

# Pathologic Differences between Placentas from Intrauterine Growth Restriction Pregnancies with and without Absent or Reversed End Diastolic Velocity of Umbilical Arteries

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**Background:** Abnormal umbilical artery Doppler velocimetry is one of the important findings of intrauterine growth restriction (IUGR) and IUGR is associated with high perinatal morbidity and mortality. In addition, this abnormal Doppler velocimetry is correlated with placental insufficiency. The aim of this study was to determine the pathologic differences in the placentas from IUGR pregnancies with and without the absent or reversed end diastolic velocity (AREDV). **Methods:** Among the cases that had undergone prenatal follow-up in our institute, a retrospective slide review was conducted for 18 cases of IUGR with AREDV and 17 cases with IUGR that had normal end-diastolic flow of the umbilical artery. **Results:** The birth weight and the other clinical parameters were not different among the two groups. Grossly, the placental weight percentiles were significantly smaller in AREDV group when they were adjusted according to gestational age. Histologically, chronic deciduitis, mural hypertrophy of the decidual arteries, an intimal fibrin cushion of the large fetal vessels, increased syncytial knots, villous agglutinations, avascular villi, villous stromal-vascular karyorrhexis, and acute atherosclerosis were more frequently found in the AREDV group and their presence showed statistical significance. **Conclusions:** These findings suggest that pathologic abnormalities due to fetal and maternal vasculopathies in the placenta may be the cornerstone for inducing AREDV in the umbilical artery.

**Key Words:** Fetal growth retardation; Umbilical arteries; Doppler velocimetry; Placenta; Pathology

The etiologies underlying intrauterine growth restriction (IUGR) are not fully understood, but histologic evaluation of the placentas from IUGR pregnancies has significantly contributed to our understanding of the involved pathophysiology involved. An impairment in the invasion of fetal trophoblast cells into the maternal decidua has been hypothesized as a cause of placental insufficiency and this leads to IUGR.<sup>1</sup> The gross findings of placentas from IUGR pregnancies include a reduced placental weight, a thin umbilical cord, and parenchymal loss. The examples of the histologic findings include changes in the terminal chorionic villi such as increase syncytial knots or villous infarcts by maternal underperfusion, fetal blood supply abnormalities due to fetal thrombotic vasculopathy, and inflammatory conditions of the placental membrane such as chorioamnionitis.<sup>1,2</sup>

The severity of IUGR has been proposed based on Doppler velocimetry of the umbilical artery and this measurement reflects different degrees of placental insufficiency.<sup>3</sup> Doppler velocimetry of the umbilical artery is used to evaluate the patholog-

ically small fetus, which is caused by aberrant uteroplacental perfusion, and a fetus with absent or reversed end diastolic velocity (AREDV) of the umbilical artery: both types of fetuses require maternal hospitalization and daily fetal monitoring because of the high fetal mortality.<sup>4</sup> Histopathologic studies have suggested that abnormal Doppler velocimetry is correlated with pathologic lesions of the placenta that are characterized by obliteration of the arterioles in the tertiary stem villi.<sup>5</sup> AREDV is a strong indication of placental insufficiency and it is a significant at-risk indication for the progression of fetal acidosis, fetal distress, a low Apgar score, and even perinatal death.<sup>6-8</sup>

There are many studies that have focused on the pathology of the placenta in various circumstances. The aim of this study was to identify the pathologic findings of the placentas in IUGR pregnancies which show different rate of occurrence between the placentas with and without AREDV, and to suggest the possible pathogenic mechanisms of AREDV at the level of the placenta.

## MATERIALS AND METHODS

### The research subjects

This study was approved by the Clinical Study Medical Ethics committee (VC10E1S10035) and written informed consent was obtained from all the subject. Among the pregnancies diagnosed with IUGR and that were delivered in the Department of Obstetrics at the Catholic University of Korea of St. Vincent's Hospital, the umbilical arterial blood flow was measured within 1 week prior to delivery. The study subjects were divided into the following two groups: IUGR with AREDV (the AREDV group,  $n=18$ ); and IUGR only (the control group,  $n=17$ ). In this study, IUGR was defined when the actual birth weight was less than the 5th percentile birth weight for the gestational age according to the definition of Seeds.<sup>9</sup>

### Research methods

The medical records from the IUGR pregnancies with or without AREDV and the pathologic examinations of the placentas were included in this study. The clinical information included the maternal age, parity, the co-existing obstetric diseases such as pre-eclampsia or gestational diabetes mellitus, the mode of delivery, the gestational age at delivery, the birth weight, gender, and the Apgar scores. Among them, the birth weights were adjusted for the gestational age.<sup>10</sup>

