First-Trimester Detection of Down Syndrome Using Fetal Ultrasound Markers Combined with Maternal Serum Assessment

Description

Ultrasound markers can potentially increase the sensitivity of biochemical measures for first trimester detection of Down syndrome. Nuchal translucency (NT) refers to the ultrasound detection of subcutaneous edema in the fetal neck between weeks 10 and 13 of gestation. Fetal nasal bone examination involves ultrasound assessment at 11-14 weeks’ gestation to identify the presence or absence of the nasal bone.

Background

Definitive diagnosis of Down syndrome and other chromosomal abnormalities requires amniocentesis or chorionic villus sampling (CVS), both of which are invasive procedures that carry a risk of miscarriage estimated at 0.5% to 1%. Because of this risk, before biochemical screening existed, diagnosis was generally only offered to women 35 years or older, for whom the risk of the procedure approximated the risk of Down syndrome. However, the majority of babies with Down syndrome are born from mothers younger than 35 years, even though the mothers are at lower individual risk. This situation created interest in developing less-invasive screening programs based on assessment of serum markers that have shown associations with Down syndrome. In the late 1980s, biochemical screening at 16 weeks’ gestation was developed and began to be offered to all pregnant women. Biochemical screening consists of maternal serum measurements of alpha-fetoprotein, human chorionic gonadotropin, and unconjugated estriol (i.e., triple screen). More recently, there has been the option of a fourth marker, inhibin-A (quadruple screen). The triple screen identifies approximately 69% of Down syndrome pregnancies and the quadruple screen 81%, both at a 5% false-positive rate.

(1) This false-positive rate refers to the proportion of all tests administered that are falsely positive at the cutoff point that produces that particular value of sensitivity. Among women who test positive, only about 2% actually have a fetus with Down syndrome.

There has also been interest in ultrasound markers to improve the accuracy of biochemical screening. One potential marker is fetal nuchal translucency (NT). This refers to the ultrasound detection of subcutaneous edema in the fetal neck and is measured as the maximal thickness of the sonolucent zone between the inner aspect of the fetal skin and the outer aspect of the soft tissue overlying the cervical spine or the occipital bone. In the early 1990s, screening studies of pregnant women reported...
an association between increased NT in the first trimester of pregnancy (10–13 weeks of gestation) and chromosomal defects, most commonly Down syndrome, but also trisomy 18 and 13. Nuchal translucency could be done alone as a first-trimester screen or in combination with the maternal serum markers, free beta subunit of human chorionic gonadotropin (B-hCG) and pregnancy-associated plasma protein-A (PAPP-A). These are different serum markers than those used in the second-trimester triple or quadruple screen.

Another potential ultrasound marker is fetal nasal bone examination. The technique for assessing the nasal bone using ultrasound involves viewing the fetal face longitudinally and exactly in the midline. The nasal bone synostosis resembles a thin echogenic line within the bridge of the nose. The nasal bones are considered to be present if this line is more echogenic than the overlying skin and absent if the echogenicity is the same or less than the skin, or if it is not visible. The absence of fetal nasal bone is considered to be a positive test result, indicating an increased risk of Down syndrome. In some cases, the sonographer will not be able to visualize the nasal area of the fetus’s face and thus cannot make a determination of the presence or absence of nasal bone. The inability to visualize the nasal bone is regarded as an unsuccessful examination, rather than a positive test result. Fetal nasal bone examination can be done from 11 weeks to just before 14 weeks’ gestation. It is sometimes recommended that, if the nasal bone is absent on ultrasound done between 11 and 12 weeks’ gestation, a second examination be done 2 weeks later. Fetal nasal bone assessment can be done along with NT, or in the second step of a 2-stage screen for cases that are borderline using other first-trimester markers.

Note: This policy only addresses the ultrasound markers nuchal translucency and fetal nasal bone assessment

Related Policies

4.01.21 Sequencing-based Tests to Determine Trisomy 21 from Maternal Plasma DNA

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

First-trimester screening for detection of Down syndrome incorporating maternal serum markers and measurement of fetal nuchal translucency may be considered medically necessary for women who are adequately counseled and desire information on the risk of having a child with Down syndrome.

First-trimester screening for detection of Down syndrome using measurement of nuchal translucency alone is investigational.

