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

There are several issues that can be discussed and recommendations to be made for clinical practice and future research.

Management of extreme early onset hypertensive disorders of pregnancy

Severe early onset preeclampsia is a rare pregnancy disorder with high maternal and neonatal mortality and morbidity. Delivery of the fetus remains the mainstay of management and is the only known cure. However, in very early onset of the hypertensive disorder, this causes challenges in clinical management, because maternal and fetal risks and benefits conflict. Prolongation of pregnancy during expectant management may improve fetal prognosis on one hand, but it also prolongs exposure to maternal risk of severe morbidity and mortality on the other. Women need to be made aware of these risks and chances.

Very high risks for maternal complications (43-65%) and perinatal death (43-82%) are reported. Sibai and Ganzevoort reviewed the different types of management in literature. They concluded that before 24 weeks of gestation, because of the absence of perinatal benefits and high maternal complication rate, an expectant management approach should not be offered routinely. But in practice, women are being expectantly managed, despite apparent international consensus.

Improved neonatal care and survival rate resulted in a new Dutch guideline regarding active neonatal resuscitation in spontaneously born premature neonates at a gestational age beyond 24 completed weeks in September 2010. Before, active neonatal resuscitation was not performed before 25 weeks of gestation, unless an active resuscitation seemed justified. If active neonatal support seems within reach at an earlier gestational age, expectant management of severe early onset of preeclampsia close to the gestational age threshold may seem defendable. This improved neonatal survival in the extreme premature period calls for more information on management options and maternal and neonatal outcomes at the threshold of viability.

Literature on management strategies is scarce. To our knowledge, only one study describes the frequency of expectant management. They included 74 women, in whom 35 (47%) an expectant management was offered. Expectant management was associated with lower incidence of neonatal and maternal complications, compared
to immediate delivery. However, they included pregnancies with preeclampsia at a later gestational age: 24 to 34 weeks, which makes it less comparable to the results of our cohort. In our study, the majority (74%) of women with preeclampsia between 22 and 26 weeks of gestation are initially managed expectantly, despite the consensus in literature to terminate these pregnancies for maternal indications.

Our cohort study endorses the consensus in literature not to prolong pregnancies complicated with severe preeclampsia, presenting before 24 weeks gestation. In our cohort, maternal complications occurred frequently (70%), but we found no differences in the occurrence of maternal complications between the management groups. In expectant management prolongation was only 4 days longer (6 versus 2 days since admittance) than in immediate delivery. Still it was less often associated with perinatal death, which seems logical, as active neonatal support was offered less often. But in 56 women (57%) that were managed expectantly, the criteria for active neonatal support were never met. And at a gestational age before 24 weeks at presentation, the benefit for neonatal survival in expectantly managed women was absent.

It would be interesting to know which pregnancies have a chance of neonatal survival, before initiating an expectant management. Looking at differences between pregnancies with and without neonatal survival, we may have identified predictors for positive outcome: higher gestational age, higher estimated fetal weight and absence of Doppler flow abnormalities. However unsurprising these findings may seem, they could offer guidance in counseling of couples that are confronted with this decision. In the future, with more data, a prediction model for fetal survival could be of much value.

Fortunately, the incidence of termination of pregnancy for HDP in the extreme premature period is very low: 6.5/100,000 births. In the Netherlands this means that in every tertiary center, a termination of pregnancy for this indication is performed only 1 or 2 times a year. The resulting lack of experience adds to the difficulty and emotions that this decision already entails. Differences in frequency and management of severe, early onset preeclampsia between centers are also considerable. It would be helpful if these difficult and uncommon clinical decisions were guided by a national protocol or a prediction model. Centralization of care for preeclampsia with very early onset, or perhaps a central advisory committee might be worthwhile to consider.

The process by which care-takers establish an infaust fetal prognosis, is also very difficult. In our study on termination of pregnancy for severe hypertension with extremely bad neonatal prognosis, this judgment was mostly based on: gestational age, estimated fetal weight, severity of the growth restriction, Doppler profiles and the amount of amniotic fluid. This complies with the results of our study on management
strategies for HDP in the extreme premature period, in which almost all of these factors were identified as possible predictors for neonatal survival. However predictable and logical this conclusion may appear, one child unexpectedly survived a termination of pregnancy. If estimation of the chance of survival had been more accurate and objective, neonatal support may have been better prepared in this case.

