

Calibrated Automated Thrombogram During Pregnancy in Unexplained Recurrent Miscarriages: A Pilot Study

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ABSTRACT: **Background:** Recurrent miscarriages are associated with a high prevalence of thrombophilia. Use of a calibrated automated thrombogram (CAT) can serve as a universal test for thrombophilia.

Objectives: To examine whether thrombin generation measured by CAT is elevated during the first trimester in women with unexplained recurrent miscarriages.

Methods: This study comprised 25 pregnant women with recurrent pregnancy loss referred for thrombophilia screening and treated with low-molecular-weight heparin (LMWH). Thrombin generation parameters were measured in women who had miscarriages or live births and who were diagnosed as positive or negative for thrombophilia.

Results: Of the pregnancies, 76% resulted in live birth and 24% ended in miscarriages. Among the women, 76% were positive for thrombophilia. Thrombin generation parameters between pregnancies that ended in miscarriage compared to live births were not significantly different, and CAT parameters failed to predict pregnancy outcome. Although the CAT parameters demonstrated a trend toward a hypercoagulable state in women with thrombophilia, there was no statistical significance ($P > 0.05$).

Conclusions: Women with unexplained pregnancy loss demonstrated similar thrombin generation in the first trimester, regardless of the pregnancy outcome. CAT parameters failed to predict pregnancy outcome in women with recurrent unexplained pregnancy loss. Our results should be interpreted with caution due to the small number of participants.

IMAJ 2019; 21: 681–685

KEY WORDS: anti-thrombotic treatment, calibrated automated thrombogram (CAT), thrombin generation, thrombophilia, recurrent miscarriages

The incidence of miscarriages in healthy women is about 15% of all pregnancies. The prevalence of recurrent miscarriages is approximately 1–2% [1]. The etiology for recurrent miscarriages can be embryonic, anatomic, chromosomal, or maternal disorders that create a hostile environment for the fetus. This happens in the case of endocrinological disorders

and congenital or acquired thrombophilia. Chromosome analysis could explain 80% of unexplained recurrent miscarriages in women more than 35 years old [2,3]. Nevertheless, a large number of miscarriages remain unexplained despite comprehensive investigation. The term recurrent miscarriages is defined as three early or two late miscarriages and has a prevalence of 1–2% in women of reproductive age [4].

Recurrent miscarriages are a predictable complication in conditions of hypercoagulation. Multiple studies have indicated a connection between recurrent miscarriages and acquired or congenital thrombophilia [5]. Mutations in factor V Leiden, protein S deficiency, protein C deficiency, or antithrombin III deficiency could increase the incidence of unexplained recurrent miscarriages. Factor V Leiden was associated with early and late recurrent miscarriages as were prothrombin mutation and protein S deficiency [6]. Moreover, the prevalence of thrombophilia in unexplained pregnancy loss was 78% [7], and there is a demonstrated link between thrombophilia and obstetric complications such as preeclampsia, placental abruption, fetal growth retardation, or stillbirth [8].

Anticoagulant treatment with low-molecular-weight heparin (LMWH) at a dosage of 40 mg once daily or other anticoagulants for women with recurrent miscarriages and thrombophilia leads to improved obstetric outcomes [9,10]. However, these findings do not prove the efficacy of heparin treatment due to a lack of control groups in the aforementioned studies [11]. Conversely, the chance for live births without treatment in these women is over 50%, thus the efficacy of anticoagulant treatment in recurrent miscarriages was inconclusive. Thus, additional randomized controlled trials (RCTs) are needed [12].

In the past, the common approach was to perform thrombophilia testing for every woman with a medical history of recurrent miscarriages or one miscarriage after gestational week 10. The cause of thrombophilia was determined in 50% of the patients. In the event of positive tests for thrombophilia, anticoagulation treatment during pregnancy was suggested. Even in the case of negative tests, anticoagulant treatment was proposed in chosen cases. Current guidelines recommend that only antiphospholipid syndrome workup be performed, without further thrombophilia diagnosis [13,14]. According to a

recently published meta-analysis of four RCTs, the benefit of LMWH could not be demonstrated [15].

