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Title: Uterine Artery Doppler Examination at 11-13+6 Weeks of Pregnancy and Prediction of Preeclampsia by PIGF, Endoglin and PAPP-A Levels in Maternal Serum

Turkish Title: 11-13+6 Gebelik Haftasında Uterin Arter Doppler İncelemesi ve Maternal Serumda PIGF, Endoglin, PAPP-A Düzeyi ile Preeklampsi Öngörüsü

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Özet

Giriş ve Amaç: Birinci trimester maternal serum PAPP-A, PIGF ve sEng belirteçleri ve uterin arter Doppler incelemesi ile preeklampsinin öngörülmesini araştırmak amaçlandı.

Yöntem ve Gereçler: 11+ 0 ile 13+ 6 haftaları arasında birinci trimester kombine tarama testi için hastanemize başvuran 193 tekil gebe çalışmaya dahil edildi. Maternal öykü, serum biyokimyasal belirteçleri (PAPP-A,PIGF, sEng) ve uterin arter Doppler incelemesi yapıldı. Olguların gebelik sonuçları kayıt edildi. Gruplar "preeklamptik ve kontrol grubu'' olarak tanımlandı. Grupların bağımsız değişkenlerinin karşılaştırılmasında Mann Whitney U ve Ki-kare testi kullanıldı. Anlamlı parametrelerin kestirim değerleri için sensitivite ve spesifisite yüzdeleri ROC analizi kullanılarak hesaplandı.

Bulgular: 193 olgunun 168'i (%87) kontrol grubu (grup I), preeklampsi gelişen 25'i (%12,9) "preeklamptik grup'' olarak tanımlandı. Preeklamptik grup; hafif preeklampsi ve GHT gelişen 20 olgu (%10,3) "grup II'', ağır preeklampsi ve HELLP gelişen 5 olgu (%2,5) "grup III'' olarak tanımlandı. Preeklamptik grup ile kontrol grubu arasında maternal serum PAPP-A, PIGF, sEng düzeylerinde istatiksel olarak anlamlı farklılık saptanmazken, uterin arter Doppler PI değerleri, preeklamptik grupta istatiksel anlamlı olarak yüksek saptandı (p=0.023). sEng düzeyi, ağır preeklampsi gelişen olgularda (grup III) hafif preeklampsi gelişen olgulara göre (grup II) istatiksel anlamlı olarak yüksek saptandı (p=0.001). ROC analizi ile uterin arter PI kestirim değeri >2.23 olarak alındığında, sensitivite %42,31, spesifisite %82,10 olarak

belirlendi.

Tartışma ve Sonuç: PIGF, PAPP-A ve sEng preeklampsi öngörüsünde etkili bulunmadı. Ancak bu belirteçler hafif preeklampsi ile ağır preeklampsi ayırımında kullanılabilir. İlk trimester uterin arter Doppler incelemesi, preeklampsi öngörüsünde etkili bir tarama yöntemidir.

Anahtar Kelimeler: Preeklampsi, Uterin Arter, PAPP-A, PIGF, sEndoglin

Abstract

Introductıon and Aim: We aim to evaluate prediction of preeclampsia by integrating maternal history, serum PAPP-A, PIGF, sEng biomarkers and uterine artery Doppler in the first trimester.

Methods: 193 pregnant women admitted to outpatient clinic at 11-13+6 weeks for first trimester combined screening test were included in the study. Maternal history was taken, uterine artery Doppler and serum biomarkers (PAPP-A, PIGF, sEndoglin) were conducted. The follow up results of pregnancy were recorded. Two groups were defined as; control and preeclampsia. Mann Whitney U and Chi-square tests were used for comparison of independent variables of groups. Sensitivity models only for statistically significant parameters were calculated from ROC curves.

