Counseling women with hypertensive disorders of pregnancy
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Introduction

Hypertensive disorders of pregnancy (HDP) are a common health problem and occur in approximately 2 to 8 per cent of all pregnancies. They comprise gestational hypertension (GH), preeclampsia (PE), superimposed PE and HELLP (Hemolysis, Elevated Liver enzymes and Low Platelets) syndrome, and in a varying percentage of cases they are related to intrauterine growth restriction.

The exact etiology remains unknown and there is important heterogeneity in clinical phenotypes and probably essential heterogeneity in related pathophysiology. There appears to be significant overlap but also some differences in underlying risk factors and processes between early-onset and late-onset preeclampsia (before and after 34 weeks). Whereas maternal endothelial dysfunction has been indicated as a central phenomenon, associated poor early placentation and maternal vascular dysfunction seems to be more involved in early preeclampsia (‘placental PE’), whereas the metabolic syndrome (a group of cardiovascular risk factors as: obesity, elevated blood pressure, elevated fasting plasma glucose and hypercholesterolemia) seems to be more associated with late preeclampsia (‘maternal PE’).

We have little information on management options for HDP in the extreme premature period. HDP also have a risk for recurrence in subsequent pregnancies. Unfortunately, consistent information on recurrence risks is lacking. Furthermore, HDP identify women at increased risk for cardiovascular disease later in life, probably due to shared risk factors and pathophysiology. Nevertheless, the pathophysiological background of these associations and the phenotypes of the cardiovascular disorders involved remain largely unclear.

In clinical practice is it of utmost importance to be able to counsel women and their partners on these matters. Besides the medical sequelae, HDP can have a major psychological impact on women and their families. Therefore there is great need for new information on management options during pregnancy, recurrence rates and long term health risks.

Management of extreme early onset hypertensive disorders of pregnancy

The options for management of hypertensive disorders of pregnancy remain limited and involve symptomatic treatment and termination of pregnancy. Conflicting interests between mother and fetus raise a dilemma in clinical decision making, especially in...
extreme early onset of the disease (before 24 weeks gestational age). Prolongation of pregnancy may improve fetal prognosis on the one hand, but increases maternal risks of severe morbidity and mortality on the other hand. It is largely unknown what management options are currently being offered to our patients in the Netherlands and what related risks are present for the mother and child.

Recurrence and recurrence prediction of hypertensive disorders in subsequent pregnancies
Recurrence of hypertensive disorders of pregnancy has been the focus of investigation in other studies as well. Many cohorts have been established, each with a specific case mix of different clinical phenotypes and each with different study methodologies, containing many potential sources of bias. This hampers interpretation of these studies. Reported recurrence rates range from a few percent, up to 65%. Similarly, heterogeneous pathophysiology and study methodology causes the performance of individualized risk prediction models to be disappointing.

New to prognostic research is Individual Participant Data (IPD) meta-analysis. In contrast to conventional meta-analysis it uses the IPD of the original studies. Next to enlarging the study population and increasing statistical power to detect subtle relationships, it permits data synthesis at an individual level, creating flexibility in choosing outcome and subgroups. Additionally, it allows redefinition of outcomes or predictors based on continuous variables and use of information that did not reach publication in the original research. These qualities make IPD meta-analysis the ideal instrument to address the inconsistent reporting of recurrence rates of HDP in literature.

Long term Health risks
Recently it has become apparent that there is a strong association between HDP and long-term maternal morbidity. As such, a pregnancy complicated by a HDP can be regarded as a window of opportunity to assess future expected health. Long term morbidity include coronary heart disease, stroke and kidney failure. These associations are likely an expression of shared underlying pathophysiology, such as the classic cardiovascular risk factors. But it may also be that HDP themselves cause persistent subclinical vascular damage after pregnancy, independently leading to later vascular disease.
Aims of the thesis

The aims of this thesis were to address several counseling issues: to describe management options in extreme early onset HDP in current clinical practice in the Netherlands, to predict recurrence of hypertensive disorders of pregnancy and to study to long term maternal health consequences after a pregnancy complicated by HDP.

