International Journal of Obstetric Anesthesia (2020) **41**, 7–13
0959-289X/$ - see front matter
https://doi.org/10.1016/j.ijoa.2019.10.003

ELSEVIER
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ORIGINAL ARTICLE

Baseline parameters for rotational thromboelastometry (ROTEM®) in healthy pregnant Australian women: a comparison of labouring and non-labouring women at term

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ABSTRACT

Background: Rotational thromboelastometry (ROTEM®) is a point-of-care coagulation test. Reference ranges in non-labouring women have recently been established from a cohort of women presenting for elective caesarean delivery using the recommended minimum sample size of 120. This study aimed to present baseline parameters for labouring and non-labouring women and to compare the mean values of these ROTEM® parameters.

Methods: Ethical approval was granted for an opt-out recruitment approach for labouring women and written consent was obtained from non-labouring women (data published previously). ROTEM® testing was performed in these two cohorts at term gestation. Women with any condition affecting coagulation were excluded. ROTEM® Delta reference ranges were derived by calculating the 2.5 and 97.5 percentiles for INTEM/EXTEM/FIBTEM amplitude at 5 min (A5), coagulation time (CT), maximum clot firmness (MCF) and clot formation time (CFT).

Results: One hundred and twenty-one labouring and 132 non-labouring women met inclusion criteria. The mean values for selected ROTEM® parameters for labouring and non-labouring women respectively were: FIBTEM A5, 21.05 and 19.7 mm (P=0.008); EXTEM A5, 54.8 and 53.2 mm (P=0.025); and EXTEM CT, 52.2 and 53.7 s (P=0.049). Significant differences between the groups were observed in measures of clotting onset and clot firmness.

Conclusions: We demonstrated a significant decrease in the mean time-to-clotting onset in labouring women compared with non-labouring women. Mean values for measures of clot firmness were greater in labouring women. In comparison to previously established ROTEM® baseline parameters for non-labouring women, this study provides evidence that there is greater hypercoagulability in labouring women.

Keywords: Coagulation; Elective caesarean deliveries; Labouring women; Non-labouring women; Reference ranges; Rotational thromboelastometry; Third trimester

Introduction

Rotational thromboelastometry (ROTEM®; Instrumentation Laboratory™, Munich, Germany) is a point-of-care visco-elastic test of coagulation that is well established in hepatic and cardiac surgery, obstetrics and trauma.[1,2] Women become more hypercoagulable as pregnancy progresses through the three trimesters and this has been measured by both thromboelastography and rotational thromboelastometry in uncomplicated pregnancies.[3] To date there has been a paucity of substantial, well-researched reference ranges for ROTEM® in pregnant labouring and non-labouring women. The

Accepted October 2019
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increasing utilisation of point-of-care coagulation testing for obstetric patients warrants proper validation of hypercoagulable changes demonstrated by ROTEM®.

Changes consistent with clotting activation occur during normal vaginal delivery.[3–5] During labour, a hypercoagulable state is accompanied by enhanced fibrinolysis and platelet activation, along with elevated fibrinogen, plasminogen activator inhibitor-1 and -2 levels, and decreased total protein S and antithrombin III activity.[6] Activation of the fibrinolytic system begins during labour, prior to placental separation, as compensation for the hypercoagulable state of pregnancy.[4–8] At the end of the first stage of labour there is a rise in tissue-type plasminogen-activator (t-PA) which can enhance endogenous fibrinolysis.[4,5] Tissue plasminogen activator and D-dimer also reach maximal levels during delivery.[7] This activation of the clotting mechanism at delivery results in decreased levels of factors XI and XII, and increased levels of fibrinopeptide A.[9,10]

We have recently published ROTEM® reference ranges in non-labouring women, presenting for elective caesarean delivery at term gestation, using the recommended minimum sample size of 120.[11] Prior reports of ROTEM® reference ranges in pregnancy included fewer than the 120 patients recommended by the International Federation of Clinical Chemistry (IFCC) for establishing reference ranges.[12–16] These studies demonstrated hypercoagulability, represented by a faster time to clot formation and increased clot firmness in pregnancy.[12–16] From the time of active labour to the postpartum period, comparison of visco-elastic testing demonstrated a dynamic shift from maximum clot formation to increased clot lysis.[3] The current study aimed to compare mean values of ROTEM® baseline parameters for labouring women to those established for non-labouring women who had presented for elective caesarean delivery at term gestation.

