Thromboelastography and peripartum coagulation profiles associated with caesarean section delivery

R Smith*, T Campbell-Owen*, H Maybury*, S Pavord† and J Waugh‡

*Obstetrics & Gynaecology, University Hospitals of Leicester, LE1 5WW; †Haematology, University Hospitals of Leicester, Leicester LE1 5WW;

‡Obstetrics & Gynaecology, Royal Victoria Infirmary, Newcastle Upon Tyne NHS Trust, Newcastle Upon Tyne NE1 4LP, UK

Summary: Thromboembolic (TE) disease remains the leading direct cause of maternal death in the UK and caesarean section increases TE risk. Women are assessed for their TE risk and may receive thromboprophylaxis. From a single blood sample thromboelastography® (TEG®) allows a test of coagulation. Blood samples from women undergoing elective caesarean sections were collected at specific stages: antenatally, following overnight 'nil-by-mouth', immediately after surgery, four hours post-delivery and 24 hours post-delivery. Analyses of the R time (time taken for blood to clot) and maximum amplitude (MA) (overall clot strength) were performed. Analyses of the high and moderate risks cohorts were performed and compared to the low risk group.

Fifty-four women were recruited. A reduction in the R time was demonstrated following pre-operative fluid restriction and a further reduction in R time occurred after surgery. The R time increased 24 hours after surgery and became comparable to pre-operative levels. The MA changed similarly due to pre-operative fluid restriction. Analysis also showed that pre-operatively, the combined high and moderate risk groups' R time was shorter than the low risk group. The high and moderate risk group, having received thromboprophylaxis, had similar R times 24 hours postoperatively compared to the low risk group. TEG® demonstrates that following pre-operative fluid restriction and surgery women become hypercoagulable but by 24 hours coagulation has returned to third trimester levels. Sub-group analysis suggests the relative pre-operative hypercoagulability of high and moderate risk women compared to low risk women, becoming comparable after 24 hours following thromboprophylaxis.

Keywords: thromboelastography, thromboembolic disease, caesarean section, pregnancy, haematology, maternal mortality

INTRODUCTION

Data from the Confidential Enquiry into maternal deaths¹ confirm that thromboembolic (TE) disease continues to be the leading *direct* cause of mortality in the UK. In the period 2003–2005, the death rate due to TE disease was 19.4 per million maternities, a drop from the peak of 21.8 per million maternities in 1994–1996.

The actual number of deaths in the 2003–2005 period was 41, compared with 48 between 1994 and 1996. Of the 41 deaths, 33 were due to pulmonary embolism and eight due to cerebral thrombosis. TE deaths following caesarean section were 15 in the period 1994–1996 and seven in the period 2003–2005. This drop in mortality over the last nine years may be attributed to the introduction of thromboprophylaxis guidelines² for women undergoing caesarean section.

The period following operative delivery has the highest TE risk. Intuitively, there are a number of interventions within the caesarean section process that may be responsible for this peak in risk. Such factors include preoperative fluid restriction, the surgery itself (blood loss and damage to vascular endothelium), prolonged immobility following anaesthesia and the acute phase changes in blood constituents, including a reactive thrombocytosis.³ Previous estimates have put the incidence of thromboembolism following

caesarean section as being between 2.5 and 20 times that following spontaneous vaginal deliveries.^{4,5}

After a formal risk assessment, thromboprophylaxis is currently advocated in the postpartum period for women delivered by caesarean section who are judged to be at moderate or high risk of thromboembolism.² In these patients, prophylaxis is continued for a minimum of five days postpartum.

Thromboelastography® (TEG®) provides a global 'bedside' test of haemostatic coagulation from a single blood sample. Current laboratory tests, e.g. platelet count, prothrombin time and activated partial thromboplastin, measure individual components of the pro-thrombotic – anti-thrombotic process. TEG®, however, measures the net product of the interaction of the coagulation components.

