

Rotational Thromboelastometry Reference Range during Pregnancy, Labor and Postpartum Period: A Systematic Review with Meta-Analysis

Abstract

Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) have become increasingly popular for urgent assessment of the hemostasis system. Accordingly, TEG and ROTEM algorithms and their corresponding cut-off values are not interchangeable. ROTEM provides fast results (including validated early clot firmness parameters [A5 and A10]), that are easy to use, and the graphical display of the results is easy to interpret. ROTEM manufacturer, Tem Innovations GmbH (Munich, Germany), mentions in the user manual that the manufacturer has not set any strict reference values for INTEM, EXTEM, FIBTEM, APTEM, and NATEM in any patient population (including pregnant women) and that these values are highly variable in healthy subjects. To date, no systematic review assessing ROTEM parameters in pregnant, parturient, and postpartum women is available. With the increasing usage of ROTEM, we conducted this systematic review and meta-analysis to determine the reference values of ROTEM parameters in pregnant, parturient, and postpartum women compared with non-pregnant population.

Keywords: Coagulopathy, hemorrhage, point-of-care testing, pregnancy, thromboelastometry

Highlights

- Pregnancy is a hypercoagulability state
- In the postpartum period, the state of hypercoagulability is still present
- FIBTEM A5 test reference ranges (clot firmness amplitude at 5 min after clotting time, CT) showed its lower limit of 11.3 mm.

Introduction

Recently, the viscoelastic tests thromboelastography (TEG) and rotational thromboelastometry (ROTEM) have become increasingly popular for urgent assessment of the hemostasis system.^[1-3] Both the tests are included in many guidelines for bleeding treatment and on their basis decisions are made on the transfusion of donor blood products.^[4-7] Some institutions even use a special term, the “TEG/ROTEM-guided transfusion algorithm” that has been introduced.^[4-7] Although the methodology of both the tests is based on recording the changes of the viscoelastic properties of the forming clot, they have their own unique features.^[8] Accordingly, TEG and ROTEM algorithms

and their corresponding cut-off values are not interchangeable.^[9,10]

ROTEM provides fast results (including validated early clot firmness parameters [A5 and A10]), which is easy to use, and the graphical display of the results is easy to interpret.^[11] The test of the hemostasis system provides general information on most of the blood coagulation links, including fibrinogen level, platelet function, coagulation cascade, fibrin cross-linking, and fibrinolysis, so that the results of rotational thromboelastometry imply specific interventions for immediate correction of hemostasis disorders in bleeding patients.^[12-14]

ROTEM manufacturer, Tem Innovations GmbH (Munich, Germany), mentions in the user manual that the manufacturer has not set any strict reference values for INTEM (ROTEM test with intrinsic coagulation pathway activation using ellagic acid), EXTEM (ROTEM test with extrinsic coagulation pathway activation using recombinant tissue factor), FIBTEM (EXTEM-based ROTEM test with platelet activity inhibited by cytochalasin D), APTEM (EXTEM-based

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ROTEM test with fibrinolysis inhibited by aprotinin), and NATEM (ROTEM test without coagulation activators) in any patient population, including pregnant women, and that these values are highly variable in healthy subjects.^[15-17] Accordingly, ROTEM users are requested to validate their own reference ranges in their specific patient populations. To date, no systematic review assessing ROTEM parameters in pregnant and parturient women in full-term and physiological pregnancies is available. With the increasing usage of ROTEM, we conducted this systematic review and meta-analysis to determine the reference values of ROTEM parameters in pregnant, parturient, and postpartum women compared with non-pregnant population.

Methods

Eligibility criteria

The evaluation of the studies (in English and in Russian) compliance with the inclusion criteria was conducted in three stages: (1) based on the title, (2) based on the abstract, and finally (3) based on the full text of the article.

The review included studies containing ROTEM parameters in pregnant women in the third trimester of pregnancy and with full-term pregnancy, in labor, and in the postpartum period.

