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fetologue

SOUND TALK WITH UNBORN

BANGALORE FETAL MEDICINE CENTRE

From The Desk

Greetings from BFMC

Worldwide the standard of practice in prenatal ultrasound is to screen for chromosomal abnormalities and detect structural abnormalities in the fetus. This can be achieved by a detailed ultrasound in the second trimester, in addition to first trimester screening.
Our next two issues will focus on soft markers in the second trimester ultrasound, also referred to as genetic sonogram. Their identification and significance are the highlights of this issue as well as the next.

Inside View

- Overview of soft markers
- Likelihood ratio
- Nuchal fold
- Ventriculomegaly
- Choroid plexus cyst

Overview of Soft Markers

Dr. Veena Acharya
MD, Consultant in Fetal Medicine

Soft markers are non-anomalous variations in fetal anatomy which form part of a genetic sonogram (GS), performed in the second trimester (18-23 weeks).

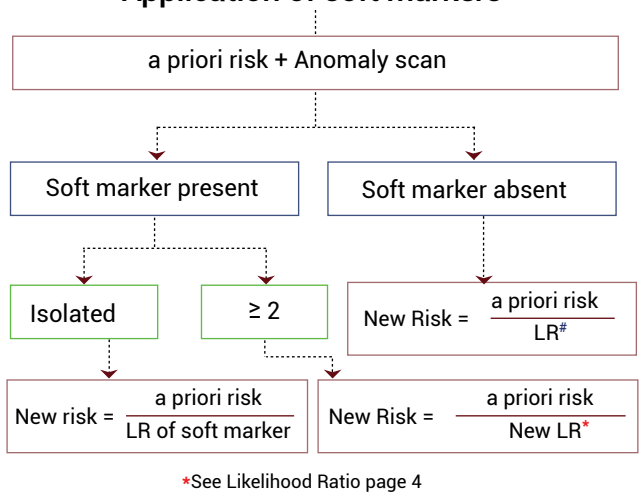
Soft Markers :

- Are frequently seen in normal fetuses
- Increase the underlying risk but are not diagnostic for fetal aneuploidy
- Are nonspecific and insignificant by themselves regarding fetal outcome
- Often transient; disappearing as the pregnancy progresses

Soft makers have been assigned a likehood ratio (LR) which are used to calculate the risks of a fetus having Down Syndrome or Trisomy 21 (T21). (refer page 3)

Minor markers - LR≤1 | Major markers - LR>1

Application of soft markers



*See Likelihood Ratio page 4

The LR to be used for risk reduction depends upon the markers that have been studied and if they are performed in a 'specialist unit'. If all major markers, including short humerus, hypoplasia of the nasal bone(s) and ARSA is excluded, then LR to be used is 0.13, implying that a 7.7 fold risk reduction can be achieved. This requires considerable expertise in scanning. However in women undergoing a routine 2nd trimester anomaly scan, in the absence of markers an LR of 0.52 is used, allowing for a 1.9 fold reduction in the risk.

Soft markers noted

- Look for other soft markers
- Detailed anomaly scan including fetal echocardiography

- If an optimal prior risk assesment is unavailable, the patient may be offered a quadruple test in the absence of a soft marker or presence of a minor marker

If the risk cut -off for Trisomy 21 after the genetic sonogram is >1 in 250, fetal karyotyping is recommended.
For Trisomy 18 and 13 the risk cut off is 1≥100.

No role if cell-free DNA testing (cfDNA) has been the modality of screening for aneuploidy, as cfDNA is a highly sensitive test with a detection rate of 99.3% for T21.

Counselling is of paramount importance when a soft marker is seen, to allay patient fears and reduce dilemmas in decision making for further invasive testing.

Implication of the genetic sonogram, against the background of an optimal first trimester screening (FTS)

FTS Low Risk
GS adds little information, reassuring.

High or intermediate risk-No marker
GS may reduce the risk sufficiently to be able to avoid an invasive testing.

High or intermediate risk-Presence of markers
Further increases the risk, and helps decision making for invasive testing.