TEG® is used in hypocoagulable states such as liver transplant surgery⁶ and cardiothoracic surgery,^{7,8} where many units use TEG® results in management algorithms. Although studies have been conducted in hypercoagulable states such as pregnancy, TEG® values are not used in any related management protocols. These studies have demonstrated that TEG® can highlight the haemostatic coagulation changes that occur. We have previously shown that TEG® values in women delivered vaginally return to normal at approximately six weeks postdelivery.⁹ Others have reported an association between TEG® and the coagulopathies associated with preeclampsia.¹⁰

The primary aim of our study was to describe, using TEG®, the changes in the global haemostatic function in women

Correspondence to: J Waugh
Email: jason.waugh@nuth.nhs.uk

undergoing caesarean section and thus generate hypotheses as to possible triggers of TE disease in this group of patients. A secondary aim was to assess whether demographic stratification of low, moderate and high TE risk subgroups, with subsequent thromboprophylaxis, relates to TEG[®] parameters; therefore possibly using TEG[®] as a surrogate for current TE risk stratification, which is based solely on demographic variables.

METHODS

After local ethical committee approval, informed consent was obtained from women undergoing elective caesarean sections between March and April 2004. Women were provided with written information about the study in the ante-natal clinic when booking for their caesarean section.

Women were risk assessed for the likelihood of having a TE event according to RCOG guidelines. Risk stratification was based on patient demographics and previous medical and obstetric histories. Table 1 summarizes the criteria used for TE risk stratification. Women in any of the TE risk categories were recruited to the study.

Prospective blood samples were taken at the following times through the caesarean section stages:

- A week prior to surgery at caesarean section booking in the ante-natal clinic, routine preoperative blood samples were also taken;
- On the day of surgery following overnight 'nil-by-mouth' and moments before administration of a combined spinal epidural;
- Immediately following wound closure, but before thromboprophylaxis;
- Four hours later in recovery;
- Twenty-four hours postoperatively.

Other operative variables such as intraoperative fluid volumes, estimated blood loss, surgical time, time of thromboprophylaxis administration and fluid given in theatre and recovery were all noted. This blinded observational study was pragmatic and thromboprophylaxis regimens were unaltered by the TEG[®] results.

Blood samples were taken as a citrated native sample from a peripheral vein via an 18-gauge needle into a vacutainer[™].

A two-syringe technique was used, i.e. the first vacutainer[™] was disregarded to minimize thromboplastin contamination. The samples were then analysed by TEG[®] between 30 and 120 minutes after capture.

TEG[®] analysis is based on the principle of changing visco-elastic properties of blood during clot formation. It is performed in a bench-top automated device. Each sample was processed by TEG[®] in a predetermined study protocol: the citrated blood in the vacutainer[™] was inverted five times, 1 mL of blood was then pipetted from the vacutainer[™] into a kaolin vial and inverted again five times and finally, 0.34 mL was pipetted from the kaolin vial into a disposable plastic cup that had been preloaded with 0.02 mL of 0.2 mmol/L calcium chloride. TEG[®] analysis was then commenced.

The disposable cup oscillates 4° 45' in either direction every 4.5 seconds. A pin is suspended in the cup of blood from a torsion wire that is electronically transduced to a computer monitor. Initially, when no clot exists, the motion of the cup does not affect the pin and a straight line is recorded. As the blood begins to clot the motion of the pin is impeded and this is transferred via the torsion wire to make a characteristic tracing¹¹

Figure 1 Schematic TEG[®] trace showing the variables measured. (*R* Time) is the distance until coagulation starts; (*k*) is the distance from *R* until the amplitude of the trace is 20 mm; (α) is the angle of the trace from the horizontal at the point when the amplitude is 20 mm; (*MA*) is the maximum amplitude achieved.

Table 1 Demographic criteria used to determine risk category and prophylactic management for thromboembolism after caesarean section

Low TE risk	Moderate TE risk (2 or more of)	High TE risk
Elective caesarean section	Age (>35 years)	Three or more moderate risk factors or
Uncomplicated pregnancy	Obesity (>80 kg)	Extended pelvic or abdominal surgery
No other risk factors	Parity (≥ 4)	Antiphospholipid antibody
	Emergency caesarean section	Paralysis or immobilization of lower limbs
	Gross varicose veins	Known personal/family history of DVT or thrombophilia
	Current infection	
	Immobility (>4 days prior to surgery)	
	Preeclampsia or pregnancy induced hypertension	
	Labour 12 hours or more	
	Major current illness (e.g. Cancer, IHD, IBD)	
Management	Management	Management
Early mobilization	UF Heparin 5000 iu s/c moments after closure	UF Heparin 5000 iu s/c moments after closure
Hydration postoperative	Fragmin 2500 iu s/c OD minimum five days	Fragmin 2500 iu s/c OD minimum five days
		Leg stockings advised

TE = thromboembolic; IHD = ischaemic heart disease, IBD = inflammatory bowel disease

(Figure 1). In our study, TEG[®] analysis was performed until the maximum amplitude (MA) of the clot had been reached.

