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Study of angiotensin converting enzyme gene polymorphism in preeclampsia

Thesis

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list of Abbreviations

Abbreviation	Full Name
ACE	Angiotensin Converting Enzyme
I/D	Insertion / Deletion
PCR	Polymerase Chain Reaction
BP	Blood pressure
SD	Standard Deviation
dNTPs	Deoxynucleoitde triphosphate
Taq polymerase	Thermus Aquaticucs polymerase enzyme
%	Percentage
n	Number
RAS	Renin Angiotensin System
Vs	Versus
χ^2	Chi square test
UV	Ultra Violet
PET	Preeclampsia toxiaemia
HTN	Hypertension
L-NAME	L-nitrorginine methyl ester
Nos	Nitric oxide synthase
AngII	Angiotensin II
GFR	Glomerular filtration rate
RPF	Renal plasma flow
MRI	Magnetic resonance imaging
Sflt 1	Soluble fms-like tyrosine kinase 1
VEGF	Vascular endothelial growth factor
PGF	Placental growth factor
ENG	Endoglin
OR	Odds Ratio
CI	Confidential interval
USA	United State of America

UK	United Kingdom
D.M	Diabetes mellitus
QTLS	Quantitative trait loci
LD	Linkage disequilibrium
$\sum$	Summation
χ	Value
O	Observed
E	Expected
EDTA	Ethylene diaminetetra acetic acid

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Introduction

Preeclampsia is a maternal disease of pregnancy associated with increased blood pressure and proteinuria after 20 weeks of gestation. It is a major cause of maternal and neonatal mortality and morbidity worldwide and has particularly high incidence in Latin American and Caribbean countries, in which hypertensive disorders during pregnancy account for 25.7% of maternal deaths ***(Khan et al., 2006).***

Preeclampsia is thought to be the result of the interplay between important genetic components and environmental influences; however, the factors and the mechanisms that lead to preeclampsia remain elusive ***(Sibai et al., 2005)***. As a result, there is a lack of effective preventive interventions ***(Villar et al., 2007)***.

With the exception of smoking, established risk factors for cardiovascular disease, including high blood pressure, diabetes, and obesity, are also risk factors for preeclampsia ***(Duckitt and Harrington, 2005)***.

In addition, women who suffer from preeclampsia have an increased risk of later cardiovascular disease, which clearly suggests a shared aetiology ***(Ray et al., 2006)***.

Inappropriate activation of the renin-angiotensin system may play a part in the development of many cardiovascular disorders, including preeclampsia ***(Shah, 2009)***.

A common insertion/ deletion polymorphism within the angiotensin converting enzyme gene *(ACE-I/D)* has been reliably associated with substantial differences in the plasma and tissue

angiogenesis-converting enzyme (ACE) activity in a codominant (additive) fashion not only in persons of European descent, but also in other populations such as Hispanics ***(Kammerer et al., 2004).***

The renin-angiotensin (RA) system has been implicated to play a role in the pathophysiology of preeclampsia (***Roberts and Coper, 2005***). Data in support of this include:-

1- Lower levels of all circulating components of the RA system

2- Activation of cellular and tissue R A components at the same time

3- Pregnancy-associated blunting of angiotensin II (All) pressor responsiveness which is owing to excessive upregulation of All receptors in a variety of tissues. However, why some women are prone to and others are protected from this disease is unknown. It has been suggested that genetic factors such as gene polymorphisms of the RA system may play an important role in the regulation of blood pressure (BP) in preeclampsia (***Roberts and Coper, 2005***).

Individuals carrying the *D* allele have higher ACE activity, which has been proposed as an intermediate phenotype of potential relevance for the development of high blood pressure and subclinical atheroma (i.e., higher intima-media thickness of the carotid artery ***(Tabtabaei et al., 2008).***

Despite the biological plausibility and the consistency of the effect of the *ACE-I/D* polymorphism on ACE activity, associations of the *ACE-I/D* polymorphism and coronary artery disease, coronary artery restenosis, stroke, and renal disease have been inconsistent. Moreover, systematic

reviews and meta-analyses have indicated the presence of (small-study bias in the published literature ***(Ng et al., 2005)***.

Several studies, also usually small in size, have reported that women carrying the D allele of the ACE I/D polymorphism have higher ACE activity and higher measures of uterine artery resistance, which is a marker for development of intrauterine growth retardation and preeclampsia ***(Shah, 2009).***

These observations lead to the proposal that the *ACE-I/D* polymorphism may be a good candidate in the search for a cause of preeclampsia. However, to date, studies evaluating the role *of ACE-I/D)* polymorphism in preeclampsia have been individually underpowered to detect plausible genetic effect sizes, being much smaller than more recent studies in cardiovascular disease.