In view of the evidence, the role of thrombophilia in recurrent miscarriages is not clear. Treatment with LMWH is also debatable due to the lack of evidence of LMWH efficacy in dealing with recurrent unexplained miscarriages with or without thrombophilia. However, the treatment with LMWH, continues, in part to encourage frustrated and disappointed couples [16].

Vincent et al. [17] demonstrated a significant increase in thrombin generation (thrombin-antithrombin complexes) in women with a history of recurrent miscarriages compared to controls. In recent years the calibrated automated thrombogram (CAT) is considered to be a good indicator for total thrombotic activity, whether hypercoagulability or hypocoagulability [18,19]. Thrombophilia may be one of the etiologies of unexplained recurrent miscarriages. Bennett and colleagues demonstrated no significant difference in CAT and rotational thromboelastometry in women with recurrent pregnancy loss compared to women without miscarriages [20]. Conversely Romagnuolo et al. [21] showed higher thrombin generation levels in the recurrent miscarriage group compared to the control group.

PATIENTS AND METHODS

The ethics committee of Emek Medical Center approved the study. Board certificate EMC 38-13. All participants gave written informed consent prior to the study. The study is registered in ClinicalTrials.gov Identifier: NCT02139670.

STUDY POPULATION AND DATA COLLECTION

Inclusion criteria included women older than 18 years of age, first trimester of pregnancy at enrollment, two or more unexplained pregnancy losses before 10 weeks of gestation or an unexplained pregnancy loss after 10 weeks, and referral by a fertility specialist after thorough investigation.

Exclusion criteria included women who received chronic anticoagulation or antiplatelet treatment and women with chromosomal, metabolic, or anatomical recurrent pregnancy loss etiologies.

All women referred to the community hypercoagulation clinic were tested for thrombophilia. Between the years 2013 and 2016 all participants provided a blood sample to measure thrombin generation. The blood samples were collected between weeks 7 and 8 of gestation during the first trimester before any treatment with LMWH began. The samples were stored at -70°C and analyzed at the end of the study using CAT. After blood collection, all the women in the cohort group received 40 mg of subcutaneous Enoxaparin without anti-factor Xa measurements. Participants were prospectively followed for outcome of the pregnancy.

DATA COLLECTION

The demographic data included age and number of miscarriages. Test results for thrombophilia included levels of protein S, protein C, antithrombin III, activated protein C resistance (APCR), lupus anticoagulant (LAC) presence, IgG and IgM antibodies to cardiolipin, genetic testing for factor V Leiden gene mutation, and prothrombin G20210A mutation.

THROMBIN GENERATION ASSAY

Six ml of blood were collected in two tubes containing sodium citrate. To obtain platelet-free plasma the samples were centrifuged twice, first for 15 minutes at 2500 RPM and then for 10 minutes at 2000 RPM. The plasma was stored at -70°C for later analysis. Thrombin generation was measured on platelet-poor plasma with the CAT technique and the use of 5 pmol/L tissue factor and 4 $\mu\text{mol/L}$ phospholipids. The thrombogram generated four parameters by dedicated software (Thrombinoscope™ B.V., Maastricht, the Netherlands): lag time, endogenous thrombin potential (ETP), peak height, and time to peak. Short lag time / time to peak and high ETP / peak height point indicated a hypercoagulable (prothrombotic) state, whereas prolonged lag time / time to peak and decreased ETP / peak height indicate a hypocoagulable (prohemorrhagic) state [18,19].

STATISTICAL ANALYSIS

Continuous variables were summarized with means and standard deviation, along with medians and interquartile ranges (IQRs). Categorical variables were summarized with numbers and proportions. The correlation between continuous variables and pregnancy outcomes was tested with the Wilcoxon two-sample test and categorical variables were tested using Fisher's exact test. Student's *t*-test was used to compare continuous variables with normal distribution. Statistical analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA). A *P* value < 0.05 was considered statistically significant.

