

# The Role of Platelet Counts in the Assessment of Inpatient Women With Preeclampsia

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## Abstract

**Objective:** Platelet count has been proposed as a screening test for generalized coagulopathy in women with preeclampsia. We performed this study to determine the relationship between platelet counts and the risk of abnormal coagulation and adverse maternal outcomes in women with preeclampsia.

**Methods:** We used data from women in the PIERS (Pre-eclampsia Integrated Estimate of RiSk) database. Abnormal coagulation was defined as either an international normalized ratio result greater than and/or a serum fibrinogen level less than the BC Women's Hospital laboratory's pregnancy-specific normal range. The relationship between platelet counts and adverse maternal outcomes was explored using a logistic regression analysis. The sensitivity, specificity, positive predictive value, and negative predictive value of platelet counts in identifying abnormal coagulation or adverse maternal outcomes were calculated.

**Results:** Abnormal coagulation occurred in 105 of 1405 eligible women (7.5%). The odds of having abnormal coagulation were increased for women with platelet counts  $< 50 \times 10^9/L$  (OR 7.78; 95% CI 3.36 to 18.03) and between 50 and  $99 \times 10^9/L$  (OR 2.69; 95% CI 1.44 to 5.01) compared with women who had platelet counts above  $150 \times 10^9/L$ . Platelet counts  $< 100 \times 10^9/L$  were associated with significantly increased odds of adverse maternal outcomes, most specifically blood transfusion. A platelet count of  $< 100 \times 10^9/L$  had good specificity in identifying abnormal coagulation and adverse maternal outcomes (92% [95% CI 91% to 94%] and 92% [95% CI 91% to 94%], respectively), but poor sensitivity (22% [95% CI 15% to 31%] and 16% [95% CI 11% to 23%], respectively).

**Conclusion:** A platelet count  $< 100 \times 10^9/L$  is associated with an increased risk of abnormal coagulation and maternal adverse outcomes in women with preeclampsia. However, the platelet count should not be used in isolation to guide care because of its poor sensitivity. Whether or not a platelet count is normal should not be used to determine whether further coagulation tests are needed.

## Résumé

**Objectif :** Le recours à la numération plaquettaire a été proposé à titre de test de dépistage visant la coagulopathie généralisée chez les femmes qui présentent une prééclampsie. Nous avons mené cette étude pour déterminer la relation entre les numérations plaquettaires et le risque de coagulation anormale et d'issues maternelles indésirables chez les femmes qui présentent une prééclampsie.

**Méthodes :** Nous avons utilisé des données issues de participantes à la base de données PIERS (*Pre-eclampsia Integrated Estimate of RiSk*). La coagulation anormale a été définie comme étant un résultat de rapport international normalisé se situant au-delà de la plage normale propre à la grossesse du laboratoire du *BC Women's Hospital* et/ou comme étant un taux sérique de fibrinogène se situant en deçà de cette plage. La relation entre les numérations plaquettaires et les issues maternelles indésirables a été explorée au moyen d'une analyse de régression logistique. La sensibilité, la spécificité, le coefficient de prévision d'un test positif et le coefficient de prévision d'un test négatif propres aux numérations plaquettaires pour ce qui est de l'identification d'une coagulation anormale ou d'issues maternelles indésirables ont été calculés.

**Résultats :** Une coagulation anormale s'est manifestée chez 105 des 1 405 femmes admissibles (7,5 %). Les risques de présenter une coagulation anormale étaient accrus chez les femmes qui comptaient des numérations plaquettaires  $< 50 \times 10^9/l$  (RC, 7,78; IC à 95 %, 3,36 - 18,03) et se situant entre 50 et  $99 \times 10^9/l$  (RC, 2,69; IC à 95 %, 1,44 - 5,01), par comparaison

**Key Words:** Preeclampsia, adverse outcomes, coagulation, platelets

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avec les femmes qui comptaient des numérations plaquettaires se situant au-delà de  $150 \times 10^9/l$ . Les numérations plaquettaires  $< 100 \times 10^9/l$  ont été associées à une hausse significative des risques de connaître des issues maternelles indésirables, plus particulièrement une transfusion sanguine. Une numération plaquettaire  $< 100 \times 10^9/l$  présentait une bonne spécificité pour ce qui est de l'identification d'une coagulation anormale et d'issues maternelles indésirables (92 % [IC à 95 %, 91 % - 94 %] et 92 % [IC à 95 %, 91 % - 94 %], respectivement), mais une faible sensibilité (22 % [IC à 95 %, 15 % - 31 %] et 16 % [IC à 95 %, 11 % - 23 %], respectivement).

**Conclusion :** Une numération plaquettaire  $< 100 \times 10^9/l$  est associée à un risque accru de coagulation anormale et d'issues maternelles indésirables chez les femmes qui présentent une prééclampsie. Toutefois, la numération plaquettaire ne devrait pas être utilisée de façon isolée pour orienter les soins, et ce, en raison de sa faible sensibilité. Le caractère normal ou non d'une numération plaquettaire ne devrait pas être utilisé pour déterminer si la tenue d'autres tests de coagulation s'avère requise.

