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RELATION OF LUPUS ANTICOAGULANT TO  
MATERNAL THROMBOPHILIA IN UNEXPLAINED  
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**Abstract**

*A successful outcome of pregnancy requires an efficient uteroplacental vascular system\* Since this system may be compromised by disorders of haemostasis associated with a prothrombotic state, we postulated that maternal thrombophiia might be risk factor for fetal loss. The relation of this thrombophilia and lupus anticoagulant is still unclear and remains to be defined. So, the aim of this work is to study the thrombogenic potential in women with recurrent miscarriage, which may be benefit for giving antithrombotic treatment. For this study, a randomly selected 15 non-pregnant women and 15 pregnant women with recurrent fetal loss were compared with another 15 non-pregnant and 15 pregnant normal women, matched for the same age (20 to 40 years) as controls. The results of this work showed that, the incidence of LA was about 46.7% in non-pregnant women while it was 40% in pregnant women. Furthermore, there was non-significant differences of activated partial thromboplastin time-sensitive LA (APTT-LA), prothrombin time (FT), thrombin time (TT), jibrinogen concentration, factor VII, factor XII and anti-thrombin III activities (ATIII) in non-pregnant women who were negative for LA. Meanwhile, factor VII and XII activities were significantly increased in pregnant women who were negative for LA ( $P<0.05$ ) compared with the corresponding control groups. On the other hand, non-pregnant women who were positive for LA had a significant increase of plasma Jibrinogen concentration ( $P<0.05$ ), APTT-LA, F VII and F XII activities ( $P<0.001$ ). Meanwhile, plasma APTT-LA, Jibrinogen concentration, F VII and F XII activities were sig-*

nificantly increased in pregnant women who were positive for LA ( $P < 0.05$ ) when compared with their corresponding control group. Plasma TT & ATIII activity showed non-statistically significant differences but PT was significantly decreased in the same group of patients.

We could conclude that although pregnancy is a hypercoagulable state; but there are certain subgroups of women who were positive for LA had a more thrombogenic potential which plays a role in recurrent miscarriage. Thus, we recommend to do AFTT-LA, which is a simple and cheap test as a screening for every woman with a past history of recurrent fetal loss. This may be of benefit for the antithrombotic treatment to improve fetal outcome.

### Introduction and aim of work

Recurrent miscarriage is defined as the occurrence of three or more consecutive clinically detectable pregnancy loss prior to the 20th week of gestation. Potential etiologies of recurrent pregnancy loss are genetic, anatomical, endocrinal, infections, immunological and unexplained factors. An immunological etiology for habitual abortion has been proposed for many couples with an otherwise unexplained etiology for their reproductive failure (Hill & Ravniker, 1990).

Antiphospholipid antibodies are autoantibodies that can be detected in plasma or serum with phospholipid dependent coagula-

tion test or solid phase immunoassays. The presence of these autoantibodies is strongly associated with an increased risk of recurrent fetal loss and thrombocytopenia (De-Groot et al, 1993).

The antiphospholipid antibody involves two antibodies. Lupus anticoagulant and anticardiolipin antibodies. Women with these antibodies along with other factors are believed to be at high risk for recurrent pregnancy loss (Festin et al., 1997).

Patients with lupus anticoagulant have an increased incidence of venous and arterial thrombosis whose pathogenesis is still unclear, (Schinco et al., 1997).

Other autoantibodies are found in patients with recurrent miscarriage such as antinuclear, anti DNA and antilymphocytes, (Laskin et al., 1997).

Activation of coagulation can be mediated by extrinsic or intrinsic pathways. The first enzyme of the extrinsic pathway is factor VII which is the enzymatically active form of the zymogen factor VII. Activated factor XII, on the other hand, is the central enzyme of the contact phase (DeMoerloose et al., 1997).

Antithrombin III which is a natural anticoagulant can be inhibited by anti-phospholipid antibodies directed against glycosaminoglycans heparin and heparan sulfate (Chamley et al., 1993).

The mechanisms of vascular thrombosis and pregnancy loss in the antiphospholipid-anibody syndrome are unknown, (Rand et al., 1997).

So, the aim of this work is to study the thrombogenic potential in patients with repeated miscarriage which may be benefit for giv-

ing antithrombotic treatment to improve fetal outcome.

