

REVIEW ARTICLE

Sonography Markers of Chromosomal Abnormality in Second Trimester

Jayprakash Shah

Chairman, Imaging Science Committee, FOGSI, Rajni Fetal Medicine Center, Ahmedabad
Honorary Sonologist, Smt NHL Municipal Medical College and Sheth VS General Hospital, Ahmedabad, Gujarat, India

Correspondence: Jayprakash Shah, 1, Sarela society, Bhd BOB, Navrangpura, Ahmedabad-380009, Gujarat, India
e-mail: rajniip@yahoo.com

ABSTRACT

Maternal age is increasing in today's world of professional carrier of women. As we know with aging of ova chromosomal abnormalities in fetus are rising. Karyotype is the final diagnostic tool for the confirmation, but it is associated with risk of abortion with the invasive procedure required for it. Sonography markers can be a good tool along with biochemical markers to reduce this risk with better pick rate of chromosomal abnormalities during prenatal period.

Keywords: Karyotype, Biochemical markers, Sonography markers.

INTRODUCTION

Sonography has become indispensable instrument in today's practice of obstetrician. With the advancing technology in availability of high-resolution sonography machines, we can see not only the details of fetal malformations including fetal cardiac malformations much earlier but can also detect soft markers. Interest and knowledge with added experience has lead us to recognize the high risk of chromosomal parkers also by sonography.

By sonography, we cannot see the chromosome, but certain findings guide us to suspect high probability of chromosomal abnormality.

Sonography markers of chromosomal abnormalities can be:

1. Soft markers
2. Certain fetal malformations
3. Multiple fetal malformations
4. Early symmetric growth retardation and polyamnios.

Soft markers are not actual malformation, but they are variant of normal finding, transient and nonspecific findings that may even resolve and may even exist in normal fetuses. They are not the indication of termination, but are the indicator of thorough fetal evaluation and further tests in form of biochemical markers and invasive testing for chromosomal abnormality.

Soft markers can be of different types:

1. Minimally increased measurement of fetal organs:
 - a. Increased nuchal fold
 - b. Borderline ventriculomegaly
 - c. Pelviectasis.
2. Normal variant in most cases but slightly increased risk of fetal problems:
 - a. Chroid plexus cyst

- b. Echogenic focus in heart
- c. Echogenic bowel
- d. Hypoplastic or absent nasal bone
- e. Shortened long bones.
3. Abnormality or malformations, which carry good fetal outcome in most fetuses:
 - a. CCAML
 - b. Umbilical vein varix
 - c. Liver calcification
 - d. Meconium pseudocyst in abdomen
 - e. Duodenal atresia
 - f. Omphalocele.

Majority of soft markers are gray zones. Sonologists and all gynecologists must know the possible outcome and a way of approach in such cases so that proper counseling can be given.

Chromosomal abnormalities are one of the leading causes of pregnancy loss:

- 95% of chromosomally abnormal fetuses are lost before term.
- Minimum 10 to 15% of all conceptions are chromosomally abnormal.
- 6 to 11% of all still births and neonatal deaths are due to chromosomal abnormality.
- High-risk group of chromosomal abnormality include:
 - Advanced maternal age > 35 years (Fig. 1)
 - Trisomy 21, 13, 18 increases with advance maternal age
 - Chromosomal abnormality like triploidy, sex chromosomal abnormality — 45 XO, 47 XXY are not affected by maternal age (Fig. 2)
 - Family history of aneuploidy
 - Abnormal 2nd trimester biochemical markers
 - Known balanced translocation, chromosomal rearrangement in parents

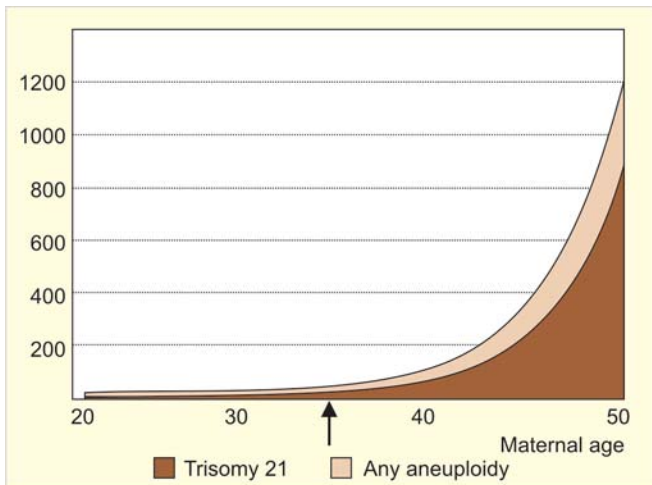


Fig. 1: Age related risk of trisomy 21 and all aneuploidy. With the advance maternal age, risk of any aneuploidy increases and more sharply after 35 years of age

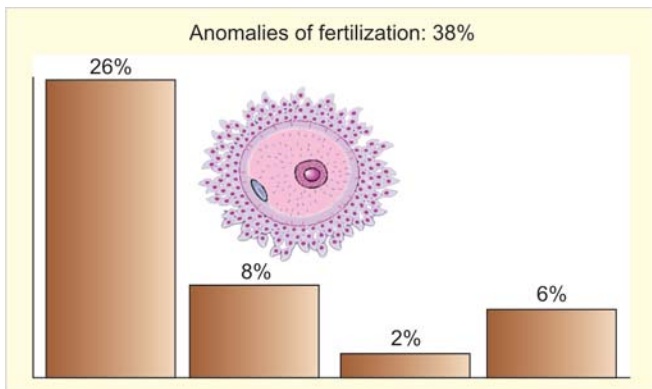
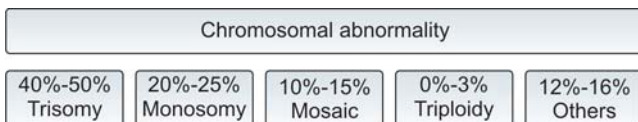


Fig. 2: Among all aneuploidy faulty ovum is responsible in 26%, faulty sperm in 8%, polyploidy in 2% and rest 6% is due to parthenogenesis

- 10 to 13% of fetuses with structural abnormality also have chromosomal abnormality
- More the number of fetal malformations—more the frequency of chromosomal abnormality (Fig. 3).

