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Prospective Longitudinal Study of Thromboelastography and Standard Hemostatic Laboratory Tests in Healthy Women During Normal Pregnancy

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BACKGROUND: Hemostatic disorders are common in obstetric complications. Thromboelastography (TEG®) simultaneously measures coagulation and fibrinolysis within 10 to 20 minutes. Our primary aim in this prospective longitudinal study was to obtain knowledge about physiological changes in TEG® variables during normal pregnancy and 8 weeks postpartum. The secondary aims were to compare TEG® variables during pregnancy with TEG® variables 8 weeks postpartum and gestational weeks 10 to 15 and to correlate TEG® variables to standard laboratory analyses.
METHODS: Blood samples were collected from 45 healthy pregnant women at gestational weeks 10 to 15, 20 to 22, 28 to 30, and 38 to 40, and at 8 weeks postpartum. The following TEG® analyses were performed: time until start of clotting (TEG®-R), time until 20-mm clot firmness (TEG®-K), angle of clotting (TEG®-Angle), maximum amplitude (TEG®-MA), and lysis after 30 minutes (TEG®-LY30). Activated partial thromboplastin time, prothrombin time, soluble fibrin, antithrombin, D-dimer, and platelet count were analyzed.
RESULTS: Compared to 8 weeks postpartum TEG®-R was at least 0.9 minutes shorter (upper limit 99% confidence intervals) until gestational weeks 28 to 30 and the mean reduction varied between 23%–26%. TEG®-K was at least 0.1 minutes shorter throughout pregnancy and the mean reduction varied between 18%–35%. TEG®-Angle was at least 2.5 degrees greater during pregnancy and the mean increase varied between 12%–20%. TEG®-MA was also at least 0.4 mm greater during pregnancy and the mean increase varied between 6%–8%. TEG®-LY30 was at least 0.03% lower during gestational weeks 28 to 30 and 38 to 40 and the mean reduction varied between 67%–73%. The routine coagulation laboratory values were within normal pregnant limits. There were no or weak correlations between TEG® and the laboratory variables.
CONCLUSIONS: TEG® demonstrates increased coagulability and decreased fibrinolysis during pregnancy. There was a faster initiation of hemostasis, with a minor increase in clot strength. Fibrinolysis decreased during late pregnancy. Alternative cutoff limits for TEG® variables may be required during pregnancy. Standard hemostatic laboratory tests were as expected during pregnancy. Future studies are needed to ascertain whether viscoelastic methods are preferable to standard hemostatic tests for the diagnosis of coagulopathy during obstetric hemorrhage. (Anesth Analg 2012;115:890–8)

Hemostatic disorders are common in obstetric complications such as preeclampsia, placental abruption, and postpartum hemorrhage.[1–4] Routine clinical chemical laboratory tests are usually used for diagnosis, but the results of these analyses are reported with a delay of about 1 to 2 hours. Immediate knowledge of hemostatic conditions is often not possible, making early goal-directed treatment difficult. However, thromboelastography (TEG®) and thromboelastometry (TEM), viscoelastic methods of assessing clotting and fibrinolysis, have been reevaluated and technically improved. These global tests simultaneously measure blood coagulation and fibrinolysis and can detect hemostatic derangement within 10 to 20 minutes.[5] Studies concerning TEG®/TEM in connection with obstetric complications have been reported.[6–12] These studies describe changes in TEG®/TEM indicating increased coagulability during different periods of pregnancy;[9,10,12,13] however, there is limited knowledge about longitudinal changes in TEG®/TEM during normal pregnancy and puerperium.

Changes in hemostasis resulting in increased coagulability during pregnancy have been reported. These changes influence results of standard laboratory analyses, such as activated partial thromboplastin time (APTT), prothrombin time (PT), and D-dimer.[14] During pregnancy, activation of blood coagulation has also been shown by increased levels of other biomarkers such as prothrombin fragment 1 + 2, thrombin-antithrombin complex, and soluble fibrin.[14,15]

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The primary aim of this prospective longitudinal study in healthy women was to obtain knowledge about changes in TEG® variables during normal pregnancy and at 8 weeks postpartum. A secondary aim was to simultaneously assess standard laboratory coagulation analyses, including APTT, PT, platelet count, antithrombin, soluble fibrin, and D-dimer, and to evaluate if there is any correlation between these variables and the TEG® variables during normal pregnancy and 8 weeks postpartum.

METHODS

Participants

This study was approved by The Regional Ethical Review Board, Gothenburg, Sweden. Informed written consent was obtained from all participants. Healthy Caucasian pregnant women were asked to participate at their first visit to the prenatal care unit in the primary care system in South Bohuslän, Sweden. The women were monitored regularly by midwives during pregnancy. Normal pregnancy was defined as the absence of obstetric complications such as preeclampsia, other placenta complications, gestational diabetes, or bleeding complications. Women with these conditions were excluded from the analyses. The course of the pregnancy and bleeding at delivery were obtained from electronic patient records (Obstetrix, Siemens AB, Healthcare Sector, Upplands Väsby, Sweden) after the last visit, at least 8 weeks postpartum.