Exclusion criteria:

- Studies reported no ROTEM parameters;
- Studies in pregnant, parturient, and postpartum women with non-obstetric conditions;
- Studies that used ROTEM in pregnant and postpartum women with postpartum hemorrhage;
- Studies that used ROTEM in pregnant and postpartum women with congenital or acquired coagulation disorders;
- Studies that used ROTEM in pregnant and postpartum women with pre-eclampsia, eclampsia, or any form of HELLP syndrome;
- Case reports;
- Duplicate articles.

Information sources

The systematic review was performed in accordance with preferred reporting items for systematic reviews and meta-analyses (PRISMA).^[18]

Two researchers (A. M. Ronenson and Yu. S. Raspopin) independently searched for articles published in English from January 1, 2000 to December 31, 2021 in PubMed, MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) databases and in Russian

from January 1, 2000 to December 31, 2021 in Google Scholar.

Search strategy

The search strategy included the words: in English “ROTEM obstetric,” “Thromboelastometry obstetric,” “ROTEM pregnancy” and “Thromboelastometry pregnancy,” “ROTEM postpartum” and “Thromboelastometry postpartum,” and in Russian “РОТЭМ у беременных” (“ROTEM in pregnant women”), “РОТЭМ у беременных” (“ROTEM in pregnant women”), “Тромбоэластометрия у беременных” (“Thromboelastometry in pregnant women”), “РОТЭМ у рожениц” (“ROTEM in parturient women”), “РОТЭМ у рожениц” (“ROTEM in parturient women”), “Тромбоэластометрия у рожениц” (“Thromboelastometry in parturient women”), “РОТЭМ после родов” (“ROTEM post partum”), “РОТЭМ после родов” (“ROTEM post partum”), “Тромбоэластометрия после родов” (“Thromboelastometry post partum”).

Selection process

All studies performed in pregnant, parturient, and postpartum women were selected for the meta-analysis. In all of the studies found, the references were examined to identify additional previously unidentified publications. Studies, titles, and abstracts were reviewed to remove possible duplicates identified by searching various databases.

Two reviewers then evaluated whether the full text of the articles met the inclusion criteria and screened each record independently.

Data collection process

Two researchers collected data from reports, they worked independently. After collecting the data, the results were combined and duplicate results were extracted.

Data items

Data from eligible publications were extracted according to predetermined criteria. The following ROTEM test parameters were extracted: CT – clotting time (sec), CFT – clot formation time (sec), AX – clot amplitude × minutes after clotting time (CT) (mm) (A5, A10, A15, A20, A30), MCF – maximal clot firmness (mm), α angle (°), LI30 – lysis index (residual clot firmness in percentage of MCF) at 30 min after CT (%), LI60 – lysis index (residual clot firmness in percentage of MCF) at 60 min after CT (%), ML – maximum

lysis (decrease in clot firmness in percentage of MCF) during run time (%).

Study risk of bias assessment

To assess the bias risks in randomized controlled trials (RCTs), the Cochrane Handbook recommendations for systematic reviews are commonly used.^[19] However, no RCTs are included in this meta-analysis because most of the studies are prospective, non-interventional.

Effect measures

For each ROTEM tests parameters (CT, CFT, A5, A10, A15, A20, A30, MCF, α angle, LI30, LI60, ML) were measured reference values (CI – confidence interval 2.5–97.5%).

Synthesis methods

Because of significant differences between the results of the studies, reflecting the heterogeneity of the sample, a random-effects model was adopted for the calculations in the meta-analysis.

In the studies selected for the meta-analysis, the variances differed significantly, and the sample distributions deviated significantly from normal distribution. These features of the synthesized data precluded the traditional method application of estimating the accumulated reference interval, in which the evaluation of study weights is based on standard deviations. Therefore, an empirical method for calculating the estimate of the accumulated reference interval was chosen, in which the weights of the studies are determined based on their sample volumes. This calculation method for the meta-analysis does not require neither equality of internal variance between studies nor specification of the distribution law of sampling within the study.

