

Screening for Birth Defects Strategies for Developing Low Resource Countries

Prashant Acharya, Jaideep Malhotra, Narendra Malhotra, S Suresh, Ashok Khurana, Chander Lulla, Hriday Acharya, Neharika Malhotra Bora, Rishabh Bora, Keshav Malhotra

ABSTRACT

Most low resource countries have no definite policies laid down for screening for fetal abnormalities and prenatal diagnostic techniques. The problem with screening scans and prenatal diagnostic techniques is the variable way in which they are conducted. There are no clear guidelines about what should, or what should not be done. What is needed is a standard for a routine anomaly scan.

In the past 10 to 15 years, major advances have been made in prenatal screening. It has been suggested that maternal age alone as a screening strategy should be abandoned, but there is still no consensus on the most cost-effective alternative, and thus no national strategy exists.

This document will provide parameters for obstetricians, radiologists and sonographers—how much screening could be accomplished within the available resources. With the help of prenatal diagnostic technique guideline we will be able to achieve a methodical, uniform and cost-effective way of fetal evaluation.

Keywords: Birth defects, Low resource, NT, Anomaly scan, Prenatal diagnostic technique, Amniocentesis, Chorion villus sampling, Aneuploidy, Nasal bone, Genetic sonogram.

How to cite this article: Acharya P, Malhotra J, Malhotra N, Suresh S, Khurana A, Lulla C, Acharya H, Bora NM, Bora R, Malhotra K. Screening for Birth Defects Strategies for Developing Low Resource Countries. *Donald School J Ultrasound Obstet Gynecol* 2013;7(4):453-461.

Source of support: Nil

Conflict of interest: None declared

INTRODUCTION

In India at present there is no definite policy laid down for the ultrasound screening for fetal abnormalities and the prenatal diagnostic techniques. The problem with screening scans and prenatal diagnostic techniques is the variable way in which they are conducted throughout the country. There are no clear guidelines about what should, or should not, be done. The present working group recommends a national standard for a routine ultrasound anomaly scan. This document will provide parameters for obstetricians, radiologists and sonographers how much screening could be accomplished within the available resources.

With the help of prenatal diagnostic technique guideline, we will be able to achieve methodical, uniform, cost-effective and better fetal evaluation. We are also aiming at lowering the prenatal invasive diagnostic procedures because of the introduction of effective screening methods.

Training and Registration

As per the law in India today, those who fulfill the criteria according to PCPNDT act, can perform the scan. He/she should be sufficiently trained to do sonography and must be registered with appropriate authority.

11 TO 13 + 6 WEEKS SCAN

The first scan in early pregnancy should be undertaken ideally between 11-13+6 weeks. The purpose of this scan is to establish:

- Gestational age accurately
- Viability
- Fetal number, and in multiple pregnancies the chorionicity/amnionicity
- Detection of gross fetal abnormalities.

Before 13 weeks, gestational age can be accurately assessed from the measurement of crown rump length (CRL).² However, from 14th weeks CRL should not be used because the fetus becomes increasingly flexed making the measurement unreliable. As an alternative to CRL, biparietal diameter, and/or head circumference should be used. The early scan can usually be performed by transabdominal and/or transvaginal route.

11 TO 13 + 6 WEEKS ANEUPLOIDY SCAN

Correct measurement of CRL, nuchal translucency (NT), heart rate must be done. NT is measured when CRL is between 45 and 84 only. Fetal anomaly scan to detect the gross fetal anomaly should be performed. Additional study of nasal bone (NB), ductus venosus and tricuspid regurgitation can improve the detection rate of fetal aneuploidy. Study of uterine artery Doppler and cervical length can be optional. Reporting of 11-, 13+6 weeks scan must include the risk assessment of trisomy 21. Consultant who is performing NT scan must be properly trained, preferably certified by Fetal Medicine Foundation, United Kingdom (FMF, UK). The software for calculating the risk of trisomy 21 is available free for those accredited by FMF in 11-13+6 weeks scan. Regular audit report ensures continuity of license for the use of software.

