CHOICE OF ANTI-COAGULANT AND ITS EFFECT ON PREGNANCY OUTCOME IN PREGNANT WOMEN WITH ANTIPHOSPHOLIPID ANTIBODY SYNDROME

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بسم الله الرحمن الرحيم

وَلَقَدْ خَلَقْنَا الْإِنْسَانَ مِنْ سُلَالَةٍ مِنْ طِينٍ * ثُمَّ جَعَلْنَاهُ نُطْفَةً فِي قَرَارٍ مَكِينٍ * ثُمَّ خَلَقْنَا النُّطْفَةَ عَلَقَةً فَخَلَقْنَا الْعَلَقَةَ مُضْغَةً فَخَلَقْنَا الْمُضْغَةَ عِظَامًا فَكَسَوْنَا الْعِظَامَ لَحْمًا ثُمَّ أَنْشَأْنَاهُ خَلْقًا آخَرَ فَتَبَارَكَ اللَّهُ أَحْسَنُ الْخَالِقِينَ

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Mohamed Ahmed Abdul-Kader Taema

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aCL	Anti-Cardiolipin Antibody
APS	Anti-Phospholipid Syndrome
aPTT	Activated Partial Thromboplastin Time
B2 GP1	Beta 2 Glycoprotien 1
BMD	Bone Mineral Density
HB-EGF	Heparin Binding Epidermal Growth Factor
HIT	Heparin Induced Thrombocytopenia
HSV	Herpes Simplex Virus
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International Normalizad Ratio
IUGR	Intra-Uterine Growth Restriction
IVF	In-vitro Fertilization
IvIg	High Dose Intravenous Immunoglobulins
LAC	Lupus Anti-Coagulant
LDA	Low Dose Aspirin
LMWH	Low Molecular Weight Heparin
LPD	Luteal Phase Defect
MTHFR	Methylene Tetrahydrofolate Reductase
PA	Phosphatidic acid
PCOS	Poly cystic ovary syndrome
PET	Pre-eclamptic Toxemia

PI	Phosphatidylinositol
PS	Phosphatidylserine
RPL	Recurrent Pregnancy Loss
SLE	Systemic Lupus erythematosus
TIA	Transient Ischemic Attack
UH (or UFH)	Un-Fractionated Heparin
VTE	Venous Thrombo-Embolism

Contents

Introduction

Historically, the first anti-phospholipid autoantibody detected was the false-positive Wassermann reaction, found especially in patients with systemic lupus erythematosus. Lupus anticoagulant was first described in the early 1950s as prolonging certain clotting assays. A few years later, lupus anticoagulant was found to be associated with the false-positive test for syphilis and (paradoxically) thrombosis. The key antigenic component of the Wassermann reaction was cardiolipin, a phospholipid found in mitochondrial membranes, and a much more sensitive immunoassay was developed in the early 1980s using cardiolipin as the solid phase antigen. Anti-cardiolipin antibodies identified in this assay proved strongly correlated with lupus anticoagulant and thrombosis. In the early 1990s, anticardiolipin autoantibodies were found to require the presence of the plasma phospholipid- binding protein 2-glycoprotein I to bind to cardiolipin. ***(Branch** et al., **2003)***

In 1963, the first description of thrombosis occurring in patients with circulating anticoagulants was soon followed by a report of similar manifestations in patients diagnosed with systemic lupus erythematosus (SLE). ***(Westney** et al., **2002)***

The anti-phospholipid syndrome has been described for the first time by Graham Hughes in 1983 as a condition connected with thrombosis or fetal losses and anti-phospholipid antibodies presence. The anti-phospholipid syndrome (APS) is a multisystemic disease, characterized by venous or arterial thrombosis, or certain obstetric complications, and the presence of anti-phospholipid antibodies. APSs are a heterogeneous group of autoantibodies that bind to negatively

charged phospholipids, phospholipid-binding protein, or a combination of the two. Lupus anticoagulant, anticardiolipin antibodies (aCL) and anti-beta 2 glycoprotein 1 antibodies are the main antibodies in this syndrome. APS occurs in isolation as a primary APS in more than 50% of the cases, but can be associated with other autoimmune diseases, most often with systemic lupus erythemathosus (SLE). ***(Haram** et al., **2012)***

