

PRENATAL SCREENING FOR FETAL ANEUPLOIDY, DOWN'S SYNDROME, WHO, WHOM, WHY & HOW?????

*Dr. Vinita Singh

*Corresponding author:

Dr. Vinita Singh, C/3103 Shanti Residency, Amrapali Society, Lalpur, Raipur, C.G. 492001
E-mail: ddvinitasingh@gmail.com



Abstract: Chromosomal abnormalities occur in 0.1% to 0.2% of live births; Trisomy 21 (Down syndrome) is the most common karyotype abnormality in live-born infants (1 per 800 live births). Trisomy 21 is the most common genetic cause of mental retardation and one of the few aneuploidies compatible with post-natal survival. The vast majority of meiotic errors leading to the trisomic condition occur in the egg, as nearly 90% of cases involve an additional maternal chromosome. The severity of each of the phenotypic features is highly variable among the patients. Besides mental retardation, present in every individual with Down syndrome (DS), Trisomy 21 is associated with more than 80 clinical traits including congenital heart disease, duodenal stenosis or atresia, imperforate anus, Hirschprung disease, muscle hypotonia, immune system deficiencies, increased risk of childhood leukemia and early onset Alzheimer's disease. The rapid changes in prenatal screening and diagnostic techniques bring new challenges. Developments in Trisomy 21 (Down syndrome) screening have sought to increase sensitivity and specificity of screening tests. Various methods have been used to identify women at risk of carrying a fetus with Trisomy 21, including consideration of maternal age, biochemical markers, amniocentesis and prenatal ultrasound. This article reviews the literature on prenatal screening for Down's syndrome which is evidence based and this extensive literature examines how appropriate widely-held understandings of Down's syndrome are, and asks whether or not practitioners and prospective parents have access to the full range screening and diagnostic test and keeping in account moral, ethical, social & financial milieu of the region and from the point of view of a regional foetal medicine unit. From the point of view of the individual woman, this means that if she chooses to participate in screening, she will have a high chance of detection of Down syndrome, and a low chance that a subsequent invasive diagnostic test will be recommended when her baby is unaffected, since invasive testing carries a low but measurable risk of foetal death.

Keywords: Down's syndrome, Non- invasive prenatal screening, screening ultrasound.

Definition

As defined by Down syndrome federation of India (DSI), Down syndrome is a naturally occurring chromosomal arrangement that has always been a part of the human condition, being universally present across racial, gender or socio-economic lines, and affects approximately one in 800 births worldwide, causing intellectual and physical disability and associated medical issues.

Down's syndrome is the most frequent live born aneuploidy affecting 4% of the clinically recognized pregnancies.¹ **The most common trisomy is Down syndrome (also called Trisomy 21) with a prevalence of 14.2 per 10,000 live births from 2006-2010.**² Down syndrome occurs in about 1 out of every 700 babies.³ The prenatal prevalence of Down syndrome is much

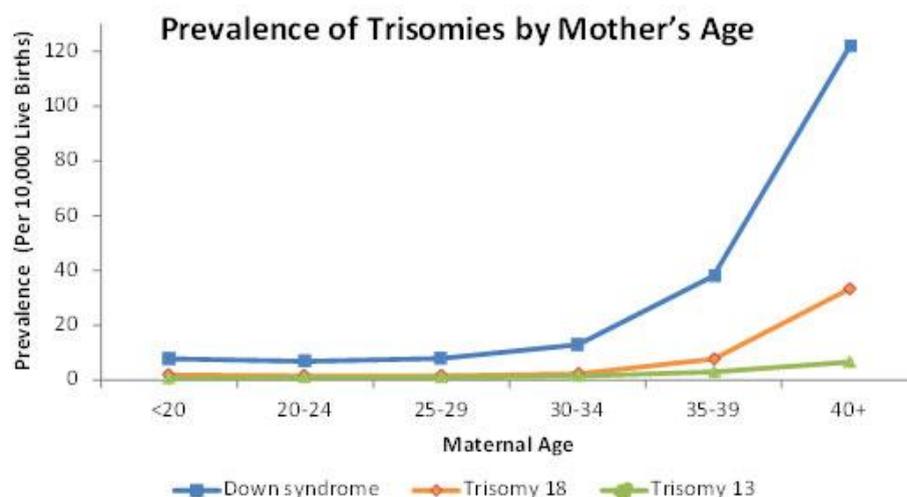
higher than among live births, with only approximately 70 percent of fetuses with Down syndrome identified in mid-second trimester surviving to term (Hook 1983)

DOWNS SYNDROME Down syndrome is usually caused by an error in cell division called meiotic nondisjunction, However, two other types of chromosomal abnormalities, mosaicism and translocation, are also implicated in Down syndrome, This additional genetic material alters the course of development and causes the characteristics associated with the syndrome.⁴⁻⁵ The karyotype shows **Trisomy 21**(About 95%) or **Translocation Down syndrome**(about 3%) or **Mosaic Down syndrome**: The latter type affects about 2% of the people with Down syndrome.

