

# Preoperative predictors of thrombocytopenia in Caesarean delivery: is routine platelet count testing necessary?

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**Background:** Peri-partum thrombocytopenia significantly impacts anaesthetic technique and increases the risk of perioperative bleeding. However, as less than 5% of normal pregnancies have significant thrombocytopenia, routine platelet testing incurs great cost for a relatively low yield. Determining whether clinical predictors, in particular HIV status, are associated with thrombocytopenia may assist clinicians in rationalising preoperative testing.

**Methods:** This was a prospective, observational, single-centre study at a South African regional hospital. We evaluated five variables as candidate predictors for mild preoperative thrombocytopenia (< 150 000/μl) in patients scheduled for both elective and emergency Caesarean delivery: HIV status, pre-eclampsia, urgency of surgery, renal impairment and liver failure. As a sub-analysis we compared the incidence of moderate thrombocytopenia (< 100 000/μl) in HIV-positive patients, with HIV-negative patients.

**Results:** We recruited 1 015 patients to this study. The incidence of mild thrombocytopenia was 10.3% (105/1 015). Only pre-eclampsia was predictive of mild thrombocytopenia (odds ratio 3.51;  $p < 0.01$ ; 95% confidence interval 2.12–5.82). The incidence of moderate thrombocytopenia was not influenced by HIV status (occurring in 1.5% of HIV-positive patients versus 1.8% in HIV-negative patients;  $p = 0.716$ ).

**Conclusions:** In this study of predominantly asymptomatic patients scheduled for Caesarean delivery, only pre-eclampsia was predictive of mild thrombocytopenia. In sub-analysis HIV status was not independently associated with moderate thrombocytopenia. All asymptomatic patients, including those who were HIV positive, had platelet counts > 70 000/μl.

**Keywords:** Caesarean delivery, HIV, obstetrics, pregnancy, thrombocytopenia

## Introduction

Thrombocytopenia in pregnancy can be classified as mild, moderate or severe, with platelet counts of between 100 000 and 150 000/μl, 50 000 and 100 000/μl and < 50 000/μl respectively.<sup>1</sup> Mild thrombocytopenia is a common haematological abnormality in pregnancy, occurring in 5–8% of parturients,<sup>2</sup> while moderate thrombocytopenia (< 100 000 /μl) occurs in approximately 1.8% of pregnancies.<sup>3</sup> This has important perioperative implications regarding mode of anaesthesia and potential requirements for platelet transfusion during surgery. South African state hospitals represent a resource-limited environment. Routine preoperative blood tests are associated with increased avoidable healthcare costs, particularly in healthy patients.<sup>4</sup> Preoperative prediction of thrombocytopenia has been incompletely explored in our context, particularly with regard to HIV status as a predictor of thrombocytopenia. The primary aim of our study was to assess predictors for mild thrombocytopenia in the pregnant patient, and our secondary aim was to further examine the role of HIV status as a predictor for mild and moderate thrombocytopenia.

## Methods

We conducted a prospective, observational study at Edendale Hospital, a regional hospital in KwaZulu-Natal, South Africa. Institutional and Department of Health approval was obtained (KZ\_2016RP30\_643) and the University of KwaZulu-Natal Bio-Ethics Committee granted ethical approval (BE478/15). Informed written consent was obtained from all patients.

## Patients and setting

We included all patients scheduled for elective and emergency Caesarean delivery (CD) who were at least 18 years old. Recruitment occurred from May 2016 until February 2017. All patients were required to have a recent full blood count (FBC), taken within the last month. Where no FBC had been taken, this was done prior to theatre; however, in accordance with departmental protocol, no patient was delayed for results purely for study purposes. Decisions to proceed with surgery without blood results were left to the attending clinicians based on the clinical scenario. Data were collected in real time by the attending anaesthetist using the collection review form attached to the consent form. Completed data forms were handed to the senior anaesthetist supervising the obstetric theatres, who forwarded them to one of the investigators in the study for storage in a secure area. Patients were allocated a study number; data were verified by study investigators, and entered into a Microsoft Excel spreadsheet (Microsoft Corporation, Redmond, WA, USA). Names of patients were not recorded in the database, and blood results were later cross-checked from the National Health Laboratory Service (NHLS) system using laboratory numbers. Participants under the age of 18, without consent, or those without blood results were excluded from the study.

