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Relationship between common interleukin 1-beta gene polymorphisms and the risk of gestational disorders: An updated meta-analysis

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Abstract

Background: To quantitatively estimate the relationship between IL-1β -511C>T, −31T>C, and +3954C>T polymorphisms and risk of gestational disorders.

Methods: In this meta-analysis, eligible publications were searched in Web of Knowledge, MEDLINE, PubMed, Scopus, and Google Scholar databases (updated April 2020), using appropriate or relevant keywords. Case-control population-based reports were included if provided with genotypic frequencies of both studied groups. Statistical analyses were performed using the MetaGenyo web tool software, where a P value less than 0.05 indicated a significant association. For the assessment of between-study variations, heterogeneity analysis was applied with the I^2 statistics.

Results: A total of thirteen studies were included. We observed a significant association between IL-1β−31T>C polymorphism and reduced risk of gestational disorders under codominant CT vs. CC [OR= 0.74, CI (0.59-0.92)], and dominant CT+TT vs. CC [OR= 0.74, CI (0.60-0.91)] contrasted genetic models. The stratified analysis considering the disease type showed that the 511C>T variant, under the recessive CC vs. CT+TT model, enhanced the risk of preterm birth by 1.29 fold.

Conclusion: Our results failed to support an association between two IL-1β polymorphisms, 511C>T and +3954C>T, with the overall risk of gestational disorders. In contrast, the 31T>C variant reduced the incidence of such diseases. Further studies are encouraged to get more precise estimates of effect sizes.

Keywords: Cytokine, Interleukin, Polymorphism, Pregnancy, Meta-analysis

Conflicts of Interest: *None declared*
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Introduction

Gestational disorders are a heterogeneous group of conditions affecting pregnant women with unknown etiology (1, 2). Notwithstanding, many of these disorders are caused by insufficient oxygen transfer and/or nutrients

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↑What is "already known" in this topic:
Gestational disorders are a heterogeneous group of conditions affecting pregnant women with unknown etiology. Regulation of inflammatory responses seems to be etiologically crucial in the pathogenesis of gestational diseases. Previous studies have shown the correlation between IL-1β gene polymorphisms and the risk of gestational disorders; still, the results showed inconsistency.

→What this article adds:
In this study, we observed a significant association between IL-1β−31T>C polymorphism and reduced risk of gestational disorders under CT vs. CC and CT+TT vs. CC genetic contrasted models. Our results failed to support an association between the other two IL-1β polymorphisms, 511C>T and +3954C>T, with the overall risk of gestational disorders.

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from mother to the fetus (3, 4). Pregnancy itself is marked by increased expression of inflammatory mediators, such as chemokines, cytokines, and pattern recognition receptors, which is often occurred during gestation (5, 6). During gestation, the balance between multiple cytokines is profoundly altered. This might trigger the production of inflammatory cytokines, which are mainly involved in adverse pregnancy outcomes (7). Through innate immune response, an organism reacts to possible perturbations in organ function, playing a substantial role in preterm birth (PTB), preeclampsia, recurrent spontaneous abortion (RSA), etc. (7, 8). Moreover, high levels of inflammatory mediators were detected in placentae affected by gestational diabetes, causing defective placentation (9). That is to say, several types of gestational disorders share a mutual phenotype of variability in inflammatory responses.

Cytokines are immunomodulatory proteins that are primarily involved in many aspects of pregnancy (10). As a multifunctional cytokine, interleukin 1 (IL1) is produced by villous syncytiotrophoblast of the human placenta during early pregnancy (11, 12).

Several genetic variants of the IL-1 gene contribute to altered IL-1 expression, causing impaired embryogenesis and abortion (13). In this regard, single-nucleotide polymorphisms (SNPs) located within coding or noncoding-regions of the IL-1β gene are well-studied. One well-studied variant is rs16944, a C-to-T substitution variant that resided in the promoter region of the IL-1β gene. The other IL-1β variant, rs1143634 (in the +3954 locus), is associated with an elevated cytokine production as a four-fold higher amount of IL-1β was observed in homozygous carriers of the T allele compared with the CC genotype carriers (14). Besides, rs1143627 is a TATA box polymorphism (genotype T/C) in the -31 locus of the IL-1β gene (15). These SNPs are high-risk candidates, and investigating their effects will provide new information in developing novel treatment strategies for subjects with etiologically different conditions.

