**Histopathological findings of pregnancy induced hypertension: Histopathology of early-onset type reflects two stage disorder theory.**

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**Abstract**

Introduction: The placental tissues of pregnancy induced hypertension (PIH) patients exhibit multiple infarctions, acute atherosis, distal villous hypoplasia, and increased syncytial knots. However, these findings are not observed in all cases of PIH, thus the significance of these changes in PIH is still unclear. We studied the frequency of histopathological changes of placental tissue in the subgroups of PIH, such as mild and severe PIH, and early onset (< 34w) and late onset (≥ 34w) PIH.

Methods: One hundred and seven cases of PIH diagnosed at the Shinshu University Hospital, Matsumoto, Japan, between 2008 and 2014 were collected. PIH includes preeclampsia and gestational hypertension. The pathologic changes evaluated in the placenta were multiple infarctions, acute atherosis, distal villous hypoplasia, and increased syncytial knots.

Results: Placental tissues of patients with early onset PIH demonstrated acute atherosis resulting from incomplete remodeling of spiral arteries, and distal villous hypoplasia and increased syncytial knots reflecting placental hypoxia/ischemia much more frequently than those with late onset PIH (all $p<0.001$). The frequencies of multiple infarctions did not show a statistical difference between early onset PIH and late onset PIH. Moreover, there were no significant differences in the frequencies of histopathological features of placental tissue between mild PIH and severe PIH.

Conclusion: Early onset PIH exhibited histopathological changes of placental tissue consistent with the two stage disorder theory more frequently than late onset PIH. These findings support the idea that early onset PIH and late onset PIH are distinct entities or different extremes of the PIH spectrum.

**Key word**

Placenta . Pregnancy induced hypertension . Preeclampsia . Two stage disorder theory

**Introduction**

Pregnancy induced hypertension (PIH) occurs in approximately 10% of all pregnancies and is a major cause of maternal and perinatal mortality and morbidity [1, 2]. PIH includes preeclampsia (PE) and gestational hypertension (GH). GH is defined as new onset hypertension after 20 weeks of gestation, but resolving up to 12 weeks postpartum. PE is defined as GH with proteinuria. PIH increases the risk of eclampsia which is an important predictor of further organ dysfunction and mortality. Eclampsia is defined as the generalized seizure in patients with PE, when the tonic-clonic sezure is not caused by other disease such as epilepsy [2]. Clinically, PIH cases are divided into mild and severe PIH depending on the severity of hypertension and proteinuria, and also divided into early onset and late onset PIH depending on the gestational week of onset [2,3,4].

Mechanisms of pregnancy induced hypertension are still unclear. However, many investigators support the two stage disorder theory [5,6,7]. The first stage arises from poor development of the early placenta. Some immunogenic maladaptation may impair extravillous trophoblast invasion into maternal spiral arteries, resulting in poor vascular remodeling and decreased maternal blood supply. Hypoxic and ischemic condition of placental tissue induces production of anti-angiogenic factor in the trophoblasts such as the soluble form of the vascular endothelial growth factor (VEGF) receptor known as soluble frm-like tyrosine kinase-1 (sFlt-1) and soluble form endoglin (sEng). In the second stage, elevated serum sFlt-1 and sEng cause vascular endothelial dysfunction and deteriorating hypoxia/ischemia, resulting in the development of fetal growth restriction, maternal hypertension, and proteinuria.

This theory is proposed on the basis of the comparison of histopathological findings [8], Doppler ultrasound assessment [9,10], and serum biomarkers, such as placental producing proteins [11-14], anti-angiogenic factors [15-18], and endothelial dysfunction factors [19], between PIH and normotensive pregnancies. On the other hand, recent studies revealed the differences in the serum biomarkers and Doppler ultrasound assessments between subgroups of PIH depending on the severity and the time point of onset, indicating different pathophysiology among subgroups of PIH.

Generally, the placenta of PIH cases have a lower placental weight, and histopathologically exhibit multiple infarctions, acute atherosis, distal villous hypoplasia, and increased syncytial knots [20]. However, these findings are not observed in all cases of PIH, thus the significance of these changes in PIH is still unclear.

