Original Research

Maternal serum α-fetoprotein screening: report of a Canadian pilot project

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A pilot project of maternal serum α-fetoprotein (MSAFP) screening was carried out in Ontario from 1982 to 1985 to examine the feasibility and acceptability of screening a prenatal population for open fetal neural tube defects. A total of 8140 patients at low genetic risk were screened. Patient acceptance was excellent. Blood samples were taken at 16 to 18 weeks' gestation. If the MSAFP level was elevated, the assay was repeated and an ultrasound examination performed. Amniocentesis was offered to 67 women with unexplained persistently elevated levels. The outcome of pregnancy was known in 7473 patients (91.8%). Seven of nine known open fetal neural tube defects were detected. All were confirmed, and no unaffected fetuses were aborted on the basis of the screening results. The rates of perinatal death (6.7%), intrauterine growth retardation (11.7%) and prematurity (23.3%) were significantly higher among the patients with unexplained elevated MSAFP levels than among those with normal levels ($p < 0.001$). Of 20 patients with unexplained low levels, 10 subsequently had spontaneous abortions and 10 gave birth to term appropriate-for-gestational-age infants. Seven of nine patients who gave birth to infants with autosomal trisomy had MSAFP values below the median. The findings indicate that MSAFP screening is feasible, accurate and acceptable in a low-risk area.

Un projet pilote de dépistage de l'alpha-foetoprotéine dans le sérum maternel (AFPSM) s'est déroulé en Ontario de 1982 à 1985. Il s'agissait d'étudier la faisabilité et l'acceptabilité du dépistage des anomalies du tube neural chez une population prénatale. Au total, 8140 patientes à faible risque congénital ont subi le test qui, par ailleurs, a été très bien accepté de celles-ci. On a prélevé des échantillons de sang de la 16e à la 18e semaine de la grossesse. Lorsque la concentration d'AFPSM était élevée, on reprenait le test et on procédait à un examen échographique. On a offert l'amniocentèse à 67 femmes qui présentaient des concentrations inexplicablement élevées persistantes. Le résultat de la grossesse de 7473 patientes (91,8%) a été connu. Sept des neuf cas des anomalies du tube neural ont été détectés. Tous ces cas ont été confirmés et dans le cas des foetus non touchés on n'a procédé à aucun avortement en fonction des résultats de dépistage. Les taux de mortalité périnatale (6,7%), de retard de croissance intra-utérine (11,7%) et de prématuration (23,3%) ont été de beaucoup plus élevés chez les patientes

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qui présentaient des concentrations inexplicablement élevées d'AFPSM que chez celles qui présentaient des concentrations normales ($p < 0,001$). Des 20 patientes présentant des concentrations inexplicablement faibles, 10 ont par la suite avorté spontanément, et 10 ont donné naissance à terme propre à l'âge de la grossesse. Sept des neuf patientes qui ont eu des bébés atteints d'une trisomie autosomique avaient présenté des concentrations d'AFPSM au-dessous de la médiane. Les résultats donnent à penser que le dépistage de l'AFPSM est faisable, précis et acceptable dans une région à risque faible.

The report by Brock and Bolton[1] in 1973 of an elevated serum α-fetoprotein (AFP) level in a patient with an anencephalic fetus heralded the possibility of mass screening for neural tube defects by means of a noninvasive test during pregnancy. After the initial work by these and other investigators,[2,3] the UK collaborative study of AFP screening[4] was carried out in 18 684 singleton and 163 twin pregnancies in 19 centres. The study showed that 88% of cases of fetal anencephaly and 79% of cases of open spina bifida could be detected with a single maternal serum AFP (MSAFP) measurement at 16 to 18 weeks' gestation using a cutoff point of 2.5 multiples of the median. Other pilot programs were carried out in Glasgow,[5] Edinburgh[6] and Oxford[7] to test the efficiency and acceptability of MSAFP screening. These studies differed in the cutoff point used and in the policy regarding repeat testing, but the results were similar: the rate of detection of anencephaly was 96% to 100% and that of open spina bifida 56% to 78%. The rate of individual acceptance of MSAFP screening, where offered, was excellent in all three centres (97% to 99%); the rate in the community varied (51% in Glasgow, 79% in Edinburgh and 72% in Oxford).

The incidence of neural tube defects in North America is about half that in the United Kingdom. In studies carried out in New York[8] and Maine[9] about 30% of the target population underwent MSAFP screening, and the detection efficiency was comparable to that in the British studies.

It has been suggested that an unexplained elevated MSAFP value (i.e., one not explained by twin pregnancy, spontaneous abortion or error in dates) is associated with an increased rate of perinatal death and an increased incidence of low birth weight.[8,10,11] Early pregnancy loss has also been found to be associated with low MSAFP values.[12] We carried out a pilot project to examine the feasibility and acceptability of MSAFP screening in a population at low risk in southern and southwestern Ontario, where the incidence of neural tube defects is 2 per 1000 births. We also examined the correlations between perinatal and fetal loss on the one hand and elevated and low MSAFP values on the other. Merkatz and colleagues[13] first described the relation between low MSAFP values and fetal autosomal trisomy; other investigators[14,15] have confirmed this finding. Their studies (all retrospective) suggested that MSAFP testing might prove useful as a method of screening for fetal Down's syndrome and other trisomy syndromes. This work was not published until after our study was virtually completed, but we have been able to evaluate this aspect of MSAFP screening in relation to our own data.

