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Outcome of fetuses with soft markers: results of 3016 cases in Ahvaz city

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Abstract

Background: Although soft markers may be seen as normal variants, they are important due to their association with chromosomal and congenital abnormalities.

Methods: This cross-sectional descriptive-analytical study was done on 3016 women who referred for perinatal care. Fetuses with any of soft markers including thickened nuchal fold (TNF), mild pyelectasis (MP), choroid plexus cyst (CPC), single umbilical artery (SUA), mega cisterna magna (MCM) and mild ventriculomegaly (MVM) were followed during pregnancy and birth. Data analysis was carried out using SPSS for Windows (version 22). Data were analyzed using chi-square and T-test. A p-value <0.050 was considered statistically significant.

Results: 285 (9.4%) fetuses with soft markers Including 148 (4.9%) fetuses with CPC, 118 (3.9%) fetuses with MP, 2 (0.1%,) fetuses with isolated TNF, 8 (0.3%) fetuses with isolated MVM, 4 (0.13%) fetuses with SUA, 4 (0.13%) fetuses with MCM were identified, and one fetus had TNF and MVM simultaneously. In cases with CPC, no abortion or major structural abnormalities were observed and all 148 neonates had normal phenotypes at birth. Among 118 cases with MP, one case had a major cardiac disorder, and 2 cases of abortions (1.7%) were reported (p=0.481). 83 cases (70.3%) were male and 35 cases (29.7%) were female (p=0.021) and all neonates had a normal phenotype. Both pregnancies with isolated TNF resulted in abortion. Of the 8 cases with isolated MVM, two cases had major structural abnormalities. 2 cases of abortion were reported and all infants had a normal phenotype. In one case, that fetus had TNF and MVM simultaneously. Amniocentesis showed no aneuploidy. No major structural abnormalities were observed in fetuses with SUA. One case of abortion was reported. Among the three births, two pre-term births were reported, and all three infants had normal phenotype. In four cases with MCM, no major structural abnormality was observed and all four neonates had normal phenotype.

Conclusion: In cases without association with other structural abnormality, mothers who have fetuses with CPC or MP should be reassured that the pregnancy outcomes are generally favorable.

Keywords: Ultrasonography, Fetus, Soft marker, Outcome

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Introduction

Many methods have been used to identify fetuses with the risk of aneuploidy, using maternal age, biochemical tests, prenatal sonography and invasive procedures like amniocentesis. For this purpose, a sonographic exam is done in the second trimester (usually at 16–20 weeks) of pregnancy. There are two types of sonographic markers of aneuploidy, including major fetal structural abnormalities and soft markers (1).

Although some soft markers can be occurred in a fetus as

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↑What is "already known" in this topic:
Although soft markers are one of the two sonographic markers suggestive of aneuploidy, they may be seen in the fetus as normal variants. Because of their relationship with aneuploidy, they become an important topic in obstetrics and a major concern among parents.

→What this article adds:
This study showed that we could reassure mothers that the pregnancy outcome is generally favorable.

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normal variants, because of increased incidence in abnormal situations such as chromosomal and congenital abnormalities and associations between some of these markers and intrauterine fetal death, pre-term birth, fetal growth restriction and congenital infection in euploid fetuses, soft markers are important (2, 3). It is estimated that isolated soft markers occur in 11% to 17% of normal fetuses (4). These markers are not identical in different races and can be isolated without association with major structural abnormalities (5).

The most commonly studied soft markers are thickened nuchal fold (TNF), mild pyelectasis (MP), choroid plexus cyst (CPC), single umbilical artery (SUA), mega cisterna magna (MCM), and mild ventriculomegaly (MVM) (1).

In this study, we aimed to identify the fetuses with soft markers in our study population and to evaluate their outcome during pregnancy and at birth.

Methods

The present study is a cross-sectional descriptive-analytical study on 3016 women who referred to Ahvaz Imam Khomeini Hospital and a private perinatology clinic, between August 2015 and March 2019 for perinatal care.

Fetuses with any oft markers including thickened nuchal fold (TNF), mild pyelectasis (MP), choroid plexus cyst (CPC), single umbilical artery (SUA), mega cisterna magna (MCM) and mild ventriculomegaly (MVM) were included in the study.