All women have chance to deliver the trisomy 21 baby which is known as 'risk a priori'.⁷ As the age increases, risk for delivering a trisomy 21 increases as shown in Appendix 1. As far as scanning for NT is concerned, current

Appendix 1: Maternal age risk 'a priori'⁷

Maternal age	Trisomy 21			
	12 weeks	16 weeks	20 weeks	40 weeks
20	1068	1200	1295	1527
25	946	1066	1147	1352
30	626	703	759	895
31	543	610	658	776
32	461	518	559	659
33	383	430	464	547
34	312	350	378	446
35	249	280	302	356
36	196	220	232	280
37	152	171	185	218
38	117	131	142	167
39	89	100	108	128
40	68	76	82	97
41	51	57	62	73
42	38	42	46	55

Table 1: Methods of screening for trisomy 21

Method of screening	% of detection at false positive rate 5%
Maternal age	30
Maternal age and maternal serum biochemistry at 15 to 18 weeks—triple/quadruple test	50-70
Maternal age and fetal NT at 11-13+6 weeks	70-80
Maternal age and fetal NT and maternal serum free beta hCG and PAPP-A at 11-13+6 weeks	90
Maternal age and fetal NT and nasal bone at 11-13+6 weeks	90
Maternal age and fetal NT and NB and maternal serum free beta-hCG and PAPP-A at 11-13+6 weeks	95

evidence suggests that this is an effective way of determining babies at risk of Down syndrome and is best performed between 11-13+6 weeks (detection rate 70-80% with false-positive rate of 5%). Adding NB to NT improves the detection rate by 10% (detection rate 90% with false-positive rate of 5%).¹¹

Adding the serum biochemistry [free beta-human chorionic gonadotropin (hCG) and pregnancy-associated plasma protein A (PAPP-A)] to NT improves the detection rate by 10% (detection rate 90% with false-positive rate of 5%). Maternal serum screening can be used to modify a woman's age-related risks. If serum testing is to be used as a method of screening for Down syndrome, accurate knowledge of gestational age is essential.^{3,9,11} In developing countries where appropriate and authentic laboratory facility for dual or Quadruple marker tests are NOT available, one should rely on NT, Nasal bone and ductus venosus by appropriately trained person for aneuploidy screening.

Comparison of the Detection Rates, for a False-positive Rate of 5%, of Different Methods of Screening for Trisomy 21 (www.fetalmedicine.com)^{8,11}

Combination of age, NT, NB, ductus venosus, tricuspid regurgitation, heart rate with serum biochemistry will produce the highest sensitivity with the lowest false positive rate (Table 1).¹

11 TO 13+ 6 WEEKS ANOMALY SCAN

Nicolaides et al²³ mentioned that almost 43.6% of fetal anomalies were detected at 11-13+6 weeks. The 11-13+6 weeks scan detected all cases of acrania, alobar holoprosencephaly, exomphalos, gastroschisis, megacystis and body stalk anomaly, 77% of absent hand or foot, 50%

of diaphragmatic hernia, 50% of lethal skeletal dysplasias, 60% of polydactyly, 34% of major cardiac defects, 5% of facial clefts and 14% of open spina bifida, but none of agenesis of the corpus callosum, cerebellar or vermian hypoplasia, echogenic lung lesions, bowel obstruction, most renal defects or talipes. NT was above the 95th percentile in 34% of fetuses with major cardiac defects. Data from various studies by Whithlow et al, Radhakrishnan et al, Suseela et al^{21,24,25} suggest that about from 22, 55 and 85% of significant abnormalities will be identified by a screening scan early in the 11-13+6 weeks scan respectively. These data proves that 11-13+6 weeks scan is very helpful in the diagnosis of significant lethal fetal anomalies, which are not compatible with life during in the first trimester of pregnancy.

'18 TO 20 WEEKS'—TARGETED ANOMALY SCAN

When 1st trimester scan is missed, the '18 to 20 weeks' targeted anomaly scan provides dating information and diagnosis of multiple pregnancy. The majority of nonviable pregnancies will be lost before the scan at 20 weeks. An attempt must be made to evaluate the fetus completely with standard views to exclude major structural anomalies in transverse, sagittal and coronal plains. The '18 to 20 weeks'—targeted anomaly scan is to reassure the woman that the fetus appears to have no obvious structural abnormalities. The primary aim should be to prove the 'normality'. Recent data⁴ from one unit suggested that about 50% of significant abnormalities would be identified by a screening scan. Recent data from Radhakrishnan et al²¹ suggested that about 55% of significant abnormalities will be identified by a screening scan early in the 11-13+6 weeks scan and detection will go to 88% after 18 to 20 weeks scan in the expert hands. The '18 to 20 weeks'—anomaly scan should

be carried out at the clinic with minimum standard described below. If a clinic considers that it cannot deliver scans to this minimum standard as described below then the '18 to 20 weeks' scan should be referred to an appropriate unit.

