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Birth Weight/ Placental Weight Ratios: Does the association differ between early- and late-onset preeclampsia?

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ABSTRACT

Objectives: Early- and late-onset preeclampsia (PE) may differ in pathophysiology and this can be reflcted in differences in birth weight/placental weight (BW/Pl) ratios. Therefore, we compared BW/Pl ratios of births with early- and those with late-onset PE.

Materials and Methods: The retrospective descriptive study included all hospital-based singleton births of 24-43 weeks' gestation between January 2007 and December 2016. A total of 51,940 pregnant women were divided into three groups: early-onset PE, late-onset PE, and pregnant women without PE. Birth weight/placental weight were compared among 3 groups.

Results: The mean (± standard deviation; SD) BW/Pl ratios were signifiantly different in early-onset PE and late-onset PE compared with the control group (3.91 ± 0.93 in early-onset PE, 4.85 ± 0.91 in late-onset PE and 5.17 ± 0.90 in the control group, $p < 0.001$). The factors signifiantly associated with BW/Pl ratios were race, infant gender, diabetes mellitus (DM), gestational age at delivery, early-onset PE, late-onset PE, small for gestational age (SGA) and large for gestational age (LGA). After adjustment for DM, gestational age at delivery, late-onset PE, SGA and LGA, the BW/Pl ratio was still associated signifiantly more with early-onset PE than with late-onset PE.

Conclusion: The BW/Pl ratios of preeclamptic women differed between early- and late-onset PE, and that early-onset PE may be commonly associated with placental efficiency. This suggests that preeclampsia consists of several different processes manifesting as a single disease.

Keywords: preeclampsia, placenta, birth weight, early onset, late onset.

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อัตราส่วนระหว่างน้ำหนักทารกแรกเกิดต่อน้ำหนักรก มีความแตกต่างกันหรือไม่ระหว่างหญิงตั้งครรภ์ที่มีภาวะครรภ์เป็นพิษชนิดเกิดขึ้นเร็ว และเกิดขึ้นช้า

พจนีย์ ผดุงเกียรติวัฒนา, ทรงพล พุทธศิริ

บทคัดย่อ

วัตถุประสงค์: *ภาวะครรภ์เป็นพิษชนิดเกิดขึ้นเร็วกับเกิดขึ้นช้า น่าจะมีพยาธิสรีรวิทยาการเกิดที่แตกต่างกันซึ่งจะส่งผลให้เกิดความแตกต่างระหว่างอัตราส่วนระหว่างน้ำหนักทารกแรกเกิดต่อน้ำหนักรก การศึกษานี้จึงมีวัตถุประสงค์เพื่อศึกษาความแตกต่างระหว่างอัตราส่วนดังกล่าวในครรภ์เป็นพิษชนิดเกิดขึ้นเร็วและเกิดขึ้นช้า*

วัสดุและวิธีการ: *เป็นการศึกษาทบทวนข้อมูลภายในโรงพยาบาล ในหญิงตั้งครรภ์เดี่ยวที่คลอดตั้งแต่อายุครรภ์ 24-43 สัปดาห์ ระหว่างเดือน มกราคม พ.ศ.2550 ถึงเดือนธันวาคม พ.ศ. 2559 คิดเป็นจำนวนหญิงตั้งครรภ์ 51,940 ราย แบ่งออกเป็น 3 กลุ่มศึกษา ได้แก่ หญิงตั้งครรภ์ที่มีภาวะครรภ์เป็นพิษชนิดเกิดขึ้นเร็ว หญิงตั้งครรภ์ที่มีภาวะครรภ์เป็นพิษชนิดเกิดขึ้นช้า และหญิงตั้งครรภ์ที่ไม่มีภาวะครรภ์เป็นพิษ ทำการเปรียบเทียบอัตราส่วนระหว่างน้ำหนักทารกแรกเกิดต่อน้ำหนักรก*

