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Association of *Interleukin-17A* rs2275913 Polymorphism with Recurrent Miscarriage: A Systematic Review and Meta-Analysis Study

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Abstract

Recurrent miscarriage (RM) is a condition defined as having three or more consecutive pregnancy losses before the 20 weeks of pregnancy. The present study was undertaken to investigate association of *Interleukin-17A (IL-17A)* rs2275913 polymorphism with RM. To this end, we searched the international databases (Web of Science, PubMed, Embase, and Scopus) and extracted studies investigating the association of *IL-17A* rs2275913 polymorphism with RM using the appropriate keywords. The collected data were analyzed with the random-effects model and STATA (version 14). A total of five studies met the eligibility criteria, and total sample size was 998 subjects. Mean age of the cases and controls were 31.41 ± 4.16 and 30.56 ± 3.5 years, respectively. Our results disclosed a significant relationship of the *IL-17A* rs2275913 AA genotype [odds ratio (OR)=1.68; 95% confidence interval (CI)=1.16-2.43; I^2=19; P=0.294) with RM. There was no statistically significant correlation between *IL-17A* rs2275913 GG genotype (OR=1.04; 95% CI=0.64-1.7; I^2=59.5; P=0.042) and GA genotype (OR=0.85; 95% CI=0.65-1.1^2; I^2=19.1; P=0.293) with RM. Our findings revealed that the *IL-17A* rs2275913 polymorphism is associated with RM, and the AA genotype of this polymorphism increased possibility of being involved in RM.

Keywords: *IL-17A* rs2275913, Polymorphism, Recurrent Miscarriage

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Introduction

Recurrent or repeated miscarriage (RM) is defined as having three or more consecutive pregnancy losses before the 20 weeks of pregnancy (1). The exact pathophysiology of RM is still unknown; however, several underlying factors, such as chromosomal abnormalities, anatomical defects, hormonal problems, thrombophilic disorders, infections, and immune system factors have been attributed to this condition (2-4). Studies showed that Th1/Th2 immune balance played a prominent role in reproductive phenomena (5), in which the dominant Th2-type response was associated with normal pregnancy, while the Th1-type response correlated with pregnancy failure (6). Cytokine production can be affected by genetic polymorphisms, particularly in the promoter regions, giving rise to high, medium, or low levels of cytokines (7). Association of the such polymorphisms and production of various cytokines has been reported as an important factor for pregnancy (8).

Interleukin (IL)-17 is a well-known proinflammatory cytokine mainly produced by a subset of T-helper cells, i.e. Th17 cells (9, 10). IL-17 family member comprises of six closely related cytokines, from *IL-17A* to *IL-17F* (11). Two of the most studied cytokines, *IL-17A* and *IL-17F*, are located in the adjacent positions on chromosome 6 with almost 50% sequence identity, targeting the same receptor, and exhibiting similar biological properties (12). IL17 is considered an important factor in inflammation and autoimmunity, and it can influence the pathogenesis of RM (6). The rs2275913 SNP, produced via replacement of the guanine (G) by adenine (A) nucleotide base in the *IL-17A* gene promoter,

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was significantly associated with a large number of diseases (13-15). Allelic variants of rs2275913 single-nucleotide polymorphism (SNP) have been indicated to differently bind to the nuclear factor of activated T cells, leading to variations in IL-17A secretion (16).

The aim of the study was to investigate the association of IL-17A rs2275913 polymorphism with RM.

Material and Methods

The present study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (17).

Search strategies

A comprehensive search was performed to extract the published studies reporting association of IL-17 polymorphisms with recurrent spontaneous abortion. The used keywords included "rs2275913", "polymorphism", "*IL17A*", "*interleukin-17*", "recurrent miscarriage", "fetal loss", "pregnancy loss", "abortion", "RM", "frequency", "mutation", "variation", and "genotype". These keywords were also combined using Boolean operators ("OR" and "AND") to search international databases, including ISI, PubMed, Embase, and Scopus. Google Scholar was searched for the studies not included in the mentioned databases. Thereafter, references of the extracted studies were checked to find potentially relevant studies. All records were then imported into the EndNote, and duplicate findings were deleted.