Blood Sampling

Blood sampling was performed at gestational weeks 10 to 15, 20 to 22, 28 to 30, and 38 to 40, and at 8 weeks postpartum. The results at 8 week postpartum were used as nonpregnant references, because the hemostatic balance is normalized at this time.[14,15] Blood was sampled between 8 and 12 AM, after 15 minutes of rest. The blood samples were taken with a butterfly device (Terumo Quick Fit, Tokyo, Japan) and the first portion (9 mL) was discarded. The second blood sample was collected with 2 mL syringe (Codan, Lensahn, Germany) for TEG® analysis, followed by sampling directly into tubes for APTT, PT, soluble fibrin, antithrombin, and D-dimer. Finally, blood was collected for platelet count.

Analyses

The TEG® 5000 version 4.2 software (Hemoscope Corporation, Niles, IL) was used for all TEG® analyses. Regular checks were performed according to the manufacturer's instructions. The activator consisted of kaolin. Kaolin reagent, cups, and pins were supplied by the manufacturer. One mL of native whole blood was gently mixed with kaolin and 360 μL of this preparation was pipetted into a TEG® cup prewarmed to 37°C. Measurements were performed within 4 minutes of blood sampling. The samples were run for 90 minutes. Anesthesia nurses were trained in performing the TEG® analyses to mimic the clinical setting.

The following TEG® variables were assessed: R time (TEG®-R), which reflects the time until the first significant clot formation; K (TEG®-K), which reflects the speed or clot kinetics to reach a certain level of clot firmness; angle (TEG®-Angle), which reflects the rate of clot growth; and MA (TEG®-MA), which reflects the maximal strength of the clot. Finally, LY30 (TEG®-LY30), measuring persistent lysis 30 minutes after MA was reached, was determined.

Blood for APTT, PT, antithrombin, soluble fibrin, and D-dimer was collected in tubes containing 0.13 M citrate. EDTA tubes were used for determination of platelet count. The blood samples were handled within 30 minutes and centrifuged at 2000 g at room temperature for 20 minutes. Plasma was frozen at −70°C until analyzed. Antithrombin, soluble fibrin, and D-dimer were analyzed serially for each individual. If PT International Normalized Ratio (INR) was <0.9, we used 0.8 in the calculations and if the D-dimer level was <0.5 mg/L, we used 0.2 in the calculations. Information about laboratory analyses is shown in the Appendix.

TEG® variables and laboratory analyses during pregnancy were compared with 8 week postpartum and gestational weeks 10 to 15. TEG® variables were also correlated to standard laboratory analyses.

Statistics

The longitudinal analysis of the data was performed with a mixed effects model, in which subject is considered a random effect. The mixed procedure in SAS version 9.2 (SAS Institute Inc, Cary, NC) was used to estimate effects over time. In considering the covariance pattern among timepoints, the autoregressive model is usually a natural choice. Compared to an unstructured matrix there was a substantial gain in model fit. Because there was no a priori design when to terminate the study, 99% confidence intervals (CIs) have been used, and Dunnett's method was applied to control the family-wise error rate of the multiple comparisons of the trimester measurements with the baseline assessment and the nonpregnant state, respectively.

According to plots of the data most of the distributions were reasonably normal. A few were less regular, namely soluble fibrin, D-dimer, TEG® LY30, and TEG®-K. We were unable to produce estimates that conformed to the data using logarithmic transformations to achieve normally distributed measurements. However, there was a close correspondence between the estimates from a fixed effects model and the mixed effects approach: CIs were somewhat wider with the mixed model, as expected. We therefore assume that the mixed model estimation was robust enough to produce valid results.

Pearson correlations between TEG® measures and laboratory data were calculated at each time point. Small values with differing sign among timepoints were considered clinically uninteresting. For higher values with consistent directions, 99% confidence limits have been supplied.

RESULTS

Sixty-one women were initially included in the study; 9 women were excluded from the final analyses because of obstetric complications, including preeclampsia ($n = 2$), gestational diabetes ($n = 2$), small for gestational age ($n = 1$), placenta previa with hemorrhage ($n = 1$), cholestasis ($n = 1$), anemia ($n = 1$), and elective abortion ($n = 1$). Seven women withdrew their consent for personal reasons, resulting in 45 women in the final analysis. Demographic and obstetric data are shown in Table 1. Three of these 45 women were delivered by planned cesarean due to breech

Table 1. Demographic and Obstetric Data

Demographic data	
Age, y	
Median	30.0
Range	21–40
BMI (kg/m^2)	
Median	23.5
Range	17.9–32.3
Nulliparous, *n*	24
Parous, *n*	21
Vaginal delivery, *n*	39
Cesarean delivery, *n*	
Emergency	3
Planned	3
EBL at delivery, mL	
Median	350
Range	200–2600
EBL >600 mL, *n*	8

Data are from 45 healthy women.
BMI = body mass index; EBL = estimated blood loss.

presentation ($n = 1$), previous cesarean ($n = 1$), and cesarean delivery on maternal request ($n = 1$). Three women were delivered by intrapartum cesarean due to malpresentation ($n = 1$), failed induction ($n = 1$), and nonreassuring fetal status ($n = 1$). All women gave birth during and after gestational week 38, but 7 women did not reach the planned fourth sampling occasion.

