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Link to publication

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Postpartum haemorrhage (PPH) remains a major causeof obstetric mortality and requires immediate multidisciplinarymedical and surgical treatment. This includes correction of coagulopathy by resuscitation with bloodcomponents.[1] The use of rotational thromboelastometry (ROTEM) is useful for rapid diagnosis of coagulopathy and reliable assessment of fibrinogen levels in PPH.[2,3] While assessment of platelet function with multiple electrode aggregometry (Multiplate, Verum Diagnostica,Munich, Germany) has been documented in trauma,[4] it has not to our knowledge been studied in obstetrics. Multiplate uses 3 mL of hirudin-anticoagulated whole blood sampled in special vacutainer tubes; analysis time is 6 min and it is easy to use at the bedside and can be set to the patient's actual temperature. It is recommended that the freshly sampled blood stabilize at room temperature before analysis, but in severe bleeding, analysis can be started immediately. Therefore, it can be advantageous compared to laboratory platelet counts. The theoretical principles and background of multiple electrode aggregometry have been previously explained.[4]
We present a case of PPH in which Multiplate was used to guide intraoperative platelet transfusion and evaluate postoperative haemostasis.

A 39-year-old G2P1 woman at 36 + 6 weeks of gestation was admitted for induction of labour due to fetal macrosomia. The patient was healthy and pregnancy had been otherwise uneventful. Induction of labour with misoprostol 0.05 mg started at 15.00 h and by 20.00 h there were regular uterine contractions. At 22.30 h, after a membrane sweep, painless vaginal bleeding with blood clots occurred which stopped spontaneously. Membrane rupture occurred at 01.00 h the next morning and at 03.00 h, following further vaginal bleeding, an oxytocin infusion was started. Laboratory results showed a normal haemoglobin (Hb), internationalized ratio (INR) and platelet count (Table 1). At approximately 06.40 h the contractions became stronger and were accompanied by significant vaginal bleeding and pathological fetal heart rate decelerations. Oxytocin was discontinued at which point blood loss was 1.5 L. As the woman complained of dizziness and altered vision, she was transferred to the operating room at 07.20 h for delivery of a healthy neonate by caesarean section under general anaesthesia. The placenta

was removed manually andno signs of abruption were seen. The patient developed severe hypotension despite intravenous crystalloid anhydroxyethyl starch. Tranexamic acid 2 g was administered as an intravenous bolus, in addition to desmopressin 30 lg infused over 30 min. The uterus initially responded to massage and oxytocin, methyl ergometrine and carboprost, but became increasingly atonic. Due to uncontrolled vaginal bleeding and persistent uterine atony, a hysterectomy was performed. At 07.30 h, transfusion of blood and blood products was started. Fibrinogen concentrate 4 g was also administered.ROTEM (EXTEM and FIBTEM assays) and Multiplate (ADP, COL, TRAP, ASPI, and RISTO assays) and Hemochrone Jr whole blood PT-INR were performed at 08.40 h together with routine coagulation analyses. In response to results for the Multiplate systems and ROTEM, which were available after 10 and 30 min, respectively (routine coagulation laboratory analyses were ready at 09.20 h), four additional units of platelets and fresh frozen plasma (FFP) were transfused together with further fibrinogen concentrate 4 g. An elevated Hemochrone Jr whole blood PT-INR guided the administration of 1500 units of prothrombin complex concentrate. In total, estimated blood loss was 8.5 L. Surgery ended at 11.00 h. Routine coagulation, ROTEM and Multiplate parameters were tested regularly during the postoperative period. Low platelet counts on days 1 and 2 were treated with platelet transfusion with no obvious effects on ROTEM, Multiplate or platelet counts. Thromboprophylaxis with low-molecular-weight heparin was started on day 3 and continued until day 9. The Multiplate data (area under curve) showed that there was profound dysfunction of the ADP receptor, the arachidonic acid pathway (metabolism to thromboxane A2 and/or the TXA2 receptor ASPI) and the vWF interaction (RISTO), whereas collagen and thrombin-induced activation (COL and TRAP, respectively) were only moderately decreased (Fig. 1). This pattern with initially low Multiplate ADP-receptor function, but no disturbance of COL/TRAP has been shown in trauma patients.[4] Multiplate results were checked against an alternative point-of-care platelet function monitor, VerifyNOW (Accumetrics, San Diego, CA, USA) which indicated normal reactivity (261 PRU). However, Vasodilator Stimulated Phosphoprotein (VASP) analysis for the ADP-P2Y12 receptor showed only 35% reactivity, corroborating our Multiplate results (the patient was not receiving platelet function altering medications). This differs from the platelet count, which remained stable after day 4 when it was >60 · 109/L. A limitation in the interpretation of these data is that the measured platelet function is correlated to the platelet count when using the Multiplate system, an effect that might be especially pronounced when the platelet concentration falls to low levels.

During the immediate postoperative period, platelet reactivity for all agonists increased; hyper-reactivity was seen in the collagen and thrombin pathways whereas the other pathways experienced a moderate increase in reactivity (still below reference intervals).

