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INFLUENCE OF ANGIOTENSIN CONVERTING ENZYME GENE POLYMORPHISM ON PREGNANCY OUTCOME IN WOMEN WITH HISTORY OF PRE-ECLAMPSIA

By

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ABSTRACT

Background: Women who have had pre-eclampsia (PE) are more prone to recurrent negative pregnancy outcomes and altered utero-placental and umbilical flows in their future pregnancy. In addition, to an increased risk of later cardiovascular diseases, which clearly suggest a shared aetiology. Yet, the mechanisms involved have not been identified. Although, the causes of PE are not well understood, there is a possibility that PE has, at least in part, a genetic basis. The "physiological remodelling" of spiral arteries throughout pregnancy is mediated by the rennin-angiotensin system (RAS). The ACE I/D polymorphism of the ACE gene accounted for 47% of total phenotypic variance of the serum Angiotensin converting enzyme (ACE), contributing much to the variability of the ACE level. Previous studies failed to reproduce a persistent link of ACE I/D genotype and PE in nulliparous women. **Objective**: In this prospective study, we analysed the association of the ACE genotype and the recurrence of PE and/or fetal growth restriction (FGR) in subsequent pregnancy in women at high risk for a previous PE as primipara, without other known risk conditions.

Patients and Methods: Sixty women with history of PE as primipara, with no known risk factors apart from nulliparity, were recruited in their second pregnancy. Their ACE genotyping were detected. Uterine arteries resistance indices (RI) and umbilical artery pulsatility index (PI), were recorded at 16^{th}, 20^{th}, 24^{th} weeks of gestation and clinical pregnancy outcome was analyzed, as well.

Results: ACE I/D genotype distribution among our cases of 90 Egyptian pregnant women were compatible to other races in literature. DD genotype was detected in 41.1% of our cases, 34.4% were ID genotype and 24.4% were II genotype. Significant difference in ACE I/D genotype and D-allele frequency were observed in cases with recurrent PE and/or FGR. Mid trimester uterine arteries resistance indices (RI) at 16^{th}, 20^{th}, 24^{th} weeks of gestation, and umbilical artery pulsatility index (PI) at 20^{th}, 24^{th} weeks were significantly higher in DD genotype group compared to ID and II genotype respectively. In addition, DD genotype group had significantly lower gestational age at time of delivery, lower birth weight and placental weight.

Conclusion: ACE DD genotype and D- allele frequency adversely affected pregnancy outcome and utero-placental and umbilical flow velocimetry in women with history of preeclampsia as nulliparous without known risk factors apart from nulliparity.

INTRODUCTION

Women who have had pre-eclampsia (PE) are more prone to recurrent negative pregnancy outcomes and alteredutero-placental and umbilical flows in their future pregnancy ***(Zeisler et al., 2016)***. Doppler studies of utero-placental ***(Myatt***

et al., 2012 and Velauthar et al., 2014) and fetal umbilical ***(Alfirevic et al., 2015)*** circulation have shown that high impedance to flow is associated with subsequent PE, fetal growth restriction (FGR) and related complications.

Generally, the risk for an adverse pregnancy outcome with history of PE is markedly higher 20-40% compared to outcome with history of normal pregnancy ***(Kessous et al., 2015 and Van Oosywaard et al., 2015)***.

Although, the causes of PE are not well understood, there is a possibility that PE has, at least in part, a genetic basis. The condition is more likely among women whose relatives also have it ***(Harmon et al., 2015)***. However, no definite genetic cause has yet been confirmed ***(Auger et al., 2015)***.

A common variant in one particular gene, Angiotensin Converting Enzyme (ACE) gene has been linked with PE in a number of different studies. The protein encoded by ACE gene is involved in controlling blood pressure and the balance of fluid and salts in the blood ***(Broekhuijsen et al., 2015)***.

Brunelli and Prefumo (2015) suggested that the physiological remodelling of spiral arteries throughout pregnancy is mediated by the renin-angiotension system (RAS). Throughout normal pregnancy, the RAS is stimulated. ***(Poon and Nicolaides, 2014)***. Pregnancy also induces refractoriness to angiotensin II pressor effects ***(Sharp and Alfirevic, 2014)***.

Inappropriate activation of the renin-angiotensin system may play a part in the development of many cardiovascular disorders (***Halscott et al., 2014)***. A common insertion/deletion polymorphism within the angiotensin converting enzyme gene (ACE/ID) has been associated with substantial differences in the plasma and tissue ACE activity in a co-dominant fashion in persons of European descent ***(Martin et al., 2014)***, Hispanics ***(Kammaerer et al., 2004)*** and Japanese ***(Kobashi et al., 2005 and Hutcheon et al., 2011)***.

