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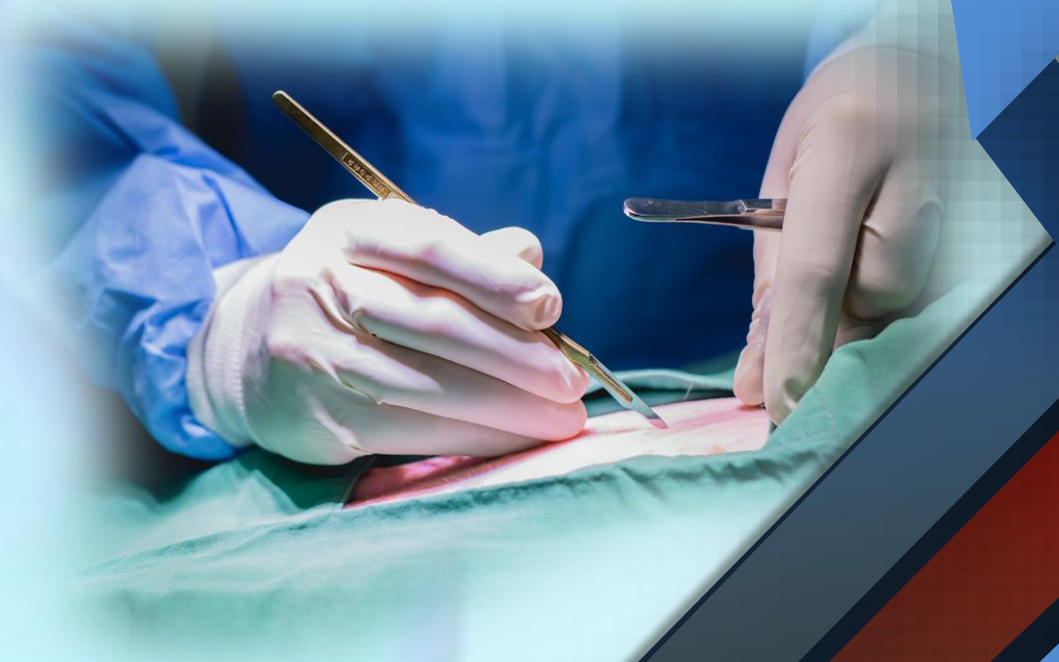

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Original article

Prevalence and Clinical Significance of Factor V Leiden Mutation in Egyptian Preeclamptic Women

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ABSTRACT

Background: Factor V [Leiden] mutation, also known as activated protein-C resistance, is the most common of the inherited thrombophilias.

Aim of the work: The present study aimed to ass the prevalence of factor V Leiden mutation in a group of Egyptian pregnant women and its relation to maternal and neonatal outcomes.

Patients and methods: The present prospective study included 130 preeclamptic women with a singleton pregnancy in the 3rd trimester. Blood samples were obtained for DNA analysis to assay factor V Leiden mutation. Transabdominal obstetric ultrasound examination was performed to confirm the fetal number, viability, presentation, estimated fetal weight, position & grade of the placenta, amount of liquor, biophysical profile, and gestational age. This was achieved through the measurements of the biparietal diameter, head circumference, abdominal circumference, and femur length. Flow velocity waveforms were obtained from each uterine artery.

Results: Factor V Leiden [FVL] mutation was identified in 20 patients [15.4 %]. Comparison between women with FVL and women without revealed a significantly higher frequency of intrauterine growth restriction [IUGR], intrauterine fetal death [IUFD], small for gestational age [SGA], preterm labor, and intensive care unit [ICU] admission among women with FVL mutation. They also have a significantly higher frequency of abnormal Doppler findings, abruptio placenta, and placental infarction.

Conclusion: The present study suggested that maternal and neonatal complications in PE patients may be related to FVL, abnormal uterine artery Doppler findings, and placental infarction.

Keywords: Factor V Leiden; Preeclampsia; Uterine artery Doppler; Mutation; Egyptian

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* Main subject and any subcategories have been classified according to the research topic.

INTRODUCTION

Thrombophilia is the term applied to a group of coagulation disorders favoring clot formation and thromboembolism. They are classified into inherited and acquired. Both types are linked to serious pregnancy complications affecting the mother and/or the baby[1]. Thrombophilia leads to a wide range of disorders, including pregnancy-induced hypertension, placental abruption, intrauterine fetal growth restriction, intrauterine fetal death, and recurrent fetal loss[2].

Inherited thrombophilia is a quite common disorder, affecting about 15% of the general population, and is detected in 20-50% of pregnant ladies with thromboembolism[3]. It can result from one or more abnormalities in the coagulation pathway, such as deficiencies of antithrombin, protein C, or protein S, and also mutations in prothrombin or factor V genes [3].