TEG®

The changes in TEG® variables during pregnancy show an increase in blood coagulation and a decrease in fibrinolysis compared to 8 week postpartum, as shown in Tables 2 and 3 and Figure 1.

Changes in TEG® Variables, Compared to 8 Weeks Postpartum

TEG®-R was at least 0.9 minutes shorter during pregnancy until gestational weeks 28 to 30 and the mean reduction varied between 23%–26%. TEG®-K was at least 0.1 minutes shorter throughout pregnancy and the mean reduction varied between 18%–35%. TEG®-Angle was at least 2.5 degrees greater throughout pregnancy and the mean increase varied between 12%–20%. TEG®-MA was at least 0.4 mm greater during pregnancy and the mean increase varied between 6%–8%. TEG®-LY30 was at least 0.03% lower during gestational weeks 28 to 30 and gestational weeks 38 to 40, and the mean reduction varied between 67%–73%. There was little overlap between the 99% CI of pregnant and postpartum results.

Changes in TEG® Variables During Pregnancy

Comparisons were made between early pregnancy (gestational weeks 10 to 15) and the other gestational periods. TEG®-R was at least 0.5 minutes longer at gestational weeks 38 to 40 and the mean increase was 23%. TEG®-K was at least 0.1 minutes longer in gestational weeks 38 to 40 and the mean increase was 26%. TEG®-Angle was at least 0.2 degrees lower in gestational weeks 38 to 40 and the mean decrease was 7%. TEG®-MA was greater during early pregnancy and remained so throughout pregnancy. TEG®-LY30 was at least 0.1% less during gestational weeks 38 to 40 and the mean decrease was 72% compared to early pregnancy. There was little overlap between the 99% CI of pregnant and postpartum results.

Clinical Laboratory Analyses

Laboratory analyses are presented in Tables 4 and 5. One woman had a slightly prolonged APTT (46 seconds) at 8 week postpartum. Further workup for increased bleeding tendency did not reveal a hemorrhagic diathesis.

Changes Compared to 8 Weeks Postpartum

APTT was at least 0.8 seconds shorter during the entire pregnancy. PT (INR) was at least 0.1 lower at gestational weeks 20 to 22, 28 to 30, and 38 to 40. Platelet count was at least 2.0×10^9/L lower during gestational weeks 10 to 15, 28 to 32, and 38 to 40 but remained within the normal

Table 2. TEG® Variables During Normal Pregnancy and 8 Weeks Postpartum

TEG®	Gestational wk	10–15	20–22	28–30	38–40	8 wk postpartum
	Women, *n*	45	43	42	38	44
R, min	Mean	6.8	7.2	7.1	8.4	9.2
	99% CI	6.1–7.6	6.5–8.0	6.4–7.9	7.6–9.2	8.5–10.0
	Median	6.9	7.3	7.2	8.0	8.4
	Range	3.7–13.2	2.8–11.1	3.2–12.4	5.7–13.7	4.1–16.2
K, min	Mean	1.8	1.9	2.0	2.2	2.7
	99% CI	1.5–2.0	1.6–2.2	1.7–2.2	1.9–2.5	2.4–3.0
	Median	1.7	1.9	1.8	1.9	2.6
	Range	0.9–4.5	0.9–2.9	1.2–4.3	1.4–4.1	1.6–5.4
Angle, degree	Mean	65.9	63.6	63.9	61.6	54.7
	99% CI	63.2–68.7	60.8–66.4	61.1–66.8	58.6–64.5	51.9–57.5
	Median	66.2	63.1	65.2	62.2	54.8
	Range	41.8–79.3	50.9–78.1	42.7–73.3	45.9–72.2	34.5–68.0
MA, mm	Mean	67.5	66.9	68.2	68.5	63.6
	99% CI	65.9–69.2	65.2–68.6	66.5–70.0	66.7–70.3	62.0–65.3
	Median	66.7	66.6	68.2	68.0	63.3
	Range	61.3–82.8	46.3–76.3	58.0–77.7	62.5–76.2	54.3–77.0
LY30, %	Mean	1.0	0.7	0.4	0.3	1.2
	99% CI	0.5–1.5	0.2–1.2	−0.1–0.9	−0.2–0.9	0.8–1.7
	Median	0.5	0.1	0.1	0.0	0.6
	Range	0.0–3.3	0.0–5.6	0.0–3.5	0.0–3.1	0.0–9.5

R = time until fibrin formation; K = time until amplitude 20 mm; Angle = angle of clotting; MA = maximum amplitude; LY30 = percent of lysis at 30 min.