Platelet reactivity increased above the reference intervals for all pathways except ADP on postoperative day 8. As high platelet counts increase the Multiplate signals, there may be an increased risk for thromboembolism.[6] However, it is unknown whether this applies to all complex deliveries. ROTEM parameters (both EXTEM and FIBTEM-MCFs) were still within reference intervals at this point, and plasma-fibrinogen levels did not show an acute phase reactant increase. In this case, our transfusion experience reflects recommendations in the trauma literature to use an increased ratio of FFP and platelets to red blood cells and the opinion that obstetric haemorrhage can be similarly managed.[7] UK guidelines for transfusion recommend a 1:1:1 transfusion ratio (RBC:FFP:platelets) in the critical care setting.[8] Supporting evidence is weaker in the obstetric setting than in trauma since there is less tissue damage and medical intervention is usually closer to hand.[8] In the immediate postoperative period we adopted a conservative approach to platelet transfusion so the platelet count did not increase above $50 \cdot 10^9$/L and Multiplate ADP/ASPI/RISTO were still low. There was no clinical evidence of ongoing bleeding, although Hb decreased to 8.1 g/dL on day 1 but increased to 9.7 g/dL following transfusion of two units of RBC. This case would support the notion that more aggressive fibrinogen replacement might be necessary during obstetric haemorrhage: a high ratio of RBC to fibrinogen concentrate may not be appropriate and more platelet transfusion may be needed.

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Table 1 Cumulative blood loss, fluid therapy and laboratory analyses

	04.50 h	07.20 h	08.40 h	09.20 h	11.00 h	16.00 h	Day 1	Day 2	Day 3	Day 4	Day 8
Blood loss (mL)		1500	4500	6000	8500						
Intravenous fluids											
Crystalloids (mL)		1500			3600	4600					
Colloids (mL)			500								
RBC (units)			8	9	10	10	12				
FFP (units)			4	6	10						
Platelets (units)			2	4	6	8	10	12			
Haemoglobin (g/dL)	12.2		8.4	10.7	7.7	8.9	8.1	9.7	10.0	10.7	11.1
Lactate (mmol/L)			5.1	3.4	1.3	0.9					
INR	1.0		2	1	1.1	1	1	1.1		0.9	1
APTT (s)	36		166	44	37	40	40	40	41	45	41
Platelet ($\times 10^9$/L)	189			21	49	40	39	40	50	62	165
Fibrinogen (g/L)	3.7			7.3	2	2.3	2.7	2.8	3.1	3.7	3.6
AT III (kIE/L)	0.82			0.25	0.63	0.69				0.86	
D-dimer (mg/L)	1.3			>10	>10	>10	6.0	4	1.3	0.45	
Fibrinogen concentrate (g)			4	8							
PCC (IU)					1500						

RBC: red blood cell concentrate; FFP: fresh frozen plasma; INR: prothrombin-international normalised ratio; APTT: activated partial thromboplastin time; AT III: antithrombin III; PCC: prothrombin complex concentrate.
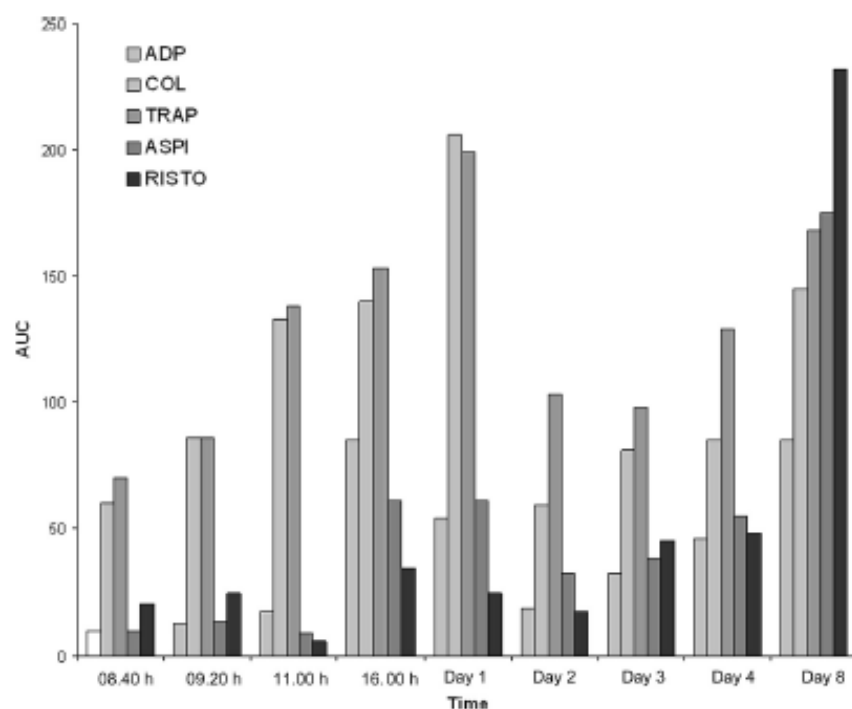
Fig. 1 Multiplate platelet aggregometry analysis with ADP, COL, TRAP, ASPI and RISTO assays