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Review article

Advances in prenatal screening for Down syndrome: II first trimester testing, integrated testing, and future directions

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Abstract

Background: The acceptability of prenatal screening and diagnosis of Down syndrome is dependent, in part, on the gestational age at which the testing is offered. First trimester screening could be advantageous if it has sufficient efficacy and can be effectively delivered. *Issues*: Two first trimester maternal serum screening markers, pregnancy-associated plasma protein-A (PAPP-A) and free β-human chorionic gonadotropin (β-hCG), are useful for identifying women at increased risk for fetal Down syndrome. In addition, measurement of an enlarged thickness of the subcutaneous fluid-filled space at the back of the neck of the developing fetus (referred to as nuchal translucency or NT) has been demonstrated to be an indicator for these high-risk pregnancies. When these three parameters are combined, estimates for Down syndrome efficacy exceed those currently attainable in the second trimester. Women who are screen-positive in the first trimester can elect to receive cytogenetic testing of a chorionic villus biopsy. The first trimester tests could also, theoretically, be combined with the second trimester maternal serum screening tests (integrated screening) to obtain even higher levels of efficacy. There are, however, several practical limitations to first trimester and integrated screening. These include scheduling of testing within relatively narrow gestational age intervals, availability of appropriately trained ultrasonographers for NT measurement, risks associated with chorionic villus biopsy, and costs. There is also increasing evidence that an enlarged NT measurement is indicative of a high risk for spontaneous abortion and for fetal abnormalities that are not detectable by cytogenetic analysis. Women whose fetuses show enlarged NT, therefore, need first trimester counseling regarding their Down syndrome risks and the possibility of other adverse pregnancy outcomes. Follow-up ultrasound and fetal echocardiography in the second trimester are also indicated. *Conclusion*: First trimester screening appears to be a highly effective method to screen for Down syndrome. Women with screen-positive results based on NT measurement appear to be at increased risk for diverse fetal abnormalities. The finding of a normal fetal karyotype may not, therefore, carry a high level of reassurance for a normal baby.

Keywords: Down syndrome; First trimester; Screening, serum tests; Ultrasound; Aneuploidy

1. Introduction

In part 1 of this review of advances on prenatal screening for Down syndrome, the efficacy of second trimester screening for Down syndrome was discussed

Abbreviations: PAPP-A, pregnancy-associated plasma protein-A; hCG, human chorionic gonadotropin; NT, nuchal translucency; NB, nose bone; MSAFP, maternal serum alpha-fetoprotein; uE3, unconjugated estriol; INH-A, inhibin-A.

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[1]. It was pointed out that second trimester maternal serum screening has become a widely accepted procedure with an estimated 63% of all pregnant women in the United States receiving this testing [2]. However, there may be far lower acceptance for the fully diagnostic amniocentesis procedure in women with screen-positive results. For example, a review of amniocentesis utilization in Connecticut for women with screen-positive results from 1993 to 1997 showed that, overall, only 52% underwent amniocentesis [3]. Multiple factors appeared to influence whether or not women received amniocentesis including the patient-specific risk provided on the screening report and the gestational age at the time of screening. Amniocentesis is an invasive procedure that carries a 0.5–1.0% risk for fetal loss [4], but this risk appears to be much more accepted when the procedure is offered earlier [3]. Although first trimester invasive testing (chorionic villus biopsy) carries a somewhat greater risk to the fetus [5], the earlier timing presents an attractive alternative for many women.

To take full advantage of earlier diagnosis, first trimester screening would be helpful, provided it has sufficient efficacy and can be effectively delivered. First trimester screening might be particularly welcomed by women of advanced maternal age or others at higher a priori risk, many of whom could receive earlier reassurance. This second part of the review considers the current status of first trimester screening and the merits of integrated first and second trimester screening.

2. First trimester serum markers

2.1. Pregnancy-associated plasma protein-A

Brambati et al. [6] first recognized the potential value of measuring maternal serum pregnancy-associated plasma protein-A (PAPP-A) in screening for fetal aneuploidy in the first trimester. Numerous studies have confirmed that PAPP-A is low in first trimester pregnancies complicated by Down syndrome [7]. Maternal serum PAPP-A concentration is normally increasing rapidly during the first trimester and, therefore, accurate gestational age assessment is critical. Based on maternal age and PAPP-A concentrations, an estimated 52% of Down syndrome pregnancies could be identified at the 5% false-positive rate (Table 1), but this value will be dependent on the time in the first trimester that the testing is performed [8]. By 15 weeks gestation, the efficacy of this marker is lost and there is no value in performing the PAPP-A test for second trimester patients.