Furthermore, acute atherosis also occurs in the placental tissue of patients with lupus erythematosus and/or antiphospholipid antibody syndrome, and the changes of chorionic villi are assumed to be the results of ischemia. Therefore, these findings are not specific to PIH. The frequency of these histopathological findings in the subgroups of PIH, such as mild and severe PIH, and early and late onset PIH, has never been examined.

In the current study we investigated the histopathological changes of placental tissue in the subgroups of PIH and compared the frequency of each pathological finding between the subgroups.

## Methods

### Cases

Clinical information of one-hundred and seven cases of PIH diagnosed at the Department of Obstetrics, Shinshu University Hospital, Matsumoto, Japan between 2008 and 2014 were collected. None of the patients developed eclampsia because there was efficient therapy. The inclusion criteria for pregnant women with PIH were: 1) singleton gestation; 2) absence of chronic hypertension, systemic lupus erythematosus, and antiphospholipid antibody syndrome; and 3) undergoing regular medical examinations. PIH includes PE and GH. GH was defined as new onset hypertension (systolic pressure ≥ 140 mmHg or diastolic pressure ≥ 90 mmHg, measured at two time points in at least a 4-hour interval) after 20 weeks of gestation, but resolving up to 12 weeks postpartum. PE was defined as GH with proteinuria (at least 300 mg in a 24-hour urine sample, or 2+ protein at dipstick test). Early onset PIH was defined as hypertension developing before 34 weeks of gestation, and late onset PIH was defined as that developing after 34 weeks of gestation. Severe PIH was diagnosed as systolic pressure ≥ 160 mmHg or diastolic pressure ≥ 110 mmHg, or two grams or more urine protein in a 24-hour urine sample.

### Placental tissue samples

Macroscopic pictures of the cut surface of placenta and histopathologic slides of placental tissues of the PIH cases were retrieved from the pathology files at the Department of Laboratory Medicine, Shinshu

University Hospital. Standard sampling of placental tissues were one specimen of fetal membrane roll, one specimen of umbilical cord, and four specimens of placental tissue [21]. All tissue samples were fixed in 10% neutral-buffered formalin and embedded in paraffin. Tissue sections (3-μm-thick) were prepared for hematoxylin and eosin staining.

This study was approved by the medical ethics committee at the Shinshu University School of Medicine.

*Pathologic evaluation*

Slides were reviewed independently by single pathologist (A.T) under the blind condition to all clinical information. The pathologic changes of placenta were evaluated for following points: 1) multiple infarctions; 2) acute atherosis; 3) distal villous hypoplasia; and 4) increased syncytial knots (Fig. 1). Multiple infarctions were defined as the presence of 2 infarctions or more overall or the presence of a large infarction with the size of 3 cm in diameter or larger accompanying many small infarctions only recognizable under microscopic examination. Infarctions exhibited crowded villi and ischemic necrosis. Acute atherosis was vasculopathy of decidual spiral artery, characterized by preserved endothelial cells, accumulation of foamy macrophages, and mural fibrin deposition. Distal villous hypoplasia was defined by the small diameter of terminal villi, ranging between 30 and 40 μm. Moreover, distal villous hypoplasia was accompanied by slender stem villi with reduced branching, which has been termed accelerated maturation [20,21,22]. Increased syncytial knots were defined as the presence of more than 100 syncytial knots per 100 villi [23].

Statistical Analysis

Statistical analysis of clinical data was performed using the *t*-test and chi-square test. Fisher's exact test was used when comparing histopathological findings of placental tissue between subgroups of PIH (early onset vs. late onset and mild vs. severe). Analyses were performed with SPSS version 22 software (IBM Corp., Armonk, NY, USA). A $p$-value $<0.05$ was considered significant.

