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Significant association between angiotensin-converting enzyme gene insertion/deletion polymorphism and risk of recurrent miscarriage: A systematic review and meta-analysis

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ABSTRACT

Background. Many studies have investigated the association between angiotensin-converting enzyme (ACE) gene insertion/deletion (I/D) polymorphism and risk of recurrent miscarriage, but the impact is unclear due to inconsistencies among those studies. This study aimed to quantify the strength of the association between ACE I/D polymorphism and recurrent miscarriage risk by performing a systematic review and meta-analysis.

Design and Methods. We searched PubMed, Embase, Web of Science, and Wanfang Medicine databases for eligible articles relating the association between ACE I/D polymorphism and risk of recurrent miscarriage in humans. We estimated the summary odds ratios (ORs) with their 95% confidence intervals (95% CIs) to assess the association.

Results. Eleven studies with a total of 3357 individuals were included in this meta-analysis. Compared to the ACE II genotype, DD and ID were both associated with increased risk of recurrent miscarriage ($OR_{DD\ versus\ II}$ = 1.81, 95% CI 1.23–2.66, P = 0.003; $OR_{ID\ versus\ II}$ = 1.50, 95% CI 1.25–1.80, P < 0.001). Sensitivity analyses further confirmed the association above. No evidence of publication bias was observed.

Conclusion. Meta-analyses of available data show a significant association between ACE I/D polymorphism and recurrent miscarriage risk, and the ACE polymorphic D allele contributes to increased risk of recurrent miscarriage.

Abbreviations: ACE, Angiotensin-converting enzyme; HWE, Hardy–Weinberg equilibrium; OR, odds ratio; 95% CI, 95% confidence interval; skewed XCI, skewed X chromosome inactivation.

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1. Introduction

Recurrent miscarriage, defined as 2 or more spontaneous abortions, affects up to 5% of reproductively active couples and an even higher proportion of women 35 years of age and older [1]. In addition, epidemiological investigations have demonstrated that the frequency of subsequent pregnancy loss is over 24% after two pregnancy losses, 30% after three and 40% after four successive pregnancy losses [2]. The cause of recurrent miscarriage is multifactorial, and several factors have been identified as being related to recurrent miscarriage including uterine anomaly, chromosomal abnormalities, endocrine dysfunction, inherited thrombophilias, immune disorders, lifestyle factors, and maternal infections [3,4]. Acquired and inherited thrombophilia is an important research avenue in the recurrent miscarriage field, and women with thrombophilias may have excessive thrombosis of the placental vessels, placental infarction, and secondary uteroplacental insufficiency, thus having an increased risk of recurrent miscarriage [5–7]. However, the etiology of most recurrent miscarriages is still unclear, and, genetic polymorphisms have been proposed as susceptibility factors in patients with recurrent miscarriage [1,3].

A normal pregnancy depends on adequate placental circulation and fetal vasculature. The development of a normal functioning vascular network requires cooperation between different cell types and various growth factors in the processes of implantation, embryo development, and placentation. Abnormalities of placental vasculature may result in several gestational complications including pregnancy loss [3,4]. Several gene polymorphisms affecting placental vasculature and circulation, including Factor V Leiden, prothrombin G20210A mutation, factor XII deficiency, and eNOS Glu298Asp, have been suggested to be associated with increased risk of recurrent miscarriage [5,6,8–10]. Angiotensin-converting enzyme (ACE) also has an important impact on vascular structure and the function of placenta, and the abnormalities of ACE may result in fetal loss or recurrent miscarriage [11–13]. The human ACE gene is located on chromosome 17q23. The ACE gene was shown to be characterized by an insertion/deletion polymorphism based on the presence (insertion [I]) or absence (deletion [D]) within intron 16 of a 287-base pair alu repeat sequence, resulting in three genotypes (DD and II homozygotes and ID heterozygotes) [14,15]. Previous studies have suggested that ACE I/D polymorphism is associated with increased risks of thrombotic disorders, such as venous thromboembolism, stroke and coronary artery disease [16–18]. Since the modified expression of ACE may result in pregnancy loss, the ACE I/D polymorphism may be a susceptibility factor that increases the risk of recurrent miscarriage [11,12,15,19]. Numerous studies have investigated the relationship between ACE I/D polymorphism and recurrent miscarriage risk, but the available evidence from those studies is weak, owing to the sparseness of data and conflicting results [20–28]. Each of these studies involved few cases and controls and failed to confirm a consistent association. Furthermore, those studies varied markedly by including different populations, sampling strategies, and genotyping procedures. To shed some light on these contradictory results and to decrease the uncertainty of the estimated risk, we presented the results of a meta-analysis of published data investigating the association between ACE I/D polymorphism and recurrent miscarriage risk.

2. Methods

2.1. Search strategy

We conducted a comprehensive search of PubMed, Embase and Wanfang databases from their inceptions through June 2012. We combined search terms for ACE I/D polymorphism and recurrent miscarriage. Search terms included ACE or angiotensin-converting enzyme; gene, polymorphism, or genetic variant; and miscarriage, pregnancy loss, or recurrent miscarriage. There was no language limitation. The retrieved studies were manually screened in their entirety to assess eligibility for this study. All references cited in the studies were also reviewed to identify additional published articles not indexed in the common database.

2.2. Study eligibility

Eligibility criteria included the following: (i) Case–control design with the genotyping of women with and without recurrent miscarriage; (ii) recurrent miscarriage defined as two or more losses in the first two trimesters of pregnancy (recurrent miscarriage defined as 3 or more miscarriages were also considered eligible); (iii) unexplained or idiopathic pregnancy losses, that is, pregnancy losses with 'known' causes being excluded; (iv) genotypes identified by DNA analysis (polymerase chain reaction); (v) provided information on genotype frequency and confirmation of Hardy–Weinberg equilibrium (HWE) in the genotype distribution of the control group. In studies with overlapping cases or controls, the most recent and/or the largest study with extractable data was included in the meta-analysis. Studies investigating progression, severity, phenotype modification, response to treatment, or survival were excluded from this review. In addition, family-based association studies were excluded because they use a different study design. Since HWE is a surrogate to assess study quality, and the effect of HWE is associated with problems in the design and conduct of genetic association studies, studies with departures from HWE were excluded [29,30].

2.3. Data extraction

Two investigators independently extracted data, and disagreements were resolved by consensus. The extracted data included the year of publication, study population, definition of recurrent miscarriage, inclusion criteria for recurrent miscarriage patients and normal controls, demographics, matching, clinical status of controls, genotyping method, and the genotype distribution of cases and controls for the ACE I/D polymorphic variant. The frequencies of the alleles were extracted or calculated for cases and controls. All data were extracted from published articles, and we did not contact individual authors for further information. The quality of the included studies was assessed using the following criteria modified from the previous report [9,10]: