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Peri-partum reference ranges for ROTEM® thromboelastometry

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Editor's key points

- Point of care visco-elastic monitoring is useful in guiding haemostatic therapy in patients with massive haemorrhage.
- There are limited data to establish reference ranges for thromboelastometric coagulation parameters in peri-partum patients.
- Reference ranges for ROTEM® coagulation monitoring were determined; these will be useful in setting thresholds for treatment of post-partum haemorrhage.

Background. Post-partum haemorrhage (PPH) causes rapidly developing deficiencies in clotting factors and contributes to substantial maternal morbidity and mortality. Rotational thromboelastometry (ROTEM®) is increasingly used as a point of care coagulation monitoring device in patients with massive haemorrhage; however, there are limited data on reference ranges in the peri-partum period. These are required due to the haemostatic changes in pregnancy.

Methods. In a Dutch multi-centre trial, 161 subjects were included; blood samples were obtained during labour (T1) and within 1 h of delivery (T2). Reference ranges of ROTEM® INTEM, EXTEM, FIBTEM, and APTEM were set and correlation with laboratory results was investigated using the guidelines of the International Federation of Clinical Chemistry.

Results. Reference ranges were obtained for clotting time (CT), clot formation time (CFT), α-angle, clot firmness at 10 and 20 min (A10, A20), maximum clot firmness (MCF), and maximum lysis (ML). These were comparable from centre to centre, and between T1 and T2. Reference ranges T1: EXTEM: CT 31–63 s, CFT 41–120 s, and MCF 42–78 mm. INTEM: CT 109–225 s, CFT 40–103, and MCF 63–78 mm. FIBTEM: CT 31–79 s and MCF 13–45 mm. APTEM: CT 33–62 s, CFT 42–118, and MCF 61–79 mm.

Conclusions. Reference values for ROTEM® parameters are reported. The previously published correlation between FIBTEM parameters and plasma fibrinogen levels by the Clauss method is confirmed. Further research is needed to define threshold values for haemostatic therapy in the course of PPH.

Clinical trial registration. NTR 2515 (http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=2515).

Keywords: blood, coagulation; haemostasis; post-partum haemorrhage; reference values; thromboelastography

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Worldwide, post-partum haemorrhage (PPH) is the leading cause of maternal morbidity and mortality.[1] The course of PPH is unpredictable. Therefore, timely recognition and adequate treatment is crucial. Guidelines and flowcharts have been published to optimize the management of PPH.[2–5] In these guidelines, laboratory tests [haemoglobin (Hb), platelet count, fibrinogen, activated partial thromboplastin time (APTT), and prothrombin time (PT)] are used to monitor haemostatic competence. However, in most cases, therapy of PPH cannot be based on the actual haemostatic capacity of the patient since laboratory tests typically require 45–60 min for results to be available. Also, most coagulation tests were intended not for monitoring clotting abnormalities, but for diagnosing single-factor

coagulation defects and monitoring the effect of anticoagulant medication.[6]

Rotational thromboelastometry (ROTEM®) and thromboelastography (TEG) are dynamic, visco-elastic coagulation tests that reflect the coagulation process from initiation of clot formation until fibrinolysis. The tests are performed on whole blood instead of plasma, which saves time and gives a quick glance at the interaction between cellular and plasmatic clotting factors. The use of ROTEM® or TEG in massive bleeding in non-obstetric patients is widely practised and has proved cost-effective.[7] Current literature[8 9] and a guideline[10] for the treatment of massive haemorrhage in trauma patients recommend the use of TEG or ROTEM®. However, ROTEM®/TEG results in non-pregnant patients cannot be compared with women during labour, as specific pregnancy and peri-partum-related haemodynamic and haemostatic changes are likely to influence ROTEM®/TEG results.

