ORIGINAL ARTICLE

Coagulation assessment in normal pregnancy: thrombelastography with citrated non activated samples

G. DELLA ROCCA [1], T. DOGARESCHI [1], T. CECCONET [1], S. BUTTERA [1], A. SPASIANO [1], P. NADBATH [1], M. ANGELINI [2], C. GALLUZZO [2], D. MARCHESONI [2]

[1]Department of Anesthesia and Intensive Care Medicine, University of Udine, Udine, Italy; [2]Department of Obstetrics and Gynecology, University of Udine, Udine, Italy

ABSTRACT

Backgound. Thrombelastography (TEG) provides an effective and convenient means of whole blood coagulation monitoring. TEG evaluates the elastic properties of whole blood and provides a global assessment of hemostatic function. Previous studies performed TEG on native blood sample, but no data are available with citrated samples in healthy pregnant women at term. The aim of this study was to investigate the effect of pregnancy on coagulation assessed by TEG and establish normal ranges of TEG values in pregnant women at term comparing them with healthy non pregnant young women.

Methods. We enrolled pregnant women at term undergoing elective cesarean section or labour induction (PREG group) and healthy non-pregnant women (CTRL group). Women with fever or inflammatory syndrome, defined as C-reactive protein (CRP) >5 mg/L and with a platelet count <150.000/mm^3 have been excluded. For each women hemochrome and standard coagulation test were assessed. At the same time we performed a thrombelastographic test with Hemoscope TEG® after sample recalcification without using any activator.

Results. One hundred thirty patients were studied, 65 for each group. There were no differences between groups regarding demographic data. Hemoglobin, platelet count, International Normalized Ratio and Activated Partial Thromboplastin Time Ratio were lower and fibrinogen was higher in PREG group. All TEG parameters resulted as being significantly different between the groups with a hypercoagulable pattern in PREG group compared to CTRL group.

Conclusion The main findings of this study confirm the hypercoagulability status of pregnant women at term. This coagulation pattern is well represented by thrombelastographic trace obtained by recalcified citrate blood sample. *(Minerva Anestesiol 2012;78:1357-64)*

Key words: Thrombelastography - Pregnancy - Blood coagulation.

Pregnancy is associated with changes in hemostasis, including increases in the levels of most clotting factors, a decrease in anticoagulants, and a reduction in fibrinolytic activity. These changes result in a state of hypercoagulability that minimizes the risk of hemorrhage during pregnancy and immediately after delivery.[1, 2]

Comment in p. 1319.

To assess the perioperative coagulation status of a patient, routine coagulation tests (*e.g.*, platelet count, prothrombin time, activated partial thromboplastin time, and fibrinogen) are still widely used despite their limitations.[3, 4] They do not provide any information on the kinetics of clot formation, on clot strength, on the interactions between the coagulation components, on platelet function, or about fibrinolysis; fur-

thermore, the generation of results is slow.[3, 4] To overcome these limitations, there is a need for a specific, sensitive, and rapid bedside test for monitoring coagulation. Thrombelastography (TEG) allows for a qualitative and dynamic analysis of the specific blood clotting process, from clot formation through its lysis, highlighting alterations at every single step in the cascade.[5] It studies the viscoelastic properties of a blood sample and their changes during coagulation process, reproducing them in a graphical trace and measuring defined parameters well explained by Di Benedetto.[5] Camezind *et al.* studied TEG using fresh native blood, but, if samples cannot be processed in few minutes, they can be citrated and then assessed at a later time following recalcification [6] as Armstrong and collagues did with ROTEM®.[7] No data are available regarding TEG for the assessment of citrated blood samples from pregnant women; furthermore, the reference values supplied by manufacturers of TEG machines are wide, and they cannot be applied to pregnant women.

The aim of this study was to investigate the effects of pregnancy on coagulation assessed by TEG and establish the normal ranges of TEG values, including: reaction time (R, minutes), clot formation time (k, minutes), α-angle (α, degrees), maximum amplitude (MA, mm), and clot lysis at 30 and 60 min (Ly30 and Ly60%). TEG values for citrated/recalcified blood taken from pregnant women at term were compared to those obtained from healthy young women confirmed not to be pregnant.

