Fetal Soft Markers in Obstetric Ultrasound

Abstract

Objective: To evaluate ultrasound “soft markers” used in fetal genetic screening.

Options: Ultrasound screening at 16 to 20 weeks is one of the most common genetic screening and (or) diagnostic tests used during pregnancy. The practical concern for ultrasound screening is false-positive and false-negative (missed or not present) results. The use and understanding of ultrasound soft markers and their screening relative risks is an important option in the care of pregnant women. Currently, the presence of a “significant” ultrasound marker adds risk to the likelihood of fetal pathology, but the absence of soft markers, except in controlled situations, should not be used to reduce fetal risk.

Key Words: Ultrasound, soft marker, prenatal screening, fetus, aneuploidy, trisomy, genetic

Outcomes: The use of ultrasound in pregnancy has significant health and economic outcomes for families and the health care system, compared with no ultrasound use. The Society of Obstetricians and Gynaecologists of Canada (SOGC) recommends a single “routine” ultrasound evaluation at 16 to 20 weeks in all pregnancies. Patients need to be counselled about the positive and negative findings that ultrasound may reveal so they are prepared for unexpected pregnancy knowledge and the possibility of further testing options being offered.

Evidence: Committee members were asked to review specific soft marker ultrasound topics after consensus was reached on the most commonly published soft markers. Medline and PubMed databases were searched for peer-reviewed English articles published from 1985 to 2003. Reviews of each soft marker topic were written by committee members with quality of evidence and classification of recommendations. These reviews were then circulated and discussed by the combined committee. Final format for the guideline was completed by the committee chairpersons.

Values: The quality of evidence and classification of recommendations followed discussion and consensus by the combined committees of Diagnostic Imaging and Genetics of the SOGC.

Benefits, Harms, Costs: It is not possible at this time to determine the benefits, harms, and costs of the guideline because this would require health surveillance and research and health resources not presently available; however, these factors need to be evaluated in a prospective approach by provincial and tertiary initiatives. Consideration of these issues is in the options and outcome section of this abstract.

Recommendations:

1. The screening ultrasound at 16 to 20 weeks should evaluate 8 markers, 5 of which (thickened nuchal fold, echogenic bowel, mild ventriculomegaly, echogenic focus in the heart, and choroid plexus cyst) are associated with an increased risk of fetal aneuploidy, and in some cases with nonchromosomal problems, while 3 (single umbilical artery, enlarged cisterna magna, and pyelectasis) are only associated with an increased risk of nonchromosomal abnormalities when seen in isolation (II-2 B).

2. Identification of soft markers for fetal aneuploidy requires correlation with other risk factors, including history, maternal age, and maternal serum testing results (II-1 A).

3. Soft markers identify a significant increase in fetal risk for genetic disease. Timely referral for confirmation, counselling, and investigation is required to maximize management options (III-B).

Validation: Peer-reviewed guideline development is part of the committee process in addition to SOGC council and editorial review.

Sponsors: SOGC.


These guidelines reflect emerging clinical and scientific advances as of the date issued and are subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed. Local institutions can dictate amendments to these opinions. They should be well documented if modified at the local level. None of these contents may be reproduced in any form without prior written permission of the SOGC.
INTRODUCTION

Providing an obstetric ultrasound at 16 to 20 weeks' gestation has become standard practice in Canada.1-3 Although there are many potential benefits, the primary reason to routinely offer this scan is for the detection of fetal abnormalities.4-6 Some obstetric ultrasound findings are considered variants of normal but are noteworthy because they also increase the risk for underlying fetal aneuploidy. These findings are known as “soft markers” and should be considered distinct from fetal anatomic malformations and (or) growth restriction that also increase perinatal and genetic risks.

The presence of soft markers increases the risk for fetal aneuploidy but is not diagnostic. Individual soft markers will vary in the degree of association with fetal aneuploidy. It has become practice to estimate the degree of association as a likelihood ratio (LR) by which the a priori background risk is altered. Detection of multiple soft markers will increase the significance of the finding, compared with seeing the same marker in isolation.7,8 Nonsonographic factors, including maternal age, gestational age, past history, and family history also influence the chance for aneuploidy and should be considered to establish an accurate a priori risk.9-12 In addition, maternal serum testing as an alternate screening tool can complement and enhance the overall screening process.13-18 Providing an accurate assessment of fetal genetic risk requires the ability to integrate known factors before patients can make an informed choice about proceeding with invasive diagnostic testing.

The purpose of this guideline is to (1) evaluate the usefulness of each ultrasound soft marker, (2) assess whether a specific soft marker should be looked for routinely on screening ultrasound, (3) review potential nonkaryotypic implications for soft markers, (4) suggest follow-up recommendations to deal with soft markers once detected, and (5) provide assessment of the quality of information regarding each marker. (See Table 1 for the quality of evidence and classification of recommendation).19

REFERENCES

ECHOCENIC INTRACARDIAC FOCUS (Figure 1)

Definition and Imaging Criteria

Echogenic intracardiac focus (EICF) is defined as a focus of echogenicity comparable to bone, in the region of the papillary muscle in either or both ventricles of the fetal heart.1–6 Eighty-eight percent are only in the left ventricle, 5% are only in the right, and 7% are biventricular.7 A grading system has been proposed comparing the echogenicity of the intracardiac focus with surrounding bone. Grade 2 suggests that echogenicity is equal to bone, and grade 3 suggests it is greater.8 Using an appropriate transducer frequency (≤ 5 MHz) and appropriate gain setting, an EICF can be diagnosed on the standard 4-chamber view of the fetal heart.

