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Fetal lateral neck cysts: the significance of associated findings

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Objectives The detection of fetal lateral neck cysts (FLNC) may create anxiety and confusion among pregnant woman and their physicians. We attempted to determine the incidence and significance of FLNC. Also, we tried to define the importance of the associated findings: the laterality of the finding, triple test results, maternal age and other ultrasonographic findings.

Methods and Materials Between January 2000 and September 2003, 80 fetuses were evaluated at our institution for FLNC out of 3350 ultrasonic scans done for fetal malformations at 14–16 weeks' gestation.

Results The incidence of FLNC was 2.4% (80/3350). The majority of cases were isolated (53/80, 66%) and unilateral (46/80,58%). Down syndrome was associated with nonisolated FLNC.

Conclusion Whether the finding was unilateral or bilateral had no significance. Associated increased nuchal translucency (NT) was of importance. Furthermore, the sole finding of increased NT is significant and the finding of the FLNC has no added value. There was no correlation between isolated FLNC without NT and fetal aneuploidy. However, other risk factors increase the risk for aneuploidy by up to 15 fold. Copyright © 2005 John Wiley & Sons, Ltd.

KEY WORDS: fetal neck cyst; Down syndrome; triple test; nuchal translucency

INTRODUCTION

The rapid advancement of the obstetrical ultrasonic equipment enables visualization of small parts of fetal systems and organs. FLNC are fluid filled accumulation found in the anterolateral region of the fetal neck and are usually part of a fetal system undergoing development. However, since the current structure is not common to all fetuses, a dilemma is created whether it has no significance or these 'soft findings' are indeed markers of high-risk group for aneuploidy in general or Down syndrome (DS) fetuses in specific. In the latter case, an invasive diagnostic procedure is warranted.

Much attention has been dedicated to the fetal neck region as one in which pathology may be associated with aneuploid fetus.

There is a conflicting data in the literature regarding the significance of FLNC. Some studies suggest that such cases are indicated for fetal karyotype analysis (Elejalde *et al*., 1985). Others concluded that isolated cases of FLNC during the early second trimester should not be considered as cystic hygroma since they do not represent pathological lesions and as such their karyotype has no need to be assessed (Schewitsch *et al*., 1980).

The present study analyzes our data regarding FLNC in terms of the associated findings and the indication to perform fetal karyotype analysis. In addition, we present the accumulative experience regarding fetal neck cysts of our and other studies based on similar population.

MATERIALS AND METHODS

Between January 2000 to September 2003, 3350 ultrasonic early (14–16 weeks) scans for fetal malformations were performed at our institution. Eighty women were referred to our Genetic Institute following finding of FLNC. Most of the patients were scanned on maternal demand and were considered to be at low risk. Only approximately 20% were classifies as high risk for fetal malformations due to family history of malformations, advanced maternal age, or maternal disease and exposure to potentially teratogenic medications. The gestational age was calculated according to the last menstrual period or the average ultrasonographic age when the difference between the two exceeded 10 days. All cases with FLNC were included in the present work. FLNC diagnosis was established when a >2.5-mm hypoechoic lesion was visualized in the lateral aspect of the fetal cervical area while scanning the neck area parallel to the bitemporal diameter plane just below the mandible (based on the fact that the lateral linear resolution of the transvaginal ultrasound transducer is in the neighborhood of 1.2 mm). Only cases of 'true FLNC' were included since the other inclusion criterion was that the nuchal translucency was within normal limits. We used a high-resolution ultrasound (ATL 5000, Bothell, WA.) with 8–4 MHz broadband vaginal probe. A complete anatomic scan of the fetus was performed in each of the

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Table 1—The characteristics of fetuses with FLNC(s)

		Karyotype		Triple test				
		Normal	Abnormal	Normal	Abnormal	Not done	Maternal age > 35	Twins
Isolated 53	Bilateral 20 (38%)	19	1[a]	13	1[a]	6	1	0
	Unilateral 33 (62%)	33	0	22	3	8	3	0
Nonisolated 27	Bilateral 14 (52%)	11	3[b]	5	1	8	1[c]	2[d]
	Unilateral 13 (48%)	13	0	9	1	3	1	2

EIF, echogenic intracardiac focus; NT, increased nuchal translucency.
[a] The same fetus: 46,XX, t(14;21); triple marker adjusted risk 1 : 166.
[b] All 3 fetuses had increased NT and in addition: T-21: EIF; T-21: EIF + hydronephrosis; T-18: cleft lip (one of twin).
[c] One of the T-21.
[d] One had T-18.

cases. The study included all cases even if additional anomalies were detected.

