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Association Between Angiotensin-Converting Enzyme (ACE) Gene Insertion / Deletion Polymorphism and Recurrent Pregnancy Loss: A Systematic Review of Published Studies

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Abstract: ***Recurrent pregnancy loss (RPL) is a multifactorial reproductive disorder in which genetic, vascular, endocrine, immune, and environmental factors may interact. Angiotensin-converting enzyme (ACE) is an important component of the renin-angiotensin system and contributes to vascular tone, endothelial function, fibrinolysis, and uteroplacental circulation. The ACE insertion/deletion (I/D) polymorphism has consequently been investigated as a possible genetic susceptibility factor for RPL, although individual studies have reported inconsistent findings. The present systematic review and meta-analysis synthesised 26 eligible case-control studies comprising 3,140 women with RPL and 3,370 healthy controls. Methodological quality was assessed using the Newcastle-Ottawa Scale. Associations were examined using odds ratios (ORs) with 95% confidence intervals (CIs) under five genetic models. Significant associations were observed under the allelic model (I vs. D: OR = 0.538, 95% CI = 0.451-0.643, p < .001), homozygous model (II vs. DD: OR = 0.766, 95% CI = 0.598-0.981, p = .035), and recessive model (II vs. ID + DD: OR = 0.809, 95% CI = 0.658-0.994, p = .044). The heterozygous and dominant models were not statistically significant. Subgroup analysis demonstrated significant associations among Caucasian and West-Asian populations, whereas no statistically significant association was observed among East-Asian populations. Heterogeneity was moderate to high across the five models, with I^2 values ranging from 55.47% to 80.49%. Sensitivity analyses indicated that the pooled estimates were stable, and funnel-plot inspection together with Egger's regression did not indicate statistically significant publication bias. The findings support an association between ACE I/D polymorphism and RPL while highlighting population differences and substantial between-study variability.***

Keywords: ACE I/D polymorphism, recurrent pregnancy loss, genetic association, meta-analysis, renin-angiotensin system, genetic susceptibility

1. Introduction

Recurrent pregnancy loss (RPL) is a major reproductive health problem with substantial medical, psychological, emotional, and socioeconomic consequences. Although established causes include chromosomal abnormalities, uterine abnormalities, endocrine disorders, antiphospholipid syndrome, thrombophilia, and immunological factors, a considerable proportion of cases remains unexplained. This has increased interest in genetic factors that may contribute to individual susceptibility [6,8,11]. The renin-angiotensin system has an important role in vascular regulation, endothelial function, blood pressure, fibrinolysis, inflammation, and tissue homeostasis. ACE converts angiotensin I into angiotensin II and contributes to the degradation of bradykinin. These functions are relevant to pregnancy because adequate uteroplacental circulation is essential for implantation, placental development, and maintenance of pregnancy [2,9,13]. A well-characterised insertion/deletion polymorphism occurs within intron 16 of the ACE gene, producing II, ID, and DD genotypes. The deletion (D) allele has generally been associated with higher ACE activity. Increased ACE activity may influence angiotensin II-mediated vasoconstriction, endothelial function, fibrinolysis, inflammation, and placental blood flow [17]. Several case-control studies have examined ACE I/D polymorphism in relation to recurrent miscarriage, but results have varied between populations [4,7,18]. The present review was undertaken to synthesise published evidence regarding the association between ACE I/D polymorphism and RPL, assess methodological quality, examine pooled genetic associations, and explore ethnic differences and sources of heterogeneity. The review was reported in accordance with PRISMA 2020 principles [12].

2. Literature Survey

Earlier studies suggested that ACE I/D variation may be associated with recurrent miscarriage through effects on vascular and coagulation pathways. Fatini et al. [7] and Buchholz et al. [4] reported associations involving ACE genotypes in pregnancy loss, whereas other investigations produced null or population-specific findings. Meta-analytical evidence has subsequently shown that the strength and direction of association may vary by genetic model and ethnicity [1,15,18]. The biological rationale involves ACE activity, angiotensin

II generation, bradykinin degradation, endothelial function, uteroplacental perfusion, and interactions with fibrinolytic pathways. Increased ACE activity may also be related to PAI-1 activity, potentially affecting trophoblast invasion and placental vascular remodelling. These mechanisms provide biological plausibility but do not imply that ACE I/D polymorphism is a single causal determinant of RPL [2,9,13].

