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A historical and practical review of first trimester aneuploidy screening

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SUMMARY

There have been tremendous advancements over the past three decades in prenatal screening for aneuploidy and we have changed our practice from screening by maternal age alone to ‘combined’ first trimester screening and circulating cell-free fetal DNA. We currently use the nuchal translucency and biochemical markers of free β -hCG and PAPP-A to determine the risk of fetal aneuploidy. The primary goal is to identify higher risk women for fetal aneuploidy early in pregnancy and give them the option to pursue invasive testing in a timely manner if desired.

Keywords

Aneuploidy; First trimester screening; Free β -human chorionic gonadotropin; Maternal serum screening tests; Nuchal translucency measurement; Pregnancy-associated plasma protein A

1. Introduction

The past 30 years have produced numerous discoveries and advances in prenatal screening for cytogenetic disorders in the fetus: ultrasound imaging, maternal serum biochemical markers, and isolation of cell free fetal DNA in maternal serum. These advancements are responsible for the options currently available for prenatal screening for aneuploidy in the first trimester. The purpose of this review article is historical and practical. Its historical aspect chronicles the origins of and innovations in first trimester screening, demonstrating how current screening for fetal aneuploidy has come into practice. On a practical side, it will highlight the available options for first trimester screening, indications for screening, first trimester screening in twin pregnancies and discuss the additional knowledge that can be obtained from a first trimester “combined” screen.

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Conflict of interest statement
None declared.

2. Origins of prenatal screening for fetal aneuploidy

Prior to the 1980s, the primary method to identify women at risk for aneuploidy was based on the concept of increased risk with advanced maternal age. Dr Lionel Penrose was the first to recognize this concept in the 1930s when he observed that there was a significant association between increasing maternal age and birth of a Down syndrome child [1]. With the advent of cytogenetic analysis on cultured amniocytes in the 1970s, all women aged >36 years were offered amniocentesis to diagnose potential fetal aneuploidy. Maternal age was a poor screening test in isolation because it only identified 25–30% of fetal aneuploidy.

The first recommendation for prenatal aneuploidy screening in the general population stemmed from the observation by Merkatz et al. [2] in 1984 that maternal serum α -fetoprotein (MSAFP) in the second trimester was significantly lower in a woman with a trisomy 18 fetus. Simultaneously, MSAFP was suggested by Cuckle [3] as a screening test for Down syndrome in the general population. This study modeled a mathematical algorithm that combined maternal age and MSAFP in the second trimester to detect 40% of cases of Down syndrome with a false-positive rate of 6.8%. This led to the first protocols for fetal aneuploidy screening in the general population across all maternal ages. After observations with MSAFP, altered maternal serum levels in affected pregnancies were observed in other analytes: free β -human chorionic gonadotropin (β -hCG), inhibin A and unconjugated estriol (uE_3) [4–6]. Wald et al. [7] combined the maternal serum markers of β -hCG, α -fetoprotein (AFP) and uE_3 with maternal age in the ‘triple screen’ in 1988. Overall, the mean levels of these analytes were expressed as a multiple of the expected value for gestational age based on a log–linear regression in the controls, multiples of the median (MoM). The mean for the analytes β -hCG, AFP and uE_3 in a second trimester pregnancy affected with Down syndrome were 2.1, 0.7 and 0.7 MoM respectively. Looking across all maternal ages, the triple screen detection rate for Down syndrome in the second trimester was 60% with a false-positive rate of 5%, essentially doubling the detection rate from age alone. Haddow et al. [8] examined dimeric inhibin A as yet another marker to be added to the second trimester screening profile and this was later dubbed the ‘quadruple screen’. Using age and the four maternal serum analytes, the detection rate for Down syndrome was 75% at a false-positive rate (FPR) of 5%.

3. First trimester maternal serum markers of free β -hCG and pregnancy-associated plasma protein A (PAPP-A)

The goals for improving prenatal screening for aneuploidy following the advent of the triple and quadruple screen were to achieve a higher detection rate, a lower FPR, reassurance to patients with a low risk and to offer diagnostic testing as early as possible. Thus, with the development of a maternal serum screening test for the general population, a logical next question was the feasibility of implementing prenatal screening earlier in pregnancy. Chorionic villus sampling (CVS) had been introduced in the 1980s, an invasive procedure that allowed for prenatal diagnosis in the first trimester, adding impetus to move screening to an earlier gestational age [9]. The clear advantages of a screening test in the first trimester included earlier reassurance to low risk patients, more time to consider options for diagnosis, and the possibility of earlier, safer termination in affected pregnancies.

