AOGS
Acta Obstetricia et Gynecologica Scandinavica

AOGS ORIGINAL RESEARCH ARTICLE

Prediction of progression to severe disease in women with late preterm hypertensive disorders of pregnancy

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Key words
Clinical prediction model, preeclampsia, gestational hypertension, chronic hypertension, high-risk pregnancy

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Conflict of interest
The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Please cite this article as: Zwertbroek EF, Broekhuijsen K, Langenveld J, van Baaren G-J, van den Berg PP, Bremer HA, et al. Prediction of progression to severe disease in women with late preterm hypertensive disorders of pregnancy. Acta Obstet Gynecol Scand 2017; 96:96–105.

Received: 2 June 2015
Accepted: 16 October 2016

DOI: 10.1111/aogs.13051

Abstract

Introduction. If hypertensive disorders of pregnancy are diagnosed before term, the benefits of immediate delivery need to be weighed against the neonatal consequences of preterm delivery. If we are able to predict which women are at high risk of progression to severe disease, they could be targeted for delivery and maternal complications might be reduced. In addition, this may prevent unnecessary preterm births in women at low risk. *Material and methods.* We developed a prediction model using data from the HYPITAT-II trail, which evaluated immediate delivery vs. expectant monitoring in women with non-severe hypertensive disorders of pregnancy between 34 and 37 weeks of gestation. Univariate and multivariate logistic regression analysis were used to identify relevant variables from clinical and laboratory parameters. The performance of the resulting prediction model was assessed by receiver operating characteristic analysis, calibration and bootstrapping, using the average predicted probabilities. *Results.* We included 519 women, 115 (22.2%) of whom developed severe hypertensive disorders of pregnancy. The prediction model included: maternal age (odds ratio 0.92 per year), gestational age (odds ratio 0.87 per week), systolic blood pressure (odds ratio 1.05 per mmHg), the presence of chronic hypertension (odds ratio 2.4), platelet count (odds ratio 0.996), creatinine (odds ratio 1.02) and lactate dehydrogenase (odds ratio 1.003). The model showed good fit ($p = 0.64$), fair discrimination (area under the curve 0.76, 95% confidence interval 0.73–0.81, $p < 0.001$) and could stratify women in three risk groups of average, intermediate and high risk (predicted probabilities <0.22, <0.44 and >0.45, respectively). *Conclusion.* In women with non-severe hypertension in pregnancy near term, progression to severe disease can be predicted. This model requires external validation before it can be applied in practice.

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; AUC, area under the curve; BP, blood pressure; CI, confidence interval; HDP, hypertensive disorders of pregnancy; HELLP, hemolysis, elevated liver enzymes, and low platelets; HYPITAT trial, HYpertension and Preeclampsia Intervention Trial in the Almost Term patient; LDH, lactate dehydrogenase; ROC curve, receiver operating characteristic curve.

Introduction

Hypertensive disorders of pregnancy (HDP) include chronic hypertension, gestational hypertension and preeclampsia, the latter either new-onset or superimposed in women with preexisting (chronic) hypertension (superimposed preeclampsia). To date, these disorders complicate approximately 10% of all pregnancies (1). Hypertensive disorders are very strongly associated with maternal morbidity and mortality such as eclampsia, placental abruption, syndrome of hemolysis, elevated liver enzymes and low platelets (HELLP), and also with neonatal stillbirth and morbidity, mainly due to iatrogenic preterm birth (2,3).

Delivery is the only effective treatment to prevent maternal or fetal complications in HDP. For women with HDP at term, delivery can be considered, in the view of similar risk of neonatal complications compared with expectant management and improved maternal outcome (4). However, preterm delivery may result in short-term neonatal morbidity such as respiratory distress syndrome, or morbidity beyond the neonatal period such as neurological developmental problems, school-related problems and impaired growth (5). Therefore, if HDP is diagnosed before term, the benefits of delivery need to be weighed against the consequences of preterm delivery.

The HYPITAT-II study could not demonstrate a significant difference in severe adverse maternal outcome after routine delivery of women with late preterm HDP (between 34 and 37 weeks of gestation). However, routine delivery did significantly increase the risk of neonatal respiratory distress syndrome when delivery was induced (6).