## INTRODUCTION

Preeclampsia is a complex, multi-system disorder that remains a significant cause of maternal morbidity and mortality worldwide.<sup>1</sup> Preeclampsia seems to result from a mismatch between fetoplacental demands and the ability of the maternal uterine blood supply to meet those demands, which leads to the release of vasoactive and innate immune activating substances in the maternal circulation, with subsequent endothelial and innate immune activation.<sup>2,3</sup> This leads to maternal clinical manifestations, which include hypertension, renal and hepatic dysfunction, systemic inflammation, and hematological abnormalities. These hematological abnormalities usually manifest as mild and indolent consumptive coagulopathies, including consumption of platelets, clotting factors, and fibrinogen. Occasionally, these abnormalities become severe, for example manifesting as disseminated intravascular coagulation, which can be life-threatening.<sup>3,4</sup>

The care of women with preeclampsia should be based on the goal of reducing maternal and perinatal risks, two priorities that may be in conflict remote from term. Several studies have supported the use of a platelet count threshold ( $100 \times 10^9/L$ ) above which even women with

severe preeclampsia are unlikely to have abnormalities in aPTT, INR, or serum fibrinogen.<sup>5-7</sup> This threshold has been endorsed by the Society of Obstetricians and Gynaecologists of Canada in the absence of placental abruption.<sup>8</sup> Standardized assessment and surveillance guidelines in British Columbia include the aforementioned laboratory assessments of coagulation, but recommend that aPTT, INR, and serum fibrinogen be measured in every woman with suspected or confirmed preeclampsia; this regimen of investigation is associated with reduced maternal risk.<sup>9,10</sup> Coagulation tests, which are expensive, are generally used to identify bleeding risk prior to Caesarean section or vaginal birth in order to avoid maternal hemorrhage, as well as to identify the risk of epidural hematoma in women requesting neuraxial blockade.<sup>11</sup>

The purpose of this study was to determine the relationship between platelet count and the risk of an abnormal coagulation test (INR or serum fibrinogen) in women with preeclampsia. A secondary aim was to establish the relationship between platelet count or the occurrence of one or more abnormal coagulation test results with blood transfusion and/or other elements of a combined adverse maternal outcome within 48 hours of hospital admission.

## METHODS

The data used for this study were extracted from PIERS database. PIERS is a prospective study of women with preeclampsia admitted to tertiary obstetric centres in which there is a general policy of expectant management of preeclampsia remote from term. Full details of the PIERS methodology have been published elsewhere.<sup>12</sup> Data were collected on women admitted from September 2003 to January 2010 to eight tertiary perinatal centres: four in Canada, two in the United Kingdom, one in New Zealand, and one in Australia. In four sites, until September 2007, women were required to give informed consent for enrolment in PIERS. In three of those four sites (after September 2007), and in all other sites since joining the study, PIERS was conducted as a continuous quality improvement project. The continuous quality improvement project entailed the introduction of predetermined guidelines for the initial assessment and ongoing surveillance of women admitted to hospital with suspected or confirmed preeclampsia. The details of these guidelines have been published elsewhere.<sup>9,10</sup>

Women were included in the PIERS study if they met any one of the following inclusion criteria: (1) BP  $\geq 140/90$  mmHg (on at least two occasions  $\geq 4$  hours apart after 20 weeks' gestation, by any method in the hospital)

## ABBREVIATIONS

aPTT	activated partial thromboplastin time
BP	blood pressure
dBp	diastolic blood pressure
HELLP	hemolysis, elevated liver enzymes, and low platelet
INR	international normalized ratio
PIERS	Pre-eclampsia Integrated Estimate of RiSk
sBP	systolic blood pressure

