

Prenatal Findings in Congenital Leukemia: A Case Report

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Established facts

- Neonatal leukemia has poor prognosis.
- Neonatal leukemia associated with Down syndrome has a natural tendency to undergo spontaneous remissions and reported mortality rate is much lower than that without Down syndrome.
- Significant number of neonatal leukemia arises in utero and fetal leukemia should be kept in mind as an important cause of intrauterine deterioration and death.
- Hepatosplenomegaly and hydrops fetalis are two characteristic prenatal features of congenital leukemia.

Novel Insights

- Prenatal course of leukemic fetus including sequential changes in the ultrasonographic findings, pulse Doppler indices, and fetal heart rate patterns is specified for the first time.
- Experience in our case suggests elevation of pulsatility index of the umbilical artery with paradoxically enlarged fetal trunk as an early sign of fetal leukemia.
- Experiences in our case and in the past reported cases suggest two distinct mechanisms for hydrops development caused by fetal leukemia. The first is leukemic cell involvement of multiple fetal organs including placenta and the second is chronic circulatory insufficiency due to hyperviscosity attributable to leukocytosis.
- Prenatal diagnoses of fetal leukemia have been reported in only 10 cases, all of which were associated with trisomy 21. This suggests that leukemic fetuses associated with Down syndrome are likely to have a milder prenatal course than those without Down syndrome, thus giving a time for cordocentesis.

Prenatal Findings in Congenital Leukemia: A Case Report

Abstract

We here describe a case of congenital leukemia that ended in intrauterine fetal demise at 30 weeks of gestation. Acute enlargement of the fetal trunk, elevated pulsatility index of the umbilical artery with concomitant decline of pulsatility index of middle cerebral artery, pleural effusion, and polyhydramnios preceded the fetal death. Diagnosis of congenital myeloid leukemia was suggested by microscopic examination of the placental tissue, revealing immature myeloid precursors filling the lumina of fetal vessels in the umbilical cord and chorionic villi. Extensive vascular involvement of the placenta by leukemic cells was considered to be a primary cause of the fetal death.

Keywords; Cordocentesis, Doppler velocimetry, Down syndrome, Hydrops fetalis, Intrauterine death, Hepatosplenomegaly

1 Introduction

2
3 Neonatal leukemia, which occurs at a rate of 1 per 5 million births, is the leading
4 cause of neonatal death due to neoplastic disease [1]. Recent molecular studies
5 indicate that significant number of neonatal leukemia arises in utero [2]. In this
6 respect, fetal leukemia should be kept in mind as an important cause of intrauterine
7 deterioration and death. However, prenatal history of congenital leukemia has not
8 been well characterized. Herein, we describe a case of congenital leukemia where
9 acute enlargement of the fetal trunk, elevated pulsatility index of the umbilical artery
10 with concomitant decline of pulsatility index of the middle cerebral artery, pleural
11 effusion, and polyhydramnios were noted before fetal demise at 30 weeks of gestation.
12
13

Case Report

A 35-year-old woman (gravida 0, para 0) at 27⁺⁵ weeks' gestation was referred and admitted to our hospital due to moderate amount of vaginal bleeding from total placenta previa. She was taking antipsychotic medication for schizophrenic disorder. Her blood screening was negative for irregular antibody or treponema pallidum. Recent infection with rubella was also excluded.

After hospitalization, bleeding gradually decreased and disappeared with bed rest and tocolytic administration. On admission, fetal measurements of biparietal diameter (BPD), fetal trunk area (FTA), and femur length (FL) were all within the normal range. No fetal malformation was noted and amniotic fluid volume was normal. Pulsatility indices of umbilical artery (UmA-PI) and middle cerebral artery (MCA-PI) measured with Doppler ultrasonography (Voluson730Pro; GE Healthcare, Austria) were all within the normal level (Figure 1A and B). Fetal heart rate (FHR) monitoring showed reassuring pattern.

At 29⁺⁶ weeks' gestation, UmA-PI was elevated beyond the normal limit (Figure 1A). MCA-PI was decreased but remained within the normal range (Figure 1B). Although BPD and FL was within the normal limits, FTA was abruptly enlarged to 64.29 cm² (+2.3SD). FHR monitoring showed reassuring pattern.

