Three-dimensional Ultrasonographic Visualization of Fetal Chromosome Abnormalities: a Preliminary Experience Report of 4 Cases

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The accurate diagnosis of fetal malformations in utero can provide both heath care providers and parents a number of management options. Three-dimensional ultrasonography is a new technique of diagnosis which has several potential advantages to allow for evaluation of specific anomalies by permitting high-quality views of body surface. We report 4 cases of fetal chromosomal abnormalities including 2 cases of trisomy 21, 1 case of trisomy 13 and 1 case of 48, XXY/+18. All cases were proved to have abnormal chromosomes by amniocentesis or percutaneous umbilical cord blood sampling. After 3D reconstruction, we can identify specific facial abnormalities which can not be visualized by conventional two-dimensional ultrasound such as low set ear, Mongolian's slant eyes, facial dysmorphism of trisomy 13 and trisomy 18. We also clearly visualized abnormalities of digits such as overlapping fingers, club hands and sandal gap. Three-dimensional reconstruction of the fetal body surface improves the antenatal diagnosis of chromosomal abnormalities characterized by a particular dysmorphism. Our report suggests that three-dimensional ultrasonography has the potential to provide novel informations on the fetal anatomy and be useful in visualization and identification of chromosomal abnormalities in utero.

Keywords : *Three-dimensional Ultrasonography, Chromosome Abnormalities, Trisomy 21, Trisomy 13, Chromosome 48, XXY/+18*

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Aneuploid fetuses affect approximately 0.5% of newborns[1-2]. Down syndrome results from the most prevalent clinically significant cytogenetic abnormality with a general population incidence of approximately 1 in 800 live births[3]. Trisomy 18 or Edwards syndrome is the second most common which has a reported incidence of 1 in 8,000 live births[4]. Most clinically important chromosome abnormalities share four common features[3] :

1. Characteristic facial/cranial characteristics.
2. Mental/developmental delay.
3. Structural abnormalities.
4. Intrauterine growth restriction.

Poor prognosis associated with such conditions has encouraged the development of screening programs to detect the most common chromosome abnormalities such as maternal serum screening test, which uses level of three serum analyses (alpha-fetoprotein [AFP], unconjugated estriol [E3] and hCG), and comprehensive prenatal ultrasonography[3, 5-8].

Generally, most fetuses with various chromosomal abnormalities have associated structural anomalies and growth restriction that can be identified and consistently reproduced during the second trimester ultrasoud examination. The improvement of technology in ultrasonography with high frequency transducer has made the detection of discrete anomalies possible. The very high specificity, positive predictive value and negative predictive value for detecting the anomalous fetuses have been reported in many studies[9,10]. One study comparing the prenatal ultrasound diagnosis with post-mortem finding in fetuses and infants with abnormal karyotype found

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the main prenatal sonography diagnosis was correct in 88% of cases[11].

There have been several studies about the clinical application of 3D ultrasound in obstetrics in the past 10 years[12,13]. Many studies have described the potential of 3D ultrasound in evaluating fetal malformations particularly facial abnormalities [14-16], head and spine anomalies[17], fetal cleft lips and palate[18-19], fetal ear anomalies[20], fetal digits and club feet[21,22] etc. In the fact that most of major chromosomal abnormalities, trisomy 21, 18 and 13 have characteristics of craniofacial abnormalities, foot and hand abnormalities and major structural abnormalities that can be benefit to be clearly identified by this novel technology.

The aim of this study was to determine whether 3D ultrasound can improve the ability to visualize the major fetal chromosomal abnormalities in utero.

Materials and Methods

Pregnant patients were referred from the hospitals in other provinces around Northeastern area of Thailand to the Division of Fetal Diagnosis and Therapy, Department of Obstetrics and Gynecology, Faculty of Medicine, Khon Kaen University, between January 2001- July 2002 because of abnormal fetal anomalies detected by 2D ultrasound.