Study selection

After eliminating the duplicate studies, title and abstract of the remaining articles were checked to find eligible studies based on the following inclusion and exclusion criteria. Inclusion criteria included original case-control studies on association of the rs2275913 polymorphism and RM with extractable data, studies with similar objectives and statistical methods, sufficient published details to estimate odds ratio (OR) and 95% confidence interval (CI), as well as selection of patients based on the standard and reliable diagnostic parameters. The exclusion criteria included review articles, meta-analyses, congressional abstracts, studies in languages other than English, and withdrawn articles. Eligible studies were selected by two authors rechecked and confirmed by all authors.

Data extraction and quality assessment

Data were extracted from the selected studies by two different authors. The data included location, publication date, genotyping method, age and the number of case and control participants, as well as *IL-17A* rs2275913 polymorphism. All data were reviewed for potential bias by the other authors and then confirmed by all authors. The Newcastle-Ottawa scale was used to assess methodology and quality of the studies. Articles with scores 0-3, 4-6, and 7-9 were considered as low, medium, and high quality respectively; none of the studies scored <4.

Data synthesis and analysis

Mean of the sample size and standard deviations of the predicted data were combined. Studies were then weighted using the inverse-variance method. The Q-test and I^2 index, with an α-level of significance (<10%), were used to verify heterogeneity of the included studies. The heterogeneous data were then analyzed by random-effects model. All data were finally entered into STATA version 14.

Risk of bias between studies

Begg's funnel plots and Egger's test were selected to evaluate publication bias of the data, and $P<0.05$ were considered statistically significant.

Results

The present meta-analysis included five original published studies investigating the association of *IL-17A* rs2275913 polymorphisms with RM (Table 1). The study selection process is illustrated in Figure 1. The total sample size was 998 subjects (440 cases and 459 controls, with mean ages of 31.41 ± 4.16 and 30.56 ± 3.5 years, respectively). For statistical calculations, the genotypes of the subjects were classified into wild type (AA), homozygotes, heterozygotes (GA), and mutant homozygotes (GG) (Table 2).

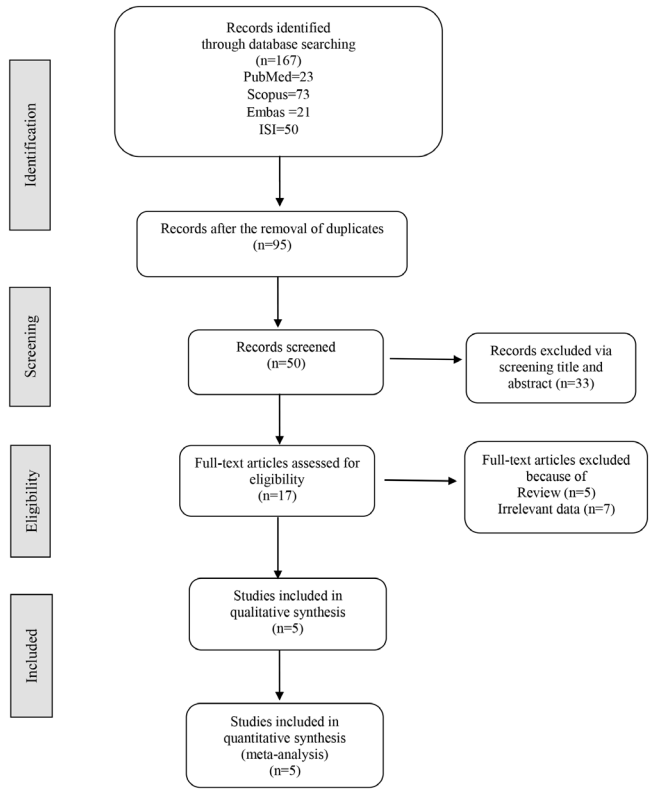

Fig.1: PRISMA flow diagram illustrating the selection of the articles.

