ISSUE 2, JULY 2016

fetologue

SOUND TALK WITH THE UNBORN

BANGALORE FETAL MEDICINE CENTRE

FROM THE DESK

Greetings from BFMC.

Thank you for the overwhelming response to our first newsletter titled "Genetics for all".

In this issue we have attempted to cover all aspects of fetal care in the first trimester, and which can be implemented in routine practice.

To quote Ian Donald, a pioneer in obstetrics ultrasound - "We are particularly interested in studying the first 12 weeks of intrauterine development which are even more interesting than the last 12 weeks. It is surely the most crucial period in any being's existence..."

We hope you find this issue informative and useful.

INSIDE VIEW

Kypros Nicolaides who gave us invaluable insights into the first 12 weeks of the fetus

Kypros Nicolaides, "The miracle maker for NHS's tiniest patients", "Father of fetal medicine" is indeed a legendary figure in the field of fetal medicine. Fondly known as "Prof" by his trainees, his name is synonymous with all aspects of the fetus, right from diagnosis to therapy. Having trained several doctors across the globe, he shares a personal rapport with every single trainee who in turn is almost always in awe with his persona. The mothers on whom he performs the scan/ procedure are totally at ease in his presence, enthralled by his "quick chat" which also reveals his inimitable sense of humour. His professional supremacy is very evident when he performs complicated procedures on the fetus where in; his technical finesse, excellent training skills and patient wellbeing come to the fore all at the same time.

Prof, as I refer to him, has an obsession with research and publishing. He has published more than 1000 articles, several books and monologues, and probably has the highest number of publications by any person in the medical field. Unknown to many, Prof has a keen interest in world politics and history. His uncompromising pursuit of scientific truth has led to immense benefits for the fetus and mother, across the world.

Dr. Prathima Radhakrishnan: *Director & Consultant in Fetal Medicine - BFMC*

DATING IN FIRST TRIMESTER

Dr Saket B Thakar *(Fellow in Fetal Medicine – BFMC)*

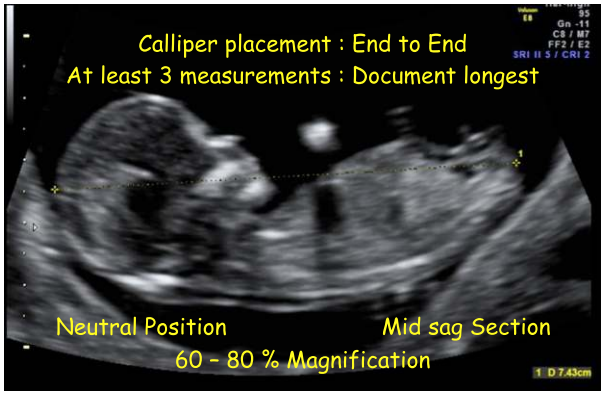
- First-trimester CRL : Best parameter for determining gestational age (GA)
- If more than one first-trimester scan with a MSD or CRL measurement is available, the earliest ultrasound with a CRL equivalent to at least 7 weeks (or 10 mm) should be used to determine the gestational age

Very early gestations: Embryo is relatively small, hence measurement errors have a more significant effect on GA assessment

Contd.

Early pregnancy

NT scan



Mid sagittal section

- Head in line with full length of the body
- Echogenic tip of the nose
- Rectangular palate
- CRL axis : 0^0 - 30^0 to the horizontal
- Clearly defined crown & rump

Neutral position

- Fluid pocket: Between fetal chin & chest
- Nasal tip: At or above the level of anterior abdominal wall

FIRST TRIMESTER SCREENING FOR ANEUPLOIDIES

Dr Saket B Thakar *(Fellow in Fetal Medicine – BFMC)*

"Every pregnant woman should have the opportunity to receive the best possible estimate of her personal risk for fetal aneuploidy". **Position statement from the Aneuploidy Screening Committee on behalf of the Board of International Society for Prenatal Diagnosis (ISPD).**

"Pregnant women may be offered screening for Down syndrome. These tests are recommended wherever possible, and not mandatory as there may be financial and logistic problems in these tests being made available everywhere, especially in remote rural areas."
FOGSI – ICOG Good clinical practice recommendations: Recommendations for routine antenatal care for healthy pregnant women; Refer 1.7.2.1 – Screening for Down Syndrome

The purpose of first trimester screening (FTS) is to assess a woman's risk for fetal aneuploidy, mainly Down syndrome (Trisomy 21), Trisomy 13 and Trisomy 18. Of these, screening for Down syndrome is most significant as other aneuploidies usually present with abnormal ultrasound findings at the nuchal translucency (NT) scan. The subcutaneous accumulation of fluid behind the fetal neck in the first trimester of pregnancy is measured as NT.

