Maternal Serum α-Fetoprotein Screening: Benefits, Risks, and Costs

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Based upon previously published reports, the benefits and risks of screening a hypothetical population of 10,000 women are analyzed, and the cost benefit of maternal serum α-fetoprotein screening is reviewed. Five hundred women would have an initially elevated serum α-fetoprotein and experience moderately severe anxiety until further tests are completed. One hundred fifty pregnancies would undergo amniocentesis with approximately one spontaneous abortion resulting from the procedure. Fifty sets of twins, 86 pregnancies with underestimated gestational age, and 50 pregnancies at risk for low birthweight or fetal death would be identified. All four anencephalics and three of four fetuses with spina bifida would be detected.

The benefits to pregnant women of prenatal screening for neural tube defects exceed the risks. At the present incidence of neural tube defects, the cost of prenatal screening to society approximately equals the economic savings. If the incidence of neural tube defects continues to fall, the benefits, risks, and costs will have to be reevaluated. There are insufficient data to determine adequately the benefits, risks, and costs of the screening for Down's syndrome with maternal serum α-fetoprotein, and such screening should be discouraged.

Since the first report of the association of elevated α-fetoprotein levels in amniotic fluid and neural tube defects in 1972,[1] use of maternal serum α-fetoprotein (MSAFP) to screen for neural tube defects and more recently Down's syndrome has been extensively studied. Large prospective trials have been reported from the United Kingdom, where the incidence of neural tube defects is high (3 to 5 in 1,000),[2,3] and the United States, where the incidence is low (1 to 2 in 1,000).[4–6] Within the genetics community there appears to be a consensus that MSAFP screening is beneficial, and that screening programs should be implemented throughout the country.[7] The process has been accelerated by recommendations by the American College of Obstetricians and Gynecologists that all pregnant patients be informed of MSAFP screening in communities where well-coordinated programs exist.[8,9] There has been significant opposition to these programs for a variety of reasons, ranging from concerns about safety,[10] efficacy,[11,12] and cost effectiveness[13] to questions about the ethical and public policy implications of such screening.[14] Many individual providers of prenatal care are uncertain as to whether to offer or recommend the test to their pregnant patients.

This article reviews the benefits, risks, and costs of MSAFP screening to pregnant women and to society. The analysis applies only to screening the low-risk population, which accounts for 90 percent of all neural tube defects.[15] The screening of women with a prior history or family history of neural tube defects is well established and not discussed here. In addition, it is assumed that the routine screening is being conducted by a well-coordinated MSAFP program that provides education, counseling, a qualified laboratory,[16] and follow-up services, including high-resolution ultrasound and amniocentesis. In the absence of such a program, screening has not been recommended[7] and should not be done. Finally, the benefits and risks to the screened fetus are not considered in this analysis and are left to wider discussions of the ethical issues involved in prenatal screening and abortion.

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TABLE 1. BENEFITS AND RISKS OF SCREENING FOR MATERNAL SERUM α-FETOPROTEIN (MSAFP)

	Incidence (per 10,000 screened)
Benefits	
Prenatal detection of:	
Neural tube defects	8
Spina bifida/anencephaly	4/4
Down's syndrome	2–5*
Twins**	50
Underestimated gestational age**	85
High-risk pregnancy** (low birthweight, fetal demise)	50
Risks***	
From amniocentesis	
Fetal death (0.5 percent)	0–1
Orthopedic anomalies or respiratory distress syndrome	1
Fetal injury (other than death)	undetectable
Abortion of normal fetus (false positive)	0
Increased maternal anxiety	
From screening	undetectable
From elevated initial MSAFP	500

** Sensitivity depends upon the cutoff and values of MSAFP*
*** Benefits of early detection have not been demonstrated*
**** Based only upon screening for neural tube defect (high MSAFP)*

TABLE 2. RESULTS OF SCREENING PROGRAMS FOR MATERNAL SERUM α-FETOPROTEIN

	North Carolina[5]	Long Island, NY[4]	Boston[6]
Number of pregnancies screened	12,084	17,703	21,000
Incidence of neural tube defect (per 1000)	1.6	1.2	1.2
Sensitivity of screening (percent)	83	91	80
Amniocentesis rate (per 100)	1.2	2.1	0.3

BENEFITS OF MSAFP SCREENING

The most commonly reported benefits and risks of MSAFP screening to pregnant women are listed in Table 1. Each of these will be dealt with separately.