**Table 1. Characteristics of women in the PIERS study (N = 1405)**

Characteristic	Abnormal coagulation* (n = 105 women)	Normal coagulation (n = 1300 women)	P**
Demographics (within 48h of eligibility)			
Maternal age at EDD (years), median (interquartile range)	30 (26 to 34)	32 (28 to 36)	0.004
Gestational age at eligibility (weeks), median (interquartile range)	32.7 (30.3 to 36.7)	36.4 (33.4 to 38.4)	<0.001
Gestational age at eligibility < 34 weeks, n (%)	59 (56.2)	362 (27.8)	<0.001
Multiple pregnancy, n (%)	10 (9.5)	142 (10.9)	0.657
Parity ≥ 1, n (%)	30 (28.6)	354 (27.2)	0.767
Smoking in this pregnancy, n (%)	15 (14.3)	138 (10.6)	0.336
Preeclampsia description			
Hypertension and proteinuria, n (%)	76 (72.4)	841 (64.7)	0.321
Hypertension and hyperuricaemia, n (%)	11 (10.5)	212 (16.3)	
HELLP without hypertension or proteinuria, n (%)	7 (6.7)	39 (3.0)	
Superimposed preeclampsia, n (%)	11 (10.5)	208 (16.0)	
Clinical (within 48h of eligibility)			
Peak blood pressure (mmHg)			
Mean arterial pressure, median (interquartile range)	121.3 (115.2 to 130.0)	121.3 (115.0 to 130.0)	0.799
sBP, median (interquartile range)	161 (150 to 180)	162 (151 to 178)	0.534
dBp	103 (100 to 110)	102 (98 to 110)	0.740
Worst dipstick proteinuria, median (interquartile range)	2 (1 to 3)	2 (1 to 3)	0.911
Highest aspartate transaminase, median (interquartile range)	37.5 (22 to 84.5)	29 (22 to 42)	0.002
Interventions			
Corticosteroid administration, n (%)	46 (43.8)	348 (26.8)	<0.001
Antihypertensive medications administered, n (%)	78 (74.3)	880 (67.7)	0.163
MgSO <sub>4</sub> administered, n (%)	55 (52.4)	437 (33.6)	<0.001
Pregnancy outcomes			
Admission-to-delivery interval (all cases) (d), median (interquartile range)	2 (1, 6)	2 (1, 5)	0.611
Gestational age at delivery (wk), median (interquartile range)	33.6 (30.6 to 36.9)	37.0 (34.5 to 38.7)	<0.001
Placental abruption, n (%)	3 (2.9)	26 (2.0)	0.473
Birth weight (g), median (interquartile range)	2387 (1270 to 3110)	2635 (1822 to 3270)	0.006
Birth weight < 3rd percentile (n babies) (41), n (%)	9 (8.6)	109 (8.4)	0.949
Intrauterine fetal death (≥ 20+0 wk and/or ≥ 500g), n (%)	1 (0.9)	12 (0.9)	0.976
Neonatal death (before 28d), n (%)	2 (1.9)	14 (1.1)	0.442
Infant death prior to hospital discharge or 6wk, n (%)	2 (1.9)	17 (1.3)	0.611

\*Elevated INR, and/or decreased fibrinogen, compared with normal third trimester range.

\*\*P calculated using Mann-Whitney U for continuous variables and Fisher exact test for categorical except preeclampsia description, which used chi-squared test

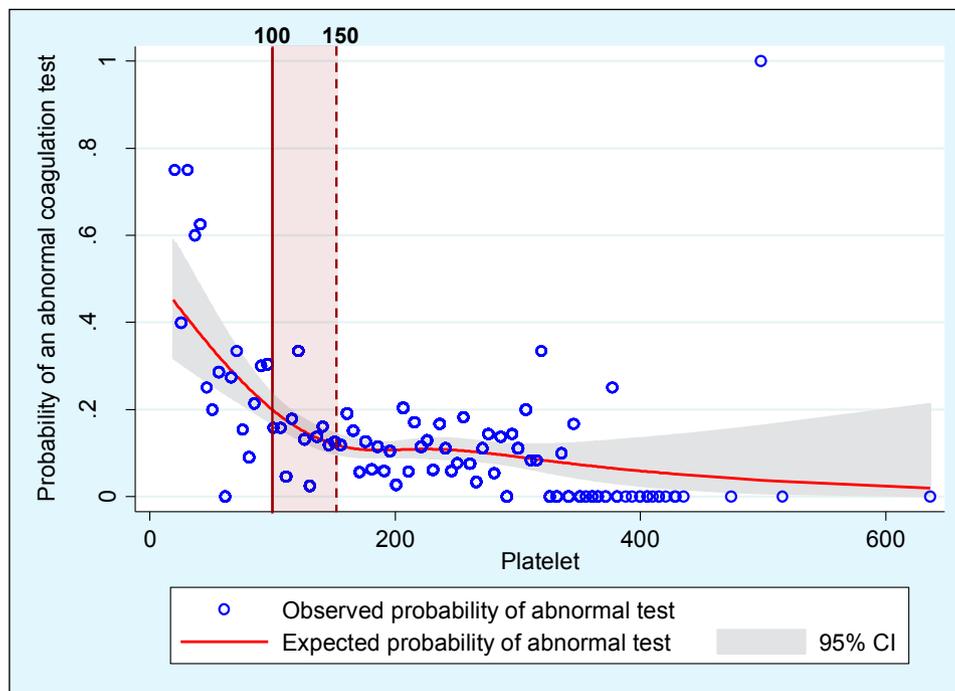
EDD: expected date of delivery

and either proteinuria (of ≥ 2+ by dipstick, ≥ 0.3 g/d by 24-hour urine collection, or > 30 mg/mmol by spot urinary protein:creatinine ratio) or hyperuricemia (greater than local upper limit of normal for non-pregnant individuals); (2) HELLP syndrome even in the absence of hypertension or proteinuria; or (3) superimposed preeclampsia, defined as pre-existing hypertension with accelerated hypertension (as diagnosed by the clinician, or defined as a sBP ≥ 170 mmHg or dBp ≥ 120 mmHg), new proteinuria, or new hyperuricemia. Women were excluded if they were admitted in active labour or if they

achieved any component of the maternal outcome prior to collection of predictors. This inclusive definition was chosen to reflect the variable and multisystem nature of preeclampsia seen in clinical practice.<sup>13-15</sup>