For nuchal fold measurement, we obtained a transverse section of the head at the level of the cavum septum pellucidum and thalami directed posteriorly to the cerebellum. The measurement was done in the midline, from the outer side of the skull bone to the outer skin. If the measurement was ≥6 mm between 15 and 23 weeks, we considered it as TNF. MP was considered as renal pelvis diameter ≥4mm and <10mm in anteroposterior dimensions in the transverse scan of the abdomen, without dilation of calyces. A CPC was considered a well-defined lucent cyst-like area within the choroid plexus of the lateral ventricle in the transverse head plane. The SUA was diagnosed by color doppler examination of the fetal pelvis to find one umbilical artery around the urinary bladder. The measurement of cisterna magna is carried out on a transverse plane of the fetal head with 15 degrees angled caudal to the canthomeatal line. The diameter is measured between the inferior-posterior surface of the cerebellar vermis to the inner surface of the occipital bone. Diameters above 10 mm were considered as MCM. The lateral ventricle was measured across the atrium of farther one from the probe, and MVM is defined as a transverse diameter greater than 10 mm at any gestational age (1, 2, 6). In case of dissatisfaction with the study and incomplete cases were excluded from the study.

Maternal age information, type of pregnancy, maternal gravidity, ultrasonography findings, gender of the fetus, screening findings during pregnancy (including biochemical tests, NT, CVS, amniocentesis, cell-free) and other pregnancy surveys (including ultrasound, fetal echocardiography), as well as infant status at births including birth weight and the need for admission to the NICU and postnatal surveys, were collected from maternal files by a questionnaire. In cases of missing data, for obtaining information, mothers were called.

Statistical Analysis

Data analysis was carried out using SPSS for Windows, (version 22). The discrete variables and nominal variables were shown as descriptive statistics such as mean and standard deviation, ratio, min-max, number of cases, frequency and percentage, where applicable. In cases of inaccessibility to information, the parameters were considered as missing data. Data were analyzed using chi-square, T-test. A p-value <0.05 was considered statistically significant.

Ethics approval

The present study was approved by the Code of Ethics: IR.AJUMS.REC.1398.543 in the Ethics Committee of Research of the Ahvaz Jundishapur University of Medical Sciences.

Results

Among the 3016 pregnant mothers who received a second-trimester screening ultrasound, 285 (9.4%) fetuses with soft markers were identified.

In this study 148 (4.9%) fetuses with CPC, 118 (3.9%) fetuses with MP, two (0.1%) fetuses with isolated TNF, eight (0.3%) fetuses with isolated MVM, four (0.13%) fetuses with SUA, four (0.13%) fetuses with MCM were identified, and one fetus had TNF and MVM simultaneously. The studied mothers had a mean (± standard deviation) age of 30.2±4 years and rangedfrom 19 to 41 years. 125 (43.8%) mothers were gravida one, 119 (41.8%) cases were gravida two, 38 (13.3%) cases were gravida three and 3 (1.1%) cases were gravida 4. 282 pregnancies were spontaneous and 3 had in vitro fertilization (IVF).

Of the 148 cases with CPC, the mean mother's age was 31.18±4 years. 56 (37.8%) cases were gravida one, 66 (44.6%) cases were gravida two, 23 (15.5%) cases were gravida three and 3 (2.1%) cases were gravida 4 (p=0.710). 145 pregnancies were spontaneous and 3 had IVF. Twenty-eight (18.9%) had cell-free tests, all of which were in the low-risk group. 107 (72.3%) cases were in the low-risk group (risk of aneuploidy), 32 (21.6%) cases were in the intermediate-risk group and 9 (6.1%) cases were in the high-risk group (p=0.280). Risk assessment performed by NT and biochemical tests in the first trimester. Fourteen fetuses underwent fetal echocardiography but no major cardiac abnormality was reported. No case of abortion or major structural abnormalities was observed in fetuses with CPC. Two (1.4%) cases had pre-term delivery and 135 (91.2%) cases had term delivery and 11 (7.4%) cases had post-term delivery. 87 (58.8%) neonates were male and 61 (41.2%) neonates were female. Two (1.4%) neonates weighed less than 2500 grams, four (2.7%) neonates weighed more than 4000 grams and 142 (95.9%) neonates weighed between 2500 and 4000 grams. Sixteen (10.8%) cases were admitted to the NICU (p=0.260). All 148 neonates with CPC at the second-trimester ultrasound had normal phenotypes at birth.