It remains unclear whether expectant monitoring is the best management strategy for all women with late preterm hypertensive disorders; delivery might be beneficial in subgroups with a high risk of developing severe disease or for those with a more advanced gestational age. If women at high risk of progression to severe disease could be identified and targeted for delivery, maternal complications may be further reduced, while at the same this may prevent unnecessary preterm births in women at low risk (7).

Several predictors of maternal morbidity in women with HDP have been studied (8–12). However, the prognostic value of these indicators in a multivariate approach is unclear for women with late preterm hypertensive disorders. Therefore, we assessed the prognostic capacity of clinical features and laboratory findings at inclusion with respect to progression to severe HDP as an indication for delivery during expectant monitoring in women with late preterm hypertensive disorders.

Material and methods

We used data from women participating in the HYPITAT-II trial who were managed by expectant monitoring. The HYPITAT-II trial was a multi-center randomized controlled trial performed in the Netherlands between March 2009 and March 2013, comparing immediate delivery to expectant monitoring for women with non-severe late preterm HDP. The trial was approved by the Institutional Review Board of the Academic Medical Centre in Amsterdam (08/244), and had local approval from the boards of the other participating hospitals.

The inclusion criteria of this study were a pregnancy complicated by gestational hypertension, preeclampsia, deteriorating chronic hypertension, or superimposed preeclampsia, and a gestational age from 34^{+0}, up to and including 36^{+6} weeks. Some women were diagnosed with HDP before 34 weeks, but were included at 34 weeks of gestation. Gestational hypertension was defined as a diastolic blood pressure (BP) ≥100 mmHg measured at two occasions at least six hours apart with its onset after 20 weeks of gestation. Preeclampsia was defined as a diastolic BP ≥90 mmHg and proteinuria. Proteinuria was defined as ≥300 mg total protein in a 24-h urine collection or a spot protein-creatinine ratio of ≥30 mg/mmol

Key Message

In women with non-severe hypertensive disorders of pregnancy late preterm or near term, unnecessary preterm births and progression to severe disease might be prevented by using a model to predict progression to severe hypertensive disorders of pregnancy.

(PCR). Women with chronic hypertension (defined as BP ≥140/90 mmHg before 20 weeks of gestation (13,14) could be included if they had either superimposed preeclampsia (defined as new onset of proteinuria) or deteriorating hypertension (defined as the need for new/additional antihypertensive medication after 34 weeks). These cases of HDP are categorized as "chronic hypertension" in this study.

Exclusion criteria were maternal age <18 years, the presence of severe hypertensive disorder (diastolic BP ≥110 mmHg and/or systolic BP ≥170 mmHg despite medication, proteinuria ≥5 g/L), HELLP syndrome, renal or heart disease, HIV seropositivity, pulmonary edema or cyanosis, non-reassuring fetal heart rate, fetal abnormalities, abnormal karyotype and ruptured membranes.

After informed consent was obtained, women were randomized to either a policy that aimed for delivery (intervention group) or a policy that aimed for expectant monitoring until 37 weeks of gestation (expectant group). Women in the expectant management group (both randomized and non-randomized) were monitored until 37 weeks of gestation or until an indication for delivery occurred, whichever was sooner. Monitoring consisted of frequent maternal BP measurements, assessments of proteinuria, laboratory tests and regular assessment of the fetal condition.

Women who refused randomization but gave informed consent to collect their data were included in a cohort group. These women were managed according to the protocol for randomized women, with the only difference that they chose their own treatment in consultation with their attending obstetrician.

In the present study, from the total HYPITAT-II population, women who were randomized for expectant monitoring were included, as well as all non-randomized women who were monitored expectantly. The study profile is shown in Figure 1.

The primary endpoint for the current study was progression to a severe hypertensive disorder as an indication for delivery. This endpoint was chosen considering two main reasons. First, it is more relevant to the clinician to predict which women will develop an indication for delivery, than to predict which women will develop adverse outcomes (regardless of the conducted management). Secondly, "severe disease" is widely accepted as an indication for delivery (13–17), which was also the case in the HYPITAT-II protocol.

Severe hypertensive disorder as an indication for delivery was defined as the occurrence of any of the following: a diastolic BP ≥110 mmHg despite medication, a systolic BP ≥160 mmHg despite medication, eclampsia, HELLP syndrome (platelet count $<100 \times 10^9$/L, aspartate transaminase (AST) >70 U/L or alanine transaminase (ALT) >70 U/L, and lactate dehydrogenase (LDH) >600 U/L), anuria (defined as a urinary production <30 mL/h lasting ≥4 h), pulmonary edema, or severe preeclamptic complaints (13,14,16,17). Cases of women who were recorded as having "severe HDP" as an indication for delivery but who did not have any of the defining characteristics of severe HDP as listed above, were assessed by the study group on an individual basis.

