THE JOURNAL OF OBSTETRICS AND GYNECOLOGY OF INDIA

The Journal of Obstetrics and Gynecology of India (January–February 2019) 69(1):56–61
https://doi.org/10.1007/s13224-018-1094-8

ORIGINAL ARTICLE

Long-Term Outcome of Fetuses with Soft Marker and Without Genetic or Structural Abnormality

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Received: 7 April 2017 / Accepted: 27 January 2018 / Published online: 10 February 2018

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Abstract

Purpose To determine long-term outcome of infants with isolated or multiple soft markers but no structural or chromosomal abnormalities.

Methods A retrospective study of 78 pregnant women who were referred for amniocentesis and found to have soft markers including echogenic intracardiac focus/foci (EIF), echogenic bowel (EB), unilateral or bilateral choroid plexus cysts, (UCPCs or BCPCs) mild pyelectasis and single umbilical artery but no structural anomalies and outcomes of the liveborns with a 4- to 9-year follow-up was conducted.

Results Among 28 fetuses with EIF, allergic asthma and epilepsy were diagnosed in two liveborns. We followed up nine pregnancies with EB, epilepsy was present in one case. Allergic asthma was detected in both UCPCs and BCPCs, whereas epilepsy and attention-deficit/hyperactivity disorder (ADHD) were diagnosed in two liveborns with BCPCs. Twelve liveborns with multiple soft markers were

evaluated; no pathology was detected in most of them except one case of allergic asthma, one case of hearing impairment and one case of ADHD.

Conclusions This study shows longer-term favorable outcomes of the liveborns with isolated or multiple soft markers without any aneuploidy and may provide insight into this debated point.

Keywords Fetus · Ultrasonography · Soft marker · Follow-up · Long-term · Outcome

Introduction

Fetal ultrasonographic scanning in the second trimester to identify major abnormalities has developed so remarkably that some findings with little or no pathological significance can be detected. These findings, such as thickened nuchal fold, echogenic intracardiac focus and echogenic bowel, commonly called "soft markers," may be seen in the normal fetus as variants but are noteworthy, because they have an increased incidence in infants with chromosomal abnormalities and congenital anomalies [1]. Therefore, researchers have long investigated the impact of isolated and multiple soft markers on the risk assessment of the aneuploidies and the invasive procedures [2–5]. However, the outcome of the infants born with these markers has been of little interest and the studies regarding this topic have reported short-term follow-up including the neonatal and infantile period of life [6–8].

The aim of this study was to determine the long-term outcome of infants with identified isolated or multiple soft markers but no structural or chromosomal abnormalities.

Materials and Methods

We conducted a retrospective study of 78 pregnant women with 15–22 weeks of singleton gestation who were referred to Ondokuz Mayis University Fetal Medicine Unit between January 2005 and January 2010 for amniocentesis and found to have isolated or multiple soft markers but no structural anomalies at the same time of procedure; and investigated the outcomes of these pregnancies and the liveborns. The study was approved by Ondokuz Mayis University Ethics Committee, and the patient records/information was anonymized and de-identified prior to analysis.

Amniocentesis was performed after obtaining informed consent from all participants if any of the following was present: advanced maternal age ($\geq$ 35), triple test (TT, maternal serum α-fetoprotein, estriol and β-human chorionic gonadotrophin) with high risk for aneuploidy (1/270 for Down syndrome), previous history of pregnancy with aneuploidy, presence of aneuploidy in first-degree relative.

Ultrasonographic soft markers included echogenic intracardiac focus/foci (EIF), echogenic bowel (EB), unilateral or bilateral choroid plexus cysts (UCPCs, BCPCs, $\geq$ 2 mm), mild pyelectasis (renal pelvis $\geq$ 4 mm), and single umbilical artery (SUA). Soft markers were considered isolated when not associated with other markers or structural anomalies. EIF was identified when a discrete area of echogenicity that is as bright as bone is noted in the heart [9]. EB was defined as echogenic if its echogenicity was similar to or greater than adjacent bone [10]. A CPC was defined as a well-circumscribed echolucent area within the choroid plexus, lateral ventricle in the axial plane of the head [11]. Mild pyelectasis was diagnosed when the renal pelvis measured $\geq$ 4 and $<$ 10 mm in anteroposterior dimensions in axial scans of the abdomen, without caliceal dilation [12]. The diagnosis of SUA was made by using color Doppler examination to find one umbilical artery surrounding one side of urinary bladder wall [12].

