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Placental Pathology in Small-for-Gestational-Age Fetuses with Different Doppler Studies

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ABSTRACT

Objectives: To describe and compare placental pathologies and neonatal outcomes in pregnancies with small-for-gestational-age (SGA) fetuses with their umbilical artery (UA) and middle cerebral artery (MCA) Doppler studies.

Materials and Methods: A retrospective study was conducted in pregnant women delivered between gestational ages of 24 to 42 week at King Chulalongkorn Memorial Hospital. Only singletons without infection, chromosomal abnormalities or major structural abnormalities were included. Those with no Doppler study within 7 days prior to delivery were excluded. Sixty-nine subjects enrolled were classified into Group 1 (n=16): normal UA and MCA pulsatility index (PI), Group 2 (n=28): normal UA but abnormal MCA PI and Group 3 (n=25): abnormal UA PI/absent or reversed end diastolic flow (AREDF). Data were compared between each group.

Results: Fetuses in Group 3 were found to be delivered at earlier gestational age with lower birth weight, higher Cesarean delivery rate, higher proportion of fetuses with Apgar score less than 7, higher NICU admission, and higher neonatal resuscitation rate than those in Group 1 and Group 2. There was no significant difference in placental weight, gross umbilical cord abnormality, and overall placental underperfusion pathology. Placental infarct in Group 3 was found to be more prevalent than those in Group 1 and Group 2.

Conclusion: Placental infarct was the only abnormal placental pathology that was significantly found in SGA fetuses with abnormal UA PI/AREDF. These SGA fetuses carried a higher morbidity and mortality than those with normal UA Doppler study regardless of normality of MCA Doppler.

Keywords: placental pathology, small-for-gestational-age, Doppler studies, umbilical artery, middle cerebral artery

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ลักษณะทางพยาธิวิทยาของรกในทารกตัวเล็กกว่าอายุครรภ์ที่มีผลการตรวจคลื่นเสียงความถี่สูงดอปเปลอร์ของเส้นเลือดแดงรูปแบบต่าง ๆ

ธนภพ บำเพ็ญเกียรติกุล, อนัญญา ตรงพิสุทธิ์ศักดิ์, พฐู ตัณฑ์ไพโรจน์, บุญชัย เอื้อไพโรจน์กิจ

บทคัดย่อ

วัตถุประสงค์: *เพื่ออธิบายและเปรียบเทียบลักษณะทางพยาธิวิทยาของรก และผลการคลอดทารกแรกเกิดในทารกตัวเล็กกว่าอายุครรภ์ที่มีผลการตรวจคลื่นเสียงความถี่สูงดอปเปลอร์ของหลอดเลือดแดงสายสะดือ (umbilical artery) และหลอดเลือดแดงสมองหลอดกลาง (middle cerebral artery) รูปแบบต่างๆ*

วัสดุและวิธีการ: *การศึกษาย้อนหลังในสตรีตั้งครรภ์ 69 คนที่คลอดระหว่างอายุครรภ์ 24-42 สัปดาห์ ที่โรงพยาบาลจุฬาลงกรณ์ที่มีผลการตรวจคลื่นเสียงความถี่สูงดอปเปลอร์ในระยะเวลา 7 วันก่อนคลอด ไม่นับรวมการตั้งครรภ์แฝด, ครรภ์ติดเชื้อ และครรภ์ที่มีความผิดปกติของโครโมโซมหรือโครงสร้าง โดยแบ่งกลุ่มเป็น 3 กลุ่ม คือ กลุ่ม 1 (16 คน): UA และ MCA pulsatility index (PI) ปกติ, กลุ่ม 2 (28 คน): UA PI ปกติ แต่ MCA PI ผิดปกติ และกลุ่ม 3 (25 คน): UA PI ผิดปกติ /absent or reversed end diastolic flow (AREDF) แล้วเปรียบเทียบข้อมูลระหว่างกลุ่ม*

