นิพนธ์ต้นฉบับ

The value of middle cerebral artery-umbilical artery pulsatility index ratio in prediction of severe fetal growth restriction

Tongta Nanthakomon, Charintip Somprasit

Abstract

Objective: To evaluate the value of the ratio of middle cerebral artery pulsatility index (MCA PI) to the umbilical artery pulsatility index (UA PI) for predicting of adverse perinatal outcome in the fetal growth restriction (FGR).

Materials and methods: A prospective study was performed on 82 pregnant women in Thammasat University Hospital between January 1, 2009 and December 31, 2009. The study population comprised 27 pregnant women who delivered FGR fetuses and 55 pregnant women whose fetuses were normal growth. The MCA PI, UA PI and MCA PI/ UA PI ratio were assessed. Mild and severe FGR were defined as a fetus having the fetal weight below the 10^{th} and 5^{th} percentile, respectively. Abnormal MCA PI/ UA PI (CU ratio) were defined as the ratio < 1.08.

Results: Of the 82 pregnant women, In FGR cases have high oligohydramnios, high cesarean section rate, lower GA at delivery, low birth weight and high rate of neonatal intensive care unit (NICU) admission compared with normal cases ($P<0.05$). 8 out of 27 women with FGR showed abnormal CU ratio but only 2 in 55 fetuses in normal group ($P <0.001$). Among these, mild and severe FGR with abnormal CU ratio were 5 (26.3%) and 3 (37.5%), respectively which was demonstrated not significantly difference ($P = 0.658$).

Conclusion: The MCA PI/ UA PI ratio could not be used as the predictor of the severe FGR from mild FGR in a particularly severe case of FGR.

Key words: Doppler Ultrasound, Fetal growth restriction, Cerebro-umbilical ratio, Middle cerebral artery, Umbilical artery

Maternal-Fetal Medicine Unit, Department of Obstetrics and Gynecology, Faculty of Medicine, Thammasat University

Introduction

Fetal Growth Restriction (FGR) indicates under development rate of fetal growth in maternal uterus in contrast to its genetic growth potential. Since the genetic growth potential cannot be practically measured, the most common practice is birthweight lower than 10 percentile of the average weight at each gestational age. The method is designed for small gestational age and thus data derived from this method should be used cautiously. These fetuses are usually known to carry a higher morbidity and mortality rates as been compared to normal fetuses. In progress reference for the management of FGR fetuses is to monitor fetal well-being and timely delivery for the compromised fetuses.[1] Doppler ultrasound has been acceptable for detected surveillance of FGR fetuses by assessment of the uteroplacental insufficiency. Diagnosis of uteroplacental insufficiency using Doppler ultrasound found umbilical artery (UA) to have high resistance to circulation. When symptom persists, resistance of UA increases. The examination using high frequency Doppler will show wave Absent End Diastolic Flow (AEDF) or Reverse End Diastolic Flow (REDF). This leads to the body adjustment for more circulation to brain known as "brain sparing phenomenon" that was showen by increase in UA resistance and a decrease in middle cerebral artery (MCA) resistance.[2]

There are many relationships and benefits of Doppler ultrasound in fetal growth restriction. Previous studies[3, 4] proved that Doppler ultrasound can be used to identify restricted growth fetus from small healthy fetus with better precision than using weight showed that Doppler ultrasound can predict the prenatal outcome of FGR and abnormal UA pulsatility index (PI) was the best indicator for abnormal prenatal outcome. The absent or reverse end diastolic flow of UA was related to bad perinatal outcomes compared to normal UA PI.[5]

In current studies have showed prenatal cerebral vasodilatation on the MCA Doppler is sensitive to a physiologic response to hypoxia and good prediction of perinatal outcome.[6] There are many studies[7, 8] use of umbilical-cerebral Doppler ratios or used Doppler cerebro-umbilical ratio (C/U ratio) in predicting fetal growth restriction in the assessment of perinatal outcome in growth-restricted and hypoxic fetuses but in previous studies were not present value to predicted specify to mild or severe FGR. This study intended to investigate the value of middle cerebral artery-umbilical artery pulsatility index ratio in prediction of severe fetal growth restriction compared to mild FGR.

