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Association of pre-pregnancy body mass index with early- and late-onset severe preeclampsia

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ABSTRACT

Objective: To determine whether maternal pre-pregnancy body mass index is associated with preeclampsia with severe features, categorized as early- or late-onset.

Study design: This retrospective cohort study was conducted at the Department of Obstetrics and Gynecology, Rajavithi Hospital. The inclusion criteria were singleton pregnant women who gave birth at Rajavithi Hospital between January 1, 2015 and October 31, 2019. The study group was pregnant women diagnosed with preeclampsia with severe features while the control group was those without preeclampsia. Body mass index was classified based on The Regional Office for the Western Pacific Region of the World Health Organization criteria. The primary outcome was association of pre-pregnancy body mass index and risk of preeclampsia with severe features, classified by gestational age into early- ($<$ 34 weeks) and late- ($\geq$ 34 weeks) onset preeclampsia. Comparisons were made using the Student's *t*-test, Chi-square, or Fisher's exact tests, as appropriate. Logistic regression was used to assess associations.

Results: There were 589 pregnant women in the control group and 519 women with preeclampsia in the study group. The study group was subdivided into early-onset (32.4 %, 168/519) and late-onset (67.6 %, 351/519) preeclampsia. Women who had preeclampsia with severe features had higher mean pre-pregnancy BMI than those without preeclampsia. Women with class I (63.6 %, 136/214) and II (81.0 %, 111/137) obesity (body mass index, 25.0–29.9 and $\geq$ 30.0 kg/m^2, respectively) had significantly increased risk of preeclampsia with severe features (adjusted odds ratio 2.71, 95 % confidence interval 1.85–4.00 and adjusted odds ratio 3.84, 95 % confidence interval 2.22–6.64, respectively). In preeclampsia subgroup analysis, class I obesity was significantly associated with late-onset severe preeclampsia (adjusted odds ratio 2.02, 95 % confidence interval 1.40–2.93), while class II obesity was significantly associated with both early- and late-onset severe preeclampsia (adjusted odds ratio 1.69, 95 % confidence interval 1.01–2.84 and adjusted odds ratio 2.13, 95 % confidence interval 1.36–3.33, respectively).

Conclusions: Class I and II obesity are significantly associated with preeclampsia with severe features. Class I obesity is significantly related to late-onset severe preeclampsia with, whereas class II obesity is associated with both early- and late-onset severe preeclampsia.

1. Introduction

Preeclampsia is a leading cause of maternal and perinatal morbidity and mortality [1], with an incidence of approximately 2–8 % of pregnant women. In preeclampsia with severe features, progressive deterioration results in serious complications for both mother and fetus, including seizures, cerebral hemorrhage, blindness, pulmonary edema, hepatic rupture, kidney failure, miscarriage, low birth weight, preterm birth, and fetal growth restriction [2]. There are several established risk factors for preeclampsia, one of which is maternal obesity which defined according to body mass index (BMI) [3], where pregnant women with obesity (BMI $>$ 30 kg/m^2) to have a higher risk of preeclampsia [4,5]. Currently, obesity is a major global problem in both developed and developing countries. In the United States, more than 1 in 3 women of reproductive age and around 25 % of women who have given birth have obesity. In addition, the pathophysiology of obesity and preeclampsia share similarities, including increased oxidative stress, inflammation, endothelial dysfunction, and vasoconstriction [6]. Therefore, pregnant

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women with obesity have higher rates of preeclampsia, with a reported three times higher risk of developing preeclampsia compared with those with healthy BMI [7]. Despite the elevated risk, it is estimated that only approximately 10 % of women with obesity will develop preeclampsia, while the remaining 90 % do not experience preeclampsia; hence, determining the differences among women with obesity who develop preeclampsia and those who do not is of considerable interest [8].

Preeclampsia has variable pathogenesis, depending on disease onset and can be classified into two phenotypes: early-onset preeclampsia, defined by onset at gestational age (GA) $<$ 34 weeks, and late-onset, occurring at $\geq$ GA 34 weeks [4]. There are differences in severity and adverse outcomes between early- and late-onset preeclampsia [9,10]. Although pregnancy in women with obesity is associated with preeclampsia, the results of some studies of preeclampsia classified as early- or late-onset have differed. For example, Sohlberg et al. found an association between obesity in pregnant women and both early- and late-onset preeclampsia [11], while other studies found no association between obesity and early-onset preeclampsia, but did identify an association with late-onset preeclampsia [5,12].

Additionally, different BMI classification systems have been established among various populations. Most previous studies have used the World Health Organization (WHO) obesity diagnosis criteria of BMI $>$ 30 kg/m^2, which differs from the criteria for Asian populations, which uses a BMI $>$ 25 kg/m^2 [13]. Since most of the pregnant women in Rajavithi Hospital were from Thai or other Southeast Asian populations, this study focused on the association between obesity in pregnant women and preeclampsia using the diagnostic criteria for obesity developed for Asian populations, with the aim of assessing the association of maternal pre-pregnancy body with severe preeclampsia categorized as early- or late-onset.

2. Material and methods

This retrospective cohort study was conducted at the Department of Obstetrics and Gynecology, Rajavithi Hospital after ethical approval by the Rajavithi Institutional Review Board (No. 129/2562). The inclusion criteria were women with singleton pregnancies who gave birth at Rajavithi Hospital between January 1, 2015 and October 31, 2019. The study group was pregnant women diagnosed with preeclampsia with severe features, while the control group was those without preeclampsia. All the singleton pregnancies with preeclampsia with severe features during the study period were included, while the participants in the control group were randomly selected. The collected data comprised maternal characteristics including: maternal age; ethnicity; parity; antenatal clinic (ANC) attendance; smoking status; obstetrics; and underling medical conditions, such as history of previous preeclampsia, gestational diabetes (GDM), hypertension, diabetes, systemic lupus erythematosus (SLE), and pre-pregnancy BMI. The pre-pregnancy BMI of each woman was documented from her body weight and height before pregnant which was obtained by history taking from her first visit at ANC in the early pregnancy period before 20 weeks of gestation. The primary outcome was the association of pre-pregnancy BMI and risk of preeclampsia with severe features, subclassified as early- and late-onset severe preeclampsia. Subjects with incomplete data were excluded.

Preeclampsia was defined as a new-onset hypertension, with or without proteinuria, occurring after 20 weeks of gestation and classified by severity as preeclampsia with or without severe features. The diagnostic criteria for preeclampsia were: systolic blood pressure $\geq$ 140 mmHg, or diastolic blood pressure $\geq$ 90 mmHg on two occasions at least 4 h apart. Proteinuria is defined as $\geq$ 300 mg/dL of protein in a 24-h urine collection, a protein to creatinine ratio of $\geq$ 0.3, or urine dipstick of 1 +, in cases where quantitative methods were not available. Preeclampsia with severe features was diagnosed by the presence of any of the following features: systolic blood pressure $\geq$ 160 mmHg; diastolic blood pressure $\geq$ 110 mmHg; thrombocytopenia (platelet count $<$ 100,000/μL); impaired liver function, as indicated by liver enzymes abnormally elevated to twice the upper limit of normal levels; severe persistent right upper quadrant or epigastric pain, unresponsive to medication and not accounted for by alternative diagnoses; renal insufficiency, defined as serum creatinine concentration $>$ 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease; pulmonary edema; and new-onset cerebral or visual disturbances [3].

Preeclampsia with severe features was further classified based on gestational age of development as early- or late-onset [4]. Early-onset preeclampsia was defined as preeclampsia that developed before 34 weeks of gestation, whereas late-onset preeclampsia occurred at or beyond 34 weeks of gestation. BMI was defined as maternal pre-pregnancy weight in kilograms divided by the square of the height in meters (kg/m^2) [13]. According to The Regional Office for the Western Pacific Region of WHO (WPRO) criteria specifically for Asian populations, BMI was categorized as follows: $<$ 18.4 kg/m^2, underweight; 18.5–22.9 kg/m^2, healthy; 23.0–24.9 kg/m^2, overweight; 25.0–29.9 kg/m^2, class I obesity; and BMI $\geq$ 30.0 kg/m^2, class II obesity [13].

All data were analyzed using SPSS software (version 22.0). Continuous variables were compared using the Student's t-test and data are presented as mean and standard deviation. Categorical variables were analyzed using the Chi-square or Fisher's exact tests, as appropriate, and the results are presented as percentages. Logistic regression was used to assess associations and the results are expressed as adjusted odds ratio (aOR) with 95 % confidence interval (CI). P $<$ 0.05 was considered significant.

3. Results

A total of 589 pregnant women were enrolled in each group. After reviewing the patients' files, 70 women with preeclampsia were excluded because of incomplete data and 519 cases were included as the study group, while the control group comprised 589 participants. Demographic data from the control and study groups were compared to assess differences in characteristic between them (Table 1). Pregnant women who had preeclampsia with severe features had significantly higher rates of previous preeclampsia, GDM, underlying medical diseases including hypertension, diabetes, SLE, and higher mean pre-pregnancy BMI than those without preeclampsia.

