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Original Research Article

Angiotensin Converting Enzyme Polymorphisms and Its Association with Hypertensive Disorders of Pregnancy in a Tertiary Care Hospital of Southern India: A Case-Control Study

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Abstract

Background: Hypertensive disorders of pregnancy (HDP) are a leading cause of maternal and perinatal morbidity worldwide, with genetic predisposition playing a significant role. The angiotensin-converting enzyme (ACE) gene insertion/deletion (I/D) polymorphism has been implicated in HDP, but data from southern India remain limited. This study aimed to assess the association between ACE gene polymorphism and HDP in a tertiary care hospital in Tamil Nadu.

Methods: A case-control study was conducted with 50 pregnant women diagnosed with HDP and 50 normotensive pregnant women as controls. Clinical and biochemical parameters were assessed, and ACE I/D polymorphism was analyzed using polymerase chain reaction (PCR). The association between genotypes and HDP risk was evaluated using chi-square tests and logistic regression analysis.

Results: A significantly higher frequency of the DD genotype was observed in preeclampsia cases (48%) compared to controls (16%) ($p = 0.000086$). The D allele was more prevalent in cases (69%) than in controls (36%) ($p < 0.00001$). Logistic regression revealed that pregnant women carrying the D allele had a 3.9 times higher risk of developing HDP (OR = 3.95; 95% CI: 2.2–7.1; $p < 0.0001$). The genotype distribution was in Hardy-Weinberg equilibrium.

Conclusion: This study provides evidence that the ACE D allele is significantly associated with an increased risk of HDP in southern Indian women. The findings support ACE genotyping as a potential tool for early risk stratification in high-risk pregnancies. Further studies with larger sample sizes and diverse populations are warranted to validate these findings and explore gene-environment interactions.

Keywords: ACE gene polymorphism, hypertensive disorders of pregnancy, preeclampsia, genetic association, case-control study, maternal health, renin-angiotensin system.

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Introduction

Hypertensive disorders of pregnancy (HDP) including gestational hypertension, preeclampsia and eclampsia are major contributors to maternal and perinatal morbidity and mortality worldwide..[1] In India, HDP account for approximately 6.7% of maternal deaths, underscoring their critical impact on public health.[2] The occurrence of hypertensive disorders of pregnancy (HDP) in India differs across studies, showing a prevalence rate between 5% and 15% among expectant mothers. Research carried out at a tertiary hospital in Tamil Nadu revealed the following breakdown of hypertensive disorders: gestational hypertension accounted for 47.4%, preeclampsia for 32.6%, and chronic hypertension for 20%.[3]

Several risk factors have been associated with the development of HDP. Women under 20 or over 35 years of age, higher Body Mass Index (BMI), primiparity, multiple gestations, pre-existing chronic conditions are at an increased risk of developing HDP.[4] Also, women with lower education levels and limited access to healthcare services have been linked to a higher incidence of HDP.[5]

Genetic factors significantly influence the onset of high blood pressure disorders during pregnancy. The

angiotensin-converting enzyme (ACE) gene, which is key to the blood pressure regulation system known as the renin-angiotensin system, has been thoroughly researched for its genetic variations, particularly the insertion/deletion (I/D) variant. According to a study by Kaur et al., there is a notable link between the ACE DD genotype and a heightened risk of pregnancy-induced hypertension (PIH). In this research, 60% of women experiencing PIH had the DD genotype, whereas only 30% of pregnant women with normal blood pressure carried this genotype. This indicates that those with the DD genotype are 3.5 times more likely to develop hypertension during pregnancy. Conversely, another study by Aggarwal et al. found no significant association between individual ACE gene polymorphisms and hypertensive disorders of pregnancy.[7]

This difference suggests possible genetic variations across different regions and highlights the importance of conducting research specific to each population. A detailed meta-analysis also reinforces the connection between the ACE I/D polymorphism and a higher risk of hypertensive pregnancy disorders, especially in Asian populations.[8] There is a lack of specific data concerning southern Indian populations, underscoring the necessity for focused genetic research in this area to gain a clearer understanding of how ACE gene polymorphisms influence hypertensive disorders of pregnancy.

We aimed to determine the association of ACE gene polymorphism with Hypertensive Disorders of Pregnancy in a tertiary hospital of Tamil Nadu.

Methods

A case–control study was conducted over a period of one year in a tertiary hospital, Trichy, Tamil Nadu. The study population consisted of 100 pregnant women visited the hospital during the study period. Pregnant women of age group 15 to 40 years, > 20 weeks with HDP were included. Normal pregnant women of similar age group were used as control. Pregnant women with pre-existing hypertension, cardiac, or renal disease were excluded. The study protocol was approved by the Institutional Ethical Committee. Written informed consent was obtained from all participants prior to enrollment in the study.

