Platelet count and -indices as postpartum haemorrhage risk factors: a retrospective cohort study

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Platelet count, platelet distribution width, mean platelet volume, immature platelet fraction, plateletcrit, thrombocytopenia, postpartum haemorrhage

Abstract

Objective: To study the relation between platelet parameters and severe postpartum haemorrhage (SPPH).

Design: Retrospective cohort study.

Setting: Birth centre of the University Medical Centre Utrecht.

Population: 23,205 deliveries between 2009 and 2017.

Methods: The predictors platelet count, mean platelet volume (MPV), plateletcrit, platelet distribution width (PDW), and immature platelet fraction (IPF) were measured within 72 hours prior to delivery. Multiple imputation was performed for missing data. Odds ratios were adjusted (aOR's) for maternal age, multiple gestation, macrosomia, induction of labour, and preeclampsia.

Main outcome measures: Severe postpartum haemorrhage (≥1,000mL of blood loss within 24 hours after delivery)

Results: Of the 2,402 (10.4%) women with thrombocytopenia (<150*10^9/L), 10.3% developed SPPH, compared to 7.6% of women with a normal platelet count (aOR: 1.34, 95%-CI: 1.14–1.57). Women with a platelet count of <50*10^9/L were most at risk (aOR of 2.19 (1.01-4.72)) compared to the reference group with normal platelet counts; the aOR was 1.20 (0.77-1.87) for the 50-99*10^9/L platelet count group, and 1.30 (1.09-1.55) for the 100-149*10^9/L platelet count group. Plateletcrit was associated with SPPH (aOR 1.15 (1.08-1.21) per 0.05% decrease), and, although rarely present, a PDW ≥23% (n=22) also increased the odds of SPPH (aOR 6.13 (2.29-16.4)).

Conclusions: Low platelet count, low plateletcrit, and a PDW ≥23% were associated with the occurrence of SPPH, independent of common PPH risk factors.

Tweetable abstract:

Retrospective cohort study of 23,205 deliveries: low platelet count is associated with postpartum haemorrhage.

Introduction

Postpartum haemorrhage (PPH) is the leading cause of maternal mortality and morbidity worldwide.[1,2] The World Health Organization defines PPH as >500mL of blood loss and severe PPH (SPPH) as >1,000mL. In the Netherlands, 4-6% of pregnancies are complicated by SPPH, and this percentage has increased in high income countries over the last decade.[3–5]

Thrombocytopenia, defined as a platelet count of $<150*10^9$/L, is a well-known risk factor for bleeding complications in non-pregnant populations. It is the second most common haematologic anomaly in pregnant women, occurring in 7-12% of pregnancies.[6,7] Thrombocytopenia in pregnancy can have multiple causes. Approximately 75% is due to gestational thrombocytopenia, 20% to preeclampsia and haemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome, and 3-5% to other causes.[8] Preeclampsia and HELLP syndrome, and HELLP syndrome severity, are established risk factors for PPH.[9–12]

Moreover, the relation between thrombocytopenia in pregnancy and PPH has been studied several times, yet these studies showed mixed results,[13–16] lacked statistical power[17–21], or only studied subgroups.[22,23] Furthermore, these studies mostly focused on PPH or PPH surrogates rather than the more clinically relevant outcome parameter SPPH. In current guidelines, women with a platelet count of $<50*10^9$/L are considered to have an increased (S)PPH risk, and platelet transfusion is recommended if the platelet count falls below $20\text{-}30*10^9$/L for vaginal delivery and $50*10^9$/L for surgical delivery. However, these recommendations are based mainly on expert opinion and more empirical evidence is needed to support them.[8,24,25]

In addition to the platelet count, most haematology analysers also routinely measure or calculate several other platelet indices. These parameters include the mean platelet volume (MPV) and the platelet distribution width (PDW), which are regarded as surrogate markers of platelet activation.[26–28] They also include the plateletcrit (PCT), which is the product of the MPV and the platelet count, and indicates the fraction of blood volume occupied by platelets, and the immature platelet fraction (IPF), which indicates the fraction of newly released platelets, that may be more hemostatically active than mature platelets. These parameters have been linked to both thrombotic and haemorrhagic events, although the evidence is non unanimous.[29–52] To date, there are no studies investigating the relation between platelet indices and (S)PPH.

