Accelerated Villous Maturation of Placentas in Spontaneous Preterm Birth

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Objective: *To determine the rate of accelerated villous maturation of placentas among spontaneous preterm births and the associated factors.*

Material and Method: *Medical records and histology results of the placentas obtained from singleton spontaneous preterm births between 2011 and 2015 at Srinagarind Hospital, Khon Kaen University were reviewed. Preterm births complicated by multiple gestations and medically indicated preterm births were excluded. Accelerated villous maturation was diagnosed by identifying diffuse terminal villi and conspicuous syncytial knotting usually observed in term placentas.*

Results: *Of 97 spontaneous preterm births, 63 (64.9%) were idiopathic. The associated obstetric complications among the remaining 34 included chorioamnionitis, intrauterine growth restriction, preeclampsia, systemic lupus erythematosus, and maternal heart disease. Accelerated villous maturation was observed in 70 placentas (72.2%). Maternal age and gestational age were significantly associated with accelerated villous maturation. The rate of accelerated villous maturation among idiopathic spontaneous preterm births was comparable with those with other obstetric conditions.*

Conclusion: *Accelerated villous maturation of placentas among spontaneous preterm births was common. Two significant factors associated with accelerated villous maturation in spontaneous preterm birth were gestational age and maternal age.*

Keywords: *Accelerated villous maturation, Placental insufficiency, Placental pathology, Preterm birth, Risk factors*

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Preterm birth (birth before 37 weeks' gestation) is an important global health problem[1-3]. Worldwide, approximately 15 million babies are born preterm annually. Preterm birth is a major cause of neonatal death accounting for more than 15% of deaths in young children[4]. Importantly, the infant survivors of preterm births often experience long-term adverse consequences affecting their physical development and functional performances[5,6]. Types of preterm birth include 1) preterm birth necessitated by maternal or fetal conditions, or the so-called "indicated preterm birth", 2) spontaneous preterm labor with intact membranes, and 3) preterm premature rupture of the membranes (PPROM)[1]. Preterm births following spontaneous labor and PPROM are together designated spontaneous preterm births[1]. Despite this high global burden, little is known about the certain etiology and how to prevent spontaneous preterm births[3].

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The placenta has been regarded as a "diary of pregnancy". Therefore, pathological examination of the placenta is an important tool for determining the potential pathomechanisms of pregnancy-related complications and may provide information necessary for management implications of the infant or the mother in the next pregnancy[7-9]. Abnormal placental structures and functions are observed in various obstetric conditions including low birth weight, preterm birth, stillbirth, and intrauterine growth restriction (IUGR)[10-15].

Accelerated villous maturation of placentas is one of maternal stromal-vascular lesions developed as a result of late maternal vascular malperfusion[7]. Accelerated villous maturation is diagnosed by identifying a diffuse pattern of term-appearing villi with increased syncytial knots, intervillous fibrin, and villous paucity due to decreased villous branching in the preterm placenta[7]. A previous study suggested that placental insufficiency secondary to maternal vascular malperfusion may play a role in stimulating spontaneous preterm birth[12]. Additional information, however, is required to make this evidence much more reliable.

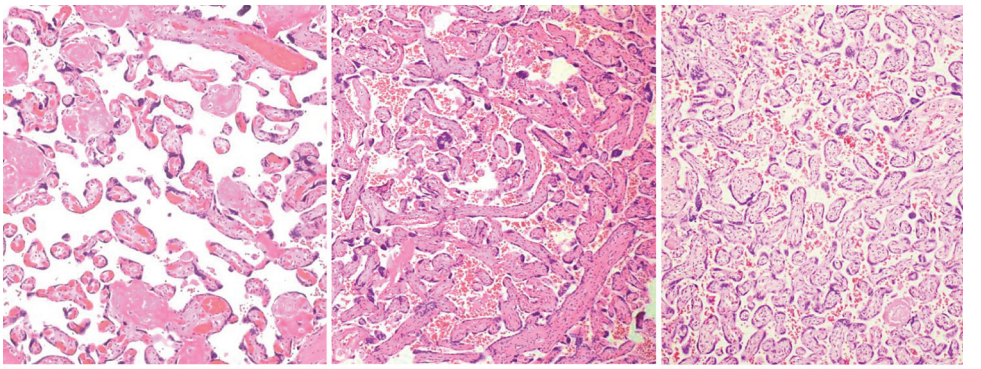

Fig. 1 Microscopic features of placental insufficiency (H&E), (A) PVH in IUGR at GA 32 weeks (x10), (B) PVH in maternal SLE with mild PIH at GA 33 weeks (x10), and (C) PVH in idiopathic spontaneous preterm birth at GA 33 weeks (x10).

