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Review

Vascular endothelial growth factor and recurrent spontaneous abortion: A meta-analysis

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ABSTRACT

To evaluate the association between vascular endothelial growth factor (VEGF) gene polymorphisms and the risk of recurrent spontaneous abortion (RSA), a meta-analysis of published case–control studies for the VEGF gene polymorphisms (gene polymorphisms reported more than three times were selected) and the risk of RSA. Odds ratios (ORs) and 95% confidence intervals (CIs) for codominant, dominant and recessive genetic models were assessed by RevMan software. Eight studies with 2813 cases and 2830 controls were included in this meta-analysis. The pooled analysis showed that −2578C/A, −1154G/A polymorphisms of VEGF were not significantly associated with the risk of RSA neither under codominant model nor under dominant model, nor under recessive model. Whereas, for −634G/C polymorphism, the pooled OR and 95% CI were 1.23 (1.01–1.49) under recessive model; and for 936C/T polymorphism, the pooled OR and 95% CI were 1.34 (1.07–1.67) and 1.40 (1.09–1.80) under codominant and dominant models, respectively. This meta-analysis suggested that VEGF gene −2578C/A, −1154G/A polymorphisms were not significantly associated with the risk of RSA, whereas, −634G/C and +936C/T polymorphisms were associated with the risk of RSA under specific genetic models.

Contents

Abbreviations: RSA, recurrent spontaneous abortion; VEGF, vascular endothelial growth factor; OR, odds ratio; CI, confidence interval; HWE, Hardy–Weinberg equilibrium; REM, random effect model; FEM, fixed effect model.

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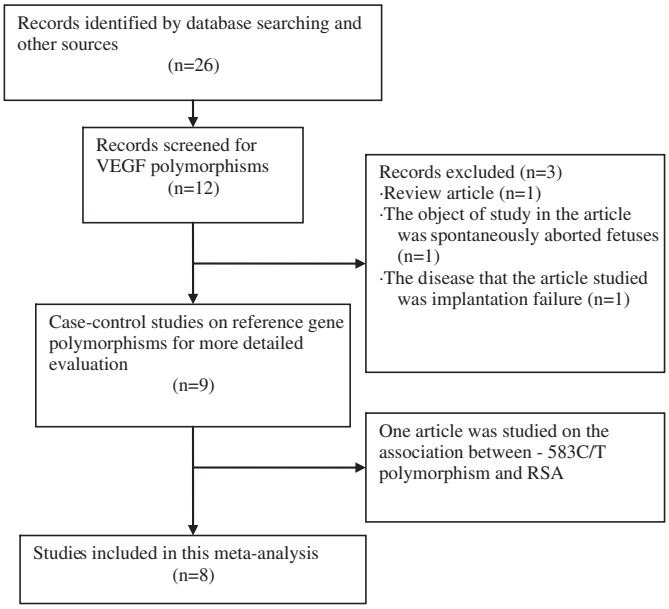

Fig. 1. The flow diagram for selection of studies.

1. Introduction

Recurrent spontaneous abortion (RSA) is defined as the occurrence of three or more clinically detectable pregnancy losses before the 20th week of gestation with the same partner (Sierra and Stephenson, 2006) and it is a major reproductive problem affecting 1–3% otherwise healthy women (Brown, 2008). The diagnosis of RSA undergoes multiple tests to detect parental chromosomal anomalies, maternal immunological, hormonal, or thrombotic disorders and anatomic abnormalities of the genital tract. However, in up to 50% of patients who experience RSA, the underlying causes remain undetermined (Li et al., 2002).