Spencer et al. [10] published their initial findings of free β -hCG as a marker for trisomies 21 and 18 in the first trimester and showed that the MoM value of free β -hCG in trisomy 21 was significantly greater and the median value in trisomy 18 was significantly lower than that in the unaffected controls. The idea of using free β -hCG was first proposed by Bogart et al. [11] who compared the ability of free versus total hCG to detect chromosomally abnormal fetuses in the second trimester. Based on Bogart's work, Spencer et al. had also examined free β -hCG in the second trimester. Compared with total hCG, free β -hCG was a better marker for detection of trisomy 21. Macri and Spencer [12] then expanded on their earlier paper using free β -hCG as an analyte from 9 to 13 weeks of gestation and showed that free β -hCG was significantly elevated (2.20 MoM) in trisomy 21 pregnancies. They concluded that this maternal serum analyte would serve as a good marker for Down syndrome in the first trimester.

Around this time, it was discovered that PAPP-A was lower in pregnancies with fetal aneuploidy. Brambati et al. [13] were the first to publish this finding in 13 cases of trisomy 21 at 8–12 weeks of gestation. The PAPP-A levels were <5th percentile. Wald et al. [14] expanded on these findings, concluding that PAPP-A was a useful marker for trisomy 21 in the first trimester (0.23 MoM). Muller et al. [15] further established PAPP-A as a potential useful marker for trisomy 21 in the first trimester with their study examining PAPP-A levels in blood samples originally collected for toxoplasmosis testing in France (median PAPP-A value for trisomy 21 was 0.42 MoM).

4. Fetal nuchal translucency: a novel approach to screen for aneuploidy

The British physician, John Langdon Down, was the first to describe Down syndrome in 1866 [16]. He noted: 'The skin has a slight dirty yellowish texture and is deficient in elasticity, giving the impression of being too large for the body.'

In the 1990s, Nicolaides et al. [17] pondered the observation of the fullness of the neck in Down syndrome neonates and the association of nuchal edema/cystic hygroma on second trimester ultrasound in fetuses with chromosomal abnormalities. Nicolaides hypothesized that increased nuchal thickness on ultrasound in the first trimester could be a marker for fetal aneuploidy. In a prospective study, 827 pregnant women who chose to have diagnostic testing underwent transabdominal ultrasound at 10–14 weeks of gestation to evaluate the fluid behind the neck in their fetuses. Visualizing a sagittal section of the crown–rump length, the maximum thickness of subcutaneous translucency between the skin and soft tissue overlying the cervical spine was measured. In the 51 fetuses with a nuchal translucency thickness of 3–8 mm, the incidence of chromosomal abnormalities was 35%. In the fetuses with smaller measurements ($n = 776$), by contrast, 1% had chromosomal abnormalities. He also noted that the abnormal fluid collection had, for the most part, resolved by the second trimester. In this study, Nicolaides reported that an increased nuchal translucency was associated with an increased risk for chromosomal defects. He introduced the term 'nuchal translucency' (NT) into the vocabulary of genetics counselors, obstetricians, ultrasound technicians, radiologists, maternal fetal medicine specialists and academic medicine. This article transformed the landscape for prenatal screening.

Based on Nicolaides' study, another prospective study by Brambati et al. [18] was performed to evaluate the technical and practical aspects of a screening program in the general population. In women undergoing CVS between 8 and 13 weeks of gestation, the NT was measured for maximum thickness. These investigators were among the first to introduce a standardized protocol: (i) two different observers scrutinize the ultrasonographic images of the posterior fetal contour in sagittal plane with the requirement to distinguish between amnion and fetal skin; and (ii) an abnormal cut-off value of 3 mm. In 70 fetuses with NT above the cut-off, 18.6% had chromosomal disorders versus 1.7% in the normal NT group. Brambati et al. affirmed that the NT increased with increasing gestational age and that an increased NT was associated with chromosomally abnormal fetuses; he also addressed the need for quality control and standardization with measurement of NT screening.

