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SCREENING FOR FETAL CHROMOSOMAL ABNORMALITIES

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Today, there are a variety of options available to pregnant women to screen for fetal chromosomal abnormalities. The assortment of screening methods currently available resulted from the advent of prenatal diagnosis, which had its beginnings in 1966. It was the work of Steele and Breg that showed that the chromosome constitution of a fetus could be determined by analysis of cultured cells from the amniotic fluid. With the well-known association that advancing maternal age correlates with increasing risk for Down syndrome, their publication directly led to the development of prenatal diagnosis. Diagnostic testing was soon available. Historically, the most commonly used test for the diagnosis of chromosome abnormalities and open neural tube defects was amniocentesis. The rate of fetal loss related to amniocentesis was quoted as approximately 1/200. Because of this risk, serum analyte screening became important as a noninvasive first step in detecting patients at risk for chromosome abnormality and open neural tube defects.

Medical screening is defined as the identification of those who are sufficiently at risk among otherwise healthy individuals to justify subsequent diagnostic testing. The condition being screened for should be clearly defined and should have a reasonable frequency in the population. The screening test should be expeditious and inexpensive on a large scale. The test should yield few screen positives. Follow-up for definitive diagnosis and management should be well-organized and prompt.

Maternal serum alpha-fetoprotein (MSAFP) testing was originally offered as a predictor for open neural tube defects only. In 1984, Merkatz, et al. in the *American Journal of Obstetrics and Gynecology* reported an association between low alpha-fetoprotein levels and an increased risk of chromosome aneuploidy, specifically Down syndrome and trisomy 18. In December of 1982 a 28-year-old woman at 38 weeks gestation delivered a baby later diagnosed with trisomy 18. The woman reviewed the course of her early pregnancy and recalled that routine alpha-fetoprotein screening reported very low levels of this analyte. Her inquiry into the association of this finding and the diagnosis of her infant sparked the study that launched AFP screening for chromosome disorders.

This initial screen, using MSAFP alone, has a detection rate of approximately 50% for Down syndrome. As shown in Figure 1, the addition of two other analytes, hCG and estriol, then called the triple screen, increases the detection rate for Down syndrome to 69%, using a risk cutoff of 1/190. The addition of inhibin A to the triple screen, now called the quad screen, detects 85% of Down syndrome cases.

While the advance of this screening protocol reduced the number of invasive procedures, test results were not available until the 17th-20th gestational week. First trimester screening was introduced in an effort to provide earlier screening

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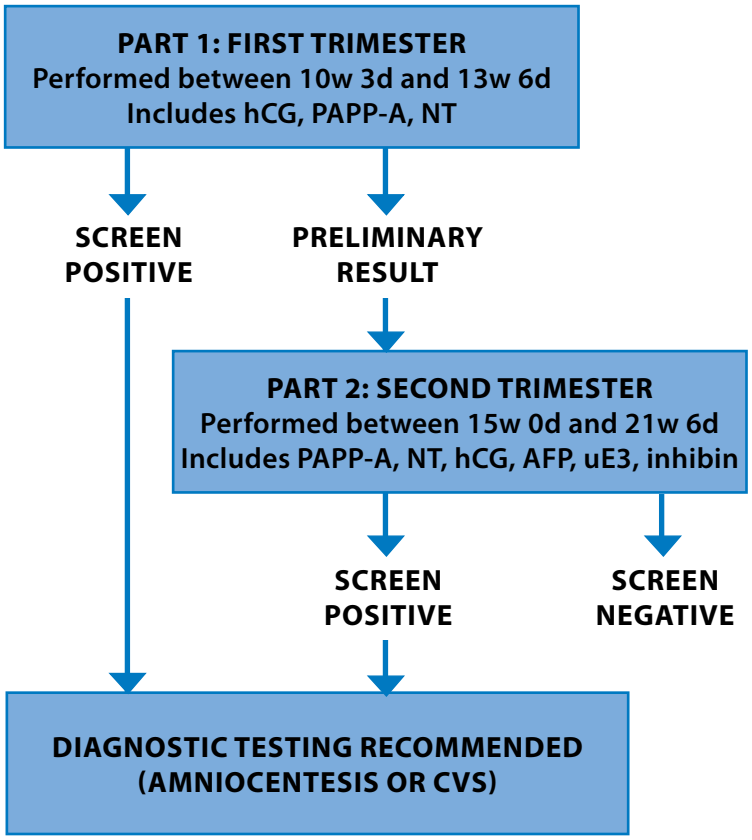
FIGURE 1: SCREENING FOR DOWN SYNDROME

SCREENING STRATEGY	ANALYTES	DOWN SYNDROME DETECTION RATE
Triple Screen	MSAFP, hCG, estriol	69%
Quadruple Screen	MSAFP, hCG, estriol, inhibin A	85%
First Trimester Screen	NT, PAPP-A, free ß-hCG	85%
Integrated Screen	NT, PAPP-A, + quad screen *(all results withheld until the second trimester)*	92%
Serum Integrated Screen	PAPP-A + quad screen	86%
Stepwise Sequential Screen	First trimester screen + quad screen *(results given after each test)*	90%

and follow-up diagnostic testing. The combination of nuchal translucency, free-ß human chorionic gonadotropin (ß-hCG) and pregnancy-associated plasma protein-A (PAPP-A) at 11-14 weeks provides a detection rate of 83% for Down syndrome and 80% for trisomy 18 with a screen positive rate of 5%. In addition, an increased nuchal translucency measurement serves as a marker for an increased risk for congenital heart disease and other genetic syndromes.