Methods

The study was carried out in two genetics centres (in Toronto and London, Ont.) and was started in May 1982. Patients were entered into the study until April 1985. A total of 23 hospitals were involved in the study, with 234 physicians (114 obstetricians and 120 family physicians) participating. Participating physicians were asked to give a brochure outlining MSAFP screening to their patients at the first prenatal visit. At the next visit patients were asked whether they were interested in screening; if so, arrangements were made to have a blood sample taken at 16 to 18 weeks' gestation. Informed consent, including permission for follow-up from hospital prenatal records, was obtained. Blood samples were drawn in hospital diagnostic centres or in private laboratories and transported to one of the two genetic centres for radioimmunoassay.

Fig. 1 outlines the design of the study. If the MSAFP level was normal, the result (the numerical value as well as the interpretation) was transmitted to the physician by mail. Case finding (i.e., ruling in or out a fetal open neural tube defect) began when the MSAFP level was found to be elevated. In this event the project coordinator in either centre contacted the physician and arranged for a second blood sample to be taken and for a level I (routine) ultrasound examination. If both the repeat MSAFP assay and the ultrasound examination gave normal results no further action was taken. If the level in the repeat assay was elevated and there was no explanation (such as missed abortion, twins or an error in dates) the patient was offered amniocentesis and detailed (level II) ultrasonography. An amniotic fluid AFP (AFAFP) assay was done (upper limit of normal, mean plus five standard deviations) as well as a gel electrophoresis acetylcholinesterase (AChE) assay (at Dr. Nancy Simpson's laboratory, Queen's University, Kingston, Ont.) and amniotic fluid cell karyotyping. If the results of these tests were normal the attending physician was notified and no further action was taken. When abnormal results indicated a high likelihood of an open neural tube defect the couple was counselled by our prenatal diagnosis team in either centre, and therapeutic abortion was one option available at the request of the couple.

In the event of an initial low MSAFP level (less than 0.25 multiples of the median) a second

blood sample was requested and a level I ultrasound examination done. Follow-up was conducted by questionnaire with the patient or, when there was an abnormal outcome, through physicians' offices and hospital record departments.

Radioimmunoassay

Toronto method: AFP antiserum and iodinated-grade AFP were supplied by the Laboratory Centre for Disease Control, Health Protection Branch, Department of National Health and Welfare. AFP standard (World Health Organization [WHO] AFP reference 72/225 [1 IU = 1.21 μg]) was supplied by the WHO, Lyon. Iodine-125-labelled AFP was iodinated according to the method described by Hunter.[16]

Generally, 50 μl of standards, controls and patients' serum samples, 500 μl of phosphate-buffered saline, 100 μl of ^{125}I-labelled AFP and 100 μl of AFP antiserum were added in sequence to polystyrene tubes measuring 12 × 75 mm. The mixture was vortexed and incubated at room temperature overnight. After 1.0 ml of goat anti-rabbit IgG was added, all tubes were centrifuged at 1500 × *g* for 10 minutes. The supernatant was discarded and the AFP level in the precipitate determined with a γ-radiation counter and data reduction; results were read from the standard curve and expressed in micrograms per litre.

On the basis of the cumulative AFP results in 3838 normal pregnancies between 1978 and 1982 the cutoff points for MSAFP at 15, 16, 17, 18 and 19 weeks of gestation were 60.0, 65.8, 70.6, 81.2 and 100.4 μg/L respectively. The values were equivalent to 2.0 multiples of the median. We used these cutoff values throughout the study.

In April 1982 we prepared a new set of AFP standards from the WHO to be used throughout the study. During the first year of the study we detected a shift in the median values (probably due to the change of AFP standards), but we decided to maintain the same cutoff values. At the end of the study median values for 15 to 19 weeks' gestation were re-established. The cutoff values described above were equivalent to 2.5 multiples of these new median values.

London method: AFP antiserum (batch AZ2942M) and ^{125}I-labelled AFP were supplied by Bohring Limited and Radioimmunoassay Inc., Scarborough, Ont. AFP standard (WHO AFP reference 72/225) was obtained from the WHO. The radioimmunoassay procedure was identical to the Toronto method. The cutoff points of 3.0 multiples of the median (95th percentile) (at 15, 16, 17, 18 and 19 weeks' gestation 71, 92, 117, 146 and 179 μg/L respectively) were derived from AFP assays in 2126 normal pregnancies at 8 to 38 weeks' gestation.

