SOFT FETAL ULTRASOUND FINDINGS

Compiled by the Genetics Team at The Credit Valley Hospital
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This document refers to the ultrasound finding of a soft sign, as compared to a clear cut structural anomaly. There is very little information about outcomes when more than one soft finding is seen on a fetal ultrasound. The information herein refers to isolated soft findings, meaning the ultrasound is otherwise unremarkable.

If the ultrasound is done at a gestation earlier than 18 weeks, a detailed fetal ultrasound around 18-19 weeks can be considered, since visualization of the fetus is better at later gestations, allowing for exclusion of other soft signs, and a better assessment of the original finding. However, in many of the soft ultrasound findings, the natural history is that the sign can disappear, but one cannot fully ignore the original finding.

The impact of Maternal Serum Screening (MSS) or Integrated Prenatal Screening (IPS) in estimating the risk of a true fetal chromosome anomaly in the presence of a soft ultrasound finding is unknown. Only for a choroid plexus cyst has the literature begun to evaluate the contribution of MSS or IPS.

It is important to remember that the risk of a significant fetal chromosome anomaly increases with maternal age. A woman is eligible for prenatal chromosome testing when she is 35 or greater at the time of delivery (32 or older if twins).

Although likelihood risks have been estimated for some of the soft signs, it is important to note that in many of the references below, the women were from high risk categories, potentially inflating the risk estimates. Also, often the number of cases reported is small.

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A small nose and midface hypoplasia are well-recognized clinical features of Down syndrome. Nasal bone ossification has been absent in a significant number of aborted fetuses with DS of varying gestations. This information provided credence to the idea of prenatal first trimester study of the nasal bone as an additional marker for DS.

Required components for nasal bone imaging have been suggested\(^{(2)}\). This includes a mid-sagittal view of the fetus with the fetus occupying most of the image with clear fetal margins.

Several studies have now been published suggesting the absence of the nasal bone in the first trimester is associated with DS. The majority of studies emerge from Cicero et al (Nicolaides group in the UK)\(^{(1)}\). Six important pieces of information have emerged:

- Nasal bone more likely to be absent at earlier gestations. In euploid fetuses with CRL between 45 and 54 mm, the nasal bone was absent in 4.7% cases. At CRL between 75 and 84 mm, the nasal bone was absent in only 1% of cases. Nasal bone assessment should be limited to first trimester fetuses with CRL > 45 mm.
- Data in the studies are from a high-risk pregnancy group. Low risk population yet to be studied. Prefumo et al\(^{(3)}\) suggest nasal bone hypoplasia performs poorly as a marker for DS in an unselected population. This raises the question of its use as a secondary marker rather than a primary marker.
- Examining a high-risk group opting for CVS, the nasal bone was absent in 43/59 (73%) trisomy 21 fetuses and only 3/603 (0.5%) euploid fetuses. If this ultrasound sign is combined with NT and biochemistry markers it is predicted the detection of DS would increase to 93% with the same false positive rate of 5%.
- The same investigators found that absence of the nasal bone is also associated with trisomy 18, trisomy 13, and monosomy X.
- There appears to be an association between absent nasal bone, fetal crown-rump length, and nuchal translucency. In aneuploid pregnancies, nasal bone absence occurs more frequently with increasing NT. When NT was at the 95th percentile or less the likelihood of absent nasal bone was greatest. The likelihood decreased as the NT increased.
- There is a relationship between ethnicity and nasal bone development.

Further evaluation of nasal bone assessment performance in a low risk population must be determined and sufficient adequately trained centres with appropriate educational and credentialing procedures must be available before this can be used as part of provincial screening in Ontario. **However, use of this ultrasound marker as an independent determinant of fetal chromosome testing cannot be ignored in first trimester fetuses with CRL>45 mm.**
References:


2. INCREASED FETAL NUCHAL TRANSLUCENCY 11-14 weeks    February 2008

Nuchal translucency (NT) is the sonographic appearance of a subcutaneous collection of fluid behind the fetal neck. The 95th percentile measurement is 3.0 mm (which advances slightly with gestational age), and 99th percentile measurement is constant at 3.5 mm. **NOTE**: reliability of the measurement is operator dependent. Typically, this measurement is done as part of Integrated Prenatal Screening (IPS) or First Trimester Screening (FTS). Screening using only the NT is to be discouraged. However, if the measurement is significantly increased, it warrants offering counselling.