To evaluate the prognostic ability of CAT, area under the receiver operating characteristics area under the curve (AUC) was calculated. Additive prognostic value of CAT to miscarriage was assessed by the increase of area under the curve using the test proposed by DeLong et al [22]

RESULTS

We enrolled 30 women who had been referred to the community hypercoagulation clinic between 2013 and 2016. Three participants were excluded because of lack of follow-up and another two were excluded for technical reasons related to the CAT test.

Overall, 19 pregnancies (76%) resulted in live births, compared to 6 (24%) that ended in miscarriages. The mean age of women in the live-birth group was 28.17 years compared to 27 in the miscarriages group. The age range in both groups was

Table 1. Comparison of demographic data and thrombophilia workup according to pregnancy outcome

	Miscarriage, n=6	Live births, n=19	P value
Age mean years (range)	28.17 (21–35)	27 (21–35)	0.8231
Gravidity	4 ± 1.41	3 ± 2.04	0.038
Parity	1.67 ± 1.21	1.16 ± 1.46	0.51
Number of living children	1.16 ± 1.16	1 ± 1.28	0.754
Number of miscarriages	4.5 ± 1.1	2 ± 1.105	0.016
Weeks of gestation	7.63 ± 4.4	7.12 ± 4.2	0.78
LAC	0 (0%)	3 (15.79%)	0.5539
Protein S deficiency	1 (16.67%)	7 (36.84%)	0.6237
Protein C deficiency	0 (0%)	2 (10.53%)	1
APCR ratio	2 (33.33%)	9 (47.37%)	0.6609
Total thrombophilia	3 (50%)	16 (84.21%)	0.1246

APCR = activated protein C resistance, LAC = lupus anticoagulant

Table 2. Thrombogram parameters as a function of pregnancy outcome

	Miscarriage, n=6	Live births, n=19	P value
Lag time, minutes			
Mean ± SD	3.2 ± 0.67	3.09 ± 0.39	0.8819
Median (IQR)	3.06 (2.67–3.33)	3.06 (2.83–3.26)	
Endogenous thrombin potential, nmol/L minutes			
Mean ± SD	2030.42 ± 529	2043.83 ± 284	0.3966
Median (IQR)	1770 (1652–2693)	1985 (1845–2249)	
Peak height, nmol/L			
Mean ± SD	371.98 ± 75	366.57 ± 38	0.5803
Median (IQR)	334.92 (324–466)	367.25 (351–380)	
Peak time, minutes			
Mean ± SD	5.67 ± 0.83	5.63 ± 0.73	0.8237
Median (IQR)	5.45 (5–6)	5.35 (5.33–5.73)	

IQR = interquartile range, SD = standard deviation

21–35 ($P = 0.8231$). The mean number of previous miscarriages was significantly higher in pregnancies that resulted in miscarriages compared to the live-birth group, 4.5 vs. 2 respectively ($P = 0.016$). The mean number of gestation weeks at the time of the testing were 7.63 in the miscarriages group, and 7.12 in the live-birth group ($P = 0.78$).

LAC was positive in 3 women (15.79%) in the live-birth group, compared to none in the miscarriage group ($P = 0.5539$). Protein S deficiency was positive in 1 woman (16.67%) in the miscarriage group vs. 7 (36.85%) in the live-birth group ($P = 0.6237$). Protein C deficiency was positive in 2 women (10.53%) in the live birth group, compared to none in the miscarriage group ($P = 1$). APCR was positive in 2 women (33.33%) in the miscarriage group vs. 9 women (47.37%) the live-birth group ($P = 0.6609$). Factor V Leiden, antibodies to cardiolipin, prothrombin mutation, and antithrombin III were negative for all participants. The prevalence of thrombophilia

