Association of Tumor Necrosis Factor-α (TFN-α) -308G>A and -238G>A Polymorphisms with Recurrent Pregnancy Loss Risk: A Meta-Analysis

Fereshteh Aslebahr, M.D.1, Hossein Neamat-zadeh, M.Sc.2, Bahareh Meibodi, M.D.4, Mojgan Karimi-Zarchi, M.D.4, Razieh Sadat Tabatabaei, M.D.4, Mahmod Noori-Shadkam, M.D.4, Mahta Mazaheri, M.D., Ph.D.2, Reihaneh Dehghani-Mohammadabadi, M.D.4

1. Department of Obstetrics and Gynecology, Semnan University of Medical Sciences, Semnan, Iran 2. Mother and Newborn Health Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran 3. Department of Medical Genetics, Shahid Sadoughi University of Medical Sciences, Yazd, Iran 4. Department of Obstetrics and Gynecology, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

Abstract

Background: Multiple studies have been carried out examining the association of tumor necrosis factor-α gene (TNF-α) promoter region polymorphisms with recurrent pregnancy loss (RPL) risk. However, the results remain controversial and incomplete. Hence, we performed a meta-analysis to evaluate the association of the TNF-α -308G>A and -238G>A polymorphisms with RPL risk.

Materials and Methods: In this meta-analysis, a comprehensive search of PubMed, Web of Knowledge and EMBASE was performed to identify relevant studies published until December 1, 2017. The associations were assessed by odds ratio (OR) and its corresponding 95% confidence interval (CI).

Results: A total of 29 case-control studies, comprising 20 studies on TNF-α -308G>A (3,461 cases and 3,895 controls) and nine studies on TNF-α -238G>A (2,589 cases and 2,664 controls), were included in the meta-analysis. Overall, we found TNF-α -308G>A to be associated with an increase in RPL risk under the homozygote (OR=1.716, 95% CI: 1.210-2.433, P=0.002) and the recessive (OR=1.554, 95% CI: 1.100-2.196, P=0.012) models. TNF-α -238G>A was also significantly associated with increased risk of RPL under the allele model (OR=1.554, 95% CI: 1.100-2.196, P=0.012). Stratified analysis revealed a more significant association between the TNF-α -308G>A polymorphism and increased RPL risk in Asians under the homozygote (OR=2.190, 95% CI: 1.465-3.274, P<0.001), the dominant (OR=1.642, 95% CI: 1.269-2.125, P<0.001) and the recessive (OR=1.456, 95% CI: 1.039-2.040, P=0.029) models, but not in Caucasians. A non-significant association was, however, identified between TNF-α -238G>A and RPL risk based on ethnicity. Moreover, TNF-α -308G>A and -238G>A polymorphisms were significantly associated with increased risk of RPL in high quality studies and polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) subgroups.

Conclusion: The present meta-analysis demonstrates that TNF-α -308G>A and -238G>A polymorphisms are associated with an increased risk of RPL.

Keywords: Meta-Analysis, Miscarriage, Pregnancy Loss, Polymorphism, Tumor Necrosis Factor-α

Introduction

Recurrent pregnancy loss (RPL) is traditionally defined as the occurrence of three or more (≥3) consecutive pregnancy losses; however, the American Society of Reproductive Medicine (ASRM) has recently redefined RPL as two or more pregnancy losses (1, 2). It is estimated that up to 3% of fertile couples have been diagnosed with RPL (3). Moreover, RPL is accompanied by an increased risk of other pregnancy complications such as preterm birth or small for gestational age newborns (4). RPL remains one of the most important issues in reproductive medicine and there are multiple barriers to the prevention, diagnosis and treatment of it (5).

Many studies have been undertaken to identify the underlying aetiology, however, the cause of miscarriage can be identified in only 50% of cases (1, 6). Maternal age and number of previous miscarriages are two independent risk factors for a further miscarriage (7). Moreover, the known causes of RPL include chromosomal and metabolic abnormalities, uterine anomalies and...