Association With Fetal Aneuploidy

The association between isolated EICF and fetal aneuploidy has been described in both retrospective and prospective studies. The evidence is best for left or biventricular EICF, but this is likely due to the greater frequency that foci are found in these locations.1–11 A meta-analysis has suggested a likelihood ratio of 2.8 (95% confidence interval [CI] 1.5–5.5);12 however, most studies were undertaken in high-risk women. When the low-risk population is evaluated, the finding of an isolated EICF is associated with lower LRs, from 0–1.8.13–17 Consensus of the SOGC Imaging and Genetics Committees suggests an LR of 2.

Although the numbers are small, studies suggest that the less frequent right-sided, biventricular, multiple, or particularly conspicuous EICF appear to be associated with a higher risk for fetal aneuploidy, compared with the more common single, left ventricular EICF.8,11,18–21

Association With Nonchromosomal Abnormalities

EICF has not been associated with congenital heart disease or other chromosomal abnormalities.22–25 There may be some ethnic difference regarding the incidence (Asian more often than Caucasian) of EICF.26

Summary

EICF is readily diagnosed on the 4-chamber view of the heart, which is an established part of the screening ultrasound at 16 to 20 weeks’ gestation.27 EICF is associated with an increased risk for fetal aneuploidy. A prevalence of 0.5% to 12% has been described in the prenatal population.23–27 If EICF is seen, it should be reported, but as an isolated finding, no further ultrasounds, including echocardiography, are required. The presence of EICF warrants evaluation of other risk factors for fetal aneuploidy, including other soft markers, maternal age, and maternal serum screening results. Based on an LR of 2, if the midtrimester risk of fetal aneuploidy is greater than 1/600 (maternal age 31 years), referral for consultation, validation, and counselling should be considered. If the background risk for fetal aneuploidy is equivalent or less than 1/600 and the EICF is isolated, no further investigations are necessary.
Recommendations

1. EICF should be evaluated as part of the 4-chamber cardiac review during the 16- to 20-week ultrasound (III-B).

2. Isolated EICF with a fetal aneuploidy risk less than 1/600 by maternal age (31 years) or maternal serum screen requires no further investigations (III-D).

3. Women with an isolated EICF and a fetal aneuploidy risk greater than 1/600 by maternal age (31 years) or maternal serum screening should be offered counselling regarding fetal karyotyping (II-2 B).

4. Women with right-sided, biventricular, multiple, particularly conspicuous, or nonisolated EICF should be offered referral for expert review and possible karyotyping (II-2 A).

References


**Figure 2. Bilateral renal pyelectasis with anterior/posterior measurement**

**MILD PYELECTASIS (Figure 2)**

**Definition and Imaging Criteria**

Mild pyelectasis is defined as a hypoechoic spherical or elliptical space within the renal pelvis that measures ≥ 5 mm and ≤ 10 mm. The measurement is taken on a transverse section through the fetal renal pelvis using the maximum anterior-to-posterior measurement. Measurements < 5 mm are normal, should not be designated as pyelectasis, and should not be reported. Pyelectasis may also be referred to as “mild renal pelvic dilatation” or “mild hydronephrosis.”

**Association With Fetal Aneuploidy**

Isolated pyelectasis is seen in 0.7% of fetuses at 16 to 26 weeks’ gestation. It is an isolated finding in fetal Down syndrome in approximately 2%. Although the likelihood ratio for Down syndrome is approximately 1.9, the 95% CI does cross 1 (0.7–5.1), indicating lack of significance. In the absence of other risk factors, the chance of Down syndrome in the presence of isolated mild pyelectasis remains small and does not justify an invasive diagnostic procedure.

**Association With Nonchromosomal Abnormalities**

Fetal pyelectasis is associated with congenital hydronephrosis, which is a commonly encountered birth defect. Renal pelvis measurements ≥ 5 mm should be considered equivalent to congenital hydronephrosis with appropriate follow-up. All fetuses with renal pelvic measurements ≥ 5 mm should have a neonatal ultrasound, and
those having measurements > 10 mm should also have a third trimester ultrasound.²

**Summary**

Evaluation of fetal kidneys, which includes possible pyelectasis, is considered part of the routine screening ultrasound at 16 to 20 weeks’ gestation and should be reported.³ The finding of isolated pyelectasis does not appear to significantly increase the risk of fetal aneuploidy in low-risk women and does not justify invasive prenatal testing, but noninvasive maternal serum screening may assist in risk assessment. Owing to the increased risk of fetal hydronephrosis, a neonatal follow-up scan should be arranged in all cases of mild isolated pyelectasis. A third trimester follow-up ultrasound should only be considered if pyelectasis is ≥ 10 mm. Referrals should be considered for women aged over 35 years and for women who have additional ultrasound findings, renal pelvis measurements > 10 mm, or maternal serum screening results showing increased chromosomal risks.

**Recommendations**

1. Evaluation of fetal kidneys is a part of the screening ultrasound at 16 to 20 weeks,’ and if pyelectasis is visualized, the renal pelvis should be measured in the anterior/posterior diameter (III-B).

2. All fetuses with renal pelvic measurements ≥ 5 mm should have a neonatal ultrasound, and those having measurements > 10 mm should be considered for a third trimester scan (II-2 A).

3. Isolated mild pyelectasis does not require fetal karyotyping (II-2 E).

4. Referral for pyelectasis should be considered with additional ultrasound findings and (or) in women at increased risk for fetal aneuploidy owing to maternal age or maternal serum screen results showing increased chromosomal risks.

