ENVIRONMENTAL RISK FACTORS FOR REPEATED PREGNANCY LOSS INPATIENTS WITH ANTIPHOSPHOLIPID SYNDROME AND PULMONARY EMBOLISM

Submitted by

Azza Moustafa Foad Hathhout

M.B.B.Ch.1986 Faculty of Medicine - Cairo University 1986
Diploma of Obstetrics and Gynecology, Faculty of medicine, Ain Shams University, 1998
Master Degree of Environmental Science, Intistute of Environmental Studies and Research,
Ain Shams University, 2014

A Thesis Submitted in Partial fulfillment
Of
The Requirement for the Doctor of Philosophy Degree
In
Environmental Sciences

Department of Environmental Medical Sciences
Institute of Environmental Studies and Research
Ain Shams University
2018

ENVIRONMENTAL RISK FACTORS FOR REPEATED PREGNANCY LOSS INPATIENTS WITH ANTIPHOSPHOLIPID SYNDROME AND PULMONARY EMBOLISM

Submitted by

Azza Moustafa Foad Hathhout

M.B.B.Ch.1986 Faculty of Medicine - Cairo University 1986
Diploma of Obstetrics and Gynecology, Faculty of medicine, Ain Shams University, 1998
Master Degree of Environmental Science, Intistute of Environmental Studies and Research,
Ain Shams University, 2014

A Thesis Submitted in Partial fulfillment
Of
The Requirement for the Doctor of Philosophy Degree
In
Environmental Sciences

Under The Supervision of

1. Professor/ Mahmoud Serri El-Bokary
Prof of Chest Diseases, Department of Environemntal Medical Sciences – Institute of Environmental Studies and Research
Ain Shams University

2. Professor/ Sherif M. Salah El-Din Abd El-Salam
Prof of Obstetrics and Gynecology
Faculty of Medicine
Menofieya University

2018

Acknowledgment

First and foremost, I feel always indebted to **ALLAH**, *the Most Kind and Most Merciful.*

I'd like to express my respectful thanks and profound gratitude to **Professor/ Mahmoud Serri El-Bokary,** *Professor of Chest Diseases, Chairman, Department of Medical Science, Faculty of Medicine- Ain Shams University for his keen guidance, kind supervision, valuable advice and continuous encouragement, which made possible the completion of this work.*

I am also delighted to express my deepest gratitude and thanks to **Professor/ Sheriff M. Salah El-Din Abd El-Salam,** *Professor of Obstetrics and Gynecology, Faculty of Medicine, Menofieya University, for his kind care, continuous supervision, valuable instructions, constant help and great assistance throughout this work.*

I would like to express my hearty thanks to all my family for their support till this work was completed.

Last but not least my sincere thanks and appreciation to all patients participated in this study.

List of Contents

List of Tables

List of Tables (Cont...)

List of Figures

List of Acronym

Acr.	Full term
acL	*Lupus anticoagulant*
apL	*Antiphospholipid antibodies*
APS	*Antiphospholipid syndrome*
BMI	*Boyd mass index*
CAPS	*Catastrophic antiphospholipid syndrome*
CI	*Confidence interval*
CI	*Confidence interval*
CMV	*Cytomegalovirus*
COPD	*Chronic obstructive pulmonary disease*
DVT	*Deep venous thrombosis*
HELLP syndrome	*Haemalytic anemia-elevated liver enzymes-low platelet count*
IgG	*Immunoglobulin G*
IgM	*Immunoglobulin M*
IUFD	*Intrauterine fetal death*
JUGR	*Intrauterine growth restriction*
LA	*Lupus anticoagulant*
OAPS	*Obstetric antiphospholipid syndrome*
PAPE	*Pregnancy associated pulmonary embolism*
PAPS	*Primary antiphospholipid syndrome*
PMB	*Premature birth*
PTD	*Preterm delivery*
PTE	*Pulmonary thrombembolism*
RAAS	*Renin-angiotensinaldosteron system*
REM	*Recurrent early miscarriage*
RRs	*Relative risks*

ABSTRACT

Introduction: Antiphospholid syndrome (APS) is an autoimmune hypercoagulable state caused by antiphospholid antibodies. Primary antiphospholipid syndrome occurs in absence of any other related disease. Secondary antiphospholipid syndrome occurs with other autoimmune disease as systemic lupus erythrematosis. The clinical features of the APS are various, but the most common clinical presentation is pregnancy loss, DVT**.** Pulmonary thromboembolism, the cardiac manifestations of APS include myocardial infarction, pericardial effusion, myocardiopathy, and coronary artery thrombosis, but the most common manifestation is valvular abnormalities.

Aim: to investigate the influence of obesity and smoking in women diagnosed as an antiphospholipid cases according to Sydney's criteria on pregnancy morbidities, vascular events, pulmonary thromboemboism and laboratory criteria.

Methods: A case control study was conducted that include women attending obstetric outpatient clinic. These women were previously diagnosed as antiphospholipid cases according to (Sydney's criteria). A total of 90 women have been equally divided into three groups: **First group** corresponds to control group which includes 30 women with normal body mass index (BMI) i.e. < 30 Kg/m^2 and, **second group** include 30 obese women with (BMI > 30 Kg/m^2) and third group include 30 women with MBI less than 30 but they were smokers.