Decision making is also compromised by the fact that ultrasound fetal weight estimation does not always comply with actual birthweight. Even though the significant mean difference in our study between estimated fetal weight (EFW) and birthweight is negligible (13 grams), in 31% the estimated fetal weight over- or underestimated the birthweight by more than 10%. We do have to keep this in mind when we counsel our patients and decide to terminate a pregnancy.

Next pregnancies frequently go without any form of HDP (69%). Most times, the HDP takes a milder course in general, present at a later gestational age and can offer good chances for neonatal survival (91%), which concurs with the findings in our IPD meta-analysis. This factor is counterintuitive for most women and their spouses whose prime interest is in the current pregnancy and who are frequently willing to fight the odds and risk maternal complications, but needs to be mentioned.

As in other studies, the interpretation of the results of our studies has limitations, since they were retrospective in design. The ideal study design for the evaluation of a treatment is obviously a randomized controlled trial. Our study on management in extreme early onset HDP compared immediate delivery to expectant management, but our study about prevalence of termination of pregnancy for HDP did not comprise a control group to compare to. On the other hand, an adequate control group would have been almost impossible to define. It would have to consist of women suffering from an extreme early onset preeclampsia, with a fetus considered viable at time of management. But this may change during prolongation, as the course of the already compromised condition of these fetuses at presentation can be unpredictable. Furthermore, a randomized controlled trial would not be ethically acceptable. Thus, a retrospective study design provides the best achievable evidence.

Interpretation was also difficult because a clinical assessment is not always converted into a database easily. For example: management was established after clinicians have counseled their patients. They base their decision on factors that are described above, but also on aspects that do not translate well into statistics. The baseline characteristics were statistically comparable in the study regarding immediate delivery versus expectant management, although a few clinical aspects
were more compatible with more severe disease in the immediate delivery group (more often eclampsia and higher maximum systolic blood pressure), explaining the more aggressive management applied. But the occurrence of HELLP syndrome is difficult to compare, because it varies in severity. The occurrence of HELLP syndrome was similar in expectant management and immediate delivery, but we do not know if HELLP syndrome or deterioration of HELLP syndrome could have been prevented by delivering the woman at an earlier stage. Nevertheless, our studies demonstrate comparable results to literature\textsuperscript{2-7} with regard to the occurrence of HELLP syndrome and other maternal complications.

All things considered, women need to be counseled carefully, weighing the risk of maternal complication versus high perinatal mortality. Before 24 weeks of gestation, expectant management should not be offered routinely, but after 24 weeks of gestation, prolongation may benefit neonatal survival without compromising maternal condition. Next pregnancies frequently go without any form of HDP and can offer good chances for neonatal survival. Guidance in decision making from a protocol or prediction model could be of much value, especially because of the rarity of the condition and associated emotions.

Recurrence rates and recurrence prediction of hypertensive disorders in subsequent pregnancies
Hypertensive disorders of pregnancy can recur in a subsequent pregnancy. Hypertensive disorders of pregnancy may have significant psychological impact on patients and their partners and many parents refrain from future pregnancies because of their earlier experiences.\textsuperscript{10} These women may have been counseled about different and rather high risks for recurrence, according to available literature. Due to the diverse methodologies and selection criteria,\textsuperscript{11} recurrence rates of hypertensive disorders of pregnancy are reported very wide-ranging in literature, from a few percent up to 65%.\textsuperscript{12} Furthermore, recurrence may not present in the same severity. There is a need to orchestrate this diversity and for individual recurrence prediction.