Regulation of inflammatory responses seems to be etiologically crucial in the pathogenesis of gestational disorders. Previous studies have established a link between IL-1β gene polymorphisms and the risk of gestational disorders (16-18). However, the results showed inconsistency. In this comprehensive study, we sought to explore a more accurate estimation of the relationship between three common IL-1β polymorphisms and susceptibility to gestational disorders.

Methods

Study selection

In this meta-analysis, we searched Web of Knowledge, MEDLINE, PubMed, Scopus, and Google Scholar databases for relevant reports (the last search on April 2020) and statistically combined the results of previous case-control studies. Keywords in the searches included "rs1143627 or IL-1β -31T or rs16944 or IL-1β -511T or rs1143634 or IL-1β -3954 C/T" and "gestation or gestational or pregnancy or labor or miscarriage or abortion or preterm or preterm or preeclampsia or preeclampsia" and "polymorphism or mutation or variant or SNP or single-nucleotide polymorphism." Also, additional eligible studies were identified by the use of hand searching of retrieved articles.

High-quality case-control population-based reports were included if provided with genotypic frequencies of both studied groups. Cohort studies, review articles, conference abstracts, publication in other languages, low-quality studies, and duplicated data were excluded. If more than one different case-controls were reported in the same article, they were treated as independent studies.

Data extraction

Information including the first author's name, publication date, country, ethnicity, number of subjects in the studied groups, genotyping method, and the genotypic distribution of IL-1β polymorphisms (-31T, -511, and -3954) in cases and controls were recorded from each publication. Data extraction was done independently by two authors (S.S. and M.H.S.) from all eligible publications. In case of disagreement, a third reviewer (N.A.) settled the discrepancy.

Risk of bias

The quality assessment (QA) was performed according to the Newcastle-Ottawa Scale (NOS) as described previously (19), and scores are presented in Tables 1-3. Studies with a score ≤ 6 were regarded as "low-quality," whereas those scored > 6 were considered "high-quality."

Statistical analysis

Data were analyzed using the MetaGenyo web tool (20) and Stata v.12 software. The Mantel-Haenszel method was used to pool Odds Ratios (ORs) with 95 % confidence intervals (CIs) for estimation of the strengths of association under the allelic and different genetic contrasted models (21). Subgroup analysis was performed by disease type, ethnicity, and score of each study. For each study, deviations from Hardy–Weinberg equilibrium (HWE in the controls) were checked using the Chi-square test. Heterogeneity analysis was applied with the I^2 statistics (>50% as heterogeneity) to assess variations between studies. When appropriate, the fixed-effect model (in the absence of between-study variation) or the random effect model (in the presence of between-study variation) was applied to pool the data from individual studies. Publication bias was estimated using Egger's tests. Analysis of sensitivity was also performed to assess the robustness of summary ORs.

Results

Study characteristics

Upon performing a comprehensive literature search, 22 reports of genetic association studies were identified regarding three IL-1β polymorphisms and the risk of gestational disorders (16-18, 22-39) containing 7574 subjects (for IL-1β -511), 2452 subjects (for IL-1β -31), and 3092 subjects (for IL-1β -3954). Eleven of these studies were performed on Asians, and eight studies were on Caucasians. Figure 1 shows the PRISMA diagram of the searching procedure. The characteristics of all included studies