In this study we therefore aimed to investigate the role of platelet count and platelet indices in the aetiology of SPPH in a population-based cohort including both vaginal and caesarean deliveries.

Methods

Study population

This retrospective cohort study was conducted in a cohort of 23,493 deliveries between 2009 to 2017 at the birth centre of the University Medical Centre Utrecht (UMCU), Utrecht, the Netherlands, including primary, secondary, and tertiary obstetric care. We included all deliveries at a gestational age of ≥20 weeks. Patients were not involved in the realisation of this article. This study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 2008,[53] and does not fall under the scope of the WMO (Medical Research Involving Human Subjects Act), as judged by the Medical Research and Ethics Committee of the UMCU.

Definitions

SPPH was defined as ≥1,000mL blood loss within 24 hours after delivery, in accordance with the World Health Organisation,[54] the American college of obstetricians and gynecologists,[2] and the Dutch association for obstetrics and gynecology.[55] Thrombocytopenia was defined as a platelet count of $<150*10^9$/L.[8]

Primary caesarean section was defined as a caesarean section that was planned before labour. Emergency caesarean section was defined as a caesarean section that was unplanned, but the need for a section arose during labour.

Pregnancies with a low or high risk of complications were defined using the Dutch midwife indication list (verloskundige indicatielijst, VIL),[56] which is a guideline used to assess if primary or secondary obstetric care is indicated. If one of the following indications for secondary care was present, the pregnancy was regarded as a high-risk pregnancy: platelet or coagulation disorders, prior SPPH, prior caesarean delivery, prior manual placenta removal, gestational age ≤37 or ≥42 weeks, HELLP or preeclampsia, multiple gestation, vasa previa, placental abruption, retained placenta, and breech presentation.

Data source and collection

For this study, demographic, obstetric, labour, postpartum and laboratory characteristics were collected from the Utrecht Patient Oriented Database (UPOD). UPOD is an infrastructure of relational databases comprising data on patient characteristics, hospital discharge diagnoses, medical procedures, medication orders, and laboratory tests for all patients treated at the UMCU.[57] As determinants the last known platelet count and platelet indices within 72 hours before delivery were used, which were available if any variable of the complete blood count was

measured by clinical indication. Platelet count and platelet indices were measured using an Abbott Diagnostics CELL-DYN Sapphire (Santa Clara, CA, USA). Blood loss was preferably measured by weighing gauzes and catching blood in a measuring cylinder, and otherwise estimated by the attending physician or midwife. There was no information available on how often blood loss was measured or estimated. To identify the presence of HELLP syndrome, preeclampsia, or other platelet disorders, the diagnosis of the attending physician was used, as noted in the medical files and correspondence. If a condition (e.g. preeclampsia or induction of labour) was not reported in medical files, we presumed women were not exposed to this condition. Data on manual placenta removal and perineal or birth tract injuries were extracted from medical files and surgical records.

Statistical analysis

To reduce bias due to missing data, we performed multiple imputation. Most data were missing in the platelet variables body mass index (BMI), blood loss, and mode of delivery (**appendix S1**). We assumed platelet count and -indices, blood loss, and mode of delivery were missing at random (i.e. missingness is random conditional on other observed patient characteristics), and BMI was missing completely at random.[58] We ran 30 multiple imputations with each 100 iterations.[59] The used imputation methods were predictive mean matching for numeric data, logistic regression imputation for binary data, and polytomous regression imputation for unordered categorical data. A list of variables used in the imputation is found in **appendix S2**. The estimates from the imputed data were pooled using Rubin's rules.[60] Separate imputations were performed for each stratified cohort. A complete case analysis was also performed, which is found in **appendix S3**.

For the summary statistics of continuous variables we reported means with standard deviation if data were normally distributed, and medians with interquartile range if data were not normally distributed. We calculated p-values for differences in baseline characteristics using Student's t-test for means, Wilcoxon rank sum test for medians, and chi-squared test for discrete variables. The Benjamini-Hochberg method was used to account for multiple testing.

