Assessment of post-partum haemorrhage risk among women with moderate thrombocytopenia

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Summary
It is unknown whether moderate thrombocytopenia represents a risk factor for post-partum haemorrhage (PPH). We assessed PPH risk among women with a platelet count of between 100 and 50 × 10^9/l and stratified the risk for O/non-O blood group. We included consecutive women undergoing vaginal delivery or caesarean section with moderate thrombocytopenia. Women with >150 × 10^9/l platelets at delivery were selected as controls and matched for age, type of birth and ethnicity. Odds ratios (ORs) with their 95% confidence intervals (95% CIs) were calculated as risk estimates. A total of 94 thrombocytopenic women and 94 controls were included in the study. The rate of PPH was significantly higher in thrombocytopenic women than in controls (37% vs. 10%, p < 0.001); there was a higher risk of PPH in the thrombocytopenic group when compared to the control group (adjusted OR 4.7, 95% CI 2.1–10.8, p < 0.01) and this association was stronger in blood group O carriers (adjusted OR 11.0, 95% CI 2.4–49.6, p < 0.01). In conclusion, our study shows that a moderate thrombocytopenia is a risk factor for PPH, especially in blood group O carriers.

KEYWORDS
ABO blood-group system, delivery, obstetric, post-partum haemorrhage, risk factors, thrombocytopenia

INTRODUCTION
Post-partum haemorrhage (PPH) is still the leading cause of maternal mortality, both in developing and advanced countries. Worldwide, it is estimated that >25% of maternal deaths are due to PPH2 and the incidence is increasing.3–4 PPH is traditionally defined as a loss of blood from the genital tract of ≥500 ml in the case of vaginal birth and ≥1000 ml in caesarean deliveries.5

Maternal, fetal and childbirth-related factors have been internationally recognised as risk factors for the development of PPH. Uterine atony accounts for the majority of PPH cases (70%–75%). Other acknowledged risk factors include a previous history of PPH, fetal macrosomia (>4000 g at birth), an increased maternal body mass index, an advanced maternal age (>35 years), nulliparity or grand multiparity (>four pregnancies), genital tract injuries, placenta accrete
spectrum (PAS) disorders, labour induction, caesarean delivery and maternal coagulopathy.\textsuperscript{3,6–9}

Thrombocytopenia, defined as a platelet (PLT) count of $<150 \times 10^9/l$, occurs in $\sim$12% of all pregnancies and can either be physiological or being a sign of an underlying pathological condition.\textsuperscript{10} Gestational thrombocytopenia is a benign condition that accounts for $\sim$75% of thrombocytopenia cases and resolves with delivery. In the remaining 25% of cases, thrombocytopenia could be an indicator of a disease arising during pregnancy.\textsuperscript{11} In only $\sim$1% of all pregnancies PLT counts at delivery are $<100 \times 10^9/l$,\textsuperscript{10} being between 100 and $50 \times 10^9/l$ most of the time,\textsuperscript{12} but the consequences of this moderate thrombocytopenia on the maternal bleeding risk are unknown.

Thrombocytopenia is a known risk factor for post-procedural bleeding in any type of surgery. In clinical practice, different PLT count thresholds have been recognised for distinct types of surgical procedures. When considering pregnancy in patients with immune thrombocytopenia (ITP), experts’ consensus suggests a PLT count of $\geq 50 \times 10^9/l$ for delivery and $\geq 80 \times 10^9/l$ for neuraxial anaesthesia as safe thresholds.\textsuperscript{10} However, to date it is not known which PLT count exposes pregnant healthy women without a history of thrombocytopenia to an increased risk of PPH. A recent study has investigated the risk of developing PPH in previously unknown thrombocytopenic patients but considering only patients delivering via caesarean section or vaginal birth after caesarean (VBAC).\textsuperscript{13}

Previous literature investigating the effect of blood group on the development of PPH is controversial.\textsuperscript{14,15} It is known that O blood group subjects carry lower levels of von Willebrand Factor (VWF),\textsuperscript{16} although rising during the third trimester of pregnancy up to its maximum level at birth. VWF is crucial to promote PLTs adhesion, but evidence on the combined effect of thrombocytopenia and low VWF levels in blood group O carriers at birth is missing.

Given this background, our study aimed to define whether moderate thrombocytopenia constitutes a risk factor for the development of PPH regardless of the type of delivery, whether a difference between vaginal birth and caesarean section exists and whether carrying blood group O may further increase the risk of PPH in thrombocytopenic women.