Biochemical markers and sonography markers are important screening modality to filter the bulk of increased risk patient based on maternal age alone. This is required to avoid the risk of invasive procedure for diagnosis of chromosomal abnormality.



Neyberg carried out a study in which he stated, if no sonography markers of increased chromosomal risk are seen then the risk of aneuploidy is reduced by half. Bahado Singh has come out with reduced risk of aneuploidy, by 8 times. Even if one remains optimistic then also Neybergs study reduces the risk of aneuploidy by nearly half. So, we can filter out the

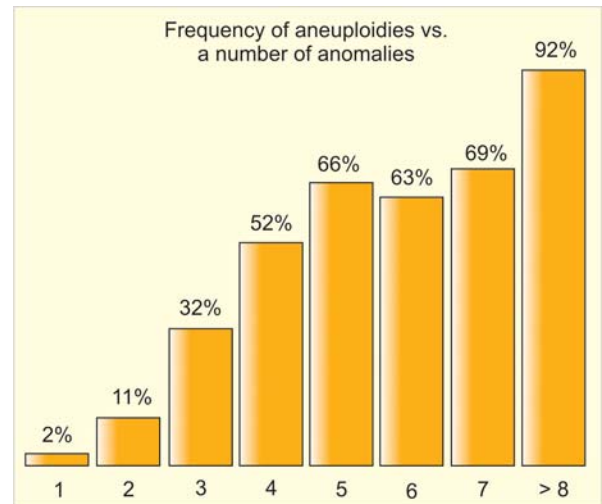
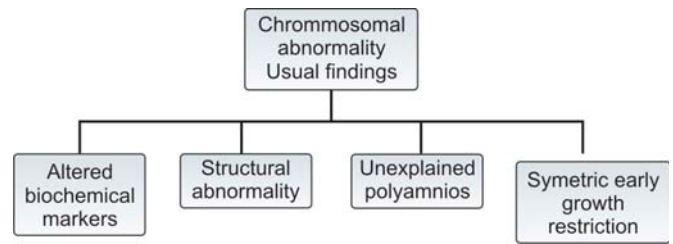


Fig. 3: The suspicious sonography markers in aneuploidy fetuses. With increasing number of anomaly identified on sonography, chances of having aneuploidy increases

Table 1: Soft markers—second trimester

- | | |
|---|---|
| <ul style="list-style-type: none"> • Ventriculomegaly • Choroid plexus cyst • Enlarged cisterna magna • Increased NF • Echogenic bowel • Brachycephaly • Nasal bone hypoplasia | <ul style="list-style-type: none"> • Echogenic focus in heart • Early symetric growth retardation • Unexplained polyamnios • Short femur • Short humerus • Macroglossia • Cystic hygroma |
|---|---|

Table 2: Malformations—second trimester

- | | |
|--|---|
| <ul style="list-style-type: none"> • Duodenal Atresia* • Holoprosencephaly* • Brachycephaly* • Strawberry shape of skull • CCAML • Macroglosia • Wormian bones • Micrognathia • Cord cyst • Pleural effusion | <ul style="list-style-type: none"> • Omphalocele* • Microcephaly* • Abnormal posterior fossa • Bilateral TEV • Meconium pseudocyst • Micro penis • Ceft lip/palate • Jelly like placenta* • Cardiac malformations* |
|--|---|

*Strong markers for chromosomal abnormality

patients by using these soft sonography markers and other markers to half.

Soft markers are as shown in Table 1 and malformations in Table 2.

| | |
|----------------------|--|
| Biochemical markers | <ul style="list-style-type: none"> • Double marker • Triple marker |
| Soft markers | <ul style="list-style-type: none"> • Common-More prevalent and strong markers • Less common markers, low L/R |
| Malformations | <ul style="list-style-type: none"> • High association with chromosomal abnormality • Less frequency |
| Unexplained findings | <ul style="list-style-type: none"> • Early symmetric growth restriction • Unexplained polyamnios |

SONO MARKERS

CNS
 Ventriculomegaly
 Holoprosencephaly
 Microcephaly
 Abnormal posterior fossa
 Choroid plexus cyst
 Dysgenesis of CC

Skull
 Brachycephaly
 Strawberry shape

Skeleton
 Short long bones
 Hand anomalies
 Foot anomalies

Face
 Cleft
 Ear
 Eyes
 Nose
 Tongue
 Micrognathia



Neck
 Nuchal lucency
 Cystic hygroma

Thorax

Miscellaneous
 Placenta and cord
 Hydrops

GIT
 Oesophageal atresia
 Duodenal atresia
 Bowel obstruction
 Echogenic bowel
 Omphalocele

Genital tract

Urinary tract

Cardiac anomaly

Growth restriction

Sonography markers have sensitivity to detect trisomy 18 to 83 to 100%, trisomy 13 to 91%.

But sensitivity to pick up trisomy 21 is low of approximately 25%.

