A 6-year Experience of Fetal Skeletal Anomalies Prenatal Diagnosis at Anomaly Clinic, Siriraj Hospital

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ABSTRACT

Objective: The purposes of this study were to review the prevalence of skeletal dysplasias among fetal anomaly cases and to demonstrate common findings detected prenatally by ultrasonography.

Methods: Twenty prenatal cases diagnosed of skeletal anomalies between January 2000 and December 2005 at Anomaly Clinic, Maternal-Fetal Medicine Unit, Siriraj Hospital were reviewed retrospectively. Demographic data such as maternal age, gravida, parity, gestational age at first diagnosis were collected, including prenatal ultrasound findings. Final diagnosis and pregnancy outcome after termination of pregnancy were also demonstrated.

Results: The prevalence of skeletal dysplasias among fetal anomaly cases in the study interval was 3.86% (20/518 cases and 95%CI=2.51%, 5.89%). Mean maternal age was 30.3 (± 5.3) years old. The most likely time of diagnosis was 26 (± 5.7) weeks of gestation. The most common type diagnosed prenatally was thanatophoric dysplasia (40%). All cases of prenatal ultrasound findings of suspected skeletal dysplasias demonstrated short limbs. Three cases were non-lethal anomalies and the parents decided to continue pregnancy. In the remaining 17 cases, the parents were counseled about lethal prognosis of their fetuses and only 11 cases decided to terminate pregnancy at our hospital. Thanatophoric dysplasia was the most common diagnosis after termination of pregnancy (9 in 11 cases).

Conclusion: Fetal skeletal dysplasias are one of fetal anomalies which can be detected prenatally by routine ultrasonography. Detection of abnormal long bone length is the important finding. Thorough scanning of all bony characteristics can help clinicians about prenatal diagnosis and pregnancy outcomes.

Keywords: Prenatal diagnosis; Skeletal dysplasias

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Skeletal anomalies or dysplasias are one of fetal anomalies detected prenatally by ultrasonography. Nowadays, there are more than 200 known skeletal dysplasias described in the literatures; however, 50 of which are recognizable at neonatal period.[1] The prevalence of skeletal dysplasias ranges from 2.3 to 7.6 per 10,000 births.[2,3,4,5] Approximately 20-40% of these result in stillbirth or neonatal death.[1,2,6]

The skeletal dysplasias represent a genetically heterogeneous group of conditions characterized by the disturbance of the normal process of bone development.[7]

They have a wide variety of frequency, mode of transmission, clinical presentation and prognosis. The International Working Group on Constitutional Diseases of Bone has published an international classification of osteochondrodysplasias that categorizes the disorders based on radiodiagnostic criteria.[2]

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However, some forms of skeletal dysplasias can be diagnosed prenatally by routine ultrasonography during antenatal period particularly in the first and second trimesters. The specific characteristics of disorders can be specified for some types of skeletal dysplasias, making genetic counseling possible. Parts of these are lethal anomalies.

Anomaly Clinic, Maternal-Fetal Medicine (MFM) Unit, Siriraj Hospital has been established since 2000. Skeletal dysplasias are one of fetal anomalies that are diagnosed at the clinic. The objectives of this study were to review the prevalence of skeletal dysplasias among fetal anomaly cases in a 6-year experience (between 2000- 2005) of our clinic, and to demonstrate common findings detected prenatally by ultrasonography.

MATERIALS AND METHODS

In this retrospective study, we reviewed the data recorded in the database program in MFM Unit. All patients

TABLE 1. The number of cases of skeletal dysplasias in each year from January 2000- December 2005.

Year	Total of anomaly cases (N)	No. of cases of skeletal dysplasias N (%)
2000	69	7 (10.14%)
2001	77	1 (1.29%)
2002	107	2 (1.86%)
2003	84	1 (1.19%)
2004	98	5 (5.10%)
2005	83	4 (4.81%)

who had fetal skeletal dysplasias diagnosed by ultrasonography between January 2000 and December 2005 were reviewed. Demographic data such as maternal age, gravida, parity, gestational age at first diagnosis were collected, including prenatal ultrasound findings. Final diagnosis and pregnancy outcome after termination of pregnancy were determined in lethal and non- lethal groups.