Methods

The study was performed in a tertiary hospital with approximately 4500 deliveries annually and a caesarean delivery rate of 35%. Ethical approval was obtained from The Royal Brisbane and Women's Hospital (RBWH) Human Research Ethics Committee (HREC/14/QRBW/497). This manuscript adheres to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) Statement.

An opt-out approach to the recruitment of labouring women was approved. Eligible women were aged 18–45 years, with a body mass index (BMI) of 18.5–30 kg/m^2, and in active labour at term gestation (>37 weeks). Labour was defined as regular uterine contractions with a cervical dilatation of at least three centimetres.

Labouring women were excluded if they had pre-existing comorbidities, pregnancy-related conditions or were taking medications affecting coagulation. Excluded pregnancy-related conditions included the following: gestational hypertension, pre-eclampsia and HELLP syndrome (haemolysis, elevated liver enzymes and low platelet count) defined according to guidelines of the Society of Obstetric Medicine of Australia and New Zealand[17]; and anaemia defined according to the World Health Organization definition.[18] Women with the following conditions were also excluded: gestational thrombocytopaenia, cholestasis of pregnancy, antepartum haemorrhage, Factor V Leiden deficiency, antiphospholipid syndrome, haemochromatosis and thalassaemia and human immunodeficiency virus. Women medicated with anticoagulants or aspirin were excluded.[11]

The recruitment and study methodology for the non-labouring women who were presenting for elective caesarean delivery at term has been described previously.[11]

For labouring women, ROTEM® sampling occurred at the time of insertion of an intravenous cannula or venepuncture for non-research related blood tests. This occurred at varying times after the onset of labour in the labouring women cohort. Samples were collected in 3.5 mL Vacutainer™ collection tubes (Becton-Dickinson, North Ryde, Australia) containing 3.2% sodium citrate. ROTEM® analysis occurred within two hours of specimen collection. ROTEM® results were reviewed retrospectively and were not used to alter clinical management.

All ROTEM® tests, performed by certified personnel on citrated whole blood, used a ROTEM® Delta analyser. INTEM, EXTEM and FIBTEM tests were performed on three parallel channels simultaneously using pipette programmes set by the manufacturer.

A minimum sample size of 120 was targeted for establishing reference values, as per IFCC recommendations for both the labouring and the non-labouring women (presenting for elective caesarean delivery at term). ROTEM® reference ranges were derived by calculating the 2.5 and 97.5 percentiles for INTEM/EXTEM/FIBTEM parameters, including the A5, A15, CT, MCF and CFT. Statistical analysis was performed using SPSS Statistics Software Version 23, IBM®, NY, USA. Categorical variables were summarised by frequencies and percentages; continuous variables by means and standard deviations (SD); and by median and interquartile ranges (IQR) for non-normally distributed variables. The means (SD) of ROTEM® parameters for the labouring and non-labouring groups were compared using an independent Student t-test and *P*-values less than 0.05 were considered statistically significant.

Results

One hundred and twenty-one women met inclusion criteria for the labouring women reference range

calculations and these women were compared to values of the 132 non-labouring women presenting for elective caesarean delivery.[11] Fig. 1 details the application of inclusion and exclusion criteria. Recruitment occurred between January and December 2016. Demographic characteristics are summarised in Table 1. Median BMI and gestation were similar between the two groups, while there was a significant difference in the mean maternal age and parity.

