Preconception/Prenatal Family History Assessment / Management Guide

Folic Acid

All Women/Couples Considering Pregnancy

No family history of neural tube defects: Folic acid supplementation of 0.4 mg/day has been shown to reduce the risk for fetal neural tube defects by 50-70% in women with no family history of neural tube defects. Patients seen for preconception visits should be advised to begin folic acid supplementation (0.4 mg/day) in the form of a daily multivitamin or prenatal vitamin prior to attempting conception. Patients should be encouraged to continue folic acid supplementation through the first trimester of pregnancy.

Previous child with a neural tube defect: Patients who have had a previous child or fetus with a neural tube defect (meningomyelocele, anencephaly, encephalocele) should be advised to begin folic acid supplementation of 4.0 mg/day at least one month prior to conception through 12 weeks gestation.

Women Currently Pregnant

Folic acid supplementation is a protective factor for neural tube defects only if taken prior to neural tube closure that occurs 30 days post-conception. Pregnant women past this gestational period will not derive protective benefits from folic acid supplementation.

Maternal Serum Multiple Marker Screening

Women under age 35 at delivery

Maternal marker screening to screen for certain chromosome abnormalities and neural tube defects during pregnancy is currently offered in a number of forms.

Second Trimester Marker Screening
2nd trimester multiple marker screening is usually performed between 15 and 20 weeks from LMP to screen for Trisomy 21, Trisomy 18, and neural tube defects. It measures AFP, unconjugated estriol (uE3) and beta-HCG in the triple screen and adds dimeric inhibin A (DIA) in the quad screen.

- Detects up to 60-80% of Trisomy 21
- Detects approximately 60% of Trisomy 18
- Detects 80% of open spina bifida and 97% of anencephaly
- Increasing age of the woman results in higher rate of positive results and higher detection rates for trisomy 18 and Down syndrome

Interpretation of results is based on the following factors. Accurate information is essential for accurate interpretation of results.

- Fetal age (based on correct LMP, or, even better, ultrasound parameters)
- Age of woman
- Maternal weight
- Ethnic background (Caucasian or African-American)
- Whether the patient is an insulin dependent diabetic
- Whether the parent or previous pregnancy/child has/had a neural tube defect

1st Trimester Screening

1st trimester multiple marker screening has recently become available and is now offered through major perinatal and prenatal genetics centers. It is usually performed at 24-84 mm CRL (between 9 and 14 weeks from LMP). The 1st trimester biochemical marker screen tests for free Beta-HGC and PAPP-A levels.

Detection rate for 1st trimester biochemical marker screening alone (without NT):

- detects up to 63% of Down syndrome
- detects 90% of trisomy 18
- does not detect neural tube defects
- Increasing age of the woman results in higher rate of positive results and higher detection rates for trisomy 18 and Down syndrome
- Interpretation factors necessary for accurate results are the same as for 2nd trimester screening (see above)

1st trimester biochemical marker testing combined with accurate CRL and nuchal translucency (NT) measurements (performed by an NT-certified sonographer), detection rates increase to:

- 90% for Down syndrome
- >90% for trisomy 18.

Biochemical screening using a dried blood sample collected between 9 and 14 weeks gestation, combined with ultrasound CRL and an accurate NT measurement is the advised method for obtaining the most accurate result with the highest detection rate and lowest false positive rate.

Integrated serum testing (IST)

IST is another recently available option for maternal marker screening. It combines both 1st and 2nd trimester serum marker testing increasing the detection rate and lowering the false positive rate. During 9 to 14 weeks gestation, patients have a fingerstick procedure. The dried blood sample is sent to the testing lab and held until the 2nd trimester sample is submitted. During 15 to 20 week gestation, the patient has a venipuncture sample drawn and submitted to the same lab. Both samples are then processed and combined results are reported to the ordering provider.

For women choosing 2nd trimester screening, integrated serum testing decreases the false positive rate, lowering the number of women needing follow-up testing. In addition, it increases the detection rate for Down syndrome and Trisomy 18 above that of 2nd trimester screening alone.

IST may be a good option for:

- Communities without NT measurement capabilities (special ultrasound equipment and a certified sonographer are needed)
- Communities without access to CVS
- Patients who are not highly anxious and are willing to wait until the 2nd trimester for results
- Patients who cannot afford a 1st trimester NT ultrasound

Women 35 or above at delivery

See next section.

