There is a return to non-pregnant coagulation parameters after four not six weeks postpartum following spontaneous vaginal delivery

H J Maybury MD MRCOG*, J J S Waugh MRCOG†, A Gornall MRCOG‡ and S Pavord FRCP FRCPATH§

*Obstetrics and Gynaecology, University Hospitals of Leicester; †Women's Services, Royal Victoria Infirmary; ‡Obstetrics and Gynaecology, Royal Shrewsbury Hospital; §Haematology, University Hospitals of Leicester

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INTRODUCTION

Changes in the coagulation status of the blood contribute to a 10-fold increased risk of venous thromboembolic disease seen in pregnancy, which rises to 25-fold in the postpartum period.¹ The widely accepted assumption that the hypercoagulable state of pregnancy resolves at six weeks postnatal is based on little scientific evidence. Individual parameters show considerable variation in their recovery to prepregnancy levels after childbirth, with some such as factor VIII and von Willebrand factor falling to baseline levels within 72 hours postpartum but others, such as the reduction in protein S, taking several weeks to recover. The cumulative effects of these is not known but could be assessed using a global test of haemostatic function such as thromboelastography (TEG). This technique evaluates the viscoelastic properties of blood during coagulation and fibrinolysis. It is able to provide information relating to the cumulative effect of several components of coagulation at a given time point and, unlike conventional clotting tests, can be performed on whole blood, thus incorporating the contribution of platelets to coagulation.

Understanding the rate of change after delivery and the time at which coagulation returns to non-pregnant levels in a population of healthy women with uncomplicated vaginal deliveries, would provide a baseline of normal physiological changes and a standard against which clinical situations associated with higher risk of thromboembolic disease can be compared. This may then inform the use of selective thromboprophylaxis to reduce morbidity and mortality related to thromboembolic disease.

We used thromboelastography to investigate the time taken for the hypercoagulable state of pregnancy to resolve in a population of healthy women with uncomplicated vaginal deliveries.

METHODS

Subjects

The study protocol was approved by Leicestershire, Northamptonshire and Rutland Ethics Committee. Women

who had uncomplicated vaginal deliveries after a normal antenatal period were approached to take part in the study. Exclusion criteria were multiple pregnancy; delivery of a baby weighing less than 2500 g; any recorded blood pressure of >140/90 mmHg either antenatally, intrapartum or postnatally; past personal or family history of thromboembolism; concurrent medical illness; and blood loss at delivery exceeding 400 mL.

Women were visited at home and gave blood samples weekly for up to 10 weeks postdelivery. A control group of 50 non-pregnant women was also recruited. These women were healthy volunteers, between 18 and 40 years of age who had no personal or family history of thromboembolism, had no medical illness and who were not taking the combined oral contraceptive pill. A single blood sample was taken from this group during the follicular phase of the menstrual cycle.

Blood sampling and analysis

Venepuncture was performed with a 21-gauge needle using minimum stasis into two 3 mL Sarstedt Monovett bottles, containing 0.3 mL of 3.2% sodium citrate. The bottles were not evacuated and a conventional syringe technique was used. The first sample was discarded to avoid contamination with tissue thromboplastin and the second was used for analysis by thromboelastography.

Thromboelastography

Twenty microlitres of 0.2 mol/L of calcium chloride were pipetted into a disposable plastic cup, which had been loaded in a prewarmed thromboelastogram. The citrated blood sample was inverted five times to ensure mixing of the sample and then 340 µL of native blood was added to the cup. Five thromboelastographic parameters were analysed: *R* time, *k* time, α angle, maximum amplitude (MA) and coagulation index (CI).

R time (reaction time) is the time from placing the blood in the cup until the first significant levels of detectable fibrin formation. This is the point at which most traditional clotting

Correspondence to: H J Maybury
Email: helenamaybury@yahoo.com

assays, including prothrombin time and activated thromboplastin time, reach their endpoints.

k Time is the time for achievement of a defined level of clot 'firmness'. It is the time from *R* time (beginning of clot formation) until a fixed level of clot firmness is reached (amplitude = 20 mm), giving a measure of the velocity of clot formation.

