age (a common complication of preeclampsia) is related to cardiovascular disease later in life.1,2 This theory is known as the “fetal origin of adult disease”.

In chapter 2 and 3 mice models with a compromised vascular system and endothelial dysfunction are used to study the pathophysiological mechanism of long-term health consequences after preeclampsia for offspring. These murine models have an impaired utero-placental perfusion and offspring of these animals experience a compromised uterine environment resembling the condition of placental insufficiency that is thought to be essential in early-onset preeclampsia.3 Chapter 2 presents a study using transgenic mice lacking endothelial nitric oxide synthase (eNOS). In vasculature eNOS is the main isofrom responsible for the production of nitric oxide. Nitric oxide is a potent vasodilator. Defects in the nitric oxide pathway have been implicated in various vascular pathologic states that include hypertension and intra-uterine growth restriction.4 Offspring of eNOS-knockout mice are growth restricted and have abnormal vascular function...
later in life, compared with the genetically identical offspring of wild-type mice. This indicates a fetal programming effect of the abnormal uterine environment. To evaluate the role of parity in the modulation of the fetal programming of the fetal growth and vascular responses oligoparous (0-2 previous pregnancies) and multiparous (5-9 previous pregnancies) mice were used. Nitric oxide synthase knockout (−/−KO) female mice were bred with nitric oxide synthase−/−KO and wild type (+/+WT) male mice to produce nitric oxide synthase−/−KO and maternally derived heterozygous (+/−Mat) litters. Nitric oxide synthase knockout and nitric oxide synthase maternally derived litters that were born to oligoparous mothers had significant growth lag compared with corresponding multiparous litters. The optimal diameter of the carotid artery from the offspring (a measure of vascular tensile properties and resistance) was decreased in oligoparous compared with multiparous female offspring. Vasorelaxation was abolished and the contractile response of the carotid artery was increased in oligoparous, but not multiparous, female offspring ($P < .05$). These data support the role of abnormal uterine environment in the fetal programming of postnatal growth and vascular function in later life. Successive pregnancies may lead to maternal uterine adaptations that bypass the lack of a functional nitric oxide synthase, which leads to improvement in postnatal growth and vascular function in the offspring. Given the reported effect of parity on the risk of preeclampsia, similar mechanisms may be operative in human pregnancy.

In chapter 3 transgenic mice are used lacking a functional low-density lipoprotein receptor (LDLR). In the process of arteriosclerosis, lipoprotein particles (especially low-density lipoprotein (LDL)) enter the arterial wall and undergo various modifications, such as oxidation. Oxidation of LDL has been proposed as an important mechanism in the pathogenesis of the arteriosclerotic process. The LDL-receptor (LDLR) is involved in the clearing of lipoproteins from the circulation, and its lack leads to hypercholesterolemia and arteriosclerosis. LDLR−/−KO mice fed a normal diet develop moderate fatty streak lesions and intima thickening with foam cells and smooth muscle cell infiltration. In this chapter the role of maternal hypercholesterolemia in fetal programming of adult vascular function is examined. Homozygous LDLR knockout mice (LDLR−/−KO) and their wild-type controls (LDLR+/+WT) were cross-bred to produce 4 litter groups: LDLR−/−KO, maternally derived heterozygous (LDLR±Mat), paternally derived heterozygous (LDLR±Pat) and LDLR+/+WT offspring. In vitro experiments using the carotid artery of the offspring at adult age showed increased contractile responses in the LDLR−/−KO and LDLR±Mat male offspring compared to the LDLR±Pat and LDLR+/+WT offspring. The contractile responses in female mice were only significantly increased in the LDLR−/−KO offspring. Despite being genomically similar, heterozygous offspring that developed in a hypercholesterolemic maternal environment
(LDLR\(^{±\text{Mat}}\)) had abnormal vascular responses later in life compared with those that developed in a normal environment (LDLR\(^{±\text{Pat}}\)). The maternal environment of hypercholesterolemia and atherosclerosis has long-term health consequence for her offspring.

