The Association of Factor V Leiden Mutation With Recurrent Pregnancy Loss Using Activated Protein C Resistance Test (Case-Control Study)

Thesis

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By

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List of Contents

Title Page No.

List of Tables i

List of Figures ii

List of Abbreviations iv

Introduction i

Aim of the Work 5

Review Of Literature

- **Chapter (1):** Recurrent Pregnancy Loss 6
- **Chapter (2):** Thrombophilia 21
- **Chapter (3):** Association Between Thrombophilia And Preganancy Outcome 30
- **Chapter (4):** Factor V Leiden And Activated Protein C Resistance Test 42

Patients And Methods 56

Results 63

Discussion 73

Conclusion And Recommendations 81

Summary 82

References 86

Arabic Summary ..... -

List of Tables

Table No.	Title	Page No.
Table (1):	Prevalences of major risk factors for VTE	22
Table (2):	Relative Risk of First and Recurrent VTE in Pregnancy on the Background of Genetic Thrombophilia	31
Table (3):	Summarizes the risk of thromboembolism in women with thrombophilia-both for asymptomatic patients and for those with a history of thromboembolism	35
Table (4):	Incidence of Factor V Leiden mutation in women with RP	37
Table (5):	Comparison between both groups as regards the mean values of age and number of successful pregnancies	64
Table (6):	Comparison between both groups as regards number of abortions and average gestational age at abortion, and their statistical significance	65
Table (7):	Comparison between both groups regarding the Number of patients with abnormal APC ratio and APC ratio values, and their statistical significance	67
Table (8):	Comparison between both groups regarding age, number of abortions, average gestational weeks at abortion, number of successful pregnancies and APC resistance test value (in case group)	69
Table (9):	Comparison between both groups regarding number of successful pregnancies and incidence of DVT	72

List of Figures

Fig. No.	Title	Page No.
Figure (1):	Workup of RPL in absence of product of conception analysis NK: natural killer, HLA: Human leukectye antigen; PCOS: polycystic ovarian syndrome; ANA: Antinuclear antibodies	14
Figure (2):	Thrombin pathway.	23
Figure (3):	Factor V Leiden and prothrombin G20210A.	24
Figure (4):	Inhibitory effect of natural anticoagulants on the coagulation cascade	29
Figure (5):	Map of Mediterranean Sea and its countries showing the prevalence of FVL in healthy population living there	48
Figure (6):	Schematic representation of blood coagulation and the protein C anticoagulant system	49
Figure (7):	Schematic drawing of different parts of the anticoagulative effects that on the vessels surface are important for regulation of the coagulation and thrombus formation. AT = antithrombin.	50
Figure (8):	The initiation and propagation of blood coagulation.	50
Figure (9):	Activation and degradation of normal FV and FV leiden	51
Figure (10):	Inactivation of FVa by APC.	52
Figure (11):	FV Leiden mutation causes hypercoagulable state through dual mechanism	55
Figure (12):	Comparison between both groups as regards number of successful pregnancies and number of abortions.	66
Figure (13):	Comparison between both groups as regards gestational age at abortion (weeks).	66
Figure (14):	Comparison between both groups as regards percentage of patients with abnormal APCR test and APCR test value	68

List of Figures

Fig. No.	Title	Page No.
Figure (15):	Comparison between number of abortion and number of successful pregnancies (in case group).	70
Figure (16):	Comparison between average gestational week at abortion (in case group)	70
Figure (17):	Comparison between APC ratio value in the case group	71
Figure (18):	Comparison between incidence of DVT in patient with Normal and abnormal APC.	72

List of Abbreviations

Abb.	Meaning
aCL	: Anticardiolipin
ANA	: Antinuclear antibody
APAS	: Antiphospholipid antibody syndrome
APC	: Activated Protein C Resistance
APCR	: Activated Protein C Resistance
AT III	: Antithrombin III
C4BP	: Complement 4 binding protein
FVL	: Factor V Leiden
G-CSF	: Granulocyte colony stimulating factor
GM-CSF	: Granulocyte-macrophage colony stimulating factor
HLA	: Human Leukocyte antigen
IUGR	: Intrauterine Growth Retardation
LA	: Lupus anticoagulant
LIT	: Lymphocyte Immunization Therapy
LPD	: Luteal phase defect
MTHFR	: Methylenetetrahydrofolate reductase
NK	: Natural Killer

List of Abbreviations

Abb.	Meaning
PAI	: Plasminogen activator inhibitor
PCOS	: Polycystic Ovarian Syndrome
POC	: product of conception
PSD	: Protein S deficiency
RPL	: Reccurent pregnancy loss
SLE	: Systemic Lupus
TM	: Thrombomodulin
VTE	: Venous Thromboembolism