METHODS

Study population

We performed a multicentre retrospective cohort study, conducted in two Obstetric Departments in Milan. All consecutive women aged 18–50 years delivering between May 2018 and November 2019 were included in the study if they had a PLT count of between 100 and $50 \times 10^9/l$ at delivery, determined on blood samples drawn within the last 24 h before childbirth. A second PLT count from a blood sample collected in a sodium citrate tube was routinely performed to exclude pseudothrombocytopenia. The inclusion criterium was a PLT count of between 100 and $50 \times 10^9/l$ at birth without prophylactic PLT transfusions or treatment with steroids or intravenous immunoglobulins. Exclusion criteria were the presence of a congenital bleeding disorder or congenital thrombocytopenia, a previous diagnosis of acquired thrombocytopenia or anti-phospholipids syndrome, an ongoing anticoagulant therapy, or the presence of active cancer.

To assess whether the presence of moderate thrombocytopenia was an independent risk factor for PPH, a cohort of healthy women delivering with a PLT count of $>150 \times 10^9/l$ were selected as controls and frequency-matched for age, type of birth and ethnicity, during the same period. Haemoglobin, PLT count, and fibrinogen levels were also retrospectively obtained within the 24 h before delivery. The study was performed in agreement with the Declaration of Helsinki.

Obstetric outcomes

Post-partum haemorrhage was defined as a blood loss of $\geq 500$ ml from the genital tract for vaginal deliveries and $\geq 1000$ ml for caesarean sections, within 24 h of delivery (primary PPH). Obstetric blood loss was quantitively measured via graduated collector bags, under-buttocks drapes in case of vaginal delivery and suction graduated canister and weight of blood saturated laparotomy pads in case of caesarean section. Our standardised algorithm for PPH prevention required administration of oxytocin 5 iu and methylergometrine 0.2 mg immediately after the shoulder delivery in case of vaginal birth. For caesarean section, our protocol indicated infusion of 20 iu diluted in 500 ml of normal saline solution, given at 40 ml/h. Uterine massage and medical treatment were adopted for blood loss of $\geq 500$ ml for vaginal birth and $\geq 1000$ ml in case of caesarean section, including use of uterotonic agents and tranexamic acid, given intravenously at a dosage of 1 g. In case of unsatisfactory control of bleeding, conservative procedures (bimanual uterine compression, uterine tamponade, compression suture) were implemented on the basis of clinician judgement and a senior obstetrician was called to review the case. Bakri balloon tamponade was the first-line approach for drug-resistant PPH. Following the PPH protocol, tranexamic acid was intravenously administered by our anaesthesiologists in case of blood loss of $\geq 500$ ml for vaginal and $\geq 1000$ ml for caesarean births. Tranexamic acid was not routinely used as prophylactic treatment in case of thrombocytopenia at delivery.

Statistical analysis

Categorical variables were expressed as counts and percentages, continuous variables as median and interquartile range (IQR). As estimates of risk, odds ratios (ORs) with their 95% confidence intervals (95% CIs) were calculated, according to the method of Woolf. Statistical analysis was performed using the chi-square test for dichotomous variables and Student’s
**RESULTS**

A total of 102 patients with a moderate thrombocytopenia at delivery were identified. Two patients were excluded for the absence of further clinical data, one patient was excluded for a type 2B von Willebrand disease, two patients were excluded for concurrent haematological neoplasms, one for antiphospholipid syndrome and ongoing anticoagulant therapy and two patients were excluded for therapeutic abortion. Therefore, a total of 94 patients were included in the analysis. To compare the risk of PPH development in thrombocytopenic women with the risk in healthy childbearing women, 94 pregnant women with a PLT count of ≥150 × 10^9/l were selected as controls over the same period and matched first by age, then by the type of birth and finally by ethnicity. The two populations did not differ for basal haemoglobin levels (114 vs. 114 g/l, p = 0.15), and the pre-partum fibrinogen levels were to some extent lower in the thrombocytopenic group than in the controls (4.29 vs. 4.63 g/l, p < 0.01), but the baseline levels in thrombocytopenic women were all normal or elevated.

