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META-ANALYSIS

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Meta-Analysis of the Association between Plasminogen Activator Inhibitor-1 4G/5G Polymorphism and Recurrent Pregnancy Loss

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BCDEF Xuejiao Li
BCD Yukun Liu
CD Rui Zhang
CD Jianping Tan
F Libin Chen
ABCDEF Yinglin Liu

Department of Obstetrics and Gynecology, Sun Yat-sen Memorial Hospital of Sun Yat-sen University, Guangzhou, Guangdong, P.R. China

Corresponding Author: Yinglin Liu, e-mail: lyl-sharry@163.com
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Background: The association between plasminogen activator inhibitor-1 (PAI-1) 4G/5G polymorphism and recurrent pregnancy loss (RPL) risk is still contradictory. We thus performed a meta-analysis.

Material/Methods: Relevant studies were searched for in PubMed, Web of Science, Embase, and Cochrane Library. An odds ratio (OR) with a 95% confidence interval (CI) was used to assess the association between PAI-1 4G/5G polymorphism and RPL risk.

Results: A total of 22 studies with 4306 cases and 3076 controls were included in this meta-analysis. We found that PAI-1 4G/5G polymorphism was significantly associated with an increased RPL risk (OR=1.89; 95% CI 1.34–2.67; *P*=0.0003). In the subgroup analysis by race, PAI-1 4G/5G polymorphism was significantly associated with an increased RPL risk in Caucasians (OR=2.23; 95% CI 1.44–3.46; *P*=0.0003). However, no significant association was observed in Asians (OR=1.47; 95% CI 0.84–2.59; *P*=0.18).

Conclusions: In conclusion, this meta-analysis suggests that PAI-1 4G/5G polymorphism might be associated with RPL development in Caucasians.

MeSH Keywords: Abortion, Habitual • Plasminogen Activator Inhibitor 1 • Polymorphism, Genetic

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Background

Recurrent pregnancy loss (RPL) is a common clinical problem that may occur during pregnancy. About 15% of clinically recognized pregnancies could suffer from RPL before the 20th week of gestation, with no known cause [1]. The pathogenesis of RPL remains unknown in many patients, and approximately 55% of patients are suspected to have thrombophilic defects [2].

Thrombophilia is a common cause of RPL and is found in 40–50% of cases [3]. Laude et al. found that levels of circulating procoagulant microparticles were higher in women with RPL when compared with controls [4]. Thrombophilia might cause a syncytiotrophoblast invasion of the maternal blood vessels, which could lead to the formation of microthrombosis at the site of implantation and result in RPL and implantation failure [5].

Plasminogen activator inhibitor-1 (PAI-1) is the urinary plasminogen activator and principal inhibitor of tissue. The main function of PAI-1 is converting plasminogen to the proteolytic enzyme plasmin [6]. Sun and colleagues found that PAI-1 4G/5G polymorphism was significant positive explanatory variable for polycystic ovary syndrome (PCOS) patients with spontaneous abortions [7]. In addition, PAI-1 4G/5G polymorphism was associated with increased PAI-1 concentrations and hypofibrinolysis and contributed to early pregnancy loss [7]. Many studies assessed the association between PAI-1 4G/5G polymorphism and RPL risk [8–29]. However, the result was still uncertain. A meta-analysis found that PAI-1 4G/5G polymorphism did not increase the risk of RPL. However, recent studies did not confirm this result [24,25,27]. Therefore, we conducted this meta-analysis to investigate the association between PAI-1 4G/5G polymorphism and RPL risk.

Material and Methods

Publication search

Relevant studies were searched for in PubMed, Web of Science, Embase, and Cochrane Library. The following terms and strategies were used for the search: ("Plasminogen activator inhibitor-1" OR "PAI-1") AND ("single nucleotide polymorphism" OR "SNP" OR "genetic variation" OR "genetic polymorphism") AND ("Recurrent pregnancy loss" OR "RPL"). To avoid possible missing of qualified trails, introduction and reference list of eligible trails identified through primary search were screened manually. No language restriction was applied when searching.

Inclusion and exclusion criteria

The following criteria were used to screen eligible studies for this meta-analysis: (1) a case–control study or cohort study that studied the association between PAI-1 4G/5G polymorphism and RPL risk; and (2) sufficient data were available for calculation of allele/genotype frequency. Only studies meeting both these criteria were included for analysis.

Data extraction

Two authors extracted the data independently. These data included: the first author, year, ethnicity, genotype distribution, and sample size. Disagreement in data extraction was resolved by group discussion by referring to original studies with a third reviewer.

