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Article

Diagnosis of fetal acrania during the first trimester nuchal translucency screening for Down syndrome

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Abstract

Objectives: Prenatal screening during the first-trimester using fetal nuchal translucency (NT) measurement and maternal serum levels of free β-human chorionic gonadotropin (hCG) and pregnancy-associated plasma protein-A (PAPP-A) has become an established method for the detection of fetal Down syndrome. Increasing evidence has shown that some of the fetal structural abnormalities could be identified during NT scanning. Second trimester maternal serum alpha-fetoprotein (MSAFP) measurements and ultrasound scans have been widely used in clinical practice to identify fetal neural tube defects (NTDs). In this study, we evaluated the effectiveness of early diagnosis of fetal acrania during NT scanning. *Methods:* We reviewed the medical records of 5890 pregnancies that were delivered in our hospital between January 1, 1999 and January 31, 2001. Among them, 3600 pregnant women received NT-based Down syndrome screening at 10–13 weeks' gestation. Pregnancies with fetal NTDs were evaluated and their maternal serum levels of free β-hCG and PAPP-A were compared with those of the normal control pregnancies. *Results:* Seven of the 3600 pregnancies were identified with fetal acrania and all of them were detected during first-trimester NT scanning. Among the seven cases, five had measurements of maternal serum concentration free β-hCG and PAPP-A concentration, yet there were not significant difference between the pregnancies with fetal acrania and those of the control pregnancies (PAPP-A, 1.13 vs. 0.96; free β-hCG, 1.10 vs. 1.06; $P > 0.05$). Two of the seven affected patients did not have maternal serum biochemical measurements due to the immediate termination of pregnancies. *Conclusions:* We demonstrated that pregnancies with fetal acrania could be easily identified at the time of NT scanning. Careful ultrasound inspection of fetal structure during NT measurements at 10–13 weeks of gestation provides an encouraging advantage for early diagnosis of fetal acrania.

Keywords: Acrania; Ultrasonography; Nuchal translucency; Free β-hCG; PAPP-A

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1. Introduction

Fetal acrania is a lethal malformation in which the flat bones of the fetal cranial vault are symmetrically absent. The reported incidence of neural tube defects (NTDs) is 0.2% in North America, yet it is only 0.12% in Taiwan. In recent years, fetal acrania was identified using maternal serum alpha-fetoprotein (MSAFP) and ultrasonography in the second trimester. Due to the improvements in techniques and developments in ultrasonography, researchers have demonstrated that such entities might be identified earlier during the first trimester [1,2].

Nuchal translucency (NT) measurement accompanied by maternal serum biochemical screening at 10–13 weeks of gestation has been increasingly used to screen fetal aneuploidies such as Down syndrome, Turner syndrome, etc. In addition, recent publications demonstrated that NT scanning during the first trimester was also beneficial for the early detection of fetal structural anomalies such as gastroschisis, omphalocele, acrania, conjoined twins, thoracic cyst, etc. However, whether maternal serum alpha-fetoprotein measurement for NTDs screening during the second trimester for those who underwent first-trimester Down syndrome screening is necessary is still debatable.

First-trimester NT-based Down syndrome screening has been optionally implemented for more than 2 years at our hospital. Whether pregnancies with fetal acrania could be successfully identified during NT scanning was evaluated in this study.

2. Materials and methods

We reviewed the medical records of 5890 pregnancies who delivered at our hospital between January 1, 1999 and January 31, 2001. Among them, 3600 women received combined test (maternal serum free β-hCG, pregnancy-associated plasma protein-A (PAPP-A), and fetal NT thickness) between 10–13 weeks of gestation for Down syndrome screening. In total seven pregnancies were identified with fetal acrania from our obstetrical database. For statistical analysis, 665 pregnancies without any adverse outcomes were chosen as control pregnancies.

Fetal nuchal translucency was measured using an Acuson 128 ultrasonography unit (Mountain View, Calif, USA) according to the criteria published by the Fetal Medicine Foundation in the UK [3] and described in our previous publication [1]. During NT measurement, fetal scanning was done thoroughly to identify whether there were any fetal structural abnormalities.

