 American Journal of Medical Genetics Part A 140A:1827–1833 (2006)

Clinical Outcome of Infants With Confined Placental Mosaicism and Intrauterine Growth Restriction of Unknown Cause

Kiyonori Miura,[1]* Koh-ichiro Yoshiura,[2,7] Shoko Miura,[1,7] Tatsuro Kondoh,[3] Naoki Harada,[4,7] Kentaro Yamasaki,[1] Yoko Fujimoto,[1] Yoko Yamasaki,[1] Terumi Tanigawa,[1] Yuriko Kitajima,[1] Takako Shimada,[1] Atsushi Yoshida,[1] Daisuke Nakayama,[1] Masato Tagawa,[3] Shuichiro Yoshimura,[1] Joseph Wagstaff,[5] Yoshihiro Jinno,[6] Tadayuki Ishimaru,[1,8] Norio Niikawa,[2,7] and Hideaki Masuzaki[1]

[1]Department of Obstetrics and Gynecology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
[2]Department of Human Genetics, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
[3]Department of Pediatrics, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
[4]Kyushu Medical Science, Nagasaki, Japan
[5]Department of Pediatrics, Clinical Genetics Program, Carolinas Medical Center, Charlotte, North Carolina
[6]Department of Molecular Genetics, University of the Ryukyus School of Medicine, Okinawa, Japan
[7]SORST, Japan Science and Technology Agency (JST), Kawaguchi, Japan
[8]Sasebo Chuo Hospital, Sasebo, Japan

Received 2 December 2005; Accepted 8 June 2006

The purpose of this study was to know a role of confined placental mosaicism (CPM) in perinatal outcome and postnatal growth and development of infants with intrauterine growth restriction (IUGR). We selected 50 infants with IUGR (<−2.0 SD) from 3,257 deliveries in a regional medical center during the past 10-year period, and carried out cytogenetic and molecular analyses in their placenta and cord blood. Of the 50 infants, 8 had CPM (CPM group) and were composed of five single (CPM2, 7, 13, 22, and 22), one double (CPM7/13), and one quadruple trisomy (CPM2/7/15/20), and one partial monosomy [del(2)(p16)]. The origin of an extra chromosome of trisomy was maternal in six cases of CPM, paternal in one, and undetermined in one. Uniparental disomy in disomic cell lines was ruled out in all these mosaics. We also compared clinical parameters for perinatal outcome between CPM group and infants without evidence of CPM (non-CPM group), such as maternal and gestational age, birth weight, *Apgar* score, cord blood pH, gender, and uterine artery patterns by Doppler ultrasonography, as well as weight, height, and developmental quotient (DQ) by Denver Developmental Screening Test at age 12 months. Phenotypic abnormalities were noted in two infants with CPM and three infants of non-CPM group: One with CPM22 had ASD and hypospadias, one with CPM7/13 had Russell–Silver syndrome (RSS), and one without CPM had polydactyly, and two without CPM had RSS. All but one infant with CPM are alive at age 12 months. Among the clinical parameters, the detection rate of a notch waveform pattern of the uterine artery was significantly higher in the CPM group ($P < 0.05$). However, no significant difference was noted in perinatal outcome of pregnancy and in DQ at age 12 months between the two groups. Interestingly, short stature (<−2 SD) at age 12 months was more frequently seen in CPM group (7/8 infants with CPM vs. 8/15 infants without CPM), although no statistically significant difference was obtained. The information obtained will be useful for perinatal care and genetic counseling for infants with IUGR and CPM. © 2006 Wiley-Liss, Inc.

Key words: confined placental mosaicism; intrauterine growth restriction; uniparental disomy; Doppler ultrasonography

How to cite this article: Miura K, Yoshiura K, Miura S, Kondoh T, Harada N, Yamasaki K, Fujimoto Y, Yamasaki Y, Tanigawa T, Kitajima Y, Shimada T, Yoshida A, Nakayama D, Tagawa M, Yoshimura S, Wagstaff J, Jinno Y, Ishimaru T, Niikawa N, Masuzaki H. 2006. Clinical outcome of infants with confined placental mosaicism and intrauterine growth restriction of unknown cause. Am J Med Genet Part A 140A:1827–1833.

Grant sponsor: Ministry of Education, Sports, Culture, Science and Technology of Japan; Grant numbers: 16591670, 17591748, 17019055; Grant sponsor: Japan Science and Technology Agency (JST).

*Correspondence to: Kiyonori Miura, Department of Obstetrics and Gynecology, Nagasaki University Graduated School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan.
E-mail: kiyonori@nagasaki-u.ac.jp
DOI 10.1002/ajmg.a.31389

INTRODUCTION

Confined placental mosaicism (CPM) may be defined as the presence of chromosomal mosaicism confined to tissues of extraembryonic origin. The mosaicism may be confined to the cytotrophoblast (type 1 CPM), the villous stroma (type 2 CPM), or both tissues (type 3 CPM) [Kalousek and Vekemans, 1996]. Chromosome mosaicism is detected in 1%–2% of chorionic villus samples (CVS) [Ledbetter et al., 1992; Wolstenholme et al., 1994; Stetten et al., 2004]. The correlation between CPM and intrauterine growth restriction (IUGR) of infants has remained controversial. Some studies showed higher frequency (6.5%–25%) of IUGR in pregnancies with CPM than those (5.0%–8.3%) in those without CPM [Kalousek et al., 1991; Ledbetter et al., 1992; Kalousek, 1994; Wolstenholme et al., 1994; Artan et al., 1995; Wilkins-Haug et al., 1995; Krishnamoorthy et al., 1995; Stipoljev et al., 2001], whereas others gave negative association between IUGR and CPM [Schwinger et al., 1989; Kennerknecht et al., 1993]. When trisomy rescue occurs (Fig. 1), one-third of fetuses may have uniparental disomy (UPD). IUGR is sometimes associated with UPD for chromosome 7, 11, 14, 15 or 16 [Ledbetter and Engel, 1995; European Collaborative Research on Mosaicism in CVS, 1999; Monk and Moore, 2004]. Maternal UPD for chromosome 7 is known to be one of the causes of Russell–Silver syndrome (RSS) that exhibits severe IUGR [Eggerding et al., 1994; Kotzot et al., 1995]. In addition, there have been two cases of IUGR who had CPM for chromosome 2 or 22 and maternal UPD for the respective chromosome [Ariel et al., 1997; Balmer et al., 1999], as well as cases of IUGR associated with CPM and maternal UPD for chromosome 16 [Eggermann et al., 2004]. In CPM-derived UPD, it is generally difficult to ascertain whether IUGR is caused by UPD in fetus or CPM in its placenta.

Clinical outcome of pregnancy and manifestations of infants with CPM varied from normal to abnormal delivery and phenotypes [Wolstenholme et al., 1994; Saks et al., 1998; Bryan et al., 2002; Roberts et al., 2003]. Abnormal outcome may depend on meiotic or mitotic origin of trisomy and on chromosomes involved in CPM [James and Jacobs, 1996]. It is also the consequence of abnormal placental functions due to abnormal karyotype, UPD or abnormal gene expression [Robinson et al., 1997]. However,

