Editorials

Screening for maternal serum α-fetoprotein: What about the low side?

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Do the relative frequency of Down's syndrome (1 to 1.5 cases per 1000 live births) and the contribution of this disorder to the burden of mental retardation and congenital heart disease justify prenatal screening for this condition?

At present the main "screening" method is determination of maternal age: pregnant women over an arbitrary age, usually 35 years, are identified and offered a diagnostic procedure, amniocentesis for fetal karyotyping. Although women in this age group are at a higher individual risk than younger women of having a child with trisomy 21, only about 20% of all cases of this disorder could be detected if all women 35 years of age or older were to request amniocentesis, since younger women are more numerous and have higher fertility rates.[1-3] Since the utilization rate of prenatal diagnosis rarely exceeds 50%,[3-6] the proportion of cases of Down's syndrome detected prenatally is unlikely to be greater than 10%. Additional screening methods are needed to identify high-risk pregnancies in the younger group. Maternal serum α-fetoprotein (MSAFP) screening appears to some to be a candidate for this job.

It is firmly established that increased levels of MSAFP identify women at increased risk of having a fetus with an open neural tube defect. This fact has become the basis for programs of screening for these malformations.[7,8] Little has been known, however, about the meaning of low values other than their association with pseudocyesis, molar pregnancy and fetal death.[9,10] In 1984 Merkatz and colleagues[11] reported an association between decreased levels of MSAFP and trisomic pregnancies. Other investigators who examined their data on low MSAFP values subsequently reported similar findings.[12-20] These observations have motivated some investigators to propose that MSAFP levels be used as a screening tool to identify women for whom amniocentesis would be appropriate because of their increased risk of having a fetus with trisomy 21,[12,13,20] and programs with this approach have begun outside Canada.[17,18]

Despite the consistency of the observations of low MSAFP values in trisomic pregnancies, we suggest that technical limitations and social policy issues currently make it inappropriate in Canada to mount a mass, purposeful program with such an approach. Although we distinguish "purposeful" screening (in which a process of looking for trisomy 21 in fetuses is set up and promoted) from "accidental" screening (in which some results requiring action are found while pregnancies are being screened in existing programs for neural tube defects), most of the factors we will consider are pertinent to both.

Technical limitations

The sensitivity and specificity of MSAFP testing in detecting trisomy 21 have been estimated with the use of different cutoff points. Multiples of the median (MoM) are used as the unit of measure since they allow comparison between centres with different distributions of MSAFP values.

As Table I shows, MSAFP testing lacks sensitivity in detecting trisomy 21. Even with very low MSAFP values (e.g., 0.4 MoM) as the cutoff, only about 15% of affected pregnancies will be detected, although 96% of unaffected pregnancies will be identified as such. As the cutoff level is increased, the proportion of trisomic pregnancies identified improves, but at the cost of an increase in the false-positive rate, which would lead to a high frequency of amniocentesis among "normal" pregnancies. The current screening test — determining the maternal age — is more efficient (if

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insufficient). By contrast, MSAFP testing has a sensitivity of 85% and a specificity of 97% when used to identify open neural tube defects, and programs of screening for these malformations have been justified only because of this ability to detect affected pregnancies.[22,23]

The predictive value of MSAFP screening[24] is also relatively poor. Since the prevalence of trisomy 21 in the general population is so low, only about 1% of women with low MSAFP values (usually taken as less than 0.5 MoM) are carrying a trisomic fetus. Thus, any program of screening for trisomy 21 that is based on MSAFP levels will have to provide extensive follow-up and counselling for women given "false-positive" results.

Another technical reason for caution in adopting MSAFP screening for trisomy 21 is the wide variation both within and between centres in the levels associated with this disorder.[21] This is not surprising since assays are oriented toward detecting the high levels associated with open neural tube defects,[25] and even then establishing standards is complex.[26] We need more information on the acccuracy and reliability of MSAFP values at the low end of the scale before we can be sure what the curve of values in trisomy 21 pregnancies looks like at different maternal and gestational ages.

Given these technical problems with sensitivity and precision, would it not be paradoxical to endorse mass, purposeful MSAFP screening for trisomy 21 when similar programs of screening for open neural tube defects have not been widely encouraged in this country? After all, MSAFP testing is more sensitive and specific for open neural tube defects than for trisomy 21: it can detect 90% and 80% of cases of anencephaly and spina bifida respectively, as compared with 40% of cases of trisomy 21, if both MSAFP and maternal age are used for screening, and neural tube defects are more common at birth than trisomy 21 in much of Canada. Yet there has been no concerted lobbying for a universally available program of screening for neural tube defects in this country. Why rush with screening for trisomy 21?

Social policy issues

Even if MSAFP testing for trisomy 21 is eventually shown to be valid, reliable, precise and repeatable, we will still need to make sociopolitical decisions before new screening programs are undertaken.[18,27] Fundamental questions include how information from screening will be used and who will make the choices.

For example, if one plans to act on information obtained from screening (to "act" may merely be to inform a woman of her MSAFP value and the risk of fetal trisomy that it suggests), one must first determine what information will be used as a basis for subsequent action, usually an offer of fetal karyotyping. The approach most frequently suggested is to use the maternal age and the MSAFP interpretation[18] jointly to establish the woman's risk and then to offer prenatal diagnosis if the risk exceeds the average for a woman 35 years of age, which varies between centres from about 1/385 to 1/200.[18] Although this approach improves the efficiency of screening, is the "35-year-old risk equivalent" really appropriate as the criterion for access to prenatal diagnosis? It was arbitrary from the start,[28] and recommendations that it be reconsidered have been made on both technical and social grounds.[29-31] Entrenching it further at this time might be ill-advised, if not retrogressive.