First-trimester screening for detection of Down syndrome incorporating fetal nasal bone assessment translucency is investigational.
In studies of first-trimester screening, the laboratory and imaging components of the screening are performed in a coordinated fashion. This process results in a set of predictions of Down syndrome, which can be summarized by receiver operator characteristic (ROC) curve analysis or sensitivity and specificity estimates. Although multiple cutoff points are possible, a standard method of presenting results is to report the sensitivity at the cutoff that produces a 5% false-positive rate. In actual practice, however, patients are not just informed of a “positive” or “negative” result but are given a numerical estimate (“1 of XX”) of the probability of Down syndrome. These probability estimates may help aid further decision making by the patient.

Trial design issues include the population of patients studied (i.e., high risk or average risk) and the quality of follow-up to avoid verification bias. Verification bias refers to a problem in which the outcome status (Down syndrome or normal) is not assessed or is not available in certain patients. In the context of Down syndrome screening, spontaneous abortion is more likely in fetuses with chromosomal anomalies. Fetuses that miscarry may be more likely to be Down syndrome fetuses and may be missed among those who have negative screening tests. Therefore, unless karyotyping is performed in all cases of spontaneous abortion or stillbirth, it is likely that a certain percentage of Down syndrome fetuses will go undetected. Therefore, to avoid verification bias, it is important to have as complete a follow-up as possible of all pregnancy outcomes with karyotypic analysis on stillbirths and live births with dysmorphic features and phenotypic assessment of other live births.

First-Trimester Screening with Nuchal Translucency and Maternal (Biochemical) Markers

There are 3 large prospective, multicenter studies on the sensitivity of first-trimester screening that include nuchal translucency (NT) measurements. The Serum, Urine, and Ultrasound Screening Study (SURUSS) study enrolled over 47,000 women, 101 of whom had fetuses with Down syndrome. (3) This study evaluated several tests in parallel, including first-trimester testing with NT and maternal markers, the triple test, second-semester quadruple test, and a combined first- and second-trimester test (both with and without NT). There were very high rates of verification, and adjustments were applied to account for miscarriages. Calculation of risk for all tests was done with a similar analytic methodology. There was no abnormal cutoff threshold for any measurement of NT or maternal serum analyte, as all measurements were entered into the regression model as continuous variables. In a direct comparison of the first-trimester test to the triple test, at a threshold of 85% detection, the first-trimester test had a false-positive rate of 6.1%, and the triple test had a false-positive rate of 9.3%. The lower false-positive rate at the same sensitivity means that the first-trimester test had superior discriminative capacity. Setting the false-positive rate at 5% resulted in a sensitivity of 83%, which was superior to what was historically expected of the triple test. The study also evaluated NT measurement alone. Its performance was considerably worse than either first-trimester testing or the triple test, with a false-positive rate of 20% at a diagnostic sensitivity of 85%.

The BUN (Blood, Urea, Nitrogen) study was also published in 2003 and evaluated first-trimester screening using the NT and the same maternal markers (human chorionic gonadotropin and pregnancy-associated plasma protein A) as the SURUSS study. (4) Approximately 8,500 patients
were enrolled, and 61 cases of Down syndrome were identified. Using a screening threshold of 1 in 270, 52 of 61 (85%) of Down syndrome cases were detected with a false-positive rate of 9.4%. If the threshold were changed to produce a false-positive rate of 5%, the detection rate was 78.7%. Taking into account possible biases due to miscarriages, the authors calculated that second-trimester screening would have to be 75% sensitive to be equivalent to the 78.7% sensitivity they found for first-trimester screening.

Another large, prospective, multicenter study similar in design to the SURUSS study was published in 2005. (5) This was the First and Second Trimester Evaluation of Risk (FASTER) trial, conducted in the U.S. and sponsored by the National Institutes of Health (NIH). The study enrolled 38,167 women, 117 of whom had a fetus with Down syndrome. All women underwent first-trimester testing with NT and maternal markers, and second-trimester quadruple screening. The study compared the results of each test, as well as stepwise sequential screening (results provided after each test analyzed), fully integrated screening (results only provided after all tests analyzed), and serum-integrated screening (similar to fully integrated but NT results not included). At a threshold of 5% false-positive rate, the rate of detection of Down syndrome was 87% for first-trimester combined screening performed at 11 weeks, 63% for NT alone at 11 weeks, 81% with second-trimester quadruple screening, 88% with serum-integrated screening, and 96% for fully integrated screening (first-trimester at 11 weeks). The detection rate of first-trimester screening was somewhat lower if performed after 11 weeks: 85% at 12 weeks and 82% at 13 weeks. Results of the FASTER trial provided further evidence that first-trimester combined screening was effective, but not NT measurement alone, and that integrated first- and second-trimester screening provided higher detection rates.