Next, pregnant women with severe preeclampsia were subdivided into early- and late-onset preeclampsia groups, comprising 168/519 (32.4 %) and 351/519 (67.6 %) participants, respectively. Comparisons of demographic data from women with early- and late-onset severe preeclampsia are presented in Table 2. Women with early-onset preeclampsia had a significantly lower rate of ANC, but a higher rate of previous preeclampsia than those with late-onset preeclampsia. Underlying medical condition rates and mean pre-pregnancy BMI did not differ significantly between women with early- and late-onset preeclampsia. Additionally, the number of women in each BMI category did not differ significantly between those with early- and late-onset preeclampsia.

Data on associations of early- and late-onset severe preeclampsia with BMI categories are presented in Table 3. After adjustment for age, ethnicity, previous preeclampsia, pre-gestational diabetes, and smoking, both class I and II obesity were significantly associated with increased risk of preeclampsia with severe features (136/214, 63.6 %, aOR 2.71, 95 % CI 1.85–4.00 and 111/137, 81.0 %, aOR 3.84, 95 % CI 2.22–6.64, respectively). Categorization of preeclampsia with severe features by gestational age demonstrated that class I obesity was specifically associated with late-onset severe preeclampsia (94/214, 43.9 %, aOR 2.02, 95 % CI 1.40–2.93), whereas class II obesity was significantly associated with both early- and late-onset severe preeclampsia (37/137, 27.0 %, aOR 1.69, 95 % CI 1.01–2.84 and 74/137, 54.0 %, aOR 2.13, 95% CI 1.36–3.33, respectively).

Table 1
Demographic variables in women with severe preeclampsia and controls.

Variable	Control (n = 589)	Severe PE (n = 519)	p-value
Maternal age (years)[a]	28.07 ± 5.52	31.36 ± 6.36	< 0.001*
Elderly gravidarum[b]	72 (12.2)	169 (32.6)	< 0.001*
Ethnicity[b]			
Thai	393 (66.7)	421 (81.1)	< 0.001*
Others[c]	196 (33.3)	98 (18.9)	
Parity[b]			
Nulliparous	222 (37.7)	218 (42.0)	0.143
Multiparous	367 (62.3)	301 (58.0)	
ANC[b]	589 (100.0)	488 (94.0)	< 0.001*
Previous preeclampsia[b]	0 (0.0)	30 (5.8)	< 0.001*
GDM[b]	0 (0.0)	94 (18.1)	< 0.001*
Underlying disease[b]	0 (0.0)	182 (35.1)	< 0.001*
DM	0 (0.0)	112 (61.5)	< 0.001*
Chronic hypertension	0 (0.0)	80 (44.0)	< 0.001*
SLE	0 (0.0)	7 (3.8)	0.009*
Other medical condition	0 (0.0)	20 (11.0)	< 0.001*
Smoking[b]	2 (0.3)	12 (2.3)	0.005*
Pre-pregnancy BMI (kg/m^2)[d]	20.89 (15.56–33.78)	24.67 (16.02–41.52)	< 0.001*
< 18.5	102 (17.3)	37 (7.1)	< 0.001*
18.5–22.99	304 (51.6)	164 (31.6)	
23–24.99	79 (13.4)	71 (13.7)	
25–29.99	78 (13.2)	136 (26.2)	
≥ 30	26 (4.4)	111 (21.4)	

Abbreviations: ANC, antenatal clinic attendance; BMI, body mass index; DM, diabetes mellitus; GDM, gestational diabetes mellitus; PE, preeclampsia; SLE, systemic lupus erythematosus.
[a] Values are presented as mean ± SD.
[b] Values are presented as number (%).
[c] Others include Myanmar, Cambodia and Laos.
[d] Values are presented as median (min–max).

Table 2
Demographic variables in pregnant women with early- and late-onset severe preeclampsia.

