NUCHAL TRANSLUCENCY GENETIC SCREENING

Background

1. Definition:
    - Fetal nuchal edema, posterior area, synonymous with "nuchal translucency" or NT
    - Nuchal fold thickness best ultrasonographic predictor of fetal trisomy 21 (Down Syndrome). [1]
    - Should be assessed as part of first-trimester scan when live fetus present[2]
    - Typically measured between 10 and 14 weeks
2. Identification of factors associated with increased risk of Down Syndrome important
    - Biochemical serum screening introduced 1984 by maternal serum alpha-fetoprotein (AFP)[3]
    - Addition of human chorionic gonadotropin (hCG) and Pregnancy-associated plasma protein-A (PAPP-A) to first trimester maternal serum screening
    - Second trimester screening combines AFP, hCG, unconjugated estriol, and inhibin-A
    - Strong association between size of fluid collection at back of fetal neck and risk of Trisomy 21 in 1990's[8]
    - Standardized guidelines for measurement of NT and specific training now exist

Pathophysiology

1. Pathology
    - Risk of fetal aneuploidy is complex
    - NT screening able to detect fetal aneuploidy
    - Disease burden of fetal aneuploidy
        - Cognitive deficits
        - Congenital heart disease
        - Gastrointestinal tract anomalies
        - Intrauterine death
2. Incidence of Trisomy:[4]
    - Frequency Trisomy 21 >> Trisomy 18 > Trisomy 13
    - Trisomy 21 risk strongly age related (advanced maternal age > 35 years)[14]
        - Age 20 – 1/1476 births
        - Age 35 – 1/352 births
        - Age 50 – 1/25 births
    - Trisomy 18 - 1/8000 births
    - Trisomy 13 - 1/12000 births
3. Risk Factors:
    - Advanced maternal age
    - History of previous pregnancy complicated by fetal trisomy
    - History of chromosomal translocation, inversion, aneuploidy in themselves or partner
4. Morbidity / Mortality:
    - Women with isolated NT thickening or isolated abnormal AFP
        - Increased risk of poor pregnancy outcomes: (SOR:B) [5]

- Increased NT: congential heart defects, abdominal wall defects, genetic syndromes, fetal loss
- Increased AFP: open neural tube defects, older fetus

- Women with false positive screening
  - Risks from unnecessary invasive testing
  - Stress and anxiety of test results
    - Less likely to participate in screening in future pregnancy[15]
    - Studies show women with false-positive mammogram results suffer significant cancer-related anxiety versus controls[16]

Diagnostics

1. Screening Options[3]
   - Combined First Trimester Screening
     - NT plus serum markers (PAPP-A and hCG)
     - MSAFP at 16-20 weeks for NTD
     - Higher false positive for women > 35 years old
   - Integrated Screening
     - First trimester plus second trimester screening
       - Risk assessed after both results obtained
       - Serum Integrated
         - PAPP-A alone at 10-13 weeks
         - Quad Test at 15-19 weeks
       - Full Integrated:
         - NT, PAPP-A at 10-13 weeks
         - Quad Test at 15-19 weeks
       - Highest sensitivity with lowest false positives (SOR:B)[3]
   - Sequential Screening
     - First trimester plus second trimester screening
     - Tests offered depend on risk assessed from first trimester screen
       - Stepwise Sequential Screening
         - High risk offered diagnostic testing
         - Low risk offered second trimester screening
       - Contingent Sequential Screening
         - High risk offered diagnostic testing
         - Intermediate risk offered second trimester testing (Quad screen)
         - Low risk not offered further testing
   - Quadruple Screening
     - Includes four serum markers (MSAFP, hCG, estriol, inhibin A)
     - Option for second trimester presentation
   - Cost
     - Integrated serum screening most cost effective screening for Down syndrome [6]
     - If cost of NT screening is lowered (below $57 in 2005), first-trimester combined screening becomes most cost effective [6]
2. Invasive Testing[5]

- Chorionic Villus Sampling (CVS)
  - Transabdominal or transcervical sampling of placental tissue
  - Performed between 10 and 13 weeks gestation
  - Allows early and definitive chromosomal analysis
  - Risk bleeding, infection, early pregnancy loss
- Amniocentesis
  - Sampling of amniotic fluid
  - Performed between 14 and 20 weeks gestation (safest at 16-18 weeks)
  - Risk: vaginal spotting, amniotic fluid leakage, infection and fetal loss