Several studies have been published on the use of thromboelastometry in pregnancy, confirming a hypercoaguable state, slightly shorter clotting time (CT), and significantly higher clot firmness during pregnancy.[11 12] Unfortunately, these studies do not have an adequate sample size and included either patients in the third trimester of pregnancy or patients already diagnosed with PPH.[13] One study[14] defined reference values for ROTEM® parameters in the post-partum period in uneventful deliveries and showed a strong correlation between thromboelastometric and conventional parameters, confirming the findings of previous studies.[12] However, the transition from the pregnant to post-partum state can induce large changes in haemostatic activity, particularly with haemorrhage. Therefore, post-partum values might not be sufficient to evaluate the peri-partum haemostatic condition.[15–18]

The increasing use of TEG or ROTEM® in massive bleeding guidelines and the haemostatic changes in pregnancy and during delivery underline the necessity of defining gestational reference ranges for thromboelastometry. The aim of this multi-centre study was to define reference ranges for the ROTEM® thromboelastometry during delivery. A second objective was to confirm the correlation between ROTEM® values and laboratory tests in women during labour after at least 24 weeks gestation.

Methods

Study population

Guidelines of the International Federation of Clinical Chemistry (IFCC) were abided by, which recommend a minimum sample size of 120 for calculating reference values.[19] The aim was to include at least 150 patients to have a sample size of 120 taking into account 20% missing values. Four centres participated in the study: Maastricht University Medical Centre (MUMC), Maxima Medical Centre Veldhoven (MMC), VU University Medical Centre Amsterdam (VUMC), and Radboud University Medical Centre (RUMCN); for patient characteristics, see Supplementary addendum online. These centres will be noted as Centres 1–4, respectively. Women attending the outpatient clinic for pregnancy check-ups were eligible to participate. The inclusion criteria were: age >18 yr, mentally competent, duration of pregnancy >24 weeks, and written informed consent. In order to have a reflection of the normal population, we included consecutive patients after informed consent. The exclusion criteria were: labour <24+0 weeks gestation, known bleeding disorders, or use of prophylactic or therapeutic anticoagulant therapy (acetylsalicylic acid within the last 10 days or low-molecular-weight heparins within the last 48 h). Women who agreed to participate were provided with oral and written information, and written informed consent was obtained. The study protocol was approved by the medical ethics committee of the Maastricht University Medical Centre (METC MUMC) and the local committees of the other participating hospitals.

Enrolment was between December 2010 and February 2012. Blood samples were collected during labour (T1) between 6 and 10 cm cervical dilatation or before elective Caesarean section and within 1 h of delivery of the placenta (T2). The participating centres received instructions about data collection and measurement of blood loss. Blood loss was estimated by weighing all absorbent towels except the first, which was changed directly after delivery of the newborn. Laboratory results were revealed to the attending caregiver; ROTEM® results were not disclosed.

Sample collection

Blood samples [(EDTA (ethylenediaminetetraacetic acid) and citrated blood)] were obtained by peripheral venipuncture and transported to the laboratory for analysis as soon as possible, within 2 h. Standard blood collection tubes (BD Vacutainer, Plymouth, UK) containing 0.105 M (Centres 1, 3, and 4) or 0.109 M (Centre 2) citrate solution, resulting in final citrate concentrations of 3.2% were used for the coagulation and ROTEM® tests and fibrinogen. Tubes containing 5.4 mg EDTA were used for the conventional haematology tests.

Laboratory tests

Laboratory tests were performed in each hospital laboratory using local protocols and methods. Although it is desirable to perform all coagulation assays in a batch using the same equipment and reagent for each test, this was not feasible because these tests were often used at each hospital site for clinical haemostatic management.

Measured at T1 and T2 were: Hb, haematocrit (Ht), platelet count, fibrinogen, D-Dimer, activated partial thromboplastin time (APTT), and prothrombin time (PT). The Hb, Ht, and platelet count were determined in whole EDTA blood by three different but comparable methods with national reference values: Sysmex XE-5000 (Sysmex, Japan) (Centres 2 and 4), Cell Dyn Sapphire (Abbott, USA) (Centre 3), and Beckman Coulter LH-750 (Beckman Coulter, the Netherlands) (Centre 1). For fibrinogen and D-Dimer, comparable methods (citrated plasma) and national reference values were used. Plasma fibrinogen concentration was measured by the Clauss method with STA-R Evolution (Roche Diagnostics, Germany) and the reagent STA Fibrinogen (Centres 2–4) and Sysmex

CA-7000 (Centre 1). D-Dimer was measured by STA-R Evolution with reagent Liatest D-DI (Centres 2 and 4), Modular Analytics (Roche Diagnostics, Germany) with reagent Tina-quant D-Dimer Gen2 (Centre 3), and Sysmex CA-700 with reagent Innovance D-Dimer (Centre 1).