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Of the 118 cases with MP, the mean mother's age was 29.7±3.5 years. 59 (50%) cases were gravida one, 44 (37.3%) cases were gravida two and 15 (12.7%) cases were gravida three (p=0.181). All cases had spontaneous pregnancy. Seven cases (5.9%) had cell free testing, all of which were in low risk group. In first trimester risk assessment for aneuploidy 98 (83.1%) cases were in the low risk group, 12 (10.2%) cases were in the intermediate risk group and 8(6.7%) cases were in the high risk group (p=0.059). 22 fetuses underwent fetal echocardiography, 21 cases were reported normal and one case had major cardiac disorder. Of the 118 fetuses with MP, two (1.7%) IUFD (Intrauterine Fetal Death) were reported (p=0.481). One case of IUFD in 21 weeks ages fetus with NT=3.5mm and another one was IUFD at 30 week in the fetus with NT=6.5mm and major cardiac disorder in a twin pregnancy. Among 116 pregnancies leading to live birth, one (0.9%) case had pre-term delivery, 111 (95.7%) cases had term delivery and 4 (3.4%) cases had post-term delivery. Six (5.2%) neonates weighed more than 4000 grams and 110 (94.8%) neonates weighed between 2500 and 4000 grams. 83 (70.3%) of fetuses were male and 35 (29.7%) cases were female. MP was significantly higher in male gender (p=0.021). Five (4.3%) cases were admitted to NICU. All 116 neonates with MP at the second trimester ultrasound had a normal phenotype at birth.

In two cases the fetus had isolated TNF. The first case was a 21 year old gravida one mother with NT=4.9, which eventually led to spontaneous abortion at 19 weeks. The second case was a 36 year old gravida 2 mother with NT=3.8mm and NF=8mm. In echocardiography the fetus had major cardiac abnormality and according to amniocentesis the fetus had trisomy 21 and finally therapeutic abortion was performed.

Of the 8 cases with isolated MVM, the mean mother's age was 25.5±5.7 years. Seven cases were gravida one, one case was gravida two, all of which had spontaneous pregnancies. Six cases were in the low risk group, one case in the intermediate risk group and one case in the high risk group. One case underwent amniocentesis, which was normal. One fetus underwent fetal echocardiography which was reported as normal. Two cases had major structural abnormality. All fetuses were female. Two cases of abortion were reported in this group. One case was a 19 year old mother with fetus in low risk group who had myelomeningocele, and Arnold chiari malformation and eventually underwent a therapeutic abortion. Another case was a 33 year old mother with a fetus in low risk group, which in the second trimester ultrasound, all of the long bones were reported less than the second percentile for gestational age and eventually resulted in abortion. Among the six live births, one case had pre-term labor and five had term births. One infant weighed less than 2500 grams and five neonates weighed between 2500 and 4000 grams. Of these, two infants were admitted to the NICU. In all six cases of birth, the infant had a normal phenotype.

In one case the fetus had TNF and MVM simultaneously. A gravida two 27 year old mother with NT=3.2mm that was in high-risk group of aneuploidy. The fetus was male and in second-trimester ultrasound had bilateral club foot furthermore TNF and MVM. She underwent amniocentesis that no aneuploidy was reported. Unfortunately, the call to collect more information was not successful. (This case is not included in Table 1)

Of the four cases with SUA, the mean mother's age was 27.2±4.5 years. All mothers were gravida two, all had spontaneous pregnancy and all were in the low-risk group. Two cases had cell-free tests that were in the low-risk group. No major structural abnormality was observed in fetuses with SUA. Two fetuses underwent fetal echocardiography tests that were reported as normal. Among four fetuses with SUA, one case of spontaneous abortion reported, in a 25 years old mother with a fetus with NT=1.7mm. Among the 3 live births, two had pre-term and one case had term births. One infant weighing less than 2500 grams and two infants

