Advanced Maternal Age and Prenatal Diagnosis: It's Time for Individual Assessment of Genetic Risks

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The association between advanced maternal age and increased risk of fetal aneuploidy has been extensively documented in large epidemiologic studies on neonates [1,2], and *in vitro* on unfertilized human oocytes [3]. A simple comparison of the age-related risk for aneuploidy with the risk of pregnancy loss associated with amniocentesis (about 1 in 200 procedures) led most European and American medical administrations to offer prenatal diagnosis to women aged 35 or older at the time of delivery [4]. In Israel, invasive prenatal diagnosis is offered when the prospective mother is 35 years or older at the time of the last menstrual period.

Screening by advanced maternal age is indeed attractive (it's inexpensive and easy to perform), but its detection rate is quite low. Since the vast majority of pregnancies occur in women younger than 35 years, most aneuploid gestations also occur in the younger population. Thus, despite the fact that more than 80% of procedures for prenatal diagnosis performed in the United States are indicated for advanced maternal age, less than 30% of aneuploid gestations are detected in this age group [5]. In Israel, about 15% of the pregnant population is older than 35 years. In 2002, about 60% of gestations affected by Down syndrome (fetuses and newborns) were observed in this age group. Prenatal diagnosis of fetal trisomy 21 was 59.7% and 29.6% in the Jewish and non-Jewish populations, respectively. Thus, despite the fact that in Israel amniocentesis is offered free of charge to women older than 35 years at conception, only 15.8% of Israeli Moslem women in this age group underwent the procedure [6]. In contrast, 47.6% of eligible Jewish women had an amniocentesis. Maternal education may modify utilization rates of invasive prenatal diagnosis and may translate into a lower rate of age-related increase in the birth prevalence of Down syndrome [7]. The decision to have an amniocentesis may be influenced also by documentation of markers for aneuploidy on ultrasound [8] or by an abnormal biochemical serum screening result [9]. In the study by Marini et al. [9], in a cohort of patients defined by advanced maternal age, utilization rates of amniocentesis were 48% when serum-screening results were positive but only 13% when serum screening was considered negative.

The relationship between low alpha-fetoprotein in maternal serum and an increased risk for fetal aneuploidy, first reported by Merkatz and colleagues [10], established the era of biochemical serum screening. Using a cutoff risk for Down syndrome at mid-trimester similar to that for a 35 year old (about 1 in 300), some 5–7% of the young population screen positive. At follow-up amniocentesis, 1 in 85 procedures will yield an abnormal result. The development of multiple marker biochemical screening in maternal serum (human chorionic gonadotropin and unconjugated estriol) improved the detection rate of affected gestations (from 45 to 65%) as well as the abnormality/amniocentesis ratio – the latter rose to 1 in 50 procedures, without changing the proportion of patients considered to be at risk [11]. The addition of dimeric Inhibin A to triple serum screening improved the sensitivity to 79%, with a false positive rate of 7.5% [12]. Moreover, it soon became apparent that in addition to Down syndrome, biochemical serum screening allowed detection of other chromosomal anomalies as well (trisomy 18 and sex chromosome aneuploidy).

Maternal age alone is an ineffective and expensive screening tool for aneuploidy

The decision to offer prenatal diagnosis is influenced by the numerical comparison between the risk of aneuploidy and the risk of pregnancy loss [4]. The latter is relatively constant and is estimated at 0.2–0.5%. However, the use of more accurate screening methods can modulate the risk of chromosomal anomalies, targeting invasive procedures (with their inherent risk of pregnancy loss) to the population at highest risk. Moreover, it appears that screening methods are more sensitive in the group that is a priori at higher risk. If triple serum screening is used in patients over 35 and amniocentesis is offered only when the combined risk of having a fetus with Down syndrome is higher than 1 in 200, irrespective of

maternal age, 89% of affected pregnancies will be detected [13]. In practice, such a policy would obviate some 75% of amniocentesis procedures.

The diagnosis of structural malformations on prenatal ultrasound is an established indication to evaluate fetal karyotype, since with some congenital anomalies (e.g., diaphragmatic hernia, omphalocele or cystic hygroma) the rate of aneuploidy may be 30–80%. Even with normal chromosomes, the prognosis in these cases is often dismal, as an effect of the malformation syndrome itself. In contrast, sonographic markers for Down syndrome are functionally inconsequential, but their presence confers an increased risk for fetal chromosomal anomalies. In experienced hands, one or multiple sonographic markers for Down syndrome will be observed in about 80% of affected fetuses, with a false positive rate of 12.5% [14]. Over 30 sonographic markers for aneuploidy have been reported but the most significant signs, appearing in over 90% of affected gestations, are those affecting the fetal neck [15]. Nuchal edema, nuchal translucency or nuchal cysts are observed in about 5% of screened pregnancies and all confer the same ominous meaning; the risk of trisomy in gestation is considered to be 1–2% in young women and more than 7% in women over age 35 [16].

