Edition 2
July 2017

Healthy Babies to Healthy Mothers

ESTD 1989
ISPAT

talkBACK

Newsletter of the Indian Society for Prenatal Diagnosis and Therapy

Meet our Team

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editor's DESK

Dr. Usha Dave

Dear ISPATIAN Friends,

While writing this Editorial, I (Dr. Dave) was going through the scientific events held so far in the year 2017. The one important change struck me was the acceptance of genomic diagnosis in majority of medical disciplines by both patients & clinicians. This was feasible due to availability of genomic technology at the fingertips of the medical doctors by a number of global genetic companies venturing into Indian market.

Dr. Seema Pandey

Noninvasive Prenatal Screening (NIPS) test using cell free DNA from maternal blood for aneuploidies is one such test which has been commercially offered for just over 2 years and the clinical use by patients and clinicians has increased significantly. As the professionals working in the prenatal field, it is crucial for us to understand the risks associated with invasive testing & provide alternative noninvasive test for assessment of aneuploidy status or other chromosomal conditions in high-risk patients. The accuracy & positivity rate of NIPS Test predicted by clinical validations around the globe demonstrates improvement in the current standard of care. Lack of invasive test infrastructure & expertise in small towns in our country will possibly make noninvasive test popular with cost-effective approach.

In this issue, we have highlighted "First Trimester Chromosomal Abnormalities" for readers & also to get exposed to newer prenatal technologies in their practice. Availability of "Maternal Blood Fetal DNA" has opened a new pandora box for a specific index case diagnosis of the genetic condition in a given family. It is for us to implement these tests judicially in our practice for the benefit of patient- the ultimate decision maker.

TRIBUTE

Remembering

DR. RAJENDRA JAIN

1953 – 2017
Hon. Secretary, AFG
Managing Committee Member, ISPAT

A Tribute to a Happy Soul

There are no words to express the loss of a Friend, a Senior Colleague, a senior practicing gynaecologist. He was a friend to everyone old and young. My tryst with him began when we started working for Association of Fellow Gynaecologist (AFG), Mumbai. As with any organization we spent several hours together building and contributing to the growth of the organization that's when we came closer. He would call anytime and even in this era of Caller Id he would always say *"Mein Dr. Rajendra Jain bol raha hu"* and I would politely reply – *"Haan Sir boleye".*

He was a learner and always wanted to learn more. He was experienced and brought that experience with him in every task we did.

He had a very vivid knowledge of his subject which would come out and enlighten all of the AFGites when he was given the task of being the editor. He would put his heart in and come out with beautiful issues of AFG TIMES. He was the guiding light to all the future editors of AFG TIMES. AFG TIMES would not have seen the light of the day if it hadn't been for him.

Our years of association rubbed on further when we were together in the managing committee of Indian Society of Prenatal Medicine and Therapy (ISPAT). Under the aegis of ISPAT we visited several cities for conferences. It's then that we grew closer. We together visited Jodhpur, Surat, Rajkot and Delhi. He never used to say no and I used to sneak him with me to all the local hangouts in the city we visited. He used to accompany me, give me company and we used to enjoy tasting the local delicacies.

In the Jodhpur conference he was accompanied by his wife. That was the time when I knew not just him but his family too. He enjoyed talking about his family – his daughters. He was happy and content.

He has left a mark and vacuum filling which is no easy task. AFG & ISPAT will miss him and his welcoming smile.

Dr. Saurabh Dani
Secretary, ISPAT
Vice President, AFG

talkBACK

president **MALHOTRA**

Dear ISPATians

Greetings and warm regards

ISPAT is growing Pan India now, and I urge each one of you to motivate at least one obstetrician, one pediatrician and one ultra-sonologist to become an ISPAT member.

Our genetics-IUGR-newborn screening CMEs are generating lots of interest nation-wide and are doing well with kind support of WB foundation.

Our book on IUGR is selling well all over the world. The work on second book of ISPAT on procedures in obstetrics for prenatal diagnosis is on and soon the contents will be released for this multi-author book.