### Placental pathologic examination

The placental sizes and weights, the gross findings of the placentas such as chorangiomas and hematomas, and the gross findings of the umbilical cords including the single umbilical artery and cord knots, were recorded. The percentage of placental weight was calculated based on the mean placental weight for the corresponding gestational age.<sup>11</sup> The placentas were fixed in formalin. From each placenta, four tissue samples were embedded in paraffin blocks for microscopic assessment, as follows: one section from the free membrane, one section from the umbilical cord, and two sections from the full thickness placenta. All the pathologic examinations were performed by one pathologist. The placental pathology has been classified differently in the various reports.<sup>12-16</sup> In this study, the pathologic findings of the placentas were divided into two groups. The one group included the lesions found in the fetal membrane, including the umbilical cord, the chorionic membrane and the decidua pari-

etalis, and the other group included the lesions found in the placenta proper. The definition of these findings was based on the criteria suggested by the Perinatal Section of the Society for Pediatric Pathology and other reports that focused on placental pathology.<sup>12,14,17-21</sup> The lesions found in the fetal membrane included acute chorioamnionitis, chronic deciduitis, mural hypertrophy of the decidual arteries, acute atherosclerosis, thrombi of the large fetal vessels and an intimal fibrin cushion of the large fetal vessels, and the lesions found in the placenta proper included villous infarct, an increased syncytial knot, villous agglutination, increased intervillous fibrin, distal villous hypoplasia, avascular villi, villous stromal-vascular karyorrhexis, chronic villitis, fetal thrombotic vasculopathy, advanced villous maturation, chorangiosis, acute atherosclerosis and persistent muscularization of the basal plate artery. Because syncytial knots are the usual finding in the ordinary placenta, only the severe syncytial knots (more than 30% of the parenchyma) were counted. Also, because acute atherosclerosis was found not only in the decidua parietalis but also in the placenta proper, it was included in both sites.

### Statistical analysis

The data is presented as the mean  $\pm$  standard deviation. Data analysis was performed with SAS ver. 8 (SAS Inc., Cary, NC, USA). Student's *t*-test was used to compare continuous variables (maternal age, gestational age, birth weight, gravidity, parity, and placental weight); a chi-square test or Fisher's exact test was used for some of the clinical categories and the placenta pathologic findings. For all the statistical analyses, a *p*-value  $< 0.05$  was considered significant.

## RESULTS

### Clinical characteristics

Table 1 shows a comparison of the clinical characteristics between the AREDV and control groups. The mean maternal age was not significantly different between the 2 groups (31.6 years and 30.6 years, respectively). Numerically, the birth weights (1,107 g and 1,862 g, respectively) were considerably lower in the AREDV group than that in the control group, but when the birth weights were adjusted according to the gestational age,<sup>10</sup> all of the neonates in both groups were in the 10th or 25th percentile, and the differences were not statistically significant. Pre-eclampsia, a non-stress test, and fetal distress were detected

**Table 1.** Maternal and neonatal characteristics between the two groups

	AREDV (n = 18)	Control (n = 17)	p-value
Maternal age (yr)	31.5 ± 4.26	30.6 ± 4.23	0.505 <sup>a</sup>
Gravidity (n)	2.11 ± 1.61	2.18 ± 2.51	0.927 <sup>a</sup>
Pre-eclampsia (%)	77.77	35.29	0.011 <sup>b</sup>
Diabetes mellitus (%)	5.55	0	0.331 <sup>c</sup>
Oligohydramnios (%)	44.44	29.41	0.358 <sup>b</sup>
Non-reactive NST (%)	72.22	11.76	0.000 <sup>c</sup>
Fetal distress (%)	100	17.65	0.000 <sup>c</sup>
Cesarean section (%)	100	70.59	-
Birth weight (g)	1,107 ± 0.36	1,862 ± 0.26	0.000 <sup>a</sup>
Birth weight percentile			0.407 <sup>b</sup>
Numbers within 10%	12	9	
Numbers within 25%	6	8	
Perinatal death (%)	5.56	0	-

<sup>a</sup>Statistical significance test was determined by student's t-test; <sup>b</sup>Statistical significance test was determined by chi-square test; <sup>c</sup>Statistical significance test was determined by Fisher's exact test.

AREDV, absent or reversed end diastolic velocity; NST, nonstress test.

**Table 2.** Gross characteristics of the placentas

	AREDV (n = 18)	Control (n = 17)	p-value
Size (cm)	14.07 ± 1.39	16.27 ± 2.07	0.001
Weight (g)	265.83 ± 54.2	432.29 ± 151.3	0.000
Placental weight percentage <sup>a</sup> (%)	75.97 ± 12.58	98.85 ± 34.93	0.003
Fetoplacental weight ratio	0.26 ± 0.06	0.23 ± 0.07	0.282
Single umbilical artery (%)	0	0	-
Membranous insertion (%)	0	0	-
Marginal insertion (%)	0	2	-
Hematoma (%)	0	0	-
Chorangioma (%)	0	0	-
Meconium staining (%)	1	0	-

<sup>a</sup>Placental weight/mean placental weight of the corresponding gestational age.

more frequently in the patients with AREDV than that in the control group.

