ORIGINAL RESEARCH

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# Maternal Plasma Levels of Hypoxia Inducible Factor 1 Alpha, Soluble Endoglin, and Transforming Growth Factor Beta1 in Preeclampsia: Cross-Sectional Research

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**ABSTRACT Objective:** To determine maternal plasma levels of hypoxia inducible factor 1 alpha (HIF-1α), soluble endoglin (sEng), and transforming growth factor beta1 (TGF-β1) in preeclampsia. **Material and Methods:** A cross-sectional study was conducted in 30 normal and 30 preeclamptic pregnant women during the third trimester of pregnancy. Plasma levels of HIF 1α, sEng, and TGF-β1 were measured by enzyme-linked immunosorbent assay (ELISA). The plasma levels were compared between preeclamptic pregnant women and normal pregnant controls. Correlation between 2 of these parameters were analyzed. **Results:** Median [interquartile range (IQR)] value of plasma HIF-1α level was significantly higher in preeclampsia (PE) group than that of normal pregnancy group, 37.10 (32.22-44.55) versus 31.09 (29.10-36.55) pg/ml, ($p<0.01$). The PE group had significantly higher plasma level of sEng than normal pregnancy group [Mean±SD: (14.02±9.05) versus (10.04±3.42) ng/ml, ($p<0.05$)]. However, there was no statistically significant difference in plasma level of TGF-β1 between PE group [Median (IQR): 4.69 (0.38-12.04) ng/ml] and normal pregnancy group [Median (IQR): 2.17 (0.392-53.75) ng/ml]. There were no significant correlations between any two of plasma HIF-1α, sEng, and TGF-β1in all pregnant women. **Conclusion:** Plasma levels of HIF-1α and sEng were significantly higher in PE than that of normal pregnancy. The hypoxia and altered angiogenic balance may be involved in the pathogenesis of preeclampsia.

**Keywords:** Hypoxia inducible factor1 alpha; soluble endoglin; transforming growth factor beta; preeclampsia

Preeclampsia (PE) is a pregnancy-related multisystem disorder characterized by new onset of hypertension and significant proteinuria after 20th week of pregnancy.[1] Globally, it estimates about 5% of pregnancy and a major leading cause of maternal and perinatal morbidity and mortality.[2]

Despite extensive researches, the pathophysiology of PE cannot be clearly explained. Many studies suggested that PE might be due to inadequate invasion of spiral arteries into maternal uterine wall resulting in shallow placentation.[3] This subsequently impaired the remodeling of spiral arteries and reduction in uteroplacental blood flow and persistent placenta ischemia/hypoxia. Chemical mediators are released from the placenta in response to hypoxic stimuli and leading to systemic vascular and endothelial dysfunction.[4] Hypoxia inducible factor 1 (HIF-1) is a heterodimeric transcriptional factor, which regulates the cellular adaptive response to decreased oxygen level in physiological and pathological conditions.[5] Previous studies reported that α isoform of HIF-1 (i.e. HIF-1α) was expressed in placentas and released into maternal circulation.[6-8]

It is currently understood that imbalance between angiogenesis and anti-angiogenesis plays an important role in the pathogenesis of PE. Excess of anti-an-

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giogenic factors, with subsequent deficiency of proangiogenic factors lead to vascular dysfunction and symptoms of preeclampsia.[9,10] The role of the anti-angiogenic factor, soluble fms-like tyrosine kinase-1 (sFlt1) and its binding ligands, vascular endothelial growth factor and placental growth factor in PE has been studied extensively. However, the studies concerning another anti-angiogenic factor, soluble form of endoglin, co-receptor of transforming growth factor beta 1 (TGF-$\beta_1$), and its ligand in PE is still limited. Moreover, the possible causative factor for the angiogenic imbalance has not been clearly identified. Thus, this study aimed to explore the maternal plasma level of HIF1α, anti-angiogenic factor soluble endoglin (sEng), and angiogenic factor TGF-$\beta_1$ in the third trimester of pregnancy and correlating the levels of HIF1α and sEng, HIF1α and TGF-$\beta_1$, sEng and TGF-$\beta_1$. This study highlighted the role of HIF1α, sEng, and TGF-$\beta_1$ in the pathogenesis of PE.

