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Association between ionised calcium and severity of postpartum haemorrhage: a retrospective cohort study

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Abstract

Background: Postpartum haemorrhage (PPH) is often complicated by impaired coagulation. We aimed to determine whether the level of ionised calcium (Ca^{2+}), an essential coagulation co-factor, at diagnosis of PPH is associated with bleeding severity.

Methods: This was a retrospective cohort study of women diagnosed with PPH during vaginal delivery between January 2009 and April 2020. Ca^{2+} levels at PPH diagnosis were compared between women who progressed to severe PPH (primary outcome) and those with less severe bleeding. Severe PPH was defined by transfusion of ≥2 blood units, arterial embolisation or emergency surgery, admission to ICU, or death. Associations between other variables (e.g. fibrinogen concentration) and bleeding severity were also assessed.

Results: For 436 patients included in the analysis, hypocalcaemia was more common among patients with severe PPH (51.5% *vs* 10.6%, $P<0.001$). In a multivariable logistic regression model, Ca^{2+} and fibrinogen were the only parameters independently associated with PPH severity with odds ratios of 1.14 for each 10 mg dl^{-1} decrease in fibrinogen (95% confidence interval [CI], 1.05–1.24; $P=0.002$) and 1.97 for each 0.1 mmol L^{-1} decrease in Ca^{2+} (95% CI, 1.25–3.1; $P=0.003$). The performance of Ca^{2+} or fibrinogen was not significantly different (area under the curve [AUC]=0.79 [95% CI, 0.75–0.83] *vs* AUC=0.86 [95% CI, 0.82–0.9]; $P=0.09$). The addition of Ca^{2+} to fibrinogen improved the model, leading to AUC of 0.9 (95% CI, 0.86–0.93), $P=0.03$.

Conclusions: Ca^{2+} level at the time of diagnosis of PPH was associated with risk of severe bleeding. Ca^{2+} monitoring may facilitate identification and treatment of high-risk patients.

Keywords: coagulation; fibrinogen; hypocalcaemia; ionised calcium; postpartum haemorrhage

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Editor's key points

- Postpartum haemorrhage (PPH) is the leading cause of maternal morbidity and mortality.
- Coagulation plays an important role in postpartum haemostasis and uterine tone, and ionised calcium is a key coagulation cofactor.
- In this retrospective, single-centre cohort study of women diagnosed with PPH, hypocalcaemia was associated with severe PPH.
- In a multivariable logistic regression model, Ca^{2+} and fibrinogen were the only parameters independently associated with PPH.
- Thus, Ca^{2+}, as a standalone parameter or when combined with fibrinogen level, can aid in identifying women with high-risk PPH.

Postpartum haemorrhage (PPH) is the leading cause of maternal morbidity and mortality worldwide with an incidence ranging from 3% to 8% of all deliveries.[1,2] Studies indicate a rising incidence of PPH in high-income countries.[1] Rapid diagnosis, risk stratification, and management of women at high risk improve maternal prognosis.[3] Uterine atony and placental abnormalities account for the majority of cases.[4] Numerous other risk factors for PPH have been identified and extensively studied. However, in the majority of cases, it is still an unpredictable emergency with a variable course.[3] There is an increasing interest in the primary and secondary coagulation alterations that occur during major PPH, as it is clear that coagulation plays an important role in postpartum haemostasis in the setting of haemorrhage.[5–7]

Calcium is an essential co-factor in the coagulation cascade and hypocalcaemia is independently associated with reduced *in vitro* clot strength in bleeding patients.[8–10] Recent studies in trauma casualties showed that admission hypocalcaemia is common and is associated with adverse outcomes. Some studies suggested that calcium may play a role in uterine contraction.[11] The roles of calcium in uterine tone and coagulation suggest that it may be a meaningful biological marker in PPH. We hypothesised that ionised calcium (Ca^{2+}) level at diagnosis of PPH may serve as an early biological marker and accurately predict women at risk of severe bleeding.

Methods

Study design and data sources

This retrospective, single-centre cohort study included women diagnosed with PPH from January 1, 2009 through April 31, 2020 in the maternity department of Rambam Health Care Campus (RHCC), a 1000-bed tertiary academic hospital serving more than 2 million residents located in Haifa, Israel.

The study was approved by the Institutional Review Board at RHCC (approval number RMB-0093-20). The need for written informed consent was waived because of the specific study design (see below). Data were analysed anonymously.

Data analysed in this study were retrieved from Prometheus, the RHCC integrated electronic medical records system. Data were collected from patient files using MDClone (Beer-Sheba, Israel), recently used in other studies.[12,13] MDClone extracts data from electronic medical records, including patients' hospitalisations, coded diagnoses, medications, surgical and other procedures, laboratory tests, patient characteristics, and administrative information. The data are presented in an anonymous and standardised format. The system allows retrieval of a wide range of variables in a defined time frame around an index event.[14]

Participants

The study population included all consecutive women who delivered vaginally and developed PPH according to discharge diagnosis (ICD-10 [International Statistical Classification of Diseases and Related Health Problems, 10th revision] code O72.1) during the study period. Each woman was counted only once (first delivery during the study period). Per hospital protocol, PPH was defined as uterine bleeding, visually estimated by a treating physician as >500 ml of blood.