ผลการศึกษา: *ค่าเฉลี่ย (± ค่าเบี่ยงเบนมาตรฐาน) ของอัตราส่วนระหว่างน้ำหนักทารกแรกเกิดต่อน้ำหนักรกมีความแตกต่างกันอย่างมีนัยสำคัญระหว่างหญิงตั้งครรภ์ที่มีภาวะครรภ์เป็นพิษชนิดเกิดขึ้นเร็วและชนิดเกิดขึ้นช้า เมื่อเทียบกับกลุ่มที่ไม่มีภาวะครรภ์เป็นพิษ (3.91±0.93 ในกลุ่มหญิงตั้งครรภ์ที่มีภาวะครรภ์เป็นพิษชนิดเกิดขึ้นเร็ว, 4.85±0.91 ในกลุ่มหญิงตั้งครรภ์ที่มีภาวะครรภ์เป็นพิษชนิดเกิดขึ้นช้าและ 5.17±0.90 ในกลุ่มที่ไม่มีภาวะครรภ์เป็นพิษ, p<0.001) ตัวแปรที่มีผลต่ออัตราส่วนระหว่างน้ำหนักทารกแรกเกิดต่อน้ำหนักรกได้แก่ โรคเบาหวาน อายุครรภ์ ภาวะครรภ์เป็นพิษชนิดเกิดขึ้นเร็วและเกิดขึ้นช้า ทารกขนาดเล็กและใหญ่กว่าอายุครรภ์ ภายหลังควบคุมตัวแปร ได้แก่ โรคเบาหวาน อายุครรภ์ ภาวะครรภ์เป็นพิษชนิดเกิดขึ้นเร็วและเกิดขึ้นช้าและทารกขนาดเล็กและใหญ่กว่าอายุครรภ์ อัตราส่วนระหว่างน้ำหนักทารกแรกเกิดต่อน้ำหนักรกยังคงสัมพันธ์กับภาวะครรภ์เป็นพิษชนิดเกิดขึ้นเร็วมากกว่าภาวะครรภ์เป็นพิษชนิดเกิดขึ้นช้า*

สรุป: *อัตราส่วนระหว่างน้ำหนักทารกแรกเกิดต่อน้ำหนักรกในหญิงตั้งครรภ์ที่มีภาวะครรภ์เป็นพิษชนิดเกิดขึ้นเร็วและเกิดขึ้นช้า มีความแตกต่างกันอย่างมีนัยสำคัญ และพบว่ามีผลมากกว่าในกลุ่มที่มีภาวะครรภ์เป็นพิษชนิดเกิดขึ้นเร็ว อาจเนื่องมาจากภาวะครรภ์เป็นพิษชนิดเกิดขึ้นเร็วมีผลจากรกเสื่อมมากกว่า และภาวะครรภ์เป็นพิษน่าจะเกิดได้จากหลายกระบวนการ*

คำสำคัญ: *ครรภ์เป็นพิษ, รก, น้ำหนักทารกแรกเกิด, เกิดขึ้นเร็ว, เกิดขึ้นช้า*

Introduction

Birth weight/placental weight ratios (BW/Pl ratio), calculated as the grams of fetal birth weight per gram of placenta weight, reflect placental efficiency or placental function[1,2]. The ability of the placenta to maintain nutrient delivery to the fetus has an influence on fetal birth weight, and it is well established that there is a positive correlation between placental weight and birth weight[3-5]. The BW/Pl ratio is often reduced, which may indicate a placenta that fails to adapt its nutrient transfer capacity to compensate for its small size[6].

Recent data have supported classifying preeclampsia (PE) into early-onset PE, which tends to develop before 34 weeks of gestation, and late-onset preeclampsia, which develops at or after 34 weeks of gestation[7,8]. Early- and late-onset PE have been found to be associated with different pathophysiological-specific features. Early-onset PE is commonly associated with placental dysfunction, reduction in placental volume, perinatal death and adverse maternal and neonatal outcomes[9,10]. Conversely, late-onset PE is more often associated with normal placenta, normal fetal growth and more favorable outcomes[11,12].

In this study, we hypothesized that early- and late-onset PE had different pathophysiology. Thus, we sought to compare BW/Pl ratios of early- and late-onset preeclampsia in order to explore the existence of these differences.

Materials and Methods

The present study was conducted at Rajavithi Hospital, a tertiary care teaching public hospital affiliated to Rangsit University in Bangkok, Thailand, with the ethical approval of the local institutional review board. The study included all hospital-based singleton births of 24-43 weeks' gestation between January 2007 and December 2016 (n=54,618). Deliveries after congenital anomalies (n=227), stillbirth (n=372), multiple gestations (n=994) and deliveries with missing gestational age, placental weight or birth weight (n=953) were excluded.