Odds ratios (OR's) for SPPH were calculated using multivariate logistic regression. A separate model was made for each platelet variable of interest: platelet count, MPV, plateletcrit, PDW, and IPF. The platelet count was categorized in $<50*10^9$/L, 50-99$*10^9$/L, 100-149$*10^9$/L, 150-350$*10^9$/L (reference category), and $\geq 350*10^9$/L based on previous literature. For the stratified analysis we combined the 50-99$*10^9$/L and the 100-149$*10^9$/L categories into one group, to retain statistical power. For the other platelet indices, literature was sparse, thus categorization of data, if necessary, was based on the distribution of data in our cohort (**figure 2**). We analysed the MPV and the plateletcrit as continuous measures, as they had a linear relationship with SPPH, and the PDW and IPF with cut off values of 23% and 6% respectively. To adjust for confounding, we included maternal age, multiple gestation, macrosomia, defined as a birth weight ≥4,000g, induction of labour, and preeclampsia in the logistic regression models. We did not include HELLP syndrome and Obesity in the models to adjust for confounding, as these two factors had no additional influence on the OR's of the adjusted model. The analyses were stratified by mode of delivery, because this might influence bleeding risk, and because previous research focused on these subgroups. A sensitivity analysis was performed to assess whether the relationship differed between high and low risk pregnancies (**appendix S4**). For the complete case analysis IBM SPSS (release 25.0.0.2) was used. For the imputation and the analysis of the

imputed dataset, RStudio (Version 1.1.456) was used. Imputation was performed using the MICE (Multivariate Imputation by Chained Equations, version 3.8.0) package.

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This study was funded by the University Medical Centre Utrecht (UMCU). All but one authors are employed by the UMCU, and one author is a student at the UMCU.

Results

Of the 23,493 eligible deliveries, 23,205 met the inclusion criterion (**figure 1**). The imputed cases (with ≥1 variable used in the analysis missing, n=11,430, 49.3%) overall comprised lower-risk pregnancies, with a lower rate of nulliparity, multiple gestation, caesarean delivery, induction of labour, SPPH, pregnancy complications, prior SPPH, and prior caesarean delivery (**appendix S1**).

The baseline characteristics of deliveries with and without thrombocytopenia are depicted in **table 1**. The groups differed significantly regarding multiple gestation (adjusted p<0.001), mode of delivery (adjusted p<0.001), HELLP syndrome (adjusted p<0.001), maternal age (adjusted p<0.001), preeclampsia (adjusted p<0.001), BMI (adjusted p<0.001), macrosomia (p=0.013), and induction of labour (p=0.047). In total, 2,402 (10.4%) deliveries were complicated by thrombocytopenia, of which 2,109 (9.1%) had a platelet count of 100-149*10^9/L, 241 (1.0%) a platelet count of 50-99*10^9/L, and 52 (0.2%) a platelet count of <50*10^9/L. The baseline characteristics per platelet count group are depicted in **appendix S5**.

In total, 1,819 (7.8%) deliveries were complicated by SPPH. SPPH occurred more frequently in patients with thrombocytopenia (10.3% versus 7.6% in patients without thrombocytopenia; OR:

1.46, 95%-CI: 1.24-1.71; adjusted OR: 1.34, 95%-CI: 1.14-1.57). Generally, the risk of SPPH increased as the platelet count decreased (**figure 2**). The proportion SPPH was highest in the group with $<50*10^9$ platelets/L (15.4%).

Both unadjusted and adjusted OR's of SPPH for platelet count and platelet indices are shown in **table 2**. A platelet count of $<150*10^9$/L, a low plateletcrit, and a PDW ≥23% were associated with an increased SPPH risk after adjusting for known PPH risk factors. The adjustment for confounders did not considerably influence the relationships between platelet count and indices, and SPPH.

Figure 3 shows the aOR's for platelet count stratified by mode of delivery. The aOR's for the other platelet indices are shown in **table 3**. There were not enough subjects to calculate aOR's for PDW ≥23% stratified by mode of delivery. In both vaginal and emergency caesarean deliveries, women with a low platelet count had a higher SPPH risk (aOR's for <50: 2.45 (0.82-7.34) and 2.19 (0.45-10.6); for 50-149: 1.37 (1.12-1.68) and 1.59 (1.07-2.37) respectively). Women with a platelet count of $\geq 350*10^9$/L had a lower SPPH risk (OR: 0.56 (0.39-0.80) and 0.89 (0.44-1.80) respectively). In primary caesarean deliveries, platelet count was not related to SPPH. In this group only a decreasing MPV conferred a higher SPPH risk (**table 3**). In vaginal and emergency caesarean deliveries, a low plateletcrit was related to an increased SPPH risk.