Blood samples were collected from the pregnant women at the time of fetal nuchal translucency scan, and the serum was separated into aliquots at −20 °C the same day. Maternal serum concentrations of free β-hCG and PAPP-A were determined within 1 week using microtiter plate enzyme-linked immunosorbent (ELISA) according to the manufacturer's protocol (Genemed Biotechnologies, USA). Maternal serum free β-hCG levels were divided by the day-specific median to determine the multiple of median (MoM) using Alpha antenatal screening software.

Table 1
Clinical data of the seven pregnancies with fetal acrania

Case	1	2	3	4	5	6	7
Maternal age	28	28	23	28	37	29	35
CRL (mm)	59	69	56	44	95	53	34
PAPP-A (MoM)	0.65	0.95	2.3	0.49	–	1.27	–
Free β-hCG (MoM)	1.35	1.13	0.46	1.54	–	1.04	–
NT (MoM)	1.20	1.00	1.11	1.44	1.30	1.01	0.80
GA at termination	13.3	14	13	12	15	15	12

CRL, crown-rump length; NT, nuchal translucency; GA, gestational age (weeks); PAPP-A, pregnancy associated plasma protein-A; hCG, human chorionic gonadotropin.

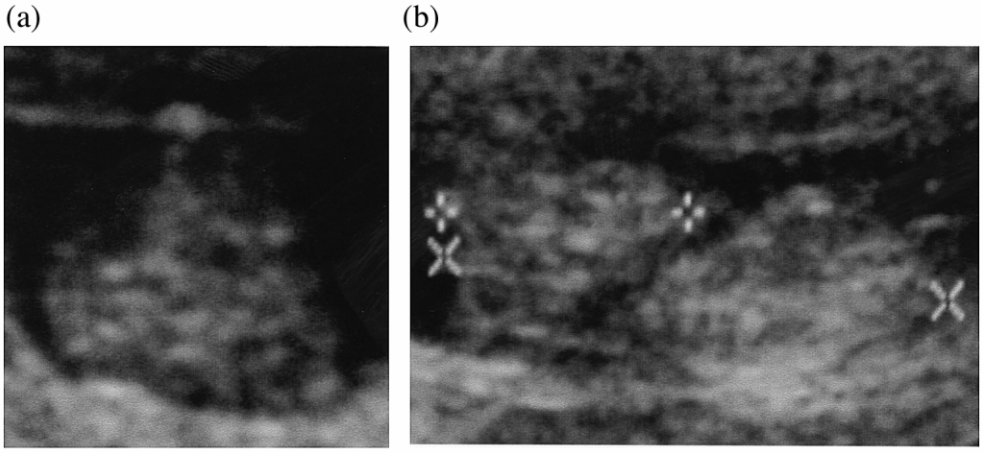

Fig. 1. (a) 'Mickey-Mouse' sign shown in coronal view of fetal acrania. (b) Sagittal view showed abundant brain tissue surround with a thin membrane.

Statistical differences between the two groups were evaluated using SPSS. A *P*-value of less than 0.05 was considered statistically significant.

3. Results

All of the seven pregnancies with fetal acrania were successfully detected using ultrasound scanning during NT measurement in this study population and their clinical data are shown in Table 1. Figs. 1–4 show the progression of sonograms of the fetal acrania by week during the first trimester. The sonograms of the fetal head revealed an absence of the skull bones but the unprotected cerebral hemispheres exposed to amniotic fluid covered only by a thin membrane. Thus, with the coronal view, the so-called 'Mickey-Mouse' sign was noted (photo 'a' of Figs. 1–4); while the sagittal image showed a lower value of the crown–chin length (photo 'b' of Figs. 1–4).

