

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

Submitted by;
MOHAMED AHMED ABDUL-KADER MOHAMED TAEMA
M.B.B.Ch

In Fulfillment of Master Degree
In Obstetrics & Gynecology

Supervised by
Prof. RAFAAT MOHAMED REIAD

Professor of Obstetrics & Gynecology
Faculty of Medicine
Cairo University

Dr. AHMED MAHMOUD HUSSEIN

Lecturer of Obstetrics & Gynecology
Faculty of Medicine
Cairo University

Dr. SHERIEF AL-ANWARY

Lecturer of Pediatrics
Faculty of Medicine
Cairo University

2014

اختيار موانع تجلط الدم وأثره على نتيجة الحمل في النساء الحوامل المصابات بمتلازمة أضداد الفوسفوليبيد

رسالة مقدمة لاستكمال درجة الماجستير
في أمراض النساء والتوليد

من الطبيب / محمد أحمد عبد القادر طعيمة
بكالوريوس الطب والجراحة
جامعة عين شمس

تحت إشراف

الأستاذ الدكتور / رأفت محمد رياض
أستاذ أمراض النساء والتوليد
كلية الطب - جامعة القاهرة

دكتور / أحمد محمود حسين
مدرس أمراض النساء والتوليد
كلية الطب - جامعة القاهرة

دكتور / شريف الأنوري
مدرس أمراض الأطفال
كلية الطب - جامعة القاهرة

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

وَلَقَدْ خَلَقْنَا الْإِنْسَانَ مِنْ سُلَالَةٍ مِنْ طِينٍ * ثُمَّ
جَعَلْنَاهُ نُطْفَةً فِي قَرَارٍ مَكِينٍ * ثُمَّ خَلَقْنَا النُّطْفَةَ
مَلَكَةً فَخَلَقْنَا الْعِلْقَةَ مَضْغَةً فَخَلَقْنَا الْمَضْغَةَ عِظَامًا
فَنَسَوْنَا الْعِظَامَ لَحْمًا ثُمَّ أَنشَأْنَاهُ خَلْقًا آخَرَ
فَتَبَارَكَ اللَّهُ أَحْسَنُ الْخَالِقِينَ

صَدَقَ اللَّهُ الْعَظِيمُ

ACKNOWLEDGEMENT

*First and foremost, thanks to **Allah**, the source of all knowledge, understanding and wisdom.*

*Words can never express my deepest gratitude and sincere appreciation to **Prof. Dr. Rafaat Mohamed Reiad**, Professor of Obstetrics and Gynecology, Faculty of Medicine, Cairo University, for his kind encouragement, constructive guidance, and provision of much of his time and effort.*

*I wish to express my deep thanks to **Dr. Ahmed Mahmoud Hussein**, Lecturer of Obstetrics and Gynecology, Faculty of Medicine, Cairo University, for his patience, great help and valuable ideas throughout the work, without whom this work could've never been done.*

*I wish to express my deepest thanks, gratitude and appreciation to **Dr. Sherief Al-Anwary**, Lecturer of Pediatrics, Faculty of Medicine, Cairo University, for her sincere effort, continuous guidance, and generous help.*

I would like to thank the Obstetric High Risk Unit of Cairo University for their technical support, and thank all the patients for their compliance and co-operation.

Special thanks full of love and gratitude to my wife and parents for their constant help and support. Being by my side all through the work helped me overcome all obstacles in my way.

And last but not least, to my son Ali; thanks for giving me a hug and a smile when I really needed that.

Mohamed Ahmed Abdul-Kader Taema

LIST OF TABLES

	Table	Page
1.	Revised classification criteria for the Anti-phospholipid antibody syndrome.	3
2.	Revised Sapporo or Sidney criteria for classification of antiphospholipid antibody syndrome.	9
3.	Studies on live birth rates in treated women with APS and fetal loss, SLE, thrombosis or combinations of these.	16
4.	Studies on live-birth rates related to pharmacological treatment in women with APS and recurrent early pregnancy loss or at least one fetal loss in absence of SLE or previous thrombosis.	19
5.	Comparison of three trials comparing pregnancy outcome for treatment with low dose aspirin (LDA) and LDA plus heparin.	21
6.	Different types of LMWH.	32
7.	Age and characteristics of obstetric history of the two studied groups.	67
8.	Frequency of criteria of diagnosis of antiphospholipid syndrome in the two studied groups.	69
9.	Laboratory characteristics in the two studied groups.	70
10.	Ultrasound characteristics of the two studied groups at delivery.	70
11.	Comparison of resistance index of umbilical artery in both groups	71
12.	Correlation between RI of umbilical artery and APGAR score and gestational age at delivery	72
13.	Mode of delivery of the two studied groups.	74
14.	Neonatal outcome in the two studied groups.	76

LIST OF FIGURES

	Figure	Page
1.	Algorithm for pharmacologic treatment of women with lupus anticoagulant (LAC), medium or high levels of anticardiolipin antibodies (aCL), or a combination of these during pregnancy and the postpartum period.	25
2.	Mechanism of action: UFH vs LMWH.	30
3.	Medison SonoAce R5, the ultrasound device used in this study.	58
4.	Cardiotocograph (CTG) device used	63
5.	Frequency of diagnostic criteria of APS in the two studied groups.	68
6.	Resistance index of umbilical artery in both groups	71
7.	Correlation between the resistance index of the umbilical artery and APGAR score at delivery	72
8.	Correlation between the resistance index of the umbilical artery and gestational age at delivery	73
9.	Gestational age at delivery in the two groups.	74
10.	Indication of cesarean delivery in relation to antiphospholipid complications.	75
11.	Measurement of the abdominal circumference at 25 weeks	82
12.	Measurement of the Biparital Diameter and Head Circumference at 26 weeks	83
13.	Measurement of Femoral Length at 31 weeks	83
14.	Measurement of Umbilical artery at 30 weeks gestation with a RI of 0.64	84
15.	Measurement of the Rt Middle Cerebral Artery with a RI of 0.83	84

16.	Category I (reassuring) Cardiotocogram with FHR of 160/min.	87
17.	Category III Cardiotocogram presenting with FHR of 120/min, but with loss of beat to beat variability	87
18.	Category III Cardiotocogram presenting with variable decelerations	88
19.	Category I Cardiotocogram presenting with early decelerations	88
20.	Category II Cardiotocogram presenting with late decelerations	89

LIST OF ABBREVIATIONS

aCL	Anti-Cardiolipin Antibody
APS	Anti-Phospholipid Syndrome
aPTT	Activated Partial Thromboplastin Time
B2 GP1	Beta 2 Glycoprotein 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 Normalized 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

	Page
Review of literature.	
Introduction	1
Aim of the work.	7
- The Obstetric Anti-Phospholipid Syndrome.	8
- Heparin & Low Molecular Weight Heparin: A Review of Pharmacology	26
- The Use of Unfractionated Heparin and Low Molecular Weight Heparin during pregnancy.	35
The use of low-molecular-weight heparins in pregnancy — how safe are they?	45
Patients and methods.	52
Results.	67
Discussion.	77
Summary & Conclusion.	90
Appendix I	94
Appendix II	95
References.	96

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 erythematosus (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 (<i>one or more</i>)	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 (<i>one or more, present on 2 or more occasions at least 12 weeks apart using recommended procedures</i>)	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*)