PAPP-A is produced by placental trophoblasts and its function is largely unknown [9]. There are data to suggest that low maternal serum PAPP-A concentrations are predictive for subsequent spontaneous abortion [10]. Whether or not detecting low concentrations of PAPP-A preferentially identifies those Down syndrome pregnancies with the highest risk for fetal death is unknown.

2.2. Human chorionic gonadotropin

There has been some controversy as to the value of total hCG in first trimester screening for Down syndrome. Some studies show good distinction between affected and unaffected pregnancies [11], while others appear to show minimal utility [12]. This discrepancy appears to be explainable by differences in the gestational ages for the samples used in the various studies [13]. Total hCG would appear to be useful for screening performed after 11 weeks gestational age, but not before that time.

Free β-human chorionic gonadotropin (β-hCG) is substantially elevated at 8–14 weeks gestation in Down syndrome pregnancies [14]. It is estimated that, at the usual 5% false-positive rate, the combination of maternal age and free β-hCG measurement could result

Table 1
Expected detection rates for first trimester and integrated testing when the false-positive rate is held at 5%

Screening test	Detection rate (%)	Reference
First trimester, maternal age plus		
PAPP-A	52	[8]
Free β-hCG	42	[8]
PAPP-A+free β-hCG	65	[8]
Nuchal translucency (NT)	73	[28]
NT+PAPP-A+free β-hCG	86	[8]
Integrated, maternal age plus		
PAPP-A+MSAFP+hCG+uE3+INH-A	85	[62]
NT+PAPP-A+MSAFP+hCG+uE3+INH-A	94	[62]

in a 42% detection rate [8]. Peak concentrations of maternal serum free β-hCG normally occur at 8–10 weeks in unaffected pregnancies [15]. The observation that free β-hCG is elevated in Down syndrome pregnancies at 8–10 weeks would, therefore, indicate that these anomalous concentrations cannot be attributed to a relative developmental immaturity of the affected pregnancies.

Free α-hCG does not appear to be useful for Down syndrome screening in the first trimester [14].

2.3. Other biochemical markers

The other serum analytes routinely used in second trimester screening (MS-AFP, unconjugated estriol (uE3), and inhibin-A (INH-A)) show either modest or no differences in Down syndrome pregnancies, and these are, therefore, of little or no value in first trimester screening [14]. Pregnancy-specific β_1 glycoprotein (SP-1) is lower very early in pregnancy in women with a Down syndrome-affected fetus [16], but this marker has not been incorporated in routine screening. Some of the newer markers previously discussed for second trimester screening, notably, eosinophil major basic protein p43 [17] and isoferritin p43 [18], may also prove to have utility in the first trimester.

Maternal urine markers have also been evaluated in the first trimester. Free β-hCG, β-core hCG, and total estriol showed promise [19], but the consensus data would indicate that, at least for β-core hCG, there are insufficient differences between affected and unaffected pregnancies for clinical utility [20,21]. Efforts to develop a urine-based screening test are currently focussed on hyperglycysolated hCG (invasive trophoblastic antigen) [22].

3. First trimester ultrasound markers

3.1. Nuchal translucency

Considerable progress has been made in using first trimester ultrasound markers in screening for Down syndrome. Most important of these markers is the measurement of nuchal translucency (NT), the thickness of the subcutaneous fluid-filled space at the back of the neck of the developing fetus.

In 1990, Szabó and Gellén [23] recognized the potential value of measuring first trimester NT as a screening tool for Down syndrome. Subsequently, Nicolaides et al. [24] reviewed fetal NT measurements present in predominantly high-risk women undergoing chorionic villi biopsy because of advanced maternal age or family history of chromosome abnormality. Using a fixed cut-off for the NT measurement of 3 mm, 18 of 28 (64%) of chromosomally abnormal cases could be identified, while only 33 of the 799 (4.1%) fetuses with normal karyotypes showed similar NT enlargement. Numerous studies have confirmed this association [25]. Pandya et al. [26] refined the approach to use a variable cut-off that was dependent on the gestational age and established a set of likelihood ratios that could be used to modify maternal age-specific risk for fetal Down syndrome. A further refinement was the development of a Gaussian model for the NT variable that allowed this test to be readily combined with other markers [27,28]. Using NT measurements and age alone, it was estimated that 73% of affected pregnancies would be identified if the false-positive rate is set at 5% [28]. The ultrasound examination is carried out at 10–14 weeks gestational age.

