

# THE UNIVERSITY OF NEW SOUTH WALES



*Faculty of Medicine*

**MFAC 4503: Independent Learning Project 3**

***The detection of clotting abnormalities by  
thromboelastography in women with repeated  
implantation failure***

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**Submission date: March 14<sup>th</sup>, 2011**

**Abstract word count: 249**

**Word Count: 4234**

## Abstract

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**BACKGROUND:** A large proportion of the underlying cause of repeated implantation failure remains unclear, but there is extensive research that highlights the possibility of thrombophilias as a cause. There has been shown a link between thromboelastograph parameters, most notably a high maximum amplitude, and repeated implantation failure. The objective of the study was to determine if thromboelastography can be used as an initial screening test for thrombophilias in women with three or more recurrent miscarriages or repeated IVF failures.

**METHODS:** This was a retrospective study encompassing 230 women (median age: 40, range: 27-52) with a history of miscarriage. Two groups were established on the basis of their thromboelastography results. Subjects with a maximum amplitude of 64.0→68.9 comprised one grouping and those with  $\geq 69.0$  comprised the other. The percentage of women with thrombophilic gene mutations and other associated factors was compared between these two groups. **RESULTS:** There was no statistically significant increase in the incidence of the thrombophilic factors in women with a higher maximum amplitude, except for those with increased homocysteine ( $P = 0.0269$ ). However, when low positive anticardiolipin antibodies was considered as being a negative value, there was an increased incidence in anticardiolipin IgM antibodies ( $P = 0.0331$ ) and in women with at least 1 thrombophilic factor ( $P = 0.0409$ ). **CONCLUSION:** From this study, thromboelastography cannot be used as an initial screening tool for thrombophilic genes in women with repeated pregnancy loss. Further study is required to elucidate what role the maximum amplitude has on repeated implantation failure.

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## Introduction

Repeated implantation failure is a significant complication that is taken to mean at least three recurring miscarriages or repeated IVF failures. Recurring miscarriages are known to affect approximately 1-3% of couples (Toth *et al.*, 2010), with strong evidence to suggest that a proportion of them can be attributed to various clotting abnormalities present in the women.

The thrombophilias that have been associated with repeated implantation failure are classified as either inherited or acquired. The more common inherited thrombophilias consist of:

- Factor V Leiden (FVL) – an autosomal dominant disorder, where the variant factor V in sufferers cannot be as easily degraded as normal
- Prothrombin gene mutation (G20210A/Factor II) (PGM) – this mutation leads to an increased amount of thrombin in the bloodstream, ultimately leading to excess coagulation of the blood
- Methylenetetrahydrofolate reductase (MTHFR) C677T mutation – this leads to hyperhomocysteinemia, an abnormally large level of homocysteine in the blood stream which damages the lining of blood vessels, increasing the likelihood of blood clots developing

The rarer forms of inherited thrombophilias are antithrombin (ATIII) deficiency, protein C (PC) deficiency and protein S (PS) deficiency. ATIII, PC and PS all normally act to inhibit various coagulation enzymes to an extent, and so their deficiencies cause the coagulation cascade to be prolonged.

Antiphospholipid syndrome (APS) is an acquired thrombophilia that has been associated with repeated implantation failure, most notably due to the antiphospholipid antibodies of the lupus anticoagulant (LA) and anticardiolipin (aCL) antibodies. APS is an autoimmune disorder where the body makes antibodies that attack normal components of the body. The exact mechanism by which LA and aCL work to produce a hypercoagulable state is still as

yet unknown, but there is ongoing research to explain how the coagulation cascade is activated (University of Illinois College of Medicine and Carle Cancer Center, 2001).

The statistics on the relationship between thrombophilic gene mutations and repeated implantation failure are many and varied. In general, thrombophilias are present in only a small percentage of the population. There have been numerous studies that have been carried out to determine the association between thrombophilias and repeated pregnancy loss with a sample of these studies shown in Table 1.

**Table 1: Percentage of thrombophilic genes in women with recurring miscarriage and repeated IVF failure in comparison with control subjects (values adapted from Azem *et al.*, 2004; Qublan *et al.*, 2006; Rodger *et al.*, 2008; Ayadurai *et al.*, 2009; Ivanov *et al.*, 2009; Mukhopadhyay *et al.*, 2009; Yenicesu *et al.*, 2010)**

Thrombophilia		Recurrent Miscarriage	Repeated IVF Failure	Control
<b>Factor V Leiden</b>	Total	1 – 42%	6.7 – 14.4%	0 – 7%
	Heterozygous	12.4%	10%	1.1 – 7%
	Homozygous	0.7%	4.4%	0%
<b>MTHFR C677T</b>	Total	10.71 – 51.5%	22.2%	2.5 – 33.3%
	Heterozygous		7.8%	8.9 - 9%
	Homozygous		14.4 – 17.8%	2 – 13.3%
<b>Prothrombin</b>	Total	0.3 – 17%	6.7 – 8.9%	1.0 – 7.3%
<b>G20210A Gene Mutation</b>	Heterozygous	15.7%	5.6%	2.3 – 3.3%
	Homozygous	1.3%	1.1%	0 – 1.1%
<b>Antithrombin Deficiency</b>		0 – 0.3%	1.1 – 2.2%	0 – 1%
<b>Protein C Deficiency</b>		1.5 – 1.57%	0 – 2.2%	0 – 1.1%

<b>Protein S</b>		11.2 – 14.72%	3.3 – 8.9%	0 – 3%
<b>Deficiency</b>				
<b>APS</b>	Total	3 – 15%	18.9%	0 – 2%
	LA	9.1%	8.9%	2 – 2.2%
	aCL	5.5%	10%	2.2 – 3%

Table 1 gives a clear indication that women with a thrombophilic gene mutation have a much greater chance of recurrent miscarriage or repeated IVF failure than those without.

These thrombophilias can be detected by standard blood coagulation tests carried out on the patient’s blood sample. Thromboelastography (TEG) can also be used to determine the haemostatic profile of patients, and has proven to be a quick, near-patient method that can substitute and reduce costs compared to conventional blood tests (Salooja *et al.*, 2001).

TEG is a tool used to measure blood coagulation that has proved to be a reliable and efficient test, with the ability to supply the relevant information on a patient’s coagulation status within 30 minutes (Vig *et al.*, 2001). It gives a graphic representation of aspects of clot formation and lysis, by visualizing the viscoelastic changes which normally occur within the body due to the polymerization of fibrin in the blood (Reikvam *et al.*, 2009). The test is performed on the basis of changes that are normally occurring during coagulation of a whole blood sample in vitro, and so provides an ability to evaluate the initiation, propagation, strength and fibrinolysis of the clot (Lang *et al.*, 2005).

TEG is already widely used in the clinical setting for hepatic and cardiac surgical patients. In both instances, TEG can be used as a point-of-care test perioperatively, to aid in monitoring the haemostasis of patients before, during and after surgery, in order to better anticipate postoperative complications (Herbstreit *et al.*, 2010). This makes it easily available in the obstetric setting, if further studies demonstrate its effectiveness in the area.

In recent times, TEG has been tested in the obstetric setting and the relationship between the values obtained from a TEG trace and recurrent pregnancy loss has been studied in detail. According to laboratory results, an abnormal MA is equivalent to 69.0 or above. Rai *et al.* (2003) studied the ability of TEG to be used in the obstetric setting and discovered that an MA value of 64.0 and over was deemed to be a predictor of miscarriage. However, how MA affects implantation is unknown, and its relationship with thrombophilias has yet to be studied. The aim of the study was to see if high MA values could be used to identify women with thrombophilias and in turn, be used as a screening tool for thrombophilic genes in women with repeated implantation failure.

## Materials and Methods

### Subjects

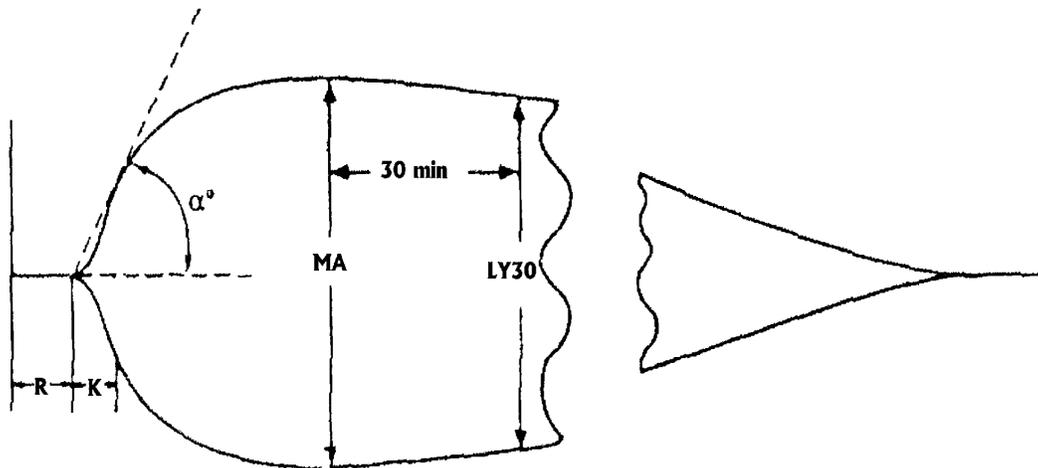
A retrospective study was undertaken, with data obtained from patients with a history of recurrent implantation failure (taken as 3 or more miscarriages or IVF failures), who had undertaken a TEG test. In total, there were 800 patients who had a TEG test performed, on a history of repeated implantation failure.

Of these women, 310 were deemed to have a significant MA value of over 64.0, the value obtained by Rai *et al.* (2003). However, the subjects in this study differ from the aforementioned, as this study had patients of mixed race and who had recurrent miscarriage as well as repeated IVF failure. In total, data for 230 of the 310 women was found, with a median age of 40 years and ranging between 27 and 52.

### Thromboelastography

The process of TEG as used in the St George laboratory, involves a 0.36mL whole blood sample placed in a cup heated to 37°C, with a vertical pin suspended in the blood by a torsion wire that

acts as the detecting system (Luddington, 2005). This blood is prepared with added citrate, which prevents coagulation. Once preparation is completed, the cup oscillates alternately clockwise and anticlockwise at 4 degrees and 45 minutes, every 10 seconds (Srinivasa *et al.*, 2001). Once the coagulation cascade has been activated in the blood due to the addition of kaolin, thrombin is formed, with successive conversion of fibrinogen to fibrin (Reikvam *et al.*, 2009). As the cup continues to spin, the blood begins to clot due to aggregates of fibrin and platelets forming between the suspended pin and the inner wall of the cup (Jackson *et al.*, 2009). This clot formation and ensuing impediment of the pin, results in torque on the pin, and eventually, a stable clot is formed. The ultimate strength of the clot will influence the oscillation of the pin, and these changes are converted to an electrical signal that is seen as the TEG trace (Reikvam *et al.*, 2009). During the test, each anticlockwise and clockwise rotation of the cup causes an upward and downward deflection, as seen on the computer monitor. The trace is subsequently obtained from the outline of the electrical signal, and the necessary measurements can be attained from that resultant diagram (Figure 1).