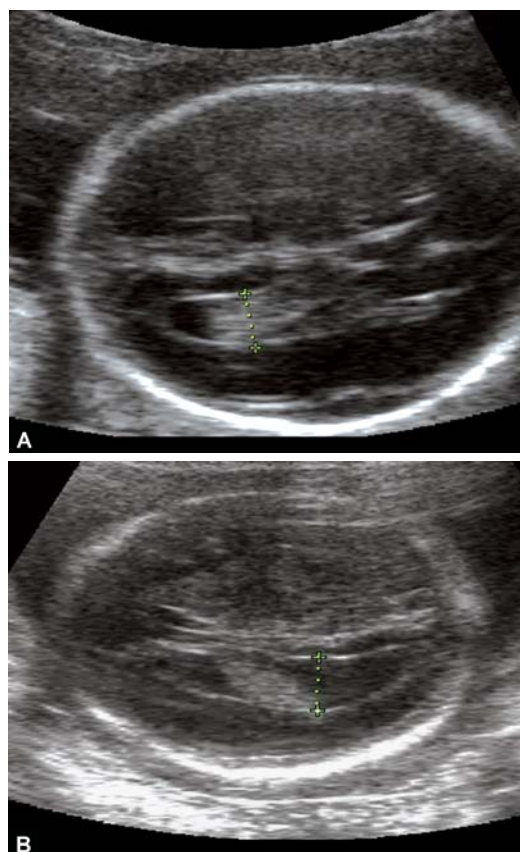
VENTRICULOMEGALY

- Dilation of lateral ventricle measuring more than 10 mm in absence of any CNS malformation is called borderline ventriculomegaly.

To stamp it as borderline ventriculomegaly, following structure has to be seen in transventricular view (Figs 4A and B).

- Falx in center
- Bilateral symmetry
- Cavum septum pellucidum
- Lateral ventricle with both medial and lateral wall visible
- Intact calvarium
- Incidence 5 to 25:10,000 delivery
 - Normal atrium of lateral ventricle measures < 10 mm.
 - More than 15 mm is suggestive of hydrocephalus.

Between 10 and 15 mm is suggestive of borderline ventriculomegaly. Let me specify that it is again a G. age related finding. Choroid plexus normally touches both the wall of lateral ventricles, but when it fails to touch both the wall, think of ventriculomegaly (Figs 5A and B). In that case, measure the



Figs 4A and B: (A) Normal ventricle, (B) Ventriculomegaly



Figs 5A and B: Borderline ventriculomegaly; (A) coronal view (B) parasagittal view

distance between medial border of lateral ventricle to medial border of choroid plexus; it has to measure less than 3 mm in normal ventricle.

Ventriculomegaly is diematic condition due to its poor outcome in nearly 20% of cases. In one study of it was observed chromosomal association in 3.8% of cases, associated malformations in:

| | | |
|---|--------|-------|
| • Aneuploidies | 9/234 | 3.8% |
| • Malformations undiagnosed <i>in utero</i> | 19/221 | 8.6% |
| • Perinatal deaths | 8/209 | 3.7% |
| • Abnormal development | 24/209 | 11.5% |
| • Abnormal outcome (overall) | 43/219 | 19.6% |

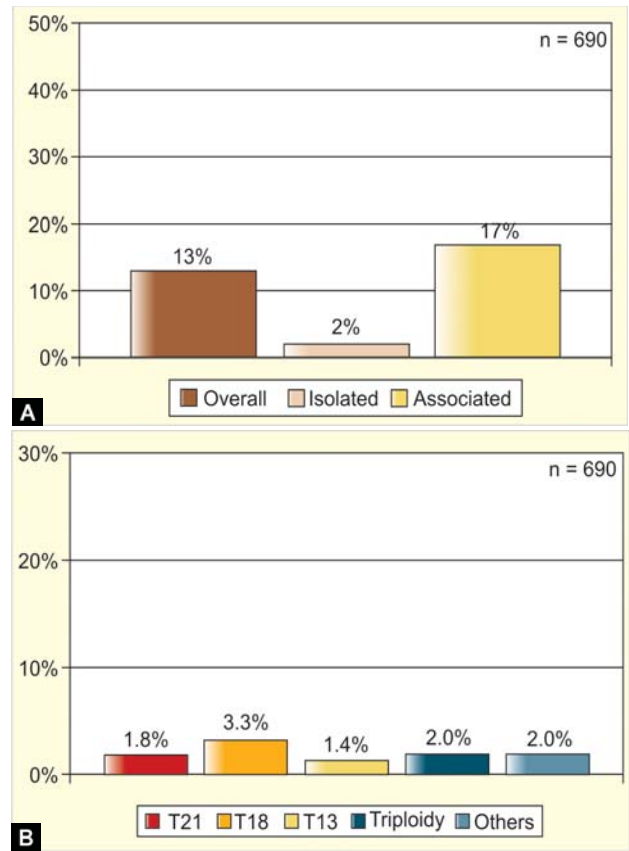
Goldstein observed that none cases of isolated ventriculomegaly died (Figs 6A and B). When it was associated with other malformations, 56% died.

Benacerraf recorded the incidence of 12% aneuploidy in 44 borderline ventriculomegaly.

Male fetuses were likely to have larger ventricles. Among borderline ventriculomegaly, 75% of male were normal while among females 50% turn out to be normal (Patel and coworkers).

How to Proceed?

- Rule out other CNS malformations
- Counseling
- Chromosomal analysis



Figs 6A and B: (A) Prevalence of aneuploidy in cases of isolated ventriculomegaly, (B) distribution of aneuploidy among isolated ventriculomegaly (Philipe jeanty)

- Regular and close follow-up
- May resolve spontaneously.

CHOROID PLEXUS CYST

Sonolucent cystic space noted in the substance of choroid plexus. It can be single, multiple, large, small, bilateral (Fig. 7) or unilateral. Almost exclusively seen between 16 and 21 weeks. Appears to be transient and disappears after 23 weeks. Likelihood ratio < 2. Incidence 1% of normal population normal variant (45/47).

Among trisomy 18, fetuses 30 to 60% show the choroid plexus. At the same time 97% of trisomy 18, fetuses show some other structural abnormality also along with CP cyst (Fig. 8).

Gross and colleagues had done retrospective analysis of 13 large published studies with overall risk of 0.27% for aneuploidy in isolated CP cyst. When associated with other marker/malformation, risk is 33%.