The calculations were carried out according to the formulas and algorithm described by Siegel *et al.*^[20] using Excel spreadsheets.

Where results were presented as median and interquartile range, median and 95% confidence interval, median and minimum and maximum values, they were converted to mean and standard deviation using the formula of Wan *et al.*^[21]; the error of the mean was converted to standard deviation by multiplying by the square root of the sample size.^[21]

Results

Studies selection

The search in English identified 628 potentially relevant studies of which 612 studies were excluded after reviewing the title or abstract. As a result, 16 articles were selected for a detailed review.^[22–37] Articles by Lee *et al.*^[32–34] were excluded because the later paper by the same authors probably included previously described ROTEM parameters, and it was impossible to rule out duplicate

data, given that the studies were performed at the same institution.^[35] Data obtained only during pregnancy from van Rheenen-Flach *et al.*^[26] and Duraj *et al.*^[28] studies were included in the meta-analysis because postpartum ROTEM parameters were obtained at 41–68 days and 6–8 weeks after delivery, respectively.

The search in Russian identified 336 potentially relevant studies of which 330 were excluded after reviewing the title or abstract. The full texts of six articles were considered for inclusion. Of these, two articles met at least one exclusion criterion. As a result, four articles were selected for detailed review.^[38–41] The selection process for the publications included in the meta-analysis is described in Figure 1.

Study characteristics included in the meta-analysis

Data from 17 studies (13 studies in English and 4 studies in Russian) were included in the final analysis; In some studies, only data complying the inclusion criteria were included. The resulting meta-analysis included 1569 pregnant women, 121 parturient women, and 352 postpartum women with various ROTEM tests performed. The data from the included studies are presented in Table 1. The parameters of various tests in pregnant and parturient women are presented in Supplement File 1 and in postpartum women in Supplement File 2.

Risk of bias

The following possible risk factors for bias were identified: current labor activity, obesity (BMI ≥ 30 kg/m²), and ethnicity. However, a detailed analysis of the studies showed that according to the study by Lee *et al.*,^[33] despite the statistically significant difference in the mean values of INTEM, EXTEM,

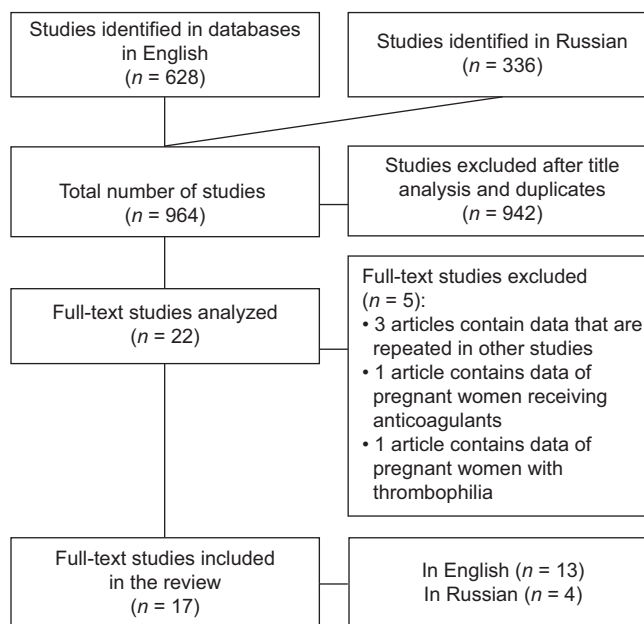


Figure 1: Flow diagram of studies selection for systematic review according to PRISMA checklist