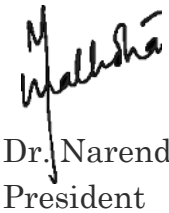
After Noida, we are going to Ranchi on 23rd July, Agra on 30th, Allahabad on 5th August and Lucknow on 6th August. That covers north, after this plan is to move south and west. Mumbai is planned on 17th September.

Also, we are going to be connected to the world through Eco connect, a unique CME on nutrition and fetal origin of adult diseases. We are likely to get a full session in AICOG-2017 at Bhubaneshwar.

This newsletter will come to you regularly. Its your newsletter please contribute regularly in form of review article, tips and tricks, how I do it, letter to editor and any humor in medicine.

Let's work towards our goal of healthy baby to a healthy mother.

Season's greetings for a good monsoon



Dr. Narendra Malhotra
President

What's in **NEWS** these days

Britain's first pregnant man gives birth to girl

Gene that could play key role in depression identified

Breastfeeding lowers the risk of maternal cardiovascular disease : Study

14 year old Yemeni boy with Clubfoot cured at Jaypee Hospital

upcoming **EVENTS**

2nd Annual Medical Complications in Pregnancy Course, September 7-8, 2017, Chicago

Genetics & Genomics: A Focus on Women's Health, September 7, 2017, Cleveland

15th Annual Fetal Imaging and Perinatal Care Conference, September 22-23, 2017, Colorado

ESTD 1989
ISPAT

eCONNECT
A NATIONAL NUTRITION CONSENSUS INITIATIVE

Prof. Narendra Malhotra
M.D., F.I.C.O.G., F.I.C.M.C.H, F.R.C.O.G., F.I.C.S., F.M.A.S.

President's Message,

Indian Society for Prenatal Diagnosis and Therapy (ISPAT) is a multidisciplinary society established in 1989 by liked minded doctors, scientists and philanthropist, interested in prevention and management of birth defects of genetic and non-genetic origin.

This society was formed to help promote, educate and train all the medical personnel, paramedical and any other like-minded persons, who wish to handle high risk pregnant patients and families in their practice.

The science of perinatology has to ensure every baby is born healthy and every mother remains healthy. To achieve this goal of ours we need to educate and sensitize 35000 plus obstetricians of India and the neonatologist and the geneticists and the primary health care physicians.

We have planned the next two years keeping our goals in mind. Our slogan is **"HEALTHY BABY TO A HEALTHY MOTHER"**

Keeping in mind this slogan we are embarking on a mission to understand & bridge the gaps in women's nutrition. As we all are aware there are gaps in terms of the information we have on the nutritional requirements of women in every stage of her life. The Indian College of Obstetrics & Gynaecology last year released the National Nutritional Consensus to fill in this gap. This consensus is essentially a set of recommendations collectively addressing the issues pertaining to nutrition during all the important life-stages of a woman. Medical science is an ever-evolving process enriched, revised and modified continuously by the cumulative work of clinicians, as well as scientists. ICOG, entrenched in the evidence based approach to the practice of modern medicine, has developed this set of guidelines by evaluating the body of existing evidence. This was a mammoth task, both in its scope as well as rigor. It will fill an important void; the lack of up-to-date information on various aspects of nutrition related to women's health. The science of nutrition is undergoing a revolution, as more and more evidence accumulates and past paradigms are replaced in quick succession by new ones. These recommendations and guidelines serve as a ready reckoner to aid the practitioners of modern medicine, provide informed and evidence-based advice.

I am happy to announce that ISPAT has taken up this mantle to spread awareness about this consensus developed by ICOG through a web based program called **"E-connect"**. As part of this program we have developed 4 video modules pertaining to various aspects of nutrition which will be followed by series of webinars which will help dispel the myths & various Q & A's about nutrition.

This will be followed by a self-assessment program & certification. All participants for the above program will be awarded a joint certificate by ISPAT & ICOG.

I hope you all will participate in this initiative wholeheartedly & make it a grand success.

I thank the ICOG Team of Dr. Krishnendu Gupta (Chairperson ICOG), Dr. Shantakumari (Secretary - ICOG), Dr. Jaideep Malhtora (President Elect - FOGSI), Dr. Rajalaxmi Walawalkar (Chairperson RCOG India liason group) for putting this consensus together & agreeing to partner with ISPAT.