Table 3. TEG® Variables During Normal Pregnancy Compared to 8 Weeks Postpartum and During Pregnancy Compared to Gestational Week 10–15

TEG®	Gestational wk	10–15	20–22	28–30	38–40
	Women, *n*	45	43	42	38
R, min					
A	Δ between means, absolute	−2.4	−2.0	−2.1	−0.8
	99% CI, absolute	−3.7 to −1.2	−3.2 to −0.7	−3.4 to −0.9	−2.0 to 0.4
	Δ between means, %	−26.2	−21.6	−22.8	−8.8
B	Δ between means, absolute	—	0.4	0.3	1.6
	99% CI, absolute	—	−0.5 to 1.4	−0.8 to 1.4	0.5 to 2.7
	Δ between means, %	—	6.3	4.5	23.3
K, min					
A	Δ between means, absolute	−1.0	−0.8	−0.7	−0.5
	99% CI, absolute	−1.4 to −0.5	−1.3 to −0.4	−1.2 to −0.3	−0.9 to −0.1
	Δ between means, %	−35.2	−30.0	−27.0	−18.1
B	Δ between means, absolute	—	0.1	0.2	0.5
	99% CI, absolute	—	−0.2 to 0.5	−0.2 to 0.6	0.1 to 0.8
	Δ between means, %	—	8.0	12.6	26.3
Angle, degree					
A	Δ between means, absolute	11.2	8.8	9.2	6.9
	99% CI, absolute	6.7 to 15.8	4.3 to 13.4	4.7 to 13.8	2.5 to 11.2
	Δ between means, %	20.5	16.2	16.9	12.5
B	Δ between means, absolute	—	−2.4	−2.0	−4.4
	99% CI, absolute	—	−5.9 to 1.2	−5.9 to 2.0	−8.5 to −0.2
	Δ between means, %	—	−3.6	−3.0	−6.6
MA, mm					
A	Δ between means, absolute	3.9	3.2	4.6	4.8
	99% CI, absolute	1.1 to 6.6	0.4 to 6.0	1.8 to 7.3	2.2 to 7.5
	Δ between means, %	6.1	5.1	7.2	7.6
B	Δ between means. absolute	—	−0.6	0.7	1.0
	99% CI, absolute	—	−3.1 to 1.8	−2.0 to 3.4	−1.7 to 3.8
	Δ between means, %	—	−0.9	1.1	1.6
LY30, %					
A	Δ between means, absolute	−0.2	−0.5	−0.8	−0.9
	99% CI, absolute	−1.0 to 0.6	−1.3 to 0.3	−1.6 to −0.03	−1.6 to −0.2
	Δ between means, %	−20.2	−42.7	−66.9	−73.4
B	Δ between means, absolute	—	−0.3	−0.6	−0.7
	99% CI, absolute	—	−0.8 to 0.3	−1.2 to 0.0	−1.3 to −0.1
	Δ between means, %	—	−29.3	−58.6	−71.7

A = changes compared to 8 wk postpartum; B = changes compared to gestational wk 10–15; R = time until fibrin formation; K = time until amplitude 20 mm; Angle = angle of clotting; MA = maximum amplitude; LY30 = percent of lysis at 30 min; Δ = changes.

nonpregnant range. Antithrombin was at least 0.01 kIU/L lower throughout pregnancy but remained within the normal nonpregnant range.

Changes During Pregnancy

Comparisons were made between early pregnancy (gestational weeks 10 to 15) and the other gestational periods. APTT remained decreased throughout pregnancy. PT (INR) was at least 0.1 lower from gestational weeks 20 to 22. Platelet count and antithrombin did not change further compared to early pregnancy.

Soluble Fibrin and D-Dimer

Soluble fibrin, D-dimer, and TEG®-LY30 are shown in Figure 2. Soluble fibrin had marked interindividual variation. Compared to 8 week postpartum D-dimer was at least 0.1 mg/mL greater from gestational weeks 28 to 30 until delivery and the mean increase varied between 140%–297%.

Correlations Between TEG® and Laboratory Analyses

There were no or weak correlations ($r < 0.5$ or $r < -0.5$) between TEG® variables and laboratory analyses.

Women with Bleeding Complications

The 8 women who bled >600 mL at delivery were analyzed as a subgroup. There were no changes in TEG® variables or standard laboratory tests indicating increased bleeding tendency before delivery. Estimated blood loss ranged between 650 to 2600 mL and associated with retained placenta (3), uterine atony (3), and cesarean delivery (1), and normal spontaneous vaginal delivery without any complications (1).

DISCUSSION

The main findings of this prospective, longitudinal, observational study of TEG® during normal pregnancy in Scandinavian Caucasian women were that the TEG® method showed increased coagulability with decreased fibrinolysis during pregnancy compared to 8 weeks postpartum.

