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Associations of intrauterine growth restriction with placental pathological factors, maternal factors and fetal factors; clinicopathological findings of 257 Japanese cases

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Summary. Intrauterine growth restriction (IUGR) is the leading cause of fetal mortality and morbidity. As an etiology, each of placental findings, maternal factors and fetal factors has been reported to be associated with IUGR, although a comprehensive approach to examine all of these parameters as a cause of IUGR has not been reported. In the present study, therefore, we comprehensively examined the placental findings and maternal and fetal factors in the cases of IUGR (n=257, mean maternal age, 30 years; gestational weeks, 34 weeks) and normal growth pregnancies (n=258, mean maternal age, 30 years; gestational weeks, 33 weeks), and determined risk factors for IUGR. The prevalence of pregnancy hypertension (PHT) (19% vs. 8%, P<0.01), smoking habit (3% vs. 0.7%, P<0.05) and fetal anomaly (3.5% vs. 0.8%, P<0.05) were higher in IUGR cases than normal growth pregnancies. Pathologically, the prevalence of infarction (33% vs. 14%, P<0.05), fetal vessel thrombosis (22% vs. 6%, P<0.001) and chronic villitis (11% vs. 3%, P<0.001) were higher in IUGR cases than those in normal growth pregnancies. A multivariable regression analysis revealed that maternal factors (PHT), fetal factors (anomaly), and placental findings (infarction, fetal vessel thrombosis, and chronic villitis) are independently associated with increased risk of IUGR (all P<0.01).

Key words: Intrauterine growth restriction, Placental findings, Maternal factors, Fetal factors

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Introduction

Intrauterine growth restriction (IUGR) is the leading cause of fetal mortality and morbidity (McIntire et al., 1999; Garite et al., 2004). Certain maternal conditions, such as hypertension, smoking, and collagen-vascular diseases, or fetal conditions, such as chromosomal disease and structural malformations, are associated with IUGR (Carlson, 1988; Reichlin, 1998; Villar et al., 2006), although the etiology of substantial number of cases of IUGR remains unknown.

The placenta, as an ephemeral organ interposed between the mother and fetus is often the target of insults directed at the fetus. A careful examination of properly sampled placenta may reveal the past events, and that may be potentially associated with the outcome of pregnancy. The College of American Pathologists Conference XIX on the examination of placenta has recommended the routine pathological examination of placentas, especially in the cases of IUGR and pregnancy hypertension (PHT) (Altshuler and Deppisch, 1991). Until now, many histological studies of placentas from IUGR infants showed a marked reduction in the overall volume of terminal villi, villous fibrosis or thickening of basement membrane (Salafia et al., 1992; Mitra et al., 2000; Ansari et al, 2003; Mayhew et al., 2004), infarction, fetal vessel thrombosis and chronic villitis (Knox and Fox, 1984; Redline and Pappin, 1995; Becroft et al., 2003). However, these placental pathological findings were affected by maternal factors, such as PHT and smoking (Larsen et al., 2002; Moldenhauer et al., 2003). Therefore, whether or not the association between placental abnormalities and IUGR is

independent of maternal factors remains unclear.

In the present study, therefore, we comprehensively examined the placental pathological findings and maternal and fetal factors in the cases of both IUGR and normal growth pregnancies, and determined the risk factors for IUGR.

Material and methods

Study population

We assessed placentas obtained from singleton IUGR Japanese infants at the University of Miyazaki Hospital between 1998 and 2010. A retrospective review of maternal and infant pair charts was conducted. Authors were blinded to the clinical records and histology. Multiple pregnancies or cases with stillborn infants were excluded from this study. Of these referrals, placentas with 257 cases were from IUGR infants. Control placentas, which were not complicated by IUGR, were selected randomly (n=258). The rate of Caesarian birth was 68% in the IUGR cases and 62% in the control cases. IUGR was defined as birth weight below the 10th percentile of the standard Japanese growth curve (Ogawa et al., 1998). Maternal factors of interest were age, history of pregnancy hypertension (PHT), gestational diabetes mellitus (GDM), collagen disease, smoking habit during pregnancy and past history of IUGR. PHT was defined as blood pressure of ≥140 mm Hg systolic and or ≥90 mm Hg diastolic during pregnancy, and PHT included gestational hypertension, preeclampsia, and chronic hypertension. Gestational hypertension was defined as only hypertension without proteinuria, preeclampsia was defined as PHT with proteinuria, and chronic hypertension was defined as PHT before pregnancy (Higgins and de Swiet, 2001). Fetal factors of interest were chromosomal disease or malformation. We classified the subgroups of IUGR cases, such as IUGR with maternal factors, IUGR with fetal factors, and IUGR without maternal or fetal factors. Gestational ages were estimated from the data of the last menstruation supported by ultrasound and clinical examination. The Ethics Committee of University of Miyazaki approved the present study (No.470).