Methods

A prospective study was performed on singleton pregnant women in Thammasat University Hospital after having been approved by Institutional Ethics Committee between January 1, 2009 and December 31, 2009. Inclusion criteria were accurate gestational age (GA), which was defined by a reliable last menstrual period and confirmed by first or second trimester sonography, delivery between 32-40 weeks' gestation in Thammasat University Hospital. Incomplete data, no antenatal UA and MCA Doppler studies and cases with structural or chromosomal anomalies detected at birth were excluded.

To accept the rationale of the study, the authors classified the patients into 3 groups according to the birthweight based on reference range. Group 1 was normal fetal growth and birth weight, Group 2 was mild FGR defined as a fetus having the fetal weight below the 10^{th} percentile and Group 3 was severe FGR with fetal weight below the 5^{th} percentile for the gestational age at birth. Doppler studies of UA, MCA, were performed by color Doppler system. The Doppler flow velocimetry in umbilical artery was obtained at free loop of UA, angle of ultrasound beam to blood flow was less

than 30° and showed at least five waveforms, then recorded of pulsatility index (PI), resistance index (RI) and uniform of wave-forms (positive absent or reverse end diastolic flow). The Doppler of MCA was recorded PI, RI and MCA PI/ UA PI ratio (cerebro-umbilical ratio; CU ratio) were assessed and results of UA and MCA Doppler define based on Harrington's chart[9] and abnormal MCA PI/ UA PI was defined as the ratio < 1.08.[10] The frequency of Doppler study depended on severity of case. Nonstress test, biophysical profile was performed differently in each case depending on indication of the test and gestational age.

Maternal characteristics including age, parity, GA at last ultrasound, GA at delivery, presence of oligohydramnios, mode of delivery, and results of Doppler study were collected. Neonatal outcomes were collected for birth weight, 1 minute Apgar score and neonatal morbidity.

Results were evaluation of maternal and neonatal characteristics were presented as mean ± standard deviation (SD) or percentage. Comparison of maternal and neonatal characteristics between groups of FGR fetuses were performed using one way ANOVA for continuous variable or Chi-square test for categorized variable. A *p-value* < 0.05 was considered statistically significant.

Results

Initially, there were 82 pregnant women recruited. The study population comprised 55 pregnant women whose fetuses were normal growth (group 1) and 27 pregnant women who delivered FGR fetuses. Among 19 patients with FGR classified in mild FGR (group 2) and 8 patients in severe FGR. Fifty-five (67%) pregnant women were classified as normal group, 19 (23.2%) patients as mild FGR and 8 (9.8%) patients as severe FGR

Maternal characteristics are offered in Table 1. The mean maternal age of FGR fetuses were not significantly different with normal growth fetuses 25.59 ± 6.24 and 31.22 ± 5.98 years respectively

Table 1 Maternal and neonatal characteristic in normal fetal growth and fetal growth restriction

	Normal (n = 55) (%)	**FGR (n = 27) (%)**	**P value**
Maternal Age, years*	31.22 ± 5.98 (17 - 42)	25.59 ± 6.24 (16 - 39)	0.805
Primipara	20(36.4)	21(77.8)	<0.001
Oligohydramnios	1(1.8)	13(48.1)	<0.001
CU ratio < 1.08	2(3.6)	8(29.6)	<0.001
Route of delivery			
Vaginal delivery	43(78.2)	12(21.8)	<0.001
Cesarean section	112(21.8)	18(66.7)	<0.001
GA at delivery, weeks*	37.38 ± 0.65 (36-38)	37.18 ± 1.61 (32-39)	0.039
EFW, grams*	2733 ± 430.94 (2060 - 4322)	1968.5 ± 366.55 (740 - 2400)	<0.001
NICU admission	2(3.6)	13(48.1)	<0.001

FGR = fetal growth restriction, CU = crerbro-umbilical ratio; middle cerebral artery pulsatility index / umbilical artery pulsatility index, GA = gestational age, C/S = cesarean section

