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Review

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.

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.

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

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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 >95th 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;