All ultrasonographic examination (2 and 3-dimensional scanning) were performed with the Voluson 530D (MT) (Medison-Kretztechnik, Austria). Four patients were suspected of having chromosomal abnormalities when 2D ultrasound detected multiple structural anomalies. After patients were informed, they were examined at least once by 3D ultrasound. A broad frequency trans-abdominal volume probe (S- VAW 3-5) was used to acquire the volume data sets. For 3-dimensional ultrasonography a volume box of the region of interest, consisting of 60 (low resolution) to 250 (high-resolution) 2-dimensional images, was sampled automatically within 2-6 seconds per volume, and acquisitions were repeated if fetal movement occurred during acquisition.

Approximately 2-4 volume data sets were obtained per anomaly. Data was stored on removable magneto-optical disk. The volume were then rendered by using computer software to produce 3D rendered images by surface-rendering mode allowing the study of the surface of the region under consideration. Light-weighted and surface rending with additional threshoding was used to create an image of the surface of the fetal face.

The ultrasound findings and fetal karyotyping were discussed with the patients. Two patients accepted percutaneous umbilical cord blood sampling while other two accepted amniocentesis for fetal karyotyping. Options for the pregnancy and pregnancy termination were discussed after the result of the karyotyping.

Results

First Case

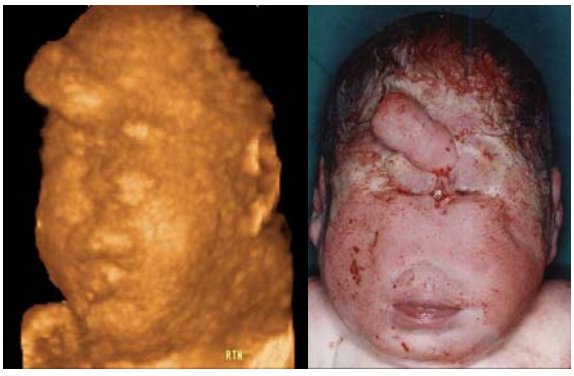
The first case was a 31-year-old, G3P1-0-1-1 at 32 weeks of gestation. She was referred to our unit because of the ventriculomegaly detected by ultrasound.

The 2D ultrasound examination revealed that the fetus had multiple structural anomalies including holoprosencephaly, proboscis, hypoplastic left heart syndrome and symmetrical IUGR.

The 3D ultrasound clearly visualized facial dysmorphism characteristics of Trisomy13 which were proboscis, cyclopia, low set ear and nasal dysplasia. (Fig. 1 and 2). Percutaneous umbilical cord blood sampling for karyotyping showed 47,XX,+13. The patient's pregnancy had been terminated at 33 weeks of gestation.

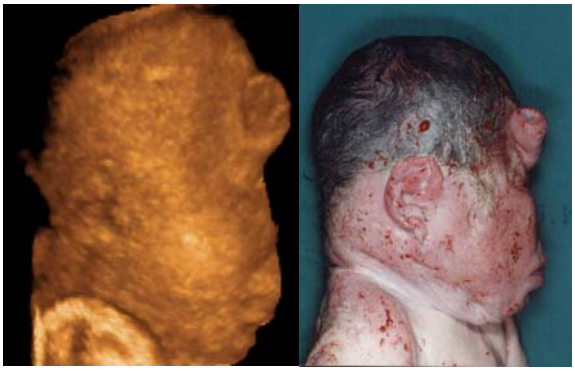
Second Case

The second case was a 21-year-old, G1P0 at 33 weeks of gestation. She was referred from rural hospital due to the problem of large for gestational age.



A B

Fig. 1 Three-dimensional surface rendered ultrasound image of a 32-week fetus with facial dysmorphism characteristics of Trisomy13 showing severe midfacial hypoplasia, proboscis, cyclopia, low set ear and nasal dysplasia (A). The same baby after termination of pregnancy at 33 weeks gestation (B).



A B

Fig. 2 Surface-renderd 3D ultrasound image of the same us on side view clearly demonstrates severe midfacial hypoplasia, proboscis and low set ear (A). The same baby after termination of pregnancy (B).

The 2D examination revealed that the fetus had micrognathia, bilateral club hands and clenched hands, rocker bottom feet, polyhydramnios and symmetrical IUGR.

