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Chapter 5

Prenatal Diagnosis of Down Syndrome

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Abstract

The chapter’s contribution to the book explores the prenatal modalities to diagnose Down syndrome (DS). The current knowledge in the field of genetic sonographic markers is presented, along the performance of current policies as well as the potential of new emerging genetic techniques. Besides the screening or testing pregnancy algorithms, the chapter describes the power of prenatal diagnostic techniques, namely, the advantages and the complications of the invasive genetic maneuvers. The progress in prenatal diagnosis of Down syndrome is one of the most important in prenatal medicine in the last decades. The methods vary in terms of detection rates, acceptability, costs, and potential complications. Although the early genetic screening was improved, ultrasound evaluation should not be dismissed, as the first-trimester sonography has the potential to diagnose the majority of major fetal abnormalities.

Keywords: Down syndrome, prenatal diagnosis, ultrasound, first trimester, nuchal translucency, nasal bone, facial angle, cell-free DNA, combined test, genetic ultrasonogram

1. Introduction

More than 1 in 1000 newborns is affected by Down syndrome (DS) [1], a disease that necessitates significant societal financial and legal support, because about 85% of infants survive the first year and 50% of those will live longer than 50 years [2]. As aneuploidies are major causes of perinatal death and childhood handicap, screening for fetal chromosomal abnormalities should be available to all pregnant women as an essential part of antenatal care and comprehensive counseling. Fortunately, DS can be suspected during pregnancy by combined ultrasound and serologic screening and confirmed by invasive genetic techniques [3]. Also, genetic noninvasive tests were recently developed that reach near certitude detection rates. First-trimester detection of
fetal major abnormalities, including trisomy 21, is important, because it offers the couples the advantages of early termination of pregnancy: less medical complications, reduced economical costs to the health system, and minor emotional impact of the couple. And we should keep in mind that the abortion rates in DS-affected pregnancies have increased to 67–92% in the United States and Europe [4].

Today, the screening methods for trisomy 21 fetuses are multiple, and patients need to choose early and comfortable. All pregnant women should be offered screening for aneuploidies, even if not all patients will accept. The expertise of a genetics counselor, preconceptual or in the first trimester, is beneficial for comprehensive counseling.

2. Historical aspects of aneuploidy screening: evolution and efficiency

The prenatal screening for chromosomal abnormalities was traditionally addressed to DS [5], because this is the most common chromosomal disease in fetuses and accounts for 8% of all congenital abnormal newborns.

It is well known that the chance of having a child with this condition increases as a woman gets older [6, 7], thus, in the 1970s and many decades after, maternal age represented the main screening method for fetal aneuploidy, by offering the option of genetic amniocentesis to all pregnant women over 35 years [8]. In the 1980s, determination of maternal serum alpha-fetoprotein (AFP) was proposed for screening, as decreased levels associated with an increased risk for DS [9]. During the last decades, diagnostic ultrasonography in obstetrics had a dramatic impact in prenatal medicine care, providing valuable information regarding fetal physiology, development, and abnormal conditions, including markers for fetal aneuploidies since the early 1990s [10, 11]. Human chorionic-gonadotrophin (HCG) and unconjugated estriol (uE3) testing were added along AFP determination, resulting in the serology triple test screen [12], and the detection rates were reported up to 73%, in the early 1990s [13].

The quad test was introduced after 1996, by including inhibin-A as a fourth marker to the triple test with a sensitivity of 81% at a 5% screen-positive rate [14, 15]. Also, during the 1990s, Kypros Nicolaides identified a powerful ultrasound marker measurable in the first trimester, namely, increased nuchal translucency (NT) thickness [16]. A first-trimester scan, also named nuchal scan or the genetic scan, was proposed as method for screening of major aneuploidies in combination with maternal age and serum testing (beta human chorionic gonadotropin (beta HCG) and pregnancy-associated plasma protein-A (PAPP-A)). Increased nuchal translucency, reduced PAPP-A levels, and an increased HCG are associated with a higher risk for DS, and using specific calculators, these ultrasound and serologic parameters assist practitioners in identifying pregnancies at risk, by using specific calculators, as the software developed by The Fetal Medicine Foundation [17, 18]. The detection rates for trisomy 21 were reported as 70–82% for first-trimester NT and 87% for first-trimester NT and serum. Additional evaluation of several ultrasound markers increases the detection rate to 90%, when the nasal bone is screened, and 95% with supplementary assessment of the blood flow through the tricuspid valve and ductus venosus (DV), which is similar to the technique that combines first-trimester NT and serum and second-trimester serologic QUAD test [19].
3. Strategies to perform aneuploidy screening