The list of adverse maternal outcomes recorded by PIERS was developed by iterative Delphi consensus<sup>16,17</sup> and includes maternal mortality and any of the following maternal morbidities: hepatic dysfunction, hematoma, or rupture; eclampsia; Glasgow Coma Scale score < 13; stroke; reversible ischemic neurological deficit; transient ischemic

**Platelet versus predicted probability of abnormal coagulation (INR and/or fibrinogen). Platelet count range of 100 to 150 × 10<sup>9</sup>/L indicated by vertical bars and grey shaded area. The points on the graph represent the average observed probability for each platelet count × 10<sup>9</sup>/L. The solid line represents the expected probability of outcome based on a logistic regression model with platelet count fitted as a restricted cubic spline with 5 knots.**



attack; posterior reversible encephalopathy; cortical blindness or retinal detachment; need for positive inotrope support; infusion of a third parenteral antihypertensive; myocardial ischemia or infarction; acute renal insufficiency (in women without prior renal disease)<sup>18</sup>; acute renal failure (in women with prior renal disease)<sup>18</sup>; dialysis; pulmonary edema; oxygen saturation by pulse oximetry < 90%; requirement of  $\geq 50\%$  FiO<sub>2</sub> for > 1 hour; intubation (other than solely for Caesarean section); placental abruption; and transfusion of any blood product.

The lowest platelet count within 48 hours of eligibility was used for analysis. For women with an adverse outcome, the lowest value prior to the occurrence of an adverse outcome was used. Abnormal coagulation was defined as an INR result greater than and/or a serum fibrinogen level less than the third trimester pregnancy ranges at the BC Women's Hospital and Health Centre in British Columbia. These threshold levels are INR > 1.06 and serum fibrinogen < 3.54 g/L. Only women with a platelet count and recorded values for INR and fibrinogen within 12 hours of their relevant platelet count were included in the study. We excluded aPTT from the definition of this outcome because of the high proportion of patients

in whom the test was never performed and also because of the possibility that aPTT could be prolonged by the presence of antiphospholipid antibodies or high doses of heparin given for thromboprophylaxis.

The demographics of women with or without abnormal coagulation were compared using a Mann-Whitney *U* test for continuous variables and a Fisher exact test for categorical variables, except in the case of the description of preeclampsia, for which a chi-squared test was used. To explore the possibility of a non-linear relationship between platelet count and abnormal coagulation, platelet count was modeled as a restricted cubic spline with 5 knots. This allowed a smooth, curvilinear relationship to be generated, which was used to identify logical threshold values for further analysis. Threshold values of 100 × 10<sup>9</sup>/L and 50 × 10<sup>9</sup>/L were also analyzed to be consistent with current clinical practice. The occurrence of each abnormal coagulation test result, any adverse maternal outcome within 48 hours of eligibility for the study, and the need for blood transfusion were assessed using logistic regression. The regression models generated for this study were univariable, and included only platelets or abnormal coagulation as individual predictors. For platelets, the variables were entered into the regression model as

**Table 2. Platelet count among women with preeclampsia and odds of abnormal coagulation or adverse maternal outcome (n = 1405)**

Outcome	Platelet count ( $\times 10^9/L$ )			
	< 50	50 to 99	100 to 149	$\geq 150$
	27	95	273	1010
<b>Abnormal coagulation*</b>				
n (%)	9 (33.3)	14 (14.7)	21 (7.7)	61 (6.0)
OR (95% CI)	7.78† (3.36 to 18.04)	2.69† (1.44 to 5.02)	1.30 (0.78 to 2.17)	reference
<b>Adverse maternal outcome</b>				
n (%)	15 (55.5)	9 (9.5)	26 (9.5)	102 (10.1)
OR (95% CI)	11.32† (5.19 to 24.68)	2.21† (1.36 to 3.58)	1.29 (0.90 to 1.85)	reference
<b>Blood transfusion</b>				
n (%)	12 (44.4)	7 (7.4)	10 (3.7)	31 (3.1)
OR (95% CI)	25.27† (10.92 to 58.47)	2.51† (1.08 to 5.87)	1.20 (0.58 to 2.48)	reference

\*Elevated INR, and/or decreased fibrinogen, compared with normal third trimester range.  
†Marked results found to be significant ( $P < 0.05$ ).

multiple dummy variables, one for each platelet range, with the highest range ( $> 150 \times 10^9/L$ ) used as the reference group. Abnormal coagulation was assessed as a categorical variable that was based on the patient either meeting or not meeting our research definition for abnormal coagulation. We assessed the diagnostic value of different platelet count thresholds by calculating sensitivity, specificity, positive predictive value, and negative predictive value. Statistical analyses were performed using STATA version 10.0 or SPSS version 18.0 (IBM Corp., Somers NY).

Research Ethics Board approval was obtained at all sites.