We evaluated whether our primary outcome measure (HDP as indication for delivery) could be predicted with several characteristics at hospital admission. Candidate

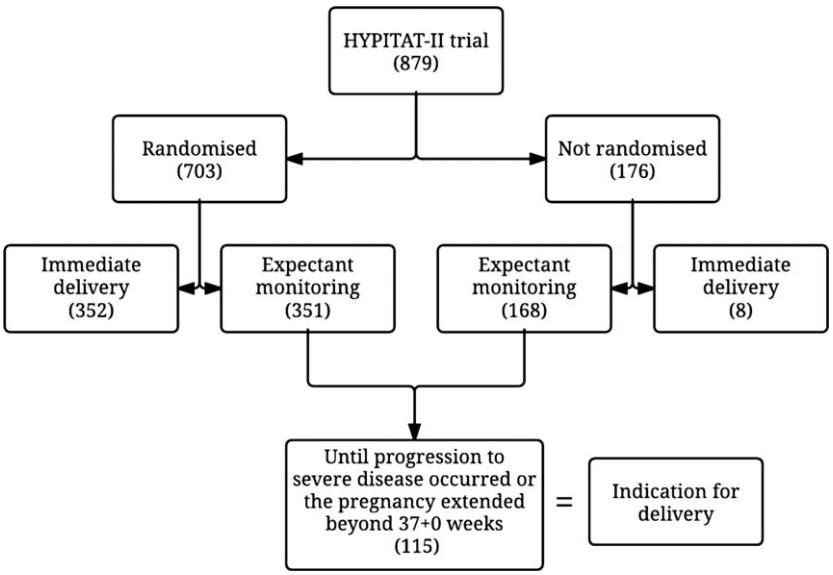

Figure 1. Study profile.

predictors were selected based on previous studies (4,8,10–12,18–26). Selected predictors were maternal characteristics (ethnicity, maternal age, education, smoking), clinical characteristics (diastolic BP, systolic BP, body mass index, gravidity, parity, gestational age at diagnosis, previous abortion, previous cesarean section, type of HDP, history of HDP, comorbidity) or laboratory findings (proteinuria, ALT, AST, LDH, creatinine, uric acid, platelets, hematocrit, hemoglobin) measured at baseline.

The current study population consisted of all 519 women who were managed expectantly in the HYPITAT-II study. With the observed prevalence of an indication for delivery, this sample size provided sufficient power to study up to 10 predictors.

Our primary outcome measure, severe HDP necessitating delivery, had no missing data. However, a few potentially prognostic variables did have a percentage of missing values >5% (for example the proteinuria variables had up to 40% missing values). Exclusion of cases with missing values would have led to loss of statistical power in the multivariable approach and, more seriously, potentially biased results (27). Therefore, we used multiple imputation to handle these missing values (28). Ten multiple imputed datasets were generated using predictive mean matching. Appropriate confidence intervals for the 10 imputed datasets were calculated using Rubins Rules (29). This type of multiple imputation provided a sensitivity analysis to evaluate the influence of imputation.

Statistical analysis

Descriptive statistics were generated using PASW Statistics 22.0 (IBM Corp., Armonk, NY). Baseline characteristics were compared between women who developed severe disease and women who did not. *p*-values were calculated using univariate logistic regression analysis based on original data. Univariate logistic regression was performed to assess the predictive value of all candidate predictors using the imputed datasets. We calculated pooled odds ratios, 95% confidence intervals and *p*-values from the 10 datasets. Predictors with a *p*-value <0.157 were selected for the multivariate logistic regression analysis (28,30). We used backward stepwise selection to generate the prediction model (28). The model performance was assessed by calibration and the Hosmer Lemeshow test for goodness of fit, with p-values closer to one indicating better fit. To evaluate the discriminative performance in the model, area under the receiver-operating characteristic (ROC) curve was calculated using the predicted and the actual outcome. The mean predicted probabilities were calculated across the ten imputations. The calibration of the model was assessed by plotting observed and predicted events for 10 subgroups of women based on deciles of the predicted probability of severe disease. In every subgroup the mean predicted and mean observed probability were calculated. If the predicted probability equals the observed probability all points would be on the line $x = y$ and the calibration would be perfect. The model was internally validated with bootstrapping using R-project software 3.0.2. 2013 (https://www.r-project.org/) (package rms, with the same model parameters as in the final multivariate model). For a detailed statistical report see Appendix S1.

