Ultrasonographic soft markers of aneuploidy in second trimester fetuses

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Bahman ۱۳۹۷

- Chromosomal abnormalities are one of the leading causes of **pregnancy loss.** Chromosome abnormalities occur in ۰.۱-۰.۲% of all live births .
- Trisomy ۲۱ is the most common karyotypic abnormality in live born infants .
- Second trimester ultrasound detects **two types** of sonographic findings suggestive of aneuploidy.

- Detection of **major fetal** structural anomalies comprises the first group.
- The second group includes **soft markers** that are non **specific often transient** and can be detected during ۲nd trimester ultrasound scan.

Ultrasound Soft Marker

- Absent or hypoplastic nasal bone
- Aberrant right subclavian artery
- Increased nuchal fold thickness
- Ventriculomegaly
- Echogenic bowel
- Intracardiac echogenic focus
- Mild hydronephrosis
- Short femur Shortened humerus
- Increased nuchal fold thickness
- Choroid plexus cyst
- Single umbelical artery
- Prefrontal space ratio.(PFSR)

- There is nothing on the morphology scan that signifies that a baby **DEFINITELY** has an aneuploidy, but there are signs that significantly increase (or decrease) the risk of aneuploidy and that warrant offering further **invasive, confirmatory testing**.

Ultrasound Soft Markers of Aneuploidy

Likelihood Ratios[1]

ISOLATED soft marker	LR T21	Recommendation
Aberrant right subclavian artery	3.9	Recalculate risk of T21 and refer for counselling and further testing
Absent or hypoplastic nasal bone	6.6	Recalculate risk of T21, and refer for counselling and further testing
Echogenic bowel	1.7	Recalculate risk of T21 and consider testing for CF and CMV; recommend uterine artery Dopplers and follow-up growth ultrasound 28 and 32 weeks
Increased nuchal fold ≥ 6mm	3.8	Recalculate risk of T21, and refer for counselling and further testing
Ventriculomegaly	3.8	Recalculate risk of T21 and refer for counselling and further testing
Choroid plexus cyst (CPC)	No increase	If CPC ≥ 5mm and hands are not seen to open, recalculate risk for T18 with likelihood ratio of 5.6 and refer for counselling and further testing
Intracardiac echogenic focus	No increase	Reassure
Mild hydronephrosis	No increase	Repeat ultrasound third trimester for worsening hydronephrosis
Shortened humerus	No increase	If less than 2.5th percentile, check all long bones and consider referral to tertiary MFM unit (possible skeletal dysplasia)
Shortened femur	No increase	If less than 2.5th percentile, check all long bones and consider referral to tertiary MFM unit (possible skeletal dysplasia)
Single umbilical artery	No increase	Recommend uterine artery Dopplers and third trimester ultrasound for growth as associated with FGR

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Table 1 Major and soft markers of aneuploidy.

System	Major	Soft markers
CNS	Ventriculomegaly, Holoprosencephaly, Microcephaly, Abnormal posterior fossa-dandy walker complex	Choroid plexus cyst
Musculoskeletal	Hand and feet anomalies – syndactyly, clinodactyly, clenched hand, radial ray aplasia, Clubfoot, a sandal gap, rocker-bottom foot	Short long bones
Face	Cleft palate and lips micrognathia, macroglossia, hypo- and hypertelorism, low set ears, small ear	–
Neck	Cystic hygroma	Nuchal fold thickening
Cardiac	Endocardial cushion defect, ventricular septal defect, hypoplastic left heart syndrome, tetralogy of Fallot, and other complex cardiac anomalies Echogenic focus	Echogenic focus
Gastrointestinal tract	Esophageal and duodenal atresia, small bowel obstruction, diaphragmatic hernia and Omphalocele	Echogenic bowel
Genitourinary tract	Moderate to severe hydronephrosis, dysplastic renal disease, and renal agenesis	Mild pyelectasis
Other	Symmetrical IUGR	Single umbilical artery

Meta-analysis of second-trimester markers for trisomy ٢١

- firstly,if a systematic second-trimester ultrasound examination demonstrates the absence of all major defects and markers there is **a ٧.٧-fold** reduction in risk for trisomy ٢١;
- secondly, the detection of any one of the markers during the scan should stimulate the sonographer to look for all other markers or defects.
- thirdly, the post-test odds for trisomy ٢١ is derived by multiplying the pre-test odds by the positive LR for each detected marker and the negative LR for each marker demonstrated to be absent.
- fourthly, in the case of most isolated markers, including intracardiac echogenic focus, echogenic bowel, mild hydronephrosis and short femur, there is only a small effect on modifying the pre-test odds.