### Placental characteristics

The placental gross findings are summarized in Table 2. The placental histopathologic characteristics are shown in Table 3. The placental diameter and weight were considerably less in the AREDV group (14.07 ± 1.39 cm and 265.83 ± 54.2 g, respectively) compared with that in the control group (16.27 ± 2.07 cm and 432.29 ± 151 g, respectively). When the placental weight was adjusted for gestational age, the placental weight percentiles were significantly lower in the AREDV group than that in the control group.<sup>11</sup> The fetoplacental weight ratio was not significantly different between the two groups. Two cases of mar-

**Table 3.** Histopathologic findings of placentas

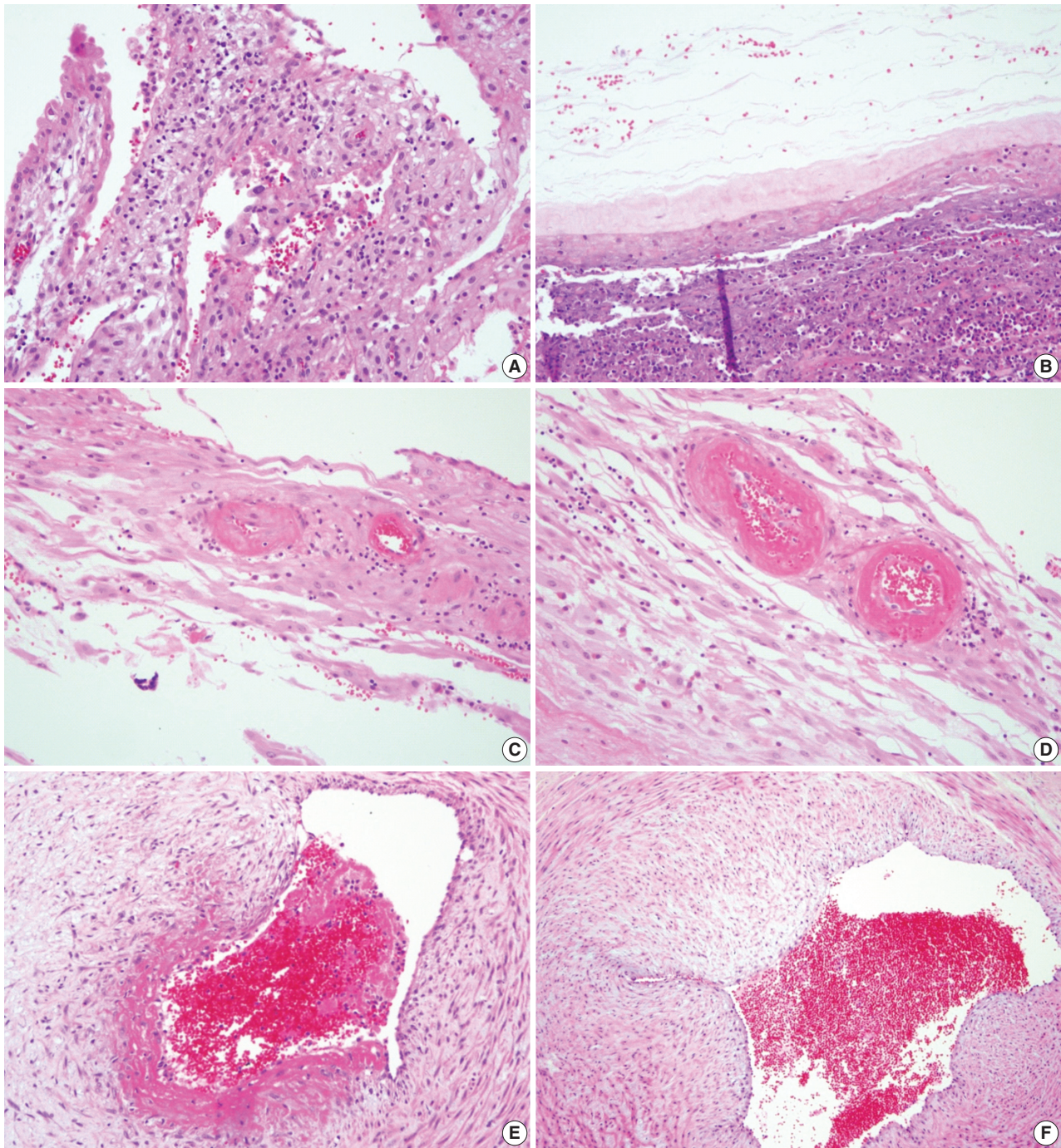
	AREDV (n = 18)	Control (n = 17)	p-value
Lesions of umbilical cord, chorionic membrane and decidua parietalis			
Funisitis and umbilical vasculitis	0	0	-
Acute chorioamnionitis	1	0	1.000
Chronic deciduitis	13	4	0.007
Mural hypertrophy of decidual arteries	5	0	0.045
Acute atherosclerosis	8	2	0.060
Thrombi of large fetal vessels	1	1	1.000
Intimal fibrin cushions of large fetal vessels	12	5	0.044
Lesions of placenta proper and implantation site			
Villous infarct	7	2	0.121
Increased syncytial knots	15	3	0.000
Villous agglutination	10	1	0.003
Increased intervillous fibrin	7	8	0.738
Distal villous hypoplasia	8	4	0.289
Avascular villi	10	3	0.035
Villous stromal-vascular karyorrhexis	10	1	0.003
Chronic villitis (VUE)	1	0	1.000
Fetal thrombotic vasculopathy	2	1	1.000
Advanced villous maturation	3	0	0.229
Chorangiosis	3	0	0.229
Acute atherosclerosis	6	0	0.019
Persistent muscularization of basal plate arteries	0	0	-

AREDV, absent or reversed end diastolic velocity; VUE, villitis of unknown etiology.

ginal insertion of the umbilical cord were detected in the control group and one case of meconium staining occurred in the AREDV group. No other gross pathologic findings, such as a single umbilical artery, hematomas, and chorangiomas, were found in either group.