Results

Between March 2009 and March 2013, 897 women were included in the HYPITAT-II trial. The expectant monitoring group consist of 351 (39.0%) women who were randomized to this group and 168 (18.8%) women were non-randomized and monitored expectantly. In total, 519 women underwent expectant monitoring in the HYPITAT-II trial and were included in our study. From our total cohort, 163 (31%) women were diagnosed with gestational hypertension, 292 (56%) with preeclampsia and 64 (12%) women had chronic hypertension at inclusion. Severe hypertensive disorder as an indication for delivery occurred in 115 (22%) women.

Baseline characteristics comparing women with and without development of severe HDP are presented in Table 1. Women who developed a severe hypertensive disorder were younger ($p = 0.008$) and had a lower gestational age at diagnosis ($p = 0.003$) compared to women who did not. Women with existing pre-pregnancy chronic hypertension were more likely to progress to severe HDP when compared to women with preeclampsia or gestational hypertension ($p < 0.0001$), while women with preeclampsia were more likely to develop severe HDP compared to women with gestational hypertension. Women who developed severe HDP had higher systolic ($p < 0.0001$) and diastolic ($p = 0.015$) blood pressures and had more severe proteinuria as measured in 24-h urine collections ($p = 0.003$). Lower levels of platelets ($p = 0.008$) and creatinine ($p = 0.043$) and higher levels of uric acid ($p = 0.011$) and LDH ($p = 0.012$) were associated with progression to severe HDP.

Table 2 shows the pooled results of the univariate analyses, based on the imputed datasets. The following continuous variables were considered for multivariable analysis: maternal age, gestational age at diagnosis, diastolic and systolic blood pressure, PCR, 24-h proteinuria, platelets, creatinine, uric acid and LDH. Binary variables were comorbidity, presence of proteinuria and diagnosis of chronic hypertension. Presence of proteinuria was chosen from the three proteinuria variables that were eligible

Table 1. Baseline patient characteristics: progression vs. no progression to severe hypertensive disorder of pregnancy (HDP) as indication for delivery. Original data.