Procedure

The minimum standard for an '18 to 20 weeks' targeted anomaly scan, gestational age can be established by measurement of biparietal diameter, head circumference, abdominal circumference and femur length.

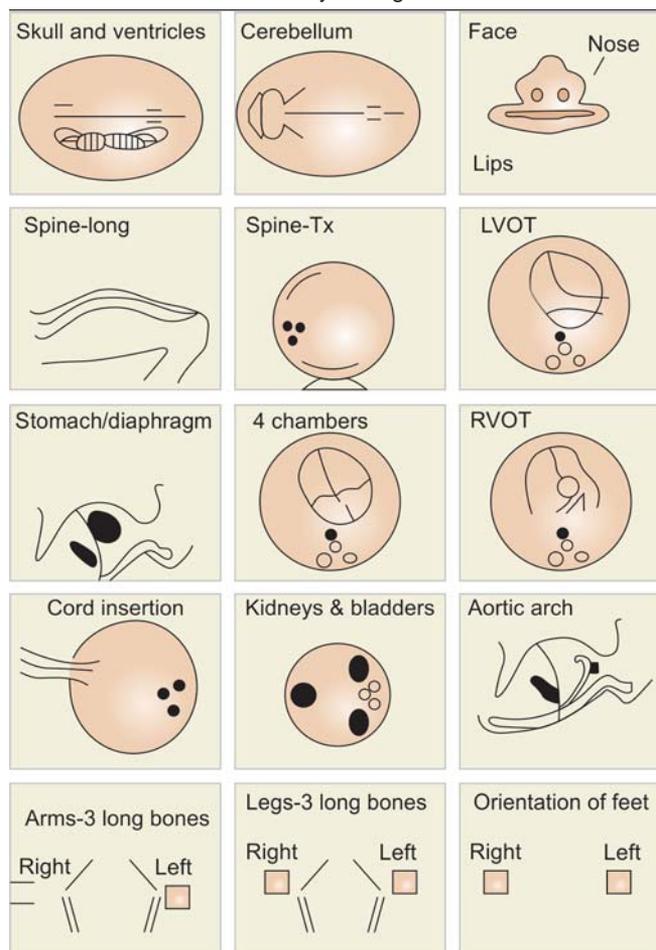
Fetal Normality

- Head size, shape + internal structures cavum pellucidum cerebellum ventricular size at atrium/parieto-occipital sulcus
- Face, lips with face profile to show nasal bone
- Spine: longitudinal, sagittal and transverse
- Thorax at level of 4-chamber cardiac view and three vessel views
- Abdominal shape and content at level of stomach
- Renal pelvis measurement
- Abdominal shape and content at level of kidneys and umbilicus
- Arms: three bones and hand (not counting fingers)
- Legs: three bones and foot (not counting toes).

If resources are available uterine artery Doppler and the measurement of cervical length should be included in the extended scan. Adding these parameters will improve in identifying the patients at risk of preterm delivery and the consequences of improper placentation, respectively. Fetal heart examination should be carried out in detail with suspected/confirm other fetal anomalies and in all medical situation where the incidence of congenital heart diseases is increased.

A checklist for the baseline fetal anomaly scan is included as Appendix 2. Detection rate of major fetal anomaly is included in Appendix 3. The risk of aneuploidy should be mentioned when scan is performed between 11 and 13+6 weeks scan with the help of software. The risk of aneuploidy should be mentioned when scan is performed between 16 and 20 weeks with the help of software or can be calculated with the help of likelihood ratio (LR) for all the soft markers. Use of Indian fetal biometry and growth charts should be encouraged for better prediction of fetal age and the fetal growth for Indian population. Acharya et al¹⁰ showed the distinct advantages of using the Indian fetal biometry over the western fetal biometry for Indian population. Like wise, use of Biometry and growth charts derived from local race and population will be more helpful in identifying the appropriate fetal growth with better

Appendix 2: Ultrasound screening for aneuploidy and baseline fetal anomaly scan guidance



All small copies of basic scan: Basic views of BPD, HC, AC and FL; Extended views to add face profile

Appendix 3: Potential detection rates based on present screening strategy

Fetal anomaly chance of being seen	Detection rate of different fetal anomaly
Spina bifida	90%
Anencephaly	99%
Hydrocephalus	60%
Major congenital heart problems	25%
Diaphragmatic hernia	60%
Exomphalos/gastroschisis	90%
Major kidney problems	85%
Major limb abnormalities	90%
Cerebral palsy spasticity: never seen	
Autism: never seen	

accuracy. Women should receive written details about their scan result. All scans should be carefully documented and archived. Accurate record keeping is needed too with the pregnancy outcome recorded with sufficient detail. Use of the computer-based record keeping with the use of software should be encouraged and preferred which also helps in checking the quality and the audit of the unit/consultant. Regular audit of pregnancy outcome should be checked.