**Associations**:  
An increased NT per se does not constitute a fetal abnormality. The larger the NT measurement, the greater is the risk of an adverse outcome.

- Chromosome anomalies (50% trisomy 21, 25 % trisomy 13/18, 10% Turner syndrome, 10% other)
- Congenital heart disease (>99th centile -> overall likelihood ratio of 22.5 X population risk, with 1% of screened population ≥ 99th centile, somewhat correlates with the size of the NT
- Single gene conditions, (with or without mental handicap)
- Other anatomic anomalies –Likelihood ratio correlates with size of NT for lethal/severe anomalies,
- Fetal demise – Likelihood ratio = 5 X but does not correlate with the size of the NT

With normal chromosomes, a normal 19 week ultrasound and echocardiogram, and with regression of the NT, there is up to a 95% chance of normal pregnancy outcome, without major malformations.

**Counselling and Management**:  
- Chromosome testing is offered, by CVS if gestation allows, or by amniocentesis. If IPS has been started, the patient can finish the screen, but if the NT is >4 mm, the result will be screen positive. A screen negative result does not rule out fetal trisomy 18 or 21. Chromosome testing includes the offer of microarray analysis if G-banded analysis is normal.
- When gestation allows, the patient can consider an ultrasound at 15 weeks, to assess viability and progression/regression of the finding, before having invasive fetal chromosome testing by amniocentesis.
- Ultrasound at 19–20 weeks gestation to look for fetal structural anomalies
- Echocardiogram of the heart and great vessels at 19-20 weeks if NT≥3.5 mm. If below 99th centile, careful ultrasound, with examination of the great vessels and heart is appropriate.
- Newborn physical examination by a clinician aware of the prenatal ultrasound finding.
References:


Hyett J et al. (1999). Using fetal nuchal translucency to screen for major congenital cardiac defects at 10-14 weeks of gestation: population based cohort study. BMJ 318:81-85.  (See also the accompanying editorial on page 70-71)


SECOND TRIMESTER SOFT SIGNS

1. Choroid Plexus Cyst (CPC)  February 2008

As the choroid plexus develops, the covering epithelium changes and choroidal villi are formed. The spaces between these projections (villi) may be enlarged by fluid or debris to create choroid plexus cysts.

**Natural History:**
- 1-4% of all pregnancies:
- almost all disappear by 28 weeks gestation
- no long term clinical consequences for cerebral development
- size, location and number do not appear to influence outcome

**Association:**
- increased risk of trisomy 18, which becomes significant only for those ≥35 at delivery
- weakly associated with trisomy 21 (Down syndrome)

**Counselling:**
- Maternal age <35, prenatal screen negative – likely risk of trisomy 18 does not warrant invasive testing; however one cannot deny amniocentesis if the patient wishes this.
- Maternal age <35, prenatal screening not done – if gestation permits, consider MSS, see also a) above.
- Maternal age 35 or >, prenatal screen negative - amniocentesis available based on age, amniocentesis should be considered, although most likely the infant is not affected.
- Maternal age 35 or >, prenatal screen not done – amniocentesis is available based on age, amniocentesis should be considered, - if patient is not keen on amniocentesis and if gestation permits, MSS could be undertaken, for if it is screen negative, likely the risk of trisomy 18 is diminished.
- If there are any additional soft signs, referral for counselling and the offer of fetal chromosome is appropriate.

**References:**


2. DROOPING CHOROID (dangling choroid)  

February 2008

The medial wall of the lateral ventricle appears to be separated from the choroid. The normal measurement should be less than 3 mm. The normal size of the lateral ventricular atrial measurement is less than 10 mm.

**Natural History:**

Unknown – often resolves by the subsequent ultrasound.

**Associations:**

There are no clear associations with a recognized adverse clinical outcome. However, there is a small concern this might be the prelude to cerebral ventriculomegaly (which has a clear association with increased adverse outcomes).