In Sweden, pregnant women usually present at the prenatal care units between gestational weeks 10 and 15. Changes in the hemostasis are more limited during early pregnancy than later in pregnancy, allowing a more extended initial period of blood sampling without major influence on the results. Missing data were mainly due to delivery before blood sampling in the gestational weeks 38

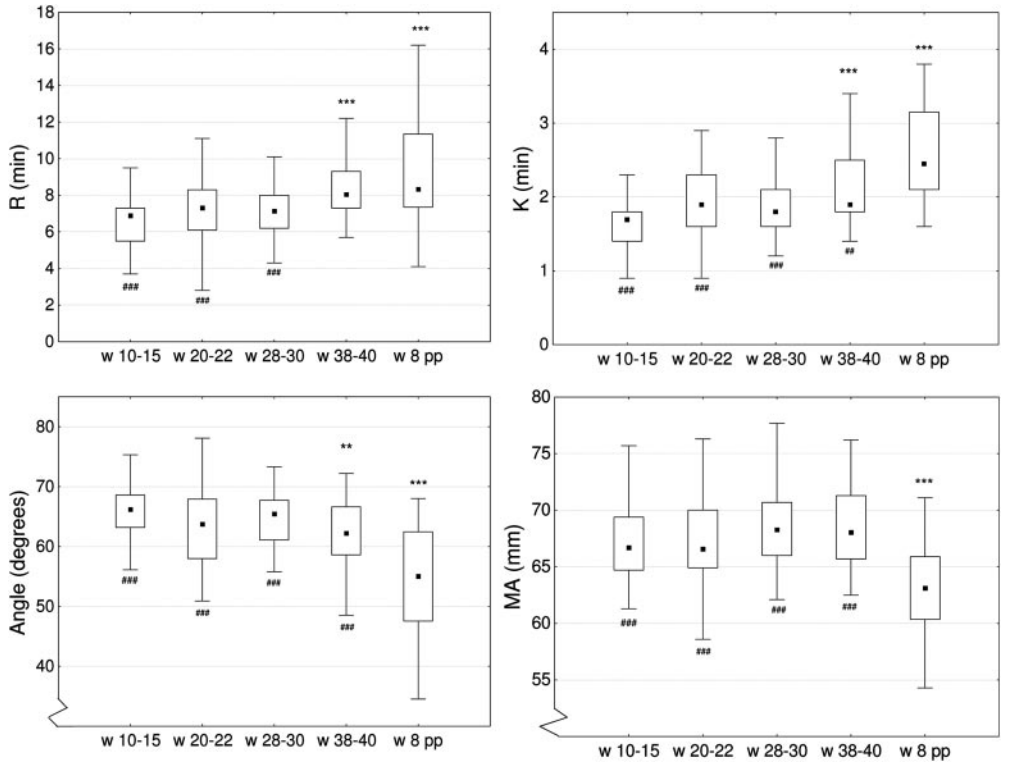

Figure 1. Thromboelastographic variables during pregnancy (gestational weeks 10 to 15, 20 to 22, 28 to 30 and 38 to 40) and 8 wk postpartum. Box-whisker plots with median (square), 25%–75% percentile, minimum, and maximum. *r* = time until fibrin formation; K = time until amplitude of 20 mm; Angle = rate of clot growth; MA = maximum amplitude; w = gestational week; pp = postpartum. **P* < 0.05, ***P* < 0.01, ****P* < 0.001 vs gestational weeks 10 to 15. #*P* < 0.05, ##*P* < 0.01, ###*P* < 0.001 vs 8 wk postpartum.

Table 4. Laboratory Analyses During Normal Pregnancy and 8 Weeks Postpartum

Laboratory analyses	Gestational wk	10–15	20–22	28–30	38–40	8 wk postpartum
	Women, *n*	43	44	43	37	44
APTT, s	Mean	32.0	32.0	31.5	31.2	34.2
	99% CI	31.0–33.1	31.1–33.1	30.5–32.5	30.2–32.3	33.2–35.3
	Median	32.0	32.0	31.0	30.0	33.5
	Range	25–38	28–39	27–39	27–37	29–46
PT (INR)	Mean	1.0	0.8	0.8	0.7	1.0
	99% CI	0.9–1.0	0.7–0.9	0.7–0.8	0.6–0.8	0.9–1.1
	Median	1.0	0.9	0.9	0.9	1.0
	Range	0.5–1.3	0.5–1.1	0.5–1.1	0.5–1.0	0.5–1.2
Platelet count	Mean	265	271	263	237	300
	99% CI	241–289	246–295	239–288	212–262	276–325
	Median	272	272	260	233	290
	Range	170–417	154–554	158–438	152–390	208–512
AT kIU/L	Mean	0.97	0.98	1.01	0.99	1.07
	99% CI	0.93–1.01	0.95–1.02	0.97–1.05	0.95–1.03	1.03–1.11
	Median	0.96	1.00	1.01	0.98	1.08
	Range	0.81–1.21	0.82–1.22	0.84–1.23	0.84–1.34	0.90–1.27
D-dimer mg/L	Mean	0.4	0.7	0.8	1.4	0.4
	99% CI	0.2–0.7	0.4–0.9	0.6–1.1	1.1–1.7	0.1–0.6
	Median	0.3	0.5	0.7	1.0	0.2
	Range	0.1–3.0	0.1–3.2	0.2–3.2	0.3–5.6	0.1–3.2
Soluble fibrin mg/L	Mean	4.6	7.7	7.1	8.3	4.8
	99% CI	0.7–8.5	4.0–11.3	3.5–10.8	4.5–12.1	1.2–8.5
	Median	2.3	4.0	4.2	5.8	3.6
	Range	0.4–49.6	0.0–56.4	0.0–48.4	1.8–48.1	0.2–15.1