In 1983, a solid-phase immunoassay for anti-cardiolipin antibodies was developed. This assay was several hundred times more sensitive than the VDRL test for detecting anti-cardiolipin antibodies in patients with systemic lupus erythematosus, and the anti-cardiolipin antibodies detected were strongly associated with lupus anticoagulant antibodies, false positive VDRL tests, and thrombosis. **(Harris** *et al.*, **1983)**

Whether anti-phospholipid antibodies per se are the cause of adverse obstetric outcomes associated with the antibodies remains a subject of debate. Working with mice, some investigators found administration of human anti-phospholipid antibodies results in clinical manifestations of anti-phospholipid syndrome, including fetal loss. The induction of fetal loss in this model is, however, variable. One group has used a mouse venous thrombosis model to show that circulating human and mouse antiphospholipid antibodies are associated with larger and more persistent thrombi than in mice treated with control antibodies. ***(Pierangeli** et al., **2000)***

In October 1998, participants in a workshop in Sapporo, Japan, devised classification criteria for the anti-phospholipid syndrome (APS).

According to the Sapporo criteria, APS is present in patients with one clinical and one laboratory criterion. ***(Wilson, 1999)***

The preliminary criteria for APS were revised in Sydney, Australia in 2004. The differences between the original and the revised criteria were:

1. The addition of exclusionary criteria, in particular, older age (males 55 and older, females 65 and older, because of competing alternative causes for thromboembolic disease in older age groups);

2. An increase in the required interval from 6 to 12 weeks, during which two consecutive tests be positive because infection-induced auto-antibodies can be positive for more than 6 weeks. ***(Miyakis** et al., **2006)***

Table 1. Revised classification criteria for the Anti-phospholipid antibody syndrome.

Clinical criteria *(one or more)*	**1. Vascular thrombosis:**	One or more objectively confirmed episodes of arterial, venous or small vessel thrombosis occurring in any tissue or organ
	2. Pregnancy morbidity:	**a)** One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation; or
		b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia, pre-eclampsia or placental insufficiency; or
		c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation
Laboratory criteria *(one or more, present on 2 or more occasions at least 12 weeks apart using recommended procedures)*	**1.Lupus anticoagulant**	detected according to the guidelines of the International Society on Thrombosis and Hemostasis
	2.Anti-cardiolipin antibody	of IgG and/or IgM isotype, present in medium or high titer (greater than 40 GPL or MPL, or greater Than the 99th percentile), measured by a standardized ELISA
	3.Anti β2-glycoprotein-1 antibody	of IgG and/or IgM isotype, Present in titer greater than the 99th percentile, measured by a standardized ELISA

(Pierangeli** et al**., 2008)

Women with anti-phospholipid syndrome (APS) have live birth rates as low as 10% to 50% in pregnancy without pharmacological treatment. Fetal losses in APS have been attributed to thrombosis of the utero-placental vasculature and placental infarction. Not surprisingly, therapy for pregnant women with APS is now focused on preventing thrombosis at the maternal—fetal interface. ***(Levine** et al., **2002)***

A variety of mechanisms by which anti-phospholipid antibodies may cause pregnancy loss and thrombosis have been suggested. Anti-phospholipid antibodies may interfere with the normal in vivo function of phospholipids or phospholipid-binding proteins that are crucial to the regulation of coagulation. Candidate molecules or pathways that might be adversely affected include B2-glycoprotein I (which has anticoagulant properties), prostacyclin, prothrombin, protein C, annexin V, and tissue factor. Anti-phospholipid antibodies may activate endothelial cells, as indicated by increased expression of adhesion molecules, secretion of cytokines, and production of arachidonic acid metabolites. ***(Branch** et al.*, ***2003)***

The presence of APS has been clearly shown to have an adverse effect on pregnancy outcome. These effects may be apparent in the first trimester, presenting as recurrent pregnancy loss, or may be associated with the later development of PET, IUGR, placental abruption, pre-term delivery, and intrauterine death. What appears to be the most important in the etiology, initially; are the factors that disturb the vital interaction between the embryonic trophoblastic tissue and the host (maternal) endometrial tissue. ***(A. Vashisht, L Regan 2005)***