Neural Tube Defects

Anencephaly is a 100 percent fatal anomaly, and most affected infants are born dead or die within hours of birth. The benefits of its detection are limited to sparing parents the continuation of the pregnancy and delivery of a grossly deformed infant. Most infants with spina bifida survive until adulthood and have normal or near normal intelligence. Depending upon the level of the lesion, they have severe handicaps including paraplegia, bowel and bladder incontinence, and multiple other health problems requiring extensive medical care, rehabilitation, and special schooling. Because of the anatomy of the neural defects, anencephaly produces higher amniotic and maternal serum α-fetoprotein levels than spina bifida.[17] Virtually all cases of anencephaly have been picked up in reported screening programs (95 percent sensitivity), while 70 to 80 percent of fetuses with spina bifida are detected.[7]

The results of a hypothetical MSAFP screening program, based upon the published results of several screening programs (Table 2), are diagrammed in Figure 1. A population of 10,000 is chosen for convenience because it approximates the number of pregnancies per year in many communities where MSAFP screening programs are being implemented. These results apply for 1986 and will change over time with more experience and changes in the incidence of neural tube defect. Large-scale monitoring programs indicate that the incidence of neural tube defects in the United States is falling dramatically, from 1.3 in 1,000 in 1970 to 0.8 in 1,000 in 1982.[18,19]

If 10,000 pregnant patients were offered and accepted MSAFP screening, all four cases of anencephaly would be picked up by ultrasound, 150 women (1.5 percent) would undergo amniocentesis because of elevated MSAFP levels, and 75 percent of the cases of spina bifida would be detected (75 percent sensitivity). In most published studies the parents of one in four to five fetuses with detected neural tube defects elected to continue the pregnancy. One or two less-serious anomalies (eg, omphalocele, esophageal atresia, gastroschisis) would be detected by screening. The major benefit would be to prevent the human suffering resulting from the delivery and long-term care of three cases of spina bifida. An additional benefit would be the prevention of the emotional trauma associated with the delivery of four cases of anencephaly.

Down's Syndrome

A series of recent reports has demonstrated an association between low MSAFP and Down's syndrome[20–25] with mean MSAFP levels in pregnancies with Down's syndrome ranging from 0.65 to 0.82 times normal. Cuckle and colleagues[21] proposed a screening strategy based upon age and MSAFP that would offer amniocentesis to all the women with a calculated risk of Down's syndrome roughly equal to that of a 38-year-old woman (1 in 200), the age

at which amniocentesis is offered to women in the United Kingdom. Using these cutoff levels retrospectively on their population, they calculated that 6.8 percent of the screened population would undergo amniocentesis and 40 percent of the fetuses affected with Down's syndrome would be detected. These figures, however, are very much dependent upon the distribution of MSAFP levels in fetuses affected by Down's syndrome. When Spencer and Carpenter[26] applied these same age-dependent cutoffs to their data, the sensitivity of the test fell to 30 percent and the amniocentesis rate rose to 11.6 percent.

In the United States amniocentesis is offered routinely to women aged 35 years or older who have a risk of Down's syndrome of 1 in 365 or greater. Many programs are using age-dependent cutoffs for MSAFP and offer amniocentesis to women whose risk is equal to or greater than that of a 35-year-old.[27] The sensitivity and the amniocentesis rate of such a screening strategy are not known and will depend upon the mean MSAFP levels for the pregnancies affected by Down's syndrome. However, the amniocentesis rate may rise as high as 15 percent (including 2 percent for neural tube defects).