We sought to evaluate five candidate variables: HIV status, pre-eclampsia, urgency of surgery, renal impairment, and liver failure, as possible predictors of mild thrombocytopenia. Liver failure was defined by the attending physician, based on clinical assessment and laboratory investigations. Renal impairment was

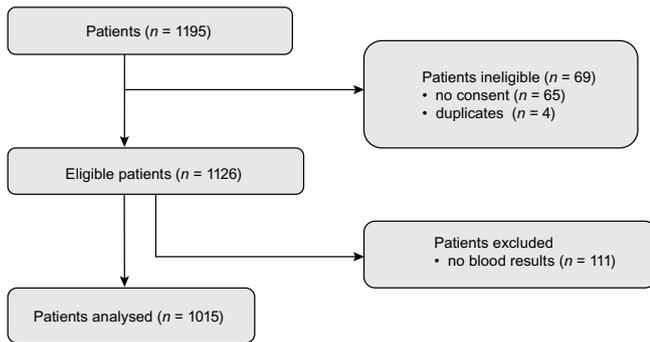


Figure 1: Patient flow chart.  
Note: n = number.

defined using the Kidney Disease Improving Outcomes (KDIGO) classification.<sup>5</sup> HIV status and CD4 count results were obtained from antenatal booking booklets and confirmed by participating women. Patients with unknown HIV status were tested on admission as part of routine obstetric care.

### Statistical analysis

We estimated the incidence of mild thrombocytopenia (< 150 000/ $\mu$ l) to be approximately 7.5%. To avoid model over-fitting it is suggested to have at least 10–15 events per variable tested in a regression model.<sup>6,7</sup> To evaluate five variables, we therefore required 75 events and 1 000 patients. The primary outcome was to assess preoperative predictors of mild thrombocytopenia (< 150 000/ $\mu$ l). The secondary outcome was to compare the incidence of moderate thrombocytopenia (< 100 000/ $\mu$ l) in otherwise well HIV-positive women with that in HIV-negative women.

Baseline characteristics of the patients were reported as mean (standard deviation [SD]) for continuous normally distributed variables; median and range for data not normally distributed; and count (percent) for categorical variables. Comparisons between normally distributed continuous data were done using Student's t-test, and for data not normally distributed, the Wilcoxon Mann-Whitney test was used. Categorical data was analysed using the chi-square test. The Shapiro-Wilk test was used for normality testing. For all analysis a *p*-value of < 0.05 defined statistical significance and the acceptable power was 80%.

To address the primary endpoint we first determined the proportion of patients who had mild thrombocytopenia, together with associated 95% confidence intervals. We then performed multivariate binary logistic regression analysis using the candidate variables to determine their association with the primary outcome. We assessed collinearity using the variance inflation factor (VIF), and we considered variables with VIF > 10 collinear. For the regression model, we reported the odds ratios (OR), corresponding standard error, 95% confidence intervals (CI) and associated *p*-values. We reported *p*-values to 3 decimal places, with *p*-values less than 0.001 reported as *p* < 0.001. We then applied the model for the prediction of mild thrombocytopenia and tested its validity for the prediction of moderate thrombocytopenia.

To assess the secondary endpoint we first determined the proportion of patients who had moderate thrombocytopenia. We then performed a chi-square test to analyse an association with HIV status.

Table 1: Incidence of thrombocytopenia by category among Caesarean delivery patients

Platelet cut-off	Total (n = 1 015)	Standard error	95% confidence interval
< 150 000/ $\mu$ l	105 (10.3%)	0.01	8.61–12.38
< 100 000/ $\mu$ l	17 (1.7%)	< 0.01	1.04–2.68
< 75 000/ $\mu$ l	10 (1%)	< 0.01	0.53–1.82
< 50 000/ $\mu$ l	5 (0.5%)	< 0.01	0.2–1.18

Note: n = number.

Table 2: Incidence of candidate risk prediction variables among caesarean delivery patients

Candidate variable	Total (n = 1 015)	Standard error	95% confidence interval
HIV positive	522 (51.4%)	0.02	48.35–54.50
Pre-eclampsia	117 (11.5%)	0.01	9.7–13.65
Renal impairment	5 (0.5%)	< 0.01	0.2–1.18
Liver failure	2 (0.2%)	< 0.01	0.05–0.79
Urgency of surgery	609 (60%)	0.02	56.95–62.98

Notes: HIV = human immunodeficiency virus, n = number.

