European Journal of Obstetrics & Gynecology and Reproductive Biology 200 (2016) 51–57

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Meta-analyses of associations between interleukin-10 polymorphisms and susceptibility to recurrent pregnancy loss

Young Ho Lee *, Jae-Hoon Kim, Gwan Gyu Song

Division of Rheumatology, Department of Internal Medicine, Korea University College of Medicine, Seoul, Republic of Korea

ARTICLE INFO

Article history:
Received 2 November 2015
Received in revised form 12 February 2016
Accepted 19 February 2016

Keywords:
RPL
Interleukin-10
Polymorphism
Meta-analysis

ABSTRACT

Objective: The aim of this study was to investigate whether interleukin-10 (IL-10) polymorphisms are associated with susceptibility to recurrent pregnancy loss (RPL).
Methods: We conducted a literature search using the PubMed and EMBASE databases and performed meta-analyses on the associations between IL-10 −1082 G/A, −819 C/T, and −592 C/A polymorphisms and RPL, using fixed- or random-effects models.
Results: A total of 15 papers involving 1858 RPL patients and 1949 controls were considered in this study. Meta-analysis of IL-10 −1082 G/A polymorphism revealed no association between RPL and the IL-10 −1082 G allele (OR = 0.999, 95% CI = 0.815–1.223, $p = 0.989$). However, meta-analysis of IL-10 −819 C/T polymorphism in all study subjects revealed an association between RPL and the IL-10 −819 C allele (OR = 0.680, 95% CI = 0.498–0.927, $p = 0.015$). Stratification by ethnicity indicated an association between the IL-10 −819 C allele and RPL in the Asian group (OR = 0.421, 95% CI = 0.226–0.783, $p = 0.006$), but not in the Caucasian and Arab groups (OR = 1.053, 95% CI = 0.218–5.077, $p = 0.949$, and OR = 0.800, 95% CI = 0.606–1.081, $p = 0.152$, respectively). Furthermore, a relationship between the IL-10 −592 C allele and RPL was identified in the Asian group (OR = 0.763, 95% CI = 0.633–0.919, $p = 0.004$), but not in the Caucasian and Arab groups.
Conclusions: The meta-analyses demonstrate that IL-10 −819 C/T and −592 C/A polymorphisms are associated with RPL susceptibility in Asian women, but not in the Caucasian and Arab populations.

Introduction

Recurrent pregnancy loss (RPL) is defined as two or more losses of pregnancies that had lasted less than 20 weeks, and involves a multifactorial etiology. Although a number of etiological factors have been identified, the cause of RPL remains unclear in approximately 50% of cases [1]. These unexplained occurrences may be due to immunological and genetic factors [2].

Successful pregnancy may be dependent on a balance between T-helper 1 (Th1)-mediated and T-helper 2 (Th2)-mediated immunity [3]. Abnormal immune reactivity in the context of the Th1/Th2 paradigm has been observed in RPL [4], and there is evidence of a diminished Th2 immune response to placental antigens in women with this condition [5]. Specifically, a change of cytokine balance in favor of Th2 cytokines such as interleukin-10 (IL-10) is considered essential for maintaining a normal pregnancy [6]. IL-10, produced by activated Th2 cells, is a multifunctional cytokine that possesses anti-inflammatory properties and the abilities to downregulate antigen presentation and macrophage activation. IL-10 acts as an inhibitory factor during the production of Th1 cytokines [7] and also has a key role in balancing the anti-inflammatory and pro-inflammatory milieu at the fetomaternal interface. It can regulate vascular activity and blunt inflammation-mediated vascular dysfunction at the fetomaternal interface as a potent vascular cytokine. Significantly lower levels of IL-10 are present in patients with RPL than in healthy pregnant women [8]. Owing to these known functions of IL-10, it is considered to be involved in the pathogenesis of RPL.

The *IL-10* gene maps to 1q31-32 and exhibits polymorphisms in its promoter region, which appears to be correlated with variations in transcription. Three of several polymorphisms of IL-10 have been studied in some detail; namely, −1082 G/A (rs1800896), −819 C/T (rs1800871), and −592 C/A (rs1800872). These three polymorphisms are located at the putative regulatory regions of

* Corresponding author at: Division of Rheumatology, Department of Internal Medicine, Korea University Anam Hospital, Korea University College of Medicine, 73, Inchon-ro, Seongbuk-gu, Seoul 02841, Republic of Korea. Tel.: +82 2 920 5645; fax: +82 2 922 5974.
E-mail address: lyhcgh@korea.ac.kr (Y.H. Lee).

http://dx.doi.org/10.1016/j.ejogrb.2016.02.032
0301-2115/

the IL-10 promoter [9]. The IL-10 −1082 G/A polymorphism lies within a putative Ets transcription factor-binding site, whereas −819 C/T lies within a putative positive regulatory region, and −592 C/A is within a putative STAT-3-binding site and a negative regulatory region. Thus, polymorphisms at these sites may modify the transcription factor-binding sites and affect IL-10 production.

Several studies have examined the association between IL-10 polymorphisms and RPL susceptibility, albeit with contradictory results, probably because of the low statistical powers of the individual studies [10–24]. Therefore, in this investigation of whether IL-10 −1082 G/A, −819 C/T, and −592 C/A polymorphisms are associated with RPL susceptibility, we used meta-analysis so as to overcome the limitations of interpretation of individual studies, resolve inconsistencies in reported data, and reduce the probability of random errors that cause false-positive or false-negative associations [25–27].