Fetal karyotype was obtained following chorionic villus sampling or amniocentesis. All couples received genetic counseling. All aneuploid pregnancies were terminated. The newborns with normal karyotype were examined after delivery by a neonatologist.

The complete ultrasonic, genetic, obstetric and neonatal information for all the cases was available for evaluation.

The data was assessed for statistical significance using the Fisher's exact test.

RESULTS

FLNC were found in 80 cases (2.4%) out of 3350 scans performed (Table 1). The majority of the findings were isolated (53/80; 66%) and unilateral (46/80; 58%) cases. However, these observations were statistically nonsignificant. DS was associated with nonisolated FLNC except for one fetus who had isolated bilateral FLNC and was found to have DS; however, the mother had an adjusted risk of 1 : 166 by triple test results (Table 2). The other three cases with aneuploidy had, in addition, an echogenic intracardiac focus (EIF) and increased nuchal translucency (NT) of 3.8-mm trisomy 21(T-21), EIF, NT and hydronephrosis (T-21) and a cleft lip and NT of 4.3 mm (T-18).

The adjusted risk by the triple test results was above normal (1 : 380) in four cases of isolated findings. Three of them had normal karyotype and one, as mentioned earlier, had T-21. Two cases of nonisolated findings had abnormal triple test results and both of them had normal karyotype.

Table 2—The associated anomalies of fetuses with FLNC(s)

Type	Cases	EIF	NT	Other
Bilateral	14	9[a]	5[a]	2[c]
Unilateral	13	5[b]	4[b]	5[d]

VSD, ventricular septal defect; CPC, choroid plexus cyst; EIF, echogenic intracardiac focus.
[a] Two fetuses with both EIF + NT.
[b] One fetus with both EIF + NT.
[c] VSD + hydronephrosis.
[d] VSD; CPC; Ectopic kidney; Echogenic bowel.

Forty-one percent (11/27) of the patients with nonisolated FLNC were not tested for the triple test and elected to have amniocentesis. However, only 26% (14/53) of patients with isolated finding opted directly for amniocentesis. This difference was statistically nonsignificant.

Four patients over 35 years of age, who were eligible for amniocentesis, had isolated FLNC and three of them were unilateral (Table 2). Two patients in this advanced-maternal-age group had nonisolated findings. In one of them, the finding was bilateral and the fetus was found to have DS.

Our patients with twin pregnancy had only nonisolated findings affecting only one fetus. In two couples, the FLNC were unilateral, whereas in the other two sets, the findings were bilateral. In one of the latter group, T-18 was found (Table 2).

Although not reaching statistical significance, there was slight left-side preponderance among our patient with unilateral FLNC.

DISCUSSION

FLNC finding, also referred to as 'nonseptated cystic hygroma', and its relationship with fetal aneuploidy has regained attention following the implementation of first-trimester screening programs (Nicolaides *et al*., 1994).

The significance of this embryological finding should be assessed in light of the process that leads to its creation. At 40 days of the intrauterine life, the lymphatic vessels that initially drain into large sacs lateral to the jugular veins connect to the venous system as the terminal portion of the right lymphatic duct and the thoracic duct (Chytiat *et al*., 1989). FLNC are the consequence of delay or failure of this process to happen (Moscoso,1995).

Nuchal cysts have been shown to be associated with couple of entities: (1) Cystic nuchal blebs present in otherwise normal fetuses as a postmortem change. (2) 45,X0 fetuses that have a particular appearance and multiple congenital malformations. (3) An apparently autosomal recessive syndrome of multiple cysts (that extend into deep muscular planes), generalized edema, cleft palate, peculiar skeletal characteristics, acutely

Table 3—The incidence (percentage) of fetal neck cyst(s) isolated and with associated anomalies and the fetal karyotype