### **Subjects and Methods**

This study included 60 fertile women, aged from 20 to 40 years. They were selected from Gynecology & Obstetric out-patients Clinic, Benha University Hospital. All subjects were classified into the following groups:

**Group I** : they included 15 non-pregnant women without past history of recurrent miscarriage as a control.

**Group II** : they included 15 pregnant women without past history of recurrent miscarriage as another control.

**Group III** : they included 15 non-pregnant women with past history of recurrent miscarriage.

**Group IV** : they included 15 pregnant women with past history of recurrent miscarriage. All cases had a recurrent miscarriage in the first trimester and the number of abortions ranged from 3 to 4 times.

**All women were subjected to the following :**

- Complete history and clinical examination.
- ECG tracer and blood pressure estimation.
- Abdominal ultrasonography scanning.
- Body mass index (BMI) as an index of obesity (National diabetes data group, 1979).
- Sampling :

5 cc venous blood sample was taken in the fasting state and divided into 2 parts. The first part was left to be clotted. The sera separated were used for determination of :-

- Anti-DNA antibody for detection of lupus erythematosus, (Greenwald, 1978).
- Fasting serum glucose (Trinder, 1969).
- Serum albumin (Grant & Kachmer, 1970).
- Serum GPT (Reitman & Frankel, 1957).
- Serum creatinine (Henry, 1974).

The second part of the sample was added to trisodium citrate solution (3.2%) in a ratio of 9:1. The sample was centrifuged at a high speed (2500 gravity) for

15 minutes. Plasma separated were kept frozen at - 80°C, until assay of:

- Lupus anticoagulant - Sensitive activated partial thromboplastin time (APTT-LA), (Brandt et al., 1995).
- Prothrombin time (PT)(Hirsh et al., 1992).
- Thrombin time (TT) (Robertson et al., 1975).
- Fibrinogen concentration, (Cooper & Douglas, 1991).
- Factor VII activity, (Furie & Furie, 1988).
- Factor XII activity, (Mammen, 1983).
- Antithrombin III activity, (Karges & Heimburger, 1987).

The instrument used for determination of different coagulation parameter was the Behring fibrin timer II (BF II). Also, all the kits were supplied by Behring Company, Germany except APTT-LA from Stago Diagnostica company, France and TT from Diamed Company, Switzerland.

**Exclusion criteria :**

- Patients with liver diseases.
- Diabetics.

- Hypertensives.
- Patients with systemic lupus erythematosus.
- Patients had recurrent abortions in the second or third trimester.
- Obese patients.
- Non-pregnant aborters more than 3 months.

The results were tabulated as mean  $\pm$ SE values, and statistically analyzed using student-t test, the results were considered significant at  $P < 0.05$ . A cut-off value, equal to (mean +2SD) was used to differentiate between positive and negative cases for lupus anticoagulant.

## Results & Discussion

**Table 1 :** Distribution of lupus anticoagulant in control and non-pregnant women with recurrent abortion groups.

Lupus anticoagulant	Control group		Non-pregnant group	
	No.	%	No.	%
Positive	0	0	7	46.7
Negative	15	100	8	53.3

**Cut-off value = 48.981 sec.**

**Table 2 :** Distribution of lupus anticoagulant in control and pregnant women with recurrent abortion groups.

Lupus anticoagulant	Control group		Non-pregnant group	
	No.	%	No.	%
Positive	0	0	6	40
Negative	15	100	9	60

**Cut-off value = 53.515 sec.**

**Table 3:** Mean,  $\pm$  SE and P values for plasma APTT-LA, PT, TT, Fibrinogen conc., F VII, F XII and AT III activities in non-pregnant women with habitual abortion Compared with the control group.

Biochemical Parameters / Studied groups	Plasma APTT-LA sec.	Plasma PT sec.	Plasma TT sec.	Plasma Fibrinogen Conc .g/L	Plasma FVH Activity %	Plasma FXH Activity %	Plasma AT III Activity %
Control group (n = 15)	44.127 $\pm 0.627$	13.04 $\pm 0.185$	17.913 $\pm 0.361$	2.872 $\pm 0.118$	107 $\pm 5.258$	108.2 $\pm 5.629$	113.067 $\pm 5.138$
Negative LA (1*5*8)	44.075 $\pm 1.688$ P>0.05	12.875 $\pm 0.423$ P>0.05	18.138 $\pm 0.753$ P>0.05	3.021 $\pm 0.234$ P>0.05	121.25 $\pm 6.48$ P>0.05	123.75 $\pm 5.573$ P>0.05	105.875 $\pm 7.472$ P>0.05
Positive LA (n = 7)	60.3 $\pm 2.672$ P<0.001 P^O.001	12.7 $\pm 0.216$ P>0.05 P^O.05	18.457 $\pm 0.367$ P>0.05 P^O.05	3.360 $\pm 0.198$ P<0.05 P^O.05	167.857 $\pm 6.988$ P<0.001 P^O.001	157.143 $\pm 6.377$ P<0.001 P^O.002	112.857 $\pm 4.723$ P>0.05 P^O.05
All cases (n=15)	51.647 $\pm 2.595$ P<0.05	12.793 $\pm 0.248$ P>0.05	18.287 $\pm 0.438$ P>0.05	3.179 $\pm 0.161$ P>0.05	143 $\pm 7.657$ P<0.001	139.333 $\pm 6.016$ P<0.001	109.133 $\pm 4.642$ P>0.05