Table 1: Characterizations of articles reviewed in the present study

First author (reference)	Publication year	Location	Genotyping method	Sample size		Mean age ± SD		Quality assessment score*
				Case	Control	Case	Control	
Baqer et al. (8)	2021	Iraq	Real-time PCR	50	50			5
Najafi et al. (18)	2014	Iran	PCR-RFLP	85	85	30.84 ± 5.2	29 ± 4.4	5
Alkhuriji (19)	2017	Saudi Arabia	Real-time PCR	100	100	33.2 ± 0. 62	33.1 ± 0.73	5
Bahadori et al. (20)	2014	Iran	PCR-RFLP	85	104			5
Zidan et al. (21)	2015	Egypt	PCR-RFLP	120	120	31.6 ± 6 28	30.6 ± 7.8	6

*; The Newcastle-Ottawa (NOS) scale. PCR-RFLP; Polymerase chain reaction-restriction fragment length polymorphism.

Table 2: The frequency of *IL-17A* rs2275913 genotypes and alleles in recurrent miscarriage (RM) and control group

First author (reference)	Cases				Controls				Cases		Controls	
	Total	AA	GG	GA	Total	AA	GG	GA	A allele	G allele	A allele	G allele
Baqer et al. (8)	50	0	33	17	50	2	28	20	17	83	24	76
Najafi et al. (18)	85	52	7	26	85	46	3	36	130	40	128	42
Alkhuriji (19)	100	11	56	33	100	3	67	30	36	164	55	145
Bahadori et al. (20)	85	7	41	37	104	7	39	58	70	100	79	129
Zidan et al. (21)	120	36	34	50	120	22	49	49	122	118	93	147

According to the random-effects model, there was no statistically significant relationship between IL-17 rs2275913 A allele (OR=0.98; 95% CI=0.66-1.45; I^2=70.9; P=0.008) and G allele (OR=1.02; 95% CI=0.69-1.51; I^2=70.9; P=0.008) with recurrent spontaneous abortion. In line with the fixed-effects model, a statistically significant association was detected between *IL-17A* rs2275913 AA (OR=1.68; 95% CI=1.16-2.43; I^2=19; P=0.294) genotype and RM. The presence of the *IL-17A* rs2275913 AA genotype in women showed an increased risk of RM by 1.68-fold (Fig.2). Furthermore, based on the random-effects model, there was no statistically significant relationship between the *IL-17A* rs2275913 GG genotype (OR=1.04; 95% CI=0.64-1.7; I^2=59.5; P=0.042) and GA genotype (OR=0.85; 95% CI=0.65-1.12; I^2=19.1; P=0.293) with RM (Figs.3, 4).

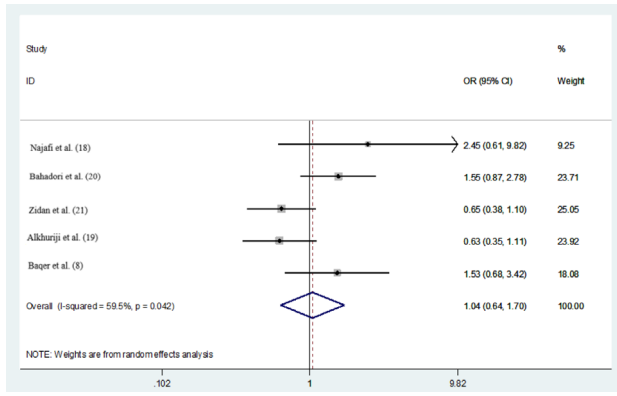

Fig.3: Forest plots for GG genotype showing the relationship of IL-17 rs2275913 polymorphism with RM. Studies are ordered by the date of publication and authors' name based on a fixed-effects model. Square represents the effect estimate of individual studies with more than 95% confidence intervals with the size of squares proportional to the weight assigned to the study in the meta-analysis. Diamond denotes the overall estimation. OR; Odds ratio and CI; Confidence interval.

