Perinatal Outcome in Women Using Oral Warfarin for Improving Pregnancy Outcome in Recurrent Pregnancy Loss

A retrospective analysis of 5-year experience at Ain Shams University Maternity Hospital

Thesis

Submitted as Partial Fulfillment of Master Degree In Obstetrics and Gynecology

BY

Mohammed Walid Yousef Zimmo
M.B.B.Ch
Misr University for Science and Technology – 2007

Under Supervision of

Prof. Mahmoud Aly Ahmed El Shourbagy
Professor of Obstetrics and Gynecology
Ain Shams University

Prof. Salah Taha Fayed
Professor of Obstetrics and Gynecology
Ain Shams University

Dr. Ahmed Hamdy Naguib Abdul Rahman
Assistant Professor of Obstetrics and Gynecology
Ain Shams University

Faculty of medicine
Ain Shams University
2011

تأثير إستخدام مضادات التخثر بالفم(وارفارين) لعلاج حالات الإجهاض المتكرر على الأم والجنين

تحليل ذو أثر رجعي من خمسة سنوات
في مستشفى جامعة عين شمس للنساء والولادة

رسالـة

توطئة لنيل درجة الماجستير فى أمراض النساء والتوليد

مقدمة من

محمـد وليـد يوسـف زمـو

بكالوريوس الطب و الجراحة (٢٠٠٧)
جامعة مصر للعلوم و التكنولوجيا

تحت إشراف

الأستاذ الدكتور/ محمود علي أحمد الشوربجي

أستاذ أمراض النساء و التوليد
كلية الطب – جامعة عين شمس

الأستاذ الدكتور/ صلاح طه فايد

أستاذ أمراض النساء و التوليد
كلية الطب – جامعة عين شمس

الدكتور/ أحمد حمدي نجيب عبد الرحمن

أستاذ مساعد أمراض النساء و التوليد
كلية الطب – جامعة عين شمس

كليــة الطـب
جامعة عين شمس
٢٠١١

Acknowledgement

First and foremost I would like to thank "Allah" for every thing. This would not be achieved without the support of "Allah".

I would like to express my deepest thanks and gratful appreciation to **Prof. Mahmoud Aly Ahmed El Shourbagy,** Professor of Obstetrics and Gynrcology, Faculty of Medicine, Ain Shams University, to whom I owe more than words can express. His limitless help , valuable advise and kind encouragement.

I owe special greatfulness and much regards to **Prof. Dr. Salah Taha Fayed,** Professor of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, for his helpful and close experienced supervision. His encouragement, guidance and valuable advise were behind the accomplishment of this work.

I would like to display my very indebtedness to Assistant **Prof. Dr. Ahmed Hamdy Naguib,** Assistant Professor of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, for his constructive supervision and his help in constructing the work. I received a great deal of help from hem, that words cannot express.

Special thanks to **Dr. Mohammed Faris,** Assistant Lecture of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University: for his scholarly advice and kind assistance during preparation of this work.

Last, but not least, I would like to thank my ***family*** for their continuous help and support. Also I am grateful to every one helped me to accomplish this work.

Mohammed Walid Yousef Zimmo

List of Contents

Title	Page No.
Introduction	1
Aim of the work	4
Review of literature	5
♦ Antiphospholipid Syndrome During Pregnancy	5
♦ Anticoagulants During Pregnancy	37
Patients and methods	62
Results	67
Discussion	97
Summary	109
Conclusions	111
Recommendation	112
References	113
Arabic Summary	137

List of Table

Table No.	Title	Page No.
Table (1):	Recommendations for anticoagulation of pregnant women with antiphospholipid antibodies	36
Table (2):	Changes in coagulation during pregnancy	38
Table (3):	Antenatal prophylactic and therapeutic doses of low-molecular-weight heparin:	59
Table (4):	Summary of protocol for thromboprophylaxis in women with previous VTE and/or thrombophiliaa:	60
Table (5):	Demographic Data of Included Women	69
Table (6):	Associated Medical Conditions of Included Women	69
Table (7):	Consanguinity and Antiphospholipid Antibodies in Included Women	71
Table (8):	Anticoagulant Therapy in Included Women	72
Table (9):	Pregnancy Outcome in Included Women	73
Table (10):	Perinatal Outcome in Included Women	75
Table (11):	Difference between Both Groups regarding Demographic Data	76
Table (12):	Difference between Both Groups regarding Associated Medical Conditions	77
Table (13):	Difference between Both Groups regarding Consanguinity and Antiphospholipid Antibodies	78
Table (14):	Difference between Both Groups regarding Pregnancy Outcome.	79
Table (15):	Difference between Both Groups regarding Birth Weight and Apgar Scores	80
Table (16):	Difference between Both Groups regarding Pregnancy and delivery Complications	82
Table (17):	Difference between Both Groups regarding Congenital Malformations	84
Table (18):	Difference between Both Groups regarding Adverse Neonatal or Infantile Events	85
Table (19):	Difference between Low and High Dose of Warfarin regarding Pregnancy and delivery Complications	86
Table (20):	Difference between Both Groups regarding Congenital Malformations	87
Table (21):	Difference between Both Groups regarding Adverse Neonatal or Infantile Events	88

Table (22): Difference between Both Groups diagnosed as APAS … 89
Table (23): Difference between Both Groups regarding Associated Medical Conditions 90
Table (24): Difference between Both Groups regarding Pregnancy Outcome. 91
Table (25): Difference between Both Groups regarding Birth Weight and Apgar Scores 92
Table (26): Difference between Both Groups regarding Pregnancy and delivery Complications 93
Table (27): Difference between Both Groups regarding Congenital Malformations..... 94
Table (28): Difference between Both Groups regarding Adverse Neonatal or Infantile Events 95
Table (29): Difference between Both Groups regarding Average Cost..... 96

List of Figure

Figure No.	Title	Page No.
Fig. (1):	Coagulation pathways.	61
Fig. (2):	Included Women	68
Fig. (3):	Bar-Chart showing Distribution of Associated Medical Conditions of Included Women	70
Fig. (4):	Bar-Chart showing Pregnancy and Delivery Complications in Included Women	74
Fig. (5):	Box-Plot Chart showing Difference between Both Groups regarding Birth Weight	81

List of Abbreviations

ACAs.....	Anticardiolipin antibodies
ACL.....	Anticardiolipin
APAS	Antiphospholipid antibodies syndrome
APAS.....	Antiphospholipid antibodies syndrome
APL.....	Antiphospholipid
aPTT.....	Activated partial thromboplastin time
AT	Antithrombin III
DIC	Disseminated intravascular coagulopathy
ELISA.....	Enzyme Linked Immunosorbent Assay
HELLP	A syndrome of Haemolysis, Elevated liver enzymes and Low platelet count
IgA	Immunoglobulin A
IGFBP-1 ..	Insulin like Growth Factor Binding Protien 1
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International Normalized Ratio
IRR.....	Incidence rate ratio
IUGR	Intrauterine growth retardation
IVIG.....	Intravenous Immunoglobulin
LA	Lupus anticoagulant
LDA	Low dose aspirin
LDL.....	Low density lipoprotien
LMWH.....	Low molecular weight heparin
P.....	Probability of error
P-.....	negative predictive value
P+.....	positive predictive value
RPL.....	Recurrent pregnancy loss
RATIO	Risk of arterial thrombosis in relation to oral contraception
VTE.....	Venous thromboembolism

List of Abbreviations (Cont…)

PAF.....	Platelet Activation Factor
PE	Preeclampsia
PGF.....	Platelet growth factor
PGI.....	Prostacyclin
PIH	Pregnancy induced hypertension
PTT.....	Partial thromboplastin time
RPL.....	Recurrent pregnancy loss
RSA.....	Recurrent spontaneous abortion
SD	Standard deviation
SLE.....	Systemic lupus erythematosus
TAT.....	Thrombin antithrombin complex
TN.....	true negative
TNF	Tumour necrosing factor
TP	true positive
VEFG.....	Vascular endothelial growth factor

Introduction

Antiphospholipid antibody syndrome (APAS) is defined as the presence of lupus anticoagulant or anticardiolipin antibodies of medium–high titre on two occasions eight weeks apart, found in association with a history of thrombosis (arterial or venous) or adverse pregnancy outcome (three or more unexplained miscarriages before ten weeks of gestation, a fetal death after ten weeks of gestation or a premature {less than 35 weeks} birth due to severe pre-eclampsia or intrauterine growth restriction) *(RCOG, 2004)*.

The management of women with APAS is controversial. Treatment options included oral steroids, low-dose aspirin and heparin. Combined administration of low-dose aspirin and heparin (in thromboprophylactic doses) had the best outcome *(Shehata et al., 2001)*.