A sample of 50 pregnant women with HDP as cases and 50 pregnant women without HDP as controls were included in the study. Pregnant women were chosen consecutively using a non-probability sampling method from the department of Obstetrics and Gynecology. Detailed demographic and clinical data were collected using a structured proforma.

Information on age, gestational age, obstetric history, and family history of hypertension were recorded. In the study preeclampsia was defined as a condition characterized by high blood pressure (≥140/90 mmHg) and proteinuria (≥300 mg/day) occurring after 20 weeks of pregnancy in a previously normotensive woman.

Eclampsia was defined as the onset of seizures that cannot be attributed to other causes in a woman with preeclampsia. Anthropometric measurements including weight and height were obtained using standardized procedures. Blood pressure was measured using a mercury sphygmomanometer with the patient in a supine position. Additionally, clinical examination findings and routine laboratory investigations (including serum glucose, urea, creatinine, and uric acid) were documented.

Venous blood samples (approx. 2 mL) were collected from all pregnant women under aseptic conditions. One aliquot was used for routine biochemical assays, while the remaining sample was collected in EDTA-coated tubes for genomic DNA extraction.

Biochemical analyses were performed using a semi-automated analyzer following standardized protocols. Parameters measured included fasting and postprandial blood glucose, blood urea, serum creatinine, and uric acid. Urine protein was assessed using the urine dipstick method.

Genomic DNA was isolated from EDTA-anticoagulated whole blood using a commercially available QIAGEN DNA extraction kit. The extraction process involved cell lysis using proteinase K and lysis buffer, followed by selective binding of DNA to a spin column and subsequent elution in a high-salt buffer. The purity and concentration of the extracted DNA were verified by spectrophotometry and agarose gel electrophoresis.

The ACE gene I/D polymorphism was determined by polymerase chain reaction (PCR). Specific oligonucleotide primers were designed to amplify a region within intron 16 of the ACE gene.

The amplified products were resolved by electrophoresis on a 1.5% agarose gel containing ethidium bromide. The gel was run at 8 V/cm for 45 minutes, and PCR products were visualized under UV illumination. The expected amplicon sizes were 490 bp for the D allele and 190 bp for the I allele. Accordingly, homozygous DD individuals displayed a single band at 490 bp, homozygous II individuals showed a band at 190 bp, and heterozygous ID individuals exhibited both bands.

Data were analyzed using the Statistical Package for Social Sciences (SPSS) software. Continuous variables were expressed as mean ± standard deviation (SD) and compared using the student's t test. Genotype distributions were analyzed using the chi-square (χ^2) test. Logistic regression analysis was employed to calculate the odds ratios (OR) and 95%

confidence intervals (CI) for the association between ACE polymorphism and HDP. A p-value of <0.05 was considered statistically significant. Furthermore, the genotype frequencies were tested for Hardy–Weinberg equilibrium.

Results

A total of 100 pregnant women were enrolled, comprising 50 Pregnant Women with HDP and 50 normotensive controls. Mean age of cases was 25.6 years and controls was 24.9 years. The age distribution among cases and controls is presented in Table 1. The mean values of various clinical and biochemical parameters between cases and controls are summarized in Table 2. Systolic and diastolic blood pressures were significantly higher in preeclampsia cases compared to controls. Significant differences were observed in urea, albumin, bilirubin, uric acid, AST, ALT, and platelet counts between cases and controls ($p < 0.00001$). No significant differences were found in glucose and creatinine levels.

ACE Gene Polymorphism Analysis: The distribution of ACE gene polymorphisms among cases and controls is detailed in Table 3. A higher frequency of the DD genotype was observed in preeclampsia cases (48%) compared to controls (16%), with a chi-square value of 18.7 and a p-value of 0.000086, indicating statistical significance. Distribution of allele among cases and control is presented in Table 4. The D allele was more prevalent in cases (69%) than in controls (36%), with a chi-square value of 21.8 and a p-value of <0.00001, suggesting a significant association between the D allele and HDP. Logistic regression analysis revealed that pregnant women carrying the D allele had a 3.9 times higher risk of developing HDP compared to those with the I allele (95% CI: 2.2 – 7.1, $p < 0.0001$).

The Hardy-Weinberg equilibrium (HWE) analysis for the ACE I/D polymorphism in the study population was conducted to assess whether the observed genotype frequencies aligned with the expected frequencies under HWE conditions. The genotype distribution for the ACE gene polymorphism was as follows: II (27%), ID (41%), and DD (32%). The expected genotype frequencies were 22.6% for II, 49.9% for ID, and 27.6% for DD. A chi-square (χ^2) test value of 3.16 was obtained, with a p-value of 0.075, indicating no significant deviation from Hardy-Weinberg equilibrium in the study population. This suggests that the allele distribution within the population is stable and not influenced by evolutionary forces such as selection, mutation, or genetic drift.