In RHCC, all women admitted to the delivery room are routinely tested for blood type and crossmatch is performed. A complete blood count is also carried out at admission. When PPH is diagnosed additional laboratory tests are performed, at the discretion of the attending physician, including a coagulation profile, repeat blood count, renal function, electrolytes, and arterial or venous blood gases (including ionised calcium). In concordance with current international and local guidelines, all women are treated with uterotonic agents (usually oxytocin) when PPH was diagnosed. Tranexamic acid was administrated when initial medical therapy failed, at the discretion of the attending physician.[15]

Patients were included in the final analysis if they had Ca^{2+} measurements performed before any blood product transfusion to avoid confounding by a possible effect of citrate, which is used as an anticoagulant in stored blood products, on plasma Ca^{2+}. We also excluded patients treated with antepartum anticoagulants.

Outcome measures and variables

The primary outcome of this study was the occurrence of severe PPH. We defined severe PPH as requiring at least one of the following: (1) ICU admission, (2) transfusion of two or more blood product units (either fresh frozen plasma or red blood cells), (3) need for an urgent haemostatic intervention (surgical or angiographic), or (4) death during the index admission.

Although risk factors for development of PPH have been well identified and studied, the risk factors for bleeding aggravation are vague. We selected candidate variables as potential risk factors for severe PPH based on literature review and clinical plausibility.[5,6,16] Candidate variables included the following (information was retrieved from electronic medical records using the MDClone system):

1. Basic characteristics: age, BMI, parity, multiple pregnancies.
2. Pregnancy complications: diabetes mellitus (DM) and hypertension (HTN).
3. Antepartum drug therapy: low-molecular-weight heparins and aspirin.
4. Laboratory profile at admission: haemoglobin (Hb) and platelet count.
5. Laboratory tests performed at diagnosis of PPH: pH, lactate, Ca^{2+}, fibrinogen level, prothrombin time (PT), and partial thromboplastin time (PTT), platelet count, and Hb.
6. Interventions: vacuum extraction, number of blood products (red blood cells [RBCs] and fresh frozen plasma [FFP], the primary plasma used in RHCC) transfused (identified by blood bank records), ICU admission (according to

administrative information), urgent surgical intervention (hysterectomy, surgical arterial ligation, or uterine repair) or angiographic embolisation (censored by operative and angiography reports, respectively).

Haematological values were measured using the Advia 120 Hematology Analyzer (Siemens Healthcare Diagnostics, Deerfield, IL, USA). PT, PTT, and fibrinogen were measured using the BCS XP System (Siemens Healthcare Diagnostics). Blood gas analysis (pH, lactate, and Ca^{2+}) was performed using GEM 3500 blood gas analyser (Instrumentation Laboratories, Bedford, MA, USA). The analyser reports Ca^{2+} values normalised to a pH of 7.4.

At RHCC, Ca^{2+} is routinely reported as part of venous and arterial blood gas analysis. There is a good correlation between arterial and venous samples.[17] The normal range for Ca^{2+} in our laboratory is 1.16–1.31 mmol L^{-1}. Hypocalcaemia was defined as Ca^{2+}<1.16 mmol L^{-1}. Low fibrinogen was defined as <200 mg dl^{-1}.[18]

Statistical analysis

Patient characteristics were summarised with descriptive statistics. Mean (standard deviation [SD]) and median (interquartile range [IQR]) were used for description of normally and non-normally distributed quantitative variables, respectively. Distribution normality was determined using histograms. Normally distributed values were compared using independent samples Student's *t*-test, whereas the Mann–Whitney *U*-test was used for non-normally distributed covariates. The χ^2 test was used to analyse the differences between categorical variables.

Univariable analysis was performed to assess candidate variables as risk factors for severe PPH; associations between potential risk factors and outcome were quantified by OR and 95% confidence interval (CI). Multivariable forward stepwise logistic regression was performed to assess the relationship between patient characteristics and the occurrence of severe PPH. Variables were selected as candidates for multivariable analysis based on the level of significance of the bivariate association (P<0.1). Ca^{2+} and fibrinogen were included in the univariable analysis both as continuous and binary variables. Model discrimination was measured using receiver operating characteristics (ROC) derived area under the curve (AUC). AUCs were compared as described,[19] with the higher *P*-value presented. Multicollinearity between Ca^{2+} and all other independent variables was assessed using variance inflation factor (VIF), with VIF >5 considered suggestive for multicollinearity.[20] The negative predictive value for development of severe PPH was calculated using Bayes' theorem (Ca^{2+} and fibrinogen were used as binary variables for this purpose). Missing data were handled using list-wise deletion. All available data were used for graph generation.