Protocol for FTS with detection rates for T21, for a 5% false positive rate

- **Combined screen:** NT + FHR + biochemical markers (free β-hCG +PAPP-A)- 85–90%
- **NT alone:** 75-80%
- **Serum biochemistry alone:** 60-70%

Pretest counselling: Nature of the test, possible outcomes and options thereafter.

Optimal Screening

✓ NT scan at 11 - 13^{+6} weeks (CRL 45mm - 84mm)

+

✓ Serum biochemistry: Best 10 - 11 weeks, anytime between 9 - 13^{+6} weeks (CRL >35mm)

Contd.

FTS risk estimate: Low / Intermediate / High

Low risk
<1 in 1000

Proceed to anomaly scan at 18-20 weeks.
Quadruple test (QT) is optional.

Combined FTS + QT: DR - 92-95%

Intermediate risk
1 in 251 - 1 in 1000

Fetal US markers:
- Nasal bone
- Tricuspid flow
- Ductus venosus flow

→ Low risk (See above)
→ High risk (See below)
→ Intermediate risk

↓

QT + Genetic Sonogram (18-20 weeks)

High risk >1 in 250

↓

First trimester anomaly scan

Counsel

Normal

Abnormal

Non-invasive prenatal testing (NIPT)
~Cell free DNA

CVS - definitive test
~Miscarriage risk : 1 in 250

Low risk
- Anomaly scan (18-20 weeks)

High risk

→ **Amniocentesis** - definitive test
~Miscarriage risk: 1 in 250

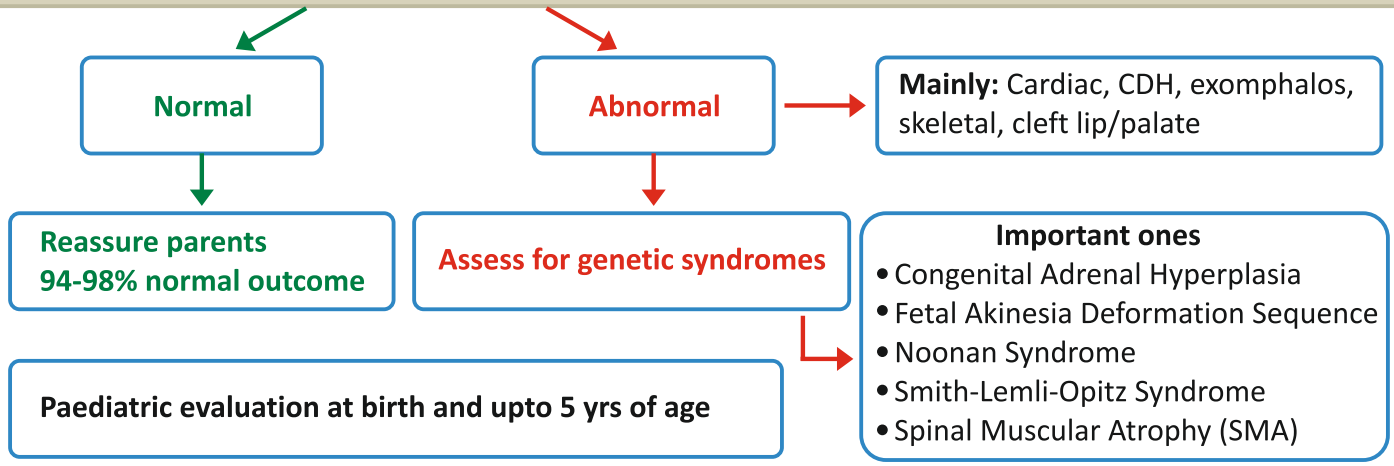
Contd.

High risk >1 in 250

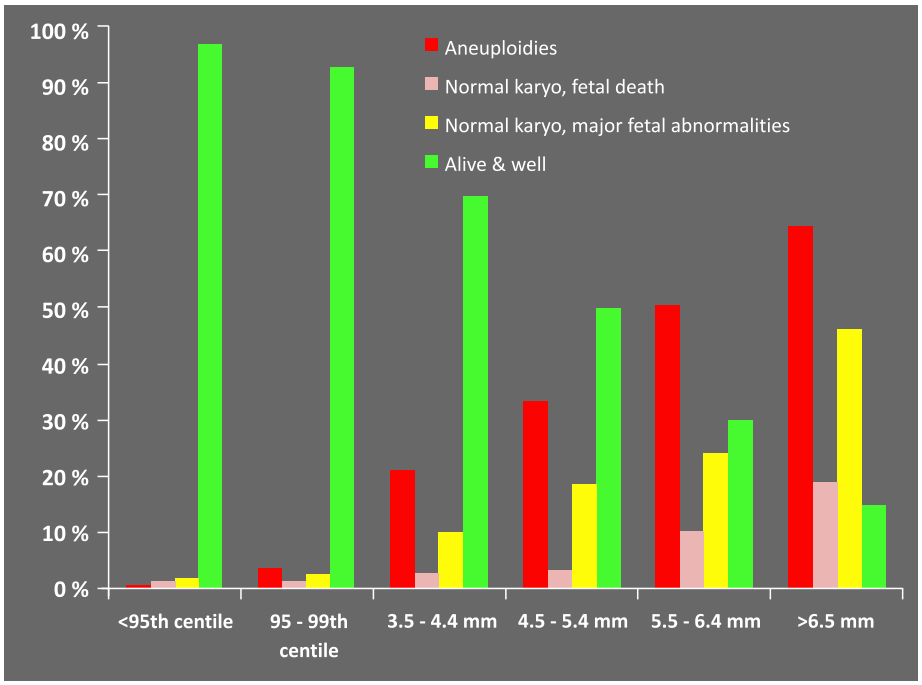
If fetal karyotype is normal and NT is below the 99th centile, the woman should be scheduled for a detailed anomaly scan at 18-20 weeks, including a fetal echocardiography.

If the fetal karyotype is normal and NT is above the 99th centile, the woman should have an early anomaly scan at 16 weeks. At this scan assess:

1. Fetal viability
2. Fetal morphology: If structural abnormalities are found, assess for possibility of genetic syndromes.
3. Evolution of NT
   a. Resolves
   b. Nuchal edema/ hydrops
   i. Maternal blood – Toxoplasmosis, CMV and parvovirus B19
   ii. DNA analysis to rule out genetic syndromes, especially if there is a family history.
4. In addition, the woman should have a detailed anomaly scan (18-20 weeks), including fetal echocardiography.



- If unexplained nuchal edema is present at anomaly scan, schedule follow up scans every 4 weeks. Parents should be counselled that there is a 10% risk of evolution to hydrops and perinatal death or a live birth with a genetic syndrome.



FMF(2004): The 11- 13^{+6} weeks scan

Increased NT and long term neurodevelopmental outcome

✓ NT < 99th centile: Neurodevelopmental outcome is same as the general population
✓ NT > 99th centile: <1 % risk of mental retardation and ASD (Autism Spectrum Disorders)

Role of the Obstetrician

✓ Recommend FTS
✓ Ensure that tests are carried out as per standards
✓ Maintain a follow-up regarding the antenatal course and outcome of pregnancies that have undergone FTS

