Prenatal Sonographic Markers of Trisomy 21

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Abstract

Objective : To describe the sonographic characteristics of fetuses with trisomy 21.

Design : A prospective descriptive analysis.

Setting : Department of Obstetrics and Gynecology, Faculty of Medicine, Maharaj Nakorn Chiang Mai Hospital, Chiang Mai University.

Subjects : Pregnancies at risk of trisomy 21 between 14-27 weeks' gestation.

Results : Thirty-six fetuses with subsequently proven trisomy 21 were prenatally evaluated by ultrasound in the second trimester. The main indications for detailed ultrasound examinations were advanced maternal age and abnormal findings on routine ultrasound. All of them had chromosome analysis by amniocentesis or cordocentesis. Nineteen (52.78%) had one or more abnormal findings. The common sonographic findings included thickened nuchal fold (33.33%), short femur (19.44%), and mild pyelectasis (22.22%). The other uncommon abnormalities included major anomalies (cardiac malformations, ventriculomegaly, duodenal atresia, esophageal atresia), hyperechoic bowel, echogenic intracardiac foci, abnormalities of extremities. In this study, rare minor markers but more specific markers including sandal gap, clinodactyly and mid-phalanx hypoplasia of the fifth finger were demonstrated.

Conclusion : About half of the fetuses with trisomy 21 had abnormal sonographic findings in the second trimester. The most common marker was thickened nuchal fold. Although prenatal ultrasound can not permit a definite diagnosis of trisomy 21, about half of them have sonographic markers, warranting cytogenetic testing.

Key word : Trisomy 21, Prenatal Diagnosis, Ultrasound

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Trisomy 21 (Down's syndrome) is the most common chromosomal abnormality among newborns with the incidence of 1 in 700 births[1]. Maternal non-disjunction is responsible for 95 per cent of trisomic cases. The risk of a liveborn infant with Down's syndrome increases with the age of the mother. The affected children have reduced IQs, decreased muscle tone, and mental as well as physical developmental delay. They also have a short nose, upslanting eyes and prominent epicanthal folds. A heart lesion is present in about 40 per cent of cases and A-V canal defects predominate. Duodenal atresia is common. Surgery may be needed for heart defects and occasional duodenal atresia. The major cause of mortality is heart defects. Prenatal screening for trisomy 21 has been done for many years. Initially, the screening was based on maternal age alone, but this was relatively ineffective as only a small proportion of cases could be detected while retaining an acceptable amniocentesis rate. Recently, screening based on maternal serum or ultrasonographic markers has become available, which has significantly improved the detection of trisomy-21 fetuses[2-4]. Detection in excess of 60 per cent of cases for a 5 per cent amniocentesis rate is now an accepted norm, leading to better cost-effectiveness compared with maternal age screening[2]. The advantage of using mid-second trimester scans is the capability of detecting additional features of Down's syndrome, including major malformations (heart defects, ventriculomegaly, etc.), as well as sonographic markers (pyelectasis, nuchal fold, hyperechoic bowel, echogenic intracardiac focus, and abnormal long bone biometry). However, with respect to sonographic prenatal screening for trisomy 21, there have been only a few reports studied in the Thai population. The objective of this study was to evaluate second trimester sonographic features of fetal trisomy 21 in Thai pregnant women.

MATERIAL AND METHOD

This descriptive analysis (case series) was undertaken at the Department of Obstetrics and Gynecology, Faculty of Medicine, Chiang Mai University, Thailand. The subjects were recruited from pregnant women in the second trimester who underwent prenatal sonographic examinations with various indications. The inclusion criteria was that the fetuses had to be subsequently proven to be trisomy 21 by either amniocentesis or cordocentesis.

All ultrasonographic examinations were performed with a standardized ultrasound protocol without knowledge of fetal karyotype, between June 1990 and June 1998, using convex MHz transducers (Aloka Model SSD 650, 680EX, or 1700). Indications for detailed ultrasound examinations were divided into two categories 1) sonographic evaluation before amniocentesis or cordocentesis due to genetic risk, and 2) abnormal finding on ultrasound indicated by other various obstetric indications including uncertain date, large- or small-for-date, fetal anomaly screening, etc.

RESULTS

Three thousand, three hundred and sixty two scans were done in the second trimester and all of them had genetic study. Thirty six cases of trisomy 21 were prenatally evaluated in details by ultrasound in the second trimester and followed.

The sonographic findings are presented in Table 1 and Fig. 1. The majority of cases had no obstetric complications. The maternal age ranged from 20 to 48 years and the mean age was 35.2 (±5.5) years. Sixty-six per cent (24 cases) were parous women. The mean gestational age at

Table 1. Sonographic abnormalities in 36 fetuses with trisomy 21.

