INTRODUCTION: OUTLINE AND SCOPE OF THE THESIS
**GENERAL INTRODUCTION AND OUTLINE OF THE THESIS:**

_Hypertensive disorders in pregnancy_ are one of the leading causes of maternal and neonatal morbidity and mortality worldwide. In the Netherlands, these disorders were the major cause of maternal morbidity and mortality with a Maternal Mortality Ratio (MMR, maternal mortality per 100,000 live-born children) of 3.5 in the period 1993-2005. This relatively high rate has decreased to 1.4 in the period 2006-2010. Since the underlying etiology of hypertensive disease in pregnancy is still unclear and no preventive or therapeutic interventions are available, the only causal treatment is delivery of the foetus and especially the placenta. Substandard care, for instance insufficient diagnostic testing, inadequate management of hypertension by obstetricians or inadequate stabilization of the patient before referring to tertiary care centres has been shown to contribute to maternal morbidity and mortality associated with hypertensive disease in pregnancy in the Netherlands. In addition, the conservative approach towards the management of this condition could also be a possible explanation. This led to critical evaluation of the management of hypertensive disease in the Netherlands, culminating in the HYPITAT (HYpertension and Pre-eclampsia Intervention Trial At Term) trial.

The HYPITAT trial was a nationwide multicenter randomized controlled, open label trial, performed in the Netherlands between October 2005 and March 2008. The study compared induction of labour with expectant monitoring in pregnant women with hypertensive disease at term. At that time, considerations were that induction of labour might increase the risk of assisted vaginal delivery and caesarean section, thereby generating morbidity and costs that would counteract the maternal morbidity avoided by preventing further progression of the hypertensive disorder. On the other hand, expectant monitoring might lead to severe pregnancy complications related to hypertension such as HELLP syndrome, pulmonary edema, eclampsia and/or adverse neonatal outcome originating from poor maternal condition. In short, the study included patients with a singleton pregnancy with a child in cephalic position and a gestational age between 36+0 and 41+0 weeks whose pregnancy was complicated by gestational hypertension (GH) or mild preeclampsia (PE). GH was defined as diastolic blood pressure (BP) ≥95 mmHg measured on two occasions at least six hours apart. Mild PE was defined as diastolic BP ≥90 mmHg measured on two occasions at least six hours apart combined with proteinuria. Proteinuria was defined by local protocol as ≥2+ protein on dipstick, >300 mg total protein in a 24 hour urine collection or protein/creatinine ratio ≥30 mg/mmol. Exclusion criteria included presence of severe GH or PE (defined as diastolic BP ≥110 mmHg and/or systolic BP ≥170 mmHg), proteinuria ≥5 gram in 24 hours, pre-existing hypertension treated with anti-hypertensive drugs, hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome, use of intravenous anti-hypertensive medication or a history of caesarean section. Patients who had given informed consent were randomly allocated to either induction of labour or expectant monitoring. Patients who did not give consent for randomization, but who provided consent for the use of their medical data, were treated according to local protocol. Patients in the expectant management group were monitored...
until the onset of spontaneous delivery or until there was a medical indication for delivery. Monitoring consisted of frequent maternal BP measurements, assessments of proteinuria, laboratory tests and regular assessment of foetal condition. The HYPITAT trial showed that induction of labour reduces the risk of clinical deterioration to severe disease compared to expectant monitoring in women with GH or mild PE at term. This reduction occurs without increasing the caesarean section rate and with similar neonatal outcome.

PREDICTION OF SEVERE MATERNAL AND NEONATAL MORBIDITY IN GESTATIONAL HYPERTENSION OR MILD PRE-ECLAMPSIA AT TERM.

The results of the HYPITAT trial concern an overall recommendation for the best treatment option, i.e. induction of labour in pregnancies with hypertensive disorders after 37 weeks of gestation. However, it is questionable whether induction of labour is the best treatment option in all patients with GH or mild PE at term. Ideally, medical care should be based on the individual patient's risk of having or developing a certain health condition. This risk identification can guide clinicians to more intensive monitoring or intervention specifically in patients who will benefit from it. Conversely, individual risk assessment would allow them to avoid unnecessary interventions in low-risk groups. Risk factors for GH or PE can be based on clinical characteristics (maternal age, ethnicity, parity, body mass index, diastolic BP, systolic BP, proteinuria, vaginal examination) or laboratory findings (Hb, Ht, platelets, uric acid, creatinine, LDH, AST, ALT and proteinuria). Since each factor can add prognostic information to the other(s), combining multiple factors into a clinical prediction model would allow the identification of women who are at high or low risk for a certain condition. The ultimate goal is to formulate more specific recommendations for the individual patient to improve quality of care and subsequently limit maternal and neonatal morbidity and mortality.