Factor V Leiden [FVL] mutation, also known as activated protein-C resistance, is the most common of the inherited thrombophilias. It is caused by a single gene mutation affecting one nucleotide and inherited as autosomal dominant. Therefore, there are two forms, the heterozygous and the homozygous types. Both types are more common in white races than Asians and Africans[4]. The heterozygous form is found in 3-8% of the general white population and about 1 % of Asians and Africans. The homozygous form is found in 1/2500-1/5000 of the white population and is rare in other races [3].

The homozygous form is considered a high-risk thrombophilia, and its relation to thrombo-embolism and other adverse pregnancy outcomes is well established. Even the heterozygous form carries have a 2-3 fold increase in the incidence of recurrent pregnancy loss [4].

AIM OF THE WORK

The present study aimed to assess the prevalence of FVL mutation in a group of Egyptian pregnant women with preeclampsia [PE] and its relation to maternal and neonatal outcomes.

PATIENTS AND METHODS

The present prospective study was conducted at Said Galal Hospital between December 2018 and September 2019. The local ethical committee approved the study protocol, and informed consent was obtained from the studied patients. The study included 130 preeclamptic women with a singleton pregnancy in the 3rd trimester. PE was diagnosed according to the criteria of the American College of Obstetrics and Gynecology[5]. Exclusion criteria were congenital fetal anomalies, diabetes, and impaired renal function, women with chronic hypertension or previous history of hypertension, or multiple pregnancies.

The study women were subjected to careful history taking, thorough clinical examination, standard laboratory investigations [CBC, renal functions, liver functions, coagulation profile, and urinalysis]. Patients were diagnosed with severe preeclampsia if they had proteinuria ≥5gr/24 hour, oliguria ≤500cc/day, platelet count ≤ 100000, elevated hepatic enzymes with persistent epigastric or right upper quadrant pain, blood pressure ≥160/110, pulmonary edema, severe headache, or visual disturbance. Eclampsia was diagnosed by the occurrence of seizure without any other etiology. Women with HELLP [[hemolysis, elevated liver enzyme levels, and low platelet levels]] syndrome or eclampsia were classified as severe preeclampsia.

Blood samples were obtained for DNA analysis to assay the presence of FVL mutation. Mutation was assessed using real-time polymerase chain reactions [rt-PCR] [Applied Biosystems, USA]. Transabdominal obstetric ultrasound examination was performed for confirmation of fetal number, viability, presentation, estimated fetal weight, position and grade of the placenta, amount of liquor, biophysical profile, and gestational age through measurements of the biparietal diameter, head circumference, abdominal circumference, and femur length. Flow velocity waveforms were obtained from each uterine artery. The recorded indices included: S/D ratio [peak systolic/ late diastolic velocity ratio], resistance index [RI] [peak systolic velocity–end-diastolic velocity/peak systolic velocity], pulsatility index [PI] [peak systolic velocity–end-diastolic velocity/ mean velocity]. Criteria for abnormal uterine artery Doppler-derived indices were increased uterine artery PI; >95th percentile, increased resistance index >95th percentile, increased S/D ratio >95th percentile

Abnormal perinatal outcomes considered were intrauterine death, five-minute Apgar score, ICU admission, and birth weight. In this study, we recorded IUGR as fetal birth weight <10, the percentile for sex, and gestational age based on twice sonography two weeks apart. The relationship of uterine artery Doppler in 3rd trimester and FVL mutation and severity of preeclampsia and maternal outcomes were also documented.

Data obtained from the present study were presented as number and percent and compared using the Chi-square test. P-value less than 0.05 was considered statistically significant. All statistical calculations were computed using SPSS 25 [IBM, USA].

RESULTS

In the present study, FVL mutation was identified in 20 patients [15.4 %]. Comparison between women with FVL and women without revealed significantly higher frequency of IUGR [45.0 % versus 5.45 %; p<0.001], IUFD [35.0 % versus 9.09 %; p=0.002], SGA [35 % versus 10.91; p=0.005], preterm labor [50 % versus 18.18 %; p=0.002] and ICU admission [30.0 % versus 3.64 %; p=0.001] among women with FVL mutation. They also have significantly higher frequency of abnormal Doppler findings, abruptio placenta and placental infarction **[Table 1]**.

Women with abnormal Doppler findings experienced significantly higher significantly higher frequency of IUGR [30.0 % versus 3.33 %; p<0.001], SGA [25.0 % versus 10.0 %; p=0.025], preterm labor [50.0 % versus 11.11 %; p<0.001] and neonatal ICU admission [20.0 % versus 2.22 %; p=0.001], abruptio placenta [15.0 % versus 4.44 %; p=0.037] and placental infarction [75.0 % versus 11.1 %; p<0.001] **[Table-2]**.

Patients with placental infarction suffered significantly higher rates of IUGR [30.0 % versus 3.3 %; p<0.001], IUFD [42.5 % versus 0 %], SGA [37.5 % versus 4.4 %; p<0.001], , neonatal ICU admission [15.0 % versus 4.4; p=0.037] and abruptio placenta [20.0 % versus 2.2 %; p=0.001] **[Table-3]**.