### Results

The patient flow diagram is shown in Figure 1. The final analysis included 1 015 eligible patient from the possible 1 195 patients (85%). We recruited 406 of 446 eligible elective CD (91%) and 609 of 739 eligible emergency CD (82.4%).

Median patient age was 27 years (range 18–44). Median gravidity was 2 (range 1–11), parity 1 (range 0–9) and median gestational age 38 (range 20–44). Mild thrombocytopenia was present in 105/1 015 patients (10.3%, 95% CI 8.61–12.38).

The incidences of thrombocytopenia measured by differing clinically relevant cut-offs are reported in Table 1. The incidences of the candidate risk prediction variables, together with their 95% CI, are reported in Table 2.

The results of the multivariate binary logistic regression analysis are given in Table 3. There was no collinearity between candidate variables.

Pre-eclampsia predicted moderate thrombocytopenia (10/117 [8.5%] vs. 7/898 [0.8%]; *p* < 0.001). HIV-positive patients constituted 522/1 015 (51.4%). Moderate thrombocytopenia (platelets < 100 000/ $\mu$ l) was present in 17/1 015 (1.7%) of all patients (CI 1.04–2.68). There was no difference in the proportion of moderate thrombocytopenia, comparing HIV-positive patients (8/522; 1.5%) with HIV-negative patients (9/493; 1.8%); (*p* = 0.716). Only one patient was not on antiretroviral treatment (1/522; 0.2%) and the mean CD4 count was 490 cells/ $\mu$ l (range 20–1 302). Post-hoc exploratory analysis to determine a possible relationship between CD4 count and thrombocytopenia was negative.

Of the 17 patients with moderate thrombocytopenia, 13 had significant risk factors (10 pre-eclampsia, two antepartum haemorrhage, and one pre-existing thrombocytopenia). All patients with no significant preoperative comorbidities had platelet counts of > 70 000/ $\mu$ l. Two out of five patients with renal failure, and

Table 3: Multivariate binary logistic regression analysis of candidate variables for mild thrombocytopenia

Mild thrombocytopenia	Odds ratio	Standard error	p-value	95% confidence interval
HIV status	0.67	0.14	0.062	0.44–1.02
Pre-eclampsia	3.51	0.90	< 0.001*	2.12–5.82
Urgency of surgery	1.33	0.31	0.234	0.83–2.11
Renal impairment	3.70	3.64	0.184	0.54–25.43
Liver failure	1.23	1.93	0.896	0.06–26.77

Note: HIV = human immunodeficiency virus.

\*Denotes statistical significance.

one out of two with liver failure had moderate thrombocytopenia. All three patients with moderate thrombocytopenia in these two categories presented initially with eclampsia.

### Discussion

This study aimed to identify preoperative predictors of mild thrombocytopenia (platelets < 150 000/ $\mu$ l) using readily available clinical parameters as candidate variables. The overall incidence of mild thrombocytopenia was 10.3%, slightly higher than the normal range of 5–8%.<sup>2</sup> In this group, only pre-eclampsia predicted mild thrombocytopenia.<sup>8</sup> The incidence of moderate thrombocytopenia (platelets < 100 000/ $\mu$ l) was 1.7%; this is similar to the 1.8% found in a retrospective study of over 20 000 patients.<sup>3</sup> Furthermore, HIV status was not shown to be a predictor of either mild or moderate thrombocytopenia, and was not associated with moderate thrombocytopenia. Importantly, in all patients without any risk factors (i.e. renal failure, sepsis, HIV status, liver failure, or pre-eclampsia), the platelet count was > 70 000/ $\mu$ l.

Gestational thrombocytopenia is the most common cause of a low platelet count and typically accounts for 75–80% of mild thrombocytopenia in parturients.<sup>2,8</sup> Hypertensive disorders are the second most common cause, accounting for up to 20% of cases. Immune-mediated thrombocytopenia accounts for up to 4% of cases, with remaining causes being much rarer. We elected to evaluate five variables for their association with mild thrombocytopenia, specifically targeting readily available clinical parameters.