**Figure 1: The TEG trace. R = Reaction time (mins); K = Clot formation time (mins);  $\alpha$  = Clot formation rate (degrees); MA = Maximum amplitude (mm); LY30 = Clot lysis after 30min (%) (adapted from Rai *et al.*, 2003)**

It has been made apparent from a number of papers that not all of the parameters recorded from the TEG trace are vital to the establishment of an individual's haemostatic profile. In the majority

of the papers, the key factors of the TEG trace were determined to be the R, K,  $\alpha$  and MA values, with some discrepancy on the importance of the LY30 and CI values (Vig *et al.*, 2001; Rai *et al.*, 2003; Miall *et al.*, 2005). In the TEG trace, R corresponds to the reaction time in minutes, and serves as an indicator of the level of activity of the coagulation factors. The value is taken as the period from the beginning of the recording until the start of the clot formation, which is when the amplitude is 2mm. The K represents clot formation time in minutes, which is the period from the beginning of the clot formation to when the amplitude is 20mm.  $\alpha$  is the angle between the baseline and the tangent to the TEG trace in degrees, and relates to the clot formation rate. Together, K and  $\alpha$  measure the speed of clot formation. MA is the maximum clot amplitude in millimeters, and is seen as the highest point on the TEG trace. It represents the strength of the clot, and hence, assesses platelet and fibrinogen function. LY30 stands for the percentage of clot lysis after 30minutes, and is based on the reduction of the amplitude of the curve between MA and A30 (the amplitude after 30 minutes). The CI is the coagulation/clot index, and represents the whole haemostatic profile of the patient, as calculated from the R, K,  $\alpha$  and MA parameters (Narani, 2005).

The study initially looked at the R, K, alpha, MA and LY30 TEG values, but after further research, it was decided that MA and LY30 would be the only feasible parameters to look into. Unfortunately, this study was unable to analyse the LY30 values of the subjects, as the St. George Hospital pathology laboratory generally stops the TEG trace as soon as the MA has been obtained.

## Data Collection

The R, k, alpha, MA and LY30 values of the TEG tests performed on the 800 patients were recorded manually from stored data in folders located at the site of testing, in the pathology laboratory at St. George Public Hospital. They were then transferred into an Excel spreadsheet, with the names of the 310 women with an MA over 64.0 also noted. Using the IVF Australia patient database, the patient file numbers were obtained and the files located in the clinics at

Bondi Junction, Maroubra, and Kogarah. The 310 women were further divided into women with an MA between 64.0 and 68.9, of which there were 258, and 52 women who had an MA of 69.0 or above. Of the 64.0 to 68.9 patients, files were only available for 186 of the 258 (72.10%) and 44 of the 52 (84.62%) of the 69.0 and above patients. Files for 230 of the 310 women were found, with the majority of the remainder having been archived.

A proforma (Appendix 1) was created to record the relevant information of the 230 women. The proforma included presence of thrombophilic gene mutations, and other factors which have some association with thrombophilias. These categories were:

- aCL (IgG and IgM antibodies)
- LA
- activated protein C resistance (APC-R)
- FVL
- PGM
  
- MTHFR – only women who were homozygous were taken as being positive for the gene
- increased homocysteine
  
- high insulin level – thought to be a factor in polycystic ovary syndrome
  
- PC deficiency
  
- PS deficiency
  
- ATIII deficiency
  
- platelet count

Not all of the 230 patients had all the relevant values present in their files, and so the percentage of women with each thrombophilic factor had to be found as a fraction over the total number of women who did have that value. Of these patients, 186 had an MA between 64.0 and 68.9, and

44 patients had an MA of 69.0 and above. Of the 230 total patients, 33 patients didn't have any values, leaving 197 patients.

In determining the percentage of women with at least one thrombophilic factor from the remaining 197 patients, 46 patients were found to have missing values, but of those present, all were normal. These normal values included heterozygous MTHFR, decreased homocysteine and increased PC and PS. These women were disregarded on the off chance that they had one abnormal value, and left 151 patients out of the original 230. Of these 151 patients, 125 had an MA of 64.0 – 68.9 and 26 had an MA of 69.0 or above.

## Analysis

The first analysis undertaken was to compare the percentage of women with positive values per category in those with an MA between 64.0 and 68.9, and those in the 69.0 and above category. This was performed to establish whether or not women with a higher MA had a propensity for thrombophilic gene mutations or other associated causes of thrombophilias.

