Management of Gestational Hypertension and mild Pre-eclampsia at term

Corine M. Koopmans

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Chapter 1

General introduction and outline of the thesis

General introduction and outline of the thesis

Hypertensive disorders of pregnancy

Having a baby is a joyous and fulfilling experience and safe for the great majority of women in the Netherlands. Unfortunately, pregnancy and delivery can also cause a stressful life event when the mother's or baby's health is adversely affected, especially in the presence of hypertensive disorders of pregnancy.

Hypertensive disorders of pregnancy are one of the leading causes of maternal mortality and severe maternal morbidity, affecting approximately 6% to 8% of all pregnancies worldwide.[1,2,3] In the Netherlands, these disorders constitute the major cause of maternal mortality, with a Maternal Mortality Ratio (MMR, maternal mortality per 100,000 live-born children) of 3.5 in the period 1993-2005.[4] The second most frequent cause was death due to cardiovascular disease, followed by thromboembolism (both MMRs 1.6). Other main causes were obstetric haemorrhage (MMR 0.7), genital tract sepsis (MMR 0.7) and cerebrovascular disorders, as vascular dissection or rupture (MMR 0.6). The MMR of 3.5 for gestational hypertensive disorders in the Netherlands is markedly higher than the MMR of 0.9 per 100,000 maternities in the United Kingdom for the period 2003-2005.[5] In the United Kingdom the commonest cause of maternal deaths in this period are thromboembolism (MMR 1.9) and cardiovascular disorders (MMR 2.3). The major difference between the Netherlands and the United Kingdom may be caused by epidemiologic factors, classification issues, or by differences in the care of high-risk pregnancies. In the Netherlands substandard care is reported in cases of maternal mortality due to hypertensive disorders.[6] Substandard care in hypertensive disease of pregnancy causing maternal mortality, concerned insufficient diagnostic testing, inadequate management of hypertension by obstetricians, no use or inadequate use of magnesium sulphate, inadequate stabilisation before referring to tertiary care centres, failure to consider timely delivery or fluid overload in women with PE dying as a result of ARDS.[5,6] The high incidence of maternal mortality due to hypertensive disorders in the Netherlands, which is apparently partly associated to substandard care, warranted critical evaluation of the management of hypertensive disease in the Netherlands. Growing awareness among Dutch obstetric caregivers on this subject is needed to lower maternal mortality and morbidity.

The spectrum of hypertensive disorders in pregnancy ranges from mild gestational hypertension (GH) or pre-eclampsia (PE) to their severe condition. Mild GH is defined as diastolic blood pressure between 90/95 - 110 mm Hg or systolic blood pressure between 140 - 170 mm Hg and mild PE as GH combined with 300 - 5000

mg total protein within a 24-h urine collection.[7,8,9] In both conditions, women were normotensive at the start of pregnancy until week 20 of gestational age. Severe hypertension is defined as diastolic blood pressure ≥110 mm Hg or systolic blood pressure ≥170 mm Hg and severe proteinuria if ≥5000 mg total protein is present within a 24-h urine collection.[7] Hypertensive disease in pregnancy could progress into severe maternal and fetal complications such as eclampsia[10], abruptio placentae, the Haemolysis Elevated Liver enzymes and Low Platelet count syndrome (HELLP), asphyxia or even intra-uterine fetal death. In order to reduce maternal and fetal mortality and morbidity in women with hypertensive disease in pregnancy, proper antenatal care, early recognition and referral and adequate treatment is required.[11] The only causal treatment of the disease is termination of pregnancy.

In case of preterm pregnancies complicated by hypertensive disease, expectant monitoring is advocated to increase the chance of fetal maturity, as long as the risks for the mother remain acceptable. Two randomised trials performed in pregnancies between 28-34 weeks' gestation complicated with PE, concluded that expectant management was associated with a reduction in neonatal complications and duration of neonatal stay in the intensive care unit, without an increase in maternal complications.[12,13]

For the management of women with GH or mild PE at term, evidence for selection of induction of labour versus expectant monitoring is scarce. Strong practice variation exists in the Netherlands for treatment of women with GH or mild PE beyond 36 weeks' gestation. In most Dutch centres, the preferred policy is expectant monitoring, whereas in the USA and other developed countries, induction of labour is general practice in women with GH or mild PE at term.[1,14] Until this thesis these recommendations have not been based on the results of a randomised clinical trial. Induction of labour might increase the risk of assisted vaginal delivery and caesarean section, thereby generating additional morbidity and costs.[15,16,17] On the other hand, expectant monitoring might lead to severe pregnancy complications as eclampsia, HELLP syndrome, organ failure or an adverse neonatal outcome. The lack of consensus is also demonstrated by the results of an inquiry under Dutch gynaecologists and residents prior to the results of the Dutch randomised controlled trial, in which induction of labour is compared to expectant monitoring in pregnant women with hypertensive disease at term (HYPITAT trial; Hypertension and Pre-eclampsia Intervention Trial At Term) (figure 1 and 2).

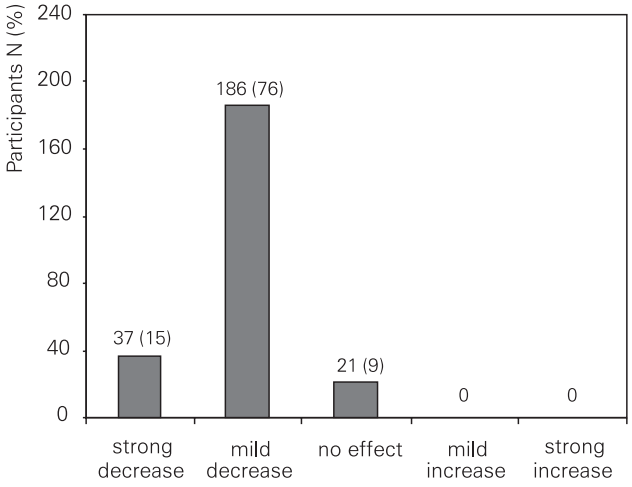

Figure 1. Prior beliefs of induction of labour on the number of maternal complications in women with mild hypertensive disease in pregnancy at term. Data from an inquire under Dutch gynaecologists and residents in March 2008.

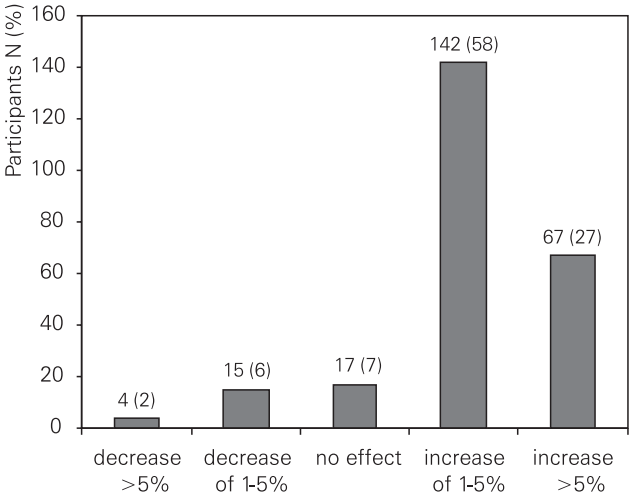

Figure 2. Prior beliefs of induction of labour on the number of unplanned caesarean section in women with mild hypertensive disease in pregnancy at term. Data from an inquire under Dutch gynaecologists and residents in March 2008.

HYPITAT study

In the first part of this thesis the (cost-) effectiveness of induction of labour and expectant monitoring in term pregnancies complicated with mild hypertensive disease is addressed. In a multicentre randomised controlled trial this issue was investigated. The study is called HYPITAT, implying '*HYpertension and Pre-eclampsia Intervention Trial At Term*'. The primary aim of this trial was to assess whether induction of labour was a beneficial treatment option compared to expectant monitoring in reducing maternal morbidity. Secondary aim was to examine methods of delivery, neonatal outcome, maternal quality of life and economic consequences of both treatment strategies.

In the field of obstetrics, important clinical questions have been addressed by multicentre randomised trials, but only a limited number of such trials have been carried out in the Netherlands. Implementation of the results from abroad is hampered, because the organisation of Dutch obstetric practice differs from that abroad. In 2003 Dutch perinatal centres offered together some important clinical issues to ZonMw. Six randomised trials, the HYPITAT trial included, were implemented within a national network, called the Dutch Obstetric Consortium. The infrastructure of the Dutch Obstetric Consortium, in which more than 40 hospitals, including all perinatal centres, participated, makes recruitment and data collection of a large group of women possible within a relative short time. This improvement of study quality and power is also important for subsequent implementation of the trial results.[18]

Prediction of severe maternal morbidity in gestational hypertension or mild pre-eclampsia

The results of the HYPITAT trial concern an overall recommendation for the best treatment option, i.e. induction of labour or expectant monitoring, in term pregnancies with hypertensive disorders. The goal of the second part of this thesis is to formulate more specific recommendations to improve quality of care and subsequently limiting maternal mortality and morbidity. For the correct choice of management for the individual patient, identification of women at increased risk of developing severe maternal outcomes is of major importance. Women who are at higher risk of developing complications during pregnancy should be identified early in pregnancy or even before conception, in order to receive preconception advice and more frequent antenatal visits. Early identification will benefit doctors and patients by helping to monitor disease severity, guide therapy and will allow clinicians to avoid unnecessary interventions in low-risk groups. High-risk pregnant women should be referred to a secondary or tertiary care centre and frequent blood pressure monitoring during the concluding weeks of pregnancy should be emphasised.

Eclampsia is still the most feared pregnancy complication in the Netherlands. The incidence of eclampsia in the Netherlands is 6.2 per 10.000 deliveries, which is markedly increased as compared with other Western European countries.[19] Although the rates of eclampsia have decreased in high-income countries since the publication of Collaborative Eclampsia trial (1995) and the Magpie trial (2002), advocating the therapeutic and prophylactic use of magnesium sulphate[20,21], accurate prediction of eclampsia still constitutes a serious clinical challenge. Therefore special attention is paid to the identification of risk indicators for eclampsia.

From literature we know that women with a pregnancy related hypertensive disorder are at increased risk of developing postpartum haemorrhage as compared to low risk populations (10% versus 1%).[22-26] Because of this 10 times higher incidence of postpartum haemorrhage, we aimed to identify women who are at increased risk of developing postpartum haemorrhage to facilitate the best management for the individual patient. Furthermore, the accuracy of serum uric acid and liver function tests in the prediction of severe maternal outcome in women with hypertensive disease is highlighted.

Outline of the thesis

The studies in this thesis discuss the best treatment option in women with a singleton (nearly) term pregnancy who are complicated with mild hypertensive disease. *Part I - The randomised trial: HYpertension and Pre-eclampsia Intervention Trial At Term (HYPITAT)* - describes the (cost-) effectiveness of induction of labour and expectant monitoring in such women. *Part II - Characteristics and tests in prediction of severe maternal morbidity in gestational hypertension or (mild) pre-eclampsia* - focuses on risk indicators, prognostic models and test accuracy for identification of the individual woman with GH or PE with increased risk of developing severe maternal complication. *Part III* contains the - *General discussion, future perspectives and summary.*

Part I

The randomised trial: HYpertension and Pre-eclampsia Intervention Trial At Term (HYPITAT)

Chapter 2 contains the study protocol of a Dutch multicentre randomised clinical trial assessing the (cost-) effectiveness of induction of labour compared to expectant management under regular monitoring in women with a singleton pregnancy complicated by GH or mild PE beyond 36 weeks' gestation (the HYPITAT trial).

Chapter 3 describes the clinical results of the HYPITAT trial.

Chapter 4 describes the maternal health-related quality of life (HR-QoL) after induction of labour versus expectant monitoring in women with GH or PE beyond 36 weeks' gestation.

Chapter 5 describes the cost-effectiveness of induction of labour compared to expectant monitoring in high-risk pregnancies due to hypertensive disorders beyond 36 weeks' gestation.

Part II

Prediction of severe maternal morbidity in gestational hypertension or (mild) pre-eclampsia

Chapter 6 describes 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.

Chapter 7 describes a case-control study in which risk indicators for the occurrence of eclampsia are identified in women with a singleton pregnancy diagnosed with GH or mild PE beyond 36 weeks' gestation.

Chapter 8 describes a cohort study in which parameters obtained before and during labour are identified to predict postpartum haemorrhage in women with a singleton pregnancy complicated with GH or mild PE beyond 36 weeks' gestation.

Chapter 9 presents a meta-analysis and decision analysis of the accuracy of serum uric acid as a predicting test for severe maternal morbidity in women diagnosed with PE.

Chapter 10 presents a systematic review in which precise estimates of maternal serum liver enzyme levels are obtained to predict adverse maternal and fetal outcomes in women with PE.

Part III

General discussion, future perspectives and summary

Chapter 11 contains the general discussion and future perspectives.

Chapter 12 contains a summary in English and in Dutch.

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Part I

The randomised trial:
HYpertension and Pre-eclampsia Intervention Trial At Term (HYPITAT)

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Chapter 2

Induction of labour versus expectant monitoring in women with gestational hypertension or mild pre-eclampsia at term: the protocol of the HYPITAT trial

BMC Pregnancy Childbirth. 2007; 7: 14

ABSTRACT

Background Hypertensive disorders, i.e. gestational hypertension and pre-eclampsia, complicate 10 to 15% of all pregnancies at term and are a major cause of maternal and perinatal morbidity and mortality. The only causal treatment is delivery. In case of preterm pregnancies conservative management is advocated if the risks for mother and child remain acceptable. In contrast, there is no consensus on how to manage mild hypertensive disease in pregnancies at term. Induction of labour might prevent maternal and neonatal complications at the expense of increased instrumental vaginal delivery rates and caesarean section rates.

Methods/ Design Women with a pregnancy complicated by gestational hypertension or mild pre-eclampsia at a gestational age between 36^{+0} and 41^{+0} weeks will be asked to participate in a multi-centre randomised controlled trial. Women will be randomised to either induction of labour or expectant management for spontaneous delivery. The primary outcome of this study is severe maternal morbidity, which can be complicated by maternal mortality in rare cases. Secondary outcome measures are neonatal mortality and morbidity, caesarean and vaginal instrumental delivery rates, maternal quality of life and costs. Analysis will be by intention to treat. In total, 720 pregnant women have to be randomised to show a reduction in severe maternal complications of hypertensive disease from 12 to 6%.

Discussion This trial will provide evidence as to whether or not induction of labour in women with gestational hypertension or mild pre-eclampsia (nearly) at term is an effective treatment to prevent severe maternal complications.

Trial Registration The protocol is registered in the clinical trial register number ISRCTN08132825.

BACKGROUND

Gestational hypertension (GH) and pre-eclampsia (PE) are common complications of pregnancy.[1] In many cases, the clinical presentation is mild, consisting only of mild hypertension and/or mild proteinuria at term. In other cases however, severe maternal and fetal complications such as eclampsia, abruptio placentae, preterm delivery, the Haemolysis Elevated Liver enzymes and Low Platelet count syndrome (HELLP), fetal growth restriction or even intra-uterine fetal death may occur. Hypertensive disorders in pregnancy make a major contribution to maternal and neonatal mortality. In the Netherlands, hypertensive disorders in pregnancy are the largest single cause of maternal mortality.[2]

Approximately 10% to 15% of all pregnancies are complicated by hypertensive disorders. The vast majority of these cases occur after 32 weeks. The only causal treatment of the disease is delivery. In case of preterm pregnancies (28-34 weeks gestational age) complicated by PE expectant monitoring is advocated to increase the chance of fetal maturity, as long as the risks for the mother remain acceptable.[3-5] Expectant management reduces neonatal complications and duration of neonatal stay in the intensive care unit in preterm pregnancies and is not associated with an increase in maternal complications.[4,5]

In case of GH or PE at term, the situation is different from preterm disease. In women with mild PE complications such as abruptio placentae and small for gestational age are similar to normotensive pregnancies. It is unclear whether in this situation expectant management is beneficial for the mother and her baby, since evidence is lacking. Despite this lack of evidence delivery is often recommended because of the unpredictability of the disease.[4,6] Recent observational studies indicate that the onset of mild GH or mild PE at or near term is associated with minimal to low maternal and neonatal morbidity.[6-8] Despite the lack of evidence that would justify intervention, many obstetricians induce labour in women at term with gestational hypertension or PE. Such a policy may increase the risk of assisted vaginal delivery and caesarean section, thus generating additional morbidity and costs.[9-11] On the other hand, expectant management might lead to severe pregnancy complications like eclampsia, severe hypertension, HELLP syndrome, organ failure or an adverse neonatal outcome.

Data from the Dutch National Obstetric Registration from 2002 showed that the yearly number of patients with hypertension (blood pressure [BP] diastolic above 90 mmHg) without proteinuria at term is 17.000. Moreover, there are 2.000 women with PE at term. The lack of consensus is demonstrated by the fact that in 9.000

women with GH or PE labour was induced, whereas labour started spontaneously in 10.000 women. Moreover, national data indicate no impact of induction of labour on neonatal outcome. In 2002 and 2003, the rate of babies born with a 5-minute Apgar score below 7 was 1.3% among women that delivered after a spontaneous onset of labour, versus 1.6% among women in whom labour was induced (OR 1.2 95% CI 1.0 to 1.5). After adjustment for potential confounders such as fetal weight, proteinuria and diastolic blood pressure, this difference became statically insignificant despite the analysis of over 35.000 patients (OR 1.1 95% CI 0.98 to 1.2). Since this equivalence is also expected from the pathophysiological background of the problem as well as from the medical literature, we anticipate no differences in neonatal outcome between both strategies.

Data from the Dutch National Obstetric Registration from Januari 2000 until Januari 2005 show that 38.170 nullipara had a singleton pregnancy in cephalic presentation complicated with GH or PE. In 18.012 women labour started spontaneously, whereas in 18.810 labour was induced. The non-elective caesarean section rate among women in whom labour started spontaneously was 14% and among women in whom labour was induced this rate was 22% (OR 1,7 95% CI 1,6 to 1,8). The vaginal instrumental delivery rates among these groups were 28% and 24% (OR 0,88 95% CI 0,84 to 0,93).

At present, there is no evidence on the effectiveness and efficiency of induction of labour in women with GH or mild PE (nearly) at term as compared with expectant management with close monitoring. In post term women and women with ruptured membranes at term, randomised trials have indicated that induction of labour does not increase the instrumental delivery rate.[12,13] However, the fact that the women were post term, might implicate that myometrial gapjunctions facilitating effective contractions were present.[12] These data can not be extrapolated to women who are (nearly) at term with GH or PE.

In view of this clinical dilemma, we propose a randomised clinical trial in which a policy of induction of labour, if necessary preceded by artificial cervical ripening, is compared with a policy of careful expectant monitoring in women with GH or mild PE (nearly) at term. At present - to our knowledge - no clinical study has been published or undertaken to investigate this issue.

METHODS/ DESIGNS

Aims

The aim of this study is to investigate whether planned induction of labour compared with expectant management in women with GH or mild PE at term will reduce severe maternal morbidity. We hypothesize that induction of labour will reduce maternal morbidity and mortality. The study will also provide insight on whether induction of labour in women with GH or PE (nearly) at term will reduce costs and improve quality of life as compared to expectant monitoring.

The proposed research concerns a multi-centre randomised controlled clinical trial in women who have GH or mild PE at gestational ages between 36^{+0} and 41^{+0} weeks. This study is set in a national Obstetric Research Consortium, in which 40 obstetric clinics in the Netherlands collaborate. Approximately 40 clinics, including academic hospitals, non-academic teaching hospitals and non-teaching hospitals will participate in this trial.

Participants/ Eligibility criteria

Patients 18 years of age or older will be eligible if they have GH or mild PE at a gestational age between 36^{+0} and 41^{+0} weeks of gestation. A diagnosis of GH is made in case the diastolic BP is equal to or above 95 mmHg at two occasions at least six hours apart in a woman who was normotensive at the start of pregnancy until week 20 of gestational age. A diagnosis of mild PE is made in case the diastolic BP is above 90 mmHg and there exists a proteinuria $>$ 300 mg total protein in a 24 hour urine collection. Women with a singleton pregnancy in cephalic presentation are eligible. Excluded were women with severe GH or PE (diastolic BP $\geq$ 110 mmHg, systolic BP $\geq$ 170 mmHg and/or proteinuria $\geq$ 5 gram in 24 hours), pre-existing hypertension (BP before 20 weeks of gestation $\geq$ 140/90 mmHg and/or using antihypertensive medication), diabetes mellitus, diabetes gravidarum requiring insulin therapy, renal disease, heart disease, HIV-seropositivity, intravenous anti-hypertensive medication, a previous caesarean section, HELLP syndrome, oliguria $<$ 500 milliliter in 24 hours, pulmonary edema or cyanosis, fetal disorders, and abnormalities at the fetal heart rate (FHR) -monitoring are not eligible for the study.

Procedures, recruitment, randomisation and collection of baseline data

Eligible women will be identified by the research coordinator and/or the staff of participating hospitals. These women will be referred to a research midwife or research nurse for counselling. Before entry into the study this person will explain

to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time during the study. They will be informed that choosing not to participate will not affect their care. In every centre an independent gynaecologist will be available for more detailed information both for patients and colleagues if required. After giving sufficient information written informed consent has to be obtained. The consent form must be signed before performance of any study-related activity. Patients who decide not to participate in this study will be treated according to one of the two protocols at the discretion of the attending obstetrician and analysed separately.

The study will be an open label study, as it is impossible to blind the health care workers involved for the strategy to which the woman is allocated. Cross-over between the two strategies would complicate the interpretation of study result. Although it will not be possible to prevent all cross-overs, both strategies will be performed according to strict criteria, as mentioned below.

After a patient has given informed consent for participation in the study cervical length will be measured using transvaginal sonography, and vaginal examination will be performed (Bishop score), both to assess cervical ripeness. At study entry all women will have baseline demographic, past obstetric and medical history recorded. After explanation of the study and informed consent, but prior to randomisation, we will perform a baseline measurement for quality of life (SF-36, HADS, EuroQol 6D3L) and additional questions on intervention preparedness and personal experience of the pregnancy. Subsequently, the patient will be randomised to either a policy that aims termination of pregnancy (intervention group) or a policy that aims expectant management for spontaneous delivery (expectant group). Randomisation will be performed through a web-based database which is hosted at the Academic Medical Centre (AMC) in Amsterdam. Randomisation will be 1:1 for intervention and expectant management, and it will be stratified for centre, parity and proteinuria according to the criteria above. Patients fill out additional quality of life questionnaires 6 weeks after delivery and 6 months after delivery (SF-36, HADS, EuroQoL 6D3L, SCL-90) and additional questions on personal experience of the delivery.

At local centres data-collection will be the responsibility of the local research coordinator and the regional research midwives or nurses. The data collected in this study will be coded and processed with adequate precautions to ensure patient confidentially.

Interventions

Intervention group

In the intervention group, patients will be induced within 24 hours after randomisation. In patients with a Bishop cervix score > 6 at vaginal examination labour will be induced by amniotomy and, if needed, augmentation with oxytocin. If this score is 6 or lower cervical ripening will be stimulated with use of intracervical or intravaginal prostaglandins according to the local protocol. In case the cervix is judged to be unripe the day after 'priming', the cervical ripening will be repeated. If the cervix remains 'unripe', day 3 will be a rest day. Cervical ripening will be repeated at day 4 and 5. All patients in the intervention group will be monitored clinically until after delivery.

Expectant group

In the expectant group, patients will be monitored until the onset of spontaneous delivery. Monitoring will consist of assessment of fetal movements as reported by the mother, as well as electronic FHR-monitoring according to the local protocol. Maternal evaluation consists primarily of frequent evaluation of blood pressure measurement and screening of urine for protein using a dipstick or protein/creatinin ratio and 24 hour urine collection for protein in case of positive screening. Blood tests (platelet count, liver enzymes and renal function) will be performed according to the local protocol.

In the expectant monitoring group, intervention is recommended in case fetal condition does not justify expectant management anymore (no fetal movements reported by the mother, non-optimal FHR-monitoring). Moreover, induction of labour is recommended in case the diastolic blood pressure is ≥ 110 mmHg or the systolic blood pressure is ≥ 170 mmHg, in case 24 hours proteinuria exceeds 5 gram, in case intravenous anti-hypertensive or prophylactic anti-convulsive medication is started, in case eclampsia or the HELLP syndrome occurs. In case in the expectant group any other indication rises for induction of labour, for example prelabour rupture of membranes for > 24 hours or meconium stained liquor, patients will be induced.

Follow up of women and infants

All details of delivery, maternal assessments and admission during pregnancy are recorded in the case record form that is accessible through the website. Maternal mortality and morbidity will be specified until date of discharge from hospital and six weeks postpartum. In case of admittance of the baby to the neonatal intensive care, high care, medium care unit or maternal ward, details of this admission are also documented. Neonatal mortality and morbidity will be specified until

date of discharge from hospital. We will register the diagnosis at discharge: small for gestational age, hypoglycemia, respiratory distress syndrome, chronic lung disease, meconium aspiration, pneumothorax, apneu, asphyxia, necrotizing enterocolitis, intraventicular haemorrhage, periventricular leucomalacia, neonatal sepsis and neonatal meningitis.
A plan for long-term follow up of the mothers is in preparation. Long-term follow up of children will not be performed, because we do not expect differences between both policies during childhood.

Outcome measures

Primary outcome measure

The primary outcome measure will be severe maternal morbidity, which can be complicated by maternal mortality in rare cases. Severe maternal morbidity will be defined as diastolic BP ≥ 110 mmHg, systolic BP ≥ 170 mmHg, proteinuria ≥ 5 g per 24 h, major postpartum haemorrhage, eclampsia, HELLP syndrome, pulmonary edema, trombo-embolic disease and/or abruptio placentae.[14] Major postpartum haemorrhage is defined as blood loss > 1000 ml within 24 hours after delivery.[15] Eclampsia is defined as severe GH or PE resulting in maternal seizures.[16] HELLP syndrome is defined as a complication of severe PE involving Haemolysis, Elevated Liver functions, and Low Platelets.[17] Trombo-embolic disease is defined as deep-vein thrombosis, pulmonary embolism or both. Patients will be examined for deep-vein thrombosis by duplex doppler if thrombosis is suspected from clinical examination. A diagnosis of pulmonary embolism will be confirmed by pulmonary angiography, computed tomography, magnetic resonance imaging or a ventilation-perfusion lung scan.[18,19,20]

Secondary outcome measures

Secondary outcomes will be neonatal mortality or neonatal morbidity, caesarean section rate, instrumental vaginal delivery rate, maternal quality of life and quality of recovery and costs. Adverse neonatal outcome will be defined as a 5-minute Apgar score below 7, an umbilical artery pH below 7.05 or admission to the neonatal intensive care.

Statistical issues

Sample size

The aim of induction of labour is to reduce the rate of severe complications of hypertensive disease, such as postpartum haemorrhage, sever hypertension (diastolic BP ≥ 110 mmHg), eclampsia and HELLP syndrome. In women with a singleton pregnancy in cephalic presentation at term (>36 weeks), the prevalence of

such complications in 2003 and 2004 was 12%.[21] To our opinion, the disadvantages of induction of labour outweigh the advantages when the complication rate is reduced to 6%. In order to detect such a difference, we will need two groups of 360 patients (two-sided test, alpha .05; beta .80).

Data analysis

The analysis will be performed by intention to treat, and stratified for centre, parity and for underlying disease (PE or GH). Quality of life as well as pain scores will be analysed using repeated measures analysis of variance.[22] Relative risks and 95% confidence intervals will be calculated for the relevant outcome measures.

Moreover, we will evaluate whether the relative benefits of induction of labour will be stronger in women with a ripe cervix at baseline and in women with a short cervical length at transvaginal sonography. In case of equivalence between outcomes, the analysis will be repeated on a par protocol basis.

Economic analysis

The process of care is distinguished into three cost stages (antenatal stage, delivery/ childbirth, postnatal stage) and three cost categories (direct medical costs [all costs in the health care sector], direct non-medical costs [costs outside the health care sector that are affected by health status or health care] and indirect costs of the pregnant women and her partner [costs of sick level]). For each stage and each cost category, costs are measured as the volumes of resources used multiplied with appropriate valuations (cost-per-unit estimates, fees, national reference prices). Cost volumes in the antenatal stage consist of direct medical costs (e.g. home/ hospital care, outpatients' visits, fetal monitoring [FHR-monitoring, ultrasound, Doppler] and maternal monitoring [various labtests; hospital care]). Direct non-medical and indirect costs in that stage may occur if role patterns or household routines shift. As we anticipate an improvement of between maternal outcomes after induction of labour the economic analysis is expected to be a cost-effectiveness analysis. Serious adverse events will be reported to an independent data safety monitoring committee. A formal interim analysis is not planned.

Ethical considerations

The study protocol has been approved by the Medical Ethical Committee of the University Medical Centre of Leiden (p04.210). The protocol is registered in the clinical trial register number ISRCTN08132825.

DISCUSSION

Gestational hypertension and pre-eclampsia are important hypertensive disorders during pregnancy which are associated with increased maternal and neonatal morbidity and mortality. There is no consensus on how to manage mild hypertensive diseases at term. Induction of labour might prevent maternal complications, but is also thought to increase the caesarean and vaginal instrumental delivery rate. This trial is designed to provide evidence on the effectiveness of induction of labour in women with mild GH or PE (nearly) at term to prevent severe maternal and neonatal complications.

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Chapter 3

Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial

The Lancet. 2009; 374: 979–88

ABSTRACT

Background Robust evidence to direct management of pregnant women with mild hypertensive disease at term is scarce. We investigated whether induction of labour in women with a singleton pregnancy complicated by gestational hypertension or mild pre-eclampsia reduces severe maternal morbidity.

Methods We undertook a multicentre, parallel, open-label randomised controlled trial in six academic and 32 nonacademic hospitals in the Netherlands between October, 2005, and March, 2008. We enrolled patients with a singleton pregnancy at 36–41 weeks' gestation, and who had gestational hypertension or mild pre-eclampsia. Participants were randomly allocated in a 1:1 ratio by block randomisation with a web-based application system to receive either induction of labour or expectant monitoring. Masking of intervention allocation was not possible. The primary outcome was a composite measure of poor maternal outcome—maternal mortality, maternal morbidity (eclampsia,
HELLP syndrome, pulmonary oedema, thromboembolic disease, and placental abruption), progression to severe hypertension or proteinuria, and major post-partum haemorrhage (>1000 mL blood loss). Analysis was by intention to treat and treatment effect is presented as relative risk. This study is registered, number ISRCTN08132825.

Findings 756 patients were allocated to receive induction of labour (n=377 patients) or expectant monitoring (n=379). 397 patients refused randomisation but authorised use of their medical records. Of women who were randomised, 117 (31%) allocated to induction of labour developed poor maternal outcome compared with 166 (44%) allocated to expectant monitoring (relative risk 0.71, 95% CI 0.59–0.86, p<0.0001). No cases of maternal or neonatal death or eclampsia were recorded.

Interpretation Induction of labour is associated with improved maternal outcome and should be advised for women with mild hypertensive disease beyond 37 weeks' gestation.

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INTRODUCTION

About 6–8% of pregnancies are complicated by hypertensive disorders.[1,2] Such disorders in pregnancy make a substantial contribution to maternal and neonatal morbidity and mortality worldwide.[3] In the Netherlands these disorders are the primary cause of maternal mortality.[4,5] Most hypertensive disorders present after 36 weeks' gestation. For the management of women with gestational hypertension (GH) or mild pre-eclampsia (PE) at term, evidence for selection of induction of labour versus expectant monitoring is scarce. Induction of labour is thought to prevent severe maternal and neonatal complications such as eclampsia, HELLP syndrome (haemolysis, elevated liver enzymes, and low platelet count), placental abruption, maternal death, and asphyxia. Conversely, induction might increase the risk of instrumental vaginal delivery and caesarean section, and thereby generate additional morbidity and costs.[6–8]

To our knowledge, no randomised clinical trial on this subject has yet been published. Strong practice variation exists in the Netherlands for treatment of women with GH or mild PE beyond 36 weeks' gestation. Therefore we aimed to assess whether induction of labour in such women reduces poor maternal outcome compared with expectant monitoring.

METHODS

Patients

We performed a multicentre, parallel, open-label randomised controlled trial in the Netherlands, in which six academic and 32 non-academic hospitals participated. We recruited women with a singleton pregnancy and a fetus in cephalic presentation at a gestational age of between 36^{+0} and 41^{+0} weeks, and who had GH or mild PE. GH was defined as diastolic blood pressure of 95 mm Hg or higher measured on two occasions at least 6 h apart. Mild PE was defined as diastolic blood pressure of 90 mm Hg or higher measured on two occasions at least 6 h apart, combined with proteinuria (two or more occurrences of protein on a dipstick, >300 mg total protein within a 24-h urine collection, or ratio of protein to creatinine >30 mg/mmol).[9–11]

Patients were excluded if they had severe GH or severe PE, defined as systolic blood pressure of 170 mm Hg or higher, diastolic blood pressure of 110 mm Hg or higher, or proteinuria of 5 g or higher per 24 h. Other exclusion criteria were

pre-existing hypertension treated with antihypertensive drugs, diabetes mellitus, gestational diabetes needing insulin treatment, renal disease, heart disease, previous caesarean section, HELLP syndrome, oliguria of less than 500 mL per 24 h, pulmonary oedema or cyanosis, HIV seropositivity, use of intravenous antihypertensive drugs, fetal anomalies, suspected intrauterine growth restriction,[12] and abnormalities detected during fetal-heart-rate monitoring.

Patients were seen by research nurses and midwives who provided counselling, obtained informed consent, monitored the study protocol in every centre and collected the data. Before randomisation, cervical length was measured by transvaginal sonography and vaginal digital examination was done. Patient data were then entered into a password-protected web-based database and a web-based application was used for block randomisation with a variable block size of 2–8. Randomisation was stratified for centre, parity, and hypertensive-related disease (GH or PE). Women were randomly allocated in a 1:1 ratio to receive either induction of labour or expectant monitoring. In this open-label trial, masking of participants, obstetricians, and outcome assessors was not possible for allocation of the randomisation number or intervention.

The trial was approved by the Institutional Review Board of the University of Leiden, and had local approval from the boards of the other participating hospitals. Written informed consent was obtained from all patients before randomisation. Patients who did not give informed consent for randomisation, but who gave authorisation for the use of their medical records, were treated according to one of the two protocols at the discretion of the attending obstetrician.

Procedures

Patients allocated to induction of labour were induced within 24 h of randomisation. If the patient had a Bishop score[13] of more than 6 at vaginal examination, labour was induced with amniotomy and, if needed, augmentation with oxytocin. If the Bishop score was 6 or lower, cervical ripening was stimulated with intracervical or intravaginale prostaglandins or a balloon catheter. Use of oxytocin or prostaglandins depended on local protocols, which were based on national guidelines of the Dutch Society for Obstetrics and Gynaecology.[14]

Patients allocated to expectant monitoring were monitored until the onset of spontaneous delivery. Maternal monitoring consisted of frequent blood pressure measurements and screening of urine for protein with a dipstick specimen or with the ratio of protein to creatinine. In cases of positive screening for protein, urine was collected for 24 h to quantify proteinuria. Laboratory tests were done on

patients with increased blood pressure or proteinuria. Fetal monitoring consisted of assessment of fetal movements as reported by the mother, as well as electronic fetal-heart-rate monitoring and ultrasound examination. Expectant monitoring was done in either a hospital or outpatient setting, dependent on the condition of the patient. Induction of labour was recommended for patients allocated to expectant monitoring if they had systolic blood pressure of 170 mm Hg or higher, diastolic blood pressure of 110 mm Hg or higher, proteinuria of 5 g or higher per 24 h, eclampsia, HELLP syndrome, suspected fetal distress, prelabour rupture of membranes lasting more than 48 h, meconium stained amniotic fluid, or a fetus with gestational age beyond 41 weeks.

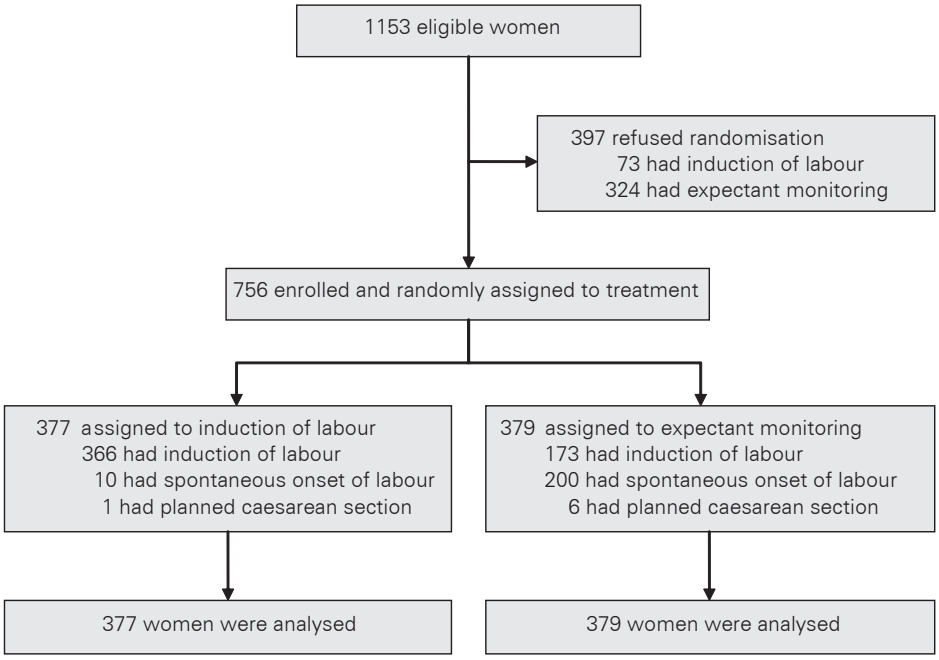

Figure 1. Trial profile

The primary outcome was a composite measure of poor maternal outcome, defined as maternal mortality, maternal morbidity (eclampsia, HELLP syndrome, pulmonary oedema, thromboembolic disease, or placental abruption), progression to severe disease (at least one measurement during ante-partum or post-partum [less than 48 h after delivery] period of systolic blood pressure ≥170 mm Hg, diastolic blood pressure ≥110 mm Hg, or proteinuria ≥5 g per 24 h),[9] and major post-partum haemorrhage. In a separate analysis, progression to severe disease was diagnosed from severe hypertension measured on at least two occasions that

were a minimum of 6 h apart. Eclampsia was defined as the presence of seizures.[15] The diagnosis of HELLP syndrome was made in patients with decreased platelet count ($<100\times10^9$/L) and increased liver enzymes (aspartate aminotransferase >70 U/L or alanine aminotransferase >70 U/L). Thromboembolic disease was defined as deep-vein thrombosis or pulmonary embolism.[16] Major post-partum haemorrhage was defined as blood loss of more than 1000 mL within 24 h of delivery.[17] Secondary outcome measures were method of delivery, neonatal mortality, and neonatal morbidity. For neonatal morbidity, we used a composite outcome consisting of a 5-min Apgar score of lower than 7, umbilical artery pH of lower than 7.05, or admission to a neonatal intensive care unit.

Statistical analysis

The composite measure of poor maternal outcome in the expectant monitoring group was thought to be 12%, on the basis of data obtained from the National Dutch Perinatal Registry of 2003 and 2004. We anticipated that induction of labour would reduce this occurrence to 6%. A sample size of 720 women, 360 women per treatment group, was needed for 80% power and a 5% type 1 error probability (two-sided).[18] We assumed a 5% protocol violation and planned to randomise 750 women.

Data were analysed on an intention-to-treat basis. All randomised women could be included in the trial analysis because missing data for relevant outcome measures were negligible. Analysis of data included comparison of maternal condition with: laboratory findings at randomisation, maternal mortality and morbidity until hospital discharge and 6 weeks post partum, neonatal mortality and morbidity until hospital discharge, method of delivery, type of hospital care, and days of maternal and neonatal hospital admission.

After we established the distribution using the Kolmogorov-Smirnov test, differences between groups with normally distributed data were tested with the Student's *t* test. For data with a skewed distribution, a non-parametric Mann-Whitney U test was applied. Categorical data were analysed with χ^2 statistics. Calculation of the percentages was based on the number of valid observations. We included footnotes in tables and figures if any observations were missing. Treatment effect is presented as relative risk (RR) with 95% CIs, and where appropriate as absolute risk reduction with 95% CIs, relative risk reduction with 95% CIs, and number needed to treat. Since the randomisation was stratified for centre, parity, and presence of proteinuria, we also did a stratified analysis using logistic regression, presented as odds ratios (ORs) for the primary outcome. A p value of less than 0.05 indicated statistical significance.

Table 1. Demographic and clinical characteristics of randomised and non-randomised patients

Characteristic	Randomised patients		Non-randomised patients	
	Induction of labour (n=377)	Expectant monitoring (n=379)	Induction of labour (n=73)	Expectant monitoring (n=324)
Nulliparous	269 (71%)	272 (72%)	52 (71%)	248 (77%)
Maternal age (years)	29.0 (26.0-33.0)	29.0 (26.0-33.0)	30.0 (27.0-33.0)	31.0 (29.0-34.0)
Gestational age (weeks)	38.4 (37.6-39.4)	38.6 (37.6-39.4)	38.4 (37.4-39.6)	38.4 (37.4-39.4)
Ethnic origin				
White	317 (84%)	298 (79%)	60 (82%)	261 (81%)
Other	35 (9%)	47 (12%)	11 (15%)	32 (10%)
Unknown	25 (7%)	34 (9%)	2 (3%)	31 (10%)
Education*				
Primary school (4 to 12 years)	6 (2%)	6 (2%)	0	0
Secondary school (12 to 16/18 years)	12 (3%)	12 (3%)	3 (4%)	7 (2%)
Lower professional school	39 (10%)	36 (9%)	6 (8%)	15 (5%)
Medium professional school	112 (30%)	106 (28%)	10 (14%)	64 (20%)
Higher professional school	55(15%)	58 (15%)	17 (23%)	49 (15%)
University	17 (5%)	12 (3%)	3 (4%)	34 (10%)
Unknown	135 (36%)	149 (39%)	34 (47%)	155 (48%)
Maternal smoking†	52 (15%)	50 (14%)	7 (10%)	23 (8%)
Body mass index (kg/m^2)				
First antenatal appointment	26.0 (22.8-30.6)	26.0 (22.7-29.7)	24.8 (22.1-28.1)	24.3 (21.9-28.4)
Baseline	32.5 (28.7-36.4)	32.3 (28.5-35.9)	30.1 (27.8-33.3)	30.5 (27.4-34.1)
Blood pressure (mmHg)				
First antenatal appointment				
Systolic	120 (110-130)	120 (111-130)	120 (110-130)	120 (110-130)
Diastolic	75 (70-80)	75 (70-80)	70 (65-80)	75 (70-80)
Baseline				
Systolic	140 (140-150)	144 (140-150)	140 (137-150)	140 (137-150)
Diastolic	100 (95-100)	100 (95-100)	100 (95-100)	98 (95-100)
Bishop score				
<2	93 (25%)	82 (22%)	–	–
2 to 6	225 (60%)	244 (64%)	–	–
>6	16 (4%)	12 (3%)	–	–
Unknown	43 (11%)	41 (11%)		
Cervical length with transvaginal sonography (mm)	30.0 (23.0-37.0)	30.0 (22.0-37.0)	–	–
Haemoglobin (mmol/L)	7.5 (7.0-8.0)	7.4 (6.9-8.0)	7.5 (6.9-8.0)	7.6 (7.1-8.1)
Packed cell volume (L/L)	0.36 (0.34-0.38)	0.36 (0.34-0.37)	0.36 (0.33-0.38)	0.36 (0.34-0.38)
Platelets (x10^9/L)	230 (192-277)	232 (192-280)	219 (177-269)	219 (189-263)
Uric acid (μmol/L)	310 (260-360)	310 (270-360)	310 (260-390)	320 (270-370)
Creatinine (μmol/L)	59.0 (52.0-70.0)	60.0 (51.8-70.0)	61.0 (55.0-73.0)	62.0 (54.0-70.0)
Aspartate aminotransferase (U/L)	20.0 (16.0-25.0)	20.0 (16.0-25.0)	20.0 (17.0-26.0)	20.0 (16.0-24.8)
Alanine amino transferase (U/L)	12.0 (9.0-17.0)	12.0 (10.0-17.0)	13.0 (9.0-18.3)	12.0 (10.0-17.0)
Lactate dehydrogenase (U/L)	294 (199-374)	287 (200-366)	331 (254-395)	316 (226-380)

Table 1. *(cont)*

Characteristic	Randomised patients		Non-randomised patients	
	Induction of labour (n=377)	Expectant monitoring (n=379)	Induction of labour (n=73)	Expectant monitoring (n=324)
Diagnosis				
Gestational hypertension	244 (65%)	252 (66%)	45 (62%)	232 (72%)
Pre-eclampsia	123 (33%)	123 (32%)	28 (38%)	84 (26%)
Unknown	10 (3%)	4 (1%)	0	8 (2%)
Proteinuria in women with pre-eclampsia (mg/24 hrs)	450 (300-1140)	600 (350-970)	735 (365-1800)	655 (463-1400)

Data are number of patients (%) or median (IQR). Data are at baseline unless otherwise indicated. –=data unavailable because not routinely measured. *Lower, medium, and higher professional schools denote preparatory, intermediate, and higher vocational education, respectively. †Data are missing for some participants: n=353 for induction of labour (randomised), n=360 for expectant monitoring (randomised), n=67 for induction of labour (non-randomised), and n=303 for expectant monitoring (non-randomised).