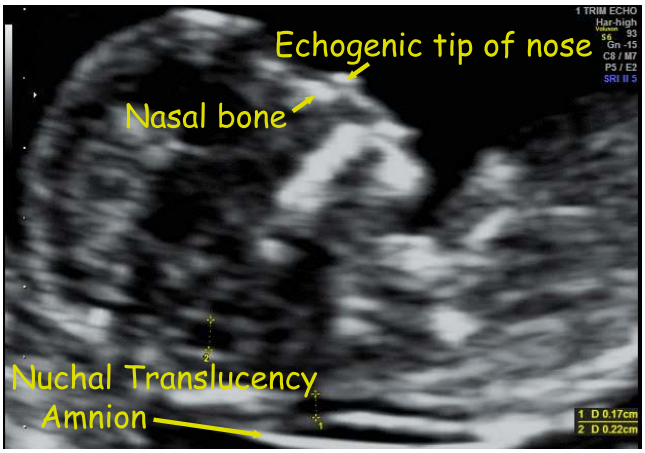
THE NT IMAGE

Dr Kavyashree K.S *(Senior Fellow In Fetal Medicine - BFMC)*

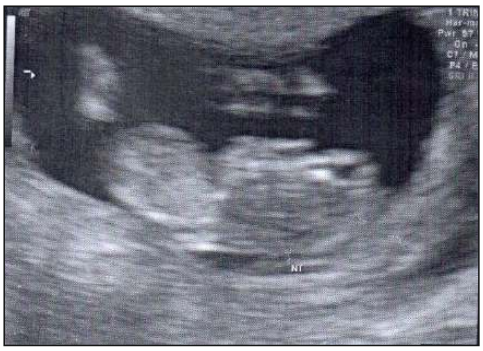
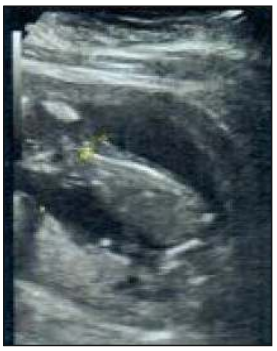
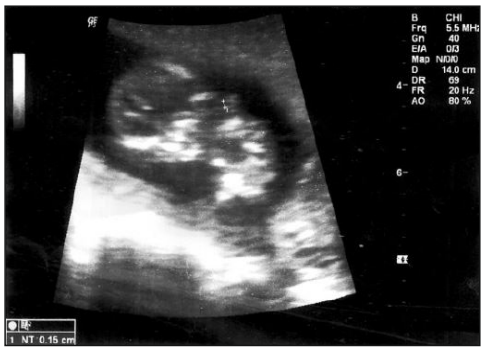
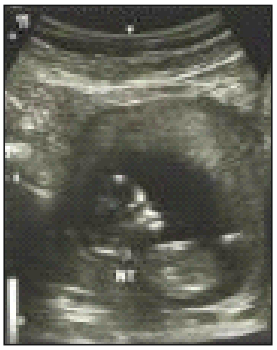
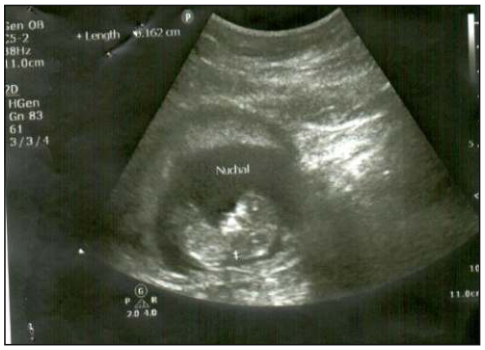
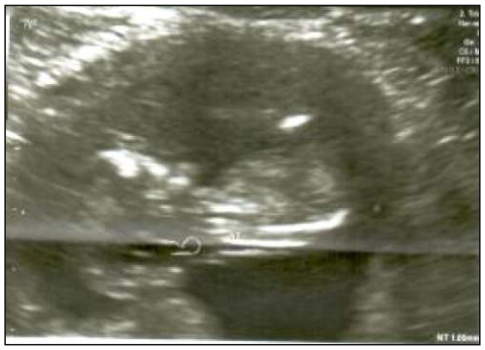
Correct NT image

The Fetal Medicine Foundation

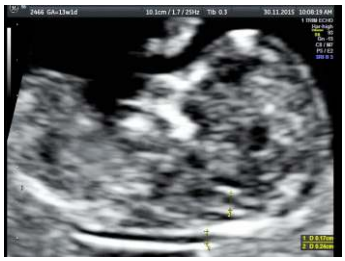
- **11 – 13^{+6} weeks or CRL 45 – 84mm (Ideal time – 12+ weeks)**
- **75% magnification** –Head & upper thorax ONLY
- **Mid sagittal view**
- Neutral position – Head in line with the spine
- **Fetal skin away** from amnion
- Measure **MAXIMUM** lucency
- **Caliper placement** – "+" - "Inner to Inner"



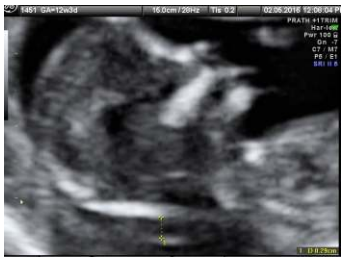
Grossly incorrect NT images

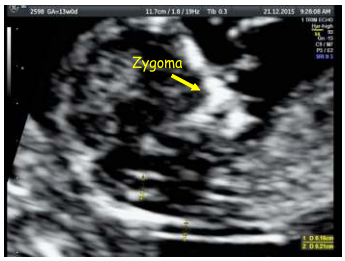
Wrong NT images



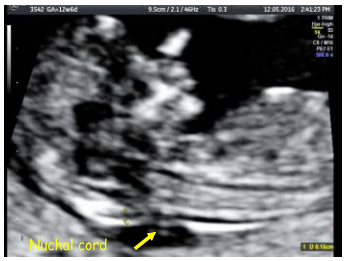
Flexed head
Falsely low NT



Extended head
Falsely high NT



Zygoma is seen – plane not midsagittal



Wrong measurement – not measured on either side of the nuchal cord

FIRST TRIMESTER BIOCHEMICAL SCREENING

Dr Rashmi Vasanth *(Consultant In Fetal Medicine -BFMC)*

First trimester biochemical screening involves measuring two proteins in the maternal serum which are produced by the placenta, and referred to as biochemical markers.

- ✓ Free β-human chorionic gonadotrophin (free β-hCG)
- ✓ Pregnancy associated plasma protein A (PAPP-A)

The measured levels are converted to MoM (multiples of the median) values to overcome gestational age dependant variation of the values. In general MoM of 1.00 is normal, a value of >2.00 is elevated and a value of <0.50 is reduced. It is important that gestational age is accurately known.

