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Use of Placental Pulsatility Index in High Risk Pregnancy to Predict Fetal Growth Restriction

Natavadee Todumrong, M.D.*,
Dhirapatara Charoenvidhya, M.D.*,
Boonchai Uerpairojkit, M.D.*

** Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand*

ABSTRACT

Objectives: The primary objective was to determine the predictive value of placental pulsatility index (PPI) in its ability to predict fetal growth restriction in singleton pregnant women at 16-24 weeks of gestation. The secondary objective was to evaluate PPI in predicting adverse perinatal outcomes and to compare the efficacy of PPI with conventional uterine artery pulsatility index (UtA PI) or umbilical artery pulsatility index (UA PI) alone.

Materials and Methods: A prospective observational study enrolled singleton pregnant women at 16- 24 weeks of gestation who were at high risk for fetal growth restriction and had prenatal care at the King Chulalongkorn Memorial Hospital between February 12, 2018, and January 28, 2019. UtA PI and UA PI were performed and calculated as PPI by transabdominal ultrasonography. Pregnancy outcomes were recorded. The optimal cut-off for PPI was derived from the receiver operating characteristic (ROC) curve to calculate the predictive values for fetal growth restriction.

Results: A total of 446 pregnant women were enrolled into the study. Twenty-seven cases (6%) developed fetal growth restriction. The optimal cut-off for PPI at 16-24 weeks of gestation was 1.38. The sensitivity, specificity, positive predictive value, and negative predictive value to predict fetal growth restriction were 66.7%, 78.8%, 16.8%, and 97.3%, respectively. The ROC curve of the PPI gave an area under the curve of 0.73 (95% CI,0.61-0.84).

Conclusion: In second-trimester high-risk pregnancies, PPI had a comparable performance in predicting FGR and adverse perinatal outcomes compared to UtA PI alone.

Keywords: placental pulsatility index, fetal growth restriction, adverse perinatal outcomes

Correspondence to: *Dhirapatara Charoenvidhya, M.D., Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand*
E-mail: dhirapatara.c@chula.ac.th

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การใช้ Placental pulsatility index ในการทำนายภาวะทารกโตช้าในครรภ์ ในสตรีตั้งครรภ์ที่มีความเสี่ยงสูง

ณัฐวดี ต่อดำรงค์, ธีระภัทร เจริญวิทย์, บุญชัย เอื้อไพโรจน์กิจ

บทคัดย่อ

วัตถุประสงค์: *วัตถุประสงค์หลักเพื่อศึกษาหาค่าคาดทำนาย (Predictive value) จากการใช้ Placental pulsatility index (PPI) ในสตรีตั้งครรภ์เดี่ยวที่มีความเสี่ยงสูง อายุครรภ์ 16-24 สัปดาห์ ต่อการเกิดภาวะทารกโตช้าในครรภ์ วัตถุประสงห์รอง คือการใช้ Placental pulsatility index (PPI) ในสตรีตั้งครรภ์เดี่ยวที่มีความเสี่ยงสูง อายุครรภ์ 16-24 สัปดาห์ ในทำนายการเกิดภาวะแทรกซ้อนของทารกหลังคลอด และเปรียบเทียบประสิทธิภาพการทำนายภาวะทารกโตช้าในครรภ์ระหว่างการใช้ Placental pulsatility index (PPI) กับการใช้ Uterine artery-PI (UtA PI) หรือ umbilical artery-PI (UA PI) เพียงอย่างเดียว*

วัสดุและวิธีการ: *รูปแบบการศึกษาเป็นการศึกษาแบบไปข้างหน้าโดยทำการศึกษาในสตรีตั้งครรภ์เดี่ยวอายุครรภ์ 16-24 สัปดาห์มีความเสี่ยงสูงที่จะเกิดภาวะทารกโตช้าในครรภ์ที่มาฝากครรภ์ที่โรงพยาบาลจุฬาลงกรณ์ ระหว่างเดือนกุมภาพันธ์ 2561 ถึงเดือน มกราคม 2562 โดยได้ทำการตรวจคลื่นเสียงความถี่สูงทางหน้าท้องวัดค่า Uterine artery-PI (UtA PI) และ umbilical artery-PI (UA PI) และคำนวณค่า Placental pulsatility index (PPI) ทำการติดตามและบันทึกผลการคลอด วิเคราะห์หาค่าที่เหมาะสมของ Placental pulsatility index (PPI) จาก receiver operating characteristic (ROC) curve เพื่อทำนายภาวะทารกโตช้าในครรภ์*