**Results**

Clinical findings

Among 107 PIH cases, 40 cases were early onset PIH (PE, n=26: GH, n=14) and 67 cases were late onset PIH (PE, n=25; GH, n=42). As for the severity, 22 cases were mild PIH (PE, n=6; GH, n=16) and 85 cases were severe PIH (PE, n=45; GH, n=40). Clinical characteristics of the cases are summarized in Table 1. In the current study, although the PIH severity was defined solely based on degree of blood pressure elevation, the PIH patients with severe manifestation, such as HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, were included in severe PIH. Patients with early onset PIH exhibited lower gestational age at delivery, placental weight, birthweight, and blood pH in the umbilical artery than those with late onset PIH (all $p<0.01$; Table 1). In addition, patients with early onset PIH had frequent severe proteinuria ($p=0.021$; Table 1) and multiparous patients ($p=0.01$; Table1). The baby's sex, severity of hypertension, diabetes mellitus, maternal body mass index, and maternal age were not significantly different between early onset PIH and late onset PIH. On the other hand, patients with severe PIH exhibited lower gestational age and birthweight than those with mild PIH (both $p<0.01$; Table 1). The baby's sex, maternal age, parity, maternal body mass index, diabetes mellitus, placental weight, and blood pH in the umbilical artery were not significantly different between mild PIH and severe PIH.

*Histopathological findings*

Histopathological features in subgroups of PIH cases are summarized in Table 2. Placental tissues of patients with early onset PIH exhibited acute atherosis, distal villous hypoplasia, and increased syncytial knots much more frequently than those with late onset PIH (all $p<0.001$; Table 2). The frequencies of multiple infarctions did not demonstrate a statistical difference between early onset PIH and late onset PIH. Moreover, there were no significant differences in the frequencies of histopathological features of placental tissue between mild PIH and severe PIH.

**Discussion**

In the current study, we found that placental tissues of early onset PIH frequently exhibited acute atherosis resulting from incomplete remodeling of spiral arteries, and increased syncytial knots and distal villous

hypoplasia reflecting placental hypoxia/ischemia. Therefore, these findings suggest that early onset PIH develops through the mechanisms suggested in the two stage disorder theory, and that late onset PIH arises from different pathophysiology. There were no significant differences in the histopathological features between mild PIH and severe PIH.

There have been several reports concerning the histopathological features of placental tissues of PIH or PE. Moldenhauer et al. have reported that the frequency of placental findings, including decidual arteriopathy, central infarction, and hypermaturity of villi, in women with PE are higher in the earlier gestational ages at the time of delivery [24]. These findings indicate that early onset PE cases exhibit frequent acute atherosis, distal villous hypoplasia, and increased syncytial knots, in agreement with our study. Zhang et al. evaluated the frequency of maternal vasculopathy characterized with acute atherosis and fibrinoid medial necrosis of spiral arteries, and they indicated a poor relationship between maternal vasculopathy and clinical manifestation [25]. Although only 21.4% of total PIH cases exhibit this vasculopathy, this lesion is found in 62% of PIH cases with a gestational age less than 30 weeks [25]. Thus, this report is consistent with our results that there was frequent acute atherosis in early onset PIH cases. Correa et al. have reported that syncytial knots are more frequently observed in patients with preterm delivery and severe PIH [26]. Their results are partly consistent with our observation that patients with early onset PIH frequently exhibited increased syncytial knots, but different from our results in that there was no significant difference in the histopathological findings of placental tissue between mild PIH and severe PIH. Furthermore, Stark et al. have demonstrated that early onset preeclampsia/eclampsia (PE/E) more frequently exhibited increased syncytial knots, distal villous hypoplasia, villous agglutination, and infarcts than late onset PE/E [27]. Their findings are in close agreement with our results, except infarcts.

The two stage disorder theory in the pathogenesis of PIH is a concept based on the studies of histopathological findings, Doppler ultrasound assessments, serum biomarkers, and hypoxic conditions of placental tissues. These findings demonstrate that impaired extravillous trophoblast invasion into decidual spiral arteries causes poor vascular remodeling and induces endothelial dysfunction [8]. Khong et al. (Amsterdam Placental Workshop Group) have recommended using the term “maternal vascular malperfusion (MVM)” as that indicating the condition induced by inadequate spiral artery remodeling [28]. Placental features being indicative of MVM include infarction, abnormalities of villous development, such as distal villous hypoplasia and increased syncytial knots, and decidual arteriopathy including acute

