

# Association between pentraxin-3 and the risk of preeclampsia

## A meta-analysis

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### Abstract

An association between circulating pentraxin-3 (PTX3) and the risk of preeclampsia (PE) remains to be established. We performed a meta-analysis of observational studies to evaluate their relationship.

The PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure, and WanFang databases were searched for related observational studies evaluating PTX3 and PE risk. A random-effects or a fixed-effects model was used in the meta-analysis, depending on the heterogeneity among the included studies.

Nine case-control studies were included, with 396 PE patients and 438 controls. The results showed that PTX3 was significantly higher in pregnant women with PE as compared to those without PE (standardized mean difference [SMD] = 2.48,  $P < .001$ ), with significant heterogeneity ( $I^2 = 98\%$ ), particularly for those over 30 years old (SMD = 3.75,  $P < .001$ ). Subsequent analyses showed that patients with severe or early-onset PE had higher PTX3 levels compared to those with mild or late-onset PE (SMD = 0.93,  $P = .01$ ), suggesting that PTX3 may be a marker of PE severity. The association between PTX3 and PE was not significantly affected by the statistical method used. Sensitivity analyses by omitting one study at a time did not significantly affect the results. However, the funnel plots were asymmetric, suggesting the potential existence of publication bias.

PTX3 may be related to the risk and severity of PE in pregnant women. These results should be evaluated and confirmed in cohort studies.

**Abbreviations:** CIs = confidence intervals, CRP = C-reactive protein, PE = preeclampsia, PTX3 = pentraxin-3, SMD = standardized mean difference.

**Keywords:** meta-analysis, pentraxin-3, preeclampsia, pregnancy outcomes

### 1. Introduction

Preeclampsia (PE) is a severe complication of pregnancy that is characterized by hypertension and proteinuria.<sup>[1]</sup> The incidence of PE is reported to be 5% to 10% worldwide.<sup>[2]</sup> Pregnant women with severe PE may have comorbidities of the central

nervous system, blood system, and other systemic organs. Currently, the etiology of PE remains poorly understood, and no effective measures have been established for the prevention and treatment of PE. For most cases of PE, the symptoms can only be improved or restrained after the termination of pregnancy, which may be an important contributor of premature birth and perinatal mortality. Therefore, the identification of patients at high risk for PE may be important for the early prevention of PE and for reducing the maternal and perinatal mortality rates of PE-related pregnancies.

Increasing evidence suggests that PE may be caused by excessive inflammatory reactions, which eventually lead to endothelial dysfunction, inflammatory factor release, and multiple organ injury. Ortegahernandez *et al.* found that the inflammatory markers of peripheral leukocytes in women with PE were similar to those with sepsis.<sup>[3]</sup> Moreover, anti-inflammatory drugs, such as aspirin, have been shown to be protective against the incidence of PE.<sup>[4]</sup> Accordingly, the levels of a few inflammatory mediators, including C-reactive protein (CRP), tumor necrosis factor-alpha, and interleukin, were found to be higher in patients with PE,<sup>[5]</sup> further confirming that PE is an inflammatory disease. However, these inflammatory factors were not specific to PE patients, which limits their application for the identification of patients with PE.

Penetrins are a family of cytokines that have recently been shown to be involved in the pathogenesis of inflammation and ischemia-related diseases.<sup>[6]</sup> Pentraxin-3 (PTX3) is the most studied member of this family. PTX3 can be rapidly induced by inflammation and infection, although it is maintained at a low level under physiological conditions in humans.<sup>[7]</sup> A previous study has demonstrated that in patients with acute myocardial

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infarction, the serum PTX3 level peaked within 6 hour of the onset of chest pain, which was much earlier than the peak of CRP.<sup>[8]</sup> In a study of patients with septic shock admitted to the intensive care unit, serum PTX3 was confirmed as an independent risk factor for predicting the severity of disease and the prognosis of patients.<sup>[9]</sup> These results suggest that changes of PTX3 levels may be a sensitive marker for the risk stratification and prognosis prediction in patients with inflammatory diseases. However, changes of PTX3 expression in women with PE as well as its relationship with the severity of PE remain to be evaluated. Therefore, in this study, we performed a meta-analysis of observational studies to evaluate the differences of serum PTX3 levels in women with and without PE as well as its correlation with the severity of PE.

## 2. Materials and methods

### 2.1. Search strategy

This study was performed in accordance with the guidelines provided by the Meta-analyses of Observational Studies in Epidemiology and the Cochrane Collaboration Network. The PubMed, Medline, Embase, and Cochrane databases, reporting studies in English, as well as the WanFang and China National Knowledge Infrastructure Chinese databases were systematically searched for relevant studies using the terms “preeclampsia” and “pentraxin-3”. The combination of the subject and free text was used for the retrieval, and the data were retrieved from the time of establishment of each database to August 2018. The search strategy for PubMed is shown in Table 1 as a representative case. The ethical approval was not necessary; this article does not contain any studies with human participants or animals performed by any of the authors.

