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Antenatal fibrinogen concentrations and postpartum haemorrhage

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ABSTRACT
Background: It is unclear whether antenatal fibrinogen concentrations are associated with postpartum haemorrhage.
Methods: This retrospective study included 871 women with a singleton pregnancy but no known risk factors for postpartum haemorrhage, in whom fibrinogen concentration was measured within the 21 days before delivery. Correlation between antenatal fibrinogen concentrations and estimated blood loss was analysed. We tested the hypothesis that the risk of postpartum haemorrhage was higher in women with antenatal fibrinogen concentrations of <3.3 g/L. Postpartum haemorrhage was defined as an estimated blood loss ⩾700 mL following vaginal delivery and ⩾1000 mL following caesarean delivery.
Results: In women delivering vaginally ($n = 337$), estimated blood loss tended to increase with decreasing antenatal fibrinogen concentration ($R = -0.107$, $P = 0.05$), median fibrinogen concentration was significantly lower in 69 women with postpartum haemorrhage than in 268 women without postpartum haemorrhage (3.93 vs. 4.18 g/L, $P = 0.025$), and postpartum haemorrhage occurred significantly more often in women with fibrinogen concentrations <3.3 g/L than in those with concentrations ⩾3.3 g/L (38% [11/29] vs. 19% [58/308], $P = 0.018$). In women undergoing caesarean delivery ($n = 534$), median fibrinogen concentration did not differ between those who experienced postpartum haemorrhage ($n = 128$) and those who did not ($n = 406$) (4.18 g/L vs. 4.07 g/L, $P = 0.43$). Antenatal fibrinogen concentrations of <3.3 g/L were not associated with higher rates of postpartum haemorrhage (26% [11/43] vs. 24% [117/491], $P = 0.80$).
Conclusions: Antenatal fibrinogen concentration <3.3 g/L may be a risk factor for postpartum haemorrhage among women following vaginal delivery.

Keywords: Postpartum haemorrhage; Fibrinogen; Vaginal delivery; Caesarean delivery

Introduction

Postpartum haemorrhage (PPH) is the leading cause of maternal mortality, accounting for approximately one third of maternal deaths in Africa and Asia,[1] and it remains a major cause of maternal mortality in developed countries. PPH has been associated with 12.5–19.1% of maternal mortality in the USA.[2,3] In Japan, the maternal mortality rate is <5 per 100 000 births according to the Japanese Ministry of Heath, Labour and Welfare[4] with PPH accounting for 14.1%, 9.7% and 6.7% of all causes of maternal mortality in Japan in 2000, 2005 and 2010, respectively.[5]

Although risk factors such as prolonged, augmented or rapid labour, history of PPH, preeclampsia, distended uterus and operative delivery are associated with PPH,[6] it can occur without warning. Causes such as uterine rupture, uterine inversion, retained placenta and birth canal injury may be identified; however, the leading aetiology of PPH is uterine atony, and many women who develop PPH from uterine atony do not have known risk factors.[2]

There is interest in how the maternal coagulation profile alters during the course of PPH and fibrinogen has been identified an important factor that may influence the magnitude of blood loss.[7–11] Studies have demonstrated that women who develop severe PPH have a low fibrinogen concentration in the initial stage of haemorrhage, that fibrinogen concentration in the initial stages of haemorrhage is a significant predictor of severity of PPH, and that decreases in fibrinogen concentration are closely correlated with the severity of blood loss. These studies have not determined whether a low fibrinogen concentration in the initial stages of PPH is caused by haemorrhage itself or reflects fibrinogen concentration before labour. It is unclear whether a low antenatal fibrinogen concentration is associated with PPH.

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This retrospective study was conducted to determine whether women with lower antenatal fibrinogen concentrations had a higher risk of developing PPH in the absence of known risk factors for PPH.

Methods

This retrospective study was conducted with the approval of the Ethics Committee of Hokkaido University Hospital. The institutional delivery database was searched for women who gave birth to a singleton infant at or after gestational week 32 at Hokkaido University Hospital between 1 April 2007 and 31 March 2013. Women who had their fibrinogen levels checked in the 21 days pre-delivery and who had no known risk factors for PPH were included. Women were divided into two groups according to whether they had a vaginal or caesarean delivery. PPH was defined as an estimated blood loss (EBL) $\geqslant$700 mL for vaginal delivery and $\geqslant$1000 mL for caesarean delivery.

