First-Year Results of Routine α-Fetoprotein Testing on Prenatal Patients in a Family Practice

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For one year all pregnant women presenting to a family practice clinic for prenatal care were routinely tested for maternal serum α-fetoprotein levels (MSAFP). Unexpectedly, 14 (15.7 percent) of 89 tested patients had low MSAFP levels.

All 14 pregnant women underwent appropriate diagnostic workups because of the low MSAFP level and were subsequently followed until delivery. Although the literature reports that low MSAFP levels are associated with chromosomal anomalies, none of the 14 women were delivered of infants with anomalies.

Reasons for the unexpectedly high rate of abnormal MSAFP levels were investigated. Investigation revealed that normal values for MSAFP tests had been derived from testing performed on high-risk pregnant women who had an inherently higher rate of abnormal pregnancies and, apparently, a different range for normal MSAFP levels than a population of unselected family practice patients.

The results of this study demonstrate that it may not be appropriate to apply diagnostic algorithms based on data derived in high-risk subspecialty clinics to unselected patients in a family practice.

In recent years measurement of maternal serum α-fetoprotein (MSAFP) levels during pregnancy has been used to facilitate antenatal detection of neural tube defects, such as anencephaly, encephalocele, and open spina bifida.[1–4] Pregnant women who have a high MSAFP level at 15 to 22 weeks' gestation can be evaluated further with ultrasound and amniotic fluid testing to determine whether a neural tube defect is present in the developing fetus.[1–4] Antenatal detection of neural tube defects allows the physician to plan for appropriate surgical management of operable defects and to provide necessary counseling to parents who desire information about aborting an affected fetus.

Low levels of MSAFP have also been associated with abnormal fetal outcomes. Women whose MSAFP levels are low are at increased risk to deliver infants with such chromosomal abnormalities as trisomy 21.[5–7]

Based on the above information, protocols for antenatal MSAFP testing have been published and widely disseminated.[2,4,8,9] National specialty societies, such as the American College of Obstetricians and Gynecologists, have recommended that MSAFP screening be offered to all pregnant women at the appropriate time during pregnancy.[10]

Nonetheless, controversy surrounds the routine use of MSAFP testing for antenatal detection of chromosomal anomalies and neural tube defects.[11–14] Some of the controversy involves the ethical issues associated with termination of pregnancies that would result in handicapped, but otherwise healthy, children.[11,12]

Much of the controversy, however, has to do with the sensitivity, specificity, and predictive value of antenatal MSAFP testing. MSAFP testing is extremely nonspecific, resulting in the application of potentially harmful technological interventions, such as amniocentesis,[15] to large numbers of women who are found ultimately to have a normal pregnancy. It has been reported that less than 20 percent of women who have an elevated MSAFP level will be delivered of an infant with a congenital defect.[1,2] The specificity of low MSAFP levels is even lower; only a small minority of women with low MSAFP levels will be shown at amniocentesis or delivery to have an infant with a chromosomal anomaly.[5–7]

When considering the predictive value of an abnormal MSAFP test, family physicians have yet another issue with which to contend. All current MSAFP screening recommendations are based on data gathered in practices of obstetricians whose patients have higher risk profiles than

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patients typically managed by family physicians. If the underlying incidence of neural tube defects and chromosomal anomalies is different among family physicians' patients than among patients of high-risk obstetricians, the predictive value of abnormal MSAFP tests will also be different in each of the two practice settings. Because the incidence of many pregnancy complications is higher in the practices of high-risk obstetricians, and interpretation of other tests differs in the practices of primary care physicians from those of obstetricians with referral practices,[16] this effect may also be important in interpreting the results of MSAFP testing.

The present study was undertaken to provide information on the results of a MSAFP screening program in a family practice. Women presenting for prenatal care were tested routinely between 15 and 22 weeks' gestation for abnormal MSAFP levels. This article reports the results of the first year of routine screening.