Subsequent studies (6-12) have confirmed that combined first-trimester screening that includes NT measurement and maternal serum markers is superior to NT measurement alone. For example, in 2013 Peuhkurinen and colleagues in Finland reported on tests performed prospectively in 35,314 pregnant women. (12) Ninety-five Down syndrome pregnancies were identified. The detection rate was 64.5% for NT alone and 72.4% for combined screening with NT and maternal serum markers. False-positive rates were 4.4% with NT alone and 4.0% with combined screening. Moreover, Ranta and colleagues, in a retrospective review of data on 76,949 women in Finland, found that combined screening with maternal serum markers and NT is especially preferable in women aged 35 years and younger. (10)

Studies continue to investigate the optimal approach to testing that balances the desires to maximize detection, minimize false-positive results, minimize unnecessary testing, and provide information to women as early in their pregnancies as possible. As stated, the SURUSS and FASTER studies have estimated the results of several approaches, including combination first-trimester testing only, stepwise sequential testing (results given after first-trimester testing, move on to second-trimester testing), and integrated screening (results given only after first- and second-trimester testing). A retrospective analysis of the prospectively collected FASTER data by Cuckle and colleagues introduced another screening approach, called "contingent screening." (13) Initial risk was calculated from first trimester NT measurement and maternal serum markers and classified as positive (i.e., greater than 1 in 20), borderline (i.e., 1 in 30–1,500), and negative (i.e., less than 1 in 1,500). Women with positive tests were offered immediate prenatal diagnosis, and those with borderline tests...
underwent second trimester quadruple screening and risks were recalculated. A final risk of greater than 1 in 270 was considered positive. This approach differs from stepwise sequential testing in that only women with borderline results continued to second-trimester testing. First-trimester testing identified 52 of 86 (60%) affected fetuses with a 1.2% false-positive rate (401 false-positive results). The final detection rate with the contingent approach was 91% with a 4.5% false-positive rate. Detection rates were similar with the stepwise approach (92% with 5.1% false-positive results) but substantially more women received second-trimester testing, 31,868 with stepwise testing versus 7,360 with contingent testing.

Another retrospective analysis of prospectively collected screening data was published by Kagan and colleagues in 2010. (14) Contingent screening resulted in a better test performance than other approaches. In this case, contingent screening involved first-stage screening using maternal age and NT thickness, with or without an additional ultrasound marker. Women with a risk of 1 in 50 or more were considered to test positive and those with a risk of less than 1 in 1,000 were considered to test negative. Patients with intermediate risk (i.e., 1 in 51 to 1 in 1,000) underwent second-stage screening with the biochemical markers free beta subunit of human chorionic gonadotropin (B-hCG) and pregnancy-associated plasma protein A (PAPP-A). An adjusted risk of at least 1 in 100 was then considered positive. The analysis used data from 21,141 singleton pregnancies, 122 of which had fetal trisomy 21.

After first-stage screening using only maternal age and NT thickness, the risk was 1 in 50 or more in 1.4% of the euploid pregnancies and 75% of the trisomy 21 pregnancies. An intermediate risk was found in 28.3% of euploid pregnancies and 23% of the trisomy 21 pregnancies. After second-stage screening with serum markers, the overall detection rate for trisomy 21 was 89%, and the false-positive rate was 3.0%. The addition of fetal nasal bone evaluation in the first-stage screening resulted in a final detection rate of 90% with a false-positive rate of 2.6%. When first-stage screening consisted of maternal age and biochemical markers, and second stage screening included fetal NT thickness and fetal nasal bone, the final detection rate was 92% with a false-positive rate of 5.2%. Other ultrasound markers, not currently addressed in this policy, were also evaluated in the Kagan et al. (2010) study. (14) With first-stage screening consisting of the marker ductus venosus flow added to maternal age and NT and second-stage screening for biochemical markers, there was a trisomy 21 pregnancy detection rate of 96% with a false-positive rate of 2.7%. When tricuspid flow was assessed instead of ductus venosus in the strategy described above, there was a detection rate of 94% and a false-positive rate of 2.6%.