| Table 1 | Demographic, obstetric and laboratory characteristics of the study population |
|---------|--------------------------------------------------|
|         | Moderate thrombocytopenia | Controls | p     |
| Number of subjects | 94 | 94 | n.s. |
| Age, years, median (IQR) | 35 (31–39) | 35 (31–39) | n.s. |
| Ethnicity, n (%) | | | |
| Caucasian | 74 (79) | 74 (79) | n.s. |
| African | 6 (6) | 6 (6) | n.s. |
| Asian | 6 (6) | 6 (6) | n.s. |
| Hispanic | 8 (9) | 8 (9) | n.s. |
| Blood group, n (%) | | | |
| O | 44 (47) | 39 (40) | 0.46 |
| Non-O | 50 (53) | 55 (60) | n.s. |
| Primiparous, n (%) | 63 (67) | 44 (47) | <0.01 |
| Gestational age, weeks, median (IQR) | 38 (36–39) | 39 (38–39.3) | <0.01 |
| First-born’s weight, g, median (IQR) | 2867 (2475–3333) | 3272 (2853–3452) | <0.01 |
| Twin pregnancies, n (%) | 14 (15) | 4 (5) | 0.01 |
| Platelets, ×10^9/l, median (IQR) | 90 (79–97) | 229 (198–260) | <0.01 |
| Admission haemoglobin, g/l, median (IQR) | 114 (101–123) | 114 (108–121) | 0.15 |
| Fibrinogen, g/l, median (IQR) | 4.29 (3.74–4.79) | 4.63 (4.02–5.24) | <0.01 |
| Pre-eclampsia, n (%) | 9 (10) | 3 (3) | 0.07 |
| HELLP syndrome, n (%) | 2 (2) | 0 | 0.15 |
| Type of delivery, n (%) | | | |
| Vaginal birth | 35 (37) | 35 (37) | n.s. |
| Caesarean section | 59 (63) | 59 (63) | n.s. |
| Induction, n (%) | 26 (28) | 17 (18) | 0.1 |
| Uterine atony, n (%) | 5 (5) | 1 (1) | 0.1 |
| Placental alterations (PAS), n (%) | 6 (6) | 1 (1) | 0.06 |

HELLP, Haemolysis Elevated Liver enzymes and Low Platelets count; n.s., not significant.

Statistical analysis has been performed using chi-square test for dichotomous variables and Student’s t-test for continuous variables.

Thrombocytopenia was associated with a fourfold increased risk of PPH, as detailed in Table 2 (OR adjusted for confounders and matching factors 4.7, 95% CI 2.1–10.8, p < 0.01). This relationship remained meaningful after adjustment for major risk factors for PPH such as uterine atony, nulliparity, fetal macrosomia, placental...
disorders, labour induction and gestational age <32 weeks (adjusted OR 3.7, 95% CI 1.5–9.4, \( p < 0.01 \)), as shown in Table 2. To investigate whether the risk increased at the diminishing of PLT count, we further stratified the thrombocytopenic patients into tertiles of PLT count distribution (highest tertile: PLT >95 × 10⁹/l; lowest tertile: PLT <83 × 10⁹/l). The choice of categorisation into tertiles rather than according to arbitrary clinical cut-offs was made to maintain the same power of analysis into the three subcategories. Each thrombocytopenic group was compared with the controls. The risk of developing PPH was significantly higher for patients with a PLT count of <83 × 10⁹/l (crude OR 12.6; 95% CI 4.7–33.6, \( p < 0.01 \)) than for the thrombocytopenic patients of the first tertile, delivering with a PLT count of >95 × 10⁹/l (crude OR 1.9; 95% CI 0.6–5.8).

Furthermore, we stratified the analysis for the type of birth, aiming to identify whether the delivery mode influenced the risk of PPH. The risk appeared to be only to some extent greater in the case of vaginal delivery (crude OR 5.6; 95% CI 1.4–22.0) than for caesarean section (crude OR 4.7; 95% CI 1.8–12.2), but the difference between the two delivering modalities was not statistically significant (Table 3).

To assess whether the blood group could influence the risk of PPH, we stratified the patients into O and non-O blood groups carriers (A, B, AB), regardless of the Rhesus (Rh) phenotype. As shown in Table 3, carrying blood group O appeared to confer a higher risk of developing PPH in

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**Table 2** Association analysis of post-partum haemorrhage (PPH) and moderate thrombocytopenia

|                          | Yes | No  | OR (95% CI), \( p \)                  | OR₁ (95% CI), \( p \)                  | OR₂ (95% CI), \( p \)                  |
|--------------------------|-----|-----|--------------------------------------|--------------------------------------|--------------------------------------|
| Controls                 | 10  | 84  | Reference                             | Reference                             | Reference                             |
| Moderate                 | 35  | 59  | 5.0 (2.3–10.8), <0.01                 | 4.7 (2.1–10.8), <0.01                 | 3.7 (1.5–9.4), <0.01                 |

Thrombocytopenic women stratified by tertiles of platelet count

- **I tertile**: 6/26; 1.9 (0.6–5.8), 0.2
- **II tertile**: 11/21; 4.4 (1.6–11.7), <0.01
- **III tertile**: 18/12; 12.6 (4.7–33.6), <0.01

Reference group: controls.