The 3D surface rendering clearly visualized facial dysmorphism of the fetus which were hypertelorism, small mouth and micrognathia (Fig. 3), bilateral club hands (Fig. 4), bilateral clenched hands (Fig. 5), and rocker bottom feet (Fig. 6). Percutaneous umbilical cord blood sampling for karyotyping showed 48,XXY,+18. The patient was delivered vaginally at 38 2/7 weeks of gestation. The infant died shortly at day 18 after birth.

Third Case

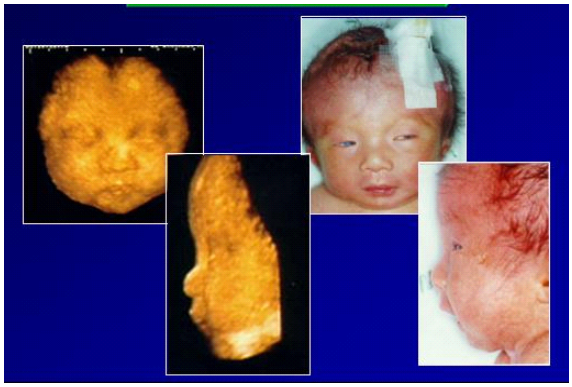
The third case was a 22-year-old, G1P0 at 34 weeks gestation. She was referred to our unit because of polyhydramnios.

The 2D ultrasound examination revealed polyhydramnios caused by duodenal obstruction (double-bubble sign). Other abnormal findings were atrioventricular septal defect and sandal gap.

The 3D surface rendering clearly visualized facial characteristics of Down syndrome manifesting in Mongolian slanted eyes and flat nasal bone (Fig. 7), and sandal gap of feet (Fig. 8). Amniocentesis for karyotyping showed 47,XY,+21. The patient underwent cesarean section due to cephalopelvic disproportion. The baby boy was 3,280 grams, Apgar score was 9 at 1 minute and 10 at 5 minute.

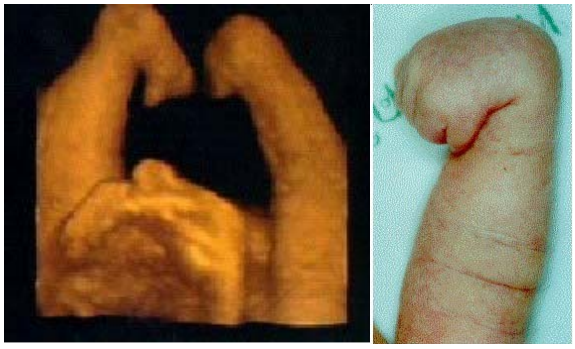
Forth Case

The fourth case was a 40-year-old, G3P2-0-0-2 at 17 weeks of gestation. She was referred to our unit for karyotyping due to advanced maternal age.



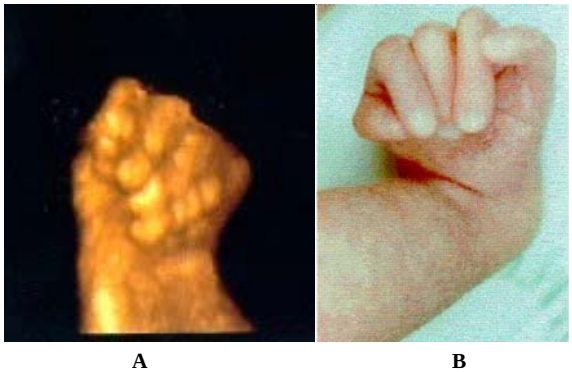
A B C D

Fig. 3 A 33-weeek fetus whose karyotyping revealed 48, XXY, +18. The three-dimensional reconstruction showing facial dysmorphism of the fetus, hypertelorism, small mouth and micrognathia on front view (A), and side view (B). The same newborn baby, a few days after delivery (C and D).