We used exploratory subgroup analyses to assess the consistency of the treatment effect in the trial between different categories of patients. Treatment effects are represented by forest plots. Patients were characterised by gestational age of the fetus (36–37, 37–38, 38–39, 39–40, and 40–41 weeks' gestation), parity (nulliparous and multiparous women), hypertensive-related diseases (GH and PE), systolic blood pressure at study entry (<140 and ≥140 mm Hg), Bishop score (<2, 2–6, and >6) and vaginal examination (cervical dilatation, effacement, consistence, position, length, and engagement). The engagement process is described with the levels of Hodge.[13] Statistical analyses were done with SPSS software (version 16.0).

This study is registered, number ISRCTN08132825.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the paper for publication. The corresponding author had full access to all data and had final responsibility for the decision to submit for publication.

RESULTS

Between October, 2005, and March, 2008, we identified 1153 eligible women, of whom 756 gave informed consent for randomisation. We randomly assigned 377 patients to induction of labour and 379 to expectant monitoring (figure 1). Of the 397 patients who refused randomisation, most (82%) had expectant monitoring and only 18% had induction of labour. Baseline characteristics of all eligible women

Table 2. Pregnancy outcome and onset of labour in randomised patients

	Induction of labour (n=377)	Expectant monitoring n=379)	Relative risk (95% CI) or p-value	Absolute risk reduction (95% CI)
Time between randomisation and onset of labour (days)	0.79 (0.67-1.0)	6.3 (3.7-10.9)	<0.0001	NA
Gestational age at delivery (weeks)	38.7 (37.9-39.8)	39.9 (38.9-40.4)	<0.0001	NA
Onset of labour				
Spontaneous	10 (3%)	200 (53%)	0.05 (0.03-0.09; <0.0001)	50.12% (44.64-55.24)
Planned caesarean section	1 (<1%)	6 (2%)	0.17 (0.02-1.39; 0.059)	NS
Induction	366 (97%)	173 (46%)	2.13 (1.90-2.38; <0.0001)	-51.44% (-56.54 to-45.93)
Indications for induction of labour*				
Randomised to treatment	366 (100%)	0	NA	NA
Maternal indications	0	94 (54%)	NA	NA
Severe hypertension (mmHg)	NA	78 (45%)	NA	NA
Severe proteinuria	NA	3 (2%)	NA	NA
HELLP syndrome	NA	7 (4%)	NA	NA
Use of anticonvulsive drugs	NA	37 (21%)	NA	NA
Use of intravenous antihypertensive drugs	NA	28 (16%)	NA	NA
Suspected fetal distress	0	18 (10%)	NA	NA
Time since prelabour rupture of membranes >48 hours	0	9 (5%)	NA	NA
Gestational age >41 weeks	0	24 (14%)	NA	NA
Chose induction	0	48 (28%)	NA	NA

Data are median (IQR) and numbers of patients (%). NA=not applicable. NS=not stated because indicator was not significantly associated. HELLP=haemolysis, elevated liver enzymes, and low platelet count. *Some patients had more than one clinical feature; percentages are given for women who were induced (366 patients randomised to induction of labour, 173 patients randomised to expectant monitoring).

(table 1) showed that women in the randomised group, compared with those in the non-randomised group, had a higher median body-mass index at their first antenatal appointment (26.0 kg/m^2, IQR 22.8–30.0 vs 24.5 kg/m^2, IQR 22.0–28.1; p<0.0001), smoked more frequently (14% [n=102 patients] vs 8% [n=30], p=0.003), and, for those whom information was available, had a lower education level (30% [n=142] vs 50% [n=103] had finished higher professional school or university, p<0.0001).

Outcome data were available for all patients who were randomised (table 2). Median time between randomisation and onset of labour was almost 1 week shorter in the induction group than the expectant monitoring group (table 2). Of the women allocated to induction of labour, few had spontaneous onset of labour (table 2). For those whose labour was induced (n=366 patients), 288 (79%) were induced

within 24 h of randomisation, 65 (18%) were induced 24–48 h after randomisation, 11 (3%) were induced 2–4 days after randomisation, and two (1%) were induced 4 days after randomisation. In 17 (5%) women the period between randomisation and successful induction was longer than expected (3 days) because the induction method with prostaglandins failed (median 4.0 days, IQR 4.0–6.5). These women were given lengthened treatment with prostaglandins, followed by treatment with

Table 3. Maternal outcome

	Induction of labour (n=377)	Expectant monitoring (n=379)	Relative risk (95% CI) or p-value	Absolute risk reduction (95% CI)
Composite adverse maternal outcome	117 (31%)	166 (44%)	0.71 (0.59-0.86; <0.0001)	12.76% (5.87-19.49%)
Maternal death	0	0	NA	NA
Severe hypertension (mmHg)				
Systolic BP	55 (15%)	88 (23%)	0.63 (0.46-0.86; 0.003)	8.63% (3.05-14.16%)
Diastolic BP	62 (17%)	103 (27%)	0.61 (0.46-0.80; <0.0001)	10.73% (4.85-16.52%)
Severe proteinuria*	3 (2%)	4 (2%)	0.91 (0.21-4.02; 0.90)	NS
HELLP syndrome	4 (1%)	11 (3%)	0.37 (0.12-1.14; 0.07)	NS
Eclampsia	0	0	NA	NA
Lung oedema	0	2 (1%)	NA	NA
Postpartum haemorrhage	35 (9%)	40 (11%)	0.88 (0.57-1.35; 0.55)	NS
Thromboembolic disease	1 (<1%)	0	NA	NA
Placental abruption	0	0	NA	NA
Severe hypertension measured twice (mmHg)				
Systolic BP	26 (7%)	44 (12%)	0.60 (0.38-0.95; 0.03)	4.71% (0.57-8.92%)
Diastolic BP	28 (7%)	50 (13%)	0.56 (0.36-0.87; 0.01)	5.77% (1.42-10.16%)
Drugs				
Oral antihypertensive	67 (18%)	111 (29%)	0.61 (0.47-0.80; <0.0001)	11.52% (5.48-17.45%)
Intravenous antihypertensive	13 (3%)	39(10%)	0.34 (0.18-0.62; <0.0001)	6.84% (3.28-10.59%)
Intravenous anticonvulsive	24 (6%)	46 (12%)	0.53 (0.33-0.84; 0.01)	5.77% (1.64-9.98%)
Maternal hospital care				
Intensive care	6 (2%)	14 (4%)	0.41 (0.16-1.07; 0.059)	NS
Medium care	14 (4%)	15 (4%)	0.90 (0.44-1.84; 0.777)	NS
Maternal ward	340 (94%)	319 (92%)	1.03 (0.99-1.07; 0.145)	NS
Unknown	17 (5%)	31 (8%)		
Duration of hospital stay (days)	2.0 (1.0-3.0)	2.0 (1.0-4.0)	0.12	NA

Data are median (IQR) or numbers of patients (%). BP=blood pressure. HELLP=haemolysis, elevated liver enzymes, and low platelet count. NA=not applicable. NS=not stated because indicator was not significantly associated.*Data are missing for some participants: n=157 for induction of labour, and n=191 for expectant monitoring.

oxytocin; five women delivered spontaneously, five had an instrumental delivery (four due to failure to progress, and one due to fetal distress), and seven had a caesarean section (six due to failure to progress, and one due to fetal distress). During induction with prostaglandins, one patient developed an allergic reaction against latex and consequently induction was discontinued. This patient then underwent a planned caesarean section because of suspected cephalopelvic disproportion.

Almost half of women allocated to expectant monitoring had their labour induced (table 2), of whom 125 (72%) had at least one medical reason for induction, and the remainder chose to be induced (table 2). Six patients had planned caesarean section, and in four of these patients, pregnancy was complicated by severe hypertension, of whom two also developed HELLP syndrome. One planned caesarean section was done because abnormalities were detected during fetal-heart-rate monitoring, and another was done for a patient with a history of total hip replacement on both sides and a triple pelvic osteotomy, who had a hip luxation during expectant monitoring.

The number of missing values for each of the variables of the primary outcome ranged from 0% for maternal mortality and eclampsia to 2% for post-partum haemorrhage. Occurrence of the primary outcome of the composite poor maternal outcome was significantly lower for women allocated to induction of labour than for those allocated to expectant monitoring (table 3; OR 0.58, 95% CI 0.43–0.78, $p<0.0001$). Therefore, allocation to induction of labour corresponded to a relative

Table 4. Method of delivery

	Induction of labour (n=377)	Expectant monitoring (n=379)	Relative risk (95% CI) or p-value
Spontaneous	273 (72%)	253 (67%)	1.09 (0.99-1.19; 0.091)
Vaginal instrumental delivery	50 (13%)	54 (14%)	0.93 (0.65-1.33; 0.694)
Caesarean section	54 (14%)	72 (19%)	0.75 (0.55-1.04; 0.085)*
Clinical features indicating that caesarean section was needed			
Arrest of first stage of labour	15 (28%)	24 (33%)	
Arrest of second stage of labour	3 (6%)	7 (10%)	
Failed instrumental delivery	4 (7%)	2 (3%)	
Fetal distress	17 (31%)	20 (27%)	
Failure to progress and fetal distress	12 (22%)	8 (11%)	
Maternal complication	2 (4%)	7 (10%)	
Elective	1 (2%)	4 (6%)	

Data are number of patients (%). *Absolute risk reduction is 4.67% (95% CI -0.65 to 9.98%).

risk reduction of 29.14% (95% CI 13.40–44.50), and a number needed to treat of 8 (95% CI 5–17). A similar treatment effect was shown by stratified analysis (OR 0.56, 95% CI 0.41–0.77, p<0.0001). No women who were randomised died from hypertensive disease in pregnancy, eclampsia, or placental abruption. One woman died 9 months post partum from sudden unexpected death due to epilepsy.

Overall, 2% (n=15) of patients developed HELLP syndrome, and the difference between intervention groups was not significant (table 3). One patient allocated to labour induction had a pulmonary embolism, and pulmonary oedema occurred in two women allocated to expectant monitoring, one of whom developed acute

Table 5. Neonatal outcome

	Induction of labour (n=377)	Expectant monitoring (n=379)	Relative risk (95% CI) or p-value
Birthweight (g)	3220 (2890-3565)	3490 (3080-3810)	<0.0001
Composite adverse neonatal outcome	24 (6%)	32 (8%)	0.75 (0.45-1.26; 0.276)*
Fetal deaths	0	0	NA
Apgar score of <7 after 5 min	7 (2%)	9 (2%)	0.79 (0.30-2.09; 0.632)
Arterial pH <7.05†	9 (3%)	19 (6%)	0.46 (0.21-1.00; 0.043))‡
Admission to intensive care	10 (3%)	8 (2%)	1.26 (0.50-3.15; 0.625)
Neonatal hospital care			
Medium care	68 (18%)	69 (18%)	0.99 (0.73-1.34; 0.952)
High care	12 (3%)	10 (3%)	1.21 (0.53-2.76; 0.656)
Intensive care	10 (3%)	8 (2%)	1.26 (0.50-3.15; 0.625)
Duration of stay in a neonatal medium, high, or intensive care unit (days)	3.0 (2.0-6.0)	4.0 (2.8-7.0)	0.077
Reasons for admission to an neonatal intensive care unit**			
Asphyxia	3 (1%)	3 (1%)	
Low birthweight	3 (1%)	0	NA
Hypoglycaemia	0	2 (1%)	NA
Infant respiratory distress syndrome	1 (<1%)	1 (<1%)	NA
Meconium aspiration	0	1 (<1%)	NA
Neonatal sepsis	0	1 (<1%)	NA
Hyperbilirubinaemia	2 (1%)	0	NA
Persistent pulmonary hypertension	0	1 (<1%)	NA
Down syndrome with congenital heart defect	1 (<1%)	0	NA
Inguinal hernias	1 (<1%)	0	NA
Interhemispheric cyst	1 (<1%)	0	NA

Data are median (IQR) or number of patients (%). NA=not applicable. *Absolute risk reduction is 2.08% (95% CI -1.71 to 5.91%). †Data are missing for some participants: n=311 for induction of labour, and n=301 for expectant monitoring. ‡Absolute risk reduction (95% CI) 3.42% (0.06 to 7.02%). **Some neonates had more than one clinical features to indicate that admission to a neonatal intensive care unit was needed.

Subgroup	Induction of labour (n=377)	Expectant monitoring (n=379)	Relative Risk (95% CI)
Gestational age at randomisation (weeks)			
36-37	18/40 (45%)	15/35 (43%)	1.05 (0.63-1.76)
37-38	32/96 (33%)	41/92 (45%)	0.75 (0.52-1.08)
38-39	27/99 (27%)	40/93 (43%)	0.63 (0.43-0.94)
39-40	27/83 (33%)	43/103 (42%)	0.78 (0.53-1.15)
40-41	13/59 (22%)	27/56 (48%)	0.46 (0.26-0.79)
Parity			
Nulliparous	83/269 (31%)	123/272 (45%)	0.68 (0.55-0.85)
Multiparous	34/108 (32%)	43/107 (40%)	0.78 (0.55-1.13)
Pregnancy related hypertension*			
Gestational hypertension	75/244 (31%)	96/252 (38%)	0.81 (0.63-1.03)
Pre-eclampsia	41/123 (33%)	67/123 (55%)	0.61 (0.45-0.82)
Systolic blood pressure at baseline (mmHg)			
<140	8/66 (12%)	29/73 (40%)	0.31 (0.15-0.62)
≥140	109/311 (35%)	137/306 (45%)	0.78 (0.64-0.95)
Bishop Score at baseline*			
<2	36/93 (39%)	45/82 (55%)	0.71 (0.51-0.97)
2 to 6	66/225 (29%)	98/244 (40%)	0.73 (0.57-0.94)
>6	9/16 (31%)	5/12 (42%)	0.75 (0.28-2.02)
Cervical dilatation at baseline (cm)*			
0	62/174 (36%)	86/163 (53%)	0.68 (0.53-0.87)
1	34/121 (28%)	48/131 (37%)	0.77 (0.53-1.10)
2	16/53 (30%)	25/55 (46%)	0.66 (0.40-1.10)
>2	4/16 (25%)	3/17 (18%)	1.41 (0.37-5.37)
Cervical effacement at baseline*			
≤25%	53/169 (31%)	78/161 (48%)	0.65 (0.49-0.85)
>25%	62/192 (32%)	81/199 (41%)	0.79 (0.61-1.03)
Cervical consistence at baseline*			
Stiff	22/61 (36%)	36/65 (55%)	0.65 (0.44-0.97)
Moderately to very weak	92/301 (31%)	125/297 (42%)	0.73 (0.59-0.90)
Engagement at baseline*			
Hodge 1	102/316 (32%)	127/304 (42%)	0.77 (0.63-0.95)
>Hodge 1	9/32 (28%)	25/48 (52%)	0.54 (0.29-1.00)
Cervical position at baseline*			
Posterior	65/207 (31%)	96/188 (51%)	0.62 (0.48-0.79)
Median to anterior	50/153 (33%)	62/168 (37%)	0.89 (0.66-1.20)
Cervical length at baseline (cm)*			
≥4	24/68 (35%)	38/64 (59%)	0.59 (0.41-0.87)
<4	90/285 (32%)	118/291 (41%)	0.78 (0.63-0.97)

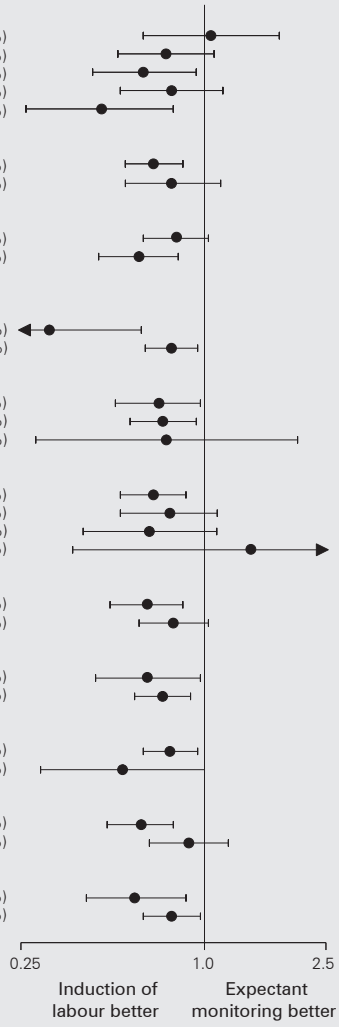

Figure 2a. Risk on composite poor maternal outcome in subgroups. *Data are missing for some participants.

respiratory distress syndrome (table 3). Progression to severe disease occurred in 88 women in the induction group and in 138 women in the expectant monitoring group (23% vs 36%; RR 0.64, 95% CI 0.51–0.80, p<0.0001); several women had more than one severe disease at the same time. The treatment effect was similar when progression to severe disease was diagnosed from high blood pressure measured on at least two occasions more than 6 h apart (11% [n=42] vs 19% [n=73]; 0.58, 0.41–0.82, p=0.002). Significantly fewer women randomised to induction,

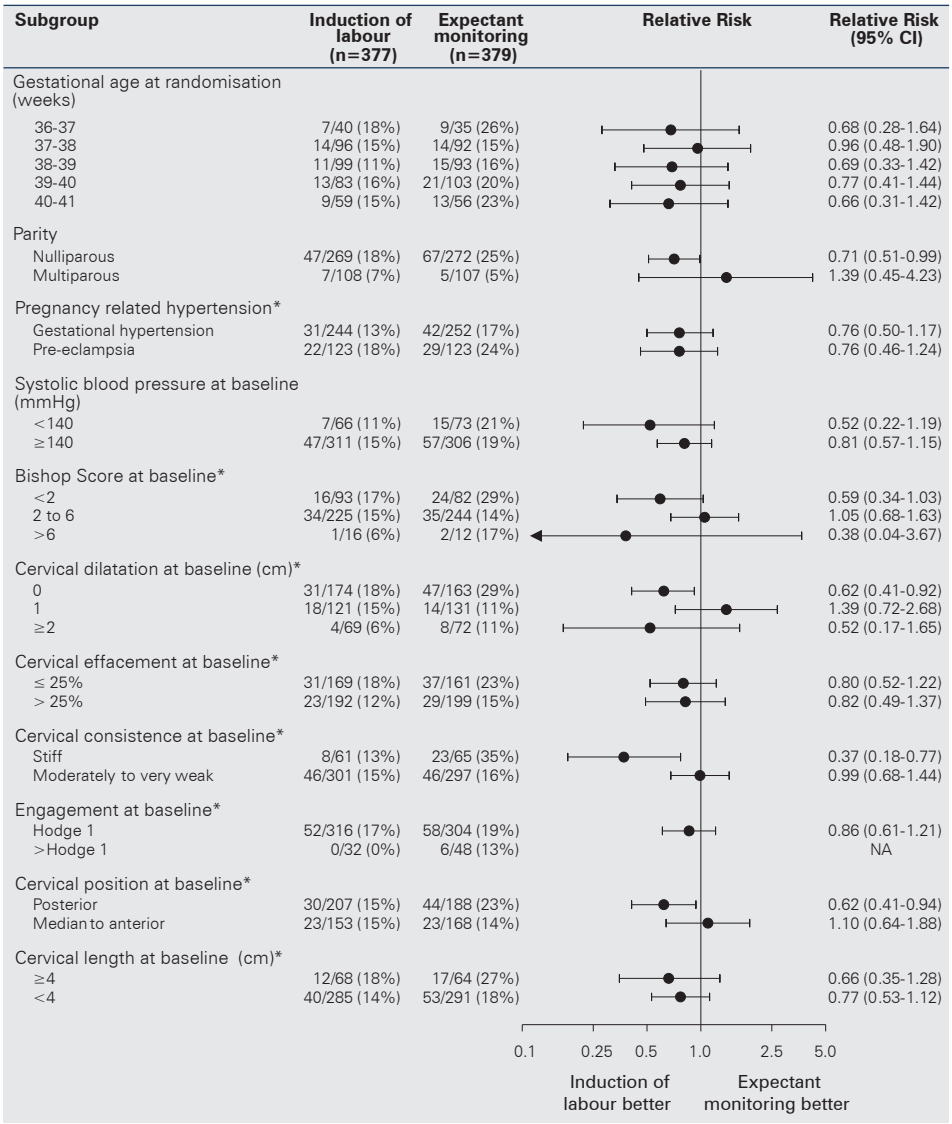

Figure 2b. Risk on caesarean section in subgroups NA=not applicable. *Data are missing for some participant.

compared with those allocated to expectant monitoring, were prescribed both oral and intravenous antihypertensive drugs (20% [n=77] vs 33% [n=124]; 0.63, 0.49–0.81, p<0.0001) and prophylactic anticonvulsive drugs.

Although fewer patients had caesarean sections in the induction group than in the expectant monitoring group, the difference was not significant (table 4). Most caesarean sections were done for patients with arrest of the first stage of labour,

failure to progress, or fetal distress (table 4). In both the induction and expectant monitoring groups, the proportion of caesarean sections was higher for women with a composite poor maternal outcome (23% [n=27] vs 27% [n=45]; 0.85, 0.56–1.29, p=0.44) than for those who were not classed as having poor maternal outcome (10% [n=27] vs 13% [n=27]; 0.82, 0.50–1.35, p=0.44). Occurrence of vaginal instrumental delivery was much the same between the induction and expectant monitoring groups (table 4).

No fetal or neonatal deaths occurred in either of the intervention groups, and the difference in composite neonatal morbidity was not significant between the interventions (table 5). However, a lower number of neonates had an arterial pH of less than 7.05 in the induction group than the expectant monitoring group (table 5). Both groups had similar proportions of neonates who had a 5-min Apgar score of lower than 7 or were admitted to an intensive care unit; table 5 shows the reasons for admission to an intensive care unit and total admission time. In the induction group, neonates were born at an earlier stage of pregnancy than in the expectant monitoring group, and therefore their birth weight was significantly lower.

In almost all subgroups a trend toward a better maternal outcome was found for patients who were induced than those who had expectant monitoring (figure 2). Only women randomised at a gestational age of 36–37 weeks or with cervical dilatation of more than 2 cm might benefit from expectant monitoring (figure 2a). Subgroup analyses on the risk of caesarean section showed that the favourable effect of induction of labour was not present in women who were multiparous, had a Bishop score of 2–6, had cervical dilatation of 1 cm, or had median or anterior position of the cervix (figure 2b).

The proportion of patients who had the composite poor maternal outcome in the non-randomised group was 43% (n=31) for those allocated to induction and 38% (n=123) for those allocated to expectant monitoring. The occurrence of caesarean sections in these patients was 4% (n=3) for those allocated to induction and 16% (n=52) for those allocated to expectant monitoring.

DISCUSSION

The results of this study show that induction of labour was associated with a lower composite risk of poor maternal outcome, which was mainly ascribed to progression to severe disease, than was expectant monitoring. Overall, 13 per 100 fewer women allocated to induction of labour had a poor maternal outcome,

corresponding with a number needed to treat of eight. Surprisingly, fewer caesarean sections were needed in the induction group than the expectant monitoring group. Adverse neonatal outcomes did not differ significantly between the groups.

The number of women with progression to severe disease was higher than expected from the sample size calculation before the trial began. Consequently, we recorded a high occurrence of the primary outcome with both interventions. This underestimation might be attributable to the absence of some useful data in the National Dutch Perinatal Registry, on which the calculation was based. First, systolic blood pressure was part of our primary outcome, but this variable was not recorded in the registry, and therefore not considered in the sample size calculation. We decided to include systolic blood pressure in our primary composite outcome since accumulating evidence suggests that systolic blood pressure is a risk factor for serious maternal morbidity, especially cerebrovascular accidents.[19,20] Second, the large number of women with high blood pressure in the trial might be explained by the fact that we used only one measurement of severe hypertension to fulfil the definition of progression to severe disease, whereas two measurements are needed for diagnosis, according to the National Dutch Perinatal Registry. Use of an endpoint based on a minimum of two measurements of high blood pressure at least 6 h apart might have underestimated the occurrence of severe hypertension, since in clinical practice the decision to treat a patient with antihypertensives or induction of labour is often based on only one measurement. However, when we recalculated the occurrence of the primary endpoint with progression to severe disease diagnosed from at least two measurements of high blood pressure, the treatment benefit of induction was also clear.

We found that fewer caesarean sections were needed in the induction group than the expectant monitoring group. Randomised trials in women with post-term pregnancies or those with pre-labour rupture of membranes at term showed similar proportions of caesarean section done for women receiving induction of labour and expectant monitoring.[21,22] The association of induction of labour with increased numbers of caesarean sections is based on results from non-randomised studies alone.[6–8] The reduced risk of caesarean section that we recorded after induction of labour could be caused by decreased occurrence of severe maternal morbidity with this intervention. To support this theory, stratified analysis in women with and without poor maternal outcome showed that an increased proportion of women with poor maternal outcome needed caesarean section, but no difference was recorded between those receiving induction of labour or expectant monitoring in either group of women.

In this trial, the primary outcome was defined as a composite measure of poor maternal outcome consisting of several conditions. We decided to include progression to severe hypertension because this disease is associated with severe maternal morbidity, such as eclampsia, pulmonary oedema, and cerebral encephalopathy or haemorrhage.[23–25] If we had restricted our primary outcome to conditions of severe morbidity, such as eclampsia, we would have had to extend the power of the study substantially. Such a target was not feasible for our study group. Moreover, since induction of labour reduces the risk of progression to severe disease, and because this intervention probably reduces the risk of caesarean section, we think that a larger study excluding progression to severe disease is not needed.

Major post-partum haemorrhage was also part of our composite primary outcome, because it has been recognised as an important risk factor in pregnant women with hypertensive disorders.[26–28] We postulated that induction of labour would reduce the risk of progression to severe disease and thereby reduce the risk of major post-partum haemorrhage. We recorded 10% of women with a major post-partum haemorrhage, which exceeded the 1.33% risk of haemorrhage (>1000 mL) that has been reported in low-risk populations,[29] but induction of labour did not reduce the occurrence of severe haemorrhage.

In the subgroup analyses we found that the beneficial effect of induction of labour was absent in women with fewer than 37 weeks' gestation, but the result is unreliable because of the low number of women in this subgroup. Our study was not sufficiently powered to detect differences in subgroup analyses,[30] and consequently we are hesitant to extrapolate trial results to women with a gestational age of 36–37 weeks.

The treatment effect that we found was pronounced in women with an unfavourable cervix (eg, cervical dilation 0 cm, cervical effacement ≤25%, or posterior position of cervix).[31] This paradoxal finding is explained by the fact that in such women who were allocated to expectant monitoring, time to delivery was longer relative to those with a favourable cervix, thereby increasing the risk that the maternal condition could deteriorate. Since the effect of an unfavourable cervix was reduced in women allocated to induction of labour, the benefit of induction increases in women with an unfavourable cervix.

Effective management of women with hypertensive disease beyond 36 weeks' gestation is strongly controversial in the Netherlands. In most participating centres, the protocol recommended expectant monitoring, which was the preferred

policy in the non-randomised groups of women. In the USA and other developed countries, induction of labour in women with GH or mild PE at term is already general practice, but until now this recommendation has not been based on the results of randomised clinical trials.[1,32]

The results of our trial are important for both developed countries in which induction of labour in women with hypertensive disease beyond 36 weeks' gestation has been controversial, and for developing countries in which maternal morbidity and mortality rates are substantially increased.[3] Our finding that induction of labour was associated with a reduced risk of severe hypertension or HELLP syndrome and subsequent reduced need for caesarean section, emphasises the importance of frequent blood pressure monitoring during the concluding weeks of pregnancy. We believe that induction of labour should be advised for women with GH and a diastolic blood pressure of 95 mm Hg or higher or mild PE at a gestational age beyond 37 weeks.

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Conflict of interest statement

All authors declare that they had no potential conflicts of interest relevant to this article.

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Chapter 4

Health-related quality of life after induction of labour versus expectant monitoring in gestational hypertension or pre-eclampsia at term

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ABSTRACT

Objective Gestational hypertension (GH) and pre-eclampsia (PE) are major contributors to maternal and neonatal morbidity and mortality. In GH or PE, labour may be either induced or monitored expectantly. We studied maternal health-related quality of life (HR-QoL) after induction of labour versus expectant monitoring in GH or PE at term. We performed the HR-QoL study alongside a multi-centre randomised controlled trial comparing induction of labour to expectant monitoring in women with GH or PE after 36 weeks.

Methods We used written questionnaires, covering background characteristics, condition-specific issues and validated measures: the Short Form (SF-36), European Quality of Life (EuroQoL 6D3L), Hospital Anxiety and Depression scale (HADS), and Symptom Check List (SCL-90). Measurements were at time points baseline, 6 weeks postpartum, and 6 months postpartum. A multivariate mixed model with repeated measures was defined to assess the effect of the treatments on the physical (PCS) and mental (MCS) components of the SF-36. Analysis was by intention to treat.

Results We analysed data of 491 randomised and 220 non-randomised women. We did not find treatment effect on long-term HR-QoL (PCS: $p=.09$; MCS: $p=.82$). The PCS improved over time ($p<.001$), and was better in non-randomised patients ($p=.02$).

Conclusion Despite a clinical benefit of induction of labour, long-term HR-QoL is equal after induction of labour and expectant management in women with GH or PE beyond 36 weeks of gestation.

INTRODUCTION

Pregnancy-related hypertensive complications are a major contribution to maternal and neonatal morbidity and mortality worldwide.[1] Gestational hypertension (GH) or pre-eclampsia (PE) occur in 6% to 8% of pregnant women, of which the majority occurs after 36 weeks of gestation.[2,3] Eventually, the only causal treatment for GH and PE is delivery. Induction of delivery is therefore thought to prevent development of severe maternal complications such as placental abruption, eclampsia, haemolysis, elevated liver enzymes, and low platelets (HELLP syndrome), even maternal death, and neonatal complications such as asphyxia. However, the benefit of induction of labour is balanced against an increased risk of instrumental vaginal delivery and caesarean section, with consequent long-term maternal morbidity.[4-6] Prior to our study, most pregnancies with GH or PE were monitored expectantly in the Netherlands in order to avoid increased risk of instrumental delivery and caesarean section, resulting in a low incidence of inductions of labour, as compared to neighbouring countries.[7] The low induction rate was caused by the lack of scientific evidence for its effectiveness in GH or PE.

In order to investigate the effectiveness and safety of induction of labour as compared to expectant monitoring, multiple outcomes need to be defined. Besides maternal and neonatal medical outcomes, information about other treatment outcomes (e.g. self-reported health on the short- and long-term, treatment burden, costs) are needed in order to gain insight into the consequences of both treatment options. Especially when differences in primary outcome are small or absent these HR-QoI measures become even more important. Only with full knowledge about the treatment options, an informed choice can be made about which treatment is best. Alongside the nationwide multi-centre randomised controlled clinical trial HYPITAT (HYpertension or Pre-eclampsia Intervention Trial At Term; ISRCT08132825) we investigated the impact of induction of labour versus expectant monitoring on the maternal health-related quality of life (HR-QoL). In the trial, the effectiveness of induction of labour was compared to expectant monitoring in women with GH or PE beyond 36 weeks of gestation.[8,9] For this study we identified the following relevant aspects of HR-QoL: short- and long-term self-reported health, anxiety, depression, and physical and mental symptoms. We also followed two non-randomised groups in order to adjust for any study participation effects.

METHODS

Participating women and clinical study

The HR-QoL study was conducted alongside the HYPITAT trial. The HYPITAT study included women with a singleton pregnancy with a fetus in cephalic presentation at study entry, between 36+0 to 41+0 weeks of gestation, complicated with GH (defined as diastolic blood pressure ≥95 mmHg) or mild PE (defined as diastolic blood pressure ≥90 mmHg, combined with ≥2+ protein on dipstick, >300 mg total protein within a 24-hour urine collection or protein/creatinine ratio >30 mg/mmol). Exclusion criteria were maternal age below 18 years, previous caesarean section, ruptured membranes, pre-existing hypertension treated with anti-hypertensive medication, severe high blood pressure (RR diastolic >110; RR systolic >170), diabetes mellitus, gestational diabetes requiring insulin therapy, renal disease, oliguria, HIV, and HELLP syndrome (Haemolysis Elevated Liver enzymes, Low Platelet count) upon presentation. Details of the study design have been described elsewhere.[8,9]

A total of 38 Dutch hospitals (six academic and 32 non-academic) participated in the HYPITAT trial. The HYPITAT trial was approved by the Institutional Review Board of the University of Leiden and had local approval from the boards of all participating hospitals. Women who were eligible for inclusion in the HYPITAT study received study information from an obstetrician, resident, or midwife during consultation, or during additional counselling by a research nurse or midwife. During the counselling, the research nurse entered the patient's clinical record form into a database using a login restricted web form. The web-based randomisation was a block randomisation with stratification for centre, parity, and hypertensive related disease (i.e. GH or PE). Women were randomly allocated to either induction of labour or expectant monitoring. Women who did not give informed consent for randomisation were asked to participate in the study as non-randomised participant, and were treated according to local protocol. Their data were also entered into the database.

Interventions and procedure

In women allocated to induction, labour was initiated within 24 hours after randomisation. Women with a Bishop score >6 were induced by amniotomy and, if needed, augmented with oxytocin. Women with a lower Bishop score were primed with intra-cervical or intra-vaginal prostaglandins. Women allocated to the expectant group were monitored either in an outpatient setting or in the hospital, with frequent assessment of the maternal condition, i.e. blood pressure

measurement, screening of urine for protein, laboratory tests, and assessment of fetal condition, i.e. fetal movements as reported by the mother, electronic fetal heart rate monitoring, and biophysical profile by ultrasound if indicated. Induction of labour was recommended in case maternal or fetal condition did not justify the assigned treatment. The study interventions have been described in more detail elsewhere.[9]

Background characteristics and clinical data (obstetric history, medical treatment, maternal and neonatal outcome, and interventions during hospital stay) were collected by local research midwives or nurses using a web-based case record form. Measures of maternal and neonatal mortality and morbidity as well as diagnoses at discharge were recorded until hospital discharge.

HR-QoL procedure and measures

For logistical reasons, inclusion to the HR-QoL study started February 2006; 5 months after the start of the clinical trial. Participating women received a folder containing HR-QoL questionnaire instructions, four HR-QoL questionnaires, four pre-stamped return envelopes, and reminder stickers –the women could stick these stickers in their agenda or on their calendar as a self-reminder for filling out a questionnaire on the appropriate date. The questionnaires included general filling instructions. Even though the validated questionnaires are straightforward, we provided a telephone number and an email address for women who needed assistance with the questionnaires.

The four HR-QoL questionnaires were to be filled out at four different time points: at baseline (inclusion) before randomisation (B1), at baseline after randomisation or participation (B2), 6 weeks postpartum (6W), and 6 months postpartum (6M). We chose 6W as the first post-partum time point because six weeks is the normal time frame for recovery after delivery; any differences between the strategy groups at that time point could be considered as relevant effects. We expected the maternal health to have stabilized at 6M, such that we considered this time point to be a good measure of long-term HR-QoL outcome. The questionnaires were available in either Dutch or English. Each questionnaire took between 10 and 30 minutes to complete. Women who did not return questionnaire 6W within 7 weeks after delivery or questionnaire 6M within 7 months after delivery received a written reminder and a new copy of the questionnaire with a pre-stamped return envelope.

Questionnaire B1 contained questions on background characteristics, e.g. date of birth, educational level, employment characteristics, household composition, obstetric history, ethnicity, length, and weight before pregnancy. The validated

measures involved the Medical Outcome Study 36-Item Short Form Health Survey (SF-36; questionnaires B1, 6W, 6M), the European Quality of Life 6 dimensions 3 levels (EuroQoL 6D3L) with subsequent general health Visual Analogue Scale (VAS; questionnaires B2, 6W, 6M), the Hospital Anxiety and Depression Scale (HADS; questionnaires B2, 6W, 6M), and the Symptom Check List (SCL-90; questionnaires B2, 6M), all validated in Dutch and English.[10-16] While some of our used measures are not typical HR-QoL measures, we chose to include these into the questionnaires because of their contribution to insight into the short- and long-term self-reported health, anxiety, depression, and physical and mental symptoms –our definition of maternal HR-QoL. The HADS and SCL-90 are more sensitive to any differences in the anxiety, depression (HADS), and physical and mental symptoms (SCL-90) planes than typical HR-QoL measures such as the SF-36. Also, while the SF-36 and EuroQoL are able to detect large effects, the HADS and SCL-90 are able to detect any potentially relevant small effects on the subscales.

The SF-36 is a generic HR-QoL questionnaire with eight health-status subscales: physical functioning, role limitations due to physical health problems, bodily pain, general health perception, vitality, social functioning, role limitations due to emotional health, and general mental health. The scores on the subscales are aggregated into the standardized summary scores Physical (PCS) and Mental Component Score (MCS). A standardized score of mean=50 and SD=10 represents the general population average.[10,11] The EuroQoL 6D3L is an instrument to describe general health status with six dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and cognitive functioning). An individual's (or population's) health description can be expressed in a value between 0 (death) and 1 (perfect health), using an algorithm to combine the six dimensions into one overall utility score.[12,17] The subsequent VAS in our study is a vertical scale ('thermometer') with values 0 'worst possible health state' (lower anchor) to 100 'best possible health state' (upper anchor). Women indicated their health state by marking the VAS, while considering the anchors.[18] The HADS is a self-report rating scale that exists of two 7-item scales: one for anxiety and one for depression each with a score range of 0 to 21; a score of 9-12 is indicative of a depressive episode.[14,19] Finally, the 90-item SCL-90 aims to measure a person's psychological symptom status. The SCL-90 exists of one overall score 'psychoneurosis', and eight symptom subscales: anxiety, agoraphobia, depression, somatic complaints, insufficiency of acting and thinking, interpersonal sensitivity, hostility, and sleeping problems. Higher scores indicate worse psychological health.[16,20]

Analysis

We checked the HR-QoL data for selective response and missing data regarding the clinical determinants composite maternal and neonatal outcome. Composite adverse maternal outcome consisted of maternal mortality, eclampsia, HELLP syndrome, pulmonary edema, thrombo-embolic disease, placental abruption, progression to severe hypertension, and/or major postpartum haemorrhage.[8] Composite adverse neonatal outcome consisted of 5-minute Apgar score <7, umbilical artery pH <7.05, and/or admission to a neonatal intensive care unit.[8] The HR-QoL data were analyzed according to the intention-to-treat (ITT) principle. We calculated difference scores between the baseline and the postpartum (6 weeks and 6 months) measures. Difference scores per summary measure were compared between randomised groups using one way ANOVA. To explain the change in the SF-36 PCS and MCS subscales over time, we used a linear mixed model regression with the following characteristics: time of assessment (baseline; 6 weeks postpartum; 6 months postpartum), intervention following ITT (expectant; induction), randomised status (randomised; not randomised), age (≤27; 28-33; ≥34), parity (nulliparous; multiparous), time before conception (<1 year; ≥1 year), pre-pregnancy BMI (≤25; >25), educational level (lower; higher), employed (no; yes), time of assessment*randomisation, and time of assessment*intervention. Analyses were conducted using SPSS 15.0 for Windows (SPSS Inc, Chicago, IL). A p-value <0.05 (two sided) was considered to indicate statistical significance.

With respect to the sample size of HR-QoL data, we considered a 5-point difference in the PCS scale and MCS scale week as clinically relevant. To find a relevant difference in HR-QoL, we needed two groups of 250 women (alpha .05; beta .80; SD 20). As the measurements at multiple time points allow for repeated measures analysis, this sample size was sufficient for testing effects over time, including overall difference and trends.

RESULTS

Baseline characteristics

Of the 1153 participants to the HYPITAT study, 756 (66%) were randomised and 397 (34%) women participated in the non-randomised part of the study. Of the randomised women, 539 (71%) also participated in the HR-QoL study, versus 282 (71%) of the non-randomised women. Overall, 711 (87%) of the women that were included in the HR-QoL study responded to at least one questionnaire (figure 1). Response rates were: 96% for questionnaire B1, 88% for B2, 74% for 6W, and 65% for 6M.

Table 1. Baseline characteristics of the randomised (RCT) and non-randomised women (i.e. with prior treatment preference, P) participants who followed induction of labour or expectant monitoring, and the women who did not return the any HR-QoL questionnaire (Non-response). Analyses of the randomised vs. non-randomised and responses vs. non-responses.

	HR-QoL response, n=711				
	Induction RCT n=245	Expectant RCT n=246	Induction P n=37	Expectant P n=183	Total Response n=711
Age: mean (SD)	30.4 (4.6)	30.2 (4.6)	30.2 (3.8)	32.0 (3.8)	30.7 (5.0)
Months to conceive: mean (SD)	9.4 (16.3)	9.2 (12.7)	4.8 (6.4)	6.9 (9.9)	8.5 (13.0)
BMI pre-pregnancy: mean (SD)	26.9 (5.5)	26.5 (5.3)	24.5 (3.2)	25.5 (4.5)	26.3 (5.1)
Dutch origin: %	92.6	88.8	94.1	92.7	85.5
Has a job: %	86.0	88.7	93.9	95.5	90.9
Lives with partner: %	96.0	97.0	97.1	98.9	97.5
Nulliparous: %	71.0	78.5	81.1	77.6	76.0
High educational level [b]: %	33.5	27.2	38.2	51.4	38.0

[a] These values are not available because they were asked by HR-QoL questionnaire
[b] Higher vocational training or university

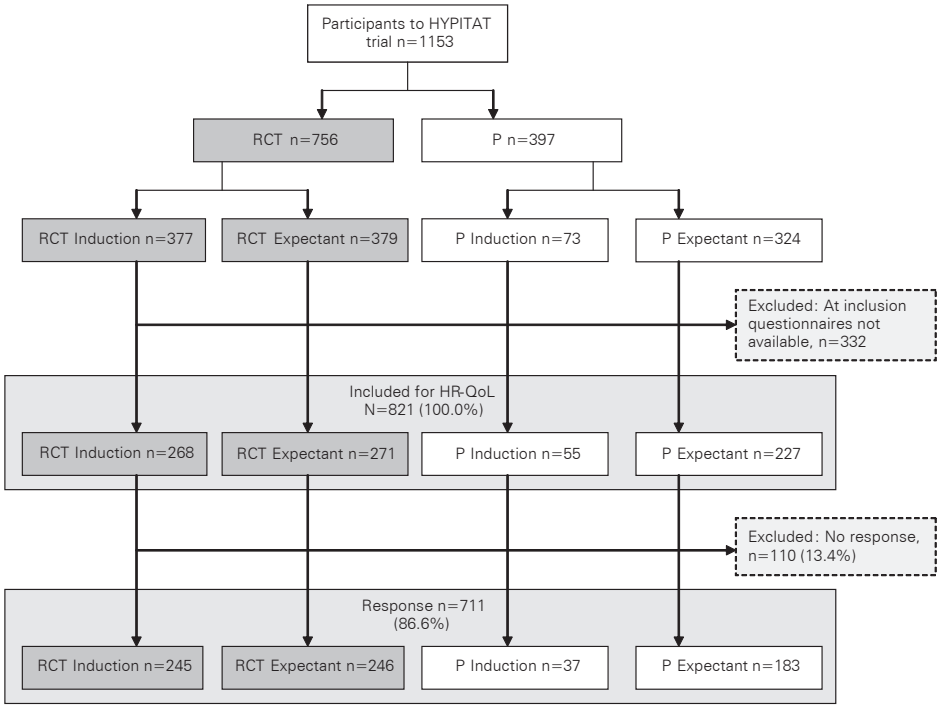

Figure 1. Flowchart of participants to the HYPITAT trial, number of inclusions in the HR-QoL study, and response percentages. HR-QoL = Health-related Quality of Life; RCT = randomised controlled trial; P = non-randomised treatment following protocol.