Table 1: Data from studies included in the systematic review and meta-analysis

Author, year, country	Number of pregnant/parturient/post partum women (after VD or CS)	ROTEM tests	Gestational age, weeks (or days after delivery)	Age (years)	BMI (kg/m ²)	Inclusion/exclusion criteria
Huissoud <i>et al.</i> , 2009, France ^[22]	58 pregnant women	INTEM EXTEM FIBTEM APTEM	≥28 weeks	–	–	Exclusion criteria: High blood pressure, hyperthermia or systemic inflammatory response syndrome, defined as C-reactive protein 5 mg/L, chronic diseases, coagulation disorders or receiving anticoagulants/antiplatelet medications
Armstrong <i>et al.</i> , 2011, United Kingdom ^[23]	54 pregnant women	INTEM EXTEM FIBTEM	38 [35-41] weeks	33.5 (5.7)	–	Exclusion criteria: <18 or >45 years, body weight <50 kg or >100 kg; personal or family history of coagulation disorders; taking medications that affect coagulation; blood transfusions or surgery within the previous 28 days; abnormal general blood count and history of smoking or comorbidities (cardiovascular, renal, malignancies, liver disease or hypertension)
Oh <i>et al.</i> , 2012, Republic of Korea ^[25]	20 pregnant women 20 pregnant women	INTEM INTEM	–	32.4 (4.85) 34.4 (2.48)	–	Inclusion criteria: Elective cesarean section, ASA I–II. Exclusion criteria: Pregnant women with hemostatic abnormalities, pre-eclampsia, placenta previa, multifetal pregnancy, bleeding, current therapy with aspirin or heparin
van Rheenen-Flach <i>et al.</i> , 2013, the Netherlands ^[26]	45 pregnant women	INTEM EXTEM	36.2 [34.1-37.4] weeks	–	–	Inclusion criteria: Only pregnant women with an uncomplicated general and obstetric history
de Lange <i>et al.</i> , 2014, the Netherlands ^[27]	155 pregnant women	INTEM EXTEM FIBTEM APTEM	39.6 weeks 1 day	31.6 [22-43]	24.6 [16.8-41.5]	Exclusion criteria: Delivery at <24 weeks gestation, current coagulation disorder or current anticoagulant therapy (acetylsalicylic acid within the last 10 days or low molecular weight heparins within the last 48 h).
Momot, 2015, Russia ^[38]	37 pregnant women 42 postpartum women	NATEM	34-36 weeks 2-3 days	–	–	Inclusion criteria: First and second pregnancies aged 18-35 years. Exclusion criteria: >35 years; history of obstetric or gynecologic complications; complicated pregnancy; history of hemorrhagic or thrombotic complications; history of assisted reproductive technology or with current pregnancy; history of surgical delivery or CS for current pregnancy; current non-obstetric condition, malignant neoplasms; taking medications that affect coagulation (antiplatelet medications, nonsteroidal anti-inflammatory drugs, anticoagulants) during the current pregnancy
Duraj <i>et al.</i> , 2015, Slovakia ^[28]	50 pregnant women	INTEM EXTEM	34-36 weeks	–	–	Inclusion criteria: Women with an uncomplicated obstetric history

Contd...

Table 1: Contd...