Current guidelines state that every pregnant woman of all ages should be offered extensive genetic counseling, screening, and invasive diagnostic testing for pregnancy with increased genetic risk before 20-week gestation [20]. Pregnant women should decide the genetic investigation technique after extensive counseling regarding the advantages, limitations, the sensibility, and false-positive results of every genetic test available [21, 22]. Still, because of limited healthcare system resources, the present screening options in the first trimester include nuchal translucency testing in combination with measurement of PAPP-A and HCG. In the second trimester, the screening tests include serum screening using triple or quadruple screening and ultrasonography. There is also the possibility for combination of first- and second-trimester screening in an integrated, stepwise sequential, or contingent sequential fashion [20, 23, 24]. Recently, some professional societies adopted the noninvasive cell-free fetal DNA in the detection protocol, for the cases with intermediate-risk cases. This relatively new test will be described separately in the chapter.

3.1. First-trimester markers and further benefit for pregnancy screening

Using only NT testing, the DS detection rate is only approximately 70% for a 5% false-positive rate [25]. However, an increased nuchal translucency greater than 3.5 mm is associated not only with genetic syndromes but also with fetal malformations, as major congenital heart defects, skeletal dysplasia, and congenital diaphragmatic hernia; thus, this marker is important for early detection of such structural abnormalities.

The first-trimester maternal serum screening includes the determination of two markers, PAPP-A and HCG. PAPP-A is a glycoprotein [26] produced by the placental syncytiotrophoblast and decidua that is decreased when placental function is abnormal, as reported in many aneuploidies and other pregnancy complications, as miscarriage and fetal growth restriction [27]. High levels of the HCG glycoprotein are usually present in DS pregnancies [28], and low levels of both markers are also associated with adverse pregnancy outcomes, such as miscarriage, stillbirth, preeclampsia, placental abruption, preterm birth, and low birth weight [29]. The serum concentration of these markers is converted to multiples of median (MoMs) and interpreted in combination with NT MoM and maternal age by dedicated software [30, 31]. The result of this combined test estimates the pregnancy genetic risk, which is considered low or increased, using a cutoff of 1/250. There are several strategies to define an intermediate risk, for example, from 1/50 or 1/100 to 1/1000. The risk in this population may be further refined with the aid of other ultrasound markers (nasal bone, tricuspid valve, and ductus venosus blood flow) or second-trimester markers, as a contingent or sequential approach [19]. More recently, the use of cell-free fetal DNA is advocated and implemented in some healthcare systems (England, Denmark, and Holland).

There are several strategies regarding the timing of the ultrasound and serological determinations. For best patient compliance, OSCAR method is preferred (one-step assessment of risk)—with biological and ultrasound evaluations, result, and parent counseling performed in one session. However, a 2–4% improvement of the detection rate is obtained, if screening is carried in two separate visits, with maternal serum testing at 9–10 weeks of gestation (when the determinations are more specific) and the ultrasound scan at 12 weeks (for a better visualization of
fetal anatomy) [32, 33]. Laboratory certification and periodically sonographer audit are important, due to the necessity of precise measurements [22].

3.2. Second-trimester screening strategies

The second-trimester maternal serum testing includes the triple and quadruple screens, with detection rates of 70 and 81%, respectively [22].

As in the first trimester, the ultrasound scan can be used for screening either alone or as an adjunct to maternal serum testing. Various sonographic features were proposed as markers for fetal chromosomal abnormalities [34, 35], and a 75% detection rate was reported for second-trimester genetic ultrasonography [36].