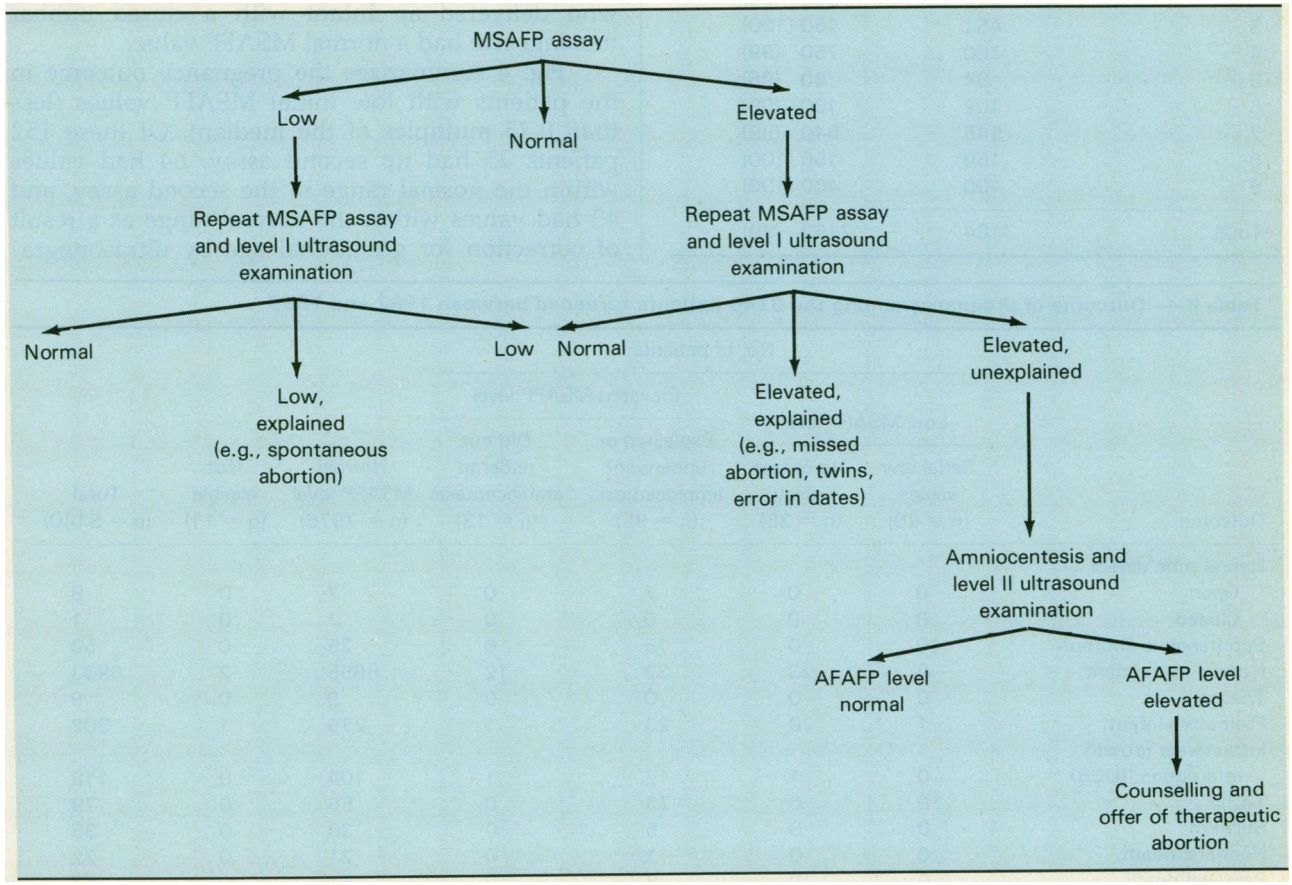

Fig. 1 — Study design for α-fetoprotein screening project. MSAFP = maternal serum α-fetoprotein; AFAFP = amniotic fluid α-fetoprotein.

Results

A total of 8140 patients (729 in London and region and 7411 in Toronto and region) were screened between May 1982 and Mar. 31, 1985. Outcome data were available for 7473 patients (91.8%).

In nine individual practices in which all patients were offered MSAFP screening, acceptance was excellent (3152 of 3184 patients [99.0%] accepting screening) (Table I).

The outcome of pregnancy among the 8140 patients is shown in Table II. Fig. 2 shows the results of screening in the 191 patients with an elevated MSAFP level in the first assay. Ultrasound gestational-age assessment resulted in 17 values falling in the normal range, and in 57 patients with initial elevated levels repeat samples gave results in the normal range. Nine patients had no second test. There were 41 patients with "explained" elevated levels in the second MSAFP assay (23 had twins, 15 a spontaneous abortion and 3 an anencephalic fetus). Of the other 67 patients with elevated MSAFP levels in the second assay 54 (0.7% of the total screened) had amniocentesis: 50 of these patients had normal results of secondary tests (AFAFP testing, AChE assay and level II ultrasonography), and 4 had abnormal results. Of the 13 patients with serial elevated "unexplained" levels, 1 was lost to follow-up, and 12 delivered infants without a neural tube defect.

