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Fetal Soft Markers in Obstetric Ultrasound

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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.

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.

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

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

1. Periodic health examination, 1992 update: 2. Routine prenatal ultrasound screening. Canadian Task Force on the Periodic Health Examination. Can Med J 1992;147(5):627–33.
2. Society of Obstetricians and Gynaecologists of Canada. Guidelines for the performance of ultrasound examination in obstetrics and gynaecology. J Soc Obstet Gynaecol Can 1995;17:263–6.
3. Society of Obstetricians and Gynaecologists of Canada. Obstetric/gynaecologic ultrasound [policy statement]. J Soc Obstet Gynaecol Can 1997;65:871–2.
4. Saari-Kemppainen A, Karjalainen O, Ylostalo P, Heinonen OP. Ultrasound screening and perinatal mortality: controlled trial on systematic one-stage screening in pregnancy. The Helsinki Ultrasound Trial. Lancet 1990;336(8712):387–91.
5. Leivo T, Tuominen R, Saari-Kemppainen A, Ylostalo P, Karjalainen O, Heinonen OP. Cost-effectiveness of one-stage ultrasound screening in pregnancy: a report from the Helsinki ultrasound trial. Ultrasound Obstet Gynecol 1996;7(5):309–14.
6. Long G, Sprigg A. A comparative study of routine versus selective fetal anomaly ultrasound scanning. J Med Screen 1998;5(1):6–10.
7. Nicolaides KH, Snijders RJ, Gosden CM, Berry C, Campbell S. Ultrasonographically detectable markers of fetal aneuploidy. Lancet 1992;340:704–7.
8. Bromley B, Lieberman E, Shipp TD, Benacerraf BR. The genetic sonogram: a method of risk assessment for Down syndrome in the second trimester. J Ultrasound Med 2002;21(10):1087–96; quiz 1097–8.
9. Stene J, Stene E, Mikkelsoen M. Risk for chromosome abnormality at amniocentesis following a child with a non-inherited chromosome aberration. Prenatal Diagn 1984;4(special issue):81–95.
10. Warburton D. Genetic Factors Influencing Aneuploidy Frequency. In: Dellarco VL, Voytek PK, Hollaender A, editors. Aneuploidy: etiology and mechanisms. New York: Plenum; 1985. p. 133–48.
11. Society of Obstetricians and Gynaecologists of Canada. Guidelines for health care providers involved in prenatal screening and diagnosis. SOGC Clinical Practice Guidelines. No. 75; August 1998.
12. Dick PT. Periodic health examination, 1996 update: 1. Prenatal screening for and diagnosis of Down syndrome. Canadian Task Force on the Periodic Health Examination. Can Med J 1996;154(4):465–79.
13. Vintzileos A, Guzman ER, Smulian JC, Yeo L, Scorza WE, Knuppel RA. Second-trimester genetic sonography in patients with advanced maternal age and normal triple screen. Obstet Gynecol 2002;99(6):993–5.
14. DeVore GR, Romero R. Combined use of genetic sonography and maternal serum triple marker screening: an effective method for increasing the detection of trisomy 21 in women younger than 35 years. J Ultrasound Med 2001;20(6):645–54.
15. Benn PA, Kaminsky LM, Ying J, Borgida AF, Egan JF. Combined second-trimester biochemical and ultrasound screening for Down syndrome. Obstet Gynecol 2002;100(6):1168–76.
16. Hobbins JC, Lezotte DC, Persutte WH, DeVore GR, Benacerraf BR, Nyberg DA, et al. An 8-center study to evaluate the utility of mid-term genetic sonograms among high-risk pregnancies. J Ultrasound Med 2003;22(1):33–8.
17. Verdin SM, Economides DL. The role of ultrasonographic markers for trisomy 21 in women with positive serum biochemistry. Br J Obstet Gynaecol 1998;105:63–7.
18. Drugan A, Reichler A, Bronstein M, Johnson MP, Sokol RJ, Evan MI. Abnormal biochemical serum screening versus 2nd trimester ultrasound – detected minor anomalies as predictors of aneuploidy in low-risk patients. Fetal Diagn Ther 1996;11:301–5.
19. Woolf SH, Battista RN, Angerson GM, Logan AG, Eel W. Canadian Task Force on the Periodic Health Exam. Ottawa: Canadian Communication Group; 1994. p. xxxvii.

Table 1. Criteria for quality of evidence assessment and classification of recommendations

Level of evidence*	Classification of recommendations†
I: Evidence obtained from at least one properly designed randomized controlled trial.	A. There is good evidence to support the recommendation for use of a diagnostic test, treatment, or intervention.
II-1: Evidence from well-designed controlled trials without randomization.	B. There is fair evidence to support the recommendation for use of a diagnostic test, treatment, or intervention.
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group.	C. There is insufficient evidence to support the recommendation for use of a diagnostic test, treatment, or intervention.
II-3: Evidence from comparisons between times or places with or without the intervention. Dramatic results from uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category.	D. There is fair evidence not to support the recommendation for a diagnostic test, treatment, or intervention.
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.	E. There is good evidence not to support the recommendation for use of a diagnostic test, treatment, or intervention.

*The quality of evidence reported in these guidelines has been adapted from the Evaluation of Evidence criteria described in the Canadian Task Force on the Periodic Health Exam.[19]
†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on the Periodic Health Exam.[19]

FETAL SOFT MARKERS USEFUL FOR SCREENING ULTRASOUND

ECHOGENIC 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]

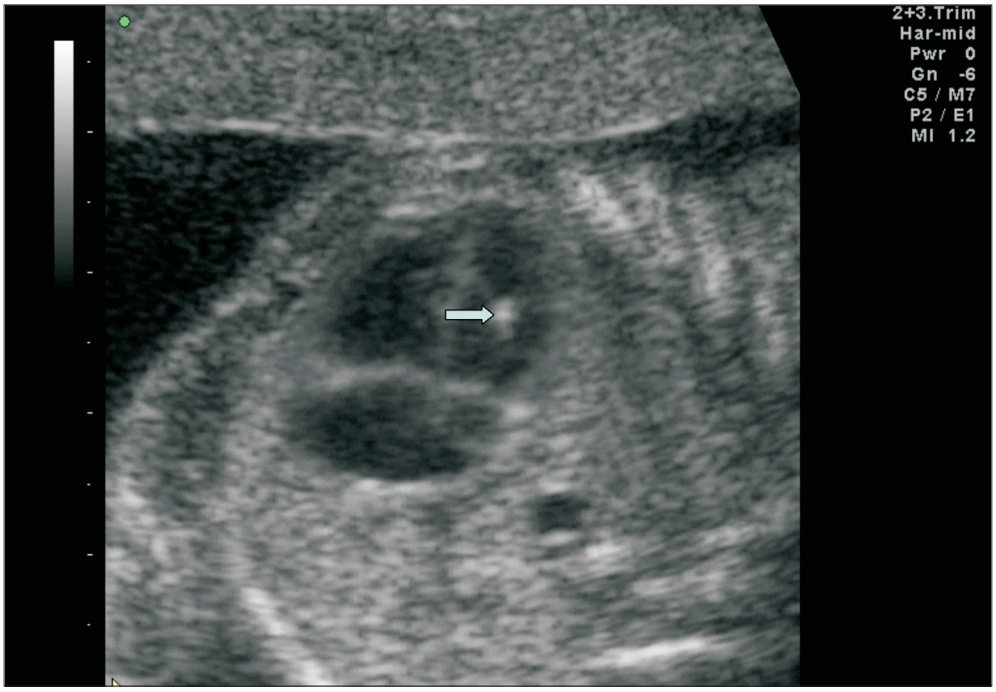
Association With Nonchromosomal Abnormalities

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.[2,17] 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.

Figure 1. Echogenic intracardiac focus in the left ventricle of the heart



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).

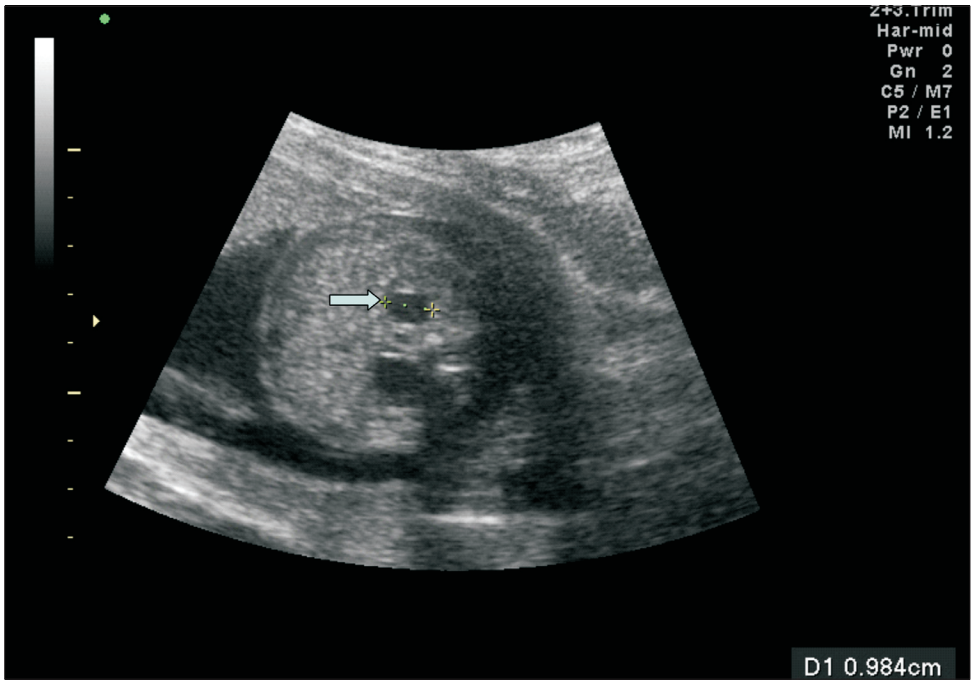
3. Women with an isolated EICF and a fetal aneuploidy risk greater than 1/600 by maternal age (31 years) or maternal serum screening should be offered counselling regarding fetal karyotyping (II-2 B).