The ACE/ID polymorphism in intron 16 of the ACE gene accounted for 47% of total phenotypic variance of the serum ACE, contributing much to the variability of the ACE level ***(Magee et al., 2014)***. A marked difference in serum ACE levels was observed between subjects in each of the 3 genotype classes: the DD is associated with higher tissue and plasma ACE levels, ID is associated with intermediate levels. Moreover, I allele has been assumed to have a sequence similar to a silencer sequence ***(Abalos et al., 2013 and Bigelow et al., 2014)***.

Nevertheless, little information is available about the effect of ACE I/D polymorphism on maternal-fetalhaemo-dynamics and adverse obstetric outcome in women with history of PE as nulliparous ***(Lisonkova et al., 2014)***.

In this study, we analysed the association of the ACE genotype and the recurrence of PE and/or FGR in subsequent pregnancy in women at high risk for a previous PE as nullipara, without other known risk conditions.

SUBJECTS AND METHODS

Women who attended the Obstetrics Clinic at Al-Zahraa University Hospital in their second pregnancy with a past history

of PE because of nulliparity without other known risk factors were recruited. A total of 60 patients were enrolled in the present study group over a period of one year from April 2015 to April 2016. The control group included 30 pregnant women with uneventful pregnancy who delivered at term of an appropriately growth fetus with no evidence of medical complications in their ex-or current pregnancy. Consent was given from all patients.

Cases with other known risk factors for cardiovascular disease including kidney disease, diabetes mellitus, thrombophilic disease, autoimmune disease, smoking and obesity were excluded from the study. Cases of multiple pregnancies were also excluded.

PE was defined as the presence of blood pressure exceeding 140/90 mmHg in a previously normotensive women associated with proteinuria in excess of 300 mg/L in a 24 hour urine collection after the 20^{th} week of pregnancy.

FGR was defined as estimated fetal weight less than 10^{th} percentile for gestational age (GA) in ultrasonographic examination and birth weight less than 10^{th} percentile for GA. Gestational age was calculated according to the date of the last menstrual period and confirmed by first -trimester ultrasonography.

The clinical pregnancy outcome variables analysed were:

1- PE with or without FGR
2- FGR without PE
3- GA at delivery
4- Birth weight
5- Placental weight

Doppler ultrasound examination: Doppler studies were performed in Al-Zahraa University Hospital. The studies were performed at 16^{th}, 20^{th}, 24^{th} weeks of pregnancy.Trans-abdominal color flow/pulsed Doppler examination of both uterine arteries and the umbilical artery were done by means of with 3.5 MHz transducer, color flow mapping, and 50-Hz high pass filter. All measurements were performed with the mother in a semirecumbent position. Color flow imaging was used to visualize the ascending branch of the uterine artery. Pulsed Doppler velocimetry was performed with a sample volume of 5 mm. A minimum of three separate recordings of resistance index (RI) was taken for each examination. Umbilical artery waveform was measured from free-floating loop of cord during fetal quiescence. The pulsatility index (PI) was measured and the average of three measurements was used.

DNA extraction and genotyping: Was done according to ***Rigat et al. (1990)***.Determination of ACE genotypes by PCR amplification on ethidium bromide-stained agarose gel is seen in Fig. 2.

Measurement of plasma ACE activities: Plasma ACE activities were measured by the method described by ***Ryan*** **(1984)** with slight modification, using (^{3}H) – hippuryl-glycyl-glycine (specitic activity, 20.5 GBq/mmol; Amersham, Arlington Heights, IL) as substrate.

Statistical Analysis: Statistical analysis was performed with *SPSS Version 7.5*. The ACE polymorphism allele frequency

was obtained by using a direct count. The Hardy-Weinberg equilibrium for genotype distribution and allele frequency was estimated by the χ^2test. Descriptive statistics was used to obtain median and mean and standard deviation. One-factor ANOVA was used to compare the means of continuous variables that followed a normal distribution. When significant differences were found by using variance analysis, pairwise comparisons were performed with the use of the least significant differences test. For data that did not follow a normal distribution and demonstrated different variances, nonparametric Kruskal-Wallis1-way AVOVA was performed.

Chi Square test was used to test the relationships between categorical variables. We used simple regression analysis to test for an association between the ACE I/D polymorphism and a risk of adverse outcome recurrence. Statistical significance was at a level of $P<0.05$.