Non-response n=117	Total RCT vs. total P p	Response vs. Non-response p
30.6 (4.9)	< .001	.820
n/a [a]	< .001	n/a
27.0 (5.8)	.009	.209
60.9	.321	<.001
n/a	.002	n/a
n/a	.135	n/a
65.5	.323	.019
16.4	< .001	<.001

Baseline characteristics of the randomised and non-randomised HR-QoL participants and of the non-responding women (i.e. women who did not respond to any questionnaire) are shown in Table 1. Randomised women were significantly younger (p<.001), had tried longer to become pregnant (p<.001), had a higher pre-pregnancy BMI (p=.01), were less often employed (p<.01), and were less likely to have had a higher educational level (p<.001) as compared to non-randomised women. Compared to the non-responding women, the responding women were more often of Dutch origin (p<.001), were more likely to be nulliparous (p=.02), and were more likely to have had a higher educational level (p<.001).

We tested if our sample contained an overrepresentation of very good or bad cases in terms of maternal outcome and neonatal outcome. At 6 weeks postpartum there were no differences between responding and non-responding women in the proportion of adverse composite maternal outcome (35% vs. 33%; p=.53), the proportion of adverse composite neonatal outcome (5.7% vs. 9.0%; p=.08), caesarean section rates (17% vs.14%; p=.22), and the proportion of assisted vaginal delivery (14% vs. 16%; p=.41). At 6 months postpartum there were also no differences between responding and non-responding women in the proportion of adverse composite maternal outcome (36% vs. 32%; p=.26), the proportion of adverse composite neonatal outcome (6.6% vs. 7.1%; p=.78), caesarean section rates (17% vs. 14%; p=.25), and the proportion of assisted delivery (13% vs. 17%; p=.14).

Summary measures

At baseline, none of the summary scores was significantly different between the randomised induction of labour and expectant management groups. One of the domain scores (i.e. a sub-measure) was significantly different between the randomised groups (SCL Hostility, difference=0.3 in favour of induction of labour, p=.04). The mean difference scores of the randomised induction of labour and expectant management groups at both 6 weeks and 6 months postpartum are

Table 2. Average HR-QoL difference scores (Δ) per summary measure: comparisons between randomised groups (Ind=induction of labour; Exp=expectant monitoring) at 6 weeks and 6 months postpartum. P-values were calculated with one-way ANOVA analyses.

Summary measure	Δ inclusion, 6 weeks postpartum, n=351			Δ inclusion, 6 months postpartum, n=313		
	Ind n=188	Exp n=163	p	Ind n=167	Exp n=146	p
SF-36 Physical Component Score	11.1	10.1	.37	15.1	14.7	.70
SF-36 Mental Component Score	-2.3	-3.0	.55	-0.6	-1.1	.67
EuroQoL summary score	0.13	0.15	.32	0.16	0.18	.30
EuroQoL Mobility	0.02	0.04	.03	0.03	0.05	.10
EuroQoL Self-care	0.02	0.01	.39	0.02	0.02	.88
EuroQoL Activity	0.07	0.07	.92	0.08	0.08	.72
EuroQoL Pain/Discomfort	0.02	0.02	.90	0.03	0.03	.56
EuroQoL Anxiety/Depression	0.00	0.01	.40	0.01	0.01	.64
VAS general health	8.5	8.4	.95	9.8	9.1	.68
HADS Anxiety	-1.45	-1.29	.63	-1.18	-1.27	.88
HADS Depression	-2.09	-2.80	.61	-1.96	-2.17	.64
SCL-90 Psychoneurosis [a]	-	-		-13.0	-13.5	.90
SCL-90 Anxiety	-	-		-1.4	-1.6	.68
SCL-90 Agoraphobia	-	-		-0.3	-0.5	.29
SCL-90 Depression	-	-		-2.5	-3.2	.50
SCL-90 Somatic complaints	-	-		-4.0	-4.3	.75
SCL-90 Insufficient acting and thinking	-	-		-2.9	-1.8	.07
SCL-90 Interpersonal sensitivity	-	-		-1.5	-0.7	.31
SCL-90 Hostility	-	-		-0.1	-0.2	.78
SCL-90 Sleeping problems	-	-		-2.9	-3.0	.891

[a] The SCL-90 has only been conducted at inclusion and at 6 months postpartum.

shown in Table 2. At 6 weeks postpartum, none of the average difference scores was significantly different between the randomised groups. Only one of the domain scores was significantly different between the randomised groups (EuroQoL Mobility, p= .03). At six months postpartum, none of the average difference scores were significantly different between the randomised groups.

Figure 2 shows the mean scores of the SF36 PCS and MCS for the randomised groups at baseline, 6 weeks postpartum, and 6 months postpartum. The PCS increased substantially over time between baseline and 6 months postpartum ($p<.001$); the PCS was even higher than the Dutch population average. The MCS decreased at 6 weeks postpartum ($p<.001$), and slightly recovered after 6 months postpartum ($p=.03$).

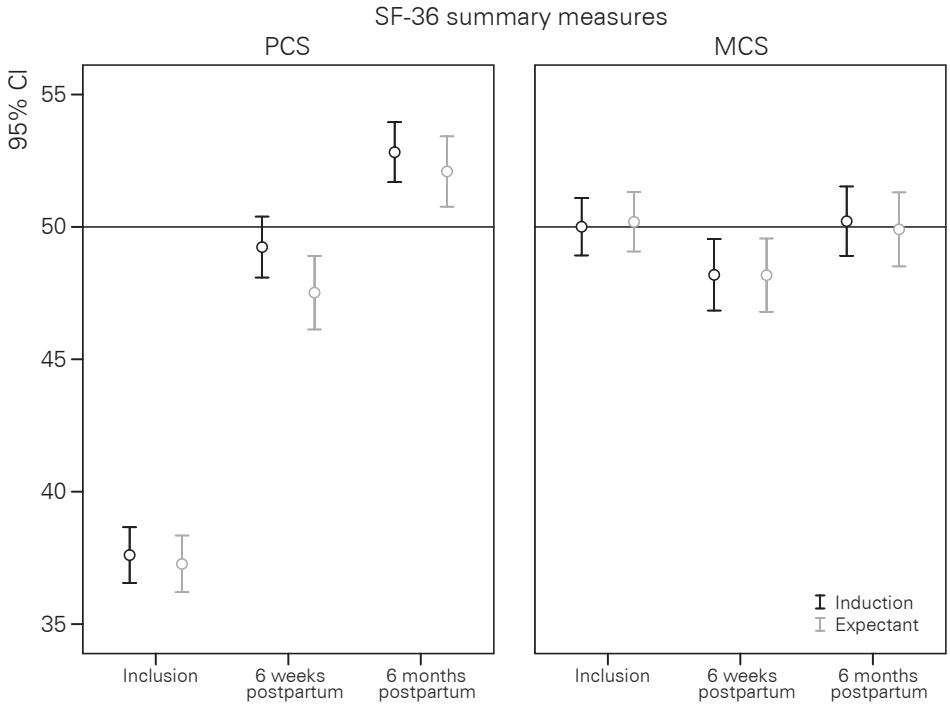

Figure 2. Error bars with 95% confidence interval (CI) of the randomised groups for induction of labour or expectant monitoring on the PCS and MCS at inclusion, at 6 weeks postpartum, and at 6 months postpartum. The horizontal lines indicate mean Dutch population norm scores.

Multivariate mixed model

Table 3 shows the results of the multivariate mixed model displaying the impact of each covariate on PCS and MCS over time, taking into account the patient's background characteristics, and characteristics of design and intervention (following ITT). The β-coefficients represent the change in PCS and MCS when the covariate changes with one unit of measurement. PCS improved substantially after childbirth (6 weeks postpartum: β=9.3, p<.001; 6 months postpartum: β=14.0, p<.001). The MCS first declined and then improved (6 weeks postpartum: β=-3.6, p<.001; 6 months postpartum: β=-1.7, p=.05). There was a significant negative effect of being randomised on PCS (β=-2.0, p=.02) but not on MCS (β=-1.1, p=.22). Intervention according ITT was not significant on either PCS (Induction of labour: β=-1.4, p=.09) or MCS (β=-0.2, p=.82). Of the background characteristics, being multiparous had a positive impact on PCS (p=.04), having a job had a positive impact on both the PCS (p<.01) and MCS (p=.01), and a higher pre-pregnancy BMI had negative impact on PCS (p<.01) but a positive impact on MCS (p=.01); none of the background characteristics had clinically significant effect (i.e. non of the betas

reached the clinical significant threshold of about 5). None of the interactions was statistically significant.

Table 3. Multivariate mixed model: estimates of main and interaction effects and covariates with 95% Confidence Interval (CI) on the SF-36 Physical Component Scale (PCS) and the Mental Component Scale (MCS). The β-coefficient represents the change in PCS and MCS when the covariate changes with one unit of measurement. n=434.

	PCS			MCS		
Parameter	Estimate (β)	95% CI	p	Estimate (β)	95% CI	p
Intercept	41.81	36.38 to 47.25	<.001	57.12	51.60 to 62.63	<.001
Time						
Baseline	Ref			Ref		
6 Weeks postpartum (6Wpp)	9.28	7.49 to 11.06	<.001	-3.63	-5.38 to -1.88	<.001
6 Months postpartum (6Mpp)	13.97	12.36 to 15.55	<.001	-1.73	-3.48 to 0.03	.054
Intervention following ITT [a]						
Expectant monitoring	Ref			Ref		
Induction of labour	1.43	-0.23 to 3.09	.091	-0.19	-1.47 to 1.86	.819
Randomisation status						
Not randomised	Ref			Ref		
Randomised	-2.01	-3.72 to -0.23	.021	-1.07	-2.78 to 0.65	.223
Age						
≤ 27 years	Ref			Ref		
28 to 33 years	0.86	-2.37 to 0.65	.263	-0.63	-2.23 to 0.96	.435
≥ 34 years	0.31	-1.49 to 2.10	.735	-0.88	-2.71 to 0.95	.347
Parity						
Nulliparous	Ref			Ref		
Multiparous	1.53	0.07 to 2.99	.040	-1.17	-2.75 to 0.40	.142
Time to conceive						
< 1 year	Ref			Ref		
≥ 1 year	0.77	-0.67 to 2.20	.294	-0.45	-2.12 to 0.97	.465
BMI pre-pregnancy						
< 25	Ref			Ref		
≥ 25	-1.80	-2.99 to -0.60	.003	1.64	0.35 to 2.92	.013
Educational level						
Lower	Ref			Ref		
Higher	0.20	-1.03 to 1.44	.749	1.03	0.98 to 2.36	.128
Employed						
No	Ref			Ref		
Yes	3.73	1.51 to 5.96	.001	3.03	0.64 to 5.42	.013
Interactions						
6Wpp * Randomized	-0.75	-3.07 to 1.58	.527	-0.93	-3.22 to 1.37	.428
6Mpp * Randomized	-0.91	-3.00 to 1.17	.388	-0.65	-2.94 to 1.64	.579
6Wpp * Induction of labour ITT	-0.79	-3.05 to 1.47	.490	-0.52	-2.74 to 1.71	.649
6Mpp * Induction of labour ITT	-0.08	-2.11 to 1.95	.940	-0.88	-3.11 to 1.36	.441

[a] ITT = Intention to treat

DISCUSSION

In this study we investigated the effect of induction of labour compared to expectant monitoring on health-related quality of life (HR-QoL) in women with gestational hypertension (GH) or mild pre-eclampsia (PE) at term. Physical health in both groups improved considerably over time while mental health was about stable. We did not find any significant impact of induction of labour or expectant monitoring on HR-QoL postpartum. Our findings in the non-randomised groups were comparable to those in the randomised groups.

In both randomised groups a part of the women crossed to the other strategy.[8] In the expectant monitoring group, labour eventually was induced in 173 (46%) of the 379 women after an average waiting period of 6.4 days (95% CI 0.83 to 19.9). In 10 (3%) of the 377 women allocated to the induction group, labour started spontaneously. Our intention to treat analysis is in agreement with real-life clinical decision-making, showing that long term HR-QoL on average is the same, regardless of whether induction or expectant monitoring is initiated. While we cannot exclude any effect of cross-over on HR-QoL, our results are generalizable in the sense that any effect of being randomised or not (-2.01 on a 0-100 scale) has no clinical significance.

Our HR-QoL study might be limited by three factors. First of all, the first postpartum assessment of HR-QoL was at 6 weeks. We did not assess HR-QoL between childbirth and 6 weeks. Low physical HR-QoL scores are typical for a limited period following childbirth, inherent to the mode of delivery and maternal morbidity postpartum. Since the caesarean section rates in the total study population differed only marginally between strategies (14% vs. 19%; RR 0.75 (95% CI 0.55-1.04)), it is unlikely that differences in mode of delivery had an impact on HR-QoL differences directly after childbirth.[8] Maternal morbidity, however, was lower after induction of labour (31% vs. 44%; RR 0.71 (95% CI 0.59-0.86)).[8] We cannot exclude that these differences may have affected short term HR-QoL after childbirth. Even if short term HR-QoL differences would exist, these apparently did not translate in long term HR-QoL differences. Second, we did not evaluate the impact of waiting on HR-QoL during expectant monitoring. Waiting may either improve HR-QoL, for example because of the more 'natural' procedure by avoiding artificial interventions. Expectant monitoring, however, may also decrease HR-QoL because of an increased level of anxiety, stress or uncertainty while waiting. One study revealed that the negative impact of anxiety and uncertainty during the waiting period on HR-QoL can be substantial.[21] The overall impact of waiting on HR-QoL, either a positive or negative impact, is probably small since the average

period of waiting is limited. Finally, while most women returned the postpartum questionnaires on time, others needed the written reminder for response, which might have delayed response –by a maximum of two weeks. We did not assess the potential impact of this study adherence on HR-QoL. Focussing on the randomised groups, however, we do not assume that there was effect of study adherence. The rationale is that study adherence is likely to be influenced by differences in baseline characteristics, which were absent in the randomised group between the strategy groups.

Our findings can be considered generalizable. First, we found several covariables of selective response (Table 1) but none these appeared to have a clinically relevant impact on HR-QoL (Table 3). Moreover, HR-QoL differences were the same in randomised and non-randomised women. Given the absence of HR-QoL differences, induction of labour appears to be a safe strategy, without compromising maternal HR-QoL on the group level. Our clinical analysis already showed a clear benefit of induction with respect to the prevention of progression to severe disease and a reduction in caesarean section rate, although the latter difference did not reach statistical significance.[8] Decision-making about the optimal treatment strategy may also be guided by economic aspects (i.e. the optimal strategy is the one with lowest costs) or, alternatively, by patient's treatment preferences. Despite the absence of differences in HR-QoL between strategies, most (82%) of the non-randomised women were managed expectantly, which supports the idea that prior preferences existed. Whether or not prior treatment preferences have an impact on treatment satisfaction and quality of life is part of future research.

Summarizing, while the HYPITAT trial shows that induction of labour resulted in significantly better maternal outcome and comparable neonatal outcome without higher caesarean section rate[8], our study adds that induction of labour in women with GH or PE at term does not affect long term maternal HR-QoL. Unless either economic analyses or analyses of patients' preferences show large advantages of expectant management, induction of labour is the preferred policy in women with GH or PE beyond 36 weeks of gestation.

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Chapter 5

An economic analysis of induction of labour and expectant monitoring in women with gestational hypertension or pre-eclampsia at term (HYPITAT trial)

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ABSTRACT

Objective To assess the economic consequences of labour induction compared to expectant monitoring in women with gestational hypertension (GH) or pre-eclampsia (PE) at term.

Design An economic analysis alongside the HYpertension and Pre-eclampsia Intervention Trial At Term (HYPITAT). Setting: Obstetric departments of 6 university and 32 teaching and district hospitals in the Netherlands.

Population Women diagnosed with GH or PE between 36^{+0} and 41^{+0} weeks gestation, randomly allocated to either induction of labour or expectant monitoring.

Methods A trial-based cost-effectiveness analysis was performed from a societal perspective during a one year time horizon. Main outcome measures: One year costs were estimated and health outcomes were expressed as the prevalence of poor maternal outcome defined as either maternal complications or progression to severe disease.

Results The average costs of induction of labour (n = 377) were €7.077 versus €7.908 for expectant monitoring (n = 379), with an average difference of -€831 (95% confidence interval: - €1.561 to - €144). This 11% difference predominantly originated from the ante partum period: per woman costs were €1.259 for induction versus €2.700 for expectant monitoring. During delivery more costs were generated following induction (€2.190) as compared to expectant monitoring (€1.210). No substantial differences were found in the postpartum, follow-up and non-medical costs.

Conclusion In women with GH or mild PE at term, induction of labour is less costly than expectant monitoring, due to differences in resource utilization in the ante partum period. As the trial already demonstrated that induction of labour results in less progression to severe disease without resulting in a higher caesarean section rate, both clinical and economic consequences are in favour of induction of labour in these women.

INTRODUCTION

Six to eight percent of all pregnancies are complicated by gestational hypertension (GH) or pre-eclampsia (PE).[1,2] Although outcome in most cases is good, hypertensive diseases remain a major cause of morbidity and mortality for both mother and child.[3] Moreover, the care for women with hypertensive disease in pregnancy imposes a substantial economic burden.

Most hypertensive diseases occur at or near term.[4] Because evidence on the choice between induction of labour and expectant monitoring for women with GH or mild PE at term is lacking, we recently performed a randomised clinical trial on that subject:[5,6] the HYpertension and Pre-eclampsia Intervention Trial At Term (HYPITAT, number ISRCTN08132825). Induction of labour significantly resulted in fewer women with progression to severe disease, whereas the caesarean section rate was lower albeit not significant. Apart from these clinical outcomes, knowledge on the cost is also of importance, in order to decide whether induction should be applied or not. At present, evidence on costs and cost-effectiveness of management of women with GH or PE at term is limited.

This study reports the results of the economic evaluation that we performed alongside the HYPITAT trial. We performed a cost-effectiveness analysis comparing induction of labour to expectant monitoring in high-risk pregnancies due to hypertensive disorders beyond 36 weeks of gestation.

METHODS

Trial design

Full details of the HYPITAT trial were reported previously.[5] The trial was approved by the Institutional Review Board of the University of Leiden (p04·210) and had local approval from the Boards of the other participating hospitals. The trial has been registered in the clinical trial register as ISRCTN08132825.

In short, the study was a multicentre randomised controlled clinical trial conducted between October 2005 and March 2008 in obstetric departments of 6 university and 32 teaching and district hospitals in the Netherlands. Women diagnosed with GH or PE beyond 36 weeks of pregnancy were allocated to either induction of labour or expectant monitoring.

In the induction group, labour was induced within 24 hours after randomisation. In case the cervix was ripe, labour was induced with amniotomy and, if labour did not start within 1 hour, augmentation with oxytocin was used. In case the cervix was judged to be 'unripe', cervical ripening was stimulated with use of intracervical or intravaginal prostaglandins, according to the local protocol.

In the expectant group, patients were monitored by local protocol until the onset of spontaneous delivery. Maternal monitoring consisted of frequent blood pressure measurements and laboratory tests. Fetal monitoring consisted of assessment of fetal movements as reported by the mother, as well as electronic FHR-monitoring and ultrasounds examination. Intervention was only recommended in case of one or more of the following conditions: diastolic blood pressure ≥110 mmHg, systolic blood pressure ≥170 mmHg, proteinuria ≥ 5 grams/ 24 hours, eclampsia, HELLP syndrome, suspected fetal distress, prelabour rupture of membranes lasting > 48 hours, meconium stained amniotic fluid or gestational age beyond 41 weeks.

Women who did not give informed consent for randomisation, but who gave authorization for the use of their medical records, were treated according to one of the two protocols at the discretion of the attending obstetrician. Data of these patients were analyzed to compare them with the randomised data.

The primary outcome in this trial was a composite measure of poor maternal outcome, defined as maternal mortality, maternal morbidity (eclampsia, HELLP syndrome, pulmonary edema, thrombo-embolic disease or placental abruption), progression to severe disease (at least one measurement during antenatal or postpartum period of diastolic blood pressure ≥110 mmHg, systolic blood pressure ≥ 170 mmHg and proteinuria ≥5 gram/ 24 hours) or major postpartum haemorrhage.[6] Secondary outcomes were: method of delivery, neonatal mortality, and neonatal morbidity. For neonatal morbidity we used a composite outcome consisting of a 5-minute Apgar score of lower than 7, umbilical artery pH of lower than 7.05, or admission to a neonatal intensive care unit (NICU).

Analysis of the clinical endpoints showed less cases of severe disease in the induction group (31% versus 44%, relative risk 0·71; 95% CI 0·59-0·86). No maternal or neonatal death or eclampsia occurred in both groups. There was no difference in neonatal morbidity rate (6% versus 8%, relative risk 0.75; 95% CI 0.45-1.26) and caesarean section rate (14% versus 19%, relative risk 0.75; 95% CI 0·55-1·04).[6]

Economic evaluation

An economic analysis was performed alongside the trial. As one strategy was found to be more effective the economic evaluation was set up as a cost-effectiveness analysis.[7,8] All unit costs were expressed in 2007 Euros using the consumer pricing index.[9]

We used a societal perspective which means that we included both medical and non-medical costs to examine the economic impact of both strategies on the whole society. We compared costs and effects from the moment of randomisation to one year postpartum. Thereby, we differentiated different cost categories (direct medical, non-medical and indirect costs) and provided details on utilization of health care resources. Discounting the costs was unnecessary because all costs occurred within one year.

Measuring resource utilization

Resources utilization was documented by extending the Case Record Form (CRF) with specific items on health care use and by administering additional questionnaires. In the CRF the following resource items were collected: maternal and neonatal admissions, method of delivery, induction method, hours in labour room and/or operation room, outpatient visits, medication, maternal laboratory tests, fetal monitoring, third stage delivery activities and neonatal monitoring.

Maternal admissions were differentiated into three phases: the antenatal, the delivery and the postpartum phase. For each admission, hospital stay was differentiated according to the level of care: intensive care, medium care, maternal ward, and home care, as different levels have different costs.

The time in the labour room was calculated as the time from admission to labour room to time of birth plus one hour extra for recovery care. Assuming that induction of labour takes place inside the labour room, it will be expected that the mean number of hours in the labour room are higher in the induction group due to time needed for induction. In case a caesarean section was performed, hours in the operation theatre were also calculated.

For each neonatal admission, hospital stay was differentiated according to the level of care as well: intensive care, high care, medium care, medium care on maternal ward, and maternal ward, as different levels have different costs. Duration of neonatal admission was calculated as the number of days between birth and hospital discharge. For neonatal admission to the maternal ward no extra costs

were generated, because it was assumed these costs were already included for the mother.

The long term use of health care from hospital discharge to one year postpartum was collected by using an additional questionnaire sent to a consecutive subsample of 99 randomised women and 48 non-randomised women one year after their childbirth. The questionnaire documented visits to health care providers and hospital admissions for their child and for themselves and medication use. In addition to these medical costs, sick leave from work (indirect non-medical costs), modes of travelling to hospital and the use of informal care given by partner and/ or family (direct non-medical costs) were assessed.

Unit costs

Different methods and sources were used to estimate unit costs as valuations for documented volumes of resource utilization (table 1). For maternal and neonatal admissions, third stage delivery and neonatal monitoring, unit cost estimates were available from the financial departments of one participating academic and one participating general hospital.

For use of the labour room and the operation theatre, unit costs were calculated per hour, using a bottom-up approach, in which all personnel, use of materials, and overhead calculated as a square meter price were integrated. Costs per type of delivery were then calculated by multiplying duration in labour room by the price for one hour in labour room and by counting up time in operation room multiplied by price per hour in operation theatre.

For some cost units (outpatient visit, specialist care, general practitioner visit, paramedical and home care, travel costs, informal care, and productivity loss) national standardized prices were used, and for laboratory testing tariffs were used.[10,11] Medication prices were estimated by using the Pharmacotherapeutic Compass.[12]

The value of productivity loss was calculated using the friction cost method from age-and sex-stratified data of the Dutch population.[10,11] This method assumes that workers that are withdrawn from work due to ill health will be replaced after some adaptation period – the "friction period". Consequently, costs from an individual woman's production loss are limited to a period of 10 weeks.

Table 1. Cost-analyses: units of resource use, unit costs, valuation method and volume source

	Unit	Unit costs	Valuation method (source)	Volume source
Medical costs				
Admission mother*				
hospital stay - ward	day	346	Top-down calculation	CRF
hospital stay - medium care	day	526	Top-down calculation	CRF
hospital-stay - intensive care	day	1,679	Top-down calculation	CRF
Admission child*				
hospital stay - medium care	day	526	Top-down calculation	CRF
hospital stay - high care	day	1,409	Top-down calculation	CRF
hospital-stay - NICU	day	1,459	Top-down calculation	CRF
Specialist care	hour	69	Dutch costing guidelines (11)	CRF/AQ
Outpatient visit*	visit	82	Top-down calculation	CRF/AQ
Psychologist	hour	34	Dutch costing guidelines (11)	AQ
Midwife	hour	34	Dutch costing guidelines (11)	AQ
General practitioner	visit	21	Dutch costing guidelines (11)	AQ
Paramedical	visit	25	Dutch costing guidelines (11)	AQ
Home care	hour	32	Dutch costing guidelines (11)	AQ
Day care	day	242	Dutch costing guidelines (11)	CRF
Induction methods**	gift	15	Pharmacotherapeutic website (12)	CRF
Antihypertensive medication and antibiotics**	dose per day	7	Pharmacotherapeutic website (12)	CRF
Analgesics during labour**	procedure	161	Top-down calculation	CRF
Neonatal monitoring**	procedure	90	Top-down calculation	CRF
Operation room*	hour	140	Bottom-up calculation	CRF
Labour room*	hour	82	Bottom-up calculation	CRF
Non-medical costs				
Travel costs- car	km	0.17	Dutch costing guidelines (11)	AQ
Travel costs- public transport	km	0.17	Dutch costing guidelines (11)	AQ
Informal care	hour	8.78	Dutch costing guidelines (11)	AQ
Productivity loss	hour	26	Dutch costing guidelines (11)	AQ

AQ= additional questionnaire; CRF= Case Report Form.
* The mean of the unit costs for an academic hospital and for a general hospital is presented.
** The mean of several methods/medications is presented.

Analyses

Group differences in resource use were tested by using the nonparametric Mann-Whitney test, as resources generally have a skewed distribution. Resource use per patient was multiplied by unit costs, and total costs per patient were calculated. Mean costs and median costs per patient were estimated, and mean cost differences between study groups were calculated. The 95% confidence intervals around the difference in mean costs, and incremental cost-effectiveness ratios (ICERs) were determined by bootstrapping. An ICER is the ratio of costs

differences versus the effectiveness differences between two interventions. Bootstrap methods are based on generating multiple replications of the statistic of interest by sampling with replacement from the original data.[7,8] Analyses were by intention-to-treat.

Thirteen univariate sensitivity analyses were performed to explore the impact of different assumptions and alternative unit-cost estimates on the results of the costs analysis. Several assumptions were made in estimating labour and operation room costs by using a bottom-up method, such as time spent in labour room and/or operation room by obstetricians and gynaecologists. In the first sensitivity analysis some variations of these assumptions were made to find out their impact on the final results (model 1). We examined several other ways of estimating the delivery costs using a top-down method (model 2) and a combination of both methods (model 3). Because most cost differences were expected ante partum due to longer maternal hospital stays in the expectant group, we wanted to find out the impact of lower valuation of the ante partum admissions by assuming several other monitoring strategies: Medium Care instead of Intensive Care (IC) admissions (model 4), day care instead of inpatient care (model 5), outpatient visits plus CTGs instead of inpatient care (model 6) and home care instead of inpatient care (model 7). In our base case analysis we included no costs for the neonatal ward admissions because we assumed this was covered by the maternal ward admissions. In model 8 we priced neonatal ward admissions to check its impact. In the base case analysis we separated all admissions into four different phases. In a sensitivity analysis we examined the impact of no separation into phases (model 9). In another sensitivity analysis (model 10) operation room costs were calculated by assuming one hour operation room time per patient instead of the actual measured hours in the original study. Finally the impact of using lower or higher unit costs during all the phases was studied in model 11, 12 and 13.

A subgroup analysis was performed to assess the consistency of the cost-effectiveness effect in patients with GH and patients with mild PE.

Statistical, economic and simulation analyses were performed using SPSS software (version 16.0, Chicago, IL) and Microsoft Excel.

RESULTS

Resource use

For the cost analysis we used data of all 756 randomised women and all 397 non-randomised women. Of the randomised women, 377 were assigned to the induction group and 379 to the expectant monitoring group. Among the 397 non-randomised patients, labour was immediately induced in 73 patients, whereas 324 patients were initially managed expectantly. Additional data on resource use during follow-up acquired by questionnaires were available for 55 randomised women, 32 allocated to induction and 23 to expectant management. In the non-randomised group 41 women returned a questionnaire, of which 6 women had been allocated to induction and 35 had been monitored expectantly.

Average volumes of resource utilization, total costs in each study group, and average costs per patient are presented in table S1a & S1b in the Appendix. Most remarkable differences in resource use between groups were generated during the antenatal and delivery period. There were more outpatient visits in the expectant group (9% in induction group versus 66% in expectant group, $p<0.001$) and a longer antenatal stay in hospital (3 days in the induction group versus 6 days in the expectant group, $p<0.001$). Stay at the labour room or operation theatre was longer for induced women (21 hours versus 10 hours, $p<0.001$). Until 1 year after childbirth women in the expectant group stayed a little longer in hospital than the women in the induction group (3.5 days induction versus 4.0 days expectant, $p<0.001$). The number of hospital days for the children were comparable between both groups (4.2 days induction and 4.3 days expectant, $p=0.014$). The average duration of sick leave after the three months permitted maternal leave as is common practice in the Netherlands, until 1 year follow-up was comparable (3.0 days versus 2.3 days, $p=0.39$).

Costs

A summary of mean and median costs per patient is presented in table 2. In the ante partum period costs per patient appeared to be higher in the expectant monitoring group because of longer maternal stays (difference: - €1.441). During delivery the costs in the induction group were higher than in the expectant monitoring group (difference: €980). This is due to longer stays in the labour room associated with the induction procedure. Until one year postpartum, women in the expectant monitoring group generated slightly more costs than women in the induction group (difference: - €398), because of longer maternal stays, longer neonatal intensive care stays, and more specialist visits. There were no substantial differences in

Table 2. Comparison of costs between randomised induction of labour and expectant monitoring

	Induction (n=377)		Expectant management (n=379)	
	Mean	**Median (IQR)**	**Mean**	**Median (IQR)**
Maternal admission	993	574 (0-1435)	2136	1215 (0-2835)
CTGs and ultrasounds	168	116 (87-203)	287	232 (145-377)
Outpatient visits	12	0 (0-0)	131	59 (0-280)
Assessments and medication	81	63 (31-116)	137	116 (62-187)
Laboratory tests	5	4 (2-6)	9	8 (4-12)
Total antepartum	**1259**	**822 (234-1786)**	**2700**	**1817 (631-3466)**
Admission because of labour	319	287 (0-574)	285	287 (0-405)
Induction material	64	45 (1-90)	20	0 (0-1)
Medication during labour	73	0 (0-161)	64	0 (0-161)
Mode of delivery	1734	960 (584-1691)	841	640 (324-1053)
Total delivery	**2190**	**1292 (815-2446)**	**1210**	**927 (567-1546)**
Maternal admission	1098	861 (574-1435)	1291	861 (574-1435)
Neonatal admission	967	0 (0-0)	1012	0 (0-0)
Paediatrician and monitoring	42	0 (0-69)	42	69 (0-69)
Total postpartum	**2105**	**1148 (810-2094)**	**2345**	**1148 (643-2417)**
Primary and specialist care	486	458 (458-559)	772	957 (957-1452)
Maternal admission	0	-	114	103 (103-146)
Neonatal admission	240	218 (218-218)	0	-
Total follow-up	**726**	**677 (677-867)**	**886**	**759 (759-1066)**
Travel costs*	22		37	
Informal care*	703		686	
Productivity loss*	72		44	
Total non-medical care	**797**		**767**	
Total cost	**7077**	**5530 (4142-7949)**	**7908**	**6235 (4508-9331)**
Differential mean cost (95% CI)***	**-831 (-1561 to -144)**			

IQR= Interquartile range
* No median and interquartile percentiles are presented, because these are extrapolated data.
**Induction minus expectant management.
*** Non-parametric confidence interval based on 1000 bootstrap replications.

non-medical costs. Overall, mean costs per patient were €7.077 (95% CI 2.326 to 19.726) for induction and €7.908 (95% CI 2.561 to 27.037) for expectant monitoring (difference - € 831 (95% CI -1.561 to -144)).

Table 3 shows mean and median costs per patient in the nonrandomised groups. Because only 6 women from the nonrandomised induced group returned the follow-up questionnaire, estimates of costs generated during follow-up and non-medical costs for this group are not very reliable. If follow-up and non-medical costs are excluded total mean costs between randomised and nonrandomised induced patients are comparable (€5554 versus €5670). Mean costs per nonrandomised

Table 3. Costs per patient in nonrandomised groups

	NR Induction (n=73)		NR Expectant management (n=324)	
	Mean	**Median (IQR)**	**Mean**	**Median (IQR)**
Maternal admission	1465	574 (0-1325)	1378	405 (0-1722)
CTGs and ultrasounds	187	145 (116-218)	233	203 (145-290)
Outpatient visits	78	0 (0-59)	142	104 (0-208)
Assessments and medication	81	54 (31-124)	117	93 (41-171)
Laboratory tests	7	6 (4-8)	7	6 (4-10)
Total antepartum	**1818**	**951 (290-1550)**	**1882**	**1113 (414-2231)**
Admission because of labour	309	287 (0-574)	257	287 (0-405)
Induction material	56	45 (1-90)	27	0 (0-45)
Medication during labour	71	0 (0-161)	60	0 (0-161)
Mode of delivery	1358	960 (589-1529)	983	653 (385-1234)
Total delivery	**1795**	**1267 (819-2364)**	**1327**	**945 (560-1711)**
Maternal admission	1309	861 (810-1435)	1110	861 (574-1435)
Neonatal admission	719	0 (0-0)	665	0 (0-0)
Paediatrician and monitoring	30	0 (0-69)	45	69 (0-69)
Total postpartum	**2057**	**1148 (836-2091)**	**1818**	**930 (724-1843)**
Primary and specialist care	491	471 (471-530)	579	526 (526-709)
Maternal admission	0	-	0	-
Neonatal admission	0	-	179	161 (161-227)
Total follow-up	**491**	**471 (471-530)**	**758**	**687 (687-933)**
Travel costs*	35		25	
Informal care*	220		403	
Productivity loss*	0		112	
Total non-medical care	**255**		**540**	
Total cost	**6416**	**4924 (3443-7151)**	**6325**	**5037 (3441-7695)**

IQR= interquartile range; NR= not randomised.
* No median and interquartile percentiles are presented, because these are extrapolated data.

patient in the expectant management group were lower than the randomised expectant monitoring patient in all phases, except for the delivery phase.

The subgroup analysis showed mean costs per woman with mild PE of € 7.870 (n=123, median € 6.347, interquartile range [IQR] € 4.826 to € 9.429) in the induction group and € 10.387 (n=123, median € 8.069, IQR € 6.019 to € 12.792) in the expectant management group. Mean costs per woman with only GH were € 6.679 (n= 244, median 5.115, IQR € 3.789 to € 7.647) in the induction group and € 6.682 (n= 252, median 5.377, IQR € 4.100 to € 7.876) in the expectant management group.

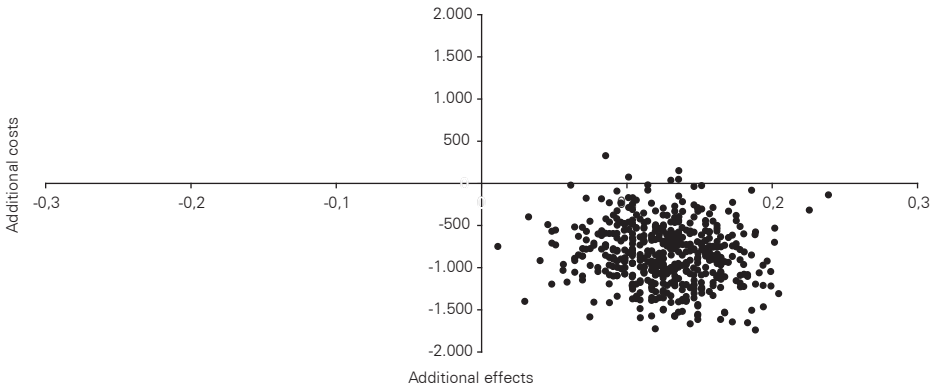

Figure 1. Cost-effectiveness plane Additional costs: difference in average costs per patient between the induction group and the expectant group (in 2007 Euros). Additional effects: difference in proportion of maternal complications between the induction group and the expectant group.

Cost-effectiveness

With an estimated difference in progression to severe disease between the two strategies of 13% in favour of induction of labour, and a mean difference in costs per patient of €831 also in favour of induction of labour, induction of labour was the dominant strategy.

We also assessed uncertainty in the estimated ICERs (bootstrap analysis), depicted in a cost effectiveness plane. Figure 1 shows that with high certainty induction is a cost saving strategy compared to expectant monitoring in pregnant women with GH or mild PE. In the upper right quadrant a strategy is considered cost-effective if the ICER is located below the line reflecting willingness-to-pay (how much one is willing to pay for one unit gain in health outcome). A strategy will always be cost-effective, irrespective of willingness-to pay, if all bootstrap estimates of incremental cost-effectiveness ratios are located in the lower right quadrant.

Sensitivity analyses

In table 4 results of the sensitivity analyses are shown. If we increase the labour and operation room costs from € 80 to € 115 and from €140 to € 224 per hour, this increases mean costs in both groups but decreases the difference to - €470, and expectant monitoring remains the most expensive strategy (model 1). Top-down calculation (model 2) or a combination of bottom-up and top-down calculation (model 3) of the delivery costs resulted in higher mean costs per patient in the expectant group and lower mean costs per induced patient. The ante partum intensive care (IC) admissions were valued for medium care prices, to find out if

Table 4. Sensitivity analyses results

Model	Description	Induction	Expectant management	Difference
	Base case scenario	€ 7,077	€ 7,908	- € 831
1	Higher labour (€115) and operation (€224) room costs	€ 7,774	€ 8,244	- € 470
2	Top-down calculation of delivery costs	€ 6,660	€ 8,456	- € 1,796
3	Bottom-up and top-down calculation of delivery costs (combining registered days of induction and top down unit prices for delivery)	€ 6,897	€ 8,551	- € 1,654
4	Ante partum IC admissions priced as Medium Care	€ 7,007	€ 7,445	- € 438
5	Value antepartum admissions by day-care prices	€ 6.817	€ 7.460	- € 643
6	Replace antepartum admissions by outpatient visits and CTGs	€ 6.438	€ 6.804	- € 366
7	Replace antepartum admissions by home care	€ 6.854	€ 7.523	- € 669
8	Value neonatal ward admissions	€ 7.579	€ 8.309	- € 730
9	Summarize all admissions without separate phases	€ 8.189	€ 8.899	- € 710
10	Standardize time in operation room to 1 hour (plus 1 hour recovery time)	€ 7.093	€ 7.939	- € 846
11	Value admissions by using academic unit prices only	€ 8,169	€ 9,665	- € 1,496
12	Value admissions by using general unit prices only	€ 6,591	€ 7,359	- € 768
13	Value admissions by using Dutch standard prices (11)	€ 7,555	€ 8,774	- € 1,219

it impacts the total costs per group. The mean costs per patient in the expectant group decreased a little. Because costs for the induced patient remained rather the same, the mean cost difference reduced to - €438 (model 4). Replacing antepartum inpatient care by other monitoring strategies (model 5, 6 and 7) decreased the mean costs per patient in both groups, but expectant management remains the most expensive strategy. Including neonatal ward admissions (model 8), summarizing all admissions without separate phases (model 9) or standardizing operation room time (model 10) increases mean costs per patient in both groups, but the differences remain rather the same. We also estimated costs by using higher and lower unit prices for hospital stay and outpatient visits. If we only use the unit costs from the academic centre, the mean costs per patient in both groups increase and the difference increases to - €1496 (model 11). If we only use the unit costs from the general hospital, the mean costs per patient decrease, but the differences between groups remain the same (model 12). If we estimate costs associated with in-patient admissions by using the Dutch national standardized unit costs the difference between groups increases (model 13).

DISCUSSION

This study assessed the economic consequences of induction of labour or an expectant monitoring strategy in pregnant women with GH or mild PE at term,

from a societal point of view. This economic analysis was performed alongside the HYPITAT trial.[6] To our knowledge it is the first economic evaluation that prospectively compared these strategies.

Our analyses show that the mean costs per patient generated by induction of labour were €831 (95% CI -1.561 to -144) lower as compared to those for expectant monitoring. Unsurprisingly, the difference in costs predominantly originated in the ante partum period, due to longer hospital stays before childbirth for women in the expectant group. On the other hand, during delivery more costs were generated following induction due to the longer duration in labour room because of induction itself. In our base-case analysis we assumed that induction was done in the labour room and we estimated delivery costs by using number of hours in labour room and unit costs for one hour in the labour room. In sensitivity analyses we examined the consequences if delivery costs were estimated using a top-down calculation, i.e. using unit costs per method of delivery. As a result the cost difference between both strategies doubled. This means that if induction time is not included separately in the costs analyses (it is assumed that these costs are already included in the costs of hospital admission), the costs difference during delivery in favour of expectant monitoring disappears and expectant monitoring even becomes more expensive. However, in our opinion top-down calculation for estimating delivery costs is not an appropriate method, because it underestimates costs due to induction and the time spent on induction itself.

In the period from childbirth until one year postpartum medical costs appeared to be €398 higher for women in the expectant monitoring group, mostly due to longer maternal and neonatal stays in the hospital and more postpartum specialist visits. Clinical results of the HYPITAT trial already indicated that induction of labour results in less progression to severe disease and that it has a lower caesarean section rate. The higher postpartum costs for women in the expectant group are a consequence of these findings. During delivery, expectant monitoring remained less costly despite more caesarean sections in this group. Higher caesarean section costs for induced patients are caused by the longer stay in the labour and operating theatre. No substantial differences were found in the non-medical costs. These costs and the above mentioned follow-up costs were estimated in a subgroup of the total trial population by using an additional questionnaire. Because of the small number of participants, this results in broad confidence intervals around the follow-up and non-medical costs, and thus higher uncertainty around these estimates. On the other hand, we were able to estimate the impact of both strategies on indirect costs and for a longer time horizon than the trial duration, which improves the relevance from a societal perspective.

In the Netherlands, women are permitted a maternal leave for three months after childbirth. In estimating the yearly costs of productivity loss we only included the remaining nine months after the maternal leave. Therefore, before generalizing non-medical costs to other countries, the local arrangements for maternal leave need to be considered.

The prospective design of the trial, the large number and diversity of participating hospitals and the well-organized structure of randomisation and data-collection within the Dutch Obstetric Consortium[13] are likely to extend both the internal and external validity of our results.

Overall, costs per randomised patient in the expectant group were higher than the costs per non-randomised patient, except for the delivery phase. From the clinical data it can be observed that randomised women had little more bad maternal outcomes after expectant management than nonrandomised women (44% versus 38%). For that reason the randomised women might be admitted more and longer in hospital before and after childbirth and this might explain the higher costs per randomised patient in these groups. Children in the randomised expectant group stayed longer in MC/HC than the nonrandomised children. This is probably not a trial effect (better monitoring in the randomised group), because this effect was not seen within the induced groups.

According to the clinical results of the HYPITAT trial induction of labour should be advised in women with GH and a diastolic blood pressure ≥95 mmHg or mild PE at a gestational age beyond 37 weeks.[6] The results as described in this economic evaluation study indicate that this strategy is also associated with lower average costs per patient.

In summary, induction of labour is found to be a less costly and more effective strategy as compared to expectant management in women with GH or PE beyond 36 weeks of gestation.

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Supporting information

The following supplementary materials are available for this article.