Prof. Narendra Malhotra
President - ISPAT

A NATIONAL NUTRITION CONSENSUS INITIATIVE

Expert Talk

Dr. Sonal Panchal
MBBS, MD. (Radiology)
Academic Director – Ian Donald School, India
Nagori's Infertility Clinic, Ahmedabad

Dr. Sonal Panchal is one of the leading infertility and ultrasound specialist in the country. She is Professor of the prestigious Dubrovnik International University. She has numerous international / national publications and scientific papers to her credit. She is a pioneer for application of Doppler, 3D-4D in infertility and also was amongst the first few people in India who mastered in 3D-4D ultrasound. Dr. Sonal is a very popular faculty and teacher and has so far delivered more than 250 lectures at various state, national and international platforms. She has undergone training in Fetal Echocardiography by STIC technology and has received the Fetal Medicine Foundation (FMF) Certificate for 11-14 wks and 18-23 wks scan.

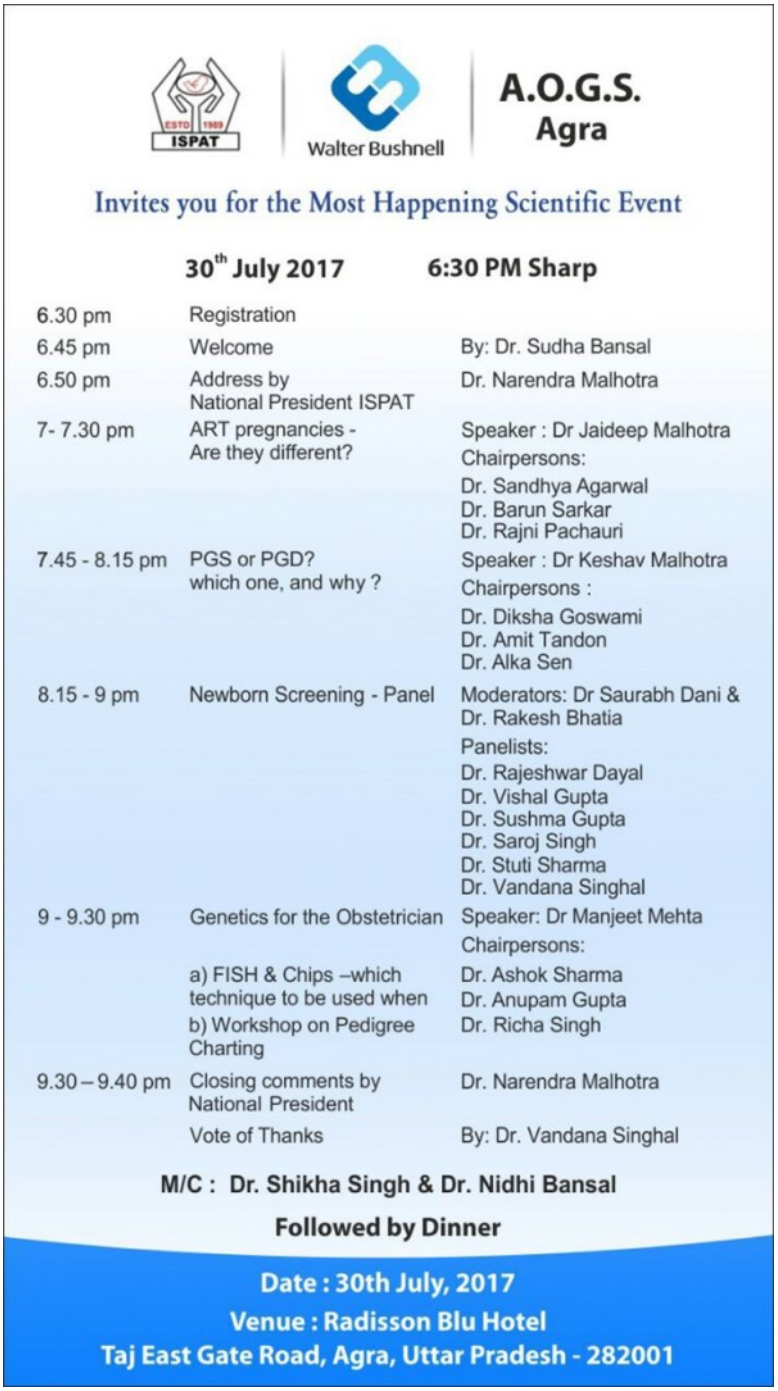
Date 22nd July 2017

Venue _____

Time _____

An educational initiative supported by
mother's Horlicks

upcoming ISPAT EVENTS



Launch of ISPAT UP Chapter

6th August 2017, 12.30pm

Hotel Clarks Awadh, Lucknow

quiz of the MONTH

1. Which are the four nucleotide bases of a DNA strand?
2. Screening test for Congenital adrenal hyperplasia (CAH) looks for which enzyme in blood?
3. Nuchal translucency (NT) scan should be done during which gestational period?
4. Which maternal biochemical markers help in predicting PIH?
5. Dose of Low dose Asprin for prevention of Preterm Preeclampsia?

Answers: Last Page

Ans (March 2017)

1 (Down Syndrome, mid 1960), 2 (All disorders where mutation is known), 3 (Ttransabdominal route, third trimester, Prochownick, Von Schultz, and Lambs in 1877), 4 (Italian biologist Giuseppe Simoni, 1983), 5 (NT, NB, Maxillary length, ductal flow, Femur and humerus length)

First Trimester Screening for Chromosomal Abnormalities

by Dr Vandana Bansal & Dr Neha Singh

BACKGROUND

Chromosomal abnormalities are major causes of perinatal death and childhood handicap. Consequently, the detection of chromosomal disorders constitutes the most frequent indication for invasive prenatal diagnosis, though both amniocentesis or chorionic villus sampling (CVS), is associated with a risk of miscarriage. In the 1970s, the main method of screening for aneuploidies was by maternal age and in the 1980s by maternal serum biochemistry and detailed ultrasonographic (USG) examination in the second trimester. In the 1990s, the emphasis shifted to the first trimester when it was realized