**Part II: Clinical research**

Chapter 4 summarizes the accuracy of various tests performed to predict the onset of preeclampsia and the effectiveness of preventative treatment. Tests to predict preeclampsia include clinical history, examination findings, laboratory and hemodynamic tests. In general, tests in early pregnancy for predicting later development of preeclampsia have a better specificity than sensitivity, as BMI (Body Mass Index) >34, alpha-fetoprotein, fibronectin and uterine artery Doppler (bilateral notching) all have specificities above 90%. Only uterine artery Doppler resistance index and combinations of indices have a sensitivity of over 60%.\(^7\) None of the tests are sufficiently accurate to recommend routine use in clinical practice. The various treatment options to prevent preeclampsia include pharmacological agents, dietary supplementation and lifestyle modification. Antiplatelet agents, primarily low-dose aspirin reduce the risk of preeclampsia by 10% (RR 0.90, 95% CI 0.84 to 0.97). Calcium only effectively prevents preeclampsia in high risk groups (RR 0.22; 95% CI 0.12 – 0.42) and in the group with low nutritional calcium intake (RR 0.36; 95% CI 0.20 -0.65).\(^8\) Pharmacological agents like low molecular weight heparin, progesterone, nitric oxide donors, anti-hypertensives and diuretics are not effective in preventing preeclampsia. Dietary supplements like magnesium, anti-oxidants, marine oils and folic acid do not reduce the incidence of preeclampsia. There is a paucity of evidence to demonstrate that lifestyle interventions like rest, exercise and reduced dietary salt intake prevent preeclampsia.

Chapter 5, 6 and 7 focus on recurrence rates of a hypertensive disorder during pregnancy after a history of a pre-term delivery due to a hypertensive disorder. The psychosocial impact of a severe hypertensive complication of pregnancy and pre-term delivery is often huge and associated with a high incidence of symptoms of post-traumatic stress disorder, depression and anxiety.\(^9\) The psychosocial condition of the mother after delivery is mainly associated with the gestational age at diagnosis.\(^10\) Evidence on the recurrence risk of hypertensive disorders is important for several reasons. From the patient perspective, the decision for future pregnancies will partly depend on this knowledge. From a medical perspective, such knowledge may influence management during the subsequent pregnancy.
Chapter 5 presents a systematic review on existing cohort studies on recurrence rates of a hypertensive disorder and pre-term delivery after a history of delivery under 34 weeks gestational age due to a hypertensive disorder. We searched Medline, Embase, and the Cochrane Library for articles published until September 2009. Recurrence rates of premature deliveries due to hypertensive disorders were calculated for each study separately. Pooled data were calculated. The search retrieved 36 relevant articles, of which 11 fulfilled the inclusion criteria. These 11 studies reported on 2,377 patients (range 18 to 1,754 patients per study), who had 2,461 deliveries. Most studies were excluded because of missing data on the exact gestational age of delivery in the subsequent pregnancy. The lack of uniform criteria for severe hypertensive disorders is another omission. Of these 11 studies, four were excluded for further calculations as they included a restricted patient population of very early onset of disease (e.g. before 28 weeks’ gestation) implicating a selection bias, leaving seven studies for further calculations. The pooled risk of a delivery before 34 weeks due to recurrence of hypertension, preeclampsia, or HELLP was 7.8% (95% confidence interval 6.7 to 9.0%). In conclusion, there is a more than 90% chance of a delivery after 34 weeks in patients’ subsequent pregnancy. As parents’ anxiety is mainly associated to the gestational age at diagnose, this finding may influence parents’ decision on a future pregnancy in a positive way.

The systematic review showed a lack of good quality cohort studies, as many studies report on a selected non-consecutive series of patients with limited numbers. Consequently, reported recurrence rates range from as high as 65% to the lowest of 5%.11,12