We used all available data from our databases within the study time frame. To place the available sample size in context, we estimated sample size using the ROC curve (Hanley and McNeil approach).[21] Although limited by an inconsistency of severe PPH definition and inclusion criteria in previous studies, sample size was determined with an expected AUC of Ca^{2+} of 0.7 and an expected incidence of severe PPH of 20% (among patients who developed PPH).[5,22] With a power of 80%, type 1 error rate of 5% (two-sided), and 10% missing data rates, the calculated sample size was 103 patients.

Data analysis was conducted with SPSS version 25.0 (IBM Corp, Armonk, NY, USA), MedCalc for Windows, version 15.0 (MedCalc Software, Ostend, Belgium), and Microsoft Excel version 14.0 (Microsoft Corporation, Redmond, WA, USA).

Results

During the study period, there were 25 550 vaginal deliveries at the RHCC, with 1032 (4%) complicated by PPH. A total of 596 patients were excluded from the analyses: Ca^{2+} measurement was not available for 571 patients, 11 patients were on chronic anticoagulants, and for additional 14 patients Ca^{2+} was measured only after administration of blood products (Fig. 1). The baseline clinical and laboratory characteristics of the 436 included patients, and those of the women not included in the analysis because of lack of Ca^{2+} measurement, are shown in Supplementary Table S1. Women for whom Ca^{2+} levels were not measured required less blood product transfusion and ICU admissions.

Of the 406 included patients, 68 (15.6%) had severe PPH. Among patients with severe PPH, 64 (94.1%) required

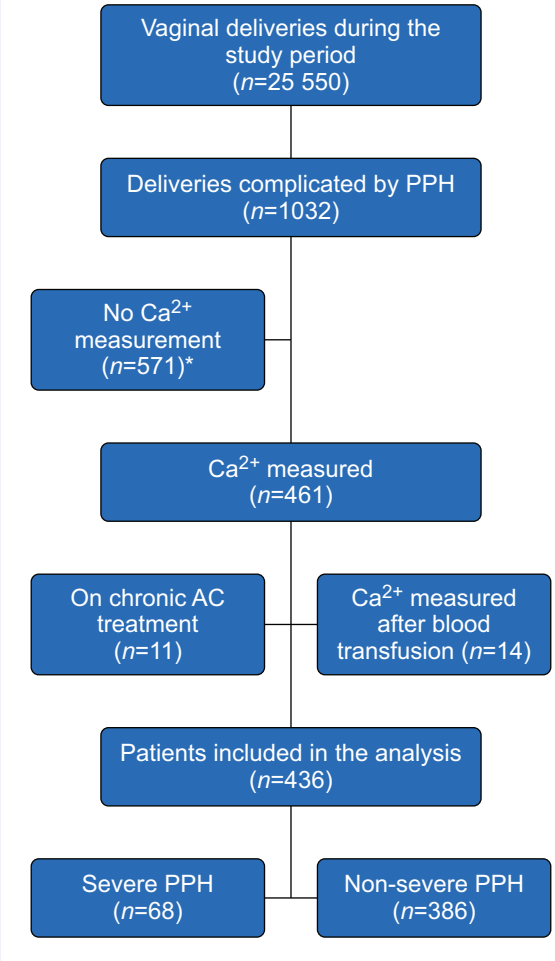

Fig 1. Flowchart of study population. *Thirteen of these 571 patients received antepartum anticoagulation. PPH, postpartum haemorrhage; Ca^{2+}, ionised calcium; AC, anticoagulants.

Table 1 Clinical and laboratory characteristics of 436 women included in the study in relation to outcome. †Odds ratio for 0.1 increase in pH. ‡Coagulation profile values were available for 367 (84.2%) patients. ¶Odds ratio for each 10 mg dl^{-1} decrease in fibrinogen. §Odds ratio for each 0.1 mmol L^{-1} decrease in Ca^{2+}. IQR, inter-quartile range; OR, odds ratio; PT, prothrombin time; PTT, partial thromboplastin time.