Appendix 4: Pooled estimates of detection rate (DR), false-positive rate (FPR) and positive and negative likelihood ratios (LR+ and LR-) of sonographic markers for trisomy 21 and estimated likelihood ratio (LR) of individual isolated markers¹⁶

Marker	DR (95% CI) (%)	FPR (95% CI) (%)	LR+ (95% CI)	LR – (95% CI)	LR isolated marker*
Intracardiac echogenic focus	24.4 (20.9-28.2)	3.9 (3.4-4.5)	5.83 (5.02-6.77)	0.80 (0.75-0.86)	0.95
Ventriculomegaly	7.5 (4.2-12.9)	0.2 (0.1-0.4)	27.52 (13.61-55.68)	0.94 (0.91-0.98)	3.81
Increased nuchal fold	26.0 (20.3-32.9)	1.0 (0.5-1.9)	23.30 (14.35-37.83)	0.80 (0.74-0.85)	3.79
Echogenic bowel	16.7 (13.4-20.7)	1.1 (0.8-1.5)	11.44 (9.05-14.47)	0.90 (0.86-0.94)	1.65
Mild hydronephrosis	13.9 (11.2-17.2)	1.7 (1.4-2.0)	7.63 (6.11-9.51)	0.92 (0.89-0.96)	1.08
Short humerus	30.3 (17.1-47.9)	4.6 (2.8-7.4)	4.81 (3.49-6.62)	0.74 (0.63-0.88)	0.78
Short femur	27.7 (19.3-38.1)	6.4 (4.7-8.8)	3.72 (2.79-4.97)	0.80 (0.73-0.88)	0.61
ARSA	30.7 (17.8-47.4)	1.5 (1.0-2.1)	21.48 (11.48-40.19)	0.71 (0.57-0.88)	3.94
Absent or hypoplastic NB	59.8 (48.9-69.9)	2.8 (1.9-4.0)	23.27 (14.23-38.06)	0.46 (0.36-0.58)	6.58

*Derived by multiplying the positive LR for the given marker by the negative LR of each of all other markers, except for short humerus. ARSA, aberrant right subclavian artery; NB, nasal bone

GENETIC SONOGRAM

The 'Genetic Sonogram' should be a part of 'anomaly scan'. The genetic sonogram will help in identifying the fetus at the risk of fetal aneuploidy.¹⁸⁻²⁰ The genetic sonogram involves the evaluation of presence or absence of soft markers between 16 and 20 weeks (Appendix 4). Soft markers are the obstetric ultrasound findings, which are considered variants of normal but are noteworthy because they also increase the risk for underlying fetal aneuploidy.^{5,6} Presence of soft markers may be associated with nonchromosomal malformations also. The presence of soft markers increases the risk for fetal aneuploidy but is not diagnostic. Individual soft markers will vary in the degree of association with fetal aneuploidy. It has become practice to estimate the degree of association as a LR by which the *a priori* background risk is altered. Detection of multiple soft markers will increase the significance of the finding, compared with seeing the same marker in isolation. In addition, maternal serum testing screening tool can complement and enhance the overall screening process. Providing an accurate assessment of fetal genetic risk require the ability to integrate known factors before patients can make an informed choice about proceeding with invasive diagnostic testing. Guidance on screening for aneuploidy is included in Appendix 4.

Recently, meta-analysis done by Nicolaidis and group have suggested new soft markers (ARSA, hypoplastic/ absent nasal bone, mild ventriculomegaly with likely hood ratio) as well as changed the likely hood ratios of the markers (Appendix 4).¹⁶

Thickened Nuchal Fold–Likelihood Ratio¹⁶: 3.8

1. A thickened nuchal fold significantly increases the risk of fetal aneuploidy. Expert review is recommended, and karyotyping should be offered.
2. A thickened nuchal fold is associated with congenital heart disease and rarely with other genetic syndromes.