Aetiology & Risk Factor

One factor that increases the risk for having a baby with Down syndrome is the mother's age. Women who are 35 years or older when they become pregnant are more likely to have a pregnancy affected by Down syndrome than women who become pregnant at a younger age.⁶⁻⁸

However, the majority of babies with Down syndrome are born to mothers less than 35 years old, because there are many more births among younger women.⁹⁻¹⁰



Source: Frequency of Trisomy Conditions using Birth Defects Tracking Programs in the United States, 2006-2010, CDC, 2011

Other factors involved is previous child with Down' Syndrome or any other chromosomal abnormality, parental balanced translocation and parents with chromosomal disorders.

Discussion

In screening programme terms, the relevant parameters for programme participants are the Down syndrome detection rate and the invasive test rate, and national guidance determines the 'optimal' balance between these two, which changes as the sensitivity and specificity of the tests are improved

Can it be diagnosed antenatally? "Prenatal screening and diagnosis"

Doctors can diagnose Down syndrome during pregnancy or after the baby is born. Some families want to know during pregnancy whether their baby has Down syndrome. Diagnosis of Down syndrome during pregnancy can allow parents and families to prepare for their baby's special needs. There are different types of prenatal testing that can be done to evaluate the

chance of a fetus having Down syndrome or determine the diagnosis of Down syndrome. A screening test establishes the chance of a fetus having Down syndrome. It does not provide a definite diagnosis. A diagnostic test studies the chromosomes from the fetus. The American College of Obstetricians & Gynecologists (ACOG) currently recommends screening all pregnancies for fetal chromosomal anomalies, including Down syndrome (Trisomy 21).

During pregnancy

There are two basic types of tests available to detect Down syndrome during pregnancy. Screening tests are one type and diagnostic tests are another type. A screening test can tell a woman and her healthcare provider whether her pregnancy has a lower or higher chance of having Down syndrome. So screening tests help decide whether a diagnostic test might be needed. Screening tests do not provide an absolute diagnosis, but they are safer for the mother and the baby. Diagnostic tests can typically detect whether or not a baby will have Down syndrome, but they can be more risky for the mother and baby. Neither screening nor diagnostic tests can predict the full impact of Down syndrome on a baby; no one can predict this.

Screening Tests

Screening tests often include a combination of a blood test, which measures the amount of various substances i.e. hormones or proteins in the mother's blood (e.g., MS-AFP, Triple Screen, Quad-screen), and an ultrasound, which creates a picture of the baby. During an ultrasound, one of the things the technician looks at is the fluid behind the baby's neck. Extra fluid in this region could indicate a genetic problem or look for specific physical characteristics on fetal ultrasound. Screening is usually done in the first or second trimester of pregnancy. Abnormal levels can mean a statistically increased risk of having a baby with Down syndrome. These screening tests can help determine the baby's risk of Down syndrome. Rarely, screening tests can give an abnormal result even when there is nothing wrong with the baby. Sometimes, the test results are normal and yet they miss a problem that does exist. A new test available since 2010 for certain chromosome problems, including Down syndrome, screens the mother's blood to detect small pieces of the developing baby's DNA that are circulating in the mother's blood. This test is recommended for women who are more likely to have a pregnancy affected by Down syndrome. The test is typically completed during the first trimester (first 3 months of pregnancy) and it is becoming more widely available. As with all prenatal screening test, there will be "false positive" results meaning that although the screening result is abnormal, the fetus does not have Down syndrome.

Diagnostic Tests

Diagnostic tests are usually performed after a positive screening test in order to confirm a Down syndrome diagnosis. Types of diagnostic tests include:

- Chorionic villus sampling (CVS)—examines material from the placenta
- Amniocentesis—examines the amniotic fluid (the fluid from the sac surrounding the baby)
- Percutaneous umbilical blood sampling (PUBS)—examines blood from the umbilical cord

These tests look for changes in the chromosomes that would indicate a Down syndrome diagnosis.

Techniques available for prenatal diagnosis of Down syndrome include amniocentesis, chorionic villus sampling, chromosome analysis and fluorescent in situ hybridization Table 2. Amniocentesis looks at the baby's chromosomes from a small amount of amniotic fluid. Amniocentesis poses inherent risks such as miscarriage (.05%), injury to the foetus, and maternal infection. In general, however, the procedure is relatively safe. A complete chromosome analysis (karyotype) takes several weeks to perform.