**References**


**SINGLE UMBILICAL ARTERY (Figure 3)**

**Definition and Imaging Criteria**

Single umbilical artery (SUA) is the absence of one of the arteries surrounding the fetal bladder and in the fetal umbilical cord. Assessment of the umbilical arteries can be made from the cord itself in either transverse or longitudinal sections.³ The umbilical arteries can also be assessed at the cord insertion site into the fetal abdomen and on either side of the fetal bladder as the vessels originate from the iliac arteries. If needed, the assessment can be enhanced with colour flow Doppler.

**Association With Fetal Aneuploidy**

Isolated SUA has not been found to be significantly associated with fetal aneuploidy.¹–⁶

**Association With Nonchromosomal Abnormalities**

Isolated SUA has been associated with both underlying fetal renal and cardiac abnormalities,¹–³ ⁷–⁹ as well as low birth weight.²,⁵

**Summary**

Assessment of cord vessels is considered a part of the routine obstetric ultrasound at 16 to 20 weeks.¹⁰ The finding of a single umbilical artery warrants a detailed review of fetal anatomy, including kidneys and heart (fetal echo). Appropriate fetal growth should be confirmed through clinical evaluation with follow-up ultrasound for clinical concerns. An isolated SUA does not warrant invasive testing for fetal aneuploidy.

**Recommendations**

1. Assessment of cord vessels is considered a part of the routine obstetric ultrasound at 16 to 20 weeks (III-A).
2. The finding of a single umbilical artery requires a more detailed review of fetal anatomy, including kidneys and heart (fetal echo) (II-2 B).
3. An isolated single umbilical artery does not warrant invasive testing for fetal aneuploidy (II-2 A).

**References**

Figure 3. Single umbilical artery on cross-section of cord

ECHOCGENIC BOWEL (Figure 4)

Definition and Imaging Criteria

Echogenic bowel is defined as fetal bowel with homogeneous areas of echogenicity that are equal to or greater than that of surrounding bone. The echogenicity has been classified as either focal or multifocal. There have been various techniques used to define echogenic bowel, partially because of concerns raised about intra- and interobserver variability. A grading system based on comparison of the echogenicity of fetal bowel and surrounding bone relative to the ultrasound machine gain setting minimizes observer variability and should be used. Grade 2 suggests that echogenicity is equal to bone whereas grade 3 suggests that it is greater. Whenever echogenic bowel is suspected, the gain setting should be lowered to enable this comparison and to ensure that bowel hyperechogenicity is real. This should help to minimize a false-positive diagnosis of hyperechogenicity.

Association With Fetal Aneuploidy

The presence of echogenic bowel is associated with an increased risk for fetal aneuploidy, including trisomy 13, 18, 21, and the sex chromosomes. It has been detected in 0.6% to 2.4% of all second trimester fetuses and as an isolated finding in 9% of fetuses with aneuploidy (2.8% to 25%). As a result, it has been suggested that the likelihood ratio for this marker is 6 (CI 2.7–6.8).

Association With Nonchromosomal Abnormalities

The presence of echogenic bowel has been associated with an increased risk for cystic fibrosis in the fetus, congenital infection, intra-amniotic bleeding, congenital malformations of the bowel, and other perinatal complications, including intrauterine growth restriction. The risk of cystic fibrosis in the fetus with echogenic bowel is approximately 2% (0 to 13%). The a priori risk will change if the
parental carrier status is known. The association between congenital infection and hyperechogenic bowel has been noted for the most common pathogens known to cause fetal infections (cytomegalovirus [CMV], herpes, parvovirus, rubella, varicella, and toxoplasmosis).3,4,6,11,12,14,18,19 Intra-amniotic bleeding has also been identified as an etiology of echogenic bowel. This can result from intra-amniotic bleeding owing to placental abruptions or invasive procedures.18,19,22–24 Congenital malformations of the fetal bowel can lead to increased echogenicity. Studies have suggested that this is more likely with upper gastrointestinal (GI) lesions. Other ultrasound features, such as ascites and dilated loops of bowel, will often be present in this circumstance.18,19,25–27 Echogenic bowel has also been reported with poor fetal growth, which is associated with an increase in perinatal morbidity and mortality.4–6,10–14,18,19,28

Summary

Evaluation of the fetal abdomen is an established component of the screening obstetric ultrasound at 16 to 20 weeks.29 This includes an evaluation of bowel echogenicity using an appropriate transducer (5 MHZ or less) and ultrasound gain setting. Echogenic bowel is associated with a significantly increased risk for both chromosomal and nonchromosomal fetal abnormalities. Timely referral for validation, consultation, and further investigation is important.

Further evaluations may include a detailed review of fetal anatomy, growth, and placental characteristics. Laboratory investigations may include a fetal karyotype, DNA testing for cystic fibrosis, and testing for congenital infections (maternal serum titres, fetal amniotic culture, or polymerase chain reaction [PCR] for viral DNA). A maternal serum screen may be considered because elevations in alpha fetoprotein and hCG in the presence of echogenic bowel may further define a population at increased risk for perinatal morbidity and mortality. Obstetric and ultrasound follow-up may also be important.