Methods

Identification of eligible studies and data extraction

A literature search was conducted to identify studies that examined associations between IL-10 polymorphisms and RPL susceptibility. The PubMed and EMBASE citation indices were used to locate articles published before October 2015, in which the presence of IL-10 polymorphisms had been determined in RPL patients and controls. Combinations of keywords such as "interleukin-10," "IL-10," "polymorphism," "recurrent miscarriage," and "recurrent pregnancy loss" were entered as both Medical Subject Headings and Text Words. In addition, all references cited in the retrieved articles were reviewed to identify additional studies not indexed by PubMed and EMBASE. Studies were included in the analysis if they met all of the following criteria: (i) they were case-control studies; (ii) they included patients with RPL, which was defined as two or more unexplained pregnancy losses in the first two trimesters of pregnancy; and (iii) they included genotype data concerning IL-10 −1082 G/A, −819 C/T, and −592 C/A polymorphisms. No language restriction was applied. The following were excluded: (i) studies containing overlapping data; (ii) studies in which genotype data could not be ascertained; (iii) reviews; and (iv) studies in which family members had been included and the analysis was based on linkage considerations. Information relating to the methods and results of the included investigations was extracted by two independent researchers. Disagreements were resolved by consensus or by the adjudication of a third researcher. The following information was extracted from each study: author(s), year of publication, ethnicity of the study population, number of cases and controls, and the genotype and allele frequencies of the IL-10 −1082 G/A, −819 C/T, and −592 C/A polymorphisms. Ethnicity is derived from the same historical founder population, and can be defined as a group of people who shares a common and distinctive culture, religion, or language. Most of the studies did not define specifically their ethnicities. Thus, we classified ethnic group based on the continent, language or religion. For example, we assumed if the study was done in China, all subjects were Asian.

Evaluations of statistical associations

We performed meta-analyses using allelic contrast, homozygote contrast, and recessive and dominant models. IL-10 allele frequencies in the relevant studies were determined using the allele counting method. The chi-square test was used to establish whether observed genotype frequencies in the control groups conformed to Hardy–Weinberg equilibrium (HWE). Point estimates of risks, odds ratios (ORs), and 95% confidence intervals (CIs) were determined for each study, and Cochran's Q statistic was used to assess within-study and between-study variation and heterogeneity [28]. The heterogeneity test was used to assess the probability of the null hypothesis that all studies were evaluating the same effect. When a significant Q statistic ($p < 0.10$) indicated heterogeneity across studies, a random-effects model was used in the meta-analysis, whereas a fixed-effects model was used in the absence of such heterogeneity. The fixed-effects model assumes that genetic factors have similar effects on RPL susceptibility across all studies and that observed variations between studies are caused by chance alone [29]. On the other hand, the random-effects model assumes substantial diversity among different investigations, and assesses both within-study sampling errors and between-study variance [30]. We quantified the effect of heterogeneity using I^2, which is equal to $100\% \times (Q - df)/Q$, where "Q" represents Cochran's Q and "df" is the degrees of freedom [31]. This measure ranges between 0 and 100%, and represents the proportion of inter-study variation attributable to heterogeneity rather than chance. I^2 values of 25%, 50%, and 75% were defined as low, moderate, and high estimates, respectively. Statistical tests were carried out using the Comprehensive Meta-Analysis computer program (Biostat, Englewood, NJ, USA).

Evaluation of heterogeneity and publication bias

To examine the potential source of heterogeneity observed in this meta-analysis, meta-regression was performed using the following variables: HWE and ethnicity. Although funnel plots are often used to detect publication bias, this type of plotting requires diverse study types of varying sample sizes and involves subjective judgments. Accordingly, we evaluated any publication bias by using Egger's linear regression test [32], which measures funnel plot asymmetry using a natural logarithmic scale of ORs.

Results

Studies included in the meta-analysis

Sixty-nine studies were identified by electronic and manual searches, and 19 were selected for full-text review based on the title and abstract details. Four studies were excluded because they discussed IL-10 polymorphisms other than those considered in this study, or showed insufficient data. Thus, 15 studies met our inclusion criteria [10–24], which involved 1858 RPL patients and 1949 controls belonging to five Caucasian, five Asian, and five Arab populations (Table 1). As such, ethnicity-specific meta-analysis was conducted only on the Caucasian, Asian, and Arab populations. Details of the IL-10 polymorphisms studied are summarized in Table 1.

Meta-analyses of IL-10 −1082 G/A, −819 C/T, and −592 C/A polymorphisms and RPL susceptibility

Meta-analysis of IL-10 −1082 G/A polymorphism revealed no association between RPL and the IL-10 −1082 G allele (OR = 0.999, 95% CI = 0.815–1.223, $p = 0.989$) (Table 2). Stratification by ethnicity indicated no association between the IL-10 −1082 G allele and RPL in the Caucasian, Asian, and Arab populations (Table 2, Fig. 1). No association was recorded between RPL and IL-10 −1082 G/A polymorphism by the analysis using the recessive or dominant models or contrast of homozygotes (Table 2). Meta-analysis of IL-10 −819 C/T polymorphism in all study subjects revealed an association between RPL and the IL-10 −819 C allele (OR = 0.680, 95% CI = 0.498–0.927, $p = 0.015$) (Table 3A). Stratification by ethnicity indicated an association between the IL-10 −819 C allele and RPL in the Asian group (OR = 0.421, 95% CI = 0.226–0.783, $p = 0.006$), but