## RESULTS

Of the 2023 women in the PIERS cohort, 1405 (69.5%) were eligible for this study. Of the 1405 included here, a total of 122 (8.7%) women had a platelet count  $< 100 \times 10^9/L$ , and 105 women (7.5%) had abnormal coagulation as defined by an abnormal INR, serum fibrinogen, or both, on the same blood sample as the worst platelet count. Of those 105 women, 23 (21.9%) had a platelet count  $< 100 \times 10^9/L$ . In total, 152 (10.8%) women had one or more adverse maternal outcomes during their hospital stay. The most common adverse outcomes were a need for blood transfusion, which occurred in 60 women (4.3%) and pulmonary edema, which occurred in 35 women (2.5%). A full list of the PIERS adverse maternal outcomes and rates within the cohort can be found elsewhere.<sup>19</sup>

The baseline characteristics of the women included in the study with and without abnormal coagulation test results

are shown in Table 1. Women with abnormal coagulation test results were younger, had earlier onset of disease (as seen by the lower gestational age at onset and delivery), had higher aspartate transaminase levels, and were more often given corticosteroids and magnesium sulphate. There was no difference between groups in the rate of placental abruption.

The relationship between platelet count and the probability of abnormal coagulation, as assessed using a logistic regression model with platelet count fitted as a restricted cubic spline, is shown in Figure. Using this figure, the additional threshold level of a platelet count of  $150 \times 10^9/L$  was identified for further analysis.

The rates of abnormal coagulation and adverse maternal outcomes corresponding to various platelet count ranges and the odds of outcome occurrence in each of these groups compared with the reference group ( $> 150 \times 10^9/L$ ) are shown in Table 2. The odds of abnormal coagulation were significantly increased among women with a platelet count of  $< 50 \times 10^9/L$  (OR 7.79; 95% CI 3.36 to 18.04) and between 50 and  $99 \times 10^9/L$  (OR 2.69; 95% CI 1.44 to 5.02) compared with women whose platelet count was  $\geq 150 \times 10^9/L$ . Odds of any adverse maternal outcome, and specifically the need for blood transfusion, were also increased with a platelet count  $\leq 50 \times 10^9/L$  or between 50 and  $99 \times 10^9/L$ .

The odds ratios for any adverse maternal outcome or blood transfusion alone were 2.55 (95% CI 1.55 to 4.19) and 3.77 (95% CI 1.97 to 7.21), respectively in women with

**Table 3. Utility of platelet counts in identifying abnormal coagulation or adverse maternal outcomes in women with preeclampsia**

Outcome	Test	Sensitivity, % (range)	Specificity, % (range)	PPV, % (range)	NPV, % (range)
Abnormal coagulation*	Platelet < 100 × 10 <sup>9</sup> /L	21.9 (14.6 to 31.2)	92.4 (90.8 to 93.7)	18.8 (12.6 to 27.2)	93.6 (92.1 to 94.9)
	Platelet < 150 × 10 <sup>9</sup> /L	41.9 (32.5 to 51.9)	73.0 (70.5 to 75.4)	11.1 (8.3 to 14.8)	94.0 (92.3 to 95.3)
Adverse maternal outcome†	Platelet < 100 × 10 <sup>9</sup> /L	15.8 (10.6 to 22.8)	92.2 (90.5 to 93.6)	19.7 (13.2 to 28.1)	90.0 (88.2 to 91.6)
	Platelet < 150 × 10 <sup>9</sup> /L	32.9 (25.6 to 41.0)	72.5 (69.9 to 74.9)	12.7 (9.6 to 16.4)	89.9 (87.8 to 91.7)
Blood transfusion	Platelet < 100 × 10 <sup>9</sup> /L	31.7 (20.6 to 45.1)	92.3 (90.8 to 93.7)	15.6 (9.9 to 23.5)	96.8 (95.6 to 97.7)
	Platelet < 150 × 10 <sup>9</sup> /L	48.3 (35.4 to 61.5)	72.8 (70.3 to 75.1)	7.3 (5.1 to 10.5)	96.9 (95.6 to 97.9)
Adverse maternal outcome†	Abnormal coagulation*	15.1 (10.0 to 22.1)	93.5 (91.9 to 94.7)	21.9 (14.7 to 31.2)	90.1 (88.3 to 91.6)
Blood transfusion	Abnormal coagulation*	21.7 (12.5 to 34.5)	93.2 (91.6 to 94.4)	12.4 (7.0 to 20.6)	96.4 (95.2 to 97.3)

NPV: negative predictive value; PPV: positive predictive value

\*Elevated INR and/or decreased fibrinogen, compared with normal third trimester range.

†See text for details.

one or more than one abnormal coagulation test results compared with those with normal coagulation test results.

We performed a sensitivity analysis examining only non-hematological outcomes, and found a significant association between a platelet count < 50 × 10<sup>9</sup>/L and the outcome (OR 5.68; 95% CI 1.85 to 17.45). A sensitivity analysis was also performed, grouping cases by diagnosis at enrolment (hypertension and proteinuria or HELLP, hypertension and hyperuricaemia, and superimposed preeclampsia), and a similar association with all outcomes was found (data not shown).