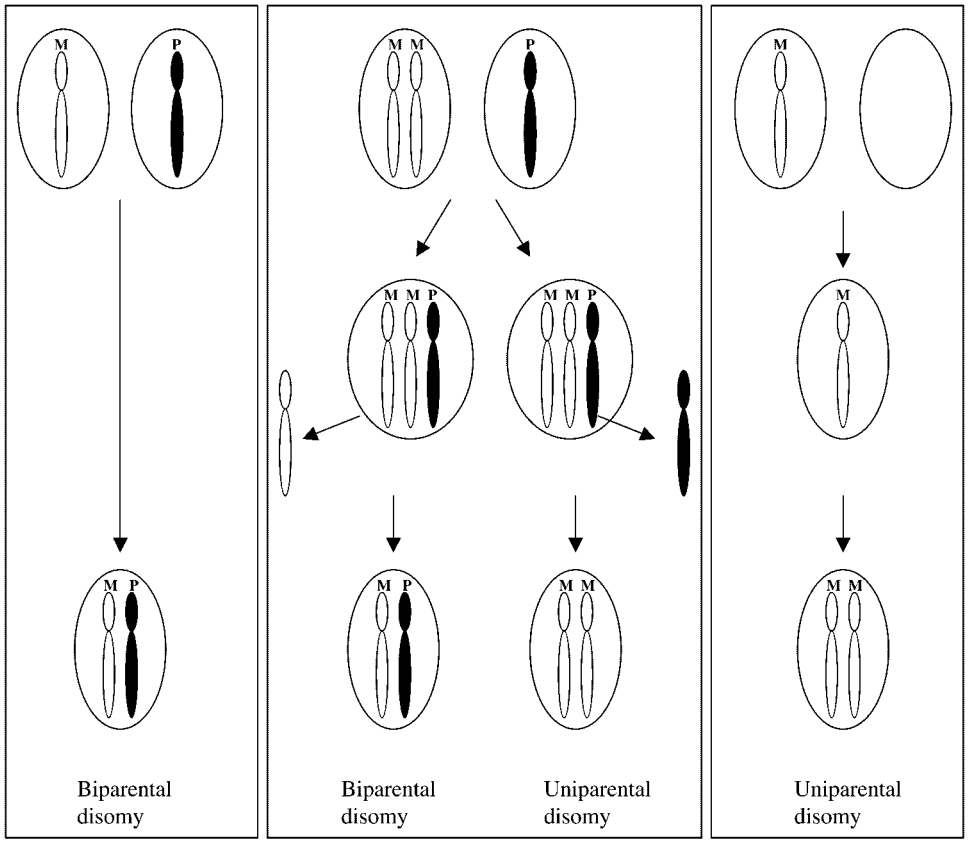

FIG. 1. Diagram illustrating the difference between biparental and uniparental disomy. **Right panel**: biparental disomy from normal fertilization. **Middle panel**: biparental and uniparental disomy from trisomic rescue. **Left panel**: monosomy duplication in a monosomic conceptus. M and P denote maternal allele and paternal allele, respectively.

it remains obscure whether CPM affects on postnatal growth and development. Therefore, molecular determination of origin of CPM may be useful to predict such outcome.

We have been following up a large series of pregnancies with IUGR of unknown cause and CPM. The purpose of this study was to know a role of CPM in perinatal outcome and postnatal growth and development of infants with IUGR.

MATERIALS AND METHODS

Patients

During a period from April 1995 to July 2004, there were 3,257 deliveries in Nagasaki University Hospital. Of these, 124 were with IUGR, judged prenatally on the basis of low estimated weight (<−2 SD) for gestational age defined by ultrasonography, and confirmed at delivery. Those with the following risk factors for IUGR were: multiple pregnancy; fetal chromosomal abnormality, infections and TORCH syndrome; maternal hypertension; maternal diabetes; maternal smoking (>20 cigarettes per day); or cord factor. Fifty fetuses without these risk factors, whose weight and length at birth were less than −2 SD, were included in the study. Biopsied chorionic villus specimens from two or more placental sites and cord blood were collected at delivery as were parental peripheral blood samples. All study protocols were approved by the Committee for the Ethical Issue on Human Genome and Gene Analysis in Nagasaki University.

Clinical Evaluation of Infants With IUGR

Clinical parameters for perinatal outcome included maternal age and gestational age at birth, birth weight, *Apgar* score, blood pH in the umbilical artery, sex, and Doppler ultrasonography of uterine artery (Fig. 2). At age 12 months after birth, the weight and length were measured of the infants, and their development was assessed using Denver Developmental Screening test (DDST) [Frankenburg and Dodds, 1967].

Cytogenetic Analysis

Tissue specimens from two or more sites of the term placenta were cultured and harvested. In each sample, 50–100 G-banded metaphases were analyzed in two flasks. Mosaicism was defined when a same chromosome abnormality was found in both two separate culture flasks.

Molecular Genetic Analysis

DNA was extracted from cord blood, placenta and parental blood using standard method. DNA samples from cases with CPM were genotyped using a microsatellite marker panel, ABI PRISM linkage-mapping set-MD10 (Applied Biosystems,

