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CASE REPORT

Prenatal Diagnosis of Congenital Hypophosphatasia : A Report of 2 Consecutive Pregnancies

Theera Tongsong MD,*
Saipin Pongsatha MD,*
Sumalee Siriangkul MD.**

* *Department of Obstetrics and Gynaecology*

** *Department of Pathology, Faculty of Medicine, Chiang Mai University, Thailand*

ABSTRACT

Hypophosphatasia, an inherited autosomal recessive, is characterized by the demineralization of bones associated with deficiency of alkaline phosphatase. The incidence is 1 in 100,000 births. Accurate prenatal diagnosis of this lethal skeletal dysplasia is now possible, and the option of pregnancy termination can be offered.

A 27 year-old primigravida, 25 weeks of gestation, presented with large-for-date uterine size. The obstetric ultrasound showed polyhydramnios, poorly ossified and globular thin cranium. The soft skull could be compressed transabdominally with ultrasound tranducer. All of bony structures were delicate, and diffusely demineralized. However, vertebral bodies, both femurs, and humerus had some degree of ossification, shortened, and bowed but had no apparent fracture. The sonographic findings were most likely related to hypophosphatasia.

Two years later, the same patient presented to the antenatal clinic with the second pregnancy at 7 weeks' gestation. The screening ultrasound at 15 weeks revealed normal with exception for rather short femurs. The follow up ultrasound at 19 weeks showed a single fetus with micromelia without fractures, thin and poorly ossified cranium, ribs, vertebrae, and all of long bones. Only three abdominal vertebral bodies were somewhat ossified. Based on the sonographic findings and previous history of first pregnancy, the diagnosis of recurrent congenital hypophosphatasia was made.

Both pregnancies were electively terminated. Postnatal radiographs, autopsies and serum alkaline phosphatase levels confirmed the prenatal diagnosis.

Key words : congenital hypophosphatasia, prenatal diagnosis, ultrasound

Hypophosphatasia is one of the rare lethal short - limbed dwarfisms occurring in approximately 1 per 100,000 births.[1] It is characterized by the demineralization of bones associated with deficiency of alkaline phosphatase. It is inherited in an autosomal recessive pattern.[2] The homozygote has a severe deficiency of tissue and serum alkaline phosphatase and excessive urinary excretion of phosphoethanolamine. Because this condition is uniformly fatal, prenatal diagnosis is important, and the option of pregnancy termination can be offered at any time during gestation. The objective of this report is to demonstrate that prenatal diagnosis by ultrasound is possible for this lethal condition.

Case Report

First pregnancy

A healthy 27-year-old primigravida was admitted to Maharaj Nakorn Chiang Mai Hospital, at 25 weeks' gestation by last menstrual period due to recurrent premature contraction. Her prior medical and familial histories were unremarkable. The patient attended our antenatal clinic since 13 weeks' gestation.

On abdominal examination, the fundal height was 28 centimetres above pubic symphysis, large-for-date uterine size. Fetal heart sound was positive. Ultrasound examination was performed to detect anomalies in cases of premature contraction and polyhydramnios. The ultrasound examination showed single fetus with breech presentation, polyhydramnios, poorly ossified and globular thin cranium through which the sulci and gyri of the brain could be easily outlined. The soft skull could be compressed transabdominally with ultrasound transducer. All of bony structures were delicate, diffusely demineralized. However, vertebral bodies, both femurs, and humerus had some degree of ossification. All of long bones were shortened, and bowed but with no apparent fracture.

Prenatal diagnosis of lethal short-limbed skeletal dysplasia was made and was most likely related with hypophosphatasia. The pregnancy was terminated vaginally. A stillborn-male infant weighing 800 grams with globular, thin, soft and compressible calvarium, shortened limbs. Postnatal radiograph showed poorly ossified globular calvarium. All of bony structures was delicate, poorly ossified. Ulna, fibula, most of metacarpal, metatarsal and phalangeal bones could not be seen. However, vertebral bodies, both femurs, and humerus had some degree of ossification. All of long bones were shortened, and bowed but no apparent fracture.

Serum alkaline phosphatase level of the abortus was extremely low, but tissue alkaline phosphatase was not determined. Autopsy findings were also compatible with the diagnosis of severe hypophosphatasia.

Second pregnancy

Two years later, at age of 29 years, she presented to the antenatal clinic, Maharaj Nakorn Chiang Mai Hospital with the second pregnancy at 7 weeks' gestation. She was healthy. Routine prenatal serologic and haematologic tests were unremarkable. Physical examination at 7, 11 and 15 weeks of gestation revealed pregnancy size consistent with dates. Ultrasound screening due to previous child with congenital hypophosphatasia was performed at 15 weeks. The sonographic findings revealed normal with exception for rather short femurs (single fetus with BPD 30 mm, HC 10.7 mm, AC 10.2 mm, placenta grade 1, normal amniotic fluid volume).