ผลการวิจัย: *พบว่าทารกในกลุ่ม 3 คลอดที่อายุครรภ์น้อยกว่า, มีน้ำหนักเมื่อแรกเกิดน้อยกว่า, อัตราการผ่าท้องทำคลอดสูงกว่า, สัดส่วนทารกที่มีคะแนนแอพการ์น้อยกว่า 7 สูงกว่า, อัตราการรับไว้ในหอผู้ป่วยทารกแรกเกิดวิกฤตและอัตราการกู้ชีพทารกแรกเกิดสูงกว่าทารกในกลุ่ม 1 และ 2 แต่ไม่มีความแตกต่างระหว่างกลุ่มในเรื่องน้ำหนักรก, ความผิดปกติของสายสะดือ และลักษณะทางพยาธิวิทยาของรกในภาพรวม พบรกขาดเลือด (Placental infarct) ในกลุ่ม 3 มากกว่าในกลุ่ม 1 และ 2*

สรุป: *ทารกตัวเล็กกว่าอายุครรภ์ที่มีผลการตรวจคลื่นเสียงความถี่สูงดอปเปลอร์ของหลอดเลือดแดงสายสะดือ (umbilical artery: UA) PI ผิดปกติ /absent or reversed end diastolic flow (AREDF) เจ็บป่วยและตายสูงกว่าทารกตัวเล็กกว่าอายุครรภ์ที่มีผลการตรวจคลื่นเสียงความถี่สูงดอปเปลอร์ของหลอดเลือดแดงสายสะดือปกติ โดยไม่คำนึงถึงผลการตรวจคลื่นเสียงความถี่สูงดอปเปลอร์ของหลอดเลือดแดงสมองหลอดกลาง (middle cerebral artery), รกขาดเลือด (Placental infarct) เป็นลักษณะทางพยาธิวิทยาของรกอย่างเดียวที่พบในกลุ่ม 3 มากกว่าในกลุ่ม 1 และ 2, ควรมีการศึกษาในอนาคตที่มีกลุ่มตัวอย่างมากขึ้นเพื่อศึกษาความสัมพันธ์ระหว่างกลุ่มย่อยต่างๆ*

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Introduction

Intrauterine fetal growth could be compromised by several factors such as prenatal infection, genetic or chromosomal abnormalities, poor maternal nutrition, maternal substance abuse, low maternal weight, and lack of oxygen supply to fetus. Among these factors, an important cause that may limit a fetus to reach its predetermined growth potential is placental abnormality. Previous study of small-for-gestational-age (SGA) fetuses has demonstrated that abnormal umbilical artery (UA) and middle cerebral artery (MCA) Doppler were strongly correlated with increased risk for cesarean section due to abnormal fetal heart rate pattern, fetal acidosis, and abnormal postnatal brain development[1]. Infants born with brain sparing phenomenon were found to have a higher incidence of behavioral problems than those without brain sparing effect[2]. SGA fetuses with normal UA impedance and abnormally low MCA pulsatility index (PI) also tended to have higher risk of neurodevelopmental deficit at 2 years of age[3].

SGA fetuses with abnormal UA Doppler have been known to have more morbidity and mortality compared to those with normal UA Doppler. Our previous study showed that SGA fetuses with normal UA and abnormal MCA PI, a late-onset IUGR, carried a significantly worse neonatal outcomes including lower birth weight, low Apgar scores at 1 and 5 minutes, increased rate of NICU admission, higher rate of respiratory distress syndrome, and needs for ventilators support; as compared to those with normal UA and MCA Doppler[4].

In correlation to placental morphology, cases with absent end-diastolic flow in UA were strongly associated with placental developmental abnormalities such as small placental size, extrachorial configuration, marginal cord insertion, and few cotyledons[5]. In microscopic evaluation, cases with absent end-diastolic flow in UA had increased risk of medial hyperplasia and luminal obliteration of stem villous vessels; while cases with reversed end-diastolic flow in UA had significantly more poorly vascularized terminal villi, villous stromal hemorrhage, hemorrhagic endovasculitis, and abnormally thin-walled fetal stem vessels[6]. Placental bed biopsy and placental pathologies are best reflected by abnormal uterine and umbilical artery velocity waveforms, respectively. The most severe clinical outcomes and perinatal mortality are present when both uterine and umbilical flow velocity are altered[7].

To the best of our knowledge, there was no placental pathology study regarding both UA and MCA Doppler studies available. The primary objective of our study is to describe neonatal outcomes and placental pathologic findings in pregnancies with SGA fetuses with different UA and MCA Doppler studies. The secondary objective is to compare neonatal outcomes and placental pathologic findings between each different UA and MCA Doppler pattern.