Pandya's and Nicolaides' group examined 1015 fetuses with NTs ≥ 3 mm and found that the incidence of chromosomal abnormalities, namely, trisomy 21, 18 and 13, was significantly associated with increased fetal NT and additively with maternal age at 10–14 weeks of gestation [19]. Another study by Pandya et al. [20] demonstrated that fetal NT increases with increasing crown–rump length, and that the likelihood of trisomy 21 varies with the degree by which a given NT deviates from the normal median at a given crown–rump length. Instead of having a specific numerical cut-off for the NT, they used the cut-off of >95 th percentile above the normal median and detected 77% of fetuses with trisomy 21 and 78% of other chromosomal abnormalities using only maternal age plus NT. For quality control, a subgroup analysis showed good reproducibility of NT measurements when ultrasound examinations were performed by different sonographers, all trained in the same fashion.

Snijders et al. [21] published one of the most comprehensive studies on fetal aneuploidy screening with maternal age and nuchal translucency from the Fetal Medicine Foundation First Trimester Screening Group. This trial, conducted at 22 centers, examined 96 127 cases of first trimester NT screening with known genetic outcomes. The median maternal age for the study group was 31 years; there was a preponderance of older-age women in this study. The NT was above the 95th percentile for a given crown–rump length in 71.8% of 326 trisomy 21 pregnancies, and in 70.5% of 325 other chromosomally abnormal pregnancies versus 4.4% of normal pregnancies. With the addition of maternal age, a risk cut-off of 1 in 300 or higher was found in 82.2% of trisomy 21 pregnancies, 77.8% of other chromosomally abnormal pregnancies and 8.3% of normal pregnancies.

Another important contribution of this study was the establishment of criteria by the Fetal Medicine Foundation to achieve a uniform 10–14-week scan among many different operators and institutions [21]. These criteria include: a proper sagittal view; magnification (fetus occupies at least 75% of the image); distinction between fetal skin and amnion; and reporting the maximum measurement obtained. The Nuchal Translucency Education and Quality Review program (NTQR) was developed in 2004 with criteria from the Society for Maternal Fetal Medicine similar to that of the Fetal Medicine Foundation for nuchal translucency screening, and these criteria have since been implemented in North America and Canada.

Another study on quality control by Whitlow et al. [22] examined how the head in an extended or flexed position distorts the NT measurement. From this publication came the recommendation to measure the fetal neck in a neutral position, as this is the most reproducible.

5. Combination of biochemistry and nuchal translucency in the first trimester

Brambati et al. [23] first reported the combination of free β -hCG and PAPP-A, attaining a detection rate of 78.9% for trisomy 21 in a small series of 13 cases of trisomy 21 and 89 unaffected controls using just these maternal serum analytes, plus maternal age. Noble et al. [24] were among the first to combine biochemistry and the NT plus age, finding that free β -hCG and NT were two independent parameters; thus their likelihood ratios could be combined. This 'combined screening' trial had a detection rate for trisomy 21 of 85% at a false-positive rate (FPR) of 5%.

Two years later, Orlandi et al. [25] published one of the first studies that prospectively assessed the combination of maternal age, biochemical screening tests of free β -hCG and PAPP-A, and NT to determine risk for fetal aneuploidy in the first trimester. The free β -hCG and PAPP-A values were divided by respective gestational day-specific median levels to determine the MoM for each analyte. Trisomy 21 pregnancies were associated with elevated free β -hCG and low PAPP-A, and trisomy 18 pregnancies were associated with low free β -hCG and PAPP-A. The likelihood ratios for each analyte, the NT, and the patient's prior age-related risk were multiplied together to determine a final risk ratio, and high risk was determined to be 1 in 380. With this combination, the detection rate for trisomy 21 was 87% with a FPR of 5% whereas the detection rate for trisomy 18 was 76% with FPR of 1%. Orlandi et al.'s study also demonstrated the utility of dried blood technology for specimen collection. The use of the dried blood spot simplified and allowed for greater flexibility in collection, shipping and processing.