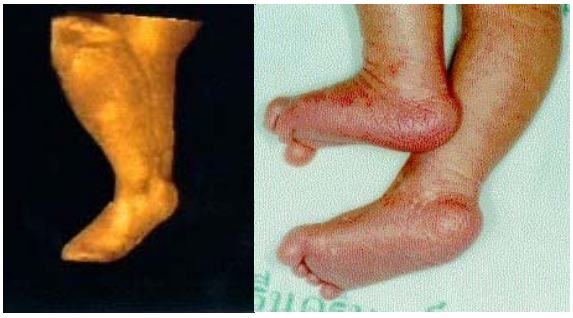
A B

Fig. 4 Three-dimensional surface rendered ultrasound image of 48, XXY, +18 fetus showing bilateral club hands (A) compare with the picture of the same baby after birth (B).



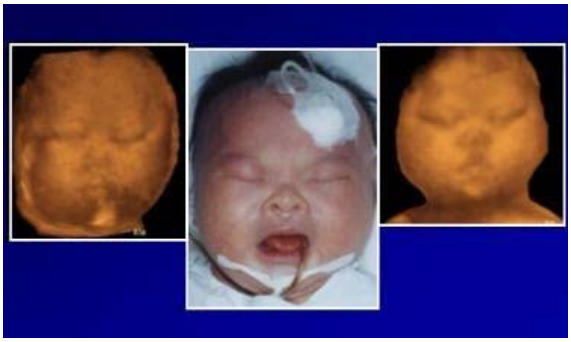
A B

Fig. 5 Three-dimensional surface rendered ultrasound age of 48, XXY, +18 fetus showing clenched hands with overlapping fingers in A compare with the picture of the same baby after birth in B.



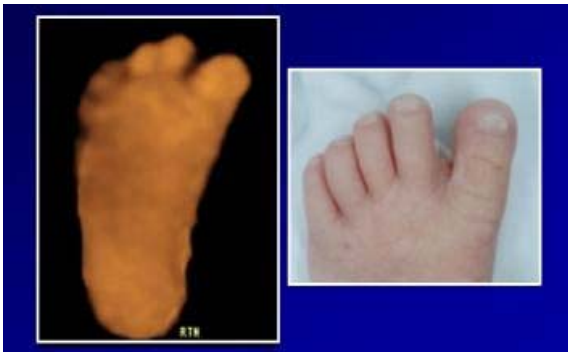
A B

Fig. 6 Three-dimensional surface rendered ultrasound image of 48, XXY, +18 fetus showing rocker bottom feet (A) compare with the picture of the same baby after birth (B)



A B C

Fig. 7 Three-dimensional surface rendered ultrasound image of a 34-week trisomy 21 fetus clearly visualize facial characteristics of Down syndrome manifesting in Mongolian slanted eyes and flat nasal bone (A and C). The same newborn baby, a few days after delivery (B).



A B

Fig. 8 Three-dimensional surface rendered ultrasound image of trisom21 fetus showing wide spaced first and second toe (sandal gap) in A compare with the picture of the same baby after birth (B).

The routine 2D ultrasound examination before amniocentesis showed a flat frontal bone, and an atrioventricular septal defect with left ventricular echogenic foci.

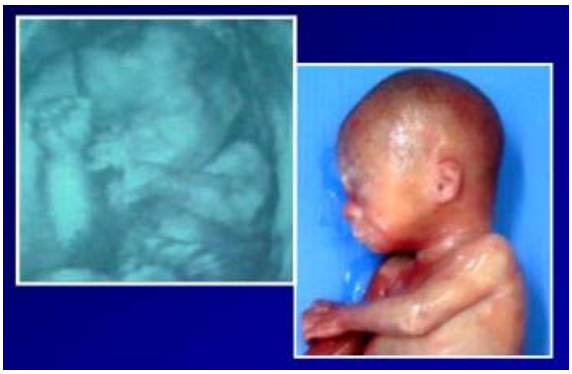
The 3D surface rendering clearly visualized the fetal face with flat frontal bone and low set ear (Fig. 9). Amniocentesis for karyotyping showed 47,XY,+21. The patient's pregnancy had been terminated at 20 weeks gestation.