METHODS

The Family Practice office is a university-based residency teaching clinic at the University of Arizona College of Medicine in Tucson. Each year approximately 22,000 patient visits are made to the facility, and family practice residents and faculty deliver approximately 120 babies.

Testing Protocol

In late 1986 physicians in the clinic began routinely measuring MSAFP on all pregnant women between 15 and 22 weeks' gestation. Women were not tested if they presented for care after 22 weeks of gestation or if they missed all prenatal visits between 15 and 22 weeks.

MSAFP assays were performed by the clinical laboratory at the University Medical Center. The University Medical Center laboratory provided a normal median value for MSAFP test results for each gestational week between 15 and 22 weeks, as the normal range for MSAFP changes with gestational age.[4] High MSAFP levels were defined as those more than 2.5 multiples of the median value; low levels were defined as those less than 0.4 multiples of the median.[2,4]

Women whose values were abnormal were referred for ultrasound examination to confirm gestational age and to exclude sonographically visible structural anomalies. If gestational age was confirmed and the sonogram findings were normal, women were offered genetic counseling by a specially trained staff. Subsequently, amniocentesis was performed on women who desired the procedure to detect chromosomal anomalies (if the MSAFP was low), or to detect elevated amniotic fluid α-fetoprotein as an indicator of neural tube defect (if the MSAFP was high).

Women who developed risk factors or complications of pregnancy that necessitated referral to an obstetrician were routinely referred to the high-risk center at the University Medical Center. Outcome information on all such patients was available and has been included in the data analysis.

Statistical Analysis

The chi-square statistic, analysis of variance techniques, and Fisher's exact test were used to detect differences between patients with normal and abnormal MSAFP test results. Significance was defined as a P value of less than or equal to .05.

RESULTS

Subjects

Of the approximately 120 patients followed for pregnancy care during the past year, 89 were receiving care during the appropriate gestational interval for measurement of MSAFP. Each of these patients had their serum tested for α-fetoprotein. These subjects represented a healthy patient population with a relatively uncomplicated reproductive history. Basic demographic and reproductive information on the patients is displayed in Table 1.

α-Fetoprotein Test Results

Of the 89 patients, 15 (16.8 percent) had an abnormal MSAFP level. Of these 15 abnormal levels, one was high and 14 were low.

High MSAFP Levels

The single patient with an elevated MSAFP level represented 1.1 percent of the total group of 89 patients (95 percent confidence limits, 0 to 3.3 percent). The patient underwent a level II ultrasound examination, which confirmed that her gestational age was correct; no sonographically visible structural anomalies were detected.

This patient was referred for genetic counseling and subsequently underwent amniocentesis. Results of studies drawn at amniocentesis were normal, including amniotic fluid α-fetoprotein levels. The patient subsequently gave birth to a healthy normal infant.

TABLE 1. CHARACTERISTICS OF TEST SUBJECTS

Characteristic	All Subjects (n = 89) No. (%)	Subjects With Normal MSAFP (n = 74) No. (%)	Subjects With Abnormal MSAFP (n = 15) No. (%)
Age (years, mean ± SD)	25.9 ± 5.74	25.5 ± 5.8	27.9 ± 5.4
Race/Ethnicity			
Hispanic	32 (40.0)	27 (40.9)	5 (35.7)
White	31 (38.8)	25 (37.9)	6 (42.9)
Black	9 (11.3)	9 (13.6)	0 (0)
Oriental	3 (3.8)	1 (1.5)	2 (13.3)
American Indian	3 (3.8)	3 (4.5)	0 (0)
Other	2 (2.5)	1 (1.5)	1 (6.7)
Prior reproductive history			
Gravidity (mean ± SD)	2.66 ± 1.56		
Parity (mean ± SD)	1.25 ± 1.33		
Prior preterm deliveries	9 (10.1)	8 (10.8)	1 (6.7)
Prior intrauterine fetal deaths	2 (2.2)	2 (2.7)	1 (0)
Prior infant deaths	3 (3.4)	2 (2.7)	1 (6.6)
Prior congenital anomalies	0 (0)	0 (0)	0 (0)

MSAFP—maternal serum α-fetoprotein; SD—standard deviation

Low MSAFP Levels

Fourteen patients had low MSAFP levels. This number represented 15.7 percent of the total group of 89 tested patients (95 percent confidence limits, 8.1 to 23.3 percent).

