Validation of the gestational week division border for subclassification of pregnancy induced hypertension

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Aim: Classification of pregnancy induced hypertension (PIH) according to the Japan Society of Obstetrics and Gynecology defines early onset PIH as that which develops before 32 weeks of gestation, and late onset PIH as that which occurs thereafter. The present study aimed to validate this cut-off point.

Methods: Clinical characteristics of the patients from 59 domestic tertiary settings of perinatal medicine were analyzed. Women with multiple pregnancies and/or any medical complications were excluded. Subgroups of mild and severe PIH were created according to the severity of hypertension.

Results: Numbers of patients with preeclampsia (PE) and gestational hypertension (GH) were 619 and 194, respectively. Severe cases accounted for 379 (333 for PE and 46 for GH) and mild cases accounted for 434 (286 for PE and 148 for GH). The difference in patterns of distribution of onset time between severe and mild cases of PIH was more remarkable than those between PE and GH. Discriminate analysis showed 32.3 weeks of gestation to be the optimal cut-off point at which severe forms of PIH were distinguishable from mild forms. Receiver operating characteristic (ROC) curve analysis of assumptive diagnostic efficacy for predicting severe hypertension with time of disease onset was most predictive at 32 weeks of gestation.

Statistical analyses revealed that the cases presenting before 32 weeks were not significantly different from the severely hypertensive cases in terms of maternal and offspring outcomes. Comparison of PIH cases occurring after 32 weeks with cases of mild hypertension were also very similar.

Conclusions: It is considered appropriate to regard 32 weeks of gestation as an optimal cut-off point for subclassification of early and late onset types of PIH.

Introduction

Pregnancy induced hypertension (PIH) is a common gestational complication defined as hypertensive disease with or without organ damage, newly recognized or superimposed on preexisting maternal hypertensive diseases during pregnancy. The American College of Obstetricians and Gynecologists (ACOG) proposed a disease classification based on the concept of hypertension in pregnancy in 1972.¹ Since then, most societies and organizations responsible for maternal and fetal medicine across the world (WHO, 1987,² NHBPEP: National High Blood Pressure Education Program, 1990³ and 2000,⁴ CHS: Canadian Hypertension Society, 1997,⁵ ISSHP: International Society for the Study of Hypertension in Pregnancy, 1998⁶ and 2001,⁷ and ASSHP: Australasian Society for the Study of Hypertension in Pregnancy, 2000⁸) have accepted this classification set by the ACOG.

The Japan Society of Obstetrics and Gynecology (JSOG) had until recently continued to use the
classification based on the classical concept of “Toxemia of pregnancy”. As this old concept was thought to obstruct a true understanding of etiology and pathophysiology of the disease, the JSOG finally decided to accept the global standard, and established a new disease definition and classification in 2005.

The new proposal defines classification in terms of pathophysiological and severity criteria. It also determines disease subclassification with regard to the time of onset. The early onset type is that which becomes overt at or before 31 weeks of gestation, and the late onset type presents thereafter. This concept of early and late onset of the disease has provided useful knowledge both for clinical practice and for basic investigations, because there are great differences in clinical features between the two types. The new Japanese definition carried on the border defined in the old definition. Subsequently, 32 weeks of gestation was selected as the empirically-defined border for gestational age.

There has not been, however, international consensus on the gestational week serving as the dividing border between early and the late onset types, and many investigators have preferred to apply 34 weeks of gestation. However, this practice is not supported by firm evidence based on disease pathophysiology.

The purpose of this study is to present scientific evidence for validation of the border week set in the new definition of PIH in Japan.

**Materials and methods**

The survey, conducted in 1995, invited 59 hospital tertiary settings for maternal-fetal medicine to participate. The person in charge of the obstetrical ward at each institute was required to fill out a questionnaire, which served as a brief report of the individual patients with pregnancy-induced hypertension managed during the preceding year. Personal data were identified only by institutional serial number. Women with multiple pregnancies and those with any medical complications were excluded.