There were nine fetuses in the study with an open neural tube defect; seven of these (all in the Toronto study) were detected by MSAFP screening (Fig. 3). In three of these cases an elevated MSAFP result was followed by detailed ultrasonography, which demonstrated fetal anencephaly (Table III). In four patients serial MSAFP values led to amniocentesis, the results of which showed elevated AFAFP values and an extra band in the gel electrophoresis AChE assay. Three of the four patients had abnormal results of level II ultrasonography (Table III). All seven patients in whom prenatal testing indicated a fetal open neural tube defect underwent mid-trimester pregnancy termination, and detailed pathological examination confirmed the diagnosis (Table III).

Two fetuses with open spina bifida were not detected by MSAFP screening (Table III). In one case the MSAFP level was below the cutoff point. In the other, because of an error in the physician's office the gestational age as determined by ultrasonography at screening was incorrectly stated to be 16 weeks rather than 14 weeks. One patient who delivered an infant with a closed lumbar meningocele had a normal MSAFP value.

Fig. 4 summarizes the pregnancy outcome in the patients with low initial MSAFP values (less than 0.25 multiples of the median). Of these 152 patients 25 had no second assay, 64 had values within the normal range in the second assay, and 43 had values within the normal range as a result of correction for gestational age by ultrasonogra-

Table I — Patient acceptance of maternal serum α-fetoprotein (MSAFP) screening in nine practices in which it was offered to all new prenatal patients

Practice no.	No. of patients	No. (and %) who accepted
1	440	432 (98)
2	242	240 (99)
3	451	450 (100)
4	760	750 (99)
5	94	90 (96)
6	102	100 (98)
7	545	540 (99)
8	150	150 (100)
9	400	400 (100)
Total	3184	3152 (99)

Table II — Outcome of pregnancy among the 8140 patients screened between 1982 and 1985

Outcome	No. of patients: Low MSAFP level — Serial low values (n = 20)	Low MSAFP level — No repeat assay (n = 25)	Elevated MSAFP level — Explained or underwent amniocentesis (n = 95)	Elevated MSAFP level — Did not undergo amniocentesis (n = 13)	Normal MSAFP level (n = 7976)	Not eligible (n = 11)	Total (n = 8140)
Neural tube defect							
Open	0	0	7	0	2	0	9
Closed	0	0	0	0	1	0	1
Spontaneous abortion	10	0	15	0	25	0	50
Normal term infant	9	23	32	12	6855	2	6933
Trisomy	0	0	0	0	9	0	9
Premature infant	1	0	23	1	276	1	302
Intrauterine growth retardation (IUGR)	0	1	12	1	104	0	118
Twins	0	0	23	0	56	0	79
Stillbirth	0	0	5	0	30	0	35
Neonatal death	0	0	1	0	21	0	22
Perinatal death	0	0	6	0	51	0	57
Unknown	0	1	0	0	658	8	667

phy. Of the 20 patients with repeat low MSAFP values 10 had a spontaneous abortion, 9 delivered term appropriate-for-dates infants, and 1 delivered a premature infant.

In this study none of the 10 women with serial low MSAFP values (less than 0.25 multiples of the median) delivered an infant with fetal trisomy. However, seven infants with trisomy 21, one infant with trisomy 13 and one infant with trisomy 18 were delivered. Seven of the nine mothers of these infants had MSAFP values below the median (Table IV).

Of the 7318 women with normal MSAFP values for whom the outcome of pregnancy was known 6857 (93.7%) delivered term (born after 37 weeks) appropriate-for-gestational-age infants. There were 104 infants (1.4%) with intrauterine growth retardation (birth weight less than the 10th percentile for gestational age), 276 premature infants (3.8%) (born at less than 37 weeks' gestation), 56 twins (0.8%), 51 perinatal deaths (7/1000 live births) and 25 spontaneous abortions (0.3%).

Of the 60 patients with serial elevated "unexplained" MSAFP values and continuing singleton pregnancies 37 (62%) delivered term appropriate-for-gestational-age infants. There were 7 infants with IUGR (12%), 14 premature infants (23%) and 4 perinatal deaths (7%). Table V summarizes the perinatal mortality and morbidity in cases of low, normal and high MSAFP values and continuing singleton pregnancies.

There were 79 twin pregnancies in our study, of which 56 were associated with normal MSAFP values and 23 with elevated values. There were four perinatal deaths (4%) in the group with normal values and two (4%) in the group with elevated values. In the group with normal values 37 out of 112 infants (33%) had IUGR (12), prematurity (27) or both (2). In the group with elevated values 19 out of 46 infants (41%) had IUGR (8), prematurity (15) or both (4). In the group with normal values there were 71 term appropriate-for-gestational-age infants (63%), compared with 25 (54%) in the group with elevated values.