Statistical analysis

The odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated to assess the association between PAI-1 4G/5G polymorphism and RPL risk. The recessive genetic model (4G/4G *vs.* 4G/5G+5G/5G) was chosen, because PAI-1 4G/4G genotype was significantly associated with increased PAI-1 production. The significance of pooled estimates was assessed with Z test. Hardy-Weinberg equilibrium (HWE) of genotype frequency in the control group was assessed by chi-square test. Between-studies heterogeneity was assessed by the chi-square-based Q test and I^2. $P<0.1$ or $I^2>50\%$ was considered as significant heterogeneity. If no significant heterogeneity was observed, fixed-effects model with Mantel-Haenszel method was used to make estimates. However, if significant heterogeneity observed, the sources of heterogeneity would be further analyzed by Galbraith plots. If there were no significant clinical or methodological differences in trails, the random effects model based on DerSimonian-Laird method was be used. Subgroup analysis was performed based on ethnicity of participants recruited in each study. A cumulative meta-analysis was conducted. Sensitivity analysis by another model, HWE, and sample size were also conducted. Publication bias was tested using Begg's test and funnel plot ($P<0.05$ was considered as significant). Statistical analysis was conducted using Stata software 11.0 (StataCorp, College Station, Texas, USA).

Results

Study characteristics

After searching and screening with preset criteria, a total of 22 studies with 4306 cases and 3076 controls were included for this meta-analysis. Four studies were conducted in Asians and 18 in Caucasians. The characteristics and the HWE results of the included studies are listed in Table 1. Four studies were not in HWE.

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

Study	Year	Ethnicity	Case	Control	Case			Control			HWE
					4G/4G	4G/5G	5G/5G	4G/4G	4G/5G	5G/5G	
Wolf	2003	Caucasian	49	102	17	25	7	32	50	20	Yes
Buchholz	2003	Caucasian	184	127	72	75	37	41	58	28	Yes
Dossenbach-Glaninger	2003	Caucasian	49	48	12	28	9	8	25	16	Yes
Guan	2005	Asian	127	117	58	52	17	20	59	38	Yes
Coulam	2006	Caucasian	150	20	11	117	22	2	13	5	Yes
Coulam	2008	Caucasian	550	41	39	396	115	6	22	13	Yes
Goodman	2009	Caucasian	120	84	38	57	25	23	48	13	Yes
Al Sallout	2010	Caucasian	100	100	16	44	40	16	48	36	Yes
Ivanov	2010	Caucasian	110	97	46	44	20	26	45	26	Yes
Ivanov	2011	Caucasian	52	125	14	23	15	26	45	26	Yes
Aarabi	2011	Caucasian	63	114	19	30	14	25	47	22	Yes
Jeddi-Tehrani	2011	Caucasian	100	100	9	31	60	1	27	72	Yes
Idali	2012	Caucasian	106	100	17	53	35	1	27	72	Yes
Torabi	2012	Caucasian	100	100	9	31	60	1	27	72	Yes
Ozdemir	2012	Caucasian	543	327	121	331	91	10	62	34	No
Parveen	2013	Asian	200	300	45	100	55	74	131	95	No
Magdoud	2013	Caucasian	304	371	37	128	139	10	104	257	Yes
Subrt	2013	Caucasian	157	74	59	75	23	10	54	10	No
Jeon	2014	Asian	308	227	129	132	47	71	117	39	Yes
Khosravi	2014	Caucasian	595	100	122	288	184	1	27	72	Yes
Kim	2014	Asian	227	304	73	123	31	102	154	48	Yes
Lino	2014	Caucasian	112	98	12	57	37	16	40	42	Yes

HWE – Hardy-Weinberg equilibrium.

Meta-analysis results

As shown in Figure 1, we found that PAI-1 4G/5G polymorphism was significantly associated with an increased RPL risk (OR=1.89; 95% CI 1.34–2.67; *P*=0.0003). In the subgroup analysis by race, PAI-1 4G/5G polymorphism was significantly associated with an increased RPL risk in Caucasians (OR=2.23; 95% CI 1.44–3.46; *P*=0.0003). However, no significant association was observed in Asians (OR=1.47; 95% CI 0.84–2.59; *P*=0.18). Results of the meta-analysis are listed in Table 2. In the sensitivity analysis, when the fixed-effects model was used, the result was still positive (OR=1.87; 95% CI 1.64–2.13; *P*<0.00001). When the studies without HWE were excluded, the result was not changed (OR=1.56; 95% CI 1.12–2.19; *P*=0.009). Furthermore, when the studies with small sample size were excluded, the result was also not changed (OR=1.98; 95% CI 1.25–3.13; *P*=0.004). The results of sensitivity analysis are listed in Table 3.

Results from the cumulative meta-analysis suggest that the evidence was consistent over time (Figure 2), indicating that the results of this meta-analysis are robust. Significant heterogeneity (I^2=81%) was detected in the recessive genetic model. Thus, we used the Galbraith plot to explore the source of the heterogeneity. As shown in Figure 3, 10 studies were considered as outliers. When these studies were excluded, the heterogeneity was decreased. No obvious heterogeneity among the remaining studies could be found (I^2=0%). Furthermore, the result was significant (OR=1.48, 95% CI 1.22–1.79, *P*<0.0001). No significant publication bias was found by Begg's funnel plot (Figure 4) and Egger's test (*P*=0.313).