Discussion

This study is the preliminary experience in using the novel technology, 3D ultrasonography, to visualize the fetal aneuploidy in utero. If fetal karyotyping had been restricted to mothers older than 35 years, large proportions about 64-97% of chromosomal abnormalities fetuses would not have been diagnosed prenatally [8].

As in the study of these four cases, 3 in 4 cases were under age 35 years old. As many reports have shown that chromosomal abnormalities were more common among fetuses with multisystem malformation than among those with isolated defect. So that many investigators have been studied and proposed the sonographic detectable markers of fetal chromosomal abnormalities for prenatal diagnosis in the first and second trimester.

The major structural abnormalities which carry a greater risk for chromosomal abnormalities includes the increased nuchal translucency, cystic hygroma, fetal hydrops, CNS anomalies, cardiac anomalies, diaphragmatic hernia, omphalocele, duodenal atresia, bladder outlet obstruction and limb anomalies [5-8].



A B

Fig. 9 Three dimensional reconstruction of A 18 week fetus of another case of trisomy 21 showing flat frontal bone and low set ear (A). The gross photograph of the same fetus (B)

The common ultrasonographic markers associated with Down syndrome or trisomy 21 are complete atrioventricular septal defect, cystic hygroma, duodenal atresia, diaphragmatic hernia, and others soft signs including short humerus and femur, nuchal thickening, clinodactyly, hypoplasia of the middle phalanx of the fifth digit, sandal gap, echogenic bowel, pyelectasis, echogenic intracardiac foci, and widening of the iliac wings.

The common ultrasonographic markers associated with Edwards' syndrome or trisomy 18 are strawberry-shaped head, Dandy-Walker malformation, omphalocele, cardiac anomalies, renal anomalies, overlapping fingers (clenched hands), and contractures of wrists (club hands).

The common ultrasonographic markers associated with Patau's syndrome or trisomy 13 are holoprosencephaly, hypotelorism and microphthalmia, severe mid facial clefting and nasal dysplasia including a proboscis, cardiac defect, renal anomalies including polycystic or enlarged kidneys and hydronephrosis, and polydactyly which is the most striking feature of this autosomal trisomy.

In this study, all of chromosomal abnormalities fetuses had sonographic findings specific to individual autosomal trisomy similarly to other studies.

Although many studies have shown the very high specificity in detecting congenital anomalies especially the lethal malformations by 2D ultrasonography, the conventional 2D ultrasound has the major disadvantage that the operator has to sweep the ultrasound beam back and forth across an organ of interest many times while mentally integrating multiple 2D images into 3D impression of the underlying anatomy or defect. This process is considered an interobserver variability.

On the contrary, with 3D ultrasonography, 3D images can be reconstructed from data obtained with a single sweep of the ultrasound beam across the involved organ. Different viewing algorithms allow the data to be displayed with a variety of technique including surface rendering, volume rendering and multiplanar reformatting. The surface image gives a photograph like impression of the fetus especially when there are lesions of the fetal surface such as facial dysmorphism, cleft lip and palate, low set ear, abdominal wall defects, for example. As well, surface rendering can give a vivid and clear demonstration of the defect.

Merz and coworkers [23] have reported their experience scanning 204 patients with congenital anomalies using both 2D and 3D ultrasonography. The patients were examined between 13-40 weeks of gestation. They found that 3D ultrasound was worthwhile in 62% of the cases while 2D and 3D provided the same information in 36% of the cases and both techniques were disadvantageous in 2% of fetuses with cardiac malformation.

In this study, by using surface rendering mode, we could clearly demonstrate the facial dysmorphism characteristic of Down syndrome, the Mongolian slanted eyes in case 3 which could not be visualized by 2D ultrasound. Also as Trisomy13, we ccould clearly visualized the classic severe midfacial hypoplasia, nasal dysplasia and a proboscis, which could lead to a degree of suspicion of this trisomy.

For the Klinefelter/trisomy18 case, which had the most features of trisomy18, 3D visualization helped to clarify the facial dysmorphism including hypertelorism, small mouth and micrognathia as well as the classical limb anomalies; bilateral clenched hands, bilateral club hands, and rocker bottom feet, which could not be clearly identified by the conventional 2D ultrasound.