Ultrasound evaluation of the fetus in the search for markers for aneuploidy has been termed "genetic" sonography. Individual ultrasound findings were assigned likelihood ratios for Down syndrome [15,17], while their absence conferred an overall negative likelihood ratio of 0.15–0.4 [14,17,18]. Regardless of the indication for fetal testing, the risk for Down syndrome following a normal second-trimester ultrasound is reduced by 83–89% [18]. This would imply a six- to sevenfold decrease in the need for invasive testing, along with a matching proportion of amniocentesis-related pregnancy losses. Combining ultrasound and serum screening may even increase the sensitivity of the test and make advanced maternal age the sole indication for invasive prenatal testing even more redundant [19,20]. The "integrated test" for Down syndrome includes evaluation of nuchal translucency, serum pregnancy-associated plasma protein-A and hCG in the first trimester and "quadruple" serum screening in the second trimester. Invasive testing for a risk equivalent to that of 35 years old will be offered to 5% of the population and will detect 94% of affected gestations [21]. First-trimester screening (at 11–14 weeks of gestation) using fetal nuchal translucency, the presence or absence of the nasal bone on ultrasound, and free beta-hCG and PAPP-A in maternal serum yields apparently similar results. In a retrospective study by Cicero et al [22], screening by these four parameters in combination with maternal age was associated with detection rates for trisomy 21 fetuses of 90.5% and 97%, yielding false positive rates of 0.5% and 5%, respectively.

In this era of limited resources allocated for public health, cost analysis is a major determinant in the evaluation of the efficacy of any screening modality. Since the billing for serum screening and for ultrasound differs in various locations, the cost of detecting one case of Down syndrome should be calculated for the specific country that is interested in evaluating its screening program. The California Department of Health Services reported that the use of triple marker prenatal serum screening led to a detection rate of 41%, and the cost per case of Down syndrome detected was US$ 35,365; the cost per case prevented was calculated as $ 110,741 [23]. The estimated cost of detecting one case of Down syndrome by the current policy of universal use of amniocentesis in all women over age 35 has been calculated as $ 138,000–181,000, with a sensitivity of less than 30% [24,25,]. However, when amniocentesis was offered to these patients based on age and genetic sonography, the sensitivity increased to 77–97% for screen positives of 5% and 25%, respectively, and resulted in cost savings of 14.3% and 18.8% [24]. A more recent study suggests that, in comparison with universal amniocentesis, genetic sonography has a sensitivity of 75% and results in savings of 9% to the healthcare system, in addition to a decrease of 87% in pregnancies lost after amniocentesis [26].

The use of biochemical serum screening and/or ultrasound to assess the individual risk for Down syndrome in all patients will enable us to target invasive procedures to pregnancies at highest risk, resulting in a significant improvement of the cost-benefit ratio while reducing considerably the number of normal pregnancies lost after amniocentesis

It is apparent from the above that advanced maternal age is neither effective nor low cost as a screening tool for affected gestations. The incorporation of additional screening methods (biochemical serum screening and/or ultrasound) is expected to increase the percent of detected cases and to reduce the number of invasive procedures and of procedure-related losses. Moreover, the combination of screening methods may achieve all this at lower cost [Table 1]. Hartnett and associates [27] calculated that in the USA in 1999 there were 530,610 women over 35 years at 16 weeks gestation carrying an estimated 4,043 fetuses with Down syndrome. Performing amniocentesis in all of them would have resulted in 100% detection rate but would result also in 2,653 procedure-related losses. Combining age with serum screening and a genetic sonogram would detect 97.6% of affected gestations but would require only 119,791 amniocenteses and would result in only 599 related losses. The projected cost of detection of one case of Down syndrome was $ 219,109 using age alone, as compared with $155,992 using serum screening and genetic sonography.

Sequential screening was found by Biggio et al. [28] to be the least expensive strategy. Like the integrated test, sequential screening is based on first-trimester screening plus quad screening in the second trimester, the difference being that in the sequential

hCG = human chorionic gonadotropin
PAPP = pregnancy-associated plasma protein

Table 1. Comparison of cost and yield of screening modalities for Down syndrome (Adapted from ref. 25)

	Group A	Group B	Group C	Group D	Group E
Sensitivity (%)	30	69	62	51	36
Cost/Down syndrome ($ 1,000)	181	203	162	151	194

Group A: Amniocentesis for all women over 35, no screening for younger patients

Group B: Amniocentesis for all patients over 35, triple serum screening for younger patients, and amniocentesis for those who screen positive.

Group C: Triple serum screening for all patients and amniocentesis for those who screen positive.

Group D: <35 years – triple serum screening followed by ultrasound for those who screen positive; amniocentesis for patients with markers on ultrasound.
>35 years – triple serum screening with amniocentesis for screen-positive patients.

