In the Name of GOD

Second Trimester Screening

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Why We Chose to Screen for Down Syn?

- Down syndrome is the **most common** chromosome abnormality among live births and the **most frequent** form of intellectual disability caused by a demonstrable chromosomal aberration.

- The syndrome is characterized by moderate to severe learning disability (average **IQ** approximately 40) in combination with short **stature**, characteristic **facial** features, **heart** defects (40 to 50 %), **intestina**l malformations (10 %), problems with **vision** and
- **hearing** (50 %), an increased frequency of **infection.**

Rationale for Screening

Rationale FOR Screening

- The **prevalence** of Down syndrome is relatively high (**1 in 634 births**), but depends on the **maternal age** range of the population.
- There is a **significant burden of disease**: the syndrome is associated with morbidity and mortality and high financial and psychosocial cost to their families.
- Diagnostic tests that **detect** the chromosomal abnormality are readily available.
- For couples who choose to **prevent birth** of an affected infant, safe and effective options are available

BASIC APPROACH TO COUNSELING

Patients considering Down syndrome screening should be given the following information . Women weigh this information differently and come to individual decisions regarding whether to undergo prenatal testing for chromosomal abnormalities and which test to undergo.

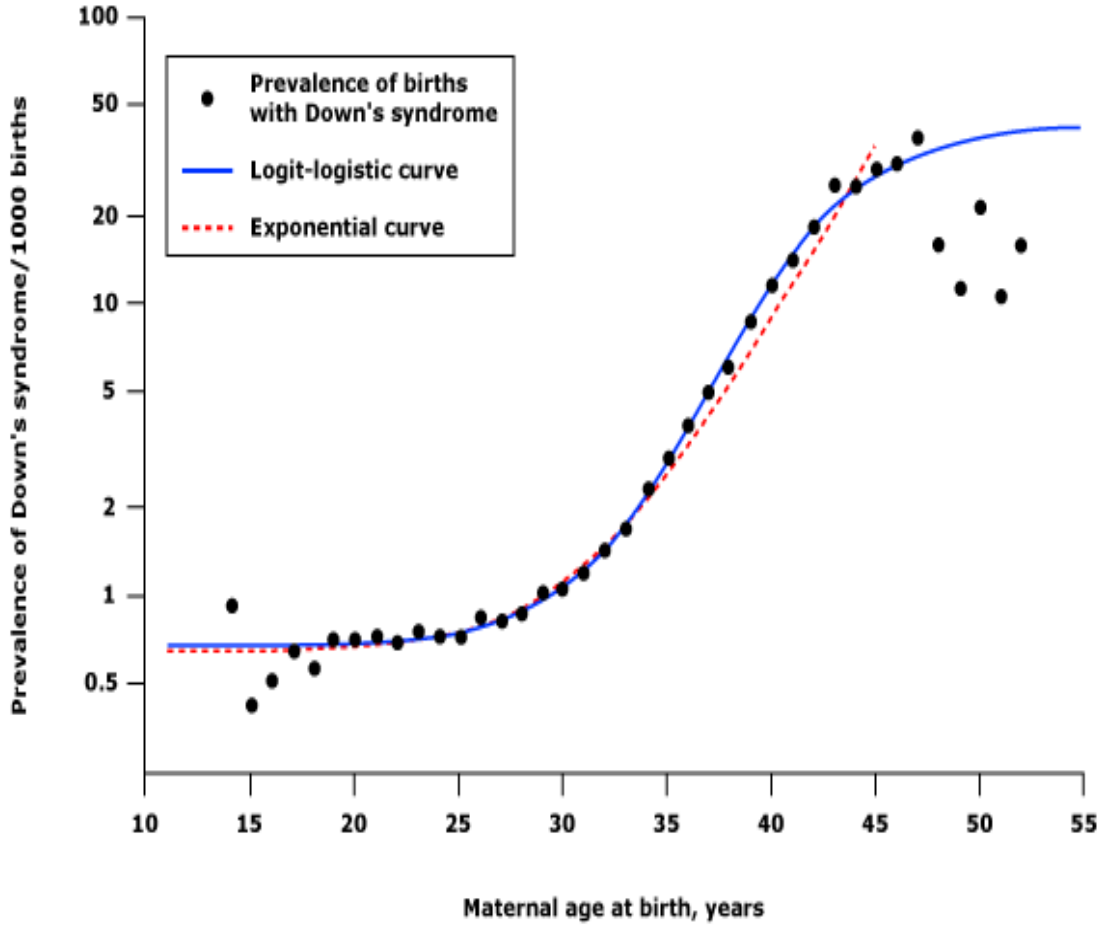
- An explanation of the **difference** between a **screening test** and a **diagnostic** test
- Screening sensitivity and specificity **compared** to diagnostic testing
- Description of the performance of **various** screening tests
- The option of diagnostic testing **instead** of screening
- The **risks** associated with prenatal diagnosis
- The psychological implications of prenatal screening and diagnosis
- The implications of **having a child** with Down syndrome
- The detection rate of chromosomal abnormalities **other than Down** syndrome, and the implications of having a child with one of these abnormalities
- Information about the length of time necessary to obtain results from screening and diagnostic testing
- Information about pregnancy termination

CANDIDATES FOR PRENATAL SCREENING AND DIAGNOSIS

- Maternal age alone: The risk of giving birth to a baby with Down syndrome as a function of maternal age is **nonlinear** and 1 in 1500 in young women to 1 in 10 in a 48-year-old.

- The use of Down syndrome risk at age 35 as a "threshold" for offering invasive testing was reached by consensus, However, these assumptions have been **challenged .**

Estimated prevalence of births with Down syndrome (95% CI) in the absence of antenatal screening in England and Wales 1990-1998: comparison of logit logistic curve with exponential curve



Reproduced with permission from: Morris, JK, Mutton, DE, Alberman, E. Revised estimates of the maternal age specific live birth prevalence of Down's syndrome. J Med Screen 2002; 9:2. Copyright ©2002 The Royal Society of Medicine Press, London.

ACOG Recommendation

In 2007

(1) **All women** be offered aneuploidy screening before 20 weeks of gestation .

(2) **All** women should have the option of **invasive testing**, regardless of maternal age .

ACOG Recommendation

ACOG also stated that a **prenatal diagnostic procedure** for fetal karyotype, rather than serum screening, should be considered in women of **any age** at high risk of Down syndrome or other fetal aneuploidies. Such women include those with:

- A **previous** pregnancy complicated by fetal trisomy
- At least **one major or two minor fetal structural** anomalies in the current pregnancy
- Chromosomal translocation, inversion, or aneuploidy in themselves or **their parent**

- Previous pregnancies with aneuploidy of a sex chromosome are not at increased risk of recurrence unless the extra chromosome was a maternally derived 'X' chromosome. Although this could be related to advanced maternal age, the derivation of the extra 'X' chromosome is not usually known.

- Screening tests are **most useful** for identification of fetuses with **Down** syndrome and trisomy **18**, but other aneuploidies **may** be suspected based on abnormal analyze levels or ultrasound findings.

- For women who first present for prenatal care > 14 wks of gestation, **the quadruple test is the best screening test** using maternal analyses.
- The final result of screening is the mother's risk of having an affected fetus.

Who IS Candidate for Screening ?

All pregnant women under 20 weeks of gestation should be offered Down syndrome/aneuploidy screening

TIMING AND COLLECTION OF MATERNAL SERUM

- Women should be encouraged to have their blood sample drawn as early in the screening time frame (**15 to 22** weeks of gestation) as possible.
- Rapid turnaround of results is important to allow time for completion of counseling and follow-up diagnostic testing, if required

- **A 10 mL** sample of blood is drawn into a red top or tiger top collection tube. Under optimal conditions, the sample should be shipped to the laboratory on the day it is obtained.

- If there is a delay in sending the sample, the **serum should be separated** from the clot and kept refrigerated until shipped.

- Analytes are stable in serum for **up to one week** when refrigerated Laboratory reports are usually available within two to three days of sample receipt.

QUADRUPLE TEST

- The quadruple test consists of:
- alpha-fetoprotein (**AFP**),
- unconjugated estriol (**uE3**),
- human chorionic gonadotropin (**hCG**),
- inhibin **A**.

- Ideally, sampling should occur between **15 to 18** weeks of gestation.

- Maternal serum **AFP and uE3** levels are, on average, **reduced** by 25 to 30 percent in pregnancies affected by Down syndrome , and **hCG and inhibin A** levels are, on average, **twice** as high as those in unaffected pregnancies .

What is the Level of detection rate?

- However The quadruple test is the **best available test** for Down syndrome screening in women who present for care in the second trimester.