At 30⁺² weeks' gestation, the patient felt diminished fetal movement. Ultrasonography showed polyhydramnios (Figure 1C) and mild fetal pleural effusion (Figure 1D). Further elevation of UmA-PI and decline of MCA-PI was noted (Figure 1A and B). Doppler waveform of bilateral uterine artery was normal. FTA was increased to 68.23 cm² (+2.6SD). FHR monitoring exhibited decreased beat-to-beat variability (Figure 2A).

At 30⁺³ weeks' gestation, FHR monitoring showed small dip-like deceleration observed on every uterine contraction, which disappeared after tocolysis (Figure 2B). UmA-PI was further elevated and MCA-PI fell below the normal limit (Figure 1A and B). Doppler waveforms of the inferior vena cava and ductus venosus were normal. Anticipating the need of expeditious premature delivery, maternal betamethasone was administered for the prevention of neonatal respiratory distress syndrome. Three hours later, mild bradycardia (100-110 beat per minute) with loss of variability was noted and fetal heartbeat suddenly became undetectable (Figure 2C). Ultrasonography

1 confirmed the fetal death.

2 Two days later, a male stillborn weighing 1872 g (+1.3SD) was delivered with
3 cesarean section indicated for total placenta previa. The newborn was macerated, but
4 no apparent external malformation was noted. The parents declined to have the
5 autopsy. Postpartum studies on the maternal serum excluded recent infection with
6 cytomegalovirus, parvovirus, herpes simplex, or toxoplasma.

7 Grossly, the placenta (410 g in weight) appeared normal. Umbilical cord (24 cm in
8 length) was inserted into the central portion of the placental disc without any sign of
9 stricture or overcoiling. The fetal surface of the placenta was translucent.
10 Microscopically, numerous small- to medium-sized atypical immature-looking cells
11 with high nuclear to cytoplasmic ratio were observed in the fetal vessels including
12 intravillous capillaries as well as medium- to large-sized veins and arteries in the
13 chorionic plate and the umbilical cord (Figure 3A, B and C). On the other hand,
14 maternal vessels in the decidual tissue and intervillous spaces were free of
15 above-mentioned atypical cells. In some areas, intervillous fibrin deposition and
16 thrombosis was identified. Immunohistochemically, these atypical cells were positive
17 for myeloperoxidase (Figure 3D) and negative for CD3 (T-cell marker) and CD20
18 (B-cell marker), indicating the myeloid lineage of differentiation. The Ki-67 (MIB-1)
19 labeling index was up to 50% (Figure 3E). This constellation of findings suggested
20 the diagnosis of acute myeloid leukemia of the fetus.

Discussion

In the current case, cause of the sudden fetal deterioration and death had been totally unknown until the placental pathology was reported. Possible causes for fetal pleural effusion associated with polyhydramnios such as cardiopulmonary anomaly, congenital infection, and erythroblastosis fetalis were excluded by the fetal ultrasonography and maternal blood tests. Numerous atypical myeloperoxidase-positive cells in the fetal vessels of the placenta and the umbilical cord suggested acute myeloid leukemia of the fetus. It is known that fetus and neonate are liable to produce leukemoid reaction in response to congenital infection or erythroblastosis fetalis [3]. Although the placental pathology could also be explained by the leukemoid reaction, exclusion of congenital infection and erythroblastosis fetalis by maternal blood tests convinced us of the diagnosis of fetal leukemia.

The FTA became abnormally large after 29⁺⁶ weeks' gestation, suggesting the development of fetal hepatosplenomegaly. Abrupt elevation of UmA-PI can be explained by occlusion of the placental and the umbilical vessels by leukemic cells, as revealed by microscopic examination. Polyhydramnios could be caused by increase of exudates from the infiltrated placental villi. Subsequent decline of MCA-PI indicated that the blood flow redistribution towards the fetal brain took place as a compensating mechanism. Since no cardiac anomaly was detected by fetal echocardiography and Doppler waveforms of inferior vena cava and ductus venosus were normal immediately prior to fetal death, the pleural effusion was considered to be due to pleural infiltration by leukemic cells rather than acute cardiac failure. Loss of variability in FHR tracing followed by dip-like deceleration concurrent with uterine contraction and prolonged bradycardia might reflect fetal hypoxia caused by impaired oxygen supply to the fetus via the occluded umbilical vein. Finally, fetal metabolic acidosis resulting from progressive hypoxia is considered to be a cause of sudden cardiac arrest. Therefore, acute circulatory failure due to placental vessel occlusion by leukemic cells is likely to be a primary cause of the sudden fetal demise.