Table S1. Resource use, mean costs per woman and total costs, medical care (2007 Euros)

Table S2. Resource use, mean costs per woman and total costs non-medical (2007 Euros).

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Table S1. Resource use, mean costs per patient and total costs, medical care (2007 Euros)

	Unit	Induction (n=377)			
		% patients using care	Mean volume*	Total Costs (€)	Mean Costs pp (€)
Total antepartum phase[a]				**474,741**	**1,259**
Maternal admission IC	days	2%	3	34,307	91
Maternal admission MC	days	11%	3.6	74,269	197
Maternal admission ward	days	52%	4.4	263,146	698
Home care	days	4%	5.5	2,639	7
CTGs and Ultrasounds	procedure	100%	8.8	63,261	168
Outpatient visits	visit	9%	3	4,807	13
Assessments and lab tests	procedure	99%	13	32,087	85
Medication#				226	0,6
Total delivery phase				**823,704**	**2,19**
Admission because of labour [b]	day	54%	1.7	120,263	319
Induction material	Gift	92%	4.7	24,087	64
Medication during labour#	Unit	50%	-	27,521	73
Spontaneous route of delivery	hours	72%	17.6	384,54	1,025
Instrumental delivery	hours	13%	26.0	105,183	279
Caesarean delivery	hours	15%	36.8	162,11	430
Total postpartum[c]				**776,62**	**2,105**
Maternal admission IC	days	2%	2.5	19,981	53
Maternal admission MC	days	4%	3.3	23,751	63
Maternal admission ward	days	90%	3.4	368,329	977
Neonatal admission IC	days	3%	4.0	64,467	171
Neonatal admission HC	days	4%	6.9	129,311	343
Neonatal admission MC	days	19%	5.0	170,781	453
Total follow-up				**273,702**	**726**
Primary care	visit	94%	15.5	122,902	326
Specialist care	visit	28%	2.4	60,32	160
Maternal admission	days	0%	0	0	0
Neonatal admission	days	3%	1	90,48	240

* of patients using care. # medication costs are an summation of several medications, therefore no unit and mean volume is given. [a] ante partum admissions: time from hospital admission to the discharge date (only if the discharge date was prior or equal to the child's birth date) or to birth date (if discharge date was after child's birth date) and if the reason of admission was not equal to labour.

Table S2. Resource use, mean costs per patient and total costs, non-medical (2007 Euros)

	Unit	Induction (n=377)			
		% patients using care	Mean volume*	Total Costs (€)	Mean Costs pp (€)
Total non-medical care				**300,469**	**797**
Travel costs (car or public transport)	km	66%	132	8,294	22
Informal care	hours	68%	80	265,031	703
Productivity loss	days	9%	3	27,144	72
Total costs				**2,668,029**	**7,077**

* of patients using care

Expectant monitoring (n=379)				
% patients using care	Mean volume*	Total Costs (€)	Mean Costs pp (€)	Difference (I-EM)
		1,023,383	**2,7**	**-1,441**
6%	8.4	223,989	591	-500
11%	4.9	112,184	296	-99
57%	7.1	463,896	1224	-526
11%	7.6	9,854	26	-19
100%	12.6	108,773	287	-119
66%	4.7	49,649	131	-118
100%	21.8	54,375	144	-58
		663	1,75	-1,15
		456,695	**1,21**	**980**
55%	1.5	108,015	285	34
41%	4.8	7,58	20	44
42%	-	24,256	64	9
67%	8.6	174,34	465	560
14%	13.1	57,608	152	127
19%	14.5	84,896	224	206
		788,699	**2,345**	**-238**
3%	5	82,622	218	-165
4%	3.5	25,393	67	-4
85%	3.7	379,758	1002	-25
2%	7.3	84,517	223	-52
3%	7.3	104,604	276	67
19%	6.0	194,427	513	-60
		462,001	**886**	**-160**
87%	16	116,732	308	18
22%	5.6	301,684	464	-304
4%	2	43,206	114	-114
0%	0	0	0	240

[b] Admission during labour: the time between admission and discharge date, if the discharge date was prior or equal to the child's birth date and the reason for admission was labour. [c] Postnatal admissions: the days between admission date after or equal to the child's birth and the discharge date.

Expectant management (n=379)				
% patients	Mean volume*	Total Costs (€)	Mean Costs pp (€)	Difference (I-EM)
using care		**290,693**	**767**	**30**
65%	225	14,023	37	-15
78%	77	259,994	686	17
22%	2.3	16,676	44	28
		2,995,995	**7,908**	**-831**

Part II

Prediction of severe maternal morbidity in gestational hypertension or (mild) pre-eclampsia

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Chapter 6

Prediction of progression to severe disease in women with gestational hypertension or mild pre-eclampsia at term

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ABSTRACT

Objective To evaluate whether progression to severe disease is predictable in women with gestational hypertension (GH) or mild pre-eclampsia (PE) at term.

Methods Women with a singleton pregnancy, a fetus in cephalic position, between 36 and 41 weeks of gestation, complicated by GH or mild PE that were managed expectantly, were selected from the HYPITAT trial. We evaluated the predictability of progression to severe disease. Logistic regression was used to determine the predictive value of clinical characteristics or laboratory findings and to generate a prediction model for clinical deterioration. The predictive value of this model was assessed with receiver-operating-characteristic (ROC) analysis, calibration and internal validation.

Results We included 703 women, of whom 244 (34.7%) had progression to severe disease. After multivariable analysis nulliparity (OR 1.87), maternal age (OR 1.05 per year), gestational age (OR 0.88 per week), previous abortion (OR 1.26), ethnicity (OR 2.05 for non-Caucasian ethnicity), diastolic (OR 1.04 per mmHg), systolic blood pressure (OR 1.02 per mmHg), and the laboratory parameters proteinuria, haemoglobin, platelets, uric acid and alanine aminotransferase were included in the final model. The area under the ROC-curve of this model was 0.71 (95% CI, 0.67-0.74). Even though the goodness of fit was moderate (p=0.40), internal validation showed the model could hold in the overall population.

Conclusion In women with GH or mild PE at term progression of severe disease can be predicted. Therefore, identified predictors can guide physicians in the treatment of an individual patient with GH or mild PE at term.

INTRODUCTION

Severe hypertension is associated with maternal morbidity, such as eclampsia, pulmonary oedema, cerebrovascular accidents encephalopathy and haemorrhage.[1-3] The majority of these hypertensive disorders occur after a gestational age of 36 weeks. Until recently, a strong controversy on the management of women with mild hypertensive disease at term existed in the Netherlands. The majority of individual hospital protocols recommended expectant monitoring, but uniformity was lacking. We performed a randomised clinical trial, which showed that induction of labour reduces the risk of clinical deterioration to severe disease compared to expectant monitoring in women with gestational hypertension (GH) or mild pre-eclampsia (PE) at term. This reduction occurs without increasing the caesarean section rate and with similar neonatal outcome.[4]

However, it is questionable if induction of labour is the best treatment option in all patients with GH or mild PE at term. For instance, in women with a uterine scar, induction of labour is associated with increased risk of uterine rupture.[5] Hence; identification of patients at increased risk of developing severe maternal morbidity is of the utmost importance. Several studies have demonstrated that factors such as parity, gestational age (GA), blood pressure, liver function, and kidney function are predictors of maternal morbidity in women with hypertensive disorders of pregnancy.[6-9] However, the prognostic value of these indicators in a multivariate approach remains unclear.

In the present study, we assessed the prognostic capacity of clinical characteristics and laboratory findings with respect to progression to severe disease in women with GH or mild PE at term. Furthermore, we propose a new prognostic model, which can aid clinicians in the treatment of individual patients.

METHODS

We used data from patients managed by expectant monitoring in the context of a randomised clinical trial in the Netherlands that was performed between October 2005 and March 2008 (the HYPITAT trial).[4] In short, patients with a singleton pregnancy with a child in cephalic position and a GA between 36+0 and 41+0 weeks whose pregnancy was complicated by GH or mild PE were asked to participate in the trial. 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 at 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 were 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, haemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome, use of intravenous anti-hypertensive medication or a caesarean section in history.

Patients who had given informed consent were randomly allocated to either induction of labour or expectant monitoring. Patients who did not give consent for randomisation, but who provided consent for the use of their medical data, were treated according to local protocol. Patients in the expectant group were monitored until the onset of spontaneous delivery or until there was a medical indication for delivery. Monitoring consisted of frequent maternal blood pressure measurements, assessments of proteinuria, laboratory tests and regular assessment of fetal condition.

The present study was limited to patients managed expectantly, and combined both the randomised and the non-randomised women in one cohort. The primary endpoint was a composite outcome of progression to severe disease which was defined as the occurrence of any of the following: eclampsia, HELLP syndrome (platelet count <100×109/L and AST >70 U/L or ALT >70 U/L), maternal mortality, diastolic BP ≥110 mmHg, systolic BP ≥170 mmHg and/or proteinuria ≥5 gram in 24 hours.

We evaluated whether this composite endpoint was predictable from clinical characteristics (maternal age, ethnicity, parity, body mass index, diastolic BP, systolic BP, proteinuria), vaginal examination (cervical dilatation, effacement, consistency, engagement, position, length and the overall Bishop score) or laboratory findings (haemoglobin, haematocrit, platelets, uric acid, creatinine, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and proteinuria) measured at baseline. Cervical length measurements (using transvaginal sonography) and vaginal digital examination were performed before randomisation. In case of non-randomisation these examinations were not always performed at baseline.

Missing data

There were no missing data for the composite endpoint, but several potentially prognostic variables had varying percentages of missing values. Missing data of the predictive variables were imputed, because exclusion would lead to a loss of

statistical power in multivariable analysis and, more seriously, potentially biased results. In multivariable prognostic research complete case analysis should be avoided and multiple imputation methods are known to be superior to other imputation methods.[10] Multiple imputation was performed using PASW Statistics 17.0 (SPSS inc. Chicago, Illinois), in which we generated 5 imputed datasets.

Data analysis

Using the imputed multiple dataset, logistic regression was performed to predict occurrence of the primary endpoint from clinical characteristics and laboratory findings. For both dichotomous and continuous variables univariate pooled odds ratios, and 95% confidence intervals (CI), as well as p-values, were calculated. Subsequently, multivariable logistic regression analysis with a stepwise backward selection procedure of predictors was performed to construct a prediction model for progression to severe disease. Confounding variables were excluded in multivariate analysis. Since the purpose of the prediction model is to reach optimal predictive power, our multivariate analysis was not limited to significant prognostic variables but considered all prognostic variables with a significance level of <0.40 in the univariate analysis.[11]

To evaluate the discriminative performance of the logistic model, the area under the Receiver Operating Characteristic (ROC) curve was calculated, comparing the actual outcome to the outcome predicted by the model.

We also evaluated the calibration of the prediction model by plotting observed and predicted event rates for 10 subgroups of patients on the basis of deciles of the predicted probability of deterioration.[12] The reliability of the model was estimated with the Hosmer and Lemeshow test for goodness-of-fit. Calculations were performed with the PASW Statistics 17.0 (SPSS inc. Chicago, Illinois) and graphs were produced using GraphPad Prism (GraphPad Software, Inc. La Jolla, USA). Internal validation and extent of overfitting of the model was assessed with bootstrapping in R.[13] Two hundred bootstrap samples were drawn from each imputation set. In each bootstrap sample, the entire modelling process was repeated. The bootstrap procedure yields an ROC area corrected for optimism and a shrinkage factor to adjust the model for overfitting.

RESULTS

We identified 1153 eligible women for participation in the HYPITAT trial. In total 756 women gave informed consent for randomisation, of whom 379 patients (50%)

were randomly allocated to expectant monitoring. Among the 397 patients who refused randomisation, 324 patients (82%) were initially managed expectantly (fig. 1). We combined both the 379 randomised and the 324 non-randomised patients who were managed expectantly into one cohort (n=703). Figure 1 also shows onset of labour and mode of delivery for both expectant management groups. In both groups labour was eventually induced in almost half of the women, of whom 50% had at least one maternal medical reason to induce (e.g. severe hypertension/ proteinuria, HELLP syndrome, use of anticonvulsive/intravenous antihypertensive drugs, prelabour rupture of membranes >48h or gestational age >41 weeks). Suspected fetal distress was the reason for induction of labour in 18 (10%, randomised group) versus 9 (6%, non-randomised group) of the women. Elective induction of labour occurred in 48 (28%) versus 46 (30%) of the patients.

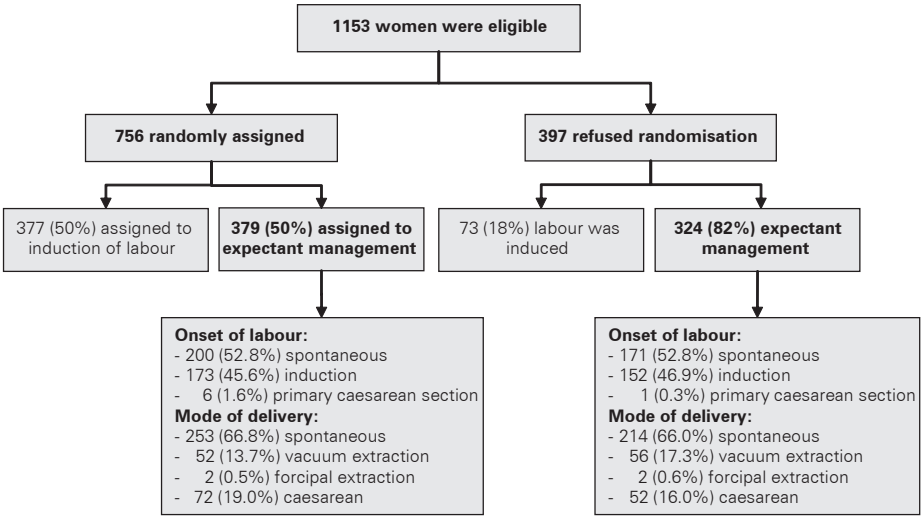

Figure 1. Trial profile of the HYPITAT trial.

Progression to severe disease occurred in 244 (34.7%) patients, as determined by one or more of the following variables: diastolic blood pressure ≥110 mmHg (n= 173, 25%); systolic blood pressure ≥170 mmHg (n= 147, 21%); proteinuria ≥5 gram (n= 8, 2.5%) and HELLP syndrome (n=17, 2.4%). Neither eclampsia nor maternal death occurred.

Baseline patient characteristics of the women with progression versus no progression to severe disease, together with the amount of missing values per variable are presented in Table 1. Primary outcome was available for all 703 women. Women in the group with progression to severe disease had younger GA at the

Table 1. Baseline patient characteristics: progression versus no progression to severe disease. Original data.

Characteristics	Progression to severe disease (n=244, 34.7%)		No progression to severe disease (n=459, 65.3%)		p
	Value	Patients with available data n (%)	Value	Patients with available data n (%)	
Nulliparous	188 (77.0%)	244 (100)	332 (72.3%)	459 (100)	.18
Maternal age (year)	30.0 (22.0-39.0)	244 (100)	30.0 (22.9-38.0)	459 (100)	.06
Gestational age (week)	38.1 (36.2-40.3)	243 (100)	38.6 (36.4-40.4)	458 (100)	.004
Previous abortion	67 (27.5%)	244 (100)	100 (21.8%)	459 (100)	.09
Maternal smoking	26 (11.4%)	228 (93)	47 (10.8%)	435 (95)	.82
Body Mass Index (kg/m^2)	31.8 (24.0-41.9)	124 (51)	31.3 (24.6-42.3)	247 (54)	.32
Ethnic origin		218 (89)		420 (92)	.02
Caucasian	182 (83.5%)		377 (89.8%)		
Non-Caucasian	36 (16.5%)		43 (10.2%)		
Education level		140 (57)		259 (56)	.72
High	52 (37.1)		101 (39.0%)		
Low	88 (62.9%)		158 (61.0%)		
Blood pressure (mmHg)					
Systolic	145 (121-169)	243 (100)	140 (120-160)	459 (100)	<.001
Diastolic	98 (90-110)	244 (100)	95 (85-105)	459 (100)	.002
Bishop Score		139 (57)		240 (52)	.02
< 2	47 (33.8)		50 (20.8)		
2-6	87 (62.6)		182 (75.8)		
> 6	5 (3.6)		8 (3.3)		
Laboratory findings					
Dipstick		195 (80)		374 (81)	.03
Negative	59 (30.3)		125 (33.4)		
Trace	42 (21.5)		110 (29.4)		
+	50 (25.6)		90 (24.1)		
++	35 (17.9)		37 (9.9)		
+++	9 (4.6)		12 (3.2)		
Haemoglobin (mmol/L)	7.40 (6.30-8.60)	230 (94)	7.60 (6.43-8.70)	424 (92)	.03
Haematocrit (L/L x 10)	3.6 (3.0-4.1)	204 (84)	3.6 (3.0-4.1)	383 (83)	.04
Platelets (x10^9/L)	217 (139-334)	228 (93)	228 (139-359)	421 (91)	.02
Uric acid (mmol/L x 10)	3.20 (2.20-4.70)	223 (91)	3.10 (1.90-4.40)	405 (88)	.08
Creatinine (μmol/L)	62.0 (45.3-86.8)	224 (92)	61.0 (43.0-83.0)	395 (86)	.03
Aspartate aminotransferase (U/L)	21.0 (10.0-42.8)	191 (78)	19.0 (10.0-37.0)	351 (76)	.10
Alanine aminotransferase (U/L)	12.0 (6.0-35.8)	191 (78)	12.0 (6.0-30.0)	358 (78)	.76
Lactate dehydrogenase (U/L)	287 (160-457)	155 (64)	305 (158-469)	312 (68)	.53
Mode of delivery		244 (100)		459 (100)	<.001
Spontaneous	142 (58.2%)		325 (70.8%)		
Vacuum/forcipal extraction	36 (14.7%)		76 (16.6%)		
Caesarean section	66 (26.6%)		58 (12.6%)		

Data are median (5th -95th percentile) or number (%).

start of expectant management (p=0.004) were more frequently of non-Caucasian ethnicity (p=0.02) had more severe proteinuria at dipstick (p=0.03), a lower Bishop Score at vaginal examination (p=0.02) and had higher systolic (p<.001) and diastolic blood pressure (p=0.002) at study entry. The laboratory findings showed lower haemoglobin (p=0.03), lower haematocrit (p=0.04) and lower platelets levels (p=0.02) as well as higher creatinine (p=0.03) in the group of women with progression to severe disease.

In the randomisation group cervical length was measured using transvaginal sonography and vaginal digital examination was performed, both prior to randomisation. In the non-randomised group vaginal examination was only performed in about 5% of the women. As a consequence Bishop Scores were

Table 2. Vaginal examination characteristics in randomised expectant monitoring group: progression versus no progression to severe disease.

Characteristics	Progression to severe disease (n=143, 37.7%)		No progression to severe disease (n=236, 62.3%)		p
	Value	Patients with available data	Value	Patients with available data	
Bishop Score		127 (89)		211 (89)	.01
< 2	42 (33.3)		40 (19.0)		
2 to 6	80 (63.0)		164 (77.7)		
> 6	5 (3.9)		7 (3.3)		
Dilatation (cm)	0.0 (0.0-2.0)	139 (97)	1.0 (0.0-3.0)	227 (96)	.03
Effacement		136 (95)		224 (95)	.14
0%	44 (32.4)		48 (21.4)		
25%	25 (18.4)		44 (19.6)		
50%	42 (30.9)		91 (40.6)		
75%	17 (12.5)		32 (14.3)		
100%	8 (5.9)		9 (4.0)		
Consistency		138 (97)		224 (95)	.07
Stiff	33 (23.9)		32 (14.3)		
Moderate	85 (61.6)		155 (69.2)		
Week	20 (14.5)		37 (16.5)		
Engagement		131 (92)		221 (94)	.66
Hodge 1	112 (85.5)		192 (86.9)		
Hodge 2	19 (14.5)		28 (12.7)		
Hodge 3	0 (0.0)		1 (0.5)		
Position		135 (94)		221 (94)	.002
Posterior	84 (62.2)		104 (47.1)		
Median	51 (37.8)		106 (48.0)		
Anterior	0 (0.0)		11 (5.0)		
Length (mm)	31 (13-48)	133 (93)	29 (10-45)	221 (94)	.001

Data are median (5th -95th percentile) or number (%).

missing in 43% of women with progression to severe disease vs. 48% of women without progression to severe disease. Multiple imputation was not possible for these variables with these percentages of missing values. We decided to evaluate the vaginal examination characteristics in the randomised group only and not to include this variable in the overall prediction model. Women with progression to severe disease had less dilatation of the cervix (p=0.03), more frequently a posterior cervix position (p=0.002) in stead of median or anterior and a longer cervix length (p=0.001) and consequently a lower Bishop Score (p=0.01) (Table 2).

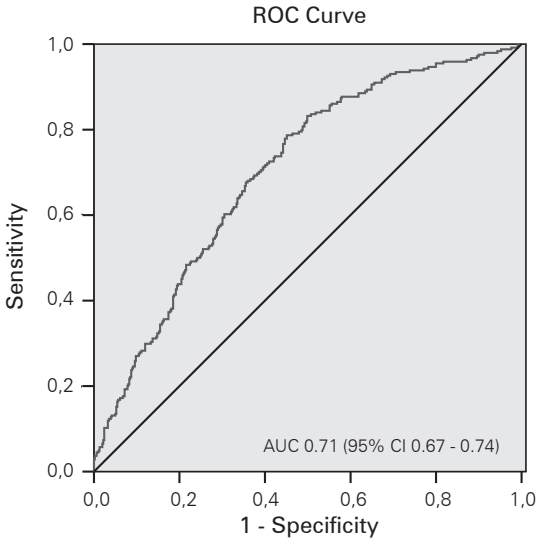

Figure 2. ROC graph of prediction model for progression to severe disease, calculated by multivariate analysis.

Factors strongly associated with progression to severe disease in the univariate analysis were GA, non-Caucasian ethnicity, high systolic and diastolic blood pressure. Of the laboratory findings, decrease of haemoglobin, haematocrit and platelets, as well as increased proteinuria, uric acid and ALT were strongly associated with progression to severe disease (Table 3). Since more liberal p-values are advocated to increase the probability that real predictors are selected in the model, we selected all prognostic variables with a significance level of p <0.40 to enter the model. Table 3 also shows this final model. The final model exists of the variables: nulliparity, maternal age, GA, previous abortion, ethnicity, blood pressures, dipstick, haemoglobin, platelets, uric acid and ALT. We averaged the 5 predicted risks of each patient, which resulted in one performance estimate. The model showed good discrimination, with an area under the ROC curve of

Table 3. Results of the univariate and multivariate analysis of predictors of progression to severe disease, pooled estimates based on imputed data.

Predictors	Univariate analysis			Multivariate analysis		
	OR	95% CI	p	OR	95% CI	p
Nulliparous	1.28	0.89 – 1.84	.18	1.87	1.09 – 2.76	.003
Maternal age (years)	1.03	0.99 – 1.07	.06	1.05	1.00 – 1.08	.02
Gestational age (weeks)	0.83	0.73 – 0.94	.004	0.88	0.97 – 1.05	.07
Previous abortion	1.36	0.95 – 1.94	.09	1.26	0.86 – 1.99	.25
Maternal smoking	1.07	0.65 – 1.76	.78			
Body Mass Index (kg/m^2)	1.01	0.97 – 1.05	.54			
Non-Caucasian ethnicity	1.74	1.09 – 2.76	.02	2.05	0.85 – 2.76	.09
Higher education level	1.03	0.67 – 1.56	.90			
Blood Pressure (mmHg)						
Systolic	1.03	1.01 – 1.04	<.001	1.02	1.01 – 1.03	.01
Diastolic	1.05	1.02 – 1.07	.001	1.04	1.02 – 1.06	.01
Laboratory findings						
Dipstick (vs negative)						
Trace	0.79	0.50 – 1.25	.32	0.81	0.99 – 1.00	.41
+	1.17	0.72 – 1.90	.53	1.09	0.99 – 1.18	.92
++	1.95	1.12 – 3.39	.02	1.71	0.69 – 2.64	.11
+++	1.37	0.57 – 3.28	.48	1.17	0.67 – 1.56	.74
Haemoglobin (mmol/L)	0.74	0.59 – 0.93	.01	0.73	0.50 – 0.95	.02
Haematocrit (L/L x 10)	0.52	0.31 – 0.89	.02			
Platelets (x10^9/L)	0.997	0.99 – 1.00	.05	0.99	0.99 – 1.00	.07
Uric acid (mmol/L x10)	1.30	1.04 – 1.64	.02	1.22	0.12 – 1.59	.12
Creatinine (μmol/L)	1.00	0.99 – 1.01	.41			
Aspartate aminotransferase (U/L)	1.01	0.99 – 1.03	.22			
Alanine aminotransferase (U/L)	1.02	1.00 – 1.03	.05	1.01	1.00 – 1.01	.12
Lactate dehydrogenase (U/L)	1.00	1.00 – 1.00	.51			

* If the variable had a p value less than .40 in the univariable analysis, it was considered in the final (multivariable) model.

0.71 (95% CI, 0.67-0.74)), but the calibration was moderate (Hosmer-Lemeshow p-value=0.40 (varying for the 5 dataset between 0.16-0.74)). Figure 3 shows the rates of progression to severe disease ranged from 14% (lowest 10 percent) to 60% (highest 10 percent). For the predicted deterioration between 30% and 45%, slight underestimation was seen. But the CIs of the group with low (<30%) risk of progression to severe disease and the group with high (>40%) risk did not overlap, indicating that distinction between these groups is possible. Bootstrapping showed little optimism (AUC varied from 0.66-0.67), indicating that the model holds for the overall population.

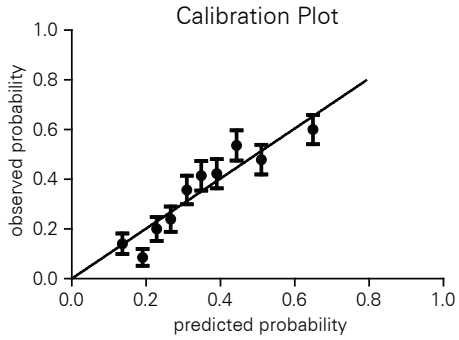

Figure 3. Calibration plot demonstrating the association between the risks of progression to severe disease as predicted by the logistic model and the observed progression to severe disease.

DISCUSSION

In this study, we elaborate on the recent findings of the HYPITAT trial, which revealed that labour should be induced in women with mild PE or GH at term.[4] We investigated if patients at increased risk of developing severe maternal outcomes, could be identified from clinical characteristics. Hereby, we aimed to facilitate the correct management for the individual patient.

Our study is important in the clinical management of women with GH or mild PE. Early prediction and identification of complications and progression to severe disease will benefit doctors and patients by guiding therapy. Moreover, increasing predictability of disease progression allows clinicians to avoid unnecessary interventions in low-risk groups.[9] For instance, the HYPITAT trial found that fewer caesarean sections were performed in women allocated to induction of labour as compared to women allocated to expectant monitoring. This can be explained by the fact that more women progressed to severe disease and needed a caesarean section (26.6% versus 12.6% of the women without progression to severe disease $P<0.01$, Table 1).

The caesarean section rates found in other countries in women in whom labour is induced as well as in women with spontaneous labour are higher than in the Netherlands. We hypothesize that this is due to the non-intervention obstetric culture in the Netherlands. For example, Verhoeven et al. reported a caesarean section rate of only 11% in a series of women in whom labour was induced.[14] We hypothesize that it is not the induction but rather the attending gynaecologist who is doing the induction who is the factor responsible for the high caesarean section rate. For example, delivery in hospital is associated with a higher risk of caesarean

section as compared to delivery at home.[15] We hypothesize that during induction of labour the attending physician is longer alongside the woman than in spontaneous labour, with also an increased risk of caesarean section.

In this analysis nearly 35% of 703 women with GH or mild PE progressed to severe disease. Variables included in the prediction model are nulliparity, maternal age, GA, previous abortion, ethnicity (Caucasian vs. non-Caucasian), systolic and diastolic blood pressure, proteinuria, haemoglobin, platelets, uric acid and ALT. Thangaratinam et al. reported a prioritized list of tests to predict complications of PE. They identified blood pressure, proteinuria, liver function tests and medical history as the most important predictors of maternal complications in PE.[9] Serum uric acid, maternal age, parity and ethnicity scored poorly in the survey of Thangaratinam, even though in clinical practice these characteristics are regarded as highly important. Several studies reported a positive correlation between elevated maternal serum uric acid levels and adverse maternal outcome but there are hardly any systematic reviews exploring the accuracy of uric acid to predict complications or progression to severe disease.[16] Koopmans et al. found serum uric acid to be a useful test in the management of PE.[17] Rinehart et al. tried to determine whether the rate of change of platelets count or LDH level in patients with severe PE could be used to determine which patients were more likely to develop the more dangerous forms of this disease.[18] They concluded that the rate of change of platelets and LDH appeared to correlate well with eventual syndrome severity. In our study decrease in platelets was also determined as an independent predictor of progression to severe disease.

Since real morbidity such as HELLP syndrome was very rare, and some true complications such as eclampsia or even maternal death did not occur at all, we used progression to severe disease as the primary outcome. We included severe hypertension since this is directly related to severe complications such as eclampsia, pulmonary oedema and cerebral encephalopathy or haemorrhage. Sibai et al. stated that the development of severe GH (without proteinuria) at anytime during pregnancy, in labor or postpartum is associated with significant maternal morbidity and should therefore be considered as part of a primary outcome for future trials for prediction or prevention of PE.[1]

The performance of our prediction model was assessed by evaluating discrimination and calibration. The ROC curve showed good discriminative capacity. However, in the assessment of performance of a prediction model, calibration is more important than discriminative capacity.[19] In fact, patients and general practitioners are not concerned about how their chance is relative to other patients (discrimination);

instead, they want to know the likelihood that they progress to severe disease with a higher risk of maternal morbidity. Consequently, the clinical aim of the model is to differentiate between women with low and high risk of progression to severe disease. And even though the performance of our model was moderate, our data on calibration and internal validation do indicate that the model can distinguish these women at low risk and women at high risk of progression to severe disease. Obviously, progression to severe disease can be observed by serially measuring blood pressure, which shows progression to severe disease afterwards. However, the clinical situation can sometimes deteriorate very quickly, and therefore prediction of progression to severe disease at baseline is of importance. The clinical utility of this model is that clinicians can differentiate between these groups, and for example immediately induce patients in the high risk group.

This distinction could especially be important for women with a prior caesarean section for instance, since induction of labour in women with a scarred uterus is associated with increased risk of uterine scar rupture.[5] Although we did not study women with a previous caesarean section, the prediction could also hold in these women. As a consequence, induction of labour could be delayed in women at low risk of complications, whereas in women at high risk a repeat caesarean section could earlier be considered.

The fact that we had varying percentages of missing values can be considered a limitation of our study. The missing data of the predictive variables were imputed to prevent a loss of statistical power in the multivariable analysis and, more seriously, reduce the possibility of bias. Since vaginal examination was not done routinely in the non-randomised study group, the percentage of missing data was particularly high. Imputation of these data was not possible, with the consequence that we had to exclude these variables from the prediction model. In the sub analysis of the randomised group an unfavourable cervical examination (dilatation, consistency, position and length) are predictors of progression to severe disease as well (data not shown). So even though most clinicians would previously choose expectant management in this situation, our data indicates that women with an unfavourable cervix are good candidates for induction of labour. This decreases the risk of progression to severe disease without increasing the caesarean section rate.[4]

In conclusion, in the prediction of progression to severe disease, in women with GH or mild PE at term, a distinction can be made between women with a low risk and women with high risk. After external validation, the identified predictors could therefore help doctors and patients in future clinical management in high

risk groups and will allow clinicians to avoid unnecessary interventions in low-risk groups of mild PIH or PE at term.

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Chapter 7

Risk indicators for eclampsia in women with gestational hypertension or mild pre-eclampsia at term

Hypertension in Pregnancy. 2010 Sep [Epub ahead of print]

ABSTRACT

Objective To evaluate whether eclampsia can be predicted in gestational hypertension or mild pre-eclampsia at term.

Methods For this case-control study we selected 76 cases with eclampsia from the LEMMoN study and 1149 controls with mild hypertensive disease of pregnancy, who did not develop eclampsia, from the HYPITAT study. Risk indicators for eclampsia, identified in multivariable logistic regression, were used to assess the predictive capacity of our model with receiver-operating-characteristic (ROC)-curve analysis. Model optimism was assessed with bootstrapping.

Results Maternal age, non-Caucasian ethnicity, systolic blood pressure >155 mmHg, ≥2+ protein on dipstick, elevated uric acid, creatinine >74 μmol/L, aspartate aminotransferase >30 U/L and lactate dehydrogenase >400 U/L were significantly associated with eclampsia. Other factors included in the model were previous fetal loss, previous miscarriage, gestational age and low platelet count. The area under the ROC-curve was 0.92. Bootstrapping showed minimal overfitting of the model.

Conclusion In women with gestational hypertension or mild pre-eclampsia at term eclampsia can be predicted.

INTRODUCTION

Hypertensive disorders of pregnancy are predominant causes of maternal and neonatal mortality and morbidity worldwide.[1,2] In the Netherlands, they are the largest single cause of maternal mortality.[3] In many cases, clinical presentation is mild, though maternal and fetal complications can develop, of which eclampsia is most feared. The incidence of eclampsia in the Netherlands is 6.2 per 10,000 deliveries, which is markedly increased as compared to other Western European countries.[4]

Recently we evaluated whether induction of labour in women with gestational hypertension (GH) or mild pre-eclampsia (PE) beyond 36 weeks of gestation was superior to expectant monitoring (HYpertension and Pre-eclampsia Intervention Trial At Term [HYPITAT trial]).[5] We found that induction of labour was associated with a reduced risk of progression to severe maternal disease, without resulting in a higher caesarean delivery rate. Overall, induction of labour appeared to be the best treatment option for women diagnosed with GH or mild PE at term.

Although we recommend a policy of induction of labour, identification of women at increased risk for complications, most seriously eclampsia, is still of major importance. Early identification could be used as a guidance to start prophylactic treatment with magnesium sulphate[6] and to induce labour immediately instead of the next morning.

After a systematic review of the medical literature we found no studies that quantify risk indicators for eclampsia in women with mild hypertensive disease beyond 36 weeks of gestation. In view of this lack of knowledge, we performed a case-control study to assess which patient characteristics may be associated with the occurrence of eclampsia among women with GH or mild PE beyond 36 weeks of gestation.

MATERIALS AND METHODS

This case-control study used data from two large studies that were published earlier.[5,7] Cases were collected from the LEMMoN study, a nationwide cohort study concerning severe maternal morbidity.[7] In this study, women with severe maternal morbidity and mortality in the Netherlands were included between August 2004 and August 2006. From this study we selected all women who developed eclampsia beyond 36 weeks of gestation. Women who already had experienced

their first seizure upon referral to the obstetrician were excluded. Eclampsia was defined as the occurrence of convulsions, which could not be attributed to other causes.[4]

Controls were women who participated in the HYPITAT trial (clinical trial register number ISRCTN 08132825).[5] This multicentre parallel randomised controlled, open label trial, was conducted in six academic and 32 non-academic hospitals in the Netherlands between October 2005 and March 2008. Induction of labour was compared to expectant monitoring in women with GH or mild PE beyond 36 weeks of gestation. GH was defined as diastolic blood pressure ≥95 mmHg measured at two occasions, performed at least six hours apart. Mild PE was defined as diastolic blood pressure ≥90 mmHg measured at two occasions, performed at least six hours apart, combined with proteinuria (defined as ≥2+ protein on dipstick, >300 mg total protein within a 24-hour urine collection or protein/creatinine ratio >30 mg/mmol).[8-10] In this trial eclampsia did not occur. Women from the randomised induction and expectant monitoring groups, as well as non-randomised women, were included in the current study, because at start of the HYPITAT trial all women had comparable baseline characteristics.

Exclusion criteria for the current study were multiple pregnancy, breech presentation, previous caesarean delivery, diabetes mellitus, renal disease, cardiac disease, pre-existing hypertension treated with antihypertensive medication, gestational diabetes requiring insulin therapy, haemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome and severe hypertension defined as systolic blood pressure >170 mmHg, diastolic blood pressure >110 mmHg and severe proteinuria (>5 grams protein in a 24 hours urine collection). Data collection included maternal age, ethnic origin, parity, obstetrical history, general history, gestational age at time of admission to the hospital (LEMMoN) or at study entry (HYPITAT), body mass index (BMI) at first antenatal appointment, smoking habits during pregnancy and educational level. We also collected systolic and diastolic blood pressures, proteinuria, use of antihypertensive drugs prior to the first eclamptic seizure and laboratory measurements (haemoglobin, haematocrit, platelets, uric acid, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and lactate dehydrogenase (LDH)) at time of admission to the hospital for cases and at study entry for controls. Furthermore, we collected information concerning the delivery, like gestational age at delivery, onset of labour and mode of delivery. Calculation of gestational age was based either on ultrasound, or on the first day of the last menstrual period.

Development of adverse maternal and neonatal outcomes was reported for cases and controls. Adverse maternal outcome measures were maternal mortality, severe hypertension (diastolic blood pressure >110 mmHg or systolic blood pressure >170 mmHg), severe proteinuria (>5 grams protein in a 24 hours urine collection), HELLP syndrome (decreased platelet count (<100 x10^9/L) and increased liver enzymes (AST >70 U/L or ALT >70 U/L)), obstetric haemorrhage (>1000 ml blood loss within 24 hours after delivery), manual delivery of the placenta, admission to an intensive care unit and prolonged stay in the hospital. Adverse neonatal outcome measures were fetal or neonatal mortality, 5-minute apgar score <7, arterial pH <7.05 and admission to a neonatal intensive care unit.

The amount of missing data at admission or at study entry varied between 0% for the variables maternal age, parity, history of fetal loss and miscarriage versus 40% for the variable educational level. Missing data of the predictive variables were imputed. In multivariable prognostic research complete case analysis should be avoided and multiple imputation methods are known to be superior to other imputation methods.[11] Multiple imputation was performed using the mice (multiple imputation by chained equations) procedure.[12] This procedure assumes that the distribution of each variable with missing values can be modeled on the basis of the other variables plus the clinical outcome of interest. Logistic regression was used for a categorical outcome variable and linear regression was used for continuous variables. The method estimates a distribution of the variable with missing values, taking all aspects of uncertainty in the imputation into account. We generated five imputed datasets.

The distribution of risk indicators among cases with and controls without eclampsia are expressed as median (5^{th}–95^{th} percentile) or number (%). The Kolmogorov–Smirnov test was applied to assess normality of the data. Group differences were tested using the unpaired Student's *t*-test in case of normal distribution and the nonparametric Mann–Whitney U test in case of skewed distribution. Categorical variables were compared using chi-square statistics. Maternal and neonatal outcomes and data concerning the delivery are presented as odds ratio (OR) with 95% confidence interval (CI).

Spearman's rank correlation test was used to find correlations between variables. Using the imputed multiple dataset, logistic regression was performed to identify risk indicators for eclampsia among clinical characteristics and laboratory findings. For both dichotomous and continuous variables univariable pooled ORs with 95% CI, as well as *p*-values, were calculated. Subsequently, multivariable logistic regression analysis with simultaneous inclusion of variables was performed to

identify risk indicators for the prediction of eclampsia. For this analysis we included all predicting variables reaching a $p<0.50$ in the univariable analysis. $p=0.20$ was used as a threshold for variables to stay in the model. The continuous variables that emerged as independent risk indicators in the multivariable analyses, were also categorized into quintiles and entered as categorical variables in the logistic regression to determine the cut-off points for increased risk of developing eclampsia.

To evaluate the discriminative performance of the logistic model, the area under the Receiver Operating Characteristic (ROC) curve was calculated, comparing the actual outcome to the predicted outcome. The ROC-curve was created after aggregating the five imputed datasets. Statistical analyses were conducted using PASW Statistics 17.0 (SPSS inc. Chicago, Illinois).

Extent of overfitting of the model, i.e. optimism, was assessed with bootstrapping in R.[13] Two hundred bootstrap samples were drawn from each imputation set. In each bootstrap sample, the entire modelling process was repeated. The bootstrap procedure yields a ROC area corrected for optimism and a shrinkage factor to adjust the model for overfitting.

RESULTS

A total of 222 eclamptic women were included in the LEMMoN study. Of nine cases, we did not receive detailed information, leaving 213 cases available for analysis. Of these, 137 women (64%) were excluded from the current study for one or more of the following reasons: eclampsia occurring before 36 weeks of gestation (n=74), diabetes mellitus (n=4), pre-existing hypertension treated with antihypertensive medication (n=3), multiple pregnancy (n=21), previous caesarean delivery (n=15), a child in breech presentation (n=8) or first eclamptic seizure occurring prior to referral to the obstetrician (n=13). Subsequently, we excluded women who had HELLP syndrome (n=7), severe hypertension (n=9) or severe proteinuria (n=9) at time of admission to the hospital. From the HYPITAT trial four patients were excluded, because they had severe hypertension at time of randomisation. Ultimately, 76 cases from the LEMMoN study were compared to 1149 controls from the HYPITAT trial.

Table 1 shows the distribution of potential risk indicators between cases and controls at time of admission to the hospital (LEMMoN) or at study entry (HYPITAT). Cases were younger (29.0 [5^{th}–95^{th} percentile 20.0–36.5] vs 30.0 [22.0–38.0] years,

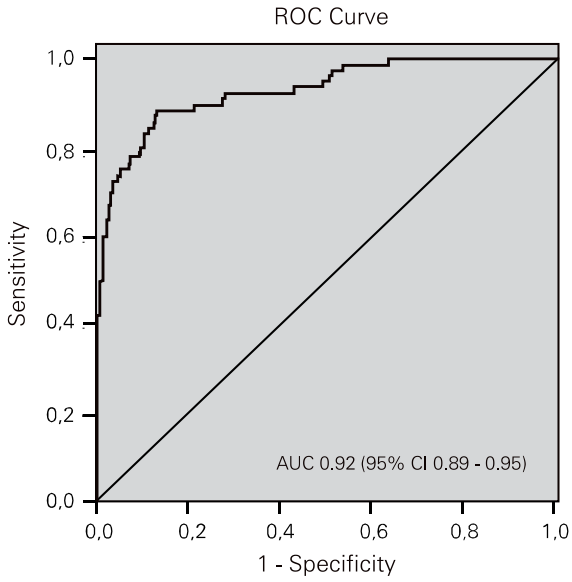

Figure 1. Receiver operating characteristic (ROC) curve of prediction model for eclampsia

p=0.04) and at admission they had higher systolic blood pressures, more often a dipstick of 2+ or 3+, and more aberrant laboratory measurements as compared to controls at study entry.

The results of the univariable and multivariable regression analysis are shown in Table 1. The clinical characteristics which appeared to be risk indicators for eclampsia in univariable analysis at admission or at study entry were maternal age, systolic blood pressure, 2+ and 3+ protein on dipstick. Laboratory measurements associated with eclampsia were platelet count, uric acid, creatinine, AST, ALT and LDH. In Spearman's rank correlation haemoglobin and haematocrit ($p<0.001$) and AST and ALT ($p<0.001$) revealed to be correlated. Therefore haematocrit and ALT were not considered in multivariable analysis. Maternal age, non-Caucasian ethnicity, systolic blood pressure, 2+ and 3+ protein on dipstick, uric acid, creatinine, AST and LDH were statistically significant associated with the development of eclampsia in multivariable analysis. Other variables included in the model were previous fetal loss, previous miscarriage, gestational age and platelets. All these risk indicators contributed to the final prediction model. The corresponding ROC curve is shown in Figure 1 with an area under the curve of 0.92 (95% CI 0.89-0.95). Bootstrapping showed minimal optimism of the model (AUC varied from 0.88 to 0.89), indicating that the model holds for the overall population.

