Serum heme oxygenase 1 (HO-1), soluble FMS like tyrosine kinase (sFlt-1) level, and neonatal outcome in early onset, late onset preeclampsia, and normal pregnancy

by Muhammad Ilham Aldika Akbar

Submission date: 11-Aug-2020 10:56AM (UTC+0800)
Submission ID: 1368288715
File name: n_early_onset,_late_onset_preeclampsia,_and_normal_pregnancy.pdf (1.01M)
Word count: 4667
Character count: 24869

Serum heme oxygenase 1 (HO-1), soluble FMS like tyrosine kinase (sFlt-1) level, and neonatal outcome in early onset, late onset preeclampsia, and normal pregnancy

Article *in* Hypertension in Pregnancy · October 2018

DOI: 10.1080/10641955.2018.1494187

CITATION
1

READS
34

14 authors, including:

Muhammad Ilham Aldika Akbar
Airlangga University
53 PUBLICATIONS **4** CITATIONS
SEE PROFILE

Rozi Aryananda
9 PUBLICATIONS **2** CITATIONS
SEE PROFILE

Nareswari Cininta
Dr Soetomo General Hospital
7 PUBLICATIONS **1** CITATION
SEE PROFILE

Manggala Pasca Wardhana
Airlangga University
11 PUBLICATIONS **13** CITATIONS
SEE PROFILE

Taylor & Francis
Taylor & Francis Group

Hypertension in Pregnancy

ISSN: 1064-1955 (Print) 1525-6065 (Online) Journal homepage: http://www.tandfonline.com/loi/ihip20

Serum heme oxygenase 1 (HO-1), soluble FMS like tyrosine kinase (sFlt-1) level, and neonatal outcome in early onset, late onset preeclampsia, and normal pregnancy

Muhammad Ilham Aldika Akbar, Mita Herdiyantini, Rozi Aditya Aryananda, Nareswari CIninta, Manggala Pasca Wardhana, Khanisyah Erza Gumilar, Budi Wicaksono, Ernawati, Agus Sulistyono, Aditiawarman, Hermanto Tri Joewono, Nadir Abdullah, Gustaaf Dekker, Erry Gumilar Dachlan & Muhammad Dikman Angsar

To cite this article: Muhammad Ilham Aldika Akbar, Mita Herdiyantini, Rozi Aditya Aryananda, Nareswari CIninta, Manggala Pasca Wardhana, Khanisyah Erza Gumilar, Budi Wicaksono, Ernawati, Agus Sulistyono, Aditiawarman, Hermanto Tri Joewono, Nadir Abdullah, Gustaaf Dekker, Erry Gumilar Dachlan & Muhammad Dikman Angsar (2018): Serum heme oxygenase 1 (HO-1), soluble FMS like tyrosine kinase (sFlt-1) level, and neonatal outcome in early onset, late onset preeclampsia, and normal pregnancy, Hypertension in Pregnancy, DOI: 10.1080/10641955.2018.1494187

To link to this article: https://doi.org/10.1080/10641955.2018.1494187

Published online: 02 Oct 2018.

HYPERTENSION IN PREGNANCY
https://doi.org/10.1080/10641955.2018.1494187

Taylor & Francis
Taylor & Francis Group

Serum heme oxygenase 1 (HO-1), soluble FMS like tyrosine kinase (sFlt-1) level, and neonatal outcome in early onset, late onset preeclampsia, and normal pregnancy

Muhammad Ilham Aldika Akbar[a], Mita Herdiyantini[a], Rozi Aditya Aryananda[a], Nareswari Clninta[a], Manggala Pasca Wardhana[a], Khanisyah Erza Gumilar[a], Budi Wicaksono[a], Ernawati[a], Agus Sulistyono[a], Aditiawarman[a], Hermanto Tri Joewono[a], Nadir Abdullah[a], Gustaaf Dekker[a,b], Erry Gumilar Dachlan[a], and Muhammad Dikman Angsar[a]

[a]Department Obstetrics & Gynecology, DR. Soetomo – UNAIR Hospital, Universitas Airlangga, Surabaya, Indonesia; [b]Department Obstetrics & Gynecology, Lyell Mc Ewin Hospital, The University of Adelaide, Adelaide, Australia

ABSTRACT

Objective: To compare the level of serum heme oxygenase 1 (HO-1), soluble FMS like tyrosine kinase (sFlt-1), and neonatal outcome in early onset preeclampsia (EO-PE), late onset preeclampsia (LO-PE), and normal pregnancy (NP).

Methods: In this prospective observational case control study, HO-1 and sFlt-1 levels were measured in blood samples within 24 h of hospital admission. Preeclampsia cases were divided into two groups based on gestational age at delivery: EO-PE (<34 weeks) and LO-PE (≥34 weeks). A total of 45 patients were involved in this study.

Result: Maternal serum level of sFlt-1 was higher in EO-PE than LO-PE and NP groups (mean ± SD; 14.50 ± 17.12 ng/ml vs 5.20 ± 6.69 ng/ml vs 2.72 ± 1.2 ng/ml [$p = 0.020$]. Maternal serum level of HO-1 was not different between EO-PE, LO-PE, and NP groups ($p = 0.681$). Birthweights were significantly lower in the EO-PE group compared with the LO-PE and NP groups (1580 ± 536 g vs 2635 ± 578 g vs 3010 ± 371 g [$p = 0.000$]). The rate of small for gestational age infant (26.7% vs 6.7% vs 0%; $p = 0.046$) and perinatal death (20% vs 0 vs 0; $p = 0.037$) was also significantly higher in EO-PE compared to LO-PE and NP. The maternal sFlt-1 level was negatively correlated with birthweight ($p = 0.006$; CC = –0.445).

Conclusion: This study did not find a correlation between maternal HO-1 levels and sFlt-1 levels. Maternal serum sFLt-1 levels in preeclampsia were higher in EO-PE and were associated with a worse perinatal outcome.

ARTICLE HISTORY
Received 26 December 2017
Accepted 24 June 2018

KEYWORDS
Heme oxygenase 1 (HO-1); soluble FMS like tyrosine kinase (sFlt-1); early onset preeclampsia; late onset preeclampsia; neonatal outcome; IUGR

Introduction

Preeclampsia is one of the leading causes of maternal–fetal mortality and morbidity worldwide, in particularly in developing countries. It is characterized by new onset of hypertension and proteinuria after 20 weeks of gestation, and variable degrees of placental involvement as reflected in a higher rate of intra-uterine growth restriction (IUGR) and iatrogenic preterm birth (1). Hypertensive disorders of pregnancy complicate roughly 5–10% of pregnancies, and are responsible for about 25,000 maternal deaths in Africa, 22,000 in Asia, 3,800 in Latin America and Caribbean, and 150 in industrialized countries (2). Preeclampsia has been divided into early and late onset preeclampsia based on the onset of the disease, with 34-weeks gestational age at time of birth as cut-off. These two phenotypes of PE have different clinical characteristics, most likely different key pathophysiological pathways involved, and also a different perinatal prognosis. Early onset preeclampsia (EO-PE) is mostly associated with more severe placental lesions, a higher rate of severe maternal clinical manifestations, fetal complications (IUGR, placental abruption), and worse perinatal prognosis compared to late onset preeclampsia (LO-PE) (3).

Research on the final common pathway leading to the characteristic endothelial cell dysfunction has recently focused on an imbalance between circulating angiogenic and anti-angiogenic factors following the landmark study of Karumanchi's group (4). The maternal syndrome preeclampsia develops because overexpression of circulating anti-angiogenic factors and low level of angiogenic factors causing endothelial dysfunction. The main pro-angiogenic factors

CONTACT Muhammad Ilham Aldika Akbar muhammad-i-a-a@fk.unair.ac.id Dept Obstetrics & Gynecology Soetomo Hospital, Faculty of Medicine Universitas Airlangga

consist of Vascular Endothelial Growth Factor (VEGF) and Placental Growth Factor (PlGF), which regulate endovascular cytotrophoblast invasion, vascular growth in placenta, and maternal endothelial cell function. The main anti-angiogenic factors contributing to the maternal manifestations of preeclampsia are soluble FMS like tyrosine kinase 1 (sFlt-1) and soluble endoglin (sEng) (5). sFlt-1 is a VEGF-soluble receptor which acts as VEGF and PIGF antagonist by inhibiting angiogenic factor interaction with the endothelial VEGF receptor on the cell surface, inducing endothelial dysfunction (5,6). Several studies have demonstrated that the imbalance between angiogenic and anti-angiogenic factor is significantly related, in time and severity, with clinical manifestation of preeclampsia. The PELICAN study has shown that a low level of PlGF can predict women with preeclampsia requiring delivery within 14 days (7–11).

One recent concept proposes that preeclampsia is caused by a failure of one of the key pregnancy protection systems during pregnancy, in addition to the aforementioned imbalance of angiogenic and anti-angiogenic factor. One of this early pregnancy protection systems known today is the heme oxygenase (HO)/carbon monoxide (CO) pathway (12,13). HO is an endoplasmic reticulum enzyme which serves to degrade heme to produce biliverdin, free iron, and CO in proportional amount. HO has two isoforms: HO-1 and HO-2. In mammalian tissue, HO-1 is induced by heme substrate, heavy metal, and other stimuli causing oxidative stress such as peroxynitrite, lipid, hypoxia, hyperoxia, ischemia, reperfusion, hyperthermia, and endotoxic shock (12). The potential mechanism by which HO-1 may exert a protective effect in normal pregnancy includes: (1) Regulation of uNK cell survival and angiogenic factors in the placental bed; fundamental in the spiral artery remodeling process, (2) protection of trophoblast cells from cellular destruction, (3) production of CO which is protective to pregnancy, (4) indirect stimulation of the production of VEGF and PIGF through CO, and (5) suppression of the production and secretion of antiangiogenic factors (sFlt-1 and sEng) (13–17). These five mechanisms have been proposed to directly or indirectly protect the pregnancy and reduce the preeclampsia risk (12).

Maternal-neonatal clinical manifestations appear to differ between EO-PE and LO-PE. EO-PE is mostly associated with superficial cytotrophoblast invasion in the spiral arteries and as such often displays abnormal uterine Doppler flow patterns, impaired fetal growth, and poorer maternal–neonatal outcomes. On the other hand, LO-PE generally is mostly associated with normal uterine artery Doppler flow resistance indices, normal fetal growth, and no adverse perinatal outcome (3,11).

We hypothesized that this discrepancy might be related to the difference levels of maternal serum HO-1 versus sFlt-1. The aims of the current study were therefore to evaluate the differences in fetal outcomes (infant birth weight, birth weight centiles, 1- and 5 min-Apgar scores) between these two subtypes of preeclampsia, in relation to maternal serum levels of HO-1 and sFlt-1, in an Indonesian population.

Methods

This was an observational cross-sectional study. The study was conducted in Dr. Soetomo Hospital (the main tertiary referral hospital in East Java), and the University of Airlangga University Hospital between January and May 2016.

Study population

The study population consisted of all preeclampsia patients admitted during this 5-month period. Inclusion criteria were singleton pregnancy diagnosed with preeclampsia with severe features. None of these patients were smoking. Blood samples were taken consecutively from all preeclamptic patients fulfilling the inclusion criteria and a control group. Patients were divided into three groups: control, EO-PE and LO-PE groups, each consisting of 15 patients. The control group consisted of normal pregnant women between 20 and 40 weeks gestation, matched by gestational age with the preeclampsia subgroups. Early and late onset preeclampsia groups were defined using 34 weeks gestational age as cut-off. Preeclampsia was diagnosed in line with the International Society for the Study of Hypertension in Pregnancy (ISSHP) criteria (2014), i.e. new onset of hypertension (blood pressure greater than 140/90 mmHg) after 20 weeks gestation with the coexistence of one of the following: proteinuria, maternal organ dysfunction, and/or IUGR (18). After diagnosis of preeclampsia was confirmed, and the patient had been stabilized, blood samples were taken, typically within 2 h after hospitalization, and not more than 24 h. The patients were followed until delivery, and neonatal outcomes (gestational age at delivery, birthweight, birthweight centile, Apgar score, oligohydramnios, Small Gestational Age (SGA), Intra Uterine Fetal Death (IUFD), NICU admission, and perinatal death) were recorded. Gestational age was recorded at delivery based on certain last menstrual periods or first-trimester ultrasound dating. Newborn birth weight was measured at delivery, and INTERGROWTH calculator determined the birth weight percentile. Oligohydramnions was

determined by ultrasound using criteria: amniotic fluid index <8 cm or single deepest pocket <2 cm. SGA was defined as a birth weight percentile <10. IUFD was diagnosed by loss of heart beat in 2D, M-Mode or Doppler examination using ultrasound, in any stage of pregnancy. NICU admission was defined as a newborn need a special care in NICU, without considering the duration of care. Perinatal death was defined using WHO criteria as a fetal death in utero (stillbirth) above 20 weeks gestation until 7 days after delivery.

Blood samples and assays

A quantity of 15 ml of blood sample was collected from untecubital vein into tube. Blood sample was left coagulated for 30 min, then centrifuged 2400 *g* for 10 min before put into fresh tube and stored at <20°C in refrigerator for later examination. Serum heme oxygenase 1 (HO-1) level was measured using HO-1 StressXpress ELISA Kit using quantitive sandwich enzyme immunoassay technique. While serum sFlt-1 level was measured using separate kit, Quantikine Human VEGF-R1 Kit with simple enzyme-linked immunosorbent assay (ELISA) methods. Laboratory staff completing the assays were blinded regarding the status of the patient (control versus preeclampsia).

Signed informed consent was obtained from all participating patients.

The ethical clearance of this study has been approved by Dr. Soetomo Medical Research Ethical Committee.

Result

Clinical characteristics and risk factors

The general characteristics and risk factors in every group are presented in Table 1. There were, as expected, significant differences among three groups in maternal age, gestational age during recruitment and delivery, and preexisting chronic hypertension. Preeclampsia groups tended to be older compared to normal control group in this study. Preexisting hypertension was more common in EO-PE group. Additional risk factors such as diabetes mellitus, renal disease, rheumatic disease, antiphospholipid syndrome, and history of familial preeclampsia were not found in any group.

Maternal serum heme oxygenase-1 and sFlt-1 level

This study found very similar maternal serum HO-1 level in the three subgroups (4.55 ± 0.98 vs 4.80 ± 1.32 vs 4.4 ± 1.08, $p = 0.681$) (Table 2, Figure 1). The level of sFlt-1 was higher in EO-PE compared with LO-PE and the control group (14.50 ± 17.12 ng/ml vs 5.20 ± 6.69 ng/ml vs 2.72 ± 1.2 ng/ml; $p = 0.020$). But there was no significant difference between maternal

Table 1. Characteristic and risk factors in early onset PE, late onset PE, and control groups.

	Early onset preeclampsia	Late onset preeclampsia	Control	*p*
Maternal Age (years)	32.94 + 5.66	33.88 + 6.58	28.9 + 6.0	0.036*
Body Mass Index (kg/m$^{(2)}$)	28.22 + 5.68	28.82 + 5.19	25.56 + 4.92	0.172
Chronic Hypertension	18%	0%	0%	0.027*
Parity				
Primi	43.8%	12.5%	28.6%	0.208
Multi	43.8%	68.8%	61.9%	
Grande Multi	12.5%	18.8%	9.5%	
Obesity	31.2%	18.8%	9.5%	0.253
Previous PE	0%	12.5%	0%	0.095
IVF Pregnancy	6.2%	0%	0%	0.315

*$p < 0.05$.

Table 2. Maternal serum level of HO, sFLT1, and neonatal outcome in early onset PE, late onset PE, and control groups.

	Early onset preeclampsia	Late onset preeclampsia	Control	*p*
Gestational age at recruitment	31.0 + 2.59	36.83 + 1.85	33.46 + 3.90	0.001*
Gestational age at delivery	32.67 + 1.303	36.83 + 1.850	38.23 + 1.103	0.000*
Birthweight	1580.33 + 536.93	2635.83 + 578.28	3010 + 371.69	0.000*
Birthweight Percentile	25.91 + 27.06	33.13 + 22.31	34.93 + 26.64	0.654
Apgar score minutes 1	5.25 + 2.67	6.33 + 1.87	7.15 + 1.41	0.047
Apgar score minutes 5	6.75 + 2.63	7.75 + 1.01	8.23 + 1.17	0.069
Oligohydramnios	2 (13.3%)	0	0	0.117
SGA (P <10th)	4 (26.7%)	1 (6.7%)	0	0.046*
IUFD	2 (13.3%)	0	0	0.117
NICU admission	7 (46.7%)	5 (33.3%)	2 (13.3%)	0.088
Perinatal death	3 (20%)	0	0	0.037*
HO	4.55 + 0.98	4.80 + 1.32	4.4 + 1.08	0.681
sFlt1	14.50 + 17.12	5.20 + 6.69	3.04 + 1.88	0.023*

*$p < 0.05$.

Table 3. Correlation between maternal serum level of HO, sFLT1, and neonatal outcome.

Variable	*P*	Coefficient correlation
HO – birthweight	0.842	−0.034
HO – percentile birthweight	0.215	−−0.209
HO – Apgar score min 1	0.041	−0.338
HO – Apgar score min 5	0.035*	−0.348
sFlt1 – birthweight	0.006*	−0.445
sFlt1 – Percentile birthweight	0.085	−0.287
sFlt1 – Apgar score min 1	0.222	−0.206
sFlt1 – Apgar score min 5	0.273	−0.185
HO – sFlt1	0.240	−0.198

* $p < 0.05$

serum sFlt-1 in LO-PE and NP, as seen in Table 2 and Figure 2. Importantly, we did not find a significant correlation between maternal serum sFlt-1 and HO-1 level ($p = 0.240$).

Neonatal outcome

Gestational age at birth was, by definition, significantly different between EO-PE vs LO-PE vs control groups (32.67 + 1.303 vs 36.83 + 1.850 vs 38.23 + 1.103 weeks), respectively. This was in conjunction with difference in infant birth weight, which was lower in EO-PE rather than LO-PE and control group (1580 ± 536 vs 2635 ± 578 vs 3010 ± 371 g; $p = 0.000$). Regarding birthweight centiles, using the INTERGROWTH calculator, there was no difference in the mean birthweight centiles between the three groups (25.91 + 27.06 vs 33.13 + 22.31 vs 34.93 + 26.64; $p = 0.654$). However, the rate of SGA infants (birthweight percentile <10th) (26.7% vs 6.7% vs 0%; $p = 0.046$) and perinatal mortality (20% vs 0 vs 0; $p = 0.037$) were significantly higher in EO-PE than LO-PE and control group. Other parameters such as minute-1 and minute-5 Apgar scores, incidence of oligohydramnios, stillbirth, and admission to NICU showed no differences between the three groups (Table 2).

The maternal sFlt-1 level was negatively correlated with actual birthweight ($p = 0.006$; CC: −0.445), while HO-1 levels had a negative correlation with the 5-min Apgar score ($p = 0.035$; CC: −0.348)(Table 3).

Discussion

This study found that the maternal serum level of HO-1 was quite similar in EO-PE vs LO-PE and vs normal control pregnant women, and the HO-1 levels did not show any correlation with sFlt-1 levels. Maternal HO-1 levels were not significantly correlated with any neonatal outcome, except the neonatal Apgar score (likely reflecting a coincidental finding).

In line with the existing literature, the maternal sFlt-1 level in the EO-PE group was significantly higher than LO-PE and control group, while the sFlt-1 levels in the LO-PE group were not different when compared with the control group (Table 2) (19–21). This finding

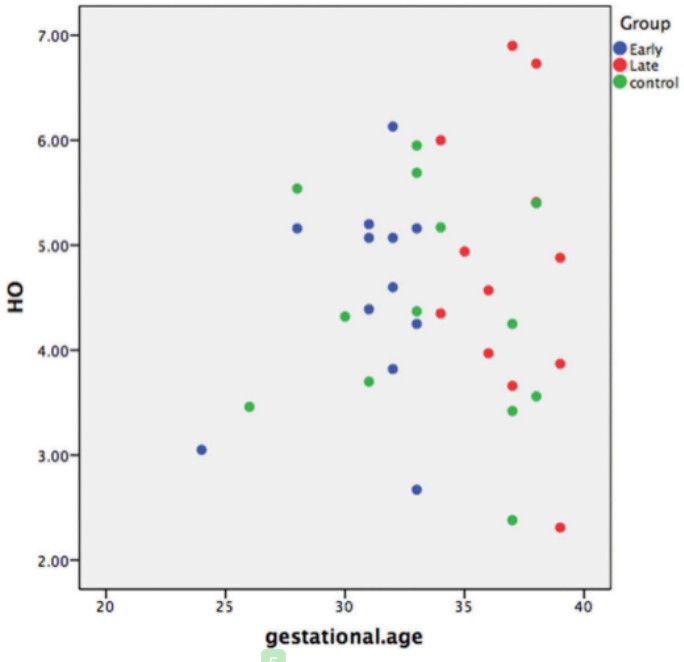

Figure 1. Plot distribution of maternal serum HO level in early onset PE, late onset PE, and control groups, based on gestational age. (Blue dot indicate EO-PE, red dot indicate LO-PE, and normal control groups as green dot).

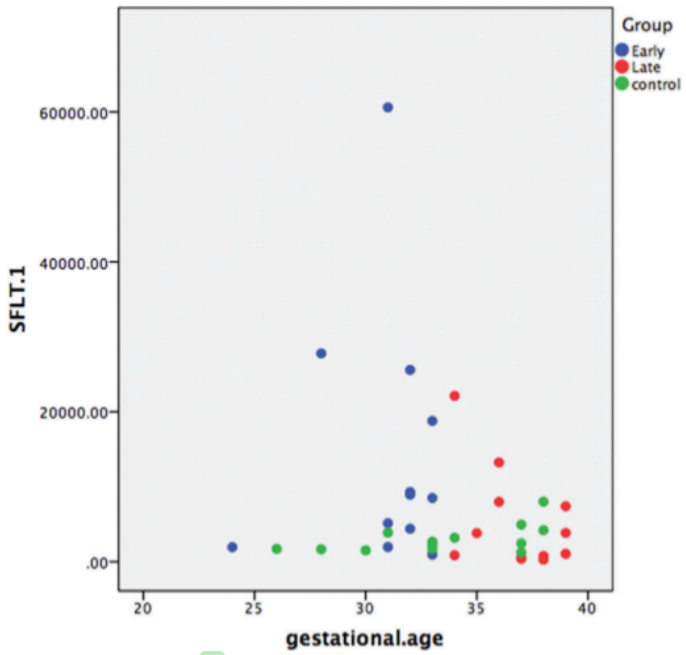

Figure 2. Plot distribution of maternal serum sFlt-1 level in early onset PE, late onset PE, and control groups, based on gestational age.

is in accordance with previous studies, showing the placental involvement/lesion in EO-PE, being minimal or absent in LO-PE. In terms of neonatal outcome, the maternal sFlt-1 level was significantly correlated with birthweight (p = 0.006, CC = −0.445).

Several studies have proposed that HO-1 is protective against preeclampsia by suppressing anti angiogenic factor activity, especially sFlt-1 and sEng. Previously, it has been shown that HO-1 deficiency in the placenta is associated with elevated sFlt-1 levels and preeclampsia itself (12,17,22). However, the maternal serum HO-1 levels and its association with PE are still unclear, because various studies had different results. In the current study, we did not find any significant difference in maternal serum HO-1 levels between the three subgroups. This finding is in line with some studies (23,24), but contradict others describing increased levels of serum HO-1 in preeclampsia groups (25–27). Vitoratos et al. were the first to study the relationship between maternal serum HO-1 and preeclampsia, involving 31 pregnant women divided into Severe PE, Mild PE, and control groups, measured at 30–34 weeks. HO-1 serum levels were measured using assay kit (EKS-800, StressXpress, New York, USA) with ELISA methods. Inter-assay and intra-assay variability was less than 10%. The severe PE group had significantly higher serum HO-1 levels compared to mild PE and normotensive groups. Maternal serum HO-1 levels were positively correlated with mean blood pressure (26). Erdemli HK et al. had similar results in their case control study involving 33 pregnant PE women with 43 normotensive pregnant women (samples taken at 27–34 weeks gestation). HO-1 serum levels were also measured using ELISA methods with available assay kit (Cusabio Biotech Co., Houston, USA. human hemeoxygenase 1, Lot no:N241161072), with intra-assay variability around 4%. Serum HO-1 levels were significantly higher in PE group compared with the control group (76.7 vs 55.9 ng/ml; p = 0.006), and a positive correlation was found between HO-1 levels with presence sign of preeclampsia (r = 0.316; p = 0.005) (25).

Karthikeyan et al. found no differences between serum HO-1 levels in their study involving 38 PE pregnant women and 38 normotensive pregnant women, in line with our findings (24). Also Varol et al. found no significant differences in serum HO-1 levels between severe and mild PE (total 46 cases) in their study (23). Serum HO-1 levels in both studies were measured using ELISA methods with different assay kits (Stressgen, Ann Arbor vs Cusabio Biotech Co Ltd) (23,24). The explanation for these divergent results is not clear, but may reflect differences in patient severity. In addition, although aforementioned papers used ELISA methods, different assay kits were used in these studies. However, importantly all these studies, including the current study agree on the fact that a lack

of HO-1 (as measured in the peripheral circulation) is apparently not the main explanation for the increased maternal sFlt-1 levels.

The data of the current study and the aforementioned studies indicate that maternal serum HO-1 is not the main defense mechanism against oxidative stress in systemic circulation (28). Further research, in particularly longitudinal studies, will be required to arrive at a better understanding on how changes in placental HO-1 expression relate to the maternal the serum HO-1 level in normal and pathological pregnancies (25).

Conclusion

This study did not find any difference between maternal serum HO-1 level of EO-PE, LO-PE, and normal pregnancy. Serum HO-1 levels also did not show any correlation with fetal outcome. Serum sFlt-1 levels were higher level in EO-PE compared with LO-PE and normal pregnancies, and increased sFlt-1 were associated with a worse perinatal outcome.

Declaration of interest

The authors report no conflicts of interest.

References

1. Dekker G, Sibai B. Primary, secondary and tertiary prevention of preeclampsia. Lancet. 2001; 357: 209–15. 10.1016/S0140-6736(00)03599-6
2. Hutcheon JA, Lisonkova S, Joseph KS. Epidemiology of pre-eclampsia and the other hypertensive disorders in pregnancy. Best Pract Res Clin Obstetrics Gynaecol. 2011; 25: 391–403. 10.1016/j.bpobgyn.2011.01.006
3. Valensise H, Vasapollo B, Gagliardi G, Novelli GP. Early and late preeclampsia: two different maternal hemodynamic states in the latent phase of the disease. Hypertension. 2008; 52: 873–80. 10.1161/HYPERTENSIONAHA.108.117358
4. Maynard SE, Venkatesha S, Thadhani R, Karumanchi SA. Soluble FMS-like tyrosine kinase 1 and endothelial dysfunction in the pathogenesis of preeclampsia. Pediatr Res. 2005; 57: 1R–7R. 10.1203/01.PDR.0000159567.85157.B7
5. Karumanchi SA, Rana S, Taylor RN. Chapter 6: angiogenesis and Preeclampsia. In Taylor R, Roberts J, Cunningham F, Lindheimer M (eds), Chesley's hypertensive disorders in pregnancy. 4th edition. Elsevier, 2015
6. De Vivo A, Baviera G, Giordano D, Todarello G, Corrado F, D'anna R. EndoglinPlGF and sFlt-1 as markers for predicting preeclampsia. Acta Obstet Gynecol Scand. 2008; 87: 837–42. 10.1080/00016340802253759
7. Chappell LC, Duckworth S, Seed PT, Griffin M, Myers J, Mackillop L, et al. Diagnostic accuracy of placental growth factor in women with suspected preeclampsia: a prospective multicenter study. Circulation. 2013; 12819: 2121–3110.1161/CIRCULATIONAHA.113.003215
8. Hagmann H, Thadhani R, Benzing T, Karumanchi SA, Stepan H. The promise of angiogenic markers for the early diagnosis and prediction of preeclampsia. Clin Chem. 2012; 585: 837–4510.1373/clinchem.2011.169094
9. Ahmad S. Elevated placental soluble vascular endothelial growth factor receptor-1 inhibits angiogenesis in preeclampsia. Circ Res. 2004; 95: 884–91. 10.1161/01.RES.0000147365.86159.f5
10. Ramma W, Buhimschi IA, Zhao G, Dulay AT, Nayeri UA, Buhimschi CS, Ahmed A. The elevation in circulating anti-angiogenic factors is independent of markers of neutrophil activation in preeclampsia. Angiogenesis. 2012; 15: 333–40. 10.1007/s10456-012-9261-5
11. Crispi F, Domínguez C, Llurba E, Martín-Gallán P, Cabero L, Gratacós E. Placental angiogenic growth factors and uterine artery doppler findings for characterization of different subsets in preeclampsia and in isolated intrauterine growth restriction. Am J Obstet Gynecol. 2006; 195: 201–07. 10.1016/j.ajog.2006.01.014
12. Ahmed A, Ramma W. Unravelling the theories of pre-eclampsia: are the protective pathways the new paradigm?. Br J Pharmacol. 2015; 172: 1574–86. 10.1111/bph.12977
13. Ahmed A, Rahman M, Zhang X, Acevedo CH, Nijjar S, Rushton I. *et al.* Induction of placental heme oxygenase-1 is protective against TNF alpha-induced cytotoxicity and promotes vessel relaxation. Mol Med. 2000; 6: 391–409
14. Linzke N, Schumacher A, Woidacki K, Croy BA, Zenclussen AC. Carbon monoxide promotes proliferation of uterine natural killer cells and remodelling of spiral arteries in pregnant hypertensive heme oxygenase-1 mutant mice. Hypertension. 2014; 63: 580–88. 10.1161/HYPERTENSIONAHA.113.02403
15. Ahmed A. Heparin-binding angiogenic growth factors in pregnancy. Trophoblast Res. 1998; 10: 215–58
16. Zenclussen ML, Linzke N, Schumacher A, Fest S, Meyer N, Casalis PA, Zenclussen AC. Heme oxygenase-1 is critically involved in placentation, spiral artery Remodelling, and blood pressure regulation during murine pregnancy. Front Pharmacol. 2015; 5Article 291: 110.3389/fphar.2014.00291
17. Cudmore M, Ahmad S, Al-Ani B, Fujisawa T, Coxall H, Chudasama K, et al. Negative regulation of soluble Flt-1 and soluble endoglin release by heme oxygenase-1. Circulation. 2007; 115: 1789–97. 10.1161/CIRCULATIONAHA.106.660134
18. Tranquilli AL, Dekker G, Magee L, Roberts J, Sibai BM, Steyn W, Zeeman GG, Brown MA. ISSHP. The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from ISSHP. Pregnancy Hypertension. 2014; 4: 97–104. 10.1016/j.preghy.2014.02.001
19. Chaiworapongsa T, Romero R, Espinoza J, Bujold E, Mee Kim Y, Gonçalves LF, Gomez R, Edwin S. Evidence supporting a role for blockade of the vascular endothelial growth factor system in the pathophysiology of preeclampsia. Young Investigator Award. Am J Obstet Gynecol. 2004; 1906: 1541–47. 10.1016/j.ajog.2004.03.043

20. Wikström A-K, Larsson A, Eriksson UJ, Nash P, Nordén-Lindeberg S, Olovsson M. Placental growth factor and soluble FMS-like tyrosine kinase-1 in early-onset and late-onset preeclampsia. Obstet Gynecol. 2007; 1096: 1368–74. 10.1097/01.AOG.0000264552.85436.a1
21. Masuyama H, Segawa T, Sumida Y, Masumoto A, Inoue S, Akahori Y, Hiramatsu Y. Different profiles of circulating angiogenic factors and adipocytokines between early- and late-onset pre-eclampsia. BJOG. 2010; 117: 314–20. 10.1111/j.1471-0528.2010.02739.x
22. Miyagami S, Koide K, Sekizawa A, Ventura W, Yotsumoto J, Oishi S, Okai T. Physiological changes in the pattern of placental gene expression early in the first trimester. Reprod Sci. 2013; 20: 710–14. 10.1177/1933719112466309
23. Varol F, Uzunoglu R, Erbas H. Sut N, Sayin C. VEGFR-1, Bcl-2, and HO-1 ratios in pregnant women with hypertension. Clin Appl Thrombosis/Hemostasis. 2013; 21(3):1–4
24. Karthikeyan VJ, Lip GY, Baghdadi S, Lane DA, Beevers DG, Blaan AD. Angiogenin and hemeoxygenase in pregnancy: influence of hypertension. Angiology. 2012; 63: 194–98.10.1177/0003319711410308
25. Erdemli HK, Yıldırımlar P, Alper TY, Kocabaş R, Salis O, Bedir A. Increased serum heme oxygenase-1 levels as a diagnostic marker of oxidative stress in preeclampsia. Hypertens Pregnancy. 2014; 334: 488–97. 10.3109/10641955.2014.946613
26. Vitoratos N, Papakonstantinou K, Deliveliotou A, Economou E, Panoulis C, Hassiakos D, Creatsas GK. Antepartum and postpartum serum heme oxygenase-1 levels in preeclamptic and normotensive pregnant women. In Vivo. 2011; 25: 445–50
27. Wantania JJ, Homenta C, Kepel BJ. Relationship of heme oxygenase-1 (HO-1) level with onset and severity in normotensive pregnancy and severe pre-eclampsia. Bali Med J. 2016; 51: 118–2210.15562/bmj.v5i1.267
28. Agarwal A, Mellado AA, Premkumar BJ, Shaman A, Gupta S. The effects of oxidative stress on female reproduction: a review. Reprod Biol Endocrinol. 2012; 10: 49

Serum heme oxygenase 1 (HO-1), soluble FMS like tyrosine kinase (sFlt-1) level, and neonatal outcome in early onset, late onset preeclampsia, and normal pregnancy

ORIGINALITY REPORT

25%	11%	24%	0%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	"Maternal Medicine", Journal of Obstetrics and Gynaecology Research, 2017 Publication	1%
2	Tobinaga, Clarissa M., Maria R. Torloni, Bárbara Y. Gueuvoghlanian-Silva, Karen P.T. Pendeloski, Patrícia A. Akita, Nelson Sass, and Silvia Daher. "Angiogenic factors and uterine Doppler velocimetry in early- and late-onset preeclampsia", Acta Obstetricia Et Gynecologica Scandinavica, 2014. Publication	1%
3	"Scientific Abstracts", Reproductive Sciences, 2012 Publication	1%
4	Muhammad Ilham Aldika Akbar, Muhammad Arief Adibrata, Aditiawarman, Rozi Aditya Aryananda et al. "Maternal and perinatal outcome related to severity of chronic hypertension in pregnancy", Pregnancy	1%

Hypertension, 2019
Publication

---

5 Jakub Kornacki, Przemysław Wirstlein, Ewa Wender-Ozegowska. "Levels of syndecan-1 and hyaluronan in early- and late-onset preeclampsia", Pregnancy Hypertension, 2019 — 1%
Publication

---

6 Aysegul Ozel, Ebru Alici Davutoglu, Asuman Firat, Hakan Erenel, Mehmet Fatih Karslı, Sevim Özge Korkmaz, Riza Madazli. "Maternal serum irisin levels in early and late-onset pre-eclamptic and healthy pregnancies", Journal of Obstetrics and Gynaecology, 2018 — 1%
Publication

---

7 Valeria Sandrim, Fernanda Borchers Coeli-Lacchini, Jose Eduardo Tanus-Santos, Riccardo Lacchini, Ricardo Carvalho Cavalli. " Circulating HO-1 levels are not associated with plasma sFLT-1 and GT polymorphism in preeclampsia ", Hypertension in Pregnancy, 2019 — 1%
Publication

---

8 "Tuesday, 4 September 2007", European Heart Journal, 09/02/2007 — 1%
Publication

---

9 Hacı Kemal Erdemli, Pınar Yıldırımlar, Tayfun Yaşar Alper, Ramazan Kocabaş, Osman Salis, Abdulkerim Bedir. "Increased serum heme — 1%

oxygenase-1 levels as a diagnostic marker of oxidative stress in preeclampsia", Hypertension in Pregnancy, 2014
Publication

10	"Scientific Abstracts", Reproductive Sciences, 2014. Publication	1%
11	jultika.oulu.fi Internet Source	1%
12	Wentao Yu, Wei Gao, Dan Rong, Zhixian Wu, Raouf A Khalil. "Molecular Determinants of Microvascular Dysfunction in Hypertensive Pregnancy and Preeclampsia", Microcirculation, 2018 Publication	1%
13	Young Nam Kim. "The relationship of the level of circulating antiangiogenic factors to the clinical manifestations of preeclampsia", Prenatal Diagnosis, 2009 Publication	<1%
14	Portelinha, A.. "Haemostatic factors in women with history of Preeclampsia", Thrombosis Research, 200905 Publication	<1%
15	Eliyahu Khankin, Caroline Royle, S. Karumanchi. "Placental Vasculature in Health and Disease", Seminars in Thrombosis and	<1%

	Hemostasis, 2010 Publication	
16	"Poster Day 1 - Oxidative Stress", Hypertension in Pregnancy, 7/2006 Publication	<1%
17	Yohei Kirino. Arthritis Research & Therapy, 2005 Publication	<1%
18	www.mdpi.com Internet Source	<1%
19	Weinai Liu, Yong Li, Wugang Wang, Junfang Li, Juan Cong. "Layer-specific longitudinal strain analysis by speckle tracking echocardiography in women with early and late onset preeclampsia", Pregnancy Hypertension, 2019 Publication	<1%
20	R Tripathi. "Soluble VEGFR-1 in pathophysiology of pregnancies complicated by hypertensive disorders: the Indian scenario", Journal of Human Hypertension, 02/23/2012 Publication	<1%
21	www.mat.or.th Internet Source	<1%
22	Wenda Ramma, Asif Ahmed. "Therapeutic potential of statins and the induction of heme oxygenase-1 in preeclampsia", Journal of	<1%

Reproductive Immunology, 2014
Publication

23	Hamid Reza Nejabati, Zeinab Latifi, Tohid Ghasemnejad, Amir Fattahi, Mohammad Nouri. "Placental growth factor (PlGF) as an angiogenic/inflammatory switcher: lesson from early pregnancy losses", Gynecological Endocrinology, 2017 Publication	<1%
24	www.oatext.com Internet Source	<1%
25	webicdn.com Internet Source	<1%
26	Tao Chen, Zai-pei Guo, Yu-hong Zhang, Ying Gao, Hong-jie Liu, Jing-yi Li. "Elevated serum heme oxygenase-1 and insulin-like growth factor-1 levels in patients with Henoch-Schonlein purpura", Rheumatology International, 2009 Publication	<1%
27	"Scientific Abstracts", Reproductive Sciences, 2011. Publication	<1%
28	Tea Kaartokallio, Siddheshwar Utge, Miira M. Klemetti, Jussi Paananen et al. "Fetal Microsatellite in the Heme Oxygenase 1 Promoter Is Associated With Severe and Early-	<1%

Onset Preeclampsia", Hypertension, 2018
Publication

29	kenney.faculty.ucdavis.edu Internet Source	<1%
30	JIMMY ESPINOZA. "ANGIOGENIC IMBALANCES IN THE PATHOGENESIS OF PREGNANCY COMPLICATIONS", Fetal and Maternal Medicine Review, 2014 Publication	<1%
31	Quinn, K.H.. "The unique pathophysiology of early-onset severe preeclampsia: role of decidual T regulatory cells", Journal of Reproductive Immunology, 201109 Publication	<1%
32	journals.sagepub.com Internet Source	<1%
33	Masuyama, H.. "Circulating angiogenic factors in preeclampsia, gestational proteinuria, and preeclampsia superimposed on chronic glomerulonephritis", American Journal of Obstetrics and Gynecology, 200602 Publication	<1%
34	William Durante. "Heme oxygenase-1 in growth control and its clinical application to vascular disease", Journal of Cellular Physiology, 06/2003 Publication	<1%

35	Pooja Wadhwani, Pradip Kumar Saha, Jaswinder Kaur Kalra, Shalini Gainder, Venkataseshan Sundaram. "A study to compare maternal and perinatal outcome in early vs. late onset preeclampsia", Obstetrics & Gynecology Science, 2020 Publication	<1%
36	Takashi Mitsui, Hisashi Masuyama, Jota Maki, Shoko Tamada et al. "Differences in uterine artery blood flow and fetal growth between the early and late onset of pregnancy-induced hypertension", Journal of Medical Ultrasonics, 2016 Publication	<1%
37	obgyn.pericles-prod.literatumonline.com Internet Source	<1%
38	Roberta B. Ness. "Cigarette Smoke Exposure and Angiogenic Factors in Pregnancy and Preeclampsia", American Journal of Hypertension, 08/2008 Publication	<1%
39	lsr.edu.in Internet Source	<1%
40	qspace.library.queensu.ca Internet Source	<1%
	Akitaka Takahashi. "The role of heme	

41	oxygenase-1 in systemic-onset juvenile idiopathic arthritis", Modern Rheumatology, 03/03/2009 Publication	<1%
42	royalsocietypublishing.org Internet Source	<1%
43	Kenneth I. Ataga. "Association of soluble fms-like tyrosine kinase-1 with pulmonary hypertension and haemolysis in sickle cell disease : sFLT-1 Associates with Pulmonary Hypertension in SCD", British Journal of Haematology, 02/2011 Publication	<1%
44	Magann, E.F.. "The amniotic fluid index, single deepest pocket, and two-diameter pocket in normal human pregnancy", American Journal of Obstetrics and Gynecology, 200006 Publication	<1%
45	Roberto Romero, Tinnakorn Chaiworapongsa, Offer Erez, Adi L. Tarca et al. "An imbalance between angiogenic and anti-angiogenic factors precedes fetal death in a subset of patients: results of a longitudinal study", The Journal of Maternal-Fetal & Neonatal Medicine, 2010 Publication	<1%
46	Eleazar Soto, Roberto Romero, Juan Pedro Kusanovic, Giovanna Ogge et al. "Late-onset	<1%

preeclampsia is associated with an imbalance of angiogenic and anti-angiogenic factors in patients with and without placental lesions consistent with maternal underperfusion", The Journal of Maternal-Fetal & Neonatal Medicine, 2011
Publication

---

47 www.nature.com <1%
Internet Source

---

48 "1-A1: Lung Cancer 1 : Poster Sessions", Respirology, 2013. <1%
Publication

---

49 Khalil, Asma, Nerea Maiz, Rosario Garcia-Mandujano, J.M. Penco, and Kypros H. Nicolaides. "Longitudinal changes in maternal serum placental growth factor and soluble fms-like tyrosine kinase-1 in women at increased risk of preeclampsia : PlGF and sFlt-1 in pre-eclampsia", Ultrasound in Obstetrics and Gynecology, 2015. <1%
Publication

---

50 Das, S., K. Pandey, V. N. Rabidas, A. Mandal, and P. Das. "Effectiveness of miltefosine treatment in targeting anti-leishmanial HO-1/Nrf-2-mediated oxidative responses in visceral leishmaniasis patients", Journal of Antimicrobial Chemotherapy, 2013. <1%
Publication

51	www.ogscience.org Internet Source	<1%
52	www.medicalgasresearch.com Internet Source	<1%
53	Huang, Qian, Lei Liu, Bihui Hu, Xiaodan Di, Shaun Patrick Brennecke, and Huishu Liu. "Decreased Seizure Threshold in an Eclampsia-Like Model Induced in Pregnant Rats with Lipopolysaccharide and Pentylenetetrazol Treatments", PLoS ONE, 2014. Publication	<1%
54	Juanjuan Chen, Raouf A. Khalil. "Matrix Metalloproteinases in Normal Pregnancy and Preeclampsia", Elsevier BV, 2017 Publication	<1%
55	www.healthmed.ba Internet Source	<1%
56	Offer Erez, Roberto Romero, Jimmy Espinoza, Wenjiang Fu et al. "The change in concentrations of angiogenic and anti-angiogenic factors in maternal plasma between the first and second trimesters in risk assessment for the subsequent development of preeclampsia and small-for-gestational age", The Journal of Maternal-Fetal & Neonatal Medicine, 2009	<1%

	Publication	
57	Theng Theng Chuah, Wan Shi Tey, Mor Jack Ng, Edward T.H. Tan, Bernard Chern, Kok Hian Tan. "Serum sFlt-1/PlGF ratio has better diagnostic ability in early- compared to late-onset pre-eclampsia", Journal of Perinatal Medicine, 2018 Publication	<1%
58	www.slideshare.net Internet Source	<1%
59	digibug.ugr.es Internet Source	<1%
60	www.fasgo.org.ar Internet Source	<1%
61	misc.medscape.com Internet Source	<1%
62	J. L. van der Merwe, D. R. Hall, C. Wright, P. Schubert, D. Grové. "Are Early and Late Preeclampsia Distinct Subclasses of the Disease—What Does the Placenta Reveal?", Hypertension in Pregnancy, 2010 Publication	<1%
63	Charity Ndwiga, George Odwe, Sripad Pooja, Omondi Ogutu, Alfred Osoti, Charlotte E. Warren. "Clinical presentation and outcomes of pre-eclampsia and eclampsia at a national	<1%

hospital, Kenya: A retrospective cohort study", PLOS ONE, 2020
Publication

---

64 Takuya Miyazaki. "Serum HO-1 is useful to make differential diagnosis of secondary hemophagocytic syndrome from other similar hematological conditions", International Journal of Hematology, 01/22/2010 <1%
Publication

---

65 Dahlia Raymond. "A Critical Review of Early-Onset and Late-Onset Preeclampsia :", Obstetrical & Gynecological Survey, 08/2011 <1%
Publication

---

66 Abdullah Serdar Açıkgöz, Abdullah Tüten, Mahmut Öncül, Şerife Eskalen et al. "Evaluation of maternal serum progranulin levels in normotensive pregnancies, and pregnancies with early- and late-onset preeclampsia", The Journal of Maternal-Fetal & Neonatal Medicine, 2015 <1%
Publication

---

67 Crispi, F.. "Placental angiogenic growth factors and uterine artery Doppler findings for characterization of different subsets in preeclampsia and in isolated intrauterine growth restriction", American Journal of Obstetrics and Gynecology, 200607 <1%
Publication

68	Kuc, Sylwia, Maria P. H. Koster, Arie Franx, Peter C. J. I. Schielen, and Gerard H. A. Visser. "Maternal Characteristics, Mean Arterial Pressure and Serum Markers in Early Prediction of Preeclampsia", PLoS ONE, 2013. Publication	<1%
69	Hisashi Masuyama, Yuji Hiramatsu. "Angiogenic proteins and adipocytokines as markers for prediction of preeclampsia", Expert Review of Obstetrics & Gynecology, 2014 Publication	<1%
70	Xiaotong Sun, Tao Qu, Xiyan He, Xueping Yang, Nan Guo, Yan Mao, Xianghong Xu, Xiaodong Sun, Xuehong Zhang, Weihua Wang. "Screening of differentially expressed proteins from syncytiotrophoblast for severe early-onset preeclampsia in women with gestational diabetes mellitus using tandem mass tag quantitative proteomics", BMC Pregnancy and Childbirth, 2018 Publication	<1%
71	Gian Carlo Di Renzo. "The role of an 'anti-angiogenic state' in complications of pregnancy", The Journal of Maternal-Fetal & Neonatal Medicine, 2009 Publication	<1%
72	Yoshimatsu, J.. "Relationship between urinary	

albumin and serum soluble fms-like tyrosine kinase 1 (sFlt-1) in normal pregnancy", European Journal of Obstetrics and Gynecology, 200609/10

Publication

<1%

Exclude quotes	On	Exclude matches	Off
Exclude bibliography	On		

Serum heme oxygenase 1 (HO-1), soluble FMS like tyrosine kinase (sFlt-1) level, and neonatal outcome in early onset, late onset preeclampsia, and normal pregnancy

GRADEMARK REPORT

FINAL GRADE

/100

GENERAL COMMENTS

Instructor

PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7

PAGE 8

PAGE 9