Hepatosplenomegaly and hydrops fetalis are two characteristic prenatal features of a leukemic fetus [4-6] [7-9]. Since extramedullary hematopoiesis physiologically occurs in liver and spleen during intrauterine period, fetuses easily develop hepatosplenomegaly in response to various hematological disorders including leukemia.

1 Hepatosplenomegaly is often revealed as abnormally enlarged FTA. In clinical
2 practice, elevation of UmA-PI is most often seen in chronic uteroplacental insufficiency
3 that is usually associated with restricted FTA growth. Thus, elevation of UmA-PI with
4 paradoxically enlarged FTA, as seen in the present case, may be an early sign of fetal
5 leukemia.

6 Hydrops fetalis is generally associated with poor prognosis [10]. Two distinct
7 mechanisms could be considered for hydrops development caused by fetal leukemia.
8 The first is leukemic cell involvement of multiple fetal organs and placenta that yields
9 excessive fluid accumulation in the fetal body and polyhydramnios. In this case,
10 multiple organ failure due to leukemic dissemination and/or acute circulatory failure
11 due to placental vessel occlusion may lead to sudden fetal demise [9]. The second is
12 chronic circulatory insufficiency due to hyperviscosity attributable to leukocytosis,
13 which is often accompanied by oligohydramnios. Hydrops fetalis in the second
14 situation often takes a slower course than that in the first situation [7, 8].

15 Prenatal diagnosis of congenital leukemia requires cordocentesis. According to our
16 PubMed search, prenatal diagnoses have been reported in only 10 cases [4, 5, 7, 8, 11,
17 12]. Interestingly, all of these cases were associated with trisomy 21 (Down
18 syndrome). This suggests that leukemic fetuses associated with Down syndrome are
19 likely to have a milder prenatal course than those without Down syndrome, thus giving
20 a time for cordocentesis. Supporting this, neonatal leukemia associated with Down
21 syndrome has a natural tendency to undergo spontaneous remissions and reported
22 mortality rate is much lower than that without Down syndrome (30% vs. 80%) [13, 14].

23 Leukemic fetuses, especially those without association of Down syndrome, usually
24 require postnatal chemotherapy. Although several reports described successful
25 chemotherapy against leukemia during the early neonatal period [15-18], these neonates
26 were in relatively stable conditions before initiating the chemotherapy. Since most of
27 the leukemic fetuses are likely to be already deteriorated in utero, the rescue might be
28 difficult even if the prenatal diagnosis was established and the delivery was expedited
29 before the fetal demise. Recently, accumulating experiences of chemotherapy against
30 pregnant women complicated with malignancies suggest that in-utero exposure to at
31 least some of chemotherapeutic agents in the second and third trimester is relatively safe
32 in terms of fetal malformation as well as both short- and long-term neonatal outcome
33 [19-21]. Therefore, intrauterine chemotherapy might be an option to rescue prenatally

1 diagnosed leukemic fetuses.