The follow up ultrasound at 19 weeks showed a single fetus with cephalic presentation. The amount of amniotic fluid was within normal

limit. The fetus had a thin, poorly ossified cranium through which the sulci and gyri of the brain could easily be seen. The thorax was rather narrow. The ossification of ribs, vertebrae, and all of long bones were markedly decreased. Only three abdominal vertebrae appeared somewhat ossified. There was severe shortening of all limbs without evidence of any fracture or callus formation. Based on these sonographic findings and previous history of first pregnancy, the diagnosis of recurrent congenital hypophosphatasia was made. (BPD 40 mm, HC 12.7 mm, AC 13.2 mm, femur length 14 and 12 mm. The placenta was normal, grade 1 and the amniotic fluid volume was normal)

After counseling and psychological support had been given, the pregnancy was terminated with transcervical misoprostol. A stillborn female fetus weighing 310 grams was spontaneously expulsed. The postnatal appearance showed thin and soft calvarium with severe shortenting of all limbs.

Postnatal radiographs showed a poorly ossified calvarium, narrow thorax, severe shortening of all long bones, absence of ossiication of ribs, long bones and all of vertebrae except for three abdominal vertebral bodies. Serum alkaline phosphatase of the abortus was extremely low, but tissue alkaline phosphatase was not determined. The autopsy findings were compatible with congenital hypophosphatasia.

Discussion

Congenital (lethal) hypophosphatasia is a rare error of inborn metabolism characterized by abnormal bone mineralization with an extreme deficiency of alkaline phosphatase.[2,3] The mechanism for the development of bone fragility in this disease is not clearly understood. Alkaline phosphatase normally acts on pyrophosphatase and other phosphate esters which leads to the accumulation of inorganic phosphates, which are critical for the malformation of bone crystals. A deficiency in alkaline phosphatase leads to deficient generation of bone crystals. The major sonographic features of congenital hypophosphatasia are short-limbed dwarfism with thin, delicate bones and decreased bone echogenicity due to diffused hypomineralization.[4,5]

A precise prenatal differentiation of severe hypophosphatasia from other skeletal dysplasia may be difficult. The major causes of short-limbed dwarfism with hypomineralization of bones include hypophosphatasia, osteogenesis imperfecta type II, and achondrogenesis.[6] The common sonographic features of achondrogenesis are absent vertebral body and sacral ossification, while calvarium is rather completely ossified, in contrast to the echolucent skull in hypophosphatasia. The degree of moderate to severe micromelia and diffused hypomineralization in hypophosphatasia may resemble that of osteogenesis imperfecta type II. However, in contrast to the thickened bones of osteogenesis imperfecta type II, the extremity bones in hypophosphatasia tend to be delicate or may even be absent,[4-8] as were indeed the cases here. The sonographic findings of diffused demineralization, short-limb dwarfism, and thin delicate bones in our cases suggested severe hypophosphatasia rather than achondrogenesis or osteogenesis imperfecta. However, the definitive diagnosis could only be confirmed by postnatal radiograph and low serum alkaline phosphatatase.[3]

Sonographic diagnosis of congenital hypophosphatasia in first trimester may be impossible due to the fact that even in normal fetus incomplete ossification at this stage of development may be difficult to discriminate from the abnormal one. At what gestational age can the sonongraphic

diagnosis of congenital hypophosphatasia be confidently made is difficult to conclude. This report suggests that the evidence of skeletal dysplasia has been already appeared as early as 15 weeks' gestation. We believe that routine ultrasound screening at midpregnancy can diagnose this lethal condition. The patient with previous history of congenital hypophosphatasia should

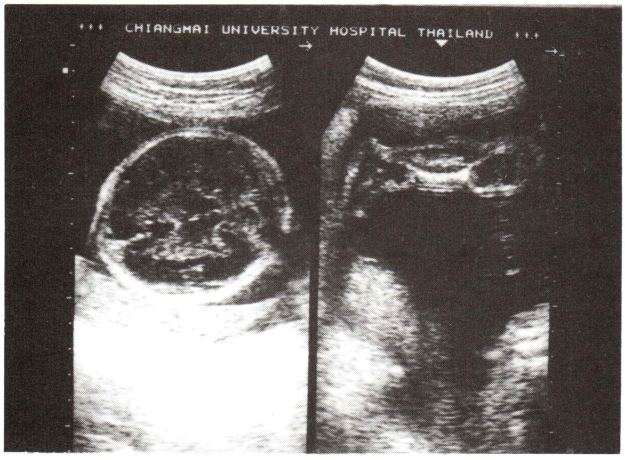


Fig. 1. (First pregnancy)
Left : The sonolucent skull through which sulci and gyri of brain could be seen.
Right : The longitudinal scan of lower extremity shows poorly ossified long bones and foot.