Recommendations

1. Evaluation of the fetal bowel should be done routinely during the 16- to 20-week obstetric ultrasound (III-B).
2. Echogenic bowel should be identified by comparison with the echogenicity of surrounding bone using an appropriate transducer and gain setting. Bowel echogenicity equal to or greater than bone is significant (grade 2 or 3) (II-2 A).
3. No further investigations are required for grade 1 echogenic bowel (II-2 D).
4. Grade 2 and 3 echogenic bowel is associated with both chromosomal and nonchromosomal abnormalities. Expert review is recommended to initiate the following: a. detailed ultrasound evaluation looking for additional structural anomalies or other soft markers of aneuploidy (II-2 A); b. detailed evaluation of the fetal abdomen looking for signs of bowel obstruction or perforation (II-2 B); and c. detailed evaluation of placental characteristics (echogenicity, thickness, position, and placental cord insertion site) (II-2 B); d. genetic counselling (II-2 A); e. laboratory investigations that
should be offered, including fetal karyotype, maternal serum screening, DNA testing for cystic fibrosis (if appropriate), and testing for congenital infection (II-2 A).

References


THICKENED NUCHAL FOLD (Figure 5)

Definition and Imaging Criteria

The nuchal fold is the skin thickness in the posterior aspect of the fetal neck. A nuchal fold measurement is obtained in a transverse section of the fetal head at the level of the cavum septum pellucidum and thalami, angled posteriorly to include the cerebellum. The measurement is taken from the outer edge of the occiput bone to the outer skin limit directly in the midline. The definition of a thickened nuchal fold has varied, although many researchers and centres now use gestational-age specific criteria. Consensus for this document is that a measurement ≥6 mm be considered significant between 18 and 24 weeks and a measurement of ≥5 mm be considered significant at 16 to 18 weeks. A thickened nuchal fold should be distinguished from cystic hygroma, in which the skin in this area has fluid-filled loculations. A thickened nuchal fold should not be confused with nuchal translucency, which is a specific measurement of fluid in the posterior aspect of the neck at 11 to 14 weeks’ gestation.

Association With Fetal Aneuploidy

A meta-analysis reviewed the performance of a thick nuchal fold at 6 mm or greater and showed that the risk for Down syndrome increased by approximately 17-fold (CI 8–35).
Association With Nonchromosomal Abnormalities

A thickened nuchal fold can be associated with single gene abnormalities, such as Noonan syndrome, multiple pterygium syndrome, and skeletal dysplasias. Thickened nuchal fold has also been associated with congenital cardiac defects.

Summary

Evaluation of the nuchal fold should be considered during the screening ultrasound at 16 to 22 weeks’ gestation. A nuchal fold of 6 mm or greater at 18 to 24 weeks or of 5 mm or greater at 16 to 18 weeks should be considered significant and should prompt referral for validation and consultation. The finding of an isolated thickened nuchal fold significantly increases the risk for fetal aneuploidy, and fetal karyotyping should be offered. Centres may use alternate definitions, taking into account gestational age and other risk factors. Nuchal index has been described as an effective method to deal with the normal increase in nuchal fold measurement that accompanies advancing gestational age. Nuchal index is the mean nuchal fold/mean biparietal diameter (BPD) × 100. A value of 11 or greater has a sensitivity of 50% and a specificity of 96%.

The suggested association of nuchal fold thickening and congenital heart defect is based on small studies. Careful detailed ultrasound examination, including the 4-chamber view and outflow tracts, should be performed. The rare occurrence of an underlying syndromic etiology for the increased nuchal fold justifies a directed, detailed anatomic survey of the fetus and a careful newborn examination.

Recommendations

1. Nuchal fold measurement should be a part of the screening obstetric ultrasound at 16 to 20 weeks (III-B).

2. A thickened nuchal fold significantly increases the risk of fetal aneuploidy. Expert review is recommended, and karyotyping should be offered (II-1 A).

3. A thickened nuchal fold is associated with congenital heart disease and rarely with other genetic syndromes. Expert review is recommended (II-2 B).

References


MILD VENTRICULOMEGALY (Figure 6)

Definition and Imaging Criteria

Cerebral ventriculomegaly is defined by atrial measurements \( \geq 10 \text{ mm} \). Mean atrial measurements are 7.6 mm, standard deviation (SD) 0.6 mm. Mild ventriculomegaly (MVM) is defined as measurements \( \geq 10 \) to \( \leq 15 \text{ mm} \). Measurements are obtained from an axial plane at the level of the thalamic nuclei just below the standard image to measure the BPD. Ventricular measurements are usually obtained in the far image field because of “typical” near-field artifacts. Cursors are positioned perpendicular to the long axis of the ventricle at the edges of the ventricular lumen, near the posterior portion of the choroid plexus.

Association With Fetal Aneuploidy

When MVM is isolated, the incidence of abnormal fetal karyotype is estimated at 3.8% (0 to 28.6%). Idiopathic lateral ventriculomegaly is found in approximately 0.15% of chromosomally-normal fetuses, whereas 1.4% of trisomy 21 fetuses in the second trimester have idiopathic ventriculomegaly. This suggests a likelihood ratio of 9 for the risk of karyotype abnormality.

Association With Nonchromosomal Abnormalities

Fetal ventriculomegaly is the most commonly detected ultrasonographic abnormality of the central nervous system. Ventriculomegaly can arise from agenesis of the corpus callosum, cerebral maldevelopment or destruction, vascular anomalies, or an obstruction within the ventricular system. Children with a prenatal diagnosis of MVM have abnormal neurodevelopment in 10% to 36% of cases dependent on associated anomalies, etiology, and ventricular measurement. In combined case series, mortality is reported at 3.7%. When MVM resolves, abnormal outcome has been reported but is infrequent (< 10%). Unilateral MVM also carries a favourable prognosis when isolated. After the prenatal diagnosis of MVM, maternal evaluation for congenital infection is recommended. Amniocentesis should be offered for karyotype and congenital infection assessment. Other imaging modalities such as magnetic resonance imaging (MRI) might be considered.

