THROMBOPHILIC GENE MUTATIONS IN CASES WITH RECURRENT MISCARRIAGE: A STUDY IN THE EGYPTIAN POPULATION

THESIS

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Abstract

Thrombophilia by definition represents acquired and/or genetic conditions that predispose patients to both venous and arterial thromboembolic events. Thrombosis is the most common cause of death worldwide. On the arterial side, myocardial infarction and stroke result in significant morbidity and mortality. Venous thromboembolic events most commonly involve the deep veins of the lower extremity with potential complications of pulmonary emboli. Pregnancy is a hypercoagulable state, and thromboembolism is the leading cause of antepartum and postpartum maternal mortality. Recent attention has focused on certain inherited thrombophilic factors that may predispose to arterial and/or venous thromboses and their possible association with pregnancy complications, including early pregnancy loss. These include a group of mostly autosomal dominant, inherited gene mutations leading to a hypercoagulable state, such as factor V Leiden G1691A, factor II or prothrombin G20210A, and hyperhomocysteinemia associated with Methylenetetrahydrofolate reductase C677f mutation. With the identification of genetic risk factors, there has been synergistic amplification of thrombotic risk when one has an abnormal gene (e.g., factor V Leiden) plus environmental issues (e.g., pregnancy). The results of our study suggested that PTH & MTHFR mutations are associated with recurrent pregnancy loss but not FVL mutations.

KEYWORDS: Recurrent pregnancy loss, thrombophilias, coagulation abnormalities, miscarriage.

Dedication

To my mother…

Thank you for the caring things you do and the kind things you say, for always being there for me each and everyday. Thank you for encouraging me to live life to the full, for the confidence that makes me see all things possible. Thank you for making me feel valued no matter what I do and for the person I've become. Mum, I owe it all to you…

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CONTENTS

List of abbreviations

ACA	:	Anticardiolipin antibody
APA	:	Antiphospholipid antibody
APCR	:	Activated Protein C Resistance
APTT	:	Activated partial thromboplastin time
C-section:		Caesarian section
CBS	:	Cystathionine-Synthase
CRP	:	C- reactive protein
CMV	:	Cytomegalovirus
DVT	:	Deep vein thrombosis
DNA	:	Deoxy ribonucleic acid
EBV	:	Epstein Barr virus
EDTA	:	Ethylenediamine tetra-acetic acid
FVL	:	Factor V Leiden
HCG	:	Human chorionic gonadotropin
IUGR	:	Intrauterine growth restriction
LMW	:	Low molecular weight
MTHFR	:	Methylenetetrahydrofolate reductase
MS	:	Methionine Synthase
PAI-1	:	Plasminogen activator inhibitor- 1
PCR	:	Polymerase chain reaction
PE	:	Pulmonary embolism
PT	:	Prothrombin time
RM	:	Recurrent miscarriage
RPL	:	Recurrent pregnancy loss
VTE	:	Venous thromboembolism

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INTRODUCTION

Thrombophilia by definition represents acquired and /or inherited conditions that predispose to both venous and arterial thrombosis. Thrombosis is the most common cause of death worldwide. Pregnancy is a hypercoaguable state and thromboembolism is a leading cause of antepartum and postpartum mortality **(Kutteh et al, 2006)**.

Recurrent miscarriage is a heterogeneous condition **(Heilmann, 2005)**. The role of acquired thrombophilia has been accepted as the aetiology of recurrent miscarriages, the contribution of specific inherited thrombophilia genes to this disorder has remained controversial **(Coulam et al, 2006)**.

Over the past few decades, genetic defects in the proteins regulating blood coagulation have been established as possible risk factors predisposing to venous thromboembolism. These genetic defects are relatively frequent **(Yoshioka et al, 2006)**.

Factor V Leiden (FVL), Prothrombin (PT) and Methylenetetrahydrofolate reductase (MTHFR) gene mutations are the three most important causes of thrombophilia **(Behjati et al, 2006)**, and are associated with high risk of recurrent miscarriages **(Kutteh et al, 2006 & Lissalde- Lavigne et al, 2005)**.

Several studies were carried out worldwide to study the prevalence of these genetic mutations (single or multiple) in association with recurrent miscarriage.

AIM OF THE WORK

The aim of this case control comparative study was to investigate the prevalence of Factor V Leiden (FVL), Prothrombin (PT) and Methylenetetrahydrofolate reductase (MTHFR) gene mutations in women with recurrent miscarriages compared to the prevalence of the same mutations in healthy age- matched fertile parous women in Egypt.

A- HISTORICAL REVIEW

In **1856, Rudolf Virchow**, a German Pathologist, proposed a hypothesis to explain the pathogenesis of thrombosis. He suggested three primary causes of venous and arterial thrombosis: stasis, injury to the vessel and abnormalities in the circulating blood. Subsequently, numerous investigators contributed the concept of a haemostatic balance between fibrin formation and fibrin dissolution. Although many families with a predisposition to thrombosis were subsequently described, it wasn't until 1965 that a Norwegian Physician, O. Egberg reported a family with antithrombin deficiency **(Egeberg, 1965).**

Thrombophilia can be defined as hereditary or acquired conditions which predispose individuals to thromboembolic events. Following Egberg's publication, additional hereditary causes of thrombophilia were identified in the 1980's including protein C and S deficiencies *(Table 1)* **(Griffin et al, 1981), (Comp et al, 1984).**

1856	Virchow	Thrombosis hypothesis
1965	Egberg	Antithrombin deficiency
1981	Griffin	Protein S deficiency
1984	Comp	Protein C deficiency
1993	Dahlback	APC-R
1994	Bertina	Factor V Leiden mutation
1996	Poort	Prothrombin mutation
1998	Van der Put	MTHFR mutation

Table 1: History of thrombophilia

"Quoted from Warde Report archives 1998; 9 (3) **(Triplett, 1998)"**