Table 1. Risk indicators for eclampsia at admission (cases) and at study entry (controls): Univariable and multivariable analysis

Characteristics	Cases (n=76)	Controls (n=1149)
Maternal age (years)*	29.0 (20.0-36.5)	30.0 (22.0-38.0)
Nulliparous	63 (83%)	838 (73%)
Non-Caucasian ethnicity	13 (17%)	124 (12%)
High education level	14 (26%)	243 (36%)
Fetal loss in history	3 (4%)	22 (2%)
Miscarriage in history	11 (15%)	269 (23%)
Body mass index at first antenatal appointment (kg/m^2)	24.9 (19.0-37.7)	25.4 (19.8-36.6)
Smoking during pregnancy	7 (13%)	131 (12%)
Gestational age	38.7 (36.0-41.2)	38.4 (36.3-40.4)
Blood pressure (mmHg)		
Systolic *	150 (123-170)	140 (125-160)
Diastolic	98 (80-110)	96 (89-105)
Dipstick *		
Negative	9 (13%)	288 (31%)
Trace	8 (11%)	234 (25%)
+	8 (11%)	246 (27%)
++	25 (36%)	109 (12%)
+++	20 (29%)	50 (5%)
Use of antihypertensive drugs	8 (11%)	151 (13%)
Laboratory measurements		
Haemoglobin (mmol/L)	7.65 (6.34-8.87)	7.50 (6.30-8.60)
Haematocrit (L/L)†	0.36 (0.30-0.43)	0.36 (0.30-0.41)
Platelets (x10^9/L) *	200 (105-319)	227 (138-346)
Uric acid (mmol/L) *†	0.37 (0.26-0.54)	0.31 (0.21-0.46)
Creatinine (μmol/L) *	77.0 (54.2-116)	61.0 (45.0-85.0)
Aspartate aminotransferase (U/L) *	30.0 (12.1-167)	20.0 (10.0-38.0)
Alanine aminotransferase (U/L) *	15.0 (5.00-127)	12.0 (6.00-31.5)
Lactate dehydrogenase (U/L) *	411 (207-708)	302 (157-475)

The distribution of risk indicators among cases with and controls without eclampsia are expressed as median (5th-95th percentile) or numbers (%). * Variables with a significant distribution between cases and controls ($p< 0.05$). OR = Odds Ratio; CI = confidence interval. If the variable had a $p< 0.50$ in the univariable analysis, it was considered in the final (multivariable) model. A $p= 0.20$ was used as a threshold for variables to stay in the final model. † Scale adapted by multiplication with a factor 10 for regression analyses.

Subsequently, the continuous variables that emerged as independent risk indicators in the multivariable analyses, were categorized into quintiles to determine cut-off points for increased risk of developing eclampsia. In case of systolic blood pressure >155 mmHg, AST >30 U/L, creatinine >74 μmol/L and LDH >400 U/L an increased risk of eclampsia was shown. For the continuous variables maternal age, gestational age, platelets and uric acid the risk for developing eclampsia increased or decreased gradually.

Univariable analysis			Multivariable analysis		
OR	95% CI	p	OR	95% CI	p
0.95	(0.90-1.00)	0.032	0.93	(0.87-0.99)	0.047
1.8	(0.98-3.31)	0.060			
1.7	(0.90-3.09)	0.106	2.8	(1.09-7.23)	0.034
0.85	(0.40-1.80)	0.686			
2.1	(0.62-7.20)	0.235	4.5	(0.77-25.7)	0.097
0.55	(0.29-1.06)	0.076	0.66	(0.29-1.50)	0.323
0.97	(0.92-1.02)	0.260			
1.10	(0.49-2.49)	0.817			
1.10	(0.88-1.38)	0.416	1.3	(0.97-1.62)	0.097
1.04	(1.02-1.06)	<0.001	1.1	(1.02-1.07)	0.001
0.98	(0.95-1.02)	0.366			
1.1	(0.41-3.02)	0.837	1.0	(0.29-3.63)	0.977
1.1	(0.42-3.08)	0.806	0.60	(0.16-2.24)	0.453
6.1	(2.73-13.7)	<0.001	3.4	(1.06-11.2)	0.050
9.7	(4.06-23.0)	<0.001	6.2	(1.97-19.5)	0.003
0.78	(0.37-1.65)	0.512			
1.2	(0.80-1.90)	0.356			
1.6	(0.56-4.29)	0.411			
0.99	(0.99-1.00)	0.002	0.995	(0.99-1.00)	0.075
1.8	(1.96-3.70)	0.004	1.8	(1.20-2.62)	0.004
1.05	(1.03-1.06)	<0.001	1.02	(1.01-1.04)	<0.001
1.05	(1.03-1.07)	<0.001	1.03	(1.00-1.04)	0.012
1.04	(1.02-1.05)	<0.001			
1.01	(1.01-1.01)	<0.001	1.01	(1.00-1.01)	<0.001

Table 2 shows maternal outcome, data concerning delivery and neonatal outcome. Maternal mortality did neither occur in cases nor in controls. Women in the case group were more often diagnosed with severe hypertension, severe proteinuria, HELLP syndrome and obstetric haemorrhage as compared to the control group. Cases were admitted more often to an intensive care unit and their duration of stay in the hospital was significantly longer.

Table 2. Maternal outcome, data concerning delivery and neonatal outcome

Characteristic	Cases (n=76)	Controls (n=1149)	OR (95% CI) or p
Maternal outcome			
Maternal mortality	0	0	
Systolic blood pressure >170 mmHg	44 (58%)	210 (18%)	6.08 (3.77-9.82)
Diastolic blood pressure >110 mmHg	43 (57%)	248 (22%)	4.68 (2.91-7.53)
Severe proteinuria (>5 g/24 hrs)	3 (4%)	12 (1%)	3.89 (1.08-14.1)
HELLP syndrome	16 (21%)	24 (2%)	12.5 (6.31-24.8)
Postpartum haemorrhage	17 (22%)	118 (10%)	2.52 (1.42-4.46)
Admission to an intensive care unit	25 (33%)	28 (2%)	19.6 (10.7-36.0)
Duration of maternal stay in hospital (days)	8.00 (4.00-16.0)	2.00 (1.00-6.00)	<0.001
Data concerning delivery			
Gestational age at delivery (weeks)	39.5 (36.7-41.8)	39.6 (37.1-41.3)	0.847
Use of analgesics during delivery			<0.001
None	21 (28%)	637 (56%)	
Pethidine/ Phenergan/ Nubaine	18 (24%)	170 (15%)	
Epidural	9 (12%)	255 (22%)	
Spinal	17 (22%)	27 (2%)	
Complete analgesia	11 (15%)	0	
Other	0	59 (5%)	
Onset of labour			<0.001
Spontaneous	28 (37%)	392 (34%)	
Induction	39 (51%)	749 (65%)	
Planned caesarean delivery	9 (12%)	8 (1%)	
Mode of delivery			<0.001
Spontaneous	16 (21%)	792 (69%)	
Vaginal instrumental delivery	28 (37%)	176 (15%)	
Caesarean delivery	32 (42%)	181 (16%)	
Delivery of the placenta			<0.001
Spontaneous	42 (55%)	920 (80%)	
Manual	2 (3%)	44 (4%)	
During caesarean delivery	32 (42%)	181 (16%)	
Neonatal outcome			
Fetal or neonatal mortality	2 (3%)	0	
Apgar Score after 5 minutes <7	5 (7%)	22 (2%)	3.69 (1.36-10.0)
Neonatal arterial pH <7.05	5 (14%)	36 (4%)	3.95 (1.45-10.8)
Admission to a neonatal intensive care unit	14 (19%)	26 (3%)	8.55 (4.24-17.2)
Gender (male)	48 (63%)	576 (50%)	1.71 (1.06-2.76)
Birth weight (g)	3185 (2430-4343)	3370 (2500-4210)	0.124

Data are median (5^{th}-95^{th} percentile) or numbers (%). OR = Odds Ratio; CI = confidence interval

Cases and controls delivered at comparable gestational age. Induction of labour and a spontaneous onset of labour can not be compared between cases and controls, because controls were randomised for either induction or expectant monitoring. Vaginal instrumental delivery rate and overall caesarean delivery rate were higher among cases.

We observed more adverse neonatal outcome measures in cases as compared to controls. Among cases one fetus died with unknown reason and one neonate died because of asphyxia whereas among controls there were no fetal or neonatal deaths.

COMMENT

In this case-control study we evaluated risk indicators for eclampsia in women diagnosed with GH or mild PE beyond 36 weeks of gestation. We found that maternal age, non-Caucasian ethnicity, systolic blood pressure >155 mmHg, ≥2+ protein on dipstick, elevated uric acid, creatinine >74 μmol/L, AST >30 U/L and LDH >400 U/L were statistically significant independent predictors for the occurrence of eclampsia. Other factors incorporated in the model were previous fetal loss, previous miscarriage, gestational age and low platelet count. The discriminative performance of the prediction model was excellent.

We think our study is of importance, because it is the first study in which risk indicators for eclampsia are identified in women with hypertensive disorders beyond 36 weeks of gestation. However, limitations are also present. First, various prognostic predictor variables had varying percentages of missing values. The missing data of the predictive variables were imputed, because deleting them would lead to a loss of statistical power in multivariable analysis and, more seriously, potentially biased results.[11] Second, case-control studies are known to give more optimistic results on the predictive capacity of a model than cohort studies, as the latter better mimic clinical reality. In case-control studies, the controls are usually patients on the 'healthy' side of the disease spectrum, whereas cases are women with the most severe presentation of disease.[14] Thus, the discriminative capacity of our model might appear to be overestimated when validated in another cohort. The third limitation of the study might be the fact that controls from the HYPITAT trial were collected from 38 hospitals in the Netherlands, whereas cases were collected from all 98 Dutch hospitals. However, we think that women in the case group are comparable to women in the control group, because local protocols are based on national guidelines of the Dutch Society for Obstetrics and Gynaecology.[15] Finally, the inclusion period was slightly different for cases and controls. However, no large studies or new guidelines on the subject were presented in this period, so it is unlikely that management over the years has been changed.
Although predictive indicators for eclampsia have been suggested in literature, evidence on the accuracy of various tests to predict eclampsia in women with hypertensive disorders in pregnancy is limited. In low-income countries the

occurrence of eclampsia is mainly associated with absent or little antenatal care.[16-18] In the Netherlands multiple pregnancy, nulliparity, young age, black ethnicity and overweight seem to be the most important risk factors for eclampsia as compared with healthy (non-preeclamptic) pregnant women.[4]

Only two case-control studies reported risk factors of eclampsia in women with hypertensive disorders in pregnancy.[19,20] In multivariable analysis Ben Salem et al. indicated vivid deep tendon reflexes and uric acid concentration ≥0.35 mmol/l as risk factors.[19] Witlin et al. found headache and deep tendon reflexes to be independent risk factors for eclampsia.[20] The predictive indicators for eclampsia suggested in these studies might very well be different from the indicators we found, because women with severe PE were also included in these studies, whereas we only investigated risk indicators in women with mild hypertensive disease of pregnancy. Moreover, these studies also concerned preterm pregnancies whereas we only considered pregnancies beyond 36 weeks of gestation. To our knowledge, studies describing risk indicators for eclampsia in pregnancies beyond 36 weeks of gestation have never been published.

It has been known that cerebral haemorrhage is an important cause of death in patients with eclampsia. Martin et al. found that a systolic blood pressure threshold of approximately 155-160 mmHg, usually without developing a diastolic blood pressure more than 105 mmHg, preceded cerebral haemorrhage in a group of 28 women with severe PE and eclampsia.[21] They concluded that women who have severe PE or eclampsia with severe systolic hypertension are especially at risk for cerebral haemorrhage. This finding is confirmed in our study, in which severe systolic blood pressure (>155 mmHg) is associated with the occurrence of eclampsia, in contrast to severe diastolic blood pressure. Thus, control of severe systolic hypertension is an important facet in the management of women with increased risk for eclampsia.[21,22]

Previously, the severity of proteinuria in PE has been considered a predictor of maternal complications, including eclampsia,[23,24] whereas others have been less sanguine about the relationship.[25,26] We identified that proteinuria of ≥2+ in a dipstick specimen strongly increased the risk of eclampsia. Therefore, although the results in literature are contrary, we think that the level or degree of proteinuria is extremely valuable for clinical decision making in preventing eclampsia.
Several studies reported a positive correlation between elevated maternal serum uric acid levels and adverse maternal outcomes but there are little data exploring the accuracy of uric acid to predict eclampsia.[27] Thangaratinam et al. identified uric acid level as a poor predictor of eclampsia, although they found that a raised serum

uric acid was associated with an almost doubled risk of eclampsia.[28] We repeated the meta-analysis with a bivariate meta-analytic model and a decision analysis to assess the value of serum uric acid in the management of women with PE and found that serum uric acid seems to be a useful test in predicting eclampsia.[29] This finding was confirmed in our current study.

Accurate prediction of eclampsia still constitutes a serious clinical challenge, and is necessary for successful management. The risk indicators found in this case-control study can be helpful in identifying women who are at highest risk for developing eclampsia and subsequently limiting mortality and morbidity caused by this life-threatening condition. In the HYPITAT trial, we already reported that in women without a previous caesarean delivery induction of labour should be the preferred strategy.[5] The present study shows that in women with high risk for developing eclampsia labour should be induced immediately, without waiting until the next morning, and that prophylactic treatment with magnesium sulphate should be applied. Magnesium sulphate halves the risk of eclampsia with a number needed to treat of 91 (95% CI 63-143), and probably reduces the risk of maternal death.[6]

In conclusion, continuous evaluation of maternal condition, complemented by haematologic and biochemical parameters, should be standard management in women with GH or mild PE at term to identify women at increased risk of developing eclampsia. The identified predictors in this study may provide physicians guidance to induce labour immediately and to start prophylactic treatment with magnesium sulphate.

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Ethics approval

The LEMMoN and HYPITAT studies were centrally approved by the medical ethics committee of Leiden University Medical Centre (LEMMoN: P04-020; HYPITAT: P04-210) and the HYPITAT trial had local approval from the boards of the other participating hospitals. The HYPITAT trial is registered in the clinical trial register as ISRCTN08132825.

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Chapter 8

Prediction of postpartum haemorrhage in women with gestational hypertension or mild pre-eclampsia at term

Submitted

ABSTRACT

Objective To assess whether postpartum haemorrhage (PPH) can be predicted in women with gestational hypertension or mild pre-eclampsia at term.

Methods For this cohort study we used data from our multicentre randomised controlled trial (HYPITAT trial). PPH was defined as blood loss >1000 ml within 24h after delivery. Two models were created to assess the predictive capacity of PPH. Model A included only antepartum variables, whereas model B included both antepartum and intrapartum variables. Logistic regression was performed to predict the occurrence of PPH. The predictive capacity of the models was assessed with receiver-operating-characteristic (ROC) analysis and calibration.

Results We included 1132 women, of whom 118 (10.4%) had PPH. Maternal age (OR 1.03), body mass index (OR 0.97), gestational age at randomisation (OR 1.19), proteinuria (OR 3.06 for +++ on dipstick), platelets (OR 0.997) and aspartate aminotransferase (OR 0.98) were independent antepartum predictors of PPH. Intrapartum variables incorporated in the model were gestational age at delivery (OR 1.21), birth weight (OR 1.36), mode of delivery (OR 1.06 and 1.67 for vaginal instrumental and caesarean delivery, respectively) and episiotomy (OR 2.1). Model A showed moderate discrimination, with an area under the ROC-curve of 0.63 (95% CI 0.57-0.69), whereas model B was slightly superior (AUC 0.69, 95% CI 0.63-0.74). Calibration was poor for model A (Hosmer-Lemeshow p-value=0.17) but better for model B (Hosmer-Lemeshow p-value=0.57).

Conclusion In women with gestational hypertension or mild pre-eclampsia at term, PPH can be predicted from antepartum and intrapartum variables. The identified predictors should alert clinicians managing labour in these women.

INTRODUCTION

Hypertensive disorders during pregnancy are associated with considerable maternal morbidity and mortality.[1-3] In literature it is described that women with hypertensive disorders are at increased risk of developing postpartum haemorrhage (PPH).[4-8] Severe PPH can result in serious morbidity, such as adult respiratory distress syndrome, coagulopathy, shock, loss of fertility, Sheehan syndrome and ultimately maternal mortality.[9,10]

Until recently, worldwide there was no evidence on how to manage women with mild hypertensive disease at term. In view of this dilemma, our study group performed a randomised controlled trial on the subject (HYPITAT trial), in which we found that induction of labour was associated with better maternal outcome as compared to expectant monitoring, without resulting in a higher caesarean delivery rate.[11] This trial result was mainly based on a difference in progression to severe diseases (systolic blood pressure ≥170 mmHg, diastolic blood pressure ≥110 mmHg or proteinuria ≥5 gram/ 24 hours) between induction of labour and expectant monitoring. Since PPH was found to be associated with hypertensive disorders of pregnancy, we included PPH as primary outcome of this study as well.[4-6] A positive effect of induction of labour on the incidence of PPH was not observed, but the overall 10% incidence of PPH found in our study was markedly higher than the 0.4-1.3% risk of PPH observed in low risk populations.[4,12] The same phenomenon has been described in the LEMMoN study which revealed an incidence for PPH of 4.0 per 1.000 deliveries in the Netherlands, whereas in 11.2% of cases PPH is accompanied by pre-eclampsia (PE).[13]

Because of this high incidence of PPH in women with a pregnancy related hypertensive disorder, identification of these women with increased risk of PPH is of major importance. We aimed at identification of women who are at increased risk of developing PPH to facilitate the best management for the individual patient. Prediction of PPH could be used as a guidance to pay particular attention to the woman during the early postpartum period and to supply effective prophylactic measures, obtaining a decrease in PPH incidence.

METHODS

For the present study we used data from the HYPITAT trial (clinical trial register number ISRCTN 08132825).[11] This multicentre parallel randomised controlled, open-label trial, was conducted in six academic and 32 non-academic hospitals in

the Netherlands between October 2005 and March 2008. In short, 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 with gestational hypertension (GH) or mild PE were randomly allocated to either induction of labour or expectant monitoring. Patients who did not give consent for randomisation, but who provided authorization for using their medical data, were treated according to local protocol. Patients allocated to induction of labour, were induced within 24 hours after randomisation. Patients in the expectant group were monitored until the onset of spontaneous delivery or until there was a medical indication for delivery. Monitoring consisted of frequent maternal blood pressure measurements, assessments of proteinuria, laboratory tests and fetal condition.

In the present study we combined the randomised and non-randomised women in one cohort. The endpoint PPH considered in this study was defined as blood loss >1000 ml within 24 hours after delivery.[9,14] Two models were created to assess whether this outcome could be predicted. First we created an antepartum model (model A) in which we evaluated whether PPH was predictable from clinical characteristics (parity, maternal age, smoking habits, prepregnancy body mass index (BMI), ethnicity, gestational age at randomisation, education level, previous abortion, diastolic and systolic blood pressure) or laboratory findings (haemoglobin, haematocrit, platelets, uric acid, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and proteinuria). The second model (model B) included these antepartum variables, as well as intrapartum variables, such as gestational age at delivery, epidural anaesthesia, duration of dilation stage or bearing down stage, use of oxytocine, onset of labour, mode of delivery, birthweight and perineal rupture. Calculation of gestational age was based either on ultrasound, or on the first day of the last menstrual period.

Several potentially prognostic variables had varying percentages of missing values. Exclusion of these variables would lead to a loss of statistical power in multivariable analysis and, more seriously, potentially biased results and therefore missing data of the predictive variables were imputed. In multivariable prognostic research complete case analysis should be avoided and multiple imputation methods are known to be superior to other imputation methods.[15] Multiple imputation was performed using PASW Statistics 17.0 (SPSS inc. Chicago, Illinois), in which we generated five imputed datasets.

Data Analysis

The Kolmogorov-Smirnov test was applied to assess normality of the data. Group differences between women with and women without PPH were tested with the

unpaired Student's *t*-test in case of normal distribution and with the nonparametric Mann-Whitney U test in case of skewed distribution. Categorical variables were compared by chi-square statistics.

Using the imputed multiple dataset, logistic regression was performed to predict the occurrence of PPH. For both dichotomous and continuous variables univariate pooled odds ratios, and 95% confidence intervals (CI), as well as p-values, were calculated. Subsequently, multivariable logistic regression analysis with a stepwise backward selection procedure of predictors was performed to construct the two prediction models for PPH. Spearman's rank correlation test was used to find correlations between variables. In case of correlated variables, the least significant variable was excluded from multivariable analysis. Since the purpose of a prediction model is to reach optimal predictive power, our multivariable analysis was not limited to significant prognostic variables but considered all prognostic variables with a significance level of <0.40 in the univariate analysis.[16]

To evaluate the discriminative performance of the logistic model, the area under the Receiver Operating Characteristic (ROC) curve was calculated, comparing the actual outcome to the outcome predicted by the model. The ROC-curve was created using aggregated average predicted probabilities from the five imputed datasets. We also evaluated the calibration of the prediction model by plotting observed and predicted event rates for 10 subgroups of patients on the basis of deciles of the predicted probability of PPH.[17] Per group, the mean predicted probability, aggregated from the five imputed datasets, as well as the mean observed PPH rate was calculated. In case of perfect calibration, all points would be situated on the line that describes X=Y, i.e. the predicted probability equals the observed probability. The reliability of the model was estimated with the Hosmer and Lemeshow test for goodness-of-fit, where low p-values indicate poor calibration. Calculations were performed with the PASW Statistics 17.0 (SPSS inc. Chicago, Illinois) and graphs were produced using GraphPad Prism (GraphPad Software, Inc. La Jolla, USA). Extent of overfitting of the model, i.e. optimism, was assessed with bootstrapping in R.[18] Two hundred bootstrap samples were drawn from each imputation set. In each bootstrap sample, the entire modelling process was repeated. The bootstrap procedure yields a ROC area corrected for optimism and a shrinkage factor to adjust the model for overfitting.

RESULTS

From the HYPITAT trial we identified 1132 eligible women for participation in the present study. Among this cohort 118 women (10.4%) developed PPH, and consequently in 1014 women (89.6%) PPH did not occur.

The distribution of potential predictors between women with and women without PPH is shown in Table 1. During the antepartum period of pregnancy there were no differences in clinical characteristics and laboratory findings between both groups. Whereas intrapartum, women who developed PPH had a higher gestational age at delivery (p=0.007), a longer bearing down stage (p=0.019), a child with a higher birth weight (p=0.009), more episiotomies (p=0.024) and more often a retained placenta which was removed manually (p<0.001).

Table 1. Distribution of predictors among patients with and patients without postpartum haemorrhage at term.

Predictors	Patients with postpartum haemorrhage (n=118)	Patients without postpartum haemorrhage (n=1014)
Clinical characteristics		
Nulliparous	90 (76%)	734 (72%)
Maternal age (years)	30.0 (23.0-39.0)	30.0 (22.0-38.0)
Maternal smoking	15 (13%)	113 (12%)
Prepregnancy body mass index (kg/m^2)	24.5 (19.0-38.1)	25.4 (19.9-36.4)
Non-Caucasian ethnicity	15 (14%)	109 (12%)
Higher education level	24 (39%)	217 (36%)
Previous abortion	29 (25%)	238 (24%)
Gestational age at randomisation	38.7 (36.7-40.6)	38.3 (36.3-40.4)
Blood pressure (mmHg)		
Systolic	140 (125-160)	140 (124-162)
Diastolic	96 (90-105)	96 (88-105)
Laboratory findings		
Dipstick		
Negative	27 (28%)	255 (31%)
Trace	26 (27%)	205 (25%)
+	26 (27%)	217 (27%)
++	11 (11%)	95 (12%)
+++	8 (8%)	42 (5%)
Haemoglobin (mmol/L)	7.5 (6.1-8.6)	7.5 (6.4-8.6)
Haematocrit (L/L)	0.36 (0.30-0.40)	0.36 (0.30-0.41)
Platelets (x10^9/L)*	209 (137-345)	228 (139-345)
Uric acid (mmol/L)	0.31 (0.19-0.46)	0.31 (0.21-0.46)
Creatinine (μmol/L)	61 (45-92)	61 (45-85)
Aspartate aminotransferase (U/L)	19.5 (9.30-38.1)	20.0 (11.0-38.7)

Table 1. *(cont.)*

Predictors	Patients with postpartum haemorrhage (n=118)	Patients without postpartum haemorrhage (n=1014)
Alanine aminotransferase (U/L)	13.0 (5.0-34.0)	12.0 (6.0-31.0)
Lactate dehydrogenase (U/L)	334 (161-472)	298 (156-476)
Data concerning delivery		
Gestational age delivery (weeks)*	39.8 (37.7-41.4)	39.6 (37.1-41.3)
Epidural anaesthesia	35 (30%)	241 (24%)
Duration of dilation stage (min)	435 (104-2044)	405 (60-2508)
Duration of bearing down stage (min)*	51 (4-167)	34 (4-156)
Use of oxytocine	70 (60%)	596 (59%)
Induction of labour	78 (66%)	668 (66%)
Mode of delivery		
Spontaneous	71 (60%)	709 (70%)
Vaginal instrumental delivery	25 (21%)	149 (15%)
Caesarean delivery	22 (19%)	156 (15%)
Birthweight (kg)*	3.50 (2.72-4.39)	3.35 (2.48-4.19)
Perineal rupture (vs none)*		
No rupture	35 (30%)	341 (34%)
1^{st} -2^{nd}	27 (23%)	330 (33%)
3^{rd}-4^{th}	2 (2%)	19 (2%)
Episiotomy	53 (45%)	320 (32%)
Placenta delivery*		
Spontaneous	66 (57%)	841 (83%)
Manual removal/ retained placenta	28 (24%)	15 (2%)
After caesarean section	22 (19%)	156 (15%)

The distribution of predictors is expressed as median (5th-95th percentile) or numbers (%). *Variables with a significant distribution between groups ($p < 0.05$).

Factors significantly associated with PPH in the univariate analysis were platelet count (OR 0.997 per unit, p=0.05), gestational age at delivery (OR 1.3 per week, p=0.003), mode of delivery (OR 1.7 for vaginal instrumental delivery and OR 1.4 for caesarean delivery versus spontaneous delivery, p=0.04 and p=0.19), birth weight (OR 1.6 per kg, p=0.008) and episiotomy (OR 1.6, p=0.03) (Table 2). Placenta delivery was in univariate analysis strongly associated with PPH (OR 25.0 for retained placenta versus spontaneous placental delivery, p<0.001). This variable was excluded from multivariable analysis, as it is obvious that retained placenta is already a strong alert for PPH.

Since more liberal p-values are advocated to increase the probability that real predictors are selected in the model, we selected all prognostic variables with a significance level of p<0.40 in the univariate analysis to enter the model. The criterion for removal from the model was a p-value >0.50. Haematocrit was excluced from

Table 2. Predictors of postpartum haemorrhage in women with mild hypertensive disease of pregnancy at term: univariable and multivariable analysis of the antepartum model (model A) and intrapartum model (model B).

Predictors	Univariable analysis		
	OR	P	95% CI
Clinical characteristics			
Nulliparous	1.2	.37	(0.79-1.9)
Multiparity (para4+)	0.78	.81	(0.10-6.1)
Maternal age (years)	1.03	.16	(0.99-1.1)
Maternal smoking	1.2	.58	(0.65-2.1)
Prepregnancy body mass index (kg/m^2)	0.97	.12	(0.93-1.01)
Non-Caucasian ethnicity	1.2	.47	(0.70-2.2)
Higher education level	1.3	.31	(0.78-2.2)
Previous abortion	1.1	.79	(0.68-1.7)
Gestational age at randomisation (weeks)	1.2	.06	(0.99-1.4)
Blood Pressure (mmHg)			
Systolic	1.003	.67	(0.99-1.02)
Diastolic	1.01	.54	(0.98-1.04)
Laboratory findings			
Dipstick (vs negative)			
Negative			
Trace	1.2	.53	(0.65-2.3)
+	1.3	.42	(0.72-2.2)
++	1.1	.73	(0.55-2.3)
+++	2.2	.08	(0.94-5.3)
Haemoglobin (mmol/L)	0.85	.25	(0.65-1.1)
Haematocrit (L/L x 10)*	0.67	.23	(0.35-1.3)
Platelets (x10^9/L)	0.997	.05	(0.99-1.00)
Uric acid (mmol/L x10)*	1.01	.94	(0.76-1.4)
Creatinine (μmol/L)	1.004	.46	(0.99-1.01)
Aspartate aminotransferase (U/L)	0.99	.27	(0.96-1.01)
Alanine aminotransferase (U/L)	1.00	.94	(0.98-1.02)
Lactate dehydrogenase (U/L)	1.00	.70	(1.00-1.00)
Intrapartum data			
Gestational age at delivery (weeks)	1.3	.003	(1.1-1.5)
Epidural anaesthesia	1.4	.16	(0.91-2.0)
Duration of dilation stage (min)	1.00	.75	(1.00-1.00)
Duration of bearing down stage (min)	1.00	.28	(0.99-1.00)
Use of oxytocine	1.04	.84	(0.70-1.5)
Induction of labour (vs spontaneous)	1.01	.96	(0.68-1.5)
Mode of delivery (vs spontaneous)			
Spontaneous			
Vaginal instrumental delivery	1.7	.04	(1.03-2.7)
Caesarean delivery	1.4	.19	(0.85-2.3)
Birthweight (kg)	1.6	.008	(1.1-2.3)
Perineal rupture (vs none)			
No rupture			
1st-2nd	0.80	.39	(0.47-1.3)
3rd-4th	1.1	.92	(0.25-4.6)
Episiotomy	1.6	.03	(1.04-2.6)

	Multivariable analysis Model A			Multivariable analysis Model B		
	OR	P	95% CI	OR	P	95% CI
	1.4	.15	(0.88-2.3)			
	1.04	.05	(1.0-1.1)	1.03	.11	(0.99-1.1)
	0.97	.17	(0.93-1.01)	0.97	.15	(0.93-1.01)
	1.2	.03	(1.02-1.4)			
	1.2	.56	(0.64-2.3)	1.2	.56	(0.64-2.3)
	1.2	.54	(0.67-2.2)	1.3	.36	(0.74-2.3)
	1.1	.83	(0.52-2.3)	1.2	.59	(0.59-2.5)
	2.1	.08	(0.93-4.8)	3.1	.01	(1.3-7.2)
	0.82	.19	(0.61-1.1)			
	0.997	.07	(0.99-1.00)	0.997	.07	(0.99-1.00)
	0.98	.12	(0.96-1.00)	0.98	.19	(0.96-1.01)
				1.2	.04	(1.01-1.5)
				1.1	.84	(0.61-1.9)
				1.7	.16	(0.82-3.4)
				1.4	.15	(0.90-2.1)
				1.1	.74	(0.57-2.2)
				1.5	.61	(0.31-7.2)
				2.1	.03	(1.07-4.0)

OR = Odds Ratio; CI = confidence interval. If the variable had a p less than .40 in the univariable analysis, it was considered in the final (multivariable) model. A p of .50 was used as a threshold for variables to stay in the final model. *Scale adapted by multiplication with a factor 10 for regression analyses.

the multivariable analysis, because haemoglobin and haematocrit were found to be strongly correlated (R=0.921, p<0.001). Results of the multivariable analysis of prediction model A, including only antepartum prognostic variables, and model B, including besides these antepartum prognostic variables also variables concerning the delivery, are shown in Table 2.

For both prediction models, we averaged the five imputed predicted risks of each patient, which resulted in one performance estimate. Model A showed moderate discrimination, with an area under the ROC curve of 0.63 (95% CI, 0.57-0.69),

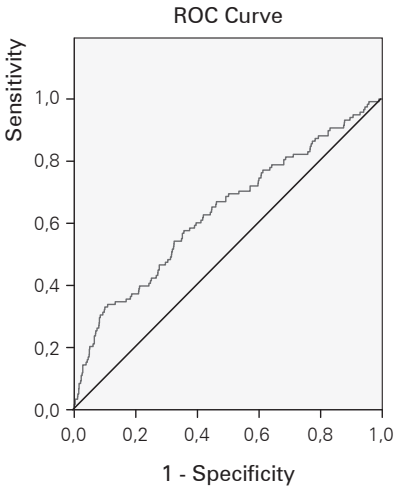

Figure 1a. ROC curve model A (antepartum variables).

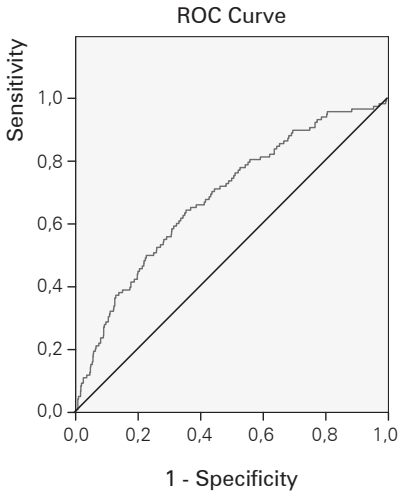

Figure 1b. ROC curve model B (antepartum and intrapartum variables).

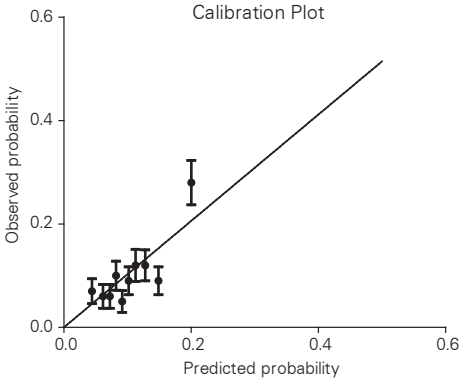

Figure 2a. Calibration plot model A (antepartum variables).

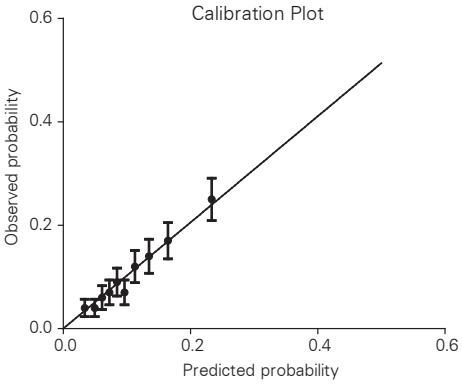

Figure 2b. Calibration plot model B (antepartum and intrapartum variables)

whereas model B showed better discrimination, with an area under the ROC curve of 0.69 (95% CI, 0.63-0.74) (figure 1a and 1b). In addition, calibration was poor for model A (Hosmer-Lemeshow p-value=0.17) and good for model B (Hosmer-Lemeshow p-value=0.57) (figure 2a and 2b). Figure 2b shows the rates of PPH ranged from 3% (lowest 10 percent) to 23% (highest 10 percent). Almost all points are situated on the line X=Y, indicating that the predicted probability equals the observed probability, except for the sixth point which shows a slight overestimation of the predicted probability. Bootstrapping indicated some overfitting with corrected ROC areas under the curve ranging from 0.57 to 0.59 for model A and from 0.61 to 0.63 for model B.

DISCUSSION

In this cohort study we evaluated predictors for PPH in women diagnosed with gestational hypertension (GH) or mild pre-eclampsia (PE) beyond 36 weeks of gestation. Prediction of PPH in these women is possible when prognostic variables in the antepartum period are combined with variables concerning delivery. Included variables in this model during antepartum period were maternal age, prepregnancy BMI, proteinuria, platelets count and AST. Variables incorporated in this model intrapartum were gestational age at delivery, mode of delivery, birth weight and perineal rupture or episiotomy.

Obstetric haemorrhage is worldwide a leading cause of maternal mortality and severe maternal morbidity, accounting for 25% of all maternal deaths.[19,20] In the Netherlands in the period 1993-2005, the most frequent cause of maternal mortality was (pre) eclampsia with a Maternal Mortality Ratio (MMR, maternal mortality per 100,000 live-born children) of 3.5. The second cause was shared by thromboembolism and cardiovascular diseases (MMR 1.6). The fourth cause was sudden death in pregnancy (MMR 0.8), followed by obstetric haemorrhage and obstetric sepsis (MMR 0.7).[3] Severe maternal morbidity caused by PPH includes adult respiratory distress syndrome, coagulopathy, shock, loss of fertility, and Sheehan syndrome.[9,10] So hypertensive disease of pregnancy as well as PPH contributes significantly to maternal mortality and severe morbidity. Thereby, the HYPITAT trial shows that PPH is more frequently found in women with hypertensive disease of pregnancy at term (10% vs 0.4-1.3% for a low risk population). Vice versa Zwart et al found that a major obstetric haemorrhage, defined as the need for transfusion of four or more units of red blood cells, or hysterectomy or arterial embolisation, was accompanied by PE in 11.2% of cases.[13] Other studies have also found a significant association between PE and PPH.[4-8] In a study on vaginal

deliveries, PPH was five times more common in pregnancies with PE[5], in two other studies, which were restricted to caesarean deliveries, PE was associated with about two-fold higher risk of PPH.[6,8] We suggest that angiogenic factors in maternal circulation can explain the association between women with hypertensive disease of pregnancy and PPH.

Because of the high incidence of PPH in women with pregnancy related hypertensive disorders, we think prediction of PPH in women with GH of PE is of major importance. Moreover, studies describing predictors for PPH in such women are scarce. But, limitations are also present. First, various prognostic predictor variables had varying percentages of missing values. The missing data of the predictive variables were imputed, because deleting them would lead to a loss of statistical power in multivariable analysis and, more seriously, potentially biased results.[15] Second, different options for the definition of PPH can be considered. We defined PPH as blood loss >1000 ml within 24 hours after delivery.[9,14] Other options to define PPH are transfusion need or drop of haemoglobin level. The latter was considered to be the most objective, but obviously depends on standardised assessment of pre- and post haemorrhage haemoglobin levels, which were not available for all patients. Probably the need of blood transfusion was the best option, however this management based criterion is depending on local transfusion policies. Although blood loss is known to be largely underestimated[21,22] we decided that blood loss >1000 ml within 24 hours after delivery was the best option, because this definition is internationally accepted.

Risk factors for PPH in the overall population include high maternal age, maternal obesity, prolonged labour, induced and augmented labour, overdistended uterus (high birth weight or macrosomia, multiple pregnancy, hydramnios), abruptio placentae, placenta praevia, PE, HELLP syndrome, previous caesarean delivery, previous postpartum haemorrhage, episiotomy, operative delivery (especially emergency caesarean delivery) and anaemia.[4,6,9,12,23] Many of the above mentioned variables were also found to be independent predictors of PPH in our study, such as increased maternal age, decreased haemoglobin rate (only for model A), decreased platelets count, decreased AST, caesarean delivery, high birth weight and episiotomy. However, prolonged labour, labour induction and augmentation with oxytocine were not included in our final model. Furthermore, multiple pregnancy, placentae praevia and previous caesarean delivery were exclusion criteria in the HYPITAT trial, and for that reason not assessed in the current study. Abruptio placenta did not occur in the HYPITAT trial and so this could not be investigated either. Noteworthy, severe PE, manifested as severe proteinuria (3+ on dipstick) was significantly related to the occurrence of PPH. Contrary to popular

belief, multiparity (para 4+) was not associated with PPH, while the risk of PPH is slightly elevated in nulliparous women, as confirmed in other studies.[12,23]

Recent studies demonstrate an increase of severe maternal morbidity related to major obstetrical haemorrhage in Western countries.[24-28] Possible explanations from these results include the increasing age of women at birth, the increasing caesarean delivery rate and a high birth weight (macrosomia), which are all confirmed in our study. Macrosomia is more and more a common lifestyle problem needing public health intervention, and is linked to maternal obesity, older age and diabetes mellitus.[29] In our study a high BMI was not associated with PPH, but in contrast a non significant trend towards a higher risk of PPH in case of smaller BMI was observed. This counter-intuitive outcome might be explained from the fact that we only included women with hypertensive disease of pregnancy, for which obesity itself is a risk factor.

Most cases of PPH are due to uterine atony and retained placenta.[9] We decided not to include uterine atony or retained placenta as variable in our prediction model, because they are already known as a strong alert for PPH and the stage of performing an active prophylactic postpartum management is already expired. Moreover, uterine atony has to be recognized clinically and is a subjective variable.

While maternal deaths are extremely rare in the Netherlands, the morbidities associated with PPH remain a major problem. The results of this study indicate that PPH can be used as a complimentary indicator to assess the quality of obstetric care. Most of the identified predictors were related to obstetric management and interventions, and are thus preventable. Including these factors in the flow charts of local protocols, could help identification of PPH and consequently lead to an optimal and quick treatment. In case of an increased risk of PPH particular attention is needed during early postpartum period and active prophylactic or therapeutic techniques can be used. So, the identified predictors should alert clinicians managing labour in women with GH and PE.

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Chapter 9

Accuracy of serum uric acid as a predictive test for maternal complications in pre-eclampsia: Bivariate meta-analysis and decision analysis

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ABSTRACT

Objective The aim of this study is to determine the accuracy and clinical value of serum uric acid in predicting maternal complications in women with pre-eclampsia.
Methods An existing meta-analysis on the subject was updated. The accuracy of serum uric acid for the prediction of maternal complications was assessed with a bivariate model estimating a summary Receiver Operating Characteristic (sROC) curve. Subsequently, a clinical decision analysis was performed, in which three alternative strategies were modelled: (I) expectant management with monitoring until spontaneous labour; (II) induction of labour; (III) serum uric acid as test for predicting maternal complications. In the latter strategy, accuracy data of serum uric acid derived from the sROC curve were used to assess the value of serum uric acid in the management of women with pre-eclampsia. In this strategy, women with an increased serum uric acid were supposed to have labour induced, whereas women with serum uric acid levels below the threshold were managed expectantly. The decision whether to use the policy expectant management, to induce labour or to test serum uric acid levels, is based on the expected utility of each strategy. The expected utility depends on the probability of occurrence of severe maternal complications (i.e. severe hypertension, haemolysis, elevated liver enzymes and low platelet count (HELLP syndrome) or eclampsia) and the mode of delivery (caesarean section versus vaginal delivery). Valuation of the outcomes was performed using a distress ratio, which expresses how much worse a complication of pre-eclampsia is valued as compared to a caesarean section.
Results Eight studies, testing 1565 women with pre-eclampsia, met the inclusion criteria. If the distress ratio was 10, the strategy regarding serum uric acid would be the preferred strategy when the probability of complications was between 2.9% and 6.3%. At higher complication rates induction of labour would be preferred, whereas at lower complication rates expectant management would be the best treatment option. These findings were stable in sensitivity analyses, using different distress ratios.
Conclusion Based on the decision analysis, serum uric acid seems to be a useful test in the management of pre-eclampsia under realistic assumptions.

INTRODUCTION

Pre-eclampsia (PE) is a leading cause of maternal and perinatal mortality and morbidity. The incidence of PE in nulliparous women is estimated between 3 and 14 percent.[1] PE is a multisystem disorder characterized by gestational hypertension (GH) after the 20th week of gestation and proteinuria.[2] It can result in maternal complications as severe hypertension, eclampsia and haemolysis, elevated liver enzymes and low platelet count (HELLP syndrome), or fetal complications such as growth restriction, fetal distress and even perinatal death. In view of the severe consequences of these complications, their prediction is of pre-eminent importance and might help to decide whether termination of pregnancy might be a better option than expectant monitoring.

Uric acid is a marker of oxidative stress, tissue injury and renal dysfunction, and therefore might be helpful in the prediction of complications of PE.[3] Uric acid is the end product of purine metabolism and is synthesized by the enzyme xanthine oxidase. Hypoxia and ischemia of the placenta and cytokines such as interferon induce the expression of xanthine oxidase and therefore increase the production of uric acid and also reactive oxygen species.[4] In uncomplicated pregnancies, serum uric acid concentration fall in early pregnancy 25–35% due to an elevation in renal clearance secondary to increased glomerular filtration rate or reduced proximal tubular reabsorption and due to changes in its production rate.[5–7] Later in pregnancy the serum uric acid levels increase, possibly due to raised fetal production, decreased binding to albumin and a decline in uric acid clearance until toward the end of pregnancy when they approach non-pregnant values.[3,8–10] The most commonly accepted explanation for the hyperuricemia in PE is increased reabsorption and decreased excretion of uric acid in the proximal tubules, although others suggest that increased uric acid is a marker of raised xanthine oxidase activity.[4]

Literature on serum uric acid as a predictor of complications of PE is conflicting. Several studies have demonstrated a correlation between elevated maternal serum uric acid levels and adverse maternal and neonatal outcome[11–16], whereas other studies showed that serum uric acid is a poor predictor of PE.[17–19] In a recent systematic review on the subject[20], a raised serum uric acid was associated with an almost doubled risk of severe complications, such as eclampsia, severe hypertension, and perinatal death. Despite this doubled risk, the authors of the review concluded that the uric acid test was not clinically useful in the management of women with PE. They stated that there was little evidence to justify the use of therapeutic measures like magnesium sulphate or early delivery aimed at

reducing maternal and fetal complications in case of increased uric acid levels. This conclusion was based on the fact that the likelihood ratio of raised serum uric acid for a pre-eclamptic patient to develop complications was two. Several concerns can be voiced on this review. First, the authors pooled likelihood ratios, which is a debatable statistical procedure.[21] Moreover, the authors only looked at one cut-off value, thereby overlooking the possibility that in patients with serum uric acid values far above this cut-off value the risk of pregnancy complications is much higher. Finally, a decision analysis, in which clinical consequences of strategies with and strategies without uric acid measurements were modelled, has never been performed.