Chorionic villus sampling (CVS) became available in the early and mid-1980s. During CVS, a piece of placental tissue is obtained either vaginally or through the abdominal wall,

usually during the eighth to twelfth week of pregnancy. The cells from the placental tissue are then used for chromosome analysis. It can be performed much earlier in pregnancy, and chromosome studies can be performed immediately, yielding much quicker test results. Studies so far have shown that the miscarriage risk (1%), associated with this procedure is slightly greater than that of amniocentesis. A technique called fluorescent in situ hybridization (FISH) allows rapid identification (48-72 hrs) of some genetic and chromosome conditions. This can be done on samples obtained by CVS, amniocentesis, or on a blood sample. Using the FISH procedure, DNA is labeled with fluorescent molecules that bind to a specific region on the target chromosome and after staining can be viewed under a fluorescence microscope. With chromosome-specific probes, a specialist quickly can determine the presence of an extra chromosome 21; instead of detecting the typical two signals (one for each chromosome 21), three signals will be observed, indicating that the fetus has Down syndrome.

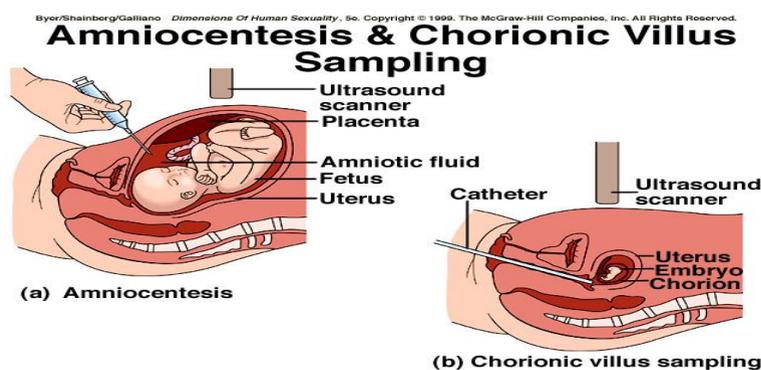


Table 1:

Summary of Prenatal Screening Methods

SCREENING TEST	TRIMESTER	BIOMARKERS	DETECTION RATE	FALSE POSITIVE RATES**
FETAL SONOGRAM	1 ST	NT	65-70%	20%
COMBINED SCREEN (11-14 wks)	1 st	NT & PAPP-A / β HCG	82-87%	5%
TRIPLE TEST (14-22 wks)	2 nd	AFP, β hcg, UE3	69%	4-8%
QUADRUPLE TEST (14-22 wks)	2 nd	AFP, β hcg, UE3 & INHIBIN-A	81%	5%
INTEGRATED (11-14 WKS & 14-22 WKS)	1 st & 2 nd	NT, PAPP-A & Quadruple	94-96%	1.3%
SERUM INTEGRATED (11-14 WKS & 14-22 WKS)	1 st & 2 nd	PAPP-A & Quadruple	85-88%	2.7%
STEP WISE SEQUENTIAL	1 st & 2 nd	1 st Combined screen & diagnostic test (amniocentesis or CVS) OR 1 st Combined screen & 2 nd triple or quadruple screen	95%	

From: FASTER Research Consortium, *New England Journal of Medicine* 353(19):2001-2011 (2005) and ACOG Practice Bulletin Number 77 *Obstetrics & Gynecology* 109(1):217-227 (2007)

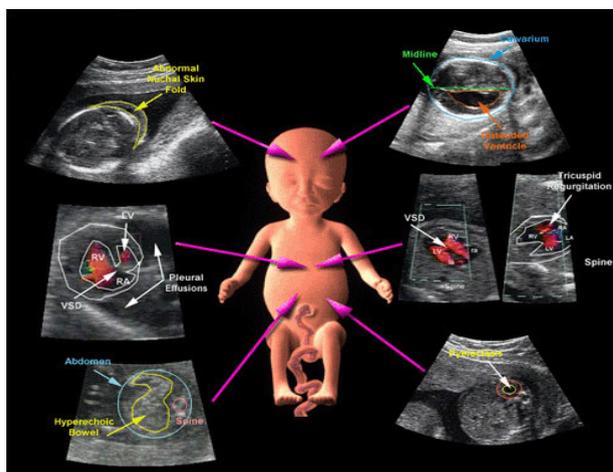
** Antenatal care: routine care for the healthy pregnant woman National Collaborating Centre for Women's and Children's Health Commissioned by the National Institute for Clinical Excellence October 2003 (RCOG Press).