Histopathologically, specific lesions were not found in the umbilical arteries of either group. In the fetal membranes, the rates of chronic deciduitis, mural hypertrophy of the decidual arteries and an intimal fibrin cushion of the large fetal vessels were significantly higher in the AREDV group compared to that of the control group ( $p = 0.007$ ,  $p = 0.045$ , and  $p = 0.004$ , respectively) (Fig. 1). In the placenta proper, the rates of increased syncytial knots, villous agglutination, avascular villi, villous stromal-vascular karyorrhexis, and acute atherosclerosis were significantly higher in the AREDV group compared to that of the control group ( $p = 0.000$ ,  $p = 0.003$ ,  $p = 0.035$ ,  $p = 0.003$ , and  $p = 0.019$ , respectively) (Fig. 2). Although villous infarct, distal villous hypoplasia, fetal thrombotic vasculopathy, advanced villous maturation and chorangiosis were more frequently found in the AREDV group compared to that in the control group, the differences were statistically insignificant (Fig. 3).





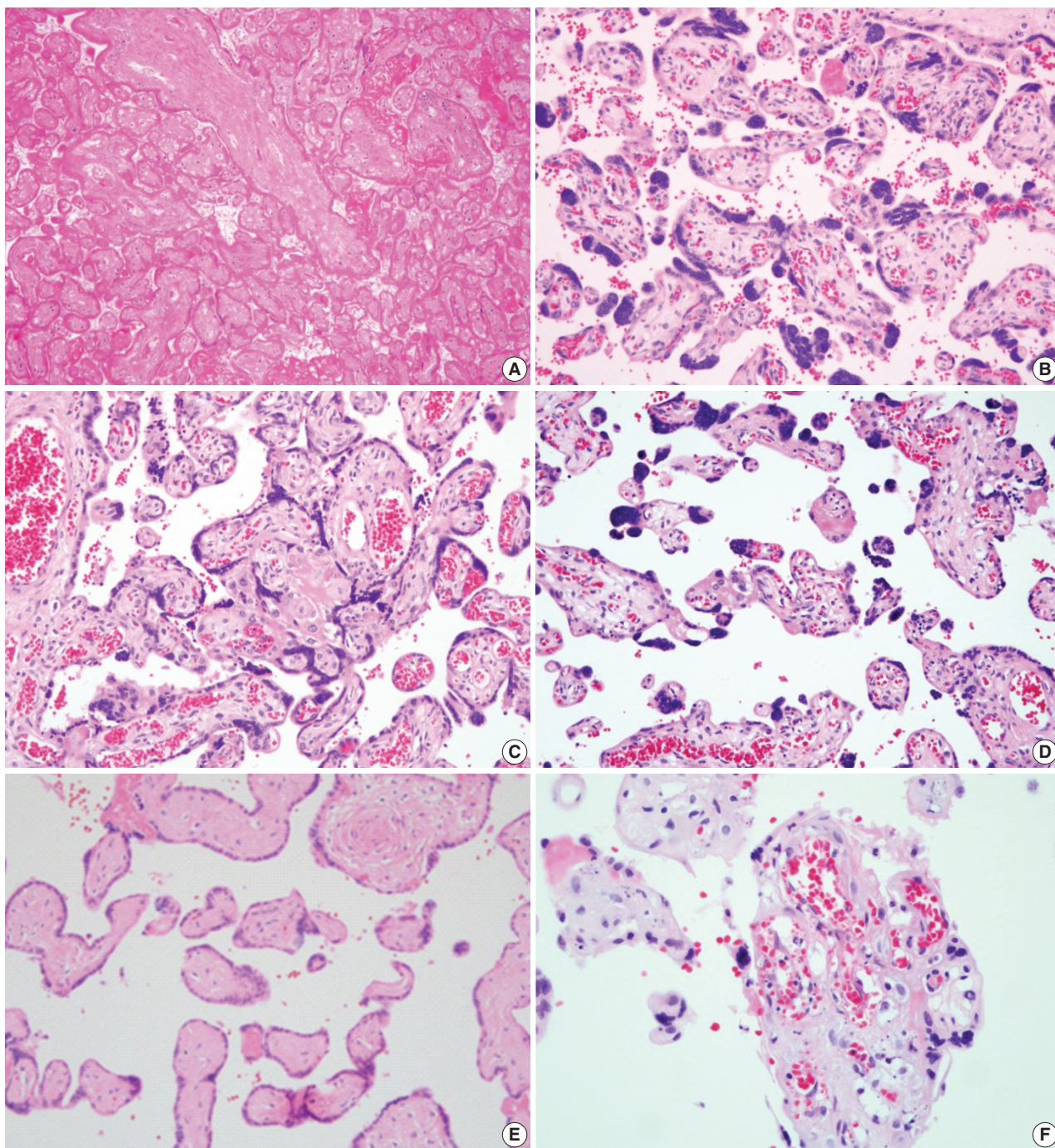
**Fig. 1.** (A) Histopathologically, chronic deciduitis is characterized by a lymphohistiocytic infiltration with plasma cells in the deciduas. (B) Necrotizing deciduitis is found in 1 case of absent or reversed end diastolic velocity group. (C) Mural hypertrophy of the arterioles in the decidua parietalis. (D) Acute atherosclerosis, which is characterized by fibrinoid necrosis of the arterial smooth muscle, is seen in the deciduas. (E) Thrombi and features of vasculitis are found in the fetal vessels in the chorionic plate. (F) An intimal fibrin cushion composed of subendothelial fibrinoid deposits is noted within the walls of the large fetal vessels.

