ANEUPLOYD DIAGNOSIS IN PREGNANCY

Aneuploid fetuses, those with abnormal chromosomal number, account for approximately 6% to 11% of all stillbirths and neonatal deaths. Chromosomal defects compatible with life but causing significant problems occur in 0.65% of newborns, and another 0.2% have structural chromosomal rearrangements that will lead to problems. Of all Down syndrome pregnancies, approximately 97% are born to families with no history of Down syndrome. Down syndrome and the other autosomal trisomies occur as a result of meiotic nondisjunction, the rate of which increases with maternal age.

The likelihood of a Down syndrome pregnancy diagnosed in the mid-trimester at 35 years of age is approximately 1/250. The risk of any aneuploidy is 1/132. At age 40, the likelihood of a Down diagnosis in the mid-trimester is 1/69, and diagnosis of 1/40 for all chromosomal aneuploidies. By 45 years of age, the likelihood of a Down diagnosis in the mid-trimester rises to 1/19 and an overall aneuploidy diagnosis rises to 1/12.

The likelihood of a live born baby with Down syndrome at 35 years of age is described at 1/384 and the likelihood of all aneuploidies at that age is 1/204 live births. By 40 years of age, the Down syndrome likelihood is increased to 1/106 and of all chromosomal aneuploidies 1/63; by 45 years of maternal age, the likelihood of Down syndrome live birth is 1/30 whereas all chromosomal aneuploidies are 1/19. The risk of having a baby with any chromosomal aneuploidy or Down syndrome is lower in term live births because of the increased association with pregnancy wastage from the mid-trimester to term.

The concept of screening tests versus diagnostic tests must be emphasized here. In years gone by, the only valid screening test for Down syndrome was maternal age. In the late 1960’s a Consensus Development Conference at the National Institute of Health determined that the appropriate maternal age for invasive genetic testing was 35 years of age because at that age the increasing likelihood of a Down baby intersected the constant likelihood of loss from amniocentesis, which at that time was described at approximately 1/287 to 1/300. The development of other screening tests has increased dramatically the likelihood of isolating pregnancies at risk for Down syndrome and for chromosomal aneuploidy. The advent of single-marker AFP testing in the 1980’s in Wales, demonstrated a correlation with low AFP and Down syndrome. Ultimately, a three-marker test was developed involving analytes estriol, alpha-fetoprotein, and total HCG. Most recently, inhibin-A has been added as a fourth analyte leading to the "Quad Screen."

New screening modalities have been developed and tested successfully over the last 8 to 10 years, principally, first-trimester Down syndrome screening. The association of an increased nuchal translucency with abnormal levels of free Beta hCG and PAPP-A have been developed.

It is a general consensus that any woman requesting invasive genetic testing should have access to these modalities: chorionic villus sampling and amniocentesis. Chorionic villus sampling should only be offered after 11 weeks of gestational age (secondary to association of earlier CVS with limb reduction defects) with amniocentesis being offered after 15 weeks gestational age.
In addition to women with abnormal screening tests and women desiring elective testing, women with the following conditions are candidates for invasive genetic testing:

1. previous pregnancies complicated by autosomal trisomy.
2. congenital anomaly identified by ultrasound.
3. prior pregnancy of a sex chromosome aneuploidy.
4. Men or women with a chromosomal translocation.
5. Men or women who are carriers of chromosomal inversions.
6. Parental aneuploidy.

A variety of screening tests are available for Down syndrome in particular. The relative efficiency is compared at a 5% false-positive screen rate. First trimester Down syndrome screening (nuchal translucency, PAPP-A, and free Beta hCG) approximately 85% detection rate; triple screen (AFP, total hCG, and unconjugated estriol) 69%; quad screen (AFP, total hCG, unconjugated estriol, and inhibin-A) 81%; stepwise sequential testing with numerous parameters approximately 95%; and contingent sequential screening at approximately 88% to 94%.

Second-trimester screening has been evaluated and compared with first-trimester screening in the FASTER trial and first trimester testing has been confirmed to have a higher sensitivity for detection of Down Syndrome. It is also clear from the FASTER trial that quad screening at the same false positive rate offers a superior sensitivity over triple screening and should be the test used going forward should a second-trimester screening strategy be employed.