In measuring APTT and PT (citrated plasma), different methods were used according to local protocol. In investigating reference values and correlation between conventional methods and ROTEM®, this was taken into account. APTT was measured by STA-R Evolution with reagent Cephascreen (Centres 2 and 4), STA-R Evolution with reagent STA APTT (Centre 3), and Sysmex CA-700 with reagent Actin FSL (Centre 4). PT was measured by STA-R Evolution with reagent Neoplastin Plus (Centres 2–4), and Sysmex CA-7000 with reagent Innovin (Centre 1). We sent a normal citrated plasma sample to all laboratories to be analysed for the purposes of standardization by calculating a ratio for APTT and PT.

ROTEM® instrument and tests

ROTEM® is a point of care coagulation monitoring device; however, in this study the assays were not performed at the bedside but in the laboratory. This was done in order to assure that the tests were performed by trained personnel. Results can be obtained as fast as in a point of care setting, provided there is real-time data transfer to a remote screen at the location of patient care.

Thromboelastometry was performed in citrated whole blood using a ROTEM® delta analyser, software version 1.6.1. (Pentapharm, Munich, Germany). Analysers were calibrated by the manufacturer. INTEM, EXTEM, FIBTEM, and APTEM tests were performed simultaneously on four parallel channels. Tests were performed using automated pipette programmes according to the instructions of the manufacturer. ROTEM® parameters: CT, clot formation time (CFT), α-angel, maximum clot firmness (MCF), amplitude at 10 min (A10), amplitude at 20 min (A20), and maximum lysis (ML) were reported and compared. The ROTEM® analyser has a continuous electronic self-control, and the manufacturer supplies standardized system controls ROTROL N and ROTROL P for weekly extrinsic quality control. A representative was available for advice on abnormal results or possible technical errors.

The INTEM assay uses Ca^{2+}, phospholipids, and ellagic acid to activate and assess coagulation through the intrinsic pathway. Tissue factor (TF) is used in EXTEM assays for activation and assessment of the extrinsic pathway. A platelet inhibitor (cytochalasin D) is added to the blood sample in the FIBTEM assay to differentiate between thrombocytopenia and fibrin polymerization. In APTEM, a fibrinolysis inhibitor (aprotinin) is used together with TF to confirm or to rule out hyperfibrinolysis.

Data analysis

Data were collected using an online registration database (InferMed MACRO Data Management) and analysed using SPSS Statistics 19 for Windows (SPSS, Inc., Chicago, IL, USA). Data were analysed by parametric and non-parametric descriptive statistics. Reference ranges for laboratory tests and ROTEM® parameters were determined according to the IFCC guidelines[19 20] calculating the 2.5 and 97.5 percentiles. Reference ranges were analysed for each centre separately and for all the centres together. For the conventional tests APTT and PT, respectively, 3 and 2 sets were calculated, in view of the different measuring methods. Correlation between conventional tests and ROTEM® parameters were calculated by means of Spearman's rank correlation coefficient.

Results

A total of 161 subjects were included in the study. Table 1 shows the basic characteristics of our study group. This population is comparable with the general Dutch obstetric population regarding maternal age, gestational age, body mass index (BMI), and percentage of planned Caesarean section (CS). Because of the fact that the study was performed in a secondary and tertiary obstetrical care population, women in the study population more often had twins, labour inductions, PPH, vaginal instrumental deliveries and emergency CS, and less spontaneous deliveries than the general population.[21]

Reference range for ROTEM® during labour

The median, inter-quartile range [IQR], and reference range for ROTEM® parameters (EXTEM, INTEM, FIBTEM, and APTEM) were

Table 1 Basic characteristics. Data are presented as mean (range) or as percentage