Descriptive analyses were performed on all study variables. Implausible values and potential errors were excluded, including birth weights above or below the mean by three standard deviations (SD), placental weights that were <100 g or >1,000 g and unknown or ambiguous genders (n= 132). The final sample was 51,940 singleton deliveries.

Preeclampsia (PE) was defined as a resting blood pressure ≥ 140/90 mmHg and proteinuria of > 300 mg/L or a 2^+ urine dipstick after 20 weeks of gestation in a previously normotensive woman[13]. Small for gestational age (SGA) was defined as infants with birth weight below the 10^{th} centile for gestational age, and large for gestational age (LGA) was defined as infants with birth weight above the 90th centile for gestational age based on the King Chulalongkorn Memorial Hospital's nomogram of birth weight for gestational age at delivery[14].

Untrimmed placenta weight (including the membranes and umbilical cord) and birth weight of the infant were weighed in grams immediately after delivery. The birth weight/placental weight ratio (BW/Pl ratio) was then calculated.

The cases were divided into three groups: early-onset PE (PE occurring at less than 34 weeks of gestation); late-onset PE (PE occurring at 34 or more weeks of gestation); and a control group (pregnancies without PE).

The data were presented as mean ± SD. Chi-square test was used to compare categorical proportion (nulliparous, race, infant gender, pre-gestational diabetes mellitus and gestational diabetes mellitus, SGA, and LGA). Multiple comparisons of maternal age, gestational age at delivery, placental weight, birth weight, and BW/Pl ratio in between groups were performed by one-way analysis of variance (ANOVA) followed by post hoc test adjustment with Bonferroni correction. Pearson's correlation, simple and multiple linear regression were analyzed for BW/Pl ratio. Data analysis was performed using the SPSS ver.16.0 (SPSS Inc., Chicago, IL, USA). A p value < 0.05 with a 95% confidence interval (CI) was considered statistically significant.

Results

From January 2007 through December 2016, a

total of 51,940 pregnant women who had singleton hospital deliveries at 24 weeks of gestation or later and met the inclusion criteria were enrolled in the study. Those diagnosed with PE accounted for 2.7% of participants, of which 339 (0.65%) had early-onset PE, and 1,111 (2.14%) had late-onset PE. The demographic data are outlined in Table 1. The mean maternal age, race, pre-gestational and gestational diabetes mellitus (DM) and gestational age at delivery were significantly different in early-onset PE and late-onset PE compared with the control group, while the proportion of infant gender was significantly different between early-onset PE and the control group. Gestational DM was significantly different in the late-onset PE compared to the control group.

Table 1. Comparison of baseline characteristics data in different groups.

Variables	Early onset-PE (n = 339)	Late onset-PE (n = 1111)	Control (n = 50,490)	p value
Maternal age (yr), mean ± SD	29.64 ± 6.60[a)]	29.9 ± 7.04[a)]	27.5 ± 6.19	< 0.001[A]
Nulliparous (%)	197 (58.1%)	592 (53.3%)	26205 (51.9%)	0.05[C]
Thai race (%)	295 (87%)[a)]	923 (83.1%)[a)]	38632 (76.5%)	< 0.001[C]
Infant male gender (%)	150 (44.2%)[a)]	543(48.9%)	26133 (51.8%)	0.004[C]
Pre-gestational DM (%)	10 (2.9%)	29 (2.6%)[a)]	132 (3%)	< 0.001[C]
Gestational DM (%)	19 (5.6%)	134 (12.1%)[a)]	2421 (4.8%)	< 0.001[C]
Gestational age at delivery (weeks), mean ± SD	30.56 ± 2.21[a)]	37.15 ± 1.88	37.15 ± 1.85	< 0.001[A]

DM, diabetes mellitus

[a)] Statistical significance ($p < 0.05$)

[A] p value was tested by ANOVA followed by post hoc test adjustment with Bonferroni correction.

[C] p value was tested by chi-square.