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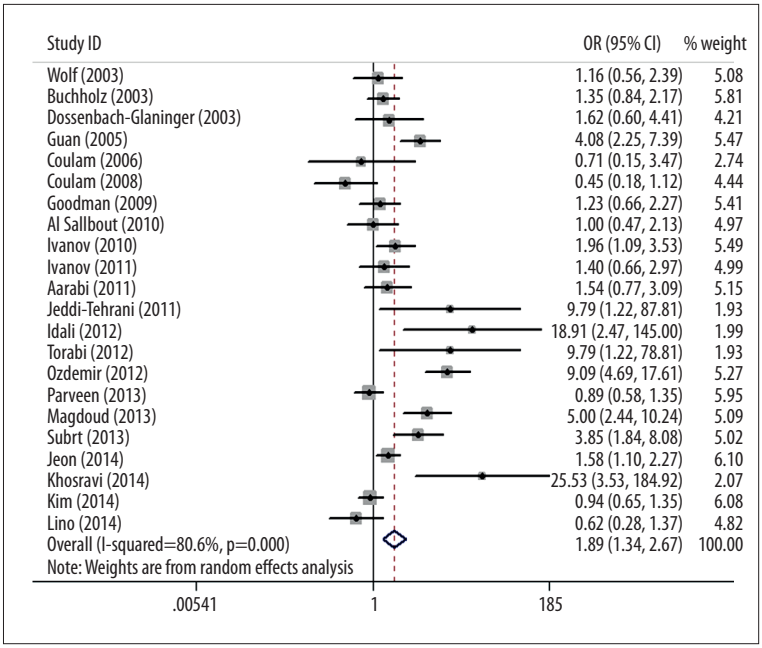

Figure 1. Forest plot of RPL risk associated with PAI-1 4G/5G polymorphism.

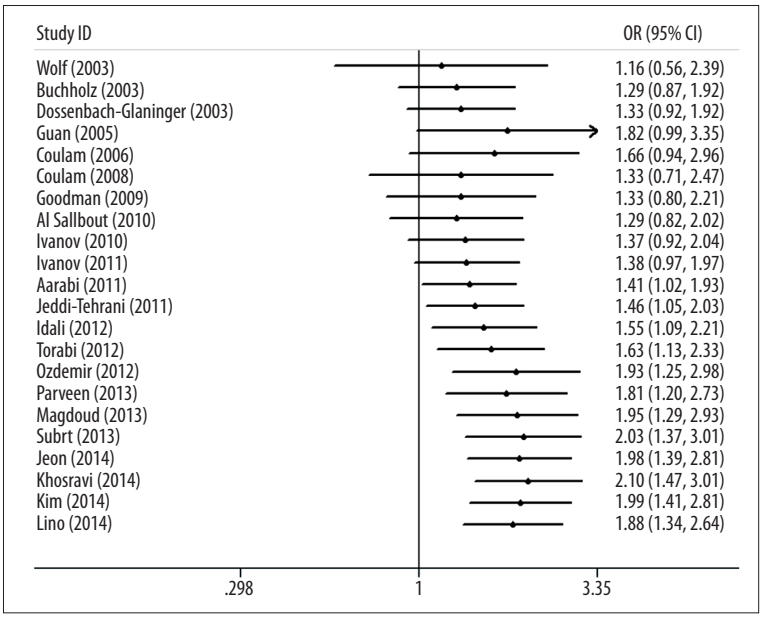

Figure 2. Cumulative meta-analysis of the association between PAI-1 4G/5G polymorphism and RPL risk.

Discussion

Our previous meta-analysis investigated the association between PAI-1 4G/5G polymorphism and RPL risk [30]. However, that meta-analysis did not find a positive association between PAI-1 4G/5G polymorphism and risk of RPL. Several new studies have been published since then. Thus, we did a new meta-analysis. When these new studies were included, we found that PAI-1 4G/5G polymorphism was significantly associated with risk of RPL, indicating that PAI-1 4G/5G polymorphism carriers might have increased RPL risk. In the subgroup analysis based on race, PAI-1 4G/5G polymorphism showed increased RPL risk in Caucasians. However, no positive association was found in Asians. Ethnic differences can occur in genotype frequencies, which might account for the different results. In addition, there were only four studies with Asians. More studies with Asian populations are needed to validate this result. We then did cumulative meta-analysis. We found that the result from our meta-analysis was stable. In the sensitivity analyses, we also found the results were not altered, indicating this meta-analysis was robust.