The fluid accumulation causing NT enlargement or nuchal cystic hygroma has been attributed to aortic isthmus narrowing or other cardiovascular defects which cause overperfusion of the head and neck [29]. This can be a transient phenomenon that spontaneously resolves in the second trimester. The NT marker should, therefore, be expected to be a marker for other conditions associated with cardiovascular defects. Other explanations for NT enlargement include abnormal or delayed development of the lymphatic system [30].

3.2. Nose bone

The absence of the nasal bone (NB) has recently been proposed as a further marker for first trimester ultrasound screening for Down syndrome. Cicero et al. [31] investigated this marker in pregnancies screen-positive by NT plus maternal age and noted that 43 of 59 (73%) Down syndrome fetuses showed absence of NB, while only 3 of 603 (0.5%) unaffected fetuses showed absence of NB. The observation needs to be confirmed in an unselected population.

4. Multiple marker first trimester screening

4.1. Optimal first trimester screening

Maternal serum analytes can be combined with each other or with the ultrasound markers to produce highly effective screening protocols. Interpretation of first trimester biochemical tests should be based on an ultrasound measurement of gestational age because the serum analyte concentrations are highly gestational age-dependent. Because of the superior discriminatory power of NT and the need for first trimester ultrasound to accurately assess gestational age, the serum tests have, thus far, been largely viewed as adjunctive to ultrasound screening. Fig. 1 shows the typical testing pathway for patients receiving first trimester screening. There is a relatively narrow time window for NT measurement and chorionic villus sampling and, therefore, careful attention must be paid to the timing of each component of the testing.

As is the case for the second trimester serum markers, it is appropriate to adjust the observed concentrations of the first trimester analytes to reflect patient race/ethnicity [32] and weight [33]. Twin pregnancies show an approximately two-fold concentration of free β-hCG and PAPP-A, allowing the computation of a pseudo-risk for an affected pregnancy [34,35]. Other factors affecting the concentrations include maternal smoking, gravidity, parity, fetal gender, gestational diabetes, and assisted reproduction [33,36–39].

Currently, measurement of NT remains a specialized technique that requires specific training. The United Kingdom Royal College of Obstetricians and Gynecologists [40] have recommended that NT screening should only be conducted where the center has staff with the appropriate high level of ultrasound competence and experience. They also recommend certification by an external agency, high-standard precision equipment, and clinical protocols that have external systems of quality assurance and ongoing audit. The feasibility and efficacy of first trimester screening is also the subject of a multicenter clinical trial in the United States (the First And Second Trimester Evaluation of Risk of fetal aneuploidy or "FASTER" trial) [41].

4.2. Expected performance

Fig. 2 presents the receiver operating characteristic curves (plots of detection rate against false-positive rate) for screening using either NT alone or NT plus free β-hCG and PAPP-A at 9–11 weeks gestation. Rates are based on modeling using established stat-

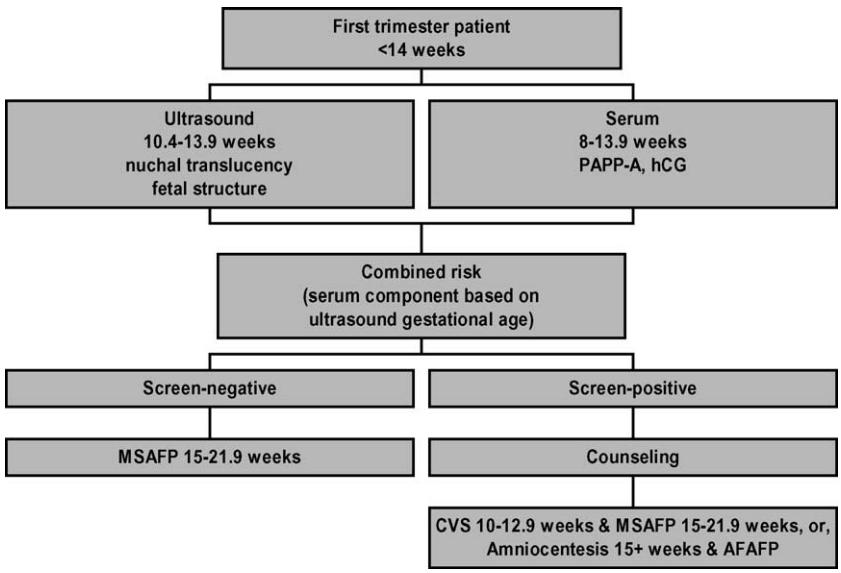

Fig. 1. Typical protocol for first trimester screening.