Table 1: Distribution of cases and control among the various age categories

Age Group (years)	Cases (n=50)	Controls (n=50)	Total (n=100)
<20	8	2	10
20–24	17	22	39
25–29	9	20	29
30–34	14	5	19
35–40	2	1	3
Mean Age	25.6	24.9	25.3

Table 2: Distribution of various clinical and biochemical parameters among the cases and controls

Parameter	Cases (Mean ± SD)	Controls (Mean ± SD)	t-value*	p-value
Systolic BP (mmHg)	145.8 ± 5.80	113.5 ± 7.40	23.69	<0.00001
Diastolic BP (mmHg)	98.24 ± 5.85	74.2 ± 4.98	22.11	<0.00001
Glucose (mg/dL)	92.1 ± 8.35	93 ± 8.55	-1.08	0.142
Urea (mg/dL)	19.16 ± 2.14	17 ± 1.79	4.86	<0.00001
Creatinine (mg/dL)	0.774 ± 0.1	0.7 ± 0.1	0.99	0.161
Albumin (g/dL)	3.32 ± 0.20	3.7 ± 0.17	-12.36	<0.00001
Bilirubin (mg/dL)	0.764 ± 0.1	0.598 ± 0.08	8.94	<0.00001
Uric Acid (mg/dL)	4.7 ± 0.23	3.7 ± 0.20	22.45	<0.00001
AST (IU/L)	37.74 ± 1.72	31 ± 2.56	20.42	<0.00001
ALT (IU/L)	41.78 ± 3.30	35 ± 1.65	23.81	<0.00001
Platelet (lakhs/cu.mm)	2.39 ± 0.33	2.87 ± 0.52	-5.47	<0.00001

***Student's T test was performed**

Table 3: Distribution of ACE polymorphism among cases and controls

Genotype	Cases (n=50)	Controls (n=50)	Total (n=100)	Chi-Square Test
II	5 (10%)	22 (44%)	27 (27%)	x^2 =21.8 p=<0.00001
ID	21 (42%)	20 (40%)	41 (41%)	
DD	24 (48%)	8 (16%)	32 (32%)	

***Chi-Square Test was performed**

Table 4: Distribution ACE gene allele among cases and controls

Allele	Cases (n=100)	Controls (n=100)	Total (n=200)	Chi-Square Test
I	31 (31%)	64 (64%)	95 (47.5%)	x^2 =21.8
D	69 (69%)	36 (36%)	105 (52.5%)	p=<0.00001

Table 5: Logistic Regression of ACE gene polymorphism and HDP status among pregnant women

HDP status	Number of Pregnant Women	Allele	Allele Count	Odds Ratio	95% Confidence Interval	p-value
Control	50	I	64%	1 (Reference)		<0.0001
Case	50	D	69%	3.9570	2.2 – 7.1	

Discussion

An increasing number of studies over the past ten years have implicated the ACE I/D polymorphism as a risk factor for preeclampsia. In our population, we found that the D allele was significantly overrepresented in preeclamptic patients compared to normotensive pregnant controls (69% vs 36%), with the DD genotype found in nearly half of the preeclamptic patients (48%) but only 16% of the controls. The ACE I/D polymorphism was strongly associated with the risk of preeclampsia ($p < 0.0001$), and the presence of the D allele was associated with a nearly four-fold increased risk of preeclampsia.

These findings align with several recent studies worldwide. A Turkish population-based study similarly found an overrepresentation of the DD genotype among preeclamptic women (with D allele frequency ~64.6% in cases vs 56.1% in controls) and a significant difference in ACE I/D genotype distributions between cases and controls.[9] In Western Iran it was observed that the ACE I/D variant increased the risk of severe preeclampsia (OR ~1.5 for the D-containing genotypes).[10]

Consistent associations have also been noted in other regions – a 2021 review highlighted that studies in Mexico and China identified the D allele as the predominant variant among preeclamptic women compared to normotensive pregnant women, suggesting the DD genotype may serve as a molecular marker of elevated preeclampsia susceptibility in those populations.[11] More recently, evidence from sub-Saharan Africa has echoed this trend. A genetic study in Nigeria (2024) focusing on multiple polymorphisms found the ACE I/D to be significantly associated with preeclampsia; the D allele frequency was substantially higher in Nigerian preeclamptic patients (44%) than in controls (30%).[12]

Similarly, research in a Russian cohort with gestational diabetes mellitus (GDM) reported that the ACE polymorphism influences preeclampsia development even in the presence of GDM – the DD genotype frequency was ~24% in GDM patients who developed preeclampsia versus 11% in those who did not, translating to a roughly three-fold increased risk.[13] This underscores that the ACE D allele's effect can compound with other risk factors like GDM to precipitate preeclampsia. Furthermore, meta-analyses lend weight to the association: a synthesis of studies reported that the D allele is associated with almost two-fold higher odds of preeclampsia overall.[14] Taken together, the preponderance of recent data from Asia, Europe, Africa, and the Americas supports the notion that the ACE D allele is a global risk factor for preeclampsia, likely via its impact on angiotensin II–mediated hypertension and endothelial injury.