### 2.2. Study selection

Studies were included if they met all of the following criteria:

- (1) Study design: case–control study in Chinese or English.
- (2) The subjects were clinically diagnosed as having PE according to the classical diagnostic criteria: systolic blood pressure  $\geq 140$  mm Hg and/or diastolic blood pressure  $\geq 90$  mm Hg after

20 weeks of gestation, accompanied by proteinuria (urinary albuminuria  $\geq 0.3$  g/24 hour, protein/creatinine  $> 0.3$  mg/dL). Many scholars believe random albuminuria  $\geq$  (++) , or negative urinary protein accords with the following new manifestations: thrombocytopenia, platelet count  $< 100,000 \times 10^9/L$ ; renal insufficiency, serum creatinine  $> 1.1$  mg/dL or 2 times higher than the normal upper limit, excluding other kidney diseases; impaired liver function, transaminase level is 2 times higher than the normal upper limit; pulmonary edema; new headache, which general medication does not alleviate, excluding other causes or blurred vision.<sup>[2]</sup>

- (3) The serum levels of PTX3 in the peripheral blood were deemed as the exposure factor and reported.
- (4) Outcome measurement: the risk of PE.
- (5) The control group consisted of normal healthy pregnant woman.

The following exclusion criteria were applied:

- (1) repetitive literature, reviews, conferences abstracts, and animal research literature;
- (2) no full-text or incomplete literature was available;
- (3) the sample size was  $< 10$  cases for a single study; or
- (4) the Newcastle–Ottawa scale (NOS) indicated that the study was of low quality.

### 2.3. Data extraction

All retrieved studies were screened according to the pre-established inclusion and exclusion criteria. First, a single researcher read the titles and abstracts, and then the obvious irrelevant studies were excluded. Furthermore, 2 researchers read the full text of each article independently to determine whether each of the remaining studies should be included. If there was a discrepancy between the 2 researchers, a third researcher was consulted.

The main content extracted included the following: the numbers of cases and controls, the average and standard deviation values of the PTX3 expression levels in the serum of each group, and the average patient age and gestational age of each group of pregnant women. Other extracted contents included the first author, date of publication, detection indicators, and research content.

### 2.4. Quality assessment of the included studies

The NOS scale was used to evaluate the quality of the included studies. Quality evaluation for the case–control studies mainly included the selection of the study population, inter-group comparability, and leakage factors. The quality scale had a total of 8 evaluation items, and each item had a score of 1 to 2. Accordingly, the total score was 9, and an NOS score  $\geq 5$  indicated that the study was reliable.

### 2.5. Statistical analyses

For some original studies that did not provide the mean and standard deviation values of the sample but only the median, range, and sample size values, the mean and standard deviation<sup>[10]</sup> were estimated according to the validated utilization median, range, and sample size below, and then the data were recorded in a table for statistical analysis.

Procedure	Search Strategy
1 pentraxin-3: ti, ab	
2 pentraxin 3: ti, ab	
3 PTX3: ti, ab	
4 1 OR 2 OR 3	
5 preeclampsia: ti, ab	
6 pre-eclampsia: ti, ab	
7 eclampsia: ti, ab	
8 PIH: ti, ab	
9 toxemia: ti, ab	
10 EPH: ti, ab	
11 edema-proteinuria-hypertension gestos: ti, ab	
12, 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11	
13 letter: pt OR review: pt OR editorial: pt OR conference: pt OR book: pt	
14, 4 AND 12 NOT 13	

ti: (title); ab: (abstract); pt: (publication type).

i) Calculation of mean

When  $n \leq 25$ ,  $M$  is estimated by the formula

$$m \cong \frac{a + 2M + b}{4}$$

When  $n > 25$ ,  $M$  is used to estimate  $m$ .

ii) Calculation of standard deviation

When  $n \leq 15$ ,  $SD$  is estimated by the formula

$$\sqrt{\frac{1}{12} \left( \frac{(a + 2M + b)^2}{4} + (b - a)^2 \right)}$$

If  $15 < n \leq 70$ ,  $SD$  is estimated by the formula

$$SD \cong \frac{R}{4}$$

If  $n > 70$ ,  $SD$  is estimated by the formula

$$SD \cong \frac{R}{6}$$

Using RevMan 5.3 software provided by the Cochrane Collaboration Network and a continuous numerical variable model, the standardized mean difference (SMD) and 95% confidence intervals (CIs) were calculated. The expression levels of PTX3 in the peripheral blood between pregnant women with and without PE as well as between those with severe or mild PE

were compared. According to the recommendation of the Cochrane System Evaluator’s Manual, the heterogeneity of the included studies was evaluated by the  $Q$ -test and the  $I^2$ -test. Significant heterogeneity was indicated if  $I^2$  was less than 50%, and the fixed-effect model was used for meta-analysis. When  $I^2$  was greater than 50%, heterogeneity among the studies was indicated, and the random-effects model was used for meta-analysis. A  $P$  value  $< .05$  was considered to be statistically significant.