First- and second-trimester screening data can be combined to improve the detection or to lower the false-positive rate to 5% [37]. Integrated screening involves a unitary report of first-trimester combined test, followed by triple or quadruple screen in the second trimester. Stepwise sequential strategy allows the patients at increased risk to opt for invasive diagnostic testing or to await the second-trimester screen to revise the genetic risk. The contingency screening is based on a stratified risk determination in the first trimester. In high-risk pregnancy, invasive diagnostic testing is offered; in low-risk patients, no further testing is required; and in intermediate group, between the two cutoffs, second-trimester screening is advised [14].

Fetal echocardiography, even if difficult to apply as a primary screening tool, can be comparable to first-trimester integrated screening in identifying over 90% of fetuses with trisomy 21 [19]. Still, it can be used after 20 weeks of gestation as genetic sonography, and when used as an adjunct to first- and/or second-trimester screening for Down syndrome, the detection rate is reported as high as 99% [19].

4. Genetic ultrasound in the first trimester

The genetic scan is also called nuchal scan, as NT measurement is the most important component of the first-trimester combined screen [38] which is performed between 11 weeks and 13 weeks + 6 days, when fetal crown-rump length (CRL) is between 45 and 84 mm. The scan approach is mainly transabdominal, using the transvaginal approach only in particular situations, when the visualization is poor [39]. International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) guidelines recommend a minimum of technical requirements for equipment: real-time, gray-scale, two-dimensional ultrasound; transabdominal and transvaginal ultrasound transducers, adjustable acoustic power output controls with output display standards; freeze frame and zoom capabilities; electronic calipers; and capacity to print/store images [40]. An accurate dating of pregnancy according to CRL measurement is important for the screening purpose, as the values of biological markers are interpreted according the gestational age [41–43].

The most important first-trimester marker is the nuchal translucency (NT) measurement, representing the thickness of the ultrasonographic sonolucency in the posterior fetal neck, between the skin and the soft tissue overlying the cervical spine [44]. To obtain an accurate and reliable
evaluation, it is necessary a sagittal view of the fetal face in the neutral position, magnification so that only the fetal head and the upper thorax are visible on the screen and the measurement of maximum thickness. Specialized training and certification are available [45, 46] (Figure 1(A)).

Semi-automated method of measuring NT thickness was developed, to avoid operator bias and either under- or overestimation of the measurement [47] (Figure 2).

Specialized software quantifies the deviation in the measured NT from the normal euploid pregnancies [47, 48]. The risk for aneuploidies, especially trisomy 21, increases exponentially with increasing NT thickness [49, 50].

The professionals should carefully explain to the patients the significance of an increased NT, as this finding has the potential to determine couples to terminate the pregnancy, worried about the possibility of an abnormal fetus [51].

4.1. Nasal bone (NB)

A common characteristic of the patients with DS is a small nose [52], and many studies have demonstrated that the absence or a hypoplastic NB in pregnancy is highly associated with

Figure 1. First-trimester ultrasound genetic markers. (A) Measurement of the cranial markers: nuchal translucency (NT), nasal bone (NB, white arrow), and fronto-maxillary facial angle (FMF, figured with red lines). (A.1) Normal values of genetic markers with small NT thickness, ossified nasal bone, and normal facial angle. (A.2) Abnormal genetic markers with increased NT thickness, absent nasal bone, and wide facial angle, of more than 90°. (B) Spectral Doppler assessment of the tricuspid flow and measurement of the fetal heart rate. (B.1) Normal tricuspid blood flow. (B.2) Regurgitation of the blood flow across the tricuspid valve. (C) Spectral Doppler assessment of the ductus venosus flow. (C.1) Normal ductal blood flow. (C.2) Abnormal ductal flow with reversed a-wave. (D) Assessment of the four-chamber view of the fetal heart in duplex mode: gray scale and color Doppler. (D.1) Normal appearance of the four-chamber view with identification of the crux cordis in gray scale and equal and separated atrioventricular flows. (D.2) Atrioventricular septal defect with common atrioventricular valve and large communication between heart cavities.
trisomy 21 [53, 54]. The correct evaluation of the nasal bone assumes a midsagittal view, similar to the one necessary for NT measurement. The angle of insonation should be perpendicular to the NB, which is evaluated in the so-called equal sign, with two echogenic lines (the skin of the nasal bridge and the NB underneath it) (Figure 1(A.1)). If the line representing the nasal bone is absent or less echogenic as the overlying skin, then the NB is noted absent or hypoplastic (Figure 1(A.2)) [49]. Seventy percent of trisomy 21 fetuses have absent nasal bone [55].