Spencer et al. [26] examined the combined first trimester screening for trisomy 21 in a retrospective analysis, and expedited the process to a 'one-stop clinic' employing new technology that allowed for results of biochemical analysis within 30 min of obtaining a blood sample. This technology resulted in precise measurements with good reproducibility and allowed for complete early fetal assessment in one visit. This study also demonstrated that each marker was independent; when combined they obtained a detection rate for trisomy 21 of 89% with FPR of 5%. Spencer et al. re-confirmed their conclusions from earlier studies that risk algorithms needed to be created that were adjusted for gestational age because detection rates varied at different gestational ages.

Krantz et al. [27] reported on the first trimester combined screening's ability to detect trisomy 18 in addition to trisomy 21. They used the dried blood spot technology previously described, and a standardized protocol outlined by the Fetal Medicine Foundation for nuchal translucency measurements. Krantz et al. showed a detection rate for trisomy 21 of 87.5% with FPR of 4.5% in women aged <35 years and detection rate of 92% with FPR of 14.3%

in women aged ≥ 35 years. For trisomy 18, there was a detection rate of 100% with FPR of 0.4–1.4% for women aged <35 and ≥ 35 years respectively.

Wapner et al. [28] published the first multicenter trial in the USA for the combined first trimester screening for trisomies 21 and 18. This study, ‘the BUN trial’, demonstrated that across multiple centers this screening method was reproducible and appropriate for use in clinical practice. The detection rate for trisomy 21 was 78.7% with FPR of 5%. The detection rate for trisomy 18 was 90.9% with FPR of 2%.

6. Comparison trials of different screening methods

Once it was demonstrated that combined first trimester screening was feasible and applicable to the general population, the next question was the comparison of combined first trimester screening to second trimester screening to determine whether one test was superior. Numerous studies showed that the detection rates for trisomy 21 in the first trimester, with a fixed FPR of 5%, ranged from 76% to 91% and this was thought to be better than the detection rates in the second trimester [25–29]. In any comparison of first and second trimester screening, however, it is important to recognize that the overestimate in detection rates in the first trimester is because the incidence of affected pregnancies is higher and a certain percentage of pregnancies detected by early prenatal screening will result in spontaneous fetal loss as gestation advances. A study by Dunstan and Nix [30], for example, provides a methodology to compare detection rates between the first and second trimester screening tests for trisomy 21 by taking into account fetal loss rates in the first trimester and incorporating this information into the comparison. Dunstan and Nix summarized that first trimester screening could only be determined to be superior to second trimester screening if the aneuploidy detection rate was at least 8.3% higher.

During this time, the ‘integrated screen’ was introduced by Wald et al. [31] and used markers from the first and second trimester to provide a single estimate of aneuploidy risk revealed during the second trimester. The detection rate for trisomy 21 was 85% with a much lower FPR of 0.9%.

Two large, multicenter, prospective trials in the UK followed: the Serum, Urine and Ultrasound Screening Study (SURUSS), and in the USA, the ‘First-Trimester and Second-Trimester Screening or Both for Down Syndrome’ (FASTER) trial. These trials sought to compare all of the different available screening methods and determine the most effective and safest method for screening for trisomy 21. In the SURUSS trial, the most effective screening test was the integrated test with a detection rate of 85% and a FPR of 0.9% [32]. For the same detection rate of 85%, the serum integrated, combined first trimester screen and quadruple second trimester screen had FPRs of 3.9%, 4.3% and 6.2% respectively. The FASTER trial had similar results. At a fixed detection rate of 85%, the FPRs of the first trimester combined, serum integrated, fully integrated, and second trimester quadruple screen were, respectively, 4.8%, 4.4%, 0.8% and 7.3% [33]. From these trials, it was concluded that the choice of screening test is individualized and depends on the woman’s gestational age, whether she desires a definitive diagnosis in the first trimester versus the best overall screening test.