Maternal Age

Women 35 or above at delivery

Women who will be 35 and older at the time of delivery have an increased risk for fetal chromosome abnormalities. A discussion about prenatal diagnosis vs. maternal marker screening should include at a minimum: the tests available, age-specific risks, and the availability of genetic counseling. Document the discussion, availability of genetic counseling, and patient decisions.

Tests Available

- **Chorionic Villus Sampling –** A diagnostic test performed in perinatal centers between 10 and 12 weeks gestation.
- **Amniocentesis** - A diagnostic test performed in perinatal centers, prenatal diagnosis clinics, or obstetrics offices between 13 and 20 weeks gestation.
- **Maternal Serum Multiple Marker Screening** – A screening test done in either the 1st or 2nd trimester, or a combined test. See section above. Increasing age of the woman results in higher rate of positive screening results and higher detection rate.

Chromosome Abnormality Risks

Maternal Age at delivery	Risk of chromosome abnormality
35	1/200 (0.5%)
36	1/165 (0.6%)
37	1/125 (0.8%)
38	1/100 (1%)
39	1/80 (1.25%)
40	1/65 (1.5%)
41	1/50 (2%)
42	1/40
43	1/30 (3%)
44	1/25
45	1/20 (5%)
>45	1/10 (10%)

Genetic Counseling - Genetic clinics offer preconception and prenatal genetic counseling to discuss issues involved in prenatal diagnosis and screening and to help the patient/couple make the best decision for themselves based on comprehensive and up-to-date information.

Paternal Age Over 45

Current evidence suggest that there is an increased risk for autosomal dominant genetic disorders caused by new mutations in offspring of fathers 45 years of age or older at the time of conception. The risk for these disorders does not increase dramatically at age 45, but rather the risk increases gradually each year.

The risk for sporadic dominant disorders as a group, is 4 to 5 times higher for fathers 45 and over than for fathers in their early 20's, although the absolute risk is still less than 1% for a given pregnancy.

Examples of autosomal dominant conditions that may be associated with advanced paternal age include achondroplasia, neurofibromatosis, Marfan syndrome, and osteogenesis imperfecta. Because there is

such a variety of dominant genetic disorders that may be related to advanced paternal age, there is no single test available for prenatal diagnosis. An ultrasound can be performed to evaluate fetal growth and development; however, the features of many dominant genetic disorders are not detectable on ultrasound examination.

Ethnic-Based Genetic Carrier Screening

- Carrier screening tests are **optional.**
- Appropriate tests should be offered to patients of particular ethnic backgrounds (see below).
- Counseling about the diseases in question, carrier testing risks/benefits and informed consent should be performed prior to any testing.
- Document carrier testing discussion and patient's decision in the medical record.
- Written information in the form of patient pamphlets or educational brochures is available for each carrier test and is a helpful adjunct to the informed decision making process.
- Many carrier screening tests detect the majority of, but not all carriers. Detection rates may differ by ethnic background of the patient. Informed consent should include the fact that negative carrier tests do not completely eliminate the risk for that genetic condition in future offspring.
- If the patient is pregnant, concurrent carrier screening (i.e. having both patient and father of baby tested at the same time) will allow more time for genetic counseling and discussion of prenatal diagnosis in the case of positive results in both members of the couple.
- Carrier screening prior to the onset of pregnancy allows more options for carrier/carrier couples (i.e. not becoming pregnant, using donor sperm from a non-carrier, prenatal diagnosis, adoption, etc).

Carrier testing procedure

1. Find the patient's and patient's reproductive partner's ethnic backgrounds on the table below.
2. Discuss appropriate carrier screening options with the patient and partner.
3. Give patient and partner written materials for review.
4. If the patient and/or partner choose to pursue screening after an informed decision-making process:
    a. Choose genetics lab. See www.genetests.org for list of labs offering carrier screening for the specific disorder in question.
    b. If patient is found to be a carrier, discuss results, autosomal recessive inheritance, and offer screening to partner/father of the baby if not already tested. Be aware that the significance of various mutations can differ as can the severity of the disorder in question. Consult with genetics about significance of a particular mutation or condition before counseling patient.
    c. If carrier/carrier couple is identified or if patient or partner has questions about results, refer to genetics for comprehensive genetic counseling and family planning/prenatal testing options.
    d. Negative results do not completely eliminate risk. Residual risk for carrier status in a given couple differs by ethnicity (see table in "Pocket Facts").