α Angle reflects the kinetics of clot development and the rate of polymerization. The angle is more comprehensive than *k* time, since there are hypocoagulable conditions in which the final level of clot firmness does not reach an amplitude of 20 mm, in which case *k* is undefined.

MA is the greatest vertical amplitude of the TEG trace. It measures the maximum strength of the developed clot, being dependent on both fibrin and platelets.

CI describes the overall coagulation and is derived from *R* time, *k* time, α angle and MA of native or kaolin-activated whole blood tracings. It is determined by the equation, $CI = -0.2454R + 0.0184K + 0.1655MA - 0.0241\alpha - 5.022$.

Statistical analysis

Statistical analysis was performed using MINITAB version 15 (Minitab Inc., PA, USA). To determine the time point at which coagulation in the postpartum women returned to that of the non-pregnant controls, non-parametric, two independent sample Mann-Whitney *U* tests were performed. A *P* value of <0.05 was considered statistically significant.

RESULTS

A total of 71 women were recruited to the study. The mean age of subjects was 28.3 years (range 17–41 years), mean weight at booking 67.7 kg (range 46.5–118 kg). The mean length of labour was 8.05 hours (range 1.08–22.4 hours) and mean blood loss 253.0 mL (range 100–400 mL). The epidural usage rate was 30% with 21 of the 71 women choosing this form of analgesia. Thirty-seven (52%) of the women were primiparous. The mean age of the control group was 29.5 years (range 18–40 years).

Sixty-one women had between two and eight samples taken, the average number of samples being 5.2. Ten women only had one sample taken due to difficult venous access (two), inability to contact patients (three) and patient choice to withdraw from study (five).

Figure 1 Interval plot of *R* time versus weeks postpartum after normal delivery

R time

The *R* time was significantly shorter in the first postpartum week (9.6 minutes vs. 13.9 minutes, $P < 0.0001$) and remained shortened in the second week (12.2 minutes vs. 13.9 minutes, $P < 0.05$) (Table 1, Figure 1). By the third week postpartum there was no significant difference when compared with the non-pregnant controls.

k Time

The *k* time shows similar changes. In the first week postpartum, the time taken to reach a defined clot strength is shortened (2.3 minutes vs. 4.4 minutes, $P < 0.0001$) and although this lengthens in the second week it is still significantly shorter than the non-pregnant controls (3.8 minutes vs. 4.4 minutes, $P < 0.05$) (Table 1). By the third postpartum week, the *k* time does not differ from the non-pregnant control population.

α Angle

The α angle is increased in the first week postpartum (59.1 vs. 43.3, $P < 0.0001$), but returns to non-pregnant values by the second postpartum week.

Table 1 TEG parameters in non-pregnant control population and after normal delivery

		R min (mean)	R min (95% CI)	K min (mean)	K min (95% CI)	Angle degree (mean)	Angle degree (95% CI)	MA, mm (mean)	MA, mm (95% CI)	Coagulation Index	
										Mean	95% CI
Controls	<i>n</i> = 50	13.9	12.9–15.0	4.4	4.0–4.8	43.3	40.1–46.5	52.7	50.6–54.8	–0.67	–1.14–0.20
Week 1	<i>n</i> = 102	9.6*	9.1–10.5	2.3*	2.1–2.5	59.1*	56.9–61.4	67.1*	65.8–68.3	2.33*	2.08–2.58
2	<i>n</i> = 34	12.2†	11.3–13.2	3.8†	3.2–4.5	46.7	41.9–51.5	61.2*	58.2–64.2	1.04*	0.51–1.58
3	<i>n</i> = 36	13.4	12.3–14.4	4.3	3.7–4.8	44.4	41.1–47.8	56.6†	53.7–59.4	0.05†	–0.45–0.56
4	<i>n</i> = 26	13.9	12.9–15.0	4.5	4.0–5.0	41.8	38.4–45.2	52.2	49.6–54.8	–0.73	–1.17–0.29
5	<i>n</i> = 36	13.4	12.4–14.3	3.8	3.5–4.2	44.5	41.7–47.3	53.2	50.9–55.4	–0.47	–0.88–0.06
6	<i>n</i> = 31	13.9	12.8–14.9	4.5	3.9–5.0	41.8	38.1–45.6	51.2	48.7–53.6	–0.84	–1.32–0.36
7–9	<i>n</i> = 26	15.1	13.1–17.2	4.9	3.7–6.0	42.5	37.6–47.4	57.3†	54.5–60.0	–0.19	–0.80–0.42
10–12	<i>n</i> = 41	15.3	14.1–16.4	4.6	4.1–5.2	42.5	39.3–45.7	53.1	51.0–55.1	–0.93	–1.31–0.54