All cases were classified into those with gestational hypertension and those with preeclampsia, according to the following criteria: those who had only hypertension were classified as those with gestational hypertension; those who were complicated with proteinuria were classified as those with preeclampsia. Disease severity was categorized into mild and severe according to the level of hypertension. Mild hypertension was a systolic blood pressure of 140 mmHg or higher but lower than 160 mmHg and/or diastolic blood pressure of 90 mmHg or higher but lower than 110 mmHg. Severe hypertension was a systolic blood pressure of 160 mmHg or higher and/or diastolic blood pressure of 110 mmHg or higher.

To compare maternal and neonatal prognosis between disease types, we estimated incidences of eclampsia and hemolysis, elevated liver enzymes, and low platelets syndrome (HELLP syndrome) as maternal complications, and of intrauterine growth restriction (IUGR) as a neonatal complication. IUGR was diagnosed growth below 1.5 standard deviations from the mean in the standard curve for newborn-infant body weights in Japan.

Disease onset in each case was determined as the point at which hypertension was first diagnosed, and was categorized into one of the following 10 intervals: 20–21, 22–23, 24–25, 26–27, 28–29, 30–31, 32–33, 34–35, 36–37, and 38 weeks of gestation or later.

To assess any statistically significant differences in incidences of the clinical problems between the early onset and the severely hypertensive form of the disease, and in those between the late onset and the mildly hypertensive form, we applied a test originally designed to reject the hypothesis that the number of incidences was significantly different between the two groups. Thus, rejection of this hypothesis would support the conclusion that classifying PIH by disease onset time might be equivalent to that by disease severity.

The gestational week division border between the early and late onset types was calculated theoretically using the Mahalanobis generalized distance method. This analysis was applied to find the gestational week which could most efficiently discriminate severe and mild cases by disease onset time using the following equation:

\[(X - X_1)/S_1 = (X_2 - X)/S_2,\]

where \(X\): discriminating week, \(X_1\) and \(X_2\): mean gestational week of disease onset in severe and mild cases, respectively, \(S_1\) and \(S_2\): standard deviation of gestational week of disease onset in severe and mild cases, respectively.

Finally, receiver operating characteristic (ROC) curve analysis was performed for assumptive efficacy of diagnosing severe PIH with the time of disease onset. Sensitivity and specificity for each two-week period were calculated using the rates of finally-confirmed severe cases in the total PIH cases having presented with the disease in the time period or previously. A regression quadric curve calculated to fit the actual ROC (KaleidaGraph 4: Hulinks Co., Ltd., Japan) was used for...
### Table 1. Clinical data of pregnancy induced hypertension (preeclampsia vs. gestational hypertension)

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Age (year)</th>
<th>Parity</th>
<th>BMI</th>
<th>sBP (mmHg)</th>
<th>dBP (mmHg)</th>
<th>Onset Week Median/IQR</th>
<th>Delivery Week Median/IQR</th>
<th>Birth Weight (g) Median/IQR</th>
<th>Complications [%]</th>
<th>FGR [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE total</td>
<td>619</td>
<td>30.2 ± 5.1</td>
<td>398/221</td>
<td>22.0 ± 4.2</td>
<td>172 ± 20*</td>
<td>106 ± 14*</td>
<td>33.5 – 36</td>
<td>2,170*</td>
<td>29 [4.7]</td>
<td>226 [36.5]*</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>333</td>
<td>29.9 ± 5.0</td>
<td>212/121</td>
<td>21.4 ± 3.5</td>
<td>177 ± 18**</td>
<td>109 ± 13**</td>
<td>31** – 35</td>
<td>1,780**</td>
<td>21 [6.3]</td>
<td>122 [36.6]**</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>286</td>
<td>30.6 ± 5.1</td>
<td>186/100</td>
<td>23.0 ± 5.1</td>
<td>158 ± 17</td>
<td>98 ± 13</td>
<td>35 – 32.5</td>
<td>2,590</td>
<td>9 [4.6]</td>
<td>48 [24.7]</td>
<td></td>
</tr>
<tr>
<td>GH total</td>
<td>194</td>
<td>30.6 ± 5.6</td>
<td>112/82</td>
<td>23.4 ± 4.3</td>
<td>165 ± 23</td>
<td>99 ± 14</td>
<td>34 – 31</td>
<td>1,990 – 3,136</td>
<td>6 [4.1]</td>
<td>35 [23.6]</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>46</td>
<td>32.8 ± 6.3</td>
<td>23/23</td>
<td>23.5 ± 4.4</td>
<td>183 ± 13**</td>
<td>108 ± 13**</td>
<td>33.5 – 27</td>
<td>2,205**</td>
<td>3 [6.5]</td>
<td>15 [32.6]</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>148</td>
<td>29.9 ± 5.1</td>
<td>89/59</td>
<td>23.3 ± 4.3</td>
<td>157 ± 18</td>
<td>95 ± 13</td>
<td>35 – 31</td>
<td>2,690</td>
<td>6 [4.1]</td>
<td>35 [23.6]</td>
<td></td>
</tr>
</tbody>
</table>