RESULTS

The distribution of ACE genotype and allele frequency among the study group with outcome history of PE were compatible with the control group (with hardy-Weinberg equilibrium). Thirty-seven(41.1%) DD homozygous, 31 (34.4%) ID heterozygous, and 22 (24.4%)II homozygous women were found. 45 of 60 patients (75%) carried the ACE D allele, D allele frequency was 0.56 (Table 1).

Table (1): ACE I/D Polymorphism Genotype distribution and allele frequency in the study & control Group.

ACE I/D / Genotype	Study group (n=60)	Control group (n=30)	Total (n=90)	P value*
DD	24 (40%)	13 (40.4%)	37 (41.1%)	P >0.05
ID	21 (35%)	10 (33.3%)	31 (34.4%)	P >0.05
II	15 (25%)	7 (26.3%)	22 (24.4%)	P >0.05
ACE D-allele frequency	%56	%59	%55	P >0.05

*P-value was calculated using Chi Square test.

There were no statistically significant difference among the control group, study group and overall group population regarding ACE I/D genotype distribution and ACE D allele frequency.

Table (2): Plasma angiotensin-converting enzyme activities according to ACE I/D polymorphism.

Gestional age (wk)	**DD (n=37)**	**ID (n=31)**	II (n=22)	**P-value***
18	**88±21**	**64±14**	**40±17**	<0.001*
25	**89±19**	**63±13**	**40±15**	<0.001*
36	**90±17**	**67±17**	**43±16**	<0.001*
38	87±24	63±19	42±18	<0.001*

*P-value was calculated using ANOVA test.

The difference between all three groups was statistically significant which is displayed in (Figure 1).

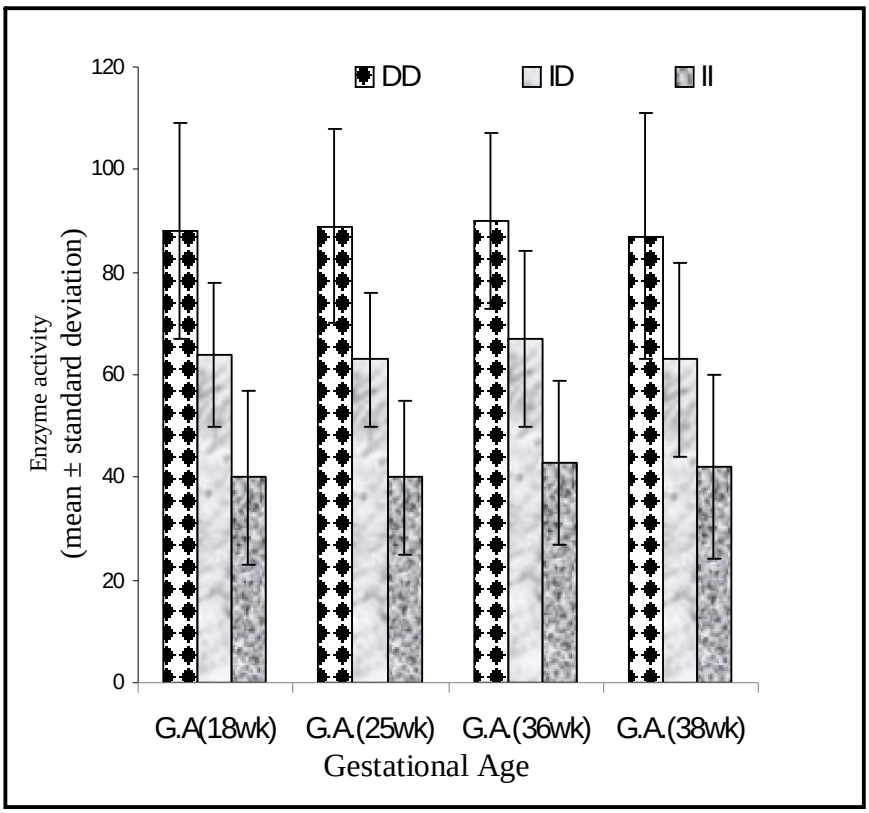

Figure (1): Angiotensin-converting enzyme activities in DD, ID and II genotype in correlation with gestational age, data were presented as mean ± standard deviation.

Clinical Pregnancy Outcome: Twenty six (43%) women of the study group developed recurrent PE and/or FGR. their D allele frequency was significantly higher (0.76); P < 0.0001.A significant difference in ACE genotype distribution and allele frequency was identified between the two subgroups of complicated and non-complicated current pregnancy. Five cases of severe early-onset PE and FGR were identified in the study group with current obstetric complications. Detailed past obstetric history revealed that all of them had an early-onset PE in their previous pregnancy. Their D allele frequency was significantly higher (0.87); P < 0.01. D allele was detected in all of the 5 cases. 4 cases were DD genotype (83%). All of these five cases undergone termination of pregnancy prior to 34th weeks of gestation (Table 3).