ABSTRACT

Background: Recurrent pregnancy loss is considered as a major devastating obstetric and gynecological health problem. Many clinicians define RPL as three or more consecutive pregnancies ending spontaneously before the 20th week of gestation. **Aim of the Work:** to investigate prevalence of FVL mutation in women with RPL using, a less time and money consuming test, APCR test. **Patients and Methods:** We compared the prevalence of FVL among 83 patients with history of 3 or more first tri-mesteric pregnancy losses (the case group) with an equal number of women with no history of RPL (the control group), recruited from the RPL outpatient clinic at the Obstetrics and Gynecology Department of Ain Shams University Maternity Hospital, during the period between April 2018 till June 2019. **Results:** Abnormal APCR test values were found in a total of 22 women in our study, 7 women in the control group (8.4%) and 15 in the case group (18.07%) with no statistically significant differences. However, in further assessment of case group, two patients in the case group with abnormal APC value, suffered from DVT episodes, representing 13.3% of 15 patient with abnormal APCR. The P value was statistically significant, which mean that the present of APCR might increase the risk for DVT **Conclusion:** Isolated FVL is unlikely to be an important cause for RPL as no statistically significant difference is found between the case and control groups.

Key words: Factor V Leiden Mutation, Recurrent Pregnancy Loss, Protein C Resistance **Abbreviation:** RPL: recurrent pregnancy loss; FVL: factor V Leiden; APCR: activated protein C resistance.

INTRODUCTION

Recurrent Pregnancy Loss (RPL) is a traumatic event, which may lead to symptoms of depression, anxiety, lowered self-esteem and other psychosocial consequences [**Kagami M et al., 2012]**.

Many clinicians define RPL as three or more consecutive pregnancies ending spontaneously before the 20th week of gestation; however, more than two pregnancy losses, including those which are not consecutive, are also recently considered as recurrent spontaneous abortions. It is an important reproductive health issue, affecting 2%-5% of couples [**El Hachem H et al., 2017]**.

There are many putative causes of first trimesteric RPL; however, only three are widely accepted: Parental chromosomal abnormalities, Antiphospholipid antibody syndrome (APAS), and a subset of uterine abnormalities. Other suspected causes are alloimmunity, endocrinopathies, environmental toxins, inherited thrombophilias and various infections [**Hyde KJ,2015].**

One of the pathophysiological pathways of interest is based on the observed association between recurrent miscarriage and thrombophilia.

Thrombophilia refers to any persistent identifiable hypercoagulable state either acquired or inherited, associated

with an increased risk of both venous and arterial thromboembolism. The most important form of acquired thrombophilia is APAS which has well established role in the incidence of RPL [**Abu-Heija A., 2014].**

Inherited thrombophilias include a group of mostly autosomal dominant, inherited gene mutations leading to hypercoagulable state, including antithrombin III (ATIII) deficiency, protein C and protein S deficiencies, and mutations in the genes encoding clotting factors as Prothrombin gene mutation (G20210A), Factor V leiden (FVL) and others. They are one of the most important predisposing factors for venous thromboembolism (VTE) in pregnancy and many studies suggested their role in many adverse pregnancy outcomes as RPL. The most common known inherited thrombophilia is FVL **[Ormesher L et al., 2016]**.

FVL is the most common known inherited thrombophilia.

It is an autosomal dominant genetic condition, which occurs as a result of a single point mutation in the factor V gene. This mutation results in a replacement of Arginine (R) 506 with Glutamine (Q) in one of the factor V cleavage sites for Activated Protein C (APC) (Arg 506) where APC acts [**Stephan Kadauke et al., 2014]**.

This substitution leads to a factor V species that cannot be degraded by APC. The rate of inactivation of FVL by APC is 10-20 fold lower compared to the rate of degradation of normal factor V, explaining the hypercoagulable state and the life-long increase risk of thrombosis [**Yusuf M et al., 2012]**.

Recently, the FVL mutation was identified as the most common genetic predisposition to thrombosis. Over the past 3 decades, many studies have suggested the strong association between FVL and many adverse pregnancy outcomes as preeclampsia, IUGR, placental abruption and RPL.

This thesis focuses on the prevalence of FVL mutation among recurrent pregnancy loss in Egyptian women using APC resistance test which is much cheaper than DNA-PCR test and see if the results will be in favor of using APC resistance test as a screening method.

Outline of the thesis

Chapter 1 Enlisted the most updated definition, etiology, investigation and treatment of reccurent pregnancy loss

Chapter 2 Descibe the thrombophilic history and discovery, and the upated information in that field

Chapter 3 Shows the relation between the RPL and thrombophilia

Chapter 4 is detailed about FVL mutation and using APC resistance test in its identification

Chapter 5 Methodology

Chapter 6 Represent results of this thesis

Chapter 7 Discussing the result of this thesis in comparsion with other thesises.

Chapter 8 Provides summary of this thesis and recommendation for future research

AIM OF THE WORK

Hypothesis:

In women with Recurrent pregnancy loss, FVL mutation may have a role in their loss.

By using the activated protein C resistance test, same ratios can be obtained as previous studies, that will be time and money saving.

Research Questions:

1- In women with RPL, does Factor V Leiden mutation have a role?

2- Will the results of this research provide a scientific rationale for screening for Factor V Leiden later on?