Several studies evaluating a particular approach to combining first- and second-trimester screening results have been published. In 2009, Wald et al. in the U.K. reported on use of the integrated screening strategy in practice. (15) Records from two London hospitals were reviewed for 15,888 women who presented in the first trimester and were screened. Ninety-eight percent accepted integrated screening, and 94% of women completed both testing stages. The Down syndrome detection rate was 87%, consistent with an estimate of 89% predicted by SURUSS. The observed false-positive rate was 2.1%. A 2013 study by Torella and colleagues in Italy reported the performance of 2-stage first-trimester combined screening. (16) Blood samples were taken at 8 weeks 0 days to 10 weeks 6 days and NT measurement was performed at 12 weeks 0 days to 12 weeks 6 days. The
combined screen was considered positive when the risk of Down syndrome was greater than 1 in 250. A total of 73 positive cases were identified among 713 women with singleton pregnancies who were screened. All 73 women underwent invasive testing and 5 cases of trisomy 21 were detected. There was also 1 false-negative case. Using this approach, the Down syndrome detection rate was 83% and the false-positive rate was 3.2%.

Studies have addressed whether women whose fetuses have large NT measurements benefit from any additional screening tests or should move directly to diagnostic testing with chorionic villus sampling (CVS). A retrospective analysis of 36,120 patients in the prospective FASTER study, published in 2009, found no added benefit in waiting for serum screening results when NT was 4.0 mm or greater, and minimal benefit when NT was 3.0 mm or greater. (17) In this study, there were 32 (0.09%) fetuses with NT of at least 4.0 mm. Among these 32 cases, the lowest final Down syndrome risk after including first-trimester serum markers was 1 in 8. Similarly, a retrospective study of 77,443 women in Quebec found that final combined first-trimester screening results were always positive in the 197 (0.3%) when NT measurements were at least 4.0 mm. (18) A study from Australia conducted first-trimester screening on 76,813 women and identified an extremely large NT (here defined as 6.5 mm or greater) in 120 cases. (19) Abnormal karyotypes were found in 89 of the 120 cases (74%).

An ongoing issue with NT measurement is the possible variability of ultrasonographic interpretation. The Fetal Medicine Foundation in the U.K. has a training program that offers an Internet-based certificate of competency in NT. (20) Continuing medical education courses in the U.S. are also available through the Fetal Medicine Foundation’s U.S. affiliate. (21) Training and certification, along with ongoing quality control, an appropriate reference database of patients and use of statistical methodology, are necessary to produce optimal diagnostic results. Two recent studies with large sample sizes (22, 23) estimated the impact of measurement error on the results of first-trimester screening by taking actual screening results and artificially altering the NT values. Both studies found that even small deviations in measurement of NT affect the false-positive and false-negative rates. For example, in the Schmidt et al. study, (23) which analyzed data from 10,116 pregnancies, underestimating the NT by 0.5 mm increased the number of false-negative results from 12 to 20 (an increase of 66.7%) and decreased the number of false-positive results from 479 to 281 (a decrease of 41.3%). On the other hand, overestimating the NT by 0.5 mm decreased the number of false-negative results from 12 to 11 (a decrease of 8.3%) and increased the number of false-positive results from 479 to 1,149 (an increase of 140%). Findings emphasize the importance of accurate measurement of NT and potential value of combining NT findings with maternal serum markers.