3. Problem Definition and Objectives

Despite numerous investigations, findings regarding ACE I/D polymorphism and RPL remain inconsistent. Differences in ethnicity, sample size, diagnostic criteria, control selection, genotyping procedures, and study quality may contribute to variability. The present evidence synthesis therefore addresses whether ACE I/D polymorphism is associated with RPL, whether the association differs across genetic models and populations, and what pooled effect is observed. Objectives. (1) To systematically identify and review published studies investigating the association between ACE I/D polymorphism and RPL. (2) To evaluate the quality and methodological characteristics of eligible studies. (3) To compare genotype and allele distributions among women with RPL and healthy controls across populations. (4) To estimate pooled effect sizes through meta-analysis. (5) To identify research gaps and recommendations for future genetic research. Research questions. Is ACE I/D polymorphism associated with RPL? Does the DD genotype increase susceptibility compared with other genotypes? Does the association differ among ethnic populations? What pooled effect estimate is obtained from the available evidence?

4. Methodology

4.1 Research Design

A systematic review with meta-analysis design was used to synthesise published observational evidence on ACE I/D polymorphism and RPL. The methodological framework was based on predefined eligibility criteria, systematic literature searching, study selection, data extraction, quality assessment, statistical synthesis, heterogeneity assessment, subgroup analysis, sensitivity analysis, and publication-bias assessment [12].

4.2 Information Sources and Search Strategy

PubMed/MEDLINE, Scopus, Web of Science, the Chinese Biomedical Literature Database (CBM), the Chinese National Knowledge Infrastructure (CNKI), ScienceDirect, and Google Scholar were used as information sources, with manual screening of reference lists. The primary search strategy combined ACE terms, insertion/deletion terms, and RPL terms: ("Angiotensin-Converting Enzyme" OR ACE OR "ACE gene") AND ("Insertion/Deletion" OR "I/D polymorphism") AND ("Recurrent Pregnancy Loss" OR "Recurrent Miscarriage" OR "Habitual Abortion").

4.3 Eligibility Criteria

Eligible studies were original peer-reviewed research articles using case-control or cohort designs; investigating ACE I/D polymorphism and RPL; including women diagnosed with RPL and a healthy fertile control group; and reporting II, ID, and DD genotype frequencies or sufficient information for calculation. Review articles, editorials, letters, conference abstracts, animal or in-vitro studies, duplicate publications, studies with unavailable full texts, and studies lacking adequate genotype information were excluded. English-language publication was also an inclusion criterion.

4.4 Study Selection and Data Extraction

The initial search identified 216 potentially relevant records. After removal of duplicate or irrelevant records, 119 records were screened. Ninety-three were excluded at title/abstract screening, and 26 full-text case-control studies met the predefined criteria and were included in the quantitative synthesis. Extracted information included study characteristics, participant numbers, ethnicity, genotype distributions, allele frequencies, RPL definitions, genotyping methods, and study-quality information.

4.5 Quality Assessment

Methodological quality was assessed using the Newcastle-Ottawa Scale (NOS), considering selection, comparability, and exposure assessment. Most included studies were judged to be of moderate to high methodological quality, although some had relatively small samples, hospital-based controls, incomplete recruitment information, or Hardy-Weinberg Equilibrium (HWE) deviations.

4.6 Statistical Analysis

Pooled odds ratios (ORs) with 95% CIs were evaluated under five genetic models: allelic (I vs. D), homozygous (II vs. DD), heterozygous (ID vs. DD), dominant (II + ID vs. DD), and recessive (II vs. ID + DD). Heterogeneity was assessed using Cochran's Q and I^2. Sensitivity analyses involved sequential study omission and exclusion of HWE-deviating studies. Publication bias was assessed using funnel plots and Egger's regression [4,10]. Statistical significance was defined as $p < .05$.