TEG[®] analysis can produce many parameters of blood coagulation as illustrated in Figure 1, four are described below:

R time: A measure of the time taken for the first fibrin strand to be formed – 'reaction time'. Thus, an elongated R time represents a deficiency of coagulation factors, inhibitors and/or activators resulting in a slow rate of thrombin formation.

α value: A measure of the rapidity of fibrin build-up and cross-linking, i.e. the speed of clot strengthening.

K time: A measure of the rapidity of reaching a 20 mm TEG[®] tracing amplitude. Like the α value, K times are affected by the availability of fibrinogen and to a lesser extent platelets.

MA: A measure of the strength of clot, strength is affected by platelet number and function and to a lesser extent the fibrinogen level.

The two parameters widely used in the literature are R time and MA, and it is these two that are used in this study.

Statistical analysis

Two analyses were performed and a *P* value of <0.05 was considered significant. For all women in the longitudinal cohort, analyses of the data by analysis of variance (ANOVA) and paired *t*-tests were performed. Separate analyses of the low, moderate and high-risk subgroups were performed using ANOVA and independent sample *t*-tests.

RESULTS

Longitudinal analysis

For the longitudinal group analysis, 54 women (14 low risk, 32 moderate risk and 8 high risk) were recruited. Demographic data for this group are shown in Table 2.

The indications for the caesarean section included: previous caesarean section (30), breech presentation (8), pre-eclampsia (6), previous perineal tear (3), placenta previa (3), fibroids (1), avoidance of instrumental delivery (1), congenital malformation (1) and macrosomia (1). The average period of 'nil-by-mouth', leading up to stage (ii), was 12 hours 50 minutes (range: 6 hour 0 minute – 18 hours 40 minutes) and the average surgical time, first incision to closure, in this series of patients was 36 minutes (range: 15–75 minutes).

Between arrival in the anaesthetic room and the commencement of surgery, an average of 875 mL (range: 500–1300 mL) of fluid was infused, intraoperatively the average was 510 mL (range: 200–1700 mL) and during four hours of recovery, the average was 625 mL (range: 350–1200 mL).

Table 3 shows a breakdown of R times and MA for the combined and individual TE risk groups throughout the caesarean section process.

Figure 2 shows the R times and MA values at the various stages of the caesarean section process for the longitudinal combined TE risk group.

Table 2 Demographic data for the longitudinal analysis of 54 mixed TE risk women and the subgroup analysis of the 14 low TE risk women, 32 moderate TE risk and eight high TE risk women

Characteristic	Mixed TE		Low TE		Moderate TE		High TE	
	Mean	Range	Mean	Range	Mean	Range	Mean	Range
Age	31.0	19–41	28.4	19–34	32.5	23–41	30.1	27–35
BMI (kg/m ²)	27.0	19–44	24.0	21–30	27.3	21–42	29.9	20–40
Gestation (weeks)	39.0	32–42	39.1	38–41	38.7	32–42	38.1	34–40

TE = thromboembolic; BMI = body mass index

Table 3 R time and maximum amplitude (MA) means for the low (14), moderate (32), high (8) and mixed (all 54 women) thromboembolic risk groups at each stage throughout the caesarean section process