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

1. Bromley B, Lieberman E, Laboda L, Benacerraf BR. Echogenic intracardiac focus: a sonographic sign for fetal Down syndrome. Obstet Gynecol 1995;86(6):998–1001.
2. Petrikovsky BM, Challenger M, Wyse LJ. Natural history of echogenic foci within ventricles of the fetal heart. Ultrasound Obstet Gynecol 1995;5(2):92–4.
3. Lim KI, Austin S, Wilson RD. Echogenic intracardiac foci: incidence laterality, and association with Down syndrome: a prospective study. J Ultrasound Med 1998;17(3):S11.
4. Manning JE, Ragavendra N, Sayre J, Laifer-Narin SL, Melany ML, Grant EG, et al. Significance of fetal intracardiac echogenic foci in relation to trisomy 21: a prospective sonographic study of high-risk pregnant women. AJR Am J Roentgenol 1998;170(4):1083–4.
5. Sohl BD, Scioscia AL, Budorick NE, Moore TR. Utility of minor ultrasonographic markers in the prediction of abnormal fetal karyotype at a prenatal diagnostic center. Am J Obstet Gynecol 1999;181(4):898–903.
6. Winter TC, Anderson AM, Cheng EY, Komarniski CA, Souter VL, Uhrich SB, et al. Echogenic intracardiac focus in 2nd-trimester fetuses with trisomy 21: usefulness as a US marker. Radiology 2000;216(2):450–6.
7. Wax JR, Mather J, Steinfeld JD, Ingardia CJ. Fetal intracardiac echogenic foci: current understanding and clinical significance. Obstet Gynecol Survey 2000;55(3):303–11.
8. Wax JR, Royer D, Mather J, Chen C, Aponte-Garcia A, Steinfeld JD, et al. A preliminary study of sonographic grading of fetal intracardiac foci: feasibility, reliability, and association with aneuploidy. Ultrasound Obstet Gynecol 2000;16(2):123–7.
9. Sepulveda W, Cullen S, Nicolaidis P, Hollingsworth J, Fisk NM. Echogenic foci in the fetal heart: a marker of aneuploidy. Br J Obstet Gynaecol 1995;102(6):490–2.
10. Bronshtein M, Jakobi P, Ofir C. Multiple fetal intracardiac echogenic foci: not always a benign sonographic finding. Prenat Diagn 1996;16(2):131–5.
11. Vibhakar NI, Budorick NE, Scioscia AL, Harby LD, Mullen ML, Sklansky MS. Prevalence of aneuploidy with a cardiac intraventricular echogenic focus in an at-risk patient population. J Ultrasound Med 1999;18(4):265–8.
12. Smith-Bindman R, Hosmer W, Feldstein VA, Deeks JJ, Goldberg JD. Second-trimester ultrasound to detect fetuses with Down syndrome–a meta-analysis. JAMA 2001;285(8):1044–55.
13. Anderson N, Jyoti R. Relationship of isolated fetal intracardiac echogenic focus to trisomy 21 at the mid-trimester sonogram in women younger than 35 years. Ultrasound Obstet Gynecol 2003;21:354–8.
14. Achiron R, Lipitz S, Gabbay U, Yagel S. Prenatal ultrasonographic diagnosis of fetal heart echogenic foci: no correlation with Down syndrome. Obstet Gynecol 1997;89:945–8.
15. Caughey AB, Lyell DJ, Filly RA, Washington AE, Norton ME. The impact of the use of the isolated echogenic intracardiac focus as a screen for Down syndrome in women under the age of 35 years. Am J Obstet Gynecol 2001;185:1021–7.
16. Bromley B, Lieberman E, Shipp TD, Benacerraf BR. The genetic sonogram: a method of risk assessment for Down syndrome in the second trimester. J Ultrasound Med 2002;21:1087–96.

Figure 2. Bilateral renal pyelectasis with anterior/posterior measurement



17. Nyberg DA, Souter VL, El-Bastawissi A, Young S, Luthhardt F, Luthy DA. Isolated sonographic markers for detection of fetal Down syndrome in the second trimester of pregnancy. J Ultrasound Med 2001;20:1053–63.

18. Petrikovsky B, Challenger M, Gross B. Unusual appearances of echogenic foci within the fetal heart: are they benign? Ultrasound Obstet Gynecol 1996;8:229–31.

19. Wax JR, Philput C. Fetal intracardiac echogenic foci: does it matter which ventricle? J Ultrasound Med 1998;17:141–4.

20. Bettelheim D, Deutinger J, Bernashek G. The value of echogenic foci ("golf balls") in the fetal heart as a marker of chromosomal abnormalities. Ultrasound Obstet Gynecol 1999;14:98–100.

21. Bromley B, Lieberman E, Shipp TD, Richardson M, Benacceraf BR. Significance of an echogenic intracardiac focus in fetuses at high and low risk for aneuploidy. J Ultrasound Med 1998;17:127–31.

22. Wolman I, Jaffa A, Geva E, Diamant S, Strauss S, Lessing JB, et al. Intracardiac echogenic focus: no apparent association with structural cardiac abnormality. Fetal Diagn Ther 2000;15(4):216–8.

23. Barsoom MJ, Feldman DM, Borgida AF, Esters D, Diana D, Egan JF. Is an isolated cardiac echogenic focus an indication for fetal echocardiography? J Ultrasound Med 2001;20(10):1043–6.

24. Homola J. Are echogenic foci in fetal heart ventricles insignificant findings? Ceska Gynekol 1997;62(5):280–2.

25. Degani S, Leibovitz Z, Shapiro I, Gonen R, Ohel G. Cardiac function in fetuses with intracardiac echogenic foci. Ultrasound Obstet Gynecol 2001;18(2):131–4.

26. Shipp TD, Bromley B, Lieberman E, Benacerraf BR. The frequency of the detection of fetal echogenic intracardiac foci with respect to maternal race. Ultrasound Obstet Gynecol 2000;15(6):460–2.

27. Van den Hof MC, Demianczuk NN. Contents of a complete ultrasound report. J Soc Obstet Gynaecol Can 2001;23(5):827–8.

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.[1–3] The measurement is taken on a transverse section through the fetal renal pelvis using the maximum anterior-to-posterior measurement.[4] 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.[5] It is an isolated finding in fetal Down syndrome in approximately 2%.[6] 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.[6] 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.[7] Renal pelvis measurements > 10 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.[8] 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 (II-2 A).

References

1. Arger PH, Coleman BH, Mintz MC, Snyder HP, Camardese T, Arensen RL, et al. Radiology 1985;156:485–9.
2. Langer B, Simeoni U, Montoya Y, Casanova R, Schlaeder G. Antenatal diagnosis of upper urinary tract dilation by ultrasonography. Fetal Diagn Ther 1996;11:191–8.
3. Wilson RD, Lynch S, Lessoway VA. Fetal pyelectasis: comparison of postnatal renal pathology with unilateral and bilateral pyelectasis. Prenat Diagn 1997;17:451–5.
4. Devore, GR. Trisomy 21: 91% detection rate using second-trimester ultrasound markers. Ultrasound Obstet Gynecol 2000;16:133–41.
5. Chudleigh PM, Chitty LS, Pembrey M, Campbell S. The association of aneuploidy and mild fetal pyelectasis in an unselected population: the result of a multicenter study. Ultrasound Obstet Gynecol 2001;17:197–202.
6. Smith-Bindman R, Hosmer W, Feldstein VA, Deeks JJ, Goldberg JD. Second-trimester ultrasound to detect fetuses with Down syndrome. A meta-analysis. JAMA 2001;285:1044–55.
7. Aviram R, Pomeran A, Sharony R, Beyth Y, Rathaus V, Tepper R. The increase of renal pelvis dilatation in the fetus and its significance. Ultrasound Obstet Gynecol 2000; 16:60–2.
8. Van den Hof MC, Demianczuk NN. Content of a complete obstetrical ultrasound report. J Soc Obstet Gynaecol Can 2001;23(5):427–8.

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.[1–3] 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,[1,7–9] as well as low birth weight.[2,3,5]

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).