Sensitivity analysis for high- and low-risk pregnancies showed that the relationship between SPPH and platelet parameters was similar in these groups (**appendix S4**).

Discussion

Main findings

In this retrospective cohort study we investigated the relationship between platelet count and platelet indices, and SPPH. We found that a low platelet count, a low plateletcrit, and a PDW ≥23%, were directly related to an increased risk of SPPH. Stratification revealed similar relations between platelet parameters and severe postpartum haemorrhage for vaginal and emergency caesarean deliveries, but not for primary caesarean deliveries.

Strengths and limitations

A strength of this study is the size of the cohort, which allowed for a high statistical precision. Overall, the documentation of patient characteristics was good (**appendix S1**). Our cohort included women with both vaginal and caesarean deliveries in both primary and secondary/tertiary care, making our results broadly applicable.

The main limitation of this study lies in the retrospective nature of the data collection. Because blood tests were ordered by medical indication, complete cases comprised more 'high-risk' pregnancies. However, our sensitivity analysis showed that the relationship between platelet characteristics and SPPH did not differ between high and low risk populations (**appendix S4**). We aimed to further reduce this bias by using multiple imputation. Furthermore, estimating rather than measuring the amount of blood loss is known to have poor accuracy, and this method was used in an unknown proportion of the cases.[61,62] Since we used SPPH as a dichotomous outcome, we expect this to have a limited effect on our results. Another limitation was the limited number of subjects in the $<50*10^9$/L platelet count group, impairing statistical precision.

Interpretation

Platelet count and SPPH

We found a relation between a lower platelet count and an increased risk of SPPH. The results of our study are consistent with the study conducted by Biguzzi et al. in a prospective cohort of 6,011 singleton vaginal deliveries, where an increased PPH risk was seen with lower platelet counts.[22] In contrast to our results, Carlson et al.[23] found that a low platelet count was related to increased clinical and laboratory evidence of bleeding in caesarean deliveries. There are two explanations for this difference. Firstly, the authors used two surrogate outcome measures rather than measuring blood loss: 1) laboratory evidence of bleeding, defined as a decrease of haemoglobin ≥4 g/dL, and 2) clinical evidence of haemorrhage, comprising medical treatment of atony, blood transfusion, coagulopathy, repeat laparotomy, peripartum hysterectomy, intensive care unit admission. These measures could reflect other conditions than PPH alone, which makes that study more vulnerable to residual confounding. Secondly, we found a relationship between the platelet count and SPPH in emergency caesarean deliveries, but not in primary caesarean deliveries, while in the study by Carlson et al. these categories were combined.

The difference in outcomes between vaginal and emergency caesarean deliveries on one hand, and primary caesarean deliveries on the other hand is remarkable. Blood loss is generally higher in caesarean deliveries than in vaginal deliveries, and it seems that haemostatic factors play a more important role in the amount of blood loss after emergency caesarean deliveries and vaginal deliveries than in primary caesarean deliveries. A possible explanation for this is that caesarean deliveries offer the opportunity to control the bleeding locally, and because primary caesarean deliveries are generally more controlled procedures than emergency caesarean deliveries, there is more time for local haemostasis.

Another finding is that women in the 50-99*10^9/L platelet count group seemed to have a lower risk of SPPH than women in the 100-149*10^9/L platelet count group. However, the first group

was relatively small, and thus possibly underpowered. Furthermore, due to the retrospective nature of the study, the results in this group might be biased by treatment effects.

Platelet indices and SPPH

The relation between other platelet indices and SPPH has not been studied before. We found that a low plateletcrit and a PDW ≥23%, were related to SPPH. A low MPV was only related to SPPH in primary caesarean deliveries. Given the mixed results of other studies regarding MPV and bleeding risk,[46–52] and the fact we have no clear explanation for this finding, we consider the MPV of limited value in clinical practice.