Author, year, country	Number of pregnant/parturient/post partum women (after VD or CS)	ROTEM tests	Gestational age, weeks (or days after delivery)	Age (years)	BMI (kg/m ²)	Inclusion/exclusion criteria
Grinevich, 2016, Belarus ^[39]	40 pregnant women	INTEM EXTEM	29-40 weeks	27 [25-30]	–	Exclusion criteria: <18 or >45 years; history of coagulation disorders and/or thromboembolism; obesity (BMI >30 kg/m ²); use of anticoagulant and/or antiplatelet drugs during pregnancy; abortion or pregnancy loss within the last 6 months; women who have not consented to participate in the study Inclusion criteria: Fertile age; physiological pregnancy; history of two or more normal births; no history of medical abortions, spontaneous miscarriages and other obstetric complications; no signs of thrombosis Exclusion criteria: Personal or family history of thrombotic or hemorrhagic complications; history of blood transfusion and obstetric complications; chronic non-obstetric conditions; taking medications (hormones) that affect coagulation
Bowden <i>et al.</i> , 2016, UK ^[39]	80 pregnant women	FIBTEM	29-40 weeks	–	–	Inclusion criteria and exclusion criteria are not indicated
Muratova, 2017, Russia ^[40]	152 pregnant women	NATEM	37-39 weeks	–	–	Inclusion criteria: Healthy pregnant women Exclusion criteria: Women with thrombophilia
Kaufner <i>et al.</i> , 2017, Germany ^[30]	181 pregnant women	EXTEM FIBTEM	39.6 [38.9 40.6] weeks	30 (6)	28 [26-32]	Inclusion criteria: Pregnant women aged >18 years, good mental health and ASA physical status II–III Exclusion criteria: Emergency cesarean section; missing blood loss data; history of hemostasis disorders; and recent medication that may affect hemostasis
Gootjes <i>et al.</i> , 2019, the Netherlands ^[31]	305 pregnant women	INTEM EXTEM FIBTEM	39.8 [32.1 42] weeks	32 [19-46]	25 [17-48]	Inclusion criteria: >18 years, gestational age >24 weeks Exclusion criteria: Personal or family history of coagulation disorders; preeclampsia; HELLP syndrome; a history of deep vein thrombosis or pulmonary embolism; deep vein thrombosis or pulmonary embolism during current pregnancy; treatment with antiplatelet medications and/or anticoagulant therapy during the pregnancy and anemia during ROTEM sampling
Lee <i>et al.</i> , 2020, Australia ^[35]	132 pregnant women	INTEM EXTEM FIBTEM	> 37 weeks	29.6 (5.4)	22.9 [21.2-27.2]	Inclusion criteria: 18-45 years; BMI of 18.5-30 kg/m ² ; full-term pregnancy (>37 weeks)

Contd...

Table 1: Contd...

Author, year, country	Number of pregnant/parturient/post partum women (after VD or CS)	ROTEM tests	Gestational age, weeks (or days after delivery)	Age (years)	BMI (kg/m ²)	Inclusion/exclusion criteria
Raspopin <i>et al.</i> , 2020, Russia ^[41]	79 pregnant women	INTEM EXTEM FIBTEM APTEM	≥32 weeks	29.9 [20; 35]	29 [21.2-34.4]	Exclusion criteria: Comorbidities; pregnancy-related conditions; receiving medications affecting coagulation (gestational hypertension, preeclampsia, and HELLP syndrome and anemia, gestational thrombocytopenia, pregnancy cholestasis, antepartum bleeding, factor V (Leiden factor) deficiency; antiphospholipid syndrome; hemochromatosis and thalassemia, and human immunodeficiency virus infection) including anticoagulants or aspirin Inclusion criteria: 18-43 years; blood loss during vaginal delivery, not 500 ml, and during cesarean section, not >1000 mL Exclusion criteria: Associated coagulation disorders; taking medications that affect hemostasis
Shamshirsaz <i>et al.</i> , 2021, USA ^[36]	41 pregnant women	INTEM EXTEM FIBTEM	Third trimester	30 (4.5)	30 (5.9)	Inclusion criteria: Healthy pregnant women, 18-45 years with a singleton gestation. Exclusion criteria: History of thrombosis, coagulopathy or thrombocytopenia of any kind, blood transfusion or surgery within the previous 30 days, current smoking, alcohol or drug use, infectious comorbidity, concurrent medical condition such as cardiovascular disease, chronic renal failure, malignancy, liver disease, infertility visit, chronic hypertension, gestational hypertension or preeclampsia before enrollment and blood draw, type 1 or type 2 diabetes, evidence of labor, multifetal gestation, and use of estrogen-containing contraceptives, aspirin, or anticoagulants
Getrajdman <i>et al.</i> , 2021, USA ^[37]	120 pregnant women	NATEM	(≥37 weeks	34 [31-36.5]	29.7 [26.1-32.8]	Inclusion criteria: Womens 18 years or older, English-speaking, and at term gestation (≥37 weeks) Exclusion criteria: active labor, had a known bleeding or clotting disorder, had a diagnosis of a hypertensive disorder (chronic hypertension, gestational hypertension or preeclampsia) or were on medication known to affect coagulation, including anti-coagulants and antiplatelets
Lee <i>et al.</i> , 2020, Australia ^[35]	121 parturient women	INTEM EXTEM FIBTEM	>37 weeks	32.7 (5.0)	23.8 [21.5-26.4]	Inclusion criteria: 18-45 years; BMI 18.5-30 kg/m ² ; full-term pregnancy (>37 weeks) Exclusion criteria: Comorbidities; pregnancy-related conditions; receiving medications affecting coagulation (gestational hypertension,

Contd...