A comparison of mean birth weight, mean placental weight, mean BW/PI ratio, SGA, and LGA is presented in Table 2. The mean (± SD) birth weights were 1,412 ± 479 grams in early-onset PE, 2,733 ± 612 grams in late-onset PE, and 3,036 ± 452 grams in the control group ($p < 0.001$). Mean (± SD) placental weights were 372 ± 127 grams in early-onset PE, 578 ± 145 in late-onset PE, and 601 ± 123 in the control group ($p < 0.001$). Mean (± SD) BW/PI ratios were 3.91 ± 0.93 grams in early-onset PE, 4.85 ± 0.91 grams in late-onset PE, and 5.17 ± 0.90 grams in the control group ($p < 0.001$), and these values were significantly different in early-onset PE and late-onset PE compared with the control group. SGA was significantly higher in early-onset PE (41.3%) and late-onset PE (10.6%) than in the control group (1.3%) ($p < 0.001$). LGA was significantly lower in early-onset PE (9.7%) than in the control group (15.7%) ($p = 0.009$).

Table 3 lists details of factors such as maternal age, race, infant gender, DM, gestational age at delivery, early-onset PE, late-onset PE, SGA and LGA that might be expected to have an influence on the BW/PI ratio. Univariate analysis indicated the factors influencing the BW/PI ratios, and showed that race, infant gender, DM, gestational age at delivery, late onset-PE, early onset-PE, LGA, and SGA were significantly associated with the BW/PI ratios. After multiple linear regression analysis, the significant factors associated with BW/PI ratio were DM, gestational age at delivery, late onset-PE, early onset-PE, LGA, and SGA (Table 4).

In all pregnant women in our study, birth

weight and placenta weight were correlated (r = 0.62, p < 0.001).

Table 2. Comparison of BW, PI, SGA, LGA and BW/PI in different groups.

Variables	Early onset-PE (n = 339)	Late onset-PE (n = 1111)	Control (n = 50,490)	p value
Mean BW ± SD (g)	1,412.4 ± 479.0[a)]	2,733.0 ± 611.7[a)]	3,036.0 ± 452.0	< 0.001[A]
Mean PI ± SD (g)	372.1 ± 127.3[a)]	577.6 ± 145.1[a)]	601.2 ± 122.7	< 0.001[A]
Mean BW/PI ± SD	3.9 ± 0.9[a)]	4.9 ± 0.9[a)]	5.2 ± 0.9	< 0.001[A]
SGA (%)	140 (41.3)[a)]	118 (10.6)[a)]	662 (1.3)	< 0.001[C]
LGA (%)	33 (9.7)[a)]	181 (16.3)	7,952 (15.7)	0.009[C]

BW, birth weight; PI, placenta weight; SGA, small for gestational age; LGA, large for gestational age.
[a)] Statistical significance (p < 0.05), [A] p value was tested by ANOVA followed by post hoc test adjustment with Bonferroni correction, [C] p value was tested by chi-square.

Table 3. Univariate analyses (95% confidence interval; CI) for BW/PI ratio.

Factors	BW/PI ratio				
	Mean	SD	B	95% CI Of B	p value
Maternal age (yr)	5.16	0.90	0.00	- 0.01, 0.01	0.871
Race					
Thai	5.13	0.91	Ref		
Others	5.25	0.87	0.12	0.10, 0.14	< 0.001
Infant gender					
Male	5.20	0.91	Ref		
Female	5.11	0.90	- 0.08	- 0.09, - 0.07	< 0.001
DM					
None	5.16	0.91	Ref		
DM	5.04	0.86	- 0.13	- 0.16, - 0.10	< 0.001
Gestational age at delivery (weeks)	5.16	0.90	0.10	0.10, 0.11	< 0.001
Preeclampsia					
None	5.17	0.90	Ref		
Late onset-PE	4.85	0.91	- 0.33	- 0.39, - 0.26	< 0.001
Early onset-PE	3.91	0.93	- 1.26	- 1.38, - 1.15	< 0.001
Fetal growth					
AGA	5.17	0.89	Ref		
LGA	5.13	0.93	- 0.04	- 0.06, - 0.01	0.002
SGA	4.72	1.18	- 0.45	- 0.52, - 0.38	< 0.001

B, beta coefficients; CI, confident interval; DM, diabetic mellitus; PE, preeclampsia; AGA, appropriate for gestational age; LGA, large for gestational age; SGA, small for gestational age

Table 4. Independent factors associated with BW/PI ratios by multiple linear regression.