Materials and methods

Inclusion and exclusion criteria

Following approval by the Ethics Committee and informed written consent, healthy women with single spontaneous pregnancies were enrolled into the study. All women were at term (gestational age >38 weeks) and scheduled for elective cesarean delivery or induction of labor (PREG group). As controls, healthy non pregnant women (under 40 years of age) scheduled for gynecological, maxilla-facial or orthopedic surgery (CTRL group) were enrolled.

Exclusion criteria were: a history of chronic or obstetric disease, coagulation disorders, or postpartum hemorrhage; the consumption of estroprogestinics, antiplatelet or anticoagulant drugs; the presence of fever or inflammatory syndrome (defined as C-reactive protein [CRP]>5 mg/L); or a platelet count <150x10^3/mm^3.

Study protocol

Following hospital admission, venous blood was collected through a single 18 gauge cannula placed in a peripheral vein. Routine blood tests were performed: hemoglobin concentration (Hb), hematocrit (Hct), platelet count (PLT), activated partial thromboplastin time ratio (aPPTr), international normalized ratio (INR), and fibrinogen (FBN); all samples were analyzed in one central laboratory. Through the same 18 gauge cannula, a consecutive blood sample was collected into a 4.5 mL tube (BD Vacutainer System, Belliver Industrial Estate, UK) containing a 3.8% sodium citrate solution (0.129 M). Within 1 h from the time of collection, TEG was performed using a Hemoscope TEG 5000 Coagulation Analyzer® (Hemoscope Corp., Niles, IL, USA) following the recalcification of 340 µL of blood with 20 µL CaCl (0.2 M) without activators by just two defined expert operators to reduce the possibility of inter-tester variability affecting the results. TEG data analyzed were: reaction time (R, minutes), clot formation time (k, minutes), α-angle (α, degrees), maximum amplitude (MA, mm) and clot lysis at 30 and 60 min (Ly30 and Ly60, respectively; %).

Statistical analysis

A preliminary analysis of TEG data of a pilot study detected a 15% difference in mean R values between the PREG and CTRL groups; so a sample size of 63 patients per group was required (α 0.05, β 0.05).

Student-t tests were used to compare the PREG and CTRL group data, except for Lys 60 data that did not have a normal distribution, so a Mann-Withney test was performed. A value of P<0.05 was considered statistically significant. Statistical analysis was conducted using Graph-

Pad Prism version 4.00 for Windows (GraphPad Software, San Diego, California, USA).

Results

Between May 2008 and November 2010, 148 women were enrolled onto the study. Eighteen women (17 in PREG group and 1 in CTRL group) were excluded due to high CRP values (14), a low platelet count (1), or distorted TEG trace due to technical problems (3); thus data were analyzed from a total of 130 women (N.=65 for each group). In the PREG group, 51 women were scheduled for elective cesarean delivery and 14 women were scheduled for induced labor. In the CTRL group, 31 women were scheduled for gynecological surgery, 26 for maxillo-facial surgery, and 8 for orthopedic surgery.

There were no significant differences between the two groups regarding age (mean±SD: PREG 33±5, CTRL 31±9 years, P=0.13) or BMI, considering BMI scores before pregnancy (PREG 23.5±3, CTRL 22.5±5, P=0.14). The mean BMI score of the pregnant women at term was 28.3±3 (kg/m^2) and the mean gestational age was 39±1 weeks.

Routine blood tests

The mean values (± SD) for each blood test are shown in Table I.

TEG values

All TEG parameters assessed, except Lys 60, resulted as being significantly different in the PREG group compared to those for the CTRL group. Mean values (± SD) for each parameter are reported in Table II for both groups. Figure 1 shows an example TEG trace obtained from a pregnant woman. The reaction time (R) minimum and maximum values in the PREG group were 2.8 and 13.7 respectively (interquartile range, 5.1-6.8) and 3.9 and 15.8 min respectively (interquartile range, 6.2-8.8) in the CTRL group (Figure 2A).