In human and animal models, PAI-1 was involved not only in fibrinolysis regulation, but also in extracellular proteolytic processes during ovulation, ovarian follicle growth, and embryo

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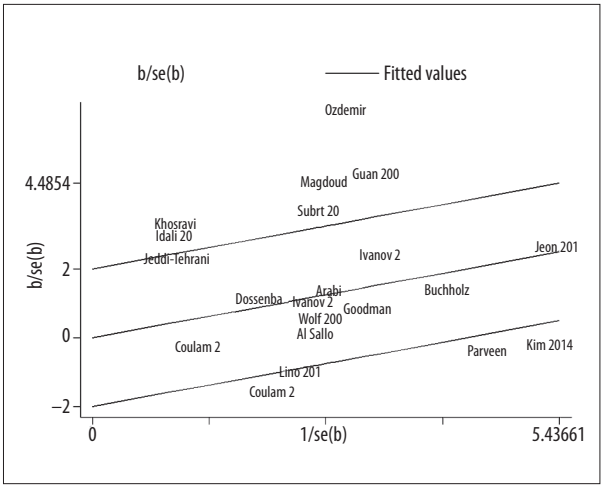

Figure 3. Galbraith plot of the association between PAI-1 4G/5G polymorphism and RPL risk.

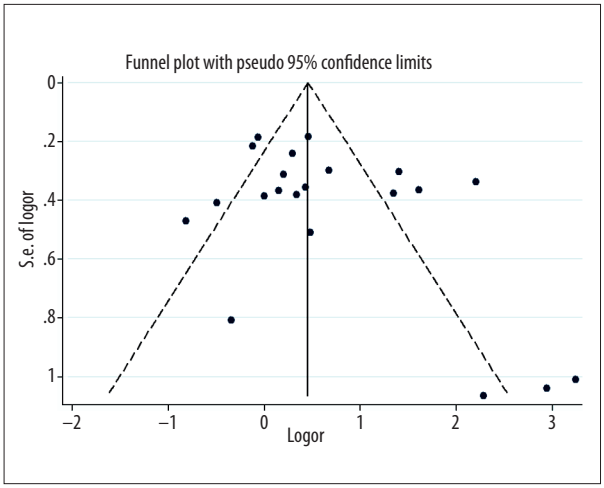

Figure 4. Funnel plot analysis to detect publication bias for PAI-1 4G/5G polymorphism and RPL risk.

Table 2. Results of meta-analysis.

Comparison	Subgroup	No. studies	OR (95% CI)	P Value	I^2 (%)
4G/4G *vs.* 4G/5G+5G/5G	Overall	22	1.89 (1.34–2.67)	0.0003	81
4G/4G *vs.* 4G/5G+5G/5G	Asian	4	1.47 (0.84–2.59)	0.18	86
4G/4G *vs.* 4G/5G+5G/5G	Caucasian	18	2.23 (1.44–3.46)	0.0003	79

Table 3. Results of sensitivity analyses.

Comparison	Subgroup	No. studies	OR (95% CI)	P Value	I^2 (%)
4G/4G *vs.* 4G/5G+5G/5G	Fixed-effect model	22	1.84 (1.61–2.09)	<0.00001	81
4G/4G *vs.* 4G/5G+5G/5G	HWE	19	1.56 (1.12–2.19)	0.009	67
4G/4G *vs.* 4G/5G+5G/5G	n<200	16	1.98 (1.25–3.13)	0.004	84

implantation [31,32]. Much evidence has suggested that abnormal levels of PAI-1 significantly increase miscarriage and complicated pregnancy rates [33]. Additionally, Glueck et al. suggested that PAI activity was a significant positive explanatory variable for the number of miscarriages [34]. Furthermore, Glueck et al. found that administration of metformin throughout pregnancy in women with PCOS reduced the risk of first-trimester spontaneous abortion [35]. Palomba and coworkers also confirmed that metformin reduced PAI-1 activity in women with PCOS and abortion risk [36]. Therefore, it might be possible that increased PAI-1 associated with high RPL risk and PAI-1 4G/5G polymorphism might influence RPL risk.

There were some limitations in this meta-analysis. First, lack of the original data limited the evaluation of gene-gene and gene-environment interactions. Second, Dawson et al. indicated that PAI-1 level was not only changed by PAI- 1 4G/5G polymorphism, but also by concentration of blood sugar, insulin, and triglycerides [37]. However, we did not adjust these factors in this meta-analysis due to lack of original data. Third, the studies included in our meta-analysis were small. Thus our meta-analysis had little statistical power to assess the association between the PAI-1 4G/5G polymorphism and RPL risk.

Conclusions

The results of this meta-analysis suggest that PAI-1 4G/5G polymorphism might be associated with RPL development in Caucasians. Large-scale studies are necessary to validate this result.

Conflict of interest

The authors declare no conflict of interest.

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