Total cases	Author, year	Number Total	Karyotype		Cases scanned
			Normal	Abnormal	
	Bronshtein *et al*., 1993	106 (1.4)	100[a]	6 (5.7)	7582
	Achiron *et al*., 1995	42 (2.8)	38	4 (9.5)	1500
	Zimmer *et al*., 1997	618 (2.6)	596	22 (3.6)	24 000
	Sharony, 2005*	80 (2.4)	76	4 (5.0)	3350
	Total	846 (2.3)	816	36 (4.2)	36 432
Isolated					
	Bronshtein *et al*., 1993	96	94	2 (2.1)	
	Achiron *et al*., 1995	26	26	0 (0)	
	Zimmer *et al*., 1997	550	543	7 (1.3)	
	Sharony, 2004	53	52	1 (1.9)[b]	
	Total	725	715	10(1.4)	
Nonisolated					
	Bronshtein *et al*., 1993	19	15	4 (21.1)	
	Achiron *et al*., 1995	16	12	4 (25.0)	
	Zimmer *et al*., 1997	68	53	15 (22.1)	
	Sharony, 2004	27	24	3 (11.1)	
	Total	130	94	26 (20.0)	

[a] Some cases lost to follow-up.
[b] Abnormal triple test result.
* The current study.

angulated ribs (producing a bell-shaped rib cage) and shortened long bones. (4) In fetuses with inherited syndromes (e.g. multiple pterygium, Roberts) and chromosomal abnormalities (e.g. T-13, T-21) as a nonspecific sign representing both primary and secondary lesions. Previously thought to be associated with Turner's syndrome, FLNC is now considered to be part of many other aneuploidies, single gene disorders and may have a familial trait (Elejalde *et al*., 1985).

Some concern could be raised as to whether the sole finding of FLNC with normal fetal karyotype is associated with adverse fetal long-term prognosis. In a series of 82 cases with cysts and sinuses in the lateral head and neck, both preauricular and lateral cervical sinuses were found to be hereditary and associated with other developmental anomalies. The authors stated that these features are lacking in the case of infra-auricular first cleft anomalies and lateral cervical cysts (Schewitsch *et al*., 1980).

The finding of FNLC is rather common and can be observed in approximately 2.5% of the fetuses during the early second trimester when fetal anatomic scan is performed (Zimmer *et al*., 1997). The cysts contain clear fluid and usually disappear before the 16th week of gestation (Wilson *et al*., 1992; Hertzberg *et al*., 1989). Another entity that is related to the lymphatic system of the fetus is cystic hygroma. The associated findings in these cases are quite different, as previously described (Bronshtein *et al*., 1989; Hertzberg *et al*., 1989; Bronshtein *et al*., 1993; Shulman *et al*., 1994; Rosati and Guariglia, 1997; Zimmer *et al*., 1997).

However, the NT that is measured as part of the first-trimester screening may regress at a later stage of fetal development, leaving behind FLNC as its mark (Zimmer *et al*., 1997; Nicolaides *et al*., 1994). Our study confirms previous observations of the benign nature of an isolated FLNC (Rosati and Guariglia, 1997; Achiron *et al*., 1995).

A comprehensive search of the English literature for publications on FLNC was undertaken and a review of large-scale studies based on similar populations is presented. The analysis shows that whether the finding is bilateral or not is of no significance (Table 3). However, the associated NT is of importance. Furthermore, the sole finding of increased NT is significant and the finding of the FLNC has no added value. Neither we nor others found a correlation between isolated FLNC without NT and fetal aneuploidy. However, the other risk factors, for example, abnormal triple test results, advanced maternal age and associated ultrasonographic findings increase the risk for aneuploidy by up to 15 fold.

Overall, isolated and nonisolated FLNC was found in 1006 out of 36 432 patients, yielding an incidence of 2.3% (range between 1.4–2.8%) of which 4.2% (3.6–9.5%) were aneuploid. The rest of the scan reported to be normal in 72%. However, 1.4% (0–2.1%) of them had an abnormal karyotype. The others (28%) had associated anomalies, and, in 20% (11.1–25.0%) of these cases, the chromosomal study was abnormal.

According to our experience, the isolated finding of FLNC including normal results of the triple test has no significance in terms of fetal karyotype. However, considering other reports, the risk of aneuploidy in FLNC exceeds 1%, and evaluation of the karyotype is indicated (Bronshtein *et al*., 1993; Zimmer *et al*., 1997).

Of note is the distribution of the affected side among our patients with unilateral FLNC. Although it did not reach significance, the left-side slight preponderance has to be further analyzed in light of the normal embryologic events (Chytiat *et al*., 1989; Moscoso, 1995).

To conclude—lately, FLNC is diagnosed more often as the result of the introduction of higher resolution

ultrasound equipment and First-Trimester Screening Program. Our findings suggest that the sole finding of FLNC is not an indication for fetal karyotype study, but this is not the case when other factors are also present.

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