- ----------BUT

- At a selected second trimester risk cut-off of about **1 in 250**, the detection rate of the quadruple test **is 80** % with a false positive rate of about **5%.**

Variety of Down syndrome screening tests

Efficiency of Down syndrome screening tests

Test*	FPR percent for 85 percent DR	DR for 5 percent FPR
Integrated test with nuchal translucency (1, 2)	0.9	94
Serum integrated test (1,2)	3.9	87
Combined test (1)	4.3	86
Quadruple test (2)	6.2	83
Triple test (2)	9.3	77

FPR: false positive rate; DR: detection rate; ( ): numbers in parentheses refer to trimester that test is obtained.
* All consider maternal age.
Data from: Wald NJ, Rodeck C, Hackshaw AK, et al. SURUSS in

REPORTING RESULTS

Several commercial software packages are available for Down syndrome screening analysis and reporting. Standard features included in the report are:

- Maternal date of birth weight DM Single /Multiple IVF
- Sample collection date
- Gestational age at the time of sample collection and method of dating
- Risk cut-off selected for a screen positive interpretation
- Risk of Down syndrome after screening
- Clear indication of a screen positive result
- Recommendation for follow-up studies in screen positive cases

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- Second trimester serum screening always includes screening for **open neural tube defects**, using the alpha-fetoprotein component of the test.
- Some screening programs include reporting of elevated risk of trisomy **18** and **Smith-Lemli-Opitz syndrome (SLOS)**, when present.

What is the Result of Screening Test?

What is the Result of Screening Test?

- **Negative test**: only for Trisomy
- **Positive test:**

What We do?

- Review The Pt Information
- Do Ultrasound for GA , NO. ,live

SECONDARY ULTRASOUND SCREENING

- We **do not** recommend use of ultrasound as a secondary screening tool because it does not have a sufficiently high detection rate for Down syndrome.

- When secondary ultrasound screening is performed on the **general obstetrical population**, a completely negative examination lowers the risk of Down syndrome by **four- to five-fold**.

- If one or more ultrasound markers of Down syndrome is observed, the risk of Down syndrome increases by **six- to seven-fold**.

- Depending on the woman's previously assigned risk (by **maternal age or quadruple testing**), the ultrasound study can change a screen negative to a screen positive result, or vice versa .

SECONDARY SCREENING WITH CIRCULATING CELL-FREE DNA

- A new test that measures circulating, free maternal and fetal DNA in maternal plasma is available for secondary screening of high risk women.

- This test has been endorsed for that purpose in an American College of Obstetricians and Gynecologists **(ACOG)** committee opinion.

- The cell-free DNA (cf DNA) test has very high sensitivity and specificity, leading to a significant reduction in the number of women falsely identified as high risk after serum screening.

- Some women with a positive serum screen may choose to undergo DNA testing because a negative DNA test may be sufficiently reassuring to allow them to avoid invasive testing for definitive diagnosis.

- The results of cf-DNA testing are typically reported 7 to 10 days after sample collection

In The Name of GOD

Obstet Gynecol. 2009 Dec;114(6):1189-96doi:
Role of second-trimester genetic sonography after Down syndrome screening.

Aagaard-Tillery KM, Malone FD, Nyberg DA

- The detection rate for a 5% false-positive rate for the genetic sonogram **alone** was **69%;**
- **the detection rate increased**
- from 81% to 90% with the **combined test**, 1
- from 81% to 90% with the **quadruple test**, 2
- from 93% to 98% with the **integrated test**,
- from 97% to 98% with the **stepwise test**, 1,2
- from 95% to 97% with the **contingent test**

- Genetic sonography can **increase detection** rates substantially for combined and quadruple tests and more **modestly** for sequential protocols.

In The Name of GOD

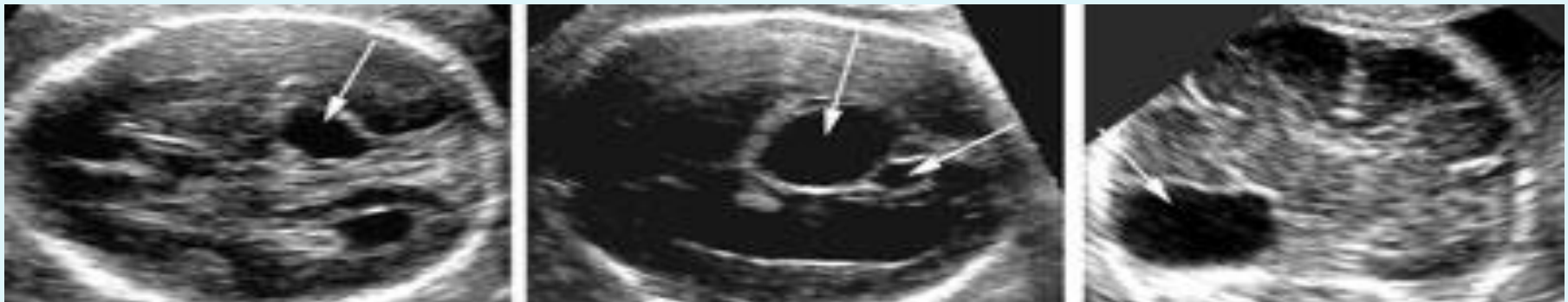
ULTRASOUND MARKERS

- The antepartum detection of **fetal aneuploidy** is a major goal of **prenatal screening** programs.

- **Sonographic examination** is useful because fetuses with abnormal karyotypes **often** have anatomic changes or anomalies.

Genetic sonogram

- A "genetic sonogram" uses ultrasound to assess the fetus for both structural anomalies and soft markers suggestive of Down synd.



What is the Significance of G.Sonogram

- The genetic sonogram can be utilized successfully to **better define** the **risk** of Down if both the presence and the number of soft markers identified are taken into account when revising the individual woman's risk of carrying an affected fetus.

- Nyberg reported the positive likelihood ratio for Down synd with no soft markers is 0.4, one marker is 2 , two markers is 10 , and three or more markers is 115 .

- Using the genetic sonogram to **modify the prior risk** from maternal age or **2nd trimester serum** screen is currently accepted practice by most centers involved in Down syndrome screening.

- When the genetic sonogram is used to modify standard serum screening results, **sensitivity** has been estimated to be at least **90 %.**

- Adding the genetic sonogram to the quadruple, integrated, stepwise, and contingent tests resulted in a rise in detection rate from 81, 93, 97, and 95 percent, respectively, to 90, 98, 98, and 97 percent

ULTRASOUND Soft MARKERS

- Soft markers are ultrasound findings of uncertain significance.

- They are often associated with normal fetuses (**normal variants**), usually have **no clinical sequelae**, and are **transient**, resolving with advancing gestation or after birth.

- They do carry an **increased risk for fetal aneuploidy**, however, and correlation with the patient's biochemical risk status should be done.

Structural Anomaly

- Fetuses with sonographic evidence of a **structural anomaly** are at **increased risk** of having a chromosomal abnormality.

- The **magnitude of risk** is highly dependent upon the **specific malformation** like omphalocel with or without liver.

ULTRASOUND Soft MARKERS

	Trimester
●Increased Nuchal Translucency (NT)	**1**
●Absent nasal bone (NB)	**1**

●Echogenic bowel	**2**
●Pyelectasis	**2**
●Shortened long bones (humerus, femur)	**2**
●Echogenic intracardiac focus	**2**
●Choroid plexus cysts	**2**

Soft Markers

- Isolated soft markers are identified in 11 to 17 %of **normal fetuses** .

- The **prevalence is higher** in aneuploid fetuses and the likelihood of aneuploidy is significantly increased when more than one marker is present.

What Do you Do ?

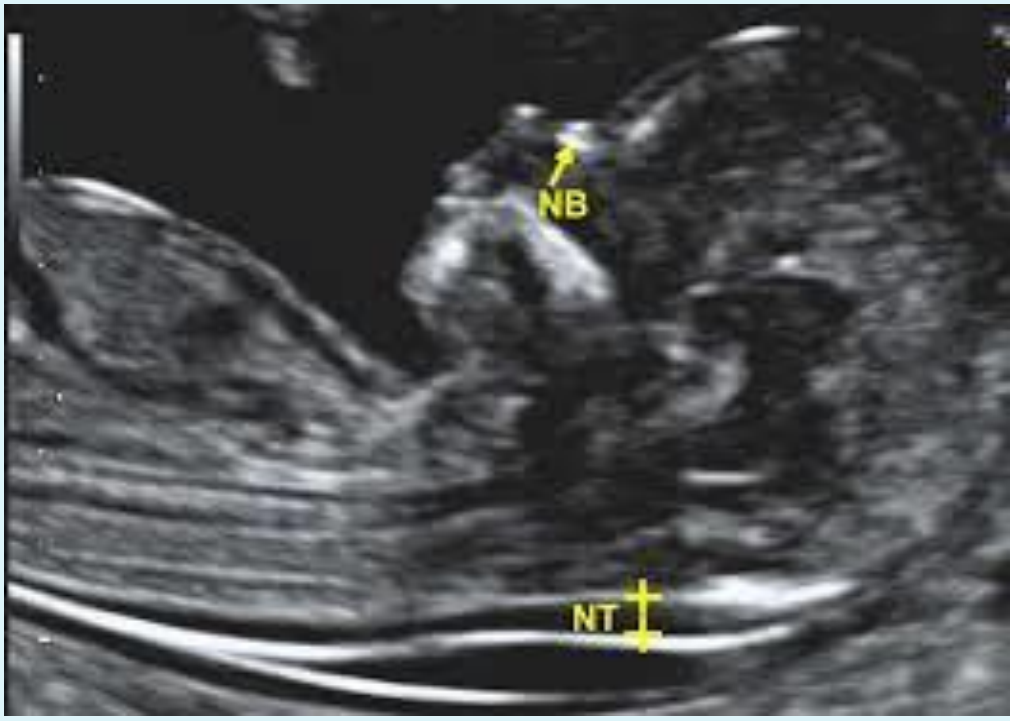
- Even in this setting, **use of soft markers** for screening for, or excluding, fetal aneuploidy is **inefficient**; however, a detailed evaluation of fetal **anatomy should** be performed **whenever one or more soft markers** has been identified.