We also found that a low plateletcrit, which is the product of MPV and platelet count, was related to an increased SPPH risk. Plateletcrit did not seem to be more strongly related to SPPH than the platelet count. This corresponds with our finding that the MPV is not significantly related to SPPH, and thus the platelet count component of the plateletcrit mainly seems to dictate its relation to SPPH risk. Since most physicians are used to working with the platelet count, and not the plateletcrit, we consider plateletcrit to be of no added value in clinical practice. However, in prediction models it might prove to be of added value.

Another finding of our study is that a PDW ≥23% was strongly related to SPPH. Only a small subset of patients met this criterion, possibly because PDW is known to have a low reproducibility and thus large variability in patients. Furthermore, this finding is remarkable as previous studies have shown that a high PDW was associated with thrombotic rather than bleeding events.[33,35] However, a high PDW has also been associated with mortality and morbidity in several non-thrombotic conditions.[63–67] Thus, a high PDW could be a surrogate marker for a

poor general condition or (subclinical) underlying conditions, and therefore be associated with SPPH.

Conclusion

Practical recommendations

We found that a low platelet count, a low plateletcrit, and a PDW ≥23%, were related to an increased risk of SPPH. Our results show that increased vigilance is needed when patients have thrombocytopenia in the days prior to delivery, even if the thrombocytopenia is mild. For clinical practice, we advise using the platelet count rather than other platelet indices to estimate the increased (S)PPH risk, as clinicians are used to work with platelet counts, and we found no evidence that other platelet indices were more strongly related to SPPH. An exception is a PDW ≥23%, which was strongly related to SPPH, but due to its rare occurrence is difficult to use in clinical practice.

Research recommendations

Further research on this topic should focus on women with thrombocytopenia, as we had limited statistical precision in the lowest platelet count group. Furthermore, the value of platelet count and platelet indices in SPPH prediction models should be investigated. Our dataset is available on request for the development and validation of such prediction models.

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Disclosure of interests

The authors report no conflict of interest.

Contribution to authorship

Conceptualization: W.D., R.S., A.L., K.G.

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Details of ethics approval

This study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 2008,[53] and does not fall under the scope of the WMO (Medical Research Involving Human Subjects Act), as judged by the Medical Research and Ethics Committee of the UMCU on the 19th of September 2018 (reference number WAG/mb/18/033284).

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Table/figure caption list

Table 1. Abbreviations: SD, standard deviation; BMI, body mass index; IQR, interquartile range; SPPH, severe postpartum haemorrhage; HELLP, haemolysis, elevated liver enzymes, low platelet count; ITP, immune thrombocytopenic purpura. *one case had both ITP and HELLP syndrome.

Table 2. Odds ratios were calculated using multivariate logistic regression. Statistically significant results are displayed in bold. †Adjusted for: maternal age, multiple gestation, macrosomia, induction of labour, and preeclampsia. Abbreviations: OR, odds ratio; SPPH, severe postpartum haemorrhage; MPV, mean platelet volume; PDW, platelet distribution width; IPF, immature platelet fraction; CI, confidence interval; NA, not applicable; ref., reference category.

Table 3. Odds ratios were calculated using multivariate logistic regression. Statistically significant results are displayed in bold. †Adjusted for: maternal age, multiple gestation, macrosomia, induction of labour, and preeclampsia. ‡Adjusted for: maternal age, multiple gestation, macrosomia, and preeclampsia. Abbreviations: aOR, adjusted odds ratio; SPPH, severe postpartum haemorrhage; CI, confidence interval; MPV, mean platelet volume; IPF, immature platelet fraction.

Figure 1. Flowchart describing study population.

Figure 2. Proportion SPPH and number of subjects in each subgroup, by platelet count and platelet indices. Abbreviations: SPPH, severe postpartum haemorrhage; MPV, mean platelet volume; PDW, platelet distribution width; IPF, immature platelet fraction.

Figure 3. Odds ratios of severe postpartum haemorrhage, calculated using multivariate logistic regression, stratified by mode of delivery. *P<0.05. †Adjusted for: maternal age, multiple gestation, macrosomia, induction of labour, and preeclampsia. ‡Adjusted for: maternal age, multiple gestation, macrosomia, and preeclampsia. Upper limits confidence intervals: a, 7.34; b, 6.52; c, 10.55. Abbreviations: OR, odds ratio; SPPH, severe postpartum haemorrhage; CI, confidence interval.