Nuchal fold, aberrant right subclavian artery (ARSA) and ventriculomegaly may be detected at GS, thereby increasing risk for T21 even in a FTS low risk setting.

Sonographic features of fetal aneuploidy

	Trisomy 21	Trisomy 18	Trisomy 13
Structural abnormalities	Cardiac abnormalities Duodenal Atresia Brachycephaly Hydrocephalus Clinodactyly Cystic hygroma and hydrops	Cardiac abnormalities Esophageal atresia Strawberry shaped head Diaphragmatic hernia Omphalocele Meningomyelocele Agenesis of corpus callosum Facial clefting Talipes Rocker bottom foot Radial aplasia Overlapping digits Umbilical cord cyst Cystic hygroma and hydrops	Cardiac abnormalities Diaphragmatic hernia Omphalocele Holoprosencephaly Facial clefting Cyclopia Agenesis of corpus callosum Rocker bottom foot Polydactyly Talipes Cystic hygroma and hydrops
Soft marker	Nuchal fold thickening Ventriculomegaly Short femur or humerus Hypoplastic nasal bone Echogenic bowel Pylectasis Sandal gap toes	Choroid plexus cyst Enlarged cistern magna Ventriculomegaly Short femur or humerus Hypoplastic nasal bone Echogenic bowel Pylectasis Single umbilical artery	Echogenic intracardiac focus Enlarged cistern magna Ventriculomegaly Pylectasis Single umbilical artery

Adapted from Breathnach et al., Amj Med genet 145(1) c62-72, 2007

Likelihood Ratio

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Director & Consultant in Fetal Medicine
• BFMC

Dr. Priya D Kumbhare
Consultant in Fetal Medicine

Likelihood Ratio (LR) is a concept which helps in decision-making in medicine. LR is the likelihood or probability that a given "marker" would be expected in a patient with the disease compared to the probability that the same "marker" would be expected in a patient without the disease. It is calculated depending upon the sensitivity and specificity.

A positive likelihood ratio (LR+) tells us how much to increase the probability of disease if the test is positive.

A negative likelihood ratio (LR-) tells us how much to decrease the probability of disease if the test is negative.

$$\text{Positive likelihood ratio (LR+)} = \frac{\text{Sensitivity}}{\text{1-Specificity}}$$

$$\text{Negative likelihood ratio (LR-)} = \frac{\text{1-Sensitivity}}{\text{Specificity}}$$

- LR > 1 - Test result is associated with the disease
- LR < 1 - Test result is associated with absence of disease
- LR = 1 - Pre & post test probablility are the same

LRs of ultrasound markers for Down syndrome (DS) based on second trimester scan

Every mother has a risk of having a baby with an aneuploidy. This risk is initially based on age alone and is termed -a-prior- risk or the "pre-test probability". If a marker (ultrasound or biochemical) is present, the risk increases as many times as the LR assigned to that marker. This new risk is termed "adjusted risk" or a -post-test probability".

MARKER	LR+	LR-	LR ISOLATED MARKER
Intracardiac echogenic focus	5.83	0.8	0.95
Ventriculomegaly	27.5	0.94	3.8
Increased nuchal fold	23.3	0.8	3.79
Echogenic bowel	11.44	0.9	1.65
Mild hydronephrosis	7.6	0.9	1.08
Short humerus	4.8	0.7	0.78
Short femur	3.72	0.8	0.61
ARSA	21.48	0.7	3.9
Absent or hypoplastic nasal bone	23.3	0.46	6.58

Meta analysis of second trimester markers for trisomy 21; M.Agathokleous et al: Ultrasound Obstet Gynecol 2013; 41: 247-261

How to use the LR at anomaly scan

1. Single marker seen

Use LR for isolated marker

Eg; 30yr Primi

a-priori risk at time of scan, based on age is 1:1000 for DS

Presence of isolated ARSA at anomaly scan - Background risk increases 3.9 times (LR of isolated ARSA)

Calculated risk = 1000/3.9 = 256. So her new risk is 1:256

2. Multiple markers seen

Calculate new LR as follows:
LR of markers seen (LR+) X LR or markers not seen on scan (LR-)

Eg; 30yr Primi

a-priori risk at time of scan based on age and first trimester screening (NT +BC) is 1:10,000 for DS
At anomaly scan ARSA and EIF are seen.