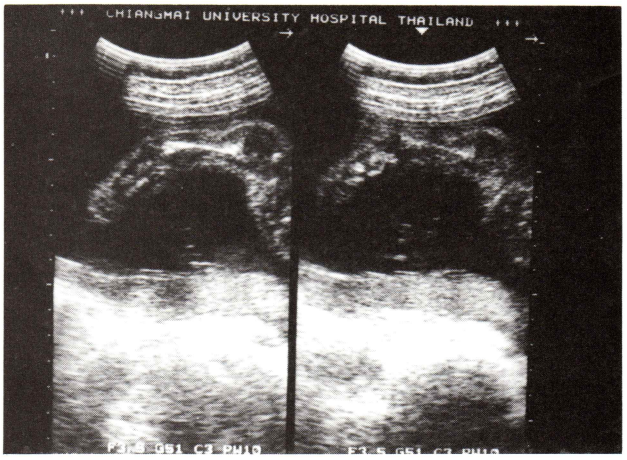


Fig. 2. (First pregnancy)
The longitudinal scan of upper extremity shows sonolucent long bones and irregular shape of ulna and radius.

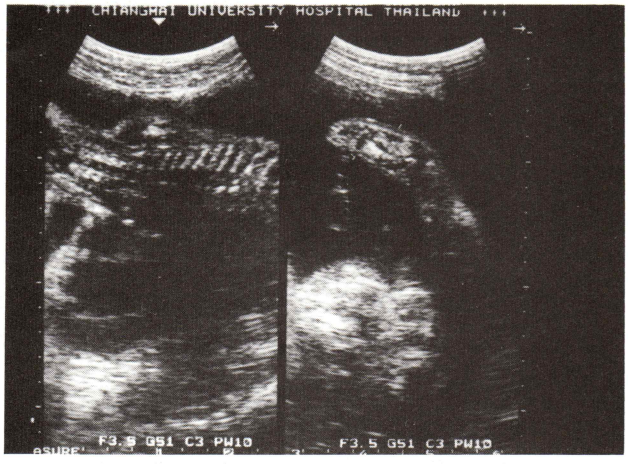


Fig. 3. (First pregnancy)
Left : The poorly ossified ribs.
Right : The poorly ossified bony structures of foot.

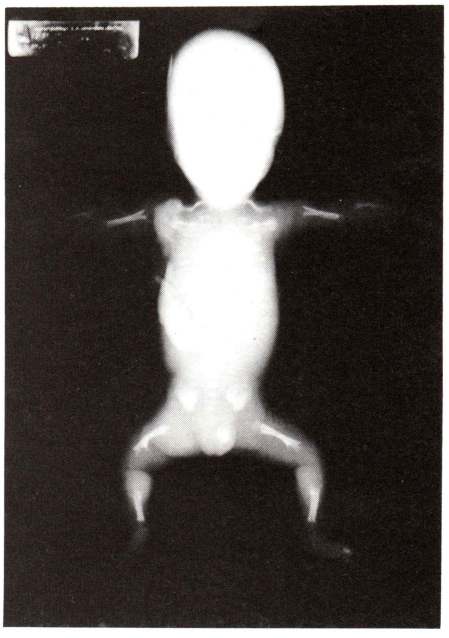


Fig. 4. (First pregnancy)
Postnatal radiograph confirms the prenatal findings.

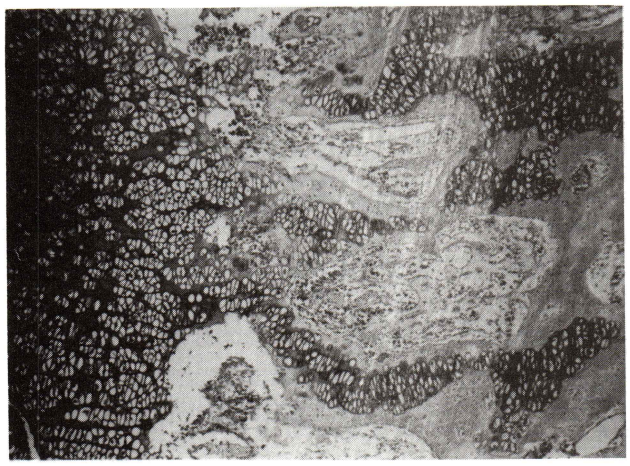


Fig. 5. (First pregnancy)
Microscopically, the zones of proliferative maturing and hypertrophic cartilage of the growth plate are widened and irregular. The cartilage also persists into the metaphysis with excessive unclassified osteoid.