Table 1: Contd...

Author, year, country	Number of pregnant/parturient/post partum women (after VD or CS)	ROTEM tests	Gestational age, weeks (or days after delivery)	Age (years)	BMI (kg/m ²)	Inclusion/exclusion criteria
Oudghiri <i>et al.</i> , 2011, France ^[24]	61 postpartum women (39 after VD, 23 after CS)	EXTEM FIBTEM APTEM	1 day	—	—	preeclampsia, and HELLP syndrome and anemia, gestational thrombocytopenia, pregnancy cholestasis, antepartum bleeding, factor V (Leiden factor) deficiency; antiphospholipid syndrome; hemochromatosis and thalassemia, and human immunodeficiency virus infection) including anticoagulants or aspirin Inclusion criteria: Pregnant women aged ≥18 years with uncomplicated pregnancy, delivered at ≥37 weeks of gestation, with acceptable blood loss (<500 mL in vaginal delivery, <1000 mL in cesarean section)
de Lange <i>et al.</i> , 2014, the Netherlands ^[27]	150 postpartum women (19% after CS)	INTEM EXTEM FIBTEM APTEM	39.6 weeks 1 day	31.6 [22-43]	24.6 [16.8-41.5]	Exclusion criteria: Delivery at <24 weeks gestation, current coagulation disorder or current anticoagulant therapy (acetylsalicylic acid within the last 10 days or low molecular weight heparins within the last 48 h)
Raspopin <i>et al.</i> , 2020, Russia ^[41]	99 postpartum women 61 after CS 38 after VD	INTEM EXTEM FIBTEM APTEM	3-5 days	30.2 [20;39] 31.8 [23;39]	30.8 [22.3;38.6] 30.4 [24.1;36.6]	Inclusion criteria: 18-43 years; blood loss during vaginal delivery, not >500 mL, and during cesarean section, not >1000 mL. Exclusion criteria: Associated coagulation disorders; taking medications that affect hemostasis

and FIBTEM between pregnant and parturient women, they fall within the reference ranges for both groups (pregnant and parturient women), which indicates a clinically insignificant difference in these mean values. Lee *et al.*^[34] found no statistically or clinically significant differences in ROTEM parameters between pregnant women with and without obesity. Tem Innovations, the manufacturer of the ROTEM device, recommends that each institution analyze ROTEM parameters of healthy subjects in its region, since geographic location may have some effect on the parameters. However, analysis of the study by Gootjes *et al.*^[31] showed no statistically and clinically significant differences in ROTEM parameters between pregnant women of different ethnic groups (Caucasian, Turkish, Moroccan, African, Hindu, Asian, etc.). It is worth noting that Gootjes *et al.*^[31] in their study appear to have divided pregnant women according to the place of birth and linguistic principles rather than ethnicity. So, this study is not substantial enough to exclude ethnicity as a potential factor introducing bias.

In general, there were no possible risk factors for endpoint bias and all the studies included in the meta-analysis were of high quality.

