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The Relationship between Factor V Leiden Mutation and Recurrent Abortion Among Palestinian Pregnant Women In The West Bank

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Thesis Approval

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Dedication

This work is dedicated to my great mother for being there for me whenever I need her, to my family; sisters and brothers for their love and motivation .To my husband's family for their love and support.

A special dedication to my dear husband Hasan for his love, support and endless patience. To my sons; Abdullah ,Mohammed Al Bashir, my sweet little baby Ayoub, and my lovely daughter Hibatallah for their understanding , love and patience .

To the memory of my father and my two beloved brothers Ali and Ayoub, may God mercy be upon them.

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Finally I would like to dedicate this work to the memory of Dr.Yaseen Jaber for the great efforts he did to the Palestinian society.

To these all I dedicate this work to represent my appreciation and grateful for all what they have done to me

U'la Daoud Khalil Abu Hilal

Declaration:

I Certify that this thesis submitted for the degree of Master is the result of my own research, except where otherwise acknowledged, and that this thesis (or part of the same) has not been submitted for a higher degree to any other university or institution.

Signed

U'la Daoud Khalil Abu Hilal

Date:

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Abstract

The Relationship between Factor V Leiden Mutation
and Recurrent Abortion Among Palestinian Pregnant Women
In The West Bank

The main objective of this study was to investigate the association between factor V Leiden mutation and Recurrent Abortion among Pregnant Women in the palestinian community in the West Bank. In order to focus the light on this major health problem and to figure out the best solutions to eliminate it from our palestinian community.

A questionnaire was developed and administered, 104 women were chosen, the case group included 54 women with no history of high blood pressure, and a history of recurrent pregnancy loss of unknown causes. The control group included 50 healthy women , who had 2 or more successful pregnancies, and none of them had a history of fetal loss or complicated pregnancy.

This research was carried out in the Medical Research Center at Al-Quds University, in Abu Dies (2007-2008), where Factor V Leiden mutation (FVL) was screened by PCR method using the ARMS test technique. Blood samples were collected from participants for DNA extraction in association with AL Hiba Center /Ramallah, Holy Family Hospital /Beithlehem and Palestinian Medical Relief society Clinic / Jericho.

The percentage of abortions among the participants in the case group was very high 68 % while all the pregnancies in the control group ended successfully. The distribution of factor V Leiden genotype among the case group was 27.8% (24.1% heterozygous alleles + 3.7 % homozygous alleles).While in the control group 22 % were heterozygous mutant ; which is statistically not significant (P value 0.324).
14% of the OCPs users among the case group were heterozygous for Factor V Leiden, while all the OCPs users among the control group were of normal genotype. The prevalence of IUFD among the participants was 11.1 % all normal for factor V genotype. There was no significance association between IUFD and Factor V Leiden mutation.

First trimester aborters were more prevalent (98.15%) than second trimester aborters (1.85%) ,the distribution of factor V Leiden mutation among the first trimester aborters (28.3 %) was higher than the second trimester aborters (0.0 %) mutant genotype.

The percentage of the primary aborters was 59.3 % whereas the secondary aborters 40.7 %. While the distribution of Factor V Leiden mutation among the secondary aborters (31.8% heterozygous alleles) was higher than those among the primary abortion (25 %= 6.30% homozygous alleles + 18.7 % heterozygous alleles).

These results indicate that statistically Factor V Leiden has no significant role in recurrent abortion. The high prevalence of Factor V Leiden among both the case and the control groups suggests that further large future studies on other DNA assays should be done for those women suffering from recurrent abortion including the genes encoding the natural anticoagulants antithrombin, protein C, and protein S, which results in a loss of anticoagulant function. Also the role of placental pathogenic mechanisms requires further evaluations.

More investigations and studies should be done taking into consideration the genotype of the women couples in order to predict fetus genotype.

Finally we recommend that we must focus our efforts on increasing the public awareness with regard to recurrent abortion and the importance of making the histopathology test for the abortuses in order to know the possible reason for abortion. The role of placental pathogenic mechanisms requires further evaluations. We should concentrate our efforts on the great role of the medical personnel among our populations in providing the necessary clinical care, including early diagnosis, medical consolations and therapy to improve the quality of lives of those people who suffered from it.

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Definitions :

ARMS: Amplification-refractory mutation system (ARMS)

Amino Acid: The basic building blocks for proteins in the body. Some Amino acids can be made by the body from other substances (nonessential) others are absorbed after ingestion of (essential) foods with protein (essential) .