* Mean ± SD (range)

(p = 0.805). 8 out of 27 women with fetal growth restriction showed abnormal MCA PI/ UA PI ratio (CU ratio <1.08) and only 2 in 55 fetuses in normal group showed abnormal CU ratio (p <0.001). In FGR cases have higher oligohydramnios, high cesarean section rate, low GA at delivery, low birth weight and high rate of neonatal intensive care unit (NICU) admission compared with normal case (p <0.05). The comparisons about characteristic of mild and severe FGR were shown in Table 2. Among these, No significant difference from mild and severe FGR in maternal age, primigravida, oligohydramnios, GA at delivery, birthweight and all of Doppler indicies. There were higher rates of cesarean section, NICU admission and lower birthweight in severe FGR cases (p <0.001, p =0.13 and p <0.001 respectively). Abnormal CU ratio were 5 (26.3%) and 3 (37.5%), respectively which did not significantly any difference (p = 0.658).

Table 2 Maternal and Neonatal characteristic in mild and severe fetal growth restriction

	Mild FGR (n = 19) (%)	**Severe FGR (n = 8) (%)**	***P value***
Maternal Age, years*	25.10 ± 6.76 (19-39)	26.75 ± 4.97 (21-34)	0.542
Primipara	16(84.2)	5(62.5)	0.045
Oligohydramnios	9(47.4)	4(50)	0.887
Route of delivery			
Vaginal delivery	9(47.4)	0(0)	<0.001
Cesarean section	10(52.6)	8(100.0)	<0.001
GA at delivery, weeks*	37.47 ± 1.30 (33-39)	36.50 ± 2.13 (32-38)	0.157
EFW, grams*	2117.6 ± 184.91 (1665-2400)	1614.4 ± 161.0 (740-2025)	<0.001
NICU admission	6(33.3)	7(87.5)	0.332
CU ratio < 1.08	5(26.3)	3(37.5)	0.013
Doppler†	1.15 ± 0.27	1.09 ± 0.25	0.635
UA PI	(0.80-1.73)	(0.78-1.47)	
UA RI	0.67 ± 0.81	0.65 ± 0.91	0.620
	(0.55-0.84)	(0.55-0.80)	
MCA PI	1.72 ± 0.68	1.37 ± 0.28	0.243
	(0.90-3.98)	(1.04-1.77)	
MCA RI	0.79 ± 1.38	0.73 ± 0.27	0.330
	(0.60-1.20)	(0.66-0.82)	
UA PI/MCA PI	0.77 ± 0.37	0.82 ± 0.30	0.739
	(0.24-1.80)	(0.55-1.41)	
MCA PI/UA PI	1.59 ± 0.81	1.30 ± 1.73	0.412
	(0.56-4.10)	(0.71-0.81)	

FGR = fetal growth restriction, CU = cere-umbilical ratio; middle cerebral artery pulsatility index/umbilical artery pulsatility index, GA = gestational age, C/S = cesarean section,

* Mean ± SD (range)

† Severe FGR group n=6 (exclude 2 cases; 1 case for absent end diastolic flow, 1 case for reverse end diastolic flow)

Discussion

Fetal Growth Restriction caused from several factors. Besides finding the cause of the symptom, one important aspect that must be investigated into is to predict the likelihood of the disease in order to avoid morbidities. Fetal birth weight analysis alone is insufficient as a tool to identify a healthy, small for gestational age fetus from fetal growth restriction, thus, further investigation into this subject is essential for treatments, counseling and management of patient. FGR caused by uteroplacental insufficiency has been confirmed to transmit an increased risk of perinatal morbidity and mortality.[5,11] Contemporary study by Bate JA. et al.[3] proved that Doppler Ultrasound can be used to identify FGR from small for gestational age. The study compared Doppler Ultrasound with weight analysis and concluded that FGR is better identified using Doppler Ultrasound and appears to be the most promising diagnostic tool for supervision of these at-risk fetuses.[11] Doppler ultrasound can be use to predict the prenatal outcome of fetal growth restriction and abnormal UA PI was the best indicator for abnormal perinatal outcome.[4] Seyam YS et al.[5] studied for the relationship between umbilical artery Doppler flow velocimetry and perinatal outcome. The study found restricted growth fetus with abnormal UA Doppler flow velocimetry to have a higher rate of admission at neonatal intensive care unit, birth weight and GA at delivery statistically lower than normal group. Gerber S et al.[12] reported that absent or reverse end diastolic flow in umbilical artery was correlated with poor perinatal outcome and some fetuses have major handicaps. The use of Doppler umbilical indices for fetal surveillance had a standard in high risk pregnancy especially in FGR follow up.[13]