Benacerraf study shows no increased risk of trisomy 21 while Gupta and coworkers showed risk of 1/880 of trisomy 21.

How to Proceed?

- Rule out other CNS malformations
- Counseling



Fig. 7: Bilateral choroid plexus cyst



Fig. 9: Brachycephaly a soft marker for T 21

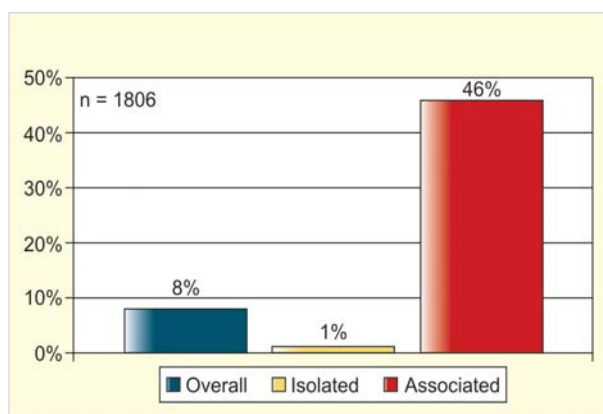


Fig. 8: Frequency of aneuploidies in fetuses with choroid plexus cysts



Fig. 10: Transcerebellar view, note the increased nuchal fold thickness

- Thorough evaluation of fetus for any other soft marker or malformation
- Isolated CP cyst, no karyotyping
- LR.

BRACHYCEPHALY

- Anteroposterior flattening of skull
- Short OFD, round shape of skull instead of ovoid
- BPD/OFD >85%
- Associated with trisomy 21 (Fig. 9)
- More reliable observation postnatal than antenatal.

How to Proceed?

- Rule out other CNS malformations
- Counseling
- Karyotyping suggested
- Rule out other associated malformations and markers.

INCREASED NUCHAL FOLD

- Benacerraf (1985) described first—between 15 and 20 weeks
- Cut off of > 6 mm—sensitivity 43% with false positive rate 0.1%

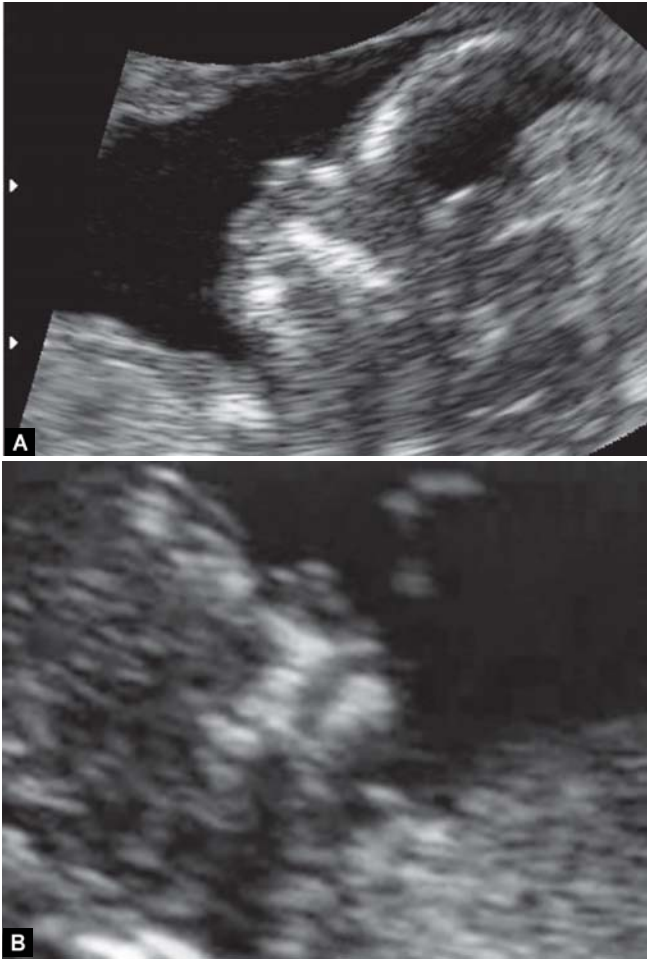
- Cut off > 5 mm—sensitivity of 77.8% with false-positive rate of 2%
- Sonolucent space with loose skin fold on the back of the neck
- Measured at transcerebellar level (Fig. 10)
- From posterior border of skull bone to posterior border of skin, including skin thickness
- > 6 mm after 18 weeks—33% aneuploidy
- Strong marker for aneuploidy, more for trisomy 18
- May persist throughout second trimester or it may resolve
- Caution: False increased NF can be seen in breech presentation, fetuses with elongated head, wrong section or when more transducer pressure is applied.

How to Proceed?

- Rule out other CNS malformations
- Counseling
- Karyotyping suggested
- Rule out other associated malformations and markers
- LR 11.

NASAL BONE HYPOPLASIA

- Absence of nasal bone or hypoplasia of nasal bone is strongly associated with aneuploidy more common with



Figs 11A and B: (A) Nasal bone visible (B) Absent nasal bone

trisomy 21 (Figs 11A and B). It can be also associated with trisomy 18, duplication, deletion of any chromosome.