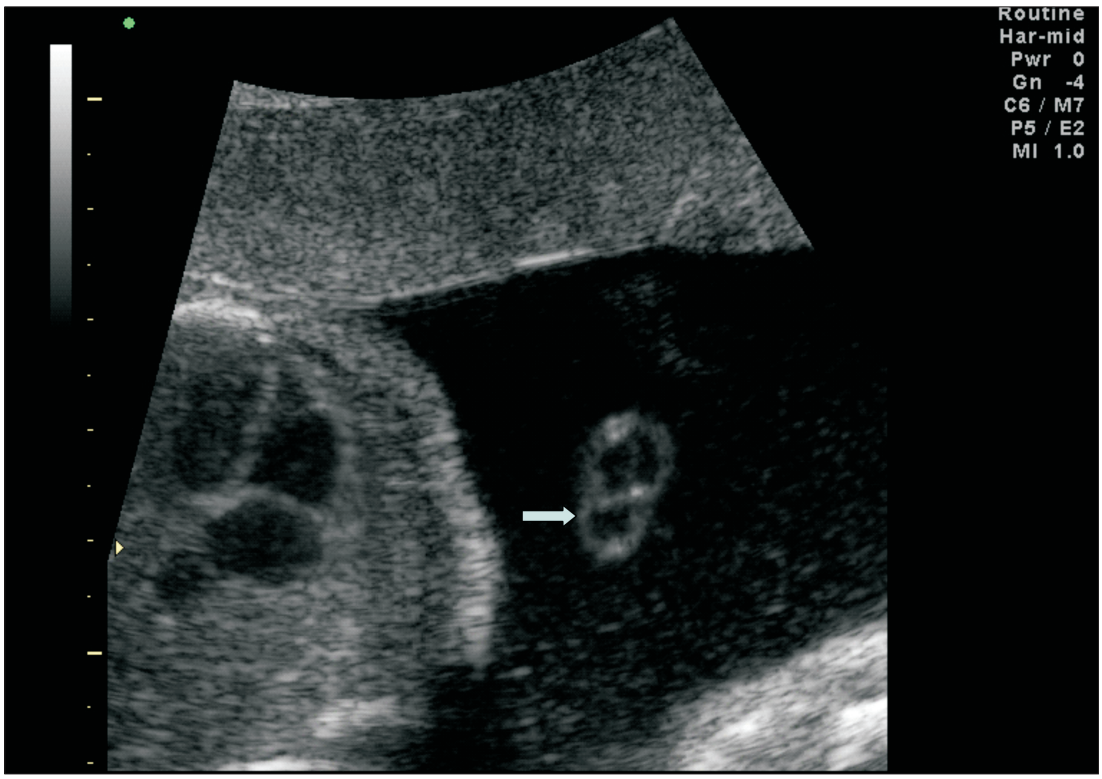
2. The finding of a single umbilical artery requires a more detailed review of fetal anatomy, including kidneys and heart (fetal echo) (II-2 B).

3. An isolated single umbilical artery does not warrant invasive testing for fetal aneuploidy (II-2 A).

References

1. Budorick NE, Kelly TE, Dunn JA, Scioscia AL. The single umbilical artery in a high-risk patient population. What should be offered? J Ultrasound Med 2001;20:619–27.
2. Farrell T, Leslie J, Owen P. Accuracy and significance of prenatal diagnosis of single umbilical artery. Ultrasound Obstet Gynecol 2000;16:667–8.
3. Geipel A, Germer U, Welp T, Schwinger E, Gembruch U. Prenatal diagnosis of single umbilical artery: determination of the absent side, associated

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



anomalies, Doppler findings and perinatal outcome. Ultrasound Obstet Gynecol 2000;15:114–7.

4. Pierce BT, Dance VD, Wagner RK, Apodaca CC, Nielsen PE, Calhoun BC. J Matern Fetal Med 2001;10:59–63.
5. Rinehart BK, Terrone DA, Taylor CW, Isler CM, Larmon JE, Roberts WE. Single umbilical artery is associated with an increased incidence of structural and chromosomal anomalies and growth restriction. Am J Perinatol 2000;17(5):229–32.
6. Murphy-Kaulbeck L, Van den Hof M. Single umbilical artery (SUA) and fetal aneuploidy. Ultrasound Obstet Gynecol 2002;20(Suppl1):67.
7. Abuhamad AZ, Shaffer W, Mari G, Copel J, Hobbins J, Evans A. Single umbilical artery: does it matter which artery is missing? Am J Obstet Gynecol 1995;173:728–32.
8. Persutte W, Hobbins J. Single umbilical artery: a clinical enigma in modern prenatal diagnosis. Ultrasound Obstet Gynecol 1995;6:216–29.
9. Van den Hof M, Murphy-Kaulbeck L. Single umbilical artery (SUA) and risk of congenital heart disease (CHD). Ultrasound Obstet Gynecol 2002;20(Suppl1):83.
10. Van den Hof MC, Demianczuk NN. Content of a complete obstetrical ultrasound report. J Soc Obstet Gynaecol Can 2001;23(5):427–8.

ECHOGENIC BOWEL (Figure 4)

Definition and Imaging Criteria

Echogenic bowel is defined as fetal bowel with homogenous areas of echogenicity that are equal to or greater than that of surrounding bone.[1] The echogenicity has been classified as either focal or multifocal.[2] There have been various techniques used to define echogenic bowel, partially because of concerns raised about intra- and interobserver variability.[3] 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.[3] Whenever echogenic bowel is suspected, the gain setting should be lowered to enable this comparison and to ensure that bowel hyperechogenicity is real.[3] This should help to minimize a false-positive diagnosis of hyperechogenicity.

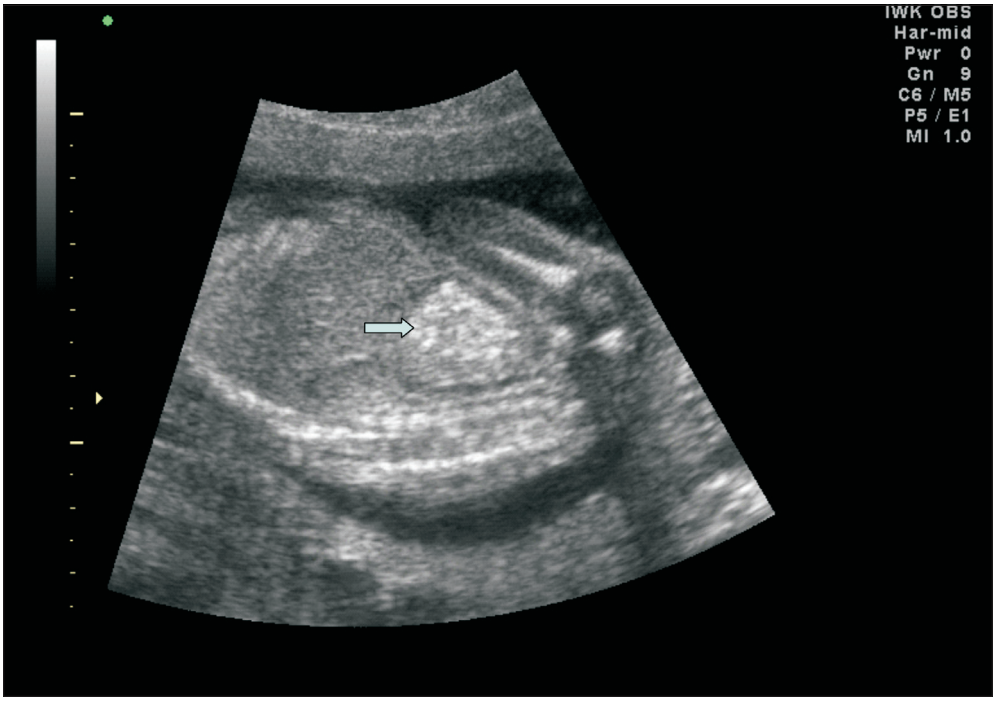
Association With Fetal Aneuploidy

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[2,4–9] and as an isolated finding in 9% of fetuses with aneuploidy (2.8% to 25%).[2–19] As a result, it has been suggested that the likelihood ratio for this marker is 6 (CI 2.7–6.8).[6]

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%).[3,10–13,18–21] The a priori risk will change if the