All 14 patients underwent level II sonographic examination, which confirmed gestational age in each case. Results of all ultrasound studies were normal; no structural defects were detected.

Only six of 14 patients agreed to be referred for genetic counseling. After counseling, four of these patients underwent amniocentesis. Chromosome analysis and other amniotic fluid studies were normal in all four patients.

Of the group of 14 patients with low MSAFP test levels, 13 were followed until delivery. All 13 gave birth to normal infants, none of which had evidence of chromosomal or structural defects. One of the 14 patients was not followed until delivery because she had moved to another city prior to term. This patient, however, was one of those who underwent amniocentesis with normal results. Thus, no evidence of chromosomal anomaly was detected in any of the 14 infants whose mother had a low MSAFP level.

MSAFP Levels and Overall Pregnancy Outcome

The 15 patients who had abnormal MSAFP levels were compared with the 74 patients who had normal levels to determine whether there were differences between the two groups for any of the demographic or historical items listed in Table 1. No significant differences were found.

Patients with normal and abnormal α-fetoprotein levels were also compared to determine whether there were differences between the two groups in various pregnancy outcomes, such as birthweight, Apgar scores, and rates of referral to the high-risk obstetrics department. No differences were found. In addition, no patient with an abnormal MSAFP had a serious adverse pregnancy outcome, such as intrauterine fetal death, neonatal death, or congenital anomalies (Table 2).

DISCUSSION

The single patient in this series who had an elevated MSAFP level represented 1.1 percent of the total group of 89 patients. This percentage is approximately the same as was expected based on reports in the literature.[1–3] This patient had a normal infant, but as the predictive value of an elevated MSAFP level is low, this outcome is not unexpected. Thus, this experience with high MSAFP levels, although limited, is in accordance with the experience of others.

On the other hand, a 15.7 percent rate of low MSAFP levels was unexpected and was much higher than reports in the literature would suggest.[5–7] Fourteen of 89 mothers had low MSAFP levels, and each of these mothers was subjected to the potential emotional distress that occurs during evaluation of an abnormal pregnancy-related laboratory test.[17] In addition, several mothers underwent invasive and potentially harmful testing (amniocentesis). While it is understood that the predictive value of MSAFP testing is poor, and that most patients with a low level

TABLE 2. PREGNANCY OUTCOMES OF TEST SUBJECTS

Outcome	All Subjects (n = 89) No. (%)	Subjects With Normal MSAFP (n = 74) No. (%)	Subjects With Abnormal MSAFP (n= 15) No. (%)
Term deliveries	79 (88.8)	66 (89.2)	13 (86.7)
Birthweight (g)	3,365 ± 541	3,381 ± 493	3,284 ± 756
Apgar, 1 minute	7.95 ± .86	7.97 ± .84	7.86 ± .95
Apgar, 5 minute	8.96 ± .40	8.96 ± .44	9.00 ± 00
Congenital anomaly	0 (0)	0 (0)	0 (0)
Preterm deliveries (<36 wk)	4 (4.5)	3 (4.1)	1 (6.6)
Spontaneous abortion	0 (0)	0 (0)	0 (0)
Therapeutic abortion	0 (0)	0 (0)	0 (0)
Intrauterine fetal death	0 (0)	0 (0)	0 (0)
Neonatal death	0 (0)	0 (0)	0 (0)
Referred to high-risk obstetrics* (delivery outcomes known)	7 (7.9)	5 (6.8)	2 (13.3)
Lost to follow-up	6 (6.7)	5 (6.8)	1 (6.6)**

** Excludes referral for genetic counseling or amniocentesis because of abnormal MSAFP*
*** This patient had normal amniotic fluid studies*
MSAFP—Maternal serum α-fetoprotein

will ultimately have a normal infant, it is nonetheless disturbing that such a high percentage of patients had abnormal test results.