Table 3. Thrombogram parameters as a function of thrombophilia workup

	With thrombophilia, n=19	Without thrombophilia, n=6	P value
Mean age in years (range)	30.17 (26–35)	26.37 (21–30)	0.1033
Number of miscarriages mean ± SD	3 ± 1.41	2.16 ± 1.3	0.1937
Lag time, minutes			
Mean ± SD	3.12 ± 0.46	3.14 ± 0.54	0.9704
Median (IQR)	3.14 (2.72–3.33)	2.95 (2.89–3.22)	
Endogenous thrombin potential, nmol/L minutes			
Mean ± SD	2094.2 ± 362.26	1896.06 ± 306.82	0.2238
Median (IQR)	1985 (1841–2352)	1818.67 (1652–2203)	
Peak height, nmol/L			
Mean ± SD	379.49 ± 46	343.04 ± 46.25	0.066
Median (IQR)	367.25 (351–415)	333.24 (302–368)	
Peak time, minutes			
Mean ± SD	5.6 ± 0.62	5.73 ± 1.06	0.7382
Median (IQR)	5.46 (5.22–5.89)	5.33 (5.11–5.78)	

IQR = interquartile range, SD = standard deviation

was 50% in the miscarriages group, compared to 84.21% in the live-birth group ($P = 0.1246$). As seen in Table 1 none of the thrombophilia tests reached statistical significance.

Table 2 compares thrombogram parameters performed by CAT according to pregnancy outcomes: the miscarriage group vs. the live-birth group. There was no significant difference between the thrombogram parameters. The mean lag time (in minutes) was 3.2 vs. 3.09 ($P = 0.8819$). The mean ETP (nmol/L min) was 2030.42 vs. 2043.83 ($P = 0.3966$). The mean peak height (nmol/L) was 371.98 vs. 366.57 ($P = 0.5803$). The mean peak time (in minutes) was 5.67 vs. 5.63 ($P = 0.82$).

Table 3 compares thrombogram parameters according to presence or absence of thrombophilia, specifically, the thrombophilia group vs. the group without thrombophilia. The mean lag time (in minutes) was 3.12 ± 0.46 vs. 3.14 ± 0.54 ($P = 0.9704$). The mean ETP (nmol/L minutes) was 2094.22 ± 362.26 vs. 1896.06 ± 306.82 ($P = 0.2238$). The mean peak height (nmol/L) was 379.49 ± 46 vs. 343.04 ± 46.25 ($P = 0.066$). The mean peak time (min) was 5.6 ± 0.62 versus 5.73 ± 1.06 ($P = 0.7382$).

We evaluated the prognostic value of several parameters for pregnancy outcome (miscarriage). The only parameter that yielded statistically significant results was the number of miscarriages. The AUC was 0.908 (95% confidence interval 0.724–0.986). Age and CAT parameters failed to predict risk of miscarriages (P value > 0.05) [Table 4].

DISCUSSION

Extensive research shows that there are numerous causes for recurrent miscarriages. When metabolic, chromosomal, or anatomical reasons are excluded, a rise in the prevalence of

Table 4. Area under the curve for calibrated automated thrombogram measurements and pregnancy outcome (miscarriage)

Parameters	Area under the curve	95% confidence interval	P value
Age	0.535	0.327-0.735	0.837
Number of miscarriages	0.908	0.724-0.986	0.0001
Endogenous thrombin potential	0.625	0.396-0.819	0.501
Peak	0.583	0.357-0.787	0.637
Time to peak	0.536	0.314-0.749	0.827
Lag time	0.526	0.305-0.740	0.876

thrombophilia is found in women with recurrent miscarriages. These findings are in agreement with our study of a small cohort, demonstrating an association between thrombophilia and recurrent miscarriages. In the present study thrombophilia was found in 76% of study participants, similar to our findings in a previous, larger retrospective cohort [22]. There was a higher prevalence of thrombophilia when compared to the general population, where the prevalence was between 3 and 8% [23]. Nevertheless, conclusions about prevalence cannot be drawn from the current study because it was not designed to assess the prevalence of thrombophilia (as the number of participants was too small).

In the present study approximately 76% of pregnancies resulted in live births compared to 72.2% in our previously retrospective cohort. Similarly, the Scottish pregnancy intervention study showed 72% live births, whether the women were treated or not with LMWH [24].

The mean number of previous miscarriages was significantly higher in the miscarriage group than the live-birth group, suggesting that pregnant women with higher numbers of previous pregnancy loss are more prone to another miscarriage [22].