New LR is calculated as follows

Positive LR = 21.48 (LR+ ARSA) X 5.83 (LR+ EIF) = 125

Negative LR = Multiply LR- of all other markers = 0.94 X 0.8 X 0.9 X 0.9 X 0.7 X 0.8 X 0.46 = 0.16

New LR = Above Positive LR X Above Negative LR = 125 x 0.16 = 20

Now the risk of DS for this fetus is increased 20 times. i.e. 10000/20 = 500.

Final adjusted risk = 1:500

The above calculations are usually done by the reporting software.

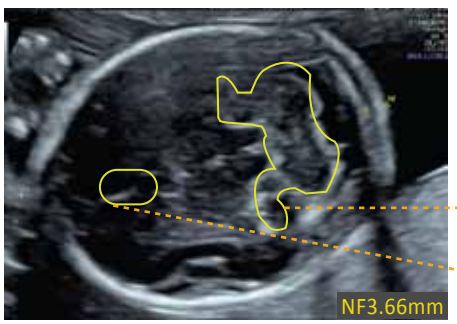
Nuchal Fold

Dr. Satyajit Chowhan
Consultant in Fetal Medicine

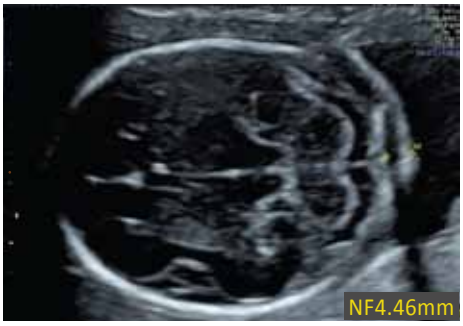
Nuchal fold (NF) is the term given to the skin fold in the posterior aspect of the fetal neck. It is one of the most sensitive and important marker for Trisomy 21 during the second trimester in low and high risk pregnancies. NF is a transient finding which usually resolves over time even in a fetus with Down Syndome. In a given fetus, measurements can vary from time to time within the second trimester.

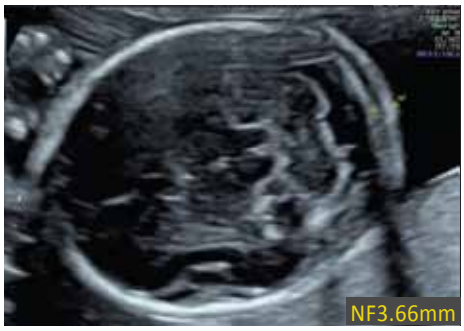
Technique

- Transcerebellar plane – Oblique plane to view CSP and cerebellum in the same plane
- Outer edge of occipital bone to outer skin, in the midline
- Avoid undue pressure on the fetal head



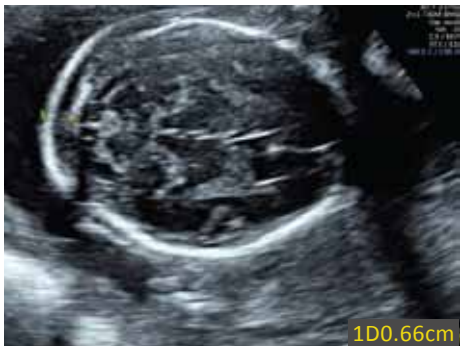
Normal
< 5 mm between 16 - 18 weeks
< 6 mm between 18 - 24 weeks





Incline US beam at an angle of 30° to the fetal head, with the occiput directed upwards. This technique should be adapted in cases of breech presentation, hyperflexed or hyperextended head which may result in a NF measurement either being over or underestimated.

Increased NF can arise de novo in the second trimester or can be a persistent increased nuchal translucency seen in the first trimester.