that the great majority of fetuses with major aneuploidies can be identified by a combination of maternal age, fetal nuchal translucency (NT) thickness and maternal serum free ß-human chorionic gonadotrophin (ß-hCG) and pregnancy-associated plasma protein-A (PAPP-A). In the last 10 years, several additional first-trimester sonographic markers have been described which improve the detection rate of aneuploidies and reduce the false-positive rate.

Now with changing trends and better ultraound technology, the 11-13^{+6} weeks scan for aneuploidy, early malformation and uterine artery Doppler screens, all patients can be grouped into low or high risk pregnancies. Pregnancies screen negative for aneuploidy and preeclampsia can be followed up as routine care but the screen positive ones undergo invasive testing for confirmation of the disorder in question and are managed under specialist care with more frequent evaluation. Thus, some congenital anomalies can be prevented. Vaccination for rubella virus, adequate intake of folic acid or iodine through fortification or supplementation and adequate antenatal care are three important methods of prevention. However secondary prevention is early detection of the anomaly so that disorders that are lethal, uncorrectable or highly morbid can be terminated, early preparation can be done in the form of early referral to a specialist, decide transfer to a centre where facilities are available for treatment of mother and the neonate at birth and correct the disease in utero by fetal therapy to optimizing best outcome for birth of a child with birth defects.

First Trimester Ultrasound Screening:

11-13^{+6} weeks Nuchal Translucency (NT) scan where in addition to looking at NT other soft markers like nasal bone, ductus venosus, tricuspid regurgitation are evaluated as a screen for aneuploidy, detection of early major malformations, dating of gestational age, no. of fetuses with their chorionicity and screening for preeclampsia and growth restriction by uterine artery dopplers.

First Trimester Aneuploidy/ Chromosomal Screening:

Overall risk of Down syndrome in general population is about 1 in 800 pregnancies; with risk increase in advanced maternal age (Age 20 yrs – risk 1 in 1500 to 1 in 100 at age of 40years). Despite these statistics, Down syndrome is undetected antenatally and discovered at birth in more younger age patients than older pregnant women. Screening for only the older subgroup of pregnant patient will detect only 30% of Down syndrome. Hence, the recommendation is Down syndrome screen should be offered to all.