Pre-eclampsia is a known risk factor for thrombocytopenia, and the incidence of pre-eclampsia in our study was 11.5%. This is higher than the estimated prevalence of 2–8%,<sup>9</sup> likely due to the fact that we conducted our study in a referral centre. This prevalence partly explains the higher incidence of both mild and moderate thrombocytopenia. Both renal and hepatic failure constitute rarer conditions: we felt it important to include these conditions in our analysis due to the relative ease of diagnosis preoperatively. We also included urgency of surgery as a separate variable due to the fact that it is often in these cases that debate occurs regarding the need for preoperative FBC. Finally, we included HIV status in both the primary outcome and the secondary outcome because there is still a paucity of data regarding its association with thrombocytopenia.

Many anaesthetists request an FBC in order to evaluate preoperative platelet count. This is particularly important given that spinal anaesthesia is currently regarded as standard of care. Most authors feel that spinal anaesthesia is permissible with a platelet count of > 75 000/ $\mu$ l,<sup>3,10–12</sup> with some suggesting that even a count > 50 000/ $\mu$ l may be acceptable in the non-pre-

eclamptic patient.<sup>13</sup> Mild thrombocytopenia is therefore not necessarily a clinically relevant end-point. However, as our study suggests, the incidence of moderate thrombocytopenia is less than 2% and this would have necessitated a prohibitively large study to evaluate the variables we chose. In addition, if a variable such as HIV status is not associated with mild thrombocytopenia, it is unlikely that it would be associated only with moderate thrombocytopenia. Further, only 4/1015 patients (0.4%) had a platelet count below 100 000/ $\mu$ l without a clear preoperative reason for this. All of these asymptomatic patients had platelet counts in excess of 70 000/ $\mu$ l and underwent uneventful spinal anaesthesia.

While previous work suggested that HIV-positive patients were prone to thrombocytopenia,<sup>14</sup> few studies have examined the association of HIV status with thrombocytopenia in pregnancy. Despite this evidence gap, it is often listed as a potential cause of maternal thrombocytopenia.<sup>2</sup> Sebitloane conducted a retrospective analysis of a prospective trial (data collection 2005–2007) on 1 311 low-risk obstetric patients.<sup>15</sup> Enrolled patients were not receiving anti-retroviral treatment, as this was not standard of care at this time, and the overall incidence of mild thrombocytopenia was 5.3%, which is lower than the 10.3% in our study. This was likely due to the exclusion of pre-eclamptic patients in the Sebitloane study. Despite not being treated for HIV, there was no association between HIV status and thrombocytopenia, and severity of immunosuppression was not linked to thrombocytopenia. In our study, the mean CD4 count when comparing HIV-positive and -negative patients was similar (490 versus 453); in the HIV group only one patient was not taking anti-retroviral treatment. We also did not limit our study to low-risk patients. Despite these differences, our prospective study confirms the findings of this retrospective analysis.

We were unable to evaluate the incidence of conditions such as gestational thrombocytopenia and immune-mediated thrombocytopenia (these are largely diagnoses of exclusion and require follow-up FBC) owing to logistical considerations. However, our results are applicable to South African regional hospitals, where the majority will be able to access renal and liver function tests. There may have been data entry errors; this was mitigated by confirmation of data entry points by the study investigators, in addition to checking laboratory results through hospital numbers. We excluded 111 patients without blood results. Successful recruitment was lower in the emergency group, possibly reflecting clinical urgency. It is possible that this group is slightly under-represented; however, 60% of patients were scheduled for emergency CD. Our study protocol also allowed for FBCs to be taken within one month of the scheduled operation; this would potentially allow for significant changes in platelet levels preoperatively. However, 98% (995/1015) of FBCs in our study were taken within the week preceding CD. We thus feel it unlikely that our results were significantly affected.

### Conclusions

In this study of predominantly asymptomatic patients scheduled for Caesarean delivery, only pre-eclampsia was predictive of mild thrombocytopenia. In a sub-analysis, HIV status was not independently associated with moderate thrombocytopenia. All asymptomatic patients, including those who were HIV positive, had platelet counts > 70 000/ $\mu$ l. Our results suggest that a routine FBC is indicated in pre-eclampsia, but not in patients without comorbidities, even if HIV positive. Further work is required to establish the incidence of thrombocytopenia in parturients with AIDS-defining disease, presenting for CD.

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