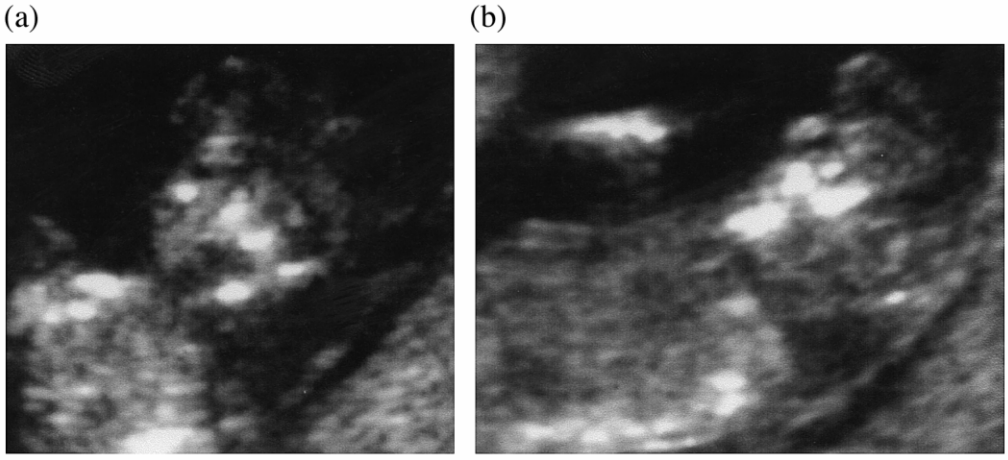

Fig. 2. (a) 'Mickey-Mouse' sign shown in coronal view of fetal acrania. (b) Sagittal view showed abundant brain tissue surround with a thin membrane.

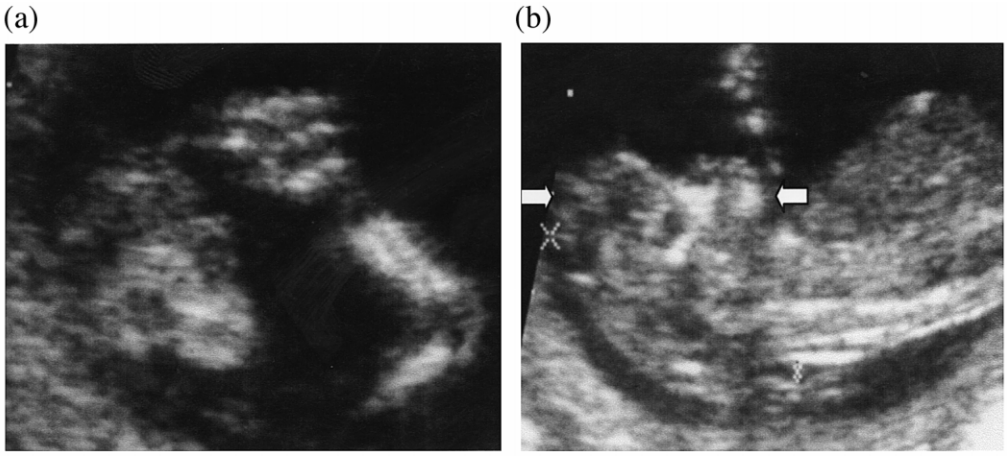

Fig. 3. (a) 'Mickey-Mouse' sign shown in coronal view of fetal acrania. (b) Sagittal view showed abundant brain tissue surround with a thin membrane.

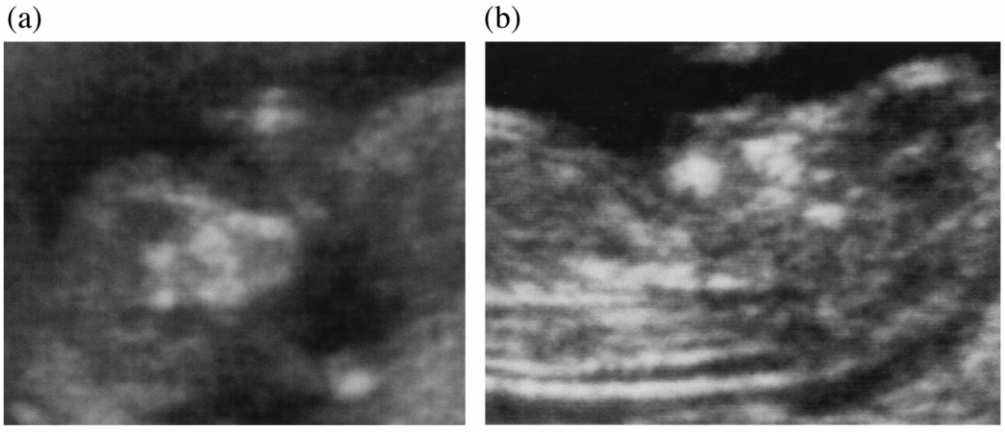

Fig. 4. (a) 'Mickey-Mouse' sign shown in coronal view of fetal acrania. (b) Sagittal view showed abundant brain tissue surround with a thin membrane.