Although the literature contains many reports on the recurrence of hypertensive disorders, it focuses mainly on early onset of the disorder (< 34 weeks of gestation). Knowledge of recurrence of late preterm and term disease is rather sparse. This presents a problem for clinical practice as hypertensive disorders do occur mostly after 34 weeks of gestation. As our two cohort studies investigate recurrence of relatively later onset disease, the results contribute to the knowledge of the risk of recurrence for many
Women. The cohort size of these cohort studies is reasonable, but we sampled detailed information on medical history and clinical hypertensive syndrome. In this way, these cohort studies distinguish themselves from the large registry based cohorts already available in the literature.13-16

Women who experienced HDP between 34 and 37 weeks of gestation in a previous pregnancy, have a risk of 51% to have recurrence of HDP in the next pregnancy. Women with HDP in the term period, have a risk of 38% for recurrence. Several predictors were indicative for individual recurrence risk prediction: higher maternal age at time of delivery in the index pregnancy, chronic hypertension, higher body mass index, non-White European ethnicity, higher maximum blood pressure during the index pregnancy and longer interpregnancy interval. A negative association with recurrence was found for the use of anticonvulsive medication during the index pregnancy. The majority of these predictors are also known as classical cardiovascular risk factors. These factors probably contribute to a susceptibility to both develop recurrent HDP and subsequent cardiovascular disease in later life. This underlines the theory that a pregnancy acts as a stress test for future cardiovascular health.17,18 Severity of HDP in the index pregnancy, indicated by the maximum blood pressure, increases the risk for recurrence. This association between severity and recurrence of HDP may be related to a woman’s susceptibility to develop HDP and her accompanying risk factors, but it may also indicate a role for vascular damage by the previous HDP in the recurrence. Inversely, anticonvulsive medication seemed to decrease the risk for recurrence. Could a more aggressive treatment for hypertension prevent vascular damage and thus recurrence of HDP? It is interesting to learn that an association has been found between the increase of maximal blood pressures, the diagnosis-to-delivery interval and the resolution time for hypertension postpartum.19 Longer exposure to higher blood pressures, associated to the amount of vascular damage, causes longer resolution-time for hypertension and proteinuria. Thus, it remains undecided if the complicated pregnancy is just an indicator of later risks, or that the duration of vascular stress and vascular damage may have more impact than previously believed.

The individual patient data (IPD) meta-analysis, allows recurrence risk estimation and risk prediction at a larger scale. We were able to show an overall recurrence risk of 21%, using a study population of 99,415 women with a hypertensive disorder in a former pregnancy. Furthermore, we learned that concomitant HELLP syndrome, delivery of a Small for Gestational Age (SGA) child and younger gestational age at delivery in the index pregnancy increases the risk for recurrence. In case of a multiple pregnancy in
their index pregnancy, the risk for recurrence is much lower, while the presence of thrombophilia seems to have no effect on recurrence of HDP at all.

We were unable to show a protective effect for low molecular weight heparin use in subsequent pregnancies after previous HDP, neither for women with or without known thrombophilia. The same seems true for use of aspirin (unpublished). Both widely discussed treatments will be further evaluated as predictors in prognostic models to be developed using this database, but we have to keep in mind that we have limited data on this specific subject and that this study was not designed to evaluate treatment effects. Only one of the studies that present a preventive effect for heparin and/or aspirin, was included in our IPD (54 women). At the same time, we included IPD of 2 studies (369 women), that showed no effect of heparin and/or aspirin on recurrence of HDP.

Many risk factors for recurrence of HDP have been identified, like parity, chronic hypertension and maternal age. However, because clinical practice and prognosis are multivariable, performance of prediction based on single risk factors has been disappointing. Multivariable prognostic models can help in the assessment of one’s individual recurrence risk for HDP. A recent review shows that prognostic models are not implemented in clinical practice, despite the existence of many prognostic models, including models for recurrence of HDP. One of the reasons is the lack of external validation of developed models. Researchers seem to neglect to follow up on their publication and many times do not validate and implement their prognostic model in clinical practice, while individual recurrence risk prediction for HDP can be very valuable for women and their partners for reasons described earlier.

Our large IPD database was used to validate existing prognostic models for recurrence of HDP and recurrence of early onset (< 34 weeks) HDP. These existing models performed variably regarding discrimination. Calibration was moderate to good, which improved after updating intercept and slope for all models.