RESULTS

Among 518 fetal anomalies diagnosed prenatally at Anomaly Clinic, MFM Unit, Siriraj Hospital between January 2000 and December 2005, there were a total of 20 cases of skeletal dysplasias (3.86%). The number of cases of skeletal dysplasias in each year is shown in Table 1. Mean maternal age was 30.3 (± 5.3) years old. Half of them were first gravida and none had history of abortion. The mean gestational age at first diagnosis at the Anomaly Clinic was 26 (± 5.7) weeks. The preliminary prenatal diagnosis of skeletal dysplasias is shown in Table 2. The most common prenatal diagnosis was thanatophoric dysplasia (8 cases = 40%). Other diagnoses were osteogenesis imperfecta (20%), and achondroplasia (5%). 35% were diagnosed as micromelia. The most common prenatal ultrasound finding of skeletal dysplasias was short limbs (20 of 20 cases) and 5 of them (25%) had bone length less than 10 percentile. Other prenatal ultrasound findings are shown in Table 3.

In 20 cases of skeletal dysplasias, 3 cases decided to continue pregnancy because their fetuses had only short limbs which were not less than 10 percentile. Fetal surveillance was scheduled at our clinic until delivery. The first case had a previous child affected by achondroplasia which is a non-lethal anomaly, and unfortunately, occurred again. This case delivered at 36^{+3} weeks gestation because of spontaneous preterm labor. The second one showed normal living male infant after delivery at 40 weeks gestation with birth weight of 3,380 grams. The last delivered at 37 weeks gestation and this case also had a previous affected child with short lower limbs without evidence of bony fracture. This case was planned for postnatal investigations along with his older brother by our geneticists but, unfortunately, both of them lost follow up and we could not find out their definite diagnosis.

Apart of these were counseled about lethal prognosis of their fetuses. All of them opted for termination of pregnancy. There were 5 referred cases in this group and 4 of these were sent back to their primary hospitals. However, we could not get the details of their definite diagnosis after termination of pregnancy. Only two cases, which were not referred cases, lost follow up after visiting at our unit. So, 11 cases were terminated at Siriraj Hospital. Two cases were counseled genetically to perform prenatal diagnosis for chromosome study which turned out to be normal and continued to terminate pregnancy. After termination of pregnancy, all of the fetuses were sent for autopsy. The final result and definite diagnosis are shown in Table 4.

TABLE 2. The first visit prenatal diagnosis of skeletal dysplasias in each year from January 2000- December 2005.

Year	The first visit prenatal diagnosis of skeletal dysplasias			
	Achondroplasia	Thanatophoric dysplasia	Osteogenesis Imperfecta	Micromelia caused?
2000	1	4	1	1
2001	-	1	-	-
2002	-	1	1	-
2003	-	-	-	1
2004	-	1	2	2
2005	-	1	-	3

TABLE 3. Abnormal prenatal ultrasound findings of skeletal dysplasias.

Abnormal U/S findings	Cases (n)	Percent (%)
Short limbs	20	100
Small thorax	12	60
Bowing or angulations	7	35
Evidence of bony fracture	4	20
Clover leaf skull	2	10
Skull change when apply pressure	2	10
Others:		
polyhydramnios	4	20
oligohydramnios	2	10
pyelectasis	2	10
heart defect	1	5
ventriculomegaly	1	5

DISCUSSION

Skeletal dysplasias can be divided into two major groups according to prognosis: non-lethal and lethal. In the non-lethal group, heterozygous achondroplasia is the most common chondrodysplasia which occurs with a frequency of approximately 1 in 15,000 births.[2] The inheritance pattern of this is autosomal dominant. However, over 80% of the cases are results of de novo gene mutations. Studies have shown that the new gene mutations are exclusively inherited from the father and that there is a positive association with advanced paternal age.[2,8] In this study, we had 1 case of this non-lethal anomaly in our 6-year experience. This case had a family history of previous affected child and decided to continue pregnancy until spontaneous delivery at the gestational age of 36 weeks 3 days. Vaginal delivery was the route of delivery and pregnancy outcome revealed a living preterm female infant. Further management was performed at neonatal period by neonatologists and geneticists.

In the lethal group, thanatophoric dysplasia is the most common prenatal diagnosis which is in accordance with many studies. It is characterized by a large cranium, a narrow thorax with short ribs, a relatively long trunk, short limbs and severe growth deficiency. There are two types of thanatophoric dysplasia. Type I is more common and is characterized by curved long bones particularly femur and very flat vertebral bodies whereas type II shows straight long bones and taller vertebral bodies. The characteristics of this anomaly are specific, particularly clover

TABLE 4. The final diagnosis and pregnancy outcome.