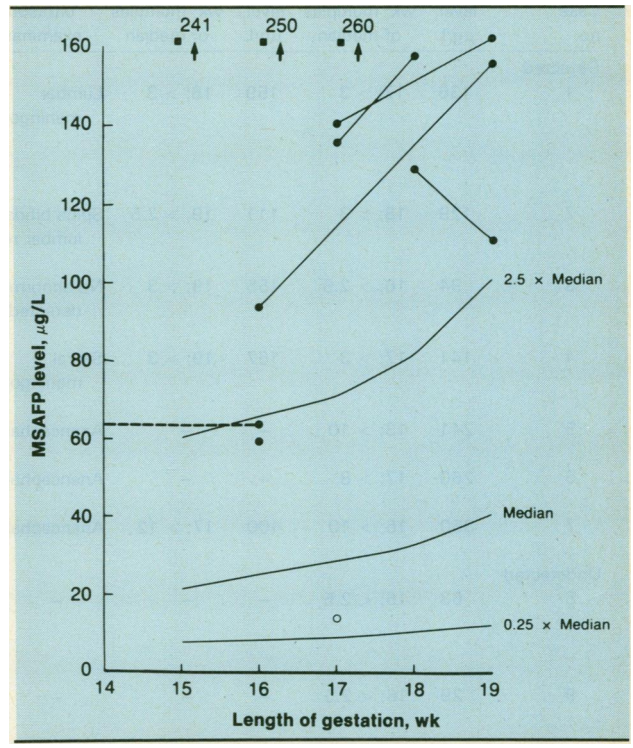

Fig. 3 — MSAFP levels in 10 patients with fetuses with neural tube defects. ■ = anencephaly; ● = meningomyelocele; ○ = closed lumbar meningocele.

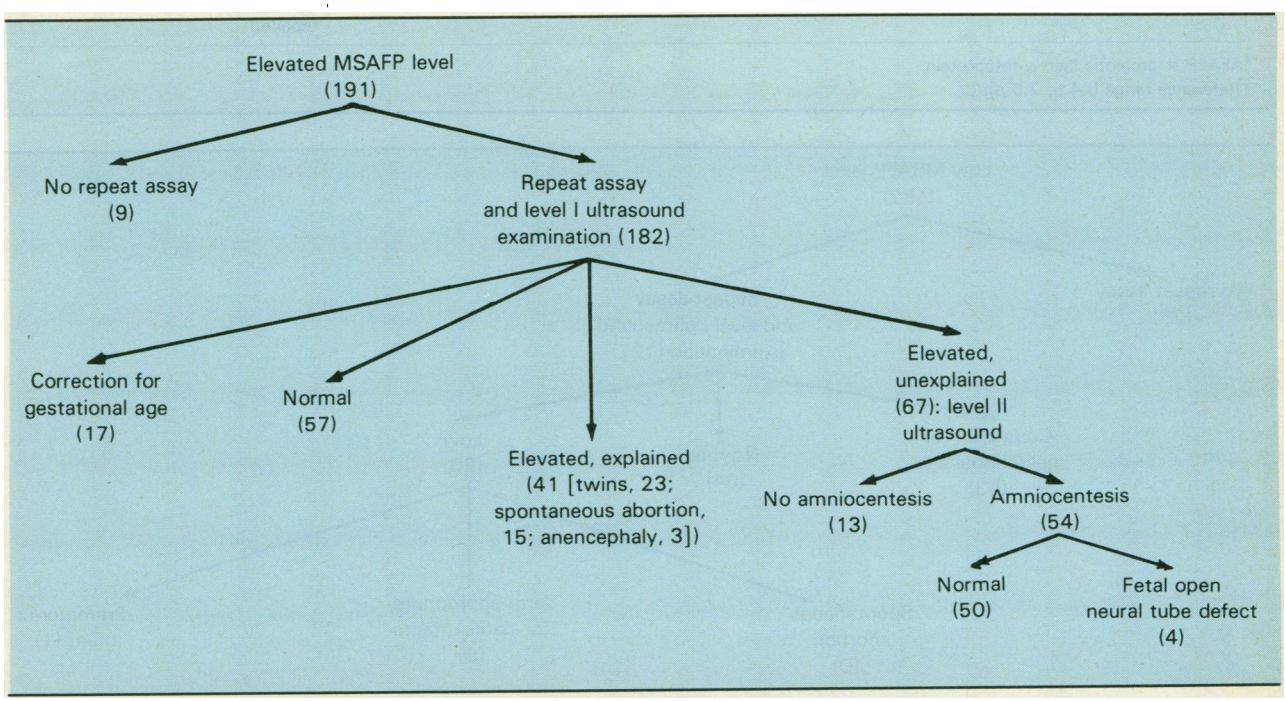

Fig. 2 — Results of screening in patients with elevated MSAFP level in first assay.

