Greetings from BFMC

We are delighted to share with you our new education portal www.fetalandgynaieimaging.com. The newsletter will continue to bring you practical knowledge in Fetal Medicine, which will come in handy in your daily practice.

The significance of soft markers noted at the mid trimester anomaly scan was the highlight of our previous issue. This issue will be a continuation and culmination of the same.

### Approach to US Soft Markers in the second Trimester

**STEP 1** – When a soft marker is identified at the anomaly scan, diligently search for other soft markers and structural abnormalities in the fetus, including the fetal cardia.

**STEP 2** – Calculate the risk of aneuploidy i.e Trisomy 21 based on likelihood ratios. This risk is calculated against a background risk based on maternal age alone or in combination with first trimester screening (NT + maternal serum biochemistry), or second trimester maternal serum screening (quadruple test).

**STEP 3** – Counsel
- Low risk – < 1 in 250
- High risk – > 1 in 250

The option for fetal karyotyping is open to either risk group, as the above protocol is a screening protocol and is not diagnostic, however meticulous the scan has been performed. When a detailed scan has been performed, the absence of soft markers confers a 7.7 fold reduction in the risk for Trisomy 21. Eg: If the background risk for Trisomy 21 is 1 in 500, the risk is reduced by 500 X 7.7. The new risk is 1 in 3850.

If a soft marker has been detected and there is no LR assigned to it, follow step 1. In the presence of other risk factors such as advanced maternal age, high risk on serum biochemistry, or 2 or more soft markers counsel for fetal karyotyping.

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

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

### Nasal Bone

The fetal nasal bone is an established soft marker for screening for Down Syndrome (Trisomy 21).

In Trisomy 21 there is a delayed maturation of the ossification centre in the nasal bone. In these fetuses the nasal bone might develop after 24 weeks and some as late as 6-8 years. Absent/ hypoplasia of the nasal bone(s) produces the typical flat facial profile.

1. **Absent nasal bone**: Uni/bilateral (each nasal bone has an independent ossification centre)
2. **Hypoplastic nasal bone**: Uni/bilateral
   - Subjective - shorter, thinner, less echogenic
   - Objective – various parameters
     - Single pre-defined threshold ≤2.5mm
     - Gestational age-based threshold: <2.5th or 5th centile, specific to the population studied.
     - Nasal bone length < 0.75 MoM. This is superior to all other measures of hypoplasia
   - BPD/NB: >9 to >12 – abnormal
   - NB present on one side, absent on the other side – Consider as nasal bone present

A true mid-sagittal view will demonstrate the suture between the two nasal bones which will give an incorrect impression of an “absent nasal bone”.

### Interpretation

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NBL can be calculated specific to GA online by using this link - http://perinatology.com/calculators/Nasal%20bone.html

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[Images of ultrasound images showing hypoplastic and absent nasal bones]
Parents need to be informed that absent/hypoplastic nasal bone has no bearing on the function of the nose.

Majority of the euploid fetuses with absence of the nasal bone in the 2nd trimester are likely to be normal. However, rarely certain genetic syndromes associated with a flat facial profile can be diagnosed later in the pregnancy. Hence, a follow up scan at 30 – 32 weeks with specific attention to the facial profile may be considered, particularly when there are other risk factors for the same.

### Absent Nasal Bone (%)

<table>
<thead>
<tr>
<th>Category</th>
<th>Absent Nasal Bone (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euploid fetus</td>
<td>0.3 to 0.7</td>
</tr>
<tr>
<td>Trisomy 21</td>
<td>30 – 40</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>45</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>53</td>
</tr>
</tbody>
</table>

### Echogenic Intracardiac Focus

An echogenic intracardiac focus (EIF) is a discrete echogenic area within the cardiac ventricle, with brightness equivalent to that of a bone. These echogenic foci have been referred to as ‘golf balls’ or ‘peas’ or ‘bright reflectors’.

EIF represent microcalcification and fibrosis of the papillary muscle or chordae tendinae. They are not associated with myocardial dysfunction or cardiac structural abnormalities, and often disappear later in pregnancy or postnatally.

