The role of placental growth factor, soluble-Fms-like tyrosine kinase-1 and diastolic notch uterine artery to predict the early onset of preeclampsia

M.P. LUBIS[1], H. HARIMAN[2], S.N. LUMBANRAJA[1], A. BACHTIAR[3]

SUMMARY: **The role of placental growth factor, soluble-Fms-like tyrosine kinase-1 and diastolic notch uterine artery to predict the early onset of preeclampsia.**

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Preeclampsia is a global problem that affects 2-8% of pregnancies, and an estimated 8.3 million pregnant women experience preeclampsia every year. In preeclampsia there will be an increase in sFlt-1 levels and decreased levels PlGF. This condition will cause disorders of vasculogenesis and angiogenesis in fetomaternal circulation which will eventually lead to preeclampsia syndrome such as proteinuria, hypertension and endothelial dysfunction.

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

Many as 50% of subjects have characteristics without a diastolic notch. A total of 27 subjects (38.6%) had unilateral diastolic notch and 8 subjects (11.4%) had bilateral diastolic notch. Pulsatility index of uterine artery with 1.228 cut-off points, Area Under Curve (AUC) of 78.2% (95% CI 59.3% - 97%), sensitivity 80%, specificity 64.6%. PIGF levels with a 441 pg/ml cut-off point, Area Under Curve (AUC) amounted to 82.5% (95% CI 61.5% - 100%), sensitivity 80%, specificity 87.7%. The level of sFlt-1 with a cut-off point of 10087.5 pg / ml, Area Under Curve (AUC) was 81.2% (95% CI 63.6% - 98.9%), sensitivity 80%, specificity 67.7 %.

From these results in pregnant women of 22-24 weeks of pregnancy, the levels of PIGF and sFlt-1 can be a predictor of early onset preeclampsia. Examination of PIGF levels alone is sufficient as a predictor of early onset preeclampsia.

KEY WORDS: Placental growth factor - Uterine artery pulsatile index - Soluble-Fms-like tyrosine kinase-1 - Preeclampsia.

Introduction

Indonesia is a country with a population of fourth in the world and a high growth rate. The maternal mortality rate in Indonesia is still high at 305 per 100,000 live births and hypertension is the second highest cause with a prevalence of 26%. One form of hypertension in pregnancy is preeclampsia which is characterized by the presence of hypertension with blood pressure $\geq$ 140/90 mmHg and protein in urine at gestational age after 20 weeks. Preeclampsia is a global problem that affects 2-8% of pregnancies (1).

In preeclampsia there will be an increase in sFlt-1 levels and a decrease in PlGF levels. This condition will cause vascular disorders in fetomaternal circulation. Change in these factors levels can occur before the clinical manifestation of preeclampsia, therefore it may be a screening or assessment of risk factors for preeclampsia (2).

Early onset preeclampsia constitutes 5-20% of all severe preeclampsia, but often causes severe clinical cases, which are associated with abnormal trophoblast invasion of the spiral arteries (3).

In a normal pregnancy, the pulsatility index (PI) and resistance index (RI) will decrease after pregnancy 24-26 weeks, so that a permanent image is

[1] Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia
[2] Department of Clinical Pathology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia
[3] Health Policy and Administration, Faculty of Public Health, Universitas Indonesia, Jakarta, Indonesia

Corresponding author: Anditha Sitompul, e-mail: anditha.namira@gmail.com

formed which is a high and almost horizontal diastolic picture. If the curve persists and the PI and RI values remain high after 20-24 weeks, it means that there is high pressure in the uterine arteries which usually results in preeclampsia or stunted fetal growth (4).

Methods

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

Results

This study followed by 70 pregnant women with gestational age 22-24 weeks that came to the Obstetrics Outpatient Clinic of the Bunda Thamrin Hospital, Tanjung Mulia Mitra Medika Hospital, Sundari Hospital and private clinic that had fulfilled the inclusion and exclusion criteria. Subjects with 24 weeks gestation were the most subjects with a total of 35 people (50%). A total of 31 subjects (44.3%) was primigravida (Table 1).

In Table 2 there are the results of diastolic notch examination of right and left uterine artery.