AIM OF THE WORK

The aim of this study is to determine the distribution of **angiotensin converting enzyme** gene polymorphism in preeclampsia (DD., DI., II.) and association between the ACE gene polymorphism with the development of preeclampsia among Egyptian women from the Nile Delta Region of Egypt.

Clinical Impacts of Preeclampsia

Preeclampsia a pregnancy specific syndrome affecting 5% of all pregnancies causes substantial maternal and fetal morbidity and mortality. The pathophysiology of preeclampsia remains largely unknown it has been hypothesized that placental ischaemia is an early event, leading to placental production of soluble factor or factors that cause maternal endothelial dysfunction, resulting in the clinical findings of hypertension, proteinuria, and edema ***(Maynard et al., 2006).***

Preeclampsia is the leading cause of maternal and neonatal mortality and morbidity. It is a complex syndrome of undetermined etiologic origin, usually diagnosed during the second half of pregnancy, by clinical features new development of hypertension (Bp > 140/90 mm Hg) proteinuria (> 300 mg/24hours urine collection or > 1+ on stick test) and edema ***(Bilodeau and Hubel, 2007).***

Preeclampsia is considered a maternal as well as fetal syndrome it affects 2-10% of nulliparous, and is more prevalent when preexisting hypertension, renal, disease, or diabetes is present. The main clinical features of the disorder are maternal hypertension, proteinuria, and abnormal renal, hepatic, and central nervous system function.

The fetal syndrome includes growth restriction, intrauterine death, and premature delivery. Abnormalities in the development of placental circulation are believed to be important causal features of pathogenesis of preeclampsia and are present early in pregnancy ***(Augest, 2008)***

While maternal diastolic blood pressure is greater than 110 mm Hg there is increased risk of severe maternal complication including eclamptic seizures, intracerebral haemorrhage, and placental abruption, pulmonary edema due to capillary leak or myocardial dysfunction and acute renal

failure due to vasospasm also hepatic dysfunction and disseminated intravascular coagulopathy ***(Gibson, 2007).***

Severe pregnancy complication have been shown to be associated with deficient uteroplacental circulation and linked with intervillous and spiral vessel thrombosis more over it has been suggested that these complications could have their basis in a deficient trophoblastic invasion in the utrine spiral arteries at stage much earlier than the clinical manifestation becomes evident ***(Yonis, 2003).***

Visual disturbances occurs in up to 25% of patients with preeclampsia. However blindness remains a rare phenomenon ***(Geburtshilfe, 2007).***

Preeclampsia is a pregnancy induced multiorganic disease. The incidence is 5-7% of all pregnant women. In Egypt the triad of haemorrhage, toxaemia and infection in this descending order of importance "45%- 23%- 12%" respectively constitute together 80% of the direct causes of the maternal deaths ***(Kassas et al., 1995).***

The overall perinatal mortality in pregnancy is around 35 per 1000 total birth in cases of severe preeclampsia the incidence may rich 160 per 1000 total birth. The most important factor determining pregnancy outcome is gestational age at time of delivery. Survival being < 40% - when delivery indicated at 28 week's gestation. Mortality is increased two folds in the fetous is small for age ***(Robson, 2006).***

Genetic Aspects of preeclampsia

Current interest in the genetics of preeclampsia can be traced back to the signal study of Leon Chesley, who follow up the remote course of 267 women who survived eclampsia during the years 1931 through 1951 (***Chesley and Cosgrove, 1976)***.

In the course of his evaluations, he noted the increased occurrence of preeclampsia-eclampsia within families (***Chesley, 1980)***.

With the advent of molecular genetics, this field is now advancing rapidly. Preeclampsia was noted to be familial disease . Some conditions "run in families" because of similar diet, habits, or environment, but published reports showed that preeclampsia is a genetic disease. Analyses of affected families suggest that one or more relatively common alleles act as "major genes" conferring susceptibility to preeclampsia. It is unlikely that any particular genotype is necessary for the disease to occur; rather, these "preeclampsia genes" act as susceptibility loci that lower a woman's threshold for developing preeclampsia. While the ultimate causes of preeclampsia remain unknown, it is perhaps obvious that genes should play a role ***(Kenneth and Marshal, 2005)***.

Mutant Genes

Mutant genes in any of dozens of pathways could affect a woman's risk of developing preeclampsia. Indeed, preeclampsia is best understood as a multifactorial, polygentic condition. Many of the aberrant genes will be "private" mutations, affecting one woman or only a handful of women. However, any mutation identified that affects woman's risk may give us new insights into the pathophysiologic cascade or lead to a treatment that is applicable to all women***(Kenneth and Marshal, 2005)***.

A more exciting outcome from genetic studies of preeclampsia