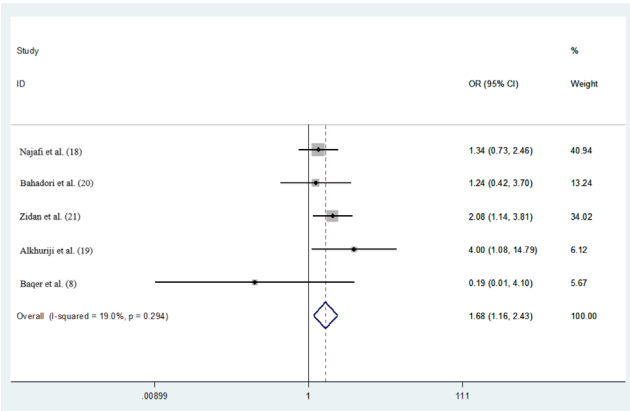

Fig.2: Forest plots for AA genotype showing the relationship of IL-17 rs2275913 polymorphism with RM. Studies are ordered by the date of publication and authors' name based on a fixed-effects model. Square represents the effect estimate of individual studies with more than 95% confidence intervals with the size of squares proportional to the weight assigned to the study in the meta-analysis. Diamond denotes the overall estimation. OR; Odds ratio and CI; Confidence interval.

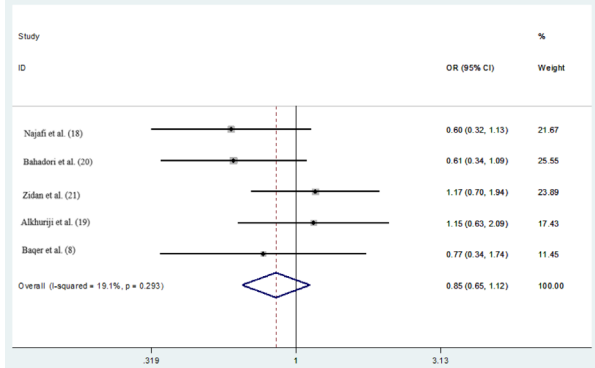

Fig.4: Forest plots for GA genotype showing the relationship of IL-17 rs2275913 polymorphism with RM. Studies are ordered by the date of publication and authors' name based on a fixed-effects model. Square represents the effect estimate of individual studies with more than 95% confidence intervals with the size of squares proportional to the weight assigned to the study in the meta-analysis. Diamond denotes the overall estimation. OR; Odds ratio and CI; Confidence interval.

Risk of bias between studies

No significant publication bias was observed for either outcome using the Begg's (P=0.052) and Egger's (P=0.166) tests. Figure 5 represents the risk of publication bias among studies based on the two above-mentioned tests.

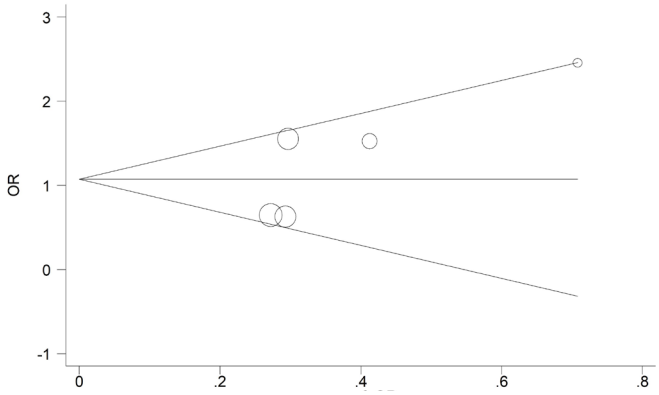

Fig.5: Beggs funnel plot for publication bias, representing a pseudo 95% confidence limit. OR; Odds ratio.