Table (3): ACE Polymorphism Genotype Distribution and Allele Frequency according to current obstetric complications.

ACE I/D Polymorphism / **ACE I/D Genotype**	**Women with PE and/or FGR (n=26)**	**Women Without PE or FGR (n=34)**
DD	17 (65.38%)	7 (20.58%)
ID	8 (30.77%)	17 (50.00%)
II	1 (3.85%)	10 (29.41%)
χ^2 =13.85; *P*< 0.001		
ACE D		
Allele frequency	0.76	0.44
χ^2 =21.3; *P* < 0.0001		
PE indicates preeclampsia; FGR, fetal growth restriction.		

The percentage of cases with PE and/or FGR was significantly higher in DD genotype (65.38%) than in either ID genotype (30.77%) or II genotype (3.85%). D-allele frequency was significantly higher in the subgroup with obstetric complications.

There was no significant difference in distribution of PE between the DD genotype groups versus ID versus II in the study group. PE complicates 25% in the DD group versus 14.2% and 6.6% for the ID and II groups. 45.8% of cases who developed FGR are DD genotype versus 23.8% for ID group. This makes significant difference between the DD versus the ID and II groups (P= 0.002).

A significantly lower gestational age at delivery was observed in women with the DD genotype. Birth weight was significantly lower in the DD group than in the ID group, which in turn showed a

lower birth weight compared with the II group.

7 of 11 women with the DD genotype who had FGR required delivery before the 34th week of pregnancy. In addition, the 5 women with early-onset severe PE and FGR in their previous and current-pregnancy carried the D allele. In this special subgroup, the D allele prevalence was 0.92.

A significant decline in placental weight among women carrying the D-allele in comparison to women with II genotype in the study group was observed, as well (Table 4).

Table (4): Clinical Pregnancy Outcome in Relation to the ACE I/D Polymorphism in the study group.

Groups / Clinical Pregnancy Outcome	DD (n=24)	ID (n=21)	II (n=15)	P value
PE, n (%)*	6 (25%)	3(14.2%)	1(6.6%)	*P*=0.3
FGR, n (%)*	11 (45.8%)	5(23.8%)	0	*P*=0.0066
Gestational age at delivery, wk: median (range)**	35 (29-39)	38(36-40)	38(37-41)	*P*<0.02
Birth weight, g: median (range)**	2530 (1400-3150)	2870 (2250-3500)	3349 (2950-3950)	*P*<0.001
Placental wt (g)**	253	386	430	*P*<0.05

*P-value was calculated using Chi Square test.

**P-value was calculated using Kruskal–Wallis test (One way ANOVA).

Maternal Utero-placental and Fetal Umbilical Circulation: Doppler is the study of choice to comment on uterine artery resistive index (RI) and umbilical artery pulsatility index (PI). Fig.3 shows the normal uterine artery RI, while fig.4 show abnormal uterine artery RI. Fig.5 shows normal umbilical artery PI, while Fig. 6,7 and 8 show abnormal umbilical artery PI.

A D-allele dose dependent effect significantly alters maternal utero-placental and fetal umbilical haemo-dynamic indices. The uterine artery RI showed a normal pattern of progressive decrease from the 16thto the 24th week of pregnancy only among ACE II genotype subgroup (table 5). At the 16thweek, the mean of the resistance indices for the uterine arteries of the ACE DD genotype was significantly higher with respect to the other 2 genotypes. Again at the 20th and 24th weeks, the ACE DD genotype had significantly higher uterine artery RI than that in the ID, which were, in turn, higher than those in the II group.

The umbilical artery PI although non-significant at 16^{th} weeks between the different genotype subgroups, was significantly higher in DD genotype versus ID genotype versus II genotype at 20^{th} and 24^{th} weeks of gestation (Table 5).

Table (5): Maternal Utero-placental and Fetal Umbilical Circulation Indices in relation to the ACE I/D Polymorphism in the study group.

