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Genetic Screening Summary – Options in pregnancy

Patient Categories:

1. Low Risk – Age less than 35, no other risk factors
2. Increased (high) Risk – Advanced maternal age, parental translocation, prior infant with fetal trisomy, abnormal ultrasound findings, positive screening test.

A "screening" test will modify or adjust the baseline risk, while a "diagnostic" test will return with a definitive result.

All Patients: Discuss and offer aneuploidy screening and testing at the first prenatal visit (most children with Down Syndrome are born to younger women, since larger proportion of all children are born to young women); the benefits and risks of diagnostic testing (amniocentesis, CVS) should also be discussed at the time of the screening discussion.

Positive screen → option for diagnostic testing
Negative screen → counsel regarding lower adjusted risk and lower residual risk; NO additional screening tests (risk for false-positive); offer diagnostic testing if additional findings emerge (U/S)

A. First Trimester Nuchal Screen

Eligibility & Timeframe

- All pregnant women are eligible, including patients with twin gestation.
- Time frame: when crown rump length measures 45mm – 84mm, or about 11w 0d – 13w 6d.
- Women who undergo this screening should be offered obstetric ultrasound in the mid-second trimester as a screen for fetal growth, fluid and anatomy. The serum MSAFP should be offered as a screen for open neural tube defects if for some reason the patient will not be offered or perform the mid-second trimester ultrasound exam.

Characteristics

- NT measurement
- Free-beta fragment of hCG & PAPP-A levels
- Nasal bone
- Also included in aneuploidy calculation: maternal age, weight, race, number of fetuses, prior history of aneuploidy

Strengths

- 91% detection rate for DS at a 5% false positive rate without nasal bone assessment
- 95% detection rate for DS at a 2% false positive rate with nasal bone assessment
- Potential for earlier diagnoses
- Ability to screen for other fetal or placental disorders

Limitations

- Lacks ability to assess the risk of open NTD and relies on availability of a certified sonographer
- Important: accurate gestational dating at time of blood sampling (inaccurate dating decreases accuracy)

B. Quadruple Marker Screen

Eligibility & Timeframe

- All pregnant women are eligible

- Time frame: 15 0/7 weeks – 22 6/7 weeks; optimal time frame: 15-19 weeks (optimizes screening for ONTD's)

Characteristics
- 4 serum analytes are measured: hCG, AFP, Inhibin A, uEstriol
- Also included in calculation: maternal age, weight, race, presence of diabetes, number of fetuses

Strengths
- Provides aneuploidy risk plus ONTD risk estimates
- Above 80% detection rate for DS at a 5% positive result rate
- Some labs offer additional screening for rare disorders (e.g. Smith-Lemli-Opitz syndrome)

Limitations
- Important: accurate gestational dating at time of blood sampling (inaccurate dating decreases accuracy)

C. <u>Ultrasound (DAFUS) screening:</u>

Eligibility
- Appropriate for patients with a known risk factor for a fetal abnormality or the need for a more detailed ultrasound that typically performed by Radiology. Can be performed as early as 18 weeks, but more optimally performed at 20 – 22 weeks.

Ultrasound Markers/Anomalies
- Major structural anomalies art typically present in fetuses affected with T13 or T18
- Major abnormalities associated with T21 (Down syndrome) include cardiac anomalies and duodenal atresia (typically identified in 3rd trimester)
- "Soft" or low-risk markers for aneuploidy are also common in unaffected fetuses; therefore, it is difficult to use these to distinguish between affected/unaffected fetuses.
- Additional follow-up for isolated U/S markers will be determined individually.
- Further counseling is recommended for fetuses with hypoplastic/absent nasal bone, echogenic bowel, or nuchal skinfold thickening, as these markers are associated with a higher risk of aneuploidy.
- As isolated finding, <u>increased NT</u> confers the highest risk for aneuploidy/genetic syndromes and isolated anomalies (heart defects, abdominal wall defects, diaphragmatic hernia) - even with normal chromosomes on diagnostic testing - offer targeted U/S and fetal echocardiography
- <u>Cystic hygroma</u> is associated with a 50% likelihood of fetal aneuploidy; half of the remaining euploid fetuses will have a major structural malformation; less than 20% will result in a healthy live-born infant at term
- If isolated low-risk markers (choroid plexus cyst; intracardiac echogenic focus) is identified, analyte screening could be offered (if not performed already)
- <u>Increased NT or cystic hygroma:</u> warrants genetic counseling and detailed ultrasound (DAFUS). Consider diagnostic testing. If normal karyotype, anatomic evaluation still needs to be offered along with fetal cardiac echo exam and further counseling regarding potential for genetic syndromes not detected by aneuploidy screening.