2

References

- 1 Bader JL, Miller RW: Us cancer incidence and mortality in the first year of
life. *Am J Dis Child* 1979;133:157-159.
- 2 Greaves M: Pre-natal origins of childhood leukemia. *Rev Clin Exp Hematol*
2003;7:233-245.
- 3 Gray ES, Balch NJ, Kohler H, Thompson WD, Simpson JG: Congenital
leukaemia: An unusual cause of stillbirth. *Arch Dis Child* 1986;61:1001-1006.
- 4 Gaedicke G, Kleihauer E, Terinde R: Acute non-lymphocytic leukaemia
versus transient leukaemoid reaction in fetuses with down syndrome. *Lancet*
1990;335:857.
- 5 Foucar K, Friedman K, Llewellyn A, McConnell T, Aisenbrey G, Argubright
K, Ballinger L: Prenatal diagnosis of transient myeloproliferative disorder via
percutaneous umbilical blood sampling. Report of two cases in fetuses affected by
down's syndrome. *Am J Clin Pathol* 1992;97:584-590.
- 6 Donnenfeld AE, Scott SC, Henselder-Kimmel M, Dampier CD: Prenatally
diagnosed non-immune hydrops caused by congenital transient leukaemia. *Prenat Diagn*
1994;14:721-724.
- 7 Baschat AA, Wagner T, Malisius R, Gembruch U: Prenatal diagnosis of a
transient myeloproliferative disorder in trisomy 21. *Prenat Diagn* 1998;18:731-736.
- 8 Robertson M, De Jong G, Mansvelt E: Prenatal diagnosis of congenital
leukemia in a fetus at 25 weeks' gestation with down syndrome: Case report and review
of the literature. *Ultrasound Obstet Gynecol* 2003;21:486-489.
- 9 Shibasaki T, Matsuda H, Kawakami Y, Furuya K: Fetal leukemia with
umbilical artery embolism and circulatory failure. *Obstet Gynecol* 2007;109:521-523.
- 10 Simpson JH, McDevitt H, Young D, Cameron AD: Severity of non-immune
hydrops fetalis at birth continues to predict survival despite advances in perinatal care.
Fetal Diagn Ther 2006;21:380-382.
- 11 Zerres K, Schwanitz G, Niesen M, Gembruch U, Hansmann M, Waldherr R:
Prenatal diagnosis of acute non-lymphoblastic leukaemia in down syndrome. *Lancet*
1990;335:117.

12 Macones GA, Johnson A, Tilley D, Wade R, Wapner R: Fetal
 hepatosplenomegaly associated with transient myeloproliferative disorder in trisomy 21.
 Fetal Diagn Ther 1995;10:131-133.

13 Homans AC, Verissimo AM, Vlachia V: Transient abnormal myelopoiesis of
 infancy associated with trisomy 21. Am J Pediatr Hematol Oncol 1993;15:392-399.

14 Isaacs H, Jr.: Fetal and neonatal leukemia. J Pediatr Hematol Oncol
 2003;25:348-361.

15 Mori T, Kaneko H, Kumagai MA, Miyauchi J, Kaneko Y, Fujimoto J,
 Tsunematsu Y: Congenital leukaemia with a mixed phenotype of megakaryoblasts and
 erythroblasts: A case report and characterization of the blasts. Br J Haematol
 1997;96:740-742.

16 Fernandez MC, Weiss B, Atwater S, Shannon K, Matthay KK: Congenital
 leukemia: Successful treatment of a newborn with t(5;11)(q31;q23). J Pediatr Hematol
 Oncol 1999;21:152-157.

17 Satter EK, Maari CH, Morel KD, Eichenfield LF, Cunningham BB,
 Friedlander SF, Bergman JN: Disseminated linear calcinosis cutis associated with the
 koebner phenomenon in an infant with congenital acute monocytic leukaemia. Br J
 Dermatol 2004;150:753-756.

18 van Dongen JC, Dalinghaus M, Kroon AA, de Vries AC, van den
 Heuvel-Eibrink MM: Successful treatment of congenital acute myeloid leukemia
 (aml-m6) in a premature infant. J Pediatr Hematol Oncol 2009;31:853-854.

19 Aviles A, Neri N: Hematological malignancies and pregnancy: A final report
 of 84 children who received chemotherapy in utero. Clin Lymphoma 2001;2:173-177.

20 Ring AE, Smith IE, Jones A, Shannon C, Galani E, Ellis PA: Chemotherapy
 for breast cancer during pregnancy: An 18-year experience from five london teaching
 hospitals. J Clin Oncol 2005;23:4192-4197.

21 Hahn KM, Johnson PH, Gordon N, Kuerer H, Middleton L, Ramirez M, Yang
 W, Perkins G, Hortobagyi GN, Theriault RL: Treatment of pregnant breast cancer
 patients and outcomes of children exposed to chemotherapy in utero. Cancer
 2006;107:1219-1226.