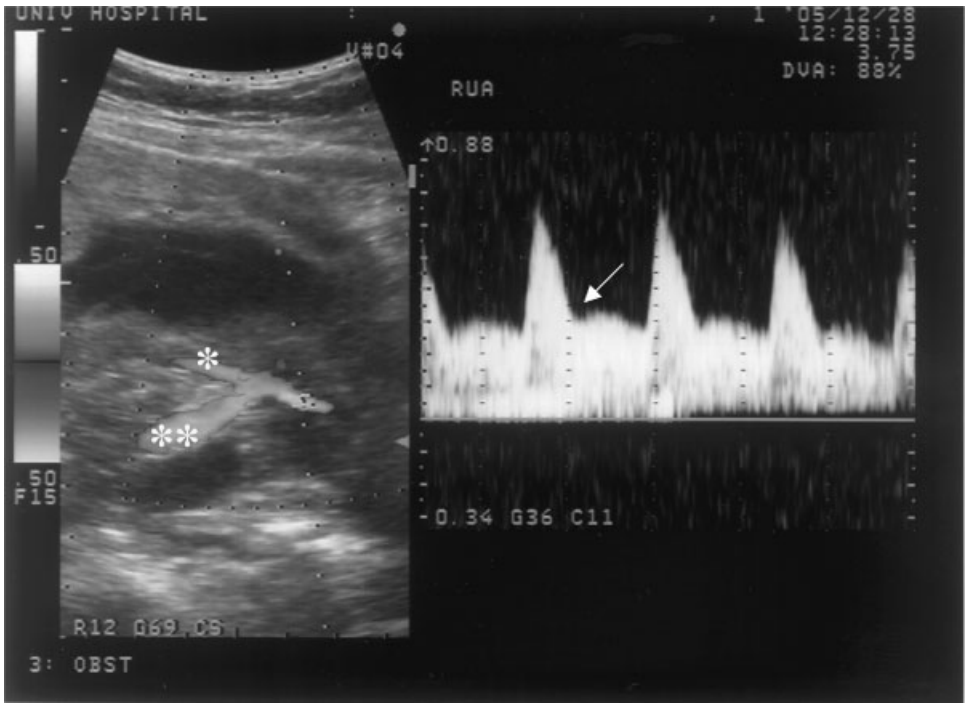

FIG. 2. Photograph of a notch-waveform ultrasonographic color-Doppler pattern of the uterine artery. White arrow points to a notch-waveform. * and ** denote uterine artery and external iliac artery, respectively.

Foster City, CA) and GeneAmp PCR System 9700 (Applied Biosystems). Each genotyping was repeated at least three times to avoid erroneous results. The PCR condition and the procedure of genotyping were described in our previous manuscript [Masuzaki et al., 2004].

Infants whose placental villi were disomy/trisomy mosaics were studied for possible UPD of the chromosome pairs involved in the trisomies. The analysis was carried out in DNA samples from the infants and their parents, using microsatellite marker panels corresponding to the chromosomes involved in the trisomies. Placental DNA samples with disomy/trisomy mosaicism were analyzed in the same manner, in order to learn about the origin of the trisomies involved.

RESULTS

Confined Placental Mosaicism

Of the 50 infants with IUGR and their placentas studied, 8 (16%) had a chromosomally abnormal cell line restricted to the placenta (Table I). Patient 1 had non-mosaic trisomy 22; Patients 2 to 5 were trisomy mosaics; Patient 6 was a double trisomy mosaic; Patient 7 a quadruple trisomy mosaics; and Patient 8 was a normal/del(2)(p16)mosaic. Cultured cord blood lymphocytes from these infants were chromosomally normal with either a 46,XX (three cases) or 46,XY (five cases) karyotype.

Origin of Placental Trisomic Cell Lines

Microsatellite markers close to the centromeres were analyzed in the six placentas with trisomic cell lines and peripheral blood samples from their parents (Table I). Analysis in Patients 1 to 4 (trisomies 22, 2, 7, and 13, respectively) indicated that their trisomic cell lines arose from maternal first meiotic non-disjunction (mat MI). Trisomy 7 in Patient 5 resulted from paternal first meiotic non-disjunction (pat MI). Trisomies 7 and 13 in Patient 6 both originated from either maternal second meiotic or mitotic non-disjunction (mat MII or mitotic), although to distinguish MII from mitotic events was impossible because the markers we used did not detect the presence of recombinations. Trisomies 2, 7, and 15 in Patient 7 likewise arose from either maternal second meiotic or mitotic events. The origin of trisomy 20 in the same infant, however, was not determined. Analysis of cord blood samples from the six infants with placental trisomic cell lines showed no instance of UPD for the chromosome pairs involved in the trisomies.