APTT = activated partial thromboplastin time; PT = prothrombin complex; INR = international normalized ratio; AT = antithrombin.

to 40 and, in a few cases, due to technical problems. The number of patients in this study is probably large enough to be representative for Scandinavian Caucasian pregnant women.

Our findings of increased coagulability are in agreement with a cross-sectional study during pregnancy, a longitudinal study including only late pregnancy and the postpartum period[12,13] and a longitudinal study using another

Table 5. Laboratory Analyses During Normal Pregnancy Compared to 8 Weeks Postpartum and During Pregnancy, Compared to Gestational Week 10–15

Laboratory analyses	Gestational wk	10–15	20–22	28–30	38–40
	Women, *n*	45	43	42	38
APTT, s					
A	Δ between means, absolute	−2.2	−2.2	−2.8	−3.0
	99% CI, absolute	−3.6 to −0.8	−3.5 to −0.9	−3.9 to −1.6	−4.0 to −2.1
	Δ between means, %	−6.4	−6.3	−8.1	−8.9
B	Δ between means, absolute	—	0.0	−0.6	−1.0
	99% CI, absolute	—	−0.8 to 0.8	−1.7 to 0.5	−2.3 to 0.3
	Δ between means, %	—	0.3	−1.8	−7.3
PT (INR)					
A	Δ between means, absolute	−0.01	−0.2	−0.2	−0.3
	99% CI, absolute	−0.1 to 0.1	−0.3 to −0.1	−0.3 to −0.1	−0.4 to −0.2
	Δ between means, %	−1.0	−18.0	−22.0	−31.0
B	Δ between means, absolute	—	−0.2	−0.2	−0.3
	99% CI, absolute	—	−0.2 to −0.1	−0.3 to −0.1	−0.4 to −0.2
	Δ between means, %	—	−17.3	−21.4	−30.6
Platelet count $\times 10^9$/L					
A	Δ between means, absolute	−35.1	−29.5	−37.0	−63.4
	99% CI, absolute	−68.3 to −2.0	−60.2 to 1.1	−63.8 to −10.3	−84.7 to −42.1
	Δ between means, %	−11.7	−9.8	−12.3	−21.1
B	Δ between means, absolute	—	5.6	−1.9	−28.2
	99% CI, absolute	—	−13.2 to 24.4	−26.8 to 23.0	−57.8 to 1.4
	Δ between means, %	—	2.1	−0.7	−10.6
AT kIU/L					
A	Δ between means, absolute	−0.10	−0.09	−0.06	−0.08
	99% CI, absolute	−0.15 to −0.04	−0.14 to −0.04	−0.11 to −0.01	−0.12 to −0.04
	Δ between means, %	−9.3	−8.4	−5.6	−7.5
B	Δ between means, absolute	—	0.01	0.04	0.02
	99% CI, absolute	—	−0.02 to 0.04	0.00 to 0.08	−0.03 to 0.07
	Δ between means, %	—	1.0	4.1	2.1
D-dimer mg/L					
A	Δ between means, absolute	0.1	0.3	0.5	1.0
	99% CI, absolute	−0.3 to 0.5	−0.1 to 0.7	0.1 to 0.9	0.7 to 1.4
	Δ between means, %	17.1	94.3	140	297
B	Δ between means, absolute	—	0.3	0.4	1.0
	99% CI, absolute	—	0.0 to 0.6	0.1 to 0.8	0.6 to 1.4
	Δ between means, %	—	66.7	102.4	238.1
Soluble fibrin mg/L					
A	Δ between means, absolute	−0.2	2.8	2.3	3.5
	99% CI, absolute	−6.4 to 5.9	−3.0 to 8.7	−3.3 to 7.8	−1.4 to 8.4
	Δ between means, %	−5.0	59.0	47.2	72.5
B	Δ between means, absolute	—	3.1	2.5	3.8
	99% CI, absolute	—	−2.1 to 8.3	−3.6 to 8.6	−2.8 to 10.4
	Δ between means, %	—	66.7	54.5	82.6