Vascular endothelial growth factor (VEGF) is a potent angiogenic factor and a survival factor for endothelial cells during physiological and tumor angiogenesis, and functions in vasodilatation, vascular permeability and anti-apoptosis (Benjamin and Keshet, 1997; Ferrara et al., 2003). VEGF plays an essential role in fetal and placental angiogenic development; mice lacking the expression of VEGF die in utero due to inadequate vascular formation (Ferrara, 2004; Hiratsuka et al., 2005). Besides, VEGF plays a critical role in oocyte maturation, decidualized endometrial vascularization, embryo implantation and placenta angiogenesis in early gestation (Jackson et al., 1994; Krüssel et al., 2000, 2001; Zygmunt et al., 2003). Several VEGF polymorphisms have been reported to affect VEGF activity and expression (Awata et al., 2002; Brogan et al., 1999; Mohammadi et al., 2009; Renner et al., 2000). The polymorphisms of VEGF −2578C/A (rs699947), −1154G/A (rs1570360), −634G/C (rs2010963) and +936C/T (rs3025039) are the four of the most commonly studied loci, and are suggested to be potentially associated with the risk of RSA. However, the currently available results are still controversial, some studies supported that the polymorphisms were risk factors for RSA (Aggarwal et al., 2011; Coulam and Jeyendran, 2008), whereas other studies drew converse conclusions (Traina et al., 2011; Xing et al., 2011). Hence, we decided to perform this meta-analysis on the effect of VEGF gene polymorphisms on the risk of RSA.

2. Materials and methods

2.1. Search strategy

Studies were identified by searches of ISI Web of Science, PubMed MEDLINE and EMBASE databases for relevant articles published in English before March 2012, using the search terms: vascular endothelial growth factor or VEGF, in combination with recurrent spontaneous abortion (RSA), recurrent pregnancy loss (RPL), recurrent miscarriage (RM) and recurrent fetal loss (RFL). Besides, the bibliographies of relevant studies, review articles and meta-analysis articles were also considered. The article search was performed independently by three investigators (Zhang, Dai, and Zhang).

2.2. Inclusion criteria

The inclusion criteria were as follows: (1) case–control study published as an original study and with clinical diagnosis criteria of RSA. RSA is defined as the occurrence of three or more clinically detectable pregnancy losses before the 20th week of gestation. (2) Only unexplained or idiopathic abortions (i.e., abortions with "known"

Table 1
Characteristics of the studies included in this meta-analysis.

Gene polymorphism	Author	Year	Country	Genotype [a]		*P* for HWE [b]
				Case	Control	
−1154G/A	Papazoglou	2005	Greece	18/19/15	42/28/12	0.055
(rs1570360)	Coulam	2008	USA	26/101/25	10/51/4	0.000
	Lee	2010	South Korea	130/80/5	81/23/9	0.000
	Su	2011	China	74/37/4	124/39/7	0.094
	Xing	2011	China	245/89/5	200/81/10	0.613
	Aggarwal	2011	India	120/48/32	135/47/18	0.000
	Eller	2011	USA	55/27/11	85/75/18	0.808
−2578C/A	Papazoglou	2005	Greece	15/21/16	27/34/21	0.132
(rs699947)	Lee	2010	South Korea	107/94/14	60/45/8	0.912
	Aggarwal	2011	India	103/74/23	116/67/17	0.111
	Eller	2011	USA	38/43/15	44/96/37	0.250
−634G/C	Papazoglou	2005	Greece	14/22/16	29/35/18	0.237
(rs2010963)	Lee	2010	South Korea	67/114/34	38/54/21	0.814
	Eller	2011	USA	36/45/15	88/73/18	0.620
	Traina	2011	Brazil	23/37/17	27/47/11	0.177
+936C/T	Papazoglou	2005	Greece	35/16/1	64/17/1	0.914
(rs3025039)	Lee	2010	South Korea	149/63/3	82/29/2	0.757
	Aggarwal	2011	India	142/52/6	164/35/1	0.549
	Eller	2011	USA	67/29/1	126/45/5	0.688
	Traina	2011	Brazil	59/20/1	101/27/1	0.578

[a] Genotype, for −1154G/A, GG/GA/AA; for −2578C/A, CC/CA/AA; for −634G/C, GG/GC/CC; and for +936C/T, CC/CT/TT.
[b] HWE, Hardy–Weinberg equilibrium.