Screening protocols continue to evolve. The 2005 First and Second Trimester Evaluation of Risk (FASTER) study by Malone, et al. published in the *New England Journal of Medicine* compared the performance of different screening tests conducted at different times during pregnancy. It compared, in a single population, first trimester screening for Down syndrome with second trimester screening and screening in both trimesters. The results demonstrated that first trimester screening for Down syndrome is highly effective, but combinations of screening markers from both the first and second trimesters yield higher detection rates and lower screen positive rates.

FIGURE 2: SEQUENTIAL SCREENING



While there are several protocols for combined screening, the focus of this discussion is on sequential screening. Sequential screening is a method to screen for Down syndrome, trisomy 18 and open neural tube defects. Illustrated in Figure 2, it incorporates a blood sample and a nuchal translucency measurement performed in the first trimester of pregnancy, preferably between 11 3/7 – 13 6/7 weeks, along with a second blood sample drawn during the second trimester, optimally between 16-18 weeks. A result is generated after both the first and second phase of testing and is reported to the patient separately.

The advantages of sequential screening are early answers with higher detection rates, reduction of patient anxiety and access to early prenatal diagnosis.

The first phase of sequential screening provides a 70% detection rate for Down syndrome with a 1.2% screen positive rate using a risk cut-off of 1/50. For trisomy 18, the first phase of screening provides an 80% detection rate with a screen positive rate of 1.2% using a risk cut-off 1/100. Patients who receive a result greater than the risk cut-off are considered screen positive and do not continue with the second phase of testing. This will serve as their final screening result and they will then be offered diagnostic testing in the form of amniocentesis or chorionic villus sampling (CVS). CVS, like amniocentesis, is diagnostic for chromosome aneuploidy. It involves the withdrawal of a small amount of chorionic tissue from the developing placenta. The procedure is usually performed between the 10th and 12th gestational week offering patients earlier diagnosis. Risk of miscarriage from the procedure is thought to be comparable to the risk of amniocentesis.

Patients who receive a result less than the screening cut-off are recommended to proceed with the second trimester blood draw. The addition of this blood draw increases the detection rate for Down syndrome to 90.4% with a screen positive rate of 3.7% using a risk cut-off of 1/270. The detection for trisomy 18 is increased to 90% with a screen positive rate of 3.7%. The risk cut-off for trisomy 18 remains the same at 1/100. A risk assessment for open neural tube defects will be generated in this second phase detecting approximately 80% of cases.

The advantages of sequential screening are early answers with higher detection rates, reduction of patient anxiety and access to early prenatal diagnosis. It is important to keep in mind that all screening is optional and requires thorough counseling with

Prenatal screening continued...

the patient. The ultimate goal of screening is to reduce the number of invasive procedures, thereby minimizing the risk of pregnancy loss. An additional benefit to reducing the number of invasive procedures is decreasing the overall costs of prenatal diagnosis.

After Part 2 (second trimester) screening, Sequential Screen offers detection rates of 90.4% of fetuses with Down syndrome (3.7% screen positive rate), 90% of fetuses with trisomy 18 (3.7% screen positive rate) and 80% of fetuses with an open neural tube defect.

Fortunately, women contemplating pregnancy today have many different screening and diagnostic options from which to choose. Of all the currently available screening tests, sequential screening appears to result in the highest detection rate at the lowest screen positive rate. However, the ultimate decision about whether to undergo screening at all, and if so, which strategy to choose, lie with the patient and her family. While screening has improved tremendously in the last 20 years reducing the number of invasive procedures, it is important to remember that these are not diagnostic tests and cannot definitively identify chromosome aneuploidy.

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Wendy was born and raised in New York City. She moved to the West Coast in 1979, completing her undergraduate education in Community Health at Oregon State University. She went on to receive her Master of Science in Human Genetics at Sarah Lawrence College in New York.

Wendy has worked in the field of medical genetics since returning to the Northwest following her graduate program. She worked for Legacy Emanuel Hospital for nearly 10 years in its Department of Medical Genetics educating patients and families on genetic screening and diagnosis and offering counseling for fetal abnormality following the diagnosis of a genetic disease. She also served as the department's clinical coordinator.Wendy has served as the clinical coordinator at Northwest Perinatal Center since joining the practice in 1994.

Wendy has been published in the *American Journal of Medical Genetics* and *Prenatal Diagnosis*. She has presented at the National Society of Genetic Counselors and the American Society of Human Genetics. She is certified in Genetic Counseling by the American Board of Medical Genetics and is a founding member of the American Board of Genetic Counseling.

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Jeri was born and raised in Portland, Oregon. She received her Bachelor of Science degree in Biology from Willamette University. She went on to attend Sarah Lawrence College in New York where she received her Master of Science degree in Human Genetics.

Jeri has been a Genetic Counselor at Northwest Perinatal Center for more than 10 years. She provides comprehensive prenatal genetic counseling and amniocentesis follow up. Her clinical experience also includes The Cystic Fibrosis Center at St. Vincent's Hospital and Medical Center, the Department of Pediatrics/OB-GYN at Nassau County Medical Center, and the March of Dimes Resource Center in New York; the Section of Genetics at St. Joseph's Hospital and Medical Center in New Jersey; and the Genetics Clinic/Prenatal Diagnosis Center at Oregon Health & Science University.

Jeri has spoken on prenatal genetics topics at various organizations, including the Oregon Society of Medical Assistants and Pediatric Services of America. She is certified by the American Board of Genetic Counseling and is a member of the National Society of Genetic Counselors.

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The clinicians of NORTHWEST PERINATAL CENTER specialize in complete medical services for the highest risk pregnancies. We are located in Portland, Oregon in the Peterkort medical offices near Providence St. Vincent Medical Center. We provide comprehensive high-risk obstetrical care that includes:

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  - fetal complications

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