Table 2 shows a comparison between the mean (SD) of each ROTEM® parameter for the labouring and non-labouring groups. There were significant differences between the two groups for most ROTEM® parameters, including the FIBTEM amplitudes at various times and the EXTEM CT. Reference ranges for selected ROTEM® parameters are shown in Table 3, with the FIBTEM, EXTEM and INTEM panels compared with previously established values from non-labouring women.[11]

Discussion

For most ROTEM® parameters, there was a significant difference between the labouring and non-labouring groups. In comparison to non-labouring women presenting for elective caesarean delivery at term gestation,[11] measures of clot firmness at various times were greater for labouring women. In addition, the onset of clot formation was significantly faster in labouring women. These differences were statistically significant for all except the alpha-angle, MaxV, EXTEM CFT and INTEM CT values. Mean values for FIBTEM/EXTEM/INTEM alpha-angle, MCF, AUC and MaxV did not significantly differ. This is consistent with the findings of Shreeve et al.[3] who demonstrated that women in established labour had a further progression toward a hypercoagulable state.

In both cohorts, measured ROTEM® parameters were obtained from three different assays (FIBTEM, EXTEM and INTEM). In keeping with other studies recruiting smaller numbers of patients, we observed changes consistent with clotting activation occurring during normal vaginal delivery.[3–5] Activation of the fibrinolytic system also begins during labour, along with platelet activation and elevated plasminogen activator inhibitor-1 and -2[5] and factor VII, prior to placental separation, likely in order to compensate for the hypercoagulable state of pregnancy.[4–8] Overall, labour is a dynamic process with consumption of platelets, and

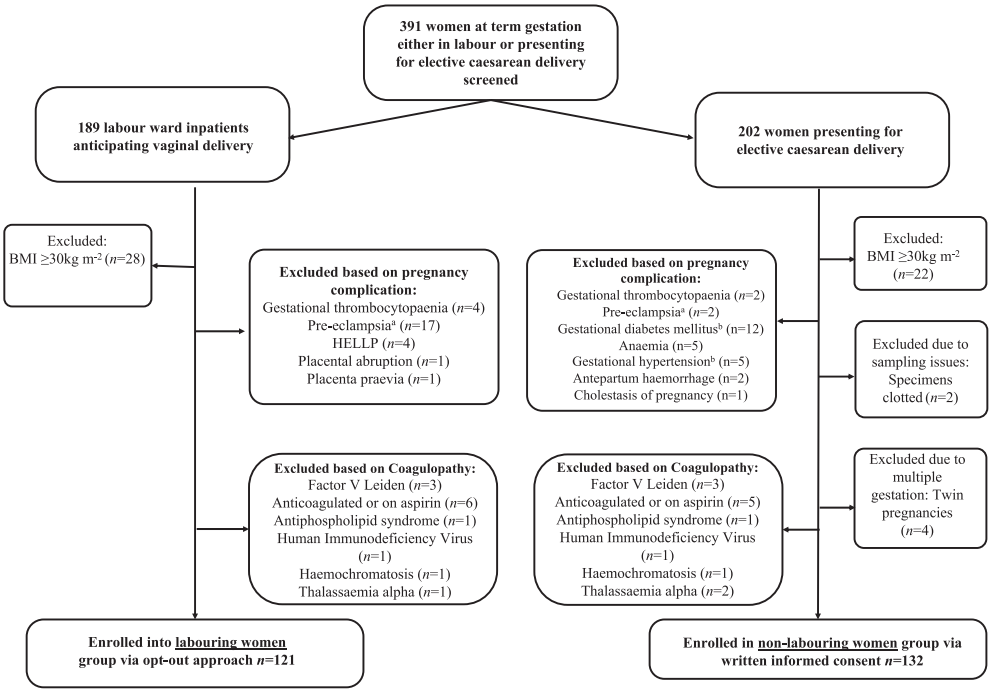

Fig. 1 Recruitment flowchart detailing participant exclusions. BMI: body mass index, HELLP: haemolysis, elevated liver enzymes and low platelets. Data for non-labouring women presenting for elective caesarean delivery at term has been previously described.[11]. [a]Pre-eclampsia and gestational hypertension as described in the SOMANZ Guidelines. Sourced from The SOMANZ Guidelines for the Management of Hypertensive Disorders of Pregnancy. https://www.somanz.org/documents/HTPregnancyGuidelineJuly2014.pdf (Accessed August 1, 2018). [b]Gestational diabetes mellitus as described in the guidelines from the Queensland Clinical Guidelines. Sourced from The Maternity and Neonatal Clinical Guideline: Gestational diabetes mellitus, published by Queensland Health, Australia. 2015. URL:// https://www.health.qld.gov.au/__data/assets/pdf_file/0023/140099/g-gdm.pdf Accessed August 1, 2018

