Who's at risk?

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CHAPTER 03

PREDICTION OF POSTPARTUM HEMORRHAGE IN WOMEN WITH GESTATIONAL HYPERTENSION OR MILD PREECLAMPSIA AT TERM.

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ABSTRACT

OBJECTIVE: To assess whether postpartum hemorrhage (PPH) can be predicted in women with gestational hypertension or mild preeclampsia at term.

DESIGN: A cohort study in which we used data from our multicenter randomized controlled trial (HYPITAT-trial).

SETTING: The study was conducted in 38 hospitals in the Netherlands between 2005 and 2008.

POPULATION: Women with gestational hypertension or mild preeclampsia at term (n=1,132).

METHODS: An antepartum model (model A) and an antepartum/intrapartum model (model B) were created using logistic regression. The predictive capacity of the models was assessed with receiver-operating-characteristic (ROC) analysis and calibration. Main outcome measure PPH, defined as blood loss >1000 ml within 24h after delivery.

RESULTS: PPH occurred in 118 (10.4%) women. Maternal age (OR 1.03), prepregnancy body mass index (OR 0.96) and women with preeclampsia (OR 1.5) were independent antepartum prognostic variables of PPH. Intrapartum variables incorporated in the model were gestational age at delivery (OR 1.2), duration of dilatation stage (OR 1.1) and episiotomy (OR 1.5). Model A and model B showed moderate discrimination, with an area under the ROC-curve of 0.59 (95% CI 0.53-0.64) and 0.64 (95% CI 0.59-0.70). Calibration was moderate for model A (Hosmer-Lemeshow p-value=0.26) but better for model B (Hosmer-Lemeshow p-value=0.36). The rates of PPH ranged from 4% (lowest 10 percent) to 22% (highest 10 percent).

CONCLUSION: In the assessment of performance of a prediction model, calibration is more important than discriminative capacity. Our prediction model shows that for women with gestational hypertension or mild preeclampsia at term distinction between low and high risk of developing PPH is possible when antepartum and intrapartum variables are combined.

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 hemorrhage (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]

Our study group performed a randomized controlled trial on the subject (HYpertension and Preeclampsia Intervention Trial At Term (HYPITAT) trial), in which we found that induction of labor 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 labor and expectant monitoring. Because PPH was found to be associated with hypertensive disorders of pregnancy, we included PPH in the composite primary outcome of our study.[4-6] Induction of labor did not increase the incidence of PPH, but the overall incidence of PPH found in our study was 10%, which was considerably higher than the 0.4-1.3% risk of PPH observed in low risk populations.[4,12] The same association has recently been described in the LEMMoN study which revealed an incidence of PPH of 4.0 per 1.000 deliveries in the Netherlands, whereas in 11.2% of cases PPH was accompanied by preeclampsia.[13]

Due to the high incidence of PPH in women with a pregnancy related hypertensive disorder, identification of women at increased risk of PPH is of major importance. Therefore we aimed to investigate whether prediction of occurrence of PPH is possible in women with gestational hypertension or mild preeclampsia at term based on antepartum or ante- and intrapartum prognostic variables. Our hypothesis was that it would be possible to identify women whose risk of PPH is elevated compared to the risk conveyed by preeclampsia alone. Consequently these patients would need particular attention during the early postpartum period to lower the incidence of PPH.

MATERIALS AND METHODS

For the present study we used data from the HYPITAT-trial (clinical trial register number ISRCTN 08132825).[11] This multicenter parallel randomized controlled, open label trial, was conducted in six academic and 32 non-academic hospitals in the Netherlands, in which 1153 women were recruited between October 2005 and March 2008. 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. Written informed consent was obtained from all patients before randomization. Women with a singleton pregnancy with a child in cephalic position and a gestational age between 36+0 and 41+0 weeks whose pregnancy was complicated by gestational