Screening for aneuploidy can be done in the first trimester as well as the 2nd trimester for trisomy 21, 18 and neural tube defects, the latter between 15 to 21 weeks gestation using detailed ultrasound (genetic sonogram) and maternal serum biochemical markers. Two commonly used screening tests are triple marker (AFP, uE3 and beta-hCG) test and quadruple screen (inhibin A added to 3 markers). Detection rate of quad screen is between 81%- 85.8% for false positive rates of 7-8.3% as compared to triple test with low detection rate of 69% only. Clinical use of triple test is now almost obsolete. Therefore, in cases where first trimester screen could not be done, quadruple test should be offered. MSAFP levels in the quadruple test are also analysed to give cut off risk for neural tube defects.

First trimester Nuchal translucency scan for aneuploidy screening

First trimester screening is currently carried out between 11^{+0} to 13^{+6} weeks' gestation, equivalent to a crown rump length of 45-84 mm. Nuchal Translucency is an objective evaluation on ultrasound of subcutaneous fluid behind the fetal head, neck and torso in the first trimester of pregnancy. Langdon Downs first noted in 1866 that individuals with Trisomy 21 characteristically have skin deficient in elasticity giving appearance of thick loose skin, being too large for the body, with flat faces and small nose (2). These characteristics have been visualized on ultrasound in late 1990s as increased Nuchal Translucency and Absent Nasal bone in intrauterine life between 11-13^{+6} weeks. About 75% of fetuses with Trisomy 21 have increased Nuchal translucency.

It is extremely important to emphasize here that the NT measurement is the single most effective screening test for fetal aneuploidy & should be taken in a standardized manner using the established Fetal Medicine Foundation criteria and adherence to a well-defined technique. Maternal age combined with fetal Nuchal Translucency at 11-13^{+6} weeks increases detection rates to 75% for fetus affected by trisomy 21 for a false positive rate of 5%. Detection rate is improved to 85-90% when maternal serum biochemical markers (free β HCG and Pregnancy Associated Plasma Protein –A) are included. Maternal serum concentration of free β HCG is higher (2MOM) and PAPP-A is lower (0.5MOM) in fetuses with Trisomy 21. In Trisomy 13 and 18 both free β HCG and PAPP-A are decreased. In sex chromosomal anomalies, only PAPP-A is low with normal free β HCG.

There is ample evidence that fetuses with thickened nuchal translucency with normal karyotype are at increased risk for other structural anomalies especially cardiac defects, genetic and non genetic syndromes. Even though fetal karyotype on Chorionic villus sampling / amniocentesis comes normal, still reassurance cannot be given, when other markers are abnormal. These fetuses with increased nuchal translucency must undergo detailed second trimester malformation scan and Fetal ECHO. However, long term outcomes of fetuses with increased NT, normal karyotype and normal anomaly scan in the second trimester have not found any increased neonatal or long term adverse outcome or neurodevelopmental delay.

Addition of **other first trimester markers** (Nasal bone/ Ductus venosus waveform/ tricuspid regurgitation) increase detection rate for Trisomy 21 to more than 95% for a false positive rate of 2.5% and 95% with false positive rate of 0.1% for Trisomy 13 and 18. About 75% of Trisomy 21 fetuses have increased NT and 60-70% of them have absent Nasal Bone at the 11-13 $^{+6}$ weeks scan. Nasal bone may not be visualized in 2% of chromosomally normal fetuses. Absent nasal bone is affected by ethinicity and is higher in Black and Asian population and least in Caucasians. Abnormality of Ductus Venosus waveform are observed in 80% of Trisomy 21 fetuses and 5% of euploid fetus. Tricuspid regurgitation is seen in 55% of Trisomy 21 fetuses but also in 1% of normal fetuses. Abnormality of ductus venosus and tricuspid regurgitation may also be seen in fetuses with cardiac defects.