The efficiency of using platelet count thresholds of 100 × 10<sup>9</sup>/L and 150 × 10<sup>9</sup>/L to identify women with abnormal coagulation, the PIERS combined adverse maternal outcome, or the need for blood transfusion specifically is shown in Table 3, presenting the sensitivity, specificity, positive predictive value, and negative predictive value. The ability of abnormal coagulation test results to predict the PIERS combined adverse maternal outcome or blood transfusion alone is also shown in Table 3. All tests showed negative predictive value and specificity > 90%, but low sensitivity and positive predictive value.

## DISCUSSION

Within our cohort of 1405 women with preeclampsia admitted to tertiary perinatal units, thrombocytopenia, defined by a platelet count < 150 × 10<sup>9</sup>/L, occurred in 395

women (28.1%). Abnormal coagulation test results were unusual in the study cohort, occurring in only 105 women (7.5%). This is consistent with previous studies and reports.<sup>5-7,20-23</sup> In addition, platelet counts < 100 × 10<sup>9</sup>/L were found to be associated with abnormal coagulation test results. As clinicians would expect, both low platelet counts and abnormal coagulation were associated with an increased risk of adverse maternal outcome(s) or blood transfusion specifically.

Our finding that a platelet count < 100 × 10<sup>9</sup>/L was not a sensitive indicator of abnormal coagulation was surprising. Even if a platelet count < 150 × 10<sup>9</sup>/L was used as the threshold for a positive test, only 42% of women with abnormal coagulation would have been correctly identified. It is important to note that of the 1283 women with a platelet count > 100 × 10<sup>9</sup>/L (91.3% of the study cohort), 82 (6.4%) had the outcome of abnormal coagulation. Although this is significantly less than the rate of abnormal coagulation found in women with platelet counts < 100 × 10<sup>9</sup>/L in this population (18.9%), it may be clinically significant, given the association found between abnormal coagulation and the adverse maternal outcomes. These results do not fully support the findings of Leduc et al.<sup>7</sup> who studied 100 women with severe preeclampsia and concluded that abnormal coagulation (defined by low serum fibrinogen or elevated aPTT) was always associated with thrombocytopenia. Other similar

studies resulted in the same conclusion for women with severe preeclampsia.<sup>5,6,22</sup> The differences in our results are likely due to our larger sample size and may also have been affected by the inclusion in our cohort of women with mild as well as severe disease.

Defining adequate sensitivity and specificity for a screening test to be used in clinical practice requires that we consider the implications of false-positive or false negative results.<sup>24,25</sup> In clinical practice, the platelet count is recommended as a screening test in women with hypertension in pregnancy to determine if further tests of coagulation are required. With a high false-negative rate, and consequently low sensitivity, platelet count screening would result in women with abnormal coagulation not being identified before interventions such as Caesarean section or neuraxial anaesthesia. When clinicians are aware of coagulation abnormalities, they will adjust practice to, for example, place an abdominal drain after a Caesarean section or withhold neuraxial anaesthesia. Although we did not have any complications of epidural anaesthesia in our cohort, this is likely because all women had tests of coagulation, beyond the platelet count, performed as part of their routine surveillance.

A high false-positive rate, in this case, would mean more women would undergo further coagulation tests (fibrinogen, aPTT, INR) than necessary, but this would not necessarily affect clinical practice adversely. Having high sensitivity is critical, more so than having high specificity. In our study, neither a cut-off platelet count of  $< 100 \times 10^9/L$  nor one of  $< 150 \times 10^9/L$  had great sensitivity for predicting abnormal coagulation. Even if the upper limit of confidence intervals around the point estimates of sensitivity was correct, we would still identify only 30% to 50% of women with abnormal coagulation. Given the consequences of a missed positive test, this yield is not adequate.

The situation is similar when considering the use of the platelet count as an independent predictor of adverse maternal outcomes. Failing to identify women who are at great risk of an adverse outcome could result in significant morbidity and possibly even mortality. This is particularly relevant when managing women in rural and remote settings. On the other hand, over-identifying women at risk may lead to unnecessary interventions and, in the case of early onset disease, iatrogenic prematurity and increased risk to the fetus. In this case, both a high sensitivity and high specificity would be required to make a treatment decision.

Using a cut-off platelet count of  $< 100 \times 10^9/L$  resulted in high specificity when predicting adverse maternal outcomes or blood transfusion alone, but low sensitivity

(16% for any adverse maternal outcome and 32% for blood transfusion alone). The high negative predictive value and specificity are likely due to the low incidence of adverse outcomes in the population and are not truly reflective of the efficacy of the test. Similar results were found when abnormal coagulation was used as a predictor of adverse maternal outcomes.