hypertension or mild preeclampsia were asked to participate in the trial. Gestational hypertension was defined as diastolic blood pressure ≥95 mmHg measured on two occasions at least six hours apart. Mild preeclampsia was defined as diastolic blood pressure ≥90 mmHg measured on two occasions at least six hours apart combined with proteinuria. Proteinuria was defined by local protocol as ≥2+ protein on dipstick, >300 mg total protein in a 24 hour urine collection or protein/creatinine ratio >30 mg/mmol. In total 756 women gave informed consent of whom 377 were randomly allocated to induction of labor and 379 women to expectant monitoring. Another 397 women did not give consent for randomization, but they provided authorization to use their medical data, and they were treated according to local protocol at the discretion of the attending obstetrician. Women allocated to induction of labor were induced within 24 hours after randomization. Women 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. For more study information we refer to the HYPITAT-trial.[11]

In the present study we combined data of randomized and non-randomized 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] In accordance with the local protocol blood loss was visually estimated or weighed. To validate the findings of our analysis, we repeated our analysis based on another endpoint, namely the need for blood transfusion.

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, education level, previous abortion), diastolic and systolic blood pressure or laboratory findings (proteinuria, hemoglobin, hematocrit, platelets, uric acid, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and women diagnosed with preeclampsia or gestational hypertension). The second model (model B) included these antepartum variables, as well as intrapartum variables, such as gestational age at delivery, pain relief, duration of dilation stage or bearing down stage, use of prostaglandins, oxytocine or magnesium sulphate, onset of labor, mode of delivery, perineum rupture and episiotomy. 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.[16,17]

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 non-parametric Mann-Whitney U test in case of skewed distribution. Categorical variables were compared by chi-square statistics.

Using the imputed multiple datasets, logistic regression was performed to predict the occurrence of PPH. For both dichotomous and continuous variables univariate pooled odds ratios (OR), and 95% confidence intervals (CI), as well as p-values, were calculated. In the case of continuous variables the OR reflects the change in probability per unit. Subsequently, multivariable logistic regression analysis was used to construct the two prognostic models for PPH. Stepwise backward selection was performed manually by combining expert opinion and apparent statistical significance. For this analysis we included all prognostic variables reaching a p-value of <0.157 in univariate analysis, based on the Akaike Information Criterion.[18]

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 prognostic model by plotting observed and predicted event rates for 10 subgroups of women on the basis of deciles of the predicted probability of PPH.[19] Per group, the mean predicted probability, aggregated from the five imputed datasets, as well as the mean observed PPH rate was calculated. In the 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 using R-project procedure 'model.val'.[20] This procedure uses the fixed set of variables in the prediction model and uses them in a logistic regression analysis with the bootstrapped data. 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 1,153 women included in the HYPITAT-trial we identified 1,132 eligible women for participation in the present study. Twenty-one women were excluded because the total amount of blood loss was unknown. Among this cohort 118 women (10.4%) developed PPH, and consequently in 1,014 women (89.6%) PPH did not occur.

Table 1. Distribution of prognostic variables among women with and women without postpartum hemorrhage at term.

Prognostic variables	*Women with postpartum hemorrhage (n=118)*	*Women without postpartum hemorrhage (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%)
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%)
Hemoglobin (mmol/L)	7.5 (6.1-8.6)	7.5 (6.4-8.6)
Hematocrit (L/L)	0.36 (0.30-0.40)	0.36 (0.30-0.41)
Platelets (x10^9/L)[1]	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)
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)
Women with PE (vs women with GH)[1]	46 (39%)	304 (30%)
Data concerning delivery		
Gestational age delivery (weeks)[1]	39.8 (37.7-41.4)	39.6 (37.1-41.3)
Pain relief		
Pethidine / phenergan / nubain	13 (11%)	153 (15%)
Epidural analgesia	35 (30%)	215 (21%)
Spinal analgesia	0 (0%)	26 (3%)
Other	8 (7%)	51 (5%)
Duration of dilation stage (min)[1]	236 (45.7-671)	200 (40.0-640)

Table 1. Distribution of prognostic variables among women with and women without postpartum hemorrhage at term.