Table 2:
Summary of Prenatal Diagnostic Methods

DIAGNOSTIC TEST	TRIMESTER	BIOMARKERS	DETECTION RATE	MISCARRIAGE RATE
Chorionic Villus Sampling	1 st (8-12 wks)	Chromosome Analysis(Karyotype) or FISH	>99%	1%
Amniocentesis	2 nd (14-18 wks)	Chromosome Analysis(Karyotype) or FISH	>99%	.05%

Sonographic Markers in Down's syndrome

It has been proved that combination of multiple sonographic markers has a better detection rate in terms of risk of aneuploidy than any single marker and that this is the most sensitive method for screening low risk populations. Several authors have presented different sonographic scores in order to achieve high detection rate in combination with an acceptable false-positive rate.



NUCHAL TRANSLUCENCY (9-13 WKS): >6MM

NASAL BONES: (11-13 wks): Failure to visualize nasal bones

ULTRASOUND exam in the second trimester 14-20 wks. There are specific characteristics identified during an ultrasound of a woman's pregnancy that are possible indicators for Down's syndrome.

The potential markers include:

- dilated brain ventricles
- mild kidney swelling
- bright spots in the heart
- 'bright' bowels
- shortening of an arm bone or thigh bone
- an abnormal artery to the upper extremities

Kypros Nicolaides, MD, of the Harris Birthright Research Centre for Fetal Medicine at King's College London in England, and team set out to examine how these markers influence risk. They looked at all research published between 1995 and 2012 that demonstrated results

on markers for Down's syndrome detected during the second trimester of pregnancies. After finding 48 reports, they determined that the most single markers have only a little impact on altering the likelihood for Down's syndrome.

The authors explained:

"This finding could have important clinical implications because currently in the United States, when a marker such as a short arm or thigh bone is detected, women are told that they are at high risk of having a child with Down's syndrome. "The researchers, however, did find some markers that indicate increased risks. **The risk increases three to four times when the following are detected:**

Increased thickness of the back of the neck, dilated brain ventricles, an abnormal artery to the upper extremities.

The risk increases six or seven times when there is an absent or small nose bone identified. "The detection of any one of the findings during the scan should prompt the sonographer to look for all other markers or abnormalities," said Prof. Nicolaides. The research also demonstrated that **the risk of having a child with Down's syndrome is reduced seven times if a comprehensive ultrasound exam during the second trimester shows that all major markers are nonexistent.** The results demonstrate that the relative significance of ultrasound markers is very different to what scientists have believed in the past. The findings from this report will be included in obstetric ultrasound scan software that alters women's risks for giving birth to a baby affected by Down's syndrome, Professor Nicolaides concluded.

**SOGC (SOCIETY OF OBS & GYN CANADA) Clinical Practice Guidelines for Risk Assessment for Aneuploidy with Fetal soft Tissue Markers Useful for screening ultrasound:
SOGC Clinical Practice Guidelines**

Table 3:

Criteria for quality of evidence assessment and classification of recommendations

Level of evidence*	Classification of recommendations#
I. Evidence obtained from at least one property designed randomized	A. There is good evidence to support the recommendations for use of a diagnostic test, treatment or intervention
II-1 Evidence from well-designed controlled trials without randomization	B. There is fair evidence to support the recommendation for use of a diagnostic test, treatment or intervention
II-2 Evidence from well-designed cohort (prospective or retrospective) or case control studies, preferably from more than one centre or research group.	C. There is insufficient evidence to support the recommendation for use of a diagnostic test, treatment or intervention
II-3 Evidence from comparisons between times or places with or without the intervention. Dramatic result from uncontrolled experiments. (Such as the result of treatment with penicillin in the 1940s) could also be included in this category.	D. There is fair evidence not to support the recommendation for use of a diagnostic test, treatment or intervention
III. Opinions of respected authorities, based on clinical experience, destructive studies, or report of expert Committee.	E. There is good evidence not to support the recommendation for use of a diagnostic test, treatment or intervention

* The quality of evidence reported in these guidelines has been adapted from the evaluation of evidence criteria described in the Canadian task force on the periodic health exam. #Recommendations included in these guidelines has been adapted from the classification of recommendations criteria in the Canadian task force on the periodic health exam.