Table 1. Demographic and clinical features and findings of the study group

Findings	All referrals	CPC	MP	TNF	MVM	SUA	MCM
Number	285	148	118	2	8	4	4
Maternal Age (years), mean±SD	30.2±4	31.18±4	29.7±3.5	28.5±10.6	25.5±5.7	27.2±4.5	27.5±2
Min-max	19-41						
Gravidity							
G1	125 (43.8%)	56 (37.8%)	59 (50%)	1	7	-	2
G2	119 (41.8%)	66 (44.6%)	44 (37.3%)	1	1	4	2
G3	38 (13.3%)	23 (15.5%)	15 (12.7%)	-		-	-
G4	3 (1.1%)	3 (2.1%)	-	-		-	-
Type of pregnancy							
Spontaneous*	282	145	118	2	8	4	4
IVF	3	3	-	-	-	-	-
Missing data	0	-	-	-	-	-	-
Cell-free test							
Low risk	38	28	7	-	-	3	-
Missing data (not did)*	247	120	111	2	8	1	4
Risk assessment							
Low	219 (76.5)	107 (72.3%)	98 (83.1%)	-	6	4	4
Intermediate	45 (16.1)	32 (21.6%)	12 (10.2%)	-	1	-	-
High*	21 (7.4)	9 (6.1%)	8 (6.7%)	2	1	-	-
Major structural abnormality*	5 (1.7%)	-	1	1	2	-	-

*One case is not included in the table
[1] Among live birth

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Table 1. Ctd

Findings	All referrals	CPC	MP	TNF	MVM	SUA	MCM
Major cardiac abnormalities							
Yes	2	-	1	1	-	-	-
No*	40	14	22	-	1	2	1
Missing data	242	134	95	1	7	2	3
Amniocentesis							
Euploid*	2	-	-	-	1	-	-
Aneuploid	1	-	-	1	-	-	-
Missing data (not don)	282	148	118	1	7	4	4
GA at delivery[1]							
Pre-term	6 (2.2%)	2 (1.4%)	1 (0.9%)	-	1	2	-
Term	256 (92.4%)	135 (91.2%)	111 (95.7%)	-	5	1	4
Post-term	15 (5.4%)	11 (7.4%)	4 (3.4%)	-	-	-	-
Abortion or IUFD*	8 (2.8%)	-	2 (1.7%)	2	2	1	-
Sex							
Male*	177 (62.5%)	87 (58.8%)	83 (70.3%)	1	-	4	2
Female	107 (37.5%)	61 (41.2%)	35 (29.7%)	1	8	-	2
Weight at delivery[1]							
<2500gr	4 (2.1%)	2 (1.4%)	-	-	1	1	-
2500-4000gr	263 (92.6%)	142 (95.8%)	110 (94.8%)	-	5	2	4
>4000gr	10 (3.9%)	4 (2.8%)	6 (5.2%)	-	-	-	-
NICU admission[1]							
Yes	24 (8.7%)	16 (10.8%)	5 (4.3%)	-	2	1	-
No	253 (91.3%)	132 (89.2%)	111 (94%)	-	4	2	4
Phenotype[1]							
Normal	277	148	116	-	6	3	4

*One case is not included in the table
[1] Among live birth

weighing between 2500 and 4000 grams. All three infants were male. One case was admitted to the NICU. In all three cases of birth, the infant had a normal phenotype.

Of the four cases with MCM, the mean age of mothers was 27.5±2 years. Two mothers were gravida one, and two were gravida two. All of the women had spontaneous pregnancies and all were in the low-risk group. No major structural abnormality was observed in these fetuses. Two fetuses were male and two of them were female. One fetus underwent fetal echocardiography which was reported as normal. Abortion was not reported in fetuses with MCM. All four neonates had term birth and weighing between 2500 and 4000 g. All four neonates had normal phenotypes, and no case of NICU admission was reported.

Demographic and clinical features and findings of the study group are shown in Table 1.

Discussion

In this study, isolated bilateral CPC was seen in 4.9% of pregnancies. There was no significant association between isolated CPC and major structural or cardiac abnormality, poor pregnancy outcome (abortion, pre-term / post-term labor, low or high birth weight) or neonatal hospitalization. All newborns had normal phenotypes. These results are similar to that reported in the literature.