Prognostic variables	*Women with postpartum hemorrhage (n=118)*	*Women without postpartum hemorrhage (n=1014)*
Duration of bearing down stage (min)[1]	36.5 (4.0-118)	26.0 (3.0-106)
Use of prostaglandins	46 (39%)	419 (41%)
Use of oxytocine	70 (60%)	596 (59%)
Use of intravenous antihypertensive	11 (10%)	65 (7%)
Use of magnesium sulphate	12 (10%)	82 (8%)
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%)
Birth weight (g)[1]	3500 (2722-4388)	3345 (2478-4191)
Perineum rupture (vs none)[1]		
No rupture	35 (30%)	341 (34%)
1st -2nd	27 (23%)	330 (33%)
3rd-4th	2 (2%)	19 (2%)
Episiotomy	53 (45%)	320 (32%)
Placenta delivery[1]		
Spontaneous	66 (57%)	841 (83%)
Retained placenta/ manual removal	28 (24%)	15 (2%)
After caesarean section	22 (19%)	156 (15%)

The distribution of prognostic variables is expressed as median (5^{th}-95^{th} percentile) or numbers (%). [1] Variables with a significant distribution between groups (p-value < .05).

The distribution of potential prognostic variables 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. Laboratory findings showed a lower amount of platelets and more women who were diagnosed with preeclampsia in the group of women who developed PPH. Intrapartum, women with PPH had a higher gestational age at delivery (p=0.007), a longer dilatation and bearing down stage (p=0.019 and 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). P-values were not shown in Table 1.

Factors significantly associated with PPH in the univariate analysis were gestational age at delivery (OR 1.3 per week, p=0.003), mode of delivery (OR 1.7 for vaginal instrumental delivery *vs.* spontaneous delivery, P=0.04), duration of dilatation stage (OR 1.1 per hour, p=0.03), birth weight (OR 1.6 per kg, p=0.008) and episiotomy (OR 1.6, p=0.04) (Table 2). Manual placenta delivery was in univariate analysis strongly

Table 2. Prognostic variables of postpartum hemorrhage 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).

	Univariate analysis			*Multivariate analysis* Model A			*Multivariate analysis* Model B		
Prognostic variables	***OR***	***95% CI***	***P***	***OR***	***95% CI***	***P***	***OR***	***95% CI***	***P***
Clinical characteristics									
Nulliparity	1.2	(0.79-1.9)	.37						
Multiparity (para4+)	0.78	(0.10-6.1)	.81						
Maternal age (years)	1.03	(0.99-1.1)	.157	1.03	(0.99-1.1)	.13	1.04	(1.0-1.1)	.08
Maternal smoking	1.1	(0.62-2.0)	.71						
Prepregnancy body mass index (kg/m^2)	0.96	(0.93-1.00)	.07	0.96	(0.93-1.00)	.07	0.96	(0.67-0.73)	.08
Non-Caucasian ethnicity	1.2	(0.64-2.1)	.60						
Higher education level	1.3	(0.75-2.2)	.36						
Previous abortion	1.1	(0.68-1.7)	.79						
Blood Pressure (mmHg)									
Systolic	1.00	(0.99-1.02)	.67						
Diastolic	1.01	(0.98-1.04)	.54						
Laboratory findings									
Dipstick (vs negative)									
Negative									
Trace	1.2	(0.64-2.4)	.60						
+	1.1	(0.72-2.2)	.63						
++	1.0	(0.55-2.3)	.91						
+++	1.8	(0.91-5.5)	.20						
Hemoglobin (mmol/L)	0.84	(0.64-1.1)	.22						
Hematocrit (L/L x 10)[1]	0.65	(0.34-1.2)	.19						
Platelets (x10^9/L)	1.00	(0.99-1.0)	.10						
Uric acid (mmol/L x10)[1]	1.01	(0.78-1.3)	.96						
Creatinine (µmol/L)	1.00	(0.99-1.01)	.49						
Aspartate aminotransferase (U/L)	0.99	(0.97-1.01)	.38						
Alanine aminotransferase (U/L)	1.00	(0.98-1.02)	.84						
Lactate dehydrogenase (U/L)	1.00	(1.00-1.0)	.53						
Women with PE (vs women with GH)	1.5	(1.01-2.2)	.05	1.5	(1.2-1.8)	.05	1.6	(1.08-2.4)	.02
Intrapartum data									
Gestational age at delivery (weeks)	1.3	(1.1-1.5)	.003				1.2	(1.06-1.5)	.01