Table [1]: Relation between perinatal outcomes and FVL mutation

	All patients N=130	FVL +ve n=20	FVL -ve n=110	P value
IUGR	15 [11.5]	9 [45.0]	6 [5.45]	<0.001
IUFD	17 [13.1]	7 [35]	10 [9.09]	0.002
SGA	19 [14.6]	7 [35]	12 [10.91]	0.005
ICU	10 [7.7]	6 [30]	4 [3.64]	0.001
Preterm	30 [23.1]	10 [50]	20 [18.18]	0.002
Abruption placenta	10 [7.7]	4 [20]	6 [5.45]	0.025
Abnormal Doppler	40 [30.8]	14 [70]	26 [23.64]	<0.001
Placenta infarction	40 [30.8]	15 [75]	25 [22.73]	<0.001

Data presented as number and percent; IUGR: Intrauterine growth retardation; IUFD: Intrauterine fetal death; SGA: Small for gestational age; ICU: Intensive care unit.

Table [2]: Relation between perinatal outcomes and Doppler findings.

	Abnormal Doppler n=40	Normal Doppler n=90	P value
IUGR	12 [30.0]	3 [3.33]	<0.001
IUFD	4 [10.0]	13 [14.4]	0.49
SGA	10 [25.0]	9 [10.0]	0.025
ICU	8 [20.0]	2 [2.22]	0.001
Preterm	20 [50.0]	10 [11.11]	<0.001
Abruption placenta	6 [15.0]	4 [4.44]	0.037
Placenta infarction	30 [75.0]	10 [11.1]	<0.001

Data presented as number and percent; IUGR: Intrauterine growth retardation; IUFD: Intrauterine fetal death; SGA: Small for gestational age; ICU: Intensive care unit.

Table [3]: Relation between perinatal outcomes and placental infarction.

	Placental infarction + n=40	Placental infarction + n=90	P value
IUGR	12 [30.0]	3 [3.3]	<0.001
IUFD	17 [42.5]	-	<0.001
SGA	15 [37.5]	4 [4.4]	<0.001
ICU admission	6 [15.0]	4 [4.4]	0.037
Preterm	22 [55.0]	8 [8.9]	<0.001
Abruption placenta	8 [20.0]	2 [2.2]	0.001

Data presented as number and percent; IUGR: Intrauterine growth retardation; IUFD: Intrauterine fetal death; SGA: Small for gestational age; ICU: Intensive care unit.

DISCUSSION

In the present study, FVL gene mutation was identified in 20 patients [15.4 %] of the 130 Egyptian women with PE. The presence of this mutation was significantly associated with maternal pathologies, including placental infarction, abruptio placenta, and abnormal uterine artery Doppler findings. Moreover, FVL gene mutation was linked to preterm labor, SGA, IUGR, and IUFD in our study. These findings accord with the conclusions of **Ahmed et al.**[6] who reported FVL variation in 9.6% of Sudanese PE patients compared with 0.6% of the healthy controls. The relation between FVL gene mutation and PE was previously documented in other populations from Iran [7], Romania [8], Macedonia[9].

In addition, the meta-analysis conducted by **Wang et al.**[10] pooling data 37 studies with 5048 PE patients and 6796 controls concluded that FVL is associated with increased risk of PE and severe PE. These conclusions were confirmed by a subsequent meta-analysis conducted in 2019 [11].

In comparison, in the study of **Deveer et al.**[12], the authors reported no significant differences between PE patients and controls regarding the prevalence of FVL gene mutation. Likewise, in the study of **Bellussi et al.**[13] suggested that women with inherited thrombophilia carrying a thrombo-philic fetus are not at increased risk of adverse pregnancy outcomes. In addition, the study of **Rodger et al.**[14] on 7343 women, including 6.9% with FVL, showed that carriers of FVL are not at increased risk of pregnancy complications. Also, the Finnish study of **Nevalainen et al.**[15] concluded that FVL mutation was not related to pregnancy complications. The discrepancy between different studies may be attributed to ethnic differences. An evidence of the ethnic influence can be derived from a Slovakian research that included two ethnicities: the Slovak majority and the Roma minority. The study noted a significant association between FVL and pregnancy complications in the Slovak women while they failed to document such relation in their ROMA counterparts **Bozikova et al.** [16].

The present study also documented a significant association between abnormal uterine artery Doppler findings and pregnancy complications, including poor placentation and neonatal complications. These findings are supported by previous studies. In an Egyptian study, higher uterine artery resistance in the third trimester was associated with an increased rate of pregnancy and neonatal complications[17]. Other studies confirmed these conclusions[18]. Furthermore, our study noted a significant association between placental infarction and maternal and neonatal complications. The association between placental infarction and maternal and neonatal morbidity is well-documented. Pathological placentation was linked to IUGR[19] low birth weight[20,21], severe PE and neonatal complications[22,23].

In conclusion, the present study suggested that maternal and neonatal complications in PE patients may be related to FVL, abnormal uterine artery Doppler findings, and placental infarction.

Financial and Non-Financial Relationships and Activities of Interest

None

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