The clot formation time (k) minimum and maximum values in the PREG group were 0.8 and 3.8 min respectively (interquartile range, 1.1-1.5) and 1.1 and 5.7 respectively (interquartile range, 1.7-2.8) in the CTRL group (Figure 2B).

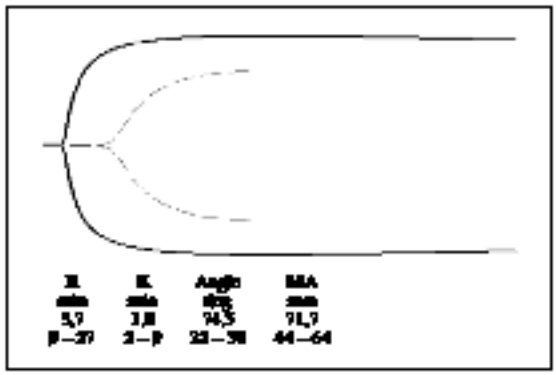

Figure 1.—Example thrombelastographic trace from a pregnant woman.
A representative TEG trace from a pregnant woman at term. Solid lines represent our patient's TEG values while dotted lines are the normal ranges provided by the manufacturer.
R: reaction time; K: coagulation time; a: alfa angle; MA: maximum amplitude.

Table I.—*Routine blood tests in the PREG and CTRL groups.*

	PREG	CTRL	p
Age (years)	33 ± 5	31 ± 9	0.13
BMI (kg/m^2)	a) 23.5 ± 3 b) 28.3 ± 3	22.5 ± 5	0.14
GA (weeks)	39 ± 1	-	-
Hb (g/dL)	11.8 ± 1.1	12.9 ± 1.1	<0.001
PLT (10^3/ mm^3)	229 ± 52	266 ± 54	<0.001
FBN (mg/dL)	588 ± 80	347 ± 75	<0.001
INR	0.93 ± 0.04	1.01 ± 0.07	<0.001
aPTTr	0.99 ± 0.08	1.05 ± 0.08	<0.001

Data are expressed as means ± SD. BMI= body max index: a) before pregnancy, b) at term.
GA: gestational age; Hb: haemoglobin; PLT: platelets; FBN: fibrinogen; INR: international normalized ratio; aPTTr: activated thromboplastin time ratio; PREG: pregnant women group; CTRL: healthy non pregnant women group.

