Maternal Serum Marker Screening for Down Syndrome

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Prenatal screening for Down syndrome is continuously being refined. Initially, the screen was limited to the health care provider's consideration of the mother's age at delivery, once the association between advanced maternal age (i.e. maternal age 35 or older at delivery) and increased risk for Down syndrome was recognized. Asking, 'How old are you?' completed the screening process. In the late 1970's a collaborative study in the United Kingdom was published which associated elevated maternal serum alpha-fetoprotein (MSAFP) with an open neural tube defects (NTD) in the fetus. Serendipitously, an association between low MSAFP and Down syndrome pregnancies was recognized, and by 1986 MSAFP alone was being utilized to achieve the detection of 30% of Down syndrome fetuses in women under the age of 35. By 1988, a complex algorithm using maternal age, and the maternal serum analytes AFP, human chorionic gonadotropin (hCG), and unconjugated estriol (uE3) was developed which achieved a 60 - 80% Down syndrome detection rate. In 1993-1994, multiple marker serum screening for all pregnant women under the age of 35 years was recommended by the American College of Obstetrics and Gynecology and the American College of Human Genetics. It has become standard of care to offer multiple marker serum screening for pregnant women under the age of 35 years and amniocentesis to those 35 years or older.

Improvements in screening the fetuses of low risk pregnant women for Down syndrome are constantly being made. For example, new analytes in the second trimester serum, as well as first trimester serum and urine are being investigated, and currently various combinations of 2,3 or 4 serum markers are offered. The variety of screening profiles available can make choices difficult for patients and primary care providers. Seeking advice from a prenatal diagnosis center is recommended. Ultrasound assessment of the fetus, including nuchal skin fold thickness, has also been proposed as a variable to adjust Down syndrome risk. Individual laboratories offer different multiple marker screens, for which they have determined their own detection rate and initial positive rate (also called false positive rate). Hence each laboratory provides its own risk figure for a given sample, based on the analytes and information provided. It is important to recognize that all screening analyses serve only to adjust the risk to the pregnant woman, and definitive diagnosis of Down syndrome can be made only by chromosome analysis of fetal tissues obtained by CVS, amniocentesis or PUBS. It is a challenge for health care providers to choose the most appropriate Down syndrome screening assessment for their patients. It would exceed the scope of this publication to address the specifics of each analyte combination, risk algorithm, risk cutoff, detection rate, and goal for the various screening profiles which are available. It is recommended that providers learn about the specific laboratory studies available to their patient population.

In multiple marker screening, the "bottom line" maternal risk calculation for Down syndrome must start from accurate patient personal information in order for the interpretation to be valid. Each piece of information about the patient and each of the laboratory's analyte levels has equal weight in the algorithm used to calculate the Down syndrome risk. The Foundation for Blood Research and the College of American Pathologists recommend that the patient report should include:

1. The gestational age (GA)
2. How the GA was calculated (LMP, US, physical exam, etc.)
3. Patient's age at delivery
4. The age-related Down syndrome risk
5. The patient's weight, race, diabetic status
6. The multiple of the median (MoM) values for each analyte
7. And the Down syndrome risk based on the above

As an added service, many laboratories also provide a written interpretation and/or suggested clinical actions based on the interpretation. One limitation of multiple marker screening is that Down syndrome risk for pregnancies with multiple fetuses cannot be assessed. The variety of available screening profiles is constantly expanding. The best use of this tool requires that the health care providers confirm patient information on the report and understand the specific screening parameters used by the laboratory. Each laboratory has a responsibility to provide information about their screening program, educate clients as needed, and discuss report specifics when indicated.

In summary, multiple marker screening is a valuable tool to assess the risk of Down syndrome in a given pregnancy, but the accuracy of any approach depends on accurate pregnancy dating and patient information as well as the reliability of the screening parameters utilized by a particular laboratory. Again, the definitive diagnosis of Down syndrome in the second trimester is made by chromosome analysis of amniocytes and the multiple marker screening should not be mistaken for a diagnostic test.

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