ผลการศึกษา: *มีสตรีที่เข้าร่วมทำการวิจัยทั้งหมด 446 ราย มีทารกโตช้าในครรภ์ 27 ราย พบว่า PPI ที่มีค่า 1.38 สามารถนำมาใช้ทำนายการเกิดภาวะทารกโตช้าในครรภ์ได้ (sensitivity 66.7%, specificity 78.8%, PPV 16.8%, NPV 97.3%, ROC curve and 95%CI 0.73 (0.61-0.84))*

สรุป: *ในสตรีตั้งครรภ์เดี่ยวที่มีความเสี่ยงสูงจะเกิดภาวะทารกโตช้าในครรภ์การใช้ PPI ไม่ได้มีประสิทธิภาพของเหนือกว่าการใช้ UtA PI ในการทำนายภาวะทารกโตช้าในครรภ์และภาวะแทรกซ้อนของทารกหลังคลอด*

คำสำคัญ: *placental pulsatility index, ภาวะทารกโตช้าในครรภ์, ภาวะแทรกซ้อนของทารกหลังคลอด*

Introduction

Fetal growth restriction (FGR) is one of the most common conditions that increase the risk of perinatal complications. The short and long-term consequences of FGR are major public health problems, especially in developing countries[1,2]. This problem increased up to 40-50% in India and Mexico, and in Thailand, it was 10-20%[3]. This results in an untoward outcome and high medical costs.

The prediction of FGR has been a matter of concern for high-risk pregnancies and may be beneficial in lowering adverse perinatal outcomes. The use of a Doppler ultrasound is currently a valuable tool in predicting fetal well-being and perinatal outcome. There has been much research regarding uterine artery pulsatility index (UtA PI) and umbilical artery pulsatility index (UA PI) to predict FGR. However, its clinical use is still limited due to its low predictive performance[5,6].

Placental pulsatility index (PPI) is a ratio that combines vascular impedance of both fetal and maternal sides of the placenta. Doppler waveforms can increase the placental vascular impedance, which is related to FGR and are signs of impending fetal asphyxia.

Recently, Gudmudsson, et al[7] conducted a retrospective study on PPI, a new parameter that reflects the placental vascular impedance in predicting FGR in high-risk pregnancies during the third trimester of gestation. They found that PPI had a sensitivity, specificity, positive predictive value, and negative predictive value of 56%, 76%, 91%, and 30%, respectively, in predicting FGR[7]. So far, there is no prospective study using PPI to predict FGR in high-risk pregnancies at an earlier gestation. This prospective study assessed the efficacy of PPI in predicting FGR in high-risk pregnancies during the second trimester of gestation.

Materials and Methods

The research protocol was reviewed and approved by the ethics committee of the King Chulalongkorn Memorial Hospital (registered number 724/60). This prospective observational study was conducted at the King Chulalongkorn Memorial Hospital between February 2018 and January 2019. The eligible criteria were singleton pregnant women at 16 - 24 weeks of gestation and had at least 1 of the inclusion criteria. The inclusion criteria were advanced maternal age (≥ 35 years), previous history of pregnancy complications i.e., FGR, preterm, pregnancy-induced hypertension (PIH), gestational diabetes mellitus (GDM), stillbirth or perinatal death, preexisting medical illness such as chronic hypertension, diabetes mellitus, vascular disease, and renal impairment. The exclusion criteria were pregnant women who had fetal anomalies, fetal chromosomal abnormalities, morbid obesity (BMI ≥ 40), uterine anomalies, and those who refused to participate in the study. The gestational age (GA) was confirmed by ultrasonography during early gestation for all participants.