Summary

Lateral ventriculomegaly can be detected on standard cranial biometry planes and should be evaluated on both screening ultrasounds as well as detailed ultrasound for higher risk women. The ventricles should be measured if they appear to be larger than the choroid plexus. The finding of ventriculomegaly should prompt a timely referral for consultation and validation. Evaluation of lateral ventriculomegaly should include a detailed examination of fetal anatomy, including the heart. Neonatal assessment and follow-up are important to rule out associated abnormalities because of the potential for abnormal neurodevelopment.

Recommendations

1. Fetal cerebral ventricles should be measured if they subjectively appear larger than the choroid plexus (III-B).

2. Cerebral ventricles greater than or equal to 10 mm are associated with chromosomal and central nervous system pathology. Expert review should be initiated to obtain the following: a. a detailed anatomic evaluation looking for additional malformations or soft markers (III-B); b. laboratory investigation for the presence of congenital infection or fetal aneuploidy (III-B); and c. MRI as a potential additional imaging technique (II-2 C).

3. Neonatal assessment and follow-up are important to rule out associated abnormalities and are important because of the potential for subsequent abnormal neurodevelopment (II-2 B).

References


CHROROID PLEXUS CYSTS (Figure 7)

Definition and Imaging Criteria

Choroid plexus cysts (CPCs) are sonographically discrete, small cysts (≥ 3 mm) found in the choroid plexus within the lateral cerebral ventricles of the developing fetus at 14 to 24 weeks’ gestation. Imaging of the choroid plexus is performed in the transverse plane of the fetal head at the same level that the lateral cerebral ventricle is evaluated. The choroid plexus should be inspected bilaterally for the presence of cysts. The size of CPCs is not of clinical relevance. Evaluation of the choroid plexus in the near field ventricle will be more difficult owing to imaging artifact.

Association With Fetal Aneuploidy

CPCs have been identified in 1% of fetuses during the second trimester screening ultrasound. The incidence of CPCs is 50% in fetuses with trisomy 18; however, only 10% of fetuses with trisomy 18 will have CPCs as the only identifiable sonographic marker on ultrasound screening. The likelihood ratio for trisomy 18 when an isolated CPC is identified is 7 (95% CI 4–12). The number of cysts and the cysts’ distribution or size does not change the risk. Although it has been suggested that an isolated CPC may increase the risk for trisomy 21 with a likelihood ratio of 1.9, the 95% CI crosses 1 (0.78–4.46) and lacks statistical significance. Association With Nonchromosomal Abnormalities

The presence of CPCs in chromosomally normal fetuses is not associated with other fetal abnormalities or abnormal postnatal development.

Summary

Evaluation of the fetal cranium, including the ventricles and choroid plexus, is considered part of the routine screening...
ultrasound at 16 to 20 weeks’ gestation. Identification and reporting of CPCs should be a part of this screening examination. With the presence of CPCs, caregivers should next evaluate maternal age risk and, if available, the maternal serum screen. CPCs increase the risk for trisomy 18. Follow-up ultrasound is not necessary for isolated CPCs. Referral for counselling and possible invasive testing is only necessary if maternal age is 35 years or older or the maternal serum screen is positive for either trisomy 18 or 21.

**Recommendations**

1. Choroid plexus should be evaluated for the presence of discrete cysts during the 16- to 20-week ultrasound (III-B).

2. Isolated CPCs require no further investigation when maternal age or the serum screen equivalent is less than the risk of a 35-year-old (II-2 E).

3. Fetal karyotyping should only be offered if isolated CPCs are found in women 35 years or older or if the maternal serum screen is positive for either trisomy 18 or 21 (II-2 A).

4. All women with fetal CPCs and additional malformation should be offered referral and karyotyping (II-2 A).

5. All women with CPCs and additional soft markers should be offered additional counselling and further ultrasound review (III-B).

**References**


ENLARGED CISTERNA MAGNA (Figure 8)

**Definition and Imaging Criteria**

The cisterna magna is measured on a transaxial view of the fetal head angled 15 degrees caudal to the canthomeatal line. The anterior/posterior diameter is taken between the inferior/posterior surface of the vermis of the cerebellum to the inner surface of the cranium. An enlarged cisterna magna is defined by an anterior/posterior diameter ≥ 10 mm. The measurement will be falsely exaggerated by a steep scan angle through the posterior fossa or dolichocephaly. The association with aneuploidy appears to be strongest in the absence of ventricular dilatation but in the presence of other anomalies. Isolated enlarged cisterna magna does not appear to be strongly associated with aneuploidy. There are no large prospective studies to evaluate this marker.

**Association With Nonchromosomal Abnormalities**

An enlarged cisterna magna is commonly seen in association with other anatomic (arachnoid cyst, Dandy Walker malformation, and Dandy Walker variant) and syndromic (oro-facial–digital syndrome, Meckel-Gruber syndrome, and DiGeorge syndrome) abnormalities.

**Summary**

Review of the fetal cerebellum and cisterna magna is a routine part of the screening ultrasound at 16 to 20 weeks' gestation. If the cisterna magna is subjectively increased, a measurement should be undertaken. The mean diameter of a normal cisterna magna is 5 mm, SD 3 mm. A measurement ≥ 10 mm is considered an abnormality and appropriate referral for consultation and validation should be initiated. A detailed fetal examination should be performed looking for other anomalies, growth restriction, or abnormal amniotic fluid volume. An isolated enlarged cisterna magna is not an indication for fetal karyotyping.