The findings of this study led to a consideration of the factors that may have contributed to the high rate of abnormally low MSAFP levels identified. Several possible factors were considered.

The first possibility is that the high rate of low MSAFP levels was merely a statistical irregularity occurring by chance in a relatively small subject population of 89 patients. This event is unlikely. Based on a sample size of 89 subjects, the calculated 95 percent confidence limits suggest that a 15.7 percent rate of abnormal findings is an accurate statistical estimate that the true frequency of abnormally low test results is at least 8.1 percent. Were the true rate as low as 8.1 percent, this frequency of abnormal tests results would still be unacceptably high for routine testing programs. If recommended protocols were followed, one of every 12 pregnant women (8 percent) might undergo amniocentesis to evaluate an abnormal MSAFP level.

A second possibility that might explain the high rate of abnormal MSAFP levels is that the currently recommended MSAFP protocols always result in such high rates of abnormal test results but that this finding has not been adequately reported in the literature. Recent reports acknowledge that low MSAFP levels occur too frequently[7,18–20] and indicate that with further modifications of MSAFP testing protocols, the specificity of the test might be improved.

For example, it has been suggested that the risk of trisomy 21 can not only be calculated as a function of MSAFP levels, but can also be adjusted for maternal age, weight, and race, and that amniocentesis should then be offered only if the calculated risk of chromosomal anomaly exceeds the risk of trisomy 21 in 35-year-old women.[18] According to the literature, this approach would set a cutoff point so that only 5 percent of women aged under 35 years are offered amniocentesis, which would be a clear improvement over the 15.7 percent found in the present study.[18]

A third possibility that may help explain the frequency of abnormal MSAFP levels found in this study is that the normative values for MSAFP were not appropriate for use in the population of patients seen by family physicians. The high rate of abnormal MSAFP values found in this study prompted a review of the source data from which the University Medical Center laboratory had established normal values.

The normative median MSAFP levels provided by the University Medical Center laboratory were based on data collected between 1979 and 1985, a period during which routine MSAFP testing was not being performed. During that time, MSAFP levels were being ordered by the University Medical Center Obstetrics Department on patients who had specific indications for the test, such as prior congenital anomalies. After a large number of tests had been performed, the laboratory reviewed the MSAFP levels from all pregnant women who produced normal infants, and used these levels to establish normal median values.

It is likely that application of these "normal" values (derived from a nonnormal referral population) to unselected primary care patients was the principal cause of

the high rate of abnormal values found among patients in the Family Practice office. The highly selected referral patients from whom the normal levels were derived probably represented a completely unique subject population, with a different incidence of congenital anomalies and different median and mean MSAFP values than would be found in an unselected normal population seen in the office of a primary care physician. This selection bias probably resulted in an inordinately large percentage of family practice patients having MSAFP levels that fell outside the "normal" range that was calculated by the University Medical Center laboratory, because the normal range was not derived from a population of normal patients.

CONCLUSIONS

This report provides the results of the first year of routine prenatal MSAFP testing in a family practice. An unacceptably high rate of abnormally low values was found, leading to the performance of unnecessary diagnostic tests.

The reason for the unexpectedly high rate of abnormal tests results was probably related to the "normal" values with which test results were compared, having been derived from a high-risk obstetric population. Since predictive values of laboratory tests are related to the prevalence of disease in the population being tested,[21] it may not be appropriate for family physicians to apply normative data derived in high-risk subspecialty clinics to their population of unselected family medicine patients.

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Commentary

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How often do primary care physicians find themselves wondering why what they learned in medical school and residency just does not seem to work in practice? How frequently do physicians' personal experiences run counter to what they read in medical journals? This was the case for Dr. Barry Weiss and his fellow physicians, as he reports in the preceding paper.[1] Their application of recommended protocols proved to be much less efficacious than they had expected. Why? As he surmises, the problem is with a number that is forgotten too frequently: the denominator.