Follow-Up/Management Recommendations

1. High risk screening tests suggesting aneuploidy
   - Invasive testing offered for further assessment of possible aneupoloidy, per patient request
2. Abnormal Screening without Evident Aneuploidy
   - Nuchal Translucency
     - Measurements $\geq$ 3.5 mm in 1st trimester associated with fetal abnormalities including: central nervous system abnormalities, facial and nuchal abnormalities, thoracic and cardiac defects, abdominal, gastrointestinal, genitourinary abnormalities, genetic syndromes, skeletal defects, neuromuscular defects, fetal anemia and more
     - Patients should be offered detailed ultrasound, fetal echo, or both [5]
   - PAPP-A
     - Level <0.4 MoM (multiples of median) in first trimester associated with early and late fetal loss, preeclampsia, preterm birth, IUGR
     - Patients should be counseled on fetal activity in second and third trimesters[7]
   - hCG
     - Level >3.0 MoM in second trimester associated with placental dysfunction leading to possible fetal loss, preeclampsia, preterm labor, IUGR
     - Patients should be counseled on signs and symptoms of preterm labor and preeclampsia[7]
   - Inhibin A
     - Level > 2.0 MoM in second trimester associated with placental dysfunction and oxidative stress leading to possible preeclampsia, IUGR, preterm birth, and late fetal loss
     - Consider ultrasound assessment of fetal growth in late second and third trimesters[7]
   - Unconjugated Estriol
     - Level < 0.25 MoM in second trimester associated with fetal diagnosis of congenital adrenal hypoplasia, steroid sulfatase deficiency, and Smith-Lemli-Opitz syndrome
     - Patients should be counseled and offered further genetic evaluation for rarer disorders[7]
   - Alpha-fetoprotein (AFP)

- Level > 2.0 MoM in second trimester associated with placental implantation abnormalities, gestational hypertension, preeclampsia, fetal loss, preterm labor, IUGR and placental abruption:
- Patients should be counseled on anticipated fetal activity in late second and third trimesters, signs and symptoms of preterm labor and preeclampsia, offered ultrasound assessment of fetal growth in late second and third trimesters; if evidence of low-lying placenta/placenta previa, potential for placenta accreta [7]

Recommendation (GRADE)

1. All pregnant women, regardless of age, offered genetic screening and invasive diagnostic testing before 20 weeks gestation: (SOR:B[5)]
2. Women presenting in first trimester: offer combined testing: (SOR:A) [5]
3. Women presenting in second trimester offered quadruple screening: (SOR:A) [5]
4. Women who pursue first trimester screening alone offered MSAFP testing in second trimester to screen for neural tube defects: (SOR:A) [5]
5. Genetics counseling and CVS or amniocentesis offered to all women with elevated risk, as determined by serum screening: (SOR:A) [5]
6. After first trimester screening, subsequent second trimester Down syndrome screening not indicated unless performed as part of integrated, stepwise sequential or contingent sequential tests: (SOR:C)[5]
7. Women have option of undergoing invasive testing without previous screening tests given potential "false negative" screening tests

Patient Education[5]

1. All patients should be offered screening or invasive testing appropriate for gestational age on presentation after discussion on difference between screening and invasive testing
2. Advantages and disadvantages of screening should be discussed
    - Advantages: increased odds of identifying abnormal fetus and reducing number of invasive diagnostic tests and procedure-related losses of normal fetuses
    - Disadvantages: not all aneuploid fetuses identified with screening; risk of false-positive screens potentially leading to invasive testing
3. Advantages and disadvantages of invasive testing should be discussed
    - Advantages: direct sampling for chromosomal analysis allows aneuploidy identification possibly missed with screening tests
    - Disadvantages: risks associated with invasive testing, including fetal injury and possible loss
4. Testing driven by the patient's choice after discussion about available tests and what patient may do with results
5. Comprehensive genetic counseling should be available to all patients

PROCEDURE

NT as a Screening Tool

1. Evidence
    - Potential of combined first trimester screening in detecting Down Syndrome demonstrated in SURUSS and BUN trials[9,10]

- FASTER trial confirmed potential with recommendation of appropriate quality control for nuchal translucency measurement[11]
- NT alone less effective than combined and should not be offered[3]
- In unselected populations, Positive Predictive Value of first trimester screening for Down's syndrome 4.7%[17]
- In control studies, PPV of first trimester screening for any aneuploidy 14.8%[18]
- Studies suggest consistent under-measurement of nuchal translucency across US[12]

2. Nuchal Translucency Quality Review Program (NTQR)[13]
   - Provides "quality controlled risk assessment"
   - US-based national consensus program covering professional activities and review for screening activities
     - Nuchal translucency
     - Nasal bone
   - Evidence based education and recommendations
   - NTQR program allows path to credentialing through successful didactic completion, examination, and image submission/review

Requirements for Offering NT screening[8]

1. Appropriate ultrasound training and ongoing quality monitoring programs are in place
2. Physician sonologists and sonographers should be NTQR certified
3. Sufficient information and resources available to provide comprehensive counseling regarding different screening options and limitations of tests
4. Access to appropriate diagnostic test available when screening tests are positive

Guidelines for NT Measurement[13]

1. Margin of NT edges visibility must allow proper caliper placement
2. Fetus must be in midsagittal plane
3. Image must be magnified so it is filled by fetal head, neck, and upper thorax
4. Fetal neck must be in neutral position, not flexed or hyperextended
5. The amnion must be seen as separate from NT line
6. The ultrasound (+) calipers must be used to perform NT measurement
7. Electronic calipers must be placed on inner borders of nuchal space with horizontal crossbar not protruding into the space
8. Calipers must be placed perpendicular to long axis of fetus
9. Measurement must be obtained at NT's widest space

Recommendations

1. Specific training, standardization, use of appropriate ultrasound equipment, and ongoing quality assessment important to achieve optimal nuchal translucency measurement for Down syndrome risk assessment; procedure should be limited to centers and individuals meeting these criteria: (SOR:A) [3]

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