The second analysis performed was to see what percentage of total women with an abnormal thrombophilic gene had a high MA. Ideally, this analysis should have been a comparison of the MA of women with a known thrombophilic gene and the MA of those without. We expected to see a greater proportion of women with a thrombophilic factor to have high MA. Since data was recorded only for women with an MA over 64.0, the total amount of women with any thrombophilic gene, and their subsequent MA was unknown. Therefore, the method used was to compare the percentage of women with thrombophilic genes in our total cohort (MA of 64.0 and above) with the general population. In the same way that we would expect a greater proportion of women with thrombophilias to have a high MA, we would expect to see a greater percentage of women with thrombophilias in our cohort, compared to the general population. However, not all of the percentages of thrombophilic gene mutations in the general population are known.

Therefore, the statistical analysis was only able to be performed on LA, APCR, FVL, PGM, MTHFR, PC deficiency and ATIII deficiency.

According to the study's supervisor, Douglass Hanly Moir Pathology, the laboratory which analyzed the majority of the study's blood tests, tends to get numerous false positive low positive aCL values. Therefore in analyzing the results, we considered both options of low positive aCL being a positive value and alternatively, low positive aCL being a negative value.

## Statistical Analysis

GraphPad Prism 5 (GraphPad Software, Inc., La Jolla, CA, USA) was used to analyze the results. This software utilized Fisher's exact test for small sample sizes or chi-square test for large sample sizes, to elucidate whether or not there was any statistical significance ( $P$ -value less than 0.05) between having a high MA and any thrombophilic factor.

## Results

There was found to be no resounding relationship between a high MA and a thrombophilic factor.

In comparing the percentage of women with thrombophilic genes in the 64.0→68.9 category with the  $\geq 69.0$  category, three factors displayed a statistical significance (Table 2 and Figure 2).

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**Table 2: Comparison of the proportion of women with positive values for thrombophilic factors in women with MA 64.0 → 68.9 and  $\geq 69.0$**