7. History of cell-free fetal DNA from maternal blood in detection of aneuploidy

Non-invasive aneuploidy screening with cell-free fetal DNA from maternal plasma is a relatively novel clinical methodology; however, the concept of isolating fetal cells and fetal cell-free DNA from maternal blood was first discovered more than 50 years ago [34]. Preliminary endeavors towards non-invasive prenatal screening were focused on detection and isolation of intact fetal cells from the maternal blood using fluorescence-activated cell sorting [35,36]. One study used isolated, nucleated fetal red blood cells via fluorescent in-situ hybridization (FISH) analysis to detect trisomy 18 [37]. A large, multicenter trial by the National Institute of Child Health and Human Development (NIFTY) used intact fetal nucleated red blood cells with cell sorting, FISH and polymerase chain reaction to detect 74% of cases of fetal aneuploidy with FPR of 0.6–4% [38]. This method of aneuploidy screening was comparable with prenatal serum screening, but had higher specificity. Before its introduction into the clinical arena, further advancement was deemed necessary.

Cell-free fetal DNA in maternal plasma was reported by Lo et al. [39] in 1997. This discovery paved the way for subsequent developments of non-invasive screening for aneuploidy. Circulating cell-free DNA comprises 3–6% of total cell-free maternal DNA. It is derived primarily from the placenta and is cleared from maternal blood within hours after delivery. Cell-free fetal DNA was first used for gender determination with X-linked disorders and for fetal Rh(D) genotyping with Rh-negative pregnant women.

In 2008, massive parallel sequencing revolutionized the detection of cell-free fetal DNA [40–42]. With this shotgun sequencing-based approach, the number of cell-free DNA fragments was quantified and fetal aneuploidy was detectable. This technological advance led to several large trials to explore the validity and feasibility of aneuploidy screening with cell-free fetal DNA [43–46]. Each of these clinical trials had slightly different methods for analysis of cell-free fetal DNA fractions. After these large clinical trials, cell-free fetal DNA screening was implemented into clinical practice for women at risk for fetal aneuploidy.

8. Practical application and other aspects of first trimester screening for aneuploidy

There are many options currently available for aneuploidy screening: the combined first trimester screen, quadruple screen, integrated screen or sequential screen. Additionally, for pregnancies at high risk for aneuploidy, cell-free fetal DNA testing is now being offered. It is important to recognize that these tests are not diagnostic and each test has associated false negatives and false positives. If a patient wants to have a definitive diagnosis of aneuploidy, chorionic villus sampling or amniocentesis are currently the only available options.

A secondary marker in the first trimester screen for aneuploidy is the presence of the nasal bone. The incorporation of the nasal bone into the first trimester screen improves the detection rate for trisomy 21 with fixed FPR, or retains a 90% detection rate with a simultaneous 10-fold decrease in the FPR from 5% to 0.5% [47].

First trimester screening in twin pregnancies is a possible and practical option. There are several factors to take into consideration with twins. The NTs can be used to determine an individual risk to each fetus; however, serum markers can only be used to obtain a pregnancy-specific risk. If there is a positive screen result, then invasive testing is generally offered for each fetus.

In addition to its use as a screening tool for aneuploidy, the first trimester combined screen has several other applications. The first trimester screen can accurately establish estimated date of confinement and chorionicity in multiple gestations, which is very important for obstetrical management. The first trimester evaluation of the nuchal translucency is, moreover, a valued examination to screen for congenital cardiac defects, diaphragmatic hernia, some skeletal dysplasias and other genetic conditions. In the future, first trimester screening may evolve to incorporate the newer technology of cell-free fetal DNA along with maternal serum analytes and NT measurement by ultrasound.

9. Conclusions

First trimester screening for aneuploidy is a valuable tool for the obstetrician and indications and methods of screening have evolved over the last quarter century. The primary goal of first trimester screen is to identify higher risk women for fetal aneuploidy and give them the option to pursue diagnostic testing in a timely manner if desired.

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Practice points

- The first trimester screen for fetal aneuploidy has evolved continuously over the past 30 years.
- The current first trimester aneuploidy screen includes maternal serum analytes for free β -hCG and PAPP-A and NT measurement on ultrasound.
- For patients at high risk for fetal aneuploidy, cell-free fetal DNA in maternal plasma has been incorporated as another screening test.
- First trimester screening has other applications such as confirmation of dating of a pregnancy, establishment of chorionicity in multiple gestations, and screening for congenital heart defects, skeletal dysplasias or other congenital malformation and conditions by increased nuchal translucency.