**3. Results**

**3.1. Database searching and study characteristics**

The flow chart of document selection is shown in Figure 1. Overall, 101 papers were retrieved by database searching, including 96 articles in English and 5 articles in Chinese. According to the inclusion and exclusion criteria, a total of nine articles that were published in English were included. The study characteristics of the included studies are shown in Table 2.

**3.2. Quality evaluation**

As shown in Table 3, a total of nine articles were included, all of which were case-control studies. The overall score was 7 to 9, based on the NOS standard.

**3.3. Meta-analysis for PTX3 levels in pregnant women with or without PE**

According to the meta-analysis of 96 cases of PE in pregnant women and 438 normal pregnant women from the 9 articles, we

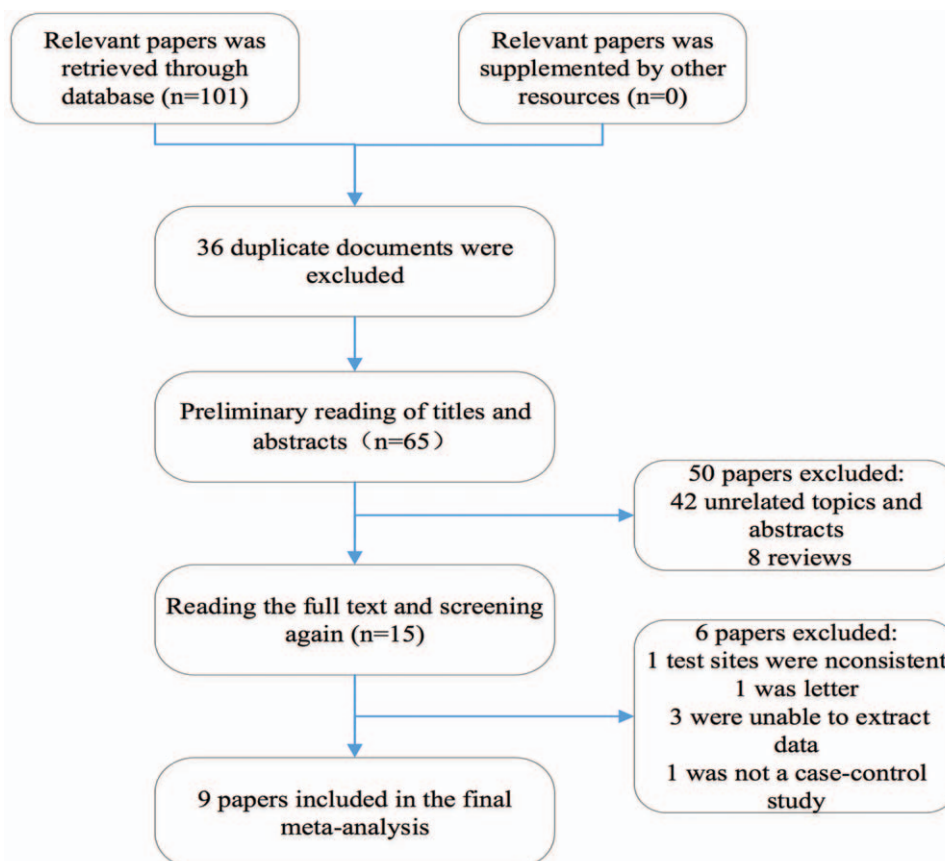


Figure 1. Flowchart of literature identification.