Phenotypic Abnormalities in the Infants With CPM

Patient 1, a boy, had an atrial septal defect (ASD) and hypospadias, both of which were surgically

TABLE I. Results of Cytogenetic and Molecular Analysis, and Clinical Outcome of Pregnancies With CPM

Case no.	Age (yrs)	Sex	Maternal age (yrs)	Karyotype: Placenta	Karyotype: Cord blood	Origin of trisomy	Gestational age (weeks)	Birth weight (SD)	Cord blood pH	Notch-waveform pattern of uterine artery	Phenotypic abnormality
1	6	M	29	47,XY,+22[50]	46,XY	Mat MI	37	−4.6	7.31	+	ASD, hypospadias
2	6	M	28	46,XY[97]/47,XY,+2[3]	46,XY	Mat MI	34	−2.5	7.27	−	—
3	3	F	25	46,XX[62]/47,XX,+7[8]	46,XX	Mat MI	37	−3.2	7.14	+	—
4	9	M	26	46,XY[45]/47,XY,+13[5]	46,XY	Mat MI	35	−2.2	7.29	−	—
5	3	F	31	46,XX[10]/47,XX,+22[40]	46,XX	Pat MI	36	−2.9	7.34	+	—
6	1[a]	M	29	46,XY[98]/48,XY,+7,+13[2]	46,XY	Mat MII or mitotic	38	−5.0	7.19	+	Russell–Silver syndrome
7	10	M	22	46,XY[48]/50,XY,+2,+7,+15,+20[2]	46,XY	Mat MII or mitotic[b]	38	−3.2	7.30	+	—
8	7	F	29	46,XX[97]/46,XX,del(2)(p16)[3]	46,XX		36	−2.9	7.25	−	—

Mat MI, maternal first meiotic non-disjunction; Mat MII, maternal second meiotic non-disjunction; Pat MI, paternal first meiotic non-disjunction.
[a]Died at age 12 months.
[b]Origin of trisomy 20 unknown.

repaired. Patient 6, a boy, had RSS with triangular face, cleft lip, and hemihypertrophy. At age 9 months, he weighed 2,680 g (−6.8 SD), measured 49.5 cm (−8.8 SD), and had developmental retardation. At age 12 months, he died of unknown cause. Analysis with a microsatellite marker panel spanning the long arm of chromosome 7 ruled out UPD for all or a part of chromosome 7.

Growth and Development of Infants With or Without CPM

Growth and development were evaluated with DDST in 7 infants with CPM and another 13 infants without CPM (Table II). In both groups, growth retardation as judged by weight was less pronounced at age 12 months than at birth, although at age 12 months 6 of the 7 infants with CPM and 8 of the 13 infants without CPM were still less than −2 SD.

There was no appreciable difference between the two groups in the frequency of delayed development. Patient 2, a boy with placental mosaicism of 46,XY/47,XY,+2, showed delayed gross and fine motor performance and delayed social ability, although his speech development was normal. Patient 17, a boy without CPM, were delayed in all categories. Patient 29, a girl without CPM, likewise were delayed in all categories tested, and had polydactyly of right preaxial finger, which was non-syndromic.

DISCUSSION

By a retrospective screening of 124 pregnancies with IUGR, we have collected 50 infants without any evidence of having risk factors for IUGR. Among them, eight infants (16%) had CPM that was detected by biopsy on two or more placental sites, followed by karyotyping on cultured preparations. The value is comparable to 8.7% obtained by Kalousek and Dill 1983 as well as to data by others [Wilkins-Haug et al., 1995; Lestou and Kalousek, 1998]. However, as our karyotyping was not done on non-cultured, direct preparation of the placenta, we did not screen for type 1 CPM or distinct between types 2 and 3. This might lead to underestimate the frequency of CPM in our series of pregnancy. Since CPM in four of the eight infants of CPM group were composed of a few trisomic cells (2–3/50 cells), the existence of trisomic cells with much lower frequency or type 1 CPM was not totally ruled out in some infants of non-CPM group. Genotyping at polymorphic allele sites examined revealed that chromosomal aberrations in five of seven infants with CPM arose at the maternal meiosis. This may reflect more frequent occurrence of meiotic non-disjunction during oogenesis than spermatogenesis [Hassold and Hunt, 2001], and meets with previously reported data that CPM of meiotic origin correlates with an increased risk of IUGR [Robinson et al., 1997]. The mean of maternal age in infants of both CPM and non-CPM groups was not high (28.6 vs. 29.1 years). It is often difficult to ascertain whether the pathological findings of pregnancy with CPM are caused by UPD in the fetus or CPM itself in the placenta. As UPD was excluded in all our infants with CPM, UPD does not explain the etiology of the majority of adverse outcome of pregnancies with CPM.