Both clinical medicine and clinical research have a numerator and a denominator, the numerator being the patients we see or study, and the denominator being all patients with a particular characteristic or disease. We tend to draw conclusions from the numerator because it represents the subjects for whom data are available. The denominator, although just as essential to clinical judgment or to the validity of a study, is much more difficult to characterize. Not only is the denominator composed of subjects whom we treat, but also of those who were lost to follow-up, those who have the disease but do not seek medical attention or seek it in another setting, and those for whom treatment was recommended but who refused to comply. If research findings are to be generalized, the pertinent denominator is the population to which the study results will be applied. Primary care physicians should be acutely aware of how the characteristics of a particular patient population affect the validity of their practice and of the research studies they may read.

Validity is the lack of systematic error.[2] In research validity is classified into two categories: internal validity, which refers to the accuracy of conclusions made from findings related to the actual subjects in a study, and external validity, which refers to the validity of inferences as they pertain to people outside the study population. Internal validity is a prerequisite for external validity.

A major threat to internal validity is selection bias, again a problem with the denominator. Are the study patients selected in such a way that the data obtained will be different from that which would have been found in the target population? In the situation described by Weiss, the target population was all prenatal patients presenting to a family practice clinic over a one-year period. Questioning why the population had such a high rate of abnormally low levels of maternal serum α-fetoprotein (MSAFP), the researchers learned that the normal median values at the laboratory used for this test were derived not from a random population of pregnant women, but rather from patients who had specific indications for the test. The established norms may have been valid for referred obstetric patients but not for those seen in the family practice.

Had the screening test been valid, the physicians still may have had disappointing results because the value of screening tests is greatly affected by the prevalence of disease within a given population—this is the issue of external validity. Is clinical research performed in referral centers on referral populations applicable to primary care? The main question the physician must ask is whether there is a difference between the patients they see in their primary care practice and patients who seek medical attention at a tertiary care center.

In most instances the answer to that question will certainly be yes. The importance of this factor was well illustrated in a paper by Ellenberg and Nelson.[3] Examining reports of unfavorable sequelae among children with febrile seizures, they found a large difference in the prevalence of poor outcomes when comparing population-based studies, ie, studies that attempted to recognize and follow up all children in a clearly defined population, with clinic-based studies, ie, investigations that involved the follow-up of children seeking medical care at hospital clinics or specialty referral units. Adverse outcomes were reported much more frequently in clinic-based studies, giving a biased picture both for the prognosis of the disease and for the need for treatment.

The difference in populations is equally important when applying screening tests (Figure 1). Even the best screening tests, the ones that are highly sensitive and very specific,

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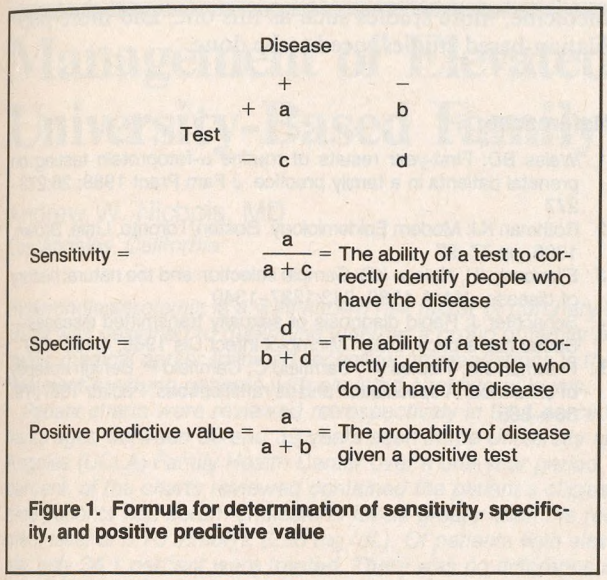