Materials and Methods

This was a retrospective study approved by Institutional Review Board with IRB No.238/57. We declared no conflict of interest in this study. All of the authors did not receive any funding or any offering from any pharmaceutical company nor any other related commercials.

We enrolled all singleton pregnant women diagnosed with International Coding of Disease, 10th revision (ICD 10) code O365: Maternal care for known or suspected poor fetal growth, who delivered between gestational age of 24 to 42 weeks at King Chulalongkorn Memorial Hospital from January 1, 2010 to December 31, 2014. Only those diagnosed as SGA based on our institute's nomogram were recruited. All participants had accurate gestational age confirmed by history and ultrasonogram prior to third trimester. Placental pathologies reported by Division of Gynecologic Pathology as well as complete Doppler studies reported by Maternal Fetal Medicine Division, had to be available for all enrolled cases. All placentas were evaluated by experienced pathologist in our institute. All Doppler studies in our institutes were performed using 3–5 MHz curvilinear probe by fellows and experienced staffs of the division. UA Doppler studies were performed at the free loop of umbilical cord. MCA Doppler studies were performed at fetal circle of Willis with transducer placed at the origin of MCA with the insonation angle of less

than 30 degree in relation to the arteries. We generally performed at least 3 cardiac cycles of uniform UA or MCA pulse waveform. PI values were obtained by automatic tracer. UA PIs were signified as abnormal if the PI values were above 95th percentile and the MCA PIs were signified as abnormal if the PI values were below the 5th percentile of nomogram based on Harrington's chart.

SGA associated with infection, chromosomal or structural abnormalities, subjects with multiple gestations, incomplete Doppler studies, no Doppler study within 7 days prior to delivery or no placental pathologic report were excluded.

Data included for statistical analysis were demographic data, neonatal outcomes, placental pathologic findings, and Doppler studies. Demographic data consisted of maternal age, gestational age at delivery and route of delivery. Neonatal outcomes included birth weight, Apgar score at 1 and 5 minutes, need for neonatal resuscitation, and NICU admission. Placental pathologies consisted of small placenta, gross umbilical cord abnormalities and underperfusion features. Small placenta was considered as placental weight less than 10th percentile of nomogram for each gestational age[8]. Gross umbilical cord abnormalities included hypercoiled cord (coiling index > 0.3 coil/cm), abnormal cord insertion (marginal, velamentous or membranous, and furcated), cord stricture, true knot, and single umbilical artery. Underperfusion pathologic features included infarct, accelerated villous maturation, increased syncytial knot, distal villous hypoplasia, and fetal thrombotic vasculopathy. Doppler studies recorded were MCA PI, UA PI, and presence of absent or reversed end diastolic flow (AREDF) of UA.

All placentas delivered in our institute were sent for pathologic evaluation if consents were obtained. The pathologic reports of all recruited cases were reviewed for gross pathology. All microscopic slides were repeatedly reviewed by experienced pathologist with expertise in placental pathology, blinded to UA and MCA Doppler study result, but not to the gestational age which is important in determining the maturity of the placenta.

The cases were subsequently classified into 3 groups based on the results of Doppler studies as follow: Group 1 with normal UA and MCA PI; Group 2 with normal UA PI but abnormal MCA PI; and Group 3 with abnormal UA PI. All clinical data, including neonatal outcomes and placental pathologic features were compared between groups.

The statistical analysis was performed using the Statistical Package for the Social Sciences software (SPSS, version 17.0; SPSS, Inc., Chicago, IL, USA). All continuous data including maternal age, gestational age at delivery and birth weight were reported as mean and standard deviation (SD) and were compared using student t-test. All other categorical data, including placental pathologic findings were reported as number and percentage and were compared using chi square test or Fisher exact test where appropriate. P-value of less than 0.05 was considered to be statistical significance.

Result

Among 69 enrolled subjects, 16 (23.2%) were classified into Group 1, 28 (40.6%) were Group 2, and 25 (36.2%) were Group 3. The maternal age was similar in each group (Table 1). More than half of cases with normal UA PI could carry the pregnancy until term; while cases with abnormal UA PI were significantly needed to be delivered at earlier gestational age, especially before 34 weeks of gestation. The most common route of delivery of all recruited cases was cesarean section with only few cases could be delivered vaginally. Group 3 also showed significantly higher rate of emergency cesarean section when compared to Group 1 and 2.