Comparisons of various parameters as indicators of perinatal outcome showed no significant difference between IUGR infants with and without CPM, except for the higher rate of notch waveform patterns in the uterine artery in the CPM group (Table III). Non-catching-up stature (<−2 SD) at age 12 months was seen in 7 (87.5%) of 8 infants with CPM and 8 (53.3%) of 15 infants without CPM, although the frequencies were not statistically different. There was no difference in motor, speech, and social development between the two groups, too. Clinical manifestations in some infants merit comments. There were three infants with RSS (one of CPM group and two of non-CPM group). Patient 2, who had CPM for del(2)(p16), showed normal developmental performance and

TABLE II. Physical and Developmental Evaluation at Age 12 Months

	With CPM	Without CPM
No. infants studied	7[a]	13
Weight (SD)	−1.7 to −3.5	−0.7 to −3.5
Length (SD)	−0.4 to −3.3	−0.7 to −3.6
Delayed development (No. delayed/total)		
Gross motor performance	1/7	2/13
Fine motor performance	1/7	2/13
Speech development	0/7	1/13
Social ability	2/7	2/13
Phenotypic abnormalities	ASD and hypospadias	Polydactyly

[a]Patient 6 was not available from study, having died of Russell–Silver syndrome.

TABLE III. Outcome of Infants With or Without Confined Placental Mosaicism

	With CPM	Without CPM
No. infants studied	8	42
Age (years)	1–10	1–10
Male/female	5/3	27/15
Maternal age (years)		
Range	22–31	23–40
Mean	28.6	29.1
Gestational age (weeks)	34–38	34–39
Birth weight (SD)	−2.2 to −5	−2 to −4.7
Cord blood pH	7.14–7.34	7.11–7.39
Notch-waveform pattern in uterine artery (present/total)	4/8	5/42
Phenotypic abnormalities		
Russell–Silver syndrome	Patient 6	Two infants
Other abnormalities	ASD, hypospadias	Polydactyly

was catching up on her growth at age 12 months. There have been two reports of infants with IUGR and CPM for partial monosomy: a liveborn with CPM for del(13)(q13) [Wolstenholme et al., 1994] and a stillbirth with CPM for del(16)(p16) [Stipoljev et al., 2001]. Our infant with CPM for del(2)(p16) is added to the list of CPM for partial monosomy that may cause IUGR. Patient 6 had RSS without UPD died at age 12 months, as did four reported cases of RSS in infancy [Imaizumi et al., 1983; Donnai et al., 1989]. The clinical severity of RSS might depend on the presence of a cell line of UPD7, though previous study suggested indistinguishable phenotypes between RSS patients with and without UPD7 [Bernard et al., 1999].

A notch-waveform ultrasonographic pattern of the uterine artery was frequently seen in the CPM group of our series of IUGR infants. This reflects high flow-resistance of the artery caused by inadequate physiological changes of spiral arteries that are important for the uteroplacental circulation [Coleman et al., 2000], and the flow-resistance is related to a reduced trophoblast migration into the myometrium. Such patterns may also be related to an association of decidual vasculopathy with CPM. Sagol et al. 1999 showed a positive association between pathological changes of the placental bed and high flow-resistance of the uterine artery in women with pre-eclampsia and IUGR. Wilkins-Haug et al. 1995 demonstrated that placental changes consistent with decidual vasculopathy were found in two cases of CPM-associated IUGR, but in none of the remaining cases of IUGR or control pregnancies. Wilkins-Haug et al. 2006 recently showed that decidual vasculopathy, placental infarcts, and intervillous thrombus were more frequently observed in infants with CPM compared to chromosomally normal placenta of infants with IUGR. On the other hand, morphologically normal placenta in many cases of either CPM or IUGR without CPM was also reported [Krishnamoorthy et al., 1995].

In conclusion, we have demonstrated associations between CPM and IUGR and between CPM and notch waveform patterns of the uterine artery. We also confirmed that perinatal outcome of pregnancy was not markedly different between IUGR infants with and without CPM. Short stature tended to be more frequently observed at age 12 months in IUGR infants with CPM than in those without CPM. The information obtained in our study will be useful for perinatal care and genetic counseling for infants with IUGR and CPM.