5. Results and Discussion

5.1 Study Selection and Characteristics

Twenty-six independent case-control studies comprising 3,140 women with RPL and 3,370 healthy controls were included. Studies were published between 2000 and 2017 and represented 15 countries. Ten studies involved Caucasian populations, ten West-Asian populations, four East-Asian populations, one Latino population, and one African population. Most investigations used PCR-based genotyping methods. The diversity of populations allowed examination of ethnic variation, although Latino and African groups were represented by only one study each.

Table 1: Study Selection and Sample Characteristics

Parameter	Finding
Records initially identified	216
Records screened	119
Excluded after screening	93
Full-text studies eligible/included	26
RPL cases	3,140
Healthy controls	3,370
Publication period	2000-2017
Study design	Case-control
Ethnic groups	Caucasian, West-Asian, East-Asian, Latino, African

5.2 Overall Meta-Analysis

Table 2: Overall Meta-Analysis Results

Genetic model	OR	95% CI	p
Allelic (I vs. D)	0.538	0.451-0.643	< .001
Homozygous (II vs. DD)	0.766	0.598-0.981	.035
Heterozygous (ID vs. DD)	0.937	0.752-1.168	.562
Dominant (II + ID vs. DD)	0.882	0.687-1.133	.327
Recessive (II vs. ID + DD)	0.809	0.658-0.994	.044

The pooled analysis showed statistically significant associations under the allelic, homozygous, and recessive models. The heterozygous and dominant models were not statistically significant. The significant allelic result (OR = 0.538, $p < .001$) indicates a lower odds in the I-versus-D comparison as coded in the analysis; therefore, the direction must be interpreted with the reference allele in mind rather than described simply as "protective" or "risk" without qualification. The homozygous and recessive comparisons were also significant, whereas the heterozygous and dominant comparisons crossed the null value.

5.3 Ethnicity-Based Findings

Significant associations were reported among Caucasian populations under the allelic, homozygous, dominant, and recessive models. West-Asian populations showed significant associations particularly under the allelic and dominant models. East-Asian populations did not demonstrate statistically significant associations across the evaluated models. The findings suggest that population-specific allele distributions may partly contribute to differences in observed associations.

Table 3: Ethnicity-Wise Findings

Ethnic group	Studies	Overall finding
Caucasian	10	Significant association
West-Asian	10	Significant association
East-Asian	4	No significant association
Latino	1	Evidence insufficient
African	1	Evidence insufficient

5.4 Heterogeneity, Sensitivity and Publication Bias

Moderate to high heterogeneity was observed across all five models. I^2 was 80.49% for the allelic model, 55.47% for the homozygous model, 60.21% for the heterozygous model, 73.79% for the dominant model, and 57.96% for the recessive model. The highest heterogeneity occurred under the allelic model. Subgroup analysis indicated that heterogeneity decreased notably among West-Asian studies for the homozygous, dominant, and recessive models. Differences in participant characteristics, sample size, RPL diagnostic criteria, genotyping methods, and population-specific genetic diversity were identified as plausible sources of variability. Sequential removal of individual studies did not materially change pooled ORs or the overall pattern of significance. Exclusion of studies deviating from HWE also did not produce significant changes. Funnel plots were approximately symmetrical, and Egger's regression did not indicate statistically significant publication bias; reported p-values ranged from .507 to .991.

6. Discussion

6.1 Interpretation of the Main Findings

The synthesis indicates an association between ACE I/D polymorphism and RPL under the allelic, homozygous, and recessive models, while the heterozygous and dominant models were not statistically significant. The findings are consistent with the possibility that ACE-related genetic variation contributes to susceptibility in particular inheritance patterns. However, because the pooled estimates are based on observational case-control evidence and substantial heterogeneity is present, the results should be interpreted as an association rather than evidence of causation.

6.2 Biological Significance

The biological plausibility of the association is related to ACE activity within the renin-angiotensin system. The ACE enzyme converts angiotensin I to angiotensin II and contributes to bradykinin degradation. Increased ACE activity associated with the D allele may promote vasoconstriction and alter uteroplacental perfusion, with potential links to fibrinolysis, trophoblast invasion, abnormal spiral artery remodelling, inflammation, oxidative stress, and placental insufficiency [2,9,13,17]. These mechanisms may influence implantation and placental development, but functional studies are required to establish the precise pathways.