- High detection rate of trisomy 21—40% sensitivity and 0.1% false positive rate.
- Measurement by:

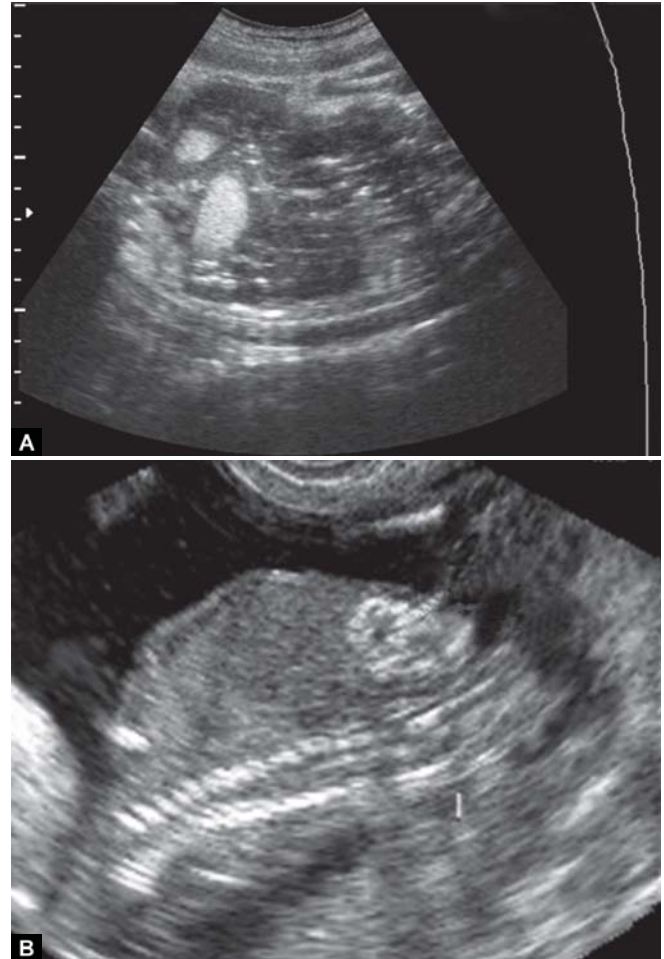
| | |
|--|--|
| <ul style="list-style-type: none"> • Profile view • Only head, neck and upper chest visible • Thin line of skin and thick NB = sign | <ul style="list-style-type: none"> • Magnification—image occupy 75% of screen • Angle of 45°/135° to avoid incorrect measurement • Observe tip of nose—thin echo. |
|--|--|
- BPD/NB > 10—suggests high aneuploidy.

How to Proceed?

- Rule out other CNS malformations
- Counseling
- Karyotyping suggested
- Rule out other associated malformations and markers
- LR.

ECHOGENIC SMALL BOWEL (FIGS 12A AND B)

- Bowel whiter than rest of the abdomen without shadows
- Bowel as echogenic as that of bone without shadow



Figs 12A and B: Echogenic small bowel

- Incidence: almost 0.5% of normal fetuses in second trimester
- Increase the risk of trisomy 21 by 6 to 7 fold (Fig. 13)
- Causes:
 - As normal variant
 - Aneuploidy
 - CMV, HSV or parvovirus infection
 - Swallow of intra-amniotic bleed due to immature enzyme system to digest it
 - Meconium ileus in third trimester, normally in large bowel
 - Meconium peritonitis with peritoneal calcifications in small bowel obstruction of severe variety
 - Cystic fibrosis—gallbladder is absent.
- Grades:
 - I*: Mild echogenic and typically diffuse—not significant finding
 - II*: Moderately echogenic and typically focal—not significant finding
 - III*: Highly echogenic equivalent to bone—only significant finding.
- *Pitfalls*: High frequency transducer can show increased echogenicity. Lower the frequency of transducer, if echogenic bowel.

How to Proceed?

- Maternal age related risk
- Counseling

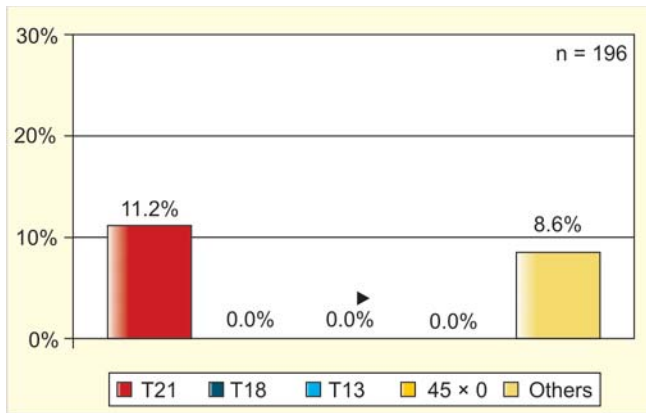


Fig. 13: The risk of type aneuploidy that is associated with echogenic bowel (Philippe jeanty et al)



Fig. 14: Echogenic cardiac focus in left ventricle.

- Rule out other associated malformations and markers
- Karyotyping suggested when grade III or some other markers are noticed
- LR 6.

ECHOGENIC CARDIAC FOCUS

- Visible in approximately 5% of fetuses.
- Discrete eye catching bright echogenic focus like bone echogenicity, more in left ventricle (Fig. 14).
- Best seen in 4 chamber view
- Can be single multiple, in one or both ventricle, large, small.
- Moves with chordae tendineae
- Due to microcalcification in chordie tendenie surrounded by fibrosis. This histopathological finding was observed in:
 - Normal fetuses—2%
 - Trisomy 13—10%
 - Trisomy 21—39%
- LR 2.

Benacerraf has studied 1334 fetuses, 66 had echogenic focus in heart. All had undergone amniocentesis and 22 of 1334 had trisomy 21. Out of 22 cases of trisomy 21, only 4 had echogenic cardiac focus.

In another study of maternal age more than 35, ECF had a detection rate of trisomy 21—6.4%.

How to Proceed?

- Counseling
- Karyotyping not suggested in isolated finding
- Rule out other associated malformations and markers
- LR
- Increased risk of trisomy 21 by 4 fold in association with other high risk factors.

Two-Vessel Cord

- Incidence 0.2 to 1% of pregnancy
- 10% may have aneuploidy like trisomy 18, 13, triploidy and monosomy X.