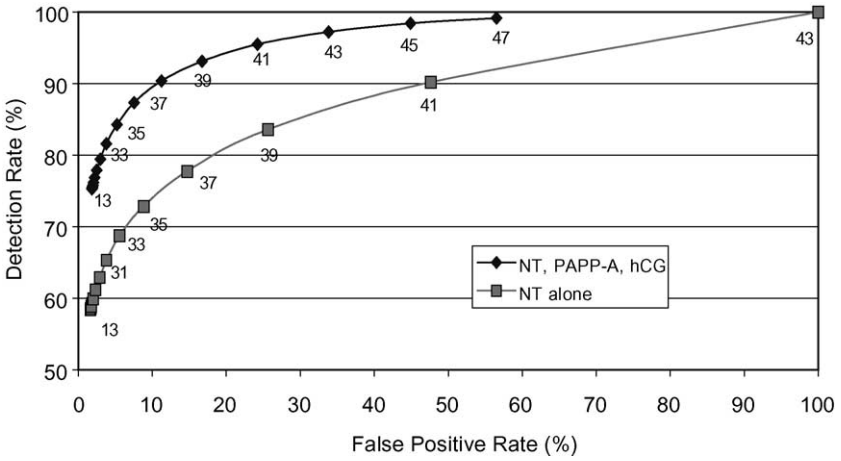

Fig. 2. Receiver-operating characteristic curves for first trimester screening by NT alone and in combination with a first PAPP-A and free β-hCG using a 1:193 first trimester risk for Down syndrome as a cut-off. Each point on the curve represents maternal age at delivery in 2-year intervals (13-43 or 13-47). Rates are based on statistical parameters in Refs. [8,28,42,43].

istical parameters for the screening tests [8,28], the 8-series Down syndrome birth prevalence rates of Bray et al. [42], and a 39% relative loss rate for affected pregnancies [43]. A first trimester cut-off of 1:193 was chosen to make the screening protocol comparable to second trimester screening. After allowing for fetal deaths, the 1:193 first trimester risk for an affected pregnancy corresponds to a second trimester risk of approximately 1:270. The first trimester maternal age-specific detection rates and false-positive rates illustrated in Fig. 2 should, therefore, be directly comparable to those second trimester efficacy rates presented earlier [1], assuming cases identified by screening are typical of all cases present in the population.

Use of NT plus maternal age should result in approximately 73% of affected pregnancies being identified when the false-positive rate is held at 5% (Table 1). Use of NT alone is not useful at the most advanced gestational ages. At age 43, or more, essentially no fetuses (affected or unaffected) have an NT measurement sufficiently small to reduce the net risk below the cut-off. Use of free β-hCG and PAPP-A at 9–11 weeks gestation, without NT biometry (Table 1), fails to achieve the level of efficacy of the second trimester triple or quadruple tests [1].

The combination of first trimester NT, PAPP-A, and hCG should detect 86% of affected pregnancies with a 5% false-positive rate (Table 1). This is superior to the second trimester quadruple test but may be less than that possible with the combination of the quadruple test and fetal biometry [1].

The expected net effect of the first trimester screening protocols when applied to a population of women with the maternal ages seen in the United States in 1999 is shown in Table 2. The predicted maternal age-specific detection rates and false-positive rates, toge-

Table 2
Summary of the expected detection rates (DR) and false-positive rates (FPR) for first and integrated test combinations for the 1999 United States pregnancy population, using a 1:193 first trimester cut-off

Screening test	DR (%)	FPR (%)	DR (%)	FPR (%)	DR (%)	FPR (%)
	Mat age<35		Mat age≥35		All	
First trimester, maternal age, plus						
NT	63	2.7	85	20.9	74	5.1
PAPP-A+free β-hCG	61	5.8	90	27.5	75	8.6
NT+PAPP-A+ free β-hCG	80	2.8	93	13.2	86	4.2
Integrated, maternal age, plus						
PAPP-A+MSAFP+ uE3+hCG+INH-A	81	3.6	94	13.5	87	4.9
NT+PAPP-A+MSAFP+ uE3+hCG+INH-A	89	1.9	96	7.2	93	2.6

Modeling based on first trimester testing at 9–11 weeks using the statistical parameters in Refs. [8,28,42,43,62,70–73].

ther with the odds of being affected given a positive result (OAPR), are also presented in Table 3.