All participants with 16-24 weeks of gestation that met the inclusion criteria were enrolled in the study. UtA PI and UA PI measurements were performed on the same day by an experienced sonographer using the standard technique. Transabdominal ultrasonography (TAS) was obtained with 4 to 9 MHz IC5-9D (Voluson E10; GE Healthcare, Milwaukee, WI). UtA PI was performed on the lower lateral quadrants of the abdomen, angled medially. Color flow mapping was used to identify the UtA at the location where it crossed the external iliac artery. Pulsed wave Doppler was used to obtaining the UtA waveform by ensuring that the angle of the insonation was less than 30 degrees and at 1 cm downstream from this crossover point. UA PI was performed at a free loop, not too close to the fetus or the placental insertions. Three similar consecutive waveforms were obtained from UtA and UA[14]. PPI was calculated using this formula : PPI = (UA PI + mean of the left and the right Ut PI)/2[7]. The sample size was calculated using Gudmudsson S, et al.'s sensitivity of PPI to predict FGR (small for gestational age < 10 centiles)[7]. At the King Chulalongkorn Memorial Hospital, the incidence of FGR in all pregnancies was 5.9%[4]. Based on this calculation, the number of participants needed was 407. When 10% attrition rate of the follow-up participants was included in the

calculation, the total sample size was scaled up to 450 pregnant women.

Information on the study was provided to all participants by the research personnel. All participants received a copy of the study information. Signed informed consent was obtained from all participants after counseling. The participants were followed, and their data were collected after delivery. The data comprised of demographic characteristics, gestational age at TAS and delivery, results of UA and UtA Doppler parameters, placental weight, mode of delivery, indication for cesarean section, birth weight, APGAR score at 5 minutes, and perinatal outcomes.

The primary outcome was the efficacy of the PPI in predicting FGR in high-risk pregnancies. Secondary outcomes were comparisons of the efficacy of the PPI and conventional UtA PI or UA PI alone in predicting adverse perinatal outcomes.

Adverse perinatal outcomes included an APGAR score less than 7 at 5 minutes, respiratory distress syndrome (RDS), transient tachypnea of the newborn (TTNB), neonatal intensive care unit (NICU) admission within 48 hours, neonatal sepsis, intraventricular hemorrhage, pulmonary hemorrhage, hypothermia, hypoglycemia, bronchopulmonary dysplasia, necrotizing enterocolitis, perinatal death, and stillbirth.

Statistical analysis was performed using SPSS Version 22 (SPSS Inc., Chicago, Ill., USA). Descriptive statistics were presented as mean (SD) with a 95% confidence interval for continuous data and n (%) for categorical data. Analysis of continuous data was done by Student t-test, and categorical data were compared using Chi-square or Fischer exact test as appropriate. P-value of less than 0.05 was considered significant. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were assessed. Receiver operating characteristic (ROC) curves were constructed for PPI with FGR and adverse perinatal outcomes.

Results

Four hundred and fifty pregnant women were enrolled into this study. Four cases were excluded because one case had trisomy 21, one had major thalassemia, and the other two had fetal anomalies. After excluding those patients, the study was left with 446 pregnant women. The data from 446 participants were analyzed. Twenty-seven (6%) cases developed FGR.

The maternal characteristics are shown in Table 1. There were no statistically significant differences in age, the number of nulliparous, body mass index (BMI), GA at first ANC, and TAS between the FGR group and appropriate for gestational age (AGA) group. When the fetuses in the FGR group was compared to the AGA group, the FGR group had significantly higher number of preterm birth (33% vs 10.5%, $p < 0.001$), adverse perinatal outcomes (33% vs 7.4%, $p < 0.001$) and NICU admission (11.1% vs 2.6%, $p = 0.046$). They also had significantly lesser neonatal birth weight. However, there were no significant differences in the need for ventilator support, the number of fetuses with APGAR score less than 7 at 5 minutes and duration of hospital stay among the FGR group and the AGA group ($p > 0.05$) (Table 2.).

Table 1. Demographic characteristics of the women with and without FGR.

	AGA (n = 419)	FGR (n = 27)	p value
Maternal age (years)	35.8 (± 3.8)	35 (± 5.8)	0.260*
Nulliparous	150 (35.8)	11 (40.7)	0.604†
GA at first ANC (weeks)	9.5 (± 2.4)	10.6 (± 2.4)	0.513*
BMI at prepregnancy (kg/m^2)	22.8 (± 3.7)	22.2 (± 3.7)	0.409*
GA at USG (weeks)	18.8 (± 2)	19 (± 1.6)	0.669*

AGA: appropriate for gestational age, FGR: fetal growth restriction, GA: gestational age, ANC: antenatal care, BMI: Body mass index. † Chi-square test, * Student's T-test. Data are presented as n (%), and mean ± SD.