Timing: Best 10 - 11 weeks, anytime between 9 – 13^{+6} weeks

Aneuploidy	Free β-hCG (MoM)	PAPP-A (MoM)	Detection rate (%)
Trisomy 21	2.15	0.15	90
Trisomy 13	0.50	0.25	90
Trisomy 18	0.28	0.18	89
45,X	1.11	0.49	≥90
Triploidy, maternal	0.18	0.06	≥90
Triploidy, paternal	8.04	0.75	≥90

Interpretation

Screen positive: Above a cut-off of 1:250, which is laboratory-specific
Screen negative: Below 1: 250

Contd.

If a pregnancy is screen positive for Trisomy 18 and Trisomy 21, it is termed as double-positive. Studies have shown that such pregnancies have a higher risk of fetal abnormalities, preterm birth and lower birth weight.

Factors influencing FT hormones that should be considered in risk assessment

Factors	Free β-hCG	PAPP-A
Increasing gestational age	↓	↑
High BMI	↓	↓
Twins	↑	↑
Assisted conception	↑	↓
Multipara	↑	↑
Smoking	No difference	↑
Vanishing twin – empty sac	No difference	No difference
Vanishing twin – fetal pole +	No difference	↑

No effect: Diabetes, previous aneuploidy

Low PAPP-A < 0.42 MoM

Outcome	Odds ratio (OR)
Birth weight < 3%ile	3.7
Preterm birth < 34 wks	2.4
Pre-eclampsia	3.7
Fetal loss < 24 wks	3.3
Fetal loss > 24 wks	1.9

Low free β-hCG < 0.41 MoM

- ✓ Increased risk of early fetal loss < 24 wks
- ✓ Association with IUGR less clear, less pronounced (OR 1.55)
- ✓ No evident association with preeclampsia or preterm birth

Neither high free β-hCG nor high PAPP-A have an association with adverse pregnancy outcomes.

There are no randomised trials evaluating the role of interventions in women found to have abnormal first trimester biochemical markers. Also there is no consensus on how such pregnancies need to be managed.

The recommendation by Society of Obstetricians and Gynaecologists of Canada Genetics Committee is as follows: "Obstetricians establish a care plan that takes into account the risks specific to individual patients. This plan may include enhanced patient education (eg, signs and symptoms of preterm labor and preeclampsia, recognition of decreased fetal movement), ultrasonography to assess fetal growth and amniotic fluid volume or cervical length, second trimester uterine artery Doppler examination to detect uteroplacental vasculopathy, and fetal surveillance (eg, biophysical profile, umbilical artery Doppler)"

TARGET 9 – FIRST TRIMESTER ANOMALY SCAN (FTAS)

Dr Anitha Shettikeri *(Consultant In Fetal Medicine -BFMC)*

- Early reassurance, early detection & genetic diagnosis
- DR: 18 – 71%, BFMC DR – 54%

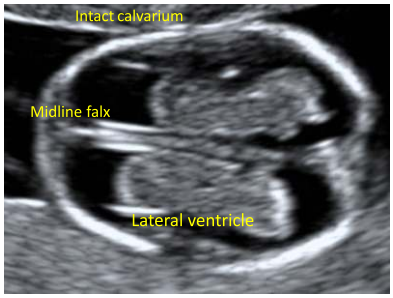
- Should FTAS be offered to all ?
  - ✓ NT < 2.5 mm - 32% of major abnormalities
  - ✓ Women < 35 yrs - 45% of major anomalies

  Hence there is a role in low and high risk group

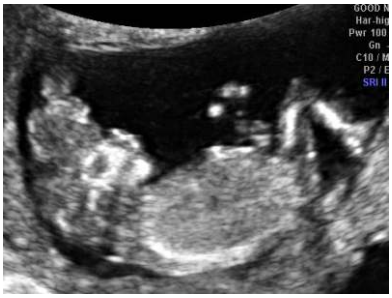
- First trimester scan includes detection of gross fetal malformations – *ISUOG practice guidelines for first trimester screening in 2012*
- Embryonic/fetal anatomy appropriate for first trimester should be assessed - *AIUM 2012*