PE: preeclampsia, GH: gestational hypertension, sBP: systolic blood pressure, dBP: diastolic blood pressure, BMI: body mass index, FGR: fetal growth restriction
Complications: eclampsia plus HELLP syndrome in Mother
*: P < 0.0001 vs. gestational hypertension
**: P < 0.0001 vs. mild form of preeclampsia or that of gestational hypertension
#: P = 0.015, vs. mild form of gestational hypertension
##: P = 0.0004, vs. mild form of gestational hypertension

### Table 2. Frequency distribution of disease onset in preeclampsia and gestational hypertension

<table>
<thead>
<tr>
<th>gestational week of disease onset</th>
<th>GH</th>
<th>Mild GH</th>
<th>Severe GH</th>
<th>PE</th>
<th>Mild PE</th>
<th>Severe PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>number</td>
<td>incidence (%)</td>
<td>number</td>
<td>incidence (%)</td>
<td>number</td>
<td>incidence (%)</td>
<td>number</td>
</tr>
<tr>
<td>20–21</td>
<td>5</td>
<td>2.6</td>
<td>3</td>
<td>2</td>
<td>4.3</td>
<td>9</td>
</tr>
<tr>
<td>22–23</td>
<td>8</td>
<td>4.1</td>
<td>4</td>
<td>2.7</td>
<td>8.7</td>
<td>11</td>
</tr>
<tr>
<td>24–25</td>
<td>8</td>
<td>4.1</td>
<td>7</td>
<td>4.7</td>
<td>2.2</td>
<td>21</td>
</tr>
<tr>
<td>26–27</td>
<td>10</td>
<td>5.2</td>
<td>5</td>
<td>3.4</td>
<td>10.9</td>
<td>42</td>
</tr>
<tr>
<td>28–29</td>
<td>7</td>
<td>3.6</td>
<td>3</td>
<td>2.0</td>
<td>8.7</td>
<td>64</td>
</tr>
<tr>
<td>30–31</td>
<td>20</td>
<td>10.3</td>
<td>16</td>
<td>10.8</td>
<td>8.7</td>
<td>81</td>
</tr>
<tr>
<td>32–33</td>
<td>27</td>
<td>13.9</td>
<td>24</td>
<td>16.3</td>
<td>6.5</td>
<td>82</td>
</tr>
<tr>
<td>34–35</td>
<td>33</td>
<td>17.0</td>
<td>20</td>
<td>13.5</td>
<td>28.3</td>
<td>94</td>
</tr>
<tr>
<td>36–37</td>
<td>41</td>
<td>21.1</td>
<td>37</td>
<td>25.0</td>
<td>8.7</td>
<td>124</td>
</tr>
<tr>
<td>38–39</td>
<td>35</td>
<td>18.0</td>
<td>29</td>
<td>19.6</td>
<td>13.0</td>
<td>91</td>
</tr>
<tr>
<td>total</td>
<td>194</td>
<td>100</td>
<td>148</td>
<td>100</td>
<td>46</td>
<td>619</td>
</tr>
</tbody>
</table>

PE: preeclampsia, GH: gestational hypertension
Early- and late-onset types of PIH

Statistical analysis
The Student’s or Welch’s t-tests and the chi-square test for dependence, as well as the Mann-Whitney U test, were applied using STAT View 5.0 for Windows.

All P values of less than 0.05 were considered to indicate statistical significance.

Results
Thirty-nine hospitals in which the institutional ethical issues had been cleared responded to the invitation (see Appendix for a complete list).

The total number of the patients was 1,466. Of these, we excluded 54 multiple pregnancies, 234 with medical complications, and 365 cases for which insufficient data were recorded. Thus, the 813 cases remaining were employed for the following analysis. The numbers of preeclampsia and gestational hypertension cases were 619 and 194, respectively.