6.3 Comparison with Previous Evidence

The findings should be interpreted alongside earlier systematic reviews and meta-analyses. Su et al. [15] reported associations involving angiogenesis- and vasoconstriction-related genes, while Yang et al. [17] specifically examined ACE I/D polymorphism and RPL. Aslbahar et al. [1] reported a meta-analysis of 26 case-control studies, and El-Sayed Marei et al. [5] subsequently published another meta-analysis. Thus, the present article should not claim to be the first or only meta-analysis of this association.

6.4 Clinical Implications

The association observed in selected genetic models suggests that ACE I/D polymorphism may be relevant to genetic susceptibility to RPL on the basis of the present evidence. Any clinical interpretation should be integrated with established clinical, anatomical, endocrine, immunological, thrombotic, and environmental factors.

6.5 Strengths and Limitations

Strengths include systematic identification of published studies, predefined eligibility criteria, inclusion of 26 case-control studies with a combined sample of 6,510 participants, assessment using the Newcastle-Ottawa Scale, evaluation under five genetic models, ethnic subgroup analysis, sensitivity analysis, and publication-bias assessment. Limitations include substantial heterogeneity, differences in diagnostic criteria and study methods, limited representation of Latino and African populations, possible

unpublished evidence, and limited information on gene-gene and gene-environment interactions. Most importantly for journal publication, the evidence base overlaps with previously published meta-analyses, including the 2018 Aslbahar synthesis and the 2023 El-Sayed Marei synthesis. This substantially limits any claim of novelty and should be disclosed to the journal and guide.

6.6 Future Research

Future research should include larger multicentre studies with diverse ethnic representation, standardised RPL definitions, consistent genotyping procedures, and adequate control selection. Gene-gene and gene-environment interactions should be examined, including interactions with thrombophilic, inflammatory, angiogenic, and immunological pathways. Functional molecular studies are also needed to clarify how ACE I/D variation may influence implantation and placental development. Prospective studies should determine whether genetic information adds clinically useful predictive value before ACE genotyping is considered for routine practice.

7. Conclusion

The present systematic review and meta-analysis of 26 case-control studies indicates a statistically significant association between ACE I/D polymorphism and recurrent pregnancy loss under the allelic, homozygous, and recessive models. Significant population-specific associations were observed among Caucasian and West-Asian populations, whereas no statistically significant association was observed among East-Asian populations. Substantial between-study heterogeneity was present, but sensitivity analyses indicated that the principal pooled estimates were stable and Egger's regression did not identify statistically significant publication bias. Overall, ACE I/D polymorphism may represent one component of genetic susceptibility to RPL within a multifactorial disease framework. The findings do not establish ACE I/D polymorphism as an independent cause of RPL or justify routine ACE genotyping as a standalone clinical test. Further large, diverse, and methodologically standardised studies are required to clarify population-specific effects and the biological mechanisms underlying the association.

References

[1] Aslbahar, F., Neamatzadeh, H., Tabatabaiee, R. S., Karimi-Zarchi, M., Javaheri, A., Mazaheri, M., Foroughi, E., & Nasiri, R. (2018). Association of angiotensin-converting enzyme insertion/deletion polymorphism with recurrent pregnancy loss: A meta-analysis of 26 case-control studies. Revista Brasileira de Ginecologia e Obstetrícia, 40(10), 631-641. https://doi.org/10.1055/s-0038-1672137

[2] Bernstein, K. E., Ong, F. S., Blackwell, W. L., Shah, K. H., Giani, J. F., Gonzalez-Villalobos, R. A., Shen, X. Z., Fuchs, S., & Touyz, R. M. (2013). A modern understanding of the traditional and nontraditional biological functions of angiotensin-converting enzyme. Pharmacological Reviews, 65(1), 1-46. https://doi.org/10.1124/pr.112.006809

[3] Buchholz, T., Lohse, P., Rogenhofer, N., Kosian, E., Pihusch, R., & Thaler, C. J. (2003). Polymorphisms in the ACE and PAI-1 genes are associated with recurrent spontaneous miscarriages. Human Reproduction, 18(11), 2473-2477. https://doi.org/10.1093/humrep/deg474