Although many studies concur on the risk conferred by the ACE D allele, the literature is not unanimous. Some populations have shown no significant association between ACE I/D genotypes and preeclampsia, reflecting the complex, multifactorial nature of the disease. For example, an analysis noted that while numerous reports from various regions linked the D allele or DD genotype to higher preeclampsia risk, other studies (including cohorts of European and East Asian ancestry) found no such relationship. Early studies in Caucasian, American, or Korean women failed to detect a significant difference in ACE I/D frequencies between preeclamptic and normotensive pregnancies. A Brazilian study similarly reported no association between ACE I/D polymorphism and preeclampsia incidence. These discrepancies could stem from several factors: ethnic differences in allele frequencies, small sample sizes or variable definitions of preeclampsia severity, as well as the possibility that ACE I/D's effect might be context-dependent, manifesting only in the presence of certain co-risk factors or in specific genetic backgrounds. It is also notable that when an association is absent, the D allele is typically neutral rather than protective, suggesting that the polymorphism's contribution may be necessary but not sufficient in isolation to cause preeclampsia.

Emerging evidence points to the importance of gene–gene interactions and maternal–fetal genotype interplay in modulating the impact of ACE I/D on preeclampsia. The pathogenesis of preeclampsia likely involves a network of polymorphic genes in angiogenic, inflammatory, and blood pressure pathways. For instance, one study demonstrated that certain combinations of maternal gene variants dramatically increased preeclampsia risk: the

angiotensin II type 2 receptor gene (AT2R) G allele appeared to interact epistatically with the ACE D allele (as well as with AT1R 1166C and MMP-9 1562T variants) to magnify the likelihood of disease.[15] In other words, women carrying a cluster of risk alleles across the RAAS and related systems had a much higher incidence of preeclampsia than those with only one risk allele.

Likewise, combinations of maternal and fetal genotypes have been shown to influence outcomes. A recent meta-analysis (2024) offered a nuanced insight: it found that the maternal ACE I/D polymorphism alone was not significantly associated with preeclampsia overall, yet the fetal ACE I/D genotype was significantly linked to preeclampsia risk in a dominant model.[16] Overall, these findings highlight that ACE I/D polymorphism acts in concert with other genetic and environmental factors. Future research integrating genomics and epigenetics is needed to fully map how ACE I/D interacts within the polygenic network underlying preeclampsia

Understanding the association between ACE I/D polymorphism and preeclampsia carries public health implications. First, the consistent observation in many populations that the D allele correlates with higher blood pressure and more severe disease suggests it could serve as a genetic marker for risk stratification. In our study, for example, women with the D allele had nearly four times greater odds of developing preeclampsia, highlighting its potential predictive value. If these findings are validated in larger multi-center cohorts, genotyping of the ACE gene early in pregnancy (or preconception) might help identify women who are genetically predisposed. This could facilitate closer monitoring, timely preventive interventions, and focused management for those at high risk. However, it is equally important to recognize the limitations before translating this into routine practice. The presence of the D allele is neither necessary nor sufficient to cause preeclampsia – many D allele carriers have normal pregnancies, and some preeclampsia patients do not carry this allele. Therefore, ACE I/D genotyping would augment, not replace, clinical risk assessment. A polygenic or multifactorial risk score that includes ACE I/D alongside other genetic markers (e.g. in angiogenic factors like VEGF, ENG, FLT1, and inflammatory genes like TNF-α) may achieve better predictive accuracy than any single polymorphism alone. These genetic insights offer hope for earlier intervention and better outcomes in preeclampsia, a condition that continues to challenge primary care physicians and jeopardize maternal-fetal wellbeing worldwide. The study used a case-control design with statistically significant findings, showing a strong association between ACE I/D polymorphism and preeclampsia. It included biochemical correlations, ensured Hardy-Weinberg equilibrium, and highlighted clinical implications for risk prediction. It lacked ACE enzyme activity measurement, had a small sample size, and did not assess postpartum outcomes.

Conclusion

This study highlights the significant association between ACE I/D polymorphism and HDP, with the D allele increasing susceptibility. The findings support its potential role in early risk stratification and targeted antenatal care. Future research should incorporate functional genomics and longitudinal follow-up to validate these findings. Integrating ACE genotyping into clinical screening programs may enhance early detection and preventive interventions.

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