The ability to modify the results of a second trimester screen with ultrasound has been evaluated for many years. This is called a Genetic Sonogram. At Desert Women's Care, we use the data of Bromley et. al, for our genetic sonogram. The following factors are considered markers: 1.) Major anomaly, 2.) short humerus, 3.) echogenic intracardiac focus, 4.) pyelectasis, and 5.) nuchal fold greater than 6 mm. Should zero markers be positive then the likelihood ratio is 0.2; should one marker be positive then the likelihood ratio is 1.9; should two markers be positive then the ratio is 6.2; and should three markers be positive then the likelihood ratio is 8. Using a genetic sonogram strategy, the Quad Screen risk of Down syndrome is multiplied by the likelihood ratio to give the new risk for Down syndrome. The decision point for amniocentesis is most commonly the 1/287 risk that we have used for years.

The BUN study, the FASTER trial, the SURUSS trial, and OSCAR trials have all demonstrated a high detection rate for Down syndrome pregnancies employing First Trimester screening. The advantage of first trimester screening is the ability to begin at 11 weeks and should invasive genetic testing be indicated, either CVS can be performed after 11 weeks or amniocentesis at approximately 15 weeks. The patient is therefore given information which she may elect to use to determine the course of her pregnancy at a much earlier date than with conventional second-trimester screening strategies.

The American College of Obstetricians and Gynecologists Practice Bulletin #77, revised in January 2007, speaks to these issues very clearly. The idea of continuous screening across all maternal ages is emphasized with the old concept of screening by age only being dismissed. It is clear that first-trimester Down syndrome screening with nuchal translucency free Beta hCG and PAPP-A at the same false positive rates yield higher Down syndrome detection rate than does quad screening or triple screening in the second trimester.

Gross variability in gestational age at initial presentation for prenatal care dictates to a large extent which testing modality is practical to implement. Should women present after 13 weeks,
first-trimester Down syndrome screening is not a viable screening alternative. Should first-trimester Down syndrome screening be elected and a screen positive result be returned, valuable considerations remain. Even in situations where invasive genetic testing does not establish chromosomal aneuploidy, those pregnancies are at increased risk for spontaneous demise, for cardiac abnormalities, and other structural abnormalities. Therefore, these patients should be offered targeted scanning in the second trimester to exclude these conditions. Patients with normal first-trimester screening also must be evaluated for open neural tube defect in the second trimester with a single-marker alpha-fetoprotein test and targeted ultrasound as warranted.

As always, it is probably not as critical to obtain information for a patient which she is not prepared to use in formulating a decision about continuing her pregnancy. Women who may not be inclined to intervene should Down Syndrome ultimately be diagnosed by invasive genetic testing may do well to avoid the risk to a normal pregnancy posed by undergoing invasive genetic testing.

Down Syndrome Update

In the March, 2011, edition of the American Journal of Obstetrics & Gynecology, Ehrich and colleagues presented a study of 480 women being screened for Down Syndrome. Maternal blood samples were collected and analyzed using a "shotgun sequencing assay for Trisomy 21 detection using circulating cell - free DNA." In other words, fetal genetic material (DNA) was isolated in maternal blood and tested. A total of 449 samples were fit for analysis. Results are graphically presented:

Of 39 fetuses diagnosed at birth with Down Syndrome, all 39 were correctly identified. Of the 410 fetuses diagnosed without Down Syndrome at birth, all but one were diagnosed correctly. In this paper Down Syndrome screening through maternal blood was 100% sensitive (every affected pregnancy was diagnosed correctly- none were missed). The specificity was 99.7% (one un-
affected child was incorrectly diagnosed). These data are better than those for 1st Trimester Down Syndrome Screening.

Additional larger studies will be required to validate this prospective trial. This technology, however, has clear merit. This is the third study with favorable results. If this technology continues to perform with these outcome parameters as the number of patients increases, it will revolutionize Down Syndrome Screening. Patients will be able to have a clear idea of the diagnosis much earlier in pregnancy than even 1st Trimester Screening can provide. When this day comes, present day screening strategies will be obviated and direct, non-invasive fetal testing will become standard of care.

The manufacturer of this technology is Sequenom. This laboratory is currently able to determine fetal gender and fetal Rh status using maternal blood. As late as last year, the only way to make these diagnoses was either through amniocentesis or cordocentesis. Sequenom assays for fetal gender and fetal Rh status are presently available at DWC. As soon as Down Syndrome screening from maternal serum is commercially available, it will be offered at DWC.