Figure 4. Fetal bowel that is as echogenic as surrounding bone



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

1. Sepulveda W, Sebire NJ. Fetal echogenic bowel: a complex scenario. Ultrasound Obstet Gynecol 2000;16:510–4.
2. Al-Kouatly HB, Chasen ST, Streltzoff J, Chervenak FA. The clinical significance of fetal echogenic bowel. Am J Obstet Gynecol 2001;185:1035–8.
3. Slotnick RN, Abuhamad AZ. Prognostic implications of fetal echogenic bowel. Lancet 1996;347:85–7.
4. Nyberg DA, Dubinsky T, Resta RG, Mahony BS, Hickock D, Luthy DA. Echogenic fetal bowel during the second trimester: clinical importance. Radiology 1993;188:527–31.
5. Bromley B, Doubilet P, Frigoletto F, Krauss C, Estroff J, Benacerraf B. Is fetal hyperechoic bowel on second trimester sonogram an indication for amniocentesis? Obstet Gyneacol 1994;83:647–51.
6. Hill LM, Fries J, Hecker J, Grzybek P. Second trimester echogenic small bowel: an increased risk of adverse perinatal outcome. Prenat Diagn 1994;14:845–50.
7. Shohl BD, Scioscia AL, Budorick NE, Moore TR. Utility of minor ultrasonographic markers in the prediction of abnormal fetal karyotype at a prenatal diagnostic center. Am J Obstet Gynecol 1999;181:898–903.
8. Nyberg DA, Souter VL, Bastawissi AE, Young S, Luthhardt F, Luthy D. Isolated sonographic markers for detection of fetal down syndrome in the second trimester of pregnancy. J Ultrasound Med 2001;20:1053–63.
9. Bromley B, Lieberman E, Shipp TD, Benacerraf BR. The genetic sonogram. A method of risk assessment for down syndrome in the second trimester. J Ultrasound Med 2002;21:1087–96.
10. Dicke JM, Crane JP. Sonographically detected hyperechoic fetal bowel: significance and implications for pregnancy management. Obstet Gynecol 1992;80:778–82.
11. Muller F, Dommergues M, Aubry MC, Simon-Bouy B, Gautier E, Oury JF, et al. Hyperechogenic fetal bowel: an ultrasonographic marker for adverse fetal and neonatal outcome. Am J Obstet Gynecol 1995;173:508–13.
12. Yaron Y, Hassan S, Geva E, Kupferminc MJ, Yavetz H, Evans MI. Evaluation of fetal echogenic bowel in the second trimester. Fetal Diagn Ther 1999;14:176–80.
13. Ghose I, Mason GC, Martinez D, Harrison KL, Evans JA, Ferriman EL, et al. Hyperechogenic fetal bowel: a prospective analysis of sixty consecutive cases. Br J Obstet Gynaecol 2000;107:426–9.
14. Stocker AM, Snijders RJ, Carlson DE, Greene N, Gregory KD, Walla CA, et al. Fetal echogenic bowel: parameters to be considered in differential diagnosis. Ultrasound Obstet Gynecol 2000;16:519–23.
15. Rotmensch S, Liberati M, Bronshtein M, Schoenfeld-Dimaio M, Shalev J, Ben-Rafael Z, et al. Pernatal sonographic findings in 187 fetuses with down syndrome. Prenat Diagn 1997;17:1001–9.
16. Smith-Bindman R, Hosmer W, Feldstein VA, Deeks JJ, Goldberg JD. Second-trimester ultrasound to detect fetuses with down syndrome: a meta-analysis. JAMA 2001;285:1044–55.
17. Shipp TD, Benacerraf BR. Second-trimester ultrasound screening for aneuploidy. Prenat Diagn 2002;22:296–307.
18. Kesrouani AK, Guibourdenche J, Muller F, Denamur E, Vuillard E, Garel C, et al. Etiology and outcome of fetal echogenic bowel. Fetal Diagn Ther 2003;18:240–6.
19. Simon-Bouy B, Satre V, Ferec C, Malinge MC, Girodon E, Denamur E, et al. Management of prenatally diagnosed hyperechogenic bowel. Am J Med Genet 121A:209,2003.
20. Sepulveda W, Leung KY, Robertson ME, Kay E, Mayall ES, Fisk NM. Prevalence of cystic fibrosis mutations in pregnancies with fetal echogenic bowel. Obstet Gynecol 1996;87:103–6.
21. Berlin BM, Norton ME, Sugarman EA, Tsipis JE, Allitto BA. Cystic fibrosis and chromosome abnormalities associated with echogenic fetal bowel. Obstet Gynecol 1999;94:135–8.
22. Sepulveda W, Reid R, Nicolaidis P, Prendiville On, Chapman RS, Fisk N. Second trimester echogenic bowel and intraamniotic bleeding: association between fetal bowel echogenicity and amniotic fluid spectrophotometry at 410 nm. Am J Obstet Gynecol 1996;174:839–42.
23. Sepulveda W. Harris Birthright Research Center, King's College Hospital School London. Fetal echogenic bowel. Lancet 1996;(34):1043.
24. Petrikovsky B, Smith-Levitin M, Hosten N. Intra-amniotic bleeding and fetal echogenic bowel. Obstet Gynecol 1999;93:684–6.
25. Phelps S, Fisher R, Partington A, Dykes E. Prenatal ultrasound diagnosis of gastrointestinal malformations. J Ped Surgery 1997;32:438–40.
26. Font GE, Solari M. Prenatal diagnosis of bowel obstruction initially manifested as isolated hyperechoic bowel. J Ultrasound Med 1998;17:721–3.
27. Shyu MK, Shih JC, Lee CN, Hwa HL, Chow SN, Hsieh FJ. Correlation of prenatal ultrasound and postnatal outcome in meconium peritonitis. Fetal Diagn Ther 2003;18:255–61.
28. Achiron R, Mazkereth R, Orvieto R, Kuint J, Lipitz S, Rotstein Z. Echogenic bowel in intrauterine growth restriction fetuses: does this jeopardize the gut. Am Obstet Gynecol 2002;100:120–5.
29. Van den Hof MC, Demianczuk NN. Contents of a complete ultrasound report. J Soc Obstet Gynaecol Can 2001;23(5):827–8.

THICKENED NUCHAL FOLD (Figure 5)

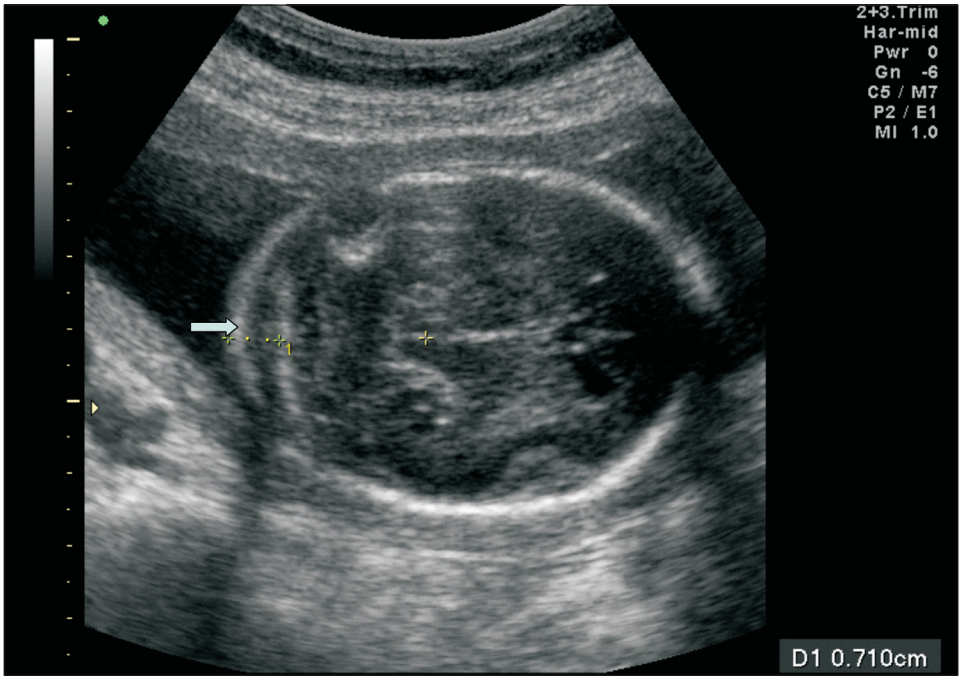
Definition and Imaging Criteria

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.[1] The definition of a thickened nuchal fold has varied,[1,2] although many researchers and centres now use gestational-age specific criteria.[3,4] 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.[1–5] 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).[6]

Figure 5. Increased nuchal fold



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.[7,8] Thickened nuchal fold has also been associated with congenital cardiac defects.[7,9,10]

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%.[11]

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.[12]

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

1. Benacerraf BR, Frigoletto FD. Soft tissue nuchal fold in the second trimester fetus: standards for normal measurements compared with those with Down syndrome. Am J Obstet Gynecol 1987;157(5):1146–9.

2. Nyberg DA, Souter VL, El-Bastawissi A, Young S, Luthhardt F, Luthy DA. Isolated sonographic markers for detection of fetal Down syndrome in the second trimester of pregnancy. J Ultrasound Med 2001;20:1053–63.

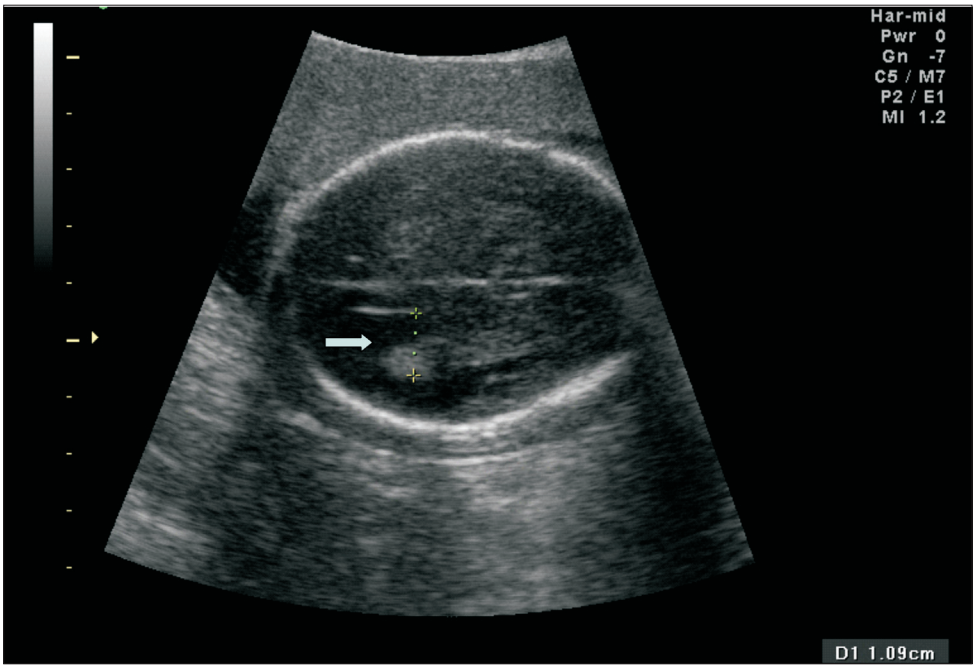
3. Locatelli A, Piccoli MG, Vergani P, Mariani E, Ghidini A, Mariana S, et al. Critical appraisal of the use of nuchal fold thickness measurements for the prediction of Down syndrome. Am J Obstet Gynecol 2000;82(1)192–8.