Double marker screen includes maternal serum levels of pregnancy associated plasma protein A (PaPP-A) and human chorionic gonadotropin (beta-hCG). Combined screen test is offered at 11-13^{+6} weeks of gestation which consists of maternal age & dual marker screen combined with nuchal translucency which gives a risk assessment for serious chromosomal anomalies, such as trisomy 21, trisomy 13, and trisomy 18 and also detect lethal congenital anomalies, such as anencephaly. This detects more than 90% of all aneuploidies (5% false positive rate) & 70-80% of major structural anomalies and a wide spectrum of pregnancy complications including miscarriage, still birth, preeclampsia, macrosomia, fetal growth restriction, preterm delivery and complications due to twin to twin transfusion.

Regardless of maternal age, screening in the first trimester is the standard of care in most guidelines & has an advantage of early reassurance of normalcy or an early definitive prenatal diagnosis. Detection of structural malformation and / or aneuploidy can help early, less physically and emotionally traumatic termination of pregnancy, if deemed necessary. Early prediction of patient specific risk for pregnancy complications may help triage pregnant population into high risk and low risk group so that individualized care, more frequent antenatal visits, close surveillance under specialist care and more

resources can be allocated to the high risk pregnant group. In addition, any preventive action may be initiated early for better impact.

The accuracy of these screening tests are optimal only if the information provided by the clinician is correctly given. For general OBGYs, the following information in referral note is a must as the maternal serum biochemistry is influenced by factors like - Correct gestational age by crown rump length or last menstral period, Maternal weight , Ethinicity, Smoking, IVF or spontaneous conception, Use of maternal or donor eggs, Number of fetuses with chorionicity, Use of drugs like beta HCG, Diabetes, Previous child with Down syndrome /any other chromosomal or genetic disorder.

First trimester screening for fetal structural anomalies

Detailed structural assessment by USG has a potential for detection of fetal abnormalities in the first trimester as many chromosomal abnormalities are associated with fetal structural abnormalities & can be detected at 18-22 weeks of gestational age. However, certain types of fetal malformations, like anencephaly, omphalocoele, limb body wall complex, holoprosencephaly, large neural tube defects and limb defects can be reliably diagnosed at 10-14 weeks of gestation. Whereas other structural anomalies like urinary tract abnormalities, certain skeletal disorders, microcephaly are detectable later in pregnancy.

With the shift in screening for aneuploidy to the first trimester, early screening and detection of congenital heart defects (CHD) at $11\text{-}13^{+6}$ weeks by early fetal ECHO has become possible. Majority of CHD show chromosomal abnormalities on karyotype testing & thus significant in future genetic counselling & prevention. However, assessment of fetal heart at so early gestation requires high level of expertise and equipment. Detection of major CHDs at 11-13 weeks scan can be improved by their association with first trimester soft markers which are easily detectable, like increased nuchal translucency, absent or reversed a wave in ductus venosus or a tricuspid regurgitation. In chromosomally normal fetus, increased NT combined with absent or reverse a wave in ductus venosus is associated with three-fold increase likelihood of major cardiac defects. Tricuspid regurgitation is a frequent finding in $1/3^{rd}$ of euploid fetuses with heart defects. Nevertheless, the second trimester scan remains the gold standard to rule out anomalies, early detection of anomalies can be achieved by meticulous scanning in the first trimester with a structured protocol.

First trimester	Detection rate	Second trimester
Nuchal translucency (NT) scan (11-13 weeks or CRL 45-84 mm)	75%	Genetic sonogram
Double marker (biochemical measurement of PaPP-A and beta HCG)	>90%(if combined with maternal age and NT Scan)	Quadruple/ triple test(81-85% vs 69%)
NIPT (non-invasive prenatal screening)	99%	Amniocentesis (gold standard)
Chorionic villous sampling (CVS)		

PRENATAL DIAGNOSIS

Diagnostic testing will confirm or exclude a suspected diagnosis of chromosomal abnormality. Over the last two decades, prenatal diagnosis has been greatly benefitted from advances in ultrasound technology and genomic prenatal tests to detect microscopic and sub-microscopic chromosome abnormalities as well as single gene disorders. At present, invasive prenatal diagnosis continues to be the gold standard for pregnancies at increased risk for chromosomal anomaly or other genetic disorders. Most commonly done invasive ultrasound procedures are chorionic villous sampling and amniocentesis in first and second trimester respectively.