Of the 11 patients with elevated MSAFP levels who delivered infants with birth defects 2 declined further testing. One gave birth to a microcephalic infant at term and the other an infant with stage IV neuroblastoma. One patient with persistently elevated MSAFP levels was closely monitored, and

Table III — Clinical and laboratory findings in 10 cases of neural tube defect

Case no.	First MSAFP assay: MSAFP level, μg/L	First MSAFP assay: Length of gestation, wk; multiples of median	Repeat MSAFP assay: MSAFP level, μg/L	Repeat MSAFP assay: Length of gestation, wk; multiples of median	Findings on level II ultrasound examination	AFAFP* level, μg/L; length of gestation, wk	Cholinesterase level, μg/L†	Outcome	Pathological findings
Detected									
1	136	17; > 3	159	18; > 3	Lumbar meningocele	7.8; 18	8.0	Therapeutic abortion	Arnold–Chiari deformity, lumbar meningocele, hydrocephalus
2	129	18; > 3	111	19; > 2.5	Spina bifida in lumbar region	6.9; 19	6.2	Therapeutic abortion	Lumbar meningomyelocele, 2.5 × 2 cm
3	94	16; > 2.5	155	19; > 3	No abnormality detected	37; 20	6.3	Therapeutic abortion	Thoracolumbar meningomyelocele, "severe"
4	141	17; > 3	167	19; > 3	Sacral meningocele	29; 19.5	6.5	Therapeutic abortion	Lumbosacral meningocele, 1 cm
5	241	13; > 10	–	–	Anencephaly	–	–	Therapeutic abortion	Anencephaly and spina bifida
6	260	17; > 8	–	–	Anencephaly	–	–	Therapeutic abortion	Anencephaly
7	350	16; > 10	400	17; > 12	Anencephaly	–	–	Therapeutic abortion	Anencephaly
Undetected									
8	63	16; < 2.5	–	–	–	–	–	Live birth at 39 wk; lumbar meningocele (small), repaired	–
9	29	16; < 2.5	–	–	–	–	–	Live birth at 40 wk; meningomyelocele, repaired (shunt subsequently inserted)	–
10	13.7	17; < 2.5	–	–	–	–	–	Live birth at 40 wk; closed lumbar meningocele, repaired	–

*AFAFP = amniotic fluid α-fetoprotein.
†Reference range 0.4 to 7.5 μg/L.

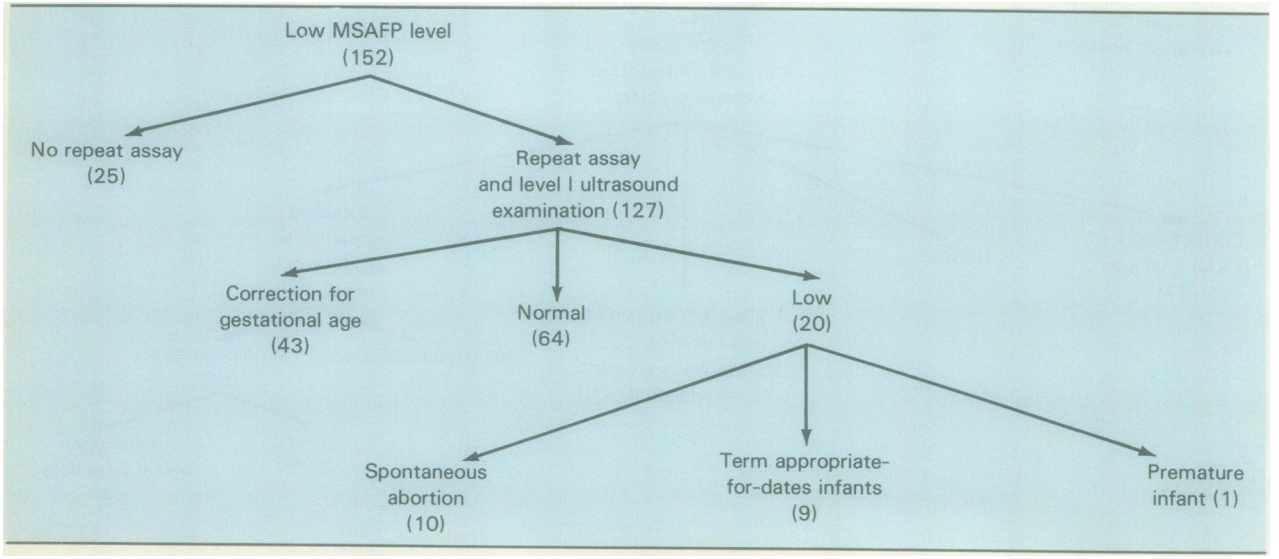

Fig. 4 — Results of screening in patients with low MSAFP level in first assay.

serial ultrasonography showed oligohydramnios with absence of fetal renal function. A stillborn infant was delivered at 28 weeks' gestation. Autopsy confirmed the diagnosis of Potter's syndrome.