Table 4:

Ultrasound “soft makers” performance summary in the detection of aneuploidy (trisomy 21, 18) and other genetic/congenital anomalies

Ultrasound “soft makers” Evidence and classification ¹	Aneuploidy (LR) ²		congenital anomaly Associations
	T21	T18	
Screening scan (16-20 weeks)			
Nuchal fold (III,A)	17	-	Congenital heart Disease
Echogenic bowel (II-2, A)	6	-	CF2%,infection 3%,GI 6%
Ventriculomegaly (II-2,a)	9	-	AC, CNS, infection, obstruction
Echogenic cardiac focus (III,A)	2	-	-
Choroid plexus cyst (II-2,A)		7	-
Single umbilical artery(III,A)	-	-	Renal cardiac
Enlarged cisterna Magna (III,A)	-	-	OFD,MG, DiG
B. Comprehensive scan (Calculation; detail)			
Clinodactyly (II-2,A)	5.6		-
Human (short) (II-2,A)	7.5		Skeletal dysplasia; IUGR
Femur (short) (II-2,A)	2.7		Skeletal dysplasia; IUGR
Nasal bone absent/hypo (II-2,A)	5.1		-
C. Research/Not useful			
Brachycephaly (III,B)	-	-	
Iliac angle (III,B)	TBD	-	-
Ear length (III,B)	3-5	-	-
Sandal toe (III,B)	-	-	-

¹ Canadian task force on periodic health examination, health Canada; quality of evidence; classification of recommendation (Ann intern med 1993; 118:731-7)

² LR: likelihood ratio; TBO to be determined

³ CF: Cystic fibrosis; CNS: central nervous system; GI: gastrointestinal; OFD: Oro-facial-digital syndrome; MG: Meckel Gruber syndrome; DiG: Di George syndrome; IUGR: intrauterine growth restriction; AC: agenesis corpus callosum

Non-invasive Prenatal Testing for Fetal Aneuploidy¹²

Non-invasive prenatal testing that uses cell free fetal DNA from the plasma of pregnant women offers tremendous potential as a screening tool for fetal aneuploidy. A negative cell free fetal DNA test result does not ensure an unaffected pregnancy. A patient with a positive test result should be referred for genetic counselling and should be offered invasive prenatal diagnosis for confirmation of test results. Circulating cell free foetal DNA, which comprises approximately 3–13% of the total cell free maternal DNA, is thought to be derived primarily from the placenta, and is cleared from the maternal blood within hours after childbirth¹³. Recently, cell free foetal DNA analysis has become clinically available for women at increased risk of foetal aneuploidy. Early attempts to detect trisomic fetuses using cell free foetal DNA required the use of multiple placental DNA or RNA markers, which made the screening test time consuming and expensive.¹⁴⁻¹⁶ Recently, a number of groups have validated a technology known as massively parallel genomic sequencing, which uses a highly sensitive assay to quantify millions of DNA

fragments in biological samples in a span of days and has been reported to accurately detect trisomy 13, trisomy 18, and trisomy 21¹⁷⁻¹⁹ as early as the 10th week of pregnancy with results available approximately 1 week after maternal sampling.

Indications for Considering the Use of Cell Free Foetal DNA

- Maternal age 35 years or older at delivery
- Foetal ultrasonography findings indicating an increased risk of aneuploidy
- History of a prior pregnancy with a Trisomy
- Positive test result for aneuploidy, including first trimester, sequential, or integrated screen, or a quadruple screen.
- Parental balanced robertsonian translocation with increased risk of foetal Trisomy 13 or Trisomy 21.

Discussion

In screening programme terms, the relevant parameters for programme participants are the Down syndrome detection rate and the invasive test rate, and national guidance determines the 'optimal' balance between these two, which changes as the sensitivity and specificity of the tests are improved so that a higher detection rate can be achieved with a lower invasive testing rate. There are various studies and recommendations which put forward their views regarding screening and diagnosis of Down's syndrome, some of them are highlighted below which can guide us to choose appropriate screening and diagnostic modalities.

Summary of Acog Practice Bullet

So that a higher detection rate can be achieved with a lower invasive testing rate. There are various studies and recommendations which put forward their views regarding screening and diagnosis of Down's syndrome, some of them are highlighted below which can guide us to choose appropriate screening and diagnostic modalities.

Summary of Acog Practice Bulletin #77

Recommendations & Conclusions, based on good and consistent scientific evidence (Level A)

- First trimester screening using both nuchal translucency measurement and biochemical Markers are an effective screening test for Down syndrome in the general population. At the same false positive rates, this screening strategy results in a higher Down syndrome detection rate than does the 2nd-trimester maternal serum triple screen and is comparable to the quadruple screen.
- Measurement of nuchal translucency alone is less effective for 1st-trimester screening than is the combined test (NT measurement & biochemical markers)
- Women found to have increased risk of aneuploidy with 1st-trimester screening should be offered genetic counseling and the option of CVS or 2nd-trimester amniocentesis.
- Specific training, standardization, use of appropriate ultrasound equipment, and ongoing quality assessments are important to achieve optimal nuchal translucency measurement and Down syndrome risk assessment, and this procedure should be limited to centers and individuals meeting these criteria.
- Neural tube defect screening should be offered in the 2nd-trimester to women who elect only 1st-trimester screening for aneuploidy.