Our experience with 3D ultrasonography demonstrated that this novel technology has a feasibility to reproduce the image in utero that allow both physician and parents to clearly understand about the malformation of fetuses without imagination. This will potentially influence the parents to choose obstetrical management plan in the future.

Although this technology was advantageous, we experienced some limitations and problems when this technique were used with patients with advanced gestational age at the time of referral for examination, which usually in the third trimester. The image quality of the fetal surface during this period is low due to less amniotic fluid around the fetus, the fetus being in contact with the placenta and uterine wall and also the position of the fetus.

In conclusion, our study suggested that 3D ultrasonography could be useful in visualization and identification of chromosomal abnormalities in utero when used in conjunction with the conventional 2D ultrasonography. Furthermore, 3D reconstruction of the fetal body surface could positively improve the antenatal diagnosis of chromosomal abnormalities characterized by a particular dysmorphism.

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การวินิจฉัยทารกในครรภ์ที่มีโครโมโซมผิดปกติด้วยคลื่นเสียงความถี่สูง 3 มิติ : รายงานจากประสบการณ์ผู้ป่วยจำนวน 4 ราย

รัตนา คำวิลัยศักดิ์, ถวัลย์วงค์ รัตนสิริ , พิไลวรรณ กลีบแก้ว

ความแม่นยำในการวินิจฉัยความผิดปกติของทารกในครรภ์จะช่วยให้แพทย์และผู้ป่วยสามารถเข้าใจและตัดสินใจเลือกวิธีการรักษาได้อย่างเหมาะสม เป็นที่ยอมรับกันว่าคลื่นเสียงความถี่สูง 3 มิติ ซึ่งเป็นเครื่องมือทันสมัยในปัจจุบันมีประโยชน์อย่างยิ่งในการวินิจฉัยความผิดปกติของทารกในครรภ์โดยเฉพาะทารกที่มีความผิดปกติของอวัยวะภายนอก ผู้เขียนได้รายงานทารกในครรภ์ที่มีโครโมโซมผิดปกติจำนวน 4 ราย ได้แก่ trisomy 21 จำนวน 2 ราย trisomy 13 จำนวน 1 ราย และ 47, XXY/+18 จำนวน 1 ราย โดยทารกในครรภ์ทั้ง 4 ราย ได้รับการตรวจโครโมโซมจากการเจาะน้ำคร่ำ หรือการเจาะเลือดจากสายสะดือ เพื่อยืนยันว่ามีโครโมโซมผิดปกติจริง หลังจากการใช้คลื่นเสียงความถี่สูง 3 มิติ ตรวจทารกในครรภ์แล้วพบว่า สามารถสร้างภาพและแสดงให้เห็นใบหน้าที่เป็นลักษณะเฉพาะของโครโมโซมแต่ละชนิดซึ่งไม่สามารถเห็นได้จากการตรวจด้วยคลื่นเสียงความถี่สูง 2 มิติ ได้แก่ หูต่ำ หางตาชี้ขึ้น ตาห่าง คางเล็กสั้น ปากเล็ก และใบหน้าผิดปกติที่พบในทารก trisomy 13 นอกจากนี้ยังสามารถมองเห็นความผิดปกติของนิ้วมือ และนิ้วเท้าได้อย่างชัดเจน เช่น นิ้วมือกำผิดปกติ ข้อมืองอ และนิ้วโป้งเท้าแยกห่างจากนิ้วชี้ ซึ่งช่วยให้การมองเห็นทารกในครรภ์ที่มีโครโมโซมผิดปกติดังกล่าวมีความชัดเจนขึ้น จากการศึกษาฉบับนี้สนับสนุนว่าคลื่นเสียงความถี่สูง 3 มิติ มีประโยชน์อย่างสูงในการนำมาใช้เพื่อตรวจวินิจฉัยทารกพิการในครรภ์ และช่วยในการมองเห็นทารกที่มีโครโมโซมผิดปกติได้ดีขึ้น