Analysis of ROTEM test parameters

A weighted mean and reference ranges (2.5–97.5%) were calculated for all ROTEM test parameters for pregnant

Table 2: INTEM test parameters during pregnancy and parturient women* compare whit non-pregnant population

Parameters	Number	Pregnant women Reference range	Non-pregnant subjects ^[16] Reference range
CT (sec)	1119	103.0-204.3	137-246
CFT (sec)	1068	32.0-86.0	40-100
α angle (°)	1011	72.7-83.6	71-82
A5 (mm)	434	41.3-62.5	
A10 (mm)	917	55.0-72.8	44-68
A15 (mm)	355	56.6-74.9	
A20 (mm)	526	60.1-76.7	50-71
A30 (mm)	337	60.1-77.3	51-72
MCF (mm)	1118	61.0-79.1	52-72
LI30 (%)	98	97.9-100.0	
ML (%)	314	0.0-15.6	0-12

* 11 studies are pooled in these results^[22,23,25–28,31,35,36,39,41]

and parturient women, and in the postpartum period. INTEM, EXTEM, FBTEM, and NATEM tests parameters are presented in Tables 2–5, compared to non-pregnant population.^[16] Other tests and parameters for pregnant and parturient women, and in the postpartum period are presented in Supplement File 3.

Table 3: EXTEM test parameters during pregnancy and parturient women* compare whit non-pregnant population

Parameters	Number	Pregnant women	Non-pregnant subjects ^[16]
		Reference range	Reference range
CT (sec)	1208**	31.0-67.6	42-74
CFT (sec)	1162	38.7-97.1	46-148
α angle (°)	1146	68.1-83.4	63-81
A5 (mm)	436	42.6-64.4	
A10 (mm)	1092	53.3-73.9	43-65
A15 (mm)	357	58.3-76.4	
A20 (mm)	522	61.2-77.3	50-69
A30 (mm)	339	62.2-78.1	50-69
MCF (mm)	1073	62.1-83.9	49-71
LI30 (%)	98	98.1-100.0	
ML (%)	310	0.0-18.5	0-18

*11 studies are pooled in these results ^[22,23,26-28,30,31,35,36,39,41]

** The study by van Rhee-Flach *et al.* was excluded, because the mean CT value is critically prolonged (92 sec), which is a deviation from the reference range according to other studies. The authors are not able to explain such critical prolongation observed

Table 4: FIBTEM test parameters during pregnancy and parturient women* compare whit non-pregnant population

Parameters	Number	Pregnant women	Non-pregnant subjects ^[16]
		Reference range	Reference range
CT (sec)	935	30.2-67.0	43-69
α angle (°)	874	67.5-86.0	
A5 (mm)	470	11.3-28.1	
A10 (mm)	823	14.3-29.9	9-24
A15 (mm)	311	13.4-32.1	
A20 (mm)	485	14.8-33.6	8-21
A30 (mm)	253	15.4-34.4	
MCF (mm)	1193	13.3-34.6	9-25
ML (%)	273	0.0-3.4	

* 9 studies are pooled in these results ^[22,23,27,29-31,35,36,41]

Discussion

In the analysis, ROTEM parameters were measured in 1569 pregnant women, 121 parturient women, and 352 postpartum women with a weighted mean age of 30.5 (7.4) years.

The meta-analysis included mostly pregnant women; the group of parturient women was small and represented data from only one study, Lee *et al.*,^[33] including 121 subjects. Lee *et al.*^[35] found statistically significant increases in the mean values of some ROTEM parameters in parturient women vs. pregnant women, such as FIBTEM A5 21.05 mm vs. 19.7 mm ($P = 0.008$); EXTEM A5 54.8 mm vs. 53.2 mm ($P = 0.025$); EXTEM CT 52.2 sec vs. 53.7 sec ($P = 0.049$). We believe, such increase has no clinical significance, considering the quite wide reference range of ROTEM test parameters. However, the issue of

the effect of childbirth on the hemostasis system remains open and requires further research in this area.

By analyzing the mean values of the ROTEM tests parameters (INTEM, EXTEM, FIBTEM, APTEM) and their standard deviations, we found significant variability between the studies included in the meta-analysis.