Table 2. Prognostic variables of postpartum hemorrhage 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).

	Univariate analysis			***Multivariate analysis*** *Model A*			***Multivariate analysis*** *Model B*		
Prognostic variables	***OR***	***95% CI***	***P***	***OR***	***95% CI***	***P***	***OR***	***95% CI***	***P***
Pain relief									
Pethidine / phenergan / nubain	0.78	(0.45-1.4)	.43						
Epidural / Spinal analgesia	1.50	(0.96-2.3)	.08						
Other	1.42	(0.64-3.1)	.39						
Duration of dilatation stage (hours)	1.07	(1.0-1.1)	.003				1.06	(0.99-1.1)	0.08
Duration of bearing down stage (min)	1.00	(1.0-1.0)	.21						
Use of prostaglandins	0.91	(0.61-1.3)	.63						
Use of oxytocine	1.02	(0.70-1.5)	.94						
Use of intravenous antihypertensive	1.50	(0.77-2.9)	.23						
Use of magnesium sulphate	1.29	(0.68-2.4)	.44						
Induction of labour (vs spontaneous)	1.01	(0.68-1.5)	.96						
Mode of delivery (vs spontaneous)									
Spontaneous									
Vaginal instrumental delivery	1.7	(1.03-2.7)	.04						
Caesarean delivery	1.4	(0.85-2.3)	.19						
Perineum rupture (vs none)									
No rupture									
1st -2nd	0.80	(0.47-1.3)	.40				0.89	(0.52-1.5)	.66
3rd-4th	0.96	(0.21-4.3)	.95				1.06	(0.24-4.8)	.94
Episiotomy	1.6	(1.03-2.5)	.04				1.5	(0.95-2.4)	.08

OR = Odds Ratio; CI = confidence interval. If the variable had a P less than .157 in the univariable analysis, it was considered in the final (multivariable) model. [1]Scale adapted by multiplication with a factor 10 for regression analyses.

associated with PPH (OR 25.0 for retained placenta *vs.* spontaneous placental delivery, p<0.001). This variable was excluded from multivariable analysis, as it is obvious that retained placenta is already a major attribute of PPH. Also birth weight was excluded as a prognostic variable as this is only known after delivery. Thereby, we did not always know the estimated birth weight by ultrasound from our patients plus, ultrasound birth weight estimates are often inaccurate.

Since more liberal p-values are advocated to increase the probability that real prognostic variables are selected in the model, we selected all prognostic variables with a significance level of p<0.157 in the univariate analysis to enter the model.