Factors	BW/PI ratio				
	Mean	SD	B	95% CI Of B	p value
DM					
None	5.16	0.91	Ref		
DM	5.04	0.86	- 0.11	- 0.14, - 0.07	< 0.001
Gestational age at delivery (weeks)	5.16	0.90	0.10	0.09, 0.10	< 0.001
Preeclampsia					
None	5.17	0.90	Ref		
Late onset-PE	4.85	0.91	- 0.20	- 0.26, - 0.15	< 0.001
Early onset-PE	3.91	0.93	- 0.43	- 0.54, - 0.33	< 0.001
Fetal growth					
AGA	5.17	0.89	Ref		
LGA	5.13	0.93	0.07	0.05, 0.09	< 0.001
SGA	4.72	1.18	- 0.20	- 0.26, - 0.14	< 0.001

B, beta coefficients; CI, confident interval; DM, diabetic mellitus; PE, preeclampsia; AGA, appropriate for gestational age; LGA, large for gestational age; SGA, small for gestational age

Discussion

In this retrospective study conducted in Thailand between 2007 and 2016, the mean BW/PI ratio was significantly lower in pregnancies with early-onset PE than in those with late-onset PE and those in the control group (3.91 ± 0.93 vs 4.85 ± 0.91 vs 5.17 ± 0.90, respectively). Similarly, Kim et al[15] reported that the mean BW/PI ratio was significantly lower in the PE group than in the control group (5.1 vs 6.0 respectively). In a previous study[16-20], variables that may affect BW/PI ration were found to include infant gender, race, DM, gestational age at delivery, SGA, and LGA. Our study found that the factors significantly associated with BW/PI were DM, gestational age at delivery, early-onset PE, late-onset PE, SGA, and LGA. After adjustment for DM, gestational age, late-onset PE, SGA, and LGA, the BW/PI ratio was still associated with early-onset PE significantly more than with late-onset PE.

The placenta is important in providing a healthy environment for the fetus and plays a central role in the pathophysiology of PE. The placenta regulates its nutrient transfer efficiency by morphological and functional adaptations which result in optimal fetal growth[2, 21, 22]. In our study, mean birth weight and mean placental weight were significantly lower in the PE group, and when birth weight was divided by placental weight, it was still lower in the PE group. It has been postulated that PE is strongly associated with small placenta and that it has an influence on placental function results in a fetus that is small with respect to its genetic potential.

PE has collectively been termed ischemic placental disease because the two types are frequently characterized by utero-placental underperfusion, chronic hypoxia and placental ischemia, which are results of abnormal spiral artery remodeling, failed trophoblast invasion and impaired transformation of decidual spiral arteries leading to abnormal placentation and influencing placental efficiency[23-27]. It has been hypothesized that placental ischemia may reduce nutrient supply so that the fetal growth may be affected. A reduction in the BW/PI ratio may be indicative of

placental dysfunction. In keeping with the results of several previous reports[15, 28,29], the BW/PI ratio in this report was found to be reduced in births with PE. Another important finding in the current study was that the BW/PI ratio was still significantly lower in early-onset PE than in late-onset PE (mean difference = -0.2 vs -0.43 respectively). This finding supports the view that PE in early-onset PE is more commonly associated with placental dysfunction than with late-onset PE. The current data suggests that distinct vascular adaptation in early and late PE could reflect different pathophysiologic mechanisms[9, 10, 30, 31]. Further studies to correlate early- and late-onset PE with the pregnancy outcomes are warranted.

The strength of this study was that it had adjusted data which made the outcomes more reliable, and that it was one of a large series with a big enough sample size to have the power to distinguish the outcomes. To the best of our knowledge, no previous hospital-based study on BW/PI ratio of early- and late-onset PE has been published.

Some limitations of this study should be noted. First, the retrospective nature of this study based on computer searches might be associated with some incomplete data and can not select only uncomplicated, healthy pregnant woman in the control group. Secondly, the weight of placentas was considered as the sum of the weight of placenta, membranes and umbilical cord (untrimmed placenta).

Conclusion

In conclusion, the BW/PI ratio of preeclamptic women differed in cases of early- and late-onset PE, and that early-onset PE may be commonly reduce placental efficiency. This suggests that PE is composed of several different processes manifesting as a single disease.

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Potential conflicts of interest

The authors declare no conflict of interest.

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