CLINICAL PREDICTION MODELS

There is an increasing interest in prediction models in clinical research. Clinical prediction models can provide an estimate of an individual's risk of the outcome in question. The predicted risk can be expressed on a scale from 0 to 100%, categorized e.g. as high, intermediate or low, or dichotomized to support clinical decision making. Developing a clinical prediction model consists of a number of steps, i.e. development, internal- and external validation and analysis of its clinical impact. The final two steps are not included in this thesis.

To date, there is not yet a widely agreed approach to developing a clinical prediction model. Preparations among others include: evaluation of the quality of the data, selection of possible predictors, deciding what to do with missing values, determining a strategy for selecting variables for the final model, evaluation of the interaction between variables and selection of measures of model performance or predictive accuracy as well as overfitting. We developed clinical prediction models
for various maternal and neonatal outcomes up to the stage of internal validation, according to best practice and expert opinion at the time the work was carried out. Over the last decade, continued interest in prediction models has resulted in development of knowledge and methodology, culminating in a recent guideline, the TRIPOD statement (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis).^{15}

In the field of obstetrics and gynecology, prediction models are also gaining interest. One could say it already started with the Apgar score for prediction of neonatal outcome in 1952. A prediction model also well integrated in clinical practice of fertility treatment is the model of Hunault. They validated 3 models developed in the 1990’s and integrated them in a new model, containing maternal age, subfertility period and primary or secondary infertility, semen motility, referral status and post-coital test.^{16} Grobman et al. developed and afterwards validated a prediction model for a vaginal delivery after a caesarean section; this is to date not yet incorporated in clinical practice.^{17,18} A prediction model already evaluated in hypertensive disease in pregnancy is the full PIERs model, in which they identified women at increased risk of adverse outcomes up to 7 days before complications arise in women with hypertensive disease during pregnancy. The model was developed to modify patient care, possibly improve the design of clinical trials, and inform biomedical investigations related to pre-eclampsia.^{19}

AIM OF THE THESIS

The aim of the research described in this thesis was to contribute towards more specific management for the individual patient to improve quality of care and subsequently limit unnecessary interventions.

To achieve this we focus on risk indicators, clinical prediction models and test accuracy for identification of the individual woman with GH or mild PE at term with increased risk of developing maternal or neonatal morbidity. In the first part of this thesis, we developed prediction models for different outcomes (progression to severe disease, postpartum hemorrhage, neonatal outcome and caesarean section) using clinical characteristics and laboratory findings. In the second part of this thesis, we evaluated the influence of cervix favorability and blood pressure patterns on the outcome of pregnancy. We also looked at the impact of the HYPITAT trial on management of these women in the Netherlands.

OUTLINE OF THE THESIS

Chapter 1 contains the aim and outline of the thesis.

Part 1: In Chapter 2, we describe a cohort study in which parameters obtained before labour are identified to predict progression to severe disease in women with a
singleton pregnancy complicated with GH or mild PE beyond 36 weeks’ gestation. Women with hypertensive disorders during pregnancy are at increased risk of developing postpartum hemorrhage. So, in Chapter 3 data from the HYPITAT cohort are used to identify parameters obtained before and during labour that can be used to predict postpartum hemorrhage (defined as blood loss > 1000 ml within 24h after delivery). Chapter 4 describes a cohort study in which parameters obtained before and during labour are identified to predict neonatal outcome in women with a singleton pregnancy complicated with GH or mild PE beyond 36 weeks’ gestation. Since this can also be an important motive to induce or manage expectantly. Chapter 5 describes a cohort study in which parameters obtained before and during labour are identified to predict caesarean section in women with a singleton pregnancy complicated with GH or mild PE beyond 36 weeks’ gestation.

Part 2: In Chapter 6 we evaluate whether cervical favorability plays a role in the decision for labour induction in women participating in the HYPITAT trial. Chapter 7 describes the course of blood pressure over time in women with GH of PE at term based on data collected in the HYPITAT cohort. In Chapter 8 we evaluate the impact of the HYPITAT trial on clinical management of GH and PE at term in the Netherlands. We wondered whether participation of hospitals in the HYPITAT trial had an impact on the implementation of its results and subsequent consequences for maternal health. Chapter 9 contains the general discussion and future perspectives. This chapter shortly describes the results of this thesis, what this means for clinical practice and the individual patient, and what will hopefully follow in the future. Finally, Chapter 10 contains a summary in English and in Dutch.

REFERENCES

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