- Usually seen at mid-trimester scan but can be seen as early as 12-13 weeks
- Left ventricle - 88%, right ventricle - 5%, bilateral - 7%
- Not attached to the ventricular wall
- Single or multiple
- Size: 1-4 mm

#### Diagnosis

- 4 chamber view of fetal cardia, preferably in apical and basal views.
- In the subcostal four chamber view it may be hidden in the specular reflections of the ventricles.
- As bright as bone.
- Turn the gain down. If EIF disappears at the same time or after bone then it is a true EIF.
- If the echogenicity is less than bone, of if no defect is seen on color flow views then it is unlikely to be an EIF.
- EIF does not produce acoustic shadows.
Aberrant right subclavian artery (ARSA) is one of the abnormalities of the aortic arch. It has been included as a soft marker for aneuploidy screening in the second trimester since 2005. In the second trimester the detection rate for ARSA is 98%.

Association
- 4–7% of euploid fetuses
- 30% in fetuses of Asian mothers
- 21-28% of fetuses with Down syndrome
- Other aneuploidies: 16% of fetuses with Trisomy 13. However, such fetuses have other associated anomalies and hence isolated EIF is unlikely to increase the risk for the same
- LR for isolated EIF is 0.95
- Isolated EIF does not increase the risk for T21 in “low risk” groups (as determined by combined first trimester or second trimester screening)
- EIF is not associated with any structural or functional abnormality of the heart. A fetal echocardiogram or follow-up ultrasound is not recommended

False EIF is due to specular reflection. Unlike a true EIF which is found in the region of the papillary muscle, a false EIF is found near the moderator band. A true EIF can be seen from more than one angle where as a false EIF is dependent on beam direction.

Aberrant Right Subclavian Artery (ARSA)

Aberrant right subclavian artery (ARSA) is one of the abnormalities of the aortic arch. It has been included as a soft marker for aneuploidy screening in the second trimester since 2005. In the second trimester the detection rate for ARSA is 98%.

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Consultant in Fetal Medicine

Andrew Averyanov et al, TheFetus.net
Normal RSA

- Transverse plane – 3 vessel tracheal view
- Fetal spine at 3 or 9 ‘o’clock
- Appropriate color Doppler settings – Low PRF
- Vessel arising from aortic arch & running a tortuous horizontal course in front of the trachea towards the right, under the clavicle

ARSA

- ARSA seen at level of three-vessel view
- Runs behind the trachea, towards the right

Prevalence

- Normal individuals: 1–2%
- Trisomy 21: 28 - 37%
- Normal karyotype with congenital heart disease: 3%

Association

- Trisomy 21: LR for an isolated ARSA is 3.9, hence isolated ARSA increases the a priori risk for Trisomy 21 by almost 4 times
Trisomy 18: 12 fold increase in risk
22q11 microdeletion
Possible inherited malformation. Incidence of maternal and fetal ARSA has been reported to be close to 1 per 10,000
Rarely dysphagia may result if ARSA is between the esophagus and fetal spine

Management
- As in any soft marker detection of ARSA should be followed by a detailed anomaly scan, fetal echocardiography and also note additional markers of 22q11 microdeletion (e.g. thymic aplasia)
- Fetal karyotyping including analysis for 22q11 microdeletion is recommended in presence of additional markers, and when the background risk for chromosomal abnormalities is high
- There is insufficient evidence to recommend fetal karyotyping in cases with isolated ARSA, when risk estimate by calculation is low
- Enquire about family history of ARSA. Maternal echocardiography may be advisable to exclude familial recurrence of ARSA

Hyperechogenic Bowel

The small bowel is not easily seen in the second trimester scan as it has the same echogenicity as the rest of the fetal abdomen. When the bowel appears as echogenic as bone, it is termed as hyperechogenic bowel (HEB). Bowel becomes echogenic due to the presence of meconium which accumulates secondary to hypoperistalsis, or decreased fluid content of the meconium. HEB is usually focal. It can be multifocal or diffuse.

Assessment
- Transducer frequency – should be 5 MHz or lower. If the frequency is high, the bowel can appear echogenic, but this will not be focal
- If the bowel is suspected to be echogenic, then turn the gain down to the lowest setting at which the bone still appears “white” ie echogenic, and the bowel is also seen

D/D of HEB is meconium peritonitis which is characterised by coarse calcifications and pseudocysts (in cases of bowel perforation meconium leaks into the abdominal cavity and sets off a fibrous reaction which give the appearance of cysts).
HEB can be a normal variant / isolated finding in up to ~70% of cases. It resolves spontaneously in majority of the cases.