Results: Among 193 women, 168 (%87) were defined as control (group I), 25 (12.9%) who developed preeclampsia were defined as preeclampsia group. In preeclampsia group; 20 (10,3%) women with GH and mild preeclampsia were defined in as group II, 5 (2.5%) women

with severe preeclampsia and HELLP were defined as group III. Maternal serum PAPP-A, PIGF, sEng levels were not significantly higher in women destined to develop preeclampsia compared with controls, whereas uterine artery PI levels were statistically higher in preeclampsia group (p=0.023). sEng levels were significantly higher in women who developed severe preeclampsia (group III) compared with mild preeclampsia (group II) (p=0.001). If uterine artery PI cut off level was taken >2.23 in ROC curve analysis, sensitivity was 42.31% and specificity was 82.10% for detecting preeclampsia.

Dıscussıon and Conclusıon: Maternal serum PAPP-A, PIGF and sEng were not found to be effective for prediction of preeclampsia but these markers can be used to differentiate mild from severe forms of preeclampsia. First trimester uterine artery Doppler study is an effective screening method in preeclampsia prediction.

Keywords: Preeclampsia, Uterine Artery, PAPP-A, PIGF, sEndoglin

INTRODUCTION

Preeclampsia (PE) affects nearly 2% of all pregnancies, and it is the most significant cause of maternal perinatal mortality and morbidity (1). Today, early detection of preeclampsia (PE) has become one of the fundamental goals of perinatal medicine. Although clinical symptoms of preeclampsia emerge after 20th weeks of gestation, trophoblast invasion that is responsible for pathogenesis occurs at first trimester (2). High resistant spiral arteries can be detected since 11 weeks of gestation by uterine artery Doppler examination (3). Therefore; first trimester uterine artery Doppler examination can be a good noninvasive method for the

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prediction of preeclampsia which reflects abnormal trophoblast invasion. Addition of maternal history and biochemical serum markers to uterine artery Doppler examination has been strongly associated with placental and endothelial dysfunction (4). These markers make screening relatively earlier; and most importantly, when they are used with first trimester Doppler sonography, they provide higher predictive value and more advanced diagnostic performance.

Placental growth factor (PIGF) and vascular endothelial growth factor (VEGF) are potent angiogenic factors and they have a stimulating effect on endothelial cell proliferation and migration. sFlt-1 (soluble fms-1ike tyrosine kinase 1) and soluble Endoglin (sEng) are anti-angiogenic factors and it is suggested that hypoxic placenta secretes increased amounts of sFlt-1 and sEng (6,7). Although there are opposite results in the studies, it is generally reported that levels of angiogenic factors, that are PIGF and VEGF, are decreased in preeclampsia and the levels of anti-angiogenic factors, that are sFlt-1 ve sEng, are increased (8).

Besides that, PAPP-A and s-ßhCG are used for chromosomal abnormality screening test, they were also investigated for the prediction of complications that are emerged at advanced gestational weeks in many studies and their availability were discussed (9). In performed studies, it was stated that especially low PAPP-A levels can be closely associated with preeclampsia (10).

Preeclampsia prediction has an important role in the prevention of preeclampsia associated complications. Based on this reality, we intended to investigate the possible relationship

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between preeclampsia development and maternal serum PIGF, sEndoglin, PAPP-A, s-βhCG levels that were measured at 11+0 and 13+6 weeks of gestation and Ut-PI values that were determined by Doppler ultrasonography.

METHODS

Singleton pregnant women who admitted for screening test at 11+0 and13+6 weeks of gestation were included in the study. The study was planned as a prospective cohort study. Ethics committee approval was taken and cases were informed about the study. Exclusion criteria were determined as pregnancy greater than 14 weeks, multiple pregnancies, chromosomal or congenital fetal abnormality, chronic hypertension, molar pregnancy, Type 1 diabetes mellitus, maternal renal disease, preeclampsia history and morbid obesity. Detailed maternal history was taken, nuchal translucency (NT) measurement and uterine artery Doppler examination were done. When consecutive similar wave patterns were obtained, PI was measured; mean PIs of right and left uterine arteries were calculated. Doppler measurement of the uterine artery PI at 11-13+6 weeks, performed by same experienced sonographer.