Discussion

Recurrent pregnancy loss or miscarriage of pregnancy is the most serious pregnancy-related disorder. Several immune-related and anatomic causes have been introduced as potential etiological reasons for RM (22, 23). However, further efforts are needed to find a detailed explanation for the pathophysiology of this condition (24). Consequently, new studies are focusing on the polymorphisms of a gene and its possible associations with RM (25). In this regard, the current meta-analysis was conducted to investigate whether the rs2275913 polymorphism is associated with RM or not (26).

As mentioned in the result section, this study included five published papers regarding the association of *IL-17A* rs2275913 polymorphism with RM. Our meta-analysis revealed the relationship of AA genotype with a higher risk of RM, but no significant association was found between single A or G alleles, as well as GA and GG genotypes with RM. According to our search, there was not any previous meta-analysis investigating the association of *IL-17A* rs2275913 polymorphism with RM or any other pregnancy-related condition. However, meta-analyses on cancer and inflammatory diseases such as rheumatoid arthritis have suggested strong associations between the *IL-17A* rs2275913 polymorphism and the mentioned diseases (27, 28).

Studies included in our meta-analysis showed controversial results regarding the association of IL-17A rs2275913 polymorphism with RM. Two studies conducted by Alkhuriji (19) and Zidan et al. (21) reported a significantly higher frequency of the AA genotype among patients than controls, while Baqer et al.'s (8) study stated a protective role for the AA genotype. Baqer's study also showed a significant association between the GG genotype and lower serum *IL-17A* concentration. However, two other studies from Iran did not suggest any significant association with any of the mentioned genotypes (18, 20).

The rs2275913 polymorphism has been studied in other pregnancy-related conditions such as preeclampsia. An original study in China displayed the association of the AG genotype and A allele with preeclampsia, a pregnancy-related inflammatory disease, with a significant role for IL-17 (29). The significant role of Th17 and IL-17 in pregnancy-related conditions, especially RM, has also been thoroughly investigated. Most of the studies in this regard have shown that the higher frequency of IL-17-producing cells and the higher serum concentration of IL-17 have a role and are associated with RM (6, 30). Disturbed Treg/Th17 balance has been exhibited to be an important feature in cases that have experienced RM. The study of Nakashima et al. (31) investigated the proportion of Th17 cells in peripheral blood at all stages of pregnancy and showed that the number of Th17 cells remained unchanged during pregnancy. According to the results of the study by Lee et al. (12). An increase in the number of Th17 cells during pregnancy as well as an increase in the ratio of pro-immune T cells versus regulatory immune T cells may lead to an inflammatory response that may contribute to the development of RM, and this results in consistent with our results which showed the association between the AA genotype of the *IL17A* rs2275913 polymorphism with RM (6).

Our study encountered some limitations that should be considered. First, insufficient sample size may compromise our ability to reveal a statistical relationship, Second, all the studies included in this meta-analysis were from middle east countries, and more worldwide studies are needed. Third, in terms of the experimental process, two studies used real-time PCR, and three studies used the PCR-RFLP method. As these two methods may have different detection accuracy, this difference could result in contradictory results.

Conclusion

The present meta-analysis study indicated that there is a consistent and significant association between the *IL-17A* rs2275913 polymorphism and RM, implying that this polymorphism is a potential marker for RM. Also, the results showed that the presence of AA genotype is associated with a higher risk of developing RM.

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Authors' Contributions

A.K.M, N.Z.; Designed the conception of the study. A.K.M., S.Z., Z.Z., S.I.; Focused on the statical analysis. N.Z., F.Sh., H.M., M.A.; Performed technical support and provided conceptual advice. All authors contributed to the

drafted the manuscript, revised it critically and approved the final version.

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