P: Probability versus control group.

P1: Probability versus negative LA.

**Table 4 :** Mean,  $\pm$  SE and P values for plasma APTT-LA, PT, TT, Fibrinogen conc., F VII, F XII and AT III activities in pregnant women with habitual abortion Compared with the control group.

Biochemical Parameters / Studied groups	Plasma APTT-LA sec.	Plasma PT sec.	Plasma TT sec.	Plasma Fibrinogen Conc .g/L	Plasma FVII Activity %	Plasma FXII Activity %	Plasma AT III Activity %
Control group (n = 15)	45.087 $\pm 1.088$	11.687 $\pm 0.224$	17.62 $\pm 0.444$	2.698 $\pm 0.164$	123.333 $\pm 6.678$	134.666 $\pm 5.607$	-123.133 $\pm 2.505$
Negative LA (n = 9)	46.600 $\pm 0.814$ P>0.05	11.111 $\pm 0.256$ P>0.05	18.633 $\pm 0.391$ P>0.05	2.952 $\pm 0.158$ P>0.05	152.778 $\pm 8.319$ P<0.05	157.778 $\pm 8.682$ P<0.05	120.889 $\pm 3.137$ P>0.05
Positive LA (n = 6)	56.967 $\pm 0.861$ P<0.001 P^O.001	10.4 $\pm 0.400$ P<0.05 PH>0.05	19.067 $\pm 0.856$ P>0.05 P^O.05	3.338 $\pm 0.203$ P<0.05 P^O.05	157.500 $\pm 10.257$ P<0.05 P^O.05	173.333 $\pm 14.077$ P<0.05 P^O.05	112.167 $\pm 8.298$ P>0.05 P>0.05
All cases (n=15)	50.747 $\pm 1.441$ P<0.05	10.827 $\pm 0.239$ P<0.05	18.807 $\pm 0.418$ P>0.05	3.107 $\pm 0.134$ P>0.05	154.667 $\pm 6.489$ P<0.05	164.000 $\pm 7.919$ P<0.05	117.4 $\pm 3.972$ P>0.05

P: probability versus control group.

P1 : Probability versus negative LA.



Antiphospholipid antibodies were first linked to pregnancy loss more than 20 years ago, and the condition known as antiphospholipid syndrome is perhaps the most convincing immunologic disturbance other than anti-erythrocyte and antiplatelet alloimmunization disorders (Branch, 1998).

The presence of antiphospholipid (apl) antibodies has been associated with thrombosis, pregnancy loss and thrombocytopenia in the antiphospholipid syndrome (Harris et al., 1998).

Women with antiphospholipid antibodies (anticardiolipin and/or lupus anticoagulant) and a history of either prior thrombotic events or pregnancy loss are at high risk during pregnancy for either another fetal death or thrombosis (Cowchock, 1998).

Our results showed a significant increase of APTT-LA in LA-positive, either non-pregnant and pregnant women with past history of recurrent fetal loss ( $P < 0.001$ ) and in all cases of non-pregnant and pregnant women ( $P < 0.05$ )

when compared with the control groups.

Also, our results showed 7 non-pregnant women (about 46.7%) with recurrent miscarriage out of 15 women had positive lupus anticoagulant. In addition, only 6 pregnant women of our cases had positive lupus anticoagulant (40%).

These results were compatible with the results of Balasch et al., (1991) and Das et al., (1991) who reported that the incidence of lupus anticoagulant in pregnant women with recurrent spontaneous abortion to be (10.7%) and (10%) respectively. Also, Parazzini et al., (1991) found lupus anticoagulant in (7%) of 220 women with unexplained recurrent abortion. Creagh et al., (1991) found that 7 out of 35 pregnant women (20%) with recurrent fetal loss were positive for lupus anticoagulant. Recently, Ghoneim et al., (1996) and Hasanein et al., (1999) reported that (25%) and (30%) had lupus anticoagulant activity, respectively among pregnant women with unexplained recurrent abortion.