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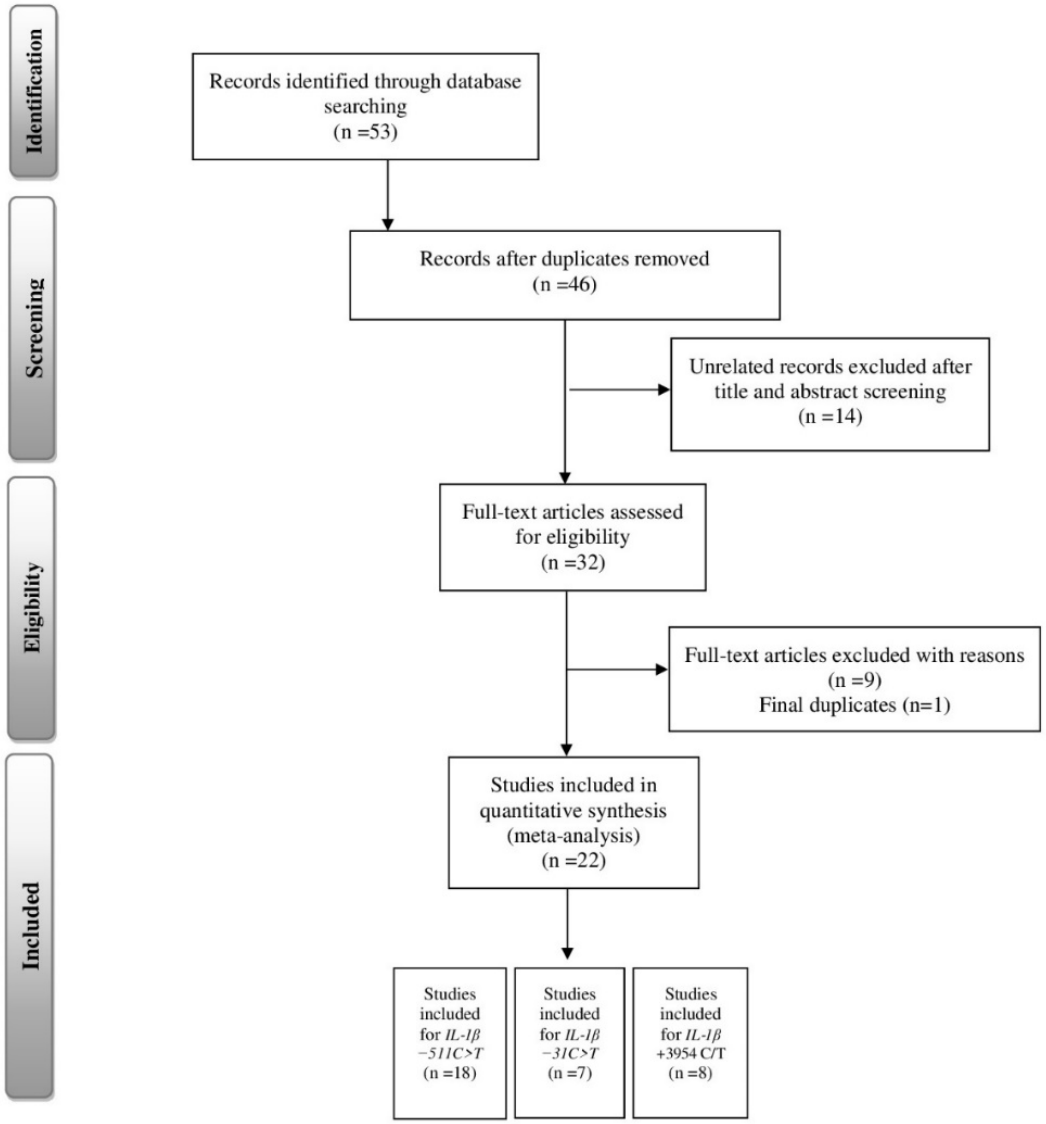

Fig. 1. Flow diagram of the study selection procedure

are summarized in Tables 1, 2, and 3.

Eight studies rated low-quality and therefore excluded. Finally, a total of 13 studies were included in the meta-analysis.

Meta-analysis results of IL1-β -511C>T polymorphism

Eleven studies with a total of 2747 women with gestational disorders and 3436 controls were included to examine the correlation of IL1-β -511C>T polymorphism and gestational disorders risk. The Meta-analysis identified no significant link between the overall risk of gestational disorders and the SNP under different genetic models (Table 4). Subgroup analysis indicated an increased PTB risk under the recessive (OR 1.29, 95% CI 1.06-1.58, p= 0.01; CC vs. CT+TT) genetic model. Besides, stratified analysis by ethnicity revealed that this polymorphism conferred a protective effect against susceptibility to gestational disorders under the heterozygous codominant model in Asians (OR 0.85, 95% CI 0.72-0.99, p= 0.036; CT vs. TT) (Table 5).

Meta-analysis results of IL1-β -31T>C polymorphism

By pooling the results of 5 studies, including 660 cases and 1433 healthy women, we found a noteworthy link between IL-1β −31T>C polymorphism and reduced the risk of gestational disorders under heterozygous codominant (OR 0.74, 95% CI 0.59-0.92, p= 0.01; CT vs. CC) and dominant (OR 0.74, 95% CI 0.60-0.91, p= 0.01; CT+TT vs. CC) models (Table 4). Stratified analysis by ethnicity revealed a significant decrease in the risk of gestational disorders under codominant (OR 0.70, 95% CI 0.55-0.89, p= 0.003; CT vs. CC) and dominant (OR 0.70, 95% CI 0.56-0.88, p= 0.002; CT+TT vs. CC) contrasted models. In this regard, no remarkable association was noticed in Caucasian women (Table 5). Figure 2 shows the forest plot for the association between the IL-1β -31T>C polymorphism and overall risk of gestational disorders under the codominant heterozygous CT vs. CC contrasted model.