The issues are addressed in the following questions:

1. What are differences in maternal and neonatal outcome after immediate delivery or expectant management for preeclampsia in extreme early onset of the disease?
2. What is the incidence of termination of pregnancy in the Netherlands for hypertensive disorders of pregnancy and which characteristics contributed to the decision to terminate after counseling?
3. What is the recurrence risk of a hypertensive disorder of pregnancy, after a hypertensive disorder of pregnancy and a delivery in the near term period?
4. What is the recurrence risk of a hypertensive disorder of pregnancy, after a hypertensive disorder of pregnancy and a delivery in the term period?
5. What is the overall recurrence risk for hypertensive disorders of pregnancy?
6. What is the performance of individual prognostic models for the recurrence of hypertensive disorders of pregnancy?
7. Are hypertensive disorders of pregnancy directly related to cardiovascular disease, stroke or hypertensive kidney disease?

Outline of the thesis

Part I Management of extreme early onset hypertensive disorders of pregnancy

In Part I—Management of extreme early onset hypertensive disorders of pregnancy—two cohort studies are described that focus on the dilemma of management of HDP at an extreme premature gestational age.

Chapter 1 answers the first question. In a nationwide cohort study we investigate the maternal and neonatal outcomes of management of hypertensive disorders of pregnancy at extreme early onset in pregnancy in the Netherlands. It addresses the dilemma between maternal and neonatal interests in management options. Also,
trends in management and outcome over the years and recurrence of preeclampsia in a subsequent pregnancy are investigated.

Chapter 2 answers the second question. In a nationwide cohort study we investigate the frequency of termination of pregnancy for hypertensive disorders prior to fetal viability in the Netherlands and the clinical characteristics involved in the decision to terminate the pregnancy.

Part II Recurrence and recurrence prediction of hypertensive disorders in subsequent pregnancies

In Part II – Recurrence and recurrence prediction of hypertensive disorders in subsequent pregnancies two cohort studies performed in the Netherlands are described, that focus on recurrence and prediction of HDP in the near-term or term gestational age period. Furthermore, an IPD project is described, based on a pooled database using original data from previous research from all over the world. It focuses again on recurrence and prediction of HDP, but this time at a much larger scale.

Chapter 3 answers the third question. In a multicenter cohort study, performed in the Netherlands, we investigated the recurrence and prediction of recurrence of hypertensive disorders of pregnancy after a history of a delivery between 34 and 37 weeks of gestation, due to a HDP. We also created a prediction model for recurrence using demographic and pregnancy characteristics.

Chapter 4 answers the fourth question. In a multicenter cohort study, performed in the Netherlands, we investigated the recurrence and prediction of recurrence of hypertensive disorders of pregnancy after a history of a delivery after 37 weeks of gestation, complicated with a HDP. We also created a prediction model for recurrence using demographic and pregnancy characteristics.

Chapter 5 answers the fifth question. In an Individual Patient Data Meta-analysis (IPD PREPARE), using data of 22 studies and 99,415 women, we studied the recurrence of hypertensive disorders of pregnancy. We also investigated recurrence for different gestational age groups and different hypertensive syndromes.

Chapter 6 answers the sixth question. In an Individual Patient Database (IPD PREPARE), was used to validate 4 existing prognostic models for recurrence of hypertensive disorders of pregnancy.
Part III Long-term health risks
In Part III—Long-term health risks—a cohort study is described that concentrates on long
term health consequences after experiencing HDP.

Chapter 7 answers the seventh question. In a cohort study we investigate the
occurrence of previous hypertensive disorders of pregnancy in women who subsequently
experienced a stroke, coronary disease or renal failure at relative young age. It explores
possible common risk factors but also investigates HDP as an independent risk factor
for later vascular disease.
Introduction, aims and outline of the Thesis

References