Table 2. Pregnancy outcomes of the women with and without FGR.

	AGA (n = 419)	FGR (n = 27)	p value
Birth weight (grams)	3,102 (± 432.4)	2,184 (± 588.4)	< 0.001*
GA at delivery (weeks)	38.3 (± 1.6)	36.9 (± 3.4)	< 0.001*
Preterm birth (< 37 weeks)	44 (10.5)	9 (33)	< 0.001†
Adverse perinatal outcome	31 (7.4)	9 (33)	< 0.001†
NICU admission	11 (2.6)	3 (11.1)	0.046‡
Need ventilator	10 (2.4)	1 (3.7)	0.501‡
APGAR score < 7 at 5 minutes	1 (0.2)	1 (3.7)	0.118‡
Duration of hospital stay (days)	4.6 (± 7.3)	4.9 (± 4.8)	0.833*

AGA: appropriate for gestational age, FGR: fetal growth restriction, GA: gestational age, NICU: Neonatal intensive care unit
† Chi-square test, ‡ Fisher's exact test, * Student's T-test. Data are presented as n (%), and mean ± SD

The ROC curve of PPI in predicting FGR gave an area under the curve of 0.73 (95% CI,0.61-0.84) with an optimal cut-off PPI of 1.38 (Fig. 1). This resulted in a sensitivity of 66.7%, a specificity of 78.8%, PPV of 16.8 %, and NPV of 97.3% for the prediction of FGR. UtA PI yielded a sensitivity of 59.3%, specificity of 87.1%, PPV of 22.9 % and NPV of 97.1% for the prediction of FGR (AUC = 0.75). UA PI yielded a sensitivity of 14.8%, a specificity of 88.8%, PPV of 7.8 %, and NPV of 94.2% for the prediction of FGR (AUC = 0.55) (Table 3).

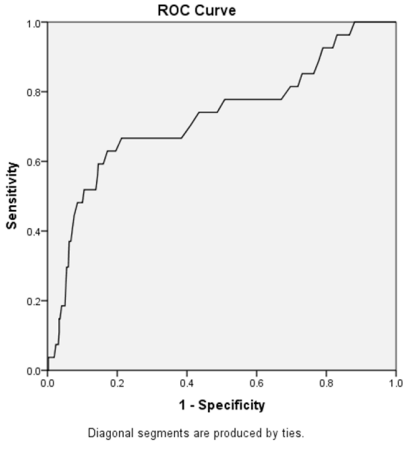

Fig. 1. Receiver operating characteristic curves of placental pulsatility index in predicting fetal growth restriction.

Table 3. Performance of PPI, UtA and UA doppler in predicting FGR.

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	ROC area and 95%CI
PPI > 1.38	66.7	78.8	16.8	97.3	0.73 (0.61-0.84)
Mean UtA PI > +2SD	59.3	87.1	22.9	97.1	0.75 (0.64-0.86)
Mean UA PI > +2SD	14.8	88.8	7.8	94.2	0.55 (0.44-0.66)

PPI: placental pulsatility index, UtA PI: uterine artery pulsatility index, UA PI: umbilical artery pulsatility index

As demonstrated in Table 4, PPI had a sensitivity of 47.4%, a specificity of 79.4%, PPV of 25.2 %, and NPV of 91.2% in predicting adverse perinatal outcomes. UtA PI had a sensitivity of 25%, a specificity of 85.2%, PPV of 14.9 %,

and NPV of 92% in predicting adverse perinatal outcomes. UA PI had a sensitivity of 10%, a specificity of 88.4%, PPV of 7.8 %, and NPV of 90.9% in predicting adverse perinatal outcomes. PPI had a higher sensitivity and PPV in predicting adverse perinatal outcomes compared to UtA PI or UA PI alone.

Table 4. Performance of PPI, UtA and UA doppler in predicting adverse perinatal outcomes.