Groups / Maternal-Fetal Circulation Indices	DD (n=24)	ID (n=21)	II (n=23)	ANOVA
Mean uterine artery (RI) (mean ± SD)				
16 wks	0.63±0.155	0.61±0.3	0.56±0.19	P > 0.05
20 wks	0.66±0.22	0.59±0.27	0.50±0.24	P > 0.05
24 wks	0.69±0.2	0.58±0.58	0.44±0.31	P > 0.05
ANOVA	P> 0.05	P> 0.05	P > 0.05	
Umbilical artery (PI) (mean ± SD)				
16 wks	1.69±0.21	1.66±0.22	1.68±0.25	P > 0.05
20 wks	1.67±0.3	1.58±0.19	1.50±0.21	P > 0.05
24 wks	1.53±0.18	1.30±0.24	1.25±0.19	P < 0.05
ANOVA	P < 0.0001	P < 0.0001	P < 0.0001	

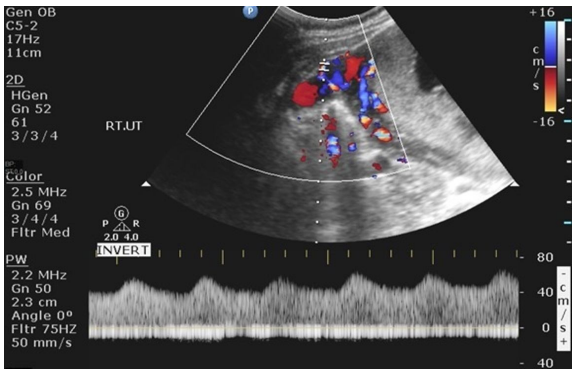

Figure (2): Normal color Doppler wave form of the uterine artery.

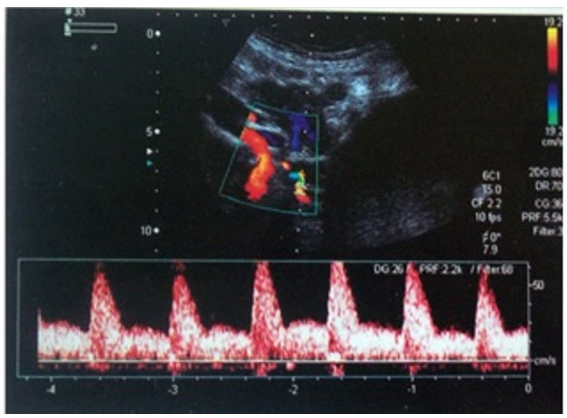

Figure (3): Abnormal color Doppler wave form of the uterine artery demonstrating low diastolic flow and an early diastolic notch.

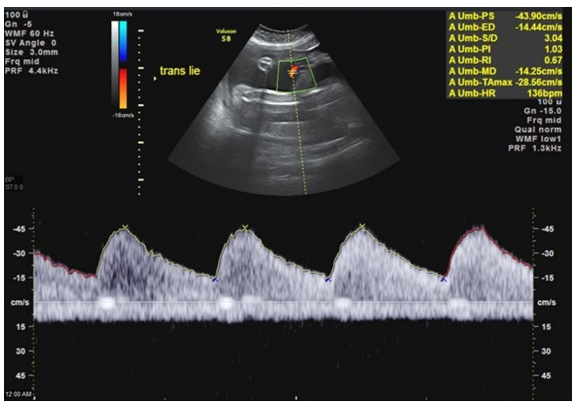

Figure (4): Normal umbilical artery flow. The pulsatility index = 1.0.

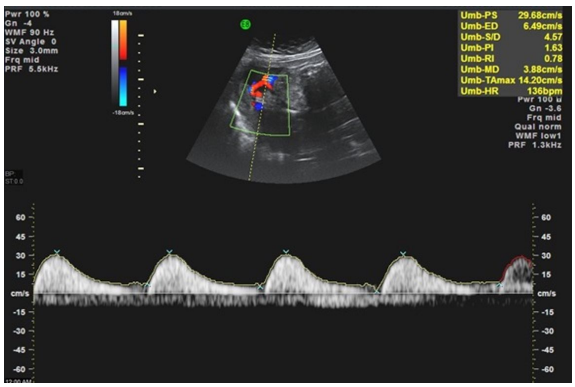

Figure (5): Abnormal Umbilical artery waves form at 24 weeks gestation. The pulsatility index (PI) of 1.63 above the normal value for this gestation.

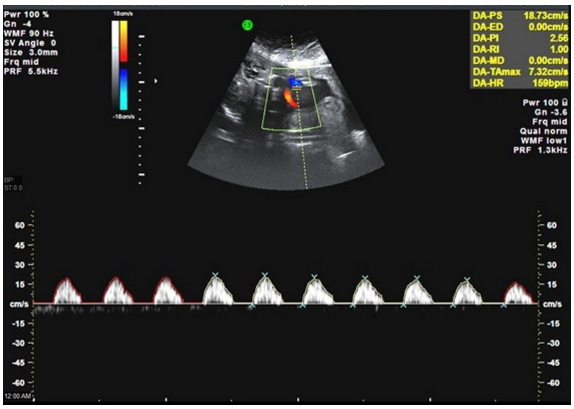

Figure (6): Abnormal color Doppler umbilical artery waveform demonstrating absent end-diastolic frequencies.