First sign of uteroplacental insufficiency is the diagnosis of increase pressure in umbilical artery. When a symptom persists, there is increased resistance in the umbilical artery. The examination using high frequency Doppler will show wave Absent End Diastolic Flow (AEDF) or Reverse End Diastolic Flow (REDF). Also, the fetus will adjust its circulation by increasing blood flow to central brain (centralization) causing "brain sparing phenomenon". When symptoms are more, blood vessels in fetal brain will lose its tuning ability causing compensatory vasodilatation.[1,4] Fetal MCA PI value below 95^{th} percentile of the normal range was found to be highly predictive of subsequent neurological outcomes.[6,14,15] The addition of placento-cerebral ratios has been shown to increase the sensitivity of these indices in detecting this pathological brain sparing effect and in predicting adverse neurological outcome.[16] Abnormal umbilical Doppler indices and cerebro-umbilical ratios are strong predictors of fetal growth restriction and of adverse perinatal outcome in pre-eclampsia, while the MCA PI alone is not a reliable indicator.[17] Such results indicate that the combination of fetal umbilical and cerebral Doppler indices to produce an umbilico-cerebral ratio can increase the utility of Doppler ultrasound in high-risk pregnancies. Obido AO et al.[10] presented cerebro-placental Doppler ratio (CPR) with categorical threshold in the prediction of adverse perinatal outcomes in growth-restricted pregnancies with a CPR threshold of less than 1.08, the sensitivity, specificity, positive and negative predictive values were 72%, 62%, 68%, and 67% respectively. The present study shows significant higher incidence of abnormal CU ratio in severe FGR compared to mild FGR. However, because of limitation of sample size, the data could not demonstrate the significant higher rate of NICU admission in severe FGR compare to mild FGR. Furthermore, the authors do not compare perinatal outcomes between FGR fetuses with normal CU ratio and abnormal CU ratio. Further investigation with a large number of cases may be needed to prove this hypothesis.

The MCA PI/ UA PI ratio could be used as the predictor for fetuses with growth restriction compared to normal cases but cannot differentiate mild from severe cases of FGR but in the study that had a small number of patients, further study that has a higher population may be need to proved this hypothesis.