CI, confidence interval; OR, crude odds ratio; OR₁, OR adjusted for matching factors and confounders (age, ethnicity, type of birth, twin pregnancy); OR₂, OR adjusted for matching factors, confounders and other risk factors for PPH (uterine atony, nulliparity, placental disorders, labour induction, gestational age <32 weeks, fetal macrosomia, pre-eclampsia and Haemolysis Elevated Liver enzymes and Low Platelets count (HELLP) syndrome.

**Table 3** Association analysis of post-partum haemorrhage (PPH) and thrombocytopenia, stratified for the type of birth (A) and O/non-O blood group (B)

(A) Type of birth

|                          | Yes | No  | OR (95% CI), \( p \)                  | OR₁ (95% CI), \( p \)                  | OR₂ (95% CI), \( p \)                  |
|--------------------------|-----|-----|--------------------------------------|--------------------------------------|--------------------------------------|
| Vaginal birth Controls   | 3   | 32  | Reference                             | Reference                             | Reference                             |
| Moderate                 | 12  | 23  | 5.6 (1.4–22.0), <0.01                 | 6.7 (1.5–29.5), 0.01                 | 4.4 (0.9–21.7), 0.07                 |
| Caesarean section Controls | 7   | 52  | Reference                             | Reference                             | Reference                             |
| Moderate                 | 23  | 36  | 4.7 (1.8–12.2), <0.01                 | 4.0 (1.4–11.1), <0.01                 | 3.2 (1.0–10.7), 0.05                 |

(B) Blood group

|                          | Yes | No  | OR (95% CI), \( p \)                  | OR₁ (95% CI), \( p \)                  | OR₂ (95% CI), \( p \)                  |
|--------------------------|-----|-----|--------------------------------------|--------------------------------------|--------------------------------------|
| Non-O Controls           | 6   | 49  | Reference                             | Reference                             | Reference                             |
| Moderate                 | 15  | 35  | 3.5 (1.2–9.9), 0.01                   | 2.7 (0.9–8.2), 0.07                   | 2.5 (0.7–8.9), 0.15                   |
| O Controls               | 4   | 35  | Reference                             | Reference                             | Reference                             |
| Moderate                 | 20  | 24  | 7.3 (2.2–24.0), <0.01                 | 11.0 (2.4–49.6), <0.01                | 14.7 (2.0–107.7), <0.01               |

CI, confidence interval; OR, crude odds ratio; OR₁, OR adjusted for matching factors and confounders (age, ethnicity, type of birth, twin pregnancy); OR₂, OR adjusted for matching factors, confounders and other risk factors for PPH (uterine atony, nulliparity, placental disorders, labour induction, gestational age <32 weeks, fetal macrosomia, pre-eclampsia and Haemolysis Elevated Liver enzymes and Low Platelets count (HELLP) syndrome.
thrombocytopenic women (crude OR 7.3; 95% CI 2.2–24.0, \(p < 0.01\)), than in healthy controls (crude OR 3.5; 95% CI 1.2–9.9). Next, we investigated the association between thrombocytopenia and O/non-O blood group. As shown in Table 4, Panel A, thrombocytopenic women with O blood group had an increased risk of PPH than the expected, suggesting a positive interaction between a moderate thrombocytopenia and the O group (OR for the combination 7.1; expected OR \([2.6–1] + [0.8–1] = 2.4\), being 1 the baseline risk). Finally, when we analysed the distribution of ABO blood groups within the tertiles, we found that the O group was more frequent in subjects with the lowest PLT count, further increasing the risk of PPH in the third tertile (adjusted OR 15.6; 95%CI 2.7 to 88.7, \(p < 0.05\)) compared to the first tertile (adjusted OR 1.0; 95%CI 0.1 to 8.0), as shown in Table 4, Panel B.

When investigating the risk of PPH with logistic regression model, this resulted in being more than fourfold higher in thrombocytopenic women than in healthy controls. When stratifying for the mode of delivery, the difference between caesarean section and vaginal birth was not significant.

Of note, when comparing PPH between thrombocytopenic and healthy women, the haemorrhages appeared to be of a greater severity in the former group. This observation is corroborated by the higher percentage of blood transfusions required in the thrombocytopenic women than in the controls in case of PPH (43% vs. 10%) and the median amount of blood loss (500 vs. 300 ml), as shown in Table 5.