Clinical characteristics
Clinical characteristics of the patients divided into groups with preeclampsia and gestational hypertension are shown in Table 1. These cases were also subdivided into severe and mild forms of preeclampsia and of gestational hypertension (Table 1).

Distribution of disease onset
Distribution of the time of disease onset in patients with preeclampsia showed a different pattern from that in patients with gestational hypertension, although both disease types showed the most frequent occurrence (the mode) at 36–37 weeks of gestation (Table 2, preeclampsia vs. gestational hypertension, P < 0.0001, Mann-Whitney U test). Those who presented with the disease at 31 weeks of gestation or earlier in the preeclampsia and gestational hypertension groups were 37% (228/619) and 30% (58/194), respectively. The difference was not statistically significant.

The mild form of gestational hypertension exhibited a different distribution pattern from that of the severe form. Almost half of the mild cases had disease onset at 36 weeks of gestation or later (66/148, 45%), while the incidence in the severe form was around one fifth (10/46, 22%, P = 0.0055, Chi-square test). The mild type formed one peak of biweekly-divided incidence of disease onset at 36–37 weeks of gestation, while the severe type formed two peaks at 26–27 and 34–35 weeks of gestation. The number of cases presenting at 31 weeks of gestation or earlier was also significantly higher in the severe type than in the mild one (20/46, 43% vs. 38/148, 26%, P < 0.021, Chi-square test).

Border of gestational age between early- and late-onset diseases
The differences in the rates of association with maternal complications and IUGR between severe and mild PIH cases were statistically significant (24/379, 6.3% vs. 14/434, 3.2%, P = 0.036, 186/379, 49% vs. 101/434, 23%, respectively; P < 0.0001, Chi-square, Table 3).

Marked differences were also revealed in the distribution pattern of disease onset between the severe and mild cases of preeclampsia (Table 2, P < 0.0001, severe vs. mild, Mann-Whitney U test). Almost half of those with mild preeclampsia (141/286, 49%) presented at 36 weeks of gestation or later, while the rate for the severe cases was significantly lower (74/333, 22%, P < 0.0001, Chi-square test). There are two small peaks of the biweekly-divided incidence of disease onset in the severe cases at 30–31 and 36–37 weeks of gestation. The number of cases presenting at 31 weeks of gestation or earlier was also significantly higher in the severe type (167/333, 50% vs. 61/286, 21%, P < 0.0001, Chi-square test).

The mild form of gestational hypertension exhibited a different distribution pattern from that of the severe form. Almost half of the mild cases had disease onset at 36 weeks of gestation or later (66/148, 45%), while the incidence in the severe form was around one fifth (10/46, 22%, P = 0.0055, Chi-square test). The mild type formed one peak of biweekly-divided incidence of disease onset at 36–37 weeks of gestation, while the severe type formed two peaks at 26–27 and 34–35 weeks of gestation. The number of cases presenting at 31 weeks of gestation or earlier was also significantly higher in the severe type than in the mild one (20/46, 43% vs. 38/148, 26%, P < 0.021, Chi-square test).

Patients with PIH onset at 31 weeks of gestation or earlier more frequently experienced maternal...
### Table 3. Clinical data of preeclampsia and gestational hypertension (Severe vs. Mild)

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Age (year)</th>
<th>Parity pp/mp</th>
<th>BMI</th>
<th>sBP (mmHg)</th>
<th>dBP (mmHg)</th>
<th>Onset Week Median/IQR</th>
<th>Delivery Week Median/IQR</th>
<th>Birth Weight (g) Median/IQR</th>
<th>Complications [%]</th>
<th>FGR [%]</th>
<th>Onset &lt;32 weeks [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>379</td>
<td>30.4 ± 5.1</td>
<td>235/143</td>
<td>21.6 ± 3.5*</td>
<td>180 ± 18*</td>
<td>110 ± 13*</td>
<td>32** 28–35</td>
<td>35.9* 32.1–38.1</td>
<td>1,825** 1,199–2,539</td>
<td>24 [6.3]**</td>
<td>137 [36]*</td>
<td>186 [49]*</td>
</tr>
</tbody>
</table>

PE: preeclampsia, GH: gestational hypertension, sBP: systolic blood pressure, dBP: diastolic blood pressure
BMI: body mass index, FGR: fetal growth restriction
pp: primipara, mp: multipara, IQR: interquartile range
*: P < 0.0001, vs. mild.