Reference

1. Intrauterine growth restriction. Clinical management guidelines for obstetrician-gynecologists. American College of Obstetricians and Gyne cologists. Int J Gynaecol Obstet 2001;72:85-96.
2. Vyas S, Nicoladies KH, Bower S, Campell S. Middle cerebral artery flow velocity waveforms in fetal hypoxaemia. Br J Obstet Gynecol 1990; 97:797-803.
3. Bates JA, Evans JA, Mason G. Differentiation of growth retarded from normally grown fetuses and prediction of intrauterine growth retardation using Doppler ultrasound. Br J Obstet Gynaecol 1996;103:670-5.
4. Fong KW, Ohlsson A, Hannah ME, Grisaru S, Kingdom J, Cohen H, et al. Prediction of perinatal outcome in fetuses suspected to have intrauterine growth restriction: Doppler US study of fetal cerebral, renal, and umbilical arteries. Radiology 1999;213:681-9.
5. Seyam YS, Al-Mahmeid MS, Al-Tamimi HK. Umbilical artery Doppler flow velocimetry in intrauterine growth restriction and its relation to perinatal outcome. Int J Gynaecol Obstet 2002; 77:131-7.
6. Chan FY, Pun TC, Lam P, Lam C, Lee CP, Lam YH. Fetal cerebral Doppler studies as a predictor of perinatal outcome and subsequent neurologic handicap. Obstet Gynecol 1996;87:981-8.
7. To WW, Chan AM, Mok KM. Use of umbilical-cerebral Doppler ratios in predicting fetal growth restriction in near-term fetuses. Aust N Z J Obstet Gynaecol 2005;45:130-6.
8. Habek D, Hodek B, Herman R, Jugovi D, Habek JC, Salinagi A. Fetal Biophysical Profile and Cerebro-Umbilical Ratio in Assessment of Perinatal Outcome in Growth-Restricted Fetuses. Fetal Diagn Ther 2003;18:12-6.
9. Harrington K. Doppler values of maternal and fetal circulation. In: Chervenak FA, Isaacson GC, Campbell S, editors. Ultrasound in obstetrics and gynecology. Boston, MA: Little, Brown & Co; 1993. 1799-801.
10. Obido AO, Riddick C, Pare E, Stamilio DM, Macones GA. Cerebroplacental Doppler ratio and adverse perinatal outcomes in intrauterine growth restriction: evaluating the impact of using gestational age-specific reference values. J Ultrasound Med 2005;24:1223-8.
11. Omtzigt AM, Reuwer PJ, Bruinse HW. A randomized controlled trial on the clinical value of umbilical Doppler velocimetry in antenatal care. Am J Obstet Gynecol 1994;170:625-34.
12. Gerber S, Hohlfeld P, Viquerat F, Tolsa JF, Vial Y. Intrauterine growth restriction and absent or reverse end-diastolic blood flow in umbilical artery (Doppler class II or III): A retrospective study of short- and long-term fetal morbidity and mortality. Eur J Obstet Gynecol Reprod Biol 2006;126:20-6.
13. Neilson JP, Alfirevic Z. Doppler ultrasound for fetal assessment in high risk pregnancies. Cochrane Database Syst Rev 2000;2. CD000073.
14. Rizzo G, Arduini D, Luciano R. Prenatal cerebral Doppler ultrasonography and neonatal neurologic outcome. J Ultrasound Med 1989;8: 237-40.
15. Eixarch E, Meker E, Iraola A, Illa M, Cripi F, Hernandez-Andrade E, et al. Neurodevelopmental outcome in 2-year-old infants who were small-for-gestational age term fetuses with cerebral blood flow redistribution Ultrasound Obstet Gynecol 2008;32:894-9.

16. Scherjon SA, Smolders-DeHaas H, Kok JH, Zondervan HA. The 'brain-sparing' effect: antenatal cerebral Doppler findings in relation to neurologic outcome in very preterm infants. Am J Obstet Gynecol 1993;169:169-75.

17. Ozeren M, Dinc H, Ekmen U, Senekayli C, Aydemir V. Umbilical and middle cerebral artery Doppler indices in patients with preeclampsia. Eur J Obstet Gynecol Reprod Biol 1999;82:11-6.

บทคัดย่อ

ความสามารถของอัตราส่วน pulsatility index ของการตรวจด้วยคลื่นเสียงความถี่สูงดอพเลอร์หลอดเลือดแดง middle cerebral กับคลื่นเสียงความถี่สูงดอพเลอร์หลอดเลือดแดงสายสะดือ ในการทำนายทารกโตช้าในครรภ์ระดับรุนแรง

ต้องตา นันทโกมล, จรินทร์ทิพย์ สมประสิทธิ์

หน่วยเวชศาสตร์มารดาและทารกในครรภ์ โครงการจัดตั้งภาควิชาสูติศาสตร์-นรีเวชวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยธรรมศาสตร์

วัตถุประสงค์: เพื่อประเมินความสามารถของอัตราส่วน pulsatility index ของคลื่นเสียงความถี่สูงดอพเลอร์หลอดเลือดแดงมิดเดิลเซเรบรัลกับคลื่นเสียงความถี่สูงดอพเลอร์หลอดเลือดแดงสายสะดือ ในการทำนายทารกโตช้าในครรภ์ระดับรุนแรง