Aside from the challenges, IPD studies contribute to the development and validation of more prognostic models and provide more knowledge and guidance in model development, validation and reporting. More importantly, we have to look at the clinical applicability of the models and implementation in clinical practice. This relies on its simplicity, availability of predictors, existence of preventive treatment, external validation and face validity (hesitation to rely on probabilities generated by the model). The 4 prognostic models validated in this IPD meta-analysis seem simple and contain routinely available predictors. Preventive treatments for HDP are still
undetermined to a certain degree. Aspirin and heparin are discussed above as preventive treatments with varying evidence for their effect. Nevertheless, predicting recurrence of HDP can have great advantages in counseling couples about a subsequent pregnancy. Couples can more rationally decide upon a subsequent pregnancy after counseling about their individual recurrence risk for HDP. Furthermore, more intense surveillance during a subsequent pregnancy can be more applied in women with a high estimated risk for recurrence.\textsuperscript{36-37} Face validity may be a more challenging issue, especially if external validation reports disappointing performance. Although one prognostic model performed very well and has potential for clinical implementation, it is focused on a specific population, leaving room for the development of new prognostic models for recurrence of HDP.

While performing this IPD meta-analysis brought about so much knowledge on the one hand, it was also hampered by many challenges on the other. To begin with, establishing contact with the authors of eligible studies proved to be very time-consuming. Failure to make contact and sometimes refusal from the authors prevented us from including the majority of studies. Not being able to obtain data for all desired studies, missing data and heterogeneity between studies seem to be a central issue for IPD studies.\textsuperscript{31,33,34} Nonetheless, the number of women with previous HDP in this database is unprecedented. Secondly, we merged data that originate from very different study methodologies. The individual studies involved reported very wide ranging recurrence risks for HDP: between 6 to 83%. And, as suspected, heterogeneity was high. Nevertheless, sensitivity analysis, in which we discriminated studies by study design and size, showed only minor discordant results.

The results of our IPD meta-analysis is useful for patients, when they are faced with insecurities regarding future pregnancies. The overall recurrence rate of 21% is lower than the most quoted recurrence rate of preeclampsia of 65%, for example, reported by Sibai et al.\textsuperscript{12} in 1991. In this study by Sibai a very high risk population is described with severe preeclampsia between 18 and 27 weeks of gestation. The recurrence rate in this population cannot be extrapolated to preeclampsia occurring at any gestational age or any severity.

We know that many women wish for a subsequent pregnancy after experiencing a HDP, but they often refrain from doing so because of to the perceived risk.\textsuperscript{38} Using individual recurrence risks by means of the now validated prognostic models, can help couples consider a future pregnancy more rationally and prevent women from abandoning a strong wish for a future child, based on unrealistic fears.
Ultimately, although this IPD meta-analysis produced a large quantity of data and generated interesting knowledge, the best outcome of the IPD study was the collaboration itself. The project led to communication and discussion with researchers and experts from all over the world. Many shared their visions and knowledge on the etiology of HDP and the mechanisms of recurrence. As a spin-off, commitments have been made to share data in the future. We plan to collaborate within an international network for the prediction of preeclampsia called ‘International Prediction of Pre-eclampsia IPD Collaborative Network (IPPIC)’. Also, we plan to create new prognostic models for the recurrence of HDP using this database of individual patient data, and include the prediction of the gestational age of recurrent HDP.

Long term health risks

Health risks in later life, as cardiovascular disease, stroke and hypertensive kidney disease, are associated with hypertensive disorders during pregnancy, but the exact relation remains unknown. This association largely reflects shared underlying causes, such as classical vascular risk factors among which the components of the metabolic syndrome. However, an independent association between HDP and vascular health has been implied in literature, but the pathophysiological mechanism of this association remains speculative.

Due to this association, HDP identify young women at risk for later health issues. After having experienced a serious condition like preeclampsia, women may also be very motivated for interventions to reduce this risk. This window of opportunity for preventive strategies makes long term health risks of HDP a very interesting field of research.