Fig. 15: Long section of cord showing 2 vessels, one large and one small, alternately arranged

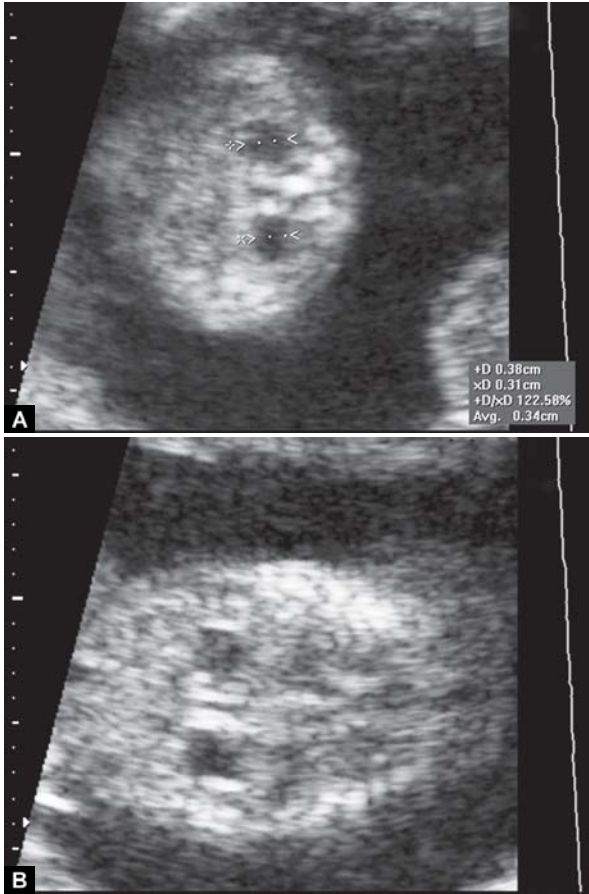
- Umbilical artery on one side is absent as continuation of Iliac vessel. Normally aorta bifurcate in Iliac vessel. In 2-vessel cord (Fig. 15), aortic bifurcation on the side of absent umbilical artery is smaller.

How to Proceed?

- Counseling
- Karyotyping not suggested in isolated finding
- Rule out other associated malformations and markers
- LR 1.

PELVIECTASIS

- Borderline renal pelvis diameter of more than 7.4 mm is said to be pelviectasis (Figs 16A and B).
- Renal pelvis to be measured in transverse section of abdomen with fetal pine at 6 or 12 o'clock positions.
- Incidence 2 to 2.8% of pregnancy
- When in doubt confirm by renal pelvis/renal diameter > 50% suggest pelviectasis.
- Slight increase in the risk of trisomy 21. Isolated pelviectasis, karyotyping not suggested.



Figs 16A and B: (A) Transverse section at kidney level showing bilateral pelviectasis, (B) Longitudinal coronal section showing borderline pelviectasis

Mild renal pelvis dilation with empty bladder has been observed to be weak marker.

Grignon and associates have put up a cut off line of 10 mm to define dilation of renal pelvis between 20 weeks and full term pregnancy. Adra and associates had an observation that when cut of 6 mm at 24 weeks and 8 mm at 31 weeks were used, obstructive uropathy was diagnosed with 100% sensitivity.

Benacerraf had observed following cut off for postnatal intervention for obstructive uropathy in renal pelvis dilation.

| G. age | Cut off for postnatal intervention |
|--|------------------------------------|
| <ul style="list-style-type: none"> • 15 to 20 weeks | 5 mm |
| <ul style="list-style-type: none"> • 20 to 30 weeks | 8 mm |
| <ul style="list-style-type: none"> • 30 weeks to term | 10 mm |

How to Proceed?

- Counseling
- Karyotyping not suggested in isolated finding
- Rule out other associated malformations and markers
- LR 1.4.

SHORT LONG BONE (FEMUR AND HUMERUS)

- Down child has shorter limbs.

| | MEASUREMENTS (mm) | MEAN (mm) | MA |
|-----|-------------------|-----------|---------------|
| BPD | 38 | 38.1 | 17W4D (± 8D) |
| HC | | | |
| AC | 98 | 98.0 | 15W6D (± 12D) |
| FL | 21 | 20.9 | 16W2D (± 10D) |
| CRL | | | |
| HUM | 22 | 22.2 | 16W5D (± 20D) |

| | MEASUREMENTS (mm) | MEAN (mm) | MA |
|-----|-------------------|-----------|---------------|
| BPD | 38 | 75.6 | 30W2D (± 22D) |
| HC | | 269.2 | 29W2D (± 14D) |
| AC | 98 | 269.1 | 31W0D (± 21D) |
| FL | 21 | 48.9 | 26W3D (± 15D) |
| CRL | | | |
| HUM | 22 | 38.1 | 23W3D (± 20D) |

Fig. 17: Biometry in cases of short long bones. Difference of G. age widens with increased G. age of fetus. Serial sonography becomes a strong proof for short long bones and is a strong marker for aneuploidy more so for T 21

- BPD/FL ≤ 90%. Short femur shall be observed in relation to BPD rather than G. age between 15 and 23 weeks, preferably between 17 and 19 weeks of pregnancy (Fig. 17).
- If isolated, slightly short femur is not strong marker.
- When combined with short humerus as well, it has LR 11.
- More commonly trisomy 21
- When associated with growth restriction, trisomy 13 and 18 are likely.

How to Proceed?

- Counseling
- Karyotyping suggested when both femur and humerus are short
- Rule out other associated malformations and markers.

GROWTH RESTRICTION

- < 1% IUGR fetuses have aneuploidy.
- Most typically associated with triploidy (5.7%), trisomy 18 (7.5%), trisomy 13 (1.7%) (Fig. 18).
- Early growth restriction in 2nd trimester—more than aneuploidy likely (Figs 19A and B).
- Large head compared to small abdomen is typical of triploidy.
- Isolated 4%.