When the efficacy of abnormal coagulation as a predictor of adverse maternal outcomes was compared with platelet count based on sensitivity, specificity, negative predictive value and positive predictive value, we found no difference. This implies that measuring INR or serum fibrinogen does not add any clinical advantage to testing for platelet count alone in these cases. This argument is further strengthened by the results of the fullPIERS model. When coagulation tests and platelet count were evaluated among several other candidate predictor variables for inclusion in the fullPIERS model, platelet count remained in the model, while coagulation tests did not.<sup>26</sup> The final variables in the fullPIERS model were gestational age at onset of preeclampsia, occurrence of chest pain or dyspnea, oxygen saturation by pulse oximetry, serum creatinine level, platelet count, and aspartate transaminase level.<sup>26</sup>

A limitation of this study is that we did not collect data on the presence of either inherited or acquired thrombophilias in past medical history. This was because in our interim analysis of the first 1250 women in the total PIERS cohort we did not find any relationship between history of thrombophilia and adverse maternal outcome in women who were admitted with preeclampsia. This does not address the issue of whether or not thrombophilias and preeclampsia coaggregate,<sup>3</sup> but it does suggest that thrombophilias do not add incrementally to the maternal risks of preeclampsia after the diagnosis has been made.

In addition, aPTT results and information on antiphospholipid antibodies were excluded from the definition of abnormal coagulation in this study because they were not uniformly performed on women in the PIERS cohort. Antiphospholipid antibodies have been reported as prevalent (10% to 30%) among women with preeclampsia.<sup>27,28</sup> Excluding aPTT from our definition of the outcome “abnormal coagulation” was felt to be appropriate because clinicians clearly did not feel it was an important investigation.

A second limitation of the study is that it had only sufficient statistical power to investigate the relationship between platelet count at a single time point and abnormal coagulation test results or need for blood transfusion, taken to be surrogates of the true risk of significant

hematological complications. Clinicians must also consider the rate of change of platelet counts over time, but we were unable to address this in our study. The PIERS combined adverse maternal outcome is also inadequate as a surrogate marker of hematological complications. Although this combined outcome was rigorously defined for the development of the PIERS models, it reflects outcomes of preeclampsia as a whole, not necessarily specific to hematological complications. The strength of modelling against the PIERS combined outcome in this study is that this reflects the real world clinical concerns associated with preeclampsia.

One strength of this study is that the data come from a large, international database of well-characterized women with rigorously defined preeclampsia. This allowed us to examine each sub-group of preeclampsia. This adds to previous studies in which the relationship between platelet count and abnormal coagulation was observed only in cases of severe preeclampsia, however defined. An additional strength of our study is that, in contrast to previous studies, we also investigated the association between platelet count and adverse maternal outcome, specifically the need for blood transfusion. Beyond identifying risk in order to guide clinical management, coagulation testing is also performed to identify women who may be at risk of epidural hematoma associated with epidural analgesia. In previous studies using thromboelastography to assess the relationship between platelet count and abnormal coagulation, a platelet count  $< 100 \times 10^9/L$  was associated with hypocoagulation in women with severe preeclampsia.<sup>5,29</sup> None of the women in these studies who received epidural analgesia had complications. In our population, neuraxial anaesthesia was used in 89.4% of women with a platelet count  $< 100 \times 10^9/L$ , and no complications, including epidural hematoma, were seen. However, we had no information about the timing of induction of neuraxial anaesthesia in relation to platelet count or the presence of the abnormal coagulation tests. Our findings support the opinion that regional anaesthesia should not be withheld from women solely because of a platelet count  $< 100 \times 10^9/L$ .<sup>11</sup>

## **CONCLUSION**

This study confirms that, among women admitted to hospital with preeclampsia, there is a significant association between both a platelet count  $< 100 \times 10^9/L$  and abnormal coagulation test results and an increased risk of adverse maternal outcome, or blood transfusion specifically. While a platelet count  $< 100 \times 10^9/L$  should alert caregivers to the real possibility of generalized coagulopathy, a normal

platelet count alone should not be used as an effective “rule out” test for mild or moderate coagulopathy because of the low sensitivity of this test.