### Table 4. Clinical data of preeclampsia and gestational hypertension (early vs. late onset)

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Age (year)</th>
<th>Parity pp/mp</th>
<th>BMI</th>
<th>sBP (mmHg)</th>
<th>dBP (mmHg)</th>
<th>Delivery Week Median/IQR</th>
<th>Birth Weight (g) Median/IQR</th>
<th>Complications [%]</th>
<th>FGR [%]</th>
<th>Severe [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>EO</td>
<td>286</td>
<td>31.0 ± 4.5</td>
<td>162/123</td>
<td>22.3 ± 4.0</td>
<td>174 ± 20*</td>
<td>107 ± 15*</td>
<td>33.3* 30.7–36.7</td>
<td>1,366** 1,021–2,207</td>
<td>25 [8.7]*</td>
<td>134 [47]*</td>
<td>189 [66]*</td>
</tr>
<tr>
<td>LO</td>
<td>527</td>
<td>30.0 ± 5.0</td>
<td>343/179</td>
<td>22.4 ± 4.4</td>
<td>167 ± 20</td>
<td>102 ± 14</td>
<td>38.2 36.9–39.6</td>
<td>2,590 2,050–3,042</td>
<td>16 [3.0]</td>
<td>140 [26]</td>
<td>208 [47]</td>
</tr>
</tbody>
</table>

PE: preeclampsia, GH: gestational hypertension, sBP: systolic blood pressure, dBP: diastolic blood pressure
BMI: body mass index, FGR: fetal growth restriction
pp: primipara, mp: multipara, IQR: interquartile range, EO: early onset, LO: late onset
*: P < 0.0001, vs. LO
complications (eclampsia + HELLP syndrome) (25/286, 8.7% vs. 16/527, 3.0%; \(P = 0.00039, \text{Chi-square test}\)) and exhibited an increased rate of impaired fetal growth (134/286, 47% vs. 140/527, 27%, \(P < 0.0001, \text{Chi-square test}\)) than those of late-onset type (Table 4).

Analysis of incidences both of maternal complications and of IUGR by identified equality between early-onset and severe hypertension (\(Z = 6.797\) and 2.543, respectively, \(P < 0.01\)) or late-onset and mild hypertension (\(Z = 8.000\) and 3.411, respectively, \(P < 0.01\)). These results confirmed that disease discrimination according to onset time is equivalent to that according to severity.

ROC curve was created with KaleidaGraph 4. Thus, the ROC curve analysis of assumptive diagnostic efficacy for predicting severe hypertension with the time of disease onset (cut-off point) revealed a dividing border of approximately 32 weeks of gestation (Figure 2).

Discriminant analysis also showed 32.8 weeks of gestation as an optimal cut-off point at which severe and mild forms of PIH could be distinguished.

**Discussion**

The present study results validated the choice of 32 weeks of gestation as the cut-off between early and late onset PIH. Although the study subjects were recruited from multi-central sites, subject race, antenatal management, and disease diagnosis were all uniform throughout the subject population. Clinical management of PIH also varied minimally across hospitals, as they follow the standard practice proposed by the JSOG. All pregnant women in Japan receive initial antenatal care on the 12\(^{th}\) week of gestation or earlier. As an ultrasonographic examination is performed in the first trimester in every case to confirm fetal development, the expected day of confinement can be considered reliable. However, the ratio of the number of mild hypertensive cases to that of severe ones may be less than the actual proportion, because the present cases were sampled mainly from tertiary settings. This is one methodological limitation of the present study.

Considerable discussion has ensued regarding the differences in clinical features of PIH between early onset and late onset type. The early onset disease tends to embody higher severity and poorer offspring outcomes, as there are more cases that involve growth-restricted fetuses. It is well known that maternal complications and/or mortality and morbidity of offspring are more common in cases of preeclampsia appearing remote from term than in those of term onset.\(^{12,21,22}\) The differences between the two subgroups of the disease may be more substantial than the characteristics apparently recognized in the clinical settings. For example, Dekker and his associates proposed a concept that thrombophilia may play an etiological role in a considerable number of patients with early onset severe disease.\(^{23}\) Many other investigators have also tried to clarify differences in etiology and/or pathophysiology between subgroups.