Stage	R time (low TE risk)	95% confidence interval	R time (moderate TE risk)	95% confidence interval	R time (high TE risk)	95% confidence interval	R time (mixed TE risk)	95% confidence interval
R time								
(i)	4.85	3.8–5.9	4.20	3.5–4.7	4.50	1.2–7.8	4.45	4.1–4.8
(ii)	4.59	4.3–4.8	3.93	3.7–4.1	4.30	2.7–5.9	4.16	4.0–4.3
(iii)	3.39	2.9–3.9	3.55	3.4–3.7	3.80	2.2–5.4	3.55	3.4–3.7
(iv)	3.75	3.1–4.4	3.80	3.6–4.0	4.10	2.4–5.9	3.83	3.7–4.0
(v)	4.10	3.5–4.7	4.23	4.0–4.4	5.10	3.3–6.8	4.32	4.1–4.5
Stage	MA time (low TE risk)	95% confidence interval	MA time (moderate TE risk)	95% confidence interval	MA time (high TE risk)	95% confidence interval	MA time (mixed TE risk)	95% confidence interval
Maximum amplitude								
(i)	60.5	57.3–63.6	63.0	58.7–67.2	67.9	11.0–124.8	62.9	59.9–66.0
(ii)	68.1	66.1–70.1	67.8	66.7–69.0	69.6	41.1–98.0	68.2	67.4–69.0
(iii)	72.5	70.0–75.0	68.3	67.3–69.3	70.1	41.6–98.5	69.6	68.8–70.5
(iv)	70.0	68.3–71.8	68.4	67.4–69.4	69.9	39.5–100.3	69.0	68.2–69.7
(v)	68.6	65.5–71.7	68.1	66.6–69.6	69.8	39.4–100.2	68.5	67.3–69.6

TE = thromboembolic

Figure 2 T-test mean R time and MA values with confidence intervals (!) at stages through the caesarean section process in longitudinal mixed TE risk analysis

R time: Analysis shows that preoperative fluid restriction leading up to stage (ii), ($P < 0.001$), and the surgical procedure (stages [ii]–[iii]), ($P < 0.0001$), both significantly reduce the time taken for clot formation to commence and thus render the mother hypercoagulable. This clot formation time significantly increases 24 hours after the procedure, (stages [iii]–[v]), ($P < 0.0001$), i.e. the woman becomes less hypercoagulable.

There was no correlation between the R time and the length of preoperative fluid restriction or length of the surgical procedure.

MA: Analysis shows a similar hypercoagulable picture after fluid restriction with significant increases in MA values ($P < 0.0006$). MA values remain significantly high after surgery (stage [iii]) ($P < 0.002$), at four hours postoperatively (stage [iv]) ($P < 0.001$) and at 24 hours postoperatively (stage [v]) ($P < 0.036$) when compared with preadmission (stage [i]).

Longitudinal subgroup analysis

For the subgroups comparative analyses between the combined high and moderate TE risk groups and the low TE risk group were performed preoperatively (stage [ii]) and at 24 hours postoperatively (stage [vi]). The high and moderate TE risk groups were combined as they both received postoperative thromboprophylaxis unlike the low TE group.

R time: In the preoperative samples (stage [ii]), the low TE risk women were less coagulable than the combined high and moderate TE risk women (4.59 versus 4.01), ($P < 0.02$). No significant difference ($P = 0.38$) was seen between the two groups at 24 hours postoperatively, when the high and moderate risk

women had received thromboprophylaxis; the low TE risk group having an R time of 4.10 and the combined high and moderate risk group having an R time of 4.39.

MA: Preoperative and 24 hours postoperative analyses did not achieve significant differences between the two groups.

DISCUSSION

In this study, TEG[®] R time and MA values suggest that (a) preoperative fluid restriction and (b) surgical intervention may be implicated in rendering a woman hypercoagulable. A degree of resolution of this hypercoagulable state is seen at 24 hours post-caesarean section as shown by an increase in R time. However, no drop in MA values was seen at the same time period. The MA analysis, therefore, corroborates the R time values, indicating a hypercoagulable state following 'starvation'. But unlike the R time, MA values do not approach preoperative levels at 24 hours postoperatively. It is hypothesized that the given MA is correlated to platelet count and that there is a reactive thrombocytosis postdelivery.³ MA will take a longer time to recover than R time.

