

Prenatal Screening for Down Syndrome

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A British physician, John Langdon Down, was the first to describe Down syndrome in 1866.¹ Dr Lionel Penrose was the first to recognize this disorder in the 1930s when he observed that there was a significant association between increasing maternal age and birth of a Down syndrome child.² Down syndrome (also known as Trisomy 21), which causes significant physical and mental health problems, is the most common incurable genetic disorder. Having a baby with Down syndrome is likely to have a significant impact on family life. With the advent of cytogenetic analysis on cultured amniocytes in the 1970s, all women aged more than 35 years were offered amniocentesis to diagnose potential fetal aneuploidy. However, this diagnostic test carries a risk from the invasive procedure such as miscarriage, infection etc. In addition, maternal age alone was a poor criteria for the screening test because it only identified 25-30% of fetal aneuploidy cases. With the advent of maternal serum biochemical analysis and ultrasound, the field of prenatal screening developed significantly. In the last decade, the introduction of non-invasive prenatal testing/screening (NIPT/S) has had a

great impact on the expansion and evolving practice of prenatal screening.

Concepts used in prenatal screening

Screening tests are designed to separate high risk from low risk patients. As with any screening test, the woman should be made aware that a “negative” test or “normal” ultrasound does not guarantee a healthy baby and a “positive” test does not mean the fetus has an abnormal condition. The woman should have both pre- and post-test counseling to discuss the meaning of her test result, and the benefits, limitations, and options for additional testing. Prenatal screening for Down syndrome consists of risk calculation based on biochemical and biometric parameters by ultrasonography, as well as maternal age, and then women with a high predicted risk can be advised of the estimated risk of a pregnancy being affected and provided with information to guide their decision about further invasive testing for diagnosis. The concepts used in prenatal screening are summarized in Table 1.³

Table 1 Concept and meaning used in prenatal screening³

Concept	Meaning
Screening test	One or more marker to select women who are screen positive for further tests or prevention.
Marker	Biophysical or biochemical measure, continuous or dichotomous, but differs between affected and unaffected pregnancies.
Screen – positive	Screening test result beyond a fixed cut off value; otherwise screen – negative
Affected	Having a specific fetal disorder or maternal condition.
Test performance	For a given cut off, the detection rate (DR) and false–positive rate (FPR). Positive predictive value (PPV) and negative predictive value (NPV) are dependent on DR, FPR, and prevalence.
DR	Proportion of affected pregnancies with positive screening.
FPR	Proportion of unaffected pregnancies with positive screening.
PPV	Proportion of screen – positives which are affected.
NPV	Proportion of screen – negatives which are affected.
Risk screening	Calculating an individual’s chance of an affected pregnancy given a marker profile and pre–test factors; derived from a likelihood ratio (LR).
LR	Proportion of affected compared with unaffected pregnancies for a given profile.
MoM	Multiple of the expected gestation–specific median, usually based on regression; allows for changes in marker levels with increasing gestation; can also be adjusted for maternal weight and other co–factors.

Serum biomarker screening

The first prenatal screening test was based on a single maternal serum marker from the second–trimester maternal serum, the α –fetoprotein (MSAFP) test for open neural tube defects (NTDs) in the mid–1970s.⁴ Simultaneously, the MSAFP was suggested by Cuckle⁵ 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. The performances which use in screening for Down’s syndrome are during the first–trimester or second–trimester or both period. First trimester combined screening includes the concentrations of

pregnancy–associated plasma protein A (PAPP–A) and free beta subunit of human chorionic gonadotropin (β –hCG) in the maternal serum, the ultrasonography nuchal translucency (NT) measurement and gestational age at 11 weeks to 13 weeks 6 days. Second–trimester screening tests are carried out using multiple markers: alpha–feto–protein, total human chorionic gonadotropin, unconjugated estriol, and inhibin A at 15 weeks to 18 weeks of gestation. Currently, the most popular algorithm used is the first–trimester combined screening test due to the cost effectiveness.⁶ The test has a detection rate of 85% with 5% FPR and PPV 1 in 46.³

Ultrasonography screening

Approximately one–third of fetuses with Down syndrome have an identifiable sonographic finding of

either a major or minor structural variation. The nuchal space is a normal and identifiable fluid-filled space behind the fetal neck that is present in all fetuses between 11 and 14 weeks of gestation. There is an association between an increased measurement of the NT and trisomy 21 which was first reported by Nicolaides et al., in 1992.⁷ Now NT measurement is routinely used in the combined screening test. The screening protocols can be improved by the use of additional ultrasound markers. The most well developed are four first trimester ultrasound markers: absence of fetal nasal bone (NB), increase of fronto-maxillary (FMF) angle, Doppler blood flow of the tricuspid valves showing regurgitation (TR), and absence or reverse flow of ductus venosus. The most useful is the fetal nasal bone absence,⁸ which demonstrates delayed ossification in fetuses with Down syndrome.