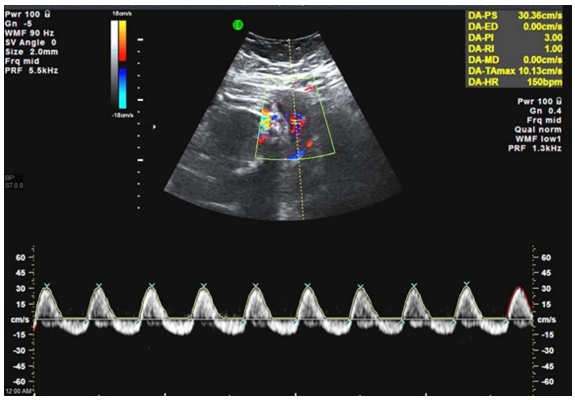

Figure (7): Abnormal color Doppler umbilical artery waveform demonstrating reversed end-diastolic frequencies.

DISCUSSION

In this study, we tested the hypothesis that genetic variability of the renin-angiotensin system may modify the pregnancy outcome in women with history of PE as primipara.

When we considered ACE genotype distribution in our overall group study population of Egyptian women; 41.1 % DD genotype, 34.4% and 24.4% for ID, II respectively, no significant difference was found in comparison to other races; white population ***(Fatini et al., 2000)***, Hispanics or Japanese ***(Kammaerer et al., 2004, Kobashi et al., 2005 and Hutcheon et al., 2011).***

Lack of significant difference in ACE genotype distribution between control group and the study group of pregnant women with past history of PE in their first pregnancy is in line with previous studies which suggested that ACE I/D genotype is not associated with risk of PE in nulliparous pregnancy ***(Serrano et al., 2006)***. However, ***Goetzinger and Odibo (2014)*** reported that in a subgroup positive for family history of hypertension, the frequency of DD genotype tended to be higher in patients with PE in their first pregnancy (25%) than in controls (8%) (P=0.061), which might indicated that carrying DD genotype may have some influence on the pathogenesis of PE, perhaps through effects on placental hypoxia. A Chinese study ***(Li et al., 2007)*** found no association of the ACE I/D polymorphism and angiotensin II type 1 receptor (AT1R) with PE. Nevertheless, ACE I/D polymorphism were associated with severe proteinuria and renal dysfunction seen in PE. They concluded that preeclamptic patients carried the D allele may be susceptible to renal dysfunction.

ACE genotype in our cases who developed recurrent obstetric complications in their second pregnancy following previous PE as primipara included; insertion homozygote II, deletion homozygote DD and insertion/deletion heterozygote ID. The gene frequency was 65.38% for DD, 30.77% for ID and 3.85% for II respectively. The frequency of deletion allotype of cases with recurrent PE and/or FGR group was significantly

higher than both control group and group of normotensive cases in the current pregnancy with previous PE. Interestingly, neither ID genotype distribution nor the ACE level differed significantly between control group and normotensive pregnant women with outcome history of PE. This indicates that nulliparity per se is a risk factor for PE (***Lisonkova et al., 2014***).

Additionally in our work, the DD genotype of ACE is associated with significant increase in the plasma ACE activities. This might appear at variance with the studies showing decreased circulating angiotensin II levels ***(Nevis et al., 2011)***. However, in decidual spiral arteries obtained from PE cases, increased angiotensin (AGT) expression has been shown, ***(Eastabrook et al., 2011)***along with up-regulated expression of AT1 receptor subtype mRNA and increased pressor responsiveness to angiotensin II ***(Crovetto et al., 2013)***. Therefore, an increased ACE activity associated with high local AGT may lead to elevated local angiotensin II level ***(Payne et al., 2011)***. In addition to the well-known vasomotor functions of the RAS components, other effects have to be considered in relation to PE. The renin-angiotensin system is involved in key events of the inflammatory process by increasing vascular permeability and contributing to the recruitment of inflammatory cells. Regarding hemostasis, several reactions are modulated by the renin-angiotensin system, and evidence exists for an association between the ACE DD genotype and increased risk of thrombotic events ***(Bouvier et al., 2014)***. Moreover, ACE by bradykinin degradation reduces nitric oxide levels, therefore contributing to endothelial dysfunction ***(Kleinrouweler et al., 2012)***.