Table 1 Patient demographics and delivery details for labouring and non-labouring women presenting to The Royal Brisbane and Women's Hospital for delivery at term gestation

Characteristics	Labouring women n=121 n (%)	Non-labouring women[11] n=132 n (%)	*P*-value
Maternal age (y), mean (SD)	29.6 (5.4)	32.7 (5.0)	<0.001
Nulliparous (n)	75 (62.0)	26 (19.7)	<0.001
Gestation (weeks), median (IQR)	39.4 (37.4–40.4)	39.0 (38.6–39.3)	0.10
Body mass index (kg/m^2), median (IQR)	22.9 (21.2–27.2)	23.8 (21.5–26.4)	0.29
Mode of birth *(n)*			
Spontaneous vaginal delivery	46 (38.0)	N/A	
Emergency caesarean section	50 (41.3)	N/A	
Induction of labour and assisted delivery	25 (20.7)	N/A	
Cervical dilatation during labour (cm), mean (SD)	4.76 (2.58)	N/A	
Ethnicities (%)			
Caucasian	57.0%	75.8%	
South East Asian	7.4%	9.1%	
Indian	5.7%	6.8%	
Other	28.9%	7.6%	
Indigenous Australian	0.8%	0.8%	

Data are presented as n (%), except where labelled mean (SD) or median (IQR). Data for non-labouring women presenting for elective caesarean delivery at term has been previously described.[11]

coagulation factors including fibrinogen and inhibitors, at delivery.[9,10]

The FIBTEM/EXTEM/INTEM amplitudes were higher in labouring women. The amplitudes at various times reflect the degree of clot firmness at those times following clot initiation. The MCF is the maximum amplitude over time and represents overall clot firmness based on the contribution of fibrinogen and platelets. The higher amplitudes found in the labouring population reflect increased hypercoagulability. The clotting time is the time from the addition of the clotting activator until the time when the clot amplitude reaches two millimetres. Narrower ranges were demonstrated for FIBTEM/EXTEM/INTEM CT, EXTEM/INTEM CFT and FIBTEM/EXTEM/INTEM alpha-angle in the labouring group.

Obstetric haemorrhage can be catastrophic if not managed effectively and immediately. When using ROTEM®-directed resuscitation, management may be less effective if test results are not interpreted for the specific reference population of labouring women at term gestation. Women with lower fibrinogen levels detected in early labour have been identified as being at risk of postpartum haemorrhage (PPH).[19] Given that FIBTEM parameters have been shown to correlate well with fibrinogen levels,[19] detection of low fibrinogen by FIBTEM assay may identify labouring women at risk of PPH. ROTEM®-guided transfusion is based on specific thresholds as triggers. Those women showing a lower degree of hypercoagulability in labour may have a reduced physiologic buffer against PPH at the time of delivery; so further studies to evaluate this possibility, and of appropriate therapeutic interventions, are needed. Further research will also involve evaluating ROTEM® at specific time points in labour, particularly during prolonged labour and in comparison with postpartum values.

The study has limitations. Our study population was restricted to pregnant women at term, either admitted in labour, anticipating vaginal delivery or admitted for elective caesarean delivery. Therefore, our results are not generalisable to pregnant women at earlier gestational ages or to non-obstetric populations. Also, the exclusion criteria were different for the two groups in that women with gestational diabetes mellitus (GDM) were excluded from the non-labouring group whilst six women with GDM were included in the labouring group. Currently, there are few data available on the impact of GDM on coagulation as measured by ROTEM®. Standard coagulation tests (PT, aPTT, fibrinogen, and platelet count) were not performed for correlation with ROTEM® values in either study cohort. In a subset of assays (FIBTEM CFT; FIBTEM/EXTEM/INTEM A30) among labouring women, fewer than 120 patient samples were analysed due to laboratory prioritisation of clinical samples over research samples. Therefore, not all of the reference ranges comply with the IFCC criteria for establishing reference ranges. Timing of our coagulation testing in relation to onset of labour or proximity to delivery was not standardised and theoretically this may have introduced some variation in the results.