- TAS and TVS are complimentary to each other

NORMAL



ACRANIA/EXENCEPHALY

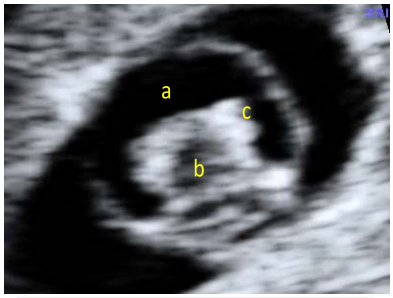


Partial/complete absence of cranial vault after 11 weeks

- ☞ **Acrania**-brain present, appears normal
- ☞ **Exencephal**-brain present, appears distorted/disrupted
- ☞ **Anencephaly**-brain absent, ill-defined heterogenous mass above level of orbits (necrotic brain tissue)

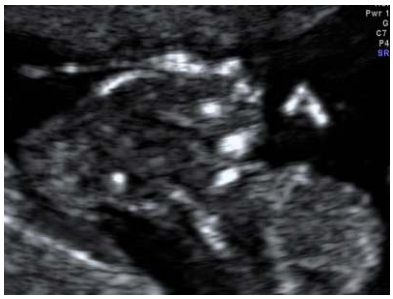
Specifically look for frontal bone ossification in axial & coronal planes

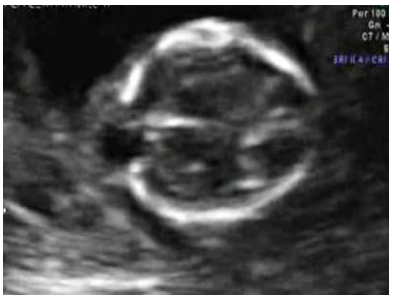
HOLOPROSENCEPHALY



- Absent falx
- Absent butterfly sign
- Large sickle shaped single cerebral ventricle[a]
- Fused thalami[b]
- Crescent-shaped frontal cortex[c]

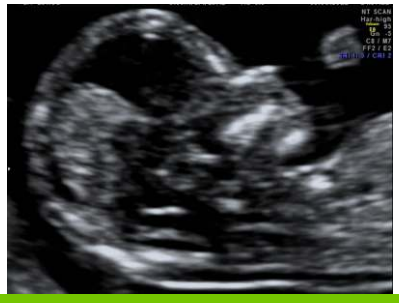
OCCIPITAL ENCEPHALOCELE



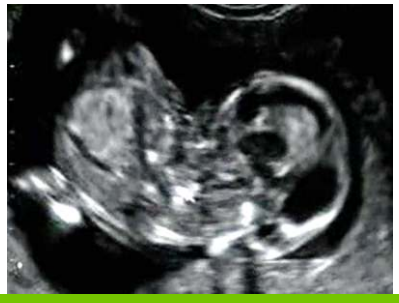


- Bony defect in skull with protrusion of a sac consisting of intracranial contents - "Bun" appearance
- D/D cystic hygroma – Intact occipital bone

NECK – NORMAL ALIGNMENT



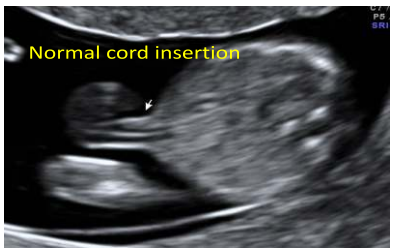
INIENCEPHALY

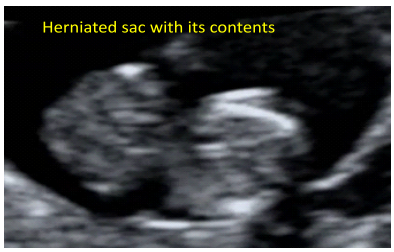


- Persistently hyperextended head
- Unable to measure CRL
- No distinct separation between head and body, posteriorly
- Abnormally short & deformed spine

Contd.

EXOMPHALOS

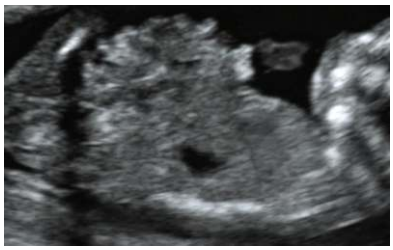




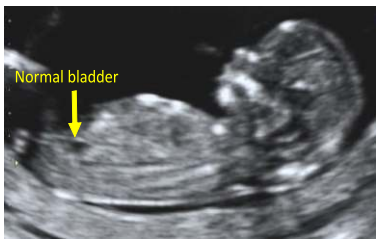
- Sac containing intestines, protruding through the fetalabdominal wall in the midline
- Umbilical cord insertion usually at the apex of the sac

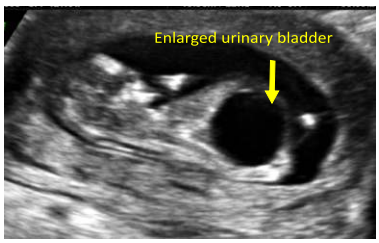
GASTROSCHISIS

- Free-floating cauliflower shaped mass (intestines) protruding through the fetal abdominal wall
- Umbilical cord is usually inserted, usually to the right of the intestinal mass