Increased NF:

- Aneuploidy - LR for Trisomy 21 is 3.79
- Structural defects
- Infections
- Genetic syndromes
- Skeletal Dysplasia

Management of increased NF

Management of increased NF is as given in overview of soft markers (page2).

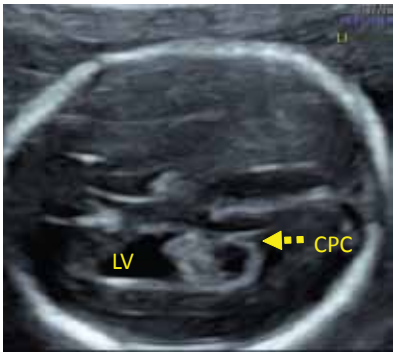
In addition:

- Evaluate for genetic syndromes
- Assess markers for fetal infection like growth restriction, hyperechogenic bowel, oligoamnios, ventriculomegaly
- Maternal serum screening for cytomegalovirus, toxoplasmosis & parvovirus B19
- Follow up scans in the third trimester particularly to assess for pulmonary stenosis which can be associated with Noonan syndrome.
- Note evolution of NF

Choroid Plexus Cyst (CPC)

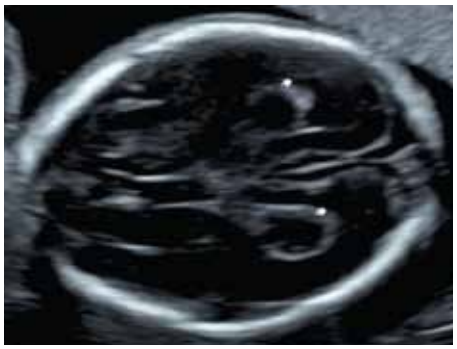
Dr. Poornima A.V
Consultant in Fetal Medicine

Choroid plexus cyst (CPC) is a small fluid filled structure within the choroid of the lateral ventricle of the fetal brain. Choroid produces cerebrospinal fluid (CSF). The cyst forms as a result of the CSF being trapped within the folds of the neuro-epithelium.
CPC is not a structural or functional abnormality in the brain

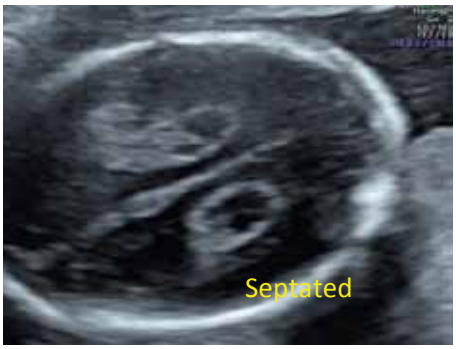


Diagnosis

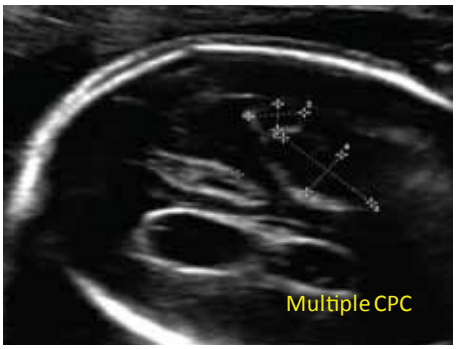
- Transverse plane of the fetal head
- Clearly visualise lateral ventricles (LV)
- CPC appears as a well defined round anechoic area within the choroid plexus
- Most often < 1cm in diameter
- Assess both the lateral ventricles
- Maybe single/multiple, unilateral/bilateral,
- unilocular/septated



Bilateral CPCs



Septated



Multiple CPCs

Cystic spaces < 2.5mm size should be considered as "mottled" choroid and unlikely to be significant.