4. Bahado-Singh RO, Oz UA, Kovanci E, Deren O, Feather M, Hsu CD, et al. Gestational age standardized nuchal thickness values for estimating mid-trimester Down syndrome risk. J Matern Fetal Med 1999;8(2):37–43.

5. Gray DL, Crane JP. Optimal nuchal skin-fold thresholds based on gestational age for prenatal detection of Down syndrome. Am J Obstet Gynecol 1994;171:1282–6.

6. Smith-Blindman R, Hosmer W, Feldstein VA, Deeks JJ, Goldberg JD. Second trimester ultrasound to detect fetuses with Down syndrome: a meta-analysis. JAMA 2001;285(8):1044–55.

Figure 6. Slightly enlarged posterior horn of the lateral ventricle



7. Souter VL, Nyberg DA, El-Bastawissi A, Zebelman A, Luthhardt F, Luthy DA. Correlation of ultrasound findings and biochemical markers in the second trimester of pregnancy in fetuses with trisomy 21. Prenat Diagn 2002;22(3):175–82.

8. Shipp TD, Benacerraf BR. Second trimester ultrasound screening for aneuploidy. Prenat Diagn 2002;22:296–307.

9. DeVore GR, Alfi O. The association between an abnormal nuchal skin fold, trisomy 21, and ultrasound abnormalities identified during the second trimester of pregnancy. Ultrasound Obstet Gynecol 1993;3:387–94.

10. Dahlgren LS, Sandor GS, Lim KI. Is the nuchal index increased in fetuses with congenital structural heart defects? Am J Obs Gynecol 2002;(Suppl 187);(6):5191.

11. Lim KI, Pugash D, Dansereau J, Wilson RD. Nuchal index: a gestational age independent ultrasound marker for the detection of Down syndrome. Prenat Diagn 2002;22(13):1233–7.

12. Baumann C, Delagarde R, Vuillard E, Oury JF. Pregnancy outcome and infant follow-up after diagnosis of nuchal anomalies at the 1st or 2nd trimester ultrasound examination. J Gynecol Obstet Biol Reprod 2001;(30 Suppl 1):68–74.

MILD VENTRICULOMEGALY (Figure 6)

Definition and Imaging Criteria

Cerebral ventriculomegaly is defined by atrial measurements ≥ 10 mm. Mean atrial measurements are 7.6 mm, standard deviation (SD) 0.6 mm. Mild ventriculomegaly (MVM) is defined as measurements ≥ 10 to ≤ 15 mm.[1] 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%).[2] Idiopathic lateral ventriculomegaly is found in approximately 0.15% of chromosomally-normal fetuses,[3] whereas 1.4% of trisomy 21 fetuses in the second trimester have idiopathic ventriculomegaly.[4] 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.[5] Ventriculomegaly can arise from agenesis of the corpus callosum, cerebral maldevelopment or destruction, vascular anomalies, or an obstruction within the ventricular system.[6] Children with a prenatal diagnosis of MVM have abnormal neurodevelopment in 10% to 36% of cases dependent on associated anomalies, etiology,[7,8] and ventricular measurement. In combined case series, mortality is reported at 3.7%.[2] When MVM resolves, abnormal outcome has been reported but is infrequent (< 10%).[9,10] Unilateral MVM also carries a favourable prognosis when isolated.[11,12] 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.[13,14]

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.[15] 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

1. Cardoza JD, Goldstein RB, Filly RA. Exclusion of fetal ventriculomegaly with a single measurement: the width of the lateral ventricular atrium. Radiology 1988;169:711–4.
2. Pilu G, Falco P, Gabrielli S, Perolo A, Sandri F, Bovicelli L. The clinical significance of fetal isolated cerebral borderline ventriculomegaly: report of 31 cases and review of the literature. Ultrasound Obstet Gynecol 1999;14:320–6.
3. Achiron R, Schimmel M, Achiron A, Mashiach S. Fetal mild idiopathic lateral ventriculomegaly: is there a correlation with fetal trisomy? Ultrasound Obstet Gynecol 1993;3:89–92.
4. Nyberg DA, Resta RG, Luthy DA, Hickox DE, Mahony BS, Hirsch JH. Prenatal sonographic findings in Down syndrome. Review of 94 cases. Obstet Gynecol 1990;76:370–7.
5. Filly RA, Cardoza JD, Goldstein RB, Barkovich AJ. Detection of fetal central nervous system anomalies: a practical level of effort for a routine sonogram. Radiology 1989;172:403–8.
6. Tsao PN, Teng RJ, Wu TJ, Yau KIT, Wang PJ. Nonprogressive congenital unilateral ventriculomegaly. Pediatr Neur 1996;14:66–8.
7. Nicolaides KH, Berry S, Snijders RJ, Thorpe-Beeston JG, Gosden C. Fetal lateral cerebral ventriculomegaly: associated malformations and chromosomal defects. Fetal Diagn Ther 1990;5(1):5–14.
8. Tomlinson MW, Treadwell MC, Bottoms SF. Isolated mild ventriculomegaly: associated karyotypic abnormalities and in utero observations. J Matern Fetal Med 1997;6:241–4.
9. Signorelli M, Tiberti A, Valseriati D, Molin E, Cerri V, Grali C, et al. Width of the fetal lateral ventricular atrium between 10 and 12 mm: a simple variation of the norm? Ultrasound Obstet Gynecol 2004;23:14–8.
10. Patel HD, Filly AL, Hersh DR, Goldstein RB. Isolated mild fetal cerebral ventriculomegaly: clinical course and outcome. Radiology 1994;192:759–64.
11. Lipitz S, Yagel S, Malinger G, Meizner I, Zalel Y, Achiron R. Outcome of fetuses with isolated borderline unilateral ventriculomegaly diagnosed at mid-gestation. Ultrasound Obstet Gynecol 1998;12(1):23–6.
12. Senat MV, Bernard JP, Schwarzler P, Britten J, Ville Y. Prenatal diagnosis and follow-up of 14 cases of unilateral ventriculomegaly. Ultrasound Obstet Gynecol 1999;14(5):327–32.
13. Levine D, Barnes PD, Madsen JR, Abbott J, Mehta T, Edelman RR. Central nervous system abnormalities assessed with prenatal magnetic resonance imaging. Obstet Gynecol 1999;94(6):1011–9.
14. Launay S, Robet Y, Valat AS, Thomas D, Devisme L, Rocourt N, et al. Cerebral fetal MRI and ventriculomegaly. J Radiol 2002;83(6 pt 1):723–30.
15. Van den Hof, MC, Deminaczuk NN. Content of a complete obstetrical ultrasound report. J Soc Obstet Gynaecol Can 2001;23(5):427–8.

CHOROID 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.[1] 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.[2] 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.[3–10] The incidence of CPCs is 50% in fetuses with trisomy 18[5,11,12]; however, only 10% of fetuses with trisomy 18 will have CPCs as the only identifiable sonographic marker on ultrasound screening.[3,4,6–9,12–16] The likelihood ratio for trisomy 18 when an isolated CPC is identified is 7 (95% CI 4–12).[9] The number of cysts and the cysts' distribution or size does not change the risk.[2] 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.[17,18]

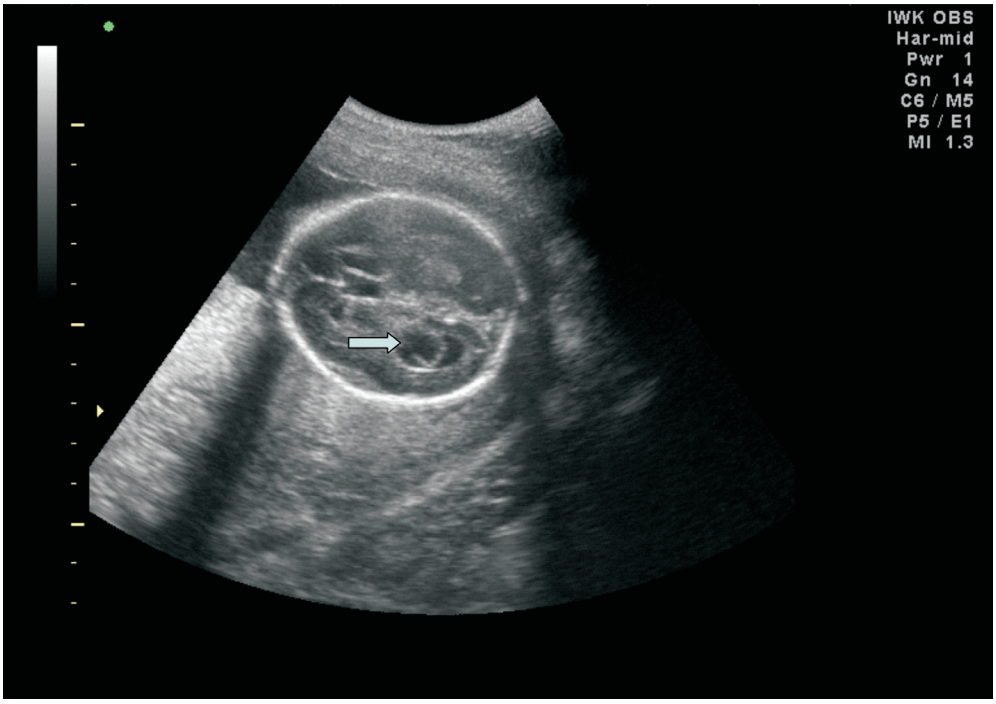
Association With Nonchromosomal Abnormalities