Accordingly, the present study was conducted to evaluate the rate of accelerated villous maturation, one of the placental histological markers indicating maternal vascular malperfusion, and the potentially associated factors among spontaneous preterm placentas.

Material and Method

After approval from the Khon Kaen University Ethics Committee for Human Research, medical records and pathological results of fresh placentas from live singleton spontaneous preterm births occurred between January 2011 and December 2015 at Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand were reviewed. It is institutional policy to routinely examine fresh placenta of all spontaneous preterm births for potential pathology. Preterm births complicated by multiple gestations and medically indicated preterm births were excluded. Abstracted data included maternal characteristics, gestational age, related-obstetric complications, and detailed placental histologic findings. The estimation of gestational age was based on a combination of the date of last menstrual period and first trimester ultrasound findings when available.

Briefly, placental weight, diameters, and type of umbilical cord insertion were recorded during gross specimen examinations. For microscopic evaluation, at least six sections were obtained from each placenta including one section of the umbilical cord, one section of placental membrane, four sections of full thickness of peripheral, and central placental parenchyma. All gross lesions that were suspicious were additionally sampled. The slides were then stained by hematoxylin and eosin. All slides were reviewed to reaffirm the placental histologic findings by an experienced perinatal pathologist (Kleebkaow P). Identifying diffused terminal villi and conspicuous syncytial knotting that were usually observed in term placenta indicated accelerated villous maturation (Fig. 1).

With an assuming 80% rate of accelerated villous maturation of the preterm placenta obtained from previous study[12], 10% margin of error, and 10% of expected rate of missing or incomplete data, the minimal sample size required for the present study was 68 preterm placentas[16].

Statistical analysis was carried out with SPSS software (IBM, Armonk, NY, USA). Data were summarized as mean ± SD or number (percentage). Univariate analyses using the Chi-square test (χ^2) were carried out to identify variables potentially associated with accelerated villous maturation, including maternal age, gestational age, and associated obstetrics conditions. A *p*-value that is smaller than 0.05 was considered statistically significant.

Results

During the study period, 97 placentas obtained from singleton spontaneous preterm births were reviewed. The mean maternal age was 27.4 years (range 14 to 41 years) and mean gestational age was 31.8 weeks (range 24 to 36 weeks). Baseline characteristics of the study samples were summarized in Table 1.

Of 97 spontaneous preterm births, 63 (64.9%) were idiopathic. The associated obstetric complications among the remaining 34 spontaneous preterm births included chorioamnionitis, IUGR, preeclampsia, systemic lupus erythematosus, and maternal heart disease. Forty-nine preterm births (50.5%) were PPROM.

Of 97 preterm placentas in the present study, 70 were reported to have accelerated villous maturation, accounting for the rate of 72.2% (95% confidence interval [CI], 62.1% to 80.8%). Placentas obtained from idiopathic spontaneous preterm births had a slightly higher rate of accelerated villous maturation than those noted in spontaneous preterm births complicated by obstetric complications (74.6%, 95% CI 62.1 to 84.7 versus 67.6%, 95% CI 49.5 to 82.6). However, this difference was not statistically significant ($p = 0.47$) (Table 2).

Maternal age and gestational age were significantly associated with accelerated villous maturation (Table 2). The rate of accelerated villous maturation was significantly decreased with increasing gestational age. About 92.3% of preterm placentas of gestational age at less than 28 weeks contained accelerated villous maturation, about 85.1% at 28 to 33 weeks, and 48.7% at 34 weeks or more. Accelerated villous maturations were significantly more common among placentas obtained from younger than 35 years woman than those from older women (86.11% versus 32.0%, $p<0.001$).