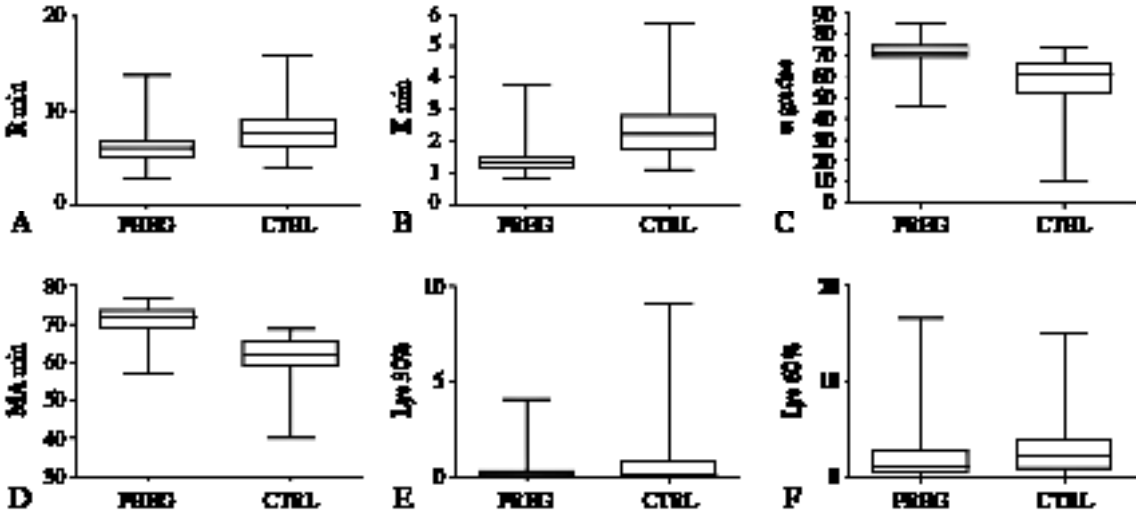

Figure 2.—TEG values for the PREG and CTRL groups.
Upper and lower quartiles; the line within each box indicates the median value, and the whiskers indicate the min and max values.
A:R values, b:K values, c:α values, d:MA values, e:Lys 30 values, f:Lys 60 values;
PREG: pregnant women group; CTRL: healthy non pregnant women group; R: reaction time; K: coagulation time; α: alfa angle; MA: maximum amplitude; Lys 30: lysis at 30 minutes; Lys 60: lysis at 60 minutes.

The α angle minimum and maximum values in the PREG group were 46.2 and 84.9 degrees respectively (interquartile range 69.1-74.2) and 10.7 and 73.8 degrees respectively (interquartile range 52-65.5) in the CTRL group (Figure 2C).

The maximum amplitude (MA) minimum and maximum values in the PREG group were 57.1 and 76.7 mm respectively (interquartile range 68.9-73.4) and 39.8 and 68.7 mm respectively (interquartile range 58.9-65.4) in the CTRL group (Figure 2D).

The clot lysis at 30 min (Lys 30) minimum and maximum values in the PREG group were 0 and 4.1 % respectively (interquartile range 0-0.3) and 0 and 9.1 % respectively (interquartile range 0-0.8) in the CTRL group (Figure 2E).

The clot lysis at 60 min (Lys 60) minimum and maximum values in the PREG group were 0 and 16.6 % respectively (interquartile range 0.4-2.7) and 0 and 15 respectively (interquartile range 0.85-4) in the CTRL group (Figure 2F).

Discussion

The results of this study into the use of TEG in pregnant women at term reveal significantly lower R and k values, and significantly higher Mα and α-angle compared to controls. Sharma and co-workers studied TEG traces of pregnant women with native blood samples and celite-activated samples and compared theme to non-pregnant women: their results are similar to ours showing a hypercoagulable pattern of pregnant women with lower R and k values and higher MA α-angle; they also found no differences in Lys 60, but they didn't record Lys 30.[8] More recently Polak published a similar paper on TEG traces in pregnant women comparing them to non pregnant women using native kaolin-activated blood samples confirming previous results and finally proposed the new TEG ranges to be used in pregnant women; unlike Sharma and us, Polak recorded a significant difference also in Lys 60, with a lower value in pregnant women as attended by physiology.[9] We didn't use activated samples, but the only difference compared to the Polak's results is a longer R parameter of PREG group (6.1 *vs.* 4.75 min) as attended; we cannot explain why there is no difference in R parameter of CTRL group (7.8 *vs.* 7.81).

In the past years, other studies have analyzed the assessment of coagulation in the obstetric population using another type of point of care device: the thrombelastometry (ROTEM®).

Table II. *Thrombelastographic values in the PREG and CTRL groups.*

	PREG	CTRL	P
R (min)	6.1±1.8	7.8±2.5	<0.001
K (min)	1.4±0.5	2.7±2.3	<0.001
a (deg)	70.6±6.5	57.7±11.6	<0.001
MA (mm)	71±3.8	61±5.9	<0.001
Ly30 (%)	0.3±0.7	0.8±1.7	0.013
Ly60 (%)	1.8±2.5	2.4±3.6	0.08

Data are expressed as means ± SD. R: reaction time; K: coagulation time; α: alfa angle; MA: maximum amplitude; Ly30: lysis at 30 minutes; Ly60: lysis at 60 minutes; PREG: pregnant women group; CTRL: healthy non pregnant women group.