The neonatal outcomes were shown in Table 2. Birthweight was significantly lower in Group 3 compared to the other two groups. Group 3 also showed significantly increased rate of neonatal resuscitation, low APGAR scores of both 1 and 5 minutes, and NICU admission. In Group 2, the needs of neonatal resuscitation and low Apgar scores at 1 and 5 minutes seemed to be much higher than those of Group 1, but there was no statistical significance. When comparing between Group 2 and 3, nearly all outcomes, except the low Apgar scores at 5 minutes, were significantly higher in Group 3.

Table 1. Demographic and clinical characteristics of the participants.

	Overall (n = 69)	Group 1 (n = 16)	Group 2 (n = 28)	Group 3 (n = 25)	P*	P**	P†
Maternal age							
Mean±SD (year)‡	30.5 ± 6.3	31.8 ± 5.7	30.3 ± 6.1	29.8 ± 7.0	0.429	0.369	0.821
• Teenage pregnancy	4 (5.8%)	1 (6.3%)	1 (3.6%)	2 (8%)	0.682	0.834	0.486
• Advanced maternal age	18 (26.1%)	5 (31.3%)	7 (25%)	6 (24%)	0.654	0.609	0.933
Gestational age at delivery							
Mean±SD (week)‡	34.4 ± 3.9	35.3 ± 4.0	35.4 ± 3.7	32.2 ± 3.1	0.947	<0.01	<0.01
• Prior to 37 weeks	44 (63.8%)	7 (43.8%)	13 (46.4%)	24 (96%)	0.864	<0.01	<0.01
• Prior to 34 weeks	29 (42.0%)	4 (25%)	8 (28.6%)	17 (68%)	0.798	<0.01	<0.01
Route of delivery							
• Vaginal delivery	8 (11.6 %)	3 (18.8%)	5 (17.9%)	0	0.941	0.025	0.026
• Emergency cesarean section	53 (85.5 %)	10 (62.5%)	20 (71.4%)	23 (92%)	0.541	0.020	0.056
• Elective cesarean section	8 (14.5 %)	3 (18.8%)	3 (10.7%)	2 (8%)	0.455	0.305	0.736

Group 1: Normal UA and MCA PI
Group 2: Normal UA PI with abnormal MCA PI
Group 3: Abnormal UA PI
* Comparison of Group 1 and 2
** Comparison of Group 1 and 3
† Comparison of Group 2 and 3

Table 2. Comparison of neonatal outcomes among 3 different Doppler study groups.

	Overall (n = 69)	Group 1 (n = 16)	Group 2 (n = 28)	Group 3 (n = 25)	P*	P**	P†
Birthweight (mean±SD, g)	1431.4 ± 508.8	1687.2 ± 474.1	1590.1 ± 435.6	1090.0 ± 430.3	0.495	< 0.01	< 0.01
Neonatal resuscitation	17 (24.6%)	1 (6.3%)	5 (17.9%)	11 (44%)	0.280	0.010	0.038
Apgar at 1 min < 7	24 (34.8%)	3 (18.8%)	7 (25%)	14 (56%)	0.634	0.018	0.021
Apgar at 5 min < 7	10 (14.5%)	0	3 (10.7%)	7 (28%)	0.175	0.020	0.108
NICU admission	32 (46.4%)	5 (31.3%)	8 (28.6%)	19 (76%)	0.851	0.002	< 0.01

Group 1: Normal UA and MCA PI, Group 2: Normal UA PI with abnormal MCA PI, Group 3: Abnormal UA PI
* Comparison of Group 1 and 2. ** Comparison of Group 1 and 3, † Comparison of Group 2 and 3

Small placenta was found the most in Group 3, followed by Group 2 and Group 1 (Table 3). However, there was no statistical difference between each group. The hypercoiling and abnormal insertion of umbilical cord were quite similar in all three groups. Although the single umbilical artery was slightly more frequently seen in Group 3, but no statistical significance was shown. In microscopic evaluation, all maternal underperfusion pathologic features were highest present in Group 3, but without significant difference from the other two groups, except only infarct. Infarct was significantly increased in Group 3 when compared to Group 1, while it was not significantly different from Group 2. Group 2 tended to show more underperfusion pathologic features than Group 1, but also without statistically difference.

Table 3. Comparison of placental pathologic features among 3 different Doppler study groups.