atherosis. Their definition of increased syncytial knots is the knots formation on more than 33% of villi, which is different from that employed in our current study [28], and wide enough to include completely our definition. When the concept of MVM is applied to our study, patients with early onset PIH frequently exhibite the features of MVM. Thus, the differences in the definition of "increased syncytial knots" do not affect the conclusion. In Doppler ultrasound assessment, a high uterine artery resistance is related to deficient spiral artery remodeling in histological examination at the early first trimester, and thus, patients with a high resistance of uterine artery flow pattern have a risk of developing PIH [9,10,29]. Furthermore, poor spiral artery remodeling can be evaluated by reduction of syncytiotrophoblast-derived peptides, such as pregnancy-associated plasma protein A (PAPP-A) and plasma protein 13 (PP-13), in maternal serum [11-14]. Recent studies, however, have indicated the differences in these findings between early onset and late onset PIH, leading to the possibility that the underlying mechanisms may be different between early onset PIH and late onset PIH. Arakaki et al. have reported that a high uterine artery pulsatility index is observed more frequently in patients with early onset PIH compared with unaffected pregnancies, but not observed in patients with late onset PIH [30]. Meta-analysis revealed that the reduction of serum PAPP-A and PP-13 are associated with early onset PE [15]. Additionally, maternal serum concentrations of anti-angiogenic factors, such as sFlt-1 and sEng, induced by placental hypoxia/ischemia vary depending on the gestational age of the onset of PIH. In particular, the placental growth factor (PLGF)/sFlt-1 ratio is higher in early onset PE [31], and reduction of PLGF levels is correlated with early onset PE [15]. These reports suggest that early onset PIH develops along the two stage disorder theory, consistent with our current study. On the other hand, late onset PIH may develop through different mechanisms.

The mechanisms of late onset PIH are associated with maternal factors such as age, obesity, and diabetes mellitus. Lisonkova et al. demonstrated that younger maternal age, nulliparity, and diabetes mellitus are strongly associated with a higher risk of late onset PE [32]. Studies of maternal hemodynamic states revealed that early onset PE seems to be linked mainly to failed spiral artery remodeling, supported with a high total vascular resistance-low cardiac output, whereas late onset PE may be linked to maternal constitutional factors, such as high body mass index, supported with a low total vascular resistance-high cardiac output [33]. These reports are partly consistent with our findings in that the patients with late onset PIH were frequently nulliparity, but different from our results in that there was no significant difference in the maternal body mass index and history of diabetes mellitus between early onset PIH and late onset PIH.

There was no significant difference in the maternal age though the patients with late onset PIH tended to be younger. Although Lisonkova et al. define that younger maternal age refers to the age under 20-year-old [32], there were no teenage patients in our current study. Furthermore, the patients who visited our hospital tended to be older because of university hospital offering advanced medical treatment.

In conclusion, early onset PIH exhibited histopathological changes consistent with the two stage disorder theory more frequently than late onset PIH. These findings support the idea that early onset PIH and late onset PIH are distinct entities or different extremes of the PIH spectrum.

**Compliance with ethical standards** This study was approved by the medical ethics committee at the Shinshu University School of Medicine (Project #3265 was approved on November 2nd, 2015).

**Conflict of interest** The authors declare that they have no conflict of interest.

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**Figure legend**

**Fig. 1**

Pathological evaluation of placenta stained with hematoxylin and eosin. **a** Placental infarctions. Villi are crowded together and attached to one another with the deposition of fibrin. **b** High power view of placental infarctions. The intervillous space is collapsed, and all cellular and nuclear structure disappears. **c** Acute atherosis. Spiral artery in section of membrane roll. Endothelial cells are present, and accumulation of foamy macrophages and mural fibrin deposition are observed. **d** Distal villous hypoplasia. Small and slender villi with wide intervillous space. **e** High power view of distal villous hypoplasia. Terminal villi exhibit a smaller diameter, ranging between 30 and 40 μm. **f** Increased syncytial knots. Syncytial knots are recognized as clusters of syncytiotrophoblastic nuclei. There are more than 100 syncytial knots per 100 villi.