**Recommendations**

1. Review of the fetal cerebellum and cisterna magna is a routine part of the screening ultrasound at 16 to 20 weeks.
If the cisterna magna is subjectively increased, a measurement should be taken (III-B).

2. An isolated enlarged cisterna magna is not an indication for fetal karyotyping (III-D).

3. With an enlarged cisterna magna, expert review is recommended for follow-up ultrasounds and possible other imaging modalities (for example, MRI) and investigations (III-B).

4. If the enlarged cisterna magna is seen in association with other abnormal findings, fetal karyotyping should be offered (III-B).

REFERENCES

FETAL SOFT MARKERS USEFUL FOR COMPREHENSIVE ULTRASOUND

SHORT FEMUR LENGTH

Definition and Imaging Criteria
A short femur length is defined as either a measurement below the 2.5th percentile for gestational age or a measurement that is less than 0.9 of that predicted by the measured biparietal diameter. The femur should be measured with the bone perpendicular to the ultrasound beam and with epiphyseal cartilages visible but not included in the measurement. The relation between bone length and head size may differ across racial groups.

Association With Fetal Aneuploidy
Short femur length has been found to have a sensitivity of 16% in the prediction of Down syndrome with a false-positive rate of 4%. A meta-analysis showed a likelihood ratio of 2.7 (95% CI 2.1-6.0).

Association With Nonchromosomal Abnormalities
Short femur length can also be associated with skeletal dysplasias or fetal growth restriction.

Summary
Short femur length is an ultrasound marker for fetal aneuploidy, particularly trisomy 21. The mathematical model used to determine a positive result is not amenable to screening ultrasound; however, it should be included in the panel of markers used by tertiary centres.

If a femur appears abnormal or its length is found to be below the 2.5th percentile for gestational age, it may be indicative of fetal growth restriction or a more general skeletal malformation. In this circumstance, other long bones should be assessed and referral with follow-up ultrasound considered.

Recommendations
1. Although femur length is standard biometry on the 16- to 20-week ultrasound, the assessment for relative shortness is not part of the screening evaluation (III-C).
2. Relative femur shortening is an ultrasound marker for trisomy 21 and should be considered during tertiary level evaluation (II-1 A).
3. If a femur appears abnormal or measures short on screening ultrasound, other long bones should be assessed and referral with follow-up ultrasound considered (III-B).

SHORT HUMERUS LENGTH

Definition and Imaging Criteria
A short humerus length is defined as a length below the 2.5th percentile for gestational age or as a measurement less than 0.9 of that predicted by the measured biparietal diameter. The humerus should be measured with the bone perpendicular to the ultrasound beam and with epiphyseal cartilages visible but not included in the measurement.
**Association With Fetal Aneuploidy**

Short humeral length has been found to have a sensitivity of 9% with a false-positive rate of 3%. A meta-analysis showed a likelihood ratio of 7.5 (95% CI 4.5–12).

**Association With Nonchromosomal Abnormalities**

Short humeral length can also be associated with skeletal dysplasias or fetal growth restriction. Humeral length has also been recorded as multiples of the median for gestational age. This allows for a graded response including a negative predictor for the relatively longer humerus.

**Summary**

Short humeral length is an ultrasound marker for fetal aneuploidy, particularly trisomy 21. Humeral length is not currently part of the screening obstetric ultrasound; however, it should be included in the panel of markers used by tertiary centres. During screening ultrasound, if the humerus appears abnormal or its length is short, other long bones should be assessed and referral with follow-up ultrasound considered.

**Recommendations**

1. Humeral length is not part of the current screening ultrasound at 16 to 20 weeks but should be considered for future inclusion (III-B).

2. Relative humeral shortening is an ultrasound marker for trisomy 21 and should be considered during tertiary level evaluation (II-1 A).

3. If the humerus is evaluated and appears abnormal or short, other long bones should be assessed and referral with follow-up ultrasound considered (III-B).

**References**


**NASAL BONE**

**Definition and Imaging Criteria**

Nasal hypoplasia has been recognized as a feature of postnatal trisomy 21.\(^1\) This has led to prenatal evaluation of the nasal bone, which has been shown to be a thin echogenic line within the bridge of the fetal nose. The fetus is imaged facing the transducer with the fetal face strictly in the midline. The angle of insonation is 90 degrees, with the longitudinal axis of the nasal bone as the reference line. Calibres are placed at each end of the nasal bone. Absence of the nasal bone or measurements below 2.5th percentile are considered significant.\(^2\)-\(^4\)

**Association With Fetal Aneuploidy**

Preliminary second trimester studies appear to confirm that hypoplastic or absent nasal bone is an ultrasound marker for fetal Down syndrome, while, conversely, a normal nasal bone would reduce significantly the risk.\(^5\)-\(^7\) The likelihood ratio for this finding varies depending on ethnic background. Although a hypoplastic nasal bone was associated with an overall likelihood ratio for Down syndrome at 51, it was found to be 132 for Caucasians and 8.5 for African Caribbeans. The negative likelihood ratio was 0.39 for Caribbeans and 0.27 for African Caribbeans.\(^8\) Nasal hypoplasia has not been associated with other aneuploidy.

**Association With Nonchromosomal Abnormalities**

An absent or hypoplastic nasal bone has not been found to be associated with chromosomal abnormalities.

**Summary**

Hypoplastic or absent nasal bone is an ultrasound marker for fetal Down syndrome, and a normal nasal bone length significantly reduces the risk. Although views of the fetal nasal bone are readily obtained by imaging the facial profile, this is not considered a part of the routine screening ultrasound.\(^8\) In circumstances where the facial profile is seen and the nasal bone is felt to be absent or hypoplastic, referral is recommended. Assessment of the nasal bone should be considered for research or tertiary level evaluation.

