

Advanced Maternal Age is No Longer so Advanced

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In the past, antenatal screening for Down's syndrome was a simple matter of noting the maternal age. Women were referred for invasive prenatal diagnosis if their age was regarded as sufficiently advanced to warrant the hazards and costs of the procedure. Local policy or national convention determined the cutoff age: usually 40, 38, 37 or 35 years. The discovery in the last 15–20 years of various maternal serum and ultrasound markers of Down syndrome has led to a major change in policy. Today, routine screening based on multiple marker determination is the norm in most countries. Information on a woman's multi-marker profile, age and family history are used to estimate the risk of Downs. Women are referred for invasive prenatal diagnosis if the risk exceeds a fixed cutoff: e.g., 1 in 250 at term in the UK, and 1 in 270 at mid-trimester in the United States, equivalent to 1 in 350 at term.

Nevertheless, in some countries a remnant of the previous policy persists. Women aged 35 or older are either offered invasive prenatal diagnosis rather than multi-marker screening, or they are screened but can obtain prenatal diagnosis regardless of the result. As Arie Dugan points out in this issue of *IMAJ* [1], from a public health standpoint this hybrid approach is not an efficient use of resources. In a system of socialized medicine the rate-limiting step is the cost of chorionic villus sampling, amniocentesis and karyotyping, or rapid DNA determination of common aneuploidies. To illustrate the point, suppose the resources are available for 5% of women to have an invasive procedure and the maternal age structure of the population is Gaussian with a mean of 27 years and standard deviation 5.5 years, close to that in the UK. An age-only policy would yield a Down syndrome detection rate of 27%, whereas for universal second-trimester screening with three serum markers – human chorionic gonadotropin, alpha-fetoprotein and unconjugated estriol – it would increase to 62% [2]. A hybrid policy with an age cutoff of 35 years would almost double the number of women having invasive procedures to 9%. The detection rate would also increase, to 67%, but universal screening with a cutoff level leading to 9% of women having invasive prenatal diagnosis would yield a 71% detection rate. There are even greater inefficiencies for the hybrid approach when second-trimester screening is further improved by substituting an assay for the free β -subunit of hCG rather than the intact molecule or adding inhibin A as a fourth serum marker.

Although those responsible for public health policy must be mindful of efficiency, it is not the sole arbiter and in the private

sector it is not necessarily an issue at all. Thus it has been argued that there is a *clinical need* for an older woman to have invasive prenatal diagnosis which overrides any universal public health policy, because of her intrinsically high risk. However, this is a spurious argument based on a common misunderstanding about the very concept of risk in this area. Unlike with screening for Mendelian genetic diseases like Tay-Sachs, being at high risk is not a fixed property of an individual or couple, which we can determine by biochemical or DNA methods. The risk of Down syndrome is simply an expression of our uncertainty as to the karyotype of the fetus, which can radically change as more information is collected. Hence, before the observation that Downs was associated with maternal age, all women had the same risk, about 1 in 700, whereas afterwards the risk ranged from 1 in 1,600 at age 15 to 1 in 28 at 45. With multi-marker screening even a 15 year old can be shown to be at high risk and many 45 year olds are at very low risk.

While the Down syndrome risk associated with advanced age is not intrinsic or immutable, it is known about from the beginning of pregnancy. Therefore, in contrast to younger women, the reproductively elderly could have the benefits of early invasive prenatal diagnosis, namely earlier reassurance, and if termination of pregnancy is necessary, it can be completed before fetal movements are felt. In experienced hands the hazards of first trimester CVS are not substantially greater than for second-trimester amniocentesis, and while there are more erroneous diagnoses due to confined placental mosaicism, these are rare. Until recently, the clinical advantage of early prenatal diagnosis for older women may have been sufficient reason to maintain a hybrid policy, but the advent of first-trimester multi-marker screening undermines this position.

In the first trimester a combination of maternal serum free β -hCG and pregnancy-associated plasma protein-A, and ultrasound nuchal translucency yields a higher detection than achievable in the second trimester even with four serum markers. When 5% of women are selected for CVS the predicted detection rate is 88%, and for 9% procedures, as with a hybrid policy, it is 92% [2]. First-trimester screening is not yet widely available in the public health sector, but when it does become routine there will be no remaining reason for a hybrid policy. Some health planners are resistant to move screening into the first trimester because suitable ultrasound equipment and appropriately skilled staff are limited, and quality management is more difficult for ultrasound than biochemistry. Additional first-trimester ultrasound markers such as nasal bone hypoplasia [3] and

hCG = human chorionic gonadotropin

CVS = chorionic villus sampling

ductus venosus blood flow [4] will considerably further increase the detection rate but require even greater skills. Eventually, a move to the first trimester is inevitable; meanwhile it is reasonable to use what facilities are available to selectively screen groups such as older women, those with a previous affected pregnancy, those who have had assisted reproduction who would particularly like to avoid invasive prenatal diagnosis, and twin pregnancies where second-trimester serum markers are relatively weak.

There is another new development in Down syndrome screening that has implications for older women. The background to this is the proposal that women have both first- and second-trimester marker determination but that the risk is not calculated until all markers have been measured [5]. This non-disclosure sequential screening policy leads to higher detection than first-trimester screening – at the 5% invasive prenatal diagnosis rate the detection rate is 94% [2]. But the long wait to complete the sequence, the loss of both early reassurance and early diagnosis, and the non-disclosure itself will make it unacceptable to many. An alternative sequential policy is known as contingent screening. Women whose risks are so high following first-trimester screening that they are unlikely to be altered by second-trimester markers are offered CVS, and those whose are so low as to be unaltered are given early reassurance. Only a small number of women with intermediate risks need then go on to second-trimester testing. Contingent screening yields a similar detection rate to non-disclosure sequential screening [6,7].

Clinicians are already informally carrying out some form of sequential screening but it is often done incorrectly. Some women have first-trimester screening, perhaps in the private sector, and later have a routine second-trimester test. In these circumstances the second-trimester risk calculation should take account of both the first- and second-trimester markers, but many clinicians do not know how to do this. Even more common is the incorrect interpretation of the late second-trimester ultrasound anomaly scan when it follows a second-trimester multi-marker serum screening test. As Arie Drugan states, information from the scan – such as nuchal skin-fold, which is unrelated to nuchal translucency, femur or humerus length – and so called 'soft markers' should be combined with the serum markers to calculate risk, rather than used *per se* to refer for invasive prenatal diagnosis [8].

Contingent screening brings universal public health policy and individual clinical need closer together and could resolve the issue of advanced maternal age. One can envisage a contingent policy beginning with a very high cutoff age, say 45, above which CVS is offered directly, and for other women a multi-marker first- and second-trimester sequence. Most of those aged 34–44 would complete screening in the first trimester, less than about one-fifth would need second-trimester serum markers, and a small fraction would have their risks modified substantially at the anomaly scan.

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Capsule

Prion fibrils aggregates and pathogenesis

Amyloid fibrils form by aggregation of diverse peptides and proteins and are involved in protein folding disorders such as Alzheimer's and prion diseases. Petkova and associates show that the morphology of fibrils formed by the beta-amyloid peptide associated with Alzheimer's disease can be controlled experimentally by variations in fibril growth conditions. Morphologic differences correlated with specific differences in molecular structure, and both morphology and molecular structure propa-

gated in a "heritable" manner when fibrils were grown *in vitro* from pre-formed seeds. The different fibril morphologies possessed significantly different toxicities in neuronal cell cultures. Thus, certain amyloid morphologies may prove to be more pathogenic than others in amyloid diseases.

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