Discussion

Within the limits of the follow-up program available to us (92% known pregnancy outcome), we found that of the nine open neural tube defects among the fetuses of this group of women seven were diagnosed by our MSAFP screening program. All three anencephalic fetuses were detected, as were four of six fetuses with open spina bifida. One case of open spina bifida was missed because the patient was screened at 14 weeks, and since the MSAFP level was above the cutoff point for 15 weeks the defect would likely have been detected if the blood sample had been taken at the correct period of gestation. Thus, five (83%) of six cases of open spina bifida were potentially detectable with this protocol. This detection rate is similar to that reported from other studies.[4-8] We feel that this potential rate of detection of fetal open neural tube defects (8/9, or 89%) is acceptable, particularly when combined with our low amniocentesis rate (0.7%).

In individual practices where each patient was offered MSAFP screening the rate of acceptance was high (99%). This finding is similar to that of other studies.[5-7] In our experience the success of MSAFP screening is vitally dependent on the individual practitioner's offering screening routinely as part of prenatal care. Since the diagnostic period is brief (16 to 18 weeks), the patient must also present early enough for prenatal care. At the end of this project approximately 19% of the prenatal population from the hospitals involved in the study were being screened. This rate could be substantially improved with increased physician and patient awareness through continuing medical education programs and the media. In our opinion both these methods are necessary to achieve optimum implementation of screening in any region.

Only birth defects associated with a skin defect in the fetus or with severe disturbances in amniotic fluid volume (i.e., Potter's syndrome) are generally associated with elevated MSAFP values. Thus, the presence of a normal MSAFP level with fetal closed spina bifida in our series was as expected, as was the elevated value associated with fetal Potter's syndrome.[17] Our one case of fetal omphalocele was associated with a normal MSAFP value and therefore was not detected. On the basis of reports of other investigators[18] one would expect that most fetal abdominal wall defects (gastroschisis and omphalocele) would be detected by MSAFP screening.

Both centres found it important to have a rapid and efficient flow of information between the patient and the attending physician on the one hand and the project personnel on the other. The essential elements for an efficient MSAFP screening program, in our experience, are as follows:

- A project coordinator to handle the day-to-day operation of the project, including both elevated and low results.
- Availability of expert ultrasonography.
- An obstetric team skilled in amniocentesis and ancillary ultrasonography.
- A laboratory capable of doing a large volume of AFP radioimmunoassays with good quality control. It is important to replot the normal range at intervals to detect and prevent any drift in values (which did occur in our study).

Table V — Outcome of pregnancy among 7307 patients with continuing singleton pregnancies

Outcome*	No. (and %) of patients; MSAFP level		
	Normal (n = 7237)	Elevated, unexplained (n = 60)	Low, unexplained (n = 10)
Term AGA infants	6856 (94.7)	37 (61.7)	9 (90.0)
IUGR infants	92 (1.3)†	7 (11.7)‡	0 (0.0)
Premature infants	249 (3.4)†	14 (23.3)‡	1 (10.0)
Perinatal mortality	47 (0.6)	4 (6.7)	0 (0.0)

*Differences between the groups with normal and elevated MSAFP values were significant at $p < 0.001$ by chi-squared testing; AGA = appropriate-for-gestational-age (37 weeks or greater).

†Seven infants were premature and had IUGR.

‡Two infants were premature and had IUGR.

Table IV — MSAFP level in nine patients who gave birth to infants with autosomal trisomy

Case no.	Type of trisomy	Length of gestation, wk	MSAFP level, μg/L	Multiples of median	Location
1	21	16	28	1.1	Toronto
2	21	17	11	0.39	Toronto
3	21	17	21	0.75	Toronto
4	21	18	64	2.0	Toronto
5	21	17	17	0.43	London, Ont.
6	21	16	29	0.94	London, Ont.
7	21	15	9	0.38	London, Ont.
8	13	16	24	0.96	Toronto
9	18	20	17	0.38	Toronto

- Laboratory capability for accurate AFAFP assay and qualitative AChE assay.

Given these prerequisites, we feel that MSAFP screening is feasible in a low-risk area and can be incorporated into routine prenatal care.

Although dating by ultrasound examination was not a necessity for entry into the study, we found that in 9% of cases of initially elevated values the levels were in fact not elevated when gestational age was corrected by ultrasonography. Similarly, one of our false-negative results was due to a calculation error after ultrasound examination. Not only should ultrasonography be done for dating in pregnancies of uncertain gestation, but also the attending physician has a responsibility to make certain that this information is correctly used to perform the assay at the appropriate period of gestation (16 to 18 weeks). We therefore feel that it is vital for the attending physician to carefully assess the pregnancy with respect to gestational age. In patients whose dates are certain and whose uterine size is consistent with the period of amenorrhea, routine dating by ultrasonography is not essential. However, if there is uncertainty about the dates or a discrepancy between the period of amenorrhea and the uterine size, an ultrasound examination is essential *before* the blood sample is taken.