All the components of the vascular RAS are expressed in andaround the remodeling spiral arteries. Moreover, local RAS generates angiotensin II, http://hyper.ahajournals.org/cgi/content/full/41/4/932 - R22-125692 so possibly causing medial hyperplasia and/or angiogenesis ***(Abdul Sultan et al., 2013).*** RAS components are increased in normalpregnancy***(Morgan et al., 1998)*** ; however, the mechanisms by which pregnancy induces refractoriness to the pressor effects of angiotesion II in women are poorly understood, but ,in animal models, a prevalent role has been attributed tonitric oxide in the modulation of maternal vascular reactivity ***(Hokas and Sibai, 1992),*** as well as to the interaction between angiotensin IItype 1 (AT1) and AT2 receptor subtypes ***(St-Louis et al., 2011)***.

Recent data have shown that up-regulation of AT1 receptor subtype in the syncytiotrophoblast could play a pathophysiological role in patients with altered uteroplacentalhaemodynamics. A significant association between the T235 molecular variant of the angiotension (AGT) gene, previously associated with essential hypertension and abnormal physiological change of uterine spiral arteries in first trimester deciduas' has been found in patients with PE ***(Vigil et al., 2013)***.

The maternal syndrome of PE and fetal syndrome of FGR during the latter half of pregnancy are believed to result from impaired placentation early in pregnancy. Impaired trophoblastic invasion of the maternal spiral arteries is shown to be

associated with increased impedance to flow in the waveforms obtained by Doppler ultrasound examination of the uterine arteries ***(Velauthar et al., 2014)***. Meanwhile, umbilical artery blood velocity waveform reflects function of the placental tertiary villous tree. Reduced villous development correlates with abnormal umbilical artery Doppler velocimetry, being severe in cases of absent or reversed end-diastolic flow velocity ***(Alfirevic et al., 2015)***. Uterine Doppler velocimetry reflects the maternal site and umbilical artery Doppler velocimetry reflects the placental site of feto-maternal circulation ***(Whitworth et al., 2015)***.

Early mid-trimester higher measures of utero-placental and fetal umbilical blood flow resistance, which is a marker for subsequent development of FGR, PE and related complications, have been observed in cases of our study group in association with D allele prevalence. At the 16th week, the mean resistance indices of uterine arteries in women with the ACE DD genotype were significantly higher with respect to the other 2 genotypes. In addition, a D allele dose-dependent effect was found at the 20th and 24th weeks. The pulsatility index for umbilical artery at the 20th and 24th weeks was significantly higher in ACE DD genotype than in ID and II women (***Alfirevic et al., 2015***).

In a report by ***De Vries et al. (2012),*** low-molecular-weight heparin lowers the recurrence rate of PE, restores the physiological vascular changes in angiotensin-converting enzyme DD Women and reduces the resistance of utero-placental flow, therefore prolonging the duration of the gestational age at delivery and the increase of birth weight, paving the way to a new approach for preventing negative outcomes in ACE DD women at risk because of previous PE as primipara. They considered the DD genotype a new marker, which may identify a thrombophilic condition.

This study supports the view that ACE/DD genotype in pregnant cases with previous PE pregnancy with unknown cause apart from nulliparity negatively affects the subsequent pregnancy outcome with increased chance of recurrent hypertensive complications and increased cases of associated FGR. High impedance to flow in uterine and umbilical arteries are even detected well in advance to these complications in pregnant women with ACE/DD genotype. These findings are in concert with previous report ***(Von Dadelszen et al., 2011)*** thatACE/ID polymorphism affects utero-placental and umbilical flow, potentially initiating the cascade of events that leads to PE.

These findings if confirmed in large scaled studies might be suggested for counselling women with PE in their first pregnancy with no known risk factors other than nulliparity as regards to the risk for recurrent complications in subsequent pregnancies. The group at risk because of ACE/DD genotype could be selected in subsequent pregnancy for more intense antenatal care, utero-placental flow studies early in pregnancy, accurate dating and assessment of fetal growth.

Meanwhile, this work suggested that ACE/ID polymorphism is not a risk factor for PE in the first pregnancy. Perhaps, the association between DD genotype and a negative pregnancy outcome comes true

only when nulliparity no longer exists. Epidemiological and clinical studies well document that nulliparity per se is a risk factor for PE, being induced by mechanisms that are not present in successive pregnancies.