Table 1. Baseline characteristics of the study samples

Characteristics	All cases (n = 97)	Associated obstetric complications	
		Idiopathic (n = 63)	Present* (n = 34)
Maternal age (years)	27.4±6.7	27.4±7.0	27.4±6.4
Gestational age (weeks)	31.8±3.4	31.7±3.5	32.1±3.2
Maternal age (years)			
≤19	16 (16.5)	12 (19.0)	4 (11.8)
20 to 34	65 (67.0)	39 (61.9)	26 (76.4)
≥35	16 (16.5)	12 (19.0)	4 (11.8)
Gestational age (weeks)			
<28	13 (13.4)	10 (15.9)	3 (8.8)
28 to 33	47 (48.5)	31 (49.2)	16 (47.1)
≥34	37 (38.1)	22 (34.9)	15 (44.1)
Accelerated villous maturation	70 (72.2)	47 (74.6)	23 (67.6)

* Including chorioamnionitis, intrauterine growth restriction, preeclampsia, systemic lupus erythematosus, and maternal heart disease

Data are present as number (percentage) or mean ± standard deviation (SD)

Table 2. Factors predicting accelerated villous maturation among 97 preterm placentas

Variables	Number of placentas with accelerated villous maturation	*p*-value
Associated obstetric complications		0.466
Absent (n = 63)	47 (74.60)	
Present* (n = 34)	23 (67.65)	
Gestational age (weeks)		<0.001
<28 (n = 13)	12 (92.31)	
28 to 33 (n = 47)	40 (85.11)	
≥34 (n = 37)	18 (48.65)	
Maternal age (years)		<0.001
<35 (n = 72)	62 (86.11)	
≥35 (n = 25)	8 (32.00)	

* Including chorioamnionitis, intrauterine growth restriction, preeclampsia, systemic lupus erythematosus, and maternal heart disease

Data are present as number (percentage)

Discussion

In the present study, accelerated villous maturation of placentas was common among spontaneous preterm births with an overall rate of 72.2%. Two factors were noted to have a significant association with accelerated villous maturation including gestational age and maternal age. There was no statistically significant difference of the rate of accelerated villous maturation in idiopathic spontaneous preterm births compared with spontaneous preterm births complicated by other obstetric conditions.

The rate of accelerated villous maturation among idiopathic spontaneous preterm placentas (74.6%) in the present study was high comparable to the rate noted among placentas obtained from spontaneous preterm births with obstetric complications (67.6%). This finding was in line with the study of Morgan et al[12] who also noted that the rate of accelerated villous maturation among idiopathic spontaneous preterm placentas was considerably higher and did not significantly differ from that observed in placentas obtained from spontaneous preterm births complicated by hypertensive disorders in pregnancy, IUGR, maternal diabetes, and placental abruption (84% versus 89%). A high rate of accelerated villous maturation across the different groups of spontaneous preterm births thus, indicates maternal vascular malperfusion as a dominating etiopathogenetic mechanism of spontaneous preterm births whether they were idiopathic or apparently related to other obstetric conditions.

There have been limited available data addressing the clinical variables associated with the risk of maternal vascular malperfusion among spontaneous preterm births[7,8,12]. In the present study, two factors reported to be associated with increased risk of having accelerated villous maturation among spontaneous preterm placentas were gestational age and maternal age. The rate of accelerated villous maturation was significantly decreased either with increasing

gestational age or maternal age (Table 2). Further studies are required to confirm these promising findings and identify potential underlying biological mechanisms.

The strength of the present study was that it examined all placentas delivered from spontaneous preterm births during the study period, thus limiting the potential of selection bias. Additionally, all placental histology results were reviewed and signed out by one perinatal pathologist who was experienced and consistently used the same diagnostic criteria for accelerated villous maturation. Lastly, the present study has highlighted the factors that are potentially associated with accelerated villous maturation among spontaneous preterm placentas, which has rarely been previously reported.

The present study had the inherent limitations associated with a retrospective analysis. Some important information including maternal health status, cigarette smoking, body mass index, and concurrently used drugs, which may impact maternal vascular perfusion could not be assessed. In addition, a relatively small sample size has precluded multivariate analyses to find independent predictors. As a result, factors associated with accelerated villous maturation in the present study have been reported based on the basis of univariate analyses.