The presence of CPCs in chromosomally normal fetuses is not associated with other fetal abnormalities or abnormal postnatal development.[15]

Summary

Evaluation of the fetal cranium, including the ventricles and choroid plexus, is considered part of the routine screening

Figure 7. Choroid plexus cyst



ultrasound at 16 to 20 weeks' gestation.[19] 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.[2] 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.[2,20]

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

1. Chitty LS, Chudleigh RP, Wright E, Campbell S, Pembrey M. The significant of choroid plexus cysts in an unselected population: results of a multicenter study. Ultrasound Obstet Gynecol 1998;12(6):391–7.

2. Gratton RJ, Hogge WA, Aston CE. Choroid plexus cysts and trisomy 18: risk of modification based on maternal age and multiple-marker screening. Am J Obstet Gynecol 1996;175(6):1493–7.

3. Walkinshaw S, Pilling D, Spriggs A. Isolated choroid plexus cysts – the need for routine offer of karyotyping. Prenat Diagn 1994;14(8):663–7.

4. Kupferminc MJ, Tamura RK, Sabbagha RE, Parilla BV, Cohen LS, Pergament E. Isolated choroid plexus cyst(s): an indication for amniocentesis. Am J Obstet Gynecol 1994;171(4):1068–71.

5. Gray DL, Winborn RC, Suessen TL, Crane JP. Is genetic amniocentesis warranted when isolated choroid plexus cysts are found? Prenat Diagn 1996;16(11):983–90.

6. Reinsch RC. Choroid plexus cysts – association with trisomy: prospective review of 16,059 patients. Am J Obstet Gynecol 1997;176(6):1381–3.

7. Geary M, Patel S, Lamont R. Isolated choroid plexus cysts and association with fetal aneuploidy in an unselected population. Ultrasound Obstet Gynecol 1997;10(3):171–3.

8. Sohn C, Gast AS, Krapfl E. Isolated fetal choroid plexus cysts: not an indication for genetics diagnosis? Fetal Diagn Ther 1997;12(5):255–9.

9. Ghidini A, Strobelt N, Locatelli A, Mariani E, Piccoli MG, Vergani P. Isolated fetal choroid plexus cysts: role of ultrasonography in establishment of the risk of trisomy 18. Am J Obstet Gynecol 2000;182(4):972–7.

10. Snijders RJ, Shawa L, Nicholaides KH. Fetal choroid plexus cysts and trisomy 18: assessment of risk based on ultrasound findings and maternal age. Prenat Diagn 1994;14(12):1119–27.

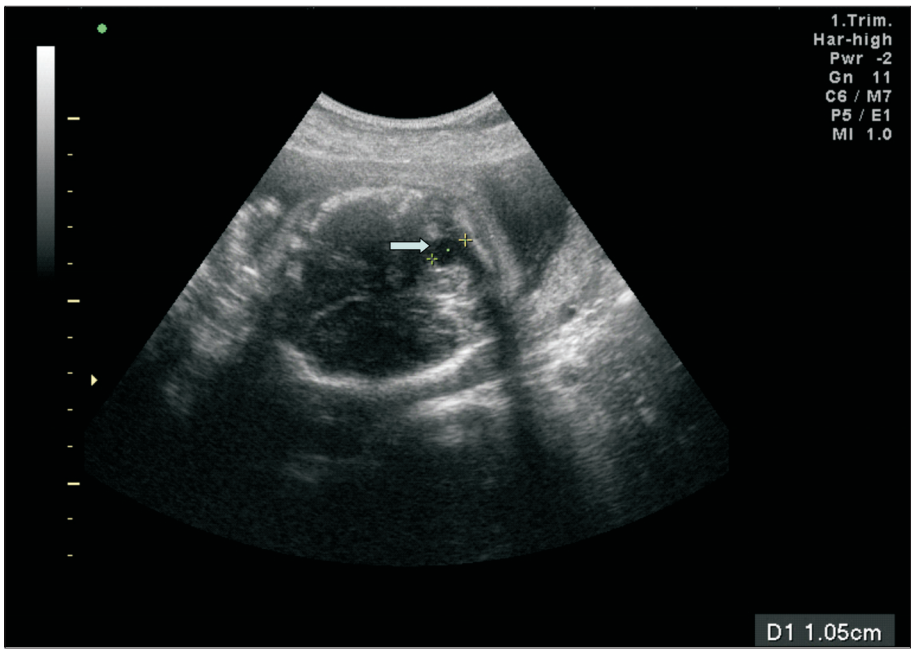
11. Denis E, Dufour P, Valat AS, Vaast P, Subtil D, Bourgeot P, et al. Choroid plexus cysts and risk of chromosome anomalies. Review of the literature and proposed management. J Gynecol Obstet Biol Reprod 1998;27(2):144–9.

12. Gonen R, Kar H, Degani S. The karyotype of fetuses with anomalies detected by second trimester ultrasonography. Europ J Obstet Gynecol Reprod Biol 1995;58(2):153–5.

13. Maieron A, Rustico M, Pecile V, Natale R, D'Ottavio G, Fischer Tamaro L, et al. The indications of the management of fetuses with choroid plexus cysts. Minerva Ginecol 1996;48(4):125–33.

14. Digiovanni LM, Quinlan MP, Verp MS. Choroid plexus cysts: infant and early childhood development outcome. Obstet Gynecol 1997;90(2):191–4.

Figure 8. Enlarged cisterna magna



15. Morcos CL, Platt LD, Carlson DE, Gregory KD, Greene NH, Korst LM. The isolated choroid plexus cyst. Obstet Gynecol 1998;92(2):232–6.

16. Sullivan A, Giudice T, Vavelidis F, Thiagaraja S. Choroid plexus cysts: is biochemical testing a valuable adjunct to targeted ultrasonography? Am J Obstet Gynecol 1999;181(2):260–5.

17. Yoder PR, Sabbagha RE, Gross SJ, Zelop CM. The second-trimester fetus with isolated choroid plexus cysts: a meta-analysis of risk of trisomies 18 and 21. Obstet Gynecol 1999;93:869–72.

18. Bromley B, Lieberman R, Benacerraf BR. Choroid plexus cysts: not associated with Down syndrome. Ultrasound Obstet Gynecol 1996;8(4):232–5.

19. Van den Hof MC, Demianczuk NN. Content of a complete obstetrical ultrasound report. J Soc Obstet Gynaecol Can 2001;23(5):427–8.

20. Demasio K, Canterino J, Ananth C, Fernandez C, Smulian J, Vintzileos A. Isolated choroid plexus cyst in low-risk women less than 35 years old. Am J Obstet Gynecol 2002;187:1246–9.

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 vemis of the cerebellum to the inner surface of the cranium. An enlarged cisternal magna is defined by an anterior/posterior diameter ≥ 10 mm.[1,2] The measurement will be falsely exaggerated by a steep scan angle through the posterior fossa or dolichocephaly.[3,4]

Association With Fetal Aneuploidy

An enlarged cisterna magna has been described in association with fetal aneuploidy, particularly trisomy 18.[5–7] The association with aneuploidy appears to be strongest in the absence of ventricular dilatation but in the presence of other anomalies.[4–6] Isolated enlarged cisterna magna does not appear to be strongly associated with aneuploidy.[2] 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)[8–10] and syndromic (oro-facial–digital syndrome, Meckel-Gruber syndrome, and DiGeorge syndrome)[4] abnormalities.