Classification of placental findings

Gross findings were recorded from the original pathology reports. Microscopic sections had been submitted on the basis of criteria developed by the College of Pathologists for submission of placental specimens for pathologic examination and were available for all cases (Altshuler and Deppisch, 1991). In all of these cases, three to six sections, representing umbilical cords, fetal membranes and villous tissue were available for review. Infarction was defined by villous necrosis adjacent to the maternal surface (Fig. 1a). Decidual vasculopathy (DV) was defined by alteration of decidual vessels with fibrin, foamy cells (atherosis), intimal hyperplasia, and thrombosis (Fig. 1b). Fetal vessel thrombosis (FVT) was defined by agglutinated platelets covered by a leukocyte-containing layer of condensed fibrin (Fig. 1c) in the fetal vessels. Tenney-Parker change (T-P change, excessive syncytial knotting) was defined by ≥30% of the tertiary villi with syncytial buds (Fig. 1d). Chronic villitis was defined as the presence of numerous lymphocytes and macrophages in villous stroma (Fig. 1e). Umbilical artery abnormality (UA) was defined by single umbilical artery or umbilical artery thrombosis (Fig. 1f). Microscopic features were assessed by review of all slides of each case by Y.S. and K.M.

Statistical analysis

All statistical analyses were performed using SPSS software version 11.0 (SPSS Inc, Chicago, IL, USA). Differences between IUGR cases and controls for all categorized numerical variables were analyzed by using the chi-squared test. Maternal and gestational ages, and placental weights were compared using the Mann-Whitney test. Multivariate logistic analysis was used to assess the independent relationships between IUGR and maternal factors, fetal factor, and pathologic findings. The hazard ratio (HR) and the 95% confidence interval (CI) of IUGR with maternal factors, fetal factors, and placental findings were calculated using Cox regression analyses with adjustments for covariates. A P-value below 0.05 was considered significant.

Results

Among the cases with IUGR (n=257), there were 78 IUGR placentas with maternal factors (30%). The number of IUGR with PHT were 49 cases (19%) which included 39 gestational hypertension, 8 preeclampsia, and 2 chronic hypertension. Eleven were cases with fetal factors (4%) including 6 cases with multiple anomalies, 2 cases with heart anomaly, 1 case with esophageal anomaly, 1 case with 18 trisomy, and 1 case with 21 trisomy. The remaining 168 cases were not associated with maternal or fetal factors (66%). To assess the association of IUGR with maternal or fetal factors we compared the prevalence of maternal or fetal factors between IUGR and normal growth groups. The incidences of PHT, smoking habit, and anomaly were higher in IUGR cases compared with those in control cases (Table 1). The prevalence of past history of IUGR (recurrence of IUGR) showed a higher tendency in the IUGR group than those in the control group, but it was not significant. There was no significant difference in maternal factors (maternal age, GDM, collagen disease) between IUGR and control cases.

To assess an association of placental abnormalities with IUGR, we compared the prevalence of placental abnormalities between IUGR and control groups (Table 2). The placental weight was significantly lower in

