American Society of Human Genetics Policy Statement for Maternal Serum Alpha-Fetoprotein Screening Programs and Quality Control for Laboratories Performing Maternal Serum and Amniotic Fluid Alpha-Fetoprotein Assays

PREAMBLE

—MSAFP values are used primarily but not solely to predict occurrence of open neural tube defects in the fetus; their use for prediction of Down syndrome is a new initiative under investigation.

—The test is a good one, as far as such a test can be, but it is imperfect, because false-negative and false-positive results both occur. In other words, it is not an infallible test.

—To use the test as effectively as is currently possible requires a program capable of supplying baseline values in sufficient number and the follow-up procedures necessary for interpretation of positive tests. In other words, it is not simply an office test.
Because there is no effective treatment to relax the burden of neural tube defects in the large majority of patients, at the present time prevention of disease involves termination of pregnancy. In other words, use of the test is value laden and controversial for some sectors of society.

— Despite its imperfections, the need for an elaborate societal structure to apply it, and its value-laden context, the test is considered by many as a necessary procedure to maintain normal standards of practice. Indeed, the American College of Obstetricians and Gynecologists (ACOG) issued a statement advising its Fellows to be aware of the availability of MSAFP testing and to discuss such testing with patients.

— It is natural that confusion about protocol and anxiety about practice and its consequences are prevalent in this context. The ASHG offers here a statement about issues that affect MSAFP testing and the attendant pitfalls.

INTRODUCTION

In 1973, it was first reported that raised levels of MSAFP were associated with fetuses who had anencephaly or open spina bifida cystica. Screening programs were then established, first in Great Britain and later in the United States and other countries, to exploit this association as a screening test for the antenatal detection of open neural tube defects. As data were accumulated, it was found that abnormal levels (both high and low) of MSAFP were also predictive of other adverse pregnancy outcomes, including imminent miscarriages, fetal demise, eventual prematurity, and more recently, Down syndrome. In May of 1985, the ACOG distributed an alert to obstetricians, and, since then, there has been a marked increase in the number of physicians and other health care personnel who utilize MSAFP screening.

The ASHG is concerned that there is frequently a lack of understanding about this test, the purpose of the alpha-fetoprotein screening, the types of conditions that can be detected, and when the test should be performed. There has also been inadequate education of physicians, other health care personnel, and, most importantly, the patients.

The ASHG has prepared this policy statement in order to communicate its views on the subject of prenatal MSAFP screening and the related functions of diagnostic testing and quality-control procedures.

Despite the promise and utility of biotechnology, it cannot be overemphasized that, even in the best circumstances, professionals in the field of human genetics will continue to practice in an environment that is somewhat characterized by doubt and uncertainty. It is the burden of professionals to have responsibility in an imperfect world. However, since procreative decision making arises from the application of MSAFP screening, it is the responsibility of professionals to provide the most accurate, nondirective, understandable, and scientifically probabilistic information to patients and their mates. Directive counseling of “screened” patients should be avoided.

The ASHG wishes to emphasize the following points:
1. MSAFP screening is a screening test and is not diagnostic.

2. MSAFP screening is becoming part of routine obstetrical care, and potential applications are still unfolding. Therefore, ongoing educational programs are urgently needed for providers of obstetrical care and for patients. Patients, especially, should be able to make a fully informed decision regarding their participation. Counseling of these patients regarding MSAFP should be nondirective and should begin early in pregnancy so that their decision is informed and unhurried.

3. MSAFP screening should be voluntary. The provider should indicate its availability, educate the patient about its potential, and allow the patient to make decisions concerning participation in screening and in consequent steps in the management of the pregnancy.

4. MSAFP testing should only be undertaken in conjunction with a competent laboratory and a comprehensive program that provides (a) prompt reporting of test results to the provider of obstetrical care, (b) appropriate counseling of patients with abnormal test results, and (c) adequate confirmatory procedures, including level II ultrasound and amniocentesis when indicated.

5. The ASHG strongly supports regulations for quality control of any laboratory involved in carrying out MSAFP screening and amniotic fluid AFP (AFAFP) determinations.

6. The program characteristics outlined above provide a framework for this policy statement. The procedures outlined in this statement may not be appropriate for women in high-risk categories, such as those with a family history of neural tube defects or Down syndrome or those who have insulin-dependent diabetes mellitus (IDDM).