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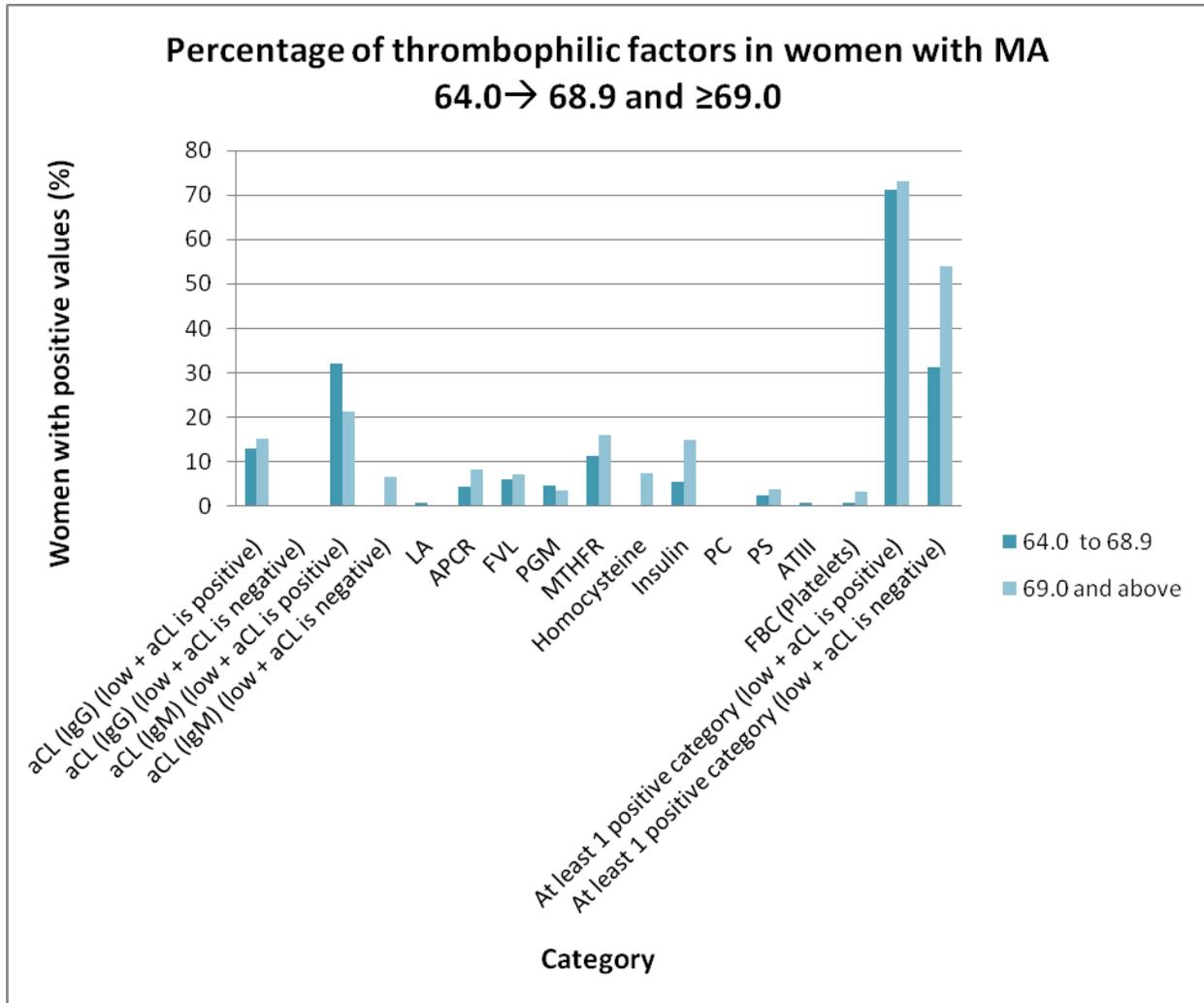
Category	64.0 → 68.9		$\geq 69.0$		$P$ -value
	Women with positive values	Women with negative values	Women with positive values	Women with negative value	

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<b>aCL (IgG) (low positive ACA is a positive value)</b>	19	127	5	28	0.7782
<b>aCL (IgG) (low positive ACA is a negative value)</b>	0	146	0	33	— *
<b>aCL (IgM) (low positive ACA is a positive value)</b>	47	99	7	26	0.2939
<b>aCL (IgM) (low positive ACA is a negative value)</b>	0	146	2	31	0.0331
<b>LA</b>	1	147	0	32	1.0000
<b>APCR</b>	5	110	2	22	0.3474
<b>FVL</b>	8	128	2	26	0.6804
<b>PGM</b>	6	127	1	27	1.0000
<b>MTHFR</b>	15	117	4	21	0.5088
<b>Homocysteine</b>	0	135	2	25	0.0269
<b>Insulin</b>	7	119	4	23	0.1052
<b>PC</b>	0	130	0	27	—*
<b>PS</b>	3	127	1	26	0.5337
<b>ATIII</b>	1	124	0	26	1.0000
<b>FBC (Platelets)</b>	1	151	1	30	0.3109
<b>At least 1 positive category (low positive aCL is a positive value)</b>	89	36	19	7	1.0000
<b>At least 1 positive category (low positive aCL is a negative value)</b>	39	86	14	12	0.0409

\* To perform a chi-square or Fischer's exact test, there must not be one row filled with zeros



**Figure 2: Comparison of the percentage of thrombophilic genes in women with MA 64.0→68.9 and ≥69.0**

An increased homocysteine was found in 0 of 135 patients (0%) in the 64.0→68.9 MA subjects, and 2 of the 27 (7.41%) patients in the ≥69.0 (*P*-value 0.0269).