ACKNOWLEDGMENTS

This study was supported in part by Grants-in-Aid for Scientific Research (Category C, No. 16591670 for K.M. and Category C, No. 17591748 for H.M.) and Grant-in-Aid on Priority Areas "Applied Genomics" (No. 17019055 for N.N.) from Ministry of Education, Sports, Culture, Science and Technology of Japan, and SORST from Japan Science and Technology Agency (JST) (for N.N.).

REFERENCES

Ariel I, Lerer I, Yagel S, Cohen R, Ben-Neriah Z, Abeliovich D. 1997. Trisomy 2: Confined placental mosaicism in a fetus with intrauterine growth retardation. Prenat Diagn 17:180–183.

Artan S, Basaran N, Hassa H, Ozalp S, Sener T, Sayli BS, Cengiz C, Ozdemir M, Durak T, Dolen I, Ozgunen T, Tuna M. 1995. Confined placental mosaicism in term placentae: Analysis of 125 cases. Prenat Diagn 15:1135–1142.

Balmer D, Baumer A, Rothlisberger B, Schinzel A. 1999. Severe intra-uterine growth retardation in a patient with maternal uniparental disomy 22 and a 22-trisomic placenta. Prenat Diagn 19:1061–1064.

Bernard LE, Penaherrera MS, Van Allen MI, Wang MS, Yong SL, Gareis F, Langlois S, Robinson WP. 1999. Clinical and molecular findings in two patients with Russell–Silver syndrome and UPD7: Comparison with non-UPD7 cases. Am J Med Genet 87:230–236.

Bryan J, Peters M, Pritchard G, Healey S, Payton D. 2002. A second case of intrauterine growth retardation and primary hypospadias associated with a trisomy 22 placenta but with biparental inheritance of chromosome 22 in the fetus. Prenat Diagn 22:137–140.

Coleman MA, McCowan LM, North RA. 2000. Mid-trimester uterine artery Doppler screening as a predictor of adverse pregnancy outcome in high-risk women. Ultrasound Obstet Gynecol 15:7–12.

Donnai D, Thompson E, Allanson J, Baraitser M. 1989. Severe Silver–Russell syndrome. J Med Genet 26:447–451.

Eggerding FA, Schonberg SA, Chehab FF, Norton ME, Cox VA, Epstein CJ. 1994. Uniparental isodisomy for paternal 7p and maternal 7q in a child with growth retardation. Am J Hum Genet 55:253–265.

Eggermann T, Curtis M, Zerres K, Hughes HE. 2004. Maternal uniparental disomy 16 and genetic counseling: New case and survey of published cases. Genet Counsel 15:183–190.

European Collaborative Research on Mosaicism in CVS. 1999. Trisomy 15 CPM: Probable origins, pregnancy outcome and risk of fetal UPD: European Collaborative Research on Mosaicism in CVS (EUCROMIC). Prenat Diagn 19:29–35.

Frankenburg WK, Dodds JB. 1967. The Denver developmental screening test. J Pediatr 71:181–191.

Hassold T, Hunt P. 2001. To err (meiotically) is human: The genesis of human aneuploidy. Nat Rev Genet 2:280–91.

Imaizumi K, Ogino T, Kajii T. 1983. Silver syndrome: An infant with necropsy findings. Jpn J Hum Genet 28:231–234.

James RS, Jacobs PA. 1996. Molecular studies of the aetiology of trisomy 8 in spontaneous abortions and the liveborn population. Hum Genet 97:283–286.

Kalousek DK. 1994. Current topic: Confined placental mosaicism and intrauterine fetal development. Placenta 15:219–230.

Kalousek DK, Dill FJ. 1983. Chromosomal mosaicism confined to the placenta in human conceptions. Science 221:665–667.

Kalousek DK, Vekemans M. 1996. Confined placental mosaicism. J Med Genet. 33:529–533.

Kalousek DK, Howard-Peebles PN, Olson SB, Barrett IJ, Dorfmann A, Black SH, Schulman JD, Wilson RD. 1991. Confirmation of CVS mosaicism in term placentae and high frequency of intrauterine growth retardation association with confined placental mosaicism. Prenat Diagn 11:743–750.