## DISCUSSION

The definition of IUGR is currently not completely settled,<sup>20</sup>

but in this study, IUGR was defined when the actual birth weight was less than the 5th percentile of birth weight for the gestational age according to the definition of Seeds.<sup>9</sup> In the present



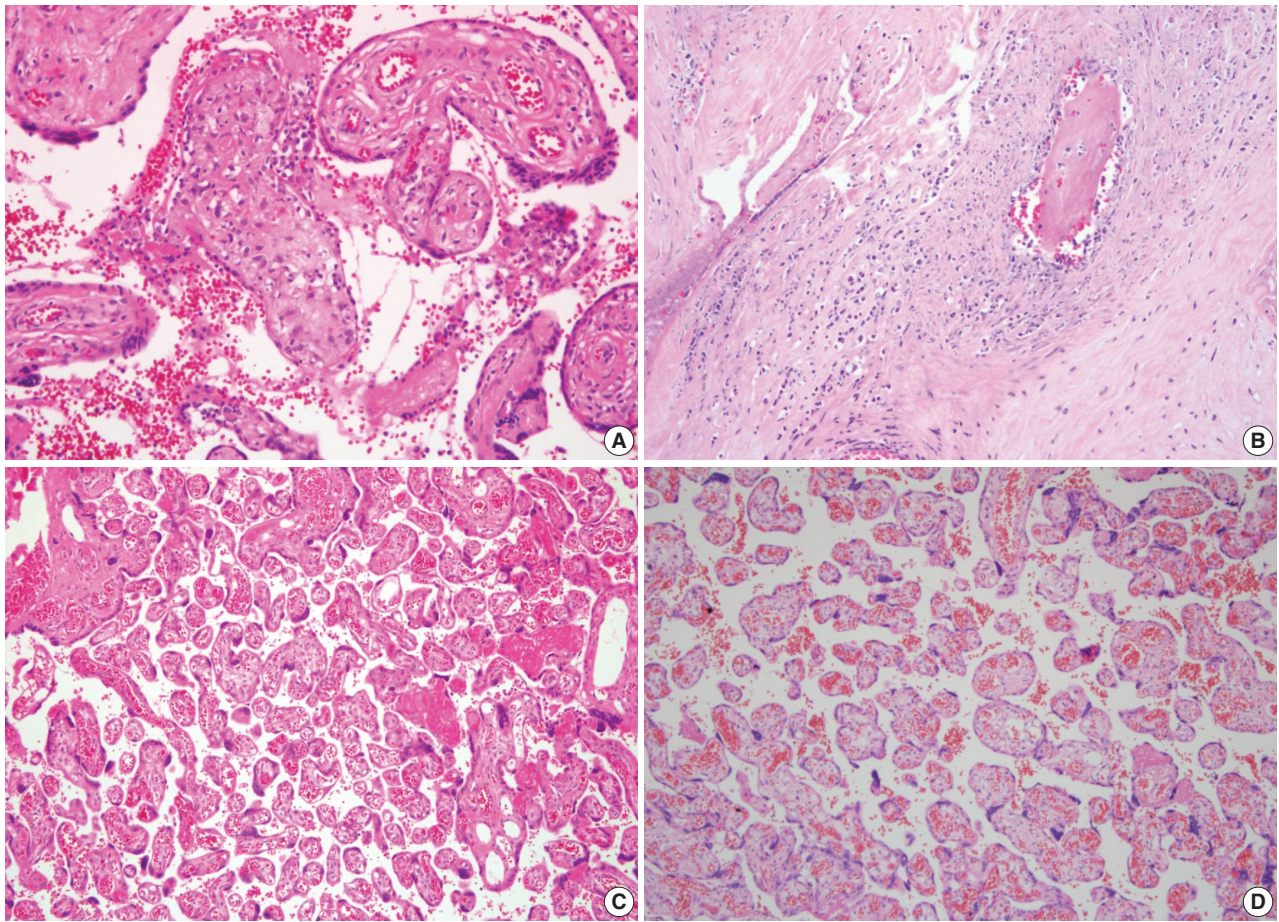


**Fig. 2.** (A) Infarction of the chorionic villi is noted near the chorionic plate. (B) Increased syncytial knots are characterized by aggregates of syncytiotrophoblast nuclei along the stem or distal villi. (C) Villous agglutination is seen as clusters of adherent distal villi agglutinated by fibrin and/or bridging syncytial knots. (D) Distal villous hypoplasia is found, which shows a small size and a decreased number of distal villi. (E) Avascular villi are characterized by terminal villi showing the total loss of villous capillaries and bland hyaline fibrosis of the villous stroma. (F) In villous stromal-vascular karyorrhexis, the nuclear debris of fetal cells can be noted in the stroma of the terminal villi.

study, differences in the histopathologic findings between the placentas from pregnancies complicated by IUGR with and without AREDV were noted. The gross and microscopic patho-

logic examinations of the placenta are invaluable tools for elucidating the pathophysiology underlying IUGR, and they can help us understand the causes and risks of recurrence.<sup>12</sup> Placen-





**Fig. 3.** (A) In chronic villitis, lymphocytic and histiocytic infiltrations are found in the villi. (B) Fetal thrombotic vasculopathy that's characterized by obliterative vasculopathy is noted in the stem villi. (C) In this case of a 27 gestational week pregnancy, advanced villous maturation is noted, which has similar histologic features as that of a near term placenta. (D) Chorangioma is characterized by increased capillaries in the terminal villi.

tal insufficiency is the most common pathophysiologic cause of IUGR. In pregnancies complicated by IUGR, some fetuses have abnormal Doppler velocimetry of the umbilical artery, whereas other fetuses have normal Doppler velocimetry of the umbilical artery. Doppler velocimetry of the umbilical artery can be useful for distinguishing small, but normally growing fetuses from pathologically small fetuses,<sup>6</sup> and it can be effective to help prevent perinatal mortality or morbidity by anticipating and planning for fetal compromise. AREDV is a severe form of placental insufficiency.

The placental pathology in IUGR pregnancies with AREDV varies and this includes an abnormal placental shape, marginal cord insertion, and maldevelopment of the peripheral chorionic villi.<sup>22-24</sup> Defective extravillous trophoblast invasion and a reduction of the inter-villous blood flow may be responsible for the development of ischemic lesions in the placenta.<sup>22,23</sup> Placental pathology has been classified into inflammatory lesions