4.3. Observed performance

The United Kingdom multicenter trial provides a substantial demonstration of the efficacy of NT screening [44]. Over 96,000 women at 22 centers received NT measurements and those women (8.8%) with first trimester risks 1:300 or greater were offered chorionic villus sampling or amniocentesis. The population studied had a median age of 31 years and, therefore, contained a higher number of older women than would be expected in a general population. Without correction for expected fetal deaths later in pregnancy, 82.2% of cases of known Down syndrome cases were identified ("observed" detection rate). Allowing for these losses, the authors estimated that this corresponded to an actual detection rate of 78–82%. However, an editorial commentary that accompanied this report suggested that the data could also be interpreted as showing a 60% detection rate [45]. After excluding other chromosome abnormalities detected (see below), the false-positive rate was 8.3%.

The combination of first trimester NT and serum tests is a relatively new concept and there is currently little prospective data on the performance. Spencer et al. [46] reported on 4190 patients of which 4088 accepted the combined first trimester screening protocol. NT measurement and biochemical testing were carried out simultaneously and results were then presented to women in as little as 1 h. The observed Down syndrome detection rate was 6/7 (86%), and the false-positive rate was approximately 6.7% (excluding trisomy 18 cases but including a number of other anomalies in the false-positive rate). An alternative approach used dried blood samples that were sent to a remote testing facility, separate from the locations at which NT measurements were performed [47]. This latter study included many advanced maternal age women. Also, based on small numbers, the authors reported an overall observed detection rate of 93.8% and false-positive rate of 7.9%.

Because a substantial proportion of first trimester Down syndrome fetuses will spontaneously abort, the possibility has to be considered that the screening preferentially identifies those affected fetuses that are most likely to be lost. This is of more concern when

Table 3
Maternal age-specific detection rates (DR), false-positive rates (FPR), minimum likelihood ratios needed for a positive result (min LR), and odds of being affected given a positive result (OAPR) for first trimester screening using NT alone and for NT plus PAPP-A and free β-hCG

Mat age	First trimester risk (1:*n*)	Min LR	NT alone			NT + PAPP-A + hCG		
			DR (%)	FPR (%)	OAPR (1:*n*)	DR (%)	FPR (%)	OAPR (1:*n*)
13	919	4.76	58.4	1.6	26	75.3	1.9	23
15	914	4.74	58.4	1.7	26	75.3	1.9	23
17	906	4.70	58.5	1.7	26	75.4	1.9	23
19	892	4.62	58.6	1.7	26	75.5	1.9	23
21	868	4.50	58.9	1.8	26	75.8	2.0	22
23	829	4.30	59.3	1.9	26	76.2	2.1	22
25	768	3.98	59.9	2.0	26	76.8	2.2	22
27	680	3.52	61.1	2.3	26	77.9	2.5	22
29	565	2.93	62.9	2.9	26	79.4	3.0	21
31	435	2.26	65.3	3.8	25	81.6	3.8	20
33	310	1.60	68.7	5.6	25	84.3	5.2	19
35	205	1.06	72.8	8.8	25	87.3	7.6	18
37	128	0.67	77.8	14.7	24	90.4	11.3	16
39	77	0.40	83.6	25.6	24	93.1	16.7	14
41	45	0.24	90.2	47.6	24	95.5	24.2	11
43	26	0.14	100.0	100.0	26	97.2	33.8	9
45	15	0.08	100.0	100.0	15	98.4	44.9	7
47	9	0.04	100.0	100.0	8	99.2	56.5	5

Based on a 1:193 first trimester cut-off. Rates were established by computer simulation using the statistical parameters in Refs. [8,28,42,43]. See footnote to Table 4, Ref. [1], for use of this table with alternative cut-offs.

considering protocols that ascertain substantially less than 100% of the cases. There is, in fact, evidence that NT screening does preferentially identify those Down syndrome affected pregnancies with the greatest likelihood for intrauterine death [48]. However, the extent to which this occurs with the combination of NT measurement and serum screening has not yet been determined.