Group E: All patients – triple serum screening followed by ultrasound for those who screen positive; amniocentesis for patients with fetal markers for Down syndrome on ultrasound.

screening strategy, positive results at each step are reported and acted upon. Sequential screening detected the most Down syndrome fetuses and averted the most Down syndrome live births but led also to the highest number of euploid losses. In contrast, the integrated screen had the fewest euploid losses and averted the second highest number of Down syndrome live births. The authors conclude that the patients' perspective on detection versus fetal safety may help define the optimal screening strategy [28].

Surprisingly enough, a multicenter longitudinal study performed on Jewish patients in Israel failed to substantiate these theoretical calculations [29]. From 1990 to 1995 the use of chromosomal studies in pregnancy increased from 11.3% to 21.6% and the percentage of Down syndrome cases detected prenatally increased from 53% to 70%. This has been accredited to the introduction and more universal use of second-trimester biochemical serum screening in the young population. From 1996 to 2000, despite the introduction of new technologies (transvaginal ultrasound evaluation at 14–16 weeks gestation and first-trimester biochemical screening), the utilization rate remained similar (about 20%) and the percentage of cases detected prenatally actually decreased to 61%. The total cost per case detected increased from $ 47,971 in 1990, through $ 75,229 in 1992 to $ 190,171 in the year 2000. Thus, the addition of new screening methods for Down syndrome in the second part of the study did not improve the percentage detected, did not reduce the amniocentesis rate, and was accompanied by an increased cost per case detected. These findings may be explained in part by the high cost of ultrasound screening but also by the continuation of the current practice that offers prenatal invasive testing to all women over age 35, despite the reassuring results from alternative screening methods.

Can we reduce the fiscal and emotional cost of prenatal diagnosis? Can we target invasive procedures to those who really need them? We already showed that sonographic screening and serum screening are equally effective in terms of detection rates, but that the former is a lot more expensive and requires a higher level of expertise while the latter is more suitable for mass screening [30]. Our report was recently substantiated by another local study [31], which estimated that in the absence of specific sonographic markers, a negative second-trimester triple test might decrease the need for amniocentesis by 60% in advanced maternal age patients. Moreover, in that study the use of ultrasound did not add new cases to those already detected by abnormal serum screening.

I suggest limiting the uniform recommendation for invasive prenatal testing to patients over the age of 40. In younger patients, the policy of screening for Downs should be changed from age-based to triple serum screening-based (from group B to group C, Table 1), with amniocentesis being offered and funded by public resources only in those patients with the combined risk for Down syndrome higher than 1 in 380 (the cutoff used today for patients under 35 years old). Incorporating the Down syndrome risk derived from ultrasound screening is optional, but not mandatory. Analysis of data from the Ministry of Health on prenatal testing performed in Israel in 2002 shows that 6,951 amniocenteses were performed for advanced maternal age in patients 35–39 years old and 1,806 procedures were performed in patients over 40. The rate of Down syndrome was 0.47% in the younger group and 2.16% in older patients ($P < 0.001$). The total aneuploidy rate was 0.8% and 3.4%, respectively ($P < 0.001$). Thus, it appears that the aneuploidy rate is five times higher in this age group, while 80% of invasive procedures for prenatal diagnosis are performed in patients between 35 and 40 years of age.

Had we applied a policy of serum screening and selective amniocentesis in patients under 40 we would have missed four cases of Down syndrome by performing only 1,738 amniocenteses in this age group – a significant improvement in yield from 211 procedures to 60 procedures per affected case. The risk-benefit ratio for the whole population would be 52 amniocenteses for detecting one case of Downs. Moreover, obviating the need for amniocentesis in 5,213 additional cases would reduce the toll on the health budget considerably, as well as avoiding some 25 needless pregnancy losses.

Obviously, arbitrarily changing the cutoffs as proposed would cause us to miss a small number of affected gestations in the older population, cases that would have been diagnosed if amniocentesis had been uniformly performed in all patients over 35. However, some cases of Down syndrome are already missed in this age group because the utilization rate of amniocentesis is far from complete. Some cases are also missed in patients younger than 35 as well, partly due to the false negative rate of screening methods and partly because screening was not opted for.

It is essential to emphasize that a numerical comparison of risks and benefits of invasive prenatal diagnosis is not necessarily correct. It is the *individual perception of risk* that is important. For a specific couple, the meaning of taking care of an affected child for the next 20 to 30 years may not be equivalent to that of pregnancy loss. People should, if possible, be in control of their own reproductive decisions. As suggested by Harris and co-workers [32], prenatal diagnosis can be cost-effective in women of all ages and level of risk for Down syndrome, depending on the woman's

preference. Thus, following appropriate screening and genetic counseling, prenatal testing should remain available for all patients at will. Who will pay for the test is a separate question with medico-legal, political and economic implications that should be deliberated and decided upon by the Ministry of Health, the Ministry of Finance and the health maintenance organizations.

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Someone's boring me. I think it's me.

Dylan Thomas (1914-53), Irish poet, most famous for Under Milkwood