A = changes compared to 8 wk postpartum; B = changes compared to gestational wk 10–15; APTT = activated partial thromboplastin time; PT = prothrombin complex; INR = international normalized ratio; AT = Antithrombin; Δ = changes.

viscoelastic method.[12,16] The hemostatic changes during pregnancy are probably estrogen induced.[14] The changes in laboratory analyses in this study concur with previous reports.[14,17]

The most pronounced decrease in TEG®-R was found at the beginning of pregnancy. A short TEG®-R indicates that clotting has started earlier. A cross-sectional study of the corresponding variable (clotting time) in the TEM system did not demonstrate shorter time to clotting start.[12] These diverging results could be due to the difference in study design or the limited number of patients in the cross-sectional study. Differences in clotting time between TEG® and TEM have been reported in nonpregnant patients.[18] TEG®-K was shorter and the TEG®-Angle was increased, compared to 8 weeks postpartum, which means that clot formation was more rapid during pregnancy. The cross-sectional study of the TEM yielded similar results.[12]

TEG®-MA was increased, meaning that the clots were stronger, during pregnancy. This increase was found early in pregnancy and did not change. The TEM study did not show increased maximum clot firmness in early pregnancy, but an increase was found in the second and third trimesters.[12] Clot firmness had the tightest correlation when TEG® and TEM were compared,[18] so the different result in the current compared to the TEM study[18] is probably due to small numbers and different populations. TEG®-MA is dependent on platelet count and fibrinogen,[6,19,20,21] and factor XIII was recently suggested to contribute as well.[22,23] Platelet count was largely unchanged during the study period, suggesting that fibrinogen may be the main contributor to the TEG®-MA results. However, factor XIII or unidentified substances might also affect this variable.

Both APTT and PT (INR) were shorter in pregnancy. The changes in APTT and PT (INR) were not found in the

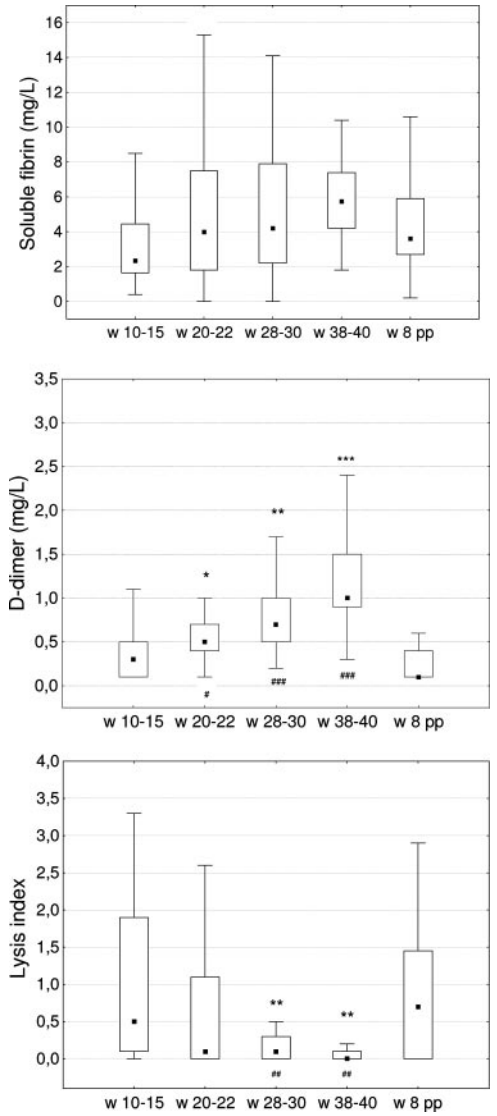

Figure 2. Soluble fibrin, D-dimer and Lysis index (TEG® LY30) during pregnancy (gestational weeks 10 to 15, 20 to 22, 28 to 30, and 38 to 40) and 8 wk postpartum. Box-whisker plots with median (square), 25%–75% percentile, minimum, and maximum. w = gestational week; pp = postpartum. $*P < 0.05$, $**P < 0.01$ $***P < 0.001$ vs gestational weeks 10 to 15. $\#P < 0.05$, $\#\#P < 0.01$, $\#\#\#P < 0.001$ vs 8 wk postpartum.

cross-sectional TEM study.[12] APTT and PT (INR) were also unchanged in a large Danish study.[17] These discrepancies may also be attributed to different study methods. The observed decrease in platelet count and antithrombin levels were consistent with previous reports.[2,24,25]

We observed marked interindividual changes in soluble fibrin, resulting in nonstatistically significant findings within nonpregnant reference levels. A few women had very high soluble fibrin levels, which not could be explained by any obstetric complications known to be associated with activation of blood coagulation. Previous reports on soluble fibrin have shown an increase during pregnancy.[15,24] This discrepancy may be due to different methods of measurements. D-dimer levels increased as pregnancy progressed, consistent with other study results.[14,15,17]

TEG®-LY30 was lower from gestational weeks 28 to 30. The decrease in TEG®-LY30 indicates decreased fibrinolysis during late pregnancy, which has been reported.[26–29] This decrease is probably due to decreased tissue plasminogen activator activity and a minor increase in thrombin-activated fibrinolysis inhibitor,[29] as well as markedly increased levels of plasminogen activator inhibitor-1 from endothelial cells and plasminogen activator inhibitor-2 from trophoblast cells.[24,30,15] This increase in inhibitors is most pronounced during the late second and the entire third trimester. The increased level of D-dimer suggests that the change in TEG®-LY30 more likely results from increased thrombin activity rather than fibrinolysis.[31]

There were no or weak correlations between standard laboratory methods and TEG® variables, which is in agreement with previous reports,[9,20] possibly due to the fact that standard laboratory methods and TEG® variables assess hemostasis differently.