Currently, valid indications for invasive prenatal testing include increased risk for fetal chromosomal abnormality, increased risk for hereditary genetic or metabolic disease and increased risk for some perinatal infections. The increased risk of fetal aneuploidy maybe derived from a screening test (first-

trimester combined test; non-invasive prenatal test (NIPT); second-trimester biochemistry, such as triple or quadruple test); abnormal ultrasound findings (fetal structural anomaly commonly associated with chromosomal abnormality); obstetric history (previous fetus or child affected by aneuploidy) or family history (parental carrier of chromosomal balanced translocation or inversion, parental aneuploidy or mosaicism. Advanced maternal age (>35years) alone should not be considered an indication, although in some countries it is still among the accepted criteria for invasive testing. Conception by assisted reproductive technique in itself is not considered a valid indication for invasive prenatal diagnosis.

The increased risk for a known genetic or biochemical disease of the fetus maybe derived from: a family hereditary disease with a known mutation or biochemical change; male fetus and carrier status of pregnant woman for a disease with X-linked chromosomal inheritance; carrier status of both parents for an autosomal recessive disorder. In the case of maternal primary infection or sero-conversion involving toxoplasma, cytomegalovirus or rubella, prenatal invasive testing may be indicated to confirm or exclude transmission of the infection to the fetus.

Adequate pre & post-test genetic counseling about the procedure and its associated risks is essential as they carry a small risk of abortion. The options available to parents after a positive diagnosis of a chromosomal abnormality must also be discussed in advance.

Non-Invasive Prenatal Screening (NIPS)Test

Maternal serum cell free DNA (cfDNA) screening for aneuploidy is a popular non-invasive test started just few years ago for common fetal aneuploidies with high sensitivity and specificity. NIPS test uses next generation sequencing to directly measure fetal DNA in the maternal circulation. Current studies suggest 99 % and 98% detection rates for trisomy 21 and trisomy 18 respectively, both for a false positive rate of <1%. This makes this test an attractive alternative to traditional serum screening for aneuploidy. Main limiting factor to its widespread use as a screening method is its cost as well as chance of inability of getting a report if the fetal fraction is low. At present, SMFM (society for maternal fetal medicine) have recommended that NIPS Test is the most appropriate screening test for high risk patients including maternal age 35 years or older at delivery, USG findings indicating increased risk for aneuploidy, previous pregnancy affected with trisomy, positive screening results for aneuploidy, including first trimester, sequential, integrated, or quadruple screen. The advances in bioinformatics & genomic technologies are overcoming the limitations of cell free DNA available & the cost factor. Larger cohort data in Indian women will soon be generated making NIPS test highly useful for low risk obstetric population. Till then, the conventional screening methods remain the most appropriate choice for first line screening in the general obstetric population.

CONCLUSION

Until the mid eighties, first trimester scan was done primarily for confirmation of intra or extra-uterine pregnancy, viability, dating and determining number of fetuses. However with the advent of high resolution ultrasound, better training and expertise and improved understanding of fetal development, the 11-13 $^{+6}$ weeks scan provides much more information for detection of aneuploidy, anomalies, cardiac defects, genetic and non-genetic syndromes and pregnancy complications. However, to maintain the high level of quality in these screening methods , adherence to strict standardized technique and extensive training and auditing cannot be overstated.

RECOMMENDED READING

Images Paediatr Cardiol. 2001 Apr-Jun; 3(2): 3–18.
PMCID: PMC3232499
http://www.who.int/mediacentre/factsheets/fs370/en/
https://www.nhp.gov.in/disease/gynaecology-and-obstetrics/congenital-anomalies-birth-defects
http://www.hoajonline.com/reproduction/2054-0841/2/1
https://www.smfm.org/publications/157-smfm-statement-maternal-serum-cell-free-dna-screening-in-low-risk-women
http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Genetics/Cell-free-DNA-Screening-for-Fetal-Aneuploidy
http://www.aafp.org/afp/2007/0901/p712.html

Answers (July 2017): 1 (Adenine, Cytosine, Guanine, Thymine), 2 (17α-hydroxyprogesterone), 3 (11-13^{+6} weeks), 4 (PlGF and PAPP-A), 5 (150mg/day)