When a low positive aCL value was taken as being negative for a thrombophilic factor, 0 of the 146 (0%) 64.0→68.9 patients and 2 of the 33 (6.06%) ≥69.0 patients were found to have the presence of aCL IgM antibodies. Also, 39 of the 125 (31.2%) 64.0→68.9 patients and 14 of the 26 (53.85%) ≥69.0 patient, were found to have at least one positive thrombophilic factor (*P*-value 0.0409).

In comparing the percentage of the 310 total women ( $\geq 64.0$ ) with the various thrombophilic genes, to that of the general population, there was found to be no significant difference in any category (Table 3).

**Table 3: Comparison of the proportion of women with positive values for thrombophilic gene mutations in total subjects and the general population (values adapted from McPhee *et al.*, 2010; Cunningham *et al.*, 2010; Lichtman *et al.*, 2010)**

Category	Total ( $\geq 64.0$ )		General Population		P-value
	Women with positive values	Women with negative values	Women with positive values	Women with negative value	
LA	1	179	3	9997	0.1033
APCR	7	132	5	95	1.0000
FVL	10	154	5	95	0.7903
PGM	7	154	2	98	0.4893
MTHFR	19	138	8	92	0.4044
PC	0	157	2	998	1.0000
ATIII	1	150	1	1999	0.3194

## Discussion

Thrombophilias have been linked to repeated implantation failure, but without the exact mechanism known. There are various hypotheses that exist on this subject matter, which attempt to explain the mechanism as to how inherited and acquired thrombophilias cause repeated implantation failure. However, the means is still unclear and the resounding notion is that there is inconclusive data.

Research has demonstrated a clear association between thrombophilias and placenta-mediated pregnancy complications but has not yet determined the causation (Said *et al.*, 2010). It has been hypothesized that there is impairment of the initial vascularisation process occurring at implantation, which can cause repeated implantation failure. Qublan *et al.* (2006) further theorized that hypercoagulation at the site of implantation leads to an unsuccessful connection between the placenta and maternal blood, thus leading to miscarriage.

To explain repeated IVF-embryo transfer which occurs at a later stage of pregnancy, it was suggested by Azem *et al.* (2004), that inherited thrombophilias might be a factor in the aetiology, with fetal thrombophilia causing placental infarcts. Regan *et al.* (2002) theorized a different reason behind recurring miscarriage. They affirmed that while research had previously found thrombi in the placental circulation to be the cause of repeated pregnancy loss, the current view of thinking is that abnormalities of early trophoblast invasion is the reason behind repeated pregnancy loss. This thought was also shared by Azem *et al.* (2004), who found numerous studies had thought that microthrombosis at the site of implantation led to miscarriage after 11-12 weeks gestation, by affecting the invasion of the maternal vessels by the syncytiotrophoblast and consequently reducing perfusion to the intervillous space.

While studies have shown that an increased MA is linked to repeated implantation failure, no study has yet looked at the relationship between an increased MA and the various thrombophilic genes which have been known to affect implantation. Since MA reflects part of the body's clotting process, it was thought that there could be found some relationship between a high MA and the various thrombophilias. However, apart from an increased homocysteine level and

presence of IgM aCL antibodies when low positive aCL was considered a negative value, this study was unable to show any other statistical significance between having a high MA and a thrombophilic gene in women with repeated implantation failure. Those two factors – increased homocysteine and presence of IgM aCL antibodies – have no relation to MA, which is a reflection of platelet and fibrinogen function.

As this study shows, high MA identifies some women which would otherwise not have been detected as they wouldn't necessarily have any thrombophilias. While this is able to provide an answer to those women who have no other explanation for repeated implantation failure, further evidence is required to elucidate the role that it can play in overcoming the problem.

This same result was also garnered by O'Donnell, *et al.* (2004), which looked at whether or not TEG could be used to test thrombophilias in patients with a family or personal history of thrombosis. They found that individuals with a hypercoagulable TEG did not necessarily have a thrombophilia, as diagnosed by conventional blood tests, and that patients who did have a thrombophilia, didn't necessarily have an abnormal TEG. Due to the differing subsets of individuals that resulted from their analysis, they came to the conclusion that TEG would be ineffective as an initial screening test for thrombophilias, but could be used as an adjunctive test.