ASHG POLICY STATEMENT FOR MSAFP SCREENING

1. Before MSAFP screening is started, the following minimal criteria should be met:
   a. Adequate physician/health-professional education
      The objective of this education is to ensure that physicians and other health care professionals understand the nature and range of severity of each of the detectable conditions and anomalies, the objectives of screening and testing, the importance of timing and reporting the low predictive value of test results, and the follow-up procedures and counseling outlined below.
   b. Access to a qualified MSAFP and AFAFP testing laboratory
      Criteria for quality control in these laboratories are detailed later in this document.
   c. Adequate facilities and personnel for follow-up of abnormally high or low MSAFP values
      Counseling, level I and level II sonography, amniocentesis, and qualitative amniotic fluid acetylcholinesterase (AChE) assay should be available.
d. Adequate patient education
   Information should be provided on the nature of the defects detectable by AFP screening, on confirmatory procedures, and on the options available should an abnormal result be confirmed.

2. The optimal time for MSAFP screening is between 16 and 18 weeks of gestation.

3. A common MSAFP screening protocol would include:
   a. First serum specimen evaluation
   b. Second serum specimen evaluation (if indicated)
   c. Counseling
   d. Ultrasonography
   e. Amniocentesis
   f. AFAFP testing (AChE and fetal blood evaluation)
   g. Karyotyping

4. Once the program is underway, physicians’ offices, laboratories, and referral centers should have staff available who can answer questions concerning procedures related to MSAFP screening. Educational brochures that are appropriate for the population being served should be made available to patients, which is to say that accurate clinical and incidence data should be clearly stated in lay language.

5. Before the specimen for MSAFP testing is obtained, the patient should have been fully informed about the procedure and its implications and should indicate her willingness to be tested. For religious and ethical reasons, some couples may not want to be confronted with the dilemmas posed by an abnormal test result. Prenatal MSAFP screening should be voluntary. The provider should indicate its availability, educate the patient about its potential, and allow the patient to make decisions concerning participation in screening and in the sequential steps in the management of pregnancies. The patient’s decision on whether or not to have MSAFP screening should be documented by such means as her written signature.

6. Both high and low MSAFP values may be predictive of a serious birth defect or adverse pregnancy outcome. Screening protocols vary in whether programs request a second sample before proceeding with follow-up. Second samples are most appropriate when (a) the first MSAFP is minimally elevated and (b) there is time for a second specimen. When the result is very elevated and expert sonography that is capable of detecting a fetal defect is available, or when the pregnancy is relatively advanced, some centers dispense with a second sample. Appropriate information and counseling should be made available to the patient during each step of the process.

7. The designation of elevated (or investigationally low) MSAFP values should depend on characteristics of the patient (e.g., age and health status) and on the prevalence of the defect in the population being screened. The risk of Down syndrome of a 35-year-old woman (i.e., 1/270 in the second trimester) would be reasonable for defining the cutoff point for low values.
8. When incorrect gestational age, multiple gestation, and fetal demise have been excluded by level I ultrasound as causes for elevated results, there should be prompt consultation or referral to a center where level II ultrasound, amniocentesis, and other confirmatory techniques are available. Both levels of ultrasound should be performed by those experienced in sonography.

9. Laboratory measurements are obtained in quantitative units (nanograms or international units per ml), frequently reported as multiples of the median (MOM). Such expressions do not address the degree of risk to the individual patient. As data are collected to permit an estimate of risk in subpopulations whose members are comparable to the woman being screened, laboratories should include in the laboratory report information about the risk to the woman on the basis of her test result.

10. Pregnant women with IDDM should be considered as a separate category. AFP levels are lower, on average, for women with IDDM, and this should be taken into consideration when interpreting results.

ASHG POLICY STATEMENT FOR QUALITY CONTROL IN MSAFP AND AFAFP TESTING LABORATORIES

The ASHG recommends that states or other licensing agencies establish reasonable guidelines for quality control of laboratories performing MSAFP and AFAFP assays.

1. A working relationship should be established to ensure appropriate and timely flow of specimens and information among the laboratory, the provider of obstetrical care, and the critical support services (a clinical genetics unit, high-risk obstetrical service, and an expert ultrasonographer).

2. Before routine screening, the laboratory should provide documentation of (a) its expertise with assays for serum AFP and for amniotic fluid and (b) its access to qualitative gel AChE and fetal hemoglobin assays.

3. Each laboratory should establish reference data for normal MSAFP and AFAFP values between 15 and 20 weeks of gestation for its own population, update the data periodically, and inform physicians and referral centers of revisions.

4. Higher volume assures better quality control. To accomplish this, screening should be centralized, especially in areas of low population density. At frequent intervals, laboratories should review the most recent results, compare them to previous results to ascertain changes in the median and dispersion of values, and investigate the causes of variation.