4.4. Other disorders identified

The UK multicenter trial [44] showed that Down syndrome screening using NT preferentially identifies many other aneuploidies. Observed detection rates were based on cases ascertained prenatally, plus those diagnosed at birth, and did not include cases that would be expected to have spontaneously aborted. Observed detection rates were given as 97/119 (81.5%) for trisomy 18, 37/46 (80%) for trisomy 13, 48/54 (89%) for Turner syndrome, 20/32 (63%) for triploidy, and 51/74 (59%) for other unbalanced karyotypes. Each of these abnormalities is associated with considerable uncertainty as to the prevalence in the first trimester and the subsequent loss rates are poorly defined. Any conversion of the observed detection rates to true detection rates is, therefore, associated with a substantial degree of uncertainty.

While the true detection rates for these other chromosome abnormalities cannot be established, it is important to note that the observed number of cases is very high, relative to the number that would be expected at birth. Based on the rates of chromosome abnormalities observed in newborns [49], it is estimated that, in the absence of screening and intervention, approximately 80% of these cases would spontaneously abort. When Down syndrome cases are combined with the other abnormalities, over half of all aneuploid cases identified would represent pregnancies that would not survive to term.

Fetal trisomy 18, trisomy 13, triploidy, and Turner syndrome are each associated with low maternal serum PAPP-A. Trisomy 18, trisomy 13, and at least some cases of triploidy will also show low levels of free β-hCG [50–54]. Screening protocols to calculate patient-specific risks have been proposed for trisomy 18 [50,51] and trisomy 13 [52]. The protocols for both of these disorders are expected to identify a high proportion of affected pregnancies with low false-positive rates. For example, the combination of maternal age, NT, PAPP-A, and free β-hCG should theoretically detect 89% of trisomy 18 fetuses with a 1% false-positive rate [51] and 90% of trisomy 13 fetuses with a 0.5% false-positive rate [52]. Because both of these trisomies are associated with similar marker patterns (enlarged NT, low PAPP-A, and low free β-hCG), some pregnancies will be screen positive by both algorithms. Some cases will also be screen-positive for Down syndrome (enlarged NT, low PAPP-A but high free β-hCG). The incremental gain in the detection and false-positive rates as a result of adding these multiple criteria for a positive screen has not yet been established.

Cardiac defects are also preferentially identified through NT screening [55–58], and other fetal anomalies may also be more frequent in this group of patients [46,56,57,59]. Early ultrasound examinations are also expected to identify a relatively high frequency of nonviable pregnancies [60]. There is also evidence that an enlarged NT is associated with increased risk for later spontaneous abortion and neonatal death [56–58]. Variable criteria have been used to define the groups with large NT and the risk for adverse outcome is not yet well defined. However, based on the limited data thus far available, these risks for a nonchromosomal abnormality or fetal death appear to be relatively high. Following the detection of an enlarged NT, the finding of a normal karyotype does not, therefore, provide the same level of reassurance as that usually conveyed following second trimester screening and karyotyping. Follow-up counseling, additional ultrasound examinations, fetal echocardiography, or other testing may be indicated for these patients [61].

5. Integrated first and second trimester screening

The term ‘‘integrated screening’’ has been applied to the situation in which Down syndrome tests are performed in both the first and second trimesters but risk is only presented to patients after the completion of the second trimester component [62]. A combination of NT and PAPP-A in the first trimester, followed by MS-AFP, hCG, uE3, and INH-A in the second trimester has been proposed. This combination has a theoretical 94% detection rate for a 5% false-positive rate. Omitting the NT component would reduce this detection rate to 85%. These estimates do not take into

consideration the fact that fetuses with the highest NT measurements may be more likely to spontaneously abort before the second trimester [48,56–58]. Therefore, these rates may somewhat overestimate both the detection rate and the false-positive rate. Projected estimates for the net detection rate and false-positive rate for the integrated test, if applied to a population with maternal ages equivalent to that in the US in 1999, are presented in Table 2.

Integrated screening, by definition, requires that women not be offered diagnostic testing (amniocentesis) until all components of the screening have been completed. Offering chorionic villus sampling to those patients who are screen-positive after the first trimester component, together with amniocentesis for those positive in the second trimester, results in a higher false-positive rate and a higher use of invasive testing and was not recommended [63,64].