Case	Prenatal diagnosis	Final diagnosis/result	Method of termination of pregnancy	Route of delivery
Non lethal				
1	Achondroplasia	Achondroplasia	Spontaneous preterm labor	Vagina
2	Micromelia caused?	Normal term infant	Spontaneous labor	Vagina
3	Osteogenesis Imperfecta	Lost follow up	Spontaneous labor	Vagina
Lethal				
4	Thanatophoric dysplasia	Thanatophoric dysplasia	Oxytocin	Vagina
5	Thanatophoric dysplasia	Thanatophoric dysplasia	Hypertonic saline	Vagina
6	Thanatophoric dysplasia	Thanatophoric dysplasia	Oxytocin	Vagina
7	Thanatophoric dysplasia	Thanatophoric dysplasia	Misoprostol	Vagina
8	Osteogenesis Imperfecta	Osteogenesis Imperfecta	Misoprostol	Vagina
9	Micromelia caused?	Thanatophoric dysplasia	Misoprostol	Vagina
10	Thanatophoric dysplasia	Thanatophoric dysplasia	Misoprostol	Vagina
11	Osteogenesis Imperfecta	Osteogenesis Imperfecta	Misoprostol	Vagina
12	Thanatophoric dysplasia	Thanatophoric dysplasia	Misoprostol	Vagina
13	Micromelia caused?	Thanatophoric dysplasia	Misoprostol	Vagina
14	Thanatophoric dysplasia	Thanatophoric dysplasia	Misoprostol	Vagina

leaf skull which is classified in type II of this disorder. Thanatophoric dysplasia is inherited in an autosomal dominant fashion with the mutant gene localized on the short arm of chromosome 4 (4p16locus).[2] The cause of death of this lethal anomaly is lung hypoplasia from small thorax which is the most common cause in the same way as other lethal skeletal anomalies.[1,9]

Osteogenesis imperfecta is one of lethal skeletal dysplasias that are characterized by bone fragility and other connective tissue abnormalities. The clinical spectrums include a perinatal lethal form and a type with a normal life span with only a mild decrease in bone mass. It is classified into 4 types and type II is a lethal form in which most affected infants are stillborn or die within the first day from respiratory failure. The characteristics of this type consist of short long bones, multiple fractures, and blue sclerae. The skull is poorly mineralized and soft. Significant undermineralization is best evaluated sonographically by the unusually easy visualization of intracranial structures in the late second and early third trimesters. In some cases, the pressure of the transducer on maternal abdomen can cause deformity of the fetal skull.[1,2]

Sillence et al.[10] subclassified this disorder into three groups based on radiologic findings. Type A has short, broad, crumpled femora, angulated tibia and beaded ribs. Type B also has short, broad, crumpled femora and angulated tibia but the ribs are normal or incomplete beading. Type C shows long, thin, inadequa-tely modeled bones with multiple fractures and thin, beaded ribs.

The significant prenatal ultrasound finding which reminds examiners to be aware of abnormality of the skeletal system is shorten-ing of bony structures especially in long bones which can be detected in all cases of skeletal dysplasias and be classified in many types: micromelia, defined as shortening of entire limbs; rhizomelia, defined as shortening of proximal part of extremities (humerus and/or femur); mesomelia, defined as shortening of middle part of extremities or intermediate segment (radius and ulnar and/or tibia and fibula); and, acromelia, defined as shortening of hand and foot. Comparison of the long bone lengths with other parameters used for gestational age assessment is particularly helpful when noting short limb lengths compared with normal measurements for gestational age and other parameters.

Furthermore, the other findings of abnormal characteristic of bony structure such as decreased bone echogenicity, bony shape such as angulation, evidence of intrauterine fracture or old fracture with callus formation (beaded- like appearance), and small chest contour can help many perinatologists and geneticists for prenatal diagnosis and counseling and to predict the prognosis of pregnancy outcome.

Polyhydramnios is also one of common ultrasound findings detected in skeletal dysplasias. The cause of this condition is difficulty of swallowing amniotic fluid from small chest contour.

In case of non-lethal anomaly, multidisciplinary approaches with neonatologists for planning of route and timing of delivery, neonatal investigation and proper management may be useful when diagnosed prenatally.

In our study, however, there were incomplete data caused by cases that were lost to follow up or had termination of pregnancy elsewhere without available report of outcome. These events are the effect of the health-service system in our country which the financial aspect still is the most important factor.