Chapter 6 presents a retrospective cohort study of significant population size, without other selection than by gestational age and hypertension. The primary aim was to determine the absolute risk of recurrence of an adverse outcome, defined as a hypertensive complications resulting in a delivery under 34 weeks’ gestation. Additionally, independent related factors were identified using a multivariate analysis for recurrence of early-onset preeclampsia. All women who developed early-onset preeclampsia (delivery <34 weeks gestation) in their first pregnancy between January 1996 and December 2004 were included, in two perinatal centers with regional function: the Academic Medical Centre Amsterdam (AMC) and the Maxima Medical Centre Veldhoven (MMC). Patients were included consecutively. Information was retrieved on the course of subsequent pregnancies. 380 Patients were identified, of whom 46 were lost to follow-up. 123 Patients refrained from subsequent pregnancy (79 (64%) due to fear of recurrence). Of the 211 patients with a subsequent pregnancy, 36 (17%, 95% CI 12% to 22%) had a recurrent delivery under 34 weeks, 30 (14%, 95% CI 9.5% to 19%) between 34 and 37 weeks and 145 (69%, 95% CI 62% to 75%) above 37 weeks of gestation. Of this last group,
only 67 (32%, 95% CI 25% to 38%) pregnancies were completely uneventful. A high diastolic blood pressure at the index pregnancy and chronic hypertension are related with an adverse outcome in the subsequent pregnancy. Chronic hypertension after the first pregnancy was associated with a 5 fold increased risk of recurrence (odds ratio 5.2, 95% CI 0.72-41). In conclusion, women with early severe preeclampsia in their first pregnancy have a 17% risk of recurrence of a delivery before 34 weeks and having chronic hypertension is an important risk factor for recurrence. Only 32% however had a completely uneventful pregnancy. Although this 32% might seem a low percentage, the question of interest for the patient and the obstetrician is recurrence of early pre-term delivery. Morbidity of the mother and her child is mainly related to this early gestational age (e.g. under 34 weeks). In that point of view a recurrence rate of 17% is most relevant.

In chapter 7 the recurrence risk of hypertensive disease in pregnancy between 34 and 37 weeks’ gestation is assessed, in a retrospective cohort study in six hospitals in the Netherlands. There are no studies published previously on recurrence of late pre-term onset of hypertensive disorders in pregnancy (e.g. between 34 and 37 weeks gestational age). There may be different underlying pathophysiological mechanisms and risk factors for early-onset preeclampsia versus term preeclampsia. Therefore recurrence risks from either early-onset or term preeclampsia may not be extrapolated to the late pre-term gestational age group. Meanwhile this group comprises a significant quantity in the non-academic setting. The primary aim was to determine the absolute risk of recurrence and assess whether cardiovascular risk factors were predictive. 425 Women were identified, of whom 351 could be contacted. In the 189 women with a subsequent pregnancy, 94 women (50%, 95% CI 43% to 57%) had recurrence of a hypertensive disorder in the subsequent pregnancy, of whom 17 women (9.0%, 95% CI 4.9% to 13%) had recurrence of a hypertensive disorder and delivered before 37 weeks of gestation. The subsequent pregnancy was uneventful in 95 women (50%). Chronic hypertension and maternal age were statistical significant predictors for recurrence. In conclusion, women with hypertensive disorders and delivery late pre-term have only a 9% chance of recurrence resulting in delivery before 37 weeks. While this percentage is relatively low, the overall recurrence rate of hypertensive disorders irrespective of gestational age in the subsequent pregnancy was 51%.

A summary of the results of chapter 6, 7 and 8 is presented in table 1.
Chapter 8 and 9 focuses on questions regarding management of hypertensive disorders in the late pre-term period. Until now, only a few studies have focused on the management of women with hypertensive disorders between 34+0 and 36+6 weeks of gestational age. The NICE guideline “hypertensive disorders during pregnancy” refers in the 2010 consensus statement to the issue of mild or moderate preeclampsia between 34 and 36 weeks of gestation in terms of a “grey zone” at which the optimal timing of birth is not clear. Although the HYPITAT trial showed that in women with mild GH or PE above a gestational age of 37 weeks induction of labour is preferable, there remains uncertainty on the best policy in the late pre-term period (34-37 weeks). The situation in these patients is different from term age because, apart from maternal morbidity, the potential neonatal consequences for premature delivery are also in the equation.

To improve the understanding on the neonatal outcome of this specific population, and its causative factors, data on neonatal morbidity in infants born from mothers with a hypertensive disorder between 34 and 37 weeks’ gestation were analysed in chapter 8. Data were obtained from the Netherlands Perinatal Registry (PRN-registry) between January 2000 and December 2006. All women who delivered between 34+0 – 36+6 weeks of gestation with gestational hypertension (n=4316), preeclampsia (n=1864) and normotensive controls (n=20749) were included. Compared to the control group, the risk of induction of labour and primary cesarean section in the PE group was strongly increased odds ratio (OR) 16 (95% CI 15 to 18) and 7.4 (95% CI 6.6 to 8.2) respectively. Children from PE mothers were more often small for gestational age (27%) than in the GH group (18%; OR 1.7, 95% CI 1.5 to 1.9) and the control group (5.3%, OR of 6.7, 95% CI 5.9 to 7.5). More children in the PE group were admitted to the high care or NICU compared to the GH and control group; OR 1.6 (95% CI 1.4 to 1.9) and OR 2.0 (95% CI 1.8 to 2.2) respectively. In the multivariable logistic regression analysis a