Section Summary: Evidence from multiple large, prospective studies establishes that the accuracy of ultrasound assessment of nuchal translucency assessment combined with maternal serum markers for detection of Down syndrome is similar or higher to other available methods. This combination of tests offers advantages over alternatives in that it can be performed earlier in the pregnancy than other methods and may lead to an earlier confirmation or exclusion of Down syndrome. The accuracy of either nuchal translucency alone or serum markers alone is less than that of the combined tests. The optimal timing of this test, and/or the optimal sequence or combination of this screening test with other tests, is not certain at this time.
Fetal Nasal Bone

Performance of Fetal Nasal Bone Assessment

A systematic review by Rosen et al for the U.S.-based Maternal Fetal Medicine Foundation Nuchal Translucency Oversight Committee identified 10 studies on fetal nasal bone performance. (24) A total of 35,312 women underwent first-trimester ultrasound assessment of fetal nasal bone. The fetal nasal bone was successfully imaged in 33,314 (94.3%) of cases and could not be imaged in 5.7% of cases. There were 479 Down syndrome fetuses, a prevalence of 13.6 in 1000. The authors note that this is 10 times the first-trimester incidence in the U.S., suggesting a high-risk population had been screened. The fetal nasal bone was absent in 310 of 479 (65%) Down syndrome cases and in 274 of 34,048 (0.8%) chromosomally normal cases.

One of the included studies, a subanalysis of the FASTER study, discussed above, involved a general population sample and had much lower rates of successful imaging than other studies. (25) Assessment of fetal nasal bone was added to the FASTER protocol during the last 7 months but did not occur in all centers. A total of 6324 women underwent fetal nasal bone sonography and pregnancy outcome data were available for 6228 (98.5%) of them. Sonographers failed to obtain an adequate view in 1523 patients (24%). Among the 4801 cases with adequate images of the fetal profile, the nasal bones were described as being absent in 22 (0.5%) of them. There were 11 identified cases of Down syndrome. Fetal nasal bone assessment did not identify any of these cases as potentially high risk. In 9 of the 11 cases (92%), the fetal nasal bones were judged to be present, and in 2 cases, were unable to determined. There were also 2 cases of trisomy 18; nasal bones were present in one and absent in the other. The FASTER investigators concluded that first-trimester fetal nasal bone sonography does not seem to have a role in general population screening for Down syndrome. Other researchers have commented on the lower rate of successful fetal nasal bone assessment in the FASTER analysis. The Rosen et al review article (24) noted that, although the sonographers were trained and experienced in NT measurement, they were new to fetal nasal bone assessment. Another review article by Sonek et al states that the likely explanation for the FASTER findings is that their techniques were different from those used by others. (26)

One study was identified that directly compared the performance of fetal nasal bone assessment in unselected and selected populations. (27) This prospective study included a total of 7672 pregnant women, 7116 of whom were at average risk and 510 at increased risk (more than 1 in 300) of Down syndrome based on age, family history, or previous pregnancy history. It was not possible to adequately assess the fetal nasal bones in 712 of 7116 (10%) in a general population sample, and in 42 of 510 (8.2%) in a high-risk sample. A total of 35 cases of Down syndrome were identified, 23 in the selected group and 12 in the unselected group. Two Down syndrome cases in the selected group were excluded because there was not a satisfactory ultrasound examination. In the remaining cases, absent fetal nasal bones identified 10 of 21 (47.6%) Down syndrome cases in the selected population and 2 of 12 (16.7%) in the unselected group. An analysis including the 2 missing cases found that fetal nasal bone assessment was able to correctly identify 10 of 23 or 43.5% of Down syndrome cases. A logistic regression model including fetal nasal bone findings, as well as NT and demographic factors,
absence of fetal nasal bone was found to be an independent predictor of trisomy 21 in the selected pregnancies group but not in the unselected pregnancies group.

A 2014 study by Chanprapaph et al in Thailand assessed the presence or absence of fetal nasal bone in 190 fetuses. (28) To be included in the study, pregnant women needed to be at increased risk for fetal aneuploidy such as advanced maternal age, previous pregnancy with abnormal chromosome, or abnormal sonographic markers or serum tests. An absent nasal bone was identified in 5 of 190 (2.6%) of the fetuses and, as a standalone marker, had a sensitivity of 28.57% and specificity of 99.43% for detecting fetal aneuploidy. In this study, other sonographic markers were measured but no serum testing was conducted. The combination of a positive NT and fetal nasal bone test had a sensitivity of 71.43% and specificity of 95.45%.

Fetal Nasal Bone Assessment in First-trimester Screening Programs

Several studies were identified that evaluated the diagnostic accuracy of first-trimester screening programs that included fetal nasal bone measurements as part of a comprehensive screening program. None of these was multicenter and none was conducted in the United States.