and vasculopathies in several reports.<sup>14,25,26</sup> For example, Salafia *et al.*<sup>25</sup> classified the lesions according to the categories of intra-placental vaso-occlusion, uteroplacental vasculopathy, and inflammatory conditions, and they found that the AREDV cases had more fetal stem villi with medial hyperplasia and luminal obliteration, more poorly vascularized terminal villi, villous stromal hemorrhage, hemorrhagic endovasculitis, and abnormal thin-walled fetal stem vessels. The Perinatal Section of the Society for Pediatric Pathology has recently classified the pathology of the placenta into inflammatory lesions, maternal vascular abnormalities and fetal vascular abnormalities. In addition, they suggested the definitions of these lesions. In this study, the interpretation of most of the pathologic items described in the histopathology were largely based on these definitions.<sup>17-19</sup> Among the lesions that occurred in the fetal membrane, acute chorioamnionitis means a diffuse-patch infiltration of neutrophils in the fibrous chorion and/or amnion. Although chronic deciduitis

was not included in this definition, it is defined as a lymphohistiocytic infiltration with plasma cells in the deciduas.<sup>20,21</sup> Mural hypertrophy of the decidual arteries is thickening (mean wall diameter > 30% of the mean circumference) of the maternal arterioles in the decidua parietalis. Acute atherosclerosis means fibrinoid necrosis of the arterial smooth muscles in the muscularized maternal arteries of basal plate, the marginal zone and/or the membranous deciduas. Thrombi of large fetal vessels means organized blood clots, occlusive or nonocclusive, of any age and that compromise the lumina of the fetal vessels in the chorionic plate or the proximal portion of the villous tree. Intimal fibrin cushion of the large fetal vessels is subendothelial or intramuscular fibrin or fibrinoid deposition within the walls of the large fetal vessels. Among the lesions that occurred in the placenta proper, villous infarct is coagulation necrosis of the chorionic villi. An increased syncytial knot means aggregates of syncytiotrophoblast nuclei along the stem villi or at one or more poles of the distal villi. Villous agglutination is defined as clusters of adherent distal villi agglutinated by fibrin and/or bridging syncytial knots accompanied by stromal fibrosis, cellular degeneration or karyorrhexis. Increased intervillous fibrin means abnormal amounts of intervillous fibrin that either coat the proximal stem villi or that are eccentrically adherent to the distal villi. Distal villous hypoplasia means the modal diameter of the distal villi is decreased. In avascular villi, three or more foci of two or more terminal villi show the total loss of villous capillaries and bland hyaline fibrosis of the villous stroma. Villous stromal-vascular karyorrhexis means three or more foci of two or more terminal villi showing karyorrhexis of fetal cells with preservation of the surrounding trophoblast. In chronic villitis lymphocytic, a histiocytic infiltration is seen in the terminal villi.<sup>14</sup> Fetal thrombotic vasculopathy is obliterative vasculopathy in the stem villi. Chorangioma, is vascular hyperplasia of the terminal chorionic villi, and this is defined as the occurrence of 10 or more villi with 10 or more capillaries in 10 low-power microscopic fields of the non-infarcted placental areas.<sup>27</sup>