Huissoud reported the first reference values of ROTEM® during pregnancy and demonstrated significant correlation between the results obtained with ROTEM® and those from standard coagulation.[2] Unlike us, Huissoud used coagulation activators, such ellagic acid or tissue factor, to speed up the analysis and facilitated more specific exploration of the intrinsic and extrinsic pathway (with INTEM and EXTEM respectively).[2]

Also Armstrong used specific activators to evaluate the extrinsic and intrinsic systems and the clotting factors alone after platelet inactivation to demonstrate the hypercoagulability of pregnancy.[7] The author defined reference ranges for ROTEM® that might be potentially useful in the hemostatic management of the parturients.[7]

Despite the fact that both devices represent the same process, the reference values are different. These findings may be explained by variations of cup size or material of the cup, but also by differences of the coagulation activators and have to be considered when using algorithms developed with one system while analyzing blood samples with the other device.[10] In order to improve the ability to differentiate between coagulopathies of different etiologies in special clinical settings, different commercially available tests have been developed for each device. The measurement reproducibility of both devices are comparable and are in a clinically acceptable range.[11, 12]

The parameters assessed by TEG provide information about each stage of whole blood clot formation: R, k, and α-angle reflect clotting factors activity; k and α-angle also evaluate the fibrin-platelet interaction, while MA is dependent on platelet concentration and function as well as platelet-fibrin interaction.[5]

The distinct form of the TEG trace observed in the pregnant women is due to an increase in the activity of coagulation factors, a decrease in endogenous anticoagulants, and an increase in platelet reactivity, despite their reduced number, that occurs during pregnancy.[8]

Even if parturient women tend to hypercoagulability as observed by TEG trace, TEG values remain beyond standard limits, but higher than "normal" patients. Standard ranges are well described in the literature.[13-15]

Hunt suggested that TEG should be available in every labor ward for assisting obstetric anesthetists in hemostatic decision making.[16] TEG can be used to assess hypercoagulable states and coagulation defects in pregnancy, for monitoring patients with pre-eclampsia or HELLP syndrome, and for assessing when blood products or procoagulant drugs need to be administered in situations like massive postpartum hemorrhage.[16] Thrombocytopenia is the most common hematologic disorder during pregnancy and a contraindication for neuroaxial anesthesia; in these cases TEG could constitute an adjunctive tool for evaluating coagulation, in association with laboratory tests and LWMH guidelines. A the moment, in literature, there are not TEG's reference values to perform neuroaxial anesthesia in pregnancy.[9]

Obstetric anesthetists are commonly asked to provide neuraxial anesthesia in women taking prophylactic heparin. A justifiable concern exists regarding its use due to the risk of neuraxial hematoma formation.[17] Low molecular weight heparin (LMWH) is often used to treat parturients with high thrombophilic risk, but guidelines are only valid for prophylactic and not therapeutic doses of LMWH.[18, 19] LMWHs are unique

in their ability to preferentially inhibit factor Xa more than factor IIa. The degree of factor Xa inhibition is directly related to its anticoagulant effect.[20] LMWHs can produce therapeutic anticoagulant effect within 2-4 hours after subcutaneous administration. Peak plasma levels occur 4 hours after subcutaneous administration and decrease to 50% of peak values 12 hours after injection. Based on these findings, it has been suggested that 10-12 hours (for prophylactic use) or 24 hours (for therapeutic use) interval occurs between the insertion of and removal of epidural needles and catheters and previous administration of LMWH dose. Despite these guidelines, bleeding risk cannot be predicted from available, standard, laboratory tests.[20]

Backe and Lyons used TEG to assess periodically the coagulation status in two pregnant women receiving therapeutic doses of LMWH.[21] TEG was able to provide them with a rapid overview of the situation, while traditional laboratory tests could not; thus influencing both the surgical and anesthetic management of the patients for a safe outcome. In the same paper the authors commented that guidelines recommend that the dose of LMWH is reduced before the induction of labor, but no guidance is given as to how women receiving this treatment should be managed in the event of early urgent delivery.[21]

Furthermore, anti-Xa assays remain the mainstay of recommended monitoring for LMWH therapy.[22] However, compared to anti-Xa assays, TEG provides a faster and simpler alternative. TEG measures the shear elasticity of blood and has been shown to be sensitive to LMWH anticoagulation.[20] TEG can help gauge the appropriate dose of LMWH for each patient, minimizing the risk of overdosing. TEG can also be used to check for residual anticoagulation before initiating invasive procedures.[23]