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Table 1. Main characteristics of the studies included in the meta-analysis for IL-1β −511C>T

Study (year)	Genotyping method	Disease	Country	Ethnicity	Case	Control	Cases					Controls					P_{HWE}	P_{HWE*}	Score
IL-1β −511C>T							CC	CT	TT	C	T	CC	CT	TT	C	T			
Hefler et al. (2002)	PCR-RFLP	RSA	Austria	Caucasian	130	67	29	90	11	148	112	20	38	9	78	56	0.17	0.52	5
Wang et al. (2002)	PCR-RFLP	RSA	USA	Caucasian	131	72	65	49	17	179	83	21	32	19	74	70	0.35	0.53	5
Linjawi et al. (2005)	PCR-RFLP	RSA	UK	Caucasian	206	224	69	117	20	255	157	85	110	29	280	168	0.48	0.57	6
Sata et al. (2009)	RT PCR	PTB	Japan	Asian	73	341	26	27	20	79	67	86	162	93	334	348	0.36	0.45	8
Ma et al. (2011)	PCR-RFLP	RSA	China	Asian	162	156	38	84	40	160	164	46	84	26	176	136	0.24	0.45	7
Agrawal et al. (2012)	PCR-RFLP	RSA	India	Asian	200	300	13	86	101	112	288	15	126	159	156	411	0.11	0.51	7
Schmid et al. (2012)	PCR and pyrosequencing	PTB	Austria	Caucasian	100	100	37	47	16	121	79	43	39	18	125	75	0.09	0.37	6
Yilmaz et al. (2012)	PCR-RFLP	PTB	Turkey	Caucasian	100	101	41	52	7	134	66	35	36	30	106	96	0.004	0.05	6
Kim et al. (2014)	PCR-RFLP	RSA	Korea	Asian	385	232	96	190	99	382	388	39	120	73	198	266	0.38	0.45	7
Wang et al. (2014)	PCR-RFLP	PE	China	Asian	232	447	52	98	82	202	262	125	214	108	464	430	0.38	0.45	7
Awasthi et al. (2015)	PCR-RFLP	PTB	India	Asian	559	559	199	223	137	621	497	166	266	127	598	520	0.30	0.45	7
Langmia et al. (2016)	Mass ARRAY	PTB	Malaysia	Asian	92	391	22	49	21	93	91	104	203	84	411	371	0.42	0.45	7
Pereyra et al. (2016)	RT PCR	PTB	Uruguay	Hispanic	142	100	44	81	17	169	115	23	61	16	107	93	0.02	0.14	7
Nasr et al. (2017)	PCR-RFLP	PE	Egypt	Arab	80	80	17	32	31	66	94	24	40	16	88	72	0.93	0.93	6
Rahmani et al. (2018)	PCR-RFLP	RSA	Iran	Caucasian	100	100	35	43	22	113	87	40	42	18	122	78	0.24	0.45	7
Wang et al. (2019)	PCR-RFLP	RSA	China	Asian	598	603	149	294	155	592	604	110	275	218	495	711	0.16	0.45	8
Majcher et al. (2019)	Taqman	GDM	Poland	Caucasian	204	207	93	93	18	279	129	86	95	26	267	147	0.98	0.98	7

RSA: Recurrent spontaneous abortion; PE: Preeclampsia; PTB: Pre term birth; GDM: Gestational diabetes mellitus; UK: United Kingdom; USA: United States; RT PCR: Real-time PCR. P_{HWE}: The P-value of chi-square test for Hardy-Weinberg in controls; P_{HWE*}: P_{HWE} corrected for multiple testing by FDR method.

Table 2. Main characteristics of the studies included in the meta-analysis for IL-1β −31T>C

Study (year)	Genotyping method	Disease	Country	Ethnicity	Case	Control	Cases					Controls					P_{HWE}	P_{HWE*}	Score
IL-1β−31T>C							CC	CT	TT	C	T	CC	CT	TT	C	T			
Wang et al. (2002)	PCR-RFLP	RSA	USA	Caucasian	127	72	19	47	61	85	155	19	33	20	71	73	0.48	0.87	5
Sata et al. (2009)	RT PCR	PTB	Japan	Asian	73	341	17	30	26	64	82	91	166	84	348	334	0.63	0.89	8
Ma et al. (2011)	PCR-RFLP	RSA	China	Asian	162	156	56	78	28	190	134	40	80	36	160	152	0.74	0.89	7
Wang et al. (2014)	PCR-RFLP	PE	China	Asian	232	447	90	90	52	270	194	117	210	120	444	450	0.20	0.61	7
Langmia et al. (2016)	MassArray	PTB	Malaysia	Asian	93	389	26	47	20	99	87	98	199	92	395	383	0.64	0.89	7
Nasr et al. (2017)	PCR-RFLP	PE	Egypt	Arab	80	80	28	28	24	84	76	20	40	20	80	80	1.00	1.00	6
Rahmani et al. (2018)	PCR-RFLP	RSA	Iran	Caucasian	100	100	37	44	19	118	82	38	42	20	118	82	0.19	0.61	7

