



## Steering the Course Between Optimal Policies and Practical Restraints

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It is with great pleasure that I welcome the launch of the Journal of Fetal Medicine. This will add to the range of publication options for researchers in the field and as a consequence it should, over time, establish a high reputation among potential readers.

Moreover, the new journal is well positioned to fill a niche currently lacking. Despite their best intentions, many existing journals do not fully reflect the range of clinical practice across the continents. These journals are rightly predominantly concerned with reporting the latest scientific discoveries. Subsequently, pilot studies designed to test the practicality of clinical implementation of the new findings, will be published in the same journals. Even when such studies involve international collaboration between multiple centers, these are usually confined to academic institutions which do not represent the full range of practical experience. In most countries, there are some centers of excellence carrying out clinical research of a high standard whilst others do not have the resources to translate them into health improvement for their patients. Between these extremes are health planners and professionals trying to manage the fine line between optimal policies and practical restraints. I see the new journal as providing a great opportunity for the middle ground to have its say in informing choice for clinicians and patients. These points can be illustrated with reference to the field where I have the most experience, namely antenatal screening.

Routine screening for Down syndrome in the first trimester of pregnancy using maternal serum free  $\beta$ -hCG and

PAPP-A together with ultrasound NT (the combined test) is now the standard of care in most developed countries. This represents a recent shift from second trimester serum-only protocols (such as the quad test) that are still the norm in many countries. It has been driven both by the much higher detection rate of the combined test and the ability to terminate affected pregnancies at an earlier gestation when the procedure is safer and less traumatic. However, quality ultrasound NT is not universally available and at first sight, it would appear that this precludes the introduction of the optimal test in all localities. This is even true for some developed countries, although the deficit is more acute worldwide. Nevertheless screening protocols exist that could be used to overcome this deficit.

In a locality without any quality NT provision at all, a first trimester serum-only protocol of free  $\beta$ -hCG, PAPP-A, PIGF and alpha-fetoprotein (AFP) (1T-quad test) can achieve a detection rate comparable with the second trimester quad test [1]. Whilst this does not provide a material detection advantage over a second trimester quad test, it does allow earlier termination of affected pregnancies. In a locality where quality NT is not generally available but there are sufficient resources to provide it to a proportion of the population, a so-called 'contingent' protocol could be used. This involves applying the 1T-quad markers to initially assess an individual woman's risk and referring those with the highest risk for an NT scan and subsequent risk revision. If just 20 % of women are selected for an NT scan the detection rate would be under 2 % less than for the standard combined test which requires quality NT ultrasound for all women [1]. Such protocols are not widely discussed in the existing journals but are clearly of importance to health planners in many countries and localities.

There is now no doubt that the universal maternal serum testing for cell-free (cf) DNA will yield the best screening

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performance for Down syndrome [2]. However, the cost of this test is very high and cost-benefit is too low to consider this strategy in public health settings [3]. The cost of cfDNA testing is likely to fall in the coming years but may still be outside the reach of public health providers in many localities. Again the most practical solution will be a contingent protocol where the cfDNA testing is selectively based on the initial risk assessment with first trimester serum and, if available, ultrasound markers [2, 4].

These possibilities assume that women will present early enough in pregnancy. However, in many localities, most do not have their first antenatal visit until the second trimester. This does not preclude Down syndrome screening with high detection provided protocols are used which combine biochemical and ultrasound markers—a type of second trimester combined test. The ultrasound options include a simple facial profile scan to determine the nuchal skinfold, rather than NT which is unreliable outside 11–13 weeks gestation, nasal bone length and prenasal thickness. Using the second trimester quad markers together with these three easy to obtain ultrasound markers will achieve detection rate comparable with the first trimester combined test [5].

Even with the simple second trimester serum-only screening tests, there are practical issues that may not be regarded as important in general but are critical in some localities. For example, maternal serum free  $\beta$ -hCG, one of the analytes in the double, triple and quad tests is subject to considerable analytical variability according to ambient temperature and duration of storage [6]. In locations where the test laboratory is some distance from the clinic and samples cannot be transported quickly and in cool conditions, the test results can be markedly affected leading to very high false-positive rates. This can be overcome by spotting the blood onto filter paper and testing with an appropriate assay method, not unlike newborn screening [7].

One disadvantage of the shift to first trimester screening is the inability to use second trimester maternal serum AFP, a component of the double, triple and quad tests, to screen for spina bifida. In countries where the staple food can be fortified with folate or where individual periconceptional supplementation with folic acid is feasible, this may not be a problem, as primary prevention of most cases can be achieved. But elsewhere new solutions are needed. First trimester ultrasound markers such as intracranial translucency are possible [8] but it is unlikely that operators sufficiently skilled to determine these measurements will be generally available. Instead, it has been shown that first trimester serum AFP and free  $\beta$ -hCG together with a simple ultrasound BPD measurement, can achieve a high detection rate [9].

It is now feasible to obtain a Down syndrome detection rate of well over 95 % and with the best available

technologies, the false-positive rate can be much  $<0.5$  %. Hence the focus of screening research is moving away from this disorder in two directions. At one extreme, using cfDNA methods, there is the possibility of screening simultaneously for all common aneuploidies and many microdeletion and microduplication syndromes. On the other side, it is becoming possible to extend the combined test to encompass adverse outcomes of pregnancy such as pre-eclampsia, growth restriction, preterm birth and gestational diabetes [10].

A meta-analysis of published clinical trials clearly demonstrates that low dose aspirin when started before 16 weeks gestation will halve the incidence of pre-eclampsia [11]. Moreover, there is a simple first trimester screening test that can identify a small group of women which includes more than 90 % of those who would develop early onset pre-eclampsia, in the absence of aspirin prevention [12]. The test is based on maternal serum PAPP-A and PIGF together with careful blood pressure measurement and a uterine artery Doppler scan. Again a contingent protocol can be devised to select women for the ultrasound phase. Despite these impressive findings there does not appear to be widespread interest in this type of screening and prevention among public health planners in developed countries. This may be connected to the low incidence of early onset pre-eclampsia in such countries. Indeed the localities most likely to benefit from this approach are those experiencing high rates of infant and maternal mortality, where eclampsia is a major contributor.

In all areas of life, globalisation has resulted in many benefits but increasingly, there is a backlash with increased interest in local issues. Ideally, both approaches can be followed in order to maximize benefits whilst minimizing disadvantages, but this will require much work from all sides. For example, I am Past President of the International Society for Prenatal Diagnosis (ISPD), a multidisciplinary society with members in over 40 countries. During my tenure as President, we began to publish position statements on topics of global interest and from a global perspective. For each topic, a working group was appointed, reflecting the highest levels of expertise, providing an international perspective, and consisting of individuals who can provide an objective assessment of the topic. At the same time, we formed the ISPD Federation comprising national groups which share the same mission to stimulate, support and promote education, research and knowledge in the field of prenatal diagnosis and therapy. This was meant to be a two-way street whereby the national groups informed ISPD of local needs and perspectives so that the position statements could reflect all views. I am confident that the Journal of Fetal Medicine can fulfil such a role too.

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