Mild Ventriculomegaly–Likelihood Ratio¹⁶: 3.81

1. Cerebral ventricles greater than or equal to 10 mm are associated with chromosomal and central nervous system pathology. Expert review should be initiated to obtain a detailed anatomic evaluation looking for additional malformations or soft markers, laboratory investigation for the presence of congenital infection or fetal aneuploidy. Fetal MRI as an additional imaging technique may be of help.
2. Neonatal assessment and follow-up are important to rule out associated abnormalities and are important because of the potential for subsequent abnormal neurodevelopment.

Echogenic Intracardiac Focus Likelihood Ratio¹⁶: 1

1. Echogenic intracardiac focus (ECF) should be evaluated and reported as part of the 4-chamber cardiac review.
2. Women with right-sided, biventricular, multiple, particularly conspicuous, or nonisolated ECF should be offer referral for expert review and possible karyotyping.

Mild Pyelectasis Likelihood Ratio¹⁶: 1

1. If pyelectasis is visualized, the renal pelvis should be measured in the anterior/posterior diameter.
2. All fetuses with renal pelvic measurements >5 mm should have a neonatal ultrasound, and those having measurements >10 mm should be considered for a regular follow-up scan.
3. Isolated mild pyelectasis does not require fetal karyotyping.
4. Referral for pyelectasis should be considered with additional ultrasound findings and (or) in women at increased risk for fetal aneuploidy owing to maternal age or maternal serum screen results.

Single Umbilical Artery

1. Assessment of cord vessels is considered a part of the routine obstetric ultrasound at 18 to 20 weeks.
2. The finding of a single umbilical artery (SUA) requires a more detailed review of fetal anatomy, including kidneys and fetal heart (fetal echo).
3. An isolated SUA does not warrant invasive testing for fetal aneuploidy.

Echogenic Bowel Likelihood Ratio¹⁶: 1.65

1. Echogenic bowel should be identified by comparison with the echogenicity of surrounding bone using an appropriate transducer and gain setting. Bowel echogenicity equal to or greater than bone is significant.
2. Echogenic bowel is associated with both chromosomal and nonchromosomal abnormalities. Expert review is recommended to initiate the detailed ultrasound evaluation looking for additional structural anomalies or other soft markers of aneuploidy, detailed evaluation of the fetal abdomen looking for signs of bowel obstruction or perforation, detailed evaluation of placental characteristics. Detailed maternal work up for serum screening tests, evaluation for cystic fibrosis and infection should be done. The genetic counseling and fetal karyotype should be considered.

Absent/Hypoplastic Nasal Bone¹⁶: LR 6.58

When Nasal bone is absent OR Hypoplastic (shorter by 1/11 of BPD) chances of Trisomy 21 increase by 6.58 times in particular black women. In Indian population, Nasal bone is absent/hypoplastic in about 10% of general population.

The incidence of an absent nasal bone is related to NT, CRL and ethnic origin as well as aneuploidy, being more common when the NT is high, the CRL is low and the mother is Black.

Choroid Plexus Cysts

1. Isolated choroid plexus cysts (CPCs) require no further investigation when maternal age or the serum screen equivalent is less than the risk of a 35-year-old.
2. Fetal karyotyping should only be offered if isolated CPCs are found in women 35 years or older or if the maternal serum screen is positive for either trisomy 18 or 21.
3. All women with fetal CPCs and additional malformation should be offered referral and karyotyping.

Mega Cisterna Magna

1. An isolated mega cisterna magna is not an indication for fetal karyotyping.

2. With a mega cisterna magna, expert review is recommended for follow-up ultrasound, fetal MRI and investigations.
3. If the mega cisterna magna is seen in association with other abnormal findings, fetal karyotyping should be offered.

Short Femur Length and Short Humerus Length Likelihood Ratio:¹⁶ 0.1 and Likelihood Ratio:¹⁶ 0.78

If a femur and/or humerus appear abnormal or measures short on screening ultrasound, other long-bones should be assessed and referral with follow-up ultrasound considered.