**Pyelectasis** refers to an anteroposterior measurement of the fetal renal pelvis of > 4mm in the transverse plane, in the second trimester. Few studies have taken a cut off > 5 mm at 20 – 30 weeks, to define pyelectasis. Renal pelvis measurement of > 10 mm is considered “at risk” for structural abnormalities of the urinary tract and a discussion on the same is out of scope for this article which is focussed on pyelectasis as a soft marker for aneuploidy.

Vesicoureteral reflux and sometimes obstruction is the cause of pyelectasis in aneuploid and euploid fetuses.

Isolated pyelectasis is seen in 0.7% of fetuses at 16 to 26 weeks' gestation. It is an isolated finding in Down syndrome in approximately 2% (SOGC 2005).

### **Pyelectasis and aneuploidy**
- Seen in unilateral and bilateral RPD
- Degree of RPD does not significantly change during the antenatal period

### **Recommendations**
- Even as an isolated finding HEB is an indicator for fetal karyotyping
- Maternal serology – CMV, Toxoplasmosis testing is indicated
- Parental carrier status in high risk ethnic groups – Cystic fibrosis (North Europeans and Caucasians). In Indian population, the carrier status for cystic fibrosis is about 1:10,000 to 1:40,000. Alpha thalassemia carrier testing is indicated in women of Southeast Asian and African descent
- Third trimester scan for detection of bowel complications such as intestinal atresia, volvulus, anal atresia and bowel perforation
- Serial growth scans as there is a risk of FGR with HEB

### **Associations**
- Aneuploidy – Trisomy 21, 18, 13, Turners and Triploidy. As an isolated finding, HEB is seen in 9% of fetuses with aneuploidy.
- Adverse pregnancy outcomes - Fetal growth restriction and intrauterine demise
- Intraamniotic bleeding
- Congenital malformations of the bowel
- Cystic fibrosis – risk is 2%
- Congenital viral infections
- Alpha thalassemia
OTHER SOFT MARKERS FOR ANEUPLOIDY

These include:
- Short long bones
- Clinodactyly
- Single umbilical artery
- Sandal gap toes
- Short ears

Except for short long bones (LR 0.6 – 0.7) none of the above soft markers have a LR. Nevertheless their presence must be reported and acted upon (refer page 1) if 2 or more such markers are seen.

Short Long Bones

Short long bones (SLB) refers to a short femur or humerus that is less than the 5th centile for that gestational age.

Short femur and/or short humerus is seen in 24 – 45% and 24 – 54% fetuses with Down Syndrome respectively. It is seen in less than 5% euploid fetuses.

A short humerus is more predictive than a short femur.

When both bones are short it might be reflective of a constitutionally small fetus, and it is important to measure the other long bones as well.

D/D for SLB - Skeletal dysplasia and early onset fetal growth restriction.

Clinodactyly

- Hypoplasia/absence of middle phalanx of 5th finger
- Seen in 21% of fetuses with Down Syndrome and 2.6% of euploid fetuses
- Has a syndromic association (Cornelia de Lange Syndrome, Feingold Syndrome, Roberts Syndrome, Russel-Silver Syndrome, Fanconi anemia)
- Clinodactyly, as an isolated finding has a good prognosis

Single Umbilical Artery (SUA)

Incidence of aneuploidy - 30% (Trisomies 13, 18, 21)

Other outcomes associated with SUA:
- Anomalies – Genitourinary and cardia
- Adverse pregnancy outcomes (15-20%)
  - Miscarriage
  - FGR
  - Intrauterine demise
  - Preterm delivery

SUA, in isolation has a good prognosis.
Sandal Gap

Medial displacement of the great toe, giving rise to a greater than normal space between the first and second toe. Sandal gap is noted in 45% of fetuses with Down Syndrome, but usually not as an isolated finding. It may also be a normal variant and hence it would be important to look at the parents’ toes.

Small Fetal Ear

- Cut off < 10th centile for the gestational age.
- How to measure - Coronal view or parasagittal view of fetal head. Measurement is taken from the superior to the inferior border of external ear.
- Incidence of aneuploidy – 60% Down Syndrome, 80-90% Trisomy 13 and 18 (in combination with other findings)
- When isolated prognosis is good

Normogram for Fetal Ear

http://www.fetalsono.com/teachfiles/EarLengX.lasso
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Skills to obtain the FMF, UK certifications - NT, Anomaly, Doppler & Cervical scans

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ONLINE / ONSITE COURSES

- Fetal Ultrasound Program (FUP)
- Gynae Ultrasound Program (GUP)

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- Fetal Echocardiography
- The First Trimester Scan
- Basic Genetics

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