Results: Obesity is independent predictor for preterm birth intrauterine fetal death and pulmonary thromboembolism also smoking was an impendent predictor for recurrent early miscarriage, preterm birth, intrauterine fetal death and pulmonary thromboembolism.

Conclusion: Obesity and smoking is associated with worth pregnancy outcomes in patients with primary antiphospholipid syndrome.

Keywords: Antiphospholipid syndrome, Obesity, Pregnancy morbidities, Vascular events, Pulmonary thromboembolism, Antiphospholipid antibodies.

INTRODUCTION

The antiphospholipid syndrome (APS) is an autoimmune disease characterize by

arterial and venous thrombosis due to antiphospholipid antibodies. The disorder is referred to as primary when it occurs in the absence of another autoimmune disease. Secondary APS occurs in the context of an autoimmune disorder such as systemic lupus erythematosus. The catastrophic APS (CAPS) is a rare life-threatening form of APS in which widespread intravascular thrombosis results in multiorgan ischemia and failure ***(Nayer and Ortega, 2014; Cervera et al., 2009).***

The other major clinical manifestations of the antiphospholipid syndrome are obstetrical. They include the unexplained death of one or more morphological normal fetuses at or beyond the 10^{th} week of gestation, the premature birth of one or more morphologically normal neonates before the 34^{th} week of gestation because of either eclampsia or severe preeclampsia, and three or more unexplained, consecutive spontaneous before the 10^{th} week of gestation ***(Giannakopoulos and Krilis, 2013; Miyakis et al., 2006).*** These Cases with poor obstetric outcome are known to have obstetric antiphospholipid syndrome (OAPS) ***(Alijotas-Reig et al., 2014; Alijotas-Reig et al., 2012).***

The clinical features of the APS are various, but the most common clinical presentation is pregnancy loss, DVT ***(Ye et al., 2005; Cervera et al., 2002).*** Pulmonary thromboembolism, the cardiac manifestations of APS included myocardial infarction, pericardial effusion,

myocardiopathy, and coronary artery thrombosis, but the most common manifestation is valvular abnormalities ***(Ye et al., 2005; Espisonsa et al., 2002).***

In this study, we investigate the influence of smoking and obesity in women with antiphospholipid syndrome on the clinical features, laboratory data fetal-maternal outcomes.

AIM OF THE WORK

The aim of the current study is to investigate the influence of smoking and obesity in women who were previously diagnosed as an antiphospholipid cases.

Chapter 1

ANTIPHOSPHOLIPID SYNDROME (APS)

APS is an autoimmune condition in which the person's immune system produces antibodies called antiphospholipid antibodies. These are abnormal antibodies that attack proteins and fats in the blood, and specifically phospholipids. The fats and proteins that are attacked are thought to be important in maintaining blood consistency. The blood becomes sticky, significantly increasing the risk of developing blood clots ***(Christian, 2010).***

APS is classified as primary or secondary, depending on its association with other autoimmune disorders.

Primary APS is diagnosed in patients demonstrating the clinical and laboratory criteria for the disease without other recognized autoimmune disease. Secondary APS is diagnosed in patients with other autoimmune disorders, such as systemic lupus erythematosus (SLE) ***(Teresa et al., 2017).***

Primary Antiphospholipid syndrome

There are Obstetric and non obstetric clinical features.

Non obstetric features of APS are as follows:

- Nontraumatic thrombosis or thromboembolism (venous or arterial).
- Stroke, especially in individuals aged 24-50 years.
- Unexplained transient ischemic attack.
- Unexplained amaurosisfugax.
- Autoimmune thrombocytopenia.
- Autoimmune hemolytic anemia.
- Unexplained prolongation of a clotting assay.
- Livedoreticularis.
- SLE or other connective tissue disorder.
- False-positive serologic test result for syphilis.

(Christian, 2010)

In 2006 an international committee proposed the following criteria **(Sydney criteria)** for defining pregnancy in the diagnosis of APS ***(Lockshin et al., 2006).***

Criteria of obstetrical APS

APS is diagnosed when at least one of the following clinical criteria and one of the following laboratory criteria are met

- **Laboratory criteria**

(i) Lupus anticoagulant (LA) present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis.

(ii) Anticardiolipin (aCL) antibody of IgG and/or IgMisotype in serum or plasma, present in medium or high titer, on two or more occasions, at least 12 weeks apart, measured by standardized ELISA.

(iii) Anti 2glycoprotein-1 antibody of IgG and/or IgM isotype in serum or plasma (in titer >99th percentile), present on two or more occasions, at least 12 weeks apart, measured by standardized ELISA ***(Marchetti et al., 2013).***

- **Clinical criteria**

(i) 1 unexplained fetal deaths ≥10 weeks of gestation with normal anatomy by prenatal ultrasound examination or direct postnatal examination.

(ii) ≥1 preterm deliveries of a morphologically normal infant before 34 weeks of gestation due to severe preeclampsia, eclampsia, or features consistent with placental insufficiency.