Soft Markers in 2nd Trimester

Nuchal Translucency

Nuchal translucency is the translucent nuchal space at the posterior fetal neck in the midsagittal plane .

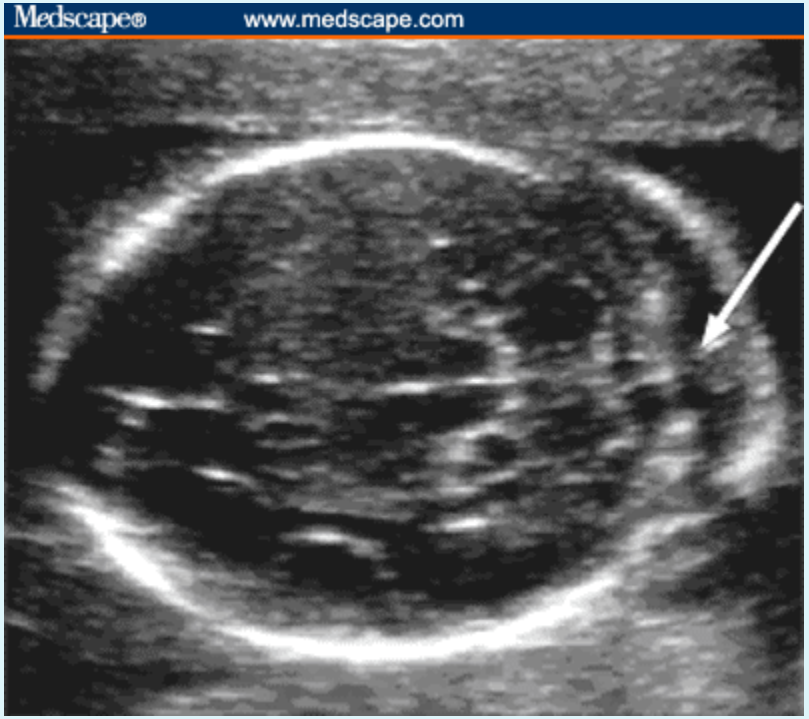
An increase in the nuchal translucency measurement is associated with an **increased risk** of fetal aneuploidy, **structural anomalies**, **genetic syndromes,** and adverse outcome.



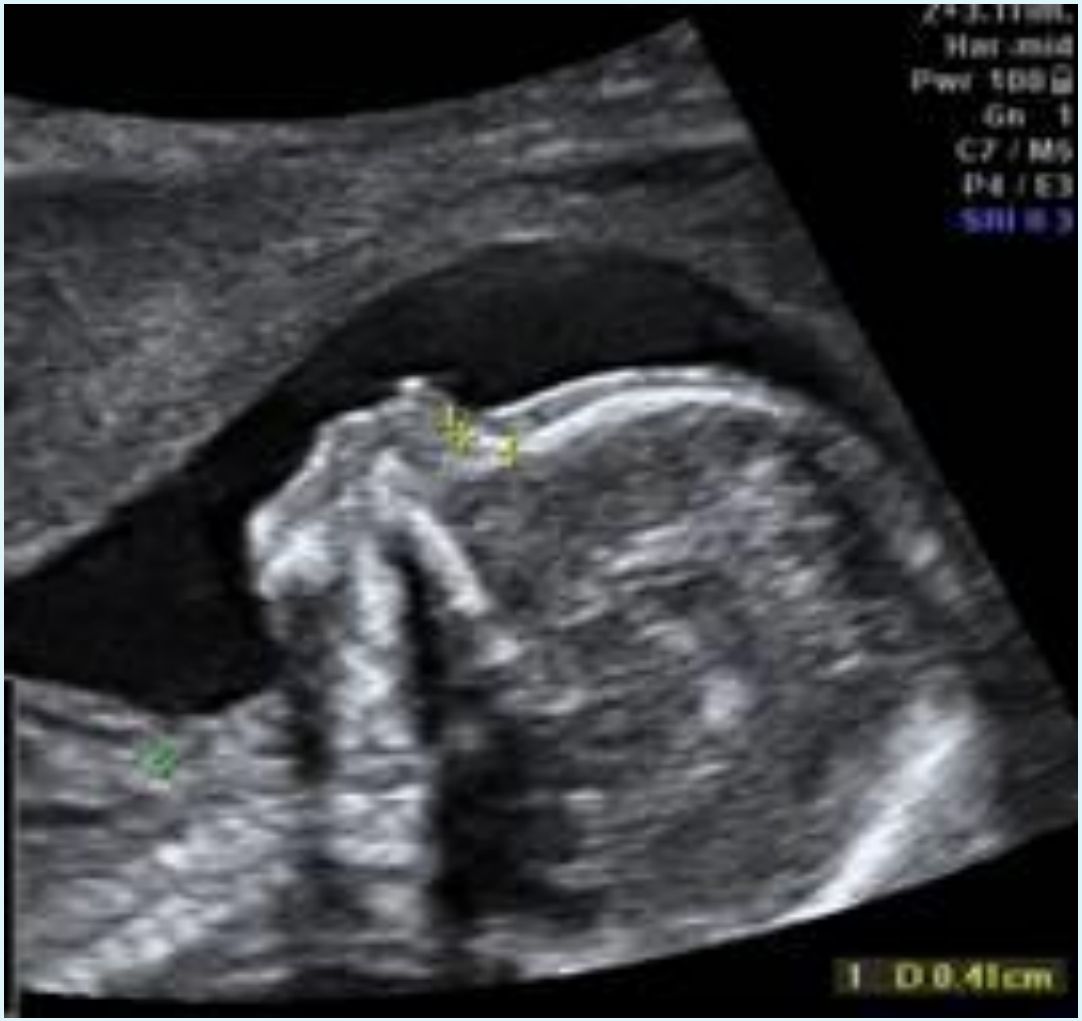
Increased Nuchal Fold

- The NF , rather than NT , is measured in the 2nd trimester.

- An increased nuchal fold is detected in **20 to 33 %** of fetuses with Down synd. and 0.5 to 2 % of euploid fetuses.



Hypoplastic Nasal Bone



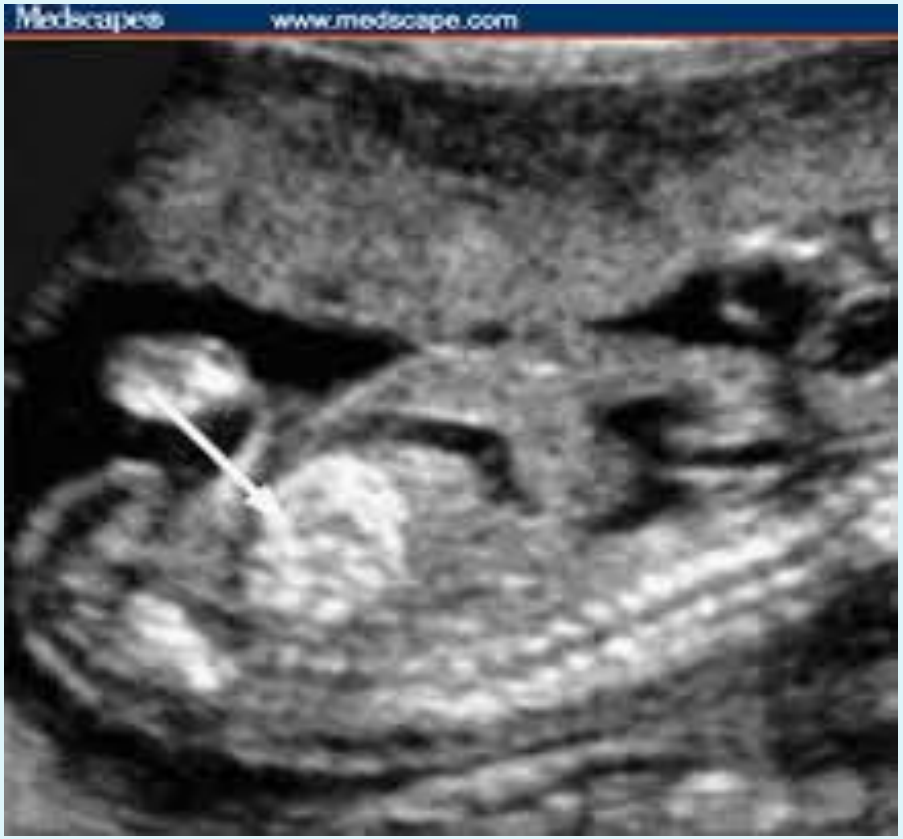
- In the **second trimester**, the reported **sensitivity** of absent nasal bone for Down is generally **lower than** in the **first** trimester.