Results of examination of uterine artery, placental growth factor (PlGF), and soluble-Fms-tyrosine kinase (sFlt-1)

The results of the uterine artery mean examination are 1.14 with SD = 0.36 with the lowest value of 0.44 and the highest of 2.08. PlGF was 834.21 with SD = 413.75, with the lowest value of 165 and the highest of 2097. The mean value of sFlt-1 was 10303.31 with SD = 7544.99 with the lowest value 1554 and highest 47236.

Incidence of early onset preeclampsia

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

In Table 3 there are the differences of uterine artery, PlGF level, and sFlt-1 level between subjects with diastolic notch and without artery diastolic notch.

Relationship of age, parity, BMI, diastolic notch and PI uterine artery levels, PlGF and sFlt-1 against the incidence of early onset preeclampsia

The results of the analysis using the Fischer's exact test showed that no significant association was found between age and the incidence of early onset preeclampsia (p = 1.000), no significant association was found between parity and the incidence of early onset preeclampsia (p = 0.251), no significant relationship between BMI and the incidence of early on-

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)
SecondGravida	23 (32.9)
Multigravidas	16 (22.9)

Table 2 - RESULTS OF DIASTOLIC NOTCH EXAMINATION OF 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)

set preeclampsia (p = 0.169), no significant association was found between uterine artery diastolic notch and the incidence of early onset preeclampsia (p = 0.054), there were differences in the mean PlGF levels between subjects with preeclampsia and those without preeclampsia (p = 0.016), and also there were differences in the mean of sFlt-1 levels between subjects with preeclampsia and those without preeclampsia (p = 0.021).

Prognostic value of PI levels uterine artery, PlGF, and sFlt-1 level in predicting early onset preeclampsia

PI Uterine Artery

From the results of analysis using the ROC curve p = 0.037 with the value of Area Under Curve (AUC) of 78.2% (95% IK 59.3% - 97%), the Cut Off value for uterine arterial IP is obtained as 1,228. By using cut off point 1,228, the uterine artery IP sensitivity value was 80% and the specificity was 64.6%.

PIGF level

From the analysis using the ROC curve the value p = 0.016 with a value of Area Under Curve (AUC) 82.5% (95% IK 61.5% - 100%). the Cut Off value for PlGF levels is obtained by 441. By using the cut off point 441, the sensitivity value of PlGF is 80% and the specificity is 87.7%.

sFlt-1 level

From the analysis using the ROC curve obtained p value = 0.021 which means that sFlt-1 in this study has the ability to predict the incidence of early onset preeclampsia with the value of Under Curve Area (AUC) amounting to 81.2% (95% IK 63.6% - 98.9%).

The Cut Off value for sFlt-1 level is 10087.5. By using a cut off point of 10087.5, the sensitivity value of PlGF is 80% and the specificity is 67.7%.

Discussion

The study was followed by as many as 70 pregnant women with gestational age 22-24 weeks who came to Bunda Thamrin Hospital, Tanjung Mulia Mitra Medika Hospital, Sundari Hospital and private clinic that have met the inclusion and exclusion criteria. Pregnant women who collected at 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%) was primigravida which 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. Another study at the same year by Lumbanraja (2013) stated that maternal age and gestational age were a risk factor of preeclampsia in < 37 weeks pregnant women with severe symptoms (5).

Using ultrasound it is known that the mean pulsatility index of the right uterine artery is 1.09 and the left is 1.18, and the total pulsatility index of uterine arteries is 1.135. Many as 50% of subjects have a

Table 3 - THE DIFFERENCES OF UTERINE ARTERY, PLGF LEVEL, AND SFLT-1 LEVEL BETWEEN SUBJECTS WITH DIASTOLIC NOTCH AND WITHOUT ARTERY DIASTOLIC NOTCH.

	Uterine Diastolic Notch		P
	+ (n = 35)	- (n = 35)	
IP a. Uterine, 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]
sFlt -1, the mean (SD)	8698.71 (6225.52)	11907.91 (8454.01)	0.006[b]

[a] T Independent, [b] Mann Whitney

normal dichotomy. A total of 27 subjects (38.6%) had unilateral diastolic notch and 8 subjects (11.4%) had 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. In a different study we found some pulsatility index mean value data, Narang et al. amounting to 1.42 (6); Gomez et al. was 1.73 (7), Yu et al. was to 1.52 (8); Figueira et al. was 0.93 (9); Sahoo et al. was to >1.4 (10); Sharma et al. amounting was > 1.55 (11).