The sensitivity and specificity of MSAFP screening for Down's syndrome are not known, and all estimates are based upon retrospective analysis of cases of Down's syndrome. Only one prospective study has published its preliminary results based upon four cases of Down's syndrome.[28] Macri,[29] one of the leaders of MSAFP screening, has strongly argued against the use of MSAFP to screen for Down's syndrome and writes, "In the absence of prospectively generated data leading to accurate risk profiles that could be made available to patients for decision making . . . , we believe that routine clinical low AFP screening places obstetricians at additional, unwarranted risk." Because the risks of using MSAFP to screen for Down's syndrome depends upon the amniocentesis rate, they cannot be accurately assessed at this time. As a result, the following analysis of the benefits, risks, and costs of MSAFP screening does not include the use of low MSAFP levels to screen for Down's syndrome.

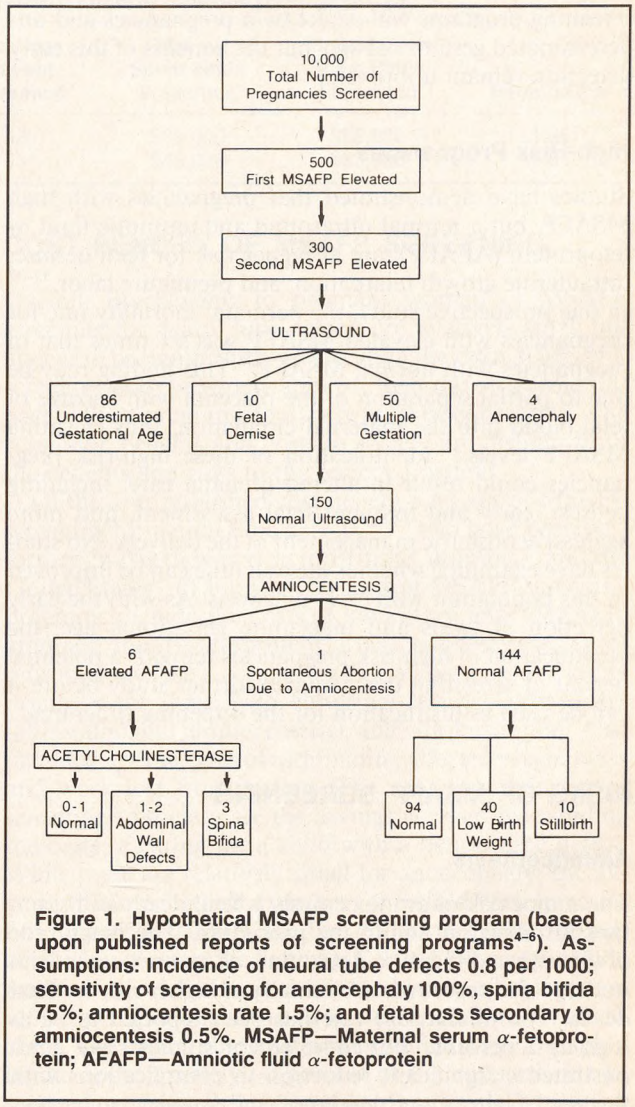

Figure 1. Hypothetical MSAFP screening program (based upon published reports of screening programs[4-6]). Assumptions: Incidence of neural tube defects 0.8 per 1000; sensitivity of screening for anencephaly 100%, spina bifida 75%; amniocentesis rate 1.5%; and fetal loss secondary to amniocentesis 0.5%. MSAFP—Maternal serum α-fetoprotein; AFAFP—Amniotic fluid α-fetoprotein

Twins and Inaccurate Gestational Age

The two most common causes of elevated MSAFP are incorrect gestational age and twins. MSAFP levels rise throughout the second trimester,[30] and an underestimated gestational age will result in falsely elevated MSAFP levels. Normal twin pregnancies also produce elevated MSAFP levels. In the hypothetical screened population, 50 cases of twins (5 percent incidence) and 90 cases of underestimated gestational age would be diagnosed with ultrasound (Figure 1). For twins, early diagnosis may result in early institution of bed rest, closer obstetric surveillance, and altered perinatal management. Correcting gestational age may lead to fewer and better managed post-term deliveries.