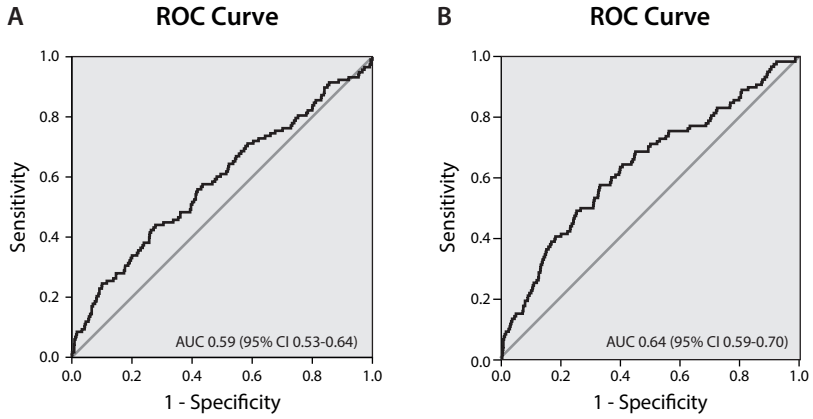

Figure 1: Receiver Operating Characteristic (ROC) curve of prediction model for postpartum hemorrhage, calculated by multivariate analysis. Figure 1a shows model A with antepartum variables and Figure 1b shows model B with antepartum and intrapartum variables.

Results of the multivariable analysis of prognostic 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 prognostic models, we averaged the five imputed predicted risks of each patient, which resulted in one performance estimate. Model A and model B showed moderate discrimination, with an area under the ROC curve of 0.59 (95% CI, 0.53-0.64) and 0.64 (95% CI, 0.59-0.70) (figure 1a and 1b). In addition, calibration was moderate for model A (Hosmer-Lemeshow p-value=0.26) but better for model B (Hosmer-Lemeshow p-value=0.36) (figure 2a and 2b). Figure 2b shows the rates of PPH ranged from 4% (lowest 10 percent) to 22% (highest 10 percent). It might be possible to differentiate between women with low and high risk of developing PPH. Bootstrapping indicated some overfitting with corrected ROC areas under the curve ranging from 0.550 to 0.554 for model A and from 0.607 to 0.612 for model B.

To validate the findings of our analysis, we repeated our analysis with the need for blood transfusion as the outcome. In this analysis, the same 1,132 women were included, of whom 52 (4.6%) needed a blood transfusion. Prepregnancy body mass index (OR 0.94 per kg/m^2, p=0.06), education level (OR 1.7 for higher education level, p=0.09) and hematocrit (OR 0.19 per unit, p=0.002) were independent antepartum prognostic variables of PPH. The intrapartum variables incorporated in the model were gestational age at delivery (OR 1.47 per week, p<0.002) and use of oxytocine (OR 1.57, p=0.15). Model A as well as model B showed moderate discrimination, with areas under the ROC curve of 0.69 (95% CI, 0.62-0.77) for model A and 0.75 (95% CI, 0.68-0.81) for model B. Calibration was also good for both models (Hosmer-Lemeshow p-value: 0.82 for model A and 0.54 for model B) (tables and figures are not shown).

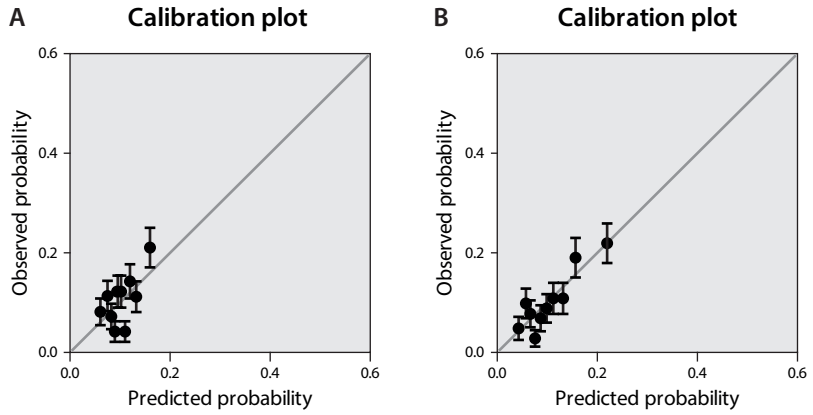

Figure 2: Calibration plot demonstrating the association between the risks of PPH as predicted by the logistic model and the observed PPH for antepartum variables (model A; Figure 2a) and antepartum and intrapartum variables (model B; Figure 2b).