In the current study, we did note significant differences in the pathologic findings such as chronic deciduitis, mural hypertrophy of the decidual arteries, an intimal fibrin cushion of the large fetal vessels, increased syncytial knots, villous agglutination, avascular villi, villous stromal-vascular karyorrhexis, and acute atherosclerosis between the IUGR pregnancies with AREDV and those without AREDV. These results show that maternal or fetal vascular abnormalities may play an essential role in the generation of placental insufficiency, which in turn causes AREDV on the Doppler velocimetry. Chronic villitis and villous stromal

hemorrhage have been reported to occur more often in the IUGR placentas by other investigators,<sup>26,28</sup> and this is in contrast to our findings. Moreover, villous infarcts and syncytiotrophoblastic knots were not reported in the AREDV group by other investigators,<sup>25</sup> yet syncytiotrophoblastic knots were found significantly more often in the current study. Of the inflammatory conditions, including acute chorioamnionitis, chronic chorioamnionitis, acute necrotizing deciduitis or chronic deciduitis, only chronic deciduitis was significantly associated with the IUGR pregnancies with AREDV. Embryologically, impairment of trophoblast invasion into the maternal spiral arteries beginning in the 1st trimester results in restriction of stem villi growth and an increase in the fetoplacental flow resistance, which displays an abnormal Doppler waveform. The villi from IUGR pregnancies with AREDV demonstrate poor vascular development, poor cytotrophoblast proliferation, syncytiotrophoblastic aging, and excessive syncytiotrophoblastic knotting.<sup>23</sup> We think that the results of our current study support this pathogenesis. These histopathologic phenomena are associated with poor transfer of oxygen and nutrients to the fetus, which results in pathologic IUGR.

We are aware of the limitations to our study. First, the gestational age was significantly different between the two groups. Second, the number of patients was small. Above all, not only the cases of AREDV, but also those of IUGR were not sufficient to compare the clinical and pathologic findings according to gestational age. Therefore, although the fetal birth weights and placental weights could be adjusted according to gestational age, there were some difficulties when comparing the pathologic findings of the placenta. But when we remember on one hand that in the developmental process of the placenta, the first and second trimesters are characterized by the formation of mesenchymal villi, immature intermediate villi and finally stem villi with the establishment of an arterio-venous network, and during the third trimester the complete form of placentas are established by the formation of mature intermediate villi and terminal villi,<sup>23,29,30</sup> and on the other hand that when comparisons of the histologic states were done between the two groups of this study and the placental formations were generally compatible with the third trimester stage, except for two cases of AREDV that showed advanced maturation of villi, we think that the comparisons of the pathologic findings of the placenta in this study were not forced into interpretation. Of course, a more precise study may be possible when sufficient cases become available. Despite these limitations, we conclude that IUGR with AREDV has more defects in the maternal and fetal vascu-



latures than does IUGR without AREDV. Thus, although pathologic examination of the placenta may not be a primary tool for the diagnosis of pathologic IUGR, the histopathologic findings can be informative for understanding the pathophysiology underlying IUGR.

In summary, we observed that the extent of maternal or fetal vascular abnormalities, and especially mural hypertrophy of the decidual arteries, an intimal fibrin cushion of large fetal vessels, increased syncytial knots, villous agglutination, avascular villi, villous stromal-vascular karyorrhexis, and acute atherosclerosis, result in abnormal blood flow of the umbilical arteries. In addition, the pathologic findings described in this study may provide helpful guidelines for the interpretation of the pathology slides of the placenta associated with IUGR.

