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Original Paper

Plasma ET-1 Concentrations Are Elevated in Pregnant Women with Hypertension - Meta-Analysis of Clinical Studies

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Key Words
Et-1 • Pregnancy • Hypertension • Meta-analysis

Abstract
Background/Aims: The ET system might be involved in the pathogenesis of hypertensive disorders during pregnancy. The objective is to analyse the impact of ET-1 in hypertensive pregnant women by a strict meta-analysis of published human clinical studies. ***Methods:*** Based on the principle of Cochrane systematic reviews, Cohort studies in PubMed (Medline), Google Scholar and China Biological Medicine Database (CBM-disc) designed to identify the role of endothelin-1 (ET-1) in the pathophysiology of gestational hypertension and preeclampsia were screened. Review Manager Version 5.0 (Rev-Man 5.0) was applied for statistical analysis. Mean difference and 95% confidence interval (CI) were shown in inverse variance (IV) fixed-effects model or IV random-effects model. ***Results:*** Sixteen published cohort studies including 1739 hypertensive cases and 409 controls were used in the meta-analysis. ET-1 plasma concentrations were higher in hypertensive pregnant women as compared to the controls (mean difference between groups: 19.02 [15.60～22.44], $P < 0.00001$,). These finding were driven by severity of hypertension and/or degree of proteinuria. ***Conclusion:*** Plasma ET-1 concentrations are elevated in hypertensive disorders during human pregnancy. In particular women with preeclampsia (hypertensive pregnant women with proteinuria) have substantially elevated plasma ET-1 concentration as compared to pregnant women with normal blood pressure.

Introduction

Approximately thirty-years ago Hickey *et al.* [1] described an endothelium-derived constricting factor in the supernatant of bovine aortic endothelial cells. This factor was

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thought to be a peptide hormone, since trypsin abolished the vasoconstrictive property of this new factor [1]. The molecular structure of this endothelium-derived constricting factor was identified by Yanagisawa *et al*. [2]. It was named endothelin, because it was isolated from the supernatant of porcine aortic endothelial cells. Endothelin produces powerful, very long-lasting constrictions of a range of mammalian blood vessels *in vitro* including human arteries and veins. It also causes long-lasting elevation of blood pressure when injected into rodents [2]. Because of these observation, scientists at this time were of the opinion that this peptide - nowadays called endothelin-1 (ET-1) plays an important role in the pathogenesis of arterial hypertension as well as pregnancy induced hypertension/preclampsia [3]. It was thus a surprising finding that ET-1 transgenic mice do not develop hypertension. This was first shown by our group in Berlin, Germany [4]. ET-2 overexpressing rats likewise do not develop hypertension [5]. Both rat and mouse ET overexpression models develop chronic kidney disease characterized by renal intestinal fibrosis and glomerulosclerosis in a blood pressure independent manner [4-10]. When going to the original publications, it was always noted that numerically the blood pressure was even somewhat lower in ET-1 transgenic mice as compared to their WT control counterparts. We recently performed a meta-analysis addressing this topic. This meta-analysis provides robust evidence that systemic ET-1 overexpression in mice lowers blood pressure in an age-dependent manner [11]. A subsequent meta-analysis – on the other hand - revealed that ET-1 plasma concentrations are elevated in humans with essential hypertension [12]. Given these contradictory findings in transgenic endothelin rodent models and humans with essential hypertension as well as the initial hypothesis that ET-1 might be involved in the pathogenesis of hypertension during pregnancy, the aim of the current study therefore was to perform a systematic review and meta-analysis of all so far published studies reporting ET-1 plasma concentrations in pregnant women. Hypertensive disorders during pregnancy remains a major cause of maternal morbidity and mortality as well as poor fetal short and long-term outcome [13-17]. Gestational hypertension is a clinical diagnosis defined by the new onset of hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) at ≥20 weeks of gestation in the absence of proteinuria or new signs of end-organ dysfunction [16-19]. Gestational hypertension is considered severe when systolic blood pressure is ≥160 mmHg and/or diastolic blood pressure is ≥110 mmHg on two consecutive blood pressure measurements at least four hours apart [16-19]. Gestational hypertension is a temporary diagnosis for hypertensive pregnant women who do not meet criteria for preeclampsia. Preeclampsia is diagnosed, if proteinuria or new signs of end-organ dysfunction develop.