DISCUSSION

In this cohort study we evaluated prognostic variables for PPH in women diagnosed with gestational hypertension or mild preeclampsia beyond 36 weeks of gestation. Whereas antepartum prediction is inaccurate, during delivery women at increased risk of PPH can be identified when prognostic variables in the antepartum period are combined with variables concerning delivery. Antepartum variables included in this model were maternal age, prepregnancy body mass index and women diagnosed with preeclampsia; intrapartum variables were gestational age at delivery, duration of dilatation stage and perineum rupture or episiotomy.

Worldwide, obstetric hemorrhage is a leading cause of maternal mortality and severe maternal morbidity, accounting for 25% of all maternal deaths.[21,22] 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 hemorrhage 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. Moreover, the HYPITAT-trial showed 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 hemorrhage, defined as the need for transfusion of four or more units of red blood cells, or hysterectomy or arterial embolization, was accompanied by preeclampsia in 11.2% of cases.[13] Other studies have also found a significant association between preeclampsia and PPH.[4-8] In

a study on vaginal deliveries, PPH was five times more common in pregnancies with preeclampsia,[5] in two other studies, which were restricted to caesarean deliveries, preeclampsia was associated with about a two-fold higher risk of PPH.[6,8] We suggest that an imbalance between angiogenic and anti-angiogenic factors in the maternal circulation may explain the association between hypertensive disease of pregnancy and PPH. Furthermore hypertension and low platelets may both affect the amount of blood loss negatively. And the association between preeclampsia and coagulopathy may worsen PPH.

Because of the high incidence of PPH in women with pregnancy related hypertensive disorders, we think prediction of PPH in women with gestational hypertension or preeclampsia is of major importance. Moreover, studies describing predictors for PPH in such women are scarce. The data collected in the context of the HYPITAT study offered a good opportunity to identify prognostic variables of PPH, but limitations were also present. The study design faces some weaknesses as it is a secondary data analysis product based on post hoc analysis of data originally collected in a study design with a distinctively different purpose - the HYPITAT study. Second, several prognostic 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.[15] Third, different options for the definition of PPH can be considered. Although blood loss is known to be largely underestimated[23,24] we decided to define PPH as blood loss >1000 ml within 24 hours after delivery,[9,14] because we used this definition in the HYPITAT-trial and it is internationally accepted. Other options to define PPH are transfusion need or drop of hemoglobin level. The latter was considered to be the most objective, but obviously depends on standardised assessment of pre- and post hemorrhage hemoglobin levels, which were not available for all women. Probably the need for blood transfusion was the best option, however this management based criterion depends on local transfusion policies. For a complete overview we repeated our analysis based on the need for transfusion, which showed even better predictability of PPH in women with gestational hypertension or mild preeclampsia (AUC: 75% vs 64%).

Risk factors for PPH in the overall population include high maternal age, maternal obesity, prolonged labor, induced and augmented labor, over distended uterus (high birth weight or macrosomia, multiple pregnancy, hydramnios), abruptio placenta, placenta praevia, preeclampsia, HELLP syndrome, previous caesarean delivery, previous postpartum hemorrhage, episiotomy, operative delivery (especially emergency caesarean delivery) and anemia.[4,6,9,12,25] Many of the above mentioned variables were also found to be independent prognostic variables of PPH in our study, like increased maternal age, preeclampsia, prolonged labor and episiotomy. High birth weight and retained placenta were strongly associated with PPH in univariate analysis. We excluded these variables from multivariable analysis, because of their high association with PPH and since these variables are only known after delivery. Decreased platelets count, labor induction and augmentation with oxytocine were not included in our final model. Augmentation with oxytocine was included in our validated model. Furthermore, multiple pregnancy, placenta 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. Contrary to popular belief, multiparity (para 4+) was not associated with PPH.