All four patients who had fetuses with open spina bifida detected in our series underwent amniocentesis, and in all four cases the AFAFP value was elevated and there was an extra band in the qualitative gel electrophoresis AChE assay. None of the remaining 50 patients who underwent amniocentesis had abnormal AFAFP or AChE results. These findings are consistent with those of the British Collaborative Acetylcholinesterase Study, in which a high degree of accuracy was noted when the AFAFP assay was combined with the AChE assay.[19] Detailed ultrasound examination by an experienced ultrasonographer failed to reveal one of four cases of fetal open spina bifida in our series, even though the examination was performed twice. This experience is similar to that of Roberts and coworkers,[20] who reported a rate of detection of open spina bifida of 80% by diagnostic ultrasonography (i.e., detailed ultrasonography in patients at risk). Our results and those of others[19] suggest that both AFAFP assay and AChE assay should be performed in all patients when amniocentesis is done because of increased risk of neural tube defect and that abnormal results of both assays indicate a high likelihood of open spina bifida even when detailed ultrasound examination fails to reveal abnormalities. Conversely, normal results of amniotic fluid biochemical tests indicate that a fetal open neural tube defect is highly unlikely.

This study showed that a normal MSAFP result was a good predictor of normal pregnancy outcome, having an accuracy of 94%. In contrast, there was only a 62% chance of a normal outcome in patients with an elevated "unexplained" MSAFP result; these patients also demonstrated an increased perinatal mortality (6.6%) and morbidity (IUGR 11%; prematurity 23%). Of the four perinatal deaths in this group (three stillbirths and one neonatal death) all three stillbirths were of unknown cause. The risk of perinatal death in this group was 11 times the risk in the normal MSAFP group. In studies by Wald and collaborators[11] and Macri and Weiss[8] the risk was increased 3.5 and 6 times respectively. Although these investigators did not attempt to separate premature infants and infants with IUGR, Wald and collaborators also found that in this group the risk of prematurity and of low birth weight was increased (5.8 and 4.7 times respectively). We found similar figures for risk of prematurity (6.8 times) and for risk of IUGR (9 times). This increased perinatal mortality and morbidity may be related to early defects in placentation that allow a greater-than-normal transplacental diffusion of AFP.[21] We therefore recommend increased surveillance of these patients in the second half of pregnancy in an effort to detect and deal appropriately with pregnancies complicated by fetal compromise. Surveillance should include frequent clinical assessments and serial biophysical monitoring (e.g., nonstress testing and ultrasound examination).

It should be emphasized that MSAFP screening has a low sensitivity in predicting perinatal mortality and morbidity. Of the 57 perinatal deaths in singleton pregnancies in our study only 4 of 51 (8%) were associated with an elevated MSAFP level. Similarly, only 7 of 99 infants (7%) with IUGR and 14 of 263 premature infants (5%) were associated with elevated MSAFP levels. Thus, in the individual patient the presence of an unexplained elevated MSAFP level indicated a high risk of fetal morbidity and mortality (36.6%), but overall only 6.1% of abnormal perinatal outcomes could be predicted by MSAFP testing. The presence of a normal MSAFP value, on the other hand, should be interpreted by the physician (and the patient) as indicating a low (but not absent) risk of fetal open neural tube defect and abnormal perinatal outcome.

We found a high rate (50%) of spontaneous abortion associated with persistently low MSAFP values. This result is similar to the findings of Davenport and Macri.[12] Interestingly, of the remaining patients with continuing pregnancies and persistently low MSAFP values, 9 out of 10 delivered normal infants at term. This indicates that low MSAFP values do not appear to be related to late pregnancy loss or a high risk of perinatal morbidity. We also were able to confirm retrospectively the relation between low MSAFP levels and fetal autosomal trisomy. If amniocentesis had been offered to patients with MSAFP levels less than 0.5 multiples of the median, four of nine fetuses with trisomy would have been detected, which is consistent with results in other series.[13-15]

In summary, we feel that MSAFP screening for open neural tube defects is feasible, accurate

and acceptable in a low-risk area. It can be incorporated without serious problems into routine prenatal care, provided that an adequate regional laboratory and a high-genetic-risk clinical team (with obstetric, genetic and ultrasonographic expertise) are available to handle the problems on a day-to-day basis. There are additional benefits to MSAFP screening related to prediction and possible prevention of late pregnancy loss and perinatal morbidity. Retrospective studies on the relation between fetal Down's syndrome and low MSAFP values hold promise; however, pilot prospective studies are needed before general introduction of this facet of MSAFP screening.

This study was supported by research grant 00846 from the Ontario Ministry of Health.

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Proper billing

The paying of a physician for attendance and the apothecary for his Medicines apart is certainly the most eligible mode of practice, both to patient and practitioner. The apothecary then, who is not obliged to spend his time in visiting patients, can afford to make up medicines at a reasonable price; and it is as desirable, as just in itself, that patients should allow fees for attendance, whatever it may be thought to deserve. They ought to know what it is they really pay for their Medicine, and what for physical advice and attendance.

— John Morgan (1735-1789)