Summary

Review of the fetal cerebellum and cisterna magna is a routine part of the screening ultrasound at 16 to 20 weeks' gestation.[11,12] 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.[3] 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

1. Comstock C, Boal D. Enlarged fetal cisterna magna: appearance and significance. Obstet Gynecol 1985;66:25S.
2. Haimovici J, Doubilet P, Benson C, Frates MC. Clinical significance of isolated enlargement of the cisterna magna (>10mm) on prenatal sonography. J Ultrasound Med 1997;16:731–4.
3. Mahoney B, Callen P, Filly R, Hoddick W. The fetal cisterna magna. Radiology 1984;153:773.
4. Nyberg D, Mahony B, Hegge F, Hickok D, Luthy D, Kapur R. Enlarged cisterna magna and the Dandy-Walker malformation: factors associated with aneuploidy. Obstet Gynecol 1991;77:436.
5. Laing FC, Frates MC, Brown DL,Bensen CB, Di Salvo D, Doubilet P. Sonography of the fetal cisterna magna: false appearance of mega-cisterna magna and Dandy-Walker variant. Radiology 1994;192:274.
6. Chen CP, Hung TH, Jan SW, Jeng CJ. Enlarged cisterna magna in the third trimester as a clue to fetal trisomy 18. Fetal Diagn Ther 1998;13:29–34.
7. Nyberg DA, Kramer D, Resta RG, Kapur R, Mahony BS, Luthy DA, et al. Prenatal sonographic findings of trisomy 18: review of 47 cases. J Ultrasound Med 1993;2:103–13.
8. Ecker JL, Shipp TD, Bromley B, Benacerraf B. The sonographic diagnosis of Dandy-Walker and Dandy-Walker variant: associated findings and outcomes. Prenat Diagn 2000;20:328–32.
9. Aletebi FA, Fung Kee Fung K. Neurodevelopmental outcome after antenatal diagnosis of posterior fossa abnormalities. J Ultrasound Med 1999;18:683–9.
10. Ulm MR, Ulm J, Bernaschek G. Dandy-Walker malformation diagnosed before 21 weeks of gestation: associated malformations and aneuploidy. Ultrasound Obstet Gynecol 1997;10:167–70.
11. Van den Hof MC, Demianczuk NN. Contents of a complete ultrasound report. J Soc Obstet Gynaecol Can 2001;23(5):827–8.
12. Society of Obstetricians and Gynaecologists of Canada. Guidelines for Performance of ultrasound. J Soc Obstet Gynaecol Can 1995;17:263–6.

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.[1] 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.[2]

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).[3]

Association With Nonchromosomal Abnormalities

Short femur length can also be associated with skeletal dysplasias or fetal growth restriction.[4]

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.[1] 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).[3]

Association With Nonchromosomal Abnormalities

Short humeral length can also be associated with skeletal dysplasias or fetal growth restriction.[4] 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.[5]

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

1. Nyberg DA, Resta RG, Luthy MA, Hickok DE, Williams MA. Humerus and femur length shortening in the detection of Down syndrome. Am J Obstet Gynecol 1993;168:534–8.
2. Shipp TD, Bromley B, Mascola M, Benacerraf B. Variation in fetal femur length with respect to maternal race. J Ultrasound Med 2001;20:141–4.
3. Smith-Bindman R, Hosmer W, Feldstein VA, Deeks JJ, Goldberg JD. Second-trimester ultrasound to detect fetuses with Down syndrome. JAMA 2001;285:1044–55.
4. Pilu G, Nicolaides KH. Diagnosis of fetal abnormalities: the 18-23-week scan. London: The Parthenon Publishing Group Inc; 1999.
5. Bahado-Singh RO, Oz AU, Kovanci E, Deren O, Copel J, Baumgarten A, et al. New Down syndrome screening algorithm: ultrasonographic biometry and multiple serum markers combined with maternal age. Am J Obstet Gynecol 1998;179:1627–31.

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 Caucasians and 0.27 for African Caribbeans.[7] 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

1. Down LJ. Observations on an ethnic classification of idiots. Clinical Lectures and Reports, London Hospital 1866;3:259–62.
2. Cicero S, Curcio P, Papageorghiou A, Sonek J, Nicolaides K. Absence of nasal bone in fetuses with trisomy 21 at 11-14 weeks of gestation: an observational study. Lancet 2001;358:1665–7.
3. Sonek JD. Nasal bone evaluation with ultrasonography: a marker for fetal aneuploidy. Ultrasound Obstet Gynecol 2003;22:11–5.
4. Minderer S, Gloning KP, Henrich W, Stoger H. The nasal bone in fetuses with trisomy 21: sonographic versus pathomorphological findings. Ultrasound Obstet Gynecol 2003;22:16–21.

5. Vintzileos A, Walters C, Yeo L. Absent nasal bone in the prenatal detection of fetuses with trisomy 21 in a high-risk population. Obstet Gynecol 2003;101(5 Part l):905–8.

6. Bromley B, Lieberman E, Shipp T, Benacerraf B. Fetal nasal bone length: a marker for Down syndrome in the second trimester. J Ultrasound Med 2002;21:1387–94.

7. Cicero S, Sonek J, McKenna D, Croom C, Johnson L, Nicolaides K. Nasal bone hypoplasia in fetuses with trisomy 21. Ultrasound Obstet Gynecol 2003;21:15–8.

8. Van den Hof MC, Demianczuk NN. Content of a complete obstetrical ultrasound report. J Soc Obstet Gynaecol Can 2001;23(5):427–8.

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.

Summary

Evaluation of the fetal fingers is not an established part of the screening obstetric ultrasound at 16 to 20 weeks' gestation. The risk for fetal aneuploidy in the presence of isolated clinodactyly has been estimated to increase by 5.5, and although this finding is considered a significant soft marker, it has not been confirmed with prospective studies. In the event that clinodactyly is seen, it is important to initiate timely referral for consultation, validation, and possibly further investigations. Tertiary centres may use evaluation for clinodactyly as part of their review for patients at increased risk for aneuploidy.

Recommendations

1. Imaging of the outstretched hand to evaluate for fifth finger clinodactyly is not an expectation during the 16- to 20-week ultrasound (III-C).

2. Fifth finger clinodactyly is associated with trisomy 21 and should be considered for research or tertiary-level evaluation (III-B).

References

1. Benacerraf BR, Osathanondh R, Frigoletto FD. Sonographic demonstration of hypoplasia of the middle phalanx of the fifth digit: a finding associated with Down syndrome. Am J Obstet Gynecol 1988;159:181–4.

2. Hall B. Mongolism in newborn infants. Clin Pediatr 1966;5:4.

3. Vintzileos AM, Campbell WA, Guzman ER, Smulian JC, McLean DA, Ananth CV. Second-trimester ultrasound markers for detection of trisomy 21: which markers are best? Obstet Gynecol 1997;89:941–4.

4. Deren O, Mahoney MJ, Copel JA, Bahado-Singh RO. Subtle ultrasonographic anomalies: do they improve the Down syndrome detection rate? Am J Obstet Gynecol 1998;178:441–5.

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.[3–8] Other calculations of frontal lobe hypoplasia have shown some screening potential in retrospective studies;[9–11] 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 18[12] 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"[12] or "lemon"[13] shapes, are associated with fetal pathology and should prompt appropriate referral.

References

1. Golden JA, Hyman BT. Development of the superior temporal neocortex is anomalous in trisomy 21. J Neuropath Experiment Neurol1994;53(5):513–20.
2. Schmidt-Sidor B, Wisniewski KE, Shepart TH, Sersen EA. Brain growth in Down syndrome subjects 15 to 22 weeks of gestational age and birth to 60 months. Clin Neuropathol 1990;9(4):181–90.
3. Borrell A, Costa D, Martinez JM, Puerto B, Carrio A, Ojuel J, Fortuny A. Brachycephaly is ineffective for detection of Down syndrome in early midtrimester fetuses. Early Human Dev 1997;47:57–61.
4. Lockwood C, Benacerraf B, Krinsky A, Blakemore K, Belanger K, Mahoney M, Hobbins J. A sonographic screening method for Down syndrome. Am J Obstet Gynecol 1987;157(4 Pt 1):803–8.
5. Shah YG, Eckl CJ, Stinson SK, Woods JR. Biparietal diameter/femur length ratio, cephalic index, and femur length measurements: not reliable screening techniques for Down syndrome. Obstet Gynecol 1990;75:186.
6. Perry TB, Benzie RJ, Cassar N, Hamilton EF, Stocker J, Toftager-Larse K, Lippman A. Fetal cephalometry by ultrasound as a screening procedure for the prenatal detection of Down syndrome. Br J Obstet Gynaecol 1984;91(2):138–43.
7. Rosati P, Guariglia L. Early transvaginal measurement of cephalic index for the detection of Down syndrome fetuses. Fetal Diagn Ther 1999;14:38–40.
8. Buttery B. Occipitofrontal-biparietal diameter ratio. An ultrasonic parameter for the antental evaluation of Down syndrome. Med J Aust 1979;2(12):662–4.
9. Bahado-Singh RO, Wyse L, Dorr MA, Copel JA, O'Connor T, Hobbins JC. Fetuses with Down syndrome have disproportionately shortened frontal lobe dimensions on ultrasonographic examination. Am J Obstet Gynecol 1992;167:1009–14.
10. Winter TC, Reichman JA, Luna JA, Cheng EY, Doll AM, Komarniski CA, et al. Frontal lobe shortening in second-trimester fetuses with trisomy 21: usefulness as an US marker. Radiology 1998;207(1):215–22.
11. Winter TC, Ostrovksy AA, Komarniski CA, Uhrich SB. Cerebellar and frontal lobe hypoplasia in fetuses with trisomy 21: usefulness as combined US markers. Radiology 2000;214(2):533–8.
12. Nicolaides KH, Salvesen DR, Snijders RJ, Gosden CM. Strawberry-shaped skull in fetal trisomy 18. Fetal Diagn Ther 1992;7(2):132–7.
13. Van den Hof MC, Nicolaides KH, Campbell J, Campbell S. Evaluation of the lemon and banana signs in one hundred thirty fetuses with open spina bifida. Am J Obstet Gynecol 1990;162(2):322–7.