Associations

- Normal variant: 1-3%
- Associated with Trisomy 18
  - 30- 50% of Trisomy 18 have CPC
  - 80% of Trisomy 18 will also have other structural abnormalities
  - CPC + minor US marker = 20% risk of T18
  - CPC + major US marker = 50% risk of T18
  - Likelihood Ratio for Trisomy 18 is 9
  - Number & size of cysts, does not influence the risk
  - Isolated CPC has no association with T21 unless other T21 markers are seen. LR is 1.0

More than 90% resolve by 28 weeks. Even if they do persist, they are asymptomatic. Resolution of the cyst does not alter the background risk of Trisomy 18. The management is as outlined in overview of soft markers (page 2).

Isolated CPC unilateral or bilateral (particularly with normal hands) in low risk does not require follow up by ultrasound or postnatal evaluation.

Ventriculomegaly (VM)

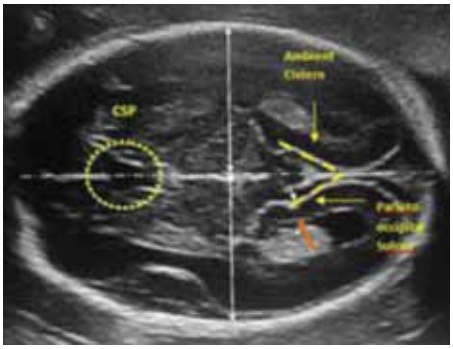
Dr. Kathy Amy Robert
Senior fellow in Fetal Medicine, BFMC

Ventriculomegaly is dilatation of the cerebral ventricles, due to the presence of excess cerebrospinal fluid.

Technique to measure the cerebral ventricle

PLANE:

- Axial plane of the fetal head, with midline falx perpendicular to the ultrasound beam



STRUCTURES TO BE VISUALISED:

- Cavum septum pellucidum seen in the anterior 1/3rd
- V shape of the parieto-occipital sulcus

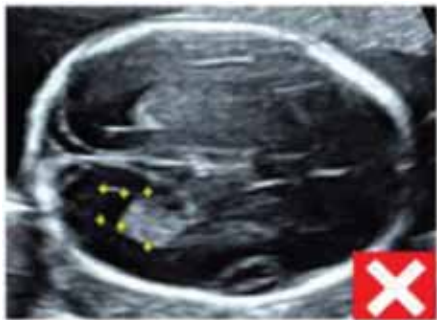
PLACEMENT OF CALLIPERS: "ON to ON"

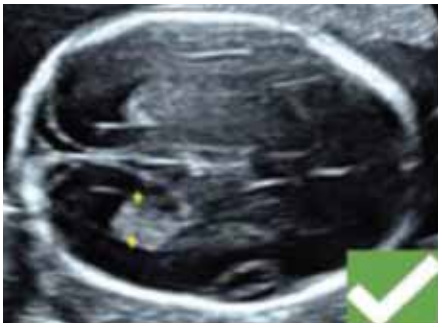
Perpendicular to the ventricle
At the level of the parieto-occipital sulcus
At glomus of Choroid plexus

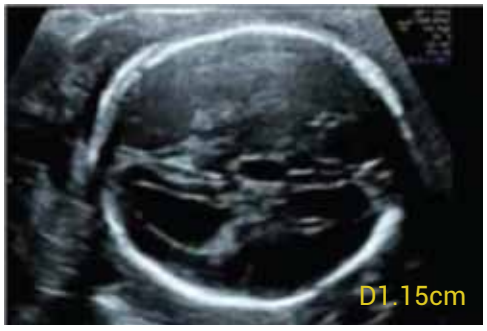
Ventriculomegaly

Interpretation:
Normal: < 10 mm
Ventriculomegaly: > 10 mm
Mild/ Borderline: 10 - 15 mm
Severe/ Overt: >15 mm

• Unilateral - 60% • Bilateral - 40%







Associations

- Isolated VM - Aneuploidies, especially Trisomy 21 (DR-7.5%) Likelihood ratio is 3.81
- Fetal infections - Toxoplasmosis, CMV
- Other cerebral structural anomalies: Cortical malformations, absence of the septum pellucidum, agenesis of the corpus callosum and agenesis of the cerebellar vermis

Majority of isolated ventriculomegaly are non-progressive. The risk of progression of ventricular dilatation is 15.7%. Anomalies not visible initially are seen in 12.8% fetuses at further assessment pre and postnatally. Outcome of those fetuses with progressive VM is worse than non-progressive VM.