Thrombin generation parameters measured during the first trimester of pregnancy by CAT failed to demonstrate a significant difference between miscarriages and live births [Table 2]. Our results demonstrated a trend to hypercoagulable state when thrombin generation parameters were compared between women with or without thrombophilia. Peak height and ETP were higher and lag time and time to peak were lower in women with thrombophilia, without statistical significance ($P > 0.05$). Although the trend toward a hypercoagulable state was to be expected, as demonstrated in previous studies of patients with thrombophilia [25], it was never demonstrated during pregnancy. Larger studies are needed to understand the role of CAT in thrombophilia in women with unexplained pregnancy loss.

Our findings suggest that thrombin generation during pregnancy, measured with CAT, failed to predict pregnancy outcomes in women with recurrent miscarriages who were treated with Enoxaparin. Our results are in concordance with previous studies, which failed to demonstrate a significant difference in thrombogram parameters in non-pregnant women with a history of

recurrent pregnancy loss, compared to women with uneventful pregnancies [20]. However, our results were incompatible with a recent study, which demonstrated an increased tendency towards a hypercoagulable state as measured by the same thrombogram parameters in recurrent pregnancy loss [21].

To the best of our knowledge, this is the first report to test CAT parameters during pregnancy in unexplained recurrent pregnancy loss demonstrating no significant difference between thrombogram parameters between live births and miscarriages. Two previous studies used the same assay in the same setting, but in non-pregnant women [20,21].

LIMITATIONS

The study had a small number of participants due to relatively slow enrollment. This result can be explained by the low rate of referral, attributed to the controversy surrounding the role of thrombophilia in recurrent pregnancy loss. In addition, the investigators had to stop the enrollment before achieving the predefined sample size of 120 of participants due to drastic changes in LMWH indications in this group of women. According to our calculation, our study reached a power of 0.8 to detect 400 nmol/L difference of ETP between women who had miscarriages vs. live births. Because of the lack of an adequate control group of pregnant women without pregnancy complications, and a small sample size our study results need to be interpreted with caution. Larger studies are needed in order to further understand the role of CAT in women with recurrent miscarriages.

CONCLUSIONS

Women with unexplained pregnancy loss demonstrated similar thrombin generation levels in the first trimester, regardless of the pregnancy outcome. There was no statistically significant difference between the thrombogram parameters in women with or without thrombophilia. Our results should be interpreted with caution due to the small number of participants.

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Capsule

Immune landscape of the human kidney

Single-cell RNA sequencing has begun to shed light on the full cellular diversity of specific organs. However, these studies rarely examine organ-specific immune cells. **Stewart** and co-authors sequenced healthy adult and fetal kidney samples at a single-cell level to define the heterogeneity in epithelial, myeloid, and lymphoid cells. From this dataset, they identified zonation of cells, with relevance to disease and the varied

perturbations that occur in different tumor settings. This profiling of the human kidney generates a comprehensive census of existing cell populations that will help inform the diagnosis and treatment of kidney-related diseases.

Science 2019; 365: 1461
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Capsule

Hinting at a herpes vaccine

A vaccine for genital herpes does not currently exist, despite the prevalence of this sexually transmitted disease. Previous attempts to make vaccines against herpes simplex virus 2 (HSV-2) included trials with protein subunit vaccine candidates that delayed infection onset but were not protective. **Awasthi** et al. described a vaccine candidate that is composed of nucleoside-modified mRNA in lipid nanoparticles that encodes the HSV-2 glycoproteins C, D, and E. This trivalent vaccine

protected mice and guinea pigs from developing genital lesions and reduced viral shedding. Neutralizing antibody and CD4+ T cell responses were detected in immunized mice. These results suggest that an mRNA-based HSV-2 vaccine may have potential for further preclinical development.

Sci Immunol 2019; 4: eaaw7083
Eitan Israeli

“Because I remember, I despair. Because I remember, I have the duty to reject despair”

Elie Wiesel (1928–2016), Romanian-born American Jewish writer, professor, political activist, Nobel Laureate and Holocaust survivor