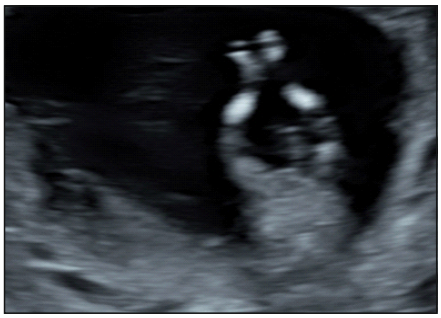
MEGACYSTIS

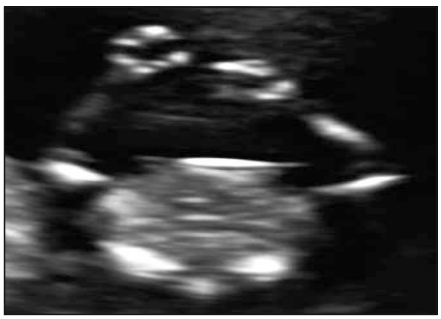




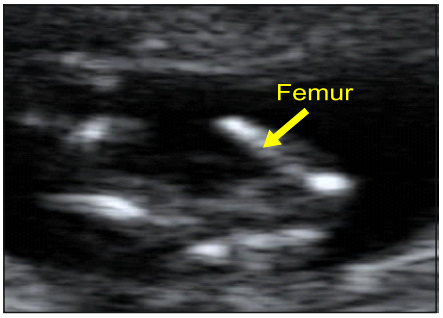
- Bladder largest longitudinal diameter > 7 mm
- Bladder measurement > 10% of CRL for any given gestational age – suspicious

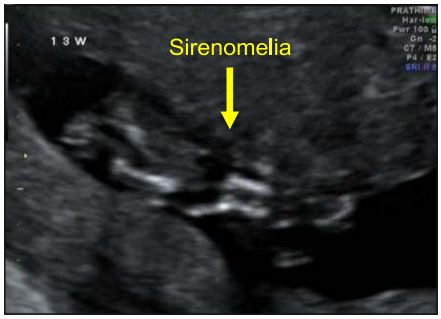
NORMAL LIMBS

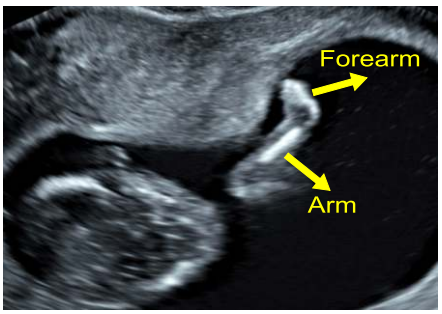




MISSING SEGMENTS / FUSED LIMBS

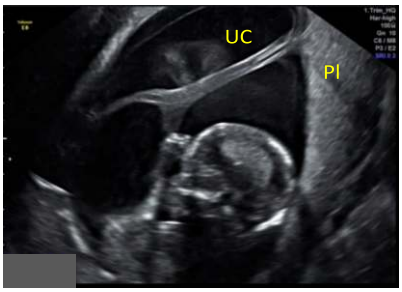






Fused lower extremities of the fetus resembling a mermaid's tail

BODY STALK ANOMALY



- Abdominal wall defect
- Kyphoscoliosis
- Short umbilical cord

CHORIONIC VILLUS SAMPLING

Dr Smita Dhengle *(Fellow in Fetal Medicine - BFMC)*

Chorionic villus sampling (CVS) involves aspiration of placental tissue. Chorionic villi are an excellent source of fetal DNA, and representative of the genetic make-up of the fetus

Indications

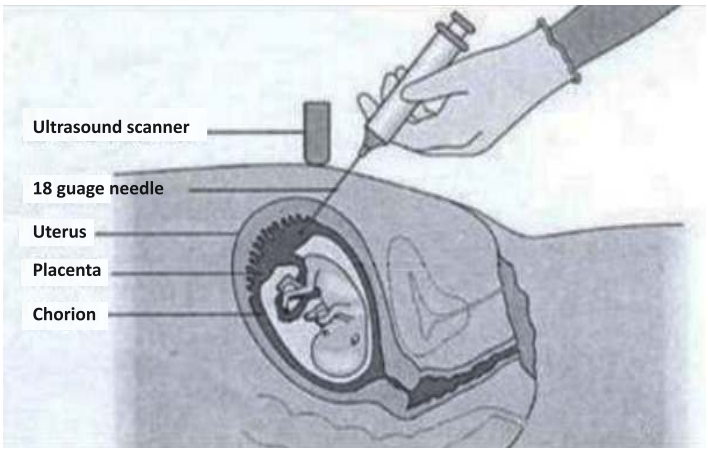
- ✓ High risk for aneuploidy based on first trimester screening or anatomic abnormality on ultrasound
- ✓ Chromosomal abnormality in parents/ previous pregnancy
- ✓ Genetic conditions where gene mutation analysis is available from index child/parent (H/O metabolic disease & hemoglobinopathies)
- ✓ DNA extraction and storage