วิธีการศึกษา: การศึกษาแบบไปข้างหน้าที่โรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติตั้งแต่ ๑ มกราคม- ๓๑ ธันวาคม ๒๕๕๒ ในสตรีตั้งครรภ์เดี่ยวที่มารับการฝากครรภ์ตรวจคลื่นเสียงความถี่สูงดอพเลอร์ที่หน่วยเวชศาสตร์มารดาและทารกในครรภ์โดยมีการตรวจวัดดัชนีต่าง ๆของคลื่นเสียงความถี่สูงดอพเลอร์หลอดเลือดแดงมิดเดิลเซเรบรัลกับคลื่นเสียงความถี่สูงดอพเลอร์หลอดเลือดแดงสายสะดือ ได้แก่ MCA pulsatility index (MCA PI), umbilical (UA) PI, UA PI/ MCA PI and MCA PI/ UA PI ทารกโตช้าในครรภ์ได้รับการแบ่งออกเป็น ๒ กลุ่มคือ กลุ่มที่น้ำหนักแรกเกิดต่ำกว่า ๑๐ เปอร์เซ็นไทล์ และกลุ่มที่เป็นทารกโตช้าในครรภ์แบบรุนแรงโดยดูจากน้ำหนักแรกเกิดต่ำกว่า ๕ เปอร์เซ็นไทล์ และให้คำนิยามความผิดปกติของอัตราส่วน pulsatility index ของคลื่นเสียงความถี่สูงดอพเลอร์หลอดเลือดแดงมิดเดิลเซเรบรัลกับคลื่นเสียงความถี่สูงดอพเลอร์หลอดเลือดแดงสายสะดือ < ๑.๐๘

ผลการศึกษา: สตรีตั้งครรภ์เดี่ยวจำนวน ๘๒ คน แบ่งเป็นทารกที่มีการเจริญเติบโตและมีน้ำหนักแรกเกิดปกติจำนวน ๕๕ คน และพบว่าเป็นทารกโตช้าในครรภ์ ๒๗ คน โดยพบว่ามีความแตกต่างกันของทั้งสองกลุ่มในเรื่อง การตั้งครรภ์ครั้งแรก ภาวะน้ำคร่ำน้อย การคลอดปรกติ อายุครรภ์ที่คลอด น้ำหนักแรกคลอด และการเข้ารับการรักษาที่หน่วยทารกแรกเกิดวิกฤต และพบว่าอัตราส่วน pulsatility index ของคลื่นเสียงความถี่สูงดอพเลอร์หลอดเลือดแดงมิดเดิลเซเรบรัลกับคลื่นเสียงความถี่สูงดอพเลอร์หลอดเลือดแดงสายสะดือที่ผิดปรกติ < ๑.๐๘ พบในทารกกลุ่มที่มีน้ำหนักแรกเกิดน้อยกว่า ๑๐ เปอร์เซ็นไทล์ ๒๖.๓% และพบในทารกที่มีน้ำหนักแรกเกิดน้อยกว่า ๕ เปอร์เซ็นไทล์ ๓๗.๕% ซึ่งไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ (ค่าพี = ๐.๖๕๘)

สรุป: ความผิดปกติของอัตราส่วน pulsatility index ของคลื่นเสียงความถี่สูงดอพเลอร์หลอดเลือดแดงมิดเดิล-เซเรบรัลกับคลื่นเสียงความถี่สูงดอพเลอร์หลอดเลือดแดงสายสะดือ ไม่สามารถใช้ในการทำนายทารกโตช้าในครรภ์ระดับรุนแรงได้อย่างมีนัยสำคัญทางสถิติ

คำสำคัญ: ทารกโตช้าในครรภ์, คลื่นเสียงความถี่สูงดอพเลอร์หลอดเลือดสายสะดือ, คลื่นเสียงความถี่สูงดอพเลอร์หลอดเลือดแดงมิดเดิลเซเรบรัล