	Non-severe postpartum haemorrhage (*n*=368)	Severe postpartum haemorrhage (*n*=68)	OR (95% CI)	*P* value
Age, yr (IQR)	29.5 (26.3–33.7)	30.8 (28.2–35.1)	1.06 (1.01–1.11)	**0.025**
Pregestational BMI, kg m^{-2} (IQR)	28.5 (25.65–31.6)	29.95 (25.75–33.35)	1.05 (0.95–1.17)	0.35
Gestational age at delivery, weeks (IQR)	40 (38–41)	39 (37.5–40)	0.94 (0.86–1.04)	0.27
Parity, *n* (IQR)	2 (1–3)	3 (1.5–3.5)	1.71 (1.19–2.46)	**0.005**
Multiple pregnancy, *n* (%)	18 (4.9)	4 (5.9)	1.22 (0.4–3.71)	0.74
Vacuum extraction, *n* (%)	116 (31.5)	12 (17.6)	0.47 (0.24–0.9)	**0.016**
Complications of pregnancy				
Diabetes mellitus, *n* (%)	6 (1.6)	0 (0)	–	–
Hypertension, *n* (%)	9 (2.4)	2 (2.9)	–	–
Aspirin treatment, *n* (%)	1 (0.3)	1 (1.5)	–	–
Laboratory at admission				
Haemoglobin, g dl^{-1} (IQR)	12.3 (11.3–13.1)	11.75 (10.75–12.75)	0.77 (0.64–0.92)	**0.005**
Platelet count, 10^3 μl^{-1} (IQR)	194 (159.5–235.5)	195 (163–235)	1 (0.99–1)	0.92
Laboratory values at postpartum haemorrhage diagnosis				
pH, (IQR)	7.29 (7.22–7.34)	7.34 (7.28–7.39)	1.95 (1.4–2.72)†	**<0.001**
Lactate, mmol L^{-1} (IQR)	3.9 (2.4–5.6)	2.9 (1.63–4.38)	0.9 (0.79–1.02)	**0.07**
Fibrinogen, mg dl^{-1} (IQR)‡	384 (319.75–444)	214 (151–284)	1.16 (1.12–1.2)¶	**<0.001**
Low fibrinogen (<200 mg dl^{-1}), *n* (%)‡	14 (4.6)	30 (48.4)	19.49 (9.37–40.51)	**<0.001**
PT, s (IQR)‡	10.5 (10–11.2)	10.4 (9.8–11)	1.11 (0.91–1.35)	0.3
PTT, s (IQR)‡	26.7 (24.8–28.65)	28.6 (25.8–33.4)	1.11 (1.05–1.17)	**<0.001**
Haemoglobin, g dl^{-1} (IQR)	10.85 (9.7–12.4)	10.1 (9.45–12)	0.88 (0.71–1.07)	0.2
Platelet count, 10^3 μl^{-1} (IQR)	187 (147–236.25)	211 (172–231)	1.01 (0.99–1.01)	0.31
Ionised calcium, mmol L^{-1} (IQR)	1.44 (1.36–1.5)	1.15 (1.05–1.36)	1.72 (1.49–1.99)§	**<0.001**
Hypocalcaemia (Ca^{2+} <1.16 mmol L^{-1}), *n* (%)	39 (10.6)	35 (51.5)	8.94 (5.01–15.97)	**<0.001**

Statistically significant p-values ($p < 0.05$) are in bold and italicized.

transfusion of two or more blood product units (FFP, RBC, or both), 20 (29.4%) were admitted to the ICU, one (1.5%) required hysterectomy, and two (2.9%) underwent angiographic embolisation. Four or more blood products were transfused in 35 (51.5%) of cases. One woman died during hospitalisation as a result of massive bleeding complications. Baseline clinical and laboratory characteristics and coagulation profile and blood gas analysis at PPH diagnosis in relation to outcome are presented in Table 1. Hypocalcaemia (Ca^{2+} <1.16 mmol L^{-1}) occurred in 74 (17%) patients, and 20 (4.6%) had Ca^{2+} <1 mmol L^{-1}. Fifty-one percent of patients were in the severe bleeding group with hypocalcaemia at diagnosis of PPH compared with 10.6% in the non-severe PPH group ($P<0.001$). Among 74 women with hypocalcaemia at diagnosis of PPH, 35 (47.3%) developed severe PPH compared with 33 of 362 (9.1%) women with normal Ca^{2+} ($P<0.001$).

In a multivariable logistic regression model, fibrinogen and Ca^{2+} concentrations were the only parameters independently associated with severity of PPH with an odds ratio (OR) of 1.14 for each 10 mg dl^{-1} decrease in fibrinogen (95% CI, 1.05–1.24; $P=0.002$) and 1.97 for each 0.1 mmol L^{-1} decrease in Ca^{2+} (95% CI, 1.25–3.1; $P=0.003$). Results of the multivariable analysis are presented in Table 2. Relationships between fibrinogen, Ca^{2+} and clinical outcome are shown in Figure 2.

The performance of Ca^{2+} or fibrinogen in predicting severe bleeding was not significantly different (AUC=0.79 [95% CI, 0.75–0.83] *vs* AUC=0.86 [95% CI, 0.82–0.9] $P=0.09$). Addition of Ca^{2+} to fibrinogen slightly improved the accuracy of fibrinogen, leading to an AUC of 0.9 (95% CI, 0.86–0.93; $P=0.03$) (Fig. 3).

Normal Ca^{2+} level (≥1.16 mmol L^{-1}) had a negative predictive value of 90.9% (95% CI, 87.5–93.7) for development of severe PPH. The negative predictive value of fibrinogen >200 mg dl^{-1} was 90.1% (95% CI, 86.3–93.1).

Discussion

Our findings show that, among high-risk patients with PPH (for whom blood gas analysis was requested), low Ca^{2+} at PPH diagnosis was associated with a higher risk for severe bleeding independently of other laboratory and clinical indicators. Thus, Ca^{2+}, as a standalone parameter or when combined with

Table 2 Results of multivariable logistic regression analysis. †Odds ratio for 0.1 increase in pH. As all VIF values were <5 (maximal VIF was 2.87), we confirmed the absence of multicollinearity. OR, odds ratio; CI, confidence interval; PTT, partial thromboplastin time; VIF, variance inflation factor.