Recent studies demonstrate an increase in severe maternal morbidity related to major obstetrical hemorrhage in Western countries.[26-30] Possible explanations for these results include the increasing age of women at birth, the increasing caesarean delivery rate and a high birth weight (macrosomia), which is confirmed in our study. Maternal obesity is an increasingly common lifestyle problem needing public health intervention and it is linked to, diabetes mellitus and macrosomia.[31] In our study, however, a higher prepregnancy BMI lowered the probability of PPH, both in the univariable and multivariable analyses. We cannot explain this contradictory result in our study population, although the relatively high prepregnancy BMI values observed in these women with a pregnancy related hypertensive disorder could play a role.

Most cases of PPH are due to uterine atony and retained placenta.[9] We decided not to include uterine atony or retained placenta as variables in our prognostic model because they are already known as a major attribute of PPH and the phase of performing an active prophylactic postpartum management has already passed. Moreover, uterine atony has to be recognized clinically and is a subjective variable.

The performance of our prediction model was assessed by evaluating discrimination and calibration. The ROC curve showed moderate discriminative capacity for both models. In the assessment of performance of a prediction model, calibration is more important than discriminative capacity. Consequently, the clinical aim of the model is to differentiate between women with low and high risk of PPH. And our data on calibration and internal validation do indicate that model B can distinguish women at low and women at higher risk of developing PPH.

While maternal deaths are extremely rare in the Netherlands, the morbidities associated with PPH remain a major problem and therefore we hope this study will motivate more people to study the cross field of PPH and hypertensive disorders of pregnancy. Our results indicate that PPH can be used as a complimentary indicator to assess the quality of obstetric care. Some of the identified prognostic variables 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 the early postpartum period and active prophylactic or therapeutic techniques can be used. Our modeling results provide a basis for further development of the model, which would involve operationalization *e.g.* by defining threshold values for continuous parameters, to produce a clinically usable model which should also be externally validated.

REFERENCES

1. Sibai BM. Diagnosis and management of gestational hypertension and preeclampsia. Obstet Gynecol. 2003;102:181–92.
2. Khan KS, Wojdyla D, Say L, Gülmezogly AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. Lancet. 2006;367:1066–74.
3. Schutte JM, Steegers EA, Schuitemaker NW, Santema JG, de Boer K, Pel M et al.; The Netherlands Maternal Mortality Committee. Rise in maternal mortality in the Netherlands. BJOG. 2010;117:399–406.
4. Sheiner E, Sarid L, Levy A, Seidman SD, Hallak M. Obstetric risk factors and outcome of pregnancies complicated with early postpartum hemorrhage: a population-based study. J Matern Fetal Neonatal Med. 2005;18:149–54.
5. Combs CA, Murphy EL, Laros RK Jr. Factors associated with postpartum hemorrhage with vaginal birth. Obstet Gynecol. 1991;77:69–76.
6. Combs CA, Murphy EL, Laros RK Jr. Factors associated with postpartum hemorrhage with cesarean deliveries. Obstet Gynecol. 1991;77:77–82.
7. Eskild A, Vatten LJ. Abnormal bleeding associated with preeclampsia: A population study of 315,085 pregnancies. Acta Obstet Gynecol Scand. 2009;88:154–8.
8. Naef RW, Chauhan SP, Chevalier SP, Roberts WE, Meydrech EF, Morrison JC. Prediction of hemorrhage at caesarean delivery. Obstet Gynecol. 1994;83:923–6.
9. Bonnar J. Massive obstetric haemorrhage. Baillieres Best Pract Res Clin Obstet Gynaecol. 2000;14:1–18.
10. American College of Obsteticians and Gynecologists. Practice bulletin. Clinical Management Guidelines for Obstetrician-Gynecologists. Number 76. Postpartum Hemorrhage. Obstet Gynecol. 2006;108:1039–47.
11. Koopmans CM, Bijlenga D, Groen H, Vijgen SMC, Aarnoudse JG, Bekedam DJ et al. Induction of labor versus expectant monitoring for gestational hypertension and preeclampsia after 36 weeks (the HYPITAT trial): a multicenter randomised controlled trial. Lancet. 2009;374:979–88.
12. Stones RW, Paterson CM, Saunders NJ. Risk factors for major obstetric haemorrhage. Eur J Obstet Gynecol Reprod Biol. 1993;48:15–8.
13. Zwart JJ, Richters JM, Öry F, de Vries JIP, Bloemenkamp KWM, van Roosmalen J. Severe maternal morbidity in the Netherlands: a nationwide population based cohort study of 371000 pregnancies. BJOG. 2008;115:842–50.
14. Mousa H, Alfirevic Z. Treatment for primary postpartum haemorrhage. Cochrane Database Syst Rev. 2007;1:CD003249.
15. Van der Heijden GJ, Donders AR, Stijnen T, Moons KG. Imputation of missing values is superior to complete case analysis and the missing-indicator method in multivariable diagnostic research: a clinical example. J Clin Epidemiol. 2006;59:1102–9.
16. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009;338:b2393–b2393.
17. Carpenter JR, Kenward MG. MAR methods for quantitative data. In: Missing data in randomised controlled trials— a practical guide. Birmingham: National Institute for Health Research, 2008 www.hta.nhs.uk/nihrmethodology/reports/1589.pdf.
18. Royston P, Moons KG, Altman DG, Vergouwe Y. Prognosis and prognostic research: Developing a prognostic model. BMJ. 2009;338:b604.