Presence of multiple soft markers at a routine morphology ultrasound

- Presence of multiple soft markers at routine morphology ultrasound has a greater than additive effect on risk of aneuploidy .
- Presence of multiple soft markers for aneuploidy should always prompt referral to a tertiary Maternal Fetal Medicine Unit for further imaging and testing .

- An online calculator for recalculating risk of T۲۱, in the presence of multiple soft markers can be found at this site (see ‘Supporting Information’ section). Please note that this does not provide confidence intervals for estimates of combined likelihood ratios:
- https://obgyn.onlinelibrary.wiley.com/doi/abs/۱۰.۱۰۰۲/uog.۱۲۳۶۴

Validity of Sonologic Soft Marker for Chromosome Abnormality

- Out of ٢٠٠ subjects included in the study ١٩ had solitary soft marker for chromosome abnormality and none of them had chromosome abnormality.
- Out of the ٩ subjects with multiple soft markers, ٢ fetuses had chromosome abnormality. There is no isolated soft marker is found to have higher risk ???for chromosome abnormality whereas cluster of markers seems to confer higher risk for aneuploidy.

Aberrant right subclavian artery

- Can be determined on ultrasound using colour flow Doppler.
- The subclavian artery is seen just above the level of the “three-vessel view” of the pulmonary artery, aorta, and superior vena cava. It is normally placed when it is in front of the trachea and aberrant when behind the trachea.
- This finding, in isolation, is associated with a likelihood ratio of ۳.۹ for T۲۱, therefore recalculation of risk of T۲۱ and referral for further counseling and testing is recommended

Absent or hypoplastic nasal bone

- The nasal bone is assessed on a sagittal view of a fetus, with the head in a neutral position and the ultrasound probe at a ۴۵-degree angle to the nasal bone. The nasal bone is seen parallel to the skin line, but just below it, and is more echogenic than skin. The length of the nasal bone should be measured and plotted on a gestational age-specific chart and is considered hypoplastic if <۲.۵th percentile for gestational age ۲.
- An absent or hypoplastic nasal bone is associated with a likelihood ratio of ۶.۶ for a diagnosis of T۲۱, therefore recalculation of risk of T۲۱ and referral for counseling and further testing is recommended.

Echogenic bowel

- Defined as bowel that has equal echogenicity to that of bone.
- In isolation, likelihood ratio of T۲۱ is ۱.۷, so recalculation of risk is recommended, with referral for counseling and further testing if now considered high risk (>۱ in ۲۵۰) for aneuploidy.
- Also associated with cystic fibrosis and congenital infections such as CMV, therefore parental testing for CF gene mutations and TORCH screen is recommended.
- Most commonly seen as a result of fetal swallowing of blood, therefore, history of maternal bleeding should be elicited.

Increased nuchal fold thickness

- Defined as nuchal fold thickness of ۶ mm or more at time of morphology ultrasound.
- As an isolated finding, associated with likelihood ratio of T۲۱ of ۳.۸, therefore risk should be recalculated and referral for counseling and further testing is recommended.

Intracardiac echogenic focus

- As an isolated finding, unlikely to be a marker for trisomy ۲۱.
- Isolated finding has likelihood ratio of ۰.۹۵, thus, in an otherwise low risk pregnancy (i.e. <۱ in ۲۵۰ risk from FTS) can be reassured as normal variant and nil further testing is required.

Mild hydronephrosis

- Defined as minimum anteroposterior diameter of the renal pelvis of ۴mm or greater.
- As an isolated finding, unlikely to be a marker for trisomy ۲۱.
- Isolated finding has likelihood ratio of ۱.۰۸, thus, in an otherwise low risk pregnancy (i.e. <۱ in ۲۵۰ risk from FTS) can be reassured and nil further testing for aneuploidy required.
- Recommend repeat ultrasound in third trimester/early neonatal review to assess for progression to hydronephrosis.

Short femur

- Defined as femur length <۲.۵th percentile from standardized gestational age-specific charts.
- Unlikely associated with T۲۱ as an isolated finding.
- However, review of lengths and appearances of other long bones, as well as other markers of skeletal dysplasia, is required and consideration of referral to a tertiary MFM unit.

Shortened humerus

- Defined as humerus length <۲.۵th percentile.
- However, review of lengths and appearances of other long bones, as well as other markers of skeletal dysplasia, is required and consideration of referral to a tertiary MFM unit.

Increased nuchal fold thickness

- Defined as nuchal fold thickness of ۶mm or more at time of morphology ultrasound.
- As an isolated finding, associated with likelihood ratio of T۲۱ of ۳.۸, therefore risk should be recalculated and referral for counseling and further testing is recommended

Ventriculomegaly

- Ventriculomegaly is defined as the diameter of the lateral cerebral ventricle of ۱۰mm or more.
- In isolation, associated with likelihood ratio of ۳.۸ for T۲۱, therefore recalculation of risk and referral for counseling and further testing is recommended.