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## REFERENCES

1. Hogan MC, Foreman KJ, Naghavi M, Ahn SY, Wang M, Makela SM, et al. Maternal mortality for 181 countries, 1980–2008: a systematic analysis of progress towards Millennium Development Goal 5. *Lancet* 2010;375:1609–23.
2. Silasi M, Cohen B, Karumanchi SA, Rana S. Abnormal placentation, angiogenic factors, and the pathogenesis of pre-eclampsia. *Obstet Gynecol Clin North Am* 2010;37:239–53.
3. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. *Lancet* 2010;376:631–44.
4. von Dadelszen P, Magee LA, Lee SK, Stewart SD, Simone C, Koren G, et al. Activated protein C in normal human pregnancy and pregnancies complicated by severe pre-eclampsia: a therapeutic opportunity? *Crit Care Med* 2002;30:1883–92.
5. Sharma SK, Philip J, Whitten CW, Padakandla UB, Landers DF. Assessment of changes in coagulation in parturients with pre-eclampsia using thromboelastography. *Anesthesiology* 1999;90:385–90.
6. Kramer RL, Izquierdo LA, Gilson GJ, Curet LB, Qualls CR. “Preeclamptic labs” for evaluating hypertension in pregnancy. *J Reprod Med* 1997;42:223–8.
7. Leduc L, Wheeler JM, Kirshon B, Mitchell P, Cotton DB. Coagulation profile in severe pre-eclampsia. *Obstet Gynecol* 1992;79:14–8.
8. Magee LA, Helewa ME, Moutquin JM, von Dadelszen P, Cardew C, Cote AM, et al. Diagnosis, evaluation and management of the hypertensive disorders of pregnancy. SOGC Clinical Practice Guidelines, No. 206, March 2008. *J Obstet Gynaecol Can* 2008;30(3 Suppl 1):S1–S48.
9. Menzies J, Magee LA, Li J, MacNab YC, Yin R, Stuart H, et al. Instituting surveillance guidelines and adverse outcomes in pre-eclampsia. *Obstet Gynecol* 2007;110:121–7.
10. von Dadelszen P, Sawchuck D, McMaster R, Douglas MJ, Lee SK, Saunders S, et al. The active implementation of pregnancy hypertension guidelines in British Columbia. *Obstet Gynecol* 2010;116:659–66.
11. Gogarten W. Pre-eclampsia and anaesthesia. *Curr Opin Anaesth* 2009;22:347–51.
12. von Dadelszen P, Payne B, Li J, Ansermino JM, Broughton-Pipkin F, Cote AM, et al. Predicting adverse maternal outcomes in pre-eclampsia: the fullPIERS model—development and validation. *Lancet* 2011;377:185–6.
13. Barton JR, O'Brien JM, Bergauer NK, Jacques DL, Sibai BM. Mild gestational hypertension remote from term: progression and outcome. *Am J Obstet Gynecol* 2001;184:979–83.
14. Homer CS, Brown MA, Mangos G, Davis GK. Non-proteinuric pre-eclampsia: a novel risk indicator in women with gestational hypertension. *J Hypertens* 2008;26:295–302.
15. Sibai BM, Stella CL. Diagnosis and management of atypical pre-eclampsia-eclampsia. *Am J Obstet Gynecol* 2009;200:481.e1–481.e7.
16. Milholland AV, Wheeler SG, Heieck JJ. Medical assessment by a Delphi group opinion technic. *N Engl J Med* 1973;288:1272–5.
17. Hutchinson A, Fowler P. Outcome measures for primary health-care: what are the research priorities? *Br J Gen Pract* 1992;42:227–31.
18. Bellomo R, Kellum JA, Ronco C. Defining and classifying acute renal failure: from advocacy to consensus and validation of the RIFLE criteria. *Intensive Care Med* 2007;33:409–13.
19. PIERS Project Resource. Full definitions of maternal adverse outcomes. Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of the fullPIERS model. Available at: <http://piers.cfri.ca/Resources.aspx>. Accessed July 7, 2011.
20. Valera M, Parant O, Vayssiere C, Arnal J, Payrastre B. Physiologic and pathologic changes of platelets in pregnancy. *Platelets* 2010;21:587–95.
21. Prieto JA, Mastrobattista JM, Blanco JD. Coagulation studies in patients with marked thrombocytopenia due to severe pre-eclampsia. *Am J Perinatol* 1995;12:220–2.
22. Barron WM, Heckerling P, Hibbard JU, Fisher S. Reducing unnecessary coagulation testing in hypertensive disorders of pregnancy. *Obstet Gynecol* 1999;94:364–70.
23. Harlow FH, Brown MA, Brighton TA, Smith SL, Trickett AE, Kwan YL, et al. Platelet activation in the hypertensive disorders of pregnancy. *Am J Obstet Gynecol* 2002;187:688–95.
24. Bewick V, Cheek L, Ball J. Statistics review 14: logistic regression. *Crit Care* 2005;9:112–8.
25. Anderson RP, Jin RY, Grunkemeier GL. Understanding logistic regression analysis in clinical reports: an introduction. *Ann Thorac Surg* 2003;75:753–7.
26. von Dadelszen P, Payne B, Li J, Ansermino JM, Pipkin FB, Cote AM, et al. Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of the fullPIERS model. *Lancet* 2011;377:219–27.
27. Saha SP, Bhattacharjee N, Ganguli RP, Sil S, Patra KK, Sengupta M, et al. Prevalence and significance of antiphospholipid antibodies in selected at-risk obstetrics cases: a comparative prospective study. *J Obstet Gynaecol* 2009;29:614–8.
28. Romero R, Mazon M, Lockwood CJ, Emamian M, Belanger KP, Hobbins JC, et al. Clinical significance, prevalence, and natural history of thrombocytopenia in pregnancy-induced hypertension. *Am J Perinatol* 1989;6:32–8.
29. Orlikowski CEP, Rocke DA, Murray WB, Gouws E, Moodley J, Kenoyer DG, et al. Thrombelastography changes in pre-eclampsia and eclampsia. *Br J Anaesth* 1996;77:157–61.