In conclusion, the current analysis confirmed the high frequency of accelerated villous maturation among spontaneous preterm placentas. Gestational age and maternal age were significant factors associated with accelerated villous maturation of preterm placentas.

What is already known on this topic?

Accelerated villous maturation of placenta has been known as histological markers indicating maternal vascular malperfusion. However, information regarding the rate and associated factor predicting accelerated villous maturation among spontaneous preterm placentas are limited.

What this study adds?

This study confirms the high frequency of accelerated villous maturation among spontaneous preterm placentas. Gestational age and maternal age were significant factors predicting accelerated villous maturation of preterm placentas.

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Potential conflicts of interest

None.

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ภาวะรกมีการเติบโตเต็มที่อย่างรวดเร็วในการคลอดก่อนกำหนดชนิดเกิดขึ้นเอง

เลอลักษณ์ ศักดาปรีชา, สุพินดา คูณมี, ทิพวรรณ เตรียมวิทยานนท์, ชำนาญ เกียรติพีรกุล, พิไลวรรณ กลีบแก้ว

วัตถุประสงค์: *เพื่อศึกษาถึงอัตราการเกิดภาวะรกมีการเติบโตเต็มที่อย่างรวดเร็วในการคลอดก่อนกำหนดชนิดเกิดขึ้นเองและปัจจัยที่มีความสัมพันธ์*

วัสดุและวิธีการ: *ทบทวนเวชระเบียนและผลพยาธิวิทยาของรกภายหลังการคลอดก่อนกำหนดชนิดเกิดขึ้นเองระหว่าง พ.ศ. 2554 ถึง พ.ศ. 2558 ที่โรงพยาบาลศรีนครินทร์ คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น การศึกษานี้ไม่รวมถึงการคลอดก่อนกำหนดที่เกิดจากการตั้งครรภ์ทารกหลายคนหรือที่เกี่ยวข้องกับข้อบ่งชี้ทางการแพทย์ ภาวะรกมีการเติบโตเต็มที่อย่างรวดเร็วจะวินิจฉัยจากการพบ terminal villi แบบกระจาย ร่วมกับ syncytial knotting ซึ่งจะพบในรกของครรภ์ครบกำหนด*

ผลการศึกษา: *จากการคลอดก่อนกำหนดชนิดเกิดขึ้นเองทั้งหมด 79 ราย ไม่พบสาเหตุที่เกี่ยวข้องจำนวน 63 ราย (ร้อยละ 64.9) ส่วนภาวะทางสูติศาสตร์ที่เกี่ยวข้องกับการคลอดก่อนกำหนดที่เหลืออีก 34 ราย ได้แก่ ติดเชื้อที่ถุงการตั้งครรภ์ ทารกเจริญเติบโตช้าในครรภ์ พรีอีแคลมเซีย (preeclampsia) ซิสเท็มมิค ลูปัส อีริทธีมาโทซัส (systemic lupus erythematosus) และโรคหัวใจในสตรีตั้งครรภ์ อัตราการเกิดภาวะรกมีการเติบโตเต็มที่อย่างรวดเร็วพบใน 70 ราย (ร้อยละ 72.2) อายุของสตรีตั้งครรภ์และอายุครรภ์มีความสัมพันธ์กับการเกิดภาวะรกมีการเติบโตเต็มที่อย่างรวดเร็วอย่างมีนัยสำคัญ อัตราการเกิดภาวะรกมีการเติบโตเต็มที่อย่างรวดเร็วในการคลอดก่อนกำหนดที่ไม่พบสาเหตุไม่แตกต่างจากการคลอดก่อนกำหนดที่สัมพันธ์กับภาวะทางสูติศาสตร์*

สรุป: *ภาวะรกมีการเติบโตเต็มที่อย่างรวดเร็วในการคลอดก่อนกำหนดชนิดเกิดขึ้นเองพบได้บ่อย ปัจจัยที่สัมพันธ์กับการเกิดภาวะดังกล่าวในการคลอดก่อนกำหนดชนิดเกิดขึ้นเองอย่างมีนัยสำคัญ ได้แก่ อายุของสตรีตั้งครรภ์และอายุครรภ์*