4.2. Doppler evaluation of the tricuspid valve: tricuspid regurgitation

Regurgitation of the blood flow across the tricuspid valve is a common marker for chromosomal defects, present in about 74% DS fetuses but also in 7% of chromosomally normal fetuses [56]. The standard evaluation is the heart apical incidence of the four-chamber view. The Doppler gate is 2–3 mm and must be placed over the tricuspid valve with a minimum angle of insonation, acceptable up to 30° (Figure 1(B.1)). Tricuspid regurgitation is diagnosed if reversed flow is noted more than 50% of ventricular systole and higher than 60 cm/s (Figure 1(B.2)) [49].

4.3. Doppler evaluation of the ductus venosus (DV)

An abnormal flow in the ductus venosus was defined as the complete cessation or a reversal forward flow of the a-wave (Figure 1(C.2)) but also an increased pulsatility index (PI) of the flow [57]. An accurate assessment of the ductal flow requires skilled operators since there is the possibility of interference from adjacent vessels: hepatic and umbilical veins [49]. Seventy-four percent of DS fetuses and 5% of chromosomally normal fetuses present abnormal DV flow [58].
4.4. Fronto-maxillary facial (FMF) angle

This angle is measured between the upper surface of the palate and the frontal bone (Figure 1(A.1)). FMF angle is significantly larger in DS fetuses (mean 88.78, range 75.4–1048) versus chromosomally normal fetuses (mean 78.18, range 66.6–89.5, P < 0.001) (Figure 1(A.2)) [49].

4.5. Fetal heart rate

Fetal heart rate should be measured routinely as part of DS screening. The studies have shown an increase of the fetal heart rate by 15% [59].

4.6. Fetal malformations

Another target of the first-trimester scan is to detect fetal severe malformations, which are either lethal or associated with severe handicap or aneuploidies [60, 61]. The abnormal fetuses detected early in pregnancy should be tested to exclude aneuploidy. Many major abnormalities can be diagnosed as early as the first-trimester scan [57, 62–66]. Other conditions vary in onset during gestation and do not have a consistent ultrasound appearance in the first trimester for a definitive and reliable diagnosis.

4.7. Screening in twin pregnancies

In cases of multiple gestations, the first-trimester scan should correctly diagnose the chorionicity of the pregnancy. In a monochorionic twin pregnancy, the false-positive rate of NT screening is higher than in dichorionic twins, because increased NT in at least one of the fetuses can be an early manifestation of twin-to-twin-transfusion syndrome, as well as a marker of chromosomal abnormalities [67]. It is recommended that, for the calculation of risk of trisomy 21, the NT of both twins should be measured and the average of the two should be considered [68].

An important advantage of screening by fetal NT is that when there is discordance for a chromosomal abnormality, the presence of a sonographically detectable marker helps to ensure the correct identification of the abnormal twin during selective termination.