Thus far, integrated screening is confined to Down syndrome risk assessment. An algorithm for trisomy 18 screening has not yet been developed. Given the high detection rate that can be achieved in the first trimester (see Section 4.4), and the fact that many of the trisomy 18-affected fetuses will spontaneously abort, the value of an integrated screen for this aneuploidy is unclear.

6. Second trimester, first trimester, or integrated screening?

First trimester screening offers the obvious advantage of potentially earlier diagnosis and intervention for those women with affected pregnancies, or reassurance for those with unaffected pregnancies. A review of the achievable detection rates and false-positive rates for other aneuploidies as well as Down syndrome also indicates that the combination of serum and ultrasound first trimester screening is superior to the second trimester serum screening protocols. However, there are a number of interrelated factors that need to be considered before successful first trimester screening can be fully implemented.

(1) For many women, comprehensive prenatal care does not begin until the second trimester and early referral of these women to maternal–fetal medicine units requires a significant change from existing clinical management.

(2) Women with screen-positive results need to consider definitive diagnosis through chorionic villus biopsy, a procedure associated with somewhat higher risk to the fetus [5]. Alternatively, they may need to wait, in a heightened state of anxiety, for amniocentesis.

(3) In pregnancies where there is an enlarged NT, and a normal karyotype, there remains an increased risk for spontaneous abortion, fetal cardiac defects, or other abnormality that may not be apparent until later in pregnancy. First trimester screening may, therefore, actually result in a prolonged period of uncertainty for some patients, rather than provide early reassurance.

(4) Earlier screening for aneuploidy needs to be linked to earlier evaluation of the risk for other genetic disorders (e.g. cystic fibrosis screening) because these other disorders may provide an additional indication for invasive testing.

(5) Screening for fetal structural abnormalities, including neural tube defects, through ultrasound and maternal serum alpha-fetoprotein (MSAFP) is still needed in the second trimester.

(6) Costs of first trimester screening may be substantially higher. These may include additional ultrasound examinations and the termination of affected pregnancies that would normally have spontaneously aborted prior to the second trimester.

Integrated screening appears to offer a compromise solution to some of the above difficulties. However, serious concerns have been raised about withholding a potentially significant first trimester finding until after the second trimester tests have been completed [65]. Women with screen-positive results based on NT need to be counseled not only about their Down syndrome risks but also the risks for other aneuploidies, fetal death, cardiac defects, and other genetic disorders [66]. The ethical issue associated with a failure to inform is not confined to the style of healthcare delivery practiced in the United States. Counseling and informed consent prior to the integrated test add additional complexity to screening and may not fully address all of the potential issues that may arise as a result of systematic withholding of information. Cuckle [67] has expressed the view that the incremental gain in Down syndrome detection does not justify waiting for results. His assessment was based on data prior to the report that nose bone was a potential marker for Down syndrome [31,68] and this, or any other further

improvement in first trimester screening, further weakens the case for delaying results.

It seems likely that, in the short-term, local factors such as the maternal age distribution of the population, availability of trained ultrasonographers, reimbursement, other resources, and the established patient referral patterns will lead to the variable utilization of first trimester and integrated screening. Increased expenditure for Down syndrome screening can be justified, at least for populations containing a high proportion of women with high a priori risk [69].

7. Future trends in Down syndrome screening

The trend towards combining maternal serum testing and sonographic markers for Down syndrome is likely to continue with the emergence of additional first and second trimester protocols that are superior to either biochemical or sonographic findings alone. The amalgamation of these two diverse types of markers will necessarily require even closer links between the clinical chemistry laboratory, maternal–fetal medicine units, clinical genetics services, and primary care physicians. In addition to new biochemical tests, refinement of the existing tests can be expected. Further clarification of co-variables (smoking, etc.) that affect analyte concentrations should also result in better screening.

The distinction between screening and the fully diagnostic tests for fetal aneuploidy will ultimately become less apparent. Amniocentesis and chorionic villus sampling may then only be offered in the few cases where an abnormality has already been established with near certainty. An achievable goal in Down syndrome screening is a level of efficacy in which amniocentesis and chorionic villus biopsy are no longer used as initial or primary diagnostic tools but, instead, are only offered to confirm and precisely define the chromosomal basis for an anomaly.

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