RSA: Recurrent spontaneous abortion; PE: Preeclampsia; PTB: Preterm birth; USA: United States; RT PCR: Real-time PCR. P_{HWE}: The P-value of chi- test for Hardy-Weinberg Equilibrium (HWE) in controls; P_{HWE*}: P_{HWE} corrected for multiple testing by FDR method.

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Table 3. Main characteristics of the studies included in the meta-analysis for IL-1β +3954C>T

Study (year)	Genotyping method	Disease	Country	Ethnicity	Case	Control	Cases					Controls					P_{HWE}	P_{HWE*}	Score
IL-1β, +3954C>T							CC	CT	TT	C	T	CC	CT	TT	C	T			
Reid et al. (2001)	PCR-RFLP	PE	UK	Caucasian	17	40	11	6	0	28	6	26	14	0	66	14	0.18	0.37	6
Ma et al. (2011)	PCR-RFLP	RSA	China	Asian	162	156	124	38	0	286	38	130	26	0	286	26	0.26	0.38	7
Mohajertehran et al. (2012)	PCR-RFLP	PE	Iran	Asian	54	50	28	20	6	76	32	28	20	2	76	24	0.49	0.59	6
Galvao et al. (2016)	RT PCR	PE	Brazil	Hispanic	168	449	5	58	105	68	268	181	87	181	449	449	0	0	7
Langmia et al. (2016)	MassArray	PTB	Malaysia	Asian	94	398	83	11	0	177	11	346	52	0	744	52	0.16	0.38	7
Tavakkol Afshari et al. (2016)	PCR-RFLP	PE	Iran	Arab	153	150	80	57	16	217	89	84	60	6	228	72	0.24	0.38	7
Wang et al. (2019)	PCR-RFLP	RSA	China	Asian	598	603	482	111	5	1075	121	474	121	8	1069	137	0.93	0.93	8

RSA: Recurrent spontaneous abortion; PE: Preeclampsia; PTB: Preterm birth; UK: United Kingdom; RT PCR: Real-time PCR. P_{HWE}: The P-value of chi- test for Hardy-Weinberg Equilibrium (HWE) in controls; P_{HWE*}: P_{HWE} corrected for multiple testing by FDR method.

Table 4. The pooled ORs and 95% CIs for the association between IL1-β polymorphisms and overall risk of gestational disorders

			Association test		Heterogeneity			Egger's test
	No	Genetic model	OR (95% CI)	p	Model	p	I^2 (%)	p
Polymorphism								
IL-1β −511C>T	11	C vs. T	1.07 (0.91-1.26)	0.39	Random	0.0001	70.44%	0.0002
	11	CT vs. TT	0.90 (0.78-1.04)	0.14	Fixed	0.32	31.32%	0.15
	11	CC vs. TT	1.15 (0.85-1.58)	0.39	Random	0.00	68.03%	0.0005
	11	CT+CC vs. TT	1.00 (0.80-1.25)	0.98	Random	0.03	57.88%	0.008
	11	CC vs. CT+TT	1.18 (0.95-1.46)	0.12	Random	0.0004	56.10%	0.011
IL-1β −31T>C	5	T vs. C	0.89 (0.71-1.11)	0.31	Random	0.04	60.10%	0.12
	5	CT vs. CC	0.74 (0.59-0.92)	0.01	Fixed	0.30	17.30%	0.01
	5	TT vs. CC	0.80 (0.54-1.20)	0.28	Random	0.08	51.94%	0.23
	5	CT+TT vs. CC	0.74 (0.60-0.91)	0.01	Fixed	0.13	44.41%	0.02
	5	TT vs. CT+CC	0.92 (0.73-1.15)	0.47	Fixed	0.16	39.31%	0.64
IL- β +3954C>T	5	T vs. C	1.44 (0.75-2.77)	0.27	Random	0.0001	93.35%	0.88
	5	CT vs. CC	1.79 (0.82-3.91)	0.14	Random	0.0001	90.95%	0.17
	3	TT vs. CC	3.37 (0.46-24.88)	0.23	Random	0.0001	91.53%	0.72
	5	CT+TT vs. CC	1.82 (0.84-3.95)	0.13	Random	0.0001	91.18%	0.16
	3	TT vs. CT+CC	1.83 (0.86-3.90)	0.12	Random	0.07	63.05%	0.54

P<0.05 is considered as statistically significant (bolded P-value).