5. Genetic ultrasound screening assessment in the second trimester

In the second trimester, the genetic ultrasound screening assessment can be used either alone or as an adjunct to maternal serum testing. The purpose of the scan is to identify fetal anomalies or chromosomal markers [69] which require invasive testing. The sonographic findings that are not generally abnormalities, but can be an indicative of fetal aneuploidy are called soft ultrasound markers. Many of them are transient. It is important to pay attention to the thickness of the nuchal fold, nasal bone appearance, or prenasal edema, but also a series of soft markers have been described: intracardiac echogenic focus, hydronephrosis, and hyperechogenic bowel were found with a higher incidence in DS fetuses than in chromosomally normal fetuses (9.6% vs. 1.5%, 17.1% vs. 5.3%, and 11.4% vs. 2.4%, respectively). The prevalence of choroid plexus cysts was not significantly different between the trisomy 21 and normal fetuses (7.5% vs. 5.0%) [70].
Nuchal fold (NF) thickness (Figure 3(A)) is often considered the most sensitive and most specific second-trimester marker for Down syndrome with false-positive rates as low as 1% [71]. It is measured on an axial section through the head at the level of the thalami, cavum septi pellucidi, and cerebellar hemispheres (i.e., in the same plane that is used to assess the posterior fossa structures). A NF > 5 mm has a sensitivity of 15% and a specificity of 97% in trisomy 21 detection, while a NF > 6 mm has a sensitivity of 12% and a specificity of 99% in trisomy 21 detection [71]. It is recommended that the nuchal thickness should not be measured after 20 gestational weeks.

Fetal ventriculomegaly (Figure 3(D)) is considered a soft marker for chromosomal abnormalities and defined as more than 10 mm across the atria of the posterior or anterior horn of lateral ventricles or alternatively, a separation of more than 3 mm of the choroid plexus from the medial wall of the lateral ventricle [72].

The nasal bone is evaluated in the standard view of fetal face profile. To define nasal bone hypoplasia (Figure 3(E)), many studies proposed various measurement criteria, and most cutoffs are more than 0.25 cm [73]. A hypoplasic nasal bone is seen in approximately 0.5–1.2% of normal fetuses [74].

The vast majority of cases with choroid plexus cysts (Figure 3(C)) have no associated abnormality, but still there is a soft association with aneuploidy, especially trisomy 18 and also trisomy 21. Their size and number of cysts are thought to affect the risk of aneuploidy [75]. Amniocentesis is not recommended when isolated, due to weak associations with genetic abnormalities. When the choroid plexus cysts are large (>1 cm), bilateral, multiple, or the maternal serum screening results are abnormal, and invasive testing is considered [76].

The echogenic intracardiac focus (EIF) represents the mineralization within the papillary muscles, usually seen at the second trimester, located in the left ventricle (Figure 3(G)). The association with trisomy 21 was demonstrated in up to 12% of fetuses, but biventricular EIFs are considered to be a higher risk for aneuploidy [77].

Figure 3. Second-trimester genetic markers: (A) increased thickness of the nuchal fold (NF), (B) prenasal edema, (C) bilateral choroid plexus cysts, (D) bilateral ventriculomegaly, (E) nasal bone hypoplasia, (F) gap sandals toes, (G) echogenic intracardiac focus, (H) bilateral pyelectasis/hydronephrosis, (I) measurement of femur length to detect shortening of the long bones, (J) non-visualization of the middle phalanx of the fifth digit, (K) echogenic bowel, (L) single umbilical artery, and (M) aberrant right subclavian artery.
Echogenic bowel (Figure 3(K)) is defined if a bowel area is brighter than the bone on an image with appropriate gain settings. Trisomy 21 was diagnosed in 15% of cases, but other several associations have been reported, such as cytomegalovirus infection, cystic fibrosis, intraamniotic hemorrhage, and intrauterine growth restriction [78].

Other second-trimester soft markers for trisomy 21 include fetal renal pyelectasia (Figure 3(H)), shortened long bones (less than third centile for gestational age) with a shortened femur or/and a shortened humerus (Figure 3(I)), single umbilical artery (Figure 3(L)), aberrant right subclavian artery (Figure 3(M)), and gap sandals toes (Figure 3(F)). When found alone, these soft markers have a weak association with DS.

As presented before, genetic sonography was used as primary screening, or as an arbitrator, to refine the initial screening result, for reassuring or when couples with positive tests did not opt for invasive testing [34, 79].