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.[2,4–8,9] 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

An 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

1. Kliewer MA, Hertzberg BS, Freed KS, DeLong DM, Kay HH, Jordan SG, et al. Dysmorphologic features of the fetal pelvis in Down syndrome: prenatal sonographic depiction and diagnostic implications of the iliac angle. Radiology 1996;201(3):681–4.
2. Bork MD, Egan JFX, Cusick W, Borgida AF, Campbell WA, Rodis JF. Iliac wing angle as a marker for trisomy 21 in the second trimester. Obstet Gynecol 1997(Part 1); 89(5):735–7.
3. Shipp TD, Bromley B, Lieberman E, Benacerraf BR. The iliac angle as a sonographic marker for Down syndrome in second-trimester fetuses. Obstet Gynecol 1997;89(3):446–50.
4. Shipp TD, Bromley B, Lieberman E, Benacerraf BR. The second-trimester fetal iliac angle as a sign of Down syndrome. Ultrasound Obstet Gynecol 1998;12(1):15–8.
5. Zook PD, Winter TC, Nyberg DA. Iliac angle as a marker for Down syndrome in second-trimester fetuses: CT measurement. Radiology 1999;211(2):447–51.
6. Freed KS, Kliewer MA, Hertzberg BS, DeLong DM, Paulson EK, Nelson RC. Pelvic CT morphometry in Down syndrome: implications for prenatal US evaluation–preliminary results. Radiology 2000;214(1):205–8.
7. Grange G, Thoury A, Dupont J-M, Pannier E, LeRhun F, Souchet M, et al. Sonographic measurement of the fetal iliac angle cannot be used alone as a marker for trisomy 21. Fetal Diagn Ther 2000;15:41–5.
8. Lee W, Blanckaert K, Bronsteen RA, Huang R, Romero R. Fetal iliac angle measurements by three-dimensional sonography. Ultrasound Obset Gynecol 2001;18:150–4.
9. Massez A, Rypens F, Metens T, Donner C, Avni FE. The iliac angle: a sonographic marker of trisomy 21 during midtrimester: dependency of fetal lying? Eur Radiol 2003; 13:2075–81.

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

1. Aase JM, Wilson AC, Smith DW. Small ear in Down's syndrome: a helpful diagnostic aid. J Pediatr 1973;82:845–7.
2. Birnholz JC, Farrell EE. Fetal ear length. Pediatrics 1988;81:555–8.
3. Shimizu T, Salvador L, Allanson J, Hughes-Benzie R, Nimrod C. Ultrasonographic measurements of fetal ear. Obstet Gynecol 1992;80:381–4.
4. Chitkara U, Lee L, El-Sayed Y, Holbrook RH, Bloch DA, Oehlert JW, et al. Sonographic ear length measurement in normal second-and third-trimester fetuses. Am J Obstet Gynecol 2000;183: 230–4.
5. Chitkara U, Lee L, Oehlert JW, Bloch DA, Holbrook RH Jr, El-Sayed YY, et al. Fetal ear length measurement: a useful predictor of aneuploidy? Ultrasound Obstet Gynecol 2002;19(2):131–5.

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

1. Wilkins I. Separation of the great toe in fetuses with Down syndrome. J Ultrasound Med 1994;13:229–31.
2. Hill LM. The sonographic detection of trisomies 13, 18, and 21. Clin Obstet Gynecol 1996;39:831–50.
3. Ranzini AC, Guzman ER, Ananth CV, Day-Salvatore D, Fisher AJ, Vintzileos AM. Sonographic identification of fetuses with Down syndrome: a matched control study. Obstet Gynecol 1999;93(5):702–6.
4. Rotmensch S, Liberati M, Bronshtein M, Schonfeld-Dimaio M, Shalev J, Ben-Rafael Z, et al. Prenatal sonographic findings in 187 fetuses with Down syndrome. Prenat Diagn 1997;17(11):1001–9.
5. Shipp TD, Benacerraf BR. Second trimester ultrasound screening for chromosomal abnormalities. Prenat Diagn 2002;22: 296–307.

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

Table 2. Ultrasound "soft markers" performance summary in the detection of aneuploidy (trisomy 21, 18) and other genetic/congenital anomalies

Ultrasound "soft markers" (evidence and classification)[1]	Aneuploidy (LR)[2] T21	Aneuploidy (LR)[2] T18	Congenital/Anomaly Association[3]
A. Screening scan (16-20 weeks)			
Nuchal fold (III, A)	17	—	Congenital heart disease
Echogenic bowel (II-2, A)	6	—	CF2%, infection 3%, GI 6%
Ventriculomegaly (II-2, A)	9	—	AC, CNS, infection, obstruction
Echogenic cardiac focus (III, A)	2	—	—
Choroid plexus cyst (II-2, A)		7	—
Single umbilical artery (III, A)	—	—	Renal, cardiac
Enlarged cisterna magna (III, A)	—	—	OFD, MG, DiG
Renal pyelectasis (II-2, A)	—	—	Hydronephrosis; reflux
B. Comprehensive scan (calculation; detail)			
Clinodactyly (II-2, A)	5.6		—
Humerus (short) (II-2, A)	7.5		skeletal dysplasia; IUGR
Femur (short) (II-2, A)	2.7		skeletal dysplasia; IUGR
Nasal bone absent/hypo (II-2, A)	51		—
C. Research/Not useful			
Brachycephaly (III, B)	—	—	—
Iliac angle (II-2, A)	TBD	—	—
Ear length (III, B)	3–5	—	—
Sandal toe (III, B)	—	—	—

[1]Canadian Task Force on Periodic Health Examination, Health Canada; Quality of Evidence;Classification of Recommendation (Ann Intern Med 1993; 118:731-7).

[2]LR: likelihood ratio; TBD: to be determined.

[3]CF: cystic fibrosis; CNS: central nervous system; GI: gastrointestinal; OFD: oro-facial-digital syndrome; MG: Meckel Gruber Syndrome; DiG: Di George Syndrome; IUGR: intrauterine growth restriction; AC: agenesis corpus callosum

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.[6–8] 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.[9,10]

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.[11–13]

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

1. Society of Obstetricians and Gynaecologists of Canada. Canadian guidelines for prenatal diagnosis, techniques of prenatal diagnosis. JOGC Clinical Practice Guidelines No. 105; July 2001.
2. Saari-Kemppainen A, Karjalainen O, Ylostalo P, Heinonen OP. Ultrasound screening and perinatal mortality: controlled trial on systematic one-stage screening in pregnancy. The Helsinki Ultrasound Trial. Lancet 1990;336(8712):387–91.
3. Leivo T, Tuominen R, Saari-Kemppainen A, Ylostalo P, Karjalainen O, Heinonen OP. Cost-effectiveness of one-stage ultrasound screening in pregnancy: a report from the Helsinki ultrasound trial. Ultrasound Obstet Gynecol 1996;7(5):309–14.
4. Long G, Sprigg A. A comparative study of routine versus selective fetal anomaly ultrasound scanning. J Med Screen 1998;5(1):6–10.
5. Kowalcek I, Huber G, Lammers C, Brunk J. Bieniakiewicz I, Gembrunch U. Anxiety scores before and after prenatal testing for congenital anomalies. Arch Gynecol Obstet 2003;267(3):126–9.
6. Vintzileos AM, Guzman ER, Smulian JC, Yeo L, Scorza WE, Knuppel RA. Down syndrome risk estimation after normal genetic sonograph. Am J Obstet Gynecol 2002;187(5):1226–9.
7. Winter TC, Uhrich SB, Souter VL, Nyberg DA. The "genetic sonogram": comparison of the index scoring system with the age-adjusted US risk assessment. Radiology 2000;215(3):775–82.
8. DeVore GR. The genetic sonogram: its use in the detection of aneuploidy in fetuses of women of advanced maternal age. Prenat Diagn 2001;21(1):40–5.
9. Bromley B, Lieberman E, Shipp TD, Benacerraf BR. The genetic sonogram: a method of risk assessment for Down syndrome in the second trimester. J Ultrasound Med 2002;21:1087–96.
10. Sohl B, Scioscia A, Budorick, NE, Moore TR. Utility of minor ultrasonographic markers in the prediction of abnormal fetal karyotype at a prenatal diagnostic center. Am J Obstet Gynecol 1999;181:898–903.
11. Verdin SM, Whitlow BJ, Lazanakis M, Kadir RA, Chatzipapas I, Economides DL. Ultrasonographic markers for aneuploidy in women with negative nuchal translucency and second trimester maternal serum biochemistry. Ultrasound Obstet Gynecol 2000;16(5):402–6.
12. Thompson MO, Thilaganathan B. Effect of routine screening for Down syndrome on the significance of isolated fetal hydronephrosis. Br J Obstet Gynaecol 1998;105(8):860–4.
13. Prefumo F, Presti F, Mavrides E, Sanusi AF, Bland JM, Campbell S, et al. Isolated echogenic foci in the fetal heart: do they increase the risk of trisomy 21 in a population previously screened by nuchal translucency? Ultrasound Obstet Gynecol 2001;18(2):126–30.