Materials and Methods

The meta-analysis was conducted according to principles and methods that we recently published [11, 12, 20, 21].

Search strategy

Two authors screened for clinical studies in PubMed (Medline) and Google Scholar relevant to the topic of ET-1 and hypertension in humans. We included studies published between January 1, 1991 and March 31, 2017. Searching keywords were “endothelin-1”, and “gestational hypertension or preeclampsia”.

Inclusion and exclusion criteria

We screened all published studies in English and Chinese published between January 1990 until June 2017. Inclusion criteria were:

(1) Clear definition of gestational hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg in at least two occasions at least 4-6 h apart after the 20th week of gestational), mild preeclampsia (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg in at

least two measurements. measured on two occasions at least 4-6 h apart after the 20th gestational week, with proteinuria >0.3 g/24h and edema), and severe preeclampsia (systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg in at least two measurements. measured on two occasions at least 4-6 h apart after the 20th gestational week, gestational hypertension with proteinuria >2.0 g/24h and edema);

(2) no twins pregnancies were allowed

(3) clear information on the study design in particular information on in-and exclusion criteria and maternal baseline characteristics.

We excluded duplicate publications, abstracts only publications, and review articles. Studies without comparison with normotensive pregnant subjects were likewise excluded. If blood sampling was not clearly defined, we also excluded these studies.

Data extraction and quality assessment

Two authors selected relevant articles, abstracted data, and evaluated the quality of enrolled studies independently. Questionable studies were resolved by discussion or consensus based on the views of a third reviewer. We contacted the authors when we encountered information that was unclear or incomplete.

The following data were extracted from the included articles: ET-1 blood concentrations, age. Data were given as mean ± SD. When data ere given as mean and range (a,b), $SD \approx [(b-a)^2 + (a-2m+b)^2/4]^{1/2}/12^{1/2}$ ($n \leq 15$) or $SD \approx (b-a)/4$ ($15 < n \leq 70$) [22]. In the sixteen included papers, ten used ng/L as ET-1 concentration unit, five papers used pg/mL, and one paper used pmol/L. So, we unified the ET-1 concentration unit as ng/L, 1 ng/L ET-1 = 1 pg/mL ET-1 = 2.4919 × pmol/L ET-1.

Table 1. Characteristics of included studies

Study ID	Variable	Normotensive		Gestational hypertension		Mild preeclampsia		Severe preeclampsia	
		Number	Value	Number	Value	Number	Value	Number	Value
Florijn, 1991	ET-1	25	2.1±0.53	-	-	25	5.0±2.6	-	-
Benigni, 1992	ET-1	19	0.48±0.53	-	-	10	0.40±0.22	-	-
	Age	19	29.3±6.1	-	-	10	31.1±4.1	-	-
Zafirovska, 1999	ET-1	178	37.36±18.07	79	42.7±16.43	-	-	-	-
	Age	178	27.6±5.4	79	28.1±6.3	-	-	-	-
Slowinski, 2002	ET-1	30	0.44±0.45	-	-	125	0.75±1.2	-	-
	Age	30	27.8±8.2	-	-	125	30.4±9.1	-	-
Vural, 2002	ET-1	20	30.85±6.25	-	-	19	37.18±15.40	-	-
	Age	20	29.2±6.7	-	-	19	28.37±5.34	-	-
Zhang, 2005	ET-1	58	21.11±6.39	60	33.23±11.80	-	-	-	-
	Age	58	21.11±6.39	60	33.23±11.80	-	-		
Lin, 2010	ET-1	42	1.78±1.33	48	3.67±2.43	-	-	38	4.83±2.75
	Age	42	27.3±3.6	86			28.6±4.1		
La, 2011	ET-1	35	68.90±14.36	-	-	-	-	46	98.24±45.04
Zhou, 2013	ET-1	40	41.78±3.48	23	48.53±3.28	24	61.44±3.84	23	74.38±4.03
	Age	40	28.38±7.48	70			29.48±8.43		
Feng, 2013	ET-1	30	95.82±30.65	28	100.23±32.83	30	122.42±27.62	22	142.65±24.33
	Age	30	27.65±7.02	80			25.43±6.92		
Shi, 2014	ET-1	40	22.13±4.55	-	-	39	33.41±5.37	40	41.29±7.18
	Age	40	28.56±5.87	-	-	39	28.38±4.29	40	28.64±5.12
Zhang, 2014	ET-1	30	29.3±4.5	-	-	20	45.3±5.1	16	52.4±6.1
	Age	30	27.1±6.3	-	-	20	26.5±6.7	16	28.1±6.4
Zhang, 2015	ET-1	40	36.17±6.28	34	45.83±9.32	58	62.31±10.72	38	75.85±11.52
	Age	40	27.56±4.31	130			27.37±2.87		
Zeng, 2015	ET-1	200	46.75±4.97	-	-	127	65.83±5.56	102	79.34±5.08
	Age	200	27.9±1.7	-	-	239		26.5±2.2	
Lu, 2016	ET-1	30	53.0±2.90	-	-	30	73.0±6.2	30	85.7±5.1
	Age	30	29.6±2.0	-	-	30	29.1±2.4	30	30.0±20.0
Lv, 2016	ET-1	120	58.26±7.22	53	82.17±19.63	43	108.29±28.31	24	124.24±36.84
	Age	120	28.36±4.23	120			29.12±3.84		

Statistical processing

Statistical analyses were conducted by Review Manager Version 5.0 (Rev-Man 5.0) software, devised by Co-chrane Collaboration as described earlier [11, 12, 18.]. Heterogeneity was assessed by *P* value and I^2. If there was no heterogeneity ($P \geq 0.1$, $I^2 \leq 50\%$), we used the IV fixed-effects model. If there was high heterogeneity ($P < 0.1$, $I^2 > 50\%$), we chose IV random-effects model. Binary outcomes were expressed as the risk ratio (RR) with 95%CI. Continuous variables were expressed as mean difference (MD) with 95% CI. In test for overall effect, the $P \leq 0.05$ was considered statistically significant.

We performed also a subgroup analysis of the hypertensive patients. subgroup 1, gestational hypertension; subgroup 2 mean SBP > 160mmHg; subgroup 3 mean SBP unclear. A comparable classification was used for diastolic blood pressure subgroups: subgroup 1, gestational hypertension; subgroup 2, mild preeclampsia; subgroup 3, severe preeclampsia. For the data of age, some papers combined gestational hypertension, mild preeclampsia, and severe preeclampsia as hypertension disorder complicating pregnancy. In this case, hypertension disorder complicating pregnancy as subgroup 4.

Results

Basic information

Based on the principle of Cochrane systematic reviews, and the inclusion and exclusion criteria of our meta-analysis, Sixteen [23-38] published cohort studies were included in

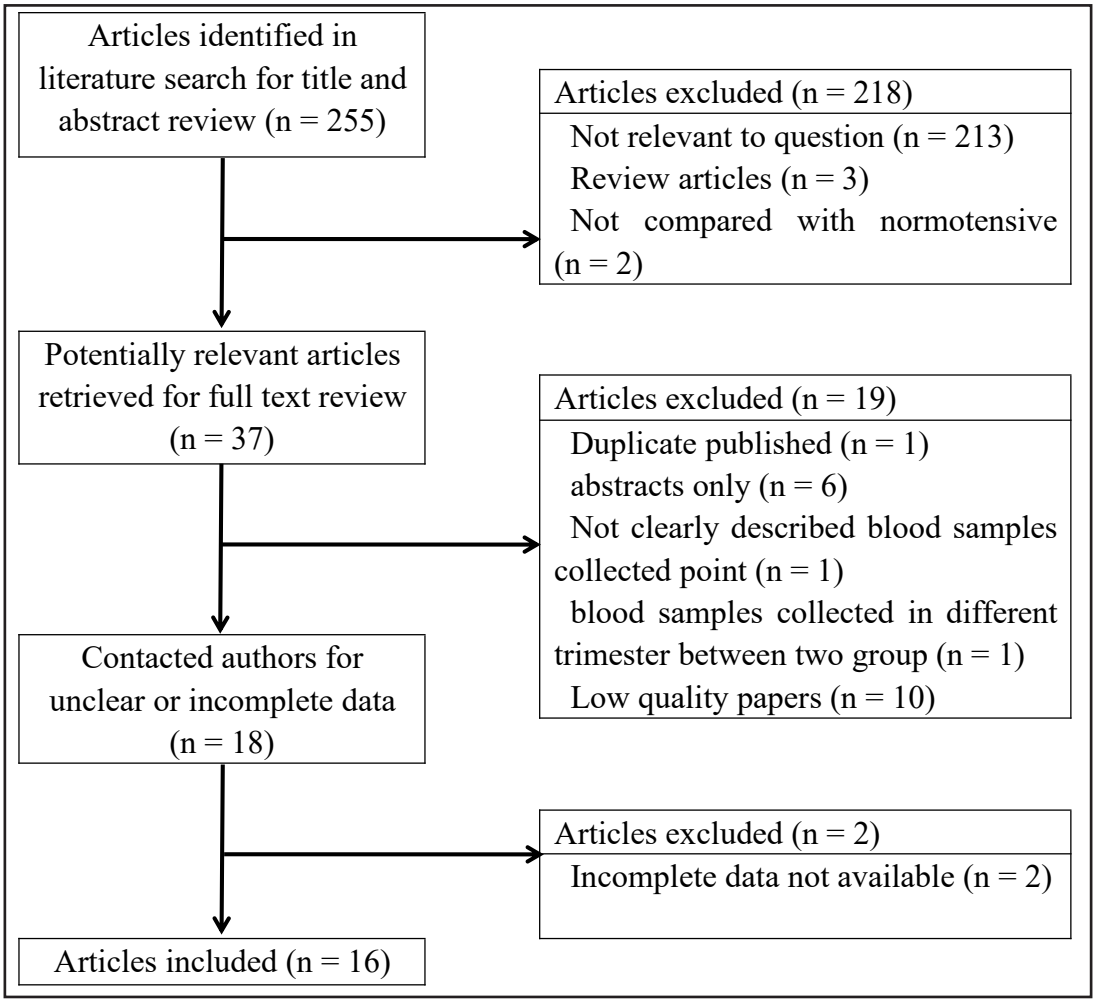

Fig. 1. Flow chart of searching article, eliminating the unmatched articles and include articles.

the present meta-analysis (1739 patients in the hypertensive group, 409 controls in the normotensive group). A more detailed description of the clinical characteristics of the included studies is given in Table 1. The study design/flow chart is given in figure 1.

ET-1 and gestational hypertension

Sixteen studies [23-38] reporting data on ET-1 and gestational hypertension and/or preeclampsia could be included into the meta-analysis.

The overall effect of the sixteen studies [23-38] showed that hypertensive pregnant women had higher ET-1 plasma concentrations than normotensive controls (mean difference: 19.02 ng/L, 95%CI [15.60～22.44], $P < 0.00001$, with high heterogeneity ($P < 0.00001$, $I^2 = 100\%$), Fig. 2). A subgroups analysis according to severity of hypertension and/or proteinuria, in the gestational hypertension group revealed that hypertensive pregnant women with no proteinuria (mean difference 9.27 ng/L, 95%CI [4.72～13.82], $P < 0.0001$, with high heterogeneity ($P < 0.00001$, $I^2 = 95\%$), Figure2), mild preeclampsia (mean difference 14.94 ng/L, 95%CI [11.52～18.36], $P < 0.00001$, with high heterogeneity ($P < 0.00001$, $I^2 = 99\%$), Figure2) as well as severe preeclampsia (mean difference 31.74 ng/L, 95%CI [20.98～42.50], $P < 0.00001$, with high heterogeneity ($P < 0.00001$, $I^2 = 100\%$),

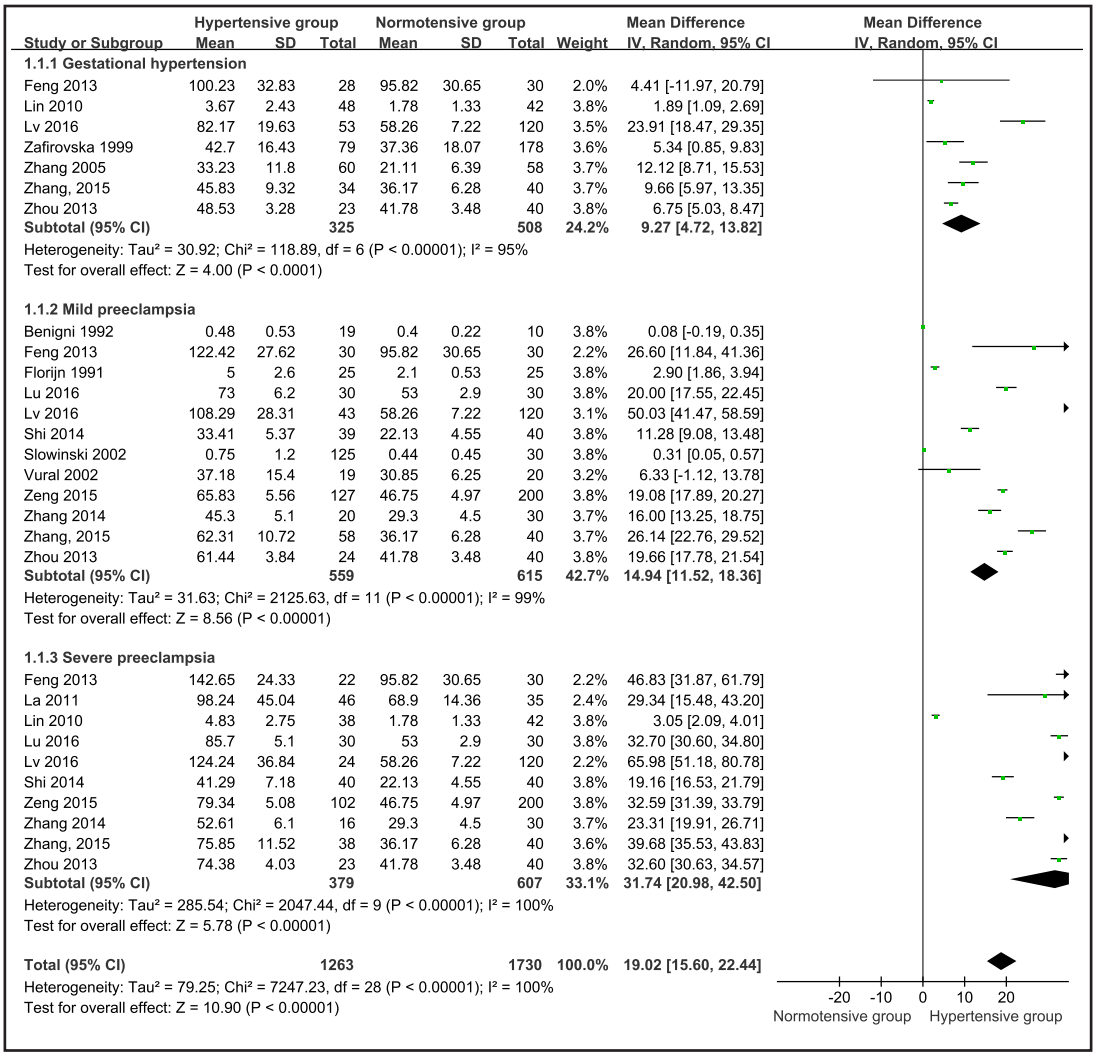

Fig. 2. Forrest blot of studies analyzing ET-1 serum concentrations in normotensive and hypertensive pregnant women.

Figure2) had higher ET-1 level than normotensive pregnant women. The age of the pregnant mothers had no impact on blood ET-1 concentration in normal and hypertensive pregnancy. Taken together, pregnant women with severe hypertension and proteinuria have higher ET-1 concentration among pregnant women with hypertension.

Discussion

The current meta-analysis revealed that plasma ET-1 concentrations are elevated in hypertensive disorders during human pregnancy. In particular women with preeclampsia (hypertensive pregnant women with proteinuria) have substantially elevated plasma ET-1 concentration as compared to pregnant women with normal blood pressure. Comparing the current study results with a recent meta-analysis in non-pregnant hypertensive patients [12], it became obvious that the ET-1 elevation is much more pronounced in hypertensive pregnant women as compared to hypertensive non-pregnant patients. Our data might suggest that ET-1 play a causal role in humans in the pathogenesis of pregnancy related hypertensive diseases.

Whole genome arrays failed so far to demonstrate a significant association between SNPs in genes of the ET system and hypertension during human pregnancy [39]. It should be taken into account that the studies investigating the genetic contributions for pregnancy-induced hypertension and preeclampsia are still limited. Only a few genetic variations were reported to be possibly associated with higher risk of pregnancy-induced hypertension and/or preeclampsia. A genome-wide association study identified a maternal copy-number deletion in the *PSG11* gene to be enriched among preeclampsia patients [40]. Another study reported that angiotensin II type 1 receptor gene *A1166C* polymorphism could be a predisposing factor for pregnancy-induced hypertension [41]. In addition, *NOS3 T*-786C SNP was reported to be associated with the occurrence of preeclampsia and its complications in a small study [42]. This is of particular interest with regard to the topic of our meta-analysis, since the ETB receptor on endothelial cells is a known activator of the endothelial NO synthase [3]. However, there – as stated above - was no signal for any component of the ET system in any genetic study in this particular field so far. Definitive answers may come from the InterPregGen study, the largest genome-wide association study of maternal and fetal genes conducted in Europe, Asia, and South America to screen for genetic risks of preeclampsia. The results of this study are awaited with interest [43].

An alternative hypothesis that might explain our findings would be that yet unknown environmental stimuli during human pregnancy might triggers epigenetic alterations of the human placenta or the vascular system including kidneys of the pregnant women [44-49] leading to an activation of the ET system in hypertensive pregnant women. An involvement of epigenetic mechanisms in the activation of the ET system has been described for diseases such as leukemia [50-53], cardiomyocyte terminal differentiation in the developing heart [54]. These studies in combination with our our meta-analysis indicating that the ET system is activated in a disease degree dependent manner in human pregnancy hypertension and the fact that there is no evidence of a genetic association of pregnancy induced hypertension and an activation of the ET system in humans should stimulate researchers to test the potential enrolments of epigenetic mechanisms in human hypertensive pregnancy diseases explaining the activation of the ET system in these diseases.

Endothelin receptor antagonists have been investigated in animal models of hypertension and also in human clinical trials in patients with essential hypertension. This treatment option, however, is not a feasible approach in human pregnancy given the embryo-toxic side effects of endothelin receptor antagonists. Similar effects on embryonic development were also observed in various gene kockout animal models of the ET system [3, 55, 56]. It is of note in this context that ECE/NEP inhibitors [57, 58] – pharmacological agents blocking the conversion of big ET-1 to ET-1 – not to have these embryo-toxic effects [55] and thus

might offer a therapeutic approach for hypertensive diseases during pregnancy. However, this requires very carefully conducted preclinical and clinical studies focusing in particular on safety.

Conclusion

Our meta-analysis clearly demonstrated an activation of the ET system in human hypertensive diseases during pregnancy. The underlying mechanisms are unknown so far. An association of genetic variations of the ET system with pregnancy hypertension was not seen in any of the genome wide association studies addressing this topic. Either epigenetic mechanisms or simply endothelial cell damage due to high blood pressure might be at least partially responsible for increased plasma ET-1 concentrations in human hypertensive diseases during pregnancy.

Disclosure statement

No competing Disclosure Statement for any of the authors.

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