Figure legends

Figure 1. Sequential changes of pulsatility indices of umbilical artery (UmA-PI) (A) and middle cerebral artery (MCA-PI) (B) and ultrasonographic findings 12 hours prior to fetal death (C and D)

(A, B) Arrows indicate the time of fetal death. Note acute elevation of UmA-PI and decline of MCA-PI from 4 days before fetal death at 30⁺³ weeks' gestation. (C) Amniotic fluid depth of 109.3mm indicates polyhydramnios. (D) Echo-free space around fetal lung (arrowheads) represents pleural effusion. * indicates fetal heart.

Figure 2. Fetal cardiograms showing fetal heart rate (FHR) tracing in the upper panels and uterine contractions in the lower panels.

(A) FHR tracing 13 hours before fetal death shows decreased beat-to-beat variability. (B) FHR tracing 4 hours before fetal death shows small dip-like deceleration on every uterine contraction. (C) FHR tracing immediately before fetal death shows mild bradycardia (100-110 beat per minute) with loss of variability followed by sudden disappearance of FHR. Arrow indicates the time of fetal death.

Figure 3. Placenta with fetal vessels showing leukocytosis. Scale bars indicate 100 μ m.

(A) Hematoxylin and Eosin (H&E) staining. (B) Magnified image of the boxed area shown in (A). Intravillous capillary vessels (arrows) are filled with small- to medium-sized immature-looking atypical cells. (C) H&E staining. Umbilical artery (arrowheads) contains an aggregate of the atypical cells. (D) Myeloperoxidase immunohistochemistry. Cytoplasmic staining of the atypical cells indicates myeloid lineage of derivation. (E) Ki-67 (MIB-1) immunohistochemistry showing high proliferative capacity of cells. Note that the labeling index reaches 50%.