In addition, it is generally accepted that differences exist in pathophysiology between preeclampsia and gestational hypertension, and that the former is a more severe form within the spectrum of disease.

However, gestational hypertension with severe elevation of blood pressure may be more deleterious to the mother and/or fetus than the mild type of preeclampsia.\(^{24}\) Furthermore, some have claimed that no distinct differences in pathophysiology exist between preeclampsia and gestational hypertension.\(^{25}\) However, the idea that preeclampsia in earlier gestational stages might indicate a poor outcome of pregnancy is still useful in the context of clinical management.

The gestational week bordering early and late onset types has been so far empirically determined. The present study is the first attempt to validate it by statistical analysis focusing on the difference in severity of hypertension. Some have recommended 34 weeks of gestation as a border gestational week,\(^{12-15}\) while others have defined 32 weeks as optimal.\(^{26}\) Still others claim that early onset should be defined as that presenting before 32 weeks, and that late onset should be set as that developing after 35 weeks.\(^{27}\) Sibai described in his review that the majority of cases of mild gestational hypertension develop at or beyond 37 weeks and that maternal and perinatal outcomes in preeclampsia are usually dependent on gestational age at onset. Moreover,
he stated that serious maternal complications are usually observed in women who develop preeclampsia before 32 gestational weeks, and that neonatal morbidities are minimal in those with severe preeclampsia beyond 35 gestational weeks.28)

In the present study, the severity of cases was determined only in terms of hypertension, and did not consider whether the patient had preeclampsia or gestational hypertension, despite the obvious etiological and pathophysiological differences between the two. Pregnancy outcome largely depended on the severity of hypertension and the disease types are hardly distinguishable at the point of hypertension appearing, because some gestational hypertension patients become preeclamptic later. Therefore, it is rational to categorize severely hypertensive women with either preeclampsia or gestational hypertension into one entity.

In line with this concept, the present data identify a difference in the distribution pattern of time of disease onset between severe and mild forms of preeclampsia, gestational hypertension, or both of them, while no statistical difference was noted for this variable between preeclampsia and gestational hypertension. In addition, the dividing line between early and late onset types of PIH was shown to be identical to that for severe and mild types in terms of maternal complication and/or fetal developmental impairment with simple comparisons and the delta analysis. Furthermore, 32 weeks of gestation, empirically defined as the border between early and late onset, was also confirmed as appropriate, through theoretically calculated discriminant and ROC analyses.

Ideally, the analysis to determine a threshold gestational week which would distinguish between early and late onset PIH would be better if it were based not only on blood pressure but also on the basis of the maternal and/or offspring prognoses. However, in the present study, only severity of hypertension was analyzed, due to the number of cases with other complications. Despite this methodological limitation, subclassification of the disease by onset time according to the border week determined in this study can effectively discriminate incidences of the complications.

In conclusion, the results suggest that the empirically determined criterion to classify disease by onset time is well supported by the evidence. Thus, treating patients presenting with a severe form of disease prior to 32 weeks of gestation appears to be reasonable. These findings should be valued by physicians who require these practical principles in their management of cases involving hypertensive women.

Acknowledgements

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The thirty six participating institutes included the following: Asahikawa Medical University, Tohoku University, JR Sendai Hospital, Fukushima Medical University, Niigata University, Gunma University, National Defense Medical College, Saitama Medical University, Saitama Medical Center Saitama Medical University, Tokyo Women’s Medical University, Nihon University Itabashi Hospital, Teikyo University, Kitazato University, Shinsyu University, Nagoya University, Nagoya City University, Aichi Medical University, University of Shiga Prefecture, Kyoto University, Kyoto Prefectural University of Medicine, Nara Medical University, Osaka City University, Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka City General Hospital, Kobe University, Okayama University, Kagawa University, Kagawa Prefectural Central Hospital, Ehime University, Kochi University, Kyusyu University, Kurume University, Kumamoto University, Miyazaki University, Kagoshima City Hospital, and Ryukyu University.

Conflict of interest

None.

References

Early- and late-onset types of PIH