However, before TEG can be introduced into the obstetric environment on a routine basis, specific reference ranges for pregnant women need to be defined. The hypercoagulability developed during pregnancy is well represented by the TEG trace, as described in the literature,[24] and confirmed by our study. To the best of our knowledge, no previous study has evaluated citrated blood samples using the Hemoscope TEG 5000 Coagulation Analyzer®. Fresh native blood is usually used, but it must be processed by TEG no longer than 6 minutes after venipuncture, and ideally after only 4 minutes.[25] The advantage of native blood is that contact activation caused by sample storage is avoided, the disadvantage, however, is that immediate analysis is not always feasible.[26] If a delay between venipuncture and starting the TEG profile cannot be avoided, citrated blood can be used; samples can be stored and then recalcified before their insertion into a hemoscope.[25-28] Camenzind and co-workers compared TEG parameters of native blood with those of citrated and recalcified blood in surgical patients.[6] They demonstrated that TEG blood parameters in recalcified blood differ from those in native blood and change significantly during 30-60 minutes of storage, but that they remain stable between 1 and 8 hours. They also revealed a state of hypercoagulability in citrated and recalcified samples. They postulated that citration may be responsible for incomplete inhibition of thrombin formation.[6] Even if citrated blood tends towards hypercoagulability, our data show evident differences in pregnant women compared to non pregnant controls that are consistent with a hypercoagulable state.

In our study, we couldn't justify this hypercoagulable state with the minutes of storage, since all samples have been processed in the same conditions within one hour from the time of collection.

On comparing the variables characterizing fibrinolysis in the two groups, we found that the values of Ly30 and Ly60 were lower in the PREG group (even if Lys 60 didn't reach statistically significance), indicating reduced fibrinolysis in pregnant women. As fibrinolysis is depressed during pregnancy, the levels of fibrin breakdown products (for example, fibrin D-dimers) will not necessarily reflect the amount of local intravascular coagulation, but it could instead denote a physiological response of the fibrinolytic system to the increase in fibrin deposition consecutive to enhanced thrombin generation.[1]

The PT and its derived measure, INR, test for factors such as FII, FV, FVII, FX, and fibrinogen. In the present study, INR and aPTTr are shorter in the pregnant subjects, even if they still

lie within normal (non pregnant) ranges; thus, these conventional global tests are not able to detect the hypercoagulable condition of pregnancy.[29]

TEG is the only single test that can provide information on the balance between thrombosis and lyses, while the battery of traditional *in vitro* coagulation tests are based on end points that do not consider the dynamics of clot formation, but rather the earliest (optical) detection of fibrin.[24] Furthermore, situations can arise in the labor ward in which it can be argued that a routine coagulation screen and full blood count do not provide enough information. TEG, on the other hand, has the capacity to provide further information; for example, it can aid in the assessment of whether a women is hemostatically fit for regional anesthesia when she has a hemostatic defect. This is certainly the case with regard to the prediction of safe regional anesthesia in women who are excluded based on present criteria. TEG constitutes a useful and promising research tool in the field of obstetrics; however, at present, few data exist to indicate that it has a role in any aspect of obstetric practice. Well-designed and adequately powered studies into the use of TEG for predicting outcomes of regional anesthesia are required.

The present study could have had some limitations: it would be more correct to standardise the exact time point of TEG analysis but, as well as technically complex, it would not correspond to real clinical practice. Sharma *et al.* demonstrated that blood becomes hypercoagulable during exposure to stress. This is due to the release of catecholamines during stress, which have a stimulatory effect on platelet aggregation, and which can, in turn, accelerate coagulability.[30] Gorton *et al.* demonstrated that the events associated with the preparation for regional anesthesia (placement of the intravenous cannula, the attachment of monitoring devices, and a 15 minutes wait adjacent to the operating theatre) induced moderate increases in the coagulation status in patients awaiting cesarean section.[31] It seems unlikely, however, that these environmental factors alone are sufficient to explain the differences in TEG values observed in pregnant women, since even non pregnant patients receive a venipuncture before surgery and are managed in the same way with no regard for an alteration in coagulation status.[31] We avoided this potential problem by collecting samples immediately after hospital arrival, a long time before the patients were prepared for, or entered the operating theatre.