Limitations:
- Lack of standardization in measurements and characteristics of 2nd trimester markers that define a positive test result ; lack of understanding how factors such as high maternal BMI, multiple gestation, machine quality, sonographer experience affect screening performance
- Least effective primary screening test for Down syndrome, only detecting 50-60% of affected fetuses. A "normal" ultrasound does not exclude the possibility of fetal Down Syndrome.

D. <u>Cell-free DNA Screening</u>

Eligibility & Timeframe

- High-risk women are eligible (see above); offer 2nd trimester U/S to evaluate for structural abnormalities
- Timeframe BMI < 40: 10 weeks –> term
- If BMI ≥ 40: timeframe 12 wks -> term
- No NT measurement needed in 1st trimester if cell-free DNA screening is performed; however, viability ultrasound is useful.
- Not yet recommended for patients with multiple gestation.

Characteristics & Strengths

- Used to screen for T13/18/21 and sex chromosome aneuploidies; determines fetal sex, determines presence of a Rh-positive fetus in a Rh negative mother; detects some paternally derived AD genetic abnormalities
- The test is most accurate for Trisomy 21, less accurate for T-18 or 13.
- Down syndrome detection rate: 98%; positive screening rate <0.5%; detection rates are lower for T13 and T18. Positive predictive value (PPV) for Down syndrome about 93%.
- PPV for T18 ~64%
- PPV for T13 ~44%
- PPV for sex chromosome aneuploidy ~39%
- Factors contributing to low fetal fraction: sampling prior to 10 weeks of gestation, high maternal BMI, fetal aneuploidy
- Low fetal fractions indicate a higher risk of aneuploidy and additional counseling should be offered.
- Confirmatory diagnostic testing is warranted prior to option of pregnancy termination.
- Residual risk of a chromosomal abnormality with normal cfDNA screening after abnormal marker screening is ~2.
- In case of positive cfDNA screen, offer diagnostic testing and U/S to evaluate for fetal structural abnormalities
- Women whose cfDNA screening test results are not reported, are indeterminate, or are uninterpretable (a no-call test result) should be offered genetic counseling and comprehensive ultrasound evaluation with maternal-fetal medicine. Consider diagnostic testing because of the potential increased risk of fetal aneuploidy.

Limitations

- Published studies have excluded those who have no reportable results, and these women are at increased risk of fetal aneuploidy
- The test cannot distinguish fetal DNA from maternal DNA – a positive screen could represent confined placental mosaicism, a resorbing twin, or rarely a maternal malignancy or maternal aneuploidy
- PPV is lower in the general obstetric population (PPV is affected by the prevalence of the disorder); in low-risk populations, there is a larger proportion of false-positive test results
- Screening for microdeletions is not validated at this time.

E. Diagnostic testing

1. Chorionic villus sampling.
    a. Typically offered at about 10 – 13 weeks gestation.
    b. Consider for the patient who has a known risk of a fetal genetic disorder, or at high-risk of fetal aneuploidy and would consider pregnancy termination.
2. Amniocentesis
    a. Can be performed at 15 weeks gestation or later.
    b. Test options:
        i. Standard karyotype
        ii. FISH – rapid assay for common trisomies, triploidy, or other specific abnormalities (e.g. 22q11 Syndrome).
        iii. Microarray – indications include the fetus with multiple anomalies identified with prenatal ultrasound, or a third trimester stillbirth when additional genetic information is desired. Should not be offered for repetitive first trimester miscarriage. Should always be accompanied by genetic counseling.

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