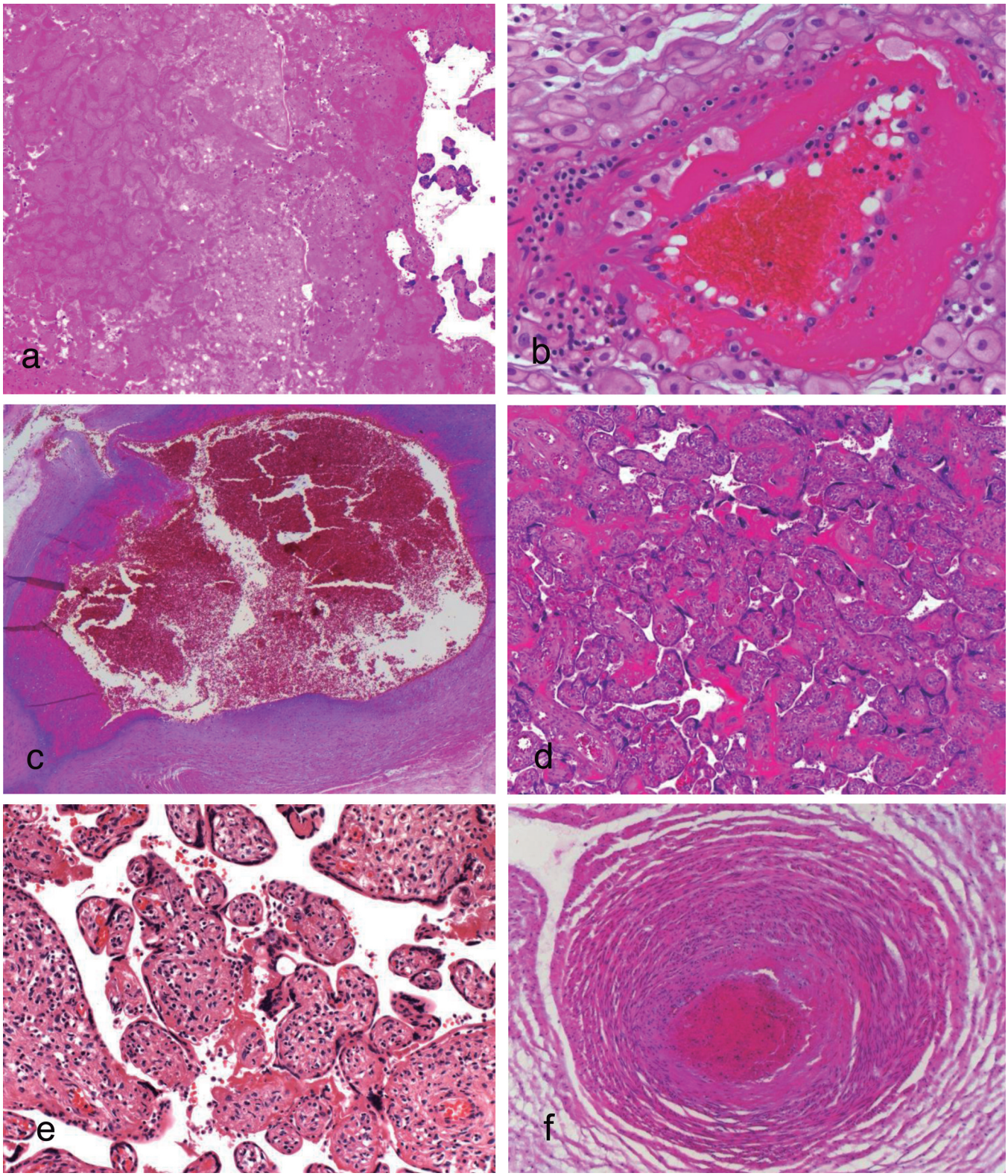

Fig. 1. Microscopical findings of placenta with IUGR. **a.** Infarction. **b.** Decidual vasculopathy (atherosis). **c.** Fetal vessel thrombosis. **d.** Tenney-Parker change. **e.** Chronic villitis. **f.** Umbilical artery thrombosis. a, d, f, x 50; b, e, x 100; c, x 25

IUGR than in the control groups. The prevalence of infarction, DV, T-P change, FVT, endothelial cushion, chronic villitis, and single umbilical artery were significantly higher in the IUGR group than in the control group. To assess an association of placental abnormalities with maternal or fetal factors, we compared the prevalence of placental abnormalities between cases with or without PHT, smoking habit, or anomaly. The prevalence of infarction is significantly higher in subjects with PHT than those without PHT (55% vs. 19%, P<0.001), but no association was found between other placental abnormalities and maternal or fetal factors (data not shown).