Management of ventriculomegaly is as outlined in overview of soft markers (page 2). In addition, maternal serum testing for cytomegalovirus and toxoplasmosis is recommended. If positive, consider fetal infection testing by PCR method, in the same amniotic fluid sample sent for fetal karyotyping.

- Repeat ultrasound to assess the evolution of VM. There is no agreement regarding the timing and frequency of follow-up; fortnightly assessment is usually practised
- MRI maybe offered to look for additional abnormalities in the fetal brain preferably after 28 weeks as some migration anomalies cannot be visualised on the ultrasound scan
- Postnatal work-up to rule out additional abnormalities of CNS
- Follow-up of developmental milestones

Neurodevelopmental Outcome in Isolated Ventriculomegaly

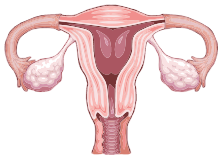
LV 10 - 12 mm - Normal > 90% of cases
LV > 12 mm - Less favourable
Neurodevelopmental delay - 17% in progressive vs 4% in the non-progression group

SERVICES PROVIDED AT BFMC CLINIC

- Fetal ultrasound – Viability, NT, anomaly, growth and fetal well-being scans
- First trimester screening: Ultrasound & biochemistry
- Fetal echocardiography
- 3D & 4D scans
- Invasive testing – amniocentesis, chorionic villus sampling, fetal blood sampling
- Intrauterine vascular/peritoneal transfusions & intrauterine shunting operations
- Fetoscopic and other minimally invasive fetal surgery
- Fetoscopic laser ablation for Twin Transfusion Syndrome – 1st team in India to perform
- Non-invasive Cell Free Fetal DNA testing for chromosomal anomalies (blood test)
- Serum Screening by UKNQAS accredited labs – Quadruple test
- Combined Fetal-Genetics Clinic
- Pre-pregnancy Counseling
- Counselling for pregnancy and fetal complications
- High risk obstetrical consultations
- Pelvic ultrasound: Basic to advanced including follicular monitoring and 3D scans.
- Emotional counselling

New from BFMC

"Gynecological Ultrasound Program" (GUP) – Onsite and Online



A comprehensive skill enhancing course pertaining to ultrasound in gynecology.

Onsite course duration: Once a month, five hours' duration, on Sunday (9 – 2 PM), over an 8-month period.

Online course: Coming soon

Faculty

Dr. Priti Venkatesh
OBG Sonologist & Fetal Medicine Specialist

Dr. Supriya Seshadri
OBG Sonologist & Fetal Medicine Specialist

Course design: Interactive lectures encompassing all aspects of gynae US, from basics to advanced. Image submission and correction will be the mainstay of this course.

Onsite course venue: Live relay from Bangalore to 35 locations across the country. Locations available in Sri lanka, Bangaldesh and Nepal as well.

Who can attend: Anyone interested in Gynae ultrasound.

To know more, mail to: gup@bangalorefetalmedicine.com or call Mob +919035 353549

Coming soon: 5th Fetal Ultrasound Program (FUP)

An in-depth training course in fetal scans, spanning over 12 months, with facilities to live stream from Bangalore to multiple locations. Image submission and correction will be at the core of this course.
Drop a mail to fup@bangalorefetalmedicine.com or call Mob +919035 353549

BANGALORE FETAL MEDICINE CENTRE

Bangalore Fetal Medicine Centre (BFMC) was set up in 2004 with the aim of providing fetal ultrasound in line with international guidelines and principles. The centre offers a wide range of services, basic to highly advanced, pertaining to Fetal Medicine, Genetics and Gynecological ultrasound. BFMC also provides training in Fetal Medicine, both onsite and online.

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Next issue

- Nasal Bone
- Echogenic Intracardiac Focus (EIF)
- ARSA
- Mild hydronephrosis
- Echogenic bowel
- Short femur/humerus

Our Partner

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