	Number	Per cent
Thickened nuchal fold	12	33.33
Mild hydronephrosis	8	22.22
Short femur	7	19.44
Short humerus	5	13.89
Ventriculomegaly	5	13.89
Cardiac anomalies	5	13.89
Abnormal hands/feet (sandal gap, clinodactyly, mid-phalanx hypoplasia of the fifth finger)	5	13.89
Brachycephaly	4	11.11
Echogenic intracardiac foci	2	5.55
Duodenal atresia	2	5.55
Hyperechoic bowel	2	5.55
Hydrops fetalis	2	5.55
Choroid plexus cyst	1	2.78
Enlarged cisterna magna	1	2.78
Cystic hygroma	1	2.78
Absent stomach	1	2.78

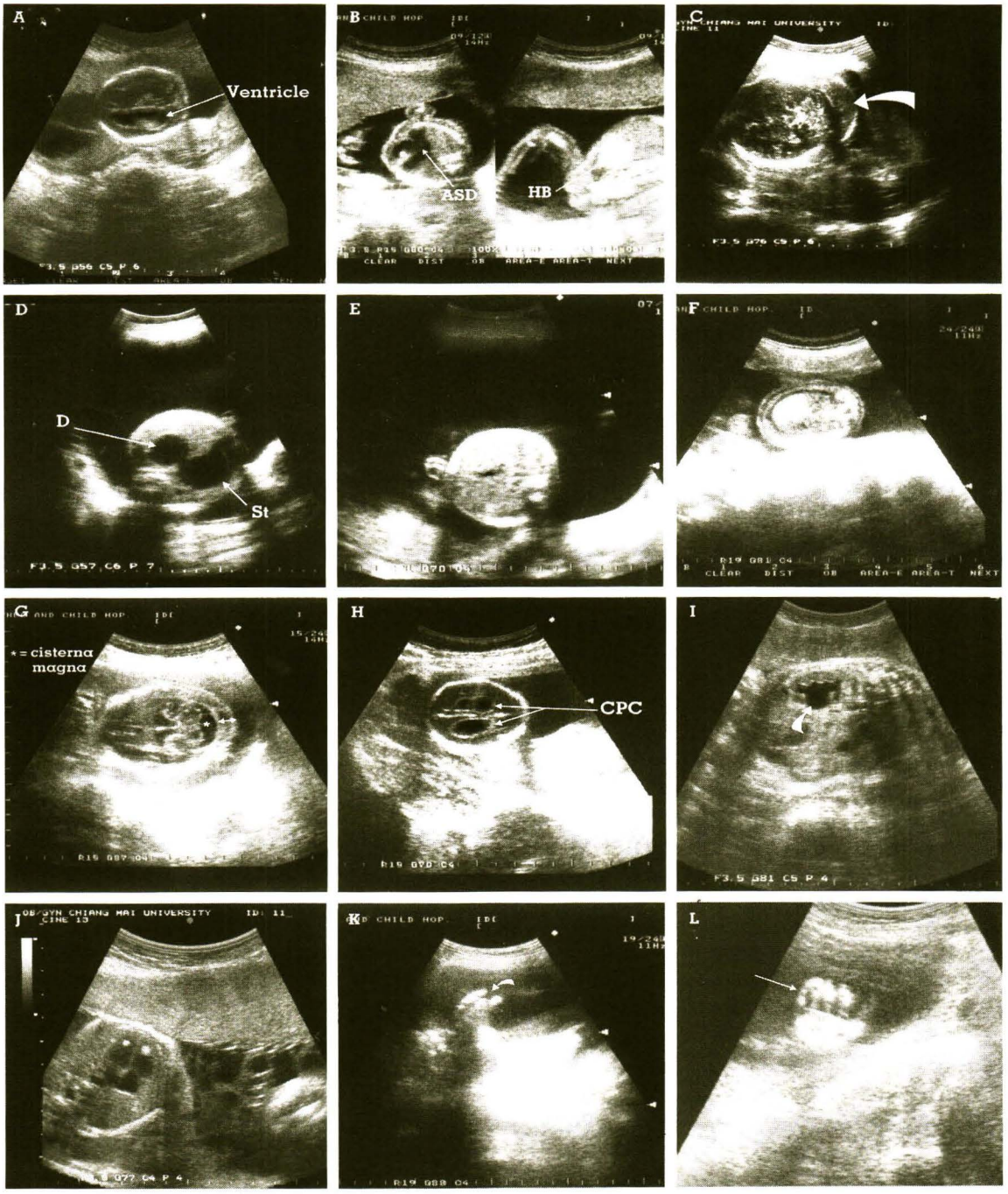

Fig. 1. Some sonographic findings in the fetuses with trisomy 21 A) mild ventriculomegaly, B) atrial septal defect (ASD) and hyperechoic bowel (HB) in the same case, C) marked thickened nuchal fold, D) double bubbles in duodenal atresia (D=duodenum, St=stomach), E) absent stomach in esophageal atresia with polyhydramnios, F) Mild hydrops fetalis; subcutaneous edema, mild ascites and hyperechoic bowel in cross-section view of abdomen, G) mild dilatation of cisterna magna and mild nuchal thickening, H) choroid plexus cysts (CPC), I) pyelectasis, J) bilateral echogenic intracardiac foci, K) sandal gap, L) hypoplasia of the middle phalanx of the fifth finger with clinodactyly (incurved).

the time of diagnosis was 19.55 weeks, range 14-27 weeks. Nineteen (52.78%) had one or more abnormal finding. Eighteen (50.00%) had one of the following; thickened nuchal fold (≥ 6 mm) short femur (the ratio of measured : expected femur length of ≤ 0.91) or humerus (the ratio of measured : expected humeral length of < 0.90), and mild pyelectasis (5-10 mm). The common sonographic findings included thickened nuchal fold (33.33%), short femur or humerus (19.44%), and mild pyelectasis (22.22%). The other uncommon abnormalities included major anomalies (cardiac malformations, ventriculomegaly, duodenal atresia, esophageal atresia), hyperechoic bowel, echogenic intracardiac foci, abnormalities of hands or feet. Moreover, we observed minor markers rarely documented prenatally but more specific including sandal gap, clinodactyly and midphalanx hypoplasia of the fifth finger. Therapeutic termination was done in all cases after proper counseling.

DISCUSSION

Although ultrasound has some limitations in demonstrating genetic markers in some fetuses with trisomy 21, this series indicates that about half of the affected fetuses have a sonographic pattern of specific abnormalities suggesting a diagnosis of trisomy 21, especially the presence of thickened nuchal fold, short long bones, and mild pyelectasis. Moreover, some minor but specific markers of trisomy 21 such as sandal gap, clinodactyly, or hypoplasia of the middle phalanx of the fifth finger, which are rarely documented prenatally, were detected in the study. These can lead to serious consideration of the possibility of this syndrome. In large western studies[5-8], it was found that second trimester ultrasound had high efficacy in identifying fetal trisomy 21. For example, Nyberg et al[5], showed that one or more ultrasound markers were detected in 68.3 per cent of fetuses with trisomy 21. Vintzileous et al[6] showed that three ultrasound markers (nuchal fold thickening, pyelectasis, and short humerus) could detect 87 per cent of the cases with a low false-positive rate of only 6.7 per cent. Bromley et al[7] found that the scoring system sonographic markers in the second trimester can identify 75.5 per cent of cases with a false-positive rate of only 5.7 per cent. Moreover, Yagel et al[8] found that midtrimester targeted fetal organ screening combined with the triple test and maternal age could detect 92.2 per cent of fetuses with trisomy 21. Our data demonstrate that half of the fetuses had one or more abnormalities but the number and severity were variable. Most findings were consistent with those reported in previous studies[5-8], although the incidence of abnormalities seem to be much lower in this study.

When any of the findings described above is found, consideration should be given to the possibility of trisomy 21 and a careful anatomic survey to look for additional sonographic signs of this trisomy should be done. Although the ultrasound in this series was not as sensitive as that in previous large series[5-8], it demonstrated the powerful capability in indentifying at least 50 per cent of fetuses with trisomy 21, much more sensitive than screening based on maternal age alone. It was difficult for this small series to specify which abnormality was the best predictor, however, it suggested that the combination of several markers was likely to be better than a single one. The data in this series is consistent with one report[9] that the nuchal fold remains the single most sensitive marker for identifying affected fetuses, however the sensitivity of only 33 per cent is less than that reported in most western series which found that a thickened nuchal fold (≥ 6 mm) has allowed the detection of Down syndrome in 40-70 per cent of affected fetuses with a false-positive rate of less than 1 per cent [5-7]. In this series, in spite of the most sensitive markers, it was much less sensitive. This may be due to several reasons including quality of equipment, or racial factor as shown by Tannirandorn et al[10], that nuchal thickness was a poor predictor of Down syndrome in the Thai population. The clinical usefulness of evaluating the various second-trimester ultrasound markers in the Thai population needs to be evaluated in prospective controlled studies.

No abnormality at all could be demonstrated in nearly half of the cases in this series. All of them were diagnosed and terminated before 20 weeks. It is possible that some abnormal sonographic findings such as duodenal atresia might have appeared later if they had been followed until late pregnancies. A normal sonographic evaluation can not exclude the possibility of this syndrome. In addition, fetal growth was not affected in this syndrome and was not helpful in prediction.