Annexin V (human placental anticoagulant protein 1): Annexin V is an anionic phospholipid (PL)-binding protein, expressed by placental and vascular endothelium. It plays a thromboregulatory role at the vascular-blood interface by shielding anionic PL from forming a complex with coagulation proteins in the circulation.

Carrier: An individual who has a recessive, disease-causing gene mutation at a particular locus on one chromosome of a pair and a normal allele at that locus on the other chromosome; may also refer to an individual with a balanced chromosome rearrangement.

Chromosome 1 is the largest human non sex chromosome, which spans about 247 million nucleotide base pairs, and represents about 8% of the total DNA in human cells. It is currently believed to have 3,148 genes and was the last completed chromosome, sequenced two decades after the beginning of the Human Genome Project. The number of variations of nucleotides (SNP or single nucleotide polymorphism) is about 740,000.

Coagulation: The process by which blood clots.

Complete abortion:- the fetus, placenta, and other tissues are passed with bleeding.

Consanguinity: Genetic relatedness between individuals descended from at least one common ancestor.

Deep Venous Thrombosis (DVT): A clot that forms in the deep veins of the legs.

DNA: (Deoxy ribo Nucleic Acid) Substance from which the genetic code is made.

Eclampsia - a severe form of pregnancy-induced hypertension resulting in seizures.

Ectopic pregnancy: an abnormal pregnancy in which the fertilized egg implants outside of uterus. About 2 percent of all pregnancies develop outside the uterus.

Embryo - conceptus between time of fertilization to 10 weeks of gestation.

Enzymes: Biological catalysts that act to speed up chemical reactions.

Exon: Coding sequence of DNA present in mature messenger RNA.

Factor: The enzymes of the coagulation cascade are referred to as clotting factors.

Fetus: from 10 weeks of gestation till time of birth.

First trimester: within the first 12 gestational weeks.

Full term: refers to the end of 36 weeks (nine months) from the first day of the woman's last menstrual period — the end of gestation. If a woman gives birth earlier than this, it is classed premature birth.

Gene: The basic unit of heredity, consisting of a segment of DNA arranged in a linear manner along a chromosome. A gene codes for a specific proteins or part of functional protein leading to a particular characteristic or function.

Genetic code: Carried on chromosomes, made up of DNA. Humans have 46 chromosomes. Each chromosome contains many genes which encode various traits.

Gestational age - time from last menstrual period (LMP) up to present.

Gravidity (G) - number of times the woman has been pregnant

Heterozygote: An individual who has two different alleles at a particular locus, where one allele is usually normal and the other abnormal.

Homozygote: An individual who has two identical alleles at a particular locus, one on each chromosome of a pair.

Hemophilia: Term describing the condition in which patients have an abnormal tendency to bleed because they are unable to adequately form clots.

Homeostasis: The process by which blood flow is stopped. This is another word to describe the processes of clot formation.

Infarction: Lack of blood supply (and thus oxygen) to an organ or tissue resulting in tissue death.

Infant - time of birth to 1 year of age.

Intrauterine Fetal Death (IUFD): term for death of the fetus inside the uterus.

Intrauterine growth restriction (IUGR) - term for slowed growth of the fetus during pregnancy.

Ischemia: Lack of blood supply (and thus oxygen) to an organ or tissue .

locus: The physical site or location of a specific gene on a chromosome .

Leiden mutation : A glutamine-for-arginine (R506Q) substitution at factor V residue 506.

Miscarriage: an early pregnancy loss or spontaneous abortion.

Missed abortion - the embryo or fetus dies, but is not passed out of the uterus. Sometimes, dark brown spotting occurs, but there is no fetal heartbeat or growth.

Mutation: A genetic term. A mutation is a change in the genetic code from what is considered normal. Mutations can occur normally and not all mutations are harmful.

Myocardial Infarction (MI): This is another term for a heart attack. This occurs when a blood vessel (an artery) to the heart is blocked.

Parity (P) - number of pregnancies with a birth beyond 20 weeks GA or an infant weighing more than 500 g.

Placenta - an organ, shaped like a flat cake that only grows during pregnancy and provides a metabolic interchange between the fetus and mother. (The fetus takes in oxygen, food, and other substances and eliminates carbon dioxide and other wastes.)