Recommendations & Conclusions, based on limited or inconsistent scientific evidence (Level B)

- Screening and invasive diagnostic testing for aneuploidy should be available to all women who present for prenatal care before 20 weeks of gestation regardless of maternal age. Women should be counseled regarding the differences between screening and invasive diagnostic testing.
- Integrated 1st- and 2nd-trimester screening is more sensitive with lower false-positive rates than 1st-trimester screening alone.
- Serum integrated screening is a useful option in pregnancies where nuchal translucency measurement is not available or cannot be obtained
- An abnormal finding on 2nd-trimester ultrasound examination identifying a major congenital anomaly significantly increases the risk of aneuploidy and warrants further counselling and the offer of a diagnostic procedure
- Patients who have a foetal nuchal translucency measurement of 3.5mm or higher, in the 1st-trimester, despite a negative aneuploidy screen, or normal foetal chromosomes should be offered a targeted ultrasound examination, foetal echocardiogram, or both
- Down syndrome risk assessment in multiple gestation using 1st- or 2nd-trimester serum Analysts is less accurate than in singleton pregnancies
- First-trimester nuchal translucency screening for Down syndrome is feasible in twin or triplet gestation but has lower sensitivity than 1st-trimester screening in singleton pregnancies

THE NATIONAL DOWN SYNDROME CONGRESS RESPONDS TO THE ACOG RECOMMENDATIONS

Human Principles

- We do not agree in principle, that ACOG, is justified in formulating Clinical Management Guidelines, on behalf of all practicing Obstetricians, which so blatantly contributes to the devaluation of life in fetuses with chromosomal anomalies including Trisomy 21.
- In formulating the ACOG Guidelines, the mere existence of fetuses, potential persons and living individuals with Trisomy 21 is more likely to be considered diminished or devalued, thereby jeopardizing the protections customarily afforded to any fetus, potential person or living individual.
- Unless specifically requested by a pregnant woman or expectant parents, Obstetricians are not justified in rendering any opinion regarding the “potential value” of the life that has been created.

NDSC (NATIONAL DOWN’S SYNDROME CONGRESS) Recommendations:

- Improve the regulation of informed consent and disclosure of information regarding Prenatal screening and diagnostic testing for all women
- Enhance training about Down syndrome for Genetic counselors, Obstetricians, Pediatricians and students in training.
- Educate and support pregnant women and couples with a positive screen or diagnosis for Trisomy 21
- Monitor statistics regarding termination and non-termination rates for all fetuses with Chromosomal anomalies, including Trisomy 21.

Screening for Down’s syndrome: NHS Fetal Anomaly Screening Programme, UK NSC Policy Recommendations 2011–2014 Model of Best Practice

Screening policy for Down’s syndrome: Programme outcomes

Service providers and commissioners are expected to implement and meet the following programme requirements within their local hospital Trust. A ministerial statement referred to by the Chief Medical Officer in 2001 informed the NHS that a Down’s syndrome screening test must

be offered to all pregnant women regardless of age. This should be accomplished adhering to and using the strategies and timeframes set out below.

Overall timeline for undertaking Down's syndrome screening: timeframe from 1 April 2011

The screening (test) will be undertaken from 10 weeks + 0 days to 20 weeks + 0 days of pregnancy.

a) From 10 weeks + 0 days the combined test (maternal serum and nuchal translucency scan). The recommended strategy.

b) From 14 weeks + 2 days to 20 weeks + 0 days, the quadruple test (maternal serum) for those presenting later.

Core screening standard: Timeframe 1 April 2011

A detection rate (DR) of more than 90%, for a screen positive rate (SPR) of less than 2% (of affected pregnancies) for England for those undergoing combined screening.

A detection rate (DR) of more than 75%, for a screen positive rate (SPR) of less than 3% (of affected pregnancies) for England for those undergoing quadruple screening.

Screening threshold: Timeframe 1 October 2011

All recommended screening strategies are set at a 1 in 150 'cut-off' at term (higher risk). Confirmatory testing for higher risk results chorionic villus sampling (CVS) or amniocentesis under direct ultrasound guidance for a "higher risk" result.