PAPP-A and s-βhCG were studied in blood samples that were taken from the patients. Measurements were performed in Immulite 2000 systems autoanalyzer by using Siemens kits and by chemiluminescence method. Measurements that were obtained were transformed to MoM values. Centrifuged blood samples were stored at -80˚C in order to analyze PIGF and sEng levels. After the completion of study groups, human soluble endoglin/CD105 Elisa (Aviscera Biscience, Inc. Santa Clara, USA) and PIGF Elisa (DRG Instruments GmbH,

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Germany) kits were tested by microELISA method by Radim Aliysei instrument in stored serum samples.

Characteristics, medical history, pregnancy outcomes, sonography findings, systolic and diastolic blood pressure values, pregnancy complications, PIGF, sEndoglin, MoM values of PAPP-A and s-βhCG of the cases were recorded in computer database. Preeclampsia diagnosis was made when two different blood pressure measurements which were measured at every 4 hours were 140/90 mm Hg and above and presence of 300 mg or more protein in the urine within 24 hours or presence of 30 mg/dL (1+dipstick) protein in spot urine sample following 20th weeks of pregnancy. According to ACOG criteria, preeclampsia group was separated into two groups including severe and mild preeclampsia (11). In case of only high blood pressure GHT diagnosis was made; and in case of addition of hemolysis, increase in liver enzymes and thrombocytopenia to preeclampsia-eclampsia table, HELLP diagnosis was made (12). Group I was composed of pregnant women who did not develop complications and Group II was composed of patients with the diagnosis of preeclampsia, GHT and HELLP.

Statistical Analysis

SPSS (Statistical Package of Social Sciences) 16,0 Evaluation Version was used in the analysis of collected data. Mann Whitney U test was used for statistical assessment and Chi-square test was used for the comparison of classifier data. The differences between mild preeclampsia, severe preeclampsia and control group in terms of independent variables were analyzed by Kruskal Wallis Test. The correlations between the variables were determined by

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Spearman correlation analyses. Results were evaluated within 95% confidence interval and significance was evaluated at $p<0.05$ level.

RESULTS

The study was performed on 250 pregnant women between 16 and 41 years old who admitted to Kocaeli University Faculty of Medicine, Department of Obstetrics and Gynecology between February 2012-2014. 57 cases from whom we could not get pregnancy results were excluded from the study. Out of patient group including 193 cases whose 11-14 week screening, Serum PAPP-A, s-βhCG,PIGF and sEng measurements were performed and whose pregnancy outcomes were known, 168 were not affected from preeclampsia whereas preeclampsia was detected in 25 cases including severe in 4 cases, mild in 18 cases, GHT in 2 cases and HELLP in one case. Patients whose pregnancy were delivered without complications were classified as group I (n=168); and patients who were diagnosed as mild preeclampsia, severe preeclampsia, GHT and HELLP were classified as group II (n=25). There was not a history of smoking or pregnancy by assisted reproductive techniques (IVF) in any of pregnant women included in the study.

Demographic characteristics and pregnancy outcomes of the patients were given in Table 1. When preeclamptic and normotensive patients were compared based on pregnancy age, gravida, number of parity, body mass index, delivery week and values, a statistically significant difference was not found ($p>0,05$) (Table 1). There was a significant difference in terms of birth weight of the newborn, mean arterial systolic pressure and mean diastolic pressure ($p<0,05$).

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No statistically significant difference was detected between preeclamptic and control groups for PIGF, sEng, PAPP-A, s-βhCG serum markers. Uterine artery PI (p=0,023) and S/D (p=0,019) ratios were found significantly higher in preeclamptic group. Groups were shown in Table 1.When we classified cases as control group (n=168), patients who developed mild preeclampsia and GHT (n=20) (group II), patients who developed severe preeclampsia and HELLP (n=5) (group III); sEng level in group III were found significantly higher than group II (Table 2). PIGF level was relatively decreased in group III compared to group II; but it was not statistically significant. PAPP-A MoM value was found to be statistically significantly low in group III compared to group II. These results were summarized in Table 2. Preeclampsia prediction can be made by ROC analysis by a PI cut-off value of >2.23, a sensitivity of 42.31% and a specificity of 82.10%. It was summarized in Table 3 and figure 1.