In a retrospective study of 40 patients referred for genetic and perinatal consultation due to isolated CPC in the Grace Prentice et al. study, all cases resulted in live birth and all neonates had no major structural or chromosomal abnormalities (7). In the Kun-Long Hung et al. study, among 2111 brain ultrasonography, CPCs were identified in 186 (8.8%) fetuses. Physical exams and phenotypes were normal for all neonates who had CPC. Furthermore, for all 179 children with 30 to 42 months follow up, the developmental outcome was normal. (8) In Enono Yhoshu et al. study to assess the prenatal and postnatal outcomes of prenatally diagnosed CPCs, 67 mothers with fetal CPCs were followed, approximately 95% of the cases showing the disappearance of cysts, mostly within 2 months from the diagnosis and according to this study persistence of CPCs in the postnatal period is uncommon and the adverse neurological outcome is not likely. (9)

In our population, isolated MP was seen in 3.9% of pregnancies. There was no significant association between isolated MP and major structural or cardiac abnormality, poor pregnancy outcome (abortion, pre-term / post-term labor, low or high birth weight) or neonatal hospitalization. All newborns had normal phenotypes. However, based on other studies, postnatal evaluation must be done for urinary tract abnormalities.

According to Claudio Coco et al. the prevalence of pyelectasis was 2.9% (366/12, 672) in the fetuses. Among these, 83.3% (305/366) of cases had isolated pyelectasis, and 16.7% (61/366) were associated with other abnormalities. The overall prevalence of trisomy 21 was 0.087% (11/12, 672) in the studied group and, among these, two had pyelectasis, one isolated, and one associated with other structural abnormalities. Based on this study, in cases of isolated pyelectasis, amniocentesis is not indicated. (10) In the Mervyn S Jaswon et al. study, 104 fetuses with MP were followed and 23 (22%) cases of VUR (vesicoureteral Reflux) were seen in postnatal studies. Based on this study, a normal postnatal ultrasound scan does not preclude the presence of VUR (11).

TNF was found in 0.1% of pregnancies in this study. Of the two fetuses with isolated TNF, one had spontaneous abortion at 19th week, and one case underwent a therapeutic abortion after approval of trisomy 21 by amniocentesis.

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Like these, in Lushan L et al. study, 72fetuses with TNF were chromosomally examined. 3.7% of cases with isolated TNF and 35.5% of cases with TNF and major structural abnormalities simultaneously were associated with chromosomal abnormalities and showed a significant increase in the rate of adverse outcomes in pregnancy (12).

In our study, MVM was observed in 0.3% of pregnancies. Of the 8 cases with isolated MVM, two cases of abortion were reported.

In the study of J Ouahba et al. which included 167 fetuses with isolated MVM, 4 cases of chromosomal abnormality, 2 cases of infection with cytomegalovirus, and 15 cases of comorbidities were reported. Termination of pregnancy was considered in 21 pregnancies (12.6%). 101 cases were followed up over a period of 19 to 127 months after birth, and in 12 cases, neurological abnormalities or psychomotor delay were observed, and in cases where ventricular dilatation was progressive during pregnancy, the outcome was worse (13).

In this study, SUA was found in 0.13% of pregnancies. No major structural abnormalities were observed. One case of spontaneous abortion was reported. In three cases of live birth, two had pre-term birth. Some studies indicated that fetuses with SUA have a higher risk of Small for Gestational Age, pre-term delivery, pregnancy-induced hypertension, admission to the neonatal intensive care unit, and perinatal mortality (3). According to a study by T. Dagklis performed on 424 fetuses with isolated SUA, no evidence of increased risk of chromosomal abnormality was observed (14).

In this study, isolated MCM was observed in 0.13% of pregnancies. No cases of major structural abnormality and abortion were reported. In Jeanne A. Hairnovici et al. study, 15 fetuses with isolated mega cisterna magna were followed during pregnancy, at birth and shortly after pregnancy. All 15 pregnancies resulted in phenotypically normal live-born infants. All eight cases were normal after a short follow-up period. According to this study, fetuses with isolated mega cisterna magna are associated with normal outcomes during and after pregnancy (15).

Conclusion

Although soft markers of aneuploidy are one of the most interesting and controversial topics in pregnancy, without synchronicity with other structural abnormalities, as mentioned above, mothers who have fetuses with CPC or MP must be reassured that the pregnancy outcomes are generally desirable.

However, further researches are required to establish standard guidelines and appropriate approach to these markers in our community.

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Conflict of Interests

The authors declare that they have no competing interests.

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