Laboratory tests, including full blood count, biochemistry and coagulation-fibrinolysis are performed for the majority of pregnant women at our clinic and for those admitted to hospital for management of obstetric and incidental complications. All blood fibrinogen data from the institutional central laboratory were obtained for each patient during the study period. In some women, fibrinogen concentration was measured several times within 21 days of delivery. The fibrinogen value determined on the day closest to delivery was used. Demographic characteristics and EBL within 24 h of delivery were recorded from medical charts. Fibrinogen concentration was measured using the Clauss thrombin clotting time method in citrated blood samples and a haematology analyzer (CS2000i, Sysmex Co. Ltd., Kobe, Japan) after centrifugation. Intra- and inter-assay coefficients of variation were <6% and 10%, respectively. Normal fibrinogen concentration at our institution, not specific for pregnancy, is 2–4 g/L.

Statistical analysis

Linear regression analysis was used to test the hypothesis that the risk of PPH was higher in women with antenatal fibrinogen concentration of <3.3 g/L than in those with antenatal fibrinogen concentration of $\geqslant$3.3 g/L. Data are presented as median [range] or mean $\pm$ standard deviation (SD). Statistical analyses were performed using the JMP10© statistical software package (SAS, Cary, NC, USA). ANOVA and Tukey–Kramer HSD (honestly significant difference) tests were used for comparison of means. The Wilcoxon/Kruskal–Wallis method was used for comparison of medians. Fisher's exact test was used for comparison of categorical variables. In all analyses, $P < 0.05$ was considered statistically significant.

Results

A total of 1473 women were identified: 766 following vaginal delivery and 707 after caesarean delivery (Fig. 1). After matching fibrinogen data with medical charts, 925 women were found to have had blood fibrinogen concentrations measured in the 21 days before delivery. Fifty-four women with known risk factors for PPH before or after delivery were excluded: 52 with placenta praevia or low-lying placenta with or without placenta accreta, one who underwent radical hysterectomy after caesarean delivery for treatment of uterine cervical cancer, and one with uterine inversion immediately after delivery. The study therefore looked at data from 871 women, representing 59% of the 1473 women originally identified. Of the 871 women, 337 delivered vaginally and 534 underwent caesarean delivery (Table 1).

For the 337 women delivering vaginally, EBL within 24 h after delivery was $\geqslant$700 mL in 67 (20%), >600 mL in 94 (28%) and >500 mL in 142 (42%). For caesarean deliveries, EBL within 24 h after delivery was $\geqslant$1000 mL in 128 of 534 women (24%).

In women delivering vaginally, median [range] fibrinogen concentration of those who had a PPH was significantly lower than that of women who did not (3.93 [2.57–5.71] g/L vs. 4.18 [2.08–6.30] g/L, $P = 0.025$). For caesarean delivery, there was no difference in median [range] fibrinogen concentration for 128 women who had a PPH compared to the 406 who did not (4.18 [2.57–6.66] g/L vs. 4.07 [1.79–8.98] g/L, $P = 0.43$).

The distribution of fibrinogen concentrations is shown in Fig. 2. Distribution did not differ between women in the vaginal and caesarean delivery groups: mean fibrinogen concentrations for women delivering vaginally or by caesarean were similar (4.13 ± 6.7 g/L vs. 4.17 ± 7.0 g/L, $P > 0.05$). Fibrinogen concentrations of <3.0 g/L and <3.3 g/L were detected in 23 (2.6%) and 72 (8.3%) of all patients, respectively.

Estimated blood loss tended to increase with decreasing antenatal fibrinogen concentration in 337 women with vaginal deliveries ($R = -0.1067$, $P = 0.05$) (Fig. 3), but not in 534 women with caesarean deliveries ($R = 0.048$, $P = 0.26$).

Among women delivering vaginally, the frequency of PPH was significantly higher in women with fibrinogen concentrations of <3.3 g/L than in those with fibrinogen concentrations of $\geqslant$3.3 g/L (Fig. 4). A fibrinogen cut-off value of 3.3 g/L yielded sensitivity of 16% (11/69), specificity of 93% (250/268), positive predictive value of 38% (11/29), and negative predictive value of 81% (250/308) for PPH. In women undergoing caesarean delivery, the frequency of PPH did not differ significantly for antenatal fibrinogen concentration above or below 3.3 g/L.