Kennerknecht I, Kramer S, Grab D, Terinde R, Vogel W. 1993. A prospective cytogenetic study of third-trimester placentae in small-for-date but otherwise normal newborns. Prenat Diagn 13:257–269.

Kotzot D, Schmitt S, Bernasconi F, Robinson WP, Lurie IW, Ilyina H, Mehes K, Hamel BC, Otten BJ, Hergersberg M. 1995. Uniparental disomy 7 in Silver–Russell syndrome and primordial growth retardation. Hum Mol Genet 4:583–587.

Krishnamoorthy A, Gowen LC, Boll KE, Knuppel RA, Sciorra LJ. 1995. Chromosome and interphase analysis of placental mosaicism in intrauterine growth retardation. J Perinatol 15: 47–50.

Ledbetter DH, Engel E. 1995. Uniparental disomy in humans: Development of an imprinting map and its implications for prenatal diagnosis. Hum Mol Genet 4:1757–1764.

Ledbetter DH, Zachary JM, Simpson JL, Golbus MS, Pergament E, Jackson L, Mahoney MJ, Desnick RJ, Schulman J, Copeland KL, Verlinsky Y, Yang-Feng T, Schonberg SA, Babu A, Tharapel A, Dorfmann A, Lubs HA, Rhoads GG, Fowler SE, De La Cruz F. 1992. Cytogenetic results from the U.S. Collaborative Study on CVS. Prenat Diagn 12:317–345.

Lestou VS, Kalousek DK. 1998. Confined placental mosaicism and intrauterine fetal growth. Arch Dis Child Fetal Neonatal Ed 79: 223–226.

Masuzaki H, Miura K, Yoshiura KI, Yoshimura S, Niikawa N, Ishimaru T. 2004. Detection of cell free placental DNA in maternal plasma: Direct evidence from three cases of confined placental mosaicism. J Med Genet 41:289–92.

Monk D, Moore GE. 2004. Intrauterine growth restriction—genetic causes and consequences. Semin Fetal Neonat Med 9:371–378.

Roberts E, Dunlop J, Davis GS, Churchill D, Davison EV. 2003. A further case of confined placental mosaicism for trisomy 2 associated with adverse pregnancy outcome. Prenat Diagn 23: 564–565.

Robinson WP, Barrett IJ, Bernard L, Telenius A, Bernasconi F, Wilson RD, Best RG, Howard-Peebles PN, Langlois S, Kalousek DK. 1997. Meiotic origin of trisomy in confined placental mosaicism is correlated with presence of fetal uniparental disomy, high levels of trisomy in trophoblast, and increased risk of fetal intrauterine growth restriction. Am J Hum Genet 60:917–927.

Sagol S, Ozkinay E, Oztekin K, Ozdemir N. 1999. The comparison of uterine artery Doppler velocimetry with the histopathology of the placental bed. Aust N Z J Obstet Gynaecol 39:324–329.

Saks E, Mccoy MC, Damron J, Kelly TE. 1998. Confined placental mosaicism for trisomy 8 and intra-uterine growth retardation. Prenat Diagn 18:1202–1204.

Schwinger E, Seidl E, Klink F, Rehder H. 1989. Chromosome mosaicism of the placenta—a cause of developmental failure of the fetus? Prenat Diagn 9:639–647.

Stetten G, Escahleeon CS, South ST, McMichael JL, Saul DO, Blakemore KJ. 2004. Reevaluating confined placental mosaicism. Am J Med Genet Part A 131A:232–239.

Stipoljev F, Latin V, Kos M, Miskovic B, Kurjak A. 2001. Correlation of confined placental mosaicism with fetal intrauterine growth retardation. A case control study of placentas at delivery. Fetal Diagn Ther 16:4–9.

Wilkins-Haug L, Roberts DJ, Morton CC. 1995. Confined placental mosaicism and intrauterine growth retardation: A case-control analysis of placentas at delivery. Am J Obstet Gynecol 172: 44–50.

Wilkins-Haug L, Quade B, Morton CC. 2006. Confined placental mosaicism as a risk factor among newborns with fetal growth restriction. Prenat Diagn 26:428–432.

Wolstenholme J, Rooney DE, Davison EV. 1994. Confined placental mosaicism, IUGR, and adverse pregnancy outcome: A controlled retrospective U.K. collaborative survey. Prenat Diagn 14:345–361.