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Table 5. Stratified analysis of IL1-β polymorphisms and gestational disorders susceptibility by type and ethnicity

	No	OR (95%CI)	P	I^2 (%)	OR (95%CI)	P	I^2 (%)	OR (95%CI)	P	I^2 (%)	OR (95%CI)	P	I^2 (%)	OR (95%CI)	P	I^2 (%)
−511C>T			C vs. T			CT vs. TT			CC vs. TT			CT+CC vs. TT			CC vs. CT+TT	
Type																
PTB	4	1.09 (0.97-1.27)	0.16	0	0.84 (0.66-1.06)	0.15	0	1.15 (0.90-1.48)	0.26	0	0.95 (0.77-1.19)	0.68	0	1.29 (1.06-1.58)	0.01	6.35
RSA	5	1.12 (0.84-1.52)	0.44	78.05	1.04 (0.84-1.30)	0.7	15.88	1.26 (0.68-2.35)	0.46	76.02	1.10 (0.76-1.59)	0.62	62.80	1.24 (0.80-1.93)	0.33	68.27
Ethnicity																
Asian	7	1.00 (0.84-1.20)	0.96	70.28	0.85 (0.72-0.99)	0.036	32.64	0.99 (0.69-1.42)	0.96	68.68	0.90 (0.71-1.13)	0.36	56.69	1.11 (0.85-1.45)	0.42	60.39
Caucasian	3	0.80 (0.50-1.26)	0.33	78.75	1.26 (0.83-1.93)	0.27	0	1.56 (0.67-3.61)	0.3	73.51	1.40 (0.75-2.59)	0.28	58.91	1.29 (0.75-2.34)	0.36	69.79
−31T>C			T vs. C			CT vs. CC			TT vs. CC			CT+TT vs. CC			TT vs. CT+CC	
Type																
PTB	2	1.08 (0.85-1.37)	0.55	59.71	0.92 (0.61-1.39)	0.70	0	1.15 (0.72-1.83)	0.57	53.67	0.99 (0.68-1.46)	0.98	0	1.23 (0.65-2.31)	0.53	63.56
RSA	2	0.83 (0.65-1.06)	0.14	24.62	0.83 (0.56-1.23)	0.36	11.18	0.70 (0.43-1.14)	0.15	17.29	0.79 (0.55-1.15)	0.22	33.59	0.78 (0.51-1.20)	0.26	0
Ethnicity																
Asian	4	0.87 (0.67-1.14)	0.32	67.87	0.70 (0.55-0.89)	0.003	6.10	0.78 (0.48-1.25)	0.30	61.71	0.70 (0.56-0.88)	0.002	46.60	0.94 (0.65-1.35)	0.74	54.45

P<0.05 is considered as statistically significant (bolded P-value).

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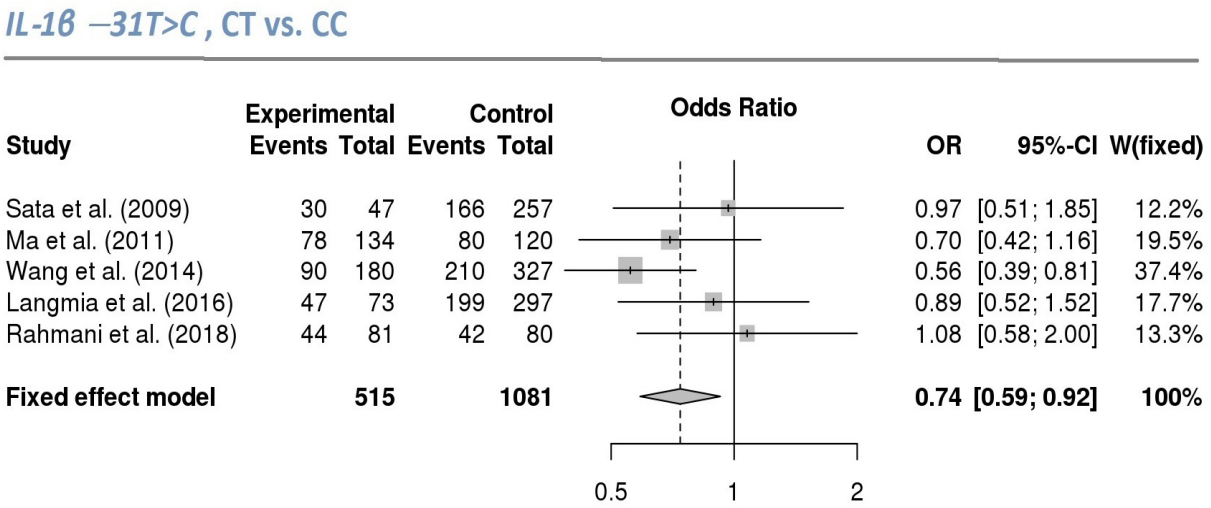