<table>
<thead>
<tr>
<th>Study design (chapter thesis)</th>
<th>Delivery index pregnancy (weeks)</th>
<th>Patients included (N)</th>
<th>Recurrence rates of a hypertensive disorder in the subsequent pregnancy*</th>
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</thead>
<tbody>
<tr>
<td></td>
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<td>Delivery &lt; 34 weeks</td>
</tr>
<tr>
<td>Systematic review (chapter 5)</td>
<td>&lt; 34</td>
<td>2188</td>
<td>7.8% (6.7 – 9.0)</td>
</tr>
<tr>
<td>Cohort study (chapter 6)</td>
<td>&lt; 34</td>
<td>211</td>
<td>17% (12 – 22)</td>
</tr>
<tr>
<td>Cohort study (chapter 7)</td>
<td>34 – 37</td>
<td>189</td>
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*Data are expressed as % (95% confidence intervals)
cesarean delivery and decreasing gestational age were independent risk factors for neonatal respiratory morbidity. Gestational hypertension or preeclampsia reduced the risk for respiratory distress syndrome compared to the control group (odds ratios of 0.81 (95% CI 0.64 – 1.0) and 0.69 (95% CI 0.49 – 0.96), respectively). In conclusion, neonatal morbidity in babies born from mothers with hypertensive disorders is still considerable in the late pre-term period, which is predominantly driven by gestational age and mode of delivery. Very interestingly, in our study the presence of a hypertensive disorder per se seems to protect for neonatal respiratory morbidity. However this protective effect is diminished by the higher cesarean rate in this group thus resulting in higher incidences of respiratory morbidity in hypertensive disorders.

As mode of delivery seems to be an important influencing factor on the neonatal outcome, one could speculate that in case of a hypertensive disorder of the mother in the late pre-term period, induction of labour is preferable before deterioration of the maternal condition occurs and a primary cesarean section is the only solution for fast improvement of the maternal condition. Choosing the right moment for delivery though, remains a difficult task for the obstetrician as with increasing gestational age the neonatal morbidity might decrease. In this perspective, the superior strategy is a randomised controlled trial comparing induction of labour to temporizing management.

**Chapter 9** provides a detailed description of the study protocol of the currently running HYPITAT-II study (Hypertension and Preeclampsia Intervention Trial in the Almost Term patients): a multicentre randomised controlled trial. The aim of this study is to investigate whether planned induction of labour compared to temporizing management in women with gestational hypertension, mild pre-eclampsia or deteriorating chronic hypertension at gestational age of 34 – 37 weeks of pregnancy, reduces maternal morbidity and / or increases neonatal morbidity. Women are randomly allocated to either delivery within 24 hours (experimental arm) or temporizing management (control arm) until 37 weeks of gestational age. The primary outcome measure is a composite endpoint of maternal mortality, maternal complications (eclampsia, HELLP syndrome, pulmonary oedema, thromboembolic disease) and progression to severe pre-eclampsia. The neonatal primary outcome is respiratory distress syndrome (RDS). Data will be analysed on an intention-to-treat basis. We aim to recruit 680 patients to show a reduction of maternal complications from 5% to 1%. The trial started recruitment in May 2009 within the structure of the Dutch consortium for studies in Obstetrics, Fertility & Gynaecology (URL: http://www.studies-obsgyn.nl/hypitat2). 49 Hospitals in the Netherlands participate in the study indicating the experienced national sense of urgency for such a trial. The expected end date of recruitment will be December 2012.
Clinical implications