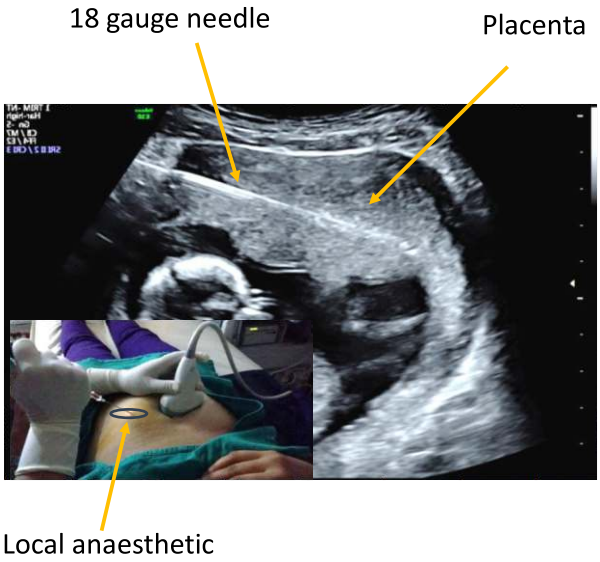
Timing of CVS: 11 -13^{+6} weeks

- ✓ < 11 weeks: difficult to perform (small uterus/ thin placenta), risk of limb reduction defects
- ✓ > 14 weeks: Laboratory issues with growing of cells in the media leading to delay in diagnosis. This can be circumvented by performing FISH/PCR analysis on the same tissue

Requisites

- ✓ Written informed consent, including risk of procedure related miscarriage
- ✓ Fill section "C" of Form F and Form G of PCPNDT
- ✓ Prophylactic antibiotic is given in some institutions
- ✓ Ultrasound guidance throughout the procedure
- ✓ If Rhesus negative, then Anti D must be administered post CVS





Complications

- Procedure related risk of miscarriage: 1 in 250
- Vaginal spotting/bleeding – very rare
- Intrauterine infection risk < 0.2%
- Laboratory failure rate: 1 – 2%
- Maternal cell contamination < 1%

Services provided at BFMC

- 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
- Combined fetal-genetics clinic
- Pre-pregnancy counselling
- Counselling for pregnancy and fetal complications
- High risk obstetric consultations
- Pelvic ultrasound: Basic to advanced including follicular monitoring and 3D scans

TRAINING AT BFMC

"Knowledge is a commodity to be shared. For knowledge to pay dividends, it should not remain the monopoly of the selected few."

The Fellowship programs at BFMC impart the best training in fetal medicine, and have been in effect since 2006. The courses are designed to expose the trainee to all aspects of fetal medicine and genetics, at the end of which he/she will acquire expertise in fetal scans as per international standards and guidelines, in-depth and superior counselling skills, as well as proficiency in performing fetal procedures depending on which course the trainee opts for. In addition, the trainee will be exposed to several advanced fetal interventional procedures.

Courses are for a duration of 1 year (Fellowship in Fetal Ultrasound) and 2 years (Fellowship in Fetal Medicine).

The 2 year course in addition to practical training in fetal medicine is aimed at enhancing the research and academic skills of the trainee through data evaluation, publication of the same in reputed journals, as well as presentations at conferences regional, national and International. At the end of the 2 year course the trainee will have obtained the FMF, UK certificates of competence in the 11-13 weeks NT scan, 18-23 weeks anomaly scan, cervical assessment, Fetal echocardiography, Doppler ultrasound and invasive procedures. Notably in this course the trainee will gain tremendous confidence in taking independent charge of scan units at the various centres affiliated to BFMC.

All trainees graduated from BFMC have made a mark in big and small cities alike.

Besides the Fellowship courses, BFMC also offers an observer course for 2 weeks. This will help the observers update themselves to the latest knowledge in fetal medicine.

If you wish to know more, kindly e-mail to secretary@bangalorefetalmedicine.com

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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.

For appointment at Genetics Clinic
Call: +91 9243 76 76 63 (24hrs), 9448894219 (9-5pm)
Online: Qikwell appointments I Email: drmbhat@chg.res.in

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