	HDP indication for delivery (n = 115)			No HDP indication for delivery (n = 404)			
		Patients with data			Patients with data		
Variable	Value	n	%	Value	n	%	p-value
Clinical characteristics							
Nulliparous	71 (61.7%)	115	100	260 (64.4%)	404	100	0.580
Gravidity	2 (1–5)	115	100	1 (1–5)	404	100	0.28
Maternal age (year)	30 (22–38)	115	100	31 (23–40)	404	100	0.008
BMI	31.1 (22.1–42.1)	64	55.6	30.8 (21.1–42.6)	191	47.3	0.584
Gestational age at diagnosis (weeks)	34.1 (28.0–36.3)	112	97.4	35.0 (30.3–36.6)	399	98.8	0.003
No of fetus							
Singleton	105 (91.3%)	115	100	383 (94.6%)	404	100	0.205
Twin	10 (8.7%)			22 (5.4%)			
Smoking	20 (17.7%)	113	98.3	50 (12.9%)	389	96.3	0.192
Blood pressure (mmHg)							
Systolic	148 (125–170)	115	100	140 (122–160)	404	100	<0.0001
Diastolic	95 (85–110)	115	100	95 (80–105)	404	100	0.015
Laboratory findings							
Proteinuria[a]	69 (98.6%)	70	60.9	240 (93%)	258	63.9	0.113
No proteinuria	1 (1.4%)			18 (7.0%)			
PCR ratio (mg/mmol)	52 (13.4–821.8)	47	40.9	40 (3.6–405)	171	42.3	0.087
24-h proteinuria (mg)	600 (8.6–4378.5)	58	50.4	400 (0–2586)	243	60.1	0.003
Dipsticks							
Negative	14 (19.2%)	73	63.5	51 (21.6%)	236	58.4	0.068
Trace	9 (12.3%)			44 (18.6%)			
+	17 (23.3%)			67 (28.4%)			
++	17 (23.3%)			52 (22.0%)			
+++	16 (21.9%)			22 (9.3%)			
Hemoglobine (mmol/L)	7.5 (6.1–8.7)	115	100	7.5 (6.3–8.6)	403	99.8	0.537
Hematocrit	0.36 (0.29–0.42)	108	93.9	0.36 (0.30–0.41)	353	87.4	0.182
Platelets ($\times 10^9$/L)	194 (124–317)	115	100	219 (129–331)	402	99.5	0.008
Creatinine(μmol/L)	58 (44–86)	114	99.1	56 (40–80)	399	98.8	0.043
Uric acid (mmol/L)	0.35 (0.21–0.48)	110	95.7	0.32 (0.19–0.46)	377	93.3	0.011
ALT (U/L)	13.0 (6.6–54.3)	110	95.7	14.0 (6.0–40.3)	366	90.6	0.737
AST (U/L)	21.0 (10.6–63.0)	91	79.1	19.0 (10.0–44.4)	303	75.0	0.351
LDH (U/L)	210.0 (137.5–457.2)	108	93.3	194.0 (134.0–390.9)	353	87.4	0.012
Social economic							
Caucasian	96 (85.0%)	113	98	336 (85.9%)	391	96.8	0.794
Non-Caucasian	17 (15.0%)			55 (14.1%)			
High education	31 (40.3%)	77	67	117 (46.8%)	250	61.9	0.314
Low education	46 (59.7%)			133 (53.2%)			
Medical history							
Preeclampsia	18 (15.7%)	115	100	52 (12.9%)	403	99.8	0.448
Cesarean section	12 (10.5%)	114	99.1	41 (10.2%)	404	99.8	0.900
Abortion[b]	38 (33.3%)	114	99.1	114 (28.2%)	404	100	0.290
Comorbidity							
Yes	31 (27.7%)	112	97.4	85 (21.5%)	395	97.8	0.172
No	81 (72.3%)			310 (78.5%)			
Diabetes mellitus	2 (1.7%)	115	100	5 (1.2%)	404	100	0.682
Gestational diabetes mellitus	5 (4.3%)	115	100	9 (2.2%)	404	100	0.224
Diagnosis							
Gestational hypertension	23 (20.0%)	115	100	109 (27.0%)	404	100	<0.0001
Preeclampsia	39 (33.9%)			187 (46.3%)			
Chronic hypertension	53 (46.1%)			108 (26.7%)			

BMI, body mass index; AST aspartate transaminase; ALT alanine transaminase; LDH lactate dehydrogenase.

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

[a]Presence of proteinuria was defined as a PCR ≥30 mg/mmol or a 24 h proteinuria ≥300 mg.

[b]Abortion could either be spontaneous or therapeutic.

Table 2. Results of the univariate analysis of predictors of progression to severe disease as indication for delivery, pooled estimates based on imputed data.

Variable	OR	95% CI	*p* value
Clinical characteristics			
Multiparity[a]	1.119	0.730–1.716	0.607
Gravidity[a]	1.080	0.714–1.634	0.716
Maternal age[b]	0.945	0.906–0.985	0.008
BMI[b]	1.019	0.977–1.062	0.370
Gestational age at diagnosis (weeks)[b]	0.890	0.822–0.963	0.004
Systolic BP[b]	1.041	1.022–1.060	<0.0001
Diastolic BP[b]	1.037	1.007–1.068	0.015
No. of fetus[b]	1.654	0.760–3.601	0.205
Smoking[a]	1.454	0.827–2.557	0.193
Laboratory findings			
Presence of proteinuria[a,f]	1.808	1.017–3.214	0.044
PCR[b,d]	1.255	1.025–1.538	0.028
24-h proteinuria[b,d]	1.098	0.962–1.255	0.161
Dipsticks (vs. negative)[c]			
Trace	0.647	0.264–1.583	0.337
+	0.808	0.394–1.657	0.559
++	1.075	0.475–2.429	0.861
+++	2.237	0.963–5.195	0.061
Hemoglobine[b]	0.913	0.683–1.220	0.539
Hematocrit[b]	0.733[e]	0.382–1.405	0.350
Platelets[b]	0.995	0.992–0.999	0.008
Creatinine[b]	1.016	1.001–1.030	0.035
Uric acid[b]	1.373[e]	1.054–1.789	0.019
ALT[b]	1.002	0.992–1.011	0.756
AST[b]	1.006	0.995–1.017	0.289
LDH[b]	1.003	1.001–1.005	0.015
Social economic			
Caucasian[a]	0.918	0.209–1.656	0.776
High education[a]	0.850	0.523–1.271	0.366
Medical history[a]			
Preeclampsia	1.245	0.696–2.227	0.460
Cesarean section	1.098	0.560–2.153	0.785
Abortion	1.270	0.813–1.984	0.293
Comorbidity[a]			
Yes	1.411	0.875–2.275	0.158
Diabetes mellitus in pregnancy	1.995	0.655–6.074	0.224
Diabetes mellitus	1.412	0.270–7.377	0.682
Diagnosis[a]			
Chronic hypertension	2.343	1.527–3.594	<0.0001
Gestational hypertension	0.677	0.408–1.123	0.131