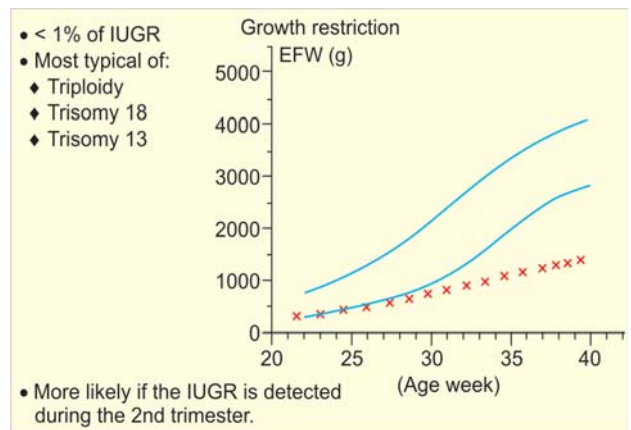
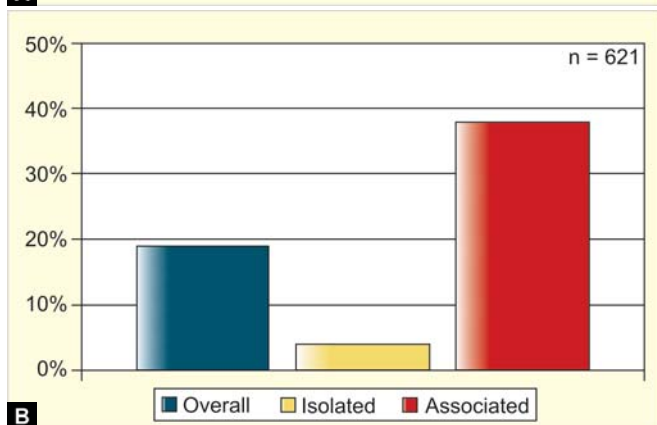
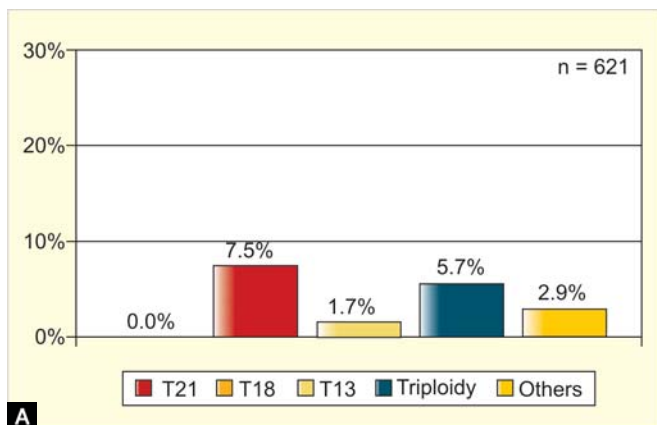


Fig. 18: Growth chart showing early growth retardation



Figs 19A and B: (A) Prevalence of aneuploidy in IUGR (B) Frequency of aneuploidy in IUGR



Figs 20A and B: (A) A case of complete AVSD (B) A case of tricuspid dysplasia with dilated right side of heart more of RA, normal placed tricuspid valve

- Other associated abnormality—4%.
- Overall 19.

How to Proceed?

- Counseling
- Karyotyping suggested in isolated finding
- Rule out other associated malformations and markers.

CARDIAC DEFECTS

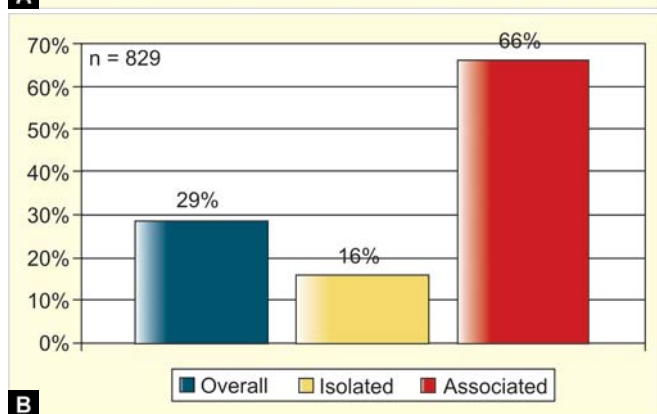
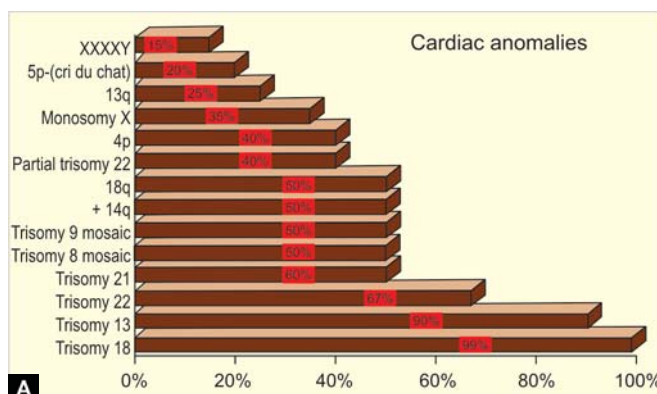
- Infants with Down’s syndrome have incidence of 50% cardiac defects, more commonly VSD, AVSD and DORV hypoplastic heart (Figs 20A and B).
- De Vore reported 76% cardiac defect in Down’s syndrome fetuses.
- Trisomy 18 and 13 have incidence of cardiac defect in > 90% cases (Figs 21A and B).
- More common aneuploidy in antenatal cardiac malformations compared to postnatal (32%/22%).

How to Proceed?

- Counseling
- Karyotyping suggested in isolated finding also
- Rule out other associated malformations and markers.

DUDENAL ATRESIA (FIG. 22)

- Recognized after 20 to 24 weeks of pregnancy.
- Two cystic mass (Bubble), one on left side of spine (stomach), another on right side of spine (Duodenum) with connection between two bubble at AC level.