PRENATAL DIAGNOSTIC TESTS

Commonly practiced invasive prenatal diagnosis techniques are chorionic villus sampling (CVS), amniocentesis, less commonly cordocentesis or percutaneous umbilical blood sampling (PUBS), fetal tissue sampling. Invasive testing can be performed in the first trimester by CVS or in the second trimester by amniocentesis; and have been the two most common prenatal diagnostic procedures for decades. Both procedures are safe, with an equivalent 0.5% risk of procedure-induced pregnancy loss.¹⁷ When performed prior to the routine sampling window of 15 weeks, amniocentesis may increase the risk of talipes equinovarus, the highest risk being encountered prior to 13 weeks' gestation. When CVS is performed prior to 9 weeks' gestation, there may be an increased risk of limb reduction defects.¹⁷ There are wide variations in utilization, operator skills, quoted procedure risks, actual observed risks, and patient choices that come from highly variable counseling as to those risks. The laboratory analysis of both procedures is reliable. CVS has a 1 to 2% incidence of confined placental mosaicism, requiring additional evaluation in some cases. Most studies comparing CVS to amniocentesis in skilled hands have found equivalency of risks. Cordocentesis has fewer indications, is performed in the late second trimester of pregnancy, but allows direct laboratory testing from fetal blood. Experienced operators should perform all invasive procedures under continuous ultrasound guidance. Patient counseling should include an evaluation of the procedural risk associated with each individual case with its background risk. In general, patients are allowed to resume most daily activities after the procedure in India. Formal informed consent for invasive procedure should be obtained before the procedure.

Chorionic Villus Sampling

CVS is a test where a small piece of chorion frondosum (placental tissue) is removed and used for genetic testing.

CVS is the most common first trimester invasive prenatal diagnosis technique for evaluation of fetal karyotype, molecular and biochemical abnormalities. CVS should not be performed before 10 weeks gestation because of the risk of transverse limb reduction defects.¹³⁻¹⁵ CVS should be performed by an operator using concurrent ultrasound. The operator should have adequate training and should continue performing sufficient numbers annually to maintain expertise.

Indications for CVS

- An abnormal first trimester screening by USG with/without serum biochemistry indicating increased risk for chromosome problems (screen positive).
- Finding of fetal abnormality on ultrasound a previous child with a chromosome abnormality.
- Parents carry a chromosome translocation (rearrangement) or evaluation for the single gene disorder like thalassemia, Tay-Sachs, sickle cell anemia and DMD/CAH/CF, etc.
- Skin disorders: epidermolysis bullosa dystrophica, albinism, ichthyosis.

Advantages of CVS

An early result is advantageous for the patient, in that, in cases of an unaffected pregnancy the anxiety is relieved and in cases of affected pregnancy early termination of pregnancy can be undertaken with lower complication rate and less emotional stress than when termination follows amniocentesis at a later gestational age.

Disadvantages and Risks of CVS

- Confined placental mosaicism:** A discrepancy between the chromosomes in the chorionic and fetal tissues, is a biologic placental factor, which is present in 1 to 2% of pregnancies
- Maternal contamination:** With decidual tissue
- Pregnancy loss:** In addition to the background risk of spontaneous pregnancy loss in the advanced maternal age group, the procedure related loss is about 1 to 2% in comparison to the 0.5 to 1% risk for amniocentesis.¹²
- Limb or facial anomalies:** The risk of limb or facial anomalies is higher if CVS is done at a gestational age earlier than 9 weeks, hence universally, CVS is generally restricted to greater than or equal to 10 weeks. These anomalies may be due to a vascular disruption sequence event, which may be associated with the CVS procedure.

Amniocentesis

Indications

Amniocentesis²² is usually performed for determination of fetal karyotype, molecular and biochemical abnormalities.

The most common test performed on the amniotic fluid is the fetal karyotype from fetal and membrane cells in the amniotic fluid after tissue culturing or fetal chromosomal evaluation by direct fluorescent *in situ* hybridization (FISH) techniques. Amniocentesis should be performed with concurrent ultrasound should be used. Amniocentesis is usually performed from 15 weeks gestation and should not routinely be performed before 14 weeks gestation because of the increased risk of adverse outcome.

Some of the most common indications for amniocentesis are:

- For chromosomal analysis in the fetus who is screen positive after USG and/or serum biochemistry
- A previous child with a chromosome abnormality or metabolic disorder
- One or both parents carry a chromosome translocation (rearrangement) or
- Both parents carriers of a genetic disease such as thalassemia minor, Tay-Sachs, sickle cell anemia, etc.
- Finding of a fetal abnormality on ultrasound suggestive of chromosomal anomaly
- Risk of fetal infection
- Sex determinations (only for X-linked disease, CAH, DMD)
- Biochemical disorders and inborn errors of metabolism screening in fetus
- Study of microdeletions in fetus.

Risks of Amniocentesis

Fetal Loss

Fetal loss after amniocentesis is 0.5 to 1% above the background loss.^{14,21}

Infection

The risk of infection introduced at the time of the amniocentesis is estimated to be 1 to 2 in 3,000 procedures.⁴

Fetal Injury

Serious fetal injuries at the time of amniocentesis are rare with continuous ultrasound guidance.

