During pregnancy the health of the mother can be severely compromised by several conditions. On the one hand there are conditions limited to pregnancy, such as preeclampsia, and on the other hand pre-existing conditions can emerge or worsen during pregnancy. When this occurs at an extremely early gestational age it can be unclear if the fetus is viable, this is called the grey zone of viability. In these cases two management strategies are available. The first strategy is termination of pregnancy without intention to intervene for fetal indications and without active neonatal management. The other management strategy is termination of pregnancy with intention to intervene for fetal indications and active neonatal management. In these cases maternal-, fetal-, legal- and ethical aspects play an important role.

The aim of this thesis is to provide contemporary information to the professional on termination of pregnancy for maternal indications at the limits of fetal viability, to enable accurate counseling and reduce unwanted practice variation. To reach this aim we investigated:

1. The incidence and different indications for termination of pregnancy for maternal indications, at the limits of fetal viability in The Netherlands
3. The outcomes of subsequent pregnancies, specifically pertaining to the recurrence risk of preeclampsia
4. The opinion of Dutch obstetricians and neonatologists regarding management, auditing and reporting cases of termination of pregnancy at the limits of fetal viability.
5. The possible differences in maternal and neonatal outcome following immediate delivery versus expectant management in cases of extreme early onset preeclampsia.
6. The optimal mode of delivery prior to 28 weeks in case of severe early onset preeclampsia.
Part I: Termination of pregnancy at the limits of fetal viability without intention to intervene for fetal indications and without active neonatal management

Maternal and fetal aspects

Literature on termination of pregnancy for maternal indications at the limits of fetal viability is scarce. In chapter 2 we describe the results of a multicenter, retrospective cohort study on the prevalence and indications of termination of pregnancy for maternal indications in The Netherlands. A total of 177 pregnancies were terminated in a ten year time period, of which 113 terminations were performed after a gestational age of 24 weeks. The majority of the pregnancies were terminated for hypertensive orders in pregnancy (74%), followed by sepsis in the presence of premature rupture of membranes (16%). The mean gestational age at termination was 171 days (GA 243/7 weeks) ± 10 days. In the hypertension group the mean gestational age was 173 days (GA 245/7) ± 9.7 days as compared to 167 days (GA 236/7) ± 10.1 days in the infection group and 162 days (GA 231/7) ± 7.0 days for the other indications. The gestational age at termination was significantly higher in the hypertension group compared to the infection group (p=0.006) and the other indications (p<0.001). The perinatal mortality was nearly 100%. Furthermore we found variation in the number of terminations per center. This might, amongst others, have been due to different local interpretation on active neonatal management at the limits of viability in a period where thresholds for active management were subject to gradual change.

As said before 74% of all terminations were performed for hypertensive disorders in pregnancy. In chapter 3 we looked into more detail to these pregnancies and furthermore we expanded the inclusion period to 15 years in total. A total of 161 women were included (11–12 per year). The mean gestational age at termination was 172 days (244/7 weeks) ± 9.4 days. The main reason to terminate the pregnancy in these cases was rapid maternal deterioration. In 75% management was initially expectant, with a mean interval between admission and start of termination of 9.3 days ± 5.4 days. Maternal morbidity was high with 75% of women developing HELLP syndrome, eclampsia or needed admission to an ICU. The perinatal mortality was 100%. In this study we also aimed to investigate the accuracy of fetal
weight estimation on which fetal prognosis was based. For the decision to refrain from fetal monitoring and active neonatal support the following parameters were taken into consideration: gestational age, estimated fetal weight, growth restriction, and lack of interval growth. In 31% of the cases estimated fetal weight was more than 10% underestimated or overestimated compared to the actual birth weight.