**Table 2****Basic characteristics of the included studies.**

Reference	Region	Age			Criteria for disease	Detection content			Research results								
		NP	SP/EOP	MP/LOP		Detection cell	Test specimen	Measurement	NP		SP / EOP		MP / LOP				
									N	Gestational Age (wk)	Mean $\pm$ SD (ng/mL)	N	Gestational Age	Mean $\pm$ SD (ng/mL)	N	Gestational Age (wk)	Mean $\pm$ SD (ng/mL)
Hamad 2011 <sup>[12]</sup>	Sweden	31 (4)	/	31 (5)	ACOG	PTX3	Plasma	ELISA	35	33 (4)	13.17 $\pm$ 2.0	/	/	/	30	35 (4)	22.64 $\pm$ 1.95
Boij 2012 <sup>[24]</sup>	Sweden	30.2	/	29.8	ACOG	PTX3	Plasma	ELISA	100	34.3	3.25 $\pm$ 0.65	31	/	9.12 $\pm$ 2.32	83	35.7	5.94 $\pm$ 1.06
Cozzi 2012 <sup>[17]</sup>	Italy	31.3 $\pm$ 5.5	/	34.1 $\pm$ 4.5	ACOG	PTX3	Plasma	ELISA	50	33.4 $\pm$ 3.6	3.8 $\pm$ 1.4	/	/	/	53	31.7 $\pm$ 3.7	24.8 $\pm$ 9.73
Turkmen 2013 <sup>[25]</sup>	Istanbul	27.17 $\pm$ 5.90	/	27.9 $\pm$ 6.43	ACOG	PTX3	Plasma	ELISA	49	34.2 $\pm$ 3.39	0.58 $\pm$ 0.39	7	/	1.15 $\pm$ 0.49	22	35.45 $\pm$ 4.5	0.61 $\pm$ 1.13
Algeri 2014 <sup>[26]</sup>	Italy	32.4 $\pm$ 5.9	/	34.6 $\pm$ 5.8	ACOG	PTX3	Plasma	ELISA	29	38.6 $\pm$ 0.9	1.3 $\pm$ 0.15	/	/	/	22	33.2 $\pm$ 4.0	3.68 $\pm$ 0.68
Estensen 2015 <sup>[27]</sup>	Norway	32 $\pm$ 5	/	32 $\pm$ 6	ACOG	PTX3	Plasma	ELISA	61	36 $\pm$ 0	2.9 $\pm$ 0.35	/	/	/	34	35 $\pm$ 5	8.2 $\pm$ 1.35
Cakmak 2017 <sup>[28]</sup>	Turkey	28 $\pm$ 5	27 $\pm$ 5	27 $\pm$ 6	ACOG	PTX3	Plasma	ELISA	40	36.29 $\pm$ 1.96	1.5 $\pm$ 0.8	45	35.71 $\pm$ 2.31	6 $\pm$ 4.1	55	35.99 $\pm$ 3.1	2.2 $\pm$ 1.3
Cui 2018 <sup>[29]</sup>	China	29.7 $\pm$ 5.9	29.6 $\pm$ 5.6	29.7 $\pm$ 5.3	ACOG	PTX3	Plasma	ELISA	62	35.7 $\pm$ 2.9	0.69 $\pm$ 0.60	25	33.7 $\pm$ 3.4	1.07 $\pm$ 1.18	85	35.4 $\pm$ 3.5	0.63 $\pm$ 0.68
Garg 2018 <sup>[30]</sup>	India	27 (23–28.5)	26 (22.5–31)	/	ACOG	PTX3	Plasma	ELISA	12	31	0.039 $\pm$ 0.11	13	21	0.051 $\pm$ 0.30	12	31	0.05 $\pm$ 0.16

ACOG = American College of Obstetricians and Gynecologists, ELISA = enzyme-linked immunosorbent assay, EOP = early-onset preeclampsia, LOP = late-onset preeclampsia, MP = mild preeclampsia, N = number, NP = normal pregnant, SP = severe preeclampsia.

found that the expression level of PTX3 in the peripheral blood of PE pregnant women was higher than that of the healthy pregnant women ( $Z = 3.73$ ;  $P = .0002$ ;  $SMD = 2.48$ ; 95%  $CI$ : 1.18–3.78) using a random-effects model ( $P < .0001$ ;  $I^2 = 98\%$ ) (Fig. 2).

### 3.4. Meta-analysis for PTX3 in early-onset PE or severe PE and late-onset PE or mild PE

Meta-analysis of 5 articles, including 121 patients with early-onset PE or severe PE and 257 patients with late-onset PE or mild PE, showed that the expression level of PTX3 in the peripheral blood of patients with early-onset PE or severe PE was higher than that of patients with late-onset PE or mild PE ( $SMD = 0.93$ ; 95%  $CI$ : 0.22–1.64;  $Z = 2.57$ ;  $P = .01$ ), with statistical heterogeneity ( $P < .00001$ ,  $I^2 = 87\%$ ), as shown in Figure 3.

### 3.5. Subgroup analysis

Because of the high heterogeneity of the studies (all  $> 90\%$ ) from our results shown in Figure 2, we divided the patients into different subgroups according to the age of the pregnant women with PE, the gestational age, and the different statistical method used.

### 3.6. Results based on the age of the pregnant women

Subgroup analysis showed that the PTX3 levels were significantly different in PE women and normal pregnant women aged 30 years old or more ( $SMD = 3.75$ ; 95%  $CI$ : 1.2–6.29;  $P = .004$ ), but not in those younger than 30 years old ( $SMD = 1.26$ , 95%  $CI$ : -0.58–3.11,  $P = .18$ ) (Fig. 4).