## REFERENCES

1. Redline RW. Placental pathology: a systematic approach with clinical correlations. *Placenta* 2008; 29 Suppl A: S86-91.
2. Aviram R, T BS, Kidron D. Placental aetiologies of foetal growth restriction: clinical and pathological differences. *Early Hum Dev* 2010; 86: 59-63.
3. Pardi G, Marconi AM, Cetin I. Placental-fetal interrelationship in IUGR fetuses: a review. *Placenta* 2002; 23 Suppl A: S136-41.
4. Haram K, Sjøteland E, Bukowski R. Intrauterine growth restriction. *Int J Gynaecol Obstet* 2006; 93: 5-12.
5. Kingdom JC, Burrell SJ, Kaufmann P. Pathology and clinical implications of abnormal umbilical artery Doppler waveforms. *Ultrasound Obstet Gynecol* 1997; 9: 271-86.
6. Byun YJ, Kim HS, Yang JJ, Kim JH, Kim HY, Chang SJ. Umbilical artery Doppler study as a predictive marker of perinatal outcome in preterm small for gestational age infants. *Yonsei Med J* 2009; 50: 39-44.
7. Wang KG, Chen CY, Chen YY. The effects of absent or reversed end-diastolic umbilical artery Doppler flow velocity. *Taiwan J Obstet Gynecol* 2009; 48: 225-31.
8. Yildirim G, Turhan E, Aslan H, *et al.* Perinatal and neonatal outcomes of growth restricted fetuses with positive end diastolic and absent or reversed umbilical artery Doppler waveforms. *Saudi Med J* 2008; 29: 403-8.
9. Seeds JW. Impaired fetal growth: definition and clinical diagnosis. *Obstet Gynecol* 1984; 64: 303-10.
10. Lee JJ, Park CG, Lee KS. Birth weight distribution by gestational age in Korean population: using finite mixture model. *Korean J Pediatr* 2005; 48: 1179-86.
11. Thompson JM, Irgens LM, Skjaerven R, Rasmussen S. Placenta weight percentile curves for singleton deliveries. *BJOG* 2007; 114: 715-20.
12. Tyson RW, Staat BC. The intrauterine growth-restricted fetus and placenta evaluation. *Semin Perinatol* 2008; 32: 166-71.
13. Gordijn SJ, Dahlstrom JE, Khong TY, Ellwood DA. Histopathological examination of the placenta: key issues for pathologists and obstetricians. *Pathology* 2008; 40: 176-9.
14. Chang KT. Pathological examination of the placenta: raison d'être, clinical relevance and medicolegal utility. *Singapore Med J* 2009; 50: 1123-33.
15. Salafia CM. Placental pathology of fetal growth restriction. *Clin Obstet Gynecol* 1997; 40: 740-9.
16. Viero S, Chaddha V, Alkazaleh F, *et al.* Prognostic value of placental ultrasound in pregnancies complicated by absent end-diastolic flow velocity in the umbilical arteries. *Placenta* 2004; 25: 735-41.
17. Redline RW, Faye-Petersen O, Heller D, *et al.* Amniotic infection syndrome: nosology and reproducibility of placental reaction patterns. *Pediatr Dev Pathol* 2003; 6: 435-48.
18. Redline RW, Ariel I, Baergen RN, *et al.* Fetal vascular obstructive lesions: nosology and reproducibility of placental reaction patterns. *Pediatr Dev Pathol* 2004; 7: 443-52.
19. Redline RW, Boyd T, Campbell V, *et al.* Maternal vascular underperfusion: nosology and reproducibility of placental reaction patterns. *Pediatr Dev Pathol* 2004; 7: 237-49.
20. Park SY, Kim MY, Kim YJ, *et al.* Placental pathology in intrauterine growth retardation. *Korean J Pathol* 2002; 36: 30-7.
21. Edmondson N, Bocking A, Machin G, Rizek R, Watson C, Keating S. The prevalence of chronic deciduitis in cases of preterm labor without clinical chorioamnionitis. *Pediatr Dev Pathol* 2009; 12: 16-21.
22. Krebs C, Macara LM, Leiser R, Bowman AW, Greer IA, Kingdom JC. Intrauterine growth restriction with absent end-diastolic flow velocity in the umbilical artery is associated with maldevelopment of the placental terminal villous tree. *Am J Obstet Gynecol* 1996; 175: 1534-42.
23. Kingdom J, Huppertz B, Seaward G, Kaufmann P. Development of the placental villous tree and its consequences for fetal growth. *Eur J Obstet Gynecol Reprod Biol* 2000; 92: 35-43.
24. Nordenvall M, Ullberg U, Laurin J, Lingman G, Sandstedt B, Ulmsten U. Placental morphology in relation to umbilical artery blood velocity waveforms. *Eur J Obstet Gynecol Reprod Biol* 1991; 40: 179-90.
25. Salafia CM, Pezzullo JC, Minior VK, Divon MY. Placental pathology of absent and reversed end-diastolic flow in growth-restricted fetuses. *Obstet Gynecol* 1997; 90: 830-6.
26. Salafia CM, Vintzileos AM, Silberman L, Bantham KF, Vogel CA.



- Placental pathology of idiopathic intrauterine growth retardation at term. *Am J Perinatol* 1992; 9: 179-84.
27. Akbulut M, Sorkun HC, Bir F, Eralp A, Duzcan E. Chorangiosis: the potential role of smoking and air pollution. *Pathol Res Pract* 2009; 205: 75-81.
28. Kovo M, Schreiber L, Ben-Haroush A, Wand S, Golan A, Bar J. Placental vascular lesion differences in pregnancy-induced hypertension and normotensive fetal growth restriction. *Am J Obstet Gynecol* 2010; 202: 561.e1-5.
29. Herr F, Baal N, Widmer-Teske R, McKinnon T, Zygmunt M. How to study placental vascular development? *Theriogenology* 2010; 73: 817-27.
30. Scifres CM, Nelson DM. Intrauterine growth restriction, human placental development and trophoblast cell death. *J Physiol* 2009; 587(Pt 14): 3453-8.