In the Cox regression analysis (Table 3), maternal factors of PHT or smoking habit were a significant risk factor for IUGR even after adjustment for the mother's age (Model 1). The association between PHT and IUGR remained significant, adjusting for fetal anomaly (Model 2), placental abnormalities with infarction (Model 3,4), FVT (Model 5, 6), chronic villitis (Model 7,8), or all (Model 9). In contrast, the IUGR risk of smoking habit was not significant after adjustment for infarction (Model 3 and Model 6).

Table 1. Relationship of maternal, fetal factors and IUGR.

	Control (n=258)	IUGR (n=257)
Gestational weeks	33	34
Mother age	30	30
PHT	20 (8%)	49 (19%)**
GDM	18 (7%)	9 (3.5%)
Collagen disease	7 (3%)	11 (4%)
Smoking	2 (0.7%)	9 (3%)*
Recurrence of IUGR	5 (2%)	12 (5%)
Anomaly	2 (0.8%)	9 (3.5%)*
Chromosomal disease	1 (0.2%)	2 (0.7%)

IUGR, intrauterine growth restriction; PHT, pregnancy hypertension; GDM, gestational diabetes mellitus; **: P<0.01, *: P<0.05

Discussion

In the present study, we found that the prevalence of PHT was significantly higher in the IUGR group than the control group (19% vs. 8%). On placental findings, the prevalence of infarction, which is the most common placental abnormality in IUGR placentas in the present study, was significantly higher in subjects with PHT than those without PHT (55% vs. 19%). In previous studies, the prevalence of placental infarction was 17-28% in IUGR pregnancies (Altshuler et al., 1975; Salafia et al., 1992; Becroft et al., 2002; Mardi and Sharma, 2003), and this prevalence is similar to our findings. Generally, infarction is considered to be a result of disturbance of the intervillous circulation, followed by an obstruction of maternal arteries in the placental floor (Benirschke and Kaufmann, 2006; Fox and Sebire, 2007). Moldenhauer et al. (2003) reported that infarction and fetal vessel thrombosis were significantly higher in subjects with PHT, particularly at early gestational ages. Salafia et al.

Table 2. Relationship of pathological findings and IUGR.

	Control (n=258)	IUGR (n=257)
Placenta weight (g)	373	296[c]
Marginal insertion	11 (4%)	15 (6%)
Velamentous insertion	3 (1%)	7 (3%)
Infarction	36 (14%)	85 (33%)[a]
DV	15 (5%)	56 (22%)[b]
T-P change	4 (1%)	30 (12%)[b]
FVT	15 (6%)	57 (22%)[c]
Endothelial cushion	31 (12%)	47 (18%)[a]
Chronic villitis	8 (3%)	28 (11%)[c]
SUA	1 (0.3%)	10 (4%)[a]
UAT	0 (0%)	5 (2%)

IUGR, intrauterine growth restriction; DV, decidual vasculopathy; T-P change, Tenney-Parker change; FVT, fetal vessels thrombosis; SUA, single umbilical artery; UAT, umbilical artery thrombosis; [a]: P<0.05, [b]: P<0.01, [c]: P<0.001

Table 3. Multiple logistic analysis of factors with IUGR placentas.

Variable	Model 1 HR	Model 2 HR	Model 3 HR	Model 4 HR	Model 5 HR	Model 6 HR	Model 7 HR	Model 8 HR	Model 9 HR
					Mother factors				
PHT	3.6 (2.0-6.4)[c]	3.9 (2.2-6.9)[c]	3.0 (1.5-6.0)[b]	2.9 (1.6-5.3)[b]	3.9 (2.0-7.7)[c]	3.7 (2.0-6.6)[c]	4.3 (2.2-8.4)[c]	3.8 (2.1-6.9)[c]	2.7 (1.5-5.1)[b]
Smoking	5.1 (1.1-24)[a]	5.1 (1.1-24)[a]	4.2 (0.8-22)	3.9 (0.8-19)	7.0 (1.2-38)[a]	5.5 (1.1-26)[a]	6.0 (1.1-32)[a]	5.6 (1.2-26)[a]	4.7 (0.9-23)
					Fetal factors				
Anomaly	-	4.7 (1.9-12)[b]	-	4.9 (1.9-12)[b]	-	4.1 (1.6-11)[b]	-	4.7 (1.8-12)[b]	3.9 (1.5-10)[b]
					Placental findings				
Infarction	-	-	2.7 (1.6-4.7)[c]	2.4 (1.5-3.8)[c]	-	-	-	-	2.3 (1.4-3.7)[b]
FVT	-	-	-	-	4.8 (2.3-9.8)[c]	4.6 (2.4-8.4)[c]	-	-	4.3 (2.2-8.1)[c]
CV	-	-	-	-	-	-	4.4 (1.6-11)[b]	5.3 (2.1-13)[c]	4.5 (1.8-11)[b]