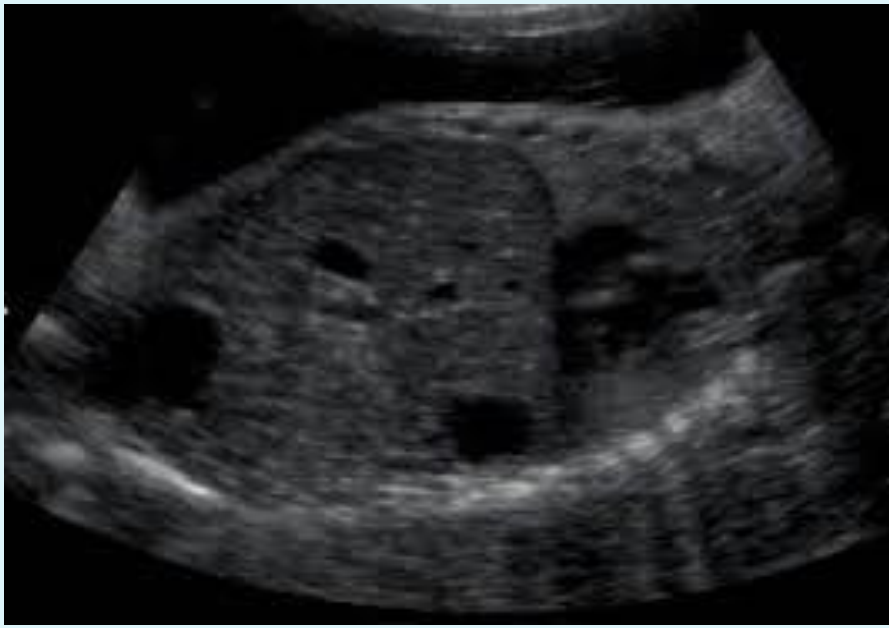
- **Absent Nasal Bone** is about 40% of Down syn fetuses and 0.7% of euploid fetuses (lower than in first trimester).

- It is **hypoplastic** in about 60% of Down fetuses and 7% of euploid fetuses In the second trimester.

- Using either nasal **hypoplasia** or **absence** as a marker **increases sensitivity**, but also the **false positive** rate.

Echogenic Bowel





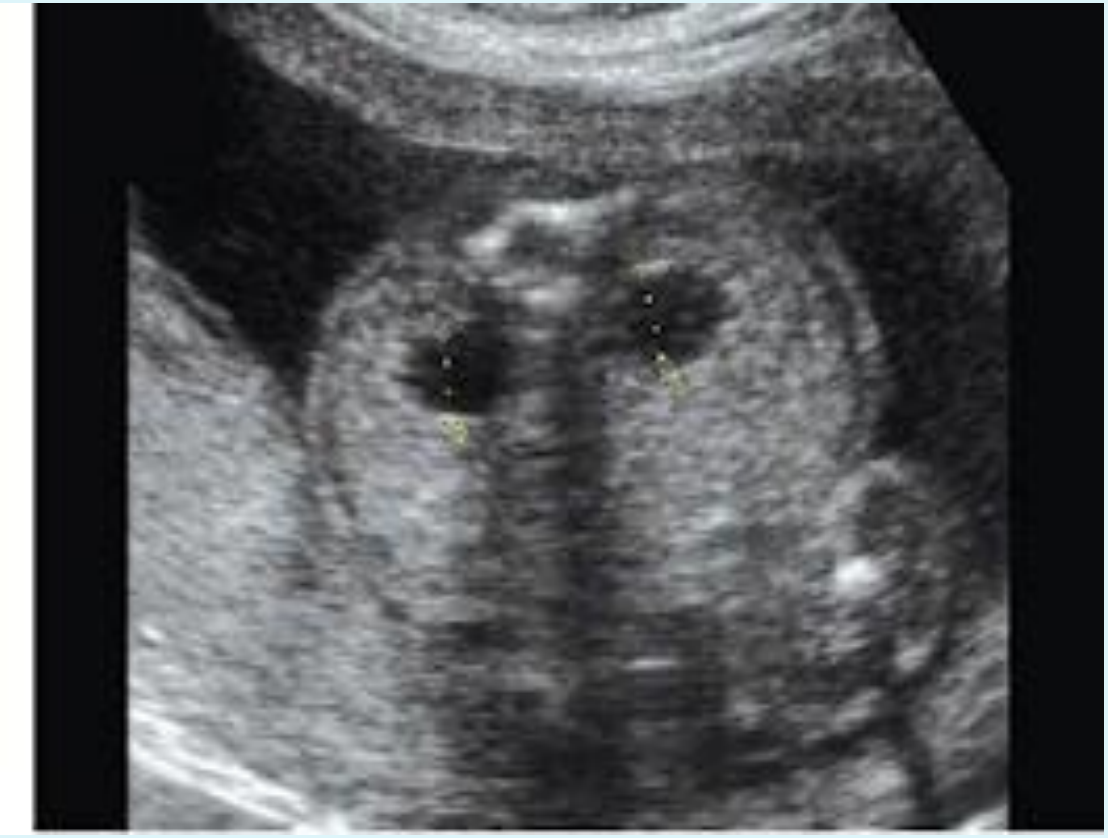
Aneuploidy has been associated with abnormal bowel function (**decreased motility, increased water absorption**) in newborns and it is possible that a similar process in the fetus could cause echogenic bowel.

- It may be first identified in the first trimester but is **more commonly** identified in the 2nd trimester.

- It has been found in 1 to 2 %of normal fetuses and 13 to 21% of fetuses with Down syn.

- A variety of complications have also been associated with this finding:
- Chromosomal defects,
- Fetal growth restriction
- Cystic fibrosis
- Congenital infection,
- Intra-amniotic bleeding
- GI obstruction

Pyelectasis

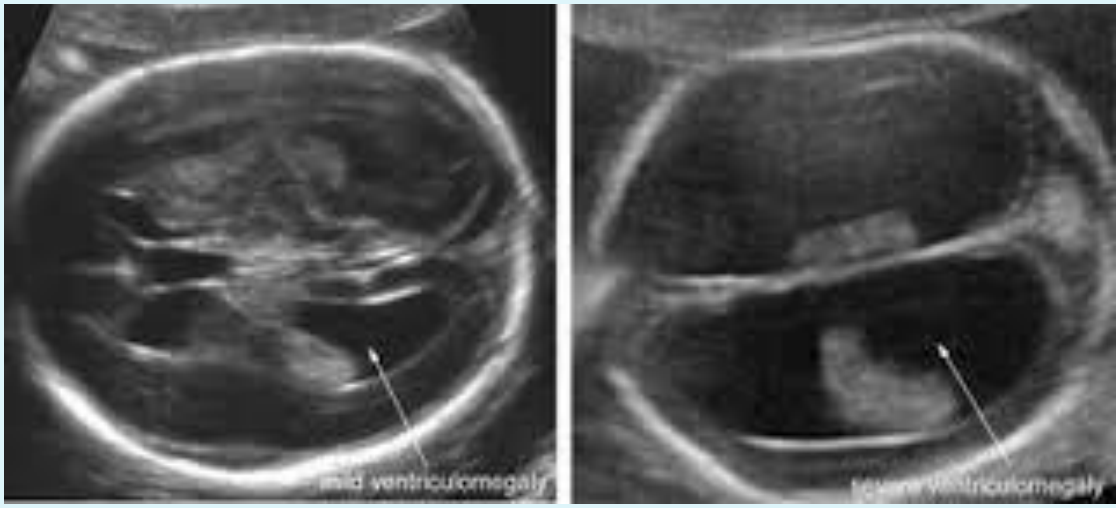


Mild dilation (4 to 7 mm in the second trimester) typically resolves over the course of gestation or in the postnatal period.

- In both euploid and aneuploid fetuses, pyelectasis is usually caused by vesicoureteral reflux, but may be related to obstruction.
- Pyelectasis is as renal pelvic diameter of 4 mm at 15 to 19 wks
- Pyelectasis in 10 to 25 % of fetuses with Down and 1 to 3 % of euploid fetuses .
- Aneuploidy is present in 0.3 to 0.9 % of fetuses with isolated pyelectasis.
- When pyelectasis is identified in an otherwise normal second trimester fetus, a normal cell-free DNA test for fetal aneuploidy can be very reassuring and obviate the need for invasive testing.

Mild ventriculomegaly is detected in 4 to 13%of fetuses with Down and 0.1 to 0.4 % of euploid fetuses.

The risk of abnormal outcome, such as Down , increases with the degree of V.megaly, progression of V.megaly, and presence of other anomalies.



- We suggest the following diagnostic evaluation when fetal ventriculomegaly is detected:

- A **comprehensive fetal sonogram**.