In the second trimester tests, the genetic sonogram markers include congenital heart defects (most commonly ventricular septal defects or endo-cardial cushion defects), ventriculomegaly, duodenal atresia, or a variety of “soft markers”, thickened nuchal skin fold, echogenic bowel, renal pyelectasis, shortened femur and humerus, and hypoplastic or absent nasal bone. A meta-analysis pooling data from 48 studies of low and high-risk women found that hypoplastic or absent nasal bone is associated with the greatest risk for Down syndrome.⁸

The second-trimester genetic sonogram for Down syndrome screening still plays a role, particularly in the following circumstances:⁹

- In countries with limited access to genetic screening, a genetic sonogram is often incorporated into the second-trimester ultrasound evaluation of fetal anatomy as a means of adjusting the risk for Down syndrome.

- The genetic sonogram may assist in the decision-making, particularly in women with risk results close to the cutoff.

- The genetic sonogram will continue to have a place in the era of cell-free DNA testing, particularly in twin and higher-order multiples.

- In cases with borderline or no results at a non-invasive prenatal test, a genetic sonogram has the potential to provide valuable information.

Non-invasive prenatal test (NIPT); cell free DNA (cfDNA) screening

Lo et al., in 1997¹⁰ discovered that fetal DNA is present in the maternal plasma and serum. Dhallan and colleagues¹¹ reported a new concept for NIPT of aneuploidies (eg, trisomy 21) by analysis of cfDNA circulating in the maternal plasma. Circulating cfDNA of fetal origin comprises approximately 3–13% of the total cell-free maternal DNA after 10 weeks of gestation and is thought to be derived primarily from the placenta. In 2011, cfDNA analysis became clinically available and the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine recommended it as a screening option for women at increased risk of fetal aneuploidy.¹² This population was defined as women 35 years old or older, fetuses with any ultrasonographic findings indicating an increased risk of aneuploidy, women with a history of trisomy-affected offspring, parents carrying a balanced Robertsonian translocation with an increased risk of trisomy 13 or trisomy 21, and women with positive first-trimester or second-trimester screening test results. Before offering cfDNA screening, counseling is recommended. This tests have high sensitivity and specificity for trisomy 18 and trisomy 21, regardless of which molecular technique is used (Table 2).¹²

One study conducted in a general obstetrical population found that prenatal testing with the use of cfDNA had significantly lower false positive rates and higher positive predictive values for detection of trisomy 21 and

Table 2 Cell-free DNA tests performance characteristics in patients who receive an interpretable result¹²

	Sensitivity (%)	Specificity (%)	Age 25 years	Age 40 years
			PPV (%)	PPV (%)
Trisomy 21	99.3	99.8	33.0	87.0
Trisomy 18	97.4	99.8	13.0	68.0
Trisomy 13	91.6	99.9	9.0	57.0
Sex chromosome aneuploidy	91.0	99.6	–	–

trisomy 18 than standard screening.¹³ The cfDNA test will screen for only the common trisomy syndromes and, if requested, sex chromosome composition. Patients should be counseled that a negative cfDNA test result does not ensure an unaffected pregnancy. Given the performance of conventional screening methods, the limitations of cfDNA screening performance, and the limited data on cost-effectiveness in the low-risk obstetric population, conventional screening methods remain the most appropriate choice for first-line screening for most women in the general obstetric population. Cuckle et al.¹⁴ concluded that universal prenatal testing using cfDNA does not provide a cost-effective replacement when compared to the standard screening methods.

Conclusion

Prenatal screening aims to identify high risk pregnant women. Effective screening methods can reduce unnecessary invasive diagnostic procedures. Prenatal screening should be offered to all women regardless of age or a-priori risk status, and the women should have both pre-and post-test counseling to discuss the benefits, limitations, and options for testing. The patients may decline all screening or diagnostic testing for aneuploidy after received the information. Standard first and second trimester

screening methods are the most cost effective and beneficial.

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