## MATERIAL AND METHODS

This cross-sectional study was carried out from January 2020 to June 2021 in the University of Medicine 2, Yangon and Department of Obstetrics and Gynecology, North Okkalapa General and Teaching Hospital (NOGTH). The study was started after getting approval from Ethics Review Committee-3 of University of Medicine 2, Yangon [date: July 24, 2019; no: 89/ERC-3 (4-2019)]. The study was performed according to the principles of Declaration of Helsinki; 2013. After clearly explaining the research procedure, written informed consent was obtained from each participant. Sixty pregnant women (30 women with PE and 30 normal pregnancies) in the 3$^{rd}$ trimester were recruited from out-patient department and obstetrics ward of NOGTH. All the participants were 18-40 years of age with singleton pregnancy. Those with cardiovascular disease, diabetes mellitus, liver disease, renal diseases, and acute and chronic infection were excluded from the study.

PE is diagnosed as resting systolic blood pressure (SBP) ≥140 mmHg and/ or diastolic blood pressure (DBP) ≥90 mmHg and proteinuria ≥300 mg in 24 hr urine specimen and/or ≥1+ on urine dipstick after the 20$^{th}$ week of pregnancy in previously normotensive women.[11] The normal pregnancies were the women with uncomplicated pregnancy with SBP <140 mmHg and DBP <90 mmHg and no proteinuria in every occasion.

### STUDY PROCEDURE

Five ml of venous blood was taken from each participant with a sterile disposable syringe under aseptic condition. The blood samples were collected into blood collecting tubes containing $K_2$ EDTA. After centrifuging, the separated plasma was transferred into Eppen tubes [Catalog no. C10010-1; Sciencewerke (Myanmar) Co.,Ltd.] and kept at -80°C until being determined for further analysis. Plasma levels of HIF-1α, sEng and TGFβ$_1$ were determined by enzyme linked-immunosorbent assay (ELISA) using commercial ELISA kits purchased from Thermofisher Scientific.

### STATISTICAL ANALYSIS

Analysis of data was done in SPSS 22.0 statistical software (SPSS Inc., Chicago, IL, USA). Plasma levels were represented as median and interquartile range (IQR) for non-normally distributed data. For data with normally distribution, they were expressed as mean±standard deviation (SD). Independent t-test was used to compare the plasma sEng level between 2 groups. Comparison of plasma HIF-1α and TGF-$\beta_1$ between 2 groups was done by the Mann-Whitney U test. Spearman's correlation test was applied to determine the correlation between 2 variables. The results were considered as statistically significant when probability value <0.05.

## RESULTS

As shown in Table 1, no significant difference was found in age of pregnant mothers, gestational age at the time of sample collection and parity in normal pregnancy and PE group.

PE group had significantly higher plasma HIF-1a level than normal pregnancy group [median (IQR): 37.10 (32.22-44.55) versus 31.09 (29.10-36.55) pg/ml, (p<0.01)] (Figure 1). The plasma level of sEng was significantly higher in PE group compared to normal pregnancy group [mean±SD: (14.02±9.05) versus (10.04±3.42) ng/ml, (p<0.05)] (Figure 2). Median IQR of plasma TGF-$\beta_1$ level ap-

**TABLE 1:** General characteristic of the subjects

| Parameters | Normal pregnancy (n=30) | Preeclampsia (n=30) | p value |
|---|---|---|---|
| Age (years) | 29±4.86 | 31.33±5.2 | 0.078 |
| Maturity (weeks) | 34.09±2.75 | 34.42±3.84 | 0.7 |
| Parity | | | |
| Nulliparity (P0) n (%) | 14(46.7)[♯] | 8(26.7)[♯] | 0.108[λ] |
| Multiparity (P1&above) n (%) | 16(53.3)[♯] | 22(73.3)[♯] | |
| SBP (mmHg) | 109.67±8.5 | 145.33±6.27 | <0.001 |
| DBP (mmHg) | 72.67±6.91 | 93±5.96 | <0.001 |
| MAP (mmHg) | 84.1±6.82 | 110.45±5.47 | <0.001 |

[♯]chi square test; [λ]chi square value Data are presented as (Mean±SD) and comparison between 2 groups by unpaired t-test except parity SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MAP: Mean arterial pressure

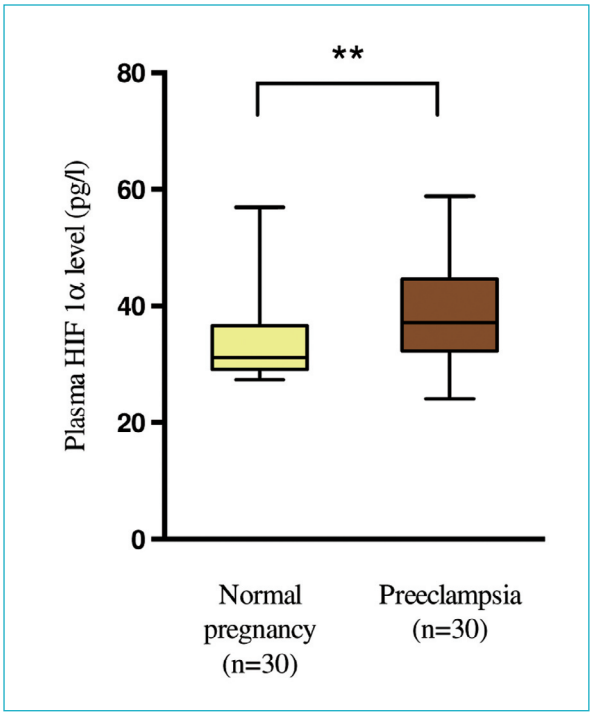


**FIGURE 1:** Comparison of plasma HIF-1 α level in preeclampsia and normal pregnancy

In the box plot, the middle bar indicates median, upper and lower end bar show 75th and 25th percentiles. The upper and lower bars represent the maximum and minimum values. Comparison was done by the Mann-Whitney test.

** Indicates significant difference (p < 0.01). HIF-1α: Hypoxia inducible factor1 alpha

peared to be higher [4.69 (0.38-12.04) ng/ml] in PE group than in normal pregnancy group [median (IQR): 2.17 (0.392-53.75) ng/ml] (Figure 3). However, a statistically significant difference was not observed in plasma TGF-$\beta_1$ level between the 2 study groups.

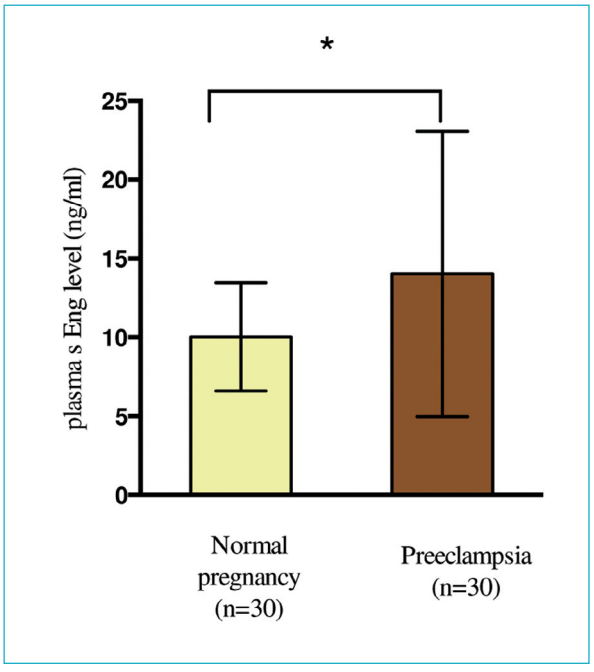


**FIGURE 2:** Comparison of plasma sEng level in preeclampsia and normal pregnancy

Error bars indicate mean±SD. Comparison was done by Independent t-test.

*Indicates significant difference (p<0.05). sEng: Soluble endoglin

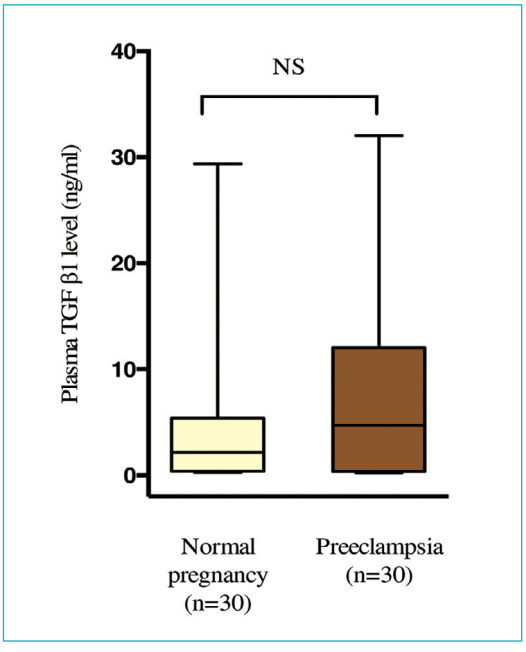


**FIGURE 3:** Comparison of plasma TGF-$\beta_1$ level in preeclampsia and normal pregnancy. In the box plot, the middle bar indicates median, upper and lower end bar show 75th and 25th percentiles. The upper and lower bars represent the maximum and minimum values. Comparison was done by the Mann-Whitney test. NS: Not significant difference

TGF-$\beta_1$: Transforming growth factor beta1

**TABLE 2A:** Correlation between plasma level of HIF-1α and sEng in all pregnant women (n=60)

| Correlation between | r | p value |
|---|---|---|
| Plasma level of HIF-1α and sEng in all pregnant women | 0.08 | 0.545 |

r- Spearman correlation coefficient
HIF-1α: Hypoxia inducible factor1 alpha; sEng: Soluble endoglin

**TABLE 2B:** Correlation between plasma level of HIF-1α and TGF-β1 in all pregnant women (n=60)

| Correlation between | r | p value |
|---|---|---|
| Plasma level of HIF1α and TGF-β1 in all pregnant women | -0.106 | 0.418 |

r- Spearman correlation coefficient
HIF-1α: Hypoxia inducible factor1 alpha; TGF-β1: Transforming growth factor beta1

**TABLE 2C:** Correlation between plasma level of sEng and TGFβ1 in all pregnant women (n=60)

| Correlation between | r | p value |
|---|---|---|
| Plasma level of sEng and TGFβ1 in all pregnant women | 0.075 | 0.567 |

r- Spearman correlation coefficient
sEng: Soluble endoglin; TGF-β1: Transforming growth factor beta1

No significant correlations were found between plasma level of HIF-1α and sEng, HIF-1α, and TGF-$\beta_1$, sEng and TGF-$\beta_1$ in all pregnant women (Table 2A, Table 2B, Table 2C).

## DISCUSSION

We studied the plasma levels of HIF-1α, sEng, and TGF-$\beta_1$ of preeclamptic pregnant woman and age-matched control in the 3rd trimester of pregnancy. Even in normal pregnancy, circulating levels of hormones or biomarkers are fluctuated throughout the gestational period according to physiological need of the mother and the fetus.[12,13] In this study, mean gestational ages were not significantly different in 2 groups. Therefore, the confounding effect of the fluctuation of biomarkers with the period of gestation can be ruled out.

Consistent with the previous studies, we found that plasma level of HIF-1 α is significantly higher in PE group than in normal pregnant group.[8,14] HIF1-α is an oxygen sensor and its level is increased in low oxygen concentration, which occurred in very early gestation of normal pregnancy.[15] HIF-1 α has a beneficial effect on trophoblastic invasion during that time. After that, HIF-1 levels falls in response to increase in placenta oxygen levels, suggesting the important role of HIF in placental development and function.[16,17] Abnormal implantation and poor trophoblastic invasion in preeclamptic placenta lead to hypoxic condition.[18,19] Many evidences showed that HIF-1α was expressed in placentas of preeclamptic women.[6,16] The cell-free level of HIF-1α mRNA and protein was significantly increased in the plasma of preeclamptic pregnant women.[7,8,20]

Under normoxic condition, HIF-1α binds with tumour suppressor protein, von Hippel-Lindau (pVHL) and after that the ubiquitin-proteasome pathway degrades that complex rapidly. In hypoxia, HIF-1α no longer binds to (pVHL), resulting in stabilization and accumulation of HIF-1α in the cytoplasm.[5,21,22] The increase in circulating level of HIF-1α in PE observed in this and other studies may be due to higher expression level as well as lesser degradation of the protein than in control group.

The significantly higher plasma level of sEng was found in preeclamptic pregnant women than that of control group. The result was similar to previous studies that reported that circulating sEng levels are increased in PE.[23-26]

These evidences implied that sEng is an crucial antiangiogenic factor involved in the pathogenesis of PE. Venkatesha et al. stated that the expression of endoglin was higher in preeclamptic placentae and serum sEng levels were also elevated in preeclamptic individuals and are positively correlated with the disease severity.[27]

The endoglin is the co-receptor for TGF-$\beta_1$ and TGF-$\beta_3$. The cleavage form of membrane bound endoglin in trophoblastic cells, sEng binds to endoglin receptor to contribute to endothelial dysfunction by inhibiting the TGF induced vasodilatation thereby promoting hypertension.[28]

TGF-$\beta_1$, involves in normal placentation through regulation of trophoblast invasion with supported evidences that circulating levels of TGF-$\beta_1$ are higher in pregnant women than in non-pregnant women.[29,30] Some investigators have observed that the level of TGF-$\beta_1$ in circulating blood was significantly higher in preeclamptic women.[31,32] However, others found no differences in circulating TGF-$\beta_1$ level between

PE and normal pregnancy.[33] Also, this study showed no statistically significant difference in plasma TGF-$\beta_1$ level between PE group and normal pregnancy group. The disparity in reports of TGF-$\beta_1$ level in PE may be due to differences in gestational age at sampling, the severity of preeclampsia, ethnicity, and assay techniques.

## CONCLUSION

The increase in circulatory level of HIF-1α and sEng in preeclamptic pregnant women in the present study contributes to the pathogenesis of PE. A slight positive correlation was observed between plasma HIF-1α and sEng although it is not significant. It is suggested that hypoxia subsequently may cause release of downstream antiangiogenic factors into circulation, HIF-1α is not the solely causative factor for the increase in level of sEng. In fact, others factors, oxidative stress, inflammation, altered immune function, and deficient catechol-o-methyl transferase may be involved in the release of antiangiogenic factor sEng.[34] The decreased effect of TGF-$\beta_1$ on endothelial cells and vascular smooth muscle in PE is more likely due to inhibition of its signaling pathway by sEng instead of low circulating level of TGF-$\beta_1$. Hypoxia is suggested to involve partly in abnormal placentation in PE. On other sides, the insults via non-hypoxic pathways may cause placenta abnormalities found in PE. The etiopathology of PE still needs to be investigated.

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***Conflict of Interest***

*No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.*

***Authorship Contributions***

***Idea/Concept:*** *Khin Thuzar Aung, Yin Thu Theint, Ohnmar Myint Thein, Sanda Kyaw, Mya Thanda Sein;* ***Design:*** *Khin Thuzar Aung, Yin Thu Theint, Ohnmar Myint Thein, Sanda Kyaw, Mya Thanda Sein;* ***Control/Supervision:*** *Khin Thuzar Aung,* ***Data Collection and/or Processing:*** *Sanda Kyaw, Mya Thanda Sein;* ***Analysis and/or Interpretation:*** *Khin Thuzar Aung, Yin Thu Theint, Ohnmar Myint Thein;* ***Literature Review:*** *Khin Thuzar Aung, Ohnmar Myint Thein, Sanda Kyaw;* ***Writing the Article:*** *Khin Thuzar Aung, Yin Thu Theint;* ***Critical Review:*** *Khin Thuzar Aung, Yin Thu Theint, Ohnmar Myint Thein, Sanda Kyaw, Mya Thanda Sein;* ***References and Fundings:*** *Khin Thuzar Aung, Mya Thanda Sein, Sanda Kyaw;* ***Materials:*** *Khin Thuzar Aung, Yin Thu Theint.*

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