	Study group
Maternal age (yr)	31.6 (22–43)
BMI	24.6 (16.8–41.5)
Gestational age (days)	277 (216–295)
Parity	
0	54%
1	33.5%
2+	12.4%
Ethnicity	
Caucasian	94.4%
Indian/Pakistani	0.6%
African	0.6%
Mediterranean	1.2%
South-American	1.2%
Other	1.2%
Twins	3.7%
Labour	
Spontaneous	48%
Induction	45%
Primary Caesarean section	7%
Blood loss (ml)	566 (100–4500)
>1000 ml	11%
Delivery mode	
Spontaneous	62%
Assisted vaginal delivery	19%
Total Caesarean section	19%
Emergency Caesarean section	11%

calculated at T1 and T2 for each centre separately. There were inter-centre variations, but the differences in the lower and upper reference limits were acceptable (5–20%) in comparison with the reference range sizes (data not presented, available on request). Therefore, pooled results from all study centres are presented in Table 2, as median, IQR in square brackets, and reference range during labour. For all ROTEM® parameters, there was no significant difference in the median between T1 and T2, suggesting little to no changes in the haemostatic equilibrium between the start of labour and within 60 min of delivery of the placenta. The EXTEM MCF at T1 is wider than at T2, while the corresponding INTEM MCF at T1 is narrower. In a secondary analysis, women with PPH ($n = 18$) were excluded. Results at T1 and T2 were similar to those for the whole group (data not presented, available on request).

Results of laboratory tests

The results obtained for laboratory tests (Tables 3 and 4) are presented as median and IQRs in square brackets in the first box and reference range from 2.5 to 97.5 percentile in the second box. The PT and APTT are reported in different groups because of the different measuring methods in the individual centres. The reference ranges for fibrinogen and D-Dimer in our study population were very wide and as expected, levels were increased when compared with non-pregnant reference ranges in the Netherlands.[22] A blood sample was sent to the four laboratories for PT and APTT ratio, showing ratios between 0.8 and 1.3, respectively.

Correlation of conventional laboratory tests and ROTEM® data

The correlation between ROTEM® test results and PT, APTT, fibrinogen, and platelet count using the Spearman test were assessed. No strong correlation was found between CT EXTEM and PT or CT INTEM and APTT. A strong and significant correlation was found between the FIBTEM clot firmness parameters (A10, A20 and MCF) and fibrinogen ($P<0.01$ and $r=0.6$). For platelet count, a significant correlation with EXTEM CFT, A10, A20, and MCF was found. Results for correlation between platelet count, fibrinogen, and ROTEM® values are given in Table 5.

In Table 6, the correlation between the early clot firmness parameters in ROTEM® EXTEM, INTEM and FIBTEM and MCF is shown. There is a strong correlation in all tests.

Discussion

Reference values for peri-partum ROTEM® thromboelastometry parameters are presented, fulfilling recommendations of the IFCC on a minimal sample size of 120. Home births were not included, so the cohort might be skewed towards more complicated deliveries. Reference ranges are comparable with data published previously. Assets are the multi-centre approach, a larger sample size, blood samples obtained before and after labour, and the prospective inclusion of women with unknown outcome with regard to development of PPH.

Published data[14] defined reference values for ROTEM® parameters in the post-partum period in uneventful deliveries. Reference values for ROTEM® parameters in the post-partum period in uneventful deliveries[14] are slightly different from our data, but within 10–20% difference in the lower and upper reference ranges. With these data on ROTEM® parameters during and within 1 h of delivery, we could not show any haemostatic differences in non-bleeding patients. The results for ROTEM® parameters at T1 (antepartum) are consistent with data published by Huissoud and colleagues[12] for 58 women in the third trimester of pregnancy. The results of conventional tests are comparable with data published on reference values for pregnant women in the third trimester.[23–25]

The presented IQRs are the same for MCF EXTEM and INTEM at T1 and T2, however the reference range (2.5–97.5 percentile) for EXTEM T1 is wider. In our database, there were 11 subjects with an MCF EXTEM <63 mm at T1. These were not subjects with PPH. Values at the lower and upper end influence the reference values when working with 2.5–97.5 percentiles. These values might be attributable to technical errors; however, we think that because of the large number of measurements the values are still valid. One could hypothesize on the possible influence of FXIII,[26] but that does not explain the difference between T1 and T2.