6. Cardiac anomalies (congenital heart defects, CHD)

CHD are present in the majority of the fetuses with DS [80] and represent one of the most common and lethal abnormalities present postnatally. Various heart conditions were reported
with significant incidence \[81\]: ventricular, atrial, and atrioventricular septal defects (Figure 4(A.1, A.2)); tricuspid stenosis; outflow tract abnormalities, as Aortic coarctation (Figure 4(B.1, B.2)), pulmonary valve stenosis, and atresia; transposition of great vessels; common truncus; and atrial stenosis. Functional conditions, as pericardial effusion and atrioventricular regurgitation, were also noted [79].

An accurate cardiac assessment as an adjunct in the first and second trimester increases the screening power to as high as 99% [19, 34] and is the only strategy to increase the mid-trimester genetic ultrasonography detection rates over 90% [36, 79]. This may be advantageous for patients who desire the highest sensitivity for DS detection (Figure 4).

7. Invasive diagnostic testing

In first-trimester screening is positive for DS, chorionic villus sampling (CVS) is proposed for a definitive genetic diagnosis, by obtaining a placental tissue sample, usually transabdominally or transcervically, if the trophoblast is situated posterior. The main advantage is represented by the early diagnosis, easing the decision-making process for couples [82]. The main disadvantage is represented by the risk of spontaneous abortion that can vary from 0.6 to 4.6% [45]. Other disadvantages include the fact that is an operator-dependent procedure and that is not available in every community [83]. There is an increased risk of limb reduction defects, if the procedure is performed before 10 weeks' gestation [83].

Amniocentesis is the most common procedure for detecting genetic abnormalities before birth. A sample of the amniotic fluid is extracted usually after 15 weeks' gestation [84], because of increased abortion risk before this gestational age. The accuracy of this invasive testing is reported to be over 99.4% [85], similar to CVS. Complications are uncommon but may include vaginal spotting, amniotic fluid leakage, chorioamnionitis, failure of fetal cells to grow in culture, fetal needle injury, and fetal loss [82], in less than 1% of cases [86].

A less frequent invasive test is percutaneous umbilical blood sampling, used in the case of severe oligoamnios or for a rapid chromosome analysis (1–3 days from fetal blood vs. 10–14 days from amniocytes). The risk of miscarriage is higher than the other two procedures [82, 83].

8. Noninvasive prenatal testing (NIPT)

In the mid-1950s, the presence of fetal cells was demonstrated in the maternal circulation [87] and in 1997 also the existence of cell-free fetal DNA, which became a feasible target for a noninvasive prenatal testing [88, 89]. Fetal DNA from maternal plasma is the result of fragmented syncytiotrophoblast cells undergoing apoptosis. NIPT allows for an earlier aneuploidy detection from as early as 4 weeks' gestation [90] but is usually recommended after nine gestational weeks, in order to obtain a sufficient fetal fraction of cell-free DNA.

This Revolutionary method, with a first clinical application in determining fetal sexing, significantly reduced the gap between the performance of conventional screening and
diagnostic testing [88, 91], because of the high sensitivity and specificity, especially for DS. Recently, a meta-analysis of 1963 cases of trisomy 21 and 223,932 non-trisomy 21 singleton pregnancies showed a weighted pooled detection rate of 99.7% for a false-positive rate of 0.04% [92].

NIPT is nowadays offered in conjunction with another method of screening for fetal aneuploidy rather than as a replacement. Some are concerned about losing the clinical value of the first-trimester screening, as during the last decades, this evaluation became an important pregnancy evaluation, aimed to detect the high-risk pregnancies not only for genetic abnormalities but also for structural malformations and other pregnancy severe complications. The main advantages of NIPT include the safety of the procedure, with no risk of miscarriage, the early timing, and the ease of testing, which is not "surgical," "stressful," or "painful," as invasive procedures may be. Among disadvantages, we should keep in in the costs and potential ethical issues, as the NIPT use for gender determination or the diagnosis of some conditions with variable prognosis [93, 94]. It is important to understand that NIPT is not a diagnostic test, and therefore, a positive NIPT result requires an invasive test to confirm the findings, as recommended by professional societies. Many chromosomally mosaic placentas are not detected by NIPT, and abnormal chromosome complements in maternal-derived cfDNA may be detected from apoptosis of maternal tumor cells [95].

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