Confirmatory testing for higher risk results: Confirmatory analysis

Confirmatory analysis for diagnostic purposes is by QF-PCR.¹¹ SOGC CLINICAL PRACTICE GUIDELINE, J Obstet Gynaecol Can 2007; 29(2):146-161

Recommendations

1. All pregnant women in Canada, regardless of age, should be offered, through an informed consent process, a prenatal screening test for the most common clinically significant fetal aneuploidies in addition to a second trimester ultrasound for dating, growth, and anomalies. (I-A)
2. Maternal age screening is a poor minimum standard for prenatal screening for aneuploidy and should be removed as an indication for invasive testing. Amniocentesis/chorionic villi sampling (CVS) should not be provided without multiple marker screening results except for women over the age of 40. Patients should be counselled accordingly. (I-A)
3. In 2007, as a minimum standard, any prenatal screen offered to Canadian women should have a 75% detection rate with no more than a 5% false positive rate for Down syndrome. The performance of the screen should be substantiated by annual audit. (III-B)
4. First trimester nuchal translucency should be interpreted for risk assessment only when performed by sonographers/sinologists trained and accredited to provide this service and with ongoing quality assurance. (II-2A) It should not be offered as a screen without biochemical markers except in the context of multiple gestation pregnancies. (I-A) For women who undertake first trimester screening (FTS), second trimester serum alpha fetoprotein (AFP) screening and/or ultrasound examination is recommended to screen for open neural tube defect (ONTD). (II-1A)
5. First trimester screening (FTS), the first step of integrated screening (with or without nuchal translucency), contingent, and sequential screening are performed in an early and relatively

- narrow time window. Timely referral is critical to ensure women are able to undergo the type of screening test they have chosen. (II-1A)
6. Soft markers or anomalies in the 18- to 20-week ultrasound can be used to modify the a priori risk of aneuploidy established by age or prior screening provided the scan is undertaken in an established centre performing tertiary level ultrasound. In the absence of ultrasound soft markers or anomalies, a negative likelihood ratio of 0.5 should be used. (II-2B) Evaluation of the fetal nasal bone in the first trimester remains technically difficult and should not be incorporated as a screen until locally established as an effective risk assessment tool. (III-D)
 7. Health care providers should be aware of the screening modalities available in their province or territory. (III-B)
 8. Screening programs should be implemented with resources that support audited screening and diagnostic laboratory services, ultrasound, genetic counselling services, patient and health care provider education, and high quality diagnostic testing, as well as resources for administration, annual clinical audit, and data management. In addition, there must be the flexibility and funding to adjust the program to new technology and protocols. (II-3B)
 9. Screening programs should show respect for the needs and quality of life of persons with disabilities. Counselling should be nondirective and should respect a woman's choice to accept or to refuse any or all of the testing or options offered at any point in the process. (III-I)
 10. By 2008, screening programs should aim to provide a screen that, as a minimum, offers women who present in first trimester a detection rate of 75% for Down syndrome, with no more than a 3% false positive rate. (III-B)

The Down Syndrome Consensus Group

The University of South Carolina's Genetic Counseling Program and the University's Center for Disability Resources hosted a meeting (Toward Concurrence: Understanding Prenatal Screening and Diagnosis of Down Syndrome from the Health Professional and Advocacy Community Perspectives) of representatives of the National Down Syndrome Society (NDSS), National Down Syndrome Congress (NDSC), American College of Obstetricians and Gynecologists (ACOG), American College of Medical Genetics (ACMG), and National Society of Genetic Counselors (NSGC) on November 16 and 17, 2008, in Columbia, South Carolina.

Common Ground: Recognizing Opportunity in Consensus: As misperceptions were clarified, areas of consensus among the five national organizations were identified. Themes reflecting agreement are listed in bold below:

1. Public education elucidating the lives and value of individuals with Down syndrome in today's society is necessary.
2. Health professional education about Down syndrome based on the most up-to-date information is necessary.
3. Education for expectant parents regarding prenatal genetic screening and prenatal diagnosis should be consistent.
4. Information and counseling provided to parents regarding a prenatal or postnatal genetic diagnosis should be complete, consistent, non-judgmental, and non-coercive.
5. Prenatal testing is a process that provides valuable information in and of itself.

Conclusion

That being said, there are specific physical differences, medical concerns and intellectual challenges faced by a person with Down syndrome. The good news is that medical treatments and other therapies have substantially improved in the last few decades and the majority of babies with Down syndrome grow up to be active and healthy, and have a long life expectancy. The call for evidence-based medical practice demands focus on these important aspects of prenatal screening and diagnosis. Non-invasive prenatal testing that uses cell free foetal DNA from the plasma of pregnant women offers tremendous potential as a screening tool for foetal

aneuploidy. Cell free foetal DNA testing should be an informed patient choice after pre-test counselling and should not be part of routine prenatal laboratory assessment.