* $P < 0.0001$ when compared with control population

† $P < 0.05$ when compared with control population

Figure 2 Interval plot of MA versus weeks postpartum after normal delivery

Maximum amplitude

MA took four weeks to return to non-pregnancy levels. It was maximally increased in the first week postpartum (67.1 mm vs. 52.7 mm, $P < 0.0001$) (Table 1, Figure 2), reduced steadily in the second week (61.2 mm vs. 52.7 mm, $P < 0.0001$) and the third week (56.6 mm vs. 52.7 mm, $P < 0.05$), but remained significantly elevated at three weeks compared with the non-pregnant controls.

Coagulation index

This parameter is increased during the first three weeks after delivery and shows a similar trend to MA. The first postpartum week demonstrates the greatest increase (2.33 vs. -0.67, $P < 0.0001$) (Table 1). In the second postpartum week the CI remains increased, but not to the level of the first week (1.04 vs. -0.67, $P < 0.0001$). In the third postpartum week there is a further reduction in CI, but the level remains significantly elevated compared with a non-pregnant population (0.05 vs. -0.67, $P < 0.05$).

By the fourth postpartum week none of the parameters differed from the non-pregnant control population, indicating resolution of the hypercoagulable state of pregnancy.

DISCUSSION

This study suggests that the hypercoagulable state of pregnancy resolves progressively after childbirth, taking four weeks to return to the non-pregnant state. This has implications for the risk of venous thrombosis in the postpartum period and the duration of thromboprophylaxis for those with additional risk factors.

We chose to use thromboelastography as this gives a cumulative measure of the numerous and varied changes in individual coagulant, anticoagulant and fibrinolytic factors that occur after childbirth. Furthermore, studies have confirmed correlation of TEG parameters with clinical risk of thrombosis in a number of clinical settings, including following elective abdominal surgery,² emergency hip fracture surgery³ and elective major non-cardiac surgery.⁴ In this study, the R and k times had recovered by three weeks postpartum but the MA remained elevated until four weeks. These results are in keeping with previous observations that fibrinogen, upon which MA is partly dependent, takes four weeks to return to baseline.⁵

The recent guidelines from the Royal College of Obstetricians and Gynaecologists, recommend risk assessment of all women in labour and after vaginal delivery has resulted in increased vigilance and more widespread use of postpartum thromboprophylaxis.⁶ However, the required duration of treatment is less certain. Currently, lower risk women receive three to five days of low molecular-weight heparin and for those at higher risk, such as with inherited thrombophilia and/or history of thrombosis, treatment is extended to six weeks. If postpartum TEG parameters do provide an accurate assessment of the totality of coagulation and correlate with clinical events, as they have been shown in other clinical settings, our data would suggest that three to five days thromboprophylaxis may be insufficient and six weeks unnecessarily excessive. Studies giving a global assessment of coagulation status in these higher risk settings and large studies to confirm a correlation with clinical events, are needed to clarify the optimum duration of postpartum thromboprophylaxis. In the meantime, this observational study of low-risk deliveries potentially provides valuable information about the resolution of the hypercoagulable state in a timeframe that has been previously ignored.

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