Fig. 1

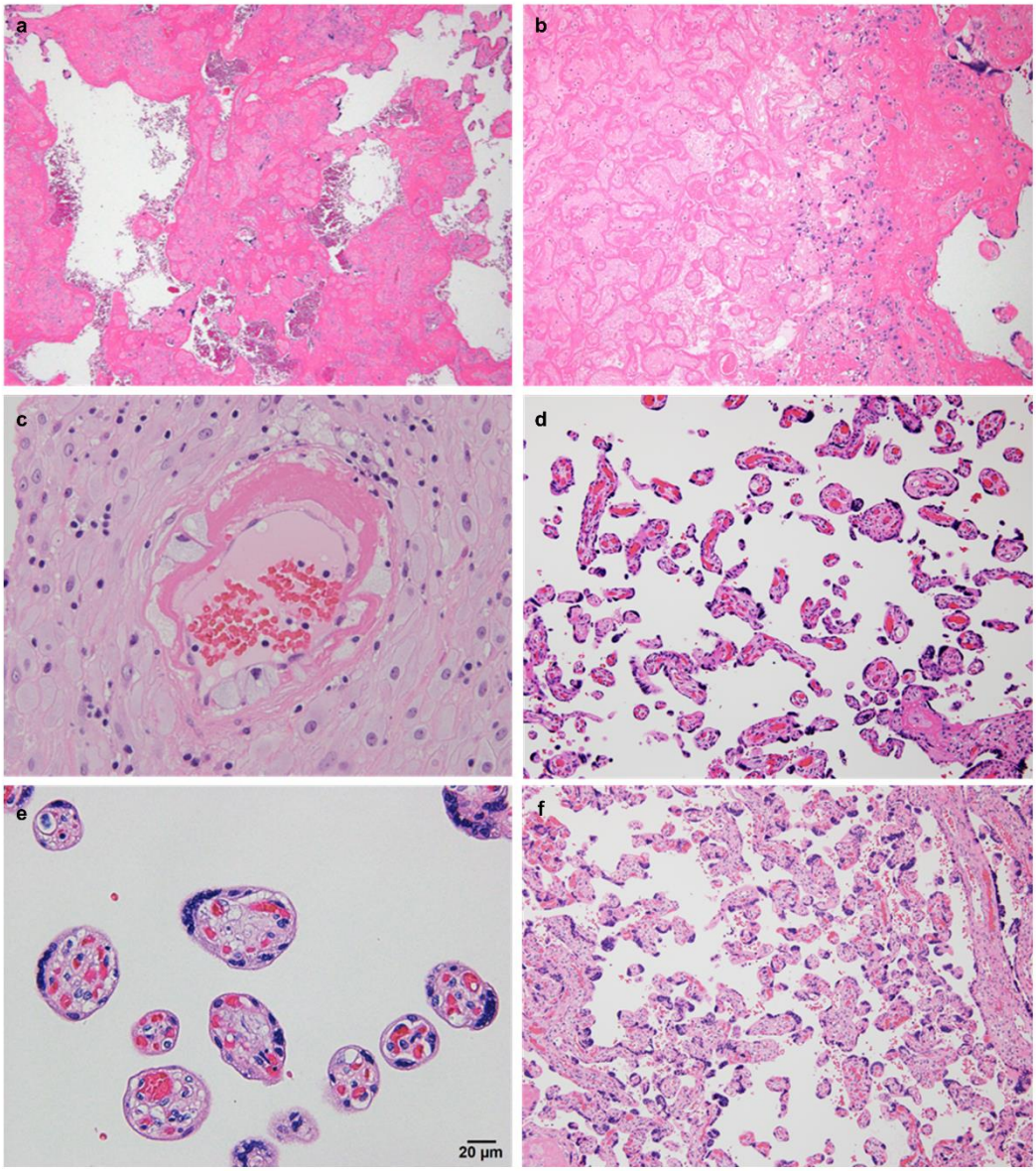

**Table 1** Clinical characteristics

| | All | Onset | | | Severity | | |
|---|---|---|---|---|---|---|---|
| | | Early onset (<34w) | Late onset (≥34w) | *P* value | Mild | Severe | *P* value |
| Case (n) | 107 | 40 | 67 | | 22 | 85 | |
| Gestational age (weeks)[a] | | | | | | | |
| Mean ± SD | 37.1±3.61 | 33.9±3.77 | 38.9±1.75 | <0.001 | 39.0±1.65 | 36.6±3.82 | <0.001 |
| Range | 27.4-42.0 | 27.4-41.1 | 34.1-42.0 | | 35.7-41.7 | 27.4-42.0 | |
| Maternal age (years)[a] | | | | | | | |
| Mean ± SD | 33.4±5.83 | 34.6±4.89 | 32.7±6.32 | 0.086 | 33.8±6.08 | 33.3±5.86 | 0.76 |
| Range | 22-51 | 22-45 | 22-51 | | 22-41 | 22-51 | |
| Maternal body mass index ($m^2$/kg)[a] | | | | | | | |
| Mean ± SD | 23.2±5.01 | 23.6±5.26 | 23.0±5.01 | 0.66 | 22.6±3.82 | 23.4±5.46 | 0.42 |
| Unknown (n) | 29 | 21 | 8 | | 0 | 29 | |
| Hypertension[b] | | | | | | | |
| Mild(≧140/90 mmHg) | 24 | 6 | 18 | | 22 | 2 | |
| Severe(≧160/110 mmHg) | 83 | 34 | 49 | 0.23 | 0 | 83 | <0.001 |
| Proteinuria[b] | | | | | | | |
| Negative | 56 | 14 | 42 | | 16 | 40 | |
| Mild (≧300 mg, <2 g) | 16 | 8 | 8 | | 6 | 10 | |
| Severe (≧2g) | 35 | 18 | 17 | 0.021 | 0 | 35 | 0.001 |
| Diabetes mellitus[b] | | | | | | | |
| Yes | 6 | 1 | 5 | | 2 | 4 | |
| No | 101 | 39 | 62 | 0.407 | 20 | 81 | 0.601 |
| Number of prior live births[b] | | | | | | | |
| 0 | 73 | 21 | 52 | | 12 | 61 | |