Other Complications

Include leakage of amniotic fluid, bleeding and uterine irritability.

These complications are estimated to occur in 1% of procedures and are generally self-limited.

Comparing various approaches of prenatal diagnostic techniques:

- Transabdominal CVS vs second trimester amniocentesis:** A subgroup of Denmark compared transabdominal CVS

with second trimester amniocentesis and found no significant difference in the total pregnancy loss between the two procedures (6.3 vs 7%; RR: 0.90; 95% CI: 0.66-1.23).

- B. *Transabdominal vs transcervical CVS*: Compared with transabdominal CVS, total pregnancy loss and spontaneous miscarriages were higher after transcervical CVS. Vaginal bleeding following the procedure was much more common after transcervical CVS, although there was no difference in the incidence of vaginal bleeding later in pregnancy. There was no significant difference in the amniotic fluid leakage following the procedure and prelabor spontaneous rupture of membranes before 28 weeks.
- C. *Early amniocentesis (EA) vs transabdominal CVS*: Spontaneous miscarriages after early amniocentesis are more common (RR: 1.76; 95% CI: 1.17-2.64).

Cordocentesis

Fetal blood sampling provides information that is not obtainable by other techniques for fetal assessment. It has tremendous fetal diagnostic and therapeutic applications, and exciting research potential. It allows the direct estimation of fetal hemoglobin, hematocrit, blood group, platelet count, reticulocyte, and white blood cell count for prenatal diagnosis of fetal anemia, thrombocytopenia, etc. Cord blood gives a better and quicker chromosomal preparation than with chorionic villi or amniotic fluid. Congenital infections can be diagnosed by serology, direct identification of the viral particles by electron microscopy of fetal blood, cultures of fetal blood, and indirect parameters like platelet count, total leukocyte count, differential count, and liver enzymes are carried out to arrive at a diagnosis. Fetal blood sampling (direct ultrasound guided fetal blood sampling) should also be performed or closely supervised by operators trained in this procedure who perform a sufficient number of such samplings to ensure technical success (i.e. sampling fetal blood), and to minimize the complication rate.

Indications

- Rh immunization–Hb, blood group, intrauterine transfusion
- Rapid fetal Karyotype (late pregnancy)
- Hematology–Hb, Factor VIII, IX deficiency, platelets
- Congenital infections–PCR, IgM (TORCH), parvovirus
- All indications similar to amniocentesis.

Indications are decreasing as prenatal diagnosis of these conditions can now be done by CVS or by amniocentesis.

The procedure-related fetal loss rate for cord blood sampling is 1 to 2.6%. The overall mortality (including background morbid condition of a diseased fetus) appears to be around 5.0% (between 3.84 and 5.87%), but fetal loss rate directly related to the procedure seems to be around 1% (between 0.88 and 0.98%) only. Fetal loss rate is closely related to the state of the fetus and indication of the procedure.

Transient bradycardia varying from 15 to 134 seconds may be seen in 3 to 9%. Complications and success in obtaining the blood sample depends on the experience of the operator.

Rhesus Status

Rhesus status should be available or obtained in every case before the prenatal invasive diagnosis. Anti-D Ig should be given to all nonsensitized RhD-negative women with Rh-positive husband after the invasive prenatal diagnosis like amniocentesis, chorion villus sampling, fetal blood sampling and other intrauterine procedures, e.g. insertion of shunts, embryo reduction. A dose of 50 mcg is recommended for prophylaxis following sensitizing events up to 20 weeks of pregnancy and for all events after 20 weeks, at least 100 mcg anti-D Ig should be given followed by a test to identify fetomaternal hemorrhage. Final dose has to be calculated after the quantification of fetomaternal hemorrhage. fetomaternal hemorrhage greater than 4 ml red cells of fetal blood, additional anti-D Ig should be given as per-requirement.

CONCLUSION

The choice between first trimester combined testing (NT with maternal serum screening), integrated screening (NT, first and second trimester maternal serum screening), CVS, amniocentesis, second trimester serum screening should be based on of informed consent. This should take into consideration the risks of the test, timing, method of termination, which may be considered (if affected), and accuracy of the test. All women should be offered first trimester (11 to 13+6 weeks) and a mid trimester (18-20 weeks) ultrasound scans with or without serum biochemistry screening. Amniocentesis and CVS are very useful techniques for fetal care, quite safe obstetric procedures in expert hands, with backup requirement of a good genetic laboratory. They require skill, and should preferably be done in referral centers to maximize safety, and optimize patient management. In addition, there is need for improved and more specific noninvasive screening methods to identify

women whose fetuses are at risk of congenital or genetic disease, to minimize number of women requiring PND procedures. Obstetricians play a key role in prenatal diagnostic and genetic services, by screening, counseling and timely referrals.

