Hypertensive disorders in pre-term pregnancy: management and long-term consequences
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General introduction and outline of the thesis
Hypertensive disorders of pregnancy, including gestational hypertension (GH) and preeclampsia (PE) complicate 10% of all pregnancies and remain one of the leading causes of maternal mortality and morbidity, both internationally as well as in The Netherlands. The clinical expression of the disease ranges from mild gestational hypertension or preeclampsia at term to severe conditions in the pre-term period. The maternal syndrome of PE is associated with severe complications (especially at early gestational ages) including eclampsia or other encephalopathies, placental abruption, stroke, pulmonary oedema, liver rupture and renal insufficiency. The fetal or neonatal consequences include intra-uterine growth restriction, stillbirth and severe morbidity related to pre-term birth. Consequently, neonatal morbidity is strongly associated with the gestational age at onset of preeclampsia, as well as the severity of the maternal syndrome and related preterm delivery.

Timing of delivery in hypertensive disorders in pregnancy

The only causal treatment of hypertensive disorders in pregnancy is delivery of the placenta and inevitably delivery of the child. Signs and symptoms of GH or PE will subside within a few days after delivery. In the pre-term period however this results in a premature born child with related severe morbidities. The dilemma of maternal morbidity versus neonatal morbidity in the pre-term period has resulted in two management approaches: the interventionist approach of stabilizing and delivery, versus a more temporizing approach. The interventionist approach is assumed to reduce the maternal risk of deterioration and the related maternal complications and the antenatal fetal risk of stillbirth. On the other hand temporizing management results in increased gestational age and therefore in reduction of neonatal morbidity and mortality. Throughout gestational ages, different levels of evidence are available concerning the best management.

Between 24 and 34 weeks gestational age there is a general consensus that temporizing management is justified if no severe maternal morbidity is present or anticipated and fetal condition is estimated to be satisfactory. Prolongation of pregnancy can be achieved without irreversible maternal morbidity and with improved neonatal outcome provided there is intensive monitoring of maternal and fetal well-being by experienced staff in a high-risk pregnancy care setting. This conclusion is based on several cohort studies and two randomized controlled trials. The difficulty of the cohort studies is the variability of inclusion criteria used per study and the different diagnostic criteria used. The two trials were
underpowered to determine safety for temporizing care. Although temporizing management seems to be permitted at early gestational ages, the exact criteria for and moment of delivery is still an area of research.

After 37 weeks perinatal outcome overall is known to be good and severe maternal morbidity is therefore not acceptable.\textsuperscript{15,16} Timing of delivery of mild GH and PE has recently been investigated in the HYPITAT trial.\textsuperscript{17} This randomized controlled trial comparing interventionist care versus temporizing care between 36\textsuperscript{+0} and 41\textsuperscript{+0} weeks gestational age, showed less severe hypertensive episodes in the interventionist approach (31\% versus 44\%, relative risk (RR) 0.71, 95\% confidence interval (CI) 0.59 to 0.86). The number of patients randomised between 36 and 37 weeks was too low to draw definite conclusions. Importantly, induction of labour in the interventionist group showed a trend to a lower cesarean section rate (RR 0.75, 95\% CI 0.55 to 1.0). Perinatal outcome was not different between groups and there was a reduction in costs and better maternal quality of life.\textsuperscript{18,19} Between 34 and 37 weeks of gestational age there remains uncertainty on the best policy (temporizing versus interventionist management) as evidence for this specific group is missing. With lack of good clinical evidence on the subject and the resulting practice variation, we focus specifically on this group in this thesis.

**Long term consequences**

A pregnancy complicated by a hypertensive disorder is a window to assess future expected health for this mother and her child. The long term health problems are related to general health conditions and psychological consequences.

General maternal health issues after a pregnancy complicated by a hypertensive disorder have been an intensively researched area in the past decade. There is abundant evidence for increased risk of cardiovascular and metabolic diseases and related death after a history of a hypertensive complication during pregnancy.\textsuperscript{20-22} Pregnancy is seen as a “stress-test” for the vascular system of the mother and having preeclampsia is an expression of a failed stress-test. Not only the future health of the mother is at state, but also the fetus may experience long-term consequences, in line with the Barker hypothesis (fetal origin of adult disease).\textsuperscript{23} Offspring from women who experienced a hypertensive disorder during their pregnancy, are at increased risk of stroke later in life.\textsuperscript{24} Additionally preeclampsia is associated with being small for gestational age (SGA) as a result of a compromised utero-placental perfusion. Being small for gestational age is related to cardiovascular disease later in life.\textsuperscript{25,26} We speculated that this SGA fetus might already have a compromised vascular system and in consequence it might have a higher risk for developing preeclampsia later in life in case of a
female fetus. With vascular reactivity studies we aimed to unravel some of the pathophysiological mechanism of preeclampsia and its long-term consequences. Apart from the general health consequences, the psychosocial impact of a pre-term delivery due to a hypertensive disorder is often huge and associated with high incidences of symptoms of post traumatic stress disorder and depression. The decision for future pregnancies largely depends on the information from the obstetrician on the estimated risk of recurrence of a pre-term delivery and the related severe maternal morbidity and serious neonatal morbidity. From a medical point of view, such counselling may influence management during the subsequent pregnancy. Information about recurrence is fragmentary and outdated, with recurrence rates ranging from as high as 65% to as low as 5%. This variation is likely because of population selection differences and small numbers. Well numbered cohort studies that consecutively included their patients are missing, as well as individual risk prediction models. In the second part of this thesis we answered questions concerning recurrence rates and prediction of hypertensive disorders in the next pregnancy.

**Outline of this thesis**

The aim of this thesis was to address specific questions concerning long term consequences, recurrence rates and management of hypertensive disorders during pregnancy in the pre-term period. **Part I – fundamental research** – describes vascular reactivity studies in offspring using mice models with a compromised vascular system in view of the “fetal origin of adult disease” hypothesis. **Part II – clinical research** – focuses on recurrence rates, prediction and management of hypertensive disorders in the pre-term period. **Part III contains the – summary and general discussion** – describing the general considerations and focuses on future research questions.

**Part I  Fundamental research**

**Chapter 2** explores the underlying pathophysiological mechanism of the impact of a compromised uterine environment on growth and vascular function of offspring and the adaptive mechanisms from successive pregnancies compared to first pregnancies.

**Chapter 3** explores the underlying pathophysiological mechanism of the long-term vascular consequences on offspring who developed in a compromised uterine environment.
Part II  Clinical research

Chapter 4 is an overview of existing literature on prediction and prevention of preeclampsia.

Chapter 5 is a systematic review of published evidence on recurrence risk of a delivery before 34 weeks of pregnancy due to a severe hypertensive disorder.

Chapter 6 is a report of a study on the recurrence risk of a delivery below 34 weeks due to a hypertensive disorder, after a history of an early onset hypertensive disorder and identifies parameters that predict adverse outcome.

Chapter 7 is a report of a study on the recurrence risk of a hypertensive disorders after a history of a delivery between 34 and 37 weeks of gestation due to a hypertensive disorder and identifies parameters that predict adverse outcome.

Chapter 8 explores the neonatal morbidity of children born between 34 and 37 weeks of gestation from pregnancies complicated by a hypertensive disorder.

Chapter 9 describes the study protocol of a Dutch multicentre randomized controlled trial assessing the (cost-) effectiveness of induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia between 34 and 37 weeks’ gestation (HYPITAT-II trial).

Part III  Summary and general discussion

Chapter 10 is a summary and general discussion of the previous chapters, and describes implications for future research.
References