Finally, the observation that patients with PE are at increased risk for chronic hypertension later in life indicates that a pre-eclamptic status during the first pregnancy may induce persistent and latent functional alterations that strengthen the D-allele dependent angiotensin II effect during the second pregnancy. Previous studies have documented that ACE DD genotype is associated with increased plasma ACE concentrations, cardiac disease such as myocardial infarction and left ventricular hypertrophy, and progression of diabetic nephropathy ***(Ray et al., 2005).***

In conclusion, although ACE/ID polymorphism is not associated with PE in nulliparous patients, it might have a role as a new susceptibility factor to a negative pregnancy outcome in future pregnancies and even possible cardiovascular complications later in life.

Investigating the etiology of recurrent preeclampsia and/or FGR as main causes of maternal and neonatal mortality and morbidity worldwide, should be a health research priority. A genetic approach may indeed be useful, but large collaborative studies will also be needed.

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تأثير تنوع جين إنزيم تحويل الأنجيوتينسين فى نتاج حمل السيدات ذوات تاريخ سابق لتسمم الحمل

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خلفية البحث: إن السيدات اللاتى تعرضن لحدوث مرض تسمم الحمل فى حملهن الأول أكثر تعرضا للمضاعفات المرضية فى الحمل المقبل، وكذا التغير السلبى فى معدل تدفق الدم فى الحبل الصرى للجنين، كما أنهن أكثر تعرضا لمخاطر أمراض القلب والدورة الدموية مع تقدم العمر. وبالرغم من ذلك فإن كيفية حدوث أى من هذه المضاعفات لم يتم التوصل إليه بعد. إلا أنه من المحتمل أن يكون هناك مرجعاً وراثياً لمرض تسمم الحمل بالرغم من أن أسبابه لم يتم التعرف عليها بصورة واضحة. والتحور الفسيولوجى لشرايين الرحم فى فترة الحمل يتم عن طريق نظام الرينين- أنجيوتنسن، ولذا فإن التغير فى نوع الجين المسئول عن إنزيم تحويل الأنجيوتنسين يساهم لدرجة كبيرة فى مستوى هذا الإنزيم فى الدم. وقد فشلت الدراسات فى تحديد علاقة ثابتة بين التنوع فى الجين المسئول عن هذا الإنزيم وحدوث تسمم الحمل فى حالات الحمل الأول للسيدات.

الهدف من البحث: تحديد العلاقة بين نوع الجين المسئول عن انزيم تحويل الأنجيوتنسين وتكرار حدوث تسمم الحمل أو صغر حجم الجنين بصورة مرضية فى الحمل المتكرر للسيدات اللاتي سبق لهن المعاناة من مرض تسمم الحمل فى حملهن الأول.

المرضى وطرق البحث: تم البحث في تحديد نوع الجين المسئول عن إنزيم تحويل الأنجيوتنسن عند ستين (60) سيدة خلال حملهن الثانى، وكان قد سبق لهن المعاناة من تسمم الحمل فى الحمل الاول. كما تم قياس معدل تدفق الدم فى كل من الشريان الرحمى والحبل السرى عن طريق الدوبلر فى الاسابيع السادس عشر والعشرين والرابع والعشرين من الحمل، كما تم تسجيل وتحليل النتاج الإكلينيكى للحمل.

النتائج: لقد كشفت هذه الدراسة أن التنوع الجينى لإنزيم تحويل الأنجيوتنسين عند تسعين سيدة مصرية مماثل للأجناس الأخرى فى الأبحاث العالمية، حيث أن النوع الجينى دى دى تم تحديده فى41,1 %، والنوع الجينى اى دى فى 34,4%، والنوع الجينى II فى 24,4% من السيدات المصريات اللاتى

خضعن للبحث. وقد كان هناك فروقاً ذات دلالة إحصائية عالية فى النوع الجينى المسئول عن تحويل الأنجيوتنسن ونسبة وجود الصفة الوراثية فى هذا الجين فى حالات السيدات التى تكرر لهن حدوث تسمم حمل أو صغر حجم الجنين فى هذه الدراسة. كما أن معدل تدفق الدم فى الشريان الرحمى والحبل السرى تأثر سلبيا إلى درجة عالية فى هذه الحالات، وكذلك فقد تأثرت سلبيا مدة الحمل وكذا وزن الجنين ووزن المشيمة .

الاستنتاج: النوع الجينى دى دى هو المسئول عن إنزيم تحويل الأنجيوتنسين، ونسبة وجود الصفة الوراثية دى، ولهذا فإن الجين يُؤثر سلبيا على نتاج الحمل ومعدل تدفق الدم فى الدورة الدموية بين الرحم والمشيمة، وكذا تدفق الدم فى الحبل السرى للجنين فى السيدات اللاتى سبق لهن التعرض لمرض تسمم الحمل بدون أسباب واضحة في حملهن الأول.