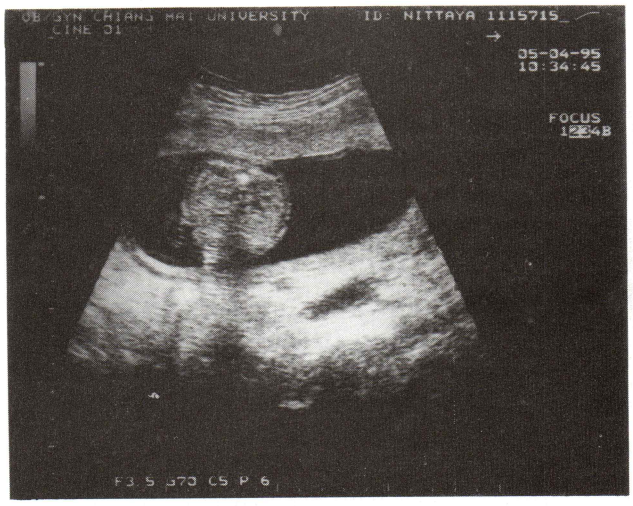


Fig. 6. (Second pregnancy)
Transverse sonographic scan of fetal abdominal spines shows the invisible posterior ossification centre and more echodense anterior body.



Fig. 7. (Second pregnancy)
The longitudinal scan shows poorly ossified vertebrae with exception for only three anterior bodies.

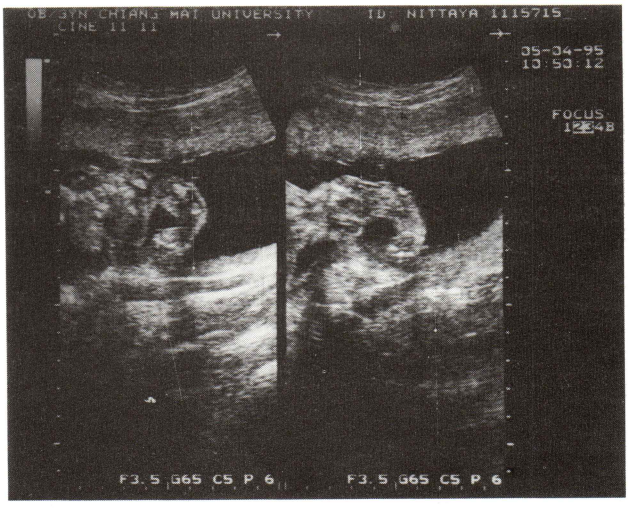


Fig. 8. (Second pregnancy)
The longitudinal scan of lower extremity shows poorly ossified and severe shortening long bones.

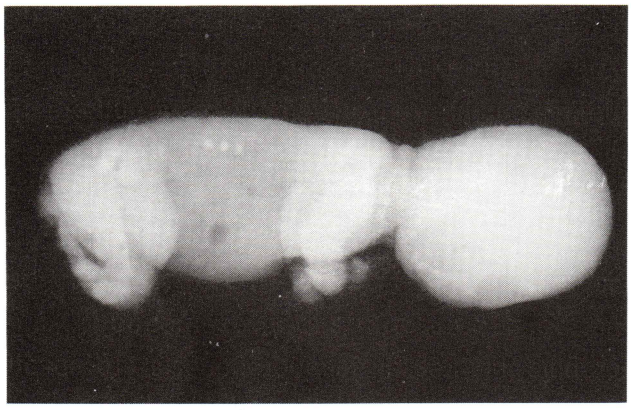


Fig. 9. (Second pregnancy)
Postnatal radiograph shows almost complete lack of mineralization of bony skeleton.

be sonographically screened at intervals from early second trimester.

Recently, prenatal diagnosis has been accomplished successfully by alkaline phosphatase assay on chorionic villus sample taken in the first trimester.[9] Congenital hypophosphatasia is an inherited autosomal recessive pattern[2] with a 25% chance of recurrence in the next pregnancy. Inspite of negative familial history, attempt must be made to exclude this condition in subsequent pregnancy. When an established confident diagnosis of this lethal skeletal dysplasia is made, the option of pregnancy termination should be offered to the patient.

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