	OR (95% CI)	*P*-value
Age, yr	0.99 (0.86–1.13)	0.90
Parity, *n*	0.94 (0.53–1.67)	0.83
Vacuum extraction, *n*	0.35 (0.02–7.19)	0.50
Haemoglobin, g dl^{-1}	0.88 (0.55–1.4)	0.60
pH†	0.31 (0.09–1.06)	0.06
Lactate, mmol L^{-1}	0.64 (0.37–1.09)	0.10
Fibrinogen,† mg dl^{-1}	1.14 (1.05–1.24)	**0.002**
PTT, s	1.01 (0.9–1.13)	0.87
Ionised calcium,† mmol L^{-1}	1.97 (1.25–3.1)	**0.003**

Statistically significant p-values ($p < 0.05$) are in bold and italicized.

fibrinogen level, can aid in identifying women with high-risk PPH.

PPH is a major cause of preventable peripartum mortality. As much as 70–93% of these deaths are deemed preventable.[23,24] Rapid diagnosis and early multidisciplinary management can improve maternal prognosis.[25] Most cases of PPH are caused by uterine atony, placental abnormalities, and genital tract trauma.[26] However, rapidly developing coagulopathy can contribute to the magnitude and duration of bleeding.[5] Administration of tranexamic acid was shown to reduce mortality and blood loss.[27] A decrease in fibrinogen level is the first sign of impaired coagulation during PPH and an important predictor for severe bleeding when measured at PPH diagnosis.[5,6] Low fibrinogen levels during the early phase of PPH predict multiple blood transfusions, need for surgical and angiographic interventions, admission to the ICU, and death.[5,6,28] It is unclear whether this relationship is associative or causative.[28]

Calcium plays an essential role in the coagulation cascade, platelet aggregation, regulation of vasomotor tone, and cardiac function. Direct point of care measurement of Ca^{2+} is widely available in most emergency departments, operating theatres, and ICUs as a feature of nearly all blood gas analysers. Hypocalcaemia is common in critically ill and trauma patients.[10,29] However, its pathogenesis and association with disease severity and outcomes are poorly defined.[10] Citrate toxicity may explain hypocalcaemia during massive transfusion, and intravenous colloid (but not crystalloid) induced haemodilution can lead to hypocalcaemia.[9,30] Other proposed mechanisms include increased sympathetic activity, altered sensitivity, and impaired parathyroid function, end-organ resistance to parathyroid hormone, altered vitamin D synthesis and action, all induced by pro-inflammatory cytokines.[10,31]

Studies in trauma casualties have shown that up to 56% of severely injured casualties are hypocalcaemic on arrival to the emergency department,[10,31] and low Ca^{2+} was associated with higher mortality and increased need for blood products. Once trauma patients begin to receive blood products, the incidence of hypocalcaemia and its severity increase.[30] Hypocalcaemia is common in critically ill patients. It correlates with Acute Physiology and Chronic Health Evaluation II (APACHE II) score and, if it persists, may be associated with increased mortality.[32] Calcium replacement was not shown to improve outcomes in this population, suggesting that the relationship between outcomes and hypocalcaemia may not be causal.[32,33] No studies have evaluated the effect of hypocalcaemia correction in trauma casualties.

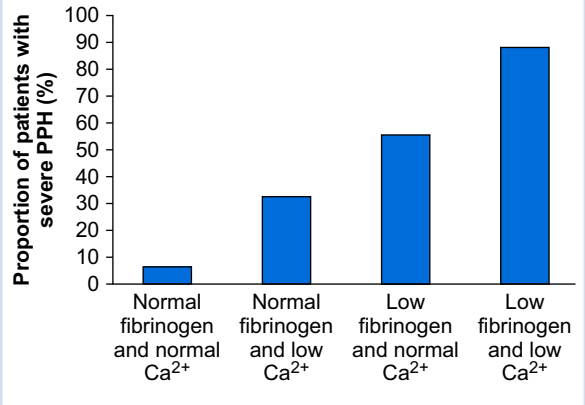

Fig 2. The relationships between fibrinogen, ionised calcium, and clinical outcome. Low fibrinogen was defined as fibrinogen <200 mg dl^{-1} and low Ca^{2+} was defined as Ca^{2+} <1.16 mmol L^{-1}. Ca^{2+}, ionised calcium; PPH, postpartum haemorrhage.