Ethnic Background	Carrier Tests
Caucasian (Northern or Southern European)	▪ Cystic Fibrosis
Hispanic (Mexican, Central American, Caribbean Hispanic)	▪ Hemoglobinopathy and Beta Thalassemia ▪ Cystic Fibrosis carrier screening is "available"
Asian, Southeast Asian, Taiwanese, Filipino	▪ Alpha Thalassemia and Beta Thalassemia
Italian, Greek, Middle Eastern	▪ Beta Thalassemia ▪ Cystic Fibrosis
Ashkenazi Jewish (Central and Eastern European Jewish descent)	It is considered standard of care for health care providers to offer carrier screening for Cystic Fibrosis, Tay-Sachs disease, and Canavan disease to all patients of Ashkenazi Jewish heritage considering or currently in a pregnancy. **Offer:** ▪ Cystic Fibrosis ▪ Tay-Sachs ▪ Canavan ▪ Familial Dysautonomia **"Make available":** ▪ Bloom syndrome ▪ Fanconi Anemia, group C ▪ Gaucher disease, type 1 ▪ Niemann-Pick disease, type A ▪ Others: (MPS IV, hereditary hearing loss, Von Gierke disease, torsion dystonia?) Consult www.genetests.org for labs offering carrier screening for these diseases. A number of labs offer "Ashkenazi Jewish carrier screening panel." Check to make sure all tests requested by patient are present in the specific panel.
French-Canadian, **Cajun**	▪ Tay-Sachs ▪ Cystic Fibrosis
African American, West African, West Indies, Caribbean (Non-Hispanic)	▪ Hemoglobinopathy (Sickle Cell + other hemoglobin variants) ▪ Beta Thalassemia ▪ Cystic Fibrosis carrier screening is "available"

Positive Family History

If there is a positive family history of a genetic disease, birth defect, chromosome abnormality, mental retardation, etc., and the patient/couple is concerned about the risks in their offspring:

1. Refer the patient/couple to genetics for comprehensive genetic counseling.
2. If referral is not possible, call a genetics center for a phone consultation on how to further assess the risks and manage the situation through your local clinic.

Family history indications for genetics referral or consultation

- Personal or family history of a known or suspected genetic disorder, birth defect, chromosome abnormality, or metabolic disorder
- Family history of mental retardation of unknown or unproven etiology

- Either parent or family member with a chromosome rearrangement
- Patient (or prospective parent) is a known carrier or has a family history of a genetic disorder, e.g. Tay-Sachs, cystic fibrosis, sickle cell disease, thalassemia, Canavan disease, etc.
- Patient (or prospective parent) is a member of an at-risk ethnic or racial group for an autosomal recessive genetic disorder and has questions about carrier testing
- Unexplained infertility or multiple pregnancy losses (three or more 1st trimester miscarriages), or previous stillbirth(s)
- Absence of the vas deferens
- Premature ovarian failure
- Strong family history of cancer or multiple cancers at a young age
- Personal or family history of stroke or blood clots before 50 years, or family history of thrombophilia genetic mutation

Maternal Medical Conditions

Consider referral to or consultation with genetics for preconception or prenatal patient with:

- Diabetes
- Seizure disorder
- Alcoholism or substance abuse
- Inherited metabolic condition (such as PKU)
- Other condition that increases the risk for birth defects and/or fetal complications

Maternal Exposures

Consider referral to or consultation with genetics if the following drugs have been used during pregnancy:

- Accutane – prior to conception or during pregnancy
- Alcohol – over 2 drinks per day or binge drinking
- Cocaine
- Coumadin
- Diethylstilbestrol
- Folic acid antagonists: aminopterin, methotrextate
- Lithium
- Seizure medications: dilantin, tegretol, trimethadione, valproate
- Streptomycin
- Therapeutic radiation
- Occupational exposures: lead, mercury

Consider referral to or consultation with genetics if the following maternal infections have occurred during pregnancy:

- Cytomegalovirus
- Hyperthermia (fever over 101 for over 2 days)
- Rubella
- Toxoplasmosis
- Varicella Zoster

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