Furthermore, if a precise numerical risk based on age and MSAFP results becomes the threshold that must be crossed to gain entry to prenatal diagnostic services, what will happen to a woman 35 years of age or older whose MSAFP values are sufficiently above the median that the posterior probability for her to have a trisomic fetus places her *below* the critical value? Logic suggests that amniocentesis would be inappropriate for her,[18] but would withdrawal of a service that has so far been universally available for women of her age be acceptable?

Other problems arise when one begins to consider who will decide what risk of trisomy 21 is "enough" to warrant further testing. Will a genetics centre establish the risk and when the threshold is passed tell the woman that the risk with her pregnancy exceeds a minimal one and that her pregnancy has therefore become "testable", or will she be told the actual probability of her fetus's being trisomic and be able to decide for herself whether to seek testing?[26,28]

Similarly unaddressed but no less important are the questions of the meaning of informed consent and genetic counselling in this context. Clearly these issues will become more salient if screening is first shown to be effective, but we believe that their consideration should not be delayed until then, for their resolution is no less important than resolution of the technical problems inherent in screening.

"Accidental" screening

Those involved in established Canadian programs of screening for neural tube defects have a responsibility to women whose MSAFP results are sufficiently below the median to suggest a risk for trisomy 21 that is greater than their maternal

Table I — Sensitivity and specificity of screening for trisomy 21 by maternal serum α-fetoprotein (MSAFP) testing and by determining maternal age[12-14, 21]

	Multiples of median MSAFP level					Maternal age ≥35 years
Variable (%)	1	≤0.7	≤0.6	≤0.5	≤0.4	
Sensitivity	80	49	34	26	15	20
Specificity	55	78	84	92	96	94

age-specific risks alone. Decisions on the management of these women cannot await the completion of even pilot studies. What should be done now in these cases of "accidental" screening for trisomy 21?

As an *interim* measure, when the objective is to minimize the possibility of missing a case of trisomy 21 in a woman already participating in a prenatal screening program, we suggest that the MSAFP values be used in conjunction with empiric maternal age-specific risk figures to determine the probability of an affected child in each case. When this calculated risk exceeds that at which amniocentesis would otherwise be made available at a particular centre, further diagnostic procedures should be offered. Such a "rule-out" policy is in line with usual clinical practice and would combine the restraint demanded by the limited sensitivity of MSAFP testing with the responsibility to provide pregnant women with all the information that might be relevant to their reproductive decisions. This policy suggests that women be informed in advance that the interpretation of both increased and decreased MSAFP values may influence the management of their pregnancies so that they can consider the full implications of their participation in a screening program.

Conclusion

We agree with those who have called mass screening for trisomy 21 using MSAFP testing "premature".[21,26,32,33] Even the most optimistic estimates suggest that using the combination of MSAFP testing and age to identify women 30 years of age or older who are at a risk greater than 1/250 of having an affected fetus would allow the diagnosis of perhaps another 10% to 20% of cases in addition to the 10% to 20% identified among women already undergoing amniocentesis only because they are 35 years of age or older.[12] For example, reducing the maternal age cutoff to 30 years would raise the proportion of fetuses in the United States identified as having Down's syndrome from 18% to 27%, if one assumes that 50% of eligible women in each age group choose prenatal diagnosis.[31] The additional cases would be identified at the potential cost of the "spontaneous" abortion of at least an equal number of chromosomally normal fetuses in cases of "false-positive" MSAFP values because of the risk attributable to amniocentesis, which may be as high as 1%.[34]

The various unresolved (and even unconsidered) technical and social policy questions about the use of MSAFP testing as a screening method lead us to suggest that it not be made available as a tool for detecting Down's syndrome in the general population of pregnant women in Canada at present. In accord with the recommendations about genetic screening made several years ago by the US National Academy of Sciences we urge that pilot studies be undertaken to establish the feasibility, effectiveness and impact of such a screening program in defined areas before its use becomes widespread[35] and that there be a broad-based discussion of its technical and policy implications.[36]

Although detecting cases of trisomy 21 in the general population with this approach appears inappropriate, using a woman's MSAFP results to diminish the chance of missing a specific case of trisomy 21 can be justified and is to be recommended to those currently screening for neural tube defects. This recommendation seems to offer an appropriate resolution to the problem of how to handle low MSAFP values for the near future: cautiously and only for decision making in individual cases.

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New challenges to medical staff organizations in hospitals

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Generally, Canadian hospitals enjoy the benefits of carefully structured medical staff organizations, which facilitate operations and allow hospital boards to delegate responsibility for quality of care. Such organizations also sustain medical participation in management, planning and educational activities, and they constitute one element of the governing triangle: board, administration and medical staff. Harmonious regulation of hospital affairs presumably serves the objectives of provincial ministries of health and promotes the provision of the best possible service to the community. Certainly in jurisdictions where coherent organizations are poor or absent, many of the accepted functions are performed badly or not at all.[1,2]

The functions and duties of medical staff organizations have been well defined and are relatively simple. For example, in Ontario the Public Hospitals Act[3] states that the hospital board shall pass bylaws that provide for the appointment and functioning of a medical staff through statutory committees to address credentials, admission and discharge policies, medical records, medical audits and tissue reviews. Thus the board is assured that its statutory responsibility is being met. Originally these basic duties of the medical staff were not particularly onerous; some have changed little, but others are becoming increasingly complex, taxing and time consuming. This complication has resulted from many forces for change, including constrained funding, rapidly expanding medical technology, increased legal liability, changes in administrative structures and pres-

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