In conclusion, in our study comparing ROTEM® results from a group of labouring women with those from a group of non-labouring women (at term and scheduled for elective caesarean delivery), we demonstrated greater hypercoagulability in labouring women. The onset of clot formation (EXTEM CT and INTEM CT, CFT) was significantly faster in labouring women and measures of clot firmness (FIBTEM/EXTEM/

Table 2 Comparison of mean values of ROTEM® parameters for labouring and non-labouring women presenting to The Royal Brisbane and Women's Hospital for delivery at term gestation

		Labouring women n=121	Non-labouring women n=132	*P*-value
FIBTEM	CT	51.7 (6.21)	53.4 (7.85)	0.065
	CFT	–	–	–
	A5	21.05 (4.10)	19.7 (3.90)	0.008
	A10	23.3 (4.54)	21.7 (4.18)	0.004
	A15	24.4 (4.76)	22.8 (4.34)	0.005
	A20	25.1 (4.93)	23.4 (4.60)	0.004
	A30	25.8 (4.93)	24.1 (4.60)	0.008
	MCF	25.8 (4.86)	24.1 (4.68)	0.007
	CFR	76.9 (2.84)	76.3 (3.45)	0.09
	α-angle	76.2 (2.93)	75.5 (3.81)	0.076
	AUC	2551.9 (485.71)	2390.9 (460.26)	0.007
	MaxV	18.1 (4.01)	17.4 (5.00)	0.25
EXTEM	CT	52.2 (5.91)	53.7 (6.26)	0.049
	CFT	62.6 (13.08)	65.7 (15.20)	0.08
	A5	54.8 (5.35)	53.2 (6.02)	0.025
	A10	64.6 (4.42)	63.2 (5.32)	0.02
	A15	68.4 (3.94)	67.0 (4.85)	0.014
	A20	70.1 (3.66)	68.8 (4.57)	0.017
	A30	71.0 (3.32)	70.0 (4.13)	0.044
	MCF	71.1 (3.36)	70.2 (4.01)	0.042
	CFR	78.5 (2.40)	78.5 (2.31)	0.08
	α-angle	77.6 (2.64)	77.4 (2.65)	0.6
	AUC	7060.8 (328.9)	6964.5 (390.7)	0.036
	MaxV	20.6 (4.23)	20.3 (4.09)	0.64
INTEM	CT	162.5 (26.19)	167.7 (32.06)	0.16
	CFT	60.47 (12.6)	64.2 (15.30)	0.035
	A5	53.06 (5.11)	51.3 (5.76)	0.012
	A10	63.0 (4.29)	61.4 (5.14)	0.007
	A15	66.9 (3.9)	65.4 (4.79)	0.009
	A20	68.7 (3.72)	67.3 (4.53)	0.008
	A30	69.6 (3.79)	68.4 (4.55)	0.028
	MCF	69.6 (3.77)	68.3 (4.43)	0.009
	CFR	78.8 (2.30)	78.2 (2.53)	0.054
	α-angle	77.7 (2.47)	77.1 (2.73)	0.11
	AUC	6925.0 (367.04)	6791.6 (429.60)	0.009
	MaxV	21.0 (4.49)	20.2 (4.48)	0.14

Data are presented as mean (SD). CT: clotting time. CFR: clot formation rate. MCF: maximum clot firmness. A5, A10, A15, A20, A30: amplitude (firmness) at x minutes. α-angle: alpha angle. AUC: area under curve. MaxV: maximum velocity.