DISCUSSION

Prediction of preeclampsia at first trimester during which maximum trophoblastic invasion occurs before the onset of the disease is definitely an important goal. Therefore; many biochemical markers that may provide preeclampsia prediction are still being investigated. An ideal test should be simple, rapid, cost effective and easy to use. Positive likelihood ratio should be >15, and negative likelihood ratio should be <0.1; its sensitivity and specificity should also be high. Today, there are not any tests that are sufficient for preeclampsia prediction alone or in combination.

While screening test which uses maternal obstetric history is quite insufficient, Harrington et al have proved during mid 1900s that preeclampsia screening might be possible by bilateral uterine artery Doppler examination that has a high sensitivity and low specificity (13).

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In a large prospective study, the relationship between uterine artery Doppler findings and the development of (RI and diastolic notch) term and preterm preeclampsia at 11 and 14weeks' of gestation was investigated, and 57 term and 33 early preeclampsia cases were detected in 3058 pregnant women. The sensitivity of uterine artery Doppler examination in the detection of preeclampsia was found to be 49% within 90 percentile. In addition, it was indicated that when RI of uterine artery Doppler was greater than 90 percentile, there was a 6 fold increase in the probability of early preeclampsia. When mean RI values of preeclamptic women at term and early preeclamptic women were compared, it was found higher in early preeclamptic women (14).

In a retrospective study, first and second trimester uterine artery Doppler indexes of 3560 pregnant women were investigated within a 7-year period and preeclampsia was detected in 126 pregnant women. It was determined by ROC analysis that PI value was the best marker in preeclampsia prediction. The difference between the mean second trimester and first trimester PI values was found to be 0.851 in preeclampsia prediction before 34 gestational weeks and 0.786 for late preeclampsia; and the authors have stated that the difference between two trimester averages of PI value might be used in preeclampsia prediction (15).

In our study, when uterine artery PI cut-off value was taken as>2.23 by ROC analysis in the prediction of preeclampsia cases, sensitivity was found as 42.31% and specificity was found as 82.10%.

In recent years, new screening protocols were introduced to the literature by Fetal Medicine Foundation with the combined evaluation of maternal characteristics, uterine artery Doppler and angiogenic-antiangiogenic markers (16).

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Addition of maternal history and biochemical serum markers to uterine artery Doppler examination was strongly associated with placental and endothelial dysfunction (4,5). Serum markers of PIGF, Endoglin, tyrosine kinase-1 (sFlt-1) and placental protein 13 (PP-13) make it possible to make screening earlier and most importantly, when they are used with first trimester Doppler sonography, they provide a higher predictive value and more advanced diagnostic performance (5).

While PAPP-A alone provides a prediction of 10-20% during preeclampsia screening, it can provide a prediction of 70% (5% false positivity ratio) when combined with uterine artery Doppler indexes (10, 17).

Spencer et al. (18) have performed PAPP-A and PP-13 measurements at first trimester and uterine artery Doppler examination at 22-24 gestational weeks. PAPP-A MoM value was found to be statistically significantly lower in preeclamptic group compared to the control group. When PAPP-A was combined with uterine artery PI value, preeclampsia could be predicted by 76% sensitivity; but there was no change in sensitivity with the addition of PP-13 to this combination.

In their study, Lorenzo et al detected a significant relationship between early-onset preeclampsia and s-βhCG value above 3.0 MoM (19). However, it was proven in many studies evaluating s-βhCG retrospectively that it could not provide preeclampsia prediction (10, 20).

In a study evaluating sEng level at 11-13 and 30-33 gestational weeks, median MoM value at 30-33 gestational weeks was found to be higher in preeclamptic group compared to control

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group, and sEng level that was tested at 11-13 gestational weeks was found to be similar between both groups. When maternal characteristics were combined with third trimester sEng levels, late-onset preeclampsia prediction was reported as 50% with a FPR of 10%. (21)

Placental growth factor (PIGF) is a proangiogenic protein and preeclampsia was associated with the production of this protein in less amounts. The decrease in concentration may present itself during the period that the disease shows clinical symptoms as well as during preclinical period; and it is present since first trimester. It was detected at first trimester that PIGF concentration was low in preeclamptic pregnant women and it was inversely proportional with the severity of the disease (22).