When comparing the data presented above with data with reference ranges in non-pregnant adults,[27] CT and CFT in EXTEM and INTEM are shorter in pregnant women, and A10, A20, and MCF are comparable for EXTEM. For INTEM and FIBTEM, the A10, A20, and MCF are higher in the upper reference limits than in non-pregnant adults, whereas the lower reference limits are comparable. These data confirm the activation of coagulation and relative hypercoaguable status of pregnant women, although Lang and colleagues[27] showed a slight trend towards faster coagulation activation and greater clot firmness in females (non-pregnant) compared with males as reported previously.[28]

A strong correlation between thromboelastometric and conventional parameters, especially FIBTEM and fibrinogen, has been shown before for women during pregnancy and labour.[12 14] On the whole, the correlation between ROTEM® EXTEM and INTEM parameters and PT and APTT, respectively, has been shown to be significant, yet with lower correlation coefficients. The known correlation between FIBTEM parameters and laboratory tests for fibrinogen was confirmed. This is important in the course of PPH as FIBTEM results are available within minutes and can be useful in targeted therapy. In a small study,[29] blood samples were obtained immediately and 2 h post-partum in 23 patients with PPH and 31 women without abnormal bleeding; in women with PPH, there was a decrease in FIBTEM A15 values 2 h earlier than the decrease in fibrinogen assessed by the Clauss method. The correlation coefficient we present for FIBTEM and MCF ($r=0.6$) is lower than most previously published correlations for non-pregnant subjects and women after labour ($r=0.83$–0.91),[14 30–32] and comparable with one study with a correlation coefficient $r=0.55$.[33] Possibly the relatively high Ht's in our patients contributed to the lower correlation.[34 35] The Ht's

Table 2 ROTEM® reference values for all centres together. T1 is antepartum between 6 and 10 cm dilatation or before planned Caesarean section, and T2 is within 1 h of delivery. Data are presented as median and IQRs in square brackets. CT, clotting time; CFT, clot formation time; α-angle, the angle between the centre line and a tangent to the curve through the 20 mm amplitude point; A10, amplitude at 10 min; A20, amplitude at 20 min; MCF, maximum clot firmness; ML, maximum lysis

	n	T1 [IQR]	Reference range	*n*	T2 [IQR]	Reference range
EXTEM						
CT (s)	150	45 [41–50]	31–63	150	45 [40–49]	34–66
CFT (s)	149	69 [62–81]	41–120	149	73 [63–86]	44–154
Alfa (°)	150	77 [74–79]	67–83	149	76 [74–79]	63–81
A10 (mm)	150	64 [61–68]	48–74	150	64 [60–67]	44–73
A20 (mm)	150	70 [68–73]	47–78	150	70 [66–72]	52–78
MCF (mm)	150	71 [69–74]	42–78	150	71 [68–74]	55–78
ML (%)	150	7 [4–12]	0–41	150	8 [3–12]	0–44
INTEM						
CT (s)	155	147 [138–164]	109–225	148	137 [127–155]	98–225
CFT (s)	154	55 [49–63]	40–103	149	57 [50–69]	37–118
Alfa (°)	155	79 [77–80]	70–82	150	78 [76–80]	67–82
A10 (mm)	155	64 [62–67]	55–72	150	64 [60–67]	46–73
A20 (mm)	154	70 [68–73]	62–77	150	70 [66–72]	49–77
MCF (mm)	154	71 [69–74]	63–78	150	71 [67–74]	48–78
ML (%)	154	5 [2–8]	0–15	149	4 [2–8]	0–15
FIBTEM						
CT (s)	153	39 [37–44]	31–79	150	39 [36–42]	31–59
Alfa (°)	150	79 [76–80]	50–83	147	78 [75–80]	65–83
A10 (mm)	153	22 [20–26]	12–38	151	21 [18–25]	12–44
A20 (mm)	153	24 [21–28]	13–40	151	23 [19–27]	12–42
MCF (mm)	151	25 [22–28]	13–45	151	24 [20–28]	12–42
ML (%)	153	0 [0–0.5]	0–6	150	0 [0–0]	0–10
APTEM						
CT (s)	152	43 [39–48]	33–62	152	41 [38–45]	31–71
CFT (s)	151	69 [59–78]	42–118	153	72 [64–85]	47–158
Alfa (°)	153	77 [75–79]	69–82	153	76 [74–78]	60–81
A10 (mm)	153	64 [60–67]	54–72	153	63 [59–66]	43–72
A20 (mm)	153	70 [67–72]	61–78	153	69 [66–72]	51–77
MCF (mm)	152	71 [69–74]	61–79	151	71 [67–73]	56–78
ML (%)	152	4 [2–8]	0–15	152	5 [2–8]	0–14