Figure 1

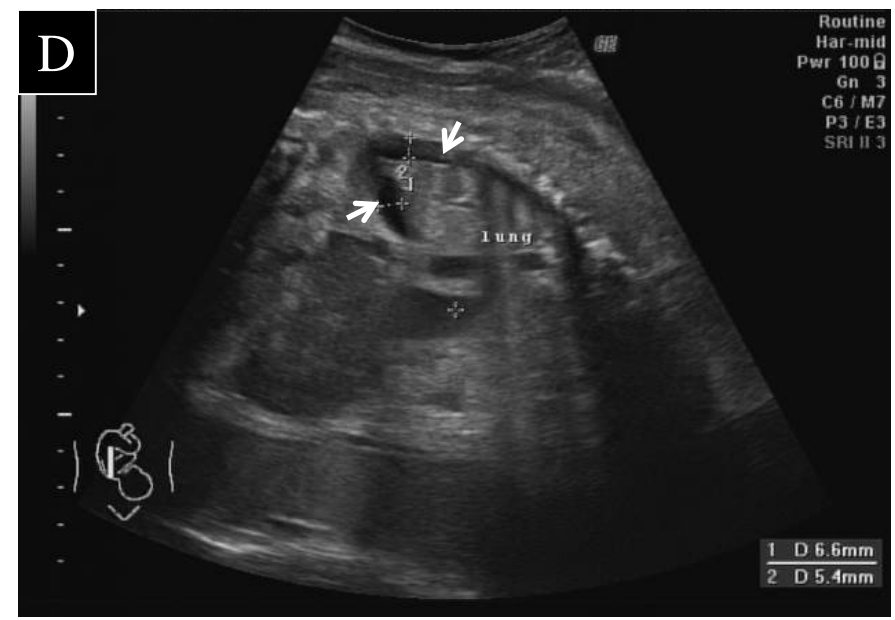
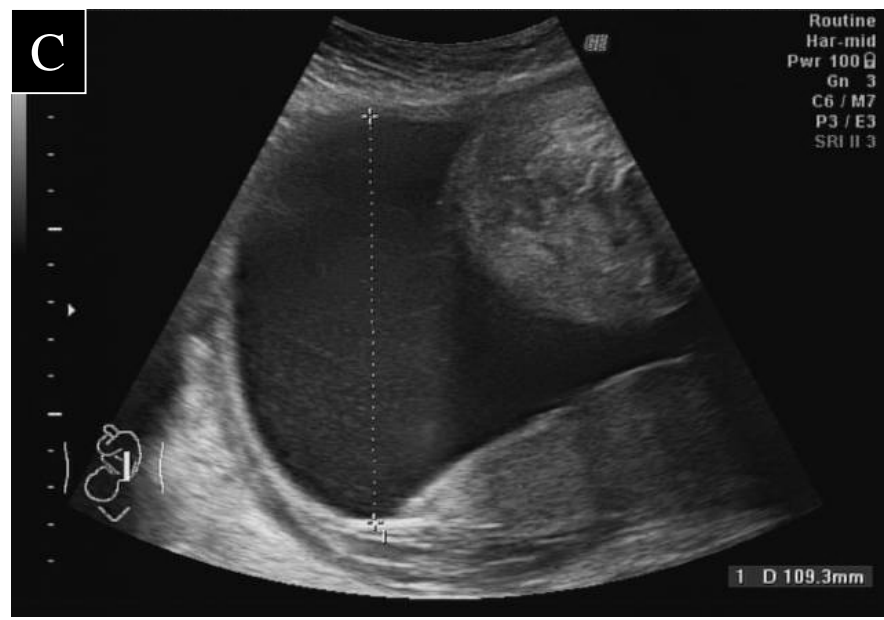
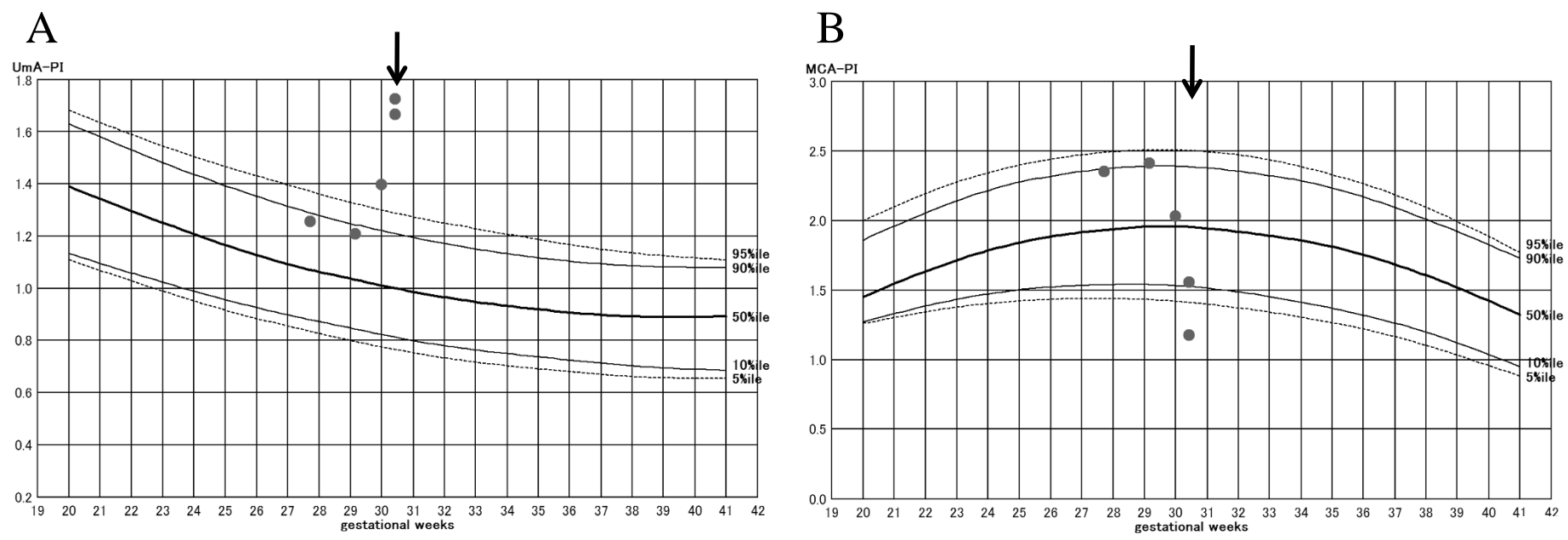


Figure 2

A



B



C



Figure 3