Fig. 2. Forest plot describing the meta-analysis for the association between the IL-1β -31T>C polymorphism and overall risk of gestational disorders under the codominant CT vs. CC contrasted model.

Meta-analysis results of IL1-β +3954C>T polymorphism

An overall analysis of 5 studies for IL1-β +3954C>T polymorphisms, including 1175 cases and 1756 controls, revealed no significant association between the SNP and risk of gestational disorders (Table 4). Unfortunately, we could not carry out the subgroup analysis for this variant due to low genotypic frequencies.

Heterogeneity and publication bias

The Egger's test showed significant publication bias regarding −511C>T and −31T>C polymorphisms in some studied models (Table 4). Except for the codominant model of −511C>T and recessive model of +3954C>T polymorphisms, high degrees of heterogeneity was found between studies under the assessed genetic models of both SNPs ($p<0.05$). As regards -31 polymorphism, heterogeneity was observed between studies under the allelic model ($p=0.04$).

Sensitivity analysis

To examine the effect of each study on summary ORs, a sensitivity analysis was carried out by deleting each study one by one in all inheritance modes. We found that ORs were not statistically influenced, which proved the accuracy of pooled results. Figure 3 shows the sensitivity analysis describing the correlation between the IL-1β -31T>C polymorphism and the risk of gestational disorders under the codominant CT vs. CC genetic model.

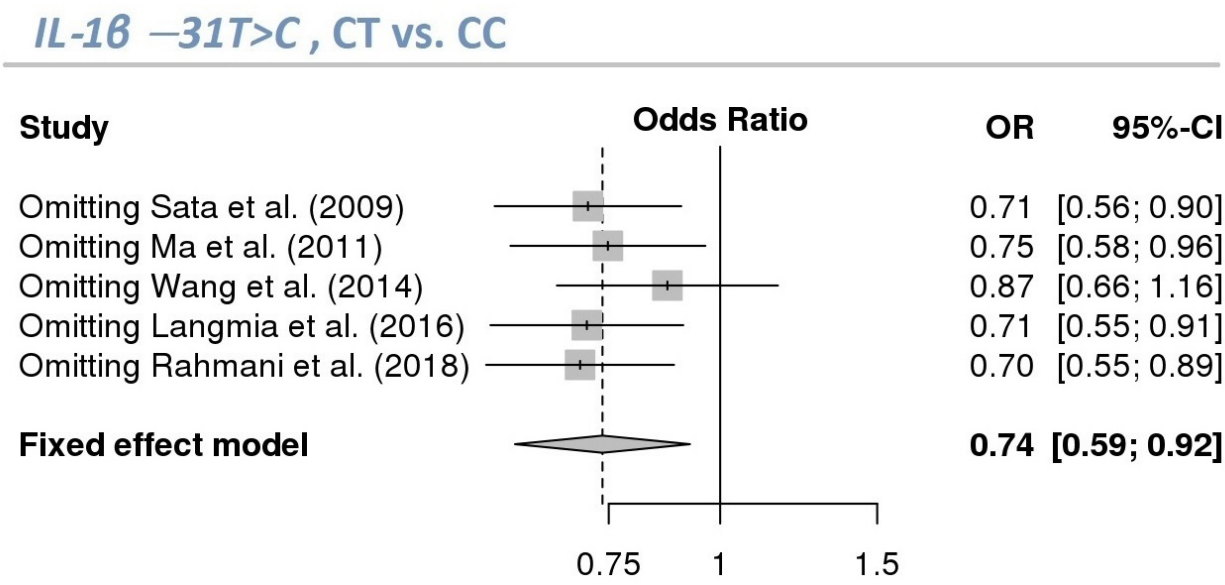

Fig. 3. Sensitivity analysis was carried out to test the effect of the each dataset on the summary ORs between the IL-1β -31T>C polymorphism and risk of gestational disorders under the codominant CT vs. CC genetic model.