Table 3 Reference values for conventional laboratory results for all centres. T1 is antepartum between 6 and 10 cm dilatation or before planned Caesarean section, and T2 is within 1 h of delivery. Data are presented as median and IQR in square brackets

Parameter	*n*	T1 median [IQR]	Reference range 2.5–97.5 percentiles	*n*	T2 median [IQR]	Reference range 2.5–97.5 percentiles
Hb (g dl^{-1})	161	12.2 [11.3–13.1]	9.1–14.3	161	11.6 [10.8–12.6]	8.5–13.9
Ht (%)	161	0.36 [0.34–0.38]	0.28–0.42	160	0.34 [0.32–0.37]	0.26–0.42
Platelets ($\times 10^6$ mm^{-3})	161	214 [179–257]	107–379	157	203 [171–246]	104–357
Fibrinogen (g $litre^{-1}$)	153	4.9 [4.4–5.8]	4.4–7.2	149	4.7 [4.1–5.4]	3.6–6.8
D-dimer (μg $litre^{-1}$)	155	1770 [1125–2611]	153–6021	151	3100 [1980–4700]	185–10460

were not mentioned in the earlier study with women during labour.[14]

In this study, the correlation between CT EXTEM and PT and CT INTEM and APTT could not be confirmed, which is probably attributable to the use of different reagents and methods of coagulation tests. The correlation between EXTEM clot firmness and platelet count can be explained by the fact that the EXTEM MCF reflects the platelet interaction with fibrinogen.

Table 4 PT and APTT calculated separately attributable to the different methods of analysis. For PT an analysis was done for Centre 1 MUMC and for Centres 2–4: VU, UMCN and MMC together because of the comparable method. For APTT an analysis was done for Centres 1 (MUMC) and 2 (VU) separately and for Centres 3 and 4 (UMCN and MMC) together

	n	T1 [IQR]	Reference range	*n*	T2 [IQR]	Reference range
PT (s)						
Centre 1 (MUMC)	40	9.8 [9.7–10.0]	9.3–10.4	39	9.9 [9.7–10.1]	9.6–10.4
Centres 2–4 (VU, UMCN, MMC)	115	13 [12.7–13.7]	11.7–14.0	109	13.7 [13.0–14.0]	12.0–17.8
APTT (s)						
MUMC	40	28 [26–29]	24–34	39	27 [26–29]	24–34
VU	26	31 [29–34]	26–34	23	32 [29–34]	27–34
UMCN/MMC	87	28 [27–29]	24–33.7	87	28 [27–30]	24–34.8

Table 5 Correlation between laboratory results and ROTEM® parameters. *$P<0.05$ and **$P<0.01$. Results presented as correlation coefficients. T1 is antepartum between 6 and 10 cm dilatation or before planned Caesarean section, and T2 is within 1 h of delivery. CT, clotting time; CFT, clot formation time; α–angle, the angle between the centre line and a tangent to the curve through the 20 mm amplitude point; A10, amplitude at 10 min; A20, amplitude at 20 min; MCF, maximum clot firmness; ML, maximum lysis

	Fibrinogen	Platelets
EXTEM T1		
CT	−0.09	0.06
CFT	−0.52**	−0.41**
A10	0.63**	0.43**
A20	0.62**	0.41**
MCF	0.60**	0.42**
EXTEM T2		
CT	−0.42	−0.17*
CFT	−0.46**	−0.43**
A10	0.52**	0.51**
A20	0.49**	0.47**
MCF	0.47**	0.44**
FIBTEM T1		
A10	0.63**	
A20	0.63**	
MCF	0.65**	
FIBTEM T2		
A10	0.57**	
A20	0.56**	
MCF	0.56**	

Table 6 Correlation between ROTEM® clot firmness parameters and MCF. *$P<0.05$ and **$P<0.01$. Correlation between ROTEM® parameters at A10, A20, and MCF. Results presented as correlation coefficients. T1 is antepartum between 6 and 10 cm dilatation or before planned Caesarean section, and T2 is within 1 h of delivery. A10, amplitude at 10 min; A20, amplitude at 20 min; MCF, maximum clot firmness

ROTEM® parameter	Correlation coefficient with MCF	
	T1	T2
EXTEM A10	0.93**	0.90**
EXTEM A20	0.96**	0.96**
INTEM A10	0.92**	0.96**
INTEM A20	0.95**	0.98**
FIBTEM A10	0.96**	0.96**
FIBTEM A20	0.98**	0.99**

It has been proposed that EXTEM MCF minus FIBTEM MCF be used to account for platelet effects.[36]

An extra analysis was performed after the recent publication of Görlinger and colleagues[37] showing a very good correlation between early clot firmness tests (A5, A10, and A15) and MCF in patients with hypo-, normo-, and hyper-coagulability. Our results are similar with high correlation coefficients, thus making it possible to start treatment at an earlier stage.