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	ROC area and 95%CI
PPI > 1.38	47.4	79.4	25.2	91.2	0.63 (0.59-0.83)
Mean UtA PI > +2SD	59.3	87.1	22.9	97.1	0.75 (0.64-0.86)
Mean UA PI > +2SD	14.8	88.8	7.8	94.2	0.55 (0.44-0.66)

PPI: placental pulsatility index, UtA PI: uterine artery pulsatility index, UA PI: umbilical artery pulsatility index

The high PPI group had a significantly increased number of FGR, lower birth weight, and higher adverse perinatal outcomes compared to the normal PPI group ($p<0.001$). Nevertheless, the differences were not significant in GA at delivery, placental weight, number of fetuses with NICU admission, the need for ventilator support, number of fetuses with APGAR score less than 7 at 5 minutes, and duration of hospital stay as shown in Table 5.

Table 5. Comparison of pregnancy outcomes among high PPI group and normal PPI group.

	High PPI group (n = 107)	Normal PPI group (n = 339)	p value
GA at delivery (weeks)	37.9 (± 2.5)	38.3 (±1.5)	0.1*
Birth weight (grams)	2,861 (± 612.5)	3,105 (± 434.8)	< 0.001*
Placental weight (grams)	578 (± 126.5)	632 (± 129)	0.493*
FGR	18 (16.8)	9 (2.7)	< 0.001†
Adverse perinatal outcome	27 (25.2)	30 (8.8)	< 0.001†
NICU admission	6 (5.6)	8 (2.4)	0.093†
Need ventilator	4 (3.7)	7 (2.1)	0.331‡
APGAR score < 7 at 5 minutes	1 (0.9)	1 (0.3)	0.388‡
Duration of hospital stay (days)	5.4 (± 8.4)	4.3 (± 6.8)	0.179*

FGR: fetal growth restriction, GA: gestational age, NICU: Neonatal intensive care unit

† Chi-square test, ‡ Fisher's exact test, * Student's T-test. Data are presented as n (%), and mean ± SD

Discussion

FGR is a leading cause of perinatal morbidity and mortality. Currently, there is no screening strategy to predict FGR due to low predictive performances of the currently available tools. This indicates that there is a need to establish a more sensitive tool to predict FGR. Recently, Gudmudsson S, et al.'s[7] retrospective study reported that during the third trimester, PPI alone might improve the detection rate of FGR compared to either UtA PI or UA PI.

This prospective study of PPI is the first of its kind to predict FGR during the second trimester of high-risk pregnancies. The best cut-off value of PPI was 1.38 according to the ROC curve (ROC curve 0.73, 95% CI (0.61-0.84). At this cut-off value, the sensitivity (66.7%) and specificity (78.8%) to predict FGR were high. These results were consistent with the findings reported in Gudmundsson S, et al.'s study[7].

However, the PPV of PPI to predict FGR in our study was lower compared to Gudmundsson S, et al.'s

study[7]. This could be due to a low prevalence of FGR (6% (27/446)) in our study when compared to Gudmundsson S, et al.'s study, which had a prevalence of 80% (273/340). The higher PPV for FGR may not reflex a real clinical situation and can be due to selection bias. Their results may not be applicable in clinical practice. In addition, they screened for FGR in the third trimester, which may have a lesser clinical benefit when compared to our study which the screening was done at an earlier gestational period.

Our study showed that PPI had a higher sensitivity and higher PPV to predict adverse perinatal outcomes compared to UtA alone (sensitivity 47.4% vs 25%, specificity 79.4% vs 85.2%, PPV 25.2% vs 14.9%, NPV 91.2% vs 92%, ROC curve 0.63 vs 0.65, respectively).

In our study, the performance of UtA PI or UA PI alone to predict FGR was consistent with the results from previous studies[8, 15]. In contrast, Pongrojpaw D, et al's study[16] showed that the UtA PI had a lower prediction performance in predicting FGR and adverse perinatal outcomes.

The strength of this study was that we obtained PPI in high-risk pregnancies from the beginning and prospectively followed them until the FGR appeared. This conforms more to the context of screening and differs from the study that was performed retrospectively. In addition, the study was conducted in an earlier gestational period which may have a better clinical benefit in implementing an intervention to ameliorate the adverse clinical outcome.

Conclusion

In conclusion, in second-trimester high-risk pregnancies, PPI had a comparable performance in predicting FGR and adverse perinatal outcomes compared to UtA PI alone. Therefore, we recommend further study about PPI use combined with other serum markers to predict FGR and adverse perinatal outcomes.

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Potential conflicts of interest

The authors declare no conflict of interest.

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