- A detailed **family and medical history** to look for **possible genetic or infectious** causes of ventriculomegaly.

- **Fetal karyotype; chromosomal microarray** should be offered to patients with isolated mild ventriculomegaly .

- **Testing for infectious** etiologies (**CMV , toxo**) ideally by PCR on amniotic fluid or by maternal serology. Testing for Zika virus or other infections may be considered if risk factors or specific exposures are present.

- **MRI** for isolated ventriculomegaly in which the etiology is **unexplained**.

- A **follow-up ultrasound examination** to assess progression or regression.

- Most children with **isolated, mild** ventriculomegaly have a normal outcome.

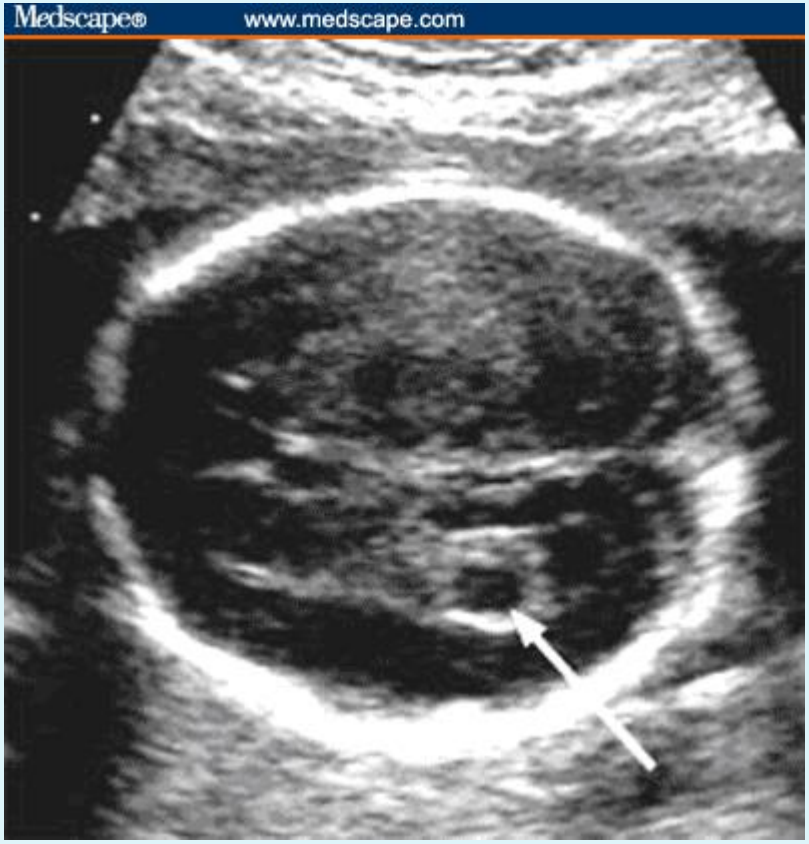
- The risk of **abnormal outcome** increases with the **severity** of ventriculomegaly, progression of ventriculomegaly, and **presence** of other anomalies.

Shortened Long Bones

- Fetuses with Down syndrome have **slightly shorter long-bones** than their normal counterparts.
- A **shortened humerus** appears to be a **better** predictor of Down syndrome than a shortened femur ,positive likelihood ratio 4.8 and 3.7.

- **Severely shortened** (<5th%) or abnormal appearing long bones may be a sign of a skeletal **dysplasia** or early onset **IUGR**.

Choroid Plexus Cyst



Results from filling of the neuroepithelial folds with CSF

- Choroid plexus cysts are present in 30 to 50 % of fetuses with **trisomy 18** compared with 0.6 to 3 % of all 2nd trimester fetuses.

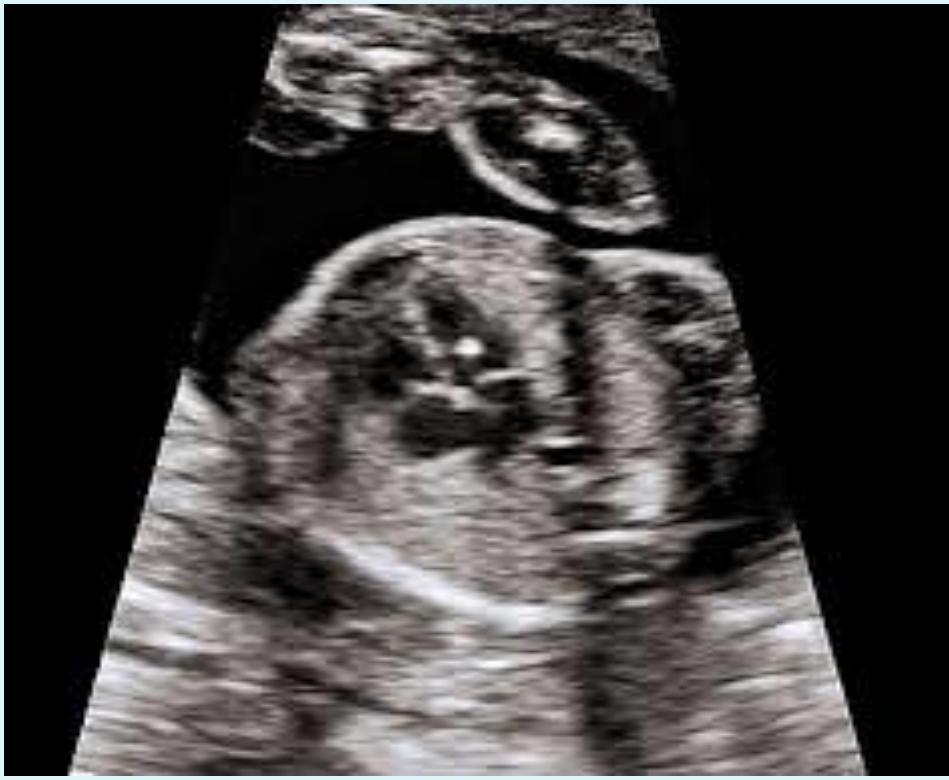
- When isolated choroid plexus cyst(s) are detected in an otherwise low risk patient , the risk of amniocentesis (1/250 chance of pregnancy loss) is higher than the risk that the fetus has **trisomy 18** (less than 1/374).

- We suggested **restricting amniocentesis** to patients with additional sonographic abnormalities or high risk factors (advanced maternal age [older **than 32 yrs** at delivery)**abnormal serum analyte** screen) .

- When choroid plexus cysts are identified in an otherwise normal 2nd-trimester fetus, a normal cell-free DNA test can be very reassuring and obviate the need for invasive testing.

Intra Cardiac Echogenic

- In the second trimester, 21 to 28 % of fetuses with Down have an echogenic intracardiac focus, while this is seen in 3 to 5 % of normals.
- Is more common in fetuses with **trisomy 13** than trisomy 21.
- When an intracardiac focus is identified in an otherwise normal 2nd trimester fetus, a normal cell-free DNA test can be very reassuring and obviate the need for invasive testing.