Figs 21A and B: (A) Prevalence of cardiac anomaly among proved aneuploidy cases, (B) Prevalence of aneuploidy among cardiac malformations



Fig. 22: Duodenal atresia

- Less associated with aneuploidy in first trimester compared to second trimester.
- Karyotype suggested in all.
- More aneuploidy with septet compared to nonseptet (76%/6%).
- Noncervical lymphangioma—no increased risk of aneuploidy.

Hydrothorax

- Isolated pleural effusion, unilateral/bilateral.
- Associated with increased risk of aneuploidy more commonly turner syndrome, but also trisomy 21 and 13.
- In one study of 82 cases, aneuploidy was observed in 4.9% of cases having trisomy 21.
- KT suggested.

Nonimmune Hydrops

- Edema all around fetus with ascites, pericardial effusion and pleural effusion.
- When detected before 18 weeks pregnancy more aneuploidy.
- 16% aneuploidy.

Diaphragmatic Hernia

- Defect in diaphragm with herniation of stomach and bowel in chest.
- 10 to 20% aneuploidy.
- Trisomy 18 is most common, can be trisomy 13 and 21 also.
- KT is suggested in all.

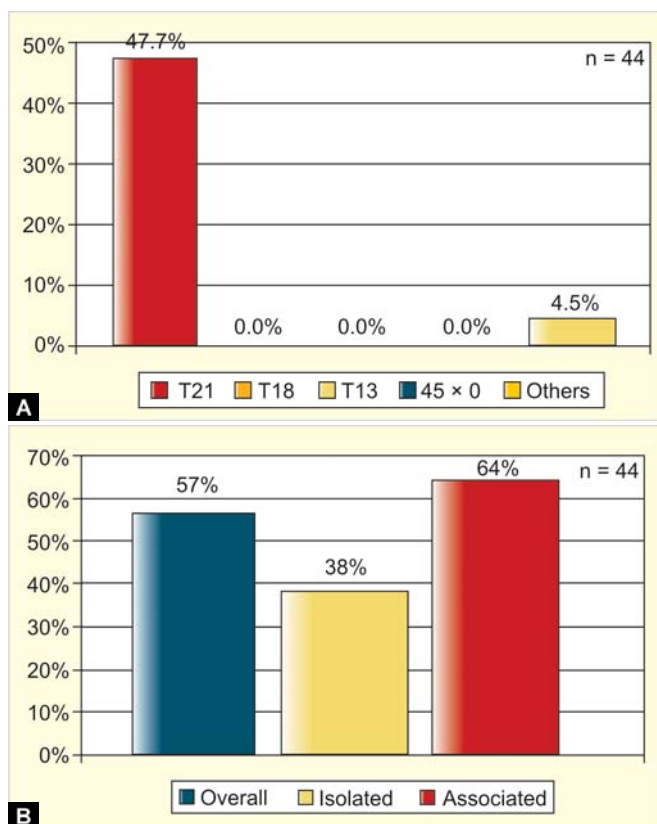
Omphalocele

- Anterior abdominal defect at the base of umbilical cord insertion with herniation of abdominal content, covered by membrane.
- Trisomy 13 and 18 are most common but can be trisomy 21, triploidy also.
- Prenatal detection associated with 30 to 40% chromosomal abnormality while 12% only in postnatal cases.
- In one study of trisomy 18 cases, 18% had omphalocele.
- In one study of 35 cases—54% were having aneuploidy.
- KT suggested.

Scoring System

Snijder and Nicolaides scoring system:

- a. Risk given as 1:!!!!.
 - b. Difficult to understand by patient.
 - c. Gives false sense of precision.
1. Benacerraf's scoring system.



Figs 23A and B: (A) Frequency of aneuploidy, (B) incidence of aneuploidy

- Strongly associated with trisomy 21 in 1/3rd of cases (Figs 23A and B).
- Cardiac malformation is also common.

How to Proceed?

- Counseling
- Karyotyping suggested in isolated finding
- Rule out other associated malformations and cardiac malformations.

Cystic Hygroma

- When cervical cystic hygroma—60% are associated with aneuploidy.

A score of 2 or more is associated with risk of aneuploidy, and karyotype is suggested.

| Finding | Score |
|-------------------------|-------|
| Major anomaly | 2 |
| Nuchal fold | 2 |
| Short femur | 2 |
| Short humerus | 2 |
| Pyelectasis > 4 mm | 1 |
| Echogenic bowel | 1 |
| Echogenic cardiac focus | 1 |
| Age < 35 years | 0 |
| Age 35 to 40 years | 1 |
| Age > 40 years | 2 |

2. Jeanty's scoring system:

- 1 major anomaly (>1% risk) omphalocele, duodenal atresia, endocardial cushion defect, crux abnormality - karyotyping indicated.
- 1 minor marker—CP cyst, echogenic cardiac focus—karyotyping not suggested.
- 2 minor marker risk > 1%—karyotyping suggested.

What is no Aneuploidy?

In many cases, fetuses with soft marker of malformations turn out to be euploidy on karyotype. In such cases, they can be associated with a vast range of syndromes. One can get the list of such syndrome from authentic website like OMIM by mentioning the findings in the search option and can even get the DNA location of abnormality, if it is known with the list of laboratory, which can carry out the testing.

CONCLUSION

To screen the whole population for chromosomal abnormality is practically impossible. At the same time, it is not possible to pick up all chromosomal malformations. Strategies shall be to use noninvasive markers like biochemical markers and sonography markers to filter the high-risk population based on maternal age and to offer invasive testing only to those filtered high-risk population to reduce the risk of abortions of normal fetuses.

High-end machines, good skill, constant vigilance, while scanning and deep interest in subject with knowledge is must.

Hoping for or relying on single parameter, which filters the aneuploidy fetus from normal is futile.

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