In order to counsel these women on future pregnancies and recurrence risk we investigated the pregnancy outcome of the first subsequent pregnancy after termination of pregnancy. These results are described in chapter 4. The cohort consisted of 131 women with a termination of pregnancy for hypertensive disorders. Data on subsequent pregnancies was available for 103 women. Eighteen women did not conceive again and seven women had a first trimester miscarriage. There were 72 ongoing pregnancies. The course of these pregnancies was uneventful in 53%. The recurrence rate for preeclampsia was 29%. The mean gestational age at delivery was $35^{6/7} \pm 4$ weeks, which is more than 11 weeks later than in the index pregnancy. The neonatal survival was 96% and the mean birth weight was $2571 \pm 938$ grams. Women with chronic hypertension had the highest recurrence rate. Furthermore prescription of low dose aspirin is advised, since women who were not given aspirin had a higher recurrence rate.

Chapter 5 describes the results of an online survey amongst obstetricians and neonatologists on management, auditing and reporting cases of termination of pregnancy for maternal indications at the limits of fetal viability. All registered obstetricians (n=197) and neonatologists (n=282) in The Netherlands were invited to participate. The survey presented 2 hypothetic cases of severe early-onset pre-eclampsia at a periviable gestational age based on historical patient records. The first case was managed by immediate termination, the second case was managed expectantly and directed towards newborn survival. The professionals were asked for their opinions on management, reporting and auditing of the two cases. The overall response rate was 37%. We found that the majority of professionals would be willing to report late termination (after 24 weeks’ gestation) for severe maternal disease to medical experts for internal audits, but not for legal auditing. Furthermore we found a significant difference in
opinion between the obstetricians and the neonatologists. The first concern of the obstetricians is usually the health of the women, where the first concern of the neonatologists is to achieve a gestational age as favorable as possible for the newborn. These differences in viewpoints should be taken into account when discussing cases in a clinical setting.

Part II: termination of pregnancy for maternal indications at the limits of fetal viability with intention to intervene for fetal viability and active neonatal support

In chapter 6 we describe the maternal and fetal outcomes and prolongation of pregnancies with severe early onset pre-eclampsia before 26 weeks of gestation. In this group of women maternal complications occurred frequently (50%) and neonatal survival was limited (19%). In the surviving neonates and neonatal morbidity was high (85%) (chapter 6). Neonatal morbidity consisted of necrotizing enterocolitis, intraventricular hemorrhage, sepsis and respiratory distress syndrome or bronchopulmonary dysplasia. Neonatal survival was poor when preeclampsia occurred prior to 24 weeks’ gestation (15%). Surviving neonates were on average 7 days older and their estimated weight was 144 grams higher than non-surviving neonates. Women need to be counselled carefully, weighing the risk for maternal complications versus high perinatal mortality.

Chapter 7 describes the results of a systematic review on the maternal and neonatal outcome in vaginal delivery versus caesarean section in severe early onset preeclampsia prior to 28 weeks’ gestation. The first aim of this systematic review was to investigate the success rate of attempted vaginal delivery in severe early onset preeclampsia prior to 28 weeks’ gestation. Furthermore we aimed to determine if there are any differences in neonatal or maternal outcome according to delivery. Results of 5 studies were included for this review, consisting of retrospective and cohort studies. Planned cesarean section rates varied from 47% to 73.2%. Success rates of vaginal delivery varied from 1.8% to 80% and rates for intercurrent cesarean delivery at some time during the process of induction of labor varied from
13% to 51%. There were no statistical differences in neonatal and maternal outcome according to mode of delivery, but the data are limited. We conclude that, giving the available evidence in the reported studies a trial of labor is a considerable option in counseling women with a pregnancy complicated by preeclampsia prior to 28 weeks’ gestation due to the similar maternal and neonatal outcome. These women should be counselled that attempted vaginal delivery has a wide range of success and is not easily predicted.

**Chapter 8** consists of a new Dutch guideline, which incorporates the clinical aspects with the legal aspects of termination of pregnancy for maternal indications at the limits of fetal viability.

**Chapter 9** is the general discussion. The results and findings of the previous chapters are discussed and suggestions are made for management and future research.