Ultrasonographic scans were carried out by a group of obstetricians highly specialized in prenatal ultrasonography diagnosis, and all cases were examined with Aloka IPC-1550 (Aloka 6-22-1 Mure, Mitaka-shi, Tokyo, Japan). Flourescence in situ hybridization, which was the standard laboratory procedure for the analysis of chromosomes 13, 18, 21, sex chromosomes and cystic fibrosis gene mutation, was used for genetic investigation at Ondokuz Mayis University Genetics Department. Demographic data, ultrasonographic findings and karyotype analyses were obtained from the database of our fetal medicine unit. The pregnant women were followed up during their routine pregnancy visits (once a month until 32nd gestation week, twice a month between 32nd and 36th gestational weeks, once a week from 36th week of gestation until delivery). After delivery, newborns and then the children were followed up by the pediatricians from at least 4 years up to 8 years and 5 months in terms of complete physical examinations and possible problems which may be associated with the soft markers found in the prenatal period such as EIF, EB and SUA. The intervals of the examinations and indications for further evaluations such as echocardiography and urinary ultrasonography were determined by the pediatricians (once in 6 months or once a year). Data on outcomes of the pregnancies and follow-up of the children were obtained by the obstetrics and pediatric electronic medical reports. In case of missing data, women were called and information was obtained about the outcome of the pregnancies and liveborns in terms of postnatal diagnosed diseases as well as prenatal diagnosis by inquiry.

Statistical Analysis

Data analysis was performed by using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, USA). The discrete variables were shown as mean ± SD or median (min–max), where applicable; otherwise, number of cases and percentages were used for nominal variables. Data were analyzed by Fisher's exact test. Odds ratios, 95% confidence interval, sensitivity, specificity, positive and negative predictive values for each soft marker were also calculated for determining the diagnostic performance. A p value < 0.05 was considered statistically significant.

Results

The study included 78 pregnant women who underwent amniocentesis and were found to have soft markers without any aneuploidy or fetal structural abnormalities between January 2005 and January 2010 and their children who were followed up for 6.5 ± 1.8 years. Demographic and clinical features of the study group are shown in Table 1.

The outcomes of the fetuses who presented with isolated and multiple soft markers at the time of amniocentesis in the second trimester were evaluated in terms of possible association between the diseases diagnosed during follow-up. Attention-deficit/hyperactivity disorder, epilepsy, allergic asthma, strabismus and hearing impairment were diagnosed in the evaluation of the children during the follow-up by pediatricians. Termination was advised for one pregnancy which was diagnosed with echogenic bowel and anhydramnios at 16th weeks of gestation by the perinatology council of Ondokuz Mayis University, Department of Obstetrics and Gynecology, and was terminated after obtaining the informed consent of the patient. The findings are shown in Table 2.

Discussion

The association between soft markers detected on second trimester ultrasonographic examination of the fetus and aneuploidy has attracted increasing interest over the last few decades as evidenced by several studies in the literature [1–4]. On the other hand, the outcome of the fetuses with identified soft markers has also long been wondered and researches have focused on perinatal outcomes of the fetuses with most common soft markers such as echogenic intracardiac focus and echogenic bowel [7, 8]. However, prognosis of such cases in the long run has been less investigated. We designed a prospective study in order to determine the outcome of the fetuses with detected isolated or multiple soft markers but no genetic or structural anomalies in 4- to 9-year follow-up.

Echogenic intracardiac focus, which was first described in 1987 and most commonly seen in the left ventricle, has a varying incidence between 0.5 and 20%. Perinatal outcome of fetuses with isolated EIF has been investigated in a few studies. One of them reported normal outcome in 95.7% of 13 patients; however, postnatal echocardiograph was performed in 11 neonates, one of which had a small ventricular septal defect, one had Tetralogy of Fallot and one had pulmonary hypertension [13]. In another study, of 31 fetuses with an isolated ICEF, outcomes of 28 fetuses are known and all neonates were reported to be normal at birth [8]. In the present study, we had a 4- to 9-year follow-up of 28 fetuses (21 isolated EIF, 7 with multiple markers); there was one neonatal death due to prematurity, and no pathology was detected except allergic asthma and epilepsy during follow-up.

Fetal echogenic bowel is another soft marker investigated in relation to perinatal outcome in the literature. EB, with 0.2–1.4% incidence, has been associated with many clinical situations including intrauterine bleeding, congenital infection such as cytomegalovirus and toxoplasma, cystic fibrosis and fetal growth restriction as well as primary fetal bowel pathology [6–14]. Isolated echogenic bowel in infants was reported as a benign condition carrying favourable prognosis, but carry poor prognosis when multiple markers are present [14]. In addition, uterine artery Doppler (UAD) screening was performed on the pregnant women diagnosed with fetal EB in another study, and pregnancies with EB and screen-positive UAD were reported at risk [8]. We followed up nine pregnancies with EB (nine isolated, five with multiple markers), and all of them had favorable prognosis except one termination owing to anhydramnios and one case was diagnosed to have epilepsy in childhood.

Fetal mild pyelectasis detected on second trimester scanning has been one of the most common soft markers with an incidence of 0.3–4.5%. Pregnancies with renal pelvis anteroposterior pelvic diameter (APPD) ≥ 6 mm were reported to be at higher risk for persistent or progressive pyelectasis. In addition, further evaluation was indicated to be unnecessary when postnatal echography was normal and APPD was moderate [15, 16]. After excluding abnormal karyotypes, seven pregnancies and the liveborns with isolated mild pyelectasis were followed up for 4 to 9 years in this study. No further evaluation for kidneys were needed and the outcomes were uneventful except allergic asthma in one case.