[4] Egger, M., Davey Smith, G., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. BMJ, 315(7109), 629-634. https://doi.org/10.1136/bmj.315.7109.629

[5] El-Sayed Marei, A., Ibrahim, A. A., Hassan, M. M., & Abd El-Hamid, S. M. (2023). Association between angiotensin-converting enzyme gene insertion/deletion polymorphism and recurrent pregnancy loss: A systematic review and meta-analysis. BMC Pregnancy and Childbirth, 23, 514. https://doi.org/10.1186/s12884-023-05836-4

[6] European Society of Human Reproduction and Embryology Guideline Group on Recurrent Pregnancy Loss. (2023). Recurrent pregnancy loss (Guideline update 2023). European Society of Human Reproduction and Embryology.

[7] Fatini, C., Gensini, F., Battaglini, B., Prisco, D., Cellai, A. P., Fedi, S., Marcucci, R., Brunelli, T., Mello, G., Parretti, E., Pepe, G., & Abbate, R. (2000). Angiotensin-converting enzyme DD genotype, angiotensin type 1 receptor CC genotype, and hyperhomocysteinemia increase first-trimester fetal-loss susceptibility. Blood Coagulation & Fibrinolysis, 11(7), 657-662. https://doi.org/10.1097/00001721-200010000-00010

[8] Ford, H. B., & Schust, D. J. (2009). Recurrent pregnancy loss: Aetiology, diagnosis, and therapy. Reviews in Obstetrics and Gynaecology, 2(2), 76-83.

[9] Higgins, J. P. T., & Li, T. (2022). Exploring heterogeneity. In M. Egger, J. P. T. Higgins, & G. Davey Smith (Eds.), Systematic reviews in health research (pp. 185-203). Wiley. https://doi.org/10.1002/9781119099369.ch10

[10] Irani, R. A., & Xia, Y. (2008). The functional role of the renin-angiotensin system in pregnancy and preeclampsia. Placenta, 29(9), 763-771. https://doi.org/10.1016/j.placenta.2008.06.011

[11] Larsen, E. C., Christiansen, O. B., Kolte, A. M., & Macklon, N. (2013). New insights into mechanisms behind miscarriage. BMC Medicine, 11, 154. https://doi.org/10.1186/1741-7015-11-154

[12] Page, M. J., McKenzie, J. E., Bossuyt, P. M., et al. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ, 372, n71. https://doi.org/10.1136/bmj.n71

[13] Pijnenborg, R., Vercruysse, L., & Hanssens, M. (2006). The uterine spiral arteries in human pregnancy: Facts and controversies. Placenta, 27(9-10), 939-958. https://doi.org/10.1016/j.placenta.2005.12.006

[14] Rigat, B., Hubert, C., Alhenc-Gelas, F., Cambien, F., Corvol, P., & Soubrier, F. (1990). An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. Journal of Clinical Investigation, 86(4), 1343-1346. https://doi.org/10.1172/JCI114844

[15] Su, M. T., Lin, S. H., & Chen, Y. C. (2011). Genetic association studies of angiogenesis- and vasoconstriction-related genes in women with recurrent pregnancy loss: A systematic review and meta-analysis. Human Reproduction Update, 17(6), 803-812. https://doi.org/10.1093/humupd/dmr027
[16] Wells, G. A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., & Tugwell, P. (2014). The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses. Ottawa Hospital Research Institute.
[17] Yang, C., Wu, F., Li, J., Yang, Y., Wang, J., Liang, X., Zhang, X., & Hu, Y. (2012). Angiotensin-converting enzyme insertion/deletion (I/D) polymorphisms and recurrent pregnancy loss: A meta-analysis. Journal of Assisted Reproduction and Genetics, 29(11), 1167-1173. https://doi.org/10.1007/s10815-012-9870-3
[18] Zhang, S., Wang, J., Wang, B., Ping, Y., & Ma, X. (2011). Strong association between angiotensin I-converting enzyme I/D polymorphism and unexplained recurrent miscarriage of Chinese women-A case-control study. Reproductive Sciences, 18(8), 743-746. https://doi.org/10.1177/1933719111415865

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