No difference was found between normotensive and preeclamptic patients in terms of PIGF levels that were tested in urine at 8-21 weeks' of pregnancy. PIGF level in preeclampsia prediction at preterm at 21-32 weeks' of pregnancy was higher compared to term preeclampsia PIGF level (23).

Akoler et al. have examined uterine artery PI, mean blood pressure, PIGF, PAPP-A values of 58 884 cases at 11-13 weeks of pregnancy; and they have reported a preeclampsia detection rate of 50% with a false positivity rate of 10% by using only maternal BMI and mean artery pressure (MAP) at 34 weeks of pregnancy, a detection rate of 75% by the addition of uterine artery PI and more than 95% by the addition of PIGF and PAPP-A values (24).

Whereas Diguisto et al. Reported the multivariate model, adjusted for laboratory and sonographic indicators, had an area under the curve (AUC) estimated at 0.76, which was not significantly different from the AUC of the univariate model adjusted only for PlGF (p=0.7).

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As a result, in a high-risk population, PlGF in the first trimester is useful for predicting preeclampsia, but neither sFlt-1 nor any UAD indices improved the prediction of preeclampsia(25).

Li L et al. demonstrated pregnancies that developed preeclampsia, the uterine artery PI at early second- trimester was increased (1.61±0.047 vs. 1.02±0.049, p<0.001). In contrast, the level of PlGF was decreased in preeclamptic group compared with the controls (0.69±0.23 vs. 1.00±0.26, P<0.001) (26).

Uterine artery PI, PAPP-A, PIGF, PP-13, inhibin-A, activin-A, soluble endoglin and mean arterial pressure were studied in 33 602 pregnant women at 11-13 weeks' of pregnancy. When only maternal factors (history), uterine artery PI, blood pressure and PAPP-A were evaluated in preeclampsia cases, early preeclampsia was predicted by a ratio of 33% with a false positivity ratio of 5%, preeclampsia that was developed between 34-37 weeks was predicted by a ratio of 27.8% and preeclampsia that was developed after 37 weeks of pregnancy was predicted by a ratio of 24.5%. Preeclampsia prediction rate was reported as 91%, 79.4% and 60.9%, respectively with the addition of other biochemical markers to maternal factors. [4]

In combined screening by maternal factors, mean arterial pressure, uterine artery PI and PLGF detection rate was 100% (95% CI 80-100) for PE at <32 weeks, 75% (95% CI 62-85) for PE at <37 weeks and 43% (95% CI 35-50) for PE at ≥37 weeks, at 10% FPR. Combination of maternal factors and biomarkers provides effective first-trimester screening for preterm-PE (27).

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Poon et al. have investigated 7797 singleton pregnant women at 11-13 weeks' of pregnancy. Authors have predicted that early-onset preeclampsia would be developed in 476 patients by logistic regression analysis using variables of uterine artery PI, mean blood pressure, serum PAPP-A, PIGF, BMI, nulliparity and an experience of preeclampsia at previous pregnancy; but preeclampsia has developed in 32 patients. While it was expected that 7321 patients would not develop preeclampsia, two patients had a diagnosis of preeclampsia. In conclusion, the sensitivity of this model was calculated as 94.1% and its specificity was determined as 94.3% (28).

In our study, when we classified the patients as group I (control group, n=168); group II (patients who developed mild preeclampsia and gestational hypertension; n=20) and group III (patients who developed severe preeclampsia and HELLP; n=5), median sEng value was calculated as 14.97 ng/mL in group II and as 19.15 ng/mL in group III; and a statistically significant difference was detected between the groups (p=0.001). sEng level in Group I was found to be higher than Group II. PIGF level was relatively decreased as 76.05 pg/mL in group II and 66.10 pg/mL in group III; but there was not a statistically significant difference. Similar to the literature, sEng was statistically higher and PIGF was lower between Group II and III. Unlike the literature; low PIGF and high sEng levels were detected in control group. Unproportional distribution of cases between groups (168/5, 168/20) and less number of preeclamptic patients may be the reason of this situation.