19. Altman DG, Royston P. What do we mean by validating a prognostic model? Stat Med. 2000;19:453–73.
20. R Development Core Team. R: A language and environment for statistical computing. Vienna: R Foundation for Statistical Computing, 2008. ISBN 3-900051-07-0. Available at: http://www.R-project.org. Retrieved November 28, 2008.
21. AbouZahr C. Global burden of maternal death and disability. Br Med Bull 2003;67:1–11.
22. World Health Organization. Maternal Mortality in 2000: Estimates Developed by WHO, UNICEF, and UNFPA. Geneva, World Health Organization, 2004.
23. Patel A, Goudar SS, Geller SE, Kodkany BS, Edlavitch SA, Wagh K et al. Drape estimation vs. visual assessment for estimating postpartum hemorrhage. Int J Gynaecol Obstet. 2006;93:220–4.
24. Zwart JJ, Yazdani ST, Harvey MS, de Vries RRP, van Roosmalen J. Underreporting of major obstetric haemorrhage in the Netherlands. Transfus Med. 2009;20:118–22.
25. Al-Zirqi I, Forsen L, Stray-Pedersen B. Prevalence and risk factors of severe obstetric haemorrhage. BJOG. 2008;115:1265–72.
26. Lewis GG (ed) 2007. The Confidential Enquiry into Maternal and Child Health (CEMACH). Saving mother's lives: reviewing maternal deaths to make motherhood safer – 2003-2005. The Seventh Report on Confidential Enquiries into Maternity Deaths in the United Kingdom. London, CEMACH, 2007.
27. Wen SW, Huang L, Liston R, Heaman M, Baskett T, Rusen ID et al. Severe maternal morbidity in Canada, 1991-2001. CMAJ. 2005;173:759–64.
28. Joseph KS, Rouleau J, Kramer MS, Young DC, Liston RM, Baskett TF. Investigation of an increase in postpartum haemorrhage in Canada. BJOG. 2007;114:751–9.
29. Roberts CL, Ford JB, Algert CS, Bell JC, Simpson JM, Morris JM. Trends in adverse maternal outcomes during childbirth: a population-based study of severe maternal morbidity. BMC Pregnancy Childbirth. 2009;9:7.
30. Kuklina EV, Meikle SF, Jamieson DJ, Whiteman MK, Barfield WD, Hillis SD et al. Severe obstetric morbidity in the United States: 1998-2005. Obstet Gynecol. 2009;113:293–9.
31. Jolly MC, Sebire NJ, Harris JP, Regan L, Robinson S. Risk factors for macrosomia and its clinical consequences: a study of 350,311 pregnancies. Eur J Obstet Gynecol Reprod Biol. 2003;111:9–14.