Figure 1. Formula for determination of sensitivity, specificity, and positive predictive value

TABLE 1. THE POSITIVE PREDICTIVE VALUES AND RESULTS OF A SCREENING TEST FOR CONGENITAL ANOMALIES, 90 PERCENT SENSITIVITY, AND 60 PERCENT SPECIFICITY

	Positive	Negative	Total
High prevalence* (10%) for 1,000 tests			
Positive	90	360	450
Negative	10	440	450
Total	100	800	900
Low prevalence** (1%) for 1,000 tests			
Positive	9	396	405
Negative	1	594	595
Total	10	990	1,000

** Positive predictive value = 20% (1 in 5 will have an anomaly)*
*** Positive predictive value = 2% (1 in 50 will have an anomaly)*

will have a low positive predictive value if a disease is rare in the population screened (Table 1).[4] The formula in Figure 1 may be used to illustrate this point when one considers the case of routine antenatal MSAFP screening. Weiss reports that 20 percent of women with elevated MSAFP will give birth to an infant with a congenital defect. If this test correctly identifies 90 percent of patients carrying an infant with a congenital anomaly (the test has a sensitivity of 90 percent), and if the incidence of congenital anomalies is 10 percent in the referred population and only 1 percent among primary care patients, the likelihood of a congenital anomaly, given a positive test, is 1 in 5 at the referral center but only 1 in 50 among the primary care patients tested. The risks and benefits of screening are very different if the positive yield is 1 in 5 compared with 1 in 50.

These considerations have far-reaching implications. Both primary care physicians and academicians need to have a greater awareness of the difference between patients seeking care at medical centers and those receiving care in the community. Patients referred to medical centers are more likely than patients cared for in a primary care setting to have pathologic conditions and probably should be approached aggressively. However, the general application of recommendations derived from studies of referred populations will lead to overuse of diagnostic tests and overtreatment. Both situations are potentially quite harmful. Not only may patients be unnecessarily subjected to risky diagnostic procedures, the psychological effects of testing, such as the effect of a woman being told she may be carrying an abnormal fetus, must be considered. In the case of febrile convulsions, recommendations based on data gathered at referral centers led to long-term anticonvulsant therapy in many children, treatment that may be worse than the disease.[5]

Because primary care physicians know their patients, work in a setting with a low prevalence of significant disease, and have the opportunity for follow-up, a less aggressive approach is often warranted. If the patient is not in acute distress and does not have a debilitating or life-threatening disease, there is time for observation; the diagnosis need not be made during the first visit. Unfortunately, this behavior is often labeled by specialists as not being thorough. This conclusion is understandable, for the specialist sees the failures of the primary care physician: those patients for whom observation or a conservative approach was not appropriate. When standards of care are recommended, a consideration of these differing characteristics of patient populations is essential.

What does this imply for the methods of teaching medical students and residents? There needs to be a greater balance between primary care and tertiary care in medical education. Through ignorance of the difference in care needed in the primary setting, residents sometimes lose respect for generalists. Too often the wise judgment of a skilled clinician is passed off as anecdotal. Quotes from journal articles are much preferred. Students and residents need to experience practice in a primary care setting to appreciate that what is appropriate at the medical center may be impractical or even harmful in the community. As Ellenberg and Nelson comment that, for common and

usually benign conditions such as febrile seizures, it may be inappropriate for specialists to base their teaching on generalizations from the potentially biased experience of the specialty clinic. Such teaching should be deferred to physicians who care for patients with a full spectrum of the given disorder or combined with teaching from a primary care perspective.

As medicine becomes increasingly technical and tertiary care centers are filled with patients with diseases that require complicated treatment, it will become even more important for practicing physicians and teachers not to forget the factor of the denominator. Skilled primary care faculty are needed in medical centers to remind specialists of the bias inherent in a referred population. Finally, for primary care physicians to practice cost-effective, careful medicine, more studies such as this one, and more population-based studies, need to be done.

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