Variable	Early-onset severe PE (n = 168)	Late-onset severe PE (n = 351)	p-value
Maternal age (years)[a]	31.10 ± 6.19	31.48 ± 6.44	0.515
Elderly gravidarum[b]	50 (29.8)	119 (33.9)	0.346
Ethnicity[b]			
Thai	139 (82.7)	282 (80.3)	0.514
Others[c]	29 (17.3)	69 (19.7)	
Parity[b]			
Nulliparous	78 (46.4)	149 (42.5)	0.158
Multiparous	90 (53.6)	202 (57.5)	
ANC[b]	156 (92.9)	332 (94.6)	0.001*
Previous preeclampsia[b]	15 (8.9)	15 (4.3)	0.033*
GDM[b]	28 (16.7)	66 (18.8)	0.780
Underlying disease[b]	55 (32.7)	127 (36.2)	0.442
DM	29 (52.7)	75 (59.1)	0.428
Chronic hypertension	26 (47.3)	54 (42.5)	0.553
SLE	2 (3.6)	5 (3.9)	1.000
Other medical condition	4 (7.3)	16 (12.6)	0.439
Smoking[b]	5 (3.0)	7 (2.0)	0.486
Pre-pregnancy BMI (kg/m^2)[d]	24.47 (16.02–42.06)	24.78 (16.02–41.52)	0.864
< 18.5	10 (5.9)	27 (7.7)	0.934
18.5–22.9	55 (32.7)	109 (31.1)	
23.0–24.9	24 (14.3)	47 (13.4)	
25.0–29.9	42 (25.0)	94 (26.8)	
≥ 30	37 (22.0)	74 (21.1)	

Abbreviations: ANC, antenatal clinic attendance; BMI, body mass index; DM, diabetes mellitus; GDM, gestational diabetes mellitus; PE, preeclampsia; SLE, systemic lupus erythematosus.
[a] Values are presented as mean ± SD.
[b] Values are presented as number (%).
[c] Others include Myanmar, Cambodia and Laos.
[d] Values are presented as median (min–max).
* Significant at $p < 0.05$.

4. Discussion

4.1. Principal findings

The findings of the present study demonstrate that several factors, including elderly primigravida; previous preeclampsia; GDM; underlying medical disease, such as diabetes, chronic hypertension, and SLE; and pre-pregnancy BMI, were significantly associated severe preeclampsia. No significant differences in demographic variables between women with early- and late-onset severe preeclampsia were detected, other than ANC and previous preeclampsia; significantly more pregnant women in the late-onset preeclampsia group received ANC relative to those in the early-onset preeclampsia group. Nevertheless, in preeclampsia subgroup analysis, class I obesity was significantly associated with late-onset severe preeclampsia, while class II obesity was significantly associated with both early- and late-onset severe preeclampsia, after adjustment for confounding factors.

4.2. Results in the context of what is known

Our results indicating associations of elderly primigravida, previous preeclampsia, GDM, underlying medical disease, and pre-pregnancy BMI are consistent with previous reports of risk factors associated with preeclampsia in the literature [4,14]. In the present study, pre-pregnancy BMI ≥ 25 kg/m^2 was significantly associated with preeclampsia, whereas other studies have concluded that women with BMI ≥ 30 kg/m^2 are at increased risk of preeclampsia [4,14]; however, we did not adjust for other factors that may have confounded our results.

Our findings on ANC attendance for women with early- and late-onset preeclampsia are inconsistent with those of a previous study of Thai women, in which Fang et al. [4] observed that not receiving prenatal care during pregnancy led to an increased risk of late-onset preeclampsia relative to women with prenatal care initiated during the first trimester.

Previous preeclampsia has been postulated to be a risk factor preeclampsia [4,14], particularly early-onset [12,15], consistent with the findings of the present study that women with previous preeclampsia were more likely to develop early-onset than late-onset preeclampsia; however, Li et al. [16] reported no significant difference in the incidence of recurrent early- and late-onset preeclampsia in women with previous preeclampsia.

Previous studies have reported significant associations between obesity and preeclampsia. A systematic review and meta-analysis of large cohort studies, including 25,356,688 pregnancies from 92 studies, found that pre-pregnancy BMI > 30 kg/m^2 was strongly associated with preeclampsia (OR = 2.8, 95 % CI 2.6–3.1) [17]. Similarly, a study of Thai women revealed that those with BMI ≥ 30 kg/m^2 had a 4.8-fold increased risk of preeclampsia (OR = 4.76, 95 % CI 1.73–13.12) compared with women who had healthy pre-pregnancy BMI [4]. Nevertheless, some studies have detected an association between preeclampsia and lower BMI in Thai women. Aksornphusitaphong and Phupong [12] reported that pre-pregnancy BMI 25–29.9 kg/m^2 and BMI ≥ 30 kg/m^2 were significantly associated with increased risk of both early- and late-onset preeclampsia. Additionally, using the WPRO criteria, Somprasit et al. [18] also found that obesity (BMI ≥ 25 kg/m^2) was significantly associated with increased risk of poor obstetric outcomes, including preeclampsia (OR = 3.70, 95 % CI 2.19–6.28). Likewise, the present study showed that increased BMI was associated with a greater risk of severe preeclampsia. Thus, the present study supports that, in the Thai population, women with BMI ≥ 25 kg/m^2 are at increased risk of preeclampsia.