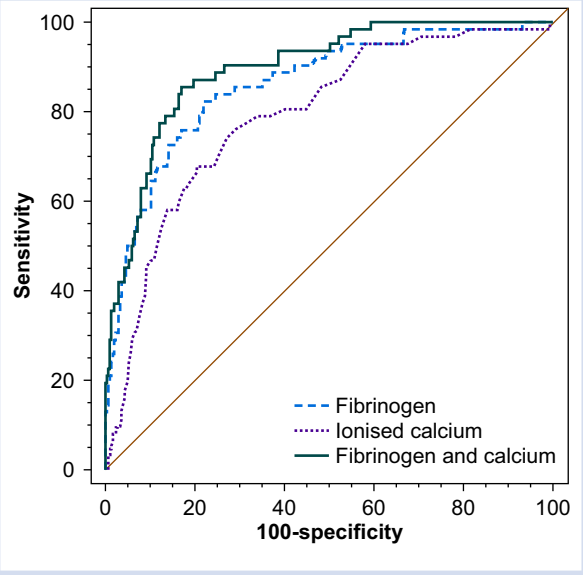

Fig 3. Receiver operating characteristic (ROC) curves of fibrinogen, ionised calcium, and combination of both for the prediction of severe postpartum haemorrhage. The areas under the curve (AUCs) for Ca^{2+} and fibrinogen were not significantly different (AUC=0.79 [95% CI, 0.75–0.83] *vs* AUC=0.86 [95% CI, 0.82–0.9]; P=0.09). Combination of Ca^{2+} and fibrinogen performed slightly better than fibrinogen alone with an AUC of 0.9 (95% CI, 0.86–0.93; P=0.03). CI, confidence interval.

Studies on healthy volunteers showed that Ca^{2+} level >0.56 mmol L^{-1} is unlikely to cause significant coagulation abnormalities *in vitro*.[34] Ho and Yip[9] showed a concentration-dependent association between Ca^{2+} level and *in vitro* clot strength measured by thromboelastography in patients at risk of bleeding or with active bleeding. Vasudeva and colleagues[31] described an association between Ca^{2+} and coagulopathy among critically injured adults without prior transfusion of any blood products. However, both studies could not exclude the possibility that hypocalcaemia may be a marker for other causes of decreased clot strength. To the best of our knowledge, no studies have evaluated the *in vitro* effect of Ca^{2+} in bleeding or critically ill patients.

Most blood gas analysers report Ca^{2+} normalised to a pH of 7.4. Acidosis decreases protein binding, resulting in increased free calcium. For each 0.1 decrease in pH, Ca^{2+} increases by ~0.05 mmol L^{-1}.[8] We speculated that the influence of hypocalcaemia may be more important during the early stages of bleeding before overt metabolic acidosis develops leading to Ca^{2+} increase. However, in patients with severe acidosis or alkalosis, Ca^{2+} measurement should be interpreted with caution (especially when calcium replacement is considered) as over- or underestimation can occur.

Although some alterations in calcium homeostasis take place during pregnancy, the level of Ca^{2+} remains stable during gestation and within the reference interval for non-

pregnant women.[35] Ca^{2+} may have a role in uterine contraction. In an *in vitro* study, normocalcaemia was associated with superior oxytocin-induced contractility, compared with contraction produced by oxytocin in uterine tissue with abnormal Ca^{2+}. The differences vanished in myometrium pretreated with oxytocin.[11] In another trial, when oxytocin was combined with calcium chloride after Caesarean delivery, no changes in uterine tone or blood loss were recorded.[36] However, a recent study suggests that a higher dose of calcium chloride (1 g) reduced the incidence of uterine atony in high-risk patients.[37] If true, a dose-dependent effect of Ca^{2+} on uterine tone may serve as an additional therapeutic target in PPH treatment.

We found that even mild hypocalcaemia during the initial stages of PPH is associated with increased risk for the development of severe PPH. The predictive ability of Ca^{2+} measured at diagnosis of PPH and before any blood transfusion is comparable with that of fibrinogen, a well-established prognostic factor. In contrast to standard laboratory coagulation tests that are time-consuming, with turnaround times above 60 min, and point-of-care technologies, such as thromboelastography and rotational thromboelastometry (ROTEM®), which are not widely available, measurement of Ca^{2+} can be accomplished within minutes.[28] Ca^{2+} measurement may be used independently or in addition to fibrinogen during the initial resuscitation and risk stratification. Patients with low fibrinogen and low Ca^{2+} levels have an especially high risk for adverse outcomes and should be monitored closely with preparations made for possible massive transfusion or an advanced surgical or angiographic intervention.

No study has assessed the benefits of early hypocalcaemia correction in the obstetric population. Our study could not determine whether the relationship between severe PPH and Ca^{2+} level is causative or represents a correlation as it was not designed to address the role of Ca^{2+} in PPH. Our study has several additional limitations. First, we included only women for whom Ca^{2+} was measured (44% of patients with PPH during the study period). Women for whom blood gas analysis was not performed are likely to have had milder bleeding reflected by lower rates of blood transfusion and ICU admission. Second, in this retrospective study, the identification of subjects with PPH relied on ICD-10 diagnostic coding at discharge. Although in our cohort the prevalence of PPH was 4%, which is comparable with reported estimates, it is possible that some women with PPH did not receive appropriate coding.[26] Studies regarding the accuracy of ICD-10 coding for PPH diagnosis are limited and revealed conflicting results.[38,39] No studies were conducted in the Israeli healthcare system. Third, the decision to transfuse RBC is mainly based on clinical judgment and visual estimation of blood loss, making standardisation challenging.[15] Fourth, the definition of severe PPH is variable, especially regarding the amount of blood transfused (ranging from 1 to 4 RBC units), making it difficult to compare our findings to the findings of others.[5,7] Fifth, the cause of PPH, which may affect bleeding severity, and exact uterotonic and antifibrinolytic treatments were not included in the analysis. Women at RHCC are routinely treated with uterotonic agents as the first-line treatment when PPH is diagnosed, and tranexamic acid is administrated when the initial medical therapy fails at the discretion of the attending physician.[15] However, the exact timing and prevalence of these therapies were not included in the analysis and may influence the results. Sixth, the prevalence of DM and HTN in our cohort was low, limiting the ability to evaluate their effect on our results and the extrapolation of our findings to populations of women with higher rates of comorbidities.