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Discussion

Immune imbalance leads to unsuccessful pregnancy (40). Aberrant function and expression of cytokines have a potential role in different pregnancy complications (41). The incidence of these complications is significantly higher in developing countries (42).

It has been well documented that polymorphisms could alter cytokine production levels and the strength of cytokine responses (43). The IL-1α and IL-1β, most-studied interleukins in pregnancy disorders, are proinflammatory cytokines that bind to the IL-1 receptor to rapidly initiate signal transduction and apply biological effects (44). The expression of the IL-1 cytokine family by the placenta in normotensive pregnancies highlights the role of this cytokine in pregnancy (45). A wealth of studies have reported the increased level of IL-1β in plasma of women with pregnancy disorders (29). Previous studies have examined the effect of IL1-β gene polymorphisms on gestational disorders. However, the reports for the association between -511C>T, −31T>C, and +3954C>T polymorphisms, as common IL1β SNPs, and various gestational disorders have shown inconsistent results in different populations. A meta-analysis of available data presents the precise estimation of the effects of the polymorphisms. Previous meta-analyses showed that IL1β polymorphisms affect the risk of various clinical conditions and cancers (46-48). However, to this date, no meta-analysis study has reported a precise correlation between IL1β polymorphisms and the risk of gestational disorders. Hence, in the current study, we combined data from the 13 genetic association studies regarding -511C>T, −31T>C, and +3954C>T polymorphisms and the risk of gestational disorders.

Pooled results from our meta-analysis revealed that IL-1β −31T>C polymorphism reduces the risk of gestational disorders under codominant CT vs. CC and dominant CT+TT vs. CC genetic models. Besides, in the overall analysis, no noteworthy association was noticed between -511C>T and +3954C>T polymorphisms and the incidence of gestational disorders. By performing the stratified analysis by disease type, our findings showed that -511C>T variant decreased the risk of PTB under the recessive genetic model. Moreover, +3954C>T did not influence the risk of gestational disorders under the assessed genetic models. For counting the potential distracting effect of population admixture, we carried out subgroup analysis by ethnicity. We found the protective effect of -511C>T and −31T>C polymorphisms against the risk of gestational disorders in Asians.

Awasthi and colleagues carried out a meta-analysis to examine the correlation between IL1β-511C/T polymorphism and the risk of PTB (30). By including four studies (consist of 832 cases and 1101 controls) in the analysis, they failed to find a link between this SNP and vulnerability to PTB under the studied genetic models. Likewise, in the present up-dated meta-analysis, we pooled the results of 11 studies, including 2747 women with gestational disorders and 3436 healthy women, and found the same results. The first meta-analysis describing the correlation between IL1β polymorphisms and risk of RSA was performed by Bombell and Mcguire in 2008 (49). By pooling the findings of three case-control studies, they failed to find a noteworthy link between -511C/T and RSA risk, although an association between -31T allele with RSA was detected by pooling trial results of two studies. Another meta-analysis by Agrawal et al. in 2012 revealed similar results for the lack of association between -511C/T and RSA susceptibility (three studies included) (27). In a recent meta-analysis, Zhang et al. pooled five studies (1052 patients and 915 controls). They observed a significant correlation between the -511C/T polymorphism and RSA incidence under the recessive genetic model (50). In our work, however, we found an enhanced risk of PTB under the recessive CC vs. CT+TT inheritance mode.

IL1 gene polymorphisms served significant roles in the development of gestational disorders. However, the findings of the former meta-analysis were controversial because of the limited sample size. Therefore, updated results can help to get more reliable details of gestational disorders' pathogenesis and find biomarkers for predicting their risk. Our meta-analysis had several limitations. First, gestational disorders are multifactorial, and gene variants cannot be considered the only underlying etiology. Second, we merely examined the role of the polymorphisms while their functional consequences were not evaluated. Third, we did not consider gene-environment interactions and haplotypes due to the unavailability of individual data in retrieved publications. Finally, heterogeneity was observed between studies, which might be due to the varied study designs, application of different genotyping methods, and ethnicity differences.

Conclusion

In conclusion, our results failed to support an association between two IL-1β polymorphisms, 511C>T and +3954C>T, with the overall risk of gestational disorders. In contrast, the 31T>C variant reduced the incidence of such diseases. Further studies are encouraged to get more precise estimates of effect sizes.

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Conflict of Interests

The authors declare that they have no competing interests.

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