In view of these limitations, we repeated the meta-analysis with a bivariate meta-analytic model, allowing us to assess test accuracy of serum uric acid in a more quantitative way. Subsequently, we performed decision analysis to assess the value of serum uric acid in the management of women with PE.

MATERIALS AND METHODS

Study identification and selection

For this review we reassessed the articles which were previously included in a systemic review written by Thangaratinam et al.[20] As these authors performed a search until 2004, we updated their search for the period 2004–2007, using a similar search strategy.

We also used similar methods as Thangaratinam et al. to assess study quality. In short, two authors (C.K. and H.G.) extracted data on study quality and test accuracy. Subsequently, accuracy data were used to construct 2 x 2 tables relating serum uric acid levels to maternal complications (severe hypertension, eclampsia and HELLP syndrome). In contrast to Thangaratinam et al., we only focused on the maternal complications.

Data synthesis

From the 2 x 2 tables, cross-classifying serum uric acid test results and the complications in pregnant women with PE, sensitivities and specificities were calculated and plotted in a Receiver Operating Characteristic (ROC) curve to visualise data. We used a bivariate meta-analysis model to calculate pooled estimates of sensitivity and specificity for several serum uric acid cut-off values and to fit a summary ROC (sROC) curve. This model incorporates the correlation

that may exist between sensitivity and specificity within studies due to possible differences in thresholds between studies. The bivariate model uses a random effects approach for both sensitivity and specificity, allowing for heterogeneity beyond chance due to clinical or methodological differences between studies.[22,23]

Clinical decision analysis

Subsequently, we used the data from the estimated sROC curve to model the use of serum uric acid measurements in the management of severe complications in pre-eclamptic pregnancies. We considered a hypothetical case of a pregnant woman with mild PE at 37 weeks of gestation. The woman had a blood pressure of 160/95 mmHg, proteinuria of 700 mg in 24 h and normal laboratory tests. The fetus was in good clinical condition, with fetal growth at the 50th percentile, normal amniotic fluid, normal fetal movements and a normal non-stress test.

A decision tree was constructed in which we modelled three alternative strategies for women with mild PE at term (Fig. 1). Strategy I is expectant management with monitoring until spontaneous labour occurs. Expectant management bears the risk of the development of severe maternal and fetal complications by deterioration of the PE. In strategy II, labour is induced immediately. This strategy is thought to prevent maternal and fetal complications, but at the expense of an increased risk of failed induction of labour and subsequent caesarean section.[24–27] In strategy III, serum uric acid is used to assess the risk of the occurrence of complications. In women with an increased serum uric acid, labour is induced whereas women with normal serum uric acid levels are managed expectantly.

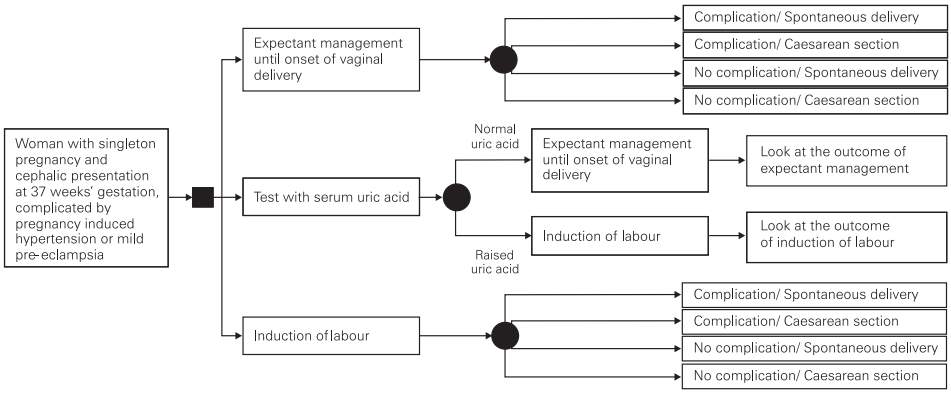

Figure 1. Decision tree for women with gestational hypertension or mild pre-eclampsia representing the three strategies for management to reduce maternal complications. The different outcomes are presented.

The decision whether to induce labour, to use the policy expectant management or to test serum uric acid levels and to induce labour in case of an increased blood value, is based on the expected utility of each strategy. The expected utility of a strategy depends on the probability of possible outcomes and the subjective values attached to the outcomes.

Outcomes and data

We considered two possible outcomes, i.e. the occurrence of a complication and the mode of delivery. The occurrence of a complication of PE was defined as severe hypertension, eclampsia and HELLP syndrome. For the mode of delivery, a caesarean section was considered as a negative outcome. For each strategy, four combinations of outcomes were possible: (I) a patient without a complication who delivered vaginally, (II) a patient with a complication who delivered vaginally, (III) a patient without a complication who delivered by caesarean section, and (IV) a patient who experienced both negative outcomes, i.e. a complication of PE and a caesarean section.

In order to compare the three different strategies, the relative valuations of the adverse pregnancy outcomes, i.e. complicated pregnancy and caesarean section, have to be taken into account. To compare the disutility caused by these two events, we used the amount of distress caused by these issues as a measure to compare the negative impact of these two outcomes. The amount of distress can be expressed on a distress scale. For an uncomplicated pregnancy resulting in a vaginal delivery the distress is considered to be zero, whereas the three other combinations of possible outcomes will generate distress. The overall valuation of the outcome of a pregnancy is determined by the distress of severe maternal complications relative to distress caused by caesarean section. In other words, how much worse is a severe maternal complication of PE valued as compared to a caesarean section? We propose the use of a distress ratio as an instrument to compare the strength of the negative impact of these two events. This ratio of the distress of 'a complication' and the distress of 'a caesarean section' is referred to as the 'distress ratio'. For example, a distress ratio of 10 for a severe complication implies that a severe complication is valued 10 times worse than a caesarean section. Understandably, this measure is subjective.[28]

Data from the Dutch National Obstetric Registration from January 2000 until January 2005 showed that the non-elective caesarean section rate among women with GH or PE in whom labour started spontaneously was 14% versus 22% in whom labour was induced (OR 1.7, 95% CI 1.6–1.8).[27] The prevalence of several complications in the expectant group was provided by the Dutch Perinatal Registry

(PRN).[29] The expected complication rate after expectant management for women with a singleton pregnancy in cephalic presentation at term (>36 weeks) and a diastolic blood pressure ≥90 mmHg was 6.2% for severe hypertension (diastolic blood pressure >110 mmHg at two occasions 6 h apart), 0.07% for eclampsia and 0.03% for HELLP syndrome, resulting in an overall complication rate of 6.3%. When labour was induced this risk was considered to be zero.

Calculation formulas

In strategy I, i.e. expectant management, the expected distress can be calculated from

(I) (Pcomp _ Exp x DIScomp) + (Psc _ Exp x DISsc) + (P(comp+sc) _ Exp x DIS(comp+sc))

The probability of a complication after expectant management (Pcomp _ Exp) was initially set at 5.0% and the probability of a caesarean section after expectant management and spontaneous onset of labour (Psc _ Exp) was set at 14%. We selected different distress ratios between 2 and 25 for a complication (DIScomp) and for caesarean section the distress was set at 1 (DISsc). For the expected distress of a complication and a caesarean section after expectant management we added the probabilities of these two outcomes (P(comp+sc) _ Exp) and the distress ratios (DIS(comp+sc)). A spontaneous delivery is assumed to bring no distress, and so is set at zero (not shown in the calculation).

In strategy II, i.e. induction of labour, the expected distress can be calculated from

(II) (Pcomp _ Ind x DIScomp) + (Psc _ Ind x DISsc) + (P(comp+sc) _ Ind x DIS(comp+sc))

The probability of a complication after induction of labour (Pcomp _ Ind) was set at 0% and the probability of a caesarean section after induction of labour (Psc _ Ind) at 22%. The expected distress of the combination of a complication and a caesarean section after induction of labour was calculated by adding the probabilities of these two outcomes (P(comp+sc) _ Ind) and the distress ratios (DIS(comp+sc)).

In strategy III, i.e. testing with serum uric acid, the expected distress is the addition of four calculations:

(IIIa) Distress for a situation with positive test and true risk of complication

(Sensitivity uric acid x Pcomp) x (Pcomp _ Ind x DIScomp + Psc _ Ind x DISsc + P(comp+sc) _ Ind x DIS(comp+sc))

(IIIb) Distress for a situation with negative test and true risk of complication
(1 - Sensitivity uric acid) x Pcomp x (Pcomp _ Exp x DIScomp + Psc _ Exp x DISsc + P(comp+sc) _ Exp x DIS(comp+sc))

(IIIc) Distress for a situation with negative test and absence of risk of complication
(Specificity uric acid) x (1 – Pcomp) x (Pcomp _ Exp x DIScomp + Psc _ Exp x DISsc + P(comp+sc) _ Exp x DIS(comp+sc))

(IIId) Distress for a situation with positive test and absence of risk of complication
(1 – Specificity uric acid) x (1- Pcomp) x (Pcomp _ Ind x DIScomp + Psc _ Ind x DISsc + P(comp+sc) _ Ind x DIS(comp+sc))

For this strategy, sensitivity and specificity were used to calculate the probability of a complication and/ or a caesarean section in case of increased or normal values of uric acid, which were derived from the estimated sROC curve.

According to the principles of decision theory, the best choice is the one with the lowest expected distress. The decision whether to use the policy expectant management, to induce labour, or to test serum uric acid levels and to induce labour in case of an increased blood value, thus depends on the expected distress of each strategy.

In subsequent sensitivity analyses, several decision models with different distress ratios were constructed to show which management should be the best option in women with mild preeclampsia. We performed multiple sensitivity analyses for the variables.

RESULTS

Study identification and eligibility

Thangaratinam et al.[20] had detected seven articles on the subject. Our search for the period 2004–2007 revealed three additional articles reporting on the association between serum uric acid and maternal complications of which we excluded two because of insufficient data to construct 2 x 2 tables. Finally, eight primary articles met the selection criteria.

Study characteristics, inclusion and exclusion criteria and the outcome measures of the included studies are listed in Table 1. In total, 1565 pregnant women with PE were included in these eight studies. The test thresholds of serum uric acid varied from 270 to 540 μmol/l in individual studies. The most common was 350 μmol/l. The commonest maternal complication assessed was severity of hypertension. Analyses of clinical characteristics suffered from unclear reporting in the studies.

Sensitivity and specificity

Table 1 also summarizes the sensitivities and specificities of serum uric acid levels in predicting severe maternal complications of PE for each study. There were six studies that reported on the capacity of serum uric acid to predict severe hypertension, two studies that reported on the prediction of eclampsia and one study that reported on the prediction of HELLP syndrome. Williams and Galerneau[19] described two complications, i.e. severe hypertension and HELLP syndrome, and used two different cut-off values of serum uric acid.

A plot of sensitivity-specificity points in ROC curve for these three severe maternal complications is shown in Fig. 2, which also contains a sROC curve constructed with the bivariate method.

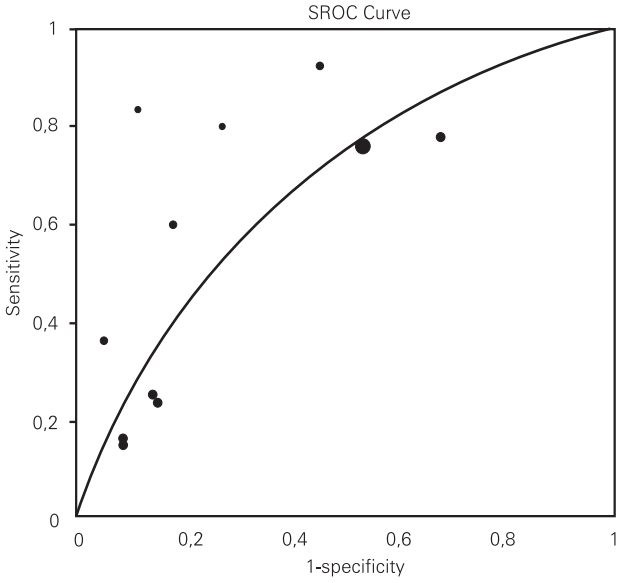

Figure 2. Summary Receiver-operating characteristic (sROC) of several studies for the prediction of maternal complications in pre-eclampsia.

Table 1. Clinical characteristics for individual studies on the predictive accuracy of uric acid in predicting maternal complications of pre-eclampsia

1st Author	Year	Country	Inclusion criteria	Number of patients (n)
Peralta Pedrero[30]	2004	Mexico	IN: BP ≥ 140/90 mmHg after 20 weeks and proteinuria ≥ 1+ and 300 mg/24 hours EX: liver and renal insufficiency and diabetes	216
Williams[19]	2002	United States	IN: BP ≥ 140/90 mmHg after 20 weeks and proteinuria ≥ 1+ or 300 mg/24 hours EX: diabetes, chronic hypertension and multiple gestations	194
Brown[31]	1996	Australia	IN: Australian Society for the Study of Hypertension in Pregnancy (ASSHP) criteria for preeclampsia32 EX: essential hypertension, secondary hypertension (predominantly renal disease)	825
Voto[33]	1988	Argentina	IN: BP ≥ 140/90 mmHg EX: essential hypertension	125
Liedholm[11]	1984	Sweden	IN: BP ≥ 140/90 mmHg during or after the first 20 gestational weeks and proteinuria ≥ 1+ on at least two occasions EX: diabetes mellitus	26
Seitchik[9]	1953	United States	IN: BP ≥ 140/90 mmHg	14
Yassaee[34]	2003	Iran	IN: severe preeclampsia	103
Fadel[35]	1969	Egypt	IN: BP > 140/ 90 mmHg and/or proteinuria in latter half of pregnancy	62

BP: blood pressure; IN: included; EX: excluded; HELLP: haemolysis, elevated liver enzymes, and low platelet count; SGOT: serum glutamic oxaloacetic transaminase; LDH: lactate dehydrogenase; TP: true positive; FN: false negative; FP: false positive; TN: true negative.

Clinical decision analysis

The probability of severe maternal complications, i.e. severe hypertension, HELLP syndrome and eclampsia, in pre-eclamptic women was set at 5.0%. In the initial analysis, we presume that the distress ratio was 10, i.e. the expected distress of severe complications was valued ten times worse than the expected distress of a caesarean section. The expected distress was 2.7 for expectant management, 2.6 for induction of labour and 2.5 for the strategy in which serum uric acid was used to decide for induction of labour or expectant management. Thus, under these assumptions, strategy III regarding serum uric acid would be the procedure of first choice, because of its lowest expected distress. However the difference with the two other strategies is small.

Outcome	Cut off value (μmol/l)	TP	FN	FP	TN	Sensitivity	Specificity
Severe hypertension (BP ≥ 160/110 mmHg)	270	119	34	43	20	0.78	0.32
Severe hypertension (systolic BP ≥ 160 and/or diastolic BP ≥ 110 mmHg on two occasions)	450 540	17 10	50 56	18 11	109 116	0.25 0.15	0.86 0.91
HELLP-syndrome (SGOT > 40 IU/L, LDH >600 IU/L, haemolysis on film and platelet count ≤ 150 x 109 /L)	450 540	13 9	42 46	21 12	118 127	0.24 0.16	0.85 0.91
Severe hypertension (systolic BP ≥ 170 and/or diastolic BP ≥ 110 mmHg)	350	130	41	351	303	0.76	0.46
Severe hypertension (BP ≥ 160/100 mmHg)	350	15	10	18	82	0.60	0.82
Severe hypertension (use of a combination therapy of beta-blocker and hydralazine)	350	12	3	3	8	0.80	0.73
Severe hypertension	350	2	.5	1	11	0.80	0.92
Eclampsia	350	12	1	41	49	0.92	0.54
Eclampsia	350	8	14	2	38	0.36	0.95

In subsequent sensitivity analyses we varied the prevalence of severe complications between 0 and 10%. Fig. 3A shows the expected distress for the three strategies, when the distress ratio is presumed to be 10. When the prevalence of severe complications was between 2.9 and 6.3%, the third strategy, looking at serum uric acid, had the lowest distress. In case of a prevalence equal or more than 6.3%, induction of labour was expected to have the lowest expected distress, whereas equal to or below a prevalence of 2.9%, expectant management would give the lowest expected distress, and so be the best treatment option.

Fig. 3B–D depicts the situation for distress ratios of 2, 5 and 25 respectively; showing that treatment concerning serum uric acid levels becomes less attractive with increasing distress ratios compared to the other two strategies. The prevalence for severe complications brings less distress regarding serum uric acid between 4.1 and 8.7% for a distress ratio of 2; between 3.2 and 7.0% for a distress ratio of

5; and between 2.7 and 5.9% for a distress ratio of 25. Until now the sensitivity and specificity values were both set to 68%. If we chose a lower sensitivity and a higher specificity combination from the sROC curve, i.e. a sensitivity of 43% and a specificity of 80%, the expected distress for serum uric acid is less advantageous however almost comparable to the situation which is shown in Fig. 3A–D. Extensive sensitivity analyses with sensitivity and specificity combinations between 40 and 80% and distress ratios varying between 2 and 25, showed that the use of serum uric acid remained of value at prevalence of complications between 3 and 9%. At higher distress ratios, the amount of distress reduced by the test was higher.

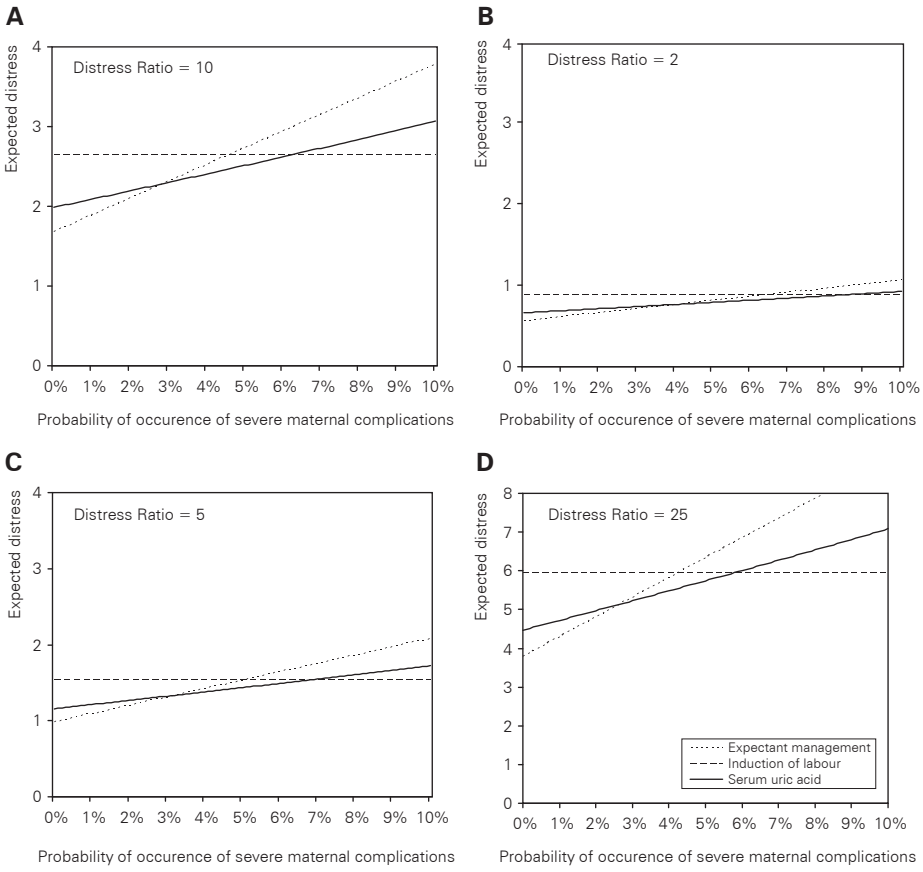

Figure 3 (A-D). Expected distress for three strategies: (I) expectant management, (II) induction of labour and (III) treatment depending on serum uric acid levels. In each figure, the prevalence of severe complications in pre-eclamptic women varies between 0 and 10% and the expected distress is calculated for the distress ratios between 2 and 25. The distress ratio represents the distress caused by severe complications as compared to the distress caused by a caesarean section. For example, a distress of 25 implies that severe complications are valued 25 times worse than a caesarean section. Sensitivity is 68% and specificity is 68%.

COMMENT

This meta-analysis summarizes the available evidence on the accuracy of serum uric acid in the prediction of severe maternal complications in pre-eclampsia (PE). The decision analysis was performed to evaluate whether the use of serum uric acid is useful in the management of women with PE. We found that under realistic assumptions, the use of serum uric acid improves the maternal outcome and should therefore be applied in patients with hypertensive disorders at term.

Evidence on the accuracy of serum uric acid in the prediction of eclampsia and HELLP syndrome is limited, since our search revealed only three studies. For this reason we added severe hypertension, which itself is not a complication, but rather a risk situation, together with eclampsia and HELLP syndrome as a composite adverse maternal outcome in the decision analysis. Progression to severe hypertension could be associated with severe maternal morbidity, as eclampsia, pulmonary edema and cerebral encephalopathy or haemorrhage.[36–38]

Inclusion of the study of Yassaee in the meta-analysis was questionable since only women with severe hypertension were included, whereas in the other studies women with mild hypertension were also included. Because of this discrepancy we repeated the meta-analysis also without the study of Yassaee. In subsequent sensitivity analyses, the clinical utility of serum uric acid measurements appeared to be comparable to our initial analysis.

The overall complication rate we used in the decision analysis was 6.3%, of which 6.2% was the complication rate of severe hypertension. Besides the much lower complication rate of eclampsia and HELLP syndrome, the distress due to eclampsia and HELLP syndrome might be much higher as compared to severe hypertension. However, as stated above, severe hypertension is also associated with poor maternal outcome. Moreover, increase of the distress ratio did not alter the conclusion of our analysis (Fig. 3A–D).

A significant limitation of this review is the heterogeneity noticed between individual studies with regard to population, test thresholds, frequency of testing, gestational age at development of PE and at delivery, interval between the test and outcome, and reference standards. Awareness is important about variations in methods for measuring uric acid levels and different therapeutic interventions such as use of antenatal steroids in reducing respiratory distress syndrome[39] and antihypertensives that might help to reduce fetal and maternal complications[40], because it could influence the outcomes.

Thangaratinam et al.[20] concluded that serum uric acid measurement was not a clinically useful test to predict maternal complications in women with PE. They based their conclusion on a likelihood ratio of two, which they found to be insufficient for clinical use. However, they based their conclusion only on test accuracy. Based on our decision analysis, in which we combined test accuracy both with the prevalence of disease and with the impact of clinical outcomes, we draw a different conclusion. Apparently, the limited accuracy of the test is still enough to make it a useful test in its clinical context.

In conclusion, measurement of serum uric acid seems to be a useful test to predict maternal complications in the management of women with PE. In patients with increased serum uric acid values labour should be induced, due to their increased risk of complications.

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Chapter 10

Accuracy of liver function tests for predicting adverse maternal and fetal outcomes in pre-eclamptic women: A systematic review

Submitted

ABSTRACT

Introduction Pre-eclampsia is one of the single largest causes of maternal and fetal mortality and morbidity. Liver function tests (LFTs) are routinely performed in women with pre-eclampsia as part of a battery of investigations to assess severity at admission and later to guide appropriate management.

Methods A systematic review of test accuracy studies to determine the accuracy with which liver function tests predict maternal and fetal complications in women with pre-eclampsia. We conducted electronic searches without language restrictions in Medline (1951-2010), Embase (1980-2010) and the Cochrane Library (2009). Primary articles that evaluated the accuracy of liver function tests in predicting complications in women with pre-eclampsia were chosen. Data was extracted by two reviewers independently. A bivariate model estimated area under summary Receiver Operating Characteristic curve (AUC), sensitivity and specificity.

Results There were 13 primary articles including a total of 3507 women assessing maternal (30 2 x 2 tables) and fetal (19 2 x 2 tables) outcomes. For predicting adverse maternal outcome, the point estimates of specificity were > 70% in 18 tables with AUC of 0.79 (95% CI 0.51–0.93). For predicting adverse fetal outcomes the AUC was 0.65 (95% CI 0.26–0.9) and the specificity of the test was >70% in 9 2 x 2 tables. Sensitivity of the test was poor for both maternal and fetal outcomes.

Conclusion LFTs performed better in predicting adverse maternal than fetal outcomes in women with pre-eclampsia. Presence of raised liver enzymes were associated with an increased probability of maternal and fetal complications, but normal liver enzymes did not rule out disease.

INTRODUCTION

Pre-eclampsia (PE) affects approximately 2–8% of all pregnancies and is associated with several complications.[1] It remains one of the single largest causes of maternal and fetal mortality and morbidity.[1-4] PE accounts for about one-fifth of antenatal admissions, two-thirds of referrals to day assessment units and a quarter of obstetric admissions to intensive care units.[5] Although the rate of complications is relatively low in PE, when present they result in adverse maternal and fetal outcomes. Clinicians need to identify the women at risk of severe complications who need effective interventions like magnesium sulphate, anti hypertensives, corticosteroids or delivery to reduce or prevent complications to the mother or baby.

Liver function tests (LFTs) are currently routinely performed in most obstetric units as part of the battery of tests in women with PE. A Delphi survey of international experts considered LFTs to be the third important predictor of maternal and fetal complications after blood pressure and proteinuria.[6] Liver enzymes, aspartate aminotransferase (AST) or serum glutamic oxalocetic transaminase (SGOT) and alanine aminotransferase (ALT) or serum glutamic pyruvic transaminase (SGPT) are often raised in PE. The clinical manifestations of liver involvement are right upper quadrant or epigastric pain, elevated liver enzymes, and in severe cases, subcapsular haemorrhage or hepatic rupture. Haemolysis, Elevated Liver functions, and Low Platelets (HELLP) syndrome is diagnosed in 10 – 20% of women with severe PE.

Prediction of PE and its complications are poor and when the condition is diagnosed there is a need to establish its severity.[7] A scientific strategy based on systematic literature review methodology help to elucidate current uncertainties and to identify gaps in the research evidence.[8] Several studies have reported a positive correlation between elevated maternal serum liver enzyme levels and adverse maternal and fetal outcomes.[9-11] However, these studies have not generally been conducted with large enough sample size to provide precise accuracy estimates and they vary widely in their definition of PE and maternal and fetal outcomes. There are no systematic reviews exploring the accuracy of liver enzymes to predict complications of PE. We therefore conducted a comprehensive systematic review to obtain precise estimates of maternal serum liver enzyme levels to predict maternal and fetal complications in women with PE.

METHODS

The review was carried out with a prospective protocol[12] using widely recommended methods.[13-16]

Identification of studies

We searched MEDLINE (1951-2010), EMBASE (1974-2010) and the Cochrane Library (2009) for relevant citations. We developed a broad and sensitive search strategy consisting of MeSH, key terms related words and word variants capturing population of PE, tests including liver function tests and maternal and fetal outcomes were employed. From this comprehensive database, the citations on liver function as a test were identified.[17] Initial generic searches were regularly updated and supplemented by specific search strategies to capture liver function tests. This was done to ensure that all relevant studies were identified. The reference lists of all known primary and review articles were hand searched to identify cited articles not captured by electronic searches. Details of the search strategy are available from the authors. We contacted corresponding authors for missing data. Language restrictions were not applied. A comprehensive database of relevant articles, published and unpublished was constructed.

Study selection and data extraction procedures

Studies which evaluated the accuracy of maternal LFTs in women with PE for the prediction of maternal or fetal complications were selected in a two-stage process. First, the electronic searches were scrutinised and full manuscripts of all citations that were likely to meet the predefined selection criteria were obtained by two independent reviewers (CMK and SI). Secondly, final inclusion or exclusion decisions were made by the reviewers (ST and CMK) after examination of these manuscripts. Studies which met the predefined and explicit criteria regarding population, tests, outcomes and study design were selected for inclusion in the review as shown below.

Population: Women with pre-eclampsia.

Index test: LFTs including AST, ALT, Lactate dehydrogenase (LDH), Gamma glutamyl transferase (GGT), Alkaline Phosphatase (ALP) and Bilirubin.

Composite adverse outcome: Maternal outcome included one of the following; eclampsia, pulmonary oedema, maternal death, abruption, disseminated intravascular coagulation (DIC), renal failure, intra cerebral haemorrhage, adult respiratory distress syndrome, retinal detachment.[12,18] Fetal outcome that included one of the following; intra uterine death, neonatal deaths, fetal distress, intra uterine growth restriction, intraventricular haemorrhage, respiratory distress syndrome, mechanical ventilation, necrotising enterocolitis, bronchopulmonary dysplasia, preterm birth.[12]

Study design: Test accuracy study allowing generation of 2 x 2 tables.
Information was extracted from each selected article on study characteristics, quality and accuracy results. Accuracy data were used to construct 2 x 2 tables of liver enzyme results and outcomes. The index test was considered positive if liver function test levels for any of the analyses were above a threshold defined in the primary study, and index test negative if these were below the threshold. When disagreements occurred, they were resolved by consensus or arbitration.

Methodological quality assessment

All manuscripts meeting the selection criteria were assessed for their methodological quality, defined as the confidence that the study design, conduct and analysis minimised bias in the estimation of test accuracy. Based on existing checklists,[14-16,19,20] quality assessment involved scrutinising study design and relevant features of the population, test and outcomes of the study. A study was considered to be of good quality if it used a prospective design, consecutive enrolment, full verification of the test result with reference standard, and had adequate test and outcome description.[15,16,19,20]

Data synthesis

For each study, we constructed a 2 x 2 table cross-classifying the LFT results and the occurrence of complications. To visualise data we plotted sensitivity and specificity in receiver operating characteristic (ROC) plots.[21] In a ROC plot the upper left corner is the ideal position because it reflects the highest sensitivity and the lowest false positive rate (highest specificity). A bivariate random effects model was used to fit a summary sROC curve.[22-25] Briefly, the bivariate model preserves the two-dimensional nature of diagnostic data in a single model incorporating the correlation that may exist between sensitivity and specificity within studies due to possible differences in threshold between studies. When more than one adverse maternal or fetal outcome was reported, we selected the test accuracy study (2 x 2 table) with the worst outcome to avoid multiple inclusions of the same patients in the meta analysis as this gives erroneous precision to the summary estimates. We refrained from pooling sensitivity and specificity or likelihood ratios separately due to differences in liver enzymes and thresholds included in the selected studies which led to heterogeneity. Area under sROC curve (AUC) presented the most suitable summary of these data. All statistical analyses were performed using MetaDisc and Stata 10.0 statistical package.

RESULTS

Literature identification and study quality

Fig. 1 summarises the process of literature identification and selection. There were 13 primary articles that met the selection criteria, consisting of 49 2 x 2 tables including a total of 3507 women.[11,26-37] Each study's salient features are provided in Table 1. Methodological quality of included studies (Fig. 2) showed that the index tests was adequately described in 5 out of 13 studies (38 %)[11,29,33,34,37] and reference standard (maternal and fetal outcomes) was adequate in all the studies.[11,26,28-37]

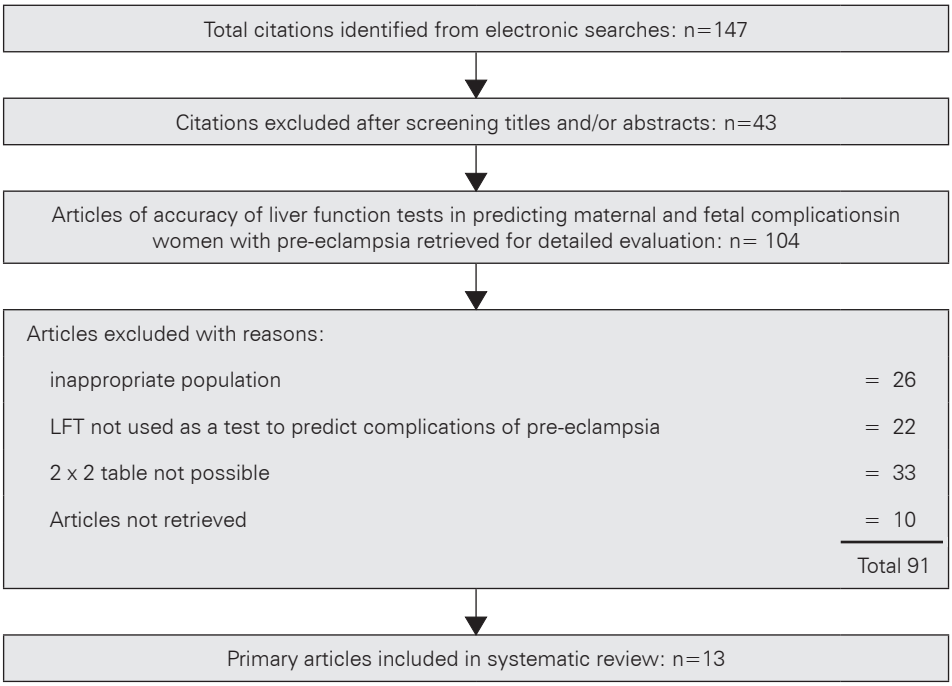

Figure 1. Study selection process for systematic review of accuracy of liver function tests in predicting maternal and fetal complications in preeclamptic women.

Five of the 13 (38%) studies were prospectively conducted[26,29-31,37] and none of the studies were blinded for outcome measurement (Fig. 2).

Study characteristics

Five of the 13 studies consisted of women with severe PE.[27,28,32-34] The gestational age of the women with PE was specified in 7 studies.[27,29,32-34,37] The liver function tests evaluated in the primary studies were mainly liver enzymes (AST,

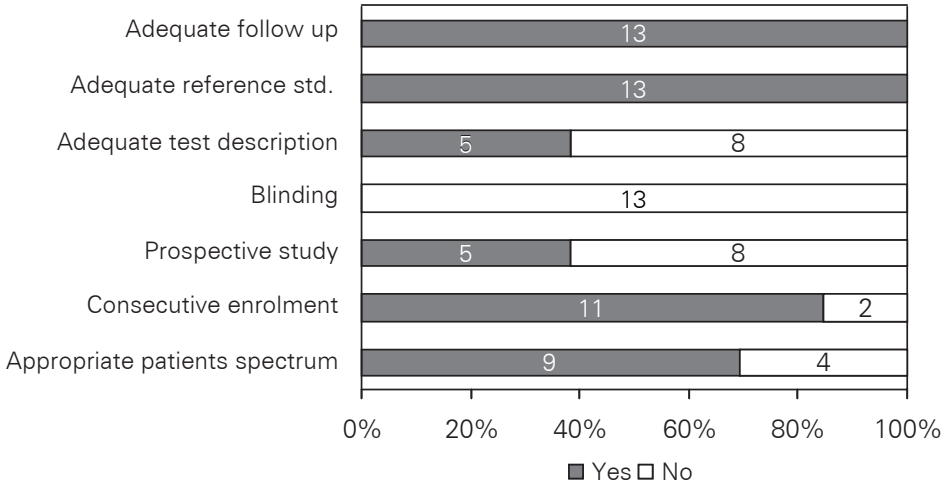

Figure 2. Quality of the included studies in the systematic review of accuracy of liver function tests in predicting maternal and fetal complications.

ALT, LDH) as reported in all studies. One study reported the accuracy of GGT and serum bilirubin.[31] The accuracy of LDH was reported with cut offs ranging from 350 to 1400 IU/l.[9,27,32-35,37] AST and ALT threshold levels were not specified in 3 studies.[29,34,36] The cut off levels of AST was reported as 2 standard deviation higher than normal in 1 study[11] and in the rest levels of AST and ALT ranged from 43 to 500 IU/l and 32 to 300 IU/l respectively. The tests were performed more than once in most studies but no data was provided on the time between the test and occurrence of outcome.

Prediction of maternal outcomes

Thirteen primary studies evaluated accuracy of LFTs to predict adverse maternal outcomes in 30 2 x 2 tables (Table 2a).[11,26-36] Eclampsia was the commonest adverse outcome that was reported. The prediction of eclampsia was evaluated through 10 2 x 2 tables in 8 studies. Prediction of eclampsia had the highest specificity of 0.97 as observed in 2 studies (95% CI 0.93–0.99; 95% CI 0.92–0.99). The cut off levels of LFTs were AST/ALT (500/300 U/l)[26] and ALT more than 60 U/l[35] for the two studies respectively. Both evaluated the role of ALT in women with broad spectrum PE. The highest predicted positive and negative likelihood ratios, LR+ 9.1 (95% CI 3.3–25.5)[26] and LR- 0.12 (95% CI 0.01–1.8)[30] were observed for eclampsia. The highest sensitivity of 0.95 (95% CI 0.63–1) was observed for LDH/AST/ALT (600/70/70 U/l) in the prediction of DIC.[28]

Table 1. Characteristics of studies included in the review of accuracy of liver function tests in predicting maternal and fetal complications in women with pre-eclampsia.

Study		Population	
Study (year) Language	**Quality**	**Number**	**Inclusion and exclusion criteria**
Odendaal (2000) English	Case control Retrospective Not consecutive patient enrolment Blinded Follow up complete	340	Early severe pre-eclampsia with a blood pressure control to around 140/90 to 150/100 mmHg, Singleton pregnancy
Audibert (1996) English	Cohort study Retrospective Consecutive enrolment Blinding not known Follow up complete	327	Severe pre-eclampsia or HELLP syndrome as defined by criteria of The American College of Obstetricians and Gynecologists (ACOG). Exclusion: Laboratory abnormalities from other disorders
Abramovici (1999) English	Cross sectional Retrospective Consecutive Blinding not known Follow up complete	269	Severe pre-eclampsia as defined by ACOG, Singleton pregnancy Exclusion: History of renal, liver or haematological abnormalities, multiple pregnancies
Haddad (2000) English	Case control Retrospective Can't tell enrolment Not blinded Follow up complete	64	Severe pre-eclampsia criteria of ACOG Exclusion: History of haematological or liver diseases. Gestation >28 weeks at admission
Martin Jr (1999) English	Retrospective Cohort Consecutive enrolment No blinding Follow up complete	568	Severe Pre-eclampsia with or without HELLP syndrome Exclusion: Eclampsia
Aali (2004) English	Cross sectional Prospective Consecutive No blinding Follow up complete	200	Pre-eclampsia according to ACOG Eclampsia: occurrence of generalized convulsion in patients with preeclampsia

	Test			Outcome
Intervention	**Gestation of testing**	**Frequency of testing**	**Cut off level**	
Nil known	>28/40	liver function tests twice weekly	LDH 350	Abruption Diagnosis of abruption placenta: ≥ 15% of the maternal surface of the placenta is covered with blood clots
Magnesium sulphate to all women with severe pre-eclampsia, glucocorticoids <34/40	Not specified	Not known	LDH 600 AST 70 ALT 70	Eclampsia Caesarean section Blood transfusion Disseminated intravascular coagulation Pleural effusion Wound Haematoma/infection Acute renal failure Abruption Pulmonary oedema Intracerebral haemorrhage Maternal death
Nil known	24/40-36/40	Not known	LDH 600 AST 70	Intrauterine growth retardation Neonatal death Respiratory distress syndrome Intraventricular haemorrhage grade 3-4 Necrotising enterocolitis grade 2-3 Bronchopulmonary dysplasia Mechanical ventilation Caesarean section
Intravenous magnesium sulphate routinely to all severe pre-eclamptics	< 28/40	Not known	LDH 600 AST 70	Eclampsia Abruptio placentae Disseminated intravascular coagulation Ascites Pulmonary oedema Pleural effusion Acute renal failure Transfusion of blood products Caesarean section Neonatal death Intraventricular Haemorrhage Respiratory Distress Syndrome
Not specified	Not specified	Admission data	LDH 1000-1400 AST 50-150 ALT 30-100	Combined maternal adverse outcome
Magnesium sulphate to all patients to prevent or control convulsions,i.v. hydralazine given when diastolic BP>110 mmHg, Betamethasone given from 24-34 weeks gestation to accelerate lung maturity	No specified	Multiple	AST 500 ALT 300	Eclampsia

Table 1. *(Cont.)*

Study		Population	
Study (year) Language	**Quality**	**Number**	**Inclusion and exclusion criteria**
Crisp (1959) English	Cohort Prospective Consecutive Follow up complete	64	Pre-eclampsia definition not specified
Borglin (1958) English	Cohort Prospective Not blinded Follow up complete	53	Symptoms of toxaemia (defined as proteinuria and increased blood pressure or pronounce edema in the last trimester)or liver damage Exclusion: Evidence of chronic nephropathy
Romero (1988) English	Cohort Retrospective Consecutive enrolment Not blinded Follow up complete	355	Pregnancy induced hypertension Exclusion: Mean Arterial Pressure<105 in 3rd trimester, chronic hypertension without superimposed PIH, multiple gestation, cholelithiasis and liver diseases causing raised SGOT
Yucesoy (2005) English	Cross sectional Retrospective Consecutive enrolment Not blinded Follow up complete	255	Mild and severe pre-eclampsia defined by National High Blood Pressure Education Programme Working Group on High Blood Pressure in Pregnancy. mild preeclampsia, defined as blood pressure ≥140/90 mmHg with albuminuria of at least 300 mg/24 h after 20 weeks of gestation. severe preeclampsia, involving eclampsia and HELLP syndrome.
Woldeselassie (2005) English	Retrospective Cross sectional Consecutive enrolment Not blinded Follow up complete	230	Pre-eclampsia Exclusion: Only symptomatic with no confirmed diagnosis
Girling (1997) English	Prospective Cross sectional Consecutive enrolment Not blinded Follow up complete	45	Pre-eclampsia 2 consecutive measurements of diastolic BP >=90 mm Hg 4 or more hours apart or a single reading >=110 mmHg, with proteinuria >0.3g/24h or >=2+ on dipstick testing Exclusion: Liver pathology, hypertension, multiple pregnancy
Menzies (2007) English	Cohort Prospective Consecutive enrolment No blinding Adequate population, test and outcome description Follow up complete	737	Pre-eclampsia of any severity Inclusion criteria: BP ≥140/90mmHg (twice ≥ 4 hours apart, after 20 weeks) and either proteinuria (≥2+by dipstick, ≥ 0.3g/24h or ≥ 30 mg/mmol by spot protein:creatinine ratio) or hyperuricemia HELLP syndrome Superimposed pre eclampsia, defined as pre existing hypertension with accelerated hypertension, new proteinuria or new hyperuricemia. Exclusion criteria: Women who have already achieved any component of the adverse maternal outcome

	Test			Outcome
Intervention	**Gestation of testing**	**Frequency of testing**	**Cut off level**	
Nil known	No specified	Multiple	AST 70	Eclampsia
Nil known	Last trimester	Multiple, weekly	Raised AST and ALT	Eclampsia
Nil known	>26/40	Multiple	AST 2SD	Pulmonary oedema Preterm delivery Respiratory distress syndrome Intrauterine growth retardation Fetal distress Neonatal death Apgar<7 @1 min Apgar<7 @5 min
Magnesium sulphate infusion in severe pre-eclampsia to prevent convulsions, Nifedipine to control high blood pressure, 2 doses of betamethasone for foetal lung maturity in 28-34 weeks gestation.	>20/40	Multiple	Increase in AST or ALT or LDH	Placental abruption Acute renal failure Disseminated intravascular coagulation Pulmonary edema Adult respiratory distress syndrome Retinal detachment Intracranial bleeding Maternal death
Anti-hypertensives and magnesium sulphate	Not specified	Multiple	ALT 60 AST 43 LDH 181	Eclampsia Severe pre-eclampsia (HELLP)
Not specified	Not specified	Multiple	Gestation specific 95% reference range Third trimester ALT 32 AST 30 Bilirubin 14 GGT 41	Maternal complications (medical complication due to pre eclampsia) Caesarean section Neonatal death Pre term delivery
Anti hypertensives, magnesium sulphate	After 20 weeks	Multiple	LDH 600 ALT/AST 40/55	Adverse maternal outcome (death or complication involving hepatic or central nervous system or renal or respiratory or haematological systems)

Table 2a. Accuracy of liver function tests in the prediction of adverse maternal outcomes in women with pre-eclampsia

Study Year	Test	Cut off	Sensitivity (95% CI)
Eclampsia			
Borglin 1958	AST/ ALT	Increased	0.67 (0.02-1.0)
Crisp 1959	AST	70	0.93 (0.52-1.0)
Romero 1988	AST	2SD	0.71 (0.29-0.96)
Aali 2004	AST/ ALT	500/ 300	0.27 (0.13-0.46)
Audibert 1996*	LDH/ AST/ ALT	600/ 70/ 70	0.27 (0.11-0.50)
Abramovici 1999*	AST	70	0.34 (0.15-0.65)
Haddad 2000*	LDH/ AST/ ALT	600/ 70/ 70	0.56 (0.21-0.86)
Woldesellasie 2005	AST	43	0.82 (0.48-0.98)
Woldesellasie 2005	ALT	60	0.04 (0.00-0.34)
Woldesellasie 2005	LDH	180	0.70 (0.35-0.93)
Pulmonary oedema			
Romero 1988	AST	2SD	0.67 (0.09-0.99)
Audibert 1996*	LDH/ AST/ ALT	600/ 70/ 70	0.50 (0.19-0.81)
Haddad 2000*	LDH/ AST/ ALT	600/ 70/ 70	0.67 (0.22-0.96)
Adverse maternal outcome			
Martin Jr 1999*	AST	150	0.70 (0.63-0.77)
Martin Jr 1999*	LDH	1400	0.72 (0.65-0.79)
Martin Jr 1999*	ALT	100	0.66 (0.59-0.73)
Girling 1997	AST/ ALT/ Bil/ GGT	30/ 32/ 14/ 41	0.93 (0.52-1.0)
Menzies 2007	ALT/ AST	40/55	0.33 (0.22-0.45)
Menzies 2007	LDH	600	0.62 (0.49-0.74)
Abruption			
Odendaal 2000*	LDH	350	0.07 (0.02-0.16)
Audibert 1996*	LDH/ AST/ ALT	600/ 70/ 70	0.40 (0.16-0.68)
Haddad 2005*	LDH/ AST/ ALT	600/ 70/ 70	0.40 (0.05-0.85)
Maternal death			
Audibert 1996*	LDH/ AST/ ALT	600/ 70/ 70	0.67(0.02-1.0)
Abramovici 1999*	AST	70	0.80(0.12-1.0)
Yucesoy 2005	AST/ ALT/ LDH	Increased	0.86(0.23-1.0)
Disseminated intravascular coagulation			
Audibert 1996*	LDH/ AST/ ALT	600/ 70/ 70	0.95 (0.63-1.0)
Haddad 2000*	LDH/ AST/ ALT	600/ 70/ 70	0.89 (0.33-1.0)
Intra cerebral haemorrhage			
Audibert 1996*	LDH/ AST/ ALT	600/ 70/ 70	0.67 (0.02-1.0)
Acute renal failure			
Audibert 1996*	LDH/ AST/ ALT	600/ 70/ 70	0.80 (0.12-1.0)
Haddad 2000*	LDH/ AST/ ALT	600/ 70/ 70	1.0 (0.03-1.0)

*severe pre-eclampsia; ALT: Alanine transaminase; AST: Aspartate transaminase; LDH: Lactate dehydrogenase; GGT: Gamma glutamyltransferase; Bi:Bilirubin; SD: Standard Deviation.

Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)
0.74 (0.54-0.89)	2.6 (0.70-9.4)	0.45 (0.05-4.4)
0.55 (0.41-0.69)	2.1 (1.5-3.0)	0.12 (0.01-1.8)
0.80 (0.75-0.85)	3.6 (2.1-6.1)	0.36 (0.11-1.2)
0.97 (0.93-0.99)	9.1 (3.3-25.5)	0.75 (0.61-0.93)
0.73 (0.66-0.78)	1.0 (0.49-2.0)	1.0 (0.77-1.31)
0.86 (0.76-0.93)	0.94 (0.37-2.4)	1.0 (0.87-1.2)
0.51 (0.37-0.65)	1.1 (0.59-2.2)	0.87 (0.40-1.90)
0.16 (0.14-0.20)	0.97 (0.73-1.3)	1.2 (0.31-4.3)
0.97 (0.92-0.99)	1.3 (0.07-23.4)	0.99 (0.87-1.1)
0.84 (0.77-0.90)	4.5 (2.5-8.0)	0.36 (0.14-0.92)
0.79 (0.74-0.84)	3.2 (1.4-7.5)	0.42 (0.08-2.1)
0.73 (0.67-0.79)	1.9 (0.97-3.6)	0.68 (0.37-1.3)
0.52 (0.38-0.65)	1.4 (0.74-2.6)	0.64 (0.2-2.1)
0.48 (0.43-0.53)	1.4 (1.2-1.5)	0.62 (0.48-0.8)
0.49 (0.44-0.54)	1.4 (1.2-1.6)	0.57 (0.44-0.74)
0.47 (0.42-0.52)	1.2 (1.1-1.4)	0.72 (0.57-0.91)
0.57 (0.37-0.76)	2.2 (1.4-3.5)	0.12 (0.01-1.7)
0.80 (0.77-0.84)	1.7 (1.2-2.4)	0.83 (0.71-0.99)
0.60 (0.56-0.64)	1.6 (1.3-1.9)	0.63 (0.46-0.86)
0.96 (0.88-0.99)	1.7 (0.41-6.7)	0.97 (0.89-1.1)
0.73 (0.67-0.79)	1.5 (0.78-2.9)	0.82 (0.54-1.2)
0.49 (0.36-0.63)	0.79 (0.26-2.4)	1.2 (0.57-2.6)
0.73 (0.67-0.78)	2.5 (0.78-7.8)	0.46 (0.05-4.4)
0.83 (0.71-0.92)	4.8 (2.1.11.1)	0.24 (0.02-2.8)
0.85 (0.78-0.90)	5.6 (3.2-9.7)	0.17 (0.01-2.2)
0.76 (0.70-0.81)	3.9 (3.0-5.1)	0.06 (0.00-0.94)
0.62 (0.47-0.75)	2.3 (1.4-3.7)	0.18 (0.01-2.5)
0.73 (0.67-0.78)	2.3 (1.4-3.7)	0.46 (0.05-4.4)
0.73 (0.67-0.79)	3.0 (1.6-5.8)	0.27 (0.02-3.3)
0.51 (0.38-0.64)	1.5 (0.66-3.5)	0.49 (0.04-5.5)

Table 2b. Accuracy of liver function tests in the prediction of adverse fetal outcomes in women with pre-eclampsia

Study Year	Test	Cut off	Sensitivity (95% CI)
Intra uterine death			
Yucesoy 2005	AST/ ALT/ LDH	Inc	0.71 (0.29-0.96)
Haddad 2000*	LDH/ AST/ ALT	600/ 70/ 70	0.63 (0.24-0.91)
Neonatal death			
Romero 1988	AST	2SD	0.50 (0.16-0.84)
Abramovici 1999*	AST	70	0.50 (0.19-0.81)
Haddad 2000*	LDH/ AST/ ALT	600/ 70/ 70	0.38 (0.09-0.76)
Intra uterine growth restriction			
Abramovici 1999*	AST	70	0.39 (0.25-0.54)
Romero 1988	AST	2SD	0.48 (0.34-0.63)
Respiratory distress syndrome			
Abramovici 1999*	AST	70	0.51 (0.38-0.64)
Romero 1988	AST	2SD	0.82 (0.60-0.95)
Haddad 2000*	LDH/ AST/ ALT	600/ 70/ 70	0.46 (0.31-0.61)
Intra ventricular haemorrhage			
Romero 1988	AST	2SD	0.60 (0.15-0.90)
Haddad 2000*	LDH/ AST/ ALT	600/ 70/ 70	0.33 (0.01-0.91)
Abramovici 1999*	AST	70	0.11 (0.00-0.67)
Necrotising enterocolitis			
Abramovici 1999*	AST	70	0.20 (0.00-0.88)
Haddad 2000*	LDH/ AST/ ALT	600/ 70/ 70	0.50 (0.07-0.93)
Bronchopulmo-nary dysplasia			
Abramovici 1999*	AST	70	0.68 (0.43-0.87)
Mechanical ventilation			
Abramovici 1999*	AST	70	0.47 (0.35-0.59)
Preterm birth			
Romero 1988	AST	2SD	0.50 (0.37-0.63)
Adverse outcome			
Girling 1997	AST/ ALT/ Bil/ GGT	30/ 32/ 14/ 41	0.86 (0.23-1.0)

*severe pre-eclampsia; ALT: Alanine transaminase; AST: Aspartate transaminase; LDH: Lactate dehydrogenase; GGT: Gamma glutamyltransferase; Bi:Bilirubin; SD: Standard Deviation

The sensitivity of the LFT to predict any maternal complication ranged from 0.04 (95% CI 0–0.34) to 0.95 (95% CI 0.63–1) and specificity from 0.16 (95% CI 0.14–0.20) to 0.97 (95% CI 0.92–0.99) respectively. Fig. 3a provides estimates of sensitivity and specificity for various maternal outcomes. The AUC for predicting any adverse maternal outcome was 0.79 (95% CI 0.51–0.93) (Fig. 4a).

Prediction of fetal outcomes

Five primary studies evaluated accuracy of LFT to predict adverse fetal outcomes in 19 2 x 2 tables (Table 2b).[11,27,31,32,36] The commonest reported adverse fetal outcomes were neonatal death, respiratory distress syndrome and intraventricular

Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)
0.86 (0.79-0.91)	4.9 (2.7-9.0)	0.33 (0.1-1.1)
0.52 (0.38-0.65)	1.3 (0.71-2.4)	0.72 (0.29-1.8)
0.80 (0.75-0.84)	2.5 (1.2-5.1)	0.63 (0.31-1.3)
0.68 (0.60-0.74)	1.5 (0.80-3.0)	0.74 (0.4-1.4)
0.50 (0.35-0.65)	0.75 (0.29-1.9)	1.3 (0.68-2.3)
0.68 (0.60-0.74)	1.2 (0.8-1.9)	0.90 (0.70-1.1)
0.85 (0.80-0.89)	3.2 (2.0-4.9)	0.61 (0.47-0.80)
0.74 (0.66-0.81)	1.9 (1.3-2.8)	0.67 (0.51-0.88)
0.84 (0.79-0.89)	5.2 (3.6-7.3)	0.22 (0.09-0.52)
0.40 (0.12-0.74)	0.76 (0.42-1.4)	1.4 (0.60-3.0)
0.80 (0.74-0.84)	3.0 (1.4-6.3)	0.50 (0.17-1.5)
0.51 (0.37-0.65)	0.68 (0.13-3.5)	1.3 (0.56-3.0)
0.66 (0.59-0.73)	0.33 (0.02-4.5)	1.3 (0.96-1.9)
0.66 (0.59-0.73)	0.59 (0.05-7.1)	1.2 (0.64-2.3)
0.52 (0.38-0.66)	1.0 (0.38-2.9)	0.96 (0.35-2.6)
0.70 (0.63-0.77)	2.3 (1.6-3.4)	0.45 (0.23-0.88)
0.74 (0.66-0.82)	1.8 (1.3-2.7)	0.71 (0.56-0.90)
0.88 (0.83-0.92)	4.2 (2.7-6.5)	0.57 (0.44-0.73)
0.50 (0.32-0.68)	1.7 (0.99-3.0)	0.27 (0.02-3.8)

haemorrhage as reported in 3 studies.[11,27,32] The sensitivity and specificity of LFT to predict any adverse fetal outcome ranged from 0.11 (95% CI 0–0.67) to 0.86 (95% CI 0.23–1) and from 0.40 (95% CI 0.12–0.74) to 0.88 (95% CI 0.83–0.92) respectively. The highest sensitivity and specificity were observed for raised ALT/AST/GGT/Bilirubin (32/30/41/14) in predicting a composite adverse fetal outcome[31] and for levels of AST (≥ 2 SD standard deviation) in predicting preterm birth respectively.[11] Fig. 3b provides estimates of sensitivity and specificity for various fetal outcomes. The best likelihood ratios of positive and negative tests for adverse fetal outcome were 5.2 (95% CI 3.6–7.3) and 0.22 (95% CI 0.09–0.52) for levels of

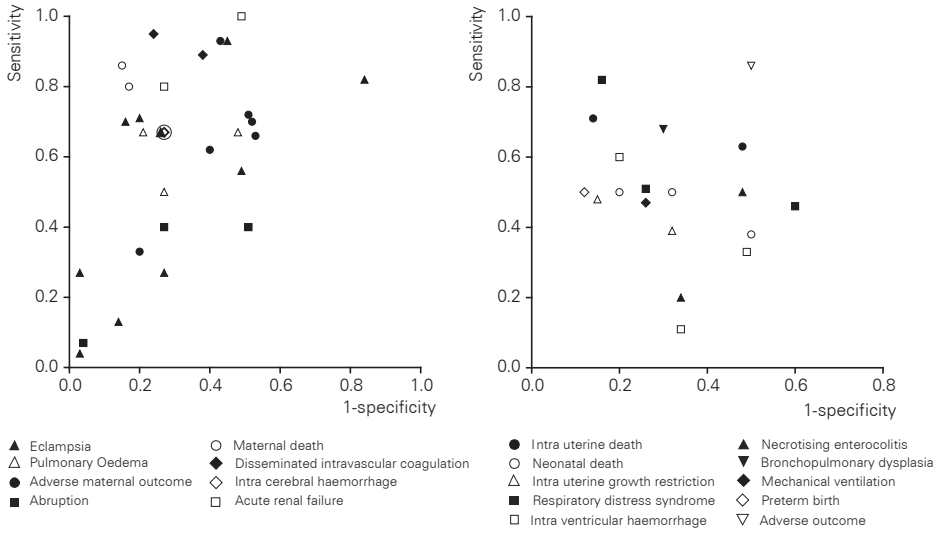

Figure 3. Receiver Operating Characteristic (ROC) plane.
3a. Adverse maternal outcomes.
3b. Adverse fetal outcomes

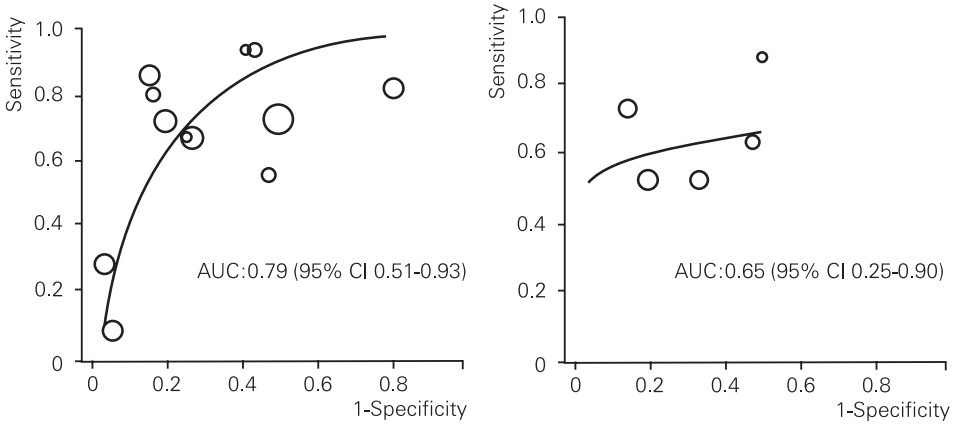

Figure 4. Summary Receiver Operating Characteristic (sROC) curve
4a. Maternal adverse outcome,
4b. Fetal adverse outcome

AST (≥ 2 SD) in predicting respiratory distress syndrome[11]. The AUC for predicting any adverse fetal outcome was 0.65 (95% CI 0.26–0.90) (Fig. 4b).

DISCUSSION

In women with pre-eclampsia (PE), LFTs were at best moderate predictors of maternal and fetal complications. The test specificity, however, was better than sensitivity. This meant that with a positive test result one could be more confident about predicting poor outcome than one could about ruling out complications with a negative result.

Current national and international classifications on severity of PE are hampered by the unknown disease aetiology. However, uteroplacental ischemia causing activation of the endothelium seems to play a major role. Endothelial dysfunction is considered to underlie many of the clinical symptoms of PE like hypertension, increased vascular permeability resulting in edema and proteinuria, and expression of inflammatory parameters leading to coagulopathy.[38-40] These changes also cause ischemia of target organs, such as brain, liver, kidney and placenta. Fibrin deposition, periportal haemorrhage, ischemic lesions and microvesicular fat deposition are histological findings observed in the livers of preeclamptic women.[41] Our published reviews have evaluated the accuracy of uric acid and proteinuria in predicting maternal and fetal complications in women with PE.[42,43] This paper adds further evidence to inform on this subject.

Amongst all maternal outcomes, studies that predicted eclampsia performed better than others with some showing significant LRs[26,30] and high specificity[26] and sensitivity.[30] The specificity was higher than 70% in 6 of the 8 studies predicting eclampsia with LFT. On further examination of these studies, Aali et al's patients were women with severe PE and a considerable number of patients had poor access to care.[26] The largest study to evaluate the role of LFTs in PE was the prospective cohort study by Menzies et al.[37] The results of this study were from unpublished data provided by the authors. The sensitivity of the LFT was better for LDH levels of 600 IU/L when compared to ALT/AST of 40/55 IU/l in predicting a composite adverse maternal outcome. The converse was true for the test specificity.

For women with raised liver enzymes, the specificity of the test for maternal outcomes was better than sensitivity with point estimates more than 70% in two-thirds of the 2 x 2 evaluations. Less than half the included 2 x 2 tables had

sensitivity more than 70%. Of those studies that showed poor specificity in comparison to sensitivity for maternal complication, the study by Crisp et al was conducted in late 50s prior with a difference in the quality of healthcare.[30] The other 2 studies consisted of women with severe PE and with large proportion of patients with HELLP syndrome in comparison to other studies.[32,33] It is likely that the test performance differs in the subgroup of women with severe PE especially those with other factors contributing to maternal complications.

The test performance in predicting adverse fetal outcomes performed similarly with the test specificity better than sensitivity. Very few studies evaluating fetal outcome had sensitivity more than 50% (Fig. 3). The low specificity observed in the studies by Haddad et al, and Abramovici et al could be attributed to the very narrow spectrum of the included patients.[27,32] The relatively low cut offs chosen in the study by Girling et al may have contributed to the low specificity but high sensitivity.[31] The overall performance of the test was marginally better in predicting adverse maternal outcomes than fetal outcomes. The difference however was not statistically significant with overlapping confidence intervals.

Our review is the first to systematically collate and appraise the existing evidence on the predictive accuracy of LFTs in women with PE. The validity of our findings depends on the methodological quality of the systematic review and the quality of the included studies. We conducted an extensive search of literature with no language restrictions to minimise the risk of missing studies and used contemporary statistical methods. There were limitations in the included studies. Firstly, the definition of PE differed between different studies. Secondly, very few studies provided details of the test methods and the gestation of testing. The test cut offs differed considerably between studies and often with no rationale for the chosen threshold values. Information on gestational age may help in better interpretation of the predictive role of the test as women with early onset PE with increased risk of maternal and fetal complications, where decision making often involves complex balancing of maternal benefits against fetal risks. Thirdly, although the tests were performed prior to the outcome, no details were available on the time elapsed between the test results and the final maternal or fetal outcome. It is possible that the outcome could have been modified by time or any interventions like anti hypertensives, magnesium sulphate, corticosteroids (treatment paradox).[44] Lack of information on the predictor variables and treatment. Fourthly, the definition of adverse outcome measures differed between the studies. Fifthly, systematic reviews and meta analyses are by their very design dependent on the primary studies for the data necessary to answer the question. The significant heterogeneity

between the studies and paucity of data on predictor variables has constrained us from performing multi regression analysis of the effect of these variables on the outcome. Although every effort had been made to obtain unpublished data, we faced limited success in this endeavour. Despite these provisos this is the best available summary of the available studies.

Through this review we have highlighted the moderate ability of abnormal LFT in correctly identifying women at increased risk of maternal and fetal complications. However, given the uncertainties in the data, making clinical recommendations or developing prediction rules for using LFTs is not possible without good quality large prospective studies. These studies should especially focus on the sub group of women with early onset PE where monitoring has a critical role in prolonging gestation.

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Part III

General discussion, future perspectives and summary

Chapter 11

General discussion and future perspectives

General discussion and future perspectives

This thesis focused on the choice between induction of labour and expectant monitoring in women with pregnancies complicated by hypertensive disease at term. The HYpertension and Pre-eclampsia Intervention Trial at Term (HYPITAT) aimed to provide clarity on the best treatment for women with a term pregnancy complicated by gestational hypertension (GH) or mild pre-eclampsia (PE). We found that induction of labour reduced the probability of progression to severe disease without increasing (and probably decreasing) the caesarean section rate. Induction of labour was also less expensive with the same maternal quality of life. The following paragraphs describe the impact of implementation of the HYPITAT study results and discuss other clinical decisions in obstetrics which arise from the HYPITAT trial.

Situation prior to HYPITAT

The Dutch Maternal Mortality Committee (1993 – 2005) and the LEMMoN study (national study into ethnicity determinants of maternal morbidity in the Netherlands; August 2004 – August 2006), describe substantially higher incidences of maternal mortality and severe morbidity due to hypertensive disorders in the Netherlands than in other Western countries.[1,2] Maternal deaths caused by hypertensive disorders were three times higher than in the UK[1,3], and the incidence of eclampsia was clearly increased as compared to other neighbouring European countries.[2] Substandard care of hypertensive disease of pregnancy was found in 91% of women with maternal death and in 60% of women with eclampsia.[1,2,4] Substandard care consisted mainly of failure to check proteinuria in case of an increased blood pressure resulting in a delay in detection of PE and suboptimal prophylactic or therapeutic treatment with anticonvulsive and antihypertensive medication.

At the start of the HYPITAT study in 2005, the optimal policy for women with pregnancies complicated by hypertensive disease (nearly) at term was not clear, due to which in the Netherlands a strong practice variation existed for the treatment of women with GH or mild PE beyond 36 weeks' gestation. This was shown by the prior beliefs of Dutch gynaecologists and residents, as stated in the introduction of this thesis. Obviously, the attending obstetricians had discordant views in this situation and management was individualized to the patient without a proper body of knowledge to rely on. In the Netherlands a conservative management was not uncommon, whereas in other developed countries a more aggressive management, namely delivery after stabilization, was the management of choice. The tendency of Dutch obstetricians of being expectant to deliver pre-eclamptic women is also reflected by the fact that gestational age at delivery in women with hypertensive

disorders is three weeks higher in the Netherlands as compared to the UK.[2,5] This discrepancy between the Netherlands and other developed countries regarding the treatment of women with hypertensive disease of pregnancy, gave us the opportunity to set up a randomised clinical trial, in which induction of labour was compared with expectant monitoring. Some hospitals in the Netherlands decided not to participate in the HYPITAT trial because they believed that the effect of an expectant management could disadvantage women's health. Their belief was based on experience, as evidence did not yet exist. In total 38 of the 93 hospitals (41%) across the Netherlands participated in the HYPITAT trial.

Impact of HYPITAT study results on doctors' behaviour and eclampsia rates in the Netherlands

The results of the HYPITAT trial showed that in women with GH or mild PE at term induction of labour improved maternal outcome, decreased the caesarean section rate and was a costs saving strategy, and should therefore be the treatment of choice in these women. We wondered whether the HYPITAT trial had impact on doctors' behaviour and provoked an increased number of inductions of labour among women with hypertensive disease of pregnancy at term. Therefore, we investigated whether participation of hospitals in the trial had impact on the implementation of its results and subsequent consequences for maternal health in the Netherlands.

We studied data from the Perinatal Registry of the Netherlands (PRN) from 2001 until 2009.[6] The HYPITAT trial was performed between October 2005 and March 2008. We identified women with GH or PE with a singleton pregnancy and a fetus in cephalic position beyond 36 weeks' gestation from the PRN, and distinguished the period before the trial (January 2001 – October 2005), the period during the trial (October 2005 – March 2008) and the period after the trial (April 2008 – December 2009). We studied trends in onset of labour and the occurrence of eclampsia, both in 38 hospitals that participated in the HYPITAT trial, and in 55 hospitals that did not.

Table 1 shows the distribution of spontaneous labour, induced labour and primary caesarean section in 22,830, 11,298 and 9,513 patients treated before, during and after the trial. The number of women in whom labour was induced increased after the HYPITAT trial (58.3% prior versus 67.1% after the trial, $p<0.01$). This change in management was mainly due to hospitals that participated in the trial (12.1% increase in inductions in participating hospitals versus 5.1% increase in non participating hospitals). Similarly, in patients with a gestational age beyond 36 weeks, there was a decrease in the risk of suffering from eclampsia: .85% prior versus .19% after the trial ($p=<0.01$). This decrease was specifically observed in

Table 1. Onset of delivery in patients with a singleton pregnancy in cephalic position after 36 weeks' gestation with gestational hypertension or mild preeclampsia.

	Onset of labour				Eclampsia
	Spontaneous n (%)	Induction n (%)	Planned CS n (%)	Missing n (%)	
All patients					
Before the trial (n=22830)	9002 (39.4%)	13313 (58.3%)	474 (2.1%)	41 (0.2%)	193 (.85%)
During the trial (n=11298)	4712 (41.7%)	6345 (56.2%)	208 (1.8%)	33 (0.3%)	34 (.30%)
After the trial (n=9513)	2976 (31.3%)	6385 (67.1%)	134 (1.4%)	18 (0.2%)	18 (.19%)
Patients who delivered in hospitals that did participate in HYPITAT					
Before the trial (n=12663)	5608 (44.3%)	6772 (53.5%)	249 (2.0%)	34 (0.3%)	120 (0.95%)
During the trial (n=6571)	3048 (46.4%)	3406 (51.8%)	90 (1.4%)	27 (0.4%)	14 (.21%)
After the trial (n=5475)	1797 (33.2%)	3593 (65.6%)	67 (1.2%)	18 (0.3%)	7 (.13%)
Patients who delivered in hospitals that did not participate in HYPITAT					
Before the trial (n=10167)	3394 (33.4%)	6541 (64.3%)	225 (2.2%)	7 (0.1%)	73 (.72%)
During the trial (n=4727)	1664 (35.2%)	2939 (62.2%)	118 (2.5%)	6 (0.1%)	20 (.42%)
After the trial (n=3945)	1143 (29.0%)	2738 (69.4%)	64 (1.6%)	0	11 (.28%)

the hospitals that participated in the HYPITAT trial, where the decrease was from 0.95% to .13%. In hospitals not participating in the HYPITAT study this decrease was .72% prior versus .28% after the trial.

Several remarks can be made on these apparent consequences of the trial. First, the number of patients who were randomised in the HYPITAT trial (n=756) or were asked for the study but refused (n=397) was only 18% of the potentially eligible patients in the participating hospitals. Second, prior to the trial, the number of inductions of labour due to hypertensive disease at term was higher in the hospitals that did not participate in the HYPITAT trial. Apparently, those hospitals that had a conservative approach prior to the study were more often willing to participate in the trial than hospitals that had *a priori* a more aggressive approach. Third, implementation of induction of labour after the trial was better in hospitals that had participated in the HYPITAT trial. This was associated with a stronger decrease of cases with eclampsia, and a decrease of number of planned caesarean section rates.

In conclusion, participation in this multicentre trial improved doctors' awareness of disease severity due to the best management in women with GH or mild PE at term, and had immediate consequences for maternal health.

Impact of the results of the HYPITAT trial in the United Kingdom

The UK National Institute of Clinical Excellence (NICE) has adapted their guidelines on 'Hypertension in Pregnancy'. They mainly mentioned that the overall maternal benefits seen in the HYPITAT trial were maintained in the subgroup of women with

mild PE and a trend to better maternal outcome was shown in the subgroup of women with GH. The Guideline Development Group recommends now induction of labour in women with GH whose diastolic blood pressure is greater than 95 mmHg with or without antihypertensive treatment after 37 weeks' gestation, and advices induction of labour within 24–48 hours after onset of mild or moderate PE beyond 37 weeks' gestation.[7]

Prediction of maternal complications in hypertensive disease of pregnancy

Over the years, relatively little progress has been made in predicting which patients will progress to severe disease, how rapid progression might occur, or how progression might be impeded once the diagnosis has been made. In this thesis several variables are identified in women with mild hypertensive disease of pregnancy with an increased risk for severe maternal morbidity, as severe hypertension, HELLP syndrome, eclampsia and postpartum haemorrhage (Chapter 6, 7 and 8). We identified clinical characteristics and specific biochemical and haematological parameters as moderate or good predictors of adverse maternal outcome, which may serve to provide guidance for the clinical management of these patients. Obesity is one of these predictors which is already known before pregnancy. In case of obesity, women should receive appropriate preconceptional advice to change their lifestyle and to loose weight prior to conception. We found that systolic blood pressure above 155 mm Hg and proteinuria equal or more than 2+ in a dipstick specimen were important predictors for severe disease and eclampsia (Chapter 6 and 7). Especially treatment of elevated systolic blood pressure has been a neglected topic. Control of severe systolic hypertension is an important aspect of the management of women with hypertensive disease of pregnancy and it would be obedient to start antihypertensive treatment in women with a systolic blood pressure of 155 mm Hg or higher. Worth mentioning are also the raised serum uric acid and liver enzymes rates, which seems to be useful predictors in the management of PE too (Chapter 10 and 11). We think it is essential to ensure that for each individual case a care plan is developed that includes the acceptable thresholds of all monitored variables we found for pregnancies. If one or more thresholds are exceeded a patient needs to be monitored frequently and after 37 weeks' of gestation an induction of labour has to be considered, particularly in women with a low Bishop Score (Chapter 3 and 6).

Future perspectives

Prediction models

GH and PE are the most common medical disorders during pregnancy and are associated with maternal and perinatal morbidity and mortality. The large majority of these cases develop at or near term and we know now that induction of labour prevents further maternal complications. Moreover new insights into the predictability of maternal complications in women with pregnancy related hypertension are described in this thesis. Knowledge on the predictors contributing to increased neonatal morbidity in women with GH or PE at term is scarce and therefore we will aim to assess whether neonatal complications can be predicted from clinical data. The identified predictors from this study may guide physicians in neonatal care. Although this is an interesting clinical issue during term pregnancies, it will be all the more important for preterm pregnancies when the risk of neonatal morbidity and mortality is much higher. Late preterm birth has been associated with significant increases in respiratory morbidity, neonatal infections, prolonged hospital stays, and neonatal mortality.[8,9] Therefore we intend to perform this investigation not only in women with hypertensive disease of pregnancy beyond 36 weeks' of gestation (HYPITAT I) but also in women with a gestational age between 34 and 37 weeks (HYPITAT II).

Furthermore, we are assessing the predictability of the caesarean section risk in women with GH or mild PE at term from clinical data during induction of labour or expectant monitoring. The HYPITAT trial showed that induction of labour was likely to reduce the risk of caesarean section in pregnant women with mild hypertensive disease at term. However, it was not clear whether this observation holds for the whole spectrum of patients, including patients with an unripe cervix. Although, the subgroup analysis already showed that in the induction group, the rate of caesarean section was lower in nulliparous women and in those with cervical Bishop score <2, refuting the belief that induction of labour especially in these women increases the rate of caesarean section. Additionally, identification of women at increased risk of developing severe maternal outcomes is especially important for women with a prior caesarean section. Induction of labour in women with a scarred uterus may be associated with increased risk of uterine scar rupture, especially when prostaglandins are used.[10] Hence, identification of women with an increased or decreased risk for caesarean section, would result in an overall reduced caesarean section rate which subsequently will diminish the incidence of women with a scarred uterus in a next pregnancy.

Ultimately, our aim is to construct clinical decision models for women with a pregnancy complicated by hypertensive disease to identify those women with an increased risk of severe maternal or neonatal morbidity. Before such models might lead to appropriate management, however, they first have to be subjected to internal and external validation. Our study group has already assessed the internal validity and extent of overfitting of some models with bootstrapping, providing preliminary information on whether the models will hold in the general population. However, external validation is needed to verify this and to improve the models for use in the general population. A valid, final decision model may make it possible to distinguish between pregnant women at high risk and at low risk of developing severe complications and to improve future management of these patients, which may result in better health care and avoidance of unnecessary interventions in low-risk groups. However, this goal is probably far ahead of us and may require a lot of additional research.

Two obstetric issues following HYPITAT: HYPITAT II and HyRAS

HYpertension and Preeclampsia Intervention Trial At near Term (HYPITAT II)

Until the HYPITAT trial, all guidelines were based on expert opinions rather than randomised trials. The HYPITAT trial is the first multicentre trial designed to compare the risks and benefits of induction of labour versus expectant monitoring for women at ≥36 weeks' gestation. A 'grey' zone still exists for GH or mild PE between 34 and 37 weeks' gestation concerning the best timing of birth. Nevertheless, there is general agreement that women with stable hypertensive disease at <37 weeks' gestation can benefit from expectant monitoring[11-16], however there is no clinical evidence. Women with mild PE may progress to severe disease with its risks, but it is not clear whether these risks outweigh the risks of planned late preterm birth for the baby. On the one hand, several retrospective and observational studies have reported that 15–30% of women during expectant monitoring will progress to severe hypertension or severe PE, with a predisposition of maternal multi-organ system involvement which is substantially associated with maternal and fetal morbidity and mortality.[17-20] On the other hand, termination of pregnancy before 37 weeks' gestation bears a risk for the neonate. In a recent cohort study, late preterm neonatal mortality rates per 1,000 live births were 1.1, 1.5, and 0.5 at 34, 35, and 36 weeks' gestation, respectively, compared with 0.2 at 39 weeks' gestation (P<.001). Neonatal morbidity was significantly increased at 34, 35, and 36 weeks' gestation, including ventilator-treated respiratory distress, transient

tachypnea, grades 1 or 2 intraventricular haemorrhage, sepsis work-ups, culture-proven sepsis, phototherapy for hyperbilirubinemia, and intubation in the delivery room. Approximately 80% of late preterm births were attributed to idiopathic preterm labour or ruptured membranes and 20% to obstetric complications. The complication rates vary from 15% at 34 weeks to below 2% at 37 weeks.[21]

There is an urgent need for randomised trials to investigate the effectiveness and efficiency of induction of labour in women with GH or mild PE with a gestational age of 34–37 weeks of pregnancy, as compared to expectant monitoring. In view of this clinical dilemma, we currently perform a randomised clinical trial in which induction of labour is compared to expectant monitoring in those women. The primary outcome will be maternal morbidity and neonatal respiratory distress syndrome. Also neonatal complications, maternal quality of life and recovery, as well as costs are compared. The study is performed in eight perinatal centres and more than 40 non-academic hospitals that already collaborate in the Obstetric Consortium in which the HYPITAT-I trial was performed.

Hypertension Risk Assessment Study (HyRAS): A 2-year follow-up on the HYPITAT study

The aim of this cohort study[22] is to provide more insight into an individuals' cardiovascular risk profile following a pregnancy complicated by GH or mild PE, so prevention against cardiovascular disease can be started at a relatively young age. Cardiovascular disease is the cause of death in 31% of women in the Netherlands.[23] Hypertensive disorders in pregnancy and cardiovascular disease in later life both show features of 'the metabolic syndrome' and atherosclerosis, so they might develop by common pathophysiologic pathways with similar vascular risk factors involved. Vascular damage occurring during GH or PE may contribute to the development of future cardiovascular disease, which has been studied in women with severe early-onset PE.[24,25] However, data concerning long term effects on cardiovascular risk of pregnancies complicated by a hypertensive disorder at term, which is more common, is lacking. Therefore, this prospective cohort study is performed to establish whether women with GH or PE at term are at increased risk for cardiovascular disease in later life. A calculated 10-year cardiovascular event risk will allow identification of those women who may benefit from primary prevention by tailored interventions, at a relatively young age.

Conclusion and recommendations

In clinical practice it is for an obstetrician always important to be aware of the risk that serious obstetric complications can develop, because obstetrics can be unpredictable and complications may have major impact. Overall, always keep in mind: the only course of action that would reliably prevent disease progression is to proceed to delivery in those patients presenting with GH or mild PE once a reasonable gestational age has been achieved.

The relatively high incidences of maternal mortality and morbidity due to hypertensive disorders of pregnancy, the evidence of substandard treatment of these disorders and the results of the HYPITAT trial, should be an alert that improvement of the Dutch care system is needed. This accumulation of evidence indeed evoked growing awareness among Dutch obstetric caregivers and they intended to be more aggressive in their practical approach. We advocate a reduction in delay of diagnosing PE and assessing and managing disease severity, which might be attained by frequent blood pressure measurements, screening of proteinuria in case of increased blood pressures and lowering thresholds for treatment with anticonvulsive and antihypertensive medication. Further improvement of obstetric care can be achieved by educating all pregnant women about the danger signs associated with serious complications of pregnancy. Development of a multi-language patient leaflet with warning signs for these complications may help to reduce delay in treating these women and to decrease severe maternal morbidity. Audits of maternal deaths and severe maternal morbidity due to hypertensive disorders may lead to better cooperation between midwives, nurses and doctors and also improve the obstetrical health care on local, regional and national level.[26] New guidelines based on good research together with more awareness of the public and adequate training of health workers will lead to better perinatal outcome for the mother and her baby in the Netherlands.

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Chapter 12

Summary
Nederlandse samenvatting

Summary

This thesis has been subdivided into two main parts. Part I describes the results of a randomised controlled trial, the HYPITAT trial (Hypertension and Pre-eclampsia Intervention Trial At Term). Part II addresses prediction of severe maternal morbidity in women with a pregnancy complicated with gestational hypertension or (mild) pre-eclampsia.

PART I

The randomised trial: HYpertension and Pre-eclampsia Intervention Trial At Term (HYPITAT)

Hypertensive disorders complicate about 6-8% of pregnancies and these disorders make a substantial contribution to maternal and neonatal morbidity and mortality worldwide. Termination of pregnancy is the only definitive treatment in this situation, but timing of delivery is debated in preterm as well as term gestation. Induction of labour is likely to improve maternal outcome, but possibly at the expense of increased probability of caesarean section and adverse neonatal outcome. In view of this dilemma, obstetricians are confronted with difficult clinical management decisions. In the Netherlands a strong practice variation existed for the treatment of women with gestational hypertension (GH) or mild pre-eclampsia (PE) beyond 36 weeks' gestation. Obviously, the attending obstetricians were either in doubt or had discordant views in these situations. In most Dutch centres, the protocol recommended expectant monitoring, whereas in the USA and other developed countries, induction of labour was more general practice in women with gestational hypertension or mild PE at term, although these recommendations were not based on the results of randomised clinical trials.

The practice variation and uncertainty on the issue in the Netherlands, gave us the opportunity to set up a nationwide multicentre randomised clinical trial, in which the effectiveness of induction of labour was compared with expectant monitoring. This trial was called the HYPITAT trial, 'HYpertension and Pre-eclampsia Intervention Trial At Term'. The trial started in October 2005 and was part of the Dutch Obstetric Consortium, which is a collaboration of obstetric clinics in the Netherlands (www.studies-obsgyn.nl/hypitat). Six academic and 32 non-academic hospitals participated. The trial was approved by the Institutional Review Board of the University of Leiden and was registered in the clinical trial register as

ISCTN08132825. Written informed consent was obtained from all patients prior to randomisation. The trial was funded by ZonMw (grant number 945-06-553).

Chapter 2 provides a detailed description of the study protocol. Women with a singleton pregnancy with a child in cephalic presentation and a gestational age between 36+0 and 41+0 weeks whose pregnancy was complicated by GH or mild PE were eligible. GH was defined as diastolic blood pressure ≥95 mmHg measured at two occasions, performed at least six hours apart. Mild PE was defined as diastolic blood pressure ≥90 mmHg measured at two occasions, performed at least six hours apart, combined with proteinuria (defined as ≥2+ protein on dipstick, >300 mg total protein within a 24-hour urine collection and/or protein/creatinine ratio >30 mg/mmol). Exclusion criteria were severe GH or severe PE, defined as diastolic blood pressure ≥110 mmHg, systolic blood pressure ≥170 mmHg and/ or proteinuria ≥5 gram within 24 hours, pre-existing hypertension, diabetes mellitus, gestational diabetes requiring insulin therapy, renal disease, heart disease, previous caesarean section, haemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome, oliguria <500 ml within 24-hours, pulmonary oedema or cyanosis, HIV seropositivity, use of intravenous antihypertensive medication, fetal anomalies, intra-uterine growth restriction and abnormalities at fetal heart rate (FHR)–monitoring.

The study was staffed by research nurses and midwives, who counselled patients, asked informed consent and monitored the study protocol in each centre. Before randomisation, cervical length and vaginal digital examination were performed. Women were randomly allocated to either induction of labour or expectant monitoring. Patients allocated to induction of labour were induced within 24 hours after randomisation with amniotomy and, if needed, augmentation with oxytocine (Bishop score >6) or with intracervical or intravaginal prostaglandins or a balloon catheter (Bishop score ≤6). Patients allocated to expectant monitoring were monitored until the onset of spontaneous delivery, except when there was a medical indication for delivery. Monitoring consisted of frequent maternal blood pressure measurements, assessments of proteinuria, laboratory tests and regular assessment of fetal condition. Patients who did not give informed consent for randomisation, but who gave authorisation for the use of their medical data, were treated according to one of the two protocols at the discretion of the attending obstetrician.

The primary outcome of this trial was a composite measure of poor maternal outcome, defined as maternal mortality, maternal morbidity (eclampsia, HELLP syndrome, pulmonary oedema, thrombo-embolic disease and/ or placental

abruption), progression to severe disease (at least one measurement of diastolic blood pressure ≥110 mmHg, systolic blood pressure ≥170 mmHg and proteinuria ≥5 gram/ 24 hours) and major postpartum haemorrhage. Secondary outcome measures were neonatal mortality, neonatal morbidity, caesarean and vaginal instrumental delivery rates, quality of life (QoL) and costs. Neonatal morbidity was defined as 5-minute Apgar score <7, umbilical artery pH <7.05 or admission to a neonatal intensive care unit.

In total 720 women had to be randomised to reduce the risk of poor maternal outcome from 12 to 6% (two-sided, α: 0.05; β: 0.80). Assuming a 5% loss to follow up, we anticipated randomisation of 750 women. Analyses were performed by intention-to-treat. Treatment effect is presented as relative risk (RR) with 95% confidence intervals (CI), adjusted for the stratified randomisation by centre, parity and underlying disease (i.e. GH or PE). After primary analysis, women were classified into subgroups based on their characteristics at trial entry: gestational age (36-37, 37-38, 38-39, 39-40 and 40-41 weeks of gestation), parity (nulli- and multiparous women), hypertensive related diseases (GH and PE), Bishop score and cervical length.

Clinical results of the trial are presented in **Chapter 3**. Between October 2005 and March 2008, we identified 1153 eligible women, of whom 756 (66%) gave informed consent for randomisation. We randomly assigned 377 women to induction of labour and 379 to expectant monitoring. Baseline characteristics of the two randomised groups were comparable. Outcome data for all 756 women were analysed. Women within the expectant monitoring group delivered approximately one week later as compared with induction of labour (0.83 [range 0.04-9.6] vs 6.4 [range 0.08-28.5] days, $p<0.001$). In 10 (3%) of the 377 women allocated to the induction group, labour started spontaneously. In 173 (46%) of the 379 women allocated to expectant monitoring, labour was induced. Among these 173 inductions, 125 women (72%) had at least one medical reason for induction, whereas induction was elective for 48 women (28%). The composite maternal outcome rates were significantly lower in women who were allocated to induction of labour as compared to women allocated to expectant monitoring (31% vs 44%, RR 0.71 [95% CI 0.59-0.86], $p<0.001$). Neither maternal death nor eclampsia or placental abruption occurred. Four women allocated to induction of labour and 11 women allocated to expectant monitoring developed HELLP syndrome (1% vs 3%, RR 0.37 [95% CI 0.12-1.14]).

Caesarean sections were performed less frequently in the induction group as compared to the expectant monitoring group (14% vs 19%, RR 0.75 [95% CI

0.55-1.04]). Both in the induction group and in the expectant monitoring group, the caesarean section rate was higher among women in whom the composite poor maternal outcome occurred. Vaginal instrumental delivery rates were comparable between both groups (13% vs 14%, RR 0.93 [95% CI 0.65-1.33]). There were no fetal or neonatal deaths in either group. The composite neonatal morbidity rate was not statistically significant (6% vs 8%, RR 0.75 [95% CI 0.45-1.26]).

In almost all subgroups a trend toward a better maternal outcome was found after induction of labour as compared to expectant monitoring. Only in women randomised at a gestational age between 36 and 37 weeks and in women with a cervical dilatation >2 cm the point estimate of the RR was above 1. Although expected otherwise, induction of labour seems to be the best policy in women with an unfavourable cervix.