If the variable had a *p*-value <0.157 in the univariate analysis, it was considered in the final (multivariate) model.

OR, odds ratio; CI, confidence interval; BMI, body mass index; BP, blood pressure; AST aspartate transaminase; ALT alanine transaminase; LDH lactate dehydrogenase.

[a]Binary variable.

[b]Continuous variable.

[c]Categorical variable.

[d]Natural logarithm was taken of this variable.

[e]OR per 0.1.

[f]Presence of proteinuria was defined as a PCR ≥ 30 mg/mmol or a 24 h proteinuria ≥300 mg.

Table 3. Multivariate analysis of predictors of progression to severe disease requiring delivery, pooled estimates based on imputed data.

Variable	OR	95% CI	β-value	*p* value
Clinical characteristics				
Maternal age (years)	0.919	0.876–0.961	−0.086	<0.0001
Gestational age at diagnosis (weeks)	0.874	0.799–0.957	−0.135	0.004
Systolic blood pressure (mmHg)	1.046	1.025–1.067	0.045	<0.0001
Comorbidity (yes/no)	1.519	0.890–2.593	0.418	0.126
Chronic hypertension (yes/no)	2.371	1.466–3.833	0.863	<0.0001
Laboratory findings				
Presence of proteinuria[a] (yes/no)	1.769	0.920–3.401	0.570	0.087
Platelets ($\times 10^9$/L)	0.996	0.992–1.000	−0.004	0.034
Creatinine (μmol/L)	1.015	0.998–1.032	0.015	0.078
Lactate dehydrogenase (U/L)	1.003	1.000–1.006	0.003	0.034

[a]Presence of proteinuria was defined as a PCR ≥30 mg/mmol or a 24 h proteinuria ≥300 mg.

for multivariate analysis. This binary variable had promising *p*-values and odds ratios compared to the other variables and above all, had less missing values.

Table 3 shows the predictors included in the final model, i.e. maternal age, presence of co-morbidity, diagnosis of deteriorating chronic hypertension or superimposed preeclampsia, gestational age at diagnosis in weeks, systolic blood pressure, platelet count, creatinine, LDH and presence of proteinuria, all measured at inclusion. The Hosmer-Lemeshow test for goodness of fit showed a good fit of the model ($p = 0.642$).

The ROC-curve is presented in Figure 2. It showed fair discriminative performance (area under the curve (AUC) 0.76, 95% CI 0.73–0.81, $p < 0.001$) in our study population. The performance of the model was fair. With regard to calibration (Figure 3) the model slightly overestimated the risk for the probabilities ranging from zero to 0.1. In terms of risk stratification, three groups could be identified, carrying a different risk of progression to severe hypertensive disorder as an indication for delivery. In the first six deciles, according to predicted probability (0.018–0.220), the observed probability did not exceed the overall risk of 22%. The 7th, 8th and 9th decile can be considered the intermediate risk group with a predicted probability ranging from 0.221 to 0.444. The 10th decile, with a predicted probability of 0.449 or higher, can be regarded as high risk. The mean risk of women in the high risk group was 0.589. Bootstrapping showed that the overfitting was small (the AUC was only 2–3% smaller than with the original data), indicating that the model could hold for