CONCLUSION

Fetal skeletal dysplasias are one of fetal anomalies which can be detected prenatally by routine ultrasonography. Detection of abnormal long bone length is the important finding particularly when compared to other parameters of fetal biometry. Thorough scanning of all bones should be considered in suspected case. Furthermore, bony characteristics such as contour, echogenicity or mineralization, evidence of fractures etc. can help examiners to diagnose skeletal dysplasias and genetic counseling.

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บทคัดย่อ

ประสบการณ์ในช่วงระยะเวลา 6 ปีของการตรวจวินิจฉัยก่อนคลอดของความผิดปกติของระบบโครงสร้างกระดูกในโรงพยาบาลศิริราช

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วัตถุประสงค์: เพื่อศึกษาความชุกของความผิดปกติของระบบโครงสร้างกระดูกที่พบในความผิดปกติของทารกในครรภ์ที่ได้รับการตรวจวินิจฉัยก่อนคลอด รวมทั้งลักษณะที่ตรวจพบได้ด้วยการตรวจอัลตราซาวนด์

วิธีการ: ได้ทำการศึกษาข้อมูลผู้ป่วยที่ตรวจพบความผิดปกติของระบบโครงสร้างกระดูกของทารกในครรภ์จำนวน 20 รายในช่วงระหว่างเดือนมกราคม พ.ศ. 2543- ธันวาคม พ.ศ. 2548 ที่หน่วยเวชศาสตร์มารดาและทารก โรงพยาบาลศิริราช ข้อมูลทั่วไปเช่นอายุ จำนวนการตั้งครรภ์ ประวัติการคลอด การแท้ง รวมทั้งอายุครรภ์ที่ตรวจพบความผิดปกติได้ถูกนำมาวิเคราะห์ นอกจากนี้ยังได้ทำการศึกษาทบทวนลักษณะของสิ่งตรวจพบด้วยอัลตราซาวนด์ รวมทั้งการวินิจฉัยโรคขั้นสุดท้ายตลอดจนผลลัพธ์ที่ได้

ผลการศึกษา: ความชุกของความผิดปกติทางโครงสร้างกระดูกของทารกในครรภ์ในช่วงระยะเวลา 6 ปี ในโรงพยาบาลศิริราชมีจำนวน 20 ราย หรือคิดเป็นร้อยละ 3.86 (95%CI=2.51%, 5.89%) ของความผิดปกติของทารกในครรภ์ที่มารับการตรวจวินิจฉัยก่อนคลอด อายุเฉลี่ยของมารดามีค่าเท่ากับ 30.3 ปี (± 5.3) และอายุครรภ์โดยเฉลี่ยที่ตรวจพบความผิดปกติมีค่าเท่ากับ 26 สัปดาห์ (± 5.7) thanatophoric dysplasia เป็นโรคที่ได้รับการวินิจฉัยก่อนคลอดมากที่สุด คิดเป็นร้อยละ 40 ลักษณะสิ่งตรวจพบทางอัลตราซาวนด์ที่พบได้ในทุกรายคือการมีความยาวของกระดูกที่สั้นกว่าปกติ มีผู้ป่วยจำนวน 3 รายที่ตรวจพบว่าเป็นความผิดปกติทางโครงสร้างกระดูกชนิดไม่รุนแรงและตัดสินใจที่จะดำเนินการตั้งครรภ์ต่อ ในขณะที่ที่เหลือ 17 ราย ตรวจพบความผิดปกติหลายอย่างและพบเป็นความผิดปกติชนิดรุนแรงที่ทารกจะไม่สามารถมีชีวิตอยู่ได้ มีเพียง 11 รายที่ตัดสินใจยุติการตั้งครรภ์ที่โรงพยาบาลศิริราช thanatophoric dysplasia ยังคงเป็นการวินิจฉัยโรคที่พบมากที่สุดหลังจากยุติการตั้งครรภ์

สรุป: ความผิดปกติทางโครงสร้างกระดูกของทารกในครรภ์สามารถตรวจวินิจฉัยก่อนคลอดได้ด้วยการตรวจอัลตราซาวนด์ การตรวจพบความยาวของกระดูกที่สั้นกว่าปกติ ตลอดจนลักษณะทางโครงสร้างอื่น ๆ ของกระดูกจะช่วยให้แพทย์ผู้ดูแลสามารถให้การวินิจฉัยก่อนคลอดและให้คำปรึกษาแนะนำเกี่ยวกับพยากรณ์โรคแก่สตรีตั้งครรภ์ได้