The early detection of twins and inaccurate gestational age results from the liberal use of ultrasound in the screening process. The benefits of early detection of either condition have not been proven, however. Randomized trials of ultrasound in pregnancy have failed to demonstrate improved outcome.[31-33] The benefits of early detection depend upon the interventions being effective and applied to the appropriate population. Yet the benefits of many obstetric interventions remain unproven. A randomized controlled trial of bedrest for twin pregnancies found that the intervention group had significantly more

complications than the routine care group.[34] Thus MSAFP screening programs will detect twin pregnancies and underestimated gestational age, but the benefits of this early detection remain unproven.

High-Risk Pregnancies

Studies have demonstrated that pregnancies with high MSAFP, but a normal ultrasound and amniotic fluid α-fetoprotein (AFAFP), are at higher risk for fetal demise, intrauterine growth retardation, and premature labor.[35–37] In one prospective study, the perinatal mortality rate for pregnancies with elevated MSAFP was six times that of pregnancies with normal MSAFP.[4] This finding may be due to partial separation of the placenta with leakage of fetal blood into the maternal circulation, thus elevating MSAFP levels.[38] Identification of these high-risk pregnancies could result in altered prenatal care, including bedrest, early and frequent fetal assessment, and more aggressive obstetric management of the delivery. No studies have examined whether the outcome can be improved in this population with early diagnosis. As with the early detection of twins and inaccurate gestational age, the identification of high-risk pregnancies remains a potential benefit of screening that requires further study before it can be used as justification for the screening programs.

RISKS OF MSAFP SCREENING

Amniocentesis

The major risk of amniocentesis is fetal death and spontaneous abortion due to the procedure. The magnitude of this risk is difficult to determine, as many women who undergo the procedure are initially at higher risk for fetal death. The miscarriage rate has been reported to be as high as 2 percent,[3] but more recent studies have demonstrated a significant reduction in complications with the use of ultrasound guidance and smaller gauge needles.[39] Higher complication rates are also associated with inexperience of the physician performing the procedure[40] and multiple needle insertions.[41] A recent study demonstrated a 0.5 percent incidence of fetal death within three weeks of amniocentesis.[39] Three large prospective studies in which pregnancies undergoing amniocentesis were matched with controls have yielded conflicting results (Table 3),[41–43] but a meta-analysis of their data indicates an approximately 0.5 percent increase in the risk of miscarriage.[44,45]

While there have been case reports of injuries from the amniocentesis needle, ranging from minor dimples in the skin[46] to the destruction of vital organs,[47–50] large prospective studies have failed to detect this risk.[41] Experimental studies in animals have demonstrated that the removal of amniotic fluid can impair fetal lung and limb development.[51] Several controlled studies have suggested an increase in respiratory distress syndrome, club feet (talipes equinovarus), and congenital dislocation of the hip in infants whose mothers had amniocentesis,[41,43,52] while others have failed to detect such an association.[52,53] Any increased risk of such problems is much less than 1 percent, and needs more study.

TABLE 3. COMPLICATIONS OF AMNIOCENTESIS*

Study Characteristics	US[41]	Canadian[49]	UK I[43]	UK II[43]
Number of subjects	2,038	1,020	2,804	2,052
Fetal losses	3.5/3.2**	3.2***	2.7/1.4	2.6/1.1
Needle marks	0.1/—		0.3/0.4	
Infants with respiratory distress syndrome	3.1/2.1		1.2/0.4	1.3/0.3
Infants with severe orthopedic postural anomalies			1.4/0	0.4/0.4

* *Adapted from Verpe and Gerbie*[45]
** *Percentage of patients undergoing amniocentesis/percentage of controls*
*** *No matched controls; comparison with Canadian vital statistics indicated no significant difference*

In this hypothetical cohort of 10,000 pregnant women, 1.5 percent, or 150, will undergo amniocentesis for elevated MSAFP. One half of 1 percent, or approximately one woman, will have a spontaneous abortion resulting from the procedure. One infant may develop orthopedic deformaties or respiratory distress syndrome from the removal of amniotic fluid.