**Counselling:**

- Monitor ventricular size and look for other anomalies with ultrasound at 18, 22-23 weeks and 32-36 weeks. If ventriculomegaly (lateral ventricle atrial measurement of 10 mm or more) is subsequently found, further counselling is warranted.

- Amniocentesis - Since there is an association of mild cerebral ventriculomegaly with an increased risk of a chromosome anomaly, amniocentesis can be offered.

**Reference:**

3. MILD CEREBRAL VENTRICULOMEGALY

Mild ventriculomegaly is defined as an axial diameter of greater than 9.9 mm, measured across the atrium of the posterior or anterior horn of the lateral ventricles at any gestation. Sometimes, it is described as a separation of more than 3 mm of the choroid plexus from the medial wall of the lateral ventricle. Ventriculomegaly is distinguished from hydrocephalus where there is an atrial diameter of greater than 15 mm. Hydrocephalus is not considered here.

**Natural History:**

- The prevalence is about 1 in 700 low risk pregnancies.

- Complete information of the natural history of isolated ventriculomegaly is not yet available, since careful long term studies have not been conducted. The size can stay the same or become smaller.

- The majority of children appear to have normal development.

- There is perhaps a 9% chance of cognitive disabilities, which can vary in severity. This can occur even with resolution. There is a suggestion in the literature that those with a smaller increase in the ventricular measurement might have a smaller chance of an abnormal outcome. However, given the lack of appropriate long-term studies, it is suggested the risk of an abnormal outcome be treated with circumspection.

- Progression to hydrocephalus can occur, but the chance of this is not well known. Progression is thought to occur in a minority of cases. There is an increased chance of other cerebral structural anomalies which might not be detectable on an antenatal ultrasound.

**Associations:**

- The chance of a fetal chromosome anomaly is estimated to be 3.8% (0-28.6%). The commonest is trisomy 21. It can be found in single gene disorders or sporadic conditions.

- Ventriculomegaly is weakly associated with fetal infections, most commonly cytomegalovirus (CMV) or toxoplasmosis.
Counselling:

- Detailed ultrasound to assess for other structural anomalies or soft signs, if not already completed.
- Additional ultrasound around 22 weeks, to look for possible progression to hydrocephalus. If persistent, another in the third trimester is suggested. Uncommonly, an MRI can detect additional anomalies, but this is not offered routinely.
- Fetal chromosome testing.
- Initial and convalescent maternal titres for CMV, toxoplasmosis, parvovirus.
- Postnatal assessment for dysmorphic features and neuroimaging, if persistent.
- Postnatal followup of developmental milestones.

References:


4. ENLARGED CISTERNA MAGNA

December 2007

The cisterna magna is a fluid collection posterior to the cerebellum. It is seen as an echo-free triangle with the point oriented towards the cerebellar vermis. Prenatally, the anterior/posterior diameter should be < 10 mm, with a normal appearing vermis, and without hydrocephalus. Visualization can be challenging, and must be done in the correct plane.

**Natural History:**
- Mega cisterna magna occurs in approximately 1/8200 pregnancies.
- When isolated, most times the finding is benign. However, there are no large prospective series, with adequate outcome data.
- Since visualization of the posterior fossa can be limited and because the development of the posterior fossa structures is a late embryologic event, there remains an unknown chance there could be other CNS anomalies, possibly detectable later in gestation, such as a Dandy-Walker malformation/variant.

**Associations:**
There might be an increased risk of a fetal chromosome anomaly, but more typically this is when the enlarged cisterna magna is found in association with other anomalies.

**Counselling:**
- When isolated, this is not an indication for fetal chromosome testing, but further investigation to look for other anomalies is indicated since some studies suggest that it is not isolated in more than 50% of cases.
- Another ultrasound at 21-23 weeks is suggested. If there is any uncertainty about the fetal brain findings, an MRI would be considered.
- The patient can consider prenatal chromosome testing.

**References:**


5. NASAL BONE HYPOPLASIA

The optimal definition for this established second trimester marker for DS seems to be multiples of the median of nasal bone for the gestational age \(^{(1, 2, 3)}\).

The regression curves used were based on NB of white fetuses. For race or ethnicity other than white a multiplicative correction factor was used to obtain MoM (African-American, Hispanic, Asian, other).