### 3.7. Results based on gestational age

The PTX3 expression in the peripheral blood of the PE group compared to the normal (control) group at gestational age  $\leq 34$  weeks ( $SMD = 3.55$ ; 95%  $CI$ : 1.1–6.01;  $P = .005$ ) and  $> 34$  weeks ( $SMD = 1.64$ ; 95%  $CI$ : 0.15–3.13;  $P = .03$ ) was significantly different. These results demonstrated that the PTX3 level in the peripheral blood was higher in early-onset PE patients or severe PE patients as well as in patients with late-onset PE or mild PE, compared to that in normal pregnant women, and it increased with the severity of the disease (Fig. 5).

### 3.8. Results based on grouping by different statistical methods

Subgroup analysis according to the statistical analysis method used showed that the association between the serum PTX3 level

**Table 3****Newcastle–Ottawa scale evaluation in the literature.**

Literature	Research population selection				Comparability between groups		Exposure factors			Total
	Case determination	Case representativeness	Contrast selection	Control determination	Control important confounding factors	Control any confounding factors	Exposure determination	Case control revealed the same exposure		
								Exposure	Non-response rate	
Hamad 2011	1	1	1	1	1	1	1	1	0	8
Boij 2012	1	1	1	1	1	1	1	1	0	8
Cozzi 2012	1	1	1	1	1	1	1	1	0	8
Turkmen 2013	1	1	1	1	1	0	1	1	0	7
Algeri 2014	1	1	1	1	1	0	1	1	0	7
Estensen 2015	1	1	1	1	1	1	1	1	1	9
Cakmak 2017	1	1	1	1	1	1	1	1	0	8
Cui 2018	1	1	1	1	1	1	1	1	0	8
Garg 2018	1	1	1	1	1	1	1	1	0	8

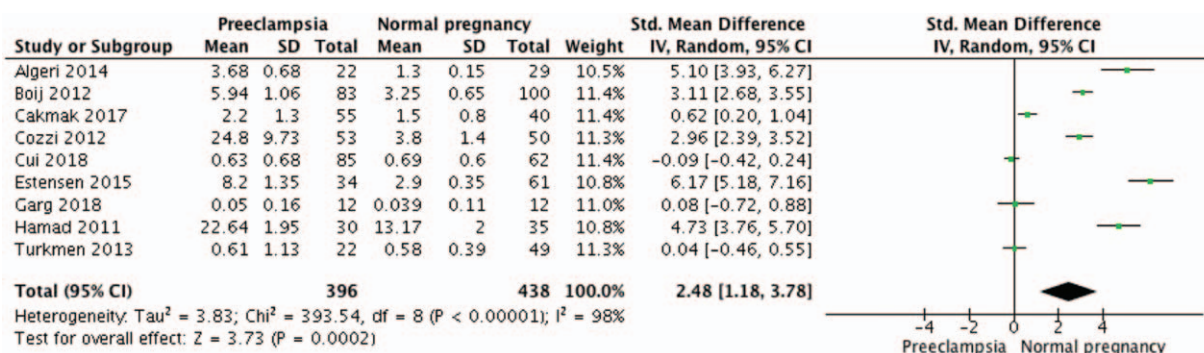


Figure 2. Meta-analysis for the difference of the PTX3 level in women with and without PE. PE = preeclampsia, PTX3 = pentraxin-3.

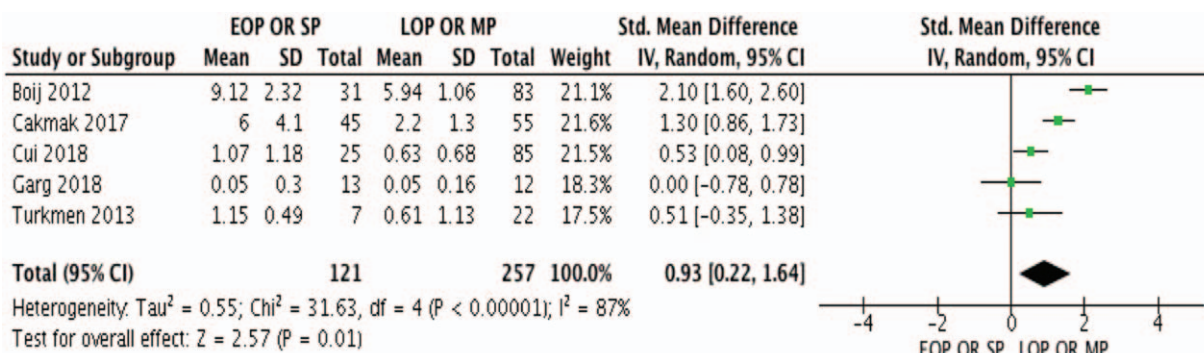


Figure 3. Meta-analysis for the difference of the PTX3 level in women with early-onset PE or severe PE and late-onset PE or mild PE. PE = Preeclampsia, PTX3 = pentraxin-3.

and PE was not significantly affected by the statistical analytical method used (P for subgroup analyses >.05; Fig. 6).