Options concerning anticoagulant therapy include unfractionated heparin (UFH), low molecular weight heparin (LMWH) and oral warfarin. The major concern about the safety of these anticoagulant drugs is the risk of bleeding and teratogenicity. Neither UFH nor LMWH crosses the placenta, thus both having almost no risk of teratogenicity. On the contrary, oral warfarin

does cross the placenta and thus having the potential risk of teratogenicity *(Chan et al., 2000)*.

Yet, UFH (and to a lesser extent, LMWH) is associated with considerable patient's discomfort related to frequent injections and is complicated by serious adverse effects with long-term therapy such as osteoporosis and heparin-induced thrombocytopenia *(Ginsberg et al., 2003)*.

The cost of heparin itself and the potential need for hospitalization to receive heparin is also of paramount importance, particularly in Egypt. It was estimated that the total cost of UFH (cal-heparin®) therapy throughout pregnancy for such cases is estimated to be about 2500 EGP (≅ 500 USD), and that of LMWH (Clexan®) to be about 4500 EGP (≅ 900 USD), compared to the total cost of oral warfarin (Marevan®) which is estimated to be about 25 – 50 EGP (≅ 5 – 10 USD).

Nevertheless, the safety of oral anticoagulants is a major obstacle to its use during pregnancy. It is universally recommended that oral anticoagulants should be withheld during the period of embryogenesis (6 – 10 weeks' gestation), as the risk of warfarin embryopathy is evident in fetuses exposed to warfarin

during this interval. However, the use of oral anticoagulants beyond this gestational age interval is yet to be allowed. The guidelines published by the Royal College of Obstetricians and Gynecologists (RCOG) still advise against the use of warfarin throughout pregnancy, except in women with heart valve prostheses, due to the unacceptably high mortality and morbidity rates with the use of heparin instead *(Abadi et al., 2002; Hung and Rahumtoola, 2003; RCOG, 2007; Bates et al., 2008)*.

Our experience in Ain Shams University Maternity Hospital actually obviates the potential risks of warfarin-related teratogenicity when used after the period of embryogenesis (i.e. after 10 weeks' gestation). During the last 5 years, annual rates between 92 and 123 women with heart valve prostheses had their antenatal care and delivery at this institute. Therefore, there is a need to revise this experience and document it retrospectively as an initial step, in preparation to plan a well-controlled prospective randomized clinical trial to study the safety of oral anticoagulation from the fetal aspect, when used beyond 10 weeks' gestation *(Fayed et al. , 2005)* .

Aim of the Work

To compare the safety or efficacy of oral warfarin use in pregnancy with the use of heparin (whether unfractionated or low-molecular-weight) as regard perinatal outcome in women with recurrent pregnancy loss.

Antiphospholipid Syndrome During Pregnancy

Antiphospholipid Syndrome is largely a non-inflammatory autoimmune disorder. The condition has come to be regarded as one of the most common autoimmune diseases. Thrombosis is the most important underlying pathological process and accounts for many of the clinical features of all forms of APS. Some patients have persistent aPL for many years and yet they only develop clinical thrombotic events when they are exposed to certain pathological or physiological events *(Ziporen et al., 2004).*

The antiphospholipid syndrome (APS) is defined by two major components:

Presence in the serum of at least one type of autoantibody known as an antiphospholipid antibody (aPL). APLs are directed against phospholipid-binding plasma proteins.

The occurrence of at least one clinical feature from a diverse list of potential disease manifestations, the most common of which are categorized as venous or arterial thrombosis, pregnancy morbidity, or thrombocytopenia *(Ziporen et al., 2004).*

Pathophysiology:

The mechanism or mechanisms by which the antiphospholipid antibodies interact with the coagulation cascade to produce clinical events are largely speculative and have not been elucidated clearly. The presence of preexisting or coincident vascular (endothelial) damage along with the identification of an aPL antibody as requisites for the emergence of a thrombotic complication has been coined the "two-hit" hypothesis.

- Possible mechanisms by which aPL might induce thrombotic events include the following:
    - aPL may combine with platelet membrane phospholipids, resulting in increased platelet adhesion and aggregation.
    - aPL may combine with the endothelial cell membrane phospholipids along with B2-GPI and induce endothelial cell damage, impaired prostacyclin production, increased platelet adhesion, and aggregation.
    - Endothelial cell damage may also result in decreased production of endothelium-derived relaxing factor and, thus, increased vasospasm and ischemia.
    - In the secondary APS, vascular endothelial cell damage has already occurred, enhancing the