Measurement of NB is performed as described by Sonek et al \(^{(4)}\). This takes into account the angle of measurement and placement of calipers for the length of the nasal bone.

Maternal age at delivery is independent of nasal bone MoM in both affected and unaffected fetuses.

There is a clear association between absent nasal bone and aneuploidy. Fetal chromosome testing should be offered in these cases. The association between Down syndrome (and possibly trisomy 18) and nasal bone hypoplasia is less clear. Amniocentesis could be offered.

References:

6. INCREASED NUCHAL FOLD

Measurement of the thickness of the skin of the posterior neck of ≥6mm in second trimester, between 16 weeks, 0 days, and <21 weeks 0 days.

**Natural History:**

- Present in 0.5% of pregnancies.
- Most have a normal outcome

**Associations:**

- clearly increased risk of fetal chromosome anomalies, most commonly trisomy 21 (Down syndrome) but also other trisomies, Turner syndrome and also less common chromosome anomalies.
- other single gene conditions
- small increased risk of congenital heart disease

**Counselling and Management:**

- Amniocentesis - The risk of a chromosome anomaly is not well established, but clearly is above the age related risk. The patient can consider amniocentesis.

- Ultrasound - 18-19 weeks – detailed fetal ultrasound, coupled with a detailed examination of the heart and great vessels, and if suspicious of heart anomaly, then an echocardiogram should be considered

- Newborn physical examination by a clinician aware of the prenatal ultrasound finding.

**References:**


7. ECHOGENIC INTRACARDIAC FOCUS

The ultrasound visualizes an area (usually of the left ventricle) which is at least as echodense as bone, about 2 mm in diameter (can be up to 6 mm.) The pathologic basis is a discrete linear mineralization of the myocardial fusiform bundle of the chordae tendinae but why it occurs is unknown.

**Natural History:**
- Found in 0.46 - 3% of pregnancies
- Might occur more frequently in fetuses of women of Asian, African and Middle Eastern ethnicities.
- No long term cardiac consequences known.
- Most disappear by the third trimester, but even when it persists, normal cardiac function is expected.

**Associations:**
- Associated with an increased risk of a chromosome problem, typically Down syndrome.
- If occurring in the right ventricle, possibly the risk of a chromosome anomaly might be higher than if located in the left.

**Counselling:**
- Controversy exists as to whether amniocentesis should be offered due to significantly different conclusions by various authors.
- Patient can consider amniocentesis.
- Further ultrasound/echocardiograms are not required.

**References:**


8. SINGLE UMBILICAL ARTERY

Natural History:

- 0.3% -1% of 19 weeks gestation (total births and late pregnancy losses)
- most have a normal outcome

Associations

- 19% had other ultrasound detectable anomalies (i.e. not isolated), often renal, cardiac or brain anomalies
- If isolated, most newborns are normal, but there remains up to a 7% risk of other structural anomalies, not seen on antenatal ultrasound (heart, brain, kidney, limbs described)
- small size (average weight 365 gm lower)
- Possible increase in risk of preterm delivery
- Slight increase in the risk of a chromosome abnormality, but usually with other structural anomalies

Counselling and Management:

- Detailed u/s at 19 weeks, including heart and great vessels
- Chance of a fetal chromosome anomaly with an isolated single umbilical artery, is low enough that fetal chromosome testing is not warranted
- Follow fetal growth with ultrasound
- Careful physical examination for additional anomalies after birth

References:


9. RENAL PYELECTASIS (pelviectasis)  

The AP diameter of renal pelvis is equal to or ≥ 5 mm at gestations up to 32 weeks, 6 days OR equal to or ≥ 7 mm at gestations of 33 weeks to term. Any measurement >10 mm is hydronephrosis.

**Natural History:**
- occurs in about 0.7%-3% of all pregnancies, more common in males
- 80% most resolve with no long term consequences, either in utero or in the first year

**Associations:**
- congenital hydronephrosis (diagnosed as > 10 mm after birth) – risk correlates with larger measurements
- vesico-ureteric reflux (VUR)
- more prevalent in fetus with trisomy 21 (isolated mild pyelectasis is present In about 2% of babies with Down syndrome). The estimated likelihood ratio is low at 1.9, with very wide confidence intervals.