The different ratios in the previous reports might be due to the method of patient selection or the difference in the sensitivity and specificity of the different tests used in the detection of lupus anticoagulant (Triplet!, 1989). In the United Kingdom, kaolin clotting time is the most popular test, while APTT as in our study is used by the majority of laboratories in USA. Moreover, not all APTT reagent were equally sensitive to the anticoagulant effect of the antiphospholipid antibodies (Brandt et al., 1987).

The recurrent fetal loss in some women with lupus anticoagulant was due to extensive placental infarction and the underlying vasculopathy in the afferent uteroplacental arteries (DeWolf et al., 1982). The cause of the fetoplacental pathologic feature remains unknown, but possible mechanisms include platelet damage with increased adhesiveness (Branch et al., 1985) and interference with antithrombin III activity (Cosgriff & Martin, 1981) were postulated.

Several investigators have demonstrated that plasma or plasma fractions that contain the lupus anticoagulant inhibit the production of prostacyclin by vascular tissues (DeWolf et al., 1982). Prostacyclin is a potent vasodilator and inhibitor of platelet aggregation that produced by vascular tissues from endogenous precursors or from prostaglandin intermediate (Moncada et al., 1977). The natural antagonist of prostacyclin appears to be thromboxane, a potent vasoconstrictor and platelet aggregation including prostaglandin that is released by aggregating platelets (Moncada & Vane, 1979). Production of prostacyclin by the endothelial cells is considered an important mechanism that protects the vascular wall from the deposition of platelet aggregates and subsequent thrombosis. Thus, the inhibition of prostacyclin as has been demonstrated in vitro with plasma that contains the lupus anticoagulant, would favor thrombosis (Branch et al., 1985).

Our results showed that; non-pregnant and pregnant women with habitual abortion, who were

negative for LA, had a non-significant decrease of prothrombin time (PT) compared with the corresponding controls. Also, non-pregnant women with habitual abortion who were positive for LA had a non-significant decrease of PT compared with their control group. These data were compatible with the results of Ogasawara et al., (1998) and contradictory to the results of Das et al., (1991) who reported that the significance prolongation of PT is unknown.

But, PT was significantly decreased in pregnant women with recurrent fetal loss and positive for LA and in all cases (positive and negative LA) compared with their control group ( $P < 0.05$ ) (Table 4).

The more shortened PT in pregnant women (positive and all cases for LA) indicates that, pregnant women were in a hypercoagulable state (Comeglio et al., 1996). The shortened FF in vitro gives an indirect explanation for the increase in activities of clotting factor V, VII, and X (Quick, 1966).

Thrombin time (TT) was not significantly increased in either non-pregnant or pregnant women with recurrent miscarriage who were positive or negative for LA ( $P > 0.05$ ) when compared with their control groups. There are no previous reports about TT in patients with recurrent fetal loss for comparison.

Our data showed that fibrinogen level was not significantly increased in either non-pregnant or pregnant women with recurrent fetal loss who were negative for LA ( $P > 0.05$ ) compared with their corresponding control group. These findings were compatible to the results of Ogasawara et al., (1998).

On the other hand, plasma fibrinogen level was significantly increased in non-pregnant and pregnant women with recurrent miscarriage who were positive for LA ( $P < 0.05$ ) compared with the corresponding control groups (Table 3 & 4).

Also, in all pregnant cases; plasma fibrinogen level was still significantly increased ( $P < 0.05$ ) compared with the control group (Table 4).

A similar association was found between elevated plasma fibrinogen level and LA in the study of Ames et al., (1995) and Gschwandtner et al., (1996).

Also, plasma fibrinogen level was recorded to be significantly increased during pregnancy by Cerneca et al., (1997) and De Moerloose et al., (1997).

Fibrinogen is an acute phase protein and its level is increased during inflammation, coronary heart disease, stroke and peripheral arterial occlusive disease (Ernst, 1990).

The elevated fibrinogen level in our results may be explained by increase synthesis of fibrinogen due to increase demand or as a result of decrease fibrinolytic activity (Dati et al., 1998) or associated inflammation in patients with lupus anticoagulant (Gschwandtner et al., 1996).