An increased homocysteine level as seen in the results is most commonly attributed to a mutation in the gene coding for the enzyme MTHFR. However, of the two women with an increased homocysteine, neither is heterozygous or homozygous for the condition. Therefore, those increases in homocysteine could be due to a mutation of cystathionine beta-synthase (CBS), another enzyme in the pathway of converting homocysteine to cysteine (University of Illinois College of Medicine and Carle Cancer Center, 2001).

In the second statistical analysis, we expected the women in our cohort have a greater percentage of thrombophilic factors compared to the general population. As there was found to be no statistical significance between any of the values, it would be possible to conclude that there would be the same amount of thrombophilic factors no matter the MA.

The only source to have studied the relationship between TEG parameters and a propensity for recurrent pregnancy loss is that of Rai *et al.* (2003). According to the paper, an increase in MA and a decrease in LY30 are the only two factors that demonstrate any statistical significance of increased rates of recurrent miscarriage.

MA is known to correspond to the platelet and to a lesser extent, the fibrinogen function. The ratio in which the two contribute to MA can be determined by using modified TEG in pregnant women. This works, by adding a monoclonal antibody fragment, known as ReoPro, to another blood sample of the patient being tested, which binds to the fibrinogen receptors on the surface of platelets. In doing so, it inhibits aggregation of the platelets and fibrinogen, and the MA of the new trace, is a representation of the contribution of fibrinogen alone, to the clot strength. Upon performing the modified TEG on 21 pregnant subjects, it was found by Gottumukkala *et al.* (1999) that on average, 55% of the clot strength was contributed to by platelets and the remaining 45% by fibrinogen.

In being able to break down the MA in this way, perhaps the treatment for women with unexplained, repeated pregnancy loss could be individualized, to provide a better result. In general, treatment for women with repeated pregnancy loss and a large MA is an anticoagulant in the form of aspirin and/or low molecular weight heparin (LMWH). While administration of the drugs has proved to be efficacious for recurrent pregnancy loss, research on the effectiveness of giving both drugs concurrently, is mixed. Some data has expressed no difference between aspirin alone and aspirin combined with LMWH, while others have seen that the best results are when the drugs are used in combination (Toth *et al.*, 2010). Doing a modified TEG on patient's blood samples may be able to help determine which form of treatment would best help overcome an individual's hypercoagulable state.

## Conclusion

To date, there is very limited research on the relationship between thrombophilias and recurrent pregnancy loss with detection by TEG. While it has been shown that MA is the key parameter in demonstrating an association with repeated implantation failure, further research is undoubtedly required on the subject. Knowing that there exists a strong association between thrombophilias and repeated implantation failure, it was thought that it would be judicious to utilize the fast and effective method of TEG to aid women with otherwise unexplained recurrent miscarriage or repeated IVF failure.

As results concluded, there was no resounding significant relationship between a high MA and the thrombophilic factors associated with repeated implantation failure. This does not dispel the usefulness of TEG as a tool in obstetric medicine as it is known there is a link between a high MA, which is known to reflect part of the body's clotting process, and repeated implantation failure.

What this study does show is that TEG is able to identify a subset of women which may have never been discovered otherwise. If the research that has already been conducted into treatment for high MA values is further studied, it could create a solution to overcome their repeated implantation failure.

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## Appendix 1: Proforma

Name	_____		
d.o.b	_____		
Clinic	_____		
MA	_____		
aCL (IgG)	-	low +	+
aCL (IgM)	-	low +	+
LA	-	+	
APC-R	-	+	

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FVL	–	hetero	homo
PGM	–	hetero	homo
MTHFR	–	hetero	homo
Homocysteine	N	↑	
Insulin	N	↑	
PC	N	↓	
PS	N	↓	
ATIII	N	↓	
FBC (platelets)	N	↑	