The possibility of inter-tester variability influencing the results of the present study was reduced by limiting the number of expert TEG operators to just two.

Most of the hypercoagulable hemostatic changes of pregnancy are also observed in women who use oral contraceptives;[32, 33] even though estroprogestinic consumption formed an exclusion criteria of this study, we cannot exclude it as a possibility, despite the fact that all participants declared not to be taking them.

Conclusions

TEG has the capacity to play an important role in the labor ward by assisting obstetric anesthetists in their decision-making processes. The targeted use of TEG during pregancy, the interpretation of TEG traces in consideration of each clinical situation, and quality control procedures are all necessary and would be beneficial for the parturient. The present study presents TEG data that could be used as reference information for the hemostatic management of pregnant women at term.

Key messages

— TEG could be useful for obstetric anesthetist in the labor ward.

— TEG traces of pregnant women are peculiar because of hypercoagulability of pregnancy.

— Our data could be used as pregnant reference ranges.

References

1. Thornton P, Douglas J. Coagulation in pregnancy. Best Pract Res Clin Obstet Gynecol 2010;24:339-52.
2. Huissoud C, Carrabin N, Benchaib M, Fontaine O, Levrat A, Massignon D *et al.* Coagulation assessment by rotation thrombelastometry in normal pregnancy. Thromb Hemost 2009;101:755-61.

