

SMFM CONSULT SERIES #57:

Evaluation and management of soft ultrasound markers for aneuploidy

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Soft markers are minor ultrasound findings identified in the midtrimester that commonly do not represent a structural abnormality. These may be normal variants but are noteworthy because of their association with an increased aneuploidy risk. Commonly identified soft markers include echogenic intracardiac focus; echogenic bowel; choroid plexus cyst(s); single umbilical artery; urinary tract dilation; shortened humerus, femur, or both; thickened nuchal fold; and absent or hypoplastic nasal bone¹⁻⁴ (Table 1).

Contemporaneously with the advancement in aneuploidy detection with soft markers was the development of improved serum screening methods to predict aneuploidy risk.^{5,6} The introduction of cell-free DNA (cfDNA) techniques greatly improved the ability to screen for common aneuploidies. Given the high sensitivity and specificity of cfDNA for trisomies 21, 18, and 13 across all age groups, in 2020, the American College

of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine endorsed the option of cfDNA screening for all patients.⁶

Q | What is the initial approach when an isolated soft marker is identified?

“Isolated” is a soft marker that has been identified in the absence of any fetal structural anomaly, growth restriction, or additional soft marker, following a detailed obstetrical ultrasound examination. Identification of a soft marker is an indication for a detailed obstetrical ultrasound examination (Current Procedural Terminology code 76811) to ensure the finding is isolated. The decision to perform a detailed examination should be made through a shared decision-making framework. In the case of multiple soft markers or structural abnormalities, the approach to evaluation should be individualized. If an isolated soft marker is confirmed, subsequent evaluation and counseling depend on prior aneuploidy screening results, additional risk factors for aneuploidy, and associations with

nonaneuploid conditions.

Traditionally, the presence or absence of specific soft markers was used to modify the probability of trisomy 21 and 18 for high-risk patients.⁷ However, the relative importance of this approach has evolved rapidly with improved prenatal screening techniques. The detection rates for aneuploidy with commonly employed serum screening strategies (ie, first-trimester screen, integrated screen, sequential screen, contingent screen, or quad screen) are high. cfDNA is the single best screening test for the common trisomies (trisomies 21, 18, and 13), and the posttest probability of a common aneuploidy after negative cfDNA screening is very low.⁸ Although a range of positive likelihood ratios (LRs) for a particular aneuploidy exists for each soft marker, even when the highest positive LRs are applied to a population that has previously had a negative cfDNA result, the risk of trisomy 21 is negligibly affected.

Only diagnostic testing removes residual risk for aneuploidy detection. Thus, a patient may elect diagnostic

CONTINUED ON PAGE 12



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TABLE 1 Isolated Soft Markers: Background and Recommended Management

Soft marker	Description	Prevalence	Range of LRs*	Aneuploidy evaluation	Follow-up	Comments
Echogenic intracardiac focus	Echogenic area < 6 mm in either cardiac ventricle that is as bright as surrounding bone and visualized in at least 2 separate planes	3%-5% in karyotypically normal fetuses	0.95-1.8	<ul style="list-style-type: none"> • cfDNA/serum screen negative: none • No prior screening: counseling for noninvasive testing for aneuploidy 	<ul style="list-style-type: none"> • Antenatal management: routine care • Follow-up imaging: N/A 	<ul style="list-style-type: none"> • Pathogenesis unclear • Do not represent a structural or functional cardiac abnormality
Echogenic bowel	Echogenic area in fetal bowel greater than or equal to that of surrounding fetal bone, typically the iliac wing	Up to 1.8% of second-trimester ultrasound examinations	1.65-8.0	<ul style="list-style-type: none"> • cfDNA/serum screen negative: none • No prior screening: counseling for noninvasive testing for aneuploidy 	<ul style="list-style-type: none"> • Antenatal management: evaluation for CF, congenital viral infection, intra-amniotic bleeding • Follow-up imaging: third-trimester ultrasound for reassessment and evaluation of growth 	<ul style="list-style-type: none"> • Associated with aneuploidy, CF, congenital viral infection, primary gastrointestinal pathology, intra-amniotic bleeding, and FGR
Choroid plexus cyst	Small, fluid-filled structure within the choroid of the lateral ventricles of the fetal brain	<ul style="list-style-type: none"> • Present in approximately 1%-2% of fetuses in the second trimester • Present in 30%-50% of fetuses with trisomy 18 	Isolated CPCs: 0.9-5.6 CPCs with a structural anomaly: 66	<ul style="list-style-type: none"> • cfDNA/serum screen negative: none • No prior screening: counseling for noninvasive testing for aneuploidy 	<ul style="list-style-type: none"> • Antenatal management: routine care • Follow-up imaging: N/A 	<ul style="list-style-type: none"> • Associated with trisomy 18 • Not considered a structural or functional brain abnormality and nearly all resolve by 28 weeks
Single umbilical artery	Umbilical cord containing 1 umbilical artery instead of 2	<ul style="list-style-type: none"> • 0.25%-1.0% of all singleton pregnancies • Up to 4.6% of twin gestations 	N/A	<ul style="list-style-type: none"> • cfDNA/serum screen negative or no prior screening: none 	<ul style="list-style-type: none"> • Antenatal management: consideration for weekly antenatal surveillance beginning at 36 0/7 weeks of gestation • Follow-up imaging: third-trimester ultrasound for evaluation of growth 	<ul style="list-style-type: none"> • Co-occurring structural abnormalities most commonly involve the cardiovascular and renal systems • Conflicting evidence regarding association with stillbirth or FGR
Urinary tract dilation	Threshold for diagnosis: <ul style="list-style-type: none"> • 16-27 weeks of gestation, AP RPD \geq 4 mm • \geq 28 weeks of gestation, AP RPD \geq 7 mm 	Occurs in 1%-2% of pregnancies	N/A	<ul style="list-style-type: none"> • cfDNA/serum screen negative: none • No prior screening: counseling for noninvasive testing for aneuploidy 	<ul style="list-style-type: none"> • Antenatal management: evaluation for persistence, with frequency of evaluation dependent on initial findings • Follow-up imaging: third-trimester ultrasound to determine whether postnatal pediatric urology or nephrology follow-up is needed 	<ul style="list-style-type: none"> • Common pathologic causes include vesicoureteral reflux (the most common etiology), ureteropelvic junction obstruction, ureterovesical junction obstruction, multicystic dysplastic kidneys, and posterior urethral valves
Shortened long bones (femur, humerus)	Ratio of observed to expected bone length (based on biparietal diameter) for diagnosis: <ul style="list-style-type: none"> • Shortened femur: ratio < 0.92 • Shortened humerus: ratio < 0.90 	N/A	<ul style="list-style-type: none"> • Shortened femur: 1.5-2.7 • Shortened humerus: 5.1-7.5 	<ul style="list-style-type: none"> • cfDNA/serum screen negative: none • No prior screening: counseling for noninvasive testing for aneuploidy 	<ul style="list-style-type: none"> • Antenatal management: evaluation for skeletal dysplasias • Follow-up imaging: third-trimester ultrasound for reassessment and evaluation of growth 	<ul style="list-style-type: none"> • Associated with skeletal dysplasia and FGR