Blood samples were obtained before and within 1 h of delivery of the placenta to be able to compare reference values. It has been hypothesized that there is maximum platelet activation, fibrin formation, and activation of fibrinolysis at the time of delivery, suggesting haemostatic changes in this period.[17 18] The laboratory results and ROTEM® parameters do not differ significantly just before and after delivery, leading us to conclude that uneventful labour itself does not induce haemostatic changes that can be detected by the laboratory tests we used, with a possible exception for D-Dimer values which were higher at T2. Although mild fibrinolysis is not always observed on ROTEM®, we saw some activation of fibrinolysis during labour; there was no difference between T1 and T2. The EXTEM ML (maximum 41%) was higher than mentioned in previous literature by Lang and colleagues[27] (0–15%). The ML in INTEM and FIBTEM was within normal ranges for non-pregnant subjects. This suggests that there might be mild, but probably not clinically relevant, fibrinolysis. If there was evident fibrinolysis, clot breakdown in EXTEM and INTEM would be similar, whereas there would be very low lysis in the APTEM assay.[38] The D-dimer levels increased at T2, which supports the theory. There was no correlation between D-dimer and ML. 8.6% of the subjects had EXTEM ML outside the normal range as described by Lang and colleagues (>15%). These were subjects with normal blood loss and no transfusions. We do not have a clear explanation for this.

Possibly some abnormal values are attributable to technical errors; however, no technical errors were reported and all analysers passed quality control.

The small difference in reference range when excluding women with PPH might be explained by the small number of women with PPH ($n=18$ with blood loss >1000 ml). We recommend use of antepartum reference ranges as these are least influenced by interventions such as medication or fluid replacement therapy. Baseline testing in every woman going into labour is not recommended; laboratory tests should be done when clinically indicated. In case of risk factors for PPH, such as obstetric risk factors or known bleeding problems, one might consider baseline testing to be able to take precautions.

There are no clear therapeutic thresholds defined for peri-partum women and no gold standard laboratory test to assess haemostasis. The value of thromboelastometry is the short interval for test results. With these reference ranges thromboelastometry can be used to monitor haemostasis during PPH. However, there are still issues that need to be addressed, such as the cut-off value for abnormal values and whether treatment in bleeding patients should be based on non-pregnant or pregnant reference values.

Conclusion

In summary, reference values of ROTEM® parameters in women during labour showed no significant differences in values before and shortly after labour. The previously published strong correlations between ROTEM® FIBTEM and fibrinogen concentration were confirmed. With these reference values ROTEM® thromboelastometry can be used to diagnose coagulopathies in early stages of PPH and monitor haemostatic therapy. Further research is needed to define intervention values and triggers for haemostatic therapy in the course of PPH.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Authors' contributions

All the authors were involved in the concept and design of the study. N.M.L.: data collection and analysis, writing first draft of the paper, and coordination of the project at MUMC, Maastricht. L.E.R.-F.: writing first draft and revisions and coordinating project at VU, Amsterdam. M.D.L.: writing the first draft of the paper and revisions. L.M.: data input and revision. M.W.: revision of the manuscript and coordinating project at UMC, Nijmegen. E.C.P.: revision of the manuscript. M.P.: revision of the manuscript and coordinating project at MMC, Veldhoven. A.C.B.: revision of the manuscript. L.S.: statistical input and revision of the manuscript. Y.M.H.: revision of the manuscript, collection of data from different laboratories, and comparison of techniques. H.C.S.: revision of the manuscript and principal investigator.

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Declaration of interest

The authors have the following conflicts of interest to declare: N.M.L. has received speaker honoraria from CSL Behring. H.C.S. received funding for this study from CSL Behring.

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