Table 3
Risk of early- and late-onset severe preeclampsia classified by BMI category.

PE with severe features	Healthy weight (Ref.)	Underweight		Overweight		Obesity I		Obesity II	
	BMI 18.5–22.9 (n = 468)	BMI < 18.5 (n = 139)		BMI 23.0–24.9 (n = 150)		BMI 25.0–29.9 (n = 214)		BMI ≥ 30 (n = 137)	
	n (%)	n (%)	aOR, 95 %CI	n (%)	aOR, 95 %CI	n (%)	aOR, 95 %CI	n (%)	aOR, 95 %CI
Total PE[a]	164 (35.0)	37 (26.6)	0.77 (0.48–1.24)	71 (47.3)	1.34 (0.87–2.08)	136 (63.6)	2.71 (1.85–4.00)[b]	111 (81.0)	3.84 (2.22–6.64)[b]
Early-onset PE[a]	55 (11.7)	10 (7.2)	0.58 (0.28–1.18)	24 (16.0)	1.23 (0.72–2.11)	42 (19.6)	1.57 (0.99–2.48)	37 (27.0)	1.69 (1.01–2.84)[b]
Late-onset PE[a]	109 (23.3)	27 (19.4)	0.91 (0.55–1.48)	47 (31.3)	1.23 (0.80–1.90)	94 (43.9)	2.02 (1.40–2.93)[b]	74 (54.0)	2.13 (1.36–3.33)[b]

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; PE, preeclampsia.
[a] Adjusted for age, ethnicity, previous preeclampsia, pre-gestational diabetes, and smoking.
[b] Statistically significant.

Our results indicated that class I obesity was associated with late-onset preeclampsia, while class II was associated with both early and late onset preeclampsia, consistent with the findings of previous studies. For example, Durst et al. [5] conducted a study of BMI at the time of admission to delivery in 881 women with preeclampsia with severe features using standard BMI criteria and found that women who were overweight or had obesity or morbid obesity were at increased risk of late-onset preeclampsia with severe features, whereas early-onset pre-eclampsia was associated only with morbid obesity. Similarly, Shao et al. [19] demonstrated that overweight (BMI $\geq$ 24 kg/m^2) or obesity (BMI $\geq$ 28 kg/m^2) was associated with an increased risk of late-onset preeclampsia using the BMI criteria established by the Working Group of Obesity in China [20].

4.3. Clinical implications

The overall consistency of previous findings and those of the present study suggests that pregnant women with higher BMI may develop preeclampsia with either early- or late-onset, while women with obesity but relatively lower BMI are more likely to be at risk of preeclampsia in the later stages of pregnancy. As pregnancy outcomes of early-onset preeclampsia are worse than those for late-onset preeclampsia [21, 22], caution should be exercised when caring for very pregnant woman with severe obesity, as they are likely to develop preeclampsia at < 34 weeks GA.

Further, our findings that ANC attendance was higher in women with late-onset than those with early-onset preeclampsia may reflect that pregnant women exposed to ANC received early preeclampsia preventative interventions, such as medication and surveillance, resulting in a decreased rate of early-onset preeclampsia.

4.4. Research implications

The present study demonstrated the significant association of obesity and preeclampsia by using the BMI criteria for ASEAN population. Nevertheless, the BMI criteria among ASEAN countries are different such as in China [20]. Further study regarding BMI criteria based on specific population may precisely identify the association between pre-pregnancy BMI and preeclampsia. In addition, due to the disadvantage of respective study, further study with a prospective format to evaluate the impact of BMI including other risk factors with early- and late-onset preeclampsia is suggested.

4.5. Strengths and limitations

The strengths of the present study are the large sample size and use of the WPRO criteria, which are guidelines specific for the Association of Southeast Asian Nations, to research the association between BMI and preeclampsia. Nevertheless, the retrospective nature of the study means that data were collected sub-optimally. In addition, the present study did not evaluate other risk factors, that may have impacted the results, because of their rare occurrence, and did not evaluate differences in outcomes between women who experienced early- and late-onset preeclampsia.

5. Conclusions

Class I and II obesity are significantly associated with preeclampsia with severe features. Class I obesity is significantly related to late-onset severe preeclampsia, whereas class II obesity is associated with both early- and late-onset preeclampsia.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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