In this thesis absolute recurrence rates of hypertensive disorder in pregnancy after a pre-term delivery due to a hypertensive disorder were calculated. Existing information about recurrence was until recently fragmentary and outdated, with the most quoted study of Sibai et al, dating from 1991.\textsuperscript{11} These data will help the obstetrician in counselling patients in considering a new pregnancy and adjust management to it in a subsequent pregnancy. The recurrence rates of a pre-term delivery were lower than expected. In women with a history of an \textit{early-onset hypertensive} disorder, 17\% had a recurrence of a delivery before 34 weeks due to a hypertensive disorder. In women with a history of a \textit{late pre-term delivery} (e.g. between 34 and 37 weeks’ gestation), 9\% had a recurrence of delivery before 37 weeks due to a hypertensive disorder. However the rate of a completely uncomplicated subsequent pregnancy was relatively low for both the early-onset group as for the late pre-term group, indicating these groups as high-risk patients (table 1). Prediction modelling indicated chronic hypertension as the strongest independent risk factor for recurrence.

This thesis also deals with management of hypertensive disorders in the late pre-term period. The neonatal morbidity is still considerable in this period. Decreasing gestational age and primary cesarean rate are independent risk factors for neonatal respiratory morbidity. Hypertensive disorders per se seem to protect for neonatal respiratory morbidity. Induction of labour may prevent maternal deterioration and a primary cesarean section, however the exact moment of induction is still debated as increasing gestational age might reduce neonatal morbidity. The HYPITAT-II study will bring the evidence concerning this management dilemma.

The implementation of the HYPITAT-II study might influence obstetric management regarding hypertensive disorders in the late pre-term period (e.g. between 34 and 37 gestational age). The HYPITAT-I study already had its influences during the trial. The number of cases of eclampsia reduced more strongly in the centres that participated in the trial.\textsuperscript{14} Moreover, after the trial the interventionist approach was implemented in the Netherlands.\textsuperscript{15} Results of this study are adapted shortly after publication in national and international guidelines. In continuation of this study the HYPITAT-II study may result in a shift from a temporizing management approach to an interventionist approach in the late pre-term period. Over ten years we might look back at “ten years after the HYPITAT-II trial” and hopefully conclude that although the induction of labour rate in this period has increased, the number of cesarean section have not, the maternal morbidity and mortality due to hypertensive disorders in the late pre-term period are reduced and neonatal morbidity did not change.
Future research

Regarding the clinical implications stated above on management of hypertensive disorders in the late pre-term period, the results of the HYPITAT-II trial will provide more insight into the best management strategy for this specific population. Results of this study will be translated into national and international guidelines. Only few follow-up studies have been performed after obstetric intervention trials, leaving long-term consequences for this specific group still unknown. With evidence available (chapter 8) for short-term neonatal morbidity after a delivery in the late pre-term period due to a hypertensive disorder, we also plan **long-term neonatal follow-up** at 2 year and 5 year old infants. The main short-term morbidities in the late pre-term period are hypoglycemia, hyperbilirubinemia and respiratory distress syndrome. All of these morbidities have the potential to cause long-term neurodevelopmental sequelae.16-18 The results of this follow-up study will influence the interpretation of the results of the HYPITAT-II trial. Since the last two decades, abundant evidence is appearing of the long-term health consequences of adverse pregnancy outcome. Pregnancy events like hypertension in pregnancy, pre-term birth, stillbirth, fetal growth restriction and gestational diabetes are associated with long-term maternal morbidity.19-22 The child itself, born from the hypertensive pregnancy, might also be at increased risk for long-term health consequences in the light of the Barker hypothesis (chapter 2 and 3). Pregnancy represents a unique opportunity to identify women and children who may be at increased risk of chronic diseases later in life. A huge field for **preventive medicine** rises up. Most of this evidence is based on retrospective case control studies. To provide more insight into an individuals’ vascular risk profile following a pregnancy complicated by a hypertensive disorder in the late pre-term period a maternal follow-up study is planned: **HyRAS-II** (Hyptiat Risk Assessment Study-II). The aim of this study is to screen women from the HYPITAT-II trial on risk factors for cardio-vascular disease, two years after their complicated pregnancy and to estimate the 10-year cardiovascular event risk in these women using validated prediction algorithms, in order to establish the proportion that is likely to benefit from preventive interventions, according to widely accepted guidelines. Another implication of **prediction models** based on individual patient data is planned on recurrence rates, so more individual tailored prediction models can be developed. Preconception care and counseling might become the most important therapeutic tool the obstetrician holds in his or her hand. A healthy mother will provide a healthy environment for herself, her child and maybe even for her grandchild.