In conclusion, in pregnant women with mild hypertensive disease beyond a gestational age of 37 weeks, induction of labour is associated with better maternal outcome as compared to expectant monitoring, without resulting in a higher caesarean section rate.

In **Chapter 4**, the maternal health-related quality of life (HR-QoL) of the HYPITAT trial is reported. As well as randomised as non-randomised women participated in the HR-QoL study. Patients were asked to fill out written validated questionnaires, covering background characteristics, condition-specific issues and the Short Form (SF-36), European Quality of Life (EuroQoL 6D3L), Hospital Anxiety and Depression scale (HADS), and Symptom Check List (SCL-90) at baseline, 6 weeks postpartum and 6 months postpartum. The SF-36 was subdivided into the standardized summary scores Physical (PCS) and Mental Component Score (MCS). We analysed data of 491 randomised and 220 non-randomised women. We did not find any HR-QoL differences between the intervention groups, e.g. the PCS and MCS were comparable after 6 weeks (p= 0.37 and p= 0.55) and after 6 months (p= 0.70 and p=0.67). We conclude that, despite the clinical benefit of induction of labour, the HR-QoL is equal after induction of labour and expectant management in women who had GH or PE beyond 36 weeks of gestation.

Besides the clinical effectiveness, it is also important to assess the economic consequences of the recommendation to induce labour in hypertensive pregnancies. In **Chapter 5** we describe the results of the short-term cost-effectiveness analysis, which was performed alongside the HYPITAT trial. We used a societal perspective. Costs and effects were compared from the moment of randomisation to one year postpartum. The process of care was differentiated into three cost categories

(direct medical, non-medical and indirect costs) and provided details on utilisation of healthcare resources. Maternal admissions were distinguished into three phases (antenatal, delivery and postpartum phase) and into three levels of care (intensive, medium, or ward). Estimated unit costs were based on several sources: top-down calculations provided by one academic and one general hospital (for maternal and neonatal admissions), bottom-up calculation (one hour use of the labour room and operating theatre), Dutch standardized prices (visits to primary and paramedical health care providers, outpatient visits and non-medical costs), and market prices medication). All unit costs were expressed in 2007 Euros using the consumer pricing index. Total costs per patient were calculated by multiplying resource use per patient by unit costs. The average costs of induction of labour (n= 377) were €7.077 versus €7.908 for expectant monitoring (n= 379), with an average difference of -€831 (95% CI - €1.561 to - €144). This 11% difference predominantly originated from the antepartum period, due to longer admission during expectant monitoring (difference - €1.441). During delivery costs in the induction group were higher than in the expectant monitoring group, due to longer time in the labour room (difference €980). Until one year postpartum, women in the expectant monitoring group generated slightly more costs (difference - €398), because of longer maternal and neonatal stays and more specialist visits. No substantial differences were found in follow-up and non-medical costs. So, induction of labour is a cost saving strategy compared to expectant monitoring in women with GH or mild PE at term.

Main conclusions of the HYPITAT trial

In pregnancies complicated with gestational hypertension or mild pre-eclampsia at term:

- Induction of labour is associated with better maternal outcome as compared to expectant monitoring (31% vs 44%, RR 0.71 [95% CI 0.59-0.86]).
- Induction of labour does not increase the caesarean section rate (14% vs 19%, RR 0.75 [95% CI 0.55-1.04]). The higher caesarean section rate in the expectant monitoring group is mainly ascribed to deterioration of the maternal condition in this group.
- Induction of labour is also the best treatment option in case of an unfavourable cervix.
- Maternal quality of life is equal after induction of labour and expectant monitoring.
- Induction of labour is a cost saving strategy compared to expectant monitoring.

Overall, induction of labour should be advised in women with gestational hypertension and a diastolic blood pressure ≥95 mmHg or mild pre-eclampsia at a gestational age beyond 37 weeks.

PART II

Prediction of severe maternal morbidity in gestational hypertension or (mild) pre-eclampsia

From the HYPITAT trial we learned that the best treatment option in women with mild hypertensive disease of pregnancy at term is induction of labour. The goal of the second part of this thesis was to formulate more specific recommendations to improve quality of care and subsequently limiting maternal mortality and morbidity. For the correct choice of management for the individual patient, identification of women at increased risk of developing severe maternal outcomes is of major importance. Early identification will benefit doctors and patients by helping to monitor disease severity, guide therapy and will allow clinicians to avoid unnecessary interventions in low-risk groups.

In **Chapter 6** a cohort study is presented, which aimed to assess whether deterioration of the clinical situation can be predicted in women with GH or mild PE at term. Women with a singleton pregnancy, a fetus in cephalic position, between 36 and 41 weeks of gestation, complicated by GH or mild PE that were managed expectantly, were selected from the HYPITAT trial. The outcome of interest was a composite outcome of progression to severe disease, defined as eclampsia, HELLP syndrome, maternal mortality, diastolic blood pressure ≥110 mmHg, systolic blood pressure ≥170 mmHg and/or proteinuria ≥5 gram in 24 hours. We used multiple imputation techniques for missing data. Logistic regression was used to determine the predictive value of clinical characteristics or laboratory findings and to generate a prediction model for clinical deterioration. The predictive value of this model was assessed with receiver-operating-characteristic (ROC) analysis and calibration. To correct for overestimated regression coefficients, the models were (internally) validated by bootstrapping techniques and shrinkage.

We included 703 women, of whom 244 (34.7%) had progression to severe disease. After multivariable analysis nulliparity (OR 1.87), maternal age (OR 1.05 per year), gestational age (OR 0.88 per week), previous abortion (OR 1.26), ethnicity (OR 2.05 for non-Caucasian ethnicity), diastolic and systolic blood pressure (OR 1.04 and 1.02 per mmHg), and the laboratory parameters proteinuria, haemoglobin, platelets, uric acid and alanine aminotransferase (ALT) were included in the final model. The area under the ROC-curve of this model was 0.71 (95% CI 0.67-0.74). Even though the goodness of fit was moderate (p=0.40) internal validation showed the model could hold in the overall population. From these results we conclude that after external

validation and proof of generalisability, these predictors may be used in obstetric clinical management in women with GH or mild PE at term.

Chapter 7 describes a case-control study, in which we aimed to evaluate whether eclampsia can be predicted in women with GH or mild PE at term. Accurate prediction of eclampsia is of major importance because in the Netherlands it is still the most feared pregnancy complication with an incidence of 6.2 per 10.000 deliveries. This is markedly increased as compared with other Western European countries. For this case-control study we selected cases with GH or mild PE who developed eclampsia from the LEMMoN study, a nationwide cohort study on severe maternal morbidity. Controls with GH or mild PE who did not develop eclampsia were selected from the HYPITAT study. Risk indicators for eclampsia, identified in multivariable logistic regression, were used to assess the predictive capacity of our model with ROC-curve analysis. Model optimism was assessed with bootstrapping.

We compared 76 cases to 1149 controls. In the multivariable analysis maternal age (OR 0.93 per year), ethnicity (OR 2.8 for non-Caucasian ethnicity), systolic blood pressure (1.1 per mm Hg), proteinuria (OR 3.4 and 6.2 for 2+ and 3+ respectively), uric acid (OR 1.8 per unit), creatinine (OR 1.02 per unit), aspartate aminotransferase (AST) (OR 1.03 per unit) and lactate dehydrogenase (LDH) (OR 1.01 per unit) showed a statistically significant association with the occurrence of eclampsia. Other variables included in the model were previous fetal loss (OR 4.5), previous miscarriage (OR 0.66), gestational age (1.3 per week) and low platelet count (OR 0.995 per unit). For some continuous variables a clear cut off point for increased risk of developing eclampsia was found: systolic blood pressure >155 mmHg, creatinine >74 μmol/L, AST >30 U/L and LDH >400 U/L. The area under the ROC-curve of this model was 0.92 (95% CI 0.89-0.95). Bootstrapping showed minimal optimism of the model, indicating that the model holds for the overall population. We concluded that eclampsia can be predicted in women with GH or mild PE at term. The identified predictors may provide physicians guidance to start prophylactic treatment with magnesium sulphate or to induce labour without delay.

Like eclampsia, postpartum haemorrhage (PPH) can also generate serious morbidity, with ultimately maternal death. Besides this, PPH has been recognized as an important risk factor in pregnant women with hypertensive disorders. In the HYPITAT trial 10% of women with GH or mild PE at term were complicated with PPH, whereas only 1 to 2% risk of HPP is observed in low risk populations. These two reasons make identification of women at increased risk for PPH of major importance. Therefore, we investigated in **Chapter 8** whether PPH can be predicted

in women with GH or mild PE. PPH was defined as blood loss >1000 ml within 24h after delivery. For this cohort study we used data from the HYPITAT trial as well. Multiple imputation techniques were used for missing data. Two models were created to assess the predictive capacity of PPH. Model A included only antepartum variables, whereas model B included both antepartum and intrapartum variables. Logistic regression was performed to predict the occurrence of PPH and bootstrapping to assess model optimism. The predictive capacity of the models was assessed with ROC analysis and calibration.

We included 1132 women, of whom 118 (10.4%) had PPH. Maternal age (OR 1.03 per year), body mass index (OR 0.97 per kg), gestational age at randomisation (OR 1.19 per week), proteinuria (OR 3.06 for +++ on dipstick), platelets (OR 0.997 per unit) and AST (OR 0.98 per unit) were independent antepartum predictors of PPH. Intrapartum variables incorporated in the model were gestational age at delivery (OR 1.21 per week), birth weight (OR 1.36 per kg), mode of delivery (OR 1.06 and 1.67 for vaginal instrumental and caesarean delivery, respectively) and episiotomy (OR 2.1). Model A showed moderate discrimination, with an area under the ROC-curve of 0.63 (95% CI 0.57-0.69), whereas model B was slightly superior (AUC 0.69, 95% CI 0.63-0.74). Calibration was poor for model A, but better for model B (Hosmer-Lemeshow p=0.17 and 0.57). Bootstrapping indicated some overfitting. From these results we concluded that in women with GH or mild PE at term, PPH can be predicted from antepartum and intrapartum variables. The identified predictors should alert clinicians managing labour in these women

In the last two chapters of this thesis two specific laboratory tests are highlighted, in which we aimed to determine the accuracy of these tests for predicting adverse outcomes in PE. **Chapter 9** presents a bivariate meta-analysis and decision analysis of the accuracy of serum uric acid as a predicting test for severe maternal morbidity in women diagnosed with PE. For this study an existing systematic review on the subject was updated. First a summary ROC-curve was estimated and subsequently a clinical decision analysis was performed. Three strategies were modelled: (I) expectant monitoring until spontaneous delivery; (II) induction of labour; (III) serum uric acid as test for predicting maternal complication. In strategy III, labour was induced in case of increased serum uric acid levels, otherwise women were managed expectantly. The decision whether to use the policy expectant monitoring, induction of labour, or to test serum uric acid levels, is based on the expected utility of each strategy. This expected utility depends on the probability of occurrence of severe maternal complications (i.e. severe hypertension, HELLP syndrome and eclampsia) and the mode of delivery (spontaneous delivery versus caesarean section). Valuation of the outcomes was performed using a distress ratio,

which expresses how much worse a complication of PE is valued as compared to a caesarean section.

For the period until 2007 our search revealed eight primary articles, which met the inclusion criteria. In total 1565 women with PE were included in this study. The most common threshold of serum uric acid was 350 μmol/l. The AUC was 68%, which was used in the clinical decision analysis. If the distress ratio was 10, the strategy regarding serum uric acid would be the preferred strategy when the probability of complications was between 2.9 and 6.3%. At higher complication rates induction of labour would be preferred, whereas at lower complication rates expectant management would be the best treatment option. These findings were stable in sensitivity analyses, using different distress ratios. We concluded that serum uric acid seems to be a useful test in the management of PE under realistic assumptions, based on our decision analysis.

Liver function tests are the second laboratory tests which are elucidated by us. These tests are currently routinely performed in most obstetric units as part of the battery of tests in women with PE. However, systematic reviews exploring the accuracy of liver enzymes to predict complications of PE have never been published. Therefore, we conducted a systematic review to obtain precise estimates of maternal serum liver enzyme levels to predict adverse maternal and fetal complications in women with PE, which is presented in **Chapter 10.** After an electronic search in Medline, Embase and the Cochrane Library and a complete examination of the manuscripts, obtained by two independent reviewers, thirteen primary studies were identified with a total of 3507 women. For the prediction of adverse maternal and fetal outcomes 30 and 19 2 x 2 tables were assessed. Eclampsia was the commonest adverse maternal outcome that was reported. The commonest reported adverse fetal outcomes were neonatal death, respiratory distress syndrome and intraventricular haemorrhage. The AUC for predicting any adverse maternal outcome was 0.79 (95% CI 0.51–0.93) and for predicting any adverse fetal outcome it was 0.65 (95% CI 0.26–0.90). For both maternal and fetal outcomes the test specificity was better than sensitivity. In conclusion, liver function tests performed better in predicting adverse maternal than fetal outcomes in women with PE. Presence of raised liver enzymes was associated with an increased probability of maternal and fetal complications, but normal liver enzymes did not rule out disease.

Nederlandse samenvatting

Dit proefschrift is opgesplitst in twee hoofddelen. In deel I worden de resultaten van een gerandomiseerde studie getoond. Deze studie heet de HYPITAT-studie (HYpertension and Pre-eclampsia Intervention Trial At Term). Deel II van dit proefschrift behandelt de predictie van ernstige maternale morbiditeit bij vrouwen met een zwangerschap die gecompliceerd is door zwangerschapshypertensie of (milde) preëclampsie.

DEEL I

De gerandomiseerde trial: HYpertension and Pre-eclampsia Intervention Trial At Term (HYPITAT)

Zwangerschapshypertensie en preëclampsie (PE) compliceren 6-8% van alle zwangerschappen. Deze aandoeningen vormen in Nederland de belangrijkste oorzaak van maternale morbiditeit en mortaliteit. Vaak is het ziektebeeld mild en wordt de diagnose gesteld in de aterme periode. Soms treden ernstige complicaties op, zoals eclampsie, abruptio placentae en het HELLP-syndroom ('haemolysis, elevated liver enzymes and low platelets'). Wereldwijd is er tot nu geen overeenstemming over het beste beleid bij vrouwen met een zwangerschapshypertensie of milde PE vanaf 36 weken amenorroe. Inleiden van de baring zou enerzijds maternale complicaties kunnen reduceren, maar anderzijds de kans op een sectio caesarea en op neonatale complicaties kunnen verhogen. In Nederland werden voor uitvoering van de trial twee verschillende behandelmethoden gebruikt: bij ongeveer de helft van de vrouwen werd de baring ingeleid en bij de andere helft werd er afgewacht. In de Verenigde Staten en andere westerse landen werd in deze situatie veel vaker de baring nagestreefd, hoewel dit niet gebaseerd was op gerandomiseerd onderzoek.

Door gebrek aan consensus en het inconsequente Nederlandse beleid, was het in Nederland mogelijk om een gerandomiseerde studie uit te voeren, waarin de effectiviteit van een inleiding van de baring werd vergeleken met een afwachtend beleid bij vrouwen met zwangerschapshypertensie of milde PE vanaf 36 weken amenorroe. Deze multicentrisch gerandomiseerde studie, de HYPITAT-studie (HYpertension and Pre-eclampsia Intervention Trial At Term), startte in oktober 2005 en werd uitgevoerd binnen het verloskundige consortium, een landelijk netwerk voor verloskundig onderzoek. In totaal werkten 6 universitaire en 32 niet-universitaire ziekenhuizen mee aan dit onderzoek. De studie werd goedgekeurd

door de Medisch Ethische Commissie van de Universiteit van Leiden (p04.210) en geregistreerd in het klinische trialregister (ISCTN08132825). Alle patiënten gaven schriftelijke toestemming voor deelname. De uitvoering van dit project werd mogelijk gemaakt door een subsidie van ZonMW (nummer 945-06-553).

In **Hoofdstuk 2** wordt het studieprotocol van de HYPITAT-studie beschreven.
Vrouwen vanaf 18 jaar met een eenlingzwangerschap gecompliceerd door zwangerschapshypertensie of milde PE tussen 36+0 en 41+0 weken amenorroe werden geïncludeerd. Zwangerschapshypertensie werd gediagnosticeerd bij een diastolische bloeddruk ≥95 mmHg en milde PE bij een diastolische bloeddruk ≥90 mmHg gecombineerd met proteïnurie; beide twee keer gemeten met een tussentijd van tenminste zes uur. Er was sprake van proteïnurie wanneer de dipstick ≥2+ proteïne liet zien, of wanneer de 24-uurs urine ≥0.3 gram was of bij een eiwit/kreatinine ratio (EKR) >30 mg/mmol. Exclusiecriteria waren diastolische bloeddruk ≥110 mmHg, systolische bloeddruk ≥170 mmHg, proteïnurie ≥5 gram/24 uur, sectiolitteken, stuitligging, pre-existente hypertensie, diabetes mellitus, diabetes gravidarum met insulinetherapie, nierziekten, hart- en vaatziekten, HIV-seropositiviteit, HELLP-syndroom, longoedeem of cyanosis, oligurie <500 mL/24 uur, intraveneuze antihypertensiva, CTG-afwijkingen, congenitale afwijkingen en intra-uteriene groeirestrictie.

Voor randomisatie werden een vaginaal toucher en cervixlengte meting verricht. De randomisatie voor inleiden van de baring dan wel afwachten was gestratificeerd voor centrum, pariteit en aanwezigheid van proteïnurie. Het inleiden van de baring geschiedde binnen 24 uur na randomisatie door middel van amniotomie of intraveneuze oxytocine bij een Bishopscore >6, en door intracervicale of intravaginale toediening van prostaglandine of ballonkatheter bij een Bishopscore ≤6. De afwachtgroep werd volgens lokaal protocol gecontroleerd totdat een spontaan begin van de baring optrad. Bij een medische indicatie, als maternale ziekte of langdurig gebroken vliezen, werd de zwangerschap alsnog beëindigd.

De primaire uitkomst was een samengestelde uitkomstmaat gedefinieerd als maternale mortaliteit, maternale morbiditeit (eclampsie, HELLP-syndroom, longoedeem, trombo-embolische ziekte of abruptio placentae), ontwikkeling van ernstige PE (tenminste één keer gemeten diastolische bloeddruk ≥110 mmHg, systolische bloeddruk ≥170 mmHg of proteïnurie ≥5 g/24 uur) of hemorrhagie postpartum. Secundaire uitkomsten waren de wijze van bevallen, neonatale mortaliteit en morbiditeit, kwaliteit van leven en kosten. Neonatale morbiditeit was een samengestelde uitkomstmaat van Apgarscore <7 na 5 minuten, arteriële pH <7.05 of IC-opname.

In totaal waren er 720 vrouwen nodig om een reductie van maternale complicaties van 12 naar 6% aan te tonen (2-zijdige test, alpha 0.05; beta 0.80). Rekening houdend met een verlies van 5% in de follow-up werden er 756 vrouwen gerandomiseerd. Het behandeleffect werd uitgedrukt in relatief risico (RR) met 95% betrouwbaarheidsintervallen (BI). Wij verrichtten exploratieve subgroepanalyses voor amenorroe (36-37, 37-38, 38-39, 39-40 en 40-41 weken), pariteit (nulli- versus multipara), proteïnurie (zwangerschapshypertensie of PE), systolische bloeddruk ($<$140 and $\geq$140 mmHg), evenals Bishopscore en cervixlengte op het moment van randomisatie. Het 'intention-to-treat' principe werd gehanteerd.

Hoofdstuk 3 beschrijft de klinische resultaten van deze studie. Tussen oktober 2005 en maart 2008 voldeden 1153 vrouwen aan de inclusiecriteria, waarvan 756 vrouwen (66%) toestemming gaven voor randomisatie. Er werden 377 patiënten gerandomiseerd voor inleiden en 379 voor afwachten. De gerandomiseerde vrouwen in de inleid- en afwachtgroep hadden vergelijkbare karakteristieken. De zwangerschapsduur was in de inleidgroep gemiddeld één week korter dan in de afwachtgroep (0.83 [0.46-2.8] vs 6.4 [0.83-19.9] dagen, $p<0.001$). Bij 10 vrouwen (3%) in de inleidgroep startte de baring spontaan. In de afwachtgroep werd de baring alsnog ingeleid bij 173 vrouwen (46%); bij 125 vrouwen (72%) om medische redenen, bij 48 vrouwen (28%) om electieve redenen. Verslechtering van de maternale uitkomst trad in de inleidgroep significant minder vaak op dan in de afwachtgroep (31% vs 44%, RR 0.71 [95% BI 0.59-0.86], $p<0.001$). Maternale sterfte, eclampsie en abruptio placentae kwamen niet voor. Bij vier vrouwen uit de inleidgroep en elf vrouwen uit de afwachtgroep werd de zwangerschap gecompliceerd door het HELLP-syndroom (1% vs 3%, RR 0.37 [95% CI 0.12-1.14]).

Het sectiopercentage in de inleidgroep was lager dan in de afwachtgroep, hoewel het verschil niet significant was (14% vs 19%, RR 0.75 [95% BI 0.55-1.04]). Zowel in de inleidgroep als in de afwachtgroep was het sectiopercentage hoger bij vrouwen met een slechte maternale uitkomst. In beide groepen werden evenveel kunstverlossingen verricht (13% vs 14%, RR 0.93 [95% CI 0.65-1.33]). De neonatale morbiditeit was ook vergelijkbaar (6% vs 8%, RR 0.75 [95% BI 0.45-1.26]). Perinatale sterfte trad niet op.

Bijna alle subgroepen toonden een trend naar reductie in maternale complicaties na inleiden in vergelijking met afwachten. Alleen tussen 36-37 weken amenorroe en bij een ontsluiting van $>$2 cm was er geen gunstig effect van inleiden op de maternale conditie. Hiermee lijkt een inleiding van de baring tegen de verwachting in gunstig te zijn voor vrouwen met een onrijpe portio.

Het inleiden van de baring bij zwangere vrouwen met een zwangerschapsgerelateerde hypertensieve aandoening vanaf 37 weken amenorroe verbetert de maternale uitkomst in vergelijking met een afwachtend beleid, zonder een verhoogde kans op een sectio caesarea.

In **Hoofdstuk 4** wordt de gezondheidsgerelateerde kwaliteit van leven (HR-QoL) van moeders in de HYPITAT-studie beschreven. Zowel vrouwen uit de gerandomiseerde groep als vrouwen uit de niet-gerandomiseerde groep werden geïncludeerd in deze studie. De vrouwen werd gevraagd om gevalideerde HR-QoL vragenlijsten in te vullen op het moment van inclusie en 6 weken en 6 maanden postpartum. De vragenlijsten betroffen de Short Form (SF-36), waarin een 'fysieke-componentscore' en een 'mentale-componentscore' gerapporteerd staan, de European Quality of Life (EuroQoL 6D3L), de Hospital Anxiety and Depression scale (HADS), en de Symptom Check List (SCL-90). In totaal werden er 491 gerandomiseerde vrouwen en 220 niet-gerandomiseerde vrouwen geanalyseerd. Op de fysieke-componentscore verbeterde de kwaliteit van leven in beide groepen substantieel tussen de uitgangswaarden en 6 weken postpartum ($p<0.001$). Tussen inleiden en afwachten werd noch op de fysieke-componentscore noch op de mentale-componentscore verschil gemeten op 6 weken (respectievelijk $p=0.37$ en $p=0.55$) en op 6 maanden postpartum (respectievelijk $p=0.70$ en $p=0.67$). De overige vragenlijsten lieten ook geen systematische verschillen zien in de HR-QoL tussen vrouwen die zijn ingeleid en die hebben afgewacht. Er zijn dus geen lange termijn verschillen tussen de maternale HR-QoL na inleiden of na afwachten bij zwangerschapshypertensie of milde PE na 36 weken zwangerschap.

Naast de onderzoeksvraag van de klinische uitkomsten in de HYPITAT-studie, is het ook belangrijk om de economische gevolgen van een inleiding van de baring of een afwachtend beleid te onderzoeken bij vrouwen met een zwangerschapsgerelateerde hypertensie na 36 weken amenorroe. In **Hoofdstuk 5** worden de resultaten beschreven van de korte-termijn kosteneffectiviteitanalyse, die naast de HYPITAT-studie werd uitgevoerd. De economische analyse werd verricht vanuit maatschappelijk perspectief en de kosten werden vergeleken vanaf het moment van randomisatie tot één jaar postpartum. Wij differentieerden de kosten in drie categorieën (direct medisch, niet-medisch en indirecte kosten). De maternale opname werd onderverdeeld in drie fasen: antenataal, perinataal en postnataal, tevens werd er onderscheid gemaakt in het niveau van de zorg: intensive care, medium care, kraamafdeling of thuiszorg. Voor maternale en neonatale opnames waren kostprijzen beschikbaar van één academisch en één perifeer ziekenhuis. De kosten van een uur verloskamer- en operatiekamergebruik werden geschat door een bottom-up-berekening waarin zowel personeel, materiaal als overhead

werden geïntegreerd. Voor andere eenheidskosten, zoals policontroles, thuiszorg of reiskosten, werden nationale standaardkostprijzen gebruikt (in euro's, prijsniveau 2007). Wij berekenden de totale kosten per patiënt door vermenigvuldiging van zorggebruik met eenheidskosten, uitgedrukt in gemiddelde kosten. Antepartum waren de kosten €1.441,- per patiënt lager in de inleidgroep, wat voornamelijk werd veroorzaakt door een kortere maternale opname. De bevalling kostte in de inleidgroep daarentegen €980,- per patiënt meer; door een langere opnameduur op de verloskamer. De postpartumkosten waren €398,- per patiënt lager in de inleidgroep. Er waren geen substantiële verschillen in de follow-up en in de niet-medische kosten. De gemiddelde kosten per patiënt waren €7.077,- voor inleiden en €7.908,- voor afwachten, een verschil van - €831,- (95% BI -€1561,- tot -€144,-). Een inleiding van de baring is dus kostenbesparend in vergelijking met een afwachtend beleid.

Belangrijkste conclusies van de HYPITAT-studie

Voor zwangerschappen gecompliceerd door zwangerschapshypertensie of milde preëclampsie vanaf een amenorroe van 37 weken, geldt:

- Inleiden van de baring verbetert de maternale uitkomst in vergelijking met een afwachtend beleid (31% vs 44%, RR 0.71 [95% BI 0.59-0.86]).
- Inleiden van de baring verhoogt het risico op een sectio caesarea niet. Er is zelfs een trend naar een lager sectiopercentage na inleiden ten opzichte van een afwachtend beleid (14% vs 19%, RR 0.75 [95% BI 0.55-1.04]). Het hogere sectiopercentage in de afwachtgroep wordt hoofdzakelijk verklaard doordat vrouwen in deze groep vaker een slechtere maternale conditie ontwikkelen.
- Ook bij een onrijpe portio is een inleiding de geïndiceerde behandelmethode.
- Inleiden van de baring leidt niet tot een slechtere maternale kwaliteit van leven op de lange termijn.
- Inleiden is aanzienlijk goedkoper dan afwachten.

DEEL II

Predictie van ernstige maternale morbiditeit bij zwangerschapshypertensie of (milde) preëclampsie

De resultaten van de HYPITAT-studie verschaffen duidelijkheid omtrent het beste beleid bij vrouwen met een milde zwangerschapsgerelateerde hypertensie aterme, namelijk een inleiding van de baring. Het doel van een inleiding is het voorkomen van ernstige maternale morbiditeit; daarom is het van belang om vrouwen met een hoger risico op een slechte maternale uitkomst zo vroeg mogelijk te

identificeren. Tijdige voorspelling leidt mogelijk tot betere zorg, want er kunnen effectievere behandelingen worden ingezet en onnodige interventies kunnen in de laagrisicogroepen worden vermeden.

Hoofdstuk 6 beschrijft welke factoren het optreden van een ernstige maternale complicatie kunnen voorspellen bij vrouwen met een zwangerschapshypertensie of milde PE aterme. Vrouwen met een eenling zwangerschap met een foetus in hoofdligging, een amenorroe tussen 36 en 41 weken, bij wie de zwangerschap gecompliceerd werd door zwangerschapshypertensie of milde PE en bij wie een afwachtend beleid werd gevoerd, werden geselecteerd uit de HYPITAT-studie. De uitkomst die bestudeerd werd was een samengestelde uitkomstmaat van ernstige maternale morbiditeit, gedefinieerd als eclampsie, HELLP-syndroom, maternale sterfte en ernstige PE (diastolische bloeddruk ≥110 mmHg, systolische bloeddruk ≥170 mmHg of proteïnurie ≥5 g/24 uur). Multipele imputatie technieken werden gebruikt voor de missende data. Met behulp van multivariabele logistische regressie werden er predictiemodellen gemaakt. De prestatie van de modellen werd onderzocht door middel van 'receiver-operating-characteristic' (ROC) analyses en kalibratie. Om te corrigeren voor een overschatting van de regressie coëfficiënten, werden de modellen (intern) gevalideerd door 'bootstrapping' technieken.

In totaal werden er 703 vrouwen geïncludeerd in deze cohort studie, waarvan 244 (35%) vrouwen ernstige maternale morbiditeit ontwikkelden. Onafhankelijke predictoren van ernstige maternale morbiditeit waren nulliparitеit (OR 1.87), maternale leeftijd (OR 1.05 per jaar), zwangerschapsduur (OR 0.88 per week), abortus in de anamnese (OR 1.26), etniciteit (OR 2.05 voor het niet-Kaukasische ras), diastolische en systolische bloeddruk (OR 1.04 en 1.02 per mmHg), en verschillende laboratorium parameters als proteïnurie, hemoglobine, trombocyten, urinezuur en alanine-aminotransferase (ALAT). De discriminerende waarde van het model was *goed* met een 'area under curve' (AUC) van 0.71 (95% CI 0.67-0.74). Ondanks de matige kalibratie (Hosmer-Lemeshow p= 0.40), laat de interne validatie zien dat het model van waarde zou kunnen zijn in de algemene populatie. Uit deze resultaten concluderen wij dat na externe validatie en een bewijs van generaliseerbaarheid van onze resultaten, de in deze studie gevonden predictoren gebruikt kunnen worden in het obstetrische klinische beleid van vrouwen met een zwangerschapshypertensie of milde PE aterme.

In **Hoofdstuk 7** worden de resultaten getoond van een case-control studie, waarin de predictie van eclampsie bij vrouwen met een zwangerschapshypertensie of milde PE in de aterme periode is onderzocht. Predictie van eclampsie is belangrijk, omdat in Nederland de incidentie van eclampsie 6.2 per 10.000 bevallingen is, een

aanzienlijk hoger cijfer dan in andere West-Europese landen. Cases waren vrouwen met een zwangerschapshypertensie of milde PE die na een zwangerschapsduur van 36 weken een eclampsie ontwikkelden. Deze vrouwen werden geselecteerd vanuit de LEMMoN-studie, een landelijke studie naar ernstige maternale morbiditeit. De controle groep bestond uit vrouwen met een zwangerschapshypertensie of milde PE zonder eclampsie, geselecteerd vanuit de HYPITAT-studie. Risico-indicatoren voor eclampsie werden geïdentificeerd met multivariabele logistische regressie en vervolgens gebruikt om de voorspellende capaciteit van ons model te testen met ROC analyse. De interne validatie werd getest met bootstrapping.

Wij vergeleken 76 cases met 1149 controles. Variabelen met een significante associatie met eclampsie waren: maternale leeftijd (OR 0.93 per jaar), etniciteit (OR 2.8 voor niet-Kaukasisch ras), systolische bloeddruk (1.1 per mm Hg), proteïnurie (OR 3.4 en 6.2 voor 2+ en 3+ respectievelijk), urinezuur (OR 1.8 per unit), kreatinine (OR 1.02 per unit), aspartaat aminotransferase (ASAT) (OR 1.03 per unit) en lactaat dehydrogenase (LDH) (OR 1.01 per unit). Andere variabelen die werden geïncludeerd in het predictiemodel waren foetale sterfte in anamnese (OR 4.5), miskraam in anamnese (OR 0.66), zwangerschapsduur (1.3 per week) en trombocyten (OR 0.995 per unit). Sommige continue variabelen hadden een duidelijk afkappunt waarboven het risico op een eclampsie sterk vergroot was: systolische bloeddruk >155 mmHg, kreatinine >74 μmol/L, ASAT >30 U/L en LDH >400 U/L. De AUC van dit model was 0.92 (95% CI 0.89-0.95) met een minimale overschatting van het model. Als conclusie stellen we dat eclampsie voorspelbaar is bij vrouwen met een zwangerschapshypertensie of milde PE in de aterme periode. De geïdentificeerde risico-indicatoren zouden de gynaecoloog leidraad kunnen geven in de profylactische behandeling met magnesiumsulfaat en het onmiddellijk inleiden van de baring.

Net als eclampsie, kan hemorrhagie postpartum (HPP) ook ernstige maternale morbiditeit genereren, en uiteindelijk leiden tot maternale sterfte. Daarnaast lijkt HPP geassocieerd te zijn met zwangerschapsgerelateerde hypertensieve aandoeningen. In de HYPITAT-studie ontwikkelde 10% van de vrouwen met zwangerschapshypertensie of milde PE een HPP, een aanmerkelijk hoger incidentiecijfer dan de 1-2% voor ongecompliceerde zwangerschappen. De twee bovengenoemde redenen laten zien dat identificatie van risicofactoren voor het optreden van HPP van groot belang is. Daarom onderzochten wij in **Hoofdstuk 8** of predictie van HPP bij vrouwen met een zwangerschapshypertensie of milde PE in de aterme periode mogelijk is. HPP werd gedefinieerd als meer dan 1000 ml bloedverlies in de eerste 24 uur na de partus. Voor deze cohort studie maakten wij gebruik van de HYPITAT database. Wij onderzochten de voorspellende capaciteit

van twee verschillende modellen. Model A betrof een antepartum model. In Model B hebben wij naast de antepartum variabelen ook de intra partum variabelen meegenomen. Multipele imputatie, logistische regressie analyse, ROC-analyse, kalibratie en bootstrapping werden eveneens toegepast om de predictie van HPP te onderzoeken.

In totaal werden er 1132 vrouwen geïncludeerd, waarvan 118 (10.4%) vrouwen een HPP kregen. Maternale leeftijd (OR 1.03 per jaar), body mass index (OR 0.97 per kg), zwangerschapsduur bij randomisatie (OR 1.19 per week), proteïnurie (OR 3.06 voor +++ dipstick), trombocyten (OR 0.997 per unit) en ASAT (OR 0.98 per unit) waren onafhankelijke, antepartum voorspellers van HPP. Intra partum variabelen die werden geïncludeerd in Model B waren zwangerschapsduur bij de bevalling (OR 1.21 per week), geboortegewicht (OR 1.36 per kg), modus van de partus (OR 1.06 en 1.67 voor een kunstbevalling en sectio caesarea, respectievelijk) en episiotomie (OR 2.1). Model A liet een matige discriminatie zien, met een AUC van 0.63 (95% CI 0.57-0.69), terwijl model B beter was (AUC 0.69, 95% CI 0.63-0.74). De kalibratie van Model A was slecht en van Model B goed (Hosmer-Lemeshow p=0.17 en 0.57), hoewel bootstrapping enige overschatting toonde. Vrouwen met een zwangerschapshypertensie of milde PE in de aterme periode hebben een verhoogde kans op HPP; de gecombineerde variabelen in de antepartum en intra partum periode kunnen samen het a priori risico op HPP verhogen of verlagen. Na externe validatie zouden deze voorspellers gebruikt kunnen worden in de kliniek.

In de laatste twee hoofdstukken van dit proefschrift worden twee specifieke laboratoriumtesten onderzocht. Wij hebben getracht om de waarde van deze testen te bepalen om zo complicaties bij vrouwen met een PE beter te kunnen voorspellen. **Hoofdstuk 9** toont een meta-analyse en beslisanalyse waarin de waarde van urinezuur wordt onderzocht om in de toekomst ernstige maternale morbiditeit bij PE te voorspellen. Voor dit onderzoek werd een bestaande systematische review geüpdatet. Eerst werd een sROC-curve opgesteld met de sensitiviteit en specificiteit van de verschillende 2 x 2 tabellen. Vervolgens werd een klinische beslisanalyse uitgevoerd; opgebouwd uit drie beslistakken: (I) afwachtend beleid, totdat de baring spontaan begint; (II) inleiden van de baring; (III) behandeling afhankelijk van de waarde van het urinezuur. In geval van strategie III zou een inleiding van de baring volgen bij een hoge waarde van het urinezuur, en zou er worden afgewacht bij een normaalwaarde van het urinezuur. De 'expected utility' van elke strategie bepaalde of er werd afgewacht, of de baring werd ingeleid of dat het beleid zou afhangen van de waarde van het urinezuur. Deze expected utility was afhankelijk van de kans op een ernstige complicatie (gedefinieerd als ernstige hypertensie, HELLP-syndroom of eclampsie) en de wijze van bevallen

(spontane partus versus sectio caesarea). Voor de waardering van de twee verschillende uitkomstmaten werd gebruik gemaakt van een 'distress ratio', die aangeeft dat een ernstige complicatie zwaarder weegt dan een sectio caesarea. Bijvoorbeeld: een distress ratio van 10 impliceert dat een ernstige complicatie 10 keer zwaarder weegt dan een sectio caesarea.

Voor de periode tot 2008 hebben wij acht geschikte artikelen gevonden, die voldeden aan de inclusiecriteria. In totaal werden er 1565 vrouwen met PE geïncludeerd. De meest voorkomende grenswaarde van urinezuur was 350 μmol. De AUC was 68%, deze waarde werd vervolgens gebruikt voor de klinische beslisanalyse. Bepaling van het urinezuur zou de beste strategie zijn als de kans op een complicatie zich bevindt tussen de 2.9 en 6.3% en er een distress ratio van 10 gehanteerd wordt. In geval van een hoger complicatiepercentage is een inleiding van de baring de beste behandeling, terwijl een afwachtend beleid juist de voorkeur geniet bij een lager complicatiepercentage. Sensitiviteitsanalyses hebben bovengenoemde bevindingen niet beïnvloed. Wij concluderen dat bepaling van de waarde van het urinezuur een nuttige test is in de behandeling van zwangere vrouwen met PE.

In het laatste hoofdstuk worden de leverfunctietesten nader onderzocht. Tegenwoordig worden deze testen routinematig uitgevoerd bij zwangere vrouwen met PE. Echter, systematische review artikelen waarin de waarde van leverfunctietesten wordt onderzocht om ernstige complicaties bij vrouwen met een PE te voorspellen, bestonden niet. In **Hoofdstuk 10** wordt daarom een systematische review beschreven waarin deze waarde van leverfunctietesten is onderzocht. Hiervoor werden de elektronische databases Medline, Embase en de Cochrane Library geraadpleegd en werden de artikelen beoordeeld door twee onafhankelijke auteurs. Dertien artikelen voldeden uiteindelijk aan de inclusiecriteria en in totaal werden er 3507 vrouwen met PE geïncludeerd. Voor een slechte maternale uitkomst en voor een slechte foetale uitkomst werden er respectievelijk 30 en 19, 2 x 2 tabellen opgesteld. De AUC voor de voorspelling van een slechte maternale uitkomst was 0.79 (95% CI 0.51–0.93) en van een slechte foetale uitkomst 0.65 (95% CI 0.26–0.90). De specificiteit van de leverfunctietesten was beter dan de sensitiviteit. Wij kunnen nu concluderen dat leverfunctietesten beter een slechte maternale uitkomst kunnen voorspellen dan een slechte foetale uitkomst bij zwangere vrouwen met PE. Daarbij zijn verhoogde leverenzymen geassocieerd met een verhoogd risico op maternale en foetale complicaties, echter normale leverfunctietesten sluiten een complicatie niet uit.

- Abbreviations
- Authors and collaborators on the HYPITAT trial and their affiliations
- Publications
- Dankwoord
- Curriculum Vitae
- Research Institute SHARE

Abbreviations

ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMC	Academic Medical Centre
AST	aspartate aminotransferase
AUC	area under curve
BMI	body mass index
BP	blood pressure
CEMACH	Confidential Enquiry into Maternal And Child Health
CI	confidence intervals
CRF	case record form
DIC	disseminated intravascular coagulation
EuroQol	European Quality of life
FHR	fetal heart rate
FN	false negative
FP	false positive
GA	gestational age
GGT	gamma glutamyl transferase
GH	gestational hypertension
HADs	Hospital Anxiety and Depression scale
HELLP	Haemolysis Elevated Liver enzymes and Low Platelet count syndrome
HR-QoL	health-related quality of live
HYPITAT	HYpertension and Pre-eclampsia Intervention Trial At Term
HyRAS	Hypertension Risk Assessment Study
IC	Intensive Care
ICER	incremental cost-effectiveness ratio
IQR	interquartile range
ISSHP	International Society for the Study of Hypertension in Preganancy
ITT	intention-to-treat
LDH	lactate dehydrogenase
LEMMoN	Landelijke studie naar Etnische determinanten van Maternale Morbiditeit in Nederland
LFT	liver function tests
MCS	Mental Component Scale
mice	multiple imputation by chained equations
MMR	maternal mortality ratio

NICU	neonatal intensive care unit
OR	odds ratio
PCS	Physical Component Scale
PE	pre-eclampsia
PPH	postpartum haemorrhage
PRN	Dutch Perinatal Registry
RCT	randomised controlled trial
ROC	receiver-operating-characteristic
RR	relative risk
SCL	Symptom Check List
SD	standard deviation
SF	Short Form
SGOT	serum glutamic oxalocetic transaminase
SGPT	serum glutamic pyruvic transaminase
sROC	summary Receiver Operating Characteristic
TIPPS	Tests in Prediction of Preeclampsia's Severity
TN	true negative
TP	true positive
UMCG	University Medical Centre Groningen
VAS	Visual Analogue Scale
ZonMw	Dutch organisation for Health Research

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Groningen, november 2010

Corine

Curriculum Vitae

Corine Koopmans werd 14 december 1979 geboren als derde kind en eerste dochter van Eelco en Ria Koopmans te Leeuwarden. In 1999 behaalde zij in deze stad haar VWO diploma aan het Slauerhoff College. Hetzelfde jaar startte zij haar studie Geneeskunde aan de Rijksuniversiteit Groningen. In 2003 deed zij een klinische stage op de afdeling Obstetrie en Gynaecologie van het 'University General Hospital' in Thessaloniki, Griekenland. Zij heeft in datzelfde jaar een wetenschappelijk onderzoeksproject gedaan op de afdeling Neonatologie van het Universitair Medisch Centrum Groningen o.l.v. prof. dr. A.F. Bos, neonatoloog. Er is gekeken naar de spontane motoriek bij gezonde zuigelingen op de leeftijd van drie maanden. Haar co-schappen in het UMCG werden afgesloten met een keuze co-schap Obstetrie en Gynaecologie in het Medisch Centrum Leeuwarden, te Leeuwarden. Daarna heeft zij haar wetenschappelijk onderzoek op de afdeling Obstetrie en Gynaecologie van het Universitair Medisch Centrum Groningen gedaan o.l.v. prof. dr. J.G. Aarnoudse en dr. M.G. van Pampus. Er werd met behulp van iontoforese onderzoek verricht naar veranderingen in de endotheelfunctie van de microcirculatie tijdens de gezonde zwangerschap en tijdens zwangerschappen gecompliceerd door intra-uteriene groeirestrictie.

Na het behalen van haar artsenbul in het voorjaar van 2006 startte zij als arts-onderzoeker met haar promotie-onderzoek, op de afdeling Obstetrie en Gynaecologie van het Universitair Medisch Centrum Groningen o.l.v. prof. dr. P.P. van den Berg (UMCG), prof. dr. J.G. Aarnoudse (UMCG), prof. dr. B.W.M. Mol (AMC), dr. M.G. van Pampus (UMCG) en dr. H. Groen (UMCG). In diezelfde periode is zij als ANIOS werkzaam geweest op de afdeling Obstetrie en Gynaecologie van het Martini Ziekenhuis te Groningen. In december 2008 werd met de opleiding tot gynaecoloog gestart in het cluster Groningen. Het eerste jaar van de opleiding heeft zij in het Medisch Centrum Leeuwarden gedaan (opleider dr. T. Spinder). Momenteel vervolgt zij haar opleiding in het Universitair Medisch Centrum Groningen (opleider prof. dr. M.J.E. Mourits).

In 2005 leerde Corine haar grote liefde Norbert kennen, met wie zij in Groningen samenwoont.

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