False-positive Test Results

The development of the acetylcholinesterase assay has substantially reduced the risk of a falsely elevated MSAFP level resulting in the elective abortion of a normal fetus. Acetylcholinesterase is secreted into cerebrospinal fluid, and its presence in amniotic fluid is relatively specific for neural tube defects. Three large US screening programs that measured amniotic acetylcholinesterase reported no abortions of normal fetuses among the 50,000 pregnancies screened.[4–6] Case reports of falsely elevated amniotic α-fetoprotein and acetylcholinesterase have been reported,[54] but it is very unlikely that a normal fetus would be aborted in a cohort of 10,000.

Psychological Risks

Many providers of prenatal care are concerned that the discussion of possible congenital anomalies and the sign-

TABLE 4. COST BENEFIT OF MATERNAL SERUM SCREENING α-FETOPROTEIN FOR NEURAL TUBE DEFECTS

Study and Location	Incidence of Neural Tube Defect (Cases/1,000)	Cost per Patient Screened	Cost per Spina Bifida Prevented	Savings per Spina Bifida Prevented	Benefit/Cost
Layde, 1979 United States[62]	1.6	$20	$35,000	$68,000	1.95
Sadovnick, 1983 British Columbia[61]	1.55	$31	$46,000	$83,000	1.81

ing of a consent form for screening may increase the woman's fears of a defective baby, either for the entire pregnancy or until the test results are available. A falsely positive initial blood test may result in severe anxiety and have a long-term effect on the pregnancy. On the other hand, women may benefit from knowing that their fetus does not have a neural tube defect.

Several studies have examined the psychological impact of screening on women who do not carry a fetus with a neural tube defect.[55–59] Women who have an initial elevated MSAFP level and their partners experience significantly increased anxiety that is moderately severe and persists until further testing is completed.[56] One study found that women who had elevated MSAFP levels for which a benign explanation (eg, underestimated gestational age) was found had higher anxiety throughout the rest of the pregnancy than women who underwent amniocentesis with normal results.[56] This finding is surprising, as the latter group is at significantly higher risk for complications. The women may have been reassured by the more invasive test, assuming that it is more definitive.

The mother's attitude toward her pregnancy does not appear to be affected by falsely positive MSAFP test or the resulting anxiety.[55] Women who agree to undergo screening for neural tube defects do not experience increased anxiety or different attitudes toward pregnancy when compared with women who refuse screening[57] or who are not offered screening.[58,59] In fact, screened women tend to be overly reassured by a normal result and assume that it assures them of a normal baby.[60] A normal MSAFP result, however, only reduces the probability of a neural tube defect from 1 in 1,000 to 1 in 5,000 (80 percent sensitivity).

In summary, for the hypothetical screened population of 10,000, 95 percent will have no detectable adverse effects from screening. Five hundred women, or 5 percent of the screened population, will have an elevated initial MSAFP level and experience moderately severe anxiety. For women who undergo amniocentesis, this anxiety will be short lived (3 to 6 weeks), but for others, it may continue until delivery. One woman, or 0.1 percent of the screened population, is likely to have a spontaneous abortion resulting from amniocentesis, and one infant may develop respiratory distress or orthopedic anomalies. The therapeutic abortion of a normal fetus from screening is extremely unlikely.

COST BENEFIT OF MSAFP SCREENING

Overall, the benefits to pregnant women of MSAFP screening for neural tube defects are relatively small but appear to be significantly greater than the risks. If MSAFP screening is to be widely applied, then the economic impact of these programs to society must be considered. The economic benefits and costs to society are distinct from the benefits and risks to the screened patient.