The strength of this study is the prospective and longitudinal design and the large number of women who participated throughout the study period. The results show the potential of TEG® as a point-of-care instrument.

One limitation of this study is the absence of prepregnancy baseline TEG® values and laboratory analyses. The results 8 weeks postpartum cannot be regarded as absolute nonpregnant values, even if most hemostatic variables are normalized at that time.[13,15,14] A major limitation is the absence of fibrinogen determination. This is due to the fact that, during the planning stage of this study, fibrinogen was

Appendix

Analysis	Reference range[a]	Laboratory method
Activated partial thromboplastin time	30–42 s	STA®-APTT/Automate 5 (Diagnostica Stago, Asnières sur Seine, France)
Prothrombin time	PT (INR) <1.2	Stago Prothrombin Complex Assay (Diagnostica Stago, Asnières sur Seine, France)
Platelet count	165–387 × 10^9/L	CellDyn Sapphire (Abbott, IL)
Antithrombin	0.80–1.20 KIE/L	Chromogenic substrate method, STAchrome ATIII (Diagnostica Stago, Asnières sur Seine, France)
Soluble fibrin	<9 mg/L	Automated latex-enhanced immunoturbidimetric assay, LPIA-latro (Mitsubishi Kagaku Iatron inc, Tokyo, Japan)[33]
D-dimer	0–0.5 mg/L	Quantitative latex agglutination assay, STA-Liatest® D-DI (Diagnostica Stago, Asnières sur Seine, France)

[a] Nonpregnant reference interval.

All chemical analyses except soluble fibrin were performed at the Department of Clinical Chemistry, Sahlgrenska University Hospital, Gothenburg, Sweden. Soluble fibrin was analyzed at the University and Regional Laboratories Region Skåne, Clinical Chemistry, University Hospital, Malmö, Sweden. Both laboratories are accredited (ISO 15189).

not included in the standard emergency hemostatic analyses, which were to be compared with the TEG® method. Another weakness of the study is that hematocrit was not determined. Retrospective checking of hemoglobin levels in medical records has, however, showed that the average hemoglobin level at gestational weeks 28 to 30 was 92.3% of the average level in early pregnancy, and 96.7% at gestational weeks 38 to 40. It is unlikely that these changes in hemoglobin levels influenced the TEG® variables.[32]

In conclusion, the TEG® method shows increased coagulability and decreased fibrinolysis during normal pregnancy in healthy women compared to 8 weeks postpartum. Alternative cutoff limits for TEG® may be required during pregnancy. Future studies are needed to ascertain whether viscoelastic methods of assessing coagulation function are preferable to standard hemostatic test in the setting of obstetric hemorrhage.

DISCLOSURES

Name: Ove Karlsson, MD.
Contribution: This author helped conduct the study, analyze the data and write the manuscript.
Attestation: Ove Karlsson has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
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Contribution: This author helped conduct the study, analyze the data and write the manuscript.
Attestation: Tommy Sporrong has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Andreas Hillarp, PhD.
Contribution: This author helped conduct the study, analyze the data, and write the manuscript.
Attestation: Andreas Hillarp has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Anders Jeppsson, MD, PhD.
Contribution: This author helped conduct the study, analyze the data, and write the manuscript.
Attestation: Anders Jeppsson has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Margareta Hellgren, MD, PhD.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Margareta Hellgren has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
This manuscript was handled by: Cynthia A. Wong, MD.

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Middle Cerebral Arterial Blood Flow Velocity Increases During Laparoscopic Cholecystectomy: Retraction

The editor in chief of *Anesthesia & Analgesia* requests the retraction of the article "Middle cerebral arterial blood flow velocity increases during laparoscopic cholecystectomy" by Yoshitaka Fujii, Hiroyoshi Tanaka, Shin Tsuruoka, Hidenori Toyooka, and Keisuke Amaha (*Anesthesia & Analgesia*, January 1994, volume 78, pages 80-3). Please see Editor's Note: Notices of Retraction in the October 2012 issue.

Reference:

Fujii Y, Tanaka H, Tsuruoka S, Toyooka H, Amaha K. Middle cerebral arterial blood flow velocity increases during laparoscopic cholecystectomy. Anesth Analg 1994;78:80-3