### 3.9. Sensitivity analysis

Sensitivity analyses by omitting 1 study at a time did not significantly change the overall results, indicating the robustness of the results.

### 3.10. Publication bias analysis

Funnel plots were used to analyze the publication bias of the nine articles. In PE pregnant women compared with healthy pregnant women, the funnel graph was poorly symmetric. A similar outcome was observed in the funnel plots of PTX3 levels in the early-onset or severe PE and late-onset or mild PE (Fig. 7A and B) groups, indicating the potential existence of publication biases.

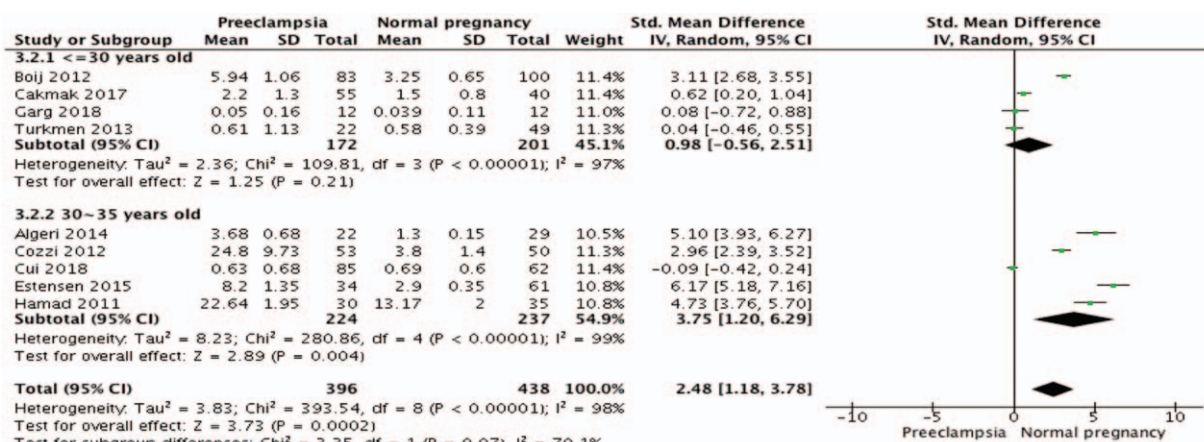


Figure 4. Meta-analysis for the difference of the PTX3 level in women with and without PE by age of the participants. PE = preeclampsia, PTX3 = pentraxin-3.

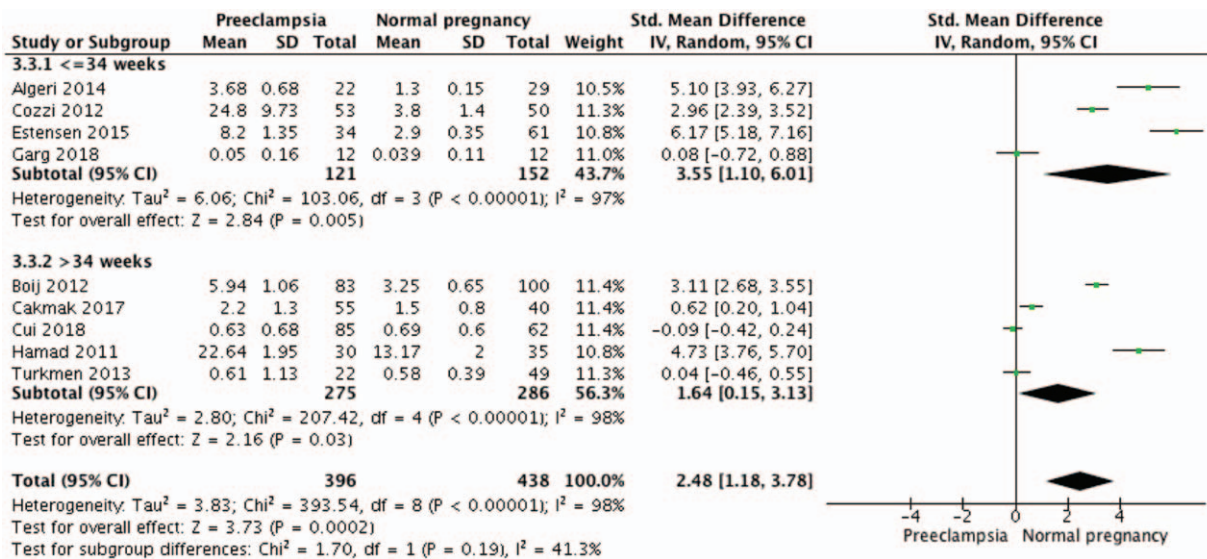


Figure 5. Meta-analysis for the difference of the PTX3 level in women with and without PE by gestational age of the participants. PE = preeclampsia, PTX3 = pentraxin-3.