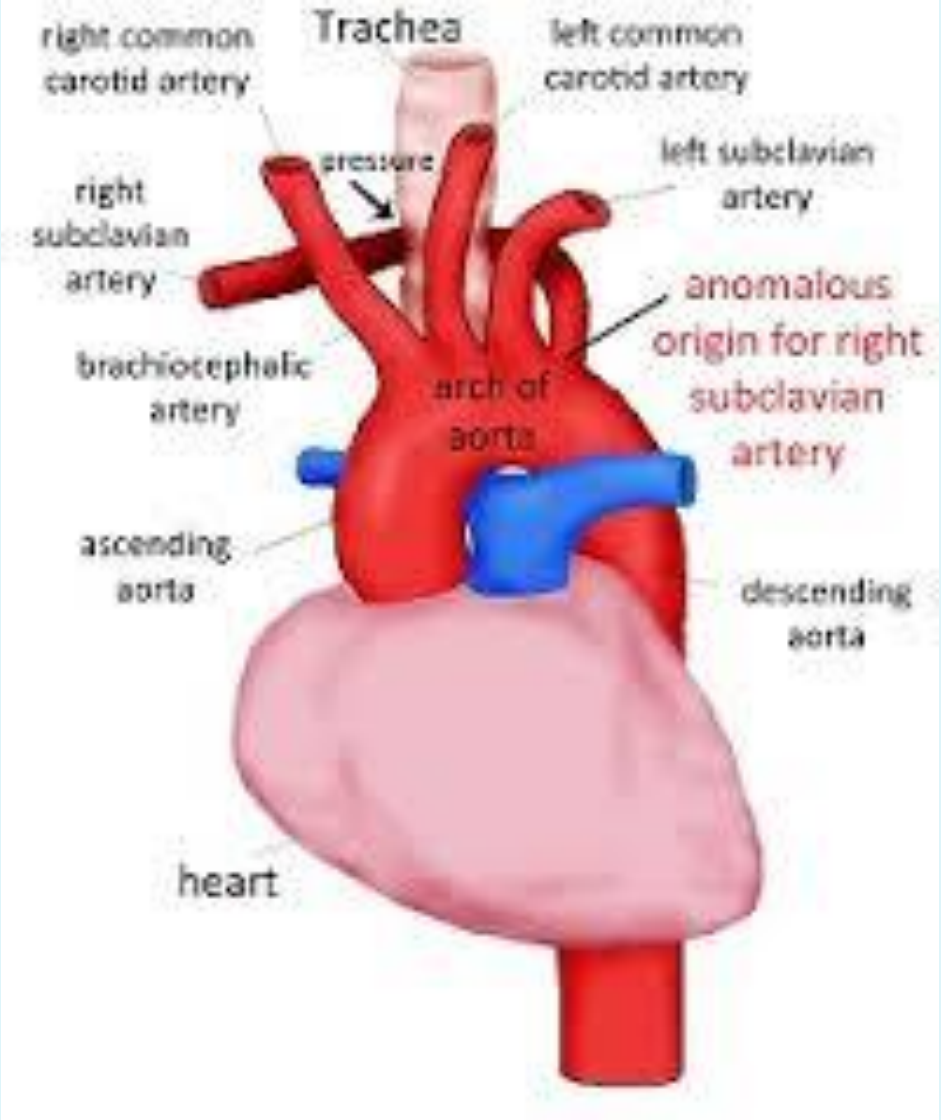
Other Markers

- Although more prevalent in patients with Down syndrome:
- Sandal gap toe
- Short ear length
- hypoplastic wedge-shaped middle phalanx of the fifth digit that causes it to curve toward the fourth finger (clinodactyly), are also common normal variants

- Micrognathia is one of the characteristics of a long list of chromosomal and nonchromosomal syndromes. Prenatal diagnosis of micrognathia can be made subjectively or objectively by comparing mandible measurements against standard tables.

ARSA

An aberrant right subclavian artery is more common in Down syndrome fetuses than euploid fetuses (prevalence 24% in Down versus about 1% in screened obstetric populations but it is usually **not an isolated** finding in Down syndrome.



Definitions of the markers

- **Ventriculomegaly:** ≥ 10 mm
- **Increased nuchal fold thickness:** ≥ 6 mm
- **Echogenic bowel:** equal echogenicity to that of bone
- **Mild hydronephrosis:** renal pelvis AP diameter varied from 3 to 4 or 5 mm
- **Hypoplastic nasal bones:** cut-off varied with gestation
- **Short femur or humerus:** cut-off varied with gestation

Meta-analysis of second trimester markers for trisomy 21

Agathokleous et al., UOG 2013

Marker	DR	FPR	LR + ve	LR – ve	Isolated marker
Cardiac echogenic focus	24.4	3.9	5.8	0.80	0.95
Ventriculomegaly	7.5	0.2	27.5	0.94	3.81
Increased nuchal fold	26.0	1.0	23.3	0.80	3.79
Echogenic bowel	16.7	1.1	11.4	0.90	1.65
Mild hydronephrosis	13.9	1.7	7.6	0.92	1.08
Short humerus	30.3	4.6	4.8	0.74	0.78
Short femur	27.7	6.4	3.7	0.80	0.61
ARSA	30.7	1.5	21.5	0.71	3.94
Absent or hypoplastic NB	59.8	2.8	23.3	0.46	6.58

No markers LR 0.13 = 7.7 fold reduction

Meta-analysis 47 studies 1995–2012

- **No markers LR 0.13 = 7.7 fold reduction**

Estimation of combined LR of multiple markers

- The LR for trisomy 21 of individual isolated markers is derived by **multiplyin**g the **+ve LR** for the given marker by the **–ve LR** of each of **all other** markers.

- The same approach when any combination of ≥ two markers are detected e.g. with mild hydronephrosis (+ve LR 7.6) and ventriculomegaly (+ve LR 27.5), the combined +ve LR is 209 (7.6 × 27.5). This must be multiplied by the **combined -ve LR** of all other markers that were not present (0.8 × 0.8 × 0.9 × 0.8 × 0.7 × 0.5 = 0.2) to derive a **final combined LR of 31.6**.

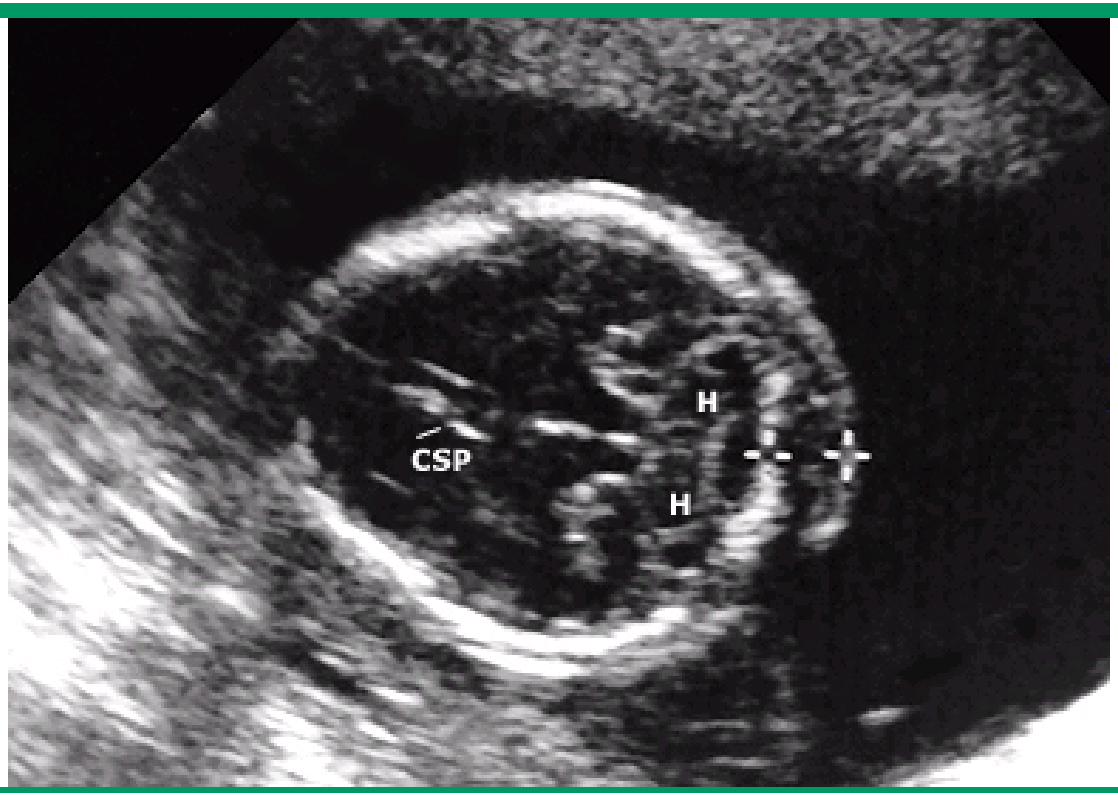
Thanks for Attention

- Screening for soft markers is not a component of a basic obstetrical ultrasound examination.
- Detection and reporting of soft is controversial because this information is anxiety-provoking for patients, requires considerable time for counseling, and may lead to invasive prenatal testing. Such testing may result in procedure-related loss of a normal fetus, and is costly.

Nuchal fold

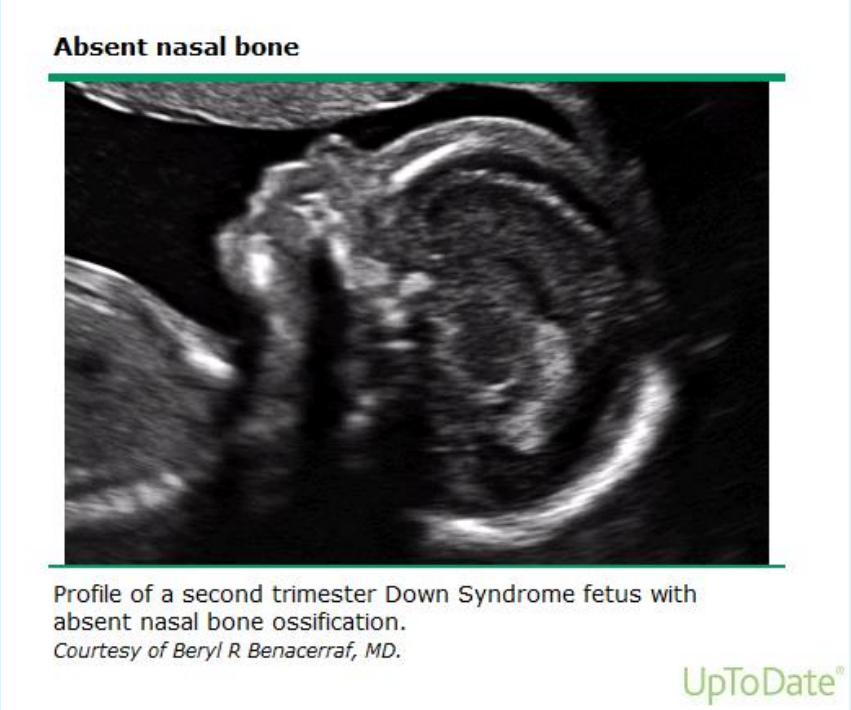
- An increase in this measurement is also associated with aneuploidy. An increased nuchal fold is detected in 20 to 33 percent of fetuses with Down syndrome and 0.5 to 2 percent of euploid fetuses