**Recommendations**

1. Assessment of the fetal nasal bone is not considered a part of the screening ultrasound at 16 to 20 weeks (III-B).

2. Hypoplastic or absence nasal bone is an ultrasound marker for fetal Down syndrome, and if suspected, expert review is recommended (II-2 B).

**References**


FIFTH FINGER CLINODACTYLY

**Definition and Imaging Criteria**

Fifth finger clinodactyly is defined by a hypoplastic or absent mid-phalanx of the fifth digit. Ultrasound identification of the fetal hand must first be undertaken and then appropriate magnification accomplished. The evaluation requires stretching of the 5 fingers. The diagnosis is established when the middle phalanx of the fifth finger is markedly smaller than normal or absent, which often causes the finger to be curved inward.1

**Association With Fetal Aneuploidy**

Fifth finger clinodactyly is found in 60% of neonates affected with Down syndrome.2 During antenatal screening, it has been found to be present in 3.4% of normal fetuses and in 18.8% of fetuses with Down syndrome. This suggests a likelihood ratio of 5.6 (95% CI 2.5–11.9).3,4

**Association With Nonchromosomal Abnormalities**

As an isolated finding, clinodactyly is not associated with other nonchromosomal anatomic or syndromic abnormalities.

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FETAL SOFT MARKERS NOT ESTABLISHED FOR CLINICAL PRACTICE

BRACHYCEPHALY

**Definition and Imaging Criteria**

 Fetuses affected with trisomy 21 are known to be at increased risk for abnormalities in brain growth and maturation.1 This is known to result in shortening of the frontal occipital brain length primarily owing to a smaller frontal lobe.2 The subsequent abnormal skull shape (brachycephaly) has been evaluated as a screening tool. Initially, brachycephaly was studied with the cephalic index—the biparietal diameter over the occipital frontal diameter. More recent investigations have specifically studied the hypoplastic frontal lobe with various biometric measurements and calculations.

**Association With Fetal Aneuploidy**

The cephalic index does not vary significantly between trisomy 21 and euploid fetuses.3-5 Other calculations of frontal lobe hypoplasia have shown some screening potential in retrospective studies;6-11 however, no prospective studies have been undertaken, and there are no calculated likelihood ratios. The “strawberry” shaped cranium has been specifically described as being associated with trisomy 1812 but has not been evaluated prospectively in a low-risk population.

**Association With Nonchromosomal Abnormalities**

Brachycephaly is not strongly associated with other chromosomal abnormalities.
Summary

Brachycephaly has not been established as an effective screen for fetal aneuploidy. No recommendations for follow-up or changes in neonatal care are advised as a result of a finding of brachycephaly or abnormalities in frontal lobe biometry. Other abnormal cranial morphologies, such as “strawberry” or “lemon” shapes, are associated with fetal pathology and should prompt appropriate referral.

References


INCREASED ILIAC ANGLE

Definition and Imaging Criteria

It has been identified that postnatal trisomy 21 is associated with a wider lateral flare of the iliac bones. Two techniques have been described to measure the fetal iliac angle.1,2 Both methods use the axial (transverse) view of the fetal pelvis. In one method, the converging lines are drawn along the posterior lateral aspect of the iliac wings, while in the second method, the converging lines are drawn through the middle of the iliac wing extremity. It has been suggested that an angle ≥ 90 degrees should be considered the upper limit of normal when screening for trisomy 21.1,3

Association With Fetal Aneuploidy

Several prospective and retrospective studies have shown the association between increased iliac angle and trisomy 21.2,4–8 Several research to date has been limited to high-risk populations. There is no screening sensitivity for this marker in the low-risk population.

Association With Nonchromosomal Abnormalities

Increased iliac angle has not been associated with specific chromosomal abnormalities.

Summary

Increased iliac angle is a possible marker for trisomy 21; however, measurement techniques do not make it amenable to a screening exam, and it has not been evaluated to be effective in a low-risk population. This marker may be useful for tertiary centres investigating high-risk patients or as a possible negative predictor.9

References

Small Fetal Ear Length

Definition and Imaging Criteria
Small low-set ears are a clinical feature in newborns with trisomy 21 and other aneuploidy.1 Although fetal ear position is difficult to determine sonographically, ear length is possible,2 and normal ranges have been established.2–4 Ear length is measured in a coronal view and defined as the maximal distance between the superior and inferior border of the external ear.

Association With Fetal Aneuploidy
A prospective study has been undertaken to evaluate fetal ear length and its association with fetal aneuploidy. A sensitivity of 32% and a specificity of 93% was found.5 This might suggest a likelihood ratio between 3 and 5; however, in 29% of fetuses, appropriate imaging was not able to be obtained. Actual likelihood ratios with confidence intervals have not been published.

Association With Nonchromosomal Abnormalities
Small, low-set, and malformed ears are associated with other genetic abnormalities; however, antenatal detection and evaluation are difficult.

Summary
Although short fetal ear length may be a marker for fetal aneuploidy, adequate evaluation has not been undertaken to establish its usefulness as either a screening tool or as part of a panel of markers for tertiary centres. The use of fetal ear length remains relegated to research protocols.

References

Sandal Gap

Definition and Imaging Criteria
Sandal gap is described as the separation of the great and second toe and has been reported to be present in 45% of newborns with trisomy 21.1,2 Prenatal diagnosis requires imaging the foot and toes from the plantar view.