Cicero et al conducted a single-center prospective screening study in the UK. (29) Down syndrome screening including fetal nasal bone assessment was conducted in 21,074 singleton pregnancies at 11 to 13 weeks’ gestation. Data from 20,418 (97%) women were available for analysis. Chromosomal abnormalities were detected in 253 of the pregnancies; this included 140 cases of Down syndrome. An adequate view of the fetal profile could not be obtained in 243 (1.2%) of cases. Of the 20,175 cases in which the fetal profile could be obtained (ie, “successful” examination), the nasal bone was recorded as absent in 238 (1.2%) of cases and present in 19,937 (97.6%). Combined screening with NT assessment and maternal serum markers achieved a detection rate of 90% at a fixed false-positive rate of 5%. With the detection rate fixed at 90%, the inclusion of nasal bone measurements using either screening strategy decreased the false-positive rate to 2.5%. In another analysis at a fixed false-positive rate of 5%, the inclusion of fetal nasal bone assessment of all women in the sample increased the detection rate to 93.6% at the 5% false-positive rate. The same increase in the detection rate, to 93.6%, was obtained when fetal nasal bone assessment was included only for women of intermediate risk (one in 51 to one in 1,000).

A study by Sahota et al conducted in Hong Kong was a retrospective analysis of 10,767 women who had been screened in a comprehensive first-trimester screening program. (30) The analysis compared several approaches to screening. Among the 10,854 fetuses with a known outcome, 32 had Down syndrome. In a screening approach that combined NT assessment and maternal serum markers in this group, 27 (94%) of the pregnancies would have been classified as high risk, 4 as low risk, and 1 as intermediate risk. The protocol included fetal nasal bone assessment of intermediate-risk pregnancies, with reclassification as high risk if the fetal nasal bone was absent. The one case classified as intermediate risk had an absent fetal nasal bone. In this study, too few cases were classified as intermediate risk to determine whether fetal nasal bone assessment in a contingent screening approach improves screening accuracy.
A 2014 prospective study conducted by Hsiao et al in Taiwan included 20,586 women who were screened with maternal serum markers and various ultrasound markers. (31) The combination of maternal serum markers and NT measurement had a 66.7% detection rate of trisomy 21. The addition of fetal nasal bone measurement increased the detection rate to 88.2%. Further inclusion of more ultrasound markers, ie, tricuspid regurgitation and the Doppler velocity waveform of the ductus venosus continued to increase the detection rate.

Techniques for evaluating fetal nasal bone images continue to be refined. A 2014 article reported on the feasibility of assessing fetal nasal bone using the retronasal triangle view. (32) A total of 1977 women pregnant with singletons were scanned using this approach. The retronasal triangle view was successfully obtained for 1970 (99.6%) fetuses. The prevalence of an absent or hypoplastic fetal nasal bone was 12 of 1728 (0.7%) in euploid fetuses and 12 of 17 (70.6%) in fetuses with trisomy 21. The sensitivity and specificity of an absent or hypoplastic fetal nasal bone for detecting trisomy 21 was 70.6% and 99.3%, respectively. Another technique under investigation is use of 3-dimensional ultrasound to measure fetal nasal bone during the first trimester. Nanni et al evaluated 161 women pregnant with singletons with both 2-dimensional and 3-dimensional US. (33) There was high intraobserver and interobserver agreement using 3-dimensional ultrasound. The agreement between 2-dimensional and 3-dimensional ultrasound was moderate (correlation coefficient: 0.77).

As with NT measurement, there are possible issues around variability of fetal nasal bone interpretation and the need for adequate training and quality control. A review article by Rosen et al states that mastering imaging of the nasal bone appears to be more difficult than mastering NT measurement. (24) The Fetal Medicine Foundation in the UK has an Internet-based certificate of competency in fetal nasal bone assessment; their website does not state how long this program has been available. (20)

Generalizability of nasal bone assessment to general clinical practice is also a consideration. A committee of the Fetal Medicine Foundation recommended further evaluation of nasal bone assessment in low-risk populations and additional availability of adequately trained centers before nasal bone assessment is introduced into general practice. They also suggested considering a contingent screening strategy. The approach they suggest is similar to that used in the Sahota et al study (30) from Hong Kong, discussed earlier, in which fetal nasal bone assessment is used only in cases that have a borderline risk determination by screening with NT and maternal serum markers. If a contingency model were used, patients could be referred to centers with developed expertise, although the authors note that this may not be feasible or practical in all areas of the United States.