Considering the tertiles of PLT count distribution, a PLT count between 100 and 95 × 10^9/l slightly increased the risk of PPH, whereas a PLT count between 83 and 95 × 10^9/l was associated with a marked increased risk of PPH (Table 2). Within the same PLT tertile, the increase of PPH risk was greater in O than non-O blood group (Table 4, Panel B). The steep gradient of rising risk at the diminishing of PLT count could therefore be explained by the positive interaction between the two risk factors (thrombocytopenia and O blood group), confirming the determinant role of O blood group.

Our results confirmed, in a population of women with moderate thrombocytopenia, the increasing risk of PPH at the decreasing of PLT count found by Carlson et al.\(^{13}\) in caesarean sections and VBAC, extending this finding also to vaginal birth. Another study evaluating 339 pregnancies

### DISCUSSION

To the best of our knowledge, this is the first study to investigate the risk of PPH in patients affected with moderate thrombocytopenia regardless of the type of delivery, further exploring the effect of the ABO blood group on the PPH risk.

Our data showed that subjects with moderate thrombocytopenia had increased risk of PPH when compared to the control group and this association was stronger in blood group O carriers.

When investigating the risk of PPH with logistic regression model, this resulted in being more than fourfold higher in thrombocytopenic women than in healthy controls. When stratifying for the mode of delivery, the difference between caesarean section and vaginal birth was not significant.

Of note, when comparing PPH between thrombocytopenic and healthy women, the haemorrhages appeared to be of a greater severity in the former group. This observation is corroborated by the higher percentage of blood transfusions required in the thrombocytopenic women than in the controls in case of PPH (43% vs. 10%) and the median amount of blood loss (500 vs. 300 ml), as shown in Table 5.

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Studies on larger cohort of patients affected with thrombocytopenia are needed to confirm or question our findings.

A limitation of our study lies in the retrospective design with the attendant bias. Nevertheless, well-documented clinical records were available for all subjects and a standardised approach to PPH management was in use for the enrolment period. Another limitation is the lack of measurement of VWF in the enrolled patients, which would be interesting to investigate in future studies among thrombocytopenic blood group O carriers at birth. Furthermore, our study was conducted on a relatively small number of patients, reflected in the wide CIs around estimates which, however, denoted a statistically significant association between thrombocytopenia and PPH in all analyses performed.

Thrombocytopenic women and controls diverged in terms of prevalence of twin pregnancies, uterine atony, and placental disorders. Twin pregnancy is a known risk factor for gestational thrombocytopenia as an effect of increased haemodilution,17,18 for uterine atony due to over-distended uterus,19 and for PPH.20 Thus, it is not surprising that three out of five uterine atonies and four out of six cases of placental disorders were observed in twin pregnancies. It would be interesting to investigate the mode of conception, as artificial reproductive techniques pregnancies have a baseline higher risk of multiple gestations and placental disorders.21 Unfortunately, information regarding the mode of conception were not available in our study. Nevertheless, all the performed statistical analyses were corrected for twin pregnancies, uterine atony and placental disorders, and the strength of the associations changed to a minor degree, remaining meaningful.

In conclusion, a moderate thrombocytopenia is associated with an increased risk of developing PPH, regardless of the type of delivery. A PLT count of between 100 and 50 × 10⁹/l appears to be a risk factor for PPH, especially in blood group O carriers. Our findings could pave the way for better prepartum risk assessment, taking into account PLT count and ABO blood group along with other known risk factors for PPH, in order to promptly recognise patients at higher risk.

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**CONFLICT OF INTEREST**

Ilaria Mancini received honoraria for participating as a speaker at educational meetings organised by Instrumentation Laboratory and Sanofi-Genzyme, outside the present work. The other authors state that they have no conflict of interest to disclose.
AUTHORS CONTRIBUTIONS
Andrea Artoni, Marco Capecchi and Gian Marco Podda designed the study. Sara Arcudi, Marco Capecchi, Alice Ronchi, Gabriella Schivardi, Gian Marco Podda, Anna Maria Marconi and Andrea Artoni assessed patients for eligibility and collected the data. Sara Arcudi performed the statistical analysis, with the contribution of Ilaria Mancini, and wrote the manuscript. Andrea Artoni, Gian Marco Podda, Enrico Iurlarlo, Manuela W. Ossola, Ilaria Mancini and Anna Maria Marconi contributed to writing the manuscript. All authors critically revised the manuscript and approved the final manuscript for submission.

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