While PIGF and PAPP-A levels decrease in preeclampsia, sEng level increases. In our study, no statistically significant difference was found between preeclamptic group and control group in terms of these markers. We consider that this result is derived from the fact that the

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distribution of the number of cases was unproportional and the number of preeclamptic cases was less than the control group. However; in subgroup analysis, it was found that PIGF level in the group including severe preeclampsia and HELLP cases was significantly decreased and sEng levels were increased compared to mild preeclampsia group.

Uterine artery PI value is detected higher in preeclamptic pregnant women compared to the control group. Similar results were obtained in our study. PI value in preeclamptic group was found significantly higher compared to control group (p=0.023). When PI cut-off value was taken as >2.23 in preeclampsia prediction, sensitivity was found as 42.31% and specificity was found as 82.10%. Uterine artery Doppler examination is an effective diagnostic tool in preeclampsia prediction.

CONCLUSION

Since uterine artery Doppler screening is simple and noninvasive and it brings very little extra time to the duration of screening, it may be included in the current sonographic examination. The sensitivity of uterine artery Doppler examination may be increased by adding one or more serum markers. Combinations provide an increase in the ability of prediction and determination compared to the tests used alone.

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Table 1. Demographic characteristics, serum biochemistry and ultrasonography results of the patients

Characteristics	Group 1 (control) (n=168)	Group 2 (preeclamptic) (n=25)	p value
Maternal age (years)	28.5±5.90	30.03±6. 39	0.494
Gravida	1.97±1.16	2.10±1.03	0.553
Parity	1.2 ± 0.9	1.5 ± 1.4	0.600
BMI (kg/m2)	28.3 ±3.3	29.3± 6.7	0.59
Delivery week	38.06±2.88	38.40±1.81	0.537
Weight of newborn (gr)	3080±53.51	2615±189.87	0.03
Mean Arter Sys. Pres	111.15±18.14	148.21±19.53	<0.0001
Mean Arter Dias. Pres.	70.54±9.45	98.05±13.18	<0.0001
PIGF(pg/mL)	71.25±0.9	67.24±1.1	0.571
sEndoglin(ng/mL)	15.38±0.2	15.82 ± 0.3	0.642
PAPP-A(MoM)	1.2	1.01	0.417
s-βhCG (MoM)	1.2	0.91	0.184
Ut- PI	1.67 ±0.35	1.93±0.23	0.023

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Ut- S/D	3.76 ± 0,2	4.85 ± 0.1	0.019

Values are mean standard deviation or n (%),ut-pı:uterine artery pulsality index measurement,ut-s/d:uterine artery systolic diastolic ratio

Table 2. Comparison of Serum Markers and Ut-PI Indexes between Mild Preeclampsia, Severe Preeclampsia and Control Groups

Median (25-75p)	**Group I (n=168)**	**Group II (n=20)**	**Group III (n=5)**	**P**
PIGF (pg/ml)	71.25 (48.08-134.58)	76.05 (41.41-134.9)	66.1 (34.39-76.68)	0.24
sEndoglin (pg/ml)	1538 (1319-1732)	1497 (1232.75-1671.75)	1915 (1804-2212.5)	**0.001**
PAPP-A MoM	1.2 (0.81-1.72)	1.18 (0.71-1.93)	0.55 (0.45-0.86)	**0.029**
S-βhCG MoM	1.02	0.93	0.74	0.15

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	(0.69-1.51)	(0.55-1.33)	(0.52-1)	
Ut-PI	1.67	1.84	2.07	**0.023**
	(1.34-2.07)	(1.5-2.55)	(1.86-2.71)	

Table 3. Uterine Artery PI Cut-Off Value in Preeclampsia Prediction

	Cut off PI	**AUC-%95 (CI)**	**LR+/LR -**	**Specificity**	**Sensitivity**
Preeklampsi	>2.23	0.639 [0.566 -0.708]	2.36/0.7	%82,10	%42,31

AUC: area under curve; LR: likelihood ratio

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Figure 1. ROC Curve of Uterine Artery Doppler PI Index for Preeclampsia Prediction