Of the four published cost-benefit analyses of MSAFP screening for neural tube defects,[61–64] two have been performed in North America: in British Columbia[63] and the United States[64] (Table 4). The costs of MSAFP screening programs include the costs of laboratory tests (MSAFP, amniotic fluid α-fetoprotein acetylcholinesterase, chromosomal analysis), counseling (for all patients and more extensive for those with abnormal results), procedures (ultrasound and amniocentesis), and administration. Also included are the costs of terminating affected pregnancies and work lost from testing. The economic benefits of screening to society are the savings accrued by avoiding the costs of caring for a child with a neural tube defect. While these are relatively small for anencephaly, the average lifetime medical expenses for a child with spina bifida exceeds $50,000 (Canadian dollars in 1984), one half of which is spent in the first year.[65] These expenses include repair of the defect and shunt for hydrocephalus, physiotherapy, specialized medical care including renal dialysis, and excess physician and hospital usage. For spina bifida, approximately 60 percent of the costs are due to medical expenses, the rest are due to the special education for approximately one fourth of those affected and residential care for less than 10 percent.

Cost-benefit analysis is an inexact procedure and often relies on assumptions and approximations that, if inaccurate, can dramatically affect the result. For example, there are controversies concerning what discount rate to use in calculating the present value of future savings and how to calculate the economic impact of a child who is born to replace the aborted fetus with neural tube defect. Despite these problems, the two studies from North America yield similar results. With an incidence of neural tube defect of 1.6 per 1,000, the economic savings equals almost twice the cost of screening. Since 1972 the incidence of neural tube defects has fallen from 1.4 in 1,000 to 0.8 in 1,000.[18] This decline results in a 40 percent de-

crease in savings or economic benefits of screening, with very little change in the costs of screening. At present, the costs of screening are estimated to be approximately equal to the savings, but will soon exceed them if the incidence of neural tube defects continues to fall.

CONCLUSIONS

Physicians must be cognizant of the risks, benefits, and costs of screening to decide whether to offer and recommend maternal serum α-fetoprotein screening to pregnant women. For neural tube defect screening, the risks of malformation, injury, or death of a normal fetus are approximately 1 in 10,000, and are due to amniocentesis. In addition, 1 in 20 screened women will experience significant anxiety during the testing period as a result of a falsely elevated MSAFP. The benefits include the detection of virtually all anencephalics and approximately 75 percent of fetuses with spina bifida. This benefit is decreasing as the incidence of neural tube defects falls below 1 in 1,000. Other proposed benefits (detection of twins, inaccurate gestational age, and high-risk pregnancies) are theoretical and have yet to be demonstrated. With the present incidence of neural tube defect (0.8 in 1,000), the economic costs of screening approximately equal the savings realized by aborting detected cases of spina bifida. The use of MSAFP to screen for Down's syndrome has only recently been proposed and has not been well studied. A calculation of the risks and costs of screening cannot be done without more data on the sensitivity of the test for Down's syndrome and the amniocentesis rate.

At the present time, mass screening for neural tube defects with MSAFP appears to be efficacious and beneficial but should be offered only where there exists a well-coordinated program that has a qualified laboratory and experienced obstetric services. The incidence of neural tube defects should be monitored, and the effect of the falling incidence on the risks, benefits, and costs assessed periodically. Studies should examine whether the early identification of twins, incorrect gestational age, and higher risk pregnancies by MSAFP screening improves outcome.

The use of MSAFP to screen routinely for Down's syndrome is premature. Data from prospective trials demonstrating the sensitivity of the screening program and the amniocentesis rates are necessary before an accurate assessment of the risks and benefits can be made and women can make an informed consent. Until these data are available, the use of MSAFP for Down's syndrome screening should be limited to the research setting, where the levels of MSAFP in affected pregnancies have already been determined.

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Addendum

Since this review was written, a large prospective study of screening for Down's syndrome with MSAFP was published (*DiMaio MA, Baumgarten A, Greenstein RM, et al. Screening for fetal Down's syndrome by measuring maternal serum alpha-fetoprotein levels. N Engl J Med 1987; 317:342–346.*) Using criteria based upon MSAFP and maternal age, weight, and race, 5 percent of the screened women underwent amniocenteses, and one third of the Down's affected pregnancies were detected. An accompanying editorial (*Pueschel SM. Maternal alpha-fetoprotein screening for Down's syndrome. N Engl J Med 1987; 317:176–178.*) discusses the implications of this study for Down's syndrome screening.