Section Summary: Assessment of fetal nasal bone by US is another method of screening for Down syndrome phenotype in utero. The accuracy of this test in the published literature is variable, and some studies have reported a relatively low sensitivity. The variability in accuracy reported may reflect the difficulty in performing and interpreting this test, and the test results are likely prone to differences in operator characteristics. Limited evidence suggests that there may be modest incremental benefit when used in combination with ultrasound nuchal translucency and serum markers, but the degree of benefit is not clear. As a result, the evidence is insufficient to determine the impact of this test on health outcomes.
Practice Guidelines, and Position Statements

In 2011, Canadian consensus guidelines on maternal screening for fetal aneuploidy were published. (34) Recommendations relevant to this policy are as follows:

Singleton pregnancies:

- All pregnant women, regardless of age, should be offered the option of pre-natal screening for significant fetal aneuploidies and a second trimester ultrasound for dating, assessment of fetal anatomy and detection of multiples.
- First trimester nuchal translucency should not be offered as a screen without biochemical markers. It should be measured by sonographers or sonologists trained and accredited for this service.

Twin pregnancies:

- Fetal nuchal translucency combined with maternal age is an acceptable first trimester screening test for aneuploidies in twin pregnancies.
- First trimester serum screening combined with nuchal translucency may be considered in twin pregnancies. It provides some improvement over the performance of screening by nuchal translucency and maternal age because the false-positive rate is lower.

In January 2007 (reaffirmed in 2011), the American College of Obstetricians and Gynecologists (ACOG) released an updated practice bulletin that recommended that all women, regardless of age, be offered aneuploidy screening before 20 weeks’ gestation. No single specific testing strategy was recommended. The recommendations state that first-trimester combined screening (nuchal translucency and maternal serum markers) is effective for testing for Down syndrome. They further state that fetal nasal bone assessment in the general population is controversial and that additional testing standardization, training for physicians and quality-control programs are needed. (1)

U.S. Preventive Services Task Force Recommendations
Not applicable

Summary

There is sufficient evidence from 2 large prospective multicenter studies (SURUSS, FASTER) and several smaller studies that first-trimester screening for Down syndrome with measurement of fetal nuchal translucency and maternal serum markers is at least as accurate as alternative tests and may allow earlier confirmation or exclusion of Down syndrome. Therefore, use of this test in the first trimester is a reasonable approach and may be considered medically necessary. The SURUSS and FASTER studies also found that overall first-trimester screening with NT alone is inferior to either first- or second-trimester combined screening therefore first-trimester screening for detection of Down syndrome using measurement of nuchal translucency alone is investigational. Additional testing may
not be necessary in those few cases when NT is at least 4.0 mm due to the high likelihood of Down syndrome in these cases.

Studies have found a high rate of successful imaging of the fetal nasal bone and an association between absent nasal bone and the presence of Down syndrome in high-risk populations. However, there is insufficient evidence on the performance of fetal nasal bone assessment in average-risk populations. Of particular concern is the low performance of fetal nasal bone assessment in a subsample of the FASTER study conducted in a general population sample. Two studies conducted outside of the U.S. have found that, when added to a first-trimester screening program evaluating maternal serum markers and nuchal translucency, fetal nasal bone assessment can result in a modest decrease in the false-positive rate. Several experts in the field are proposing that fetal nasal bone assessment be used as a second stage of screening, to screen women found to be of borderline risk using maternal serum markers and nuchal translucency. Additional studies using this contingent approach are needed before conclusions can be drawn about its utility. In summary, given the uncertainty of test performance in average-risk populations and the lack of standardization in the approach to incorporating this test into a first-trimester screening program, detection of fetal nasal bone is considered investigational.

**Medicare National Coverage**

There is no national coverage determination.

**References**


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Keywords
This policy was approved by the FEP® Pharmacy and Medical Policy Committee on June 19, 2015 and is effective July 15, 2015.

Signature on File

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