3. Luddington RJ. Thrombelastography/thromboelastometry. Clin Lab Hematol 2005;27:81-90.
4. Ganter M, Hofer CH. Coagulation monitoring: current techniques and clinical use of viscoelastic point-of-care coagulation devices. Anesth Analg 2008;106:1366-75.
5. Di Benedetto P, Baciarello M, Cabetti L, Martucci M, Chiaschi A, Bestini L. Thrombelastographyy. Present and future perspective in clinical practice. Minerva Anestesiol 2003;69:501-15.
6. Camenzind V, Bombeli T, Seifert B. Citrate storage affects thrombelastograph analysis. Anesthesiology 2000;92:1242-9.
7. Armstrong S, Fernando R, Ashpole K, Simons R, Columb M. Assessment of coagulation in the obstetric population using ROTEM® thromboelastometry. Int J Obst Anesth 2011;20:293-8.
8. Sharma SK, Philip J, Wiley J. Thromboelastographic changes in healthy parturients and postpartum women. Anesth Analg 1997;85:94-8.
9. Polak F, Kolnikova I, Lips M, Parizek A, Blaha J, Stritesky M. New recommendations for thromboelastography reference ranges for pregnant women. Thrombosis Research 2011;e14-17.
10. Nielsen VG. A comparison of the thrombelastograph and the ROTEM®. Blood Coagul Fibrinolysis 2007;18:247-52.
11. Lang T, Bauters A, Braun SL, Potzsch B, von Pape KW, Kolde HJ *et al.* Multi-center investigation on reference ranges for ROTEM® thrombelastometry. Blood Coagul Fibrinolysis 2005;16:301-10.
12. Forestier F, Belisle S, Contant C, Harel F, Janvier G, Hardy JF. Reproducibility and interchangeability of the thrombelastograph, sonoclot and hemochron activated coagulation time in cardiac surgery. Can J Anesth 2001;48:902-10.
13. Chandler WL. The Thrombelastograph and the throbelastography technique. Semin Thromb Hemost 1995;21(Suppl 4):1-6.
14. Mallet SV, Cox DJA. Thromboelastography. Br J Anesth 1992;69:307-13.
15. Coakley M, Reddy K, Mackie I, Mallert S. Transfusion triggers in orthotopic liver transplantation:a comparison of the thromboelastometry analyzer, the thrombelastogram, and conventional coagulation tests. J Cardiothorac Vasc Anesth 2006;20:548-53.
16. Hunt BJ. Thrombelastography should be available in every labour ward. Int J Obstet Anhest 2005;14:324-7.
17. Kopp SL, Horlocker TT. Anticoagulation in pregnancy and neuroaxial blocks. Anestesiol Clin 2008;16:1-22.
18. Duhl AJ, Paidas MJ, Ural SH, Branch W, Casele H, Cox-Gill J *et al.* Antithrombotic therapy and pregnancy: consensus report and recommendation for prevention and treatment of venous thromboembolism and adverse pregnancy outcomes. Am J Obstet Gynecol 2007;197:457.e1-21.
19. Samama CM, Albaladejo P, Benhamou D, Benhamou D, Bertin-Maghit M, Bruder N *et al.* Venous thromboembolism prevention in surgery and obstetrics: clinical practice guidelines. Eur J Anesthesiol 2006;23:95-116.
20. Klein SM, Slaughter TF, Vail PT, Ginsberg B, Ej-Moalem HE, Alexander R *et al.* Thrombelastography as a perioperative measure of anticoagulation resulting from low molecular weight heparin:a comparison with anti-Xa concentrations. Anesth Analg 2000;91:1091-5.
21. Backe SK, Lyons GR. High-dose tinzaparina in pregnancy and the need for urgent delivery. Br J Anesth 2002;89: 331-4.
22. Sephton V, Farquharson RG, Topping J, Quenby SM, Cowan C, Back DJ *et al.* A longitudinal study of maternal dose response to low molecular weight heparin in pregnancy. Obst Gynecol 2003;101:1307-11.
23. Carrol RG, Craft RM, Whitaker GL, Snider CC, Kirby RK, Elder RF *et al.* Thrombelastography monitoring of resistence to enoxaparin anticoagulation in thrombophilic pregnancy patients. Thromb Res 2007;120:367-70.
24. Othman M, Falcon BJ, Kadir R. Global hemostasis in pregnancy: are we using thrombelastography to its full potential? Semin Thromb Hemost 2010;36:738-45.
25. Bowbrick VA, Mikhailidis DP, Stansby G. The use of citrated whole blood in thrombelastography. Anesth Analg 2000;90:1086-8.
26. Coimbatore S, Srinivas C, Meineri M, Banks B, McCluskey SA, Karkouti K *et al.* Technical report: analysis of citrated blood with thromelastography: comparison with fresh blood samples". Can J Anesth 2008;55:284-9.
27. Zambruni A, Thalheimer U, Leandro G, Perry D, Burroughs AK. Thrombelastography with citrated blood: comparability with native blood, stability of citrate storage and effect of repeated sampling. Blood Coagul Fibrinolysis 2004;15:103-7.
28. Mancuso A, Fung K, Cox D, Mela M, Patch D, Burroughs AK. Assessment of blood coagulation in severe liver disease using thrombelastography: use of citrate storage versus native blood. Blood Coagul Fibrinolysis 2003;14:211-6.
29. Paniccia R, Domenico P, Bandinelli B, Fedi S, Giusti B, Pepe G, Abbate R *et al.* Plasma and serum levels of d- dimer and their correlation with other hemostatic parameters in pregnancy. Thromb Res 2002;105:257-62.
30. Sharma SK, Philip J. The effect of anesthetic techniques on blood coagulability in parturients as measured by Thrombelastography. Anesth Analg 1997;85:82-6.
31. Gorton H, Lyons G, Manroy P. Preparation for regional anesthesia induces changes in TEG:Br J Anesth 2000;84:403-4.
32. Knijff SCM, editor: summary of contraindications to oral contraceptives. New York:Parthenon Publishing Group; 2000.
33. Beller FK. Cardiovascular system: coagulation, thrombosis, and contraceptives steroids- is there a link? In: Goldzieher JW, Fortherby K, editors. Pharmacology of contraceptive steroid. New York: Raven Press; 1994. p. 309-34.

Funding.—No sources of financial support for the work.

The paper has been presented at the Euroanesthesia Congress, 11-14 June 2011, Amsterdam, the Netherlands.

Received on February 23, 2012 - Accepted for publication on October 29, 2012.

Corresponding author: T. Cecconet, Department of Anesthesia and Intensive Care Medicine, P.le S. Maria della Misericordia 15, 33100 Udine, Italy. E- mail: t.cecconet@gmail.com