TABLE CONTINUED ON PAGE 12

TABLE 1
CONTINUED
FROM PAGE 11

Isolated Soft Markers: Background and Recommended Management

Soft marker	Description	Prevalence	Range of LRs*	Aneuploidy evaluation	Follow-up	Comments
Thickened nuchal fold	Nuchal fold that measures ≥ 6 mm between 15 and 20 weeks of gestation	N/A	3.8-23.0	<ul style="list-style-type: none"> • cfDNA negative: none • Serum screen negative: counseling for no further testing vs noninvasive vs invasive testing for aneuploidy • No prior screening: counseling for noninvasive vs invasive testing for aneuploidy 	<ul style="list-style-type: none"> • Antenatal management: routine care • Follow-up imaging: N/A 	<ul style="list-style-type: none"> • One of the most specific markers for trisomy 21
Absent or hypoplastic nasal bone	Definition of hypoplastic nasal bone varies: <ul style="list-style-type: none"> • ≥ 10 or ≥ 11 biparietal diameter: nasal bone ratio • ≤ 2.5 mm in length • < 2.5 gestational age-based percentile • < 0.75 or ≤ 0.7 MoM 	0.1%-1.2% of euploid pregnancies	6.6-23.0	<ul style="list-style-type: none"> • cfDNA negative: none • Serum screen negative: counseling for no further testing vs noninvasive vs invasive testing for aneuploidy • No prior screening: counseling for noninvasive vs invasive testing for aneuploidy 	<ul style="list-style-type: none"> • Antenatal management: routine care • Follow-up imaging: N/A 	<ul style="list-style-type: none"> • Can be associated with other genetic syndromes

AP RPD, anterior-posterior renal pelvic diameter; CF, cystic fibrosis; cfDNA, cell-free DNA; CPC, choroid plexus cysts; FGR, fetal growth restriction; LR, likelihood ratio; MoM, multiples of the median; N/A, not applicable.

*All LRs are provided for trisomy 21, except in the setting of CPCs. The LR in the setting of CPCs is provided for trisomy 18. Accepted thresholds for positive LRs are as follows: LRs from approximately 1.5-5.0 confer a small additional increase in the likelihood of the aneuploidy; LRs between 5 and 10 confer a moderate additional increase in the likelihood of the aneuploidy; and LRs > 10 confer a significant additional increase in the likelihood of the aneuploidy.

testing for any indication. However, we do not recommend diagnostic testing for aneuploidy solely for the evaluation of an isolated soft marker following a negative serum or cfDNA screening result (grade 1B). Similarly, if a pregnant person has undergone diagnostic testing and the results indicate a normal karyotype, identification of a soft marker is insignificant with regard to aneuploidy and should be reported as such.