Conclusions

Ionised Ca^{2+} levels at the time of PPH diagnosis is a marker of the risk of severe bleeding. Identification of hypocalcaemia may facilitate rapid identification of high-risk patients requiring rapid multidisciplinary obstetric and medical management. This marker may be particularly useful as it is rapidly determined by blood gas analysis. The results of our study suggest the need to perform a randomised controlled trial that would assess the effect of calcium supplements on the clinical course of women with PPH and reduced serum Ca^{2+}. Additional studies that look at uterine atony and coagulopathy in conjunction with low Ca^{2+} are also warranted.

Authors' contributions

Study concept: DE, AK, EM, YF, AN, AR, AM
Study design: DE, NS, RA, AR, AM
Data collection: DE, NS, AK
Data analysis: DE, NS, AR, AM
Statistical analysis: DE, NS
Interpretation of results: EM, YF
Drafting of the manuscript: DE, NS
Critical review of the manuscript: AK, EM, YF, RA, AN, AR, AM
Manuscript revision: RA, AN
Approved the final version of the manuscript: AK, EM, YF, RA, AN, AR, AM
All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declarations of interest

AR is a consultant for Medtronic and is supported by the United States–Israel Binational Science Foundation (not related to this study). The other authors declare that they have no conflict interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.11.020.

References

1. Ford JB, Patterson JA, Seeho SKM, Roberts CL. Trends and outcomes of postpartum haemorrhage, 2003–2011. *BMC Pregnancy Childbirth* 2015; **15**: 334
2. Callaghan WM, Kuklina EV, Berg CJ. Trends in postpartum hemorrhage: United States, 1994–2006. *Am J Obstet Gynecol* 2010; **202**: 353. e1–6
3. Henriquez DDCA, Bloemenkamp KWM, van der Bom JG. Management of postpartum hemorrhage: how to improve maternal outcomes? *J Thromb Haemost* 2018; **16**: 1523–34
4. Chandraharan E, Krishna A. Diagnosis and management of postpartum haemorrhage. *BMJ* 2017; **358**: j3875
5. Cortet M, Deneux-Tharaux C, Dupont C, et al. Association between fibrinogen level and severity of postpartum haemorrhage: secondary analysis of a prospective trial. *Br J Anaesth* 2012; **108**: 984–9