More narrow reference ranges of CT and CFT, which characterize the rate of clot formation, in all ROTEM tests (INTEM, EXTEM, FIBTEM, APTEM) confirm the state of chronometric physiological hypercoagulation (faster start of clotting) during pregnancy, due to an increase in coagulation factors and fibrinogen concentration.^[42] The lower and upper limits of the reference ranges of A5, A10, A15, A20, A30, and MCF values in all ROTEM tests (INTEM, EXTEM, FIBTEM, APTEM, NATEM) reflecting clot density at different time points are much higher than those in non-pregnant women, indicating structural physiological hypercoagulation (denser clot formation) during pregnancy.

The FIBTEM test data are also of interest, being a surrogate for fibrinogen levels determined by the Clauss method, which remains the main predictor of the development of massive postpartum hemorrhage.^[43] Our analysis of the FIBTEM A5 test reference ranges (clot firmness amplitude at 5 min after CT) showed its lower limit of 11.3 mm. The level FBTEM A5 = 12 mm has been accepted as the lower limit in almost all the studies on postpartum bleeding for the decision to use fibrinogen concentrate or cryoprecipitate,^[44-48] and it has subsequently been accepted as the threshold below which correction of fibrinogen levels is necessary.^[49,50]

For postpartum ROTEM values, no significant clinical difference was found in the reference ranges of the various tests. It is confirmed by the study of de Lange *et al.*,^[27] which did not find any statistically and clinically significant differences between the values before and after 1 h delivery. We agree with de Lange *et al.*^[27] that it is better to use values measured during third trimester of pregnancy, to evaluate ROTEM parameters and during postpartum period about 7 days.

Study limitations

The meta-analysis has several limitations. Not all test parameters are obtained in proper number of pregnant women to draw reasonable and definitive conclusions. Some test parameters were calculated using data from a single study, which most likely does not fully reflect the reference ranges for the selected general population, especially in ROTEM tests, where were clinical difference between studies.

Analysis of the studies included in the meta-analysis showed that the geographic regions of residence, especially in European countries, often have significant differences in the pregnant and parturient women ethnicities (Caucasian,

Table 5: NATEM test parameters during pregnancy and parturient women* compare whit non-pregnant population

Parameters	Number	Pregnant women Reference range	Non-pregnant subjects ^[15] Reference range
CT (sec)	304	333.7-978.7	300-1000
CFT (sec)	309	56.8-238.4	150-700
α angle (°)	306	24.6-81.9	30-70
A10 (mm)	154	33.4-71.8	
A15 (mm)	37	27.3-62.9	
A20 (mm)	120	53.9-74.7	
MCF, mm	306	41.7-77.2	40-65
LI30 (%)	272	86.1-100.0	
LI60 (%)	120	90.9-100.0	
ML (%)	120	0.0-9.3	

* 3 studies are pooled in these results^[37,38,40]

Turkish, Moroccan, African, Hindu, Asian, etc.). Although the study by Gootjes *et al.*^[31] showed no statistically and clinically significant differences in ROTEM parameters between pregnant women of different ethnic groups, considering the large variability in coagulation test values between different ethnic groups in the general population,^[51-55] We believe further research is needed to rule out the variability in ROTEM test values depending on the ethnicity of the pregnant or parturient women.

Some authors^[22,29,36,39] reported trimester-specific reference ranges during pregnancy since they observed increasing clot firmness results during pregnancy. This was not considered in this systematic review and meta-analysis, but may be relevant for the interpretation of ROTEM results during pregnancy.

The main limitation of this study was that all included studies used "ROTEM delta" machine. In this time, Tem Innovations GmbH (Munich, Germany) produced new machine "ROTEM sigma" and the reference range parameters of this new machine may be slightly different of results to "ROTEM delta".^[56]

Conclusion

The systematic review and meta-analysis have determined reference ranges for ROTEM parameters during pregnancy and the postpartum period. The hypercoagulation state is typical for physiological pregnancy and the immediate postpartum period, which can be considered normal for this category of patients. These data can be used in daily practice and can be included in clinical guidelines for coagulation disorders, including the treatment and prevention of massive obstetric bleeding.

Disclosure

Part of this study is published as an abstract at the IJOA.^[57]

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Conflicts of interest

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