Some pregnant people may decline any aneuploidy screening following a shared decision-making process that incorporates accurate information,

accessible health care resources, and the patient’s clinical context, values, beliefs, and potential anxiety created by the identification and discussion of a soft marker.^{6,9,10} Each practice should establish a standardized protocol for how the identification of an isolated soft marker will be documented and managed for patients who have previously declined aneuploidy screening. These protocols should ensure patients are informed prior to the ultrasound examination of how findings will be handled to enhance shared decision-making and patient autonomy.

Q **What is the counseling and management regarding soft ultrasound markers?**

Table 1 summarizes the definition, prevalence, range of LRs, evaluation, and follow-up for commonly identified soft markers. **Table 2** summarizes recommendations for the evaluation and management of isolated soft ultrasound markers for aneuploidy in the second trimester. ■

FOR REFERENCES VISIT
contemporaryobgyn.net/soft-markers

TABLE 2 Summary of Recommendations		
Categories	Recommendations	Grade
1	We do not recommend diagnostic testing for aneuploidy solely for the evaluation of an isolated soft marker following a negative serum or cfDNA screening result.	1B Strong recommendation, moderate-quality evidence
2	For pregnant people with no prior aneuploidy screening and isolated echogenic intracardiac focus, echogenic bowel, urinary tract dilation, or shortened long bones, we recommend counseling to estimate the probability of trisomy 21 and discussion of options for noninvasive aneuploidy screening with cfDNA, or quad screen if cfDNA is unavailable or cost prohibitive.	1B Strong recommendation, moderate-quality evidence
3	For pregnant people with no prior aneuploidy screening and isolated thickened nuchal fold or isolated absent or hypoplastic nasal bone, we recommend counseling to estimate the probability of trisomy 21 and discussion of options for noninvasive aneuploidy screening via cfDNA, or quad screen if cfDNA is unavailable or cost prohibitive, or diagnostic testing via amniocentesis, depending on clinical circumstances and patient preference.	1B Strong recommendation, moderate-quality evidence
4	For pregnant people with no prior aneuploidy screening and isolated choroid plexus cyst(s), we recommend counseling to estimate the probability of trisomy 18 and discussion of options for noninvasive aneuploidy screening with cfDNA, or quad screen if cfDNA is unavailable or cost prohibitive.	1C Strong recommendation, low-quality evidence
5	For pregnant people with negative serum or cfDNA screening results and an isolated echogenic intracardiac focus, we recommend no further evaluation, as this finding is a normal variant of no clinical significance with no indication for fetal echocardiography, follow-up ultrasound imaging, or postnatal evaluation.	1B Strong recommendation, moderate-quality evidence
6	For pregnant people with negative serum or cfDNA screening results and isolated fetal echogenic bowel, urinary tract dilation, or shortened long bones, we recommend no further aneuploidy evaluation.	1B Strong recommendation, moderate-quality evidence
7	For pregnant people with negative serum screening results and isolated thickened nuchal fold or absent or hypoplastic nasal bone, we recommend counseling to estimate the probability of trisomy 21 and discussion of options for no further aneuploidy evaluation, noninvasive aneuploidy screening via cfDNA, or diagnostic testing via amniocentesis, depending on clinical circumstances and patient preference.	1B Strong recommendation, moderate-quality evidence
8	For pregnant people with negative cfDNA screening results and isolated thickened nuchal fold or absent or hypoplastic nasal bone, we recommend no further aneuploidy evaluation.	1B Strong recommendation, moderate-quality evidence
9	For pregnant people with negative serum or cfDNA screening results and isolated choroid plexus cyst(s), we recommend no further aneuploidy evaluation, as this finding is a normal variant of no clinical significance with no indication for follow-up ultrasound imaging or postnatal evaluation.	1C Strong recommendation, low-quality evidence
10	For fetuses with isolated echogenic bowel, we recommend evaluation for cystic fibrosis and fetal CMV infection and a third-trimester ultrasound examination for reassessment and evaluation of fetal growth.	1C Strong recommendation, low-quality evidence
11	For fetuses with an isolated single umbilical artery, we recommend no additional evaluation for aneuploidy, regardless of whether prior results of aneuploidy screening were low-risk or testing was declined. We recommend a third-trimester ultrasound examination to evaluate growth and consideration of weekly antenatal fetal surveillance beginning at 36 0/7 weeks of gestation.	1C Strong recommendation, low-quality evidence
12	For fetuses with isolated urinary tract dilation A1, we recommend an ultrasound examination at \geq 32 weeks of gestation to determine whether postnatal pediatric urology or nephrology follow-up is needed. For fetuses with urinary tract dilation A2-3, we recommend individualized follow-up ultrasound assessment with planned postnatal follow-up.	1C Strong recommendation, low-quality evidence
13	For fetuses with isolated shortened long bones, we recommend a third-trimester ultrasound examination for reassessment and evaluation of growth.	1C Strong recommendation, low-quality evidence

cfDNA, cell-free DNA; CMV, cytomegalovirus.