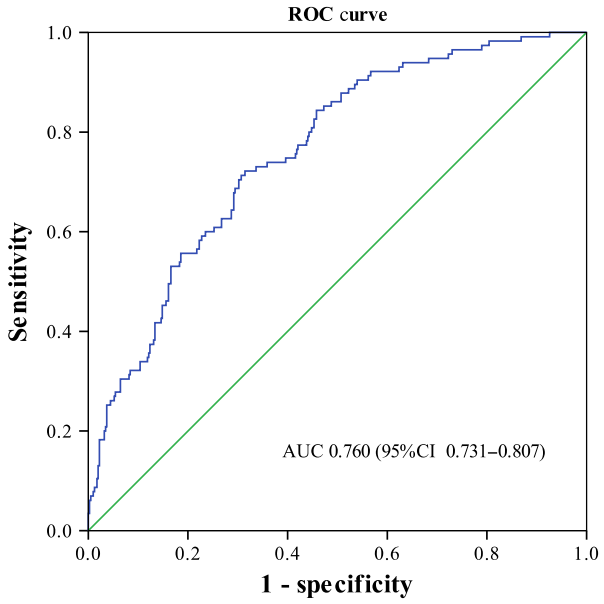

Figure 2. Receiver-operating characteristic (ROC) graph of prediction model for progression to severe disease, calculated by multivariable analysis. AUC, area under the curve; CI, confidence interval. [Color figure can be viewed at wileyonlinelibrary.com]

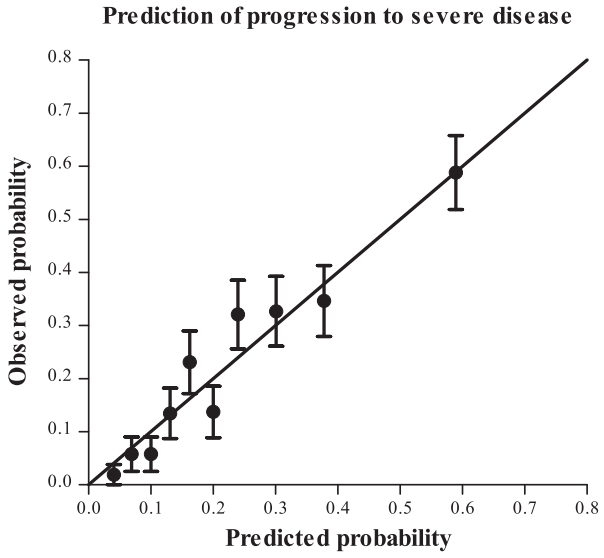

Figure 3. Calibration plot demonstrating the association between the risks of progression to severe disease as predicted by the logistic model and the observed progression to severe disease.

the overall population, although external validation has to confirm this statement.

Discussion

We developed a model to predict the progression of non-severe HDP between 34 and 37 weeks of pregnancy to become an indication for delivery. The results of our study demonstrate that among women with HDP between 34 and 37 weeks of pregnancy in our study population, women at high risk of developing severe disease can be discriminated from women at lower risk. The final model included maternal age, presence of co-morbidity, diagnosis of deteriorating chronic hypertension or superimposed preeclampsia, gestational age at diagnosis in weeks, systolic blood pressure, presence of proteinuria, platelets, creatinine and LDH.

Our model was not the first model designed to predict severe disease of HDP. Von Dadelszen et al. (10) developed a model to predict adverse outcomes. As opposed to our model, subjective maternal symptoms were included in their model. These were not available in the HYPITAT-II data. However, subjective maternal symptoms are non-quantifiable parameters and therefore the model would probably be more exact by not using these predictors (18,20–22,24). The type of hypertensive disorder was not frequently used as predictor in other prediction models. Chronic hypertension was not considered a high risk factor or an important predictor of severe disease until now. However, in our analysis, chronic hypertension was one of the strongest predictors of severe disease. Therefore, this predictor should be taken into account in further studies and the management of hypertensive disorders in pregnancy.

Our model, based on routinely available parameters in a developed world setting, showed good fit and fair discrimination for our data. However, the model slightly overestimated the risk for the probabilities ranging from zero to 0.1. For this very low risk the overestimation will not be a problem because the observed risk is still very low. The model identified three categories of women at average, intermediate and high risk of progression to severe hypertensive disease as indication for delivery. For this population of women, the overall risk of developing severe disease as an indication for delivery was 22%. Since the distinctive thresholds of medium and high risk are higher than this average risk population, the model is very useful to distinguish the medium and high risk group from the low risk group. 40% of women in our study population were at medium or high risk of developing severe disease. Regarding this large percentage, the use of this model is very relevant.

