10/21/24 ak/njm

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)

Timeline of testing

Cell free DNA:	10 0/7 weeks -> term; if BMI ≥ 40: 12 0/7 weeks-> term
Nuchal screen:	11 0/7 - 13 6/7 weeks
Chorionic villus sampling:	12 0/7 – 13 6/7 weeks
Quadruple Marker Screen:	15 0/7 – 21 6/7 weeks
AFP:	15 0/7 – 23 6/7 weeks
Amniocentesis:	≥ 15 0/7 weeks
DAFUS:	Best 20-22 weeks, but can be done as early as 18 weeks
Carrier screening:	Done at any time in pregnancy. Recommended before pregnancy

Quick Pearls

Cell free DNA:	Available to all; offer 2nd trimester U/S for structural abnormalities eval. NO Quad screen should be ordered. Instead, AFP only should be ordered
Carrier screening:	Family Hx of a heritable genetic condition (Refer for genetic counseling) Should be offered to all CO: Fragile X, CF, SMA, Hemoglobinopathies screening – regardless of family history.
Nuchal screen:	Still needs serum MSAFP to r/o open neural tube defects
Chorionic villus sampling:	A diagnostic test. If risk of a fetal genetic disorder, or fetal aneuploidy.
Quadruple Marker Screen:	15-19 weeks is best (optimizes screening for ONTD's)
AFP:	Not needed if getting Quadruple Marker Screen or if anatomy scan / DAFUS has been normal
Amniocentesis:	A diagnostic test. Many options: FISH ± reflex to karyotype or microarray. Targeted familial mutation testing / single gene testing / panel testing.
DAFUS:	If known risk factor for fetal abnormality or need for a more detailed U/S

A. Screening tests

1.) Cell-free DNA Screening

Eligibility & Timeframe

- All 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.
- Multiple gestation: No estimate regarding sex chromosome aneuploidy can be calculated

Characteristics & Strengths

- MateriniT21 (by LabCorp) is used to screen for T13/18/21 and sex chromosome aneuploidies; determines fetal sex.
- Unity screen can be ordered for additional questions such as presence of a Rh-positive fetus in a Rh negative mother and detection of Kell allele in the fetus in a Kell-negative mother.
- Panorama screen can detect some paternally derived AD genetic abnormalities.
- The test is most accurate for Trisomy 21 and Trisomy 18, less accurate for Trisomy 13.
- Sensitivities: 99.1% for T21, 99.9% for T18, 91.7% for T13, 96.2% for sex chromosome aneuploidy
- Specificities: above 99.5% for all of the above
- False-positive rate is 1/200 overall
- Positive predictive value (PPV): PPV depends on maternal age and needs to be calculated individually each time
- PPV calculator: https://www.perinatalquality.org/vendors/nsgc/nipt/
- 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 genetic counseling should be offered.
- Confirmatory diagnostic testing is recommended prior to option of pregnancy termination.
- Any patient should only be offered ONE screen (either serum screening OR cell-free fetal DNA screening). However, NIPT has higher detection rate for common trisomies.
- In case of positive cfDNA screen, refer to MFM for genetic counseling, interim ultrasound(s) as recommended by Perinatologists, diagnostic testing and DAFUS 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.
- If cell-free fetal DNA screen data did not meet quality requirements, simply re-draw.

Referral to MFM:

- Refer all AMA patients to MFM for genetic counseling and cell-free fetal DNA screening.
- Refer all women carrying twins to MFM for genetic counseling and cell-free fetal DNA screening.
- Women with positive cell-free fetal DNA screen should be referred to MFM for genetic counseling, interim ultrasound(s) as recommended by Perinatologists, diagnostic testing and DAFUS.
- Refer women with indeterminate cell-free fetal DNA screen results for genetic counseling and other possible MFM appointments.

Limitations

- Published studies have excluded those who have no reportable results, and these women are at increased risk of fetal aneuploidy
- MateriniT21 cannot distinguish fetal DNA from maternal DNA (Panorama screening can) – 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 but can be ordered if necessary.

2.) Carrier screening

- All women are eligible for the LabCorp Inheritest Core Panel which assesses carrier status for cystic fibrosis (CF), spinal muscular atrophy (SMA) and Fragile X (LabCorp test # 481776).
- All women with Southeast Asian ancestry or African American ancestry should be offered screening for hemoglobinopathies via Hemoglobinopathy Fractionation Cascade (LabCorp test # 121690).
- All women or women's partners who have a family history of a heritable genetic condition should be referred for genetic counseling (and option for carrier screening).

3.) Ultrasound screening: Detailed Anatomic Fetal US (DAFUS)

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 are typically present in fetuses affected by 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, increased NT 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
- Cystic hygroma 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) are identified, cell-free fetal DNA screening could be offered (if not performed already)
- Increased NT or cystic hygroma: warrants genetic counseling, interim ultrasound(s) as recommended by Perinatologists and detailed ultrasound (DAFUS). Discuss cell-free fetal DNA screening and diagnostic testing. If diagnostic testing (karyotype or chromosomal microarray) is normal, 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 (e.g. Noonan syndrome).

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 effect 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.

4.) AFP screening

- All women are eligible for alpha-fetoprotein 9AFP) screening for open spina bifida.
- Exception: women who have had a 2nd trimester maternal serum screen, since it includes AFP level with risk estimated for fetal open neural tube defect.
- Time frame: 15w – 23w,6d.

- Information that needs to be provided: gestational age, date on which the patient was the stated gestational age, how gestational age was determined (LMP, EDD, US), patient's weight, patient's date of birth, patient's race (white, black, other), and insulin-dependent diabetic status. Also indicate relevant patient history, such as prior neural tube defects, ultrasound anomalies, or previous maternal serum screening during this pregnancy.

5.) 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)

6.) Quadruple Marker Screen

Eligibility & Timeframe

- All pregnant women are eligible
- Time frame: 15 0/7 weeks – 21 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)

B. Diagnostic testing

1. 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. FISH with reflex to karyotype OR microarray
        iv. 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.
        v. Whole Exome sequencing (specific cases)

2. Chorionic villus sampling.
    a. Typically offered at about 12 – 13 weeks, 6 days gestation. (Dr. Barber)
    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.

References:

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