Thickened fetal nuchal skin fold in the second trimester



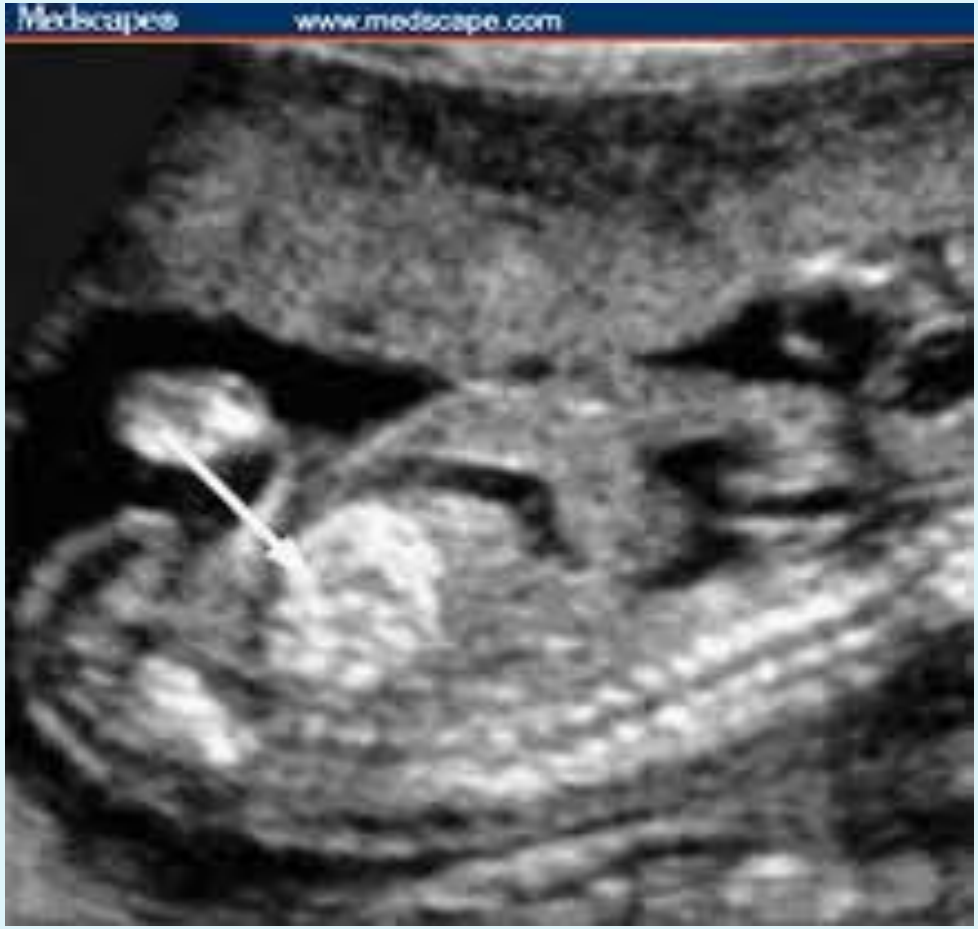
Ultrasonogram obtained during the second trimester of pregnancy to measure the thickness of the nuchal skin fold. Nuchal skin-fold thickness is measured by placing the calipers at the outer edges of the occipital bone and skin surface. The correct level is the transaxial plane containing the cavum septi pellucidum (CSP) and the cerebellar hemisphere (H).

- The nasal bone is absent in 30 to 43 percent of Down syndrome fetuses and 0.3 to 0.7 percent of euploid fetuses . Using either nasal hypoplasia or absence as a marker increases sensitivity; when either an absent or hypoplastic nasal bone is detected, sensitivity for Down syndrome is 60 percent and the false positive rate increases to 2 to 4 percent. However, the detection rate depends upon the threshold used. Options include the ratio of biparietal diameter-nasal bone length (BPD/NB >9)



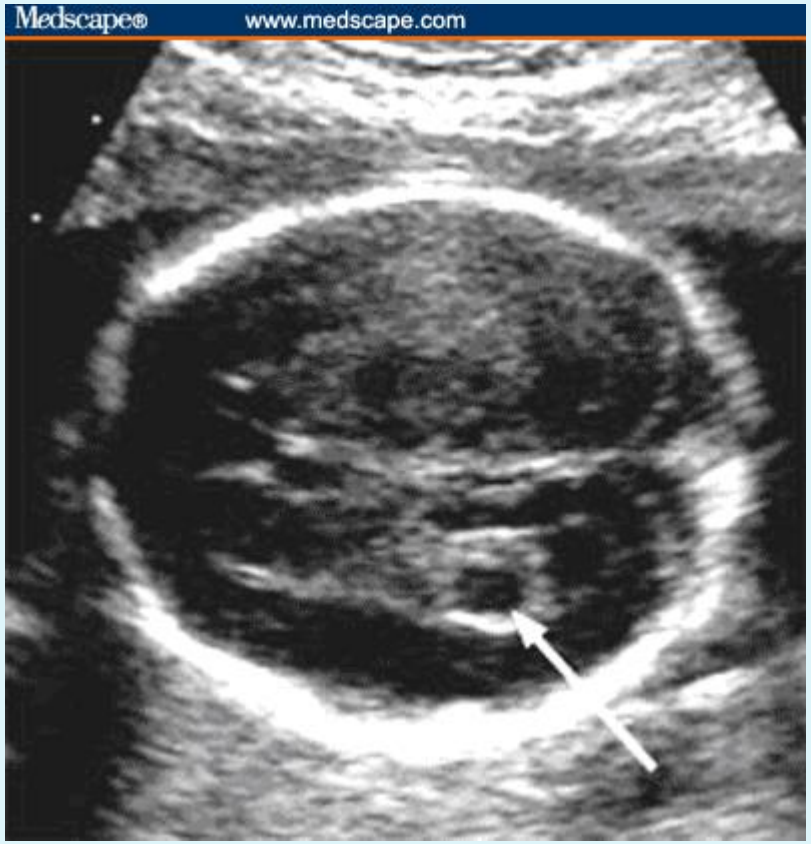
- a single pre-defined threshold for abnormal nasal bone length (≤2.5 mm), a gestational age-based threshold (<2.5th or 5th centile) based on the distribution of nasal bone length in normal fetuses , or use of multiple of the median (MoM) of nasal bone length for gestational age (**<0.75** MoM). In a comparative study, the **MoM method** appeared to have the **best combination** of **sensitivity and specificity** (49 and 92 percent, respectively, compared with 61 and 84 percent, respectively, for BPD/NB >11.

Echogenic bowel



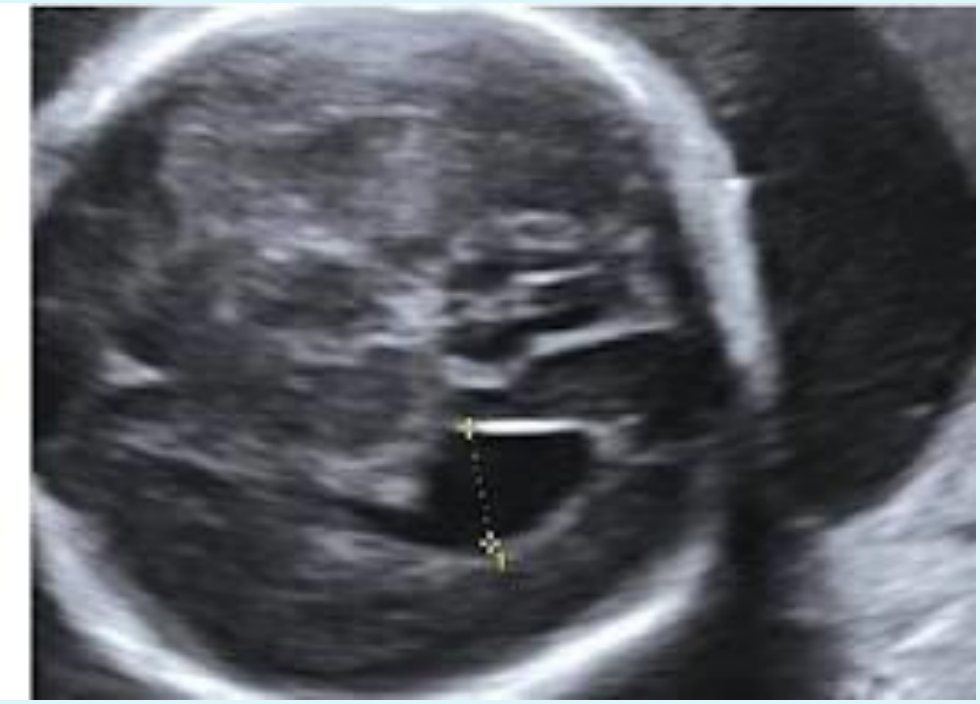
refers to increased echogenicity (brightness) of the fetal bowel noted on second trimester sonographic examination . It may be first identified in the first trimester but is more commonly identified in the second trimester. It has been found in 1 to 2 percent of normal fetuses and 13 to 21 percent of fetuses with Down syndrome. Aneuploidy has been associated with abnormal bowel function (decreased motility, increased water absorption) in newborns and it is possible that a similar process in the fetus could cause echogenic bowel

Pyelectasis



- pyelectasis as renal pelvic diameter of ≥4 mm at 15 to 19 weeks of gestation demonstrated pyelectasis in 10 to 25 percent of fetuses with Down syndrome and 1 to 3 percent of euploid fetuses.
- Aneuploidy is present in 0.3 to 0.9 percent of fetuses with isolated pyelectasis . In both euploid and aneuploid fetuses, pyelectasis is usually caused by vesicoureteral reflux, but may be related to obstruction. Mild dilation (4 to 7 mm in the second trimester) typically resolves over the course of gestation or in the postnatal period.