HR, Hazard ratio; FVT, fetal vessel thrombosis; CV, chronic villitis; PHT, pregnancy hypertension. [a]: P<0.05, [b]: P<0.01, [c]: P<0.001

(1995) also reported that the prevalence of PHT was higher in the preterm IUGR group, and that infarction was frequently observed in these placentas. In the present study, we have demonstrated that IUGR risk with PHT was reduced but remained significant after adjustment for infarction (Table 3, Model 2-4). This indicates that the association between PHT and IUGR was in part explained by placental infarction, although both PHT and placental infarction were independently associated with IUGR.

Although previous studies have reported that placentas from maternal smokers showed few morphological changes, such as an increased thickness of the villous membrane (Burton et al., 1989), or reduced dimension of villous capillaries (Larsen et al., 2002) Vedmedovska et al. (2011) recently demonstrated that the prevalence of infarction was significantly higher in the IUGR placentas with smoking habit than those of control group. Suzuki et al. (1980) and Andersen et al. (1984) have revealed reduced intervillous blood flow in women who were smoking and these findings were confirmed by Doppler studies (Lees et al., 2001; Albuquerque et al., 2004). Our data showed that the prevalence of maternal smoking is significantly higher in the IUGR group than those in the control group, and smoking in itself was an increased risk factor for IUGR (Table 1 and Model 1 in Table 3). However, the association between smoking and IUGR was not significant after adjustment for placental infarction, suggesting that the increased IUGR risk of smoking was explained by placental infarction. Placental infarction is highly associated with maternal blood flow. Our findings may support that smoking reduced maternal blood flow. However, because of the small sample size of maternal smokers in the present study, further investigation is required on this issue.

FVT was a second common finding in placentas of the IUGR group in the present study. Aviram et al. (2010) and Redline and Pappin (1995) have reported that FVT was associated with IUGR and discordant growth in monochorionic-twin placentas. Moreover, Fox and Sebire (2007) have reported that FVT was common in diabetes and PHT. In the present study, we have also demonstrated that there is a significant association between FVT and IUGR (Table 2), which was not associated with maternal factors (PHT and smoking) or fetal anomaly (Table 3). Although the mechanism underlying FVT remains uncertain, fetal vascular obstructive lesion is an important contributor for IUGR.

The incidence of circulatory disturbance findings (infarction, DV, FVT) was similar to our data in previous studies of placentas with IUGR from non-Asian countries. However the incidences of chronic villitis were higher (20-40%) (Altshuler et al., 1975; Salafia et al., 1992; Redline, 2007). Although ethnic origin has not been evaluated, Bercroft et al. (2005) reported chronic villitis to be more common in whites than either Maoris or mothers of Asian ancestry. Mardi and Sharma (2003) showed that the incidence of chronic villitis with IUGR was 12% in Indian mothers. Therefore, the incidence of chronic villitis in Asian mothers may be lower than non-Asian mothers. The reason for these differences remains unknown. Recent studies demonstrated the differences of pregnant mothers in different countries and of different ethnic origin (Engel et al., 2009; Rao et al., 2006). The differences of placental findings may be associated these ethnic factors.

In conclusion, the present study has demonstrated that each of the placental findings (infarction, FVT, chronic villitis), maternal factors (PHT), and fetal anomaly were independently associated with IUGR. This complexity in the pathophysiology of IUGR should be borne in mind by the clinicians, and some preventative approach, such as blood pressure control and smoking cessation, should be performed in the clinical setting.

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