Although it has been possible to speculate, no studies to date have been able to identify what aspect of the caesarean section process creates or triggers the high increase in TE risk associated with this procedure. TEG[®], by measuring the visco-elastic properties of blood, is able to detect hypocoagulable or hypercoagulable states. This is possible as TEG[®] provides quantitative data on the net result of the interaction of platelets with the protein coagulation cascade. Initial fibrin formation, clot rate formation and strengthening, fibrin platelet bonding via GPIIb/IIIa receptors and clot lysis are all indirectly monitored by TEG[®]. Rate, strength and stability of clot formation can all indicate whether the patient has normal, hypo- or hypercoagulable haemostasis. TEG[®] is thus able to provide dynamic information about coagulation.

It is widely assumed that dehydration is a risk factor for the development of venous TE disease; however, the literature does not reveal any large studies investigating this in a surgical setting. One study of hydration following acute ischaemic stroke, concluded that dehydration is strongly independently associated with venous TE disease.¹² Patients undergoing surgery are requested to be nil-by-mouth to avoid anaesthetic complications and for patients having elective caesarean sections, this is requested from midnight before surgery. In reality, however, most patients stop food and/or fluids much earlier than required. Thus, it is very possible for a woman to have waited in excess of 12 hours before intravenous fluids are administered, as was the case in our study.

In this series of patients, intravenous fluids were started moments before the combined spinal epidural was performed in the anaesthetic room. Therefore, given the significant hypercoagulability seen after fluid restriction, it may seem appropriate for early intravenous hydration of women awaiting an elective caesarean. However, these results would need to be reproduced in a larger and more robust study before such a change in protocol was introduced and tempered with the fact that postpartum women are at risk from non-cardiogenic pulmonary oedema from overhydration. Furthermore, preoperative 'stress' stimulating catecholamine release, with a subsequent increase in platelet activity, may be contributory to the hypercoagulability seen prior to anaesthesia and thus not solely attributable to preoperative fluid restriction.

Although there were drops in mortality rates due to TE disease over the last three trienniums, unlike other leading causes of mortality, i.e. haemorrhage and the hypertensive disorders, TE disease rates are still higher than they were 20 years ago. There may be a number of factors that contribute to this; maternal age in pregnancy is rising, women with coexisting medical problems, e.g. obesity, hypertension and renal disease, are having an increasing number of pregnancies and there has been a rise in the caesarean section rate. In Table 1, we see the medical and personal demographics used for stratification of TE risk. An unknown positive family history for TE disease or an undiagnosed thrombophilia, the latter having been implicated in up to 50% of TE in pregnancy and postpartum women,¹³ may not be identified. This lack of identification may result in thromboprophylaxis not being given to women during their pregnancy. TEG[®] may highlight these seemingly low-risk women.

Our study suggests that preoperative demographic stratification of TE risk, as described in the RCOG guidelines,² is partly reflected by TEG[®] parameters and may therefore support current TE risk groups. However, contrary to what might have been expected, preoperative TEG[®] data did not demonstrate that the high TE risk group were hypercoagulable relative to the moderate risk group. This may be as a result of the small sample size of the high TE risk group, because TEG[®] was unable to differentiate between the two higher TE risk groups or that no difference exists between the groups. Combining the two groups at stage (ii), following fluid restriction, they were found to be hypercoagulable relative to the low TE risk group. The moderate risk group, on its own, was significantly hypercoagulable compared with the low TE risk at both preoperative time points, stages (i) and (ii). Again combining the higher TE risk groups at 24 hours postoperation, and after having received thromboprophylaxis, they had similar TEG[®] values to low-risk women at 24 hours postcaesarean section.

Limitations of study

Although this study produced statistically significant results, there was significant overlap of the confidence intervals throughout the time points and as such it would have benefited from a larger sample size. To eliminate possible bias, an ideal study to examine the effects of hydration on TEG[®] values would have been a randomized control trial, comparing one group receiving overnight intravenous hydration to a group not receiving an intravenous fluid regimen. Furthermore, a control group of

women undergoing vaginal delivery would have enabled TEG[®] comparisons to the caesarean section cohort, thus, possibly quantifying any heightened TE risk associated with surgery.

It is hoped that in this study TEG[®] has generated hypotheses as to what components of an elective caesarean section may contribute to the hypercoagulability of the mother and that TEG[®] goes some way to supporting current preoperative demographic TE risk stratification guidelines.

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