There was a very high incidence of a history of HDP in pregnancy in women with vascular disease at young age. After correcting for smoking, ethnicity, hypercholesterolemia and diabetes, we were able to demonstrate an independent association between HDP and cerebrovascular disease, but not for cardiovascular disease or hypertensive kidney disease. However, the results did show an association with cardiovascular risk factors. As for other case-control studies, the interpretation of the results of our study is limited by multiple forms of bias. The most important source of bias in this study is recall bias. Furthermore, the control group did not match the case groups optimally, regarding the presence of classic cardiovascular risk factors.

In the Individual Patient Data meta-analysis described above, we have established an association between recurrence of HDP and the development of chronic hypertension.
later in life. Perhaps an association between HDP and cerebro-, cardiovascular and hypertensive kidney disease would have been stronger if we had been able to take recurrent HDP into account. This would however substantially have been subject to recall bias, which is why we did not include this as an additional factor. Recall bias can be neglected in cohort studies, when cardiovascular disease is described prospectively from a hypertensive pregnancy onward. Unfortunately, all the cohort studies included in the most recent meta-analysis by McDonald et al. are registry-based, which lack detail of potential confounders and causal relationships. For more accurate investigation and causal considerations of the association between HDP and later cardiovascular health, prospective cohort studies will have to be performed. This strategy is also challenging because follow-up from the initial event of HDP needs to be very long-term. For the time being, cohort and case-control studies deliver the best available evidence. Our study adds to the knowledge of long term consequences of HDP.

Knowing that there is an association between HDP and later health issues and identifying women at risk at a relatively young age, creates a window of opportunity for preventative strategies. It stresses the opportunity to shift from pre- and postnatal care to maternal care. Not only should women be counseled about these health risks at postnatal visits after experiencing a HDP, they should also be made mindful of ‘treatable’ cardiovascular risk factors, such as chronic hypertension, hypercholesterolemia and obesity. Screening programs with regular checks of blood pressure, cholesterol and weight, have now reached the guidelines. Even life-style intervention seems feasible and effective in decreasing cardiovascular risks.

In 2014 a multidisciplinary guideline was implemented by the Dutch scientific societies of Obstetrics and Gynecology, Cardiology and General Practitioners. The guideline advises to counsel on healthy life style and to create a cardiovascular risk profile at the age of 50, for women who experienced preeclampsia, but not gestational hypertension. It refers to another multidisciplinary guideline, in which instructions on the cardiovascular risk profile are given, considering age, gender, smoking, family history, diet, use of alcohol, physical activity, blood pressure, body-mass index, lipid spectrum, glucose level and estimated glomerular filtration rate. At this time, preeclampsia is an indication to assess a risk profile, but it is not part of the risk profile itself. The presence of other risk factors is assumed in women with preeclampsia, but this may not necessarily be true. Also, the concept of gestational hypertension and preeclampsia as entities of the same syndrome is disregarded. The more aggressive treatment of HDP since the
HYPITAT trial may add to this misinterpretation, as women may have already been delivered before hypertension progresses to preeclampsia. Furthermore, at the age of 50, the window of opportunity to screen for early development of chronic hypertension or hypercholesterolemia and lifestyle changes has passed.

Conclusions
In extreme early onset disease, women need to be counselled carefully about maternal risks and chances for neonatal survival. Before a gestational age of 24 weeks, prolongation should not be offered routinely. Gestational age, estimated fetal weight and Doppler flow abnormalities have to be taken into account to predict neonatal survival.

Recurrence rates of hypertensive disorders of pregnancy are lower than previously assumed. Women and their partners have to be counselled correspondingly. Women should not refrain from a subsequent pregnancy due to wrongly perceived risk for recurrence of a HDP because of lack of adequate counseling. Factors that influence the individual recurrence risk, as HELLP syndrome, younger gestational age and chronic hypertension, have to be taken into account.

Independently or by overlapping risk factors, an association between HDP and later health issues, identifies women at risk at a relatively young age. Women should be counselled about these health risks at postnatal visits and attend to risk factors, such as chronic hypertension, hypercholesterolemia and obesity.

There is a growing need for research to connect with clinical decision-making. In this world of communicational growth and widely available information, collaborations like in our IPD meta-analysis can enrich us with knowledge on complex diseases as preeclampsia.
Recommendations for clinical practice and future research

Using the results of this thesis, recommendations can be made for preconception counseling after experiencing a HDP, for counseling regarding management in severe early onset preeclampsia and for counseling at the postnatal visit regarding future health.