GENERAL PRINCIPLES FOR PRENATAL DIAGNOSIS PROGRAMS

1. All patients considering prenatal diagnosis should have access to professionals who are knowledgeable in the field appropriately minimally trained for doing the procedures. The prenatal diagnostic service units should use state of the art ultrasound equipment. Each specialized prenatal diagnostic service requires the services of a multidisciplinary team of a specialist in obstetric ultrasound, clinical geneticist, genetic counsellor, obstetrician (with specializing in prenatal diagnosis and management of fetal abnormality preferred), pediatrician, pediatric surgeon and laboratory. There should be at least one specialized prenatal diagnostic service center for all states of India.
2. A suggested minimum caseload of 50 invasive procedures per year is recommended per practitioner and 100 prenatal specimens for the genetic laboratory in order to maintain an appropriate level of competence. Exceptions to this minimum caseload may be justified because of unique geographic circumstances.
3. Each patient should have an appropriate assessment of family history and genetic counseling prior to undergoing invasive prenatal diagnosis.
4. Counseling should be given in a nondirective manner in order to allow an informed choice by the couple.
5. The distinction between screening and diagnostic investigations should be clarified, including the frequency of abnormal results, false-positive and false-negative tests. Accuracy of results, frequency of need for repeats testing, and risks of pregnancy loss are of particular relevance with invasive prenatal diagnosis procedures. The couple should be reminded that normal test results do not rule out every genetic or structural abnormality in their fetus.
6. Prior to embarking on prenatal diagnosis testing, couples should be made aware of the full range of options when confronted with an abnormal test result. Prior commitment to termination of pregnancy following the diagnosis of fetal abnormality is not a prerequisite for prenatal diagnosis. Each center must be aware of the local, regional, national, and international policies and protocols related to termination of pregnancy, and advise the couple of such before undertaking prenatal diagnosis. This is particularly important at gestations beyond 20 weeks.

7. Determination of fetal sex for the purpose of sex selection procedures on a nonmedical basis is inappropriate and against the law in India.
8. When a fetal anomaly is found, a multidisciplinary group should be involved for the management of the patient and the fetus.

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ABOUT THE AUTHORS

Prashant Acharya

Consultant, Department of Fetal Medicine and High Risk Obstetric Care, Paras Advanced Center for Fetal Medicine, Ahmedabad, Gujarat; Vice President, FOGSI, 2012; Ex. Chairperson, Genetic and Fetal Medicine Committee, FOGSI 2009-2012; Coordinator, IIS, India 2012 (ISUOG International Symposium)

Correspondence Address: Paras-Advanced Center for Fetal Medicine, 2/B, Virvijay Society, Opp Sanghvi High School Vijaynagar Road, Naranpura, Ahmedabad-380013, Gujarat, India e-mail: ashinprashant@hotmail.com, ashinprashant@gmail.com

Jaideep Malhotra

President Elect, ASPIRE 2014; Infertility and ART Specialist; Consultant, Department of Obstetrics and Gynecology; Director Medical Services, Rainbow Hospital, Agra, Uttar Pradesh India; Vice President, FOGSI 2010

Narendra Malhotra

Professor, Dubrovnik International University; President, FOGSI 2008; Consultant, Infertility Specialist, Department of Obstetrics and Gynecology; Managing Director, Rainbow Hospital, Agra Uttar Pradesh, India

S Suresh

Consultant, Mediscan Center, Chennai, Tamil Nadu, India

Ashok Khurana

Consultant Radiologist, Department of Radiology, New Delhi, India

Chander Lulla

Consultant Radiologist, Ria Clinic, Mumbai, Maharashtra, India

Hriday Acharya

Intern, Civil Hospital, Ahmedabad, Gujarat, India

Neharika Malhotra Bora

Lecturer, Department of Obstetrics and Gynecology, Bharati Vidyapeeth Medical College, Pune, Maharashtra, India

Rishabh Bora

2nd Year Resident, Department of Radiology, Bharati Vidyapeeth Medical College, Pune, Maharashtra, India

Keshav Malhotra

Intern, District Hospital, Agra, Uttar Pradesh, India