It was found that some other minor abnormalities, including intracardiac echogenic foci, sandal gap, clinodactyly, hypoplasia of the middle phalanx of the fifth finger etc could be visualized, however, nearly all of them had other additional markers. Therefore, it is unclear whether these isolated abnormalities are strong enough to perform invasive genetic testing or not. However, they should undoubtedly be regarded as indications for detailed ultrasound assessment. For major or multiple malformatations such as duodenal atresia, atrioventricular canal etc, cytogenetic study should always be done. These malformations are rather specific for trisomy 21.

Cardiac malformation is present with trisomy 21 in 40 per cent of cases(1), but was demostrated in only 13 per cent of cases in this study, this may be due to the fact that many minor heart lesions were difficult to visualize in some cases. Because of the high prevalence of heart defects in trisomy 21, fetal doppler echocardiography should be obtained whenever a major structural abnormality is detected(11).

Unfortunately, this study was unable to evaluate the effectiveness of nuchal translucency in prediction of trisomy 21 between 9-14 gestational weeks. Several reports showed that nuchal translucency in the first trimester can effectively predict trisomy 21 with a sensitivity of 86 per cent and a false positive rate of only 4.5 per cent(12-14). Some second trimester markers were not evaluated in our study, including iliac wing angle which has recently been shown to be a sensitive marker (15,16). Besides, this study did not evaluate sonographic markers such as the incidence of mild pyelectasis, or thickened nuchal fold in normal fetuses, therefore, it can not show the specificity of these markers in prediction.

In conclusion, half of the fetuses with trisomy 21 had one or more sonographic markers in the second trimester. The suggestive findings included nuchal thickening, pyelectasis, and shortened long bone (femur of humerus). Other rare but specific observed findings included duodenal atresia, heart defects, sandal gap, clinodactyly, etc were also visualized. Although prenatal ultrasound in this study could not make a definite diagnosis of trisomy 21, it still had the characteristic pattern of multiple markers in several cases, suggesting cytogenetic testing. However, sonographic screening for fetal anomalies requires well-trained sonographers with excellent equipment, leading to substantial financial costs. Therefore, mass screening for trisomy 21 with ultrasound has, to be seriously considered. Nonetheless, in any sonographic screening in pregnancy, attention must be paid to various sonographic markers of the fetus.

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ลักษณะทางคลื่นเสียงความถี่สูงก่อนคลอดของทารกกลุ่มอาการดาวน์

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รายงานวิเคราะห์เชิงพรรณาถึงลักษณะทางคลื่นเสียงความถี่สูงของทารกที่เป็นกลุ่มอาการดาวน์ ในไตรมาสที่สอง ซึ่งทำการศึกษาที่โรงพยาบาลมหาราชนครเชียงใหม่ มหาวิทยาลัยเชียงใหม่ ช่วงปี พ.ศ. 2533–2541 ทำการศึกษาไปข้างหน้าในสตรีตั้งครรภ์ที่มีความเสี่ยงต่อการมีทารกเป็นกลุ่มอาการดาวน์ในช่วงอายุครรภ์ 14–27 สัปดาห์พบว่าในช่วงที่ทำการศึกษามีทารกที่ได้รับการพิสูจน์ในภายหลังว่าเป็นกลุ่มอาการดาวน์และได้รับการตรวจคลื่นเสียงความถี่สูงในช่วงอายุครรภ์ 14–27 สัปดาห์จำนวน 36 รายโดย 19 ราย (ร้อยละ 52.78) มีความผิดปกติทางคลื่นเสียงความถี่สูง 1 อย่างหรือมากกว่าซึ่งที่พบบ่อยที่สุดคือ nuchal fold หนา (ร้อยละ 33.33) กระดูกต้นขาสั้น (19.44) และกรวยไตขยาย (ร้อยละ 22.22) นอกจากนั้นยังพบความผิดปกติอื่นที่พบได้ไม่บ่อยเช่น หัวใจพิการ ดูโอดีนั่มตีบ ลำไส้มีความเข้มสูง มีจุดเข้มสูงในช่องหัวใจ และความผิดปกติของมือเท้า เช่นหัวแม่เท้าแยกห่าง ข้อกลางนิ้วก้อยฝ่อ และนิ้วก้อยโค้งเข้าใน

สรุป : ประมาณครึ่งหนึ่งของทารกที่เป็นกลุ่มอาการดาวน์จะมีลักษณะจำเพาะทางคลื่นเสียงความถี่สูงซึ่งที่พบบ่อยที่สุดคือ nuchal fold หนา นับว่าการตรวจคลื่นเสียงความถี่สูงอย่างละเอียดในไตรมาสที่สองจะช่วยคัดกรองค้นหาทารกที่เป็นกลุ่มอาการดาวน์ได้ด้วยความไวดีพอสมควร

คำสำคัญ : กลุ่มอาการดาวน์, การวินิจฉัยก่อนคลอด, คลื่นเสียงความถี่สูง

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