5. Participation in and documentation of satisfactory performance in an external quality-control program specifically directed at MSAFP screening and AFAFP interpretation should be required.

6. The appropriate state agency should qualify or license laboratories to perform the specific assays. States or regions lacking such certification programs should establish them.
7. In order to evaluate test results properly, laboratories should obtain the following information for each patient:
   a. Date of birth
   b. First day of last menstrual period
   c. Results of ultrasonograph, if available, for gestational dating
   d. Patient’s weight at the time the MSAFP sample was obtained
   e. Whether the patient is an insulin-dependent diabetic
   f. Patient’s race
   g. Family history of open neural tube defect or other midline birth defects and chromosomal abnormalities
   h. Date sample was collected
   i. Geographic residence of patient

8. Protocols should exist for adjusting serum AFP values for gestational age.

9. The laboratory report should contain a quantitative expression of the AFP level or patient-specific risks for relevant genetic anomalies and conditions. The MOM should be calculated using the laboratory’s own reference data for each specific week of gestation. Such reports should include a statement regarding:
   a. The relevance of the AFP level to open neural tube defects (and, as information is collected to permit an estimate of patient-specific risks on the basis of her test result and relevant clinical data, laboratory reports should contain patient-specific risks)
   b. An age-specific risk for Down syndrome
   c. An adjusted risk for Down syndrome, as determined on the basis of MSAFP values and maternal age

10. Policies should be established for telephoning all abnormal results directly to the patient’s physician and making consultative and counseling services available to the patient.

Evolving Aspects

Understanding the evolving aspects of the field of MSAFP screening requires that screening criteria be clearly understood. MSAFP screening calls for the identification of a subgroup in which at least two criteria are met: (1) all gravidas screened into the risk subgroup should be of sufficient risk to warrant being given the option of further diagnostic testing (which in itself carries calculable risk) and (2) gravidas with fetuses with open neural tube defects should be found within the subgroup. Research is underway to establish criteria to identify another subgroup of gravidas with fetuses with chromosomal trisomic disorders.

1. Median Levels of MSAFP by Pregnancy Subgroup

The distribution of MSAFP test results is influenced by demographic and medical characteristics of the patient, including race, IDDM, and maternal weight. The effect has been well established for the first two factors, which are also associated with different rates of occurrence of neural tube de-
fects—lower in blacks than in whites and higher (as are other defects) in infants of diabetic mothers. As such factors are identified, consideration should be given to establishing separate normative values for them, individually or in combination, and reporting the results on the basis of the distribution curve most applicable to the patient.

2. Application of MSAFP Screening to the Detection of Chromosomal Trisomies

MSAFP screening for Down syndrome is being conducted on an investigational basis now. Kits for MSAFP screening have been licensed for sale only for their ability to detect defects indicated by elevated MSAFP levels, primarily neural tube defects. Before these kits are used routinely for Down syndrome, which is associated in some pregnancies with low MSAFP concentrations, they should be subjected to the same careful scrutiny as they were given in the case of defects that elevated the concentration of MSAFP. At the present time, there may be a greater chance of error for low MSAFP concentrations than for high ones.

3. Provider Modalities

MSAFP screening for open neural tube defects is a developing biomedical technology. Several provider modalities have developed thus far. These range from decentralized to moderately regulated to highly centralized or regional systems in a number of (U.S.) states and Canada.

GLOSSARY

Acetylcholinesterase (AChE). Acetylcholinesterase is an enzyme that is found in conjunction with neural tissue. An assay for the presence of this enzyme in amniotic fluid is qualitative gel electrophoresis, which is useful in identifying pregnancies with open neural tube defects.

Alpha-Fetoprotein (AFP). Alpha-fetoprotein is an alpha globulin that is an important serum protein in early fetal life. It is synthesized initially by the yolk sac and later, and more importantly, by the fetal liver. It passes into the fetal bloodstream—and hence through the kidneys into the urine—and then is excreted into the amniotic fluid (at which point it is designated AFAFP). AFP is also found in maternal blood or serum, but in much lower concentration than in the amniotic fluid. AFP can be measured in international units or in mass units such as nanograms or micrograms.

Gestational Age. Gestational age is defined as the number of days elapsed since the first day of the last normal menstrual period; when clinical information or testing shows this to be in error, gestational age may be calculated as the number of days from known or suspected conception plus 14 days.

Level I Ultrasound. Level I ultrasound involves estimation of gestational age by fetal measurements. Level II ultrasound is a detailed examination of the fetus.
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