References

1. Reeves RH, Baxter LL, Richtsmeier JT 2001. Too much of a good things: mechanisms of gene action in DS. *Trends Genet*, 17: 79-84.
2. Cara T. Mai^{1,*}, James E. Kucik¹, Jennifer Isenburg², Marcia L. Feldkamp³, Lisa K. Marengo⁴, Erin M. Bugenske², Phoebe G. Thorpe¹, Jodi M. Jackson¹, Adolfo Correa⁵, Russel Rickard⁶, C.J. Alverson¹, Russell S. Kirby⁷ and For the National Birth Defects Prevention Network, Birth Defects Research Part A: Clinical and Molecular Teratology
3. Parker SE, Mai CT, Canfield MA, et al. Updated national birth prevalence estimates for selected birth defects in the United States, 2004-2006. *Birth Defects Res A Clin Mol Teratol*. 2010; 88:1008-16.
4. NDDS (National Down's Syndrome Society)
5. Shin M, Siffel C, Correa A. Survival of children with mosaic Down syndrome. *Am J Med Genet A*. 2010;152A:800-1
6. Allen EG, Freeman SB, Druschel C, et al. Maternal age and risk for trisomy 21 assessed by the origin of chromosome nondisjunction: a report from the Atlanta and National Down Syndrome Projects. *Hum Genet*. 2009 Feb; 125(1):41-52.
7. Ghosh S, Feingold E, Dey SK. Etiology of Down syndrome: Evidence for consistent association among altered meiotic recombination, nondisjunction, and maternal age across populations. *Am J Med Genet A*. 2009 Jul; 149A (7):1415-20.
8. Sherman SL, Allen EG, Bean LH, Freeman SB. Epidemiology of Down syndrome. *Ment Retard Dev Disabil Res Rev*. 2007;13(3):221-7
9. Adams MM, Erickson JD, Layde PM, Oakley GP. Down's syndrome. Recent trends in the United States. *JAMA*. 1981 Aug 14; 246(7):758-60.
10. Olsen CL, Cross PK, Gensburg LJ, Hughes JP. The effects of prenatal diagnosis, population ageing, and changing fertility rates on the live birth prevalence of Down syndrome in New York State, 1983-1992. *Prenat Diagn*. 1996 Nov; 16(11):991-1002.
11. [Antenatal screening working standards for Down's syndrome screening 2007: National Down's syndrome screening programme for England. Exeter: NHS Fetal Anomaly Screening Programme; 2007.
12. The American College of Obstetricians and Gynecologists Committee on Genetics The Society for Maternal-Fetal Medicine Publications Committee, Number 545, December 2012
13. Lo YM, Corbetta N, Chamberlain PF, Rai V, Sargent IL, Redman CW, et al. Presence of fetal DNA in maternal plasma and serum. *Lancet* 1997; 350:485-7. [PubMed]
14. Lo YM, Tsui NB, Lau TK, Leung TN, Heung MM, et al. Plasma placental RNA allelic ratio permits noninvasive prenatal chromosomal aneuploidy detection. *Nat Med* 2007; 13:218-23. [PubMed]
15. Tong YK, Chiu RW, Akolekar R, Leung TY, Lau TK, Nicolaidis KH, et al. Epigenetic-genetic chromosome dosage approach for fetal trisomy 21 detection using an autosomal genetic reference marker. *PLoS One* 2010; 5:e15244. [PubMed] [Full Text] ⇐
16. Papageorgiou EA, Karagrigoriou A, Tsaliki E, Velissariou V, Carter NP, Patsalis PC. Fetal-specific DNA methylation ratio permits noninvasive prenatal diagnosis of trisomy 21. *Nat Med* 2011; 17:510-3. [PubMed]
17. Fan HC, Blumenfeld YJ, Chitkara U, Hudgins L, Quake SR. Noninvasive diagnosis of fetal aneuploidy by shotgun sequencing DNA from maternal blood. *Proc Natl Acad Sci U S A* 2008; 105:16266-71. [PubMed]
18. Chiu RW, Akolekar R, Zheng YW, Leung TY, Sun H, Chan KC, et al. Non-invasive prenatal assessment of trisomy 21 by multiplexed maternal plasma DNA sequencing: large scale validity study. *BMJ* 2011; 342:c7401. [PubMed]
19. Ehrich M, Deciu C, Zwiefelhofer T, Tynan JA, Cagasan L, Tim R, et al. Noninvasive detection of fetal trisomy 21 by sequencing of DNA in maternal blood: a study in a clinical setting. *Am J Obstet Gynecol* 2011; 204:205.e1-11. [PubMed]