In the present study, five pregnancies with single umbilical artery (two isolated, three with multiple markers) were followed up. The perinatal and postnatal evaluations were uncomplicated, and there was no additional maternal complication such as hypertension or fetal cardiac/urinary

Table 1 Demographic and clinical features of the study group

Features	$n = 78$
Age (years)	31.4 ± 6.9
Gravida	2 (1–8)
Parity	1 (0–7)
Indication of amniocentesis	
Previous aneuploidy	2
TT with high risk	42
FTS with high risk	4
Advanced MA	30
Gestation week at amniocentesis	20 (18–24)
Liveborn	77 (97.5%)
Neonatal death	1
Mode of delivery	
Vaginal	16 (20.8%)
C/S	61 (79.2%)
Termination of pregnancy	1 (1.3%)
Followed-up children	76
Follow-up year	6.5 ± 1.8
Karyotype	
46XX	37 (46.8%)
46XY	41 (51.9%)
Isolated soft marker	66 (84.6%)
EIF	21
EB	9
Mild pyelectasis	10
Unilateral CBC	107
Bilateral CBC	17
SUA	2
Multiple soft markers (≥ 2 marker)	12 (15.4%)

TT triple test, *FTS* first trimester screening, *SM* soft marker, *MA* maternal age, *C/S* cesarean section, *EIF* echogenic intracardiac focus, *EB* echogenic bowel, *CBC* choroid plexus cyst, SUA single umbilical artery

malformations and growth restriction which were reported to be found in several previous studies [17–20].

Choroid plexus cysts which can be single or multiple, unilateral or bilateral, are seen in about 1–2.5% of pregnancies as an isolated finding and has not been associated with abnormal development or poor prognosis in chromosomally normal fetuses [21, 22]. In the line with previous studies, we followed up fetuses with bilateral choroid plexus cyst (14 isolated, 3 with multiple markers) and 12 unilateral choroid plexus cyst (10 isolated, 2 with other soft markers). It is interesting that allergic asthma in one child with UCBCs and in one with BCPCs was detected in the liveborns with EIF and mild pyelectasis. In addition, epilepsy and attention-deficit/hyperactivity disorder were diagnosed in two liveborns with BCPCs.

When the subjects ($n = 12$) with multiple soft markers but no aneuploidy or structural abnormality were evaluated, no pathology was detected in most of them except one case of allergic asthma, one case of hearing impairment and one case of ADHD.

This study has some limitations. First, as the major limitation, the number of the study group is too small as subjects with missing data regarding the follow-up were excluded. Second, the present study did not include some soft markers such as nuchal translucency, mild ventriculomegaly and short long bones which are associated with aneuploidies. However, the present study has some interesting results regarding the pregnancy outcomes. One of the unexpected diseases detected in long-term follow-up is allergic asthma which has been diagnosed in liveborns with prenatal isolated and multiple soft markers. The other one is ADHD which has been detected in liveborns with prenatal BCPC and multiple soft markers. Epilepsy is another disease diagnosed in children with prenatal EIF and EB. Although this study has small study group to be able to comment on the possible relationship between the diseases

Table 2 Outcomes of fetuses with prenatal determined soft markers and diagnosed diseases/problems during long-term follow-up

Outcome	EIF	EB	MP	SUA	UCPC	BCPC	MSM
Healthy	17	7	6	2	9	14	9
$N = 64$							
Diagnosed diseases/problems during the long-term follow-up, which not only do not have proved relationship with the soft markers determined in the prenatal period, but also were not found to be associated with other organic causes in further investigations							
Allergic asthma	1		1		1	1	1
$N = 5$							
ADHD						1	1
$N = 2$							
Epilepsy	1	1				1	
$N = 3$							
Termination (anhydramnios at 16th gestation week)		1					
$N = 1$							
Newborn death (no determined cause)	1						
$N = 1$							
Strabismus	1						
$N = 1$							
Hearing impairment							1
$N = 1$							

EIF echogenic intracardiac focus, *EB* echogenic bowel, *MP* mild pyelectasis, *SUA* single umbilical artery, *UCPC* unilateral choroid plexus cyst, *BCPC* bilateral choroid plexus cyst, *MSM* multiple soft markers, *ADHD* attention-deficit/hyperactivity disorder

and prenatal soft markers, it may have a point on this topic and provide insight into further studies with larger groups.

Conclusion

Soft markers of aneuploidy seem to continue to be one of the most attractive and controversial topics in obstetrics. Despite several studies related to perinatal outcomes of the fetuses with these markers, the prognosis in the long run remains to be a mystery. This study shows long-term favorable outcomes of the liveborns with isolated or multiple soft markers without any aneuploidy and may provide insight into this debated point.

Acknowledgements The present study was conducted on 78 pregnant women with 15–22 weeks of singleton gestation who were referred to Ondokuz Mayis University Fetal Medicine Unit between January 2005 and January 2010 for amniocentesis and found to have isolated or multiple soft markers but no structural anomalies at the same time of procedure; and outcomes of these pregnancies and the liveborns.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Statements The study was approved by Ondokuz Mayis University Ethics Committee, and the patient records/information was anonymized and de-identified prior to analysis.

Informed Consent Informed consent was obtained from each individual participant.

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