Table 2
Mean levels of maternal serum biochemical markers of five pregnancies with acrania and 665 normal control pregnancies

	Fetal acrania	Non-affected group	Statistical results
Number of cases	5	665	
PAPP-A (MoM)	1.13 ± 0.32	0.96 ± 0.04	NS
Free β-hCG(MoM)	1.10 ± 0.18	1.06 ± 0.02	NS

NS, no statistical significance; PAPP-A, pregnancy associated plasma protein-A; hCG, human chorionic gonadotropin; MoM, multiples of median.

Five of the seven cases had maternal serum concentration measurements of free β-hCG and PAPP-A but there were no significant differences between pregnancies with fetal acrania and those of the 665 control pregnancies (MoM value of PAPP-A, 1.13 vs. 0.96; MoM value of free β-hCG, 1.10 vs. 1.06; $P > 0.05$). The data are shown in Table 2. The other two cases refused biochemical screening and termination of pregnancies after ultrasound scanning. No other cases of neural tube defects were found. The prevalence rate of NTD was 0.12% in our study population.

4. Discussion

Fetal acrania is a lethal anomaly and results from failure of mesenchymal migration. This entity occurs at the beginning of the 4th week of embryonic development, while the anterior neuropore closes. The brain tissue is covered only by a thin membrane and therefore is exposed to the amniotic fluid. Characterized by the absence of bones of the cranial vault, acrania is found in various degrees of severity [4]. Since it is a lethal anomaly, early ultrasound diagnosis allows patients to make a timely termination of the pregnancy.

Under ultrasonography, both of the exposed hemispheres of the brain are only covered by a thin membrane called the 'Mickey-Mouse' sign (Fig. 1). Most cases of acrania eventually progress to anencephaly and the features frequently seen in cases with bulging eyes called the 'frog-eye' sign (Figs. 2 and 3), which is easily diagnosed during the second trimester [5].

In acrania fetuses, crown–chin length and the ratio of the crown–chin length (Fig. 4) to the crown–rump length at 10–14 weeks of gestation were below the 5th percentile in 77% and 62% of the cases, respectively [8]. Thus, measurement of the crown–chin length also provides a technique in early recognition of fetal acrania.

In our hospital, Down syndrome screening during the first trimester has been used since 1999. It provides the benefits of a higher detection rate and earlier diagnosis than that of biochemical screening alone during the second trimester [6,7]. Recent publications showed that NT-based screening could be used to detect not only fetal aneuploidies, but increasing NT thickness was also highly correlated with fetal cardiac defects as well as adverse pregnancy outcomes (gestational hypertension, IUGR, preterm labor…, etc.) [1]. Moreover, NT scanning during the first trimester offered potential benefits for early inspection of fetal structural abnormalities.

According to the report of National Health Department of Taiwan, the incidence of NTD during the past decade was 0.12%. In this study, we demonstrated that maternal serum free β-hCG and PAPP-A during the first trimester was of little value in the diagnosis of fetal acrania because there were no statistically significant differences noted between the normal and affected pregnancies (Table 2). However, the diagnosis of acrania at 10–13 weeks of gestation could be identified using ultrasound scan during NT measurement without checking MSAFP during the second trimester.

In this study, fetal acrania was the only abnormality of the neural tube defects. Nevertheless, spinal bifida in continuity with the cranial defect or other abnormalities (cleft lip/palate, umbilical hernia, congenital heart defects or clubfeet) can be expected in such cases according to reports reviewed in the literature [8]. However, all seven of the fetal acrania cases were identified during NT scanning during the first trimester. It is worthwhile to reevaluate the economic efficacy of maternal serum alpha-fetoprotein tests for NTD screening during the second trimester for Taiwanese who underwent Down syndrome screening during the first trimester. In conclusion, careful inspection of fetal structure using ultrasound during NT measurement at 10–13 weeks of gestation provides an encouraging advantage for early diagnosis of fetal acrania.

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