In prenatal counseling of women that experienced a HDP in their previous pregnancy, it is advised to discuss the following topics:
- The overall risk of recurrence of a HDP is 20% (1/5).
- Concomitant HELLP syndrome and younger gestational age increase the risk for recurrence.
- If the HDP occurred in a multiple pregnancy, the recurrence risk of HDP is lower (11%).
- If a hypertensive disorder occurs, it will in general develop later in pregnancy and take a milder course.

In counseling about management strategy in women experiencing severe early onset preeclampsia between 22 and 26 week's gestation, it is recommended to take into account:
- Chances for neonatal survival are better at higher gestational age, higher estimated fetal weight and in absence of Doppler flow abnormalities.
- Estimated fetal weight over- or underestimates actual birth weight in 31% of cases.
- Prolongation adds a limited number of days to the gestational age at delivery.
- Risks for maternal complications are high (70%), if not already present.
- Risks for neonatal complications in surviving children are also high (85%).
- At a gestational age before 24 weeks, prolongation does not benefit neonatal survival and expectant management should not be offered routinely.
- Next pregnancies offer good chances at neonatal survival (90%) and frequently go without any form of HDP (69%) and recurrent HDP can take a milder course.

In counseling about health risks in later life it is proposed to discuss the following subjects:
- After experiencing a HDP, women have an increased risk to develop chronic hypertension (10%)
- This risk increases to 28% after recurrent HDP.
- An association exists between HDP and cardiovascular disease, stroke and hypertensive kidney disease. This risk may not entirely depend on existing cardiovascular risk factors, but it seems that HDP and future hypertensive disease are also independently associated.
- Regular checks of blood pressure and cholesterol should be performed.
- Women should be made conscious of other risk factors that can be influenced, like weight and life-style.

Future Research
Since validation of prediction models on the recurrence of HDP showed poor to moderate performance in all but one prognostic model, there is room for the development of new prognostic models for recurrence of HDP. Our IPD database could be useful in creating models that consider more predictors. We are planning to construct 4 new prognostic models using the IPD database: one to predict any recurrence (any type and any gestational age) using a multivariable logistic regression analysis (Model 1); one to predict recurrence of theoretical 'placental HDP': preeclampsia with associated SGA (Birth weight ≤ 10th percentile) and premature delivery (GA < 37 weeks) (Model 2); one to predict preeclampsia associated with the theoretical 'maternal HDP', based on the metabolic syndrome: preeclampsia without SGA (Birth weight > 10th percentile) and a term delivery (GA ≥ 37 weeks) (Model 3) and one to predict time-to-recurrence (GA) using Cox Proportional Hazards regression (Model 4). The creation of these 4 new models would complete the IPD project.

More research is needed to externally validate prognostic models and steps need to be taken towards implementation in clinical practice.

In the future, continuous updating of combined databases is needed for more accurate estimation and prediction of recurrence risks of HDP. But also, collaborations like this are needed in all fields of research.

More research is needed to investigate clinical aspects and outcomes of management choices of severe early onset preeclampsia and management. Perhaps a prognostic model for the chance of neonatal survival would be possible.

More research is needed on the pathophysiologic role of HDP themselves and concurrent vascular damage in the occurrence of cardio- and cerebrovascular disease and hypertensive kidney disease in later life. Even more important will be research looking at interventions to prevent these future health risks, dealing with relatively young women, who have the opportunity to work for years on their risk profile. In the
future we may even be able to offer a life-style intervention program, which is being evaluated in the ProActive study.  

Protocols on counseling women and their partners should be constructed, implemented and evaluated. These protocols should encompass recent knowledge about recurrence rates, management options and future health issues of HDP. In revisions of the multidisciplinary guidelines, a role for preeclampsia and other entities of the spectrum of HDP should be reconsidered as independent risk factors. Also, risk profiling earlier than at the age of 50 should be considered. Screening programs for hypertension, diabetes, hypercholesterolemia and obesity could be created and even life-style intervention programs may follow.
References


General discussion