This study has several strengths and limitations. Data were derived through a large multicenter study, including participants from a large number of hospitals throughout the Netherlands. We believe that this group is representative for women with mild HDP between 34 and 37 weeks gestational age. A limitation was the various numbers of missing values. For the multivariate approach these missing values were imputed to avoid loss of statistical power

and, more seriously, biased results. Both PCR and 24-h proteinuria had missing values, indicating that both of these techniques are used in the Netherlands to determine whether significant proteinuria is present. PCR was used more often than 24-h proteinuria. Therefore, we used the dichotomous variable 'presence of proteinuria' yes or no, to reduce the number of values that needed imputation. Proteinuria was defined as ≥300 mg total protein in a 24 h urine collection or a spot protein-creatinine ratio of ≥30 mg/mmol (PCR). Another possible limitation was the allowance of antihypertensive medication in the study. However, there was no relation between use of hypertensive medication and progression to severe disease (data not shown). We included women with gestational hypertension with a diastolic BP >100 mmHg, instead of a diastolic BP >90 mmHg, as is used in the diagnostic criteria. This may also be considered a limitation of the study. No conclusions can therefore be drawn for this subgroup of very mild gestational hypertension. However, we believe that for women with gestational hypertension and a diastolic BP of 90–100 mmHg, who probably have an even lower risk of adverse maternal outcomes than patients in our study population, expectant monitoring should be considered.

In clinical practice, this model can assist clinicians to stratify women in categories of average, intermediate and high risk. Women at average risk (ranging from 0.018 to 0.220) can be monitored according to current regular care. For the intermediate risk group (ranging from 0.221 to 0.444), more frequent monitoring or cervical ripening in case of an unripe cervix could be considered. Our model provides risk stratification based on maternal parameters and therefore the fetus should be monitored in ongoing pregnancy. The probability of developing severe disease in the high risk group ranged from 0.449 to 0.964 and the mean risk was 0.589. In this selected 10% of the population, immediate delivery should be considered, as the risk of severe maternal disease is 60% while the risk of neonatal respiratory distress syndrome for immediate delivery is 5.7% for the total population (6). The maternal benefits of delivery may outweigh the risk of the neonatal consequences of preterm delivery. These clinical recommendations could be implemented once the model is externally validated. No recommendations regarding less frequent monitoring in the average risk group can be made, since our prediction is based on the current standard of monitoring. This model provides the opportunity to calculate an individualized risk for all women, integrating all risk factors and their respective contributions into one estimate, rather than just knowing the risk factors. The calculated risk enables caretakers to identify individual women at average, intermediate or high risk.

Further research is necessary to externally validate the model to investigate whether the model holds in another less selected population. We will test the model on international data and eventually prospectively evaluate implementation in Dutch clinics. Furthermore, in this model angiogenic factors were not considered. These factors emerged as possible predictors for developing complications in women with HDP during planning and execution of the HYPITAT-II study. However, we recommend investigating these factors in future studies on hypertensive disease in pregnancy in combination with clinical and laboratory parameters to predict maternal severe disease late preterm. Nevertheless, until angiogenic factors have been studied sufficiently and have been implemented into clinical practice, our model, based on routinely available parameters, is of relevance.

In conclusion, HYPITAT-II results showed that immediate delivery cannot be recommended for all women who developed HDP during late preterm pregnancy (34–37 weeks of gestation): any decrease in the risk of adverse maternal outcomes was likely to be small, while the risk of neonatal RDS increased significantly. As delivery might be beneficial in subgroups of women with a high risk of developing severe disease, we developed a model to predict the progression of HDP between 34 and 37 weeks of pregnancy. This model stratifies women in groups of low, medium and high risk. This model has the potential to guide doctors in management of the individual women and prevent unnecessary interventions or preventable progression to severe disease after external validation.

Acknowledgments

We thank research nurses and midwives of our consortium, and residents, midwives, nurses, and gynecologists of the participating centers for their help with recruitment and data collection.

Funding

This trial was funded by "ZonMw", the Netherlands Organisation for Health Research and Development, program "Doelmatigheidsonderzoek" (Health Care Efficiency Research, grant 171102012).

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Statistical report.