	Overall (n = 69)	**Group 1 (n = 16)**	**Group 2 (n = 28)**	**Group 3 (n = 25)**	**P***	**P****	**P†**
Small placenta	44 (63.8%)	7 (43.8%)	19 (67.9%)	18 (72%)	0.118	0.070	0.743
Gross cord abnormalities	43 (62.3%)	9 (56.3%)	19 (67.9%)	15 (60%)	0.441	0.812	0.552
• Hypercoiled cord	35 (50.7%)	8 (50%)	16 (57.1%)	11 (44%)	0.647	0.707	0.339
• Marginal cord insertion	9 (13.0%)	2 (12.5%)	4 (14.3%)	3 (12%)	0.868	0.962	0.806
• Membranous cord insertion	2 (2.9%)	1 (6.3%)	1 (3.6%)	0	0.682	0.206	0.340
• Single umbilical artery	4 (5.8%)	0	1 (3.6%)	3 (12%)	0.444	0.150	0.246
Underperfusion features	46 (66.7%)	10 (62.5%)	18 (64.3%)	18 (72%)	0.906	0.524	0.548
• Infarct	31 (44.9%)	4 (25%)	11 (39.3%)	16 (64%)	0.336	0.015	0.072
• Accelerated villous maturation	13 (18.8%)	1 (6.3%)	5 (17.9%)	7 (28%)	0.280	0.086	0.378
• Increased syncytial knot	14 (20.3%)	2 (12.5%)	4 (14.3%)	8 (32%)	0.868	0.156	0.124
• Distal villous hypoplasia	7 (10.1%)	0	2 (7.1%)	5 (20%)	0.274	0.056	0.168
• Fetal thrombotic vasculopathy	12 (17.4%)	3 (18.8%)	6 (21.4%)	3 (12%)	0.832	0.551	0.361

Group 1: Normal UA and MCA PI, Group 2: Normal UA PI with abnormal MCA PI
Group 3: Abnormal UA PI
* Comparison of Group 1 and 2
** Comparison of Group 1 and 3
† Comparison of Group 2 and 3

Discussion

Our study confirmed the results of our previous study in that SGA fetuses with abnormal UA Doppler carry a higher morbidity including delivery at earlier GA, having lower birthweight, higher cesarean delivery rate, higher proportion of fetuses with Apgar score less than 7, higher NICU admission, and neonatal resuscitation rate than those with normal UA Doppler. The neonatal outcomes in Group 1 were more favorable as compared to those in Group 2 and Group 3. These finding were in agreement with previous study done by Seyam et al and Gerber et al[9, 10] and confirmed that an abnormal UA Doppler was a prognosticator of adverse pregnancy outcomes. However, in this study it was also observed that gestational age at delivery in group 3 was significantly lower than those in groups 1 and 2. As it is known that gestational age at delivery can affect neonatal outcomes, it should be cautious in interpreting these results and making a definite conclusion. In contrast to our previous study, although there was a tendency toward higher pregnancy morbidity in group 2 as compared to group 1, we could not show any significant difference in neonatal outcomes between fetuses in group 1 and 2. This finding raised the question of our recruited sample size which may be too small and might not be powered enough to distinguish the significant difference of these outcomes.

Based on placental pathologic evaluation, there were more proportion of small placenta, single umbilical artery, and nearly all maternal underperfusion features in Group 3 than Group 2 and 1. These features were also more prevalent in Group 2 than in Group 1. Although no significant difference could be demonstrated between each group, but this finding trend was still very interesting. Infarct was the only feature that showed statistically significant difference which was found between Group 1 and 3, but not between Group 2 and 3 and Group 1 and 2. These results supported the previous study of Salafia et al[6] that cases of AREDF in UA had significantly more poorly vascularized placenta.

Since this study was retrospective in nature, some limitation may exist. One main problem was a very limited sample size as there were strict criteria in sample recruitment. Many cases were excluded due to lacking of Doppler study within 7 days prior to delivery, incompleteness of the Doppler studies, and unavailability of submitted placenta for pathologic examination.

This is the first study to explore the relationship between abnormal UA with or without abnormal MCA Doppler and placental pathology. The results were still controversial due to limited number of sample size. Further prospective studies with larger number of subjects are needed to evaluate association between Doppler study and placental pathology more accurately.

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Potential conflicts of interest

The authors declare no conflict of interest.

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