The results of this work revealed that factor VII and XII activities were not significantly increased in non-pregnant women who were negative for LA while

there were a statistically significant differences ( $P < 0.001$ ) in the same group but positive for LA (Table 3) compared with the control group.

Additionally, factor VII and XII were significantly increased in pregnant women either negative or positive for LA ( $P < 0.05$ ) compared with the control group (Table 4). Also, factor VII and XII activities were **significantly** increased in all cases of non-pregnant women ( $P < 0.001$ ) (Table 3) as well as all cases of pregnant women ( $P < 0.05$ ) (Table 4) compared with the corresponding control groups.

Branch & Rodgers (1993) found that sera of patients with antiphospholipid syndrome induce the procoagulant activity of clotting factors VII and X but not factor VIII.

Also, during pregnancy factor VII activity (Morrissey et al., 1993) and factor XII activity (Coppola et al., 1996) were found to be increased.

Radcliffe et al., (1977) found That in vitro, factor VII can be acti-

vated by factor Xlla and therefore part of factor Vila detected in pregnancy can be mediated by factor Xlla (De-Moerloose et al., 1997).

Recently, Sattar et al, (1999) suggested that oestradiol-induced hypertriglyceridaemia may be a cause of indirect elevations in plasma factor VII activity, PAI and t-PA and fibrin turnover (D-dimer) during normal pregnancy, but is poorly related to the increase in Von-Willebrand factor (VWF).

The increase of factor VII activity in patients who were positive for LA may be due to induction of tissue factor expression by antiphospholipid antibodies, (Branch & Rodgers 1993). This tissue factor is responsible for activation of extrinsic pathway (De-Moerloose et al., 1997).

Our results of ATIII activity showed non-significant decrease in non-pregnant and pregnant groups who were either positive or negative for LA when compared with the control group (Table 3 & 4).

A nearly similar results were obtained by Kordich et al., 1992 but contradictory to our findings; Boey et al., (1984) and Hasselar et al., (1989) who found an increased levels of antithrombin III in patients with autoimmune disease. Boey et al., (1984) suggested that the apparent elevation of antithrombin might be due to antiphospholipid antibodies interfering with the functional antithrombin III assay in vitro.

However, Chamley et al., (1993) demonstrated that cross-reactive antiphospholipid antibodies bind to heparin and inhibit the activation of antithrombin III.

Vincent et al., (1998) found that thrombin-antithrombin (TAT) concentration were significantly raised in both antiphospholipid - positive and negative women with a history of miscarriage compared with normal control group. This may explain the increased thrombin generation in women with recurrent miscarriage. Thus the binding of antithrombin III to thrombin may be responsible for decrease of AT III activity to some extent in our study.

Comparative study of non-pregnant women, who were positive for LA versus those negatives for LA, we found that APTT-LA, factor VII and factor XII activities were all significantly increased (Table 3).

On the other hand, pregnant women who were positive for LA had only significant increase of APTT-LA when compared to those negative for LA ( $P < 0.001$ ) (Table 4).

These differences between the two groups in some of the clotting factors may be attributed to pregnancy, which is considered by some author as a hypercoagulable state (Comeglio et al., 1996).

Finally, from our study and similar reports the overall mechanism which explains the increased risk of fetal loss associated with the presence of antibodies directed against phospholipids may be proposed as during pregnancy; both extrinsic and intrinsic system were active (De-Moerloose et al., 1997). Moreover antiphospholipid antibodies release tissue factor, which activates factor VII (extrinsic pathways), (Branch &

Rodgers 1993). Thus, the common pathway will be activated with the generation of thrombin (Vincent et al., 1998), which transform fibrinogen to fibrin and thrombus formation. Also, impaired balance between prostacyclin and thromboxane A<sub>2</sub> due to ap<sub>1</sub>, which in favor of the latter leads to more platelet aggregation with more increase in thrombus formation (DeWolf et al., 1982).

On the other hand, AT III, which is a natural anticoagulant, is inhibited due to binding of antiphospholipid antibodies to heparin, which is the activator of ATIII (Chamley et al., 1993). Thus the causal mechanism seems likely to involve placenta! development and function. The net results are impaired uteroplacental circulation with recurrent miscarriage.

We could conclude that, although pregnancy is a hypercoagulable state; but there are certain subgroups of women who were positive for LA had a more thrombogenic potential, which plays a role in recurrent miscarriage. Thus, we recommend to do APTT-LA; which is simple and cheap

test as a screening for every woman with a past history of recurrent fetal loss. This may be of benefit for the antithrombotic treatment to improve fetal outcome.

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