**Counselling and Management:**
- Ultrasounds – Since pelviectasis can progress, monitoring by ultrasound at 22-23 weeks and after 28 weeks is suggested
- Ultrasound does not discriminate between obstructive and non-obstructive uropathy in the second trimester
- If persistent and greater than 10 mm after 28 weeks gestation, pediatric consultation is strongly suggested after delivery.
- VUR can still occur after birth, even with regression of pelviectasis
- Patient can consider amniocentesis.

**References:**


10. ECHOGENIC BOWEL

The appearance on ultrasound of fetal bowel with an echogenicity similar to or greater than surrounding bone.

**Natural History:**

- Found in about 0.6-2.4% of all second trimester fetuses
- Sometimes persists, sometimes disappears

**Associations:**

- usually is a normal variant
- swallowed bloody amniotic fluid from a placental abruption or an invasive procedure, intraluminal inspissated meconium, or mesenteric ischemia.

Increased risks of the following have been observed, but quantitation of the risk varies in the literature:

- chromosome anomalies (trisomy 21 and others)
- cystic fibrosis
- congenital infection (CMV, occasionally other prenatal infections)
- intrauterine growth retardation, which is associated with an increased risk of perinatal morbidity and mortality
- GI malformations
- alpha Thalassemia in Oriental population

**Counselling:**

- The patient can consider amniocentesis.
- Cystic fibrosis – the risk of an affected child will vary, depending on the ethnicity, for CF is more prevalent in persons from northern Europe. Parental CF carrier testing can detect 80% of obligate carriers when parents are of northern European background, but this is lower in other ethnic groups. If both parents are carriers, definitive prenatal diagnosis is available.
- Maternal initial and convalescent titres look for fetal infections. (CMV, herpes simplex, toxoplasmosis, parvovirus B19, varicella)
- Detailed fetal ultrasound at 19-24 weeks to look for other structural anomalies and for evidence of bowel obstruction/perforation, and at 30-32 weeks. If the finding is persistent at the later ultrasound, or if there is IUGR or a GI anomaly, newborn pediatric consultation is needed.
- Alpha Thalassemia screening of parents in Oriental families
References:


11.  SHORT FEMUR LENGTH     February 2008

A short femur length is defined as either a measurement below the 2.5\textsuperscript{th} percentile for gestational age or a measurement that is less than 0.9 multiples of that predicted by the measured BPD. The relationship between bone length and head size may differ across racial groups.

**Natural History:**
- Likely normal variant of stature
- Keep in mind ethnic differences in stature

**Associations:**
- associated with an increased risk of trisomy 21 (stronger if humeri are short too)
- if severely shortened or presence of bowing, fractures, or reduced mineralization may be an initial sign of a skeletal dysplasia
- occasionally an initial sign of IUGR

**Management:**
- Ultrasound - If gestation is < 18 weeks, suggest another 18-20 week ultrasound to assess bone growth. Other long bones should be assessed. Since there can be late detection of a skeletal dysplasia, another ultrasound around 23 weeks could be considered if there are persistent concerns on the 18-20 week ultrasound.
- Patient can consider amniocentesis

**References:**


12. SHORT HUMERUS LENGTH

February 2008

A short humerus length is defined as either a measurement below the 2.5th percentile for gestational age or a measurement that is less than 0.9 multiples of that predicted by the measured BPD. The relationship between bone length and head size may differ across racial groups.

**Natural History:**
- Likely normal variant of stature
- Keep in mind ethnic differences in stature

**Associations:**
- Associated with an increased risk of trisomy 21
- If severely shortened or presence of bowing, fractures, or reduced mineralization may be an initial sign of a skeletal dysplasia
- Occasionally an initial sign of IUGR

**Management:**
- Ultrasound - If gestation is < 18 weeks, suggest another 18-20 week ultrasound to assess bone growth. Other long bones should be assessed. Since there can be late detection of a skeletal dysplasia, another ultrasound around 23 weeks could be considered if there are persistent concerns on the 18-20 week ultrasound.
- Patient can consider amniocentesis

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