6. Butwick AJ. Postpartum hemorrhage and low fibrinogen levels: the past, present and future. *Int J Obstet Anesth* 2013; **22**: 87–91
7. Charbit B, Mandelbrot L, Samain E, et al. The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. *J Thromb Haemost* 2007; **5**: 266–73
8. Bushinsky DA, Monk RD. Calcium. *Lancet* 1998; **352**: 306–11
9. Ho KM, Yip CB. Concentration-dependent effect of hypocalcaemia on in vitro clot strength in patients at risk of bleeding: a retrospective cohort study. *Transfus Med* 2016; **26**: 57–62
10. Magnotti LJ, Bradburn EH, Webb DL, et al. Admission ionized calcium levels predict the need for multiple transfusions: a prospective study of 591 critically ill trauma patient. *J Trauma - Inj Infect Crit Care* 2011; **70**: 391–7
11. Talati C, Ramachandran N, Carvalho JCA, Kingdom J, Balki M. The Effect of extracellular calcium on oxytocin-Induced contractility in naive and oxytocin-pretreated human myometrium in vitro. *Anesth Analg* 2016; **122**: 1498–507
12. Hochberg I. Insulin detemir use is associated with higher occurrence of hypoglycemia in hospitalized patients with hypoalbuminemia. *Diabetes Care* 2018; **41**: e44–6
13. Masarweh K, Gur M, Leiba R, et al. Factors predicting length of stay in bronchiolitis. *Respir Med* 2020; **161**: 105824
14. Reiner Benaim A, Almog R, Gorelik Y, et al. Analyzing medical research results based on synthetic data and their relation to real data results: systematic comparison from five observational studies. *JMIR Med Inform* 2020; **8**, e16492
15. Shields LE, Goffman D, Caughey AB. ACOG practice bulletin: clinical management guidelines for obstetrician-gynecologists. *Obstet Gynecol* 2017; **130**: e168–86
16. Driessen M, Bouvier-Colle MH, Dupont C, Khoshnood B, Rudigoz RC, Deneux-Tharaux C. Postpartum hemorrhage resulting from uterine atony after vaginal delivery: factors associated with severity. *Obstet Gynecol* 2011; **117**: 21–31
17. Bilkovski RN, Cannon CM, Adhikari S, Nasr I. Arterial and venous ionized calcium measurements: is there a difference? *Ann Emerg Med* 2004; **44**: S56
18. Matsunaga S, Takai Y, Seki H. Fibrinogen for the management of critical obstetric hemorrhage. *J Obstet Gynaecol Res* 2019; **45**: 13–21
19. Cleves MA. Comparative assessment of three common algorithms for estimating the variance of the area under the nonparametric receiver operating characteristic curve. *Stata J Promot Commun Stat Stata* 2002; **2**: 280–9
20. Kutner MH, Nachtsheim CJ, Neter JLW. *Applied linear statistical models*. 5th Edn. New York: McGraw-Hill/Irwin; 2004
21. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982; **143**: 29–36
22. Deneux-Tharaux C, Dupont C, Colin C, et al. Multifaceted intervention to decrease the rate of severe postpartum haemorrhage: the PITHAGORE6 cluster-randomised controlled trial. *BJOG* 2010; **117**: 1278–87
23. Berg CJ, Harper MA, Atkinson SM, et al. Preventability of pregnancy-related deaths: results of a state-wide review. *Obstet Gynecol* 2005; **106**: 1228–34
24. Main EK, McCain CL, Morton CH, Holtby S, Lawton ES. Pregnancy-related mortality in California. *Obstet Gynecol* 2015; **125**: 938–47
25. Sentilhes L, Vayssière C, Deneux-Tharaux C, et al. Postpartum hemorrhage: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF): in collaboration with the French Society of Anesthesiology and Intensive Care (SFAR). *Eur J Obstet Gynecol Reprod Biol* 2016; **198**: 12–21
26. Oyelese Y, Ananth CV. Postpartum hemorrhage: epidemiology, risk factors, and causes. *Clin Obstet Gynecol* 2010; **53**: 147–56
27. Shakur H, Roberts I, Fawole B, et al. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *Lancet* 2017; **389**: 2105–16
28. Butwick AJ, Goodnough LT. Transfusion and coagulation management in major obstetric hemorrhage. *Curr Opin Anaesthesiol* 2015; **28**: 275–84
29. Byrnes MC, Huynh K, Helmer SD, Stevens C, Dort JM, Smith RS. A comparison of corrected serum calcium levels to ionized calcium levels among critically ill surgical patients. *Am J Surg* 2005; **189**: 310–4
30. Ditzel RM, Anderson JL, Eisenhart WJ, et al. A review of transfusion- and trauma-induced hypocalcemia. Is it time to change the lethal triad to the lethal diamond? *J Trauma Acute Care Surg* 2020; **88**: 434–9
31. Vasudeva M, Mathew JK, Fitzgerald MC, Cheung Z, Mitra B. Hypocalcaemia and traumatic coagulopathy: an observational analysis. *Vox Sang* 2020; **115**: 189–95
32. Steele T, Kolamunnage-Dona R, Downey C, Toh CH, Welters I. Assessment and clinical course of hypocalcemia in critical illness. *Crit Care* 2013; **17**: R106
33. Aberegg SK. Ionized calcium in the ICU should it be measured and corrected? *Chest* 2016; **149**: 846–55
34. James MFM, Roche AM. Dose-response relationship between plasma ionized calcium concentration and thrombelastography. *J Cardiothorac Vasc Anesth* 2004; **18**: 581–6
35. Dahlman T, Sjoberg HE, Bucht E. Calcium homeostasis in normal pregnancy and puerperium. A longitudinal study. *Acta Obstet Gynecol Scand* 1994; **73**: 393–8
36. Farber MK, Schultz R, Lugo L, Liu X, Huang C, Tsen LC. The effect of co-administration of intravenous calcium chloride and oxytocin on maternal hemodynamics and uterine tone following cesarean delivery: a double-blinded, randomized, placebo-controlled trial. *Int J Obstet Anesth* 2015; **24**: 217–24
37. Kalariya N, Ansar JR, Carvalho B, Riley E. Calcium chloride for the prevention of uterine atony during high risk cesarean delivery: a randomized clinical efficacy and safety study. In: *Soc Obstet Anesth Perinatol 52nd Annu Meet*; 2020. Available from: https://soap.org/wp-content/uploads/2020/09/2020_SOAP_AM_Syllabus-1.pdf. [Accessed 20 September 2020]
38. Griffin M, Mohnot S, Davis K, Pollack R, Koklanaris N, Temming L. Are ICD-10 codes accurate for identifying postpartum hemorrhage? *Am J Obstet Gynecol* 2020; **222**: S227
39. Butwick AJ, Walsh EM, Kuzniewicz M, Li SX, Escobar GJ. Accuracy of international classification of diseases, ninth revision, codes for postpartum hemorrhage among women undergoing cesarean delivery. *Transfusion* 2018; **58**: 998–1005

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