4. Discussion

PE is recognized as an inflammatory disease,<sup>[11]</sup> and PTX3 is a novel inflammatory factor<sup>[12]</sup> that has been suggested to confer an increased risk of PE.<sup>[13,14]</sup> However, due to the limited sample sizes of these previous studies, the results did not consistently demonstrate an association between PTX3 and PE. Moreover, a correlation between the PTX3 level and the severity of PE has not been fully detected. In view of the above findings, we aimed to determine the relationships between PTX3 and PE as well as between PTX3 and the severity of PE in a meta-analysis. We found that PE patients had higher PTX3 levels as compared with normal pregnant women. Furthermore, the PTX3 level was higher in those with severe or early-onset PE as compared to those with mild or late-onset PE. These results indicated that PTX3 expression in pregnant women may be a predictor of PE incidence and severity.

PTX3, CRP, and serum amyloid A belong to the pentamerin protein family; and CRP is a classic marker of acute inflammation. PTX3 is synthesized rapidly and exists for a long time in vivo. The peak value of PTX3 in an inflammatory reaction can be reached within 6 hours to 8 hours after a signal is triggered, and the increase has been shown to be much quicker than that of CRP. Therefore, PTX3 can be used to monitor inflammation initiation and development in vivo.<sup>[15,16]</sup> PTX3 can be synthesized and released in a variety of cells, such as mononuclear macrophages and vascular endothelial cells. PTX3 may increase the risk of PE by presenting persistent endothelial dysfunction.<sup>[17]</sup> First, the excessive inflammation in PE increases the levels of proinflammatory factors such as interleukin-1 and tumor necrosis factor-alpha, which in turn results in the synthesis of PTX3 and the activation of vascular and placental endothelial cells, thus leading to endothelial dysfunction.<sup>[18,19]</sup> Second, disorders in the

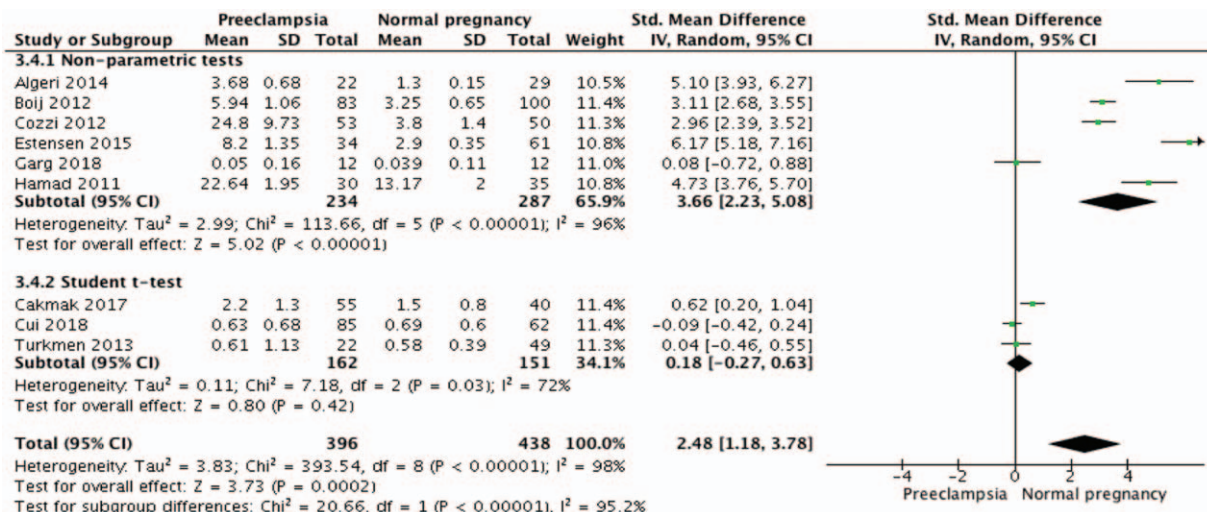
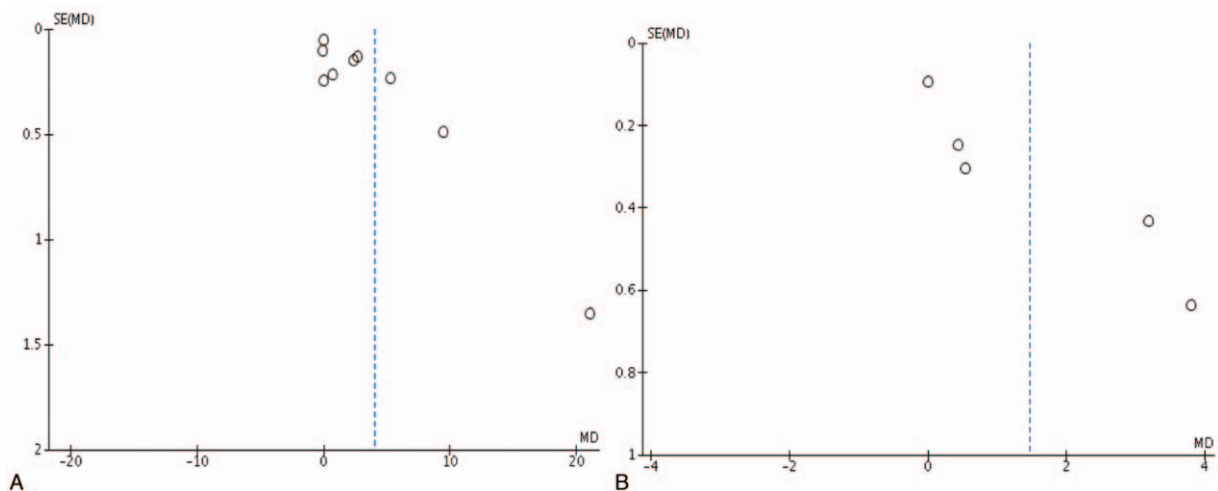