Association With Fetal Aneuploidy
Although sandal gap has been reported as a finding in fetuses with Down syndrome in the third trimester,3 it is a subtle sonographic finding in the second trimester.4,5 No studies have been undertaken to establish a risk for aneuploidy based on this finding.

Association With Nonchromosomal Abnormalities
The finding of sandal gap may be a normal variant and is not associated with other chromosomal abnormalities.

Summary
No further investigations or follow-up are necessary if isolated sandal gap is detected. It is not part of the screening ultrasound.

References

Recommendations
1. Brachycephaly, increased iliac angle, sandal gap, and fetal ear length are not considered a part of the screening ultrasound at 16 to 20 weeks (III-C).
2. Brachycephaly, increased iliac angle, sandal gap, and fetal ear length should only be evaluated in research protocols or tertiary centres (II-3 D).
3. With specific abnormal cranial morphology such as “clover leaf,” “strawberry,” or “lemon” shapes, referral should be considered (II-2 A).

Discussion
Prenatal diagnosis of fetal aneuploidy is of varying importance to individuals. Diagnosis can only be undertaken with invasive tests that are accompanied by procedure-related risks. Although uncommon, when a complication does occur, it usually results in the loss of a normal fetus. A woman’s decision to proceed with testing will involve an assessment of the risk for the procedure versus the chance of detecting an abnormality. For some, no level of risk assessment for aneuploidy will lead to invasive testing, and as such, screening for the abnormality is of less relevance. It is important to remember that the process of prenatal screening and the decision to proceed with invasive testing.
is voluntary. Caregivers who counsel women must be knowledgeable, must have the ability to integrate various risk factors, and must maintain a nondirective approach.1

The diagnosis of and screening for fetal abnormalities make the 16- to 20-week obstetric ultrasound both clinically effective and cost effective.2–4 Based on ultrasound findings, further investigations or treatment may be offered that are gestational-age dependent and thus time limited. If any fetal abnormalities or soft markers are discovered on routine ultrasound, it is important that findings be expeditiously communicated to primary caregivers. Waiting for transcription, editing, and the mail service is unacceptable in this circumstance. Persons who report these findings should do so verbally, electronically, or by fax. Primary caregivers should then relay information to the patient and offer referral for consultation, validation, and possibly further investigation. These referrals will often be to genetic and (or) prenatal diagnostic services that should be capable of urgent accommodation.

Patients who receive news of potential or real fetal abnormalities will experience anxiety and distress.5 Information should only be given to patients by individuals who can answer preliminary questions and initiate subsequent counselling, referrals and (or) investigations. Although patients will look for answers in the Diagnostic Imaging department, this is seldom the appropriate setting. Patients should
be told about general concerns and assured that their primary caregiver will receive the report as quickly as possible. Sixteen potential second trimester soft markers for fetal aneuploidy are reviewed in this document (Table 2). Only 5 markers are considered useful for evaluation for fetal aneuploidy at the time of a screening ultrasound. Increased nuchal fold, echogenic bowel, mild ventriculomegaly, echogenic foci in the heart, and choroid plexus cysts are associated with an increased risk of aneuploidy. Choroid plexus cysts are only associated with trisomy 18 and, in this circumstance, adjustment should only be made for this specific risk. The markers clinodactyly, short humerus, short femur, and hypoplastic or absent nasal bone are all associated with aneuploidy but should be used in tertiary level ultrasounds and (or) research protocols. The mathematical evaluation for short long bones is not part of the screening process and the images for clinodactyly and the nasal bone are not established as a standard part of the 16- to 20-week scan. Three other markers—single umbilical artery, enlarged cisterna magna, and pyelectasis—do not have a well-established association with aneuploidy when seen in isolation and should not be used to adjust risk when there are no other significant risk factors. However, these latter findings have other potential perinatal implications, and thus evaluation and reporting remain important during the screening process. Four markers—brachycephaly, iliac angle, ear length, and sandal gap—are not established as markers for screening a low-risk population and should not be evaluated except in a research setting or at a tertiary level.

The reduction in risk that accompanies the absence of ultrasound markers is dependent on the diligence with which an entire panel of markers is evaluated. Risk reduction has only been validated in single institutions or with prospective studies using rigorous research protocols. Although this may be recreated in dedicated prenatal diagnosis centres, a reduction should not be applied on the basis of a 16- to 20-week “screening” scan, owing to the variety of imaging locations involved. In the event that multiple (more than 2) markers are identified, it is recommended that patients be referred for confirmation, counselling, and possible further investigation. It is widely accepted that individual markers function independently, and as a result, when clustered together, they convey an even greater risk. This may be true even for markers that do not have a statistically-significant association with fetal aneuploidy when seen in isolation.

This document deals with the adjustment in risk for fetal aneuploidy based on the presence or absence of second trimester ultrasound markers; however, this risk adjustment has not been validated in a population with a lower prevalence for fetal aneuploidy owing to first trimester prenatal screening and diagnosis. As early screening (nuchal translucency, early maternal serum testing) and diagnosis (chorionic villus sampling) become established, the significance of second trimester markers will decrease and require readjustment.

In summary, the screening ultrasound at 16 to 20 weeks should evaluate 8 markers, of which 5 (thickened nuchal fold, echogenic bowel, mild ventriculomegaly, echogenic intracardiac focus, and choroid plexus cyst) are associated with an increased risk of fetal aneuploidy as well as nonchromosomal problems, while 3 (single umbilical artery, pyelectasis, and enlarged cisterna magna) are only associated with an increased risk of nonchromosomal problems when seen in isolation.

References