Diastolic notch on the incidence of early onset preeclampsia

Of 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 difference in relationship, this was probably due to the number of samples there are still a few who have preeclampsia.

Several other studies also examined diastolic notch for the incidence of preeclampsia, namely the presence or absence of diastolic notch in pregnancy patients with hypertension at 11-14 weeks' gestation in India, with a p value of 0.612 which means there is no significant difference between normal patients and patients with hypertension; Doherty also investigated this matter but including pregnant patients with obstructed fetal growth in both unilateral and bilateral diastolic notch obtained a p value of 0.7 (not significantly different).

Uterine artery pulsatility index against the incidence of early onset preeclampsia

Uterine artery pulsatility index 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.

PlGF for the incidence of early onset preeclampsia

Various special studies according to Konishi & Katabuchi focusing on soluble antiangiogenic factors such as Fms-like tyrosine kinase-1 (sFlt-1) which is a soluble vascular-1 endothelial growth factor receptor (VEGFR-1) and pro-angiogenic placental growth factor (PlGF). PlGF itself in this study found significance between the relationship between PLGF and the incidence of early onset preeclampsia with a p value of 0.016 (p <0.05). In several other studies, many supported that the decrease in PlGF levels was a predictor of the incidence of preeclampsia that had a significant relationship, according to Masuyama with PLGF mean value of preeclampsia patients 137.6 pg / ml compared to the higher PlGF values of control patients 248.6 pg / ml (p value <0.01) (12).

sFlt-1for the incidence of early onset preeclampsia

The mean sFlt-1 level in preeclampsia from the results of this study was 17.943 pg / ml which was much higher than the control ie 9715.65 pg / ml with a significant difference (p value 0.021). Based on the theory, it is also known that sFlt-1 levels tend to remember in patients who will experience preeclampsia and those who have preeclampsia, because sFlt-1 itself is also a more specific VEGF mediator if there is inflammation. A similar study was also conducted by Andersen et al. (2015) who compared the sampling and examiners using Elecsys and KRYPTOR which were the same as the Elisa type with the same results as Elecsys (p value <0,0001) and KRYPTOR (p value <0.001).

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:

	Area Under the Curve	p	Cut off point
IP uterine artery	78.2%	0.037	1.228
PGIF	82.5%	0.016	441
sFlt-1	81.2%	0.021	10087.5

In the previous selection combined with other variables namely sFlt-1 and USG examination and history of the patient characteristics it was found that the p value was also <0.05 which was significant for

examination, although it turned out that only one examination was enough as a predictor of early onset preeclampsia. The results of this study were very useful as they produced effective costs for financing the diagnosis of preeclampsia itself, and were carried out at 22-24 weeks of gestation.

Conclusions

1. In pregnant women 22-24 weeks of gestation, diastolic notch findings in uterine arteries cannot predict the incidence of early onset preeclampsia. PlGF and sFlt-1 levels can be a predictor of early onset preeclampsia.
2. 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, pulsatile value of uterine artery index, PLGF levels, sFlt-1.
   b. It was found that there was a significant difference between the pulsatile value of the uterine artery index and the incidence of early onset preeclampsia.
   c. It was found that there were significant differences between PlGF levels and the incidence of early onset preeclampsia.

   d. There were significant differences between sFlt-1 levels and the incidence of early onset preeclampsia.
3. From this study:
   a. Significant variable cut-off point values were pulsatile uterine artery index levels with 1,228 cut-off points, Under Curve Area (AUC), amounting to 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%.
   c. The value of the variable cut-off point was significant, namely the level of sFlt-1 with a cut-off point of 10087.5 pg / ml, Area Under Curve (AUC) of 81.2% (95% IK 63.6% - 98.9%), sensitivity 80%, specificity 67.7%.
   d. From PIGF and sFlt-1 combined examination, found sensitivity 80% and specificity 98,5%.

Acknowledgement

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