Figure 6. Meta-analysis for the difference of the PTX3 level in women with and without PE by the statistical method used. PE = preeclampsia, PTX3 = pentraxin-3.



**Figure 7.** Funnel plots for the meta-analysis of the PTX3 level in early-onset or severe PE (A) and late-onset or mild PE (B). PE = preeclampsia, PTX3 = pentraxin-3.

regulation of apoptotic cells may lead to a large number of factors in the maternal blood circulation, damaging maternal endothelial cells and resulting in PE.<sup>[20]</sup> It has been shown that PTX3 can promote the differentiation of T lymphocytes into type 1 T helper cells and inhibit the recognition function of dendritic cells on late apoptotic cells, which may lead to the imbalance of apoptosis, contributing to the development of PE.<sup>[21]</sup> Therefore, it is hypothesized that PTX3 may increase the incidence of PE by impairing the function of placental vascular endothelial cells. However, this hypothesis should be confirmed in further experimental studies.

Moreover, we found that increased PTX3 levels in PE patients were mostly found in pregnant women over 30 years old. Also, PTX3 may increase more dramatically in patients with severe or early-onset PE as compared to those with mild or late-onset PE. The pathological and physiological changes of the placenta in PE are closely related to the inflammatory response of the patients. The inflammatory response is aggravated with the progression of the disease. PTX3 is a marker of vasculitis, which is closely related to the pathogenesis of PE.<sup>[22,23]</sup> These results suggest that PTX3 exerts a different pathophysiological function in early- and late-onset PE. If this is the case, PTX3 may be a novel molecular marker and a new target for the early diagnosis of PE.

However, there were still some limitations of this study. First, retrospective and observational studies were included in this study, and there was no prospective cohort study, which was more likely to introduce analysis bias. Second, the number of studies included in this study was small, the sample size was small, and the quality of the studies was moderate, which led to an overall NOS score between 7 and 9. Moreover, significant heterogeneity among the included studies was detected. The heterogeneity of this study may be related to geographical variations, statistical methods, sample size, the age of the pregnant women, and the gestational age. Since we did not have access to individual patient data, the source of the heterogeneity could not be confirmed. Finally, there was a certain publication bias. The search language was limited to Chinese and English, which may lead to bias as well.

## 5. Conclusion

This study is the first to summarize and analyze the relationship between PTX3 and the risk of PE. It was systematically

demonstrated that the expression of PTX3 in the peripheral blood was closely related to the pathogenesis of PE. The results of the meta-analysis showed that PE patients had a higher serum PTX3 level as compared with normal pregnant women. Moreover, the PTX3 level was higher in those with severe or early-onset PE as compared to those with mild or late-onset PE. These results suggest that PTX3 might be related to the risk and severity of PE in pregnant women. However, these results should be evaluated and confirmed in cohort studies.

## Author contributions

XZH: Project development, data collection, data analysis, manuscript writing. WXC: Data collection, data analysis, manuscript writing. JSC: Data analysis, manuscript writing. JMY: Data analysis, manuscript writing. CWZ: Project development, data analysis, manuscript writing.

**Data curation:** Zhihui Xiong, Xinchen Wang.

**Formal analysis:** Zhihui Xiong, Xinchen Wang, Sicong Jiang, Meiyuan Jin, Wenzeng Chen.

**Project administration:** Zhihui Xiong, Wenzeng Chen.

**Writing – original draft:** Zhihui Xiong, Xinchen Wang, Sicong Jiang, Meiyuan Jin.

**Writing – review & editing:** Wenzeng Chen.

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