Ventriculomegaly



most children with isolated, mild ventriculomegaly have a normal outcome. Mild ventriculomegaly is detected in 4 to13 % of fetuses with Down syndrome and 0.1 to 0.4 % of euploid fetuses . The risk of abnormal outcome, such as Down syndrome, increases with the degree of ventriculomegaly, progression of ventriculomegaly, and presence of other anomalies.

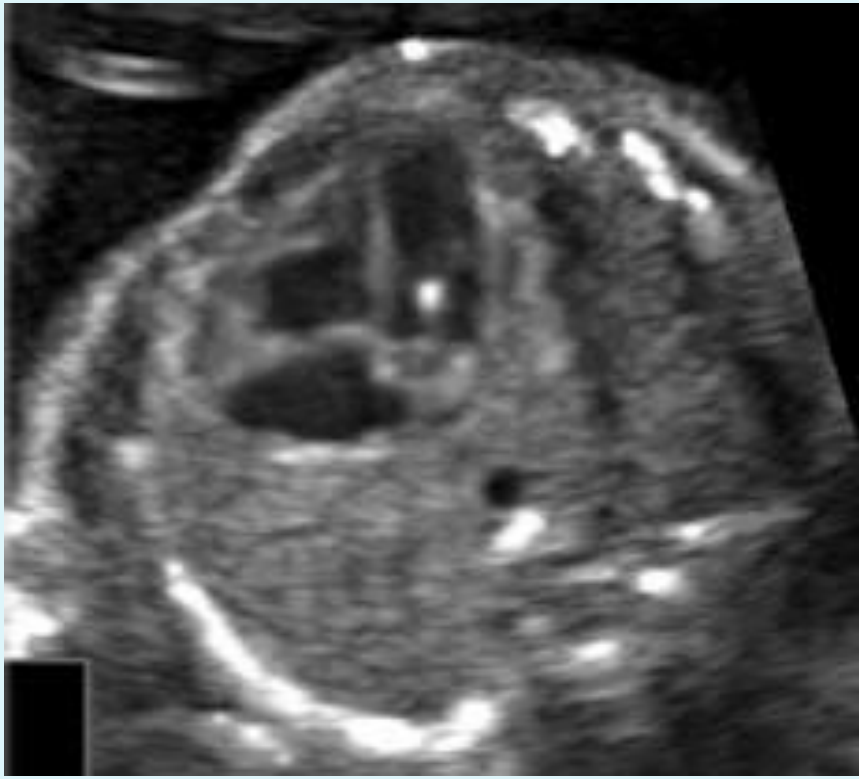
- a variety of fetal and pregnancy complications have also been associated with this finding: chromosomal defects, fetal growth restriction, cystic fibrosis, congenital infection, intraamniotic bleeding, and gastrointestinal obstruction

Shortened long bones

- Fetuses with Down syndrome have slightly shorter long-bones than their normal counterparts. A shortened humerus appears to be a better predictor of Down syndrome than a shortened femur (positive likelihood ratio 4.8 and 3.7, respectively) .
- each laboratory should develop specific standards for its own population.
- We consider abnormal an observed-to-expected length ratio (based on biparietal diameter) of less than 0.9.

- In contrast, severely shortened (<5th percentile) or abnormal appearing long bones may be a sign of a skeletal dysplasia or early onset fetal growth restriction

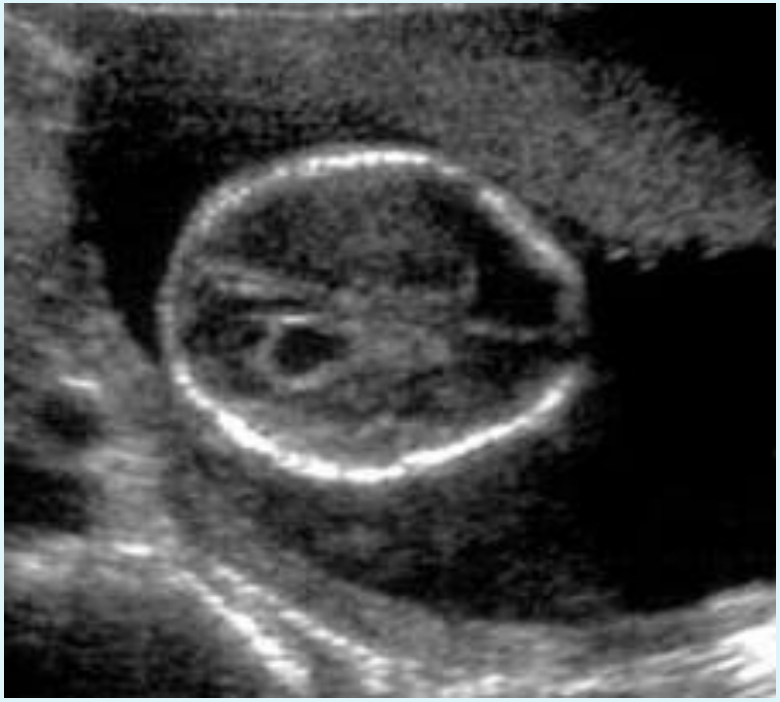
- Echogenic intracardiac foci may be first identified in the first trimester. In the second trimester, 21 to 28 percent of fetuses with Down syndrome have an echogenic intracardiac focus, while this is seen in 3 to 5 percent of normals . It is thought to be related to microcalcification and fibrosis of the papillary muscle or chordae, often disappears later. calcification was more common in fetuses with trisomy 13 than trisomy 21 (39 and 16 percent, respectively



- the general consensus about the number or location of echogenic foci have not been affects the risk of fetal aneuploidy .

Choroid plexus cysts

- Choroid plexus cysts are most common in the second .
- They usually disappear by the third trimester; those that persist are usually asymptomatic and benign.
- They appear to result from filling of the neuroepithelial folds with cerebrospinal fluid . The typical sonographic appearance is a small (usually less than 1 cm).
- A wide range of appearances are possible from unilateral single cysts to bilateral septated and multiple cysts . A targeted scan for other fetal anomalies should follow imaging of these cysts.



- in 30 to 50 percent of fetuses with trisomy 18 compared with 1 to 3 percent of all second trimester fetuses .
- The majority of large studies suggest that choroid plexus cyst(s) with an otherwise completely normal detailed structural survey (including examination of the face, heart, great vessels, and extremities) is highly reassuring of a normal karyotype. In addition, if the fetus is able to unclench its hand and hold it open, trisomy 18 is not likely. When isolated choroid plexus cyst(s) are detected in an otherwise low risk patient , the risk of amniocentesis (1/250 chance of pregnancy loss) is higher than the risk that the fetus has trisomy 18 (less than 1/374).
- We suggested restricting amniocentesis to patients with additional sonographic abnormalities or high risk factors .

- Other — Although more prevalent in patients with Down syndrome, sandal gap toe, short ear length, and a hypoplastic wedge-shaped middle phalanx of the fifth digit that causes it to curve toward the fourth finger (clinodactyly), are also common normal variants .
- Micrognathia is one of the characteristics of a long list of chromosomal and nonchromosomal syndromes . An aberrant right subclavian artery appears to be a strong predictor of Down syndrome (positive likelihood ratio 21), but has only been evaluated in two small studies . It has been detected in 18 to 47 percent of Down syndrome fetuses and 1 to 2 percent of euploid fetuses.

Abnormal Dappler

- The observation of persistent reversed end-diastolic umbilical artery flow (REDV) in the fetus with nuchal thickening appears highly predictive of aneuploidy . Persistent REDV at 10 to 14 weeks of gestation who underwent karyotyping found nine (82 percent) had aneuploidy .

- Abnormal flow in the ductus venosuseuploid fetuses (3 percent), trisomy 13 (55 percent), trisomy 18 (58 percent), and trisomy 21 (66 percent) and those with cardiac defects .

- Tricuspid regurgitation ; In one study, tricuspid regurgitation at 11 to 13 weeks was observed in 0.9 percent of euploid fetuses, 55.7 percent of fetuses with trisomy 21, 33.3 percent of fetuses with trisