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The Role of Placental Growth Factor, Soluble Endoglin, and Uterine Artery Diastolic Notch to Predict the Early Onset of Preeclampsia

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Keywords: Placental Growth Factor; sEng; Diastolic Notch; Preeclampsia

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Abstract

BACKGROUND: Reducing maternal mortality is one of the targets in the Millennium Development Goals (MDGs). In a systematic review, 4.6 per cent (95% CI 2.7-8.2) of pregnancies were complicated by preeclampsia worldwide. Preeclampsia occurs in around 10% of pregnancies in the world whereas developing countries contribute more than developed countries. In developing countries, there are 13 cases of preeclampsia in every 1,000 births, whereas in developed countries only 2-3 cases of preeclampsia are found in every 10,000 deliveries. Variations in prevalence among countries reflect, at least in part, differences in the distribution of maternal age and the proportion of nulliparous pregnant women in the population.

AIM: We aimed to investigate the role of placental growth factor, soluble endoglin, and uterine artery diastolic notch to predict the early onset of preeclampsia.

METHODS: This study used an analytical study with a nested case-control design. The study was conducted at Bunda Thamrin Hospital, Tanjung Mulia Mitra Medika Hospital, Sundari Hospital and a private clinic, from March to November 2018 with a total sample of 70 research subjects.

RESULTS: Uterine artery diastolic notch was not found in 50% of subjects. A total of 27 subjects (38.6%) had a unilateral diastolic notch, and 8 subjects (11.4%) had a bilateral diastolic notch. Cut-off point PlGF levels was 441 pg/ml, and Area Under Curve (AUC) 82.5% (95% CI 61.5%-100%), with sensitivity 80% and specificity 87.7%. The levels sEng in this study could not predict the incidence of early-onset preeclampsia (p = 0.113). Combined PlGF and pulsatile index of uterine arteries may predict early onset preeclampsia with sensitivity 40% and specificity 90.77%. From these results, pregnant women o 22-24 weeks of pregnancy, the levels of PlGF and the uterine artery pulsatility index can be a predictor of early-onset preeclampsia. Examination of PlGF levels alone is sufficient as a predictor of early-onset preeclampsia.

CONCLUSION: From these results, it can be concluded that in pregnant women of 22-24 weeks, the diastolic notches in uterine arteries cannot predict the incidence of early-onset preeclampsia. PlGF levels and pulsatile index of uterine arteries can be used as predictors of early-onset preeclampsia although examination of PlGF levels alone is sufficient as a predictor of early-onset preeclampsia.

Introduction

According to the American Family Association dividing the number of risk factors for Preeclampsia in 3 (three) groups, namely pregnancy-related factors, maternal factors and paternal factors. Maternal factors are more biologically maternal, including age, parity, race, history of preeclampsia, history of hypertension and so on. Also, many theories suggest that the pathogenesis of preeclampsia is related to the placentation process, but to date, the pathogenesis of preeclampsia is still unclear. Because the multifactorial pathogenesis of the pre-eclampsia phenotype is unexplained, prevention and prediction are still unknown, treatment of clinical symptoms must be the main thing in preventing maternal morbidity and mortality [1].

In preeclampsia, trophoblast invasion and velocimetry doppler can detect quantitative and qualitative changes in uterine arteries in waveform. In Doppler velocimetry, it can be seen the blood flow in the uterine artery, arcuate, radial and spiral around the trophoblast tissue, so that measurements can be made on the various indices needed [2], [3]. The

uterine artery wave appearance in the first trimester of pregnancy has a diastolic notch that disappears after 24 weeks of pregnancy. If the picture of this curve persists and the PI and RI values remain high after a pregnancy of 20-24 weeks, it means that there is high pressure in the uterine arteries which will usually result in preeclampsia or stunted fetal growth [4]. Endothelial dysfunction leads to progressive tissue and multiorgan damage to the mother and fetus. song is a dissolved form of a surface co-receptor transforming growth factor (TGF-β1 and TGF-β3) expressed on endothelial cells and syncytiotrophoblasts. It modulates the work of TGF-β1 and TGF-β3 which play an important role in vascular homeostasis. Concentration increases when placental perfusion is poo so that that serum levels can act as markers of changes in the impedance of the uteroplacental circulation [1], [5].

We aimed to investigate the role of placental growth factor, soluble endoglin, and uterine artery diastolic notch to predict the early onset of preeclampsia.

Methods

This study used an analytical study with a nested case-control design. The study was conducted at Bunda Thamrin Hospital, Tanjung Mulia Mitra Medika Hospital, Sundari Hospital and a private clinic, from March to November 2018 with a total sample of 70 research subjects.

Results

The research followed by 70 pregnant women with gestational age 22-24 The week came to Bunda Thamrin Hospital, Tanjung Mulia Mitra Medika Hospital, Sundari Hospital and private practice that had fulfilled the inclusion and exclusion criteria.

Table 1: Demographic Characteristics of Research Subjects

Characteristics of Subjects	n = 70
Age of Pregnancy, n (%)	
22 weeks	22 (31.4)
23 weeks	13 (18.6)
24 weeks	35 (50)
BMI, mean (SD), kg/m^2	24.47 (4.02)
Parity, n (%)	
Primigravida	31 (44.3)
Second Gravida	23 (32.9)
Multigravidas	16 (22.9)

Subjects with 24 weeks' gestation were the most subjects with a total of 35 people (50%). A total of 31 subjects (44.3%) were primigravida.

Table 2: Diastolic Notch Examination Results on Right and Left Uterine artery

Uterine Diastolic Notch, n (%)	n = 70
Without Diastolic Notch	35 (50)
Unilateral Diastolic Notch	27 (38.6)
Bilateral Diastolic Notch	8 (11.4)

Using ultrasound, it is known that as many as 50% of subjects have the one without the dichotomy. A total of 27 subjects (38.6%) had a unilateral diastolic notch, and 8 subjects (11.4%) had a bilateral diastolic notch.

Table 3: Results of Uterine artery Examination, Placental Growth Factor (PlGF) Level, and soluble Endoglin (sEng) level

	Uterine A.	PlGF	sEng
Mean	1.14	834.21	5.37
SD	0.36	413.75	1.99
Minimum	0.44	165	2.66
Maximum	2 , 08	2097	12.68
CI 95%	1.05-1.22	735.56 - 932.87	4.90 - 5.85

The results of the mean examination A. Female is 1.14 with SD = 0.36 with the lowest level was 0,44 and highest 2.08. PlGF is 834.21 with SD = 413.75, with the lowest level of 165 and the highest of 2097. The mean level of the sEng is 5.37 with SD = 1.99 with the lowest level of 2.66 and the highest 12.68.

Table 4: The incidence of Early Onset Preeclampsia

Preeclampsia	n = 70
Normal	65 (92.9)
Preeclampsia (proteinuria + 3)	2 (2.9)
Preeclampsia (proteinuria + 4)	3 (4.3)

From the results of monitoring of all subjects during the study, it was found that there were 65 subjects (92.9%) did not experience preeclampsia, 2 subjects (2.9%) had preeclampsia (proteinuria +3) and 3 subjects (4.3%) with preeclampsia (proteinuria +4).

Table 5: The difference of PlGF and sEng level between Subjects with Diastolic Notch and Without Diastolic Notch

	Uterine Diastolic Notch		P
	+ (n = 35)	(n = 35)	
IP a. Uterina, mean (SD)	1.42 (0.26)	0.85 (0.17)	< 0.001[a]
PlGF, mean (SD)	695.6 (385.69)	972.83 (398.88)	0.004[a]
sEng , mean (SD)	5.44 (2.39)	5.30 (1.51	0.533[b]

[a]*T Independent;* [b]*Mann Whitney.*

Mean A. uterina levels in subjects with diastolic notch group was 1.42 (SD = 0.26) while the mean A. uterina in the group without diastolic notch was 0.85 (SD = 0.17). Using the Independent T-test showed that there was a significant difference in uterine artery levels between subjects with diastolic notch and without diastolic notch ($p < 0.001$). The mean PlGF level in the group of subjects with a diastolic notch was 695.6 (SD = 385.69) while the mean of PlGF in the group without diastolic notch subjects was 972.83 (SD = 398.88). Using the Independent T-test showed that there was a significant difference in PLGF between subjects with diastolic notch and without diastolic notch ($p = 0.004$). The mean level in subjects in the diastolic notch group

was 5.44 (SD = 2.39) while the mean level in the group without diastolic notch subjects was 5.30 (SD = 1.51) using the Mann Whitney test indicating that there were differences in the mean sEng significant between subjects with diastolic notch and without diastolic notch (p = 0.533).

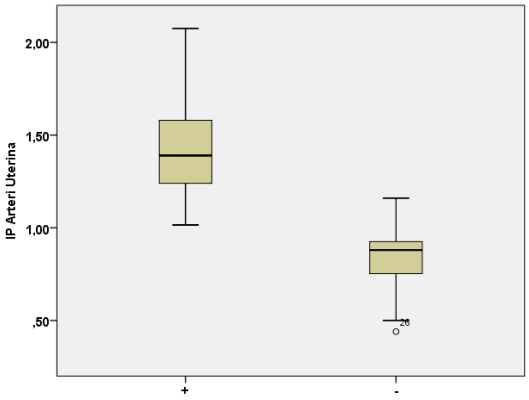

Figure 1: Boxplot Graph of PI Differences a. uterina in subjects with diastolic notch and without diastolic notch

There were no subjects over the age of 35 who had early onset preeclampsia, while there were 5 people (8.1%) subjects aged ≤ 35 years had preeclampsia. The results of the analysis using Fischer's exact test showed that no significant association was found between age and the incidence of early-onset preeclampsia (p = 1.000).

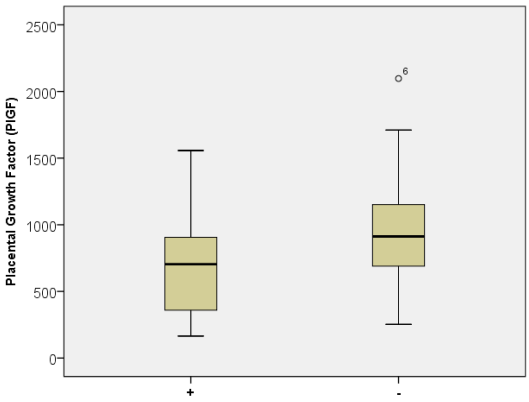

Figure 2: Boxplot graph differences in uterine arterial PlGF levels in subjects with diastolic notch and without diastolic notch

From the 31 subjects with primigravida pregnancies, there were only 3 subjects (9.6%) who had early onset preeclampsia, while there were 2 more samples with early-onset preeclampsia found in women with multigravida pregnancy. The results of the analysis using Fischer's exact test showed that there was no significant relationship between maternal parity and the incidence of early-onset preeclampsia (p = 0.251).

From the 32 subjects who had overweight and obesity BMI, there was only 1 subject (3.1%) who had early onset preeclampsia, while there were 4 people (14.8%) subjects with underweight and normoweight who had preeclampsia. The results of the analysis using Fischer's exact test showed that there was no significant relationship between BMI and the incidence of early-onset preeclampsia (p = 0.169).

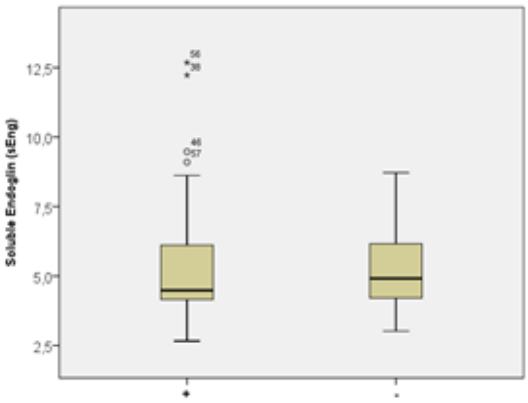

Figure 3: Boxplot graph of levels of difference in subjects with diastolic notch and without diastolic notch

From the 35 subjects who had uterine artery diastolic notch, there were 5 subjects (14.3%) who had early onset preeclampsia, while no preeclampsia was found in a subject that did not have a diastolic notch. The results of the analysis using Fischer's exact test showed that no significant association was found between uterine artery diastolic notch and the incidence of early-onset preeclampsia (p = 0.054).

Table 6: Relationship of Age, Parity, BMI, Diastolic Notch, PlGF level and sEng level early onset of preeclampsia

	Preeclampsia		p
	+ (n = 5)	- (n = 65)	
Age,n (%)			
> 35 years old	0	8 (100)	1.000[a]
≤ 35 years old	5 (8.1)	57 (91.9)	
Parity			
Primigravida	3 (9.6)	28 (90.4)	
Secundi Gravida	0	23 (100)	0.251[a]
Multigravida	2 (12.5)	14 (87.5)	
BMI, n (%)			
Overweight dan Obese	1 (3.1)	31 (96.9)	0.169[a]
Underweight dan Normoweight	4 (14.8)	23 (85.2)	
Diastolic Notch			
Found	5 (14.3)	30 (85.7)	0.054[a]
Not found	0	35 (100)	
PI mean (SD)	1.44 (0.30)	1.11 (0.35)	0.045[b]
PlGF, mean (SD)	411 (301.67)	866.77 (404.73)	0.016[c]
sEng, mean (SD)	8 (4.11)	5.17 (1.62)	0.113[c]

[a]Fischer's Exact; [b]T Independent; [c]Mann Whitney.

The mean PI uterine artery in early-onset preeclampsia subjects was lower with a mean of 1.44 (SD = 0.30) compared to subjects who did not experience preeclampsia with a mean of 1.11 (SD = 0.35). Using the Mann Whitney test showed that there were differences in the mean PI uterine artery between subjects with preeclampsia and those without preeclampsia (p = 0.045).

The mean PlGF in early-onset preeclampsia subjects was lower with a mean of 411 (SD = 301.67) than subjects who did not experience preeclampsia with a mean of 866.77 (404.73). Using the Mann Whitney test showed that there were differences in the

mean PLGF levels between subjects with preeclampsia and those without preeclampsia (p = 0.016).

The mean score in subjects with early-onset preeclampsia was seen to be higher with a mean of 8 (SD = 4.11) than subjects without preeclampsia with a mean of 5.17 (1.62). Using the Mann Whitney test showed that there was no difference in mean levels between subjects with preeclampsia and those without preeclampsia (p = 0.113).

Pulsality Index of Uterine Artery

Analysis showed that the ROC curve obtained a value of p = 0.037 which means that uterine artery IP in this study can predict the incidence of early-onset preeclampsia Area Under Curve (AUC) of 78.2% (95% IK 59.3% - 97%).

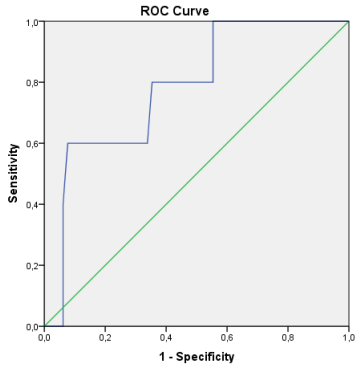

Figure 4: ROC curve of uterine artery IP against preeclampsia

Based on sensitivity and specificity curves in Figure 5, the Cut Off value for uterine arterial IP is obtained as 1,228. By using *cut-off points* 1,228, the uterine artery IP sensitivity value was 80%, and the specificity was 64.6%.

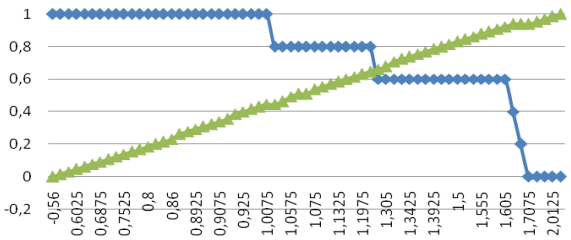

Figure 5: Uterine Arterial IP sensitivity (blue) and specificity (green) curve for the incidence of early-onset preeclampsia

PIGF

From the analysis using the ROC curve the value p = 0.016 means that PlGF in this study can predict the incidence of early onset preeclampsia with a value of Area Under Curve (AUC) 82.5% (95% IK 61.5% - 100%).

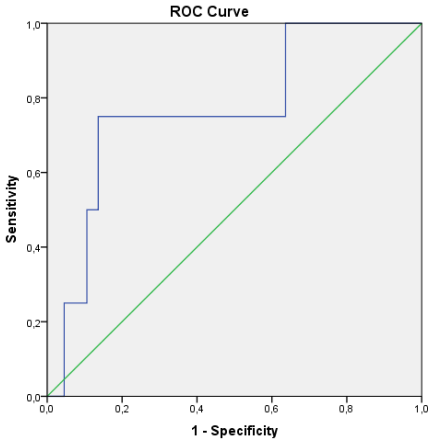

Figure 6: ROC Curve of PlGF against Preeclampsia

Based on the sensitivity and specificity curves in Figure 7, the Cut Off value for PlGF levels is obtained by 441. By using the cutoff point 441, the sensitivity value of PlGF is 80%, and the specificity is 87.7%.

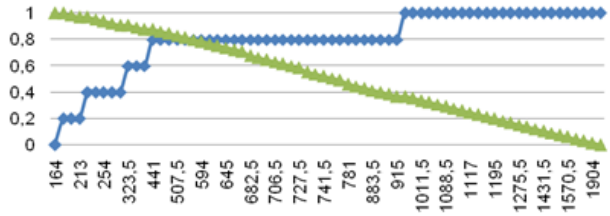

Figure 7: Curve sensitivity (blue) and specificity (green) of PlGF of genesis early-onset preeclampsia

sEng

From the results of analysis using ROC curves obtained by value p = 0,113 which means that sEng in this study could not predict the incidence of early-onset preeclampsia.

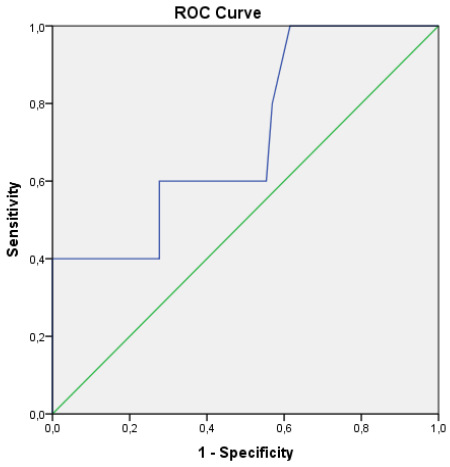

Figure 8. ROC Curves of Preeclampsia

Discussion

The research followed by 70 pregnant women aged 22-24 weeks who came to the Bunda Thamrin Hospital, Tanjung Mulia Mitra Medika Hospital, Sundari Hospital and private clinic that had met the inclusion criteria and exclusion. Pregnant women who collected a mean age of < 35 years (88.5%) dominated this study, with a mean Body Mass Index of 24.47 kg/m^2 (overweight). Subjects with 24 weeks' gestation were the most subjects with a total of 35 people (50%). A total of 31 subjects (44.3%) were primigravida who is one risk factor for early-onset preeclampsia. While the age of pregnant women > 35 years and nutritional conditions of women in overweight or obese conditions are a risk factor for the occurrence of late-onset preeclampsia, although this study still records the characteristics of the sample state [29].

Table 7: Sensitivity, specificity, the positive and negative predictive value of PI Uterine artery and PlGF level of Early-onset Preeclampsia

		Preeclampsia		Sensitivity	Specificity	NPP	NPN
		Positive	Negative				
IP.	1,228	4	2223	80%	64.6%	14., 8	97.7%
Uterina A.	<1,228	1	42				
PlGF	≤ 441	4	8	80%	87.7%	33.3%	98.3%
	> 441	1	57				
PlGF + IP Uterina A.				40%	90.77%	25%	95.16%

A total of 27 subjects (38.6%) had a unilateral diastolic notch, and 8 subjects (11.4%) had a bilateral diastolic notch. But this does not make the reference value a predictor of the incidence of early-onset preeclampsia. Different analytical methods are used to measure the reference value. Several other studies also included ultrasound examinations with the presence of diastolic notch, Kushtagi & Emani, 2016 found 38 patients with diastolic notch diagnosed with preeclampsia from a total of 48 patients with preeclampsia, Vartun, Flo, Widnes, & Acharya, 2016 found 23 samples with diastolic notch from 27 samples [6], [7].

Different studies have found that the mean PLGF level in preeclampsia is following 125 pg/ml at gestational age 20-37 weeks [8]: 95 pg/ml at midtrimester gestational age [9]; 38.7 pg/ml at 32-37 weeks gestation [10]; 54 pg/ml at 20-34 weeks gestation [11]; 83.75 pg/ml at 20-30 weeks gestation [12]; 239.75 pg/ml at 25-40 weeks' gestation [13].

The mean level sEng in this study was 8.0 ng/ml at 22-24 weeks' gestation. In other studies it can be found that the mean serum level in preeclampsia is 53.3 ng/ml at gestational age less than 34 weeks [14]; 11.08 ng/ml at gestational age 19-24 weeks [15]; 60.9 ng/ml during the first and second trimester of pregnancy [16]; 69.2 ng/ml at the third trimester of pregnancy [17] 11.58 ng/ml at gestational age less than 37 weeks [18].

Diastolic Notch and the incidence of Early Onset Preeclampsia

From the 35 samples of pregnant women who had a diastolic notch, it was found that there were 5 samples experiencing early-onset preeclampsia, with a p-value of 0.054 (> 0.05) that did not have a significant relationship, this was probably due to the number of samples there are still a few who have preeclampsia.

Other studies also found that there were significant differences between patients with normal pregnancies and patients with pregnancy who experienced preeclampsia, namely the study of Vartun, Flo, Widnes, & Acharya, 2016 with a p-value < 0.0001 (p < 0.05) very meaningful by finding 23 patients with diastolic notch who had preeclampsia compared to 4 patients with diastolic notch as well but not preeclampsia [19].

Mean Pulsatility Index of Uterine Artery for the Incidence of Early Onset Preeclampsia

Mean of IP uterine artery in subjects with early-onset preeclampsia seen higher with a mean of 1.44 (SD = 0.30) than subjects who did not experience preeclampsia with a mean of 1.11 (0.35) with a p-value of 0.045 which means that it has a significant value to distinguish cases preeclampsia. From the previous research studies, it was also dominated by significant results that were in line with this study, which made the first step to conduct a non-invasive screening. Other studies by (Vartun, Flo, Widnes, & Acharya, 2016), (Yu, Cui, Chen, & Chang, 2017), and (Narang, Agarwal, Das, Pandey, Agrawal, & Ali, 2016) with p-value very significant < 0,0001 was performed in early trimester pregnant women who ended preeclampsia [19], [20], [21].

PlGF and incidence of Early Preeclampsia

Previous studies have also been conducted by Bian, Shixia, & Duan, 2015 which showed a significant difference in the decrease in PLGF levels in preeclampsia performed in first trimester pregnant women with an mean of 115.72 pg/ml compared to control 217.30 pg/ml (p-value < 0.001) [22]; and by Gannoun, et al., in the following year (2016) which conducted a more in-depth study which divided based on gestational intervals with all the results of research on PlGF levels found to be significant at 24-29 weeks the PlGF mean levels were 58.62 pg./ml which ends early-onset preeclampsia (p-value 0.007) [21].

sEng on the incidence of Early Awakening Preeclampsia

From the results of this study, the p-value of 0.113 was found to be not significantly different between the levels of Sickness in early onset

preeclampsia with a mean value of 8 ng/ml in preeclampsia which was slightly higher than the mean in control, ie 5.17 ng/ml. In various studies, there are still various levels of sEng which have not yet become standard, as according to EL-Said, Mohammed, EL-Ashrawi, & Saad, 2013 the mean sEng levels in preeclampsia also increased (11.06 ng/ml) compared to the mean control (5, 92 ng/ml) but with p-value < 0.01 which means significant differences were found [22]. Equally with Perucci's research, 2014 which found that there was an increase in serum levels in preeclampsia, both early and late onset with a p-value of 0.001 [23]. Research by Masuyama, Nakatsukasa, Takamoto, & Hiramatsu, 2007 for very different levels of pre-eclampsia, ie 60.9 ng/ml with controls 11.2 ng/ml (p-value < 0.01) [24]. Although there are significant results from various studies above, there are other studies that are also not significantly different as significant as in this study, according to KEDuhig, 2015 with a p-value of 0.058 (p-value > 0.05) which was carried out examination in women the second trimester of pregnancy was found to have a mean level of 2.78 ng/ml which was lower than the control of 3.52 ng/ml but in the sample of other pregnant women in the third trimester of pregnancy who were also carried out in this study found significant results (p-value 0.001) [25].

The results of the study showed that the mean serum soluble endoglin (sEng) of mothers with Early Onset Preeclampsia was 41.47 ± 13.88 ng/ml while lower in Late-Onset Preeclampsia 33.19 ± 15.99 ng/ml.

Predictors of Early Onset preeclampsia

Based on bivariate data obtained significant results from a variety of predictor variables early-onset preeclampsia, which are detailed in the previous chapter with the following conclusion:

Table 8: Predictors of Early Onset Preeclampsia

	Area Under the Curve	p	cut off point
IP uterine artery	78.2%	0.037	1.228
PGIF	82.5%	0.016	441
sEng	71.4%	0.113	*

Various other studies also conducted bivariate statistics to look for cutoff values to help clinicians diagnose preeclampsia, with various cutoff values. Research by Chen (2009) has conducted an analysis of various previous studies to record the cut-off point score, although in this study it was found to be insignificant because it did not search for cut-off points, the study collected by Chen was Levine, 2006 gestational age 13-20 weeks 7.9 ng/ml, 21-32 weeks 7.2 ng/ml, 33-42 weeks 13.6 ng/ml; Salahuddin, 2007 24.8 ng/ml; Bauman, 2008 5 ng/ml; and Stepan 2008 4.14 ng/ml [27], [17], [28], [29].

Eremina et al., 2003 showed that glomerular capillary function was under VEGF control. That is when the level of VEGF in renal podocytes falls by 50%, glomerular endothelial cells swell, the capillary loop collapses, and proteinuria develops as occurs in patients with preeclampsia [30].

In pregnant women of 22-24 weeks of gestation, diastolic notch findings in uterine arteries cannot predict the incidence of early-onset preeclampsia. PlGF levels can be a predictor of early onset preeclampsia.

From this study an evaluation of the relationship between the variables on the incidence of early onset preeclampsia with the following results: a) the variables included in this study were maternal age, maternal body mass index, uterine arterial diastolic notch, pulsatility value of uterine artery index, PlGF levels, sEng; b) there were no significant differences between maternal age on the incidence of early onset preeclampsia; c) there were no significant differences between parity on the incidence of early onset preeclampsia; d) there was no significant difference between the maternal body mass index and the incidence of early onset preeclampsia; e) no significant differences were found between the presence or absence of uterine artery diastolic notch against the incidence of early onset preeclampsia; f) it was found a significant difference between the pulsatility value of the uterine artery index and the incidence of early onset preeclampsia; g) it was found that there were significant differences between PlGF levels and the incidence of early onset preeclampsia; h) no significant differences were found between sEng levels of the incidence of early onset preeclampsia.

From this study we can conclude: a) value of the variable cut-off point was significant, namely pulsatility levels of the uterine artery index with 1.228 cut-off points, Under Curve Area (AUC) 78.2% (95% IK 59.3%-97%), sensitivity 80%, specificity 64.6%; b) the value of the variable cut-off point is significant, namely PIGF levels with a 441 pg/ml cut-off point, Area Under Curve (AUC) of 82.5% (95% CI 61.5%-100%), sensitivity 80%, specificity 87.7%; and c) pulsatility index of uterine artery and PlGF combined have 40% sensitivity and specificity 90.77%.

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