INTEM A5, A10, A15, A20, A30, MCF) were significantly higher. Our results contribute to the current understanding of changes in coagulation during pregnancy, specifically during labour. Future research should assess ROTEM® values at specific time points throughout labour in order to define dynamic coagulation changes during this process and to examine the potential for the use of pre-labour ROTEM® values to predict bleeding risk.

Funding

This study was conducted at The Royal Brisbane and Women's Hospital (RBWH), Brisbane, QLD, Australia.

Pathology Queensland (SERC) provided funding for ROTEM® testing and consumables; National Blood Authority Australia, Australian Society of Anaesthetists, and The RBWH and RBWH Foundation provided funding for research nursing support and time to conduct the research. None of these organisations had any involvement in the study design, data collection, analyses, interpretation of data or the writing of this report.

Conflict of interest

The authors report no conflicts of interest

Table 3 Reference ranges for ROTEM® parameters in labouring and non-labouring women presenting to The Royal Brisbane and Women's Hospital for delivery at term gestation

ROTEM® Parameter	n	Reference range for labouring women	n	Reference range for non-labouring women[11]
FIBTEM Parameters				
CT (s)	121	41–66	132	40–74
CFR (°)	121	70–82	131*	67–82
Alpha angle (°)	121	69–81	131*	67–81
MCF (mm)	121	16–40	132	16–34
A5 (mm)	121	14–33	132	13–28
A10 (mm)	121	15–37	132	14–30
A15 (mm)	121	16–39	130*	15–32
A20 (mm)	120*	16–40	127*	16–33
A30 (mm)	116*	16–40	124*	16–34
AUC (mm x 100)	121	1589–3917	132	1634–3366
MaxV (mm min^{-1})	121	11–27	132	9–27
EXTEM Parameters				
CT (s)	121	40–65	132	43–69
CFT (s)	121	41–93	132	43–108
CFR (°)	121	73–83	132	71–82
Alpha angle (°)	121	71–82	132	69–82
MCF (mm)	121	63–77	132	60–78
A5 (mm)	121	44–67	132	39–66
A10 (mm)	121	56–74	132	50–73
A15 (mm)	120*	60–77	129*	55–76
A20 (mm)	120*	62–77	127*	57–77
A30 (mm)	115*	63–77	123*	60–78
AUC (mm x 100)	121	6562–7667	132	5960–7645
MaxV (mm min^{-1})	121	12–30	132	12–30
INTEM Parameters				
CT (s)	121	118–222	132	115–245
CFT (s)	121	36–89	132	42–103
CFR (°)	121	73–83	132	71–83
Alpha angle (°)	121	72–82	132	70–82
MCF (mm)	121	61–78	132	59–76
A5 (mm)	121	43–65	132	38–63
A10 (mm)	121	54–73	132	49–70
A15 (mm)	120*	59–80	127*	54–74
A20 (mm)	120*	60–76	127*	57–75
A30 (mm)	115*	61–78	122*	59–76
AUC (mm x 100)	121	6072–7686	132	5886–7524
MaxV (mm min^{-1})	121	13–33	132	12–31

ROTEM® reference ranges were derived by calculating the 2.5 and 97.5 percentiles. CT: clotting time. CFR: clot formation rate. MCF: maximum clot firmness. A5, A10, A15, A20, A30: amplitude (firmness) at x minutes. AUC: area under curve. MaxV: maximum velocity. *Fewer samples were analysed for these parameters due to laboratory prioritisation of clinical samples over research samples. Data for non-labouring women presenting for elective caesarean delivery at term has been previously described.[11]

Acknowledgements

We wish to acknowledge help from The National Blood Authority, The RBWH and RBWH Foundation, Pathology Queensland (SERC) and The Australian Society of Anaesthetists (ASA). The following persons made significant contributions: Sue Williams, Sue Freney and the RBWH Blood Bank Team for the processing of blood samples, collating of results and project planning; Dr Ellen Coonan (anaesthetic registrar) for help with data collection; the RBWH obstetric anaesthesia staff, anaesthetic technicians, obstetric staff, midwifery staff and research nurse team for blood sampling and patient recruitment.

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