| ≥1 | 34 | 19 | 15 | 0.01 | 10 | 24 | 0.132 |
| Placental weight (grams)[a] | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Mean ± SD | 433.2±136.45 | 324.7±121.02 | 496.7±113.41 | <0.001 | 482.00±144.92 | 425.11±139.74 | 0.19 |
| Unknown (n) | 35 | 10 | 25 | | 7 | 28 | |
| Birthweight (grams)[a] | | | | | | | |
| Mean ± SD | 2281.0±831.86 | 1591.0±743.75 | 2698.1±470.81 | <0.001 | 2636.6±617.34 | 2193.1±812.56 | <0.01 |
| Baby's sex (n)[b] | | | | | | | |
| Female | 51 | 19 | 32 | | 11 | 40 | |
| Male | 56 | 21 | 35 | 1.000 | 11 | 45 | 0.82 |
| Blood pH in umbilical artery[a] | | | | | | | |
| Mean ± SD | 7.280±0.0729 | 7.251±0.0679 | 7.298±0.0723 | <0.01 | 7.277±0.0595 | 7.283±0.0776 | 0.71 |
| Unknown | 4 | 4 | 0 | | 0 | 4 | |

[a]Analysis by *t*-test.

[b]Analysis by $\chi^2$ test.

**Table 2** Histopathological features

| Pathological features | Early onset, n=40 | Late onset, n=67 | *P* value | Mild, n=22 | Severe, n=85 | *P* value |
|---|---|---|---|---|---|---|
| Multiple infarctions [n (%)] | 18 (45.0) | 31 (46.3) | 1.000 | 10 (45.5) | 39 (45.9) | 1.000 |
| Acute atherosis [n (%)] | 24 (60.0) | 14 (20.9) | <0.001 | 4 (18.2) | 33 (38.8) | 0.082 |
| Distal villous hypoplasia [n (%)] | 30 (75.0) | 9 (13.4) | <0.001 | 4 (18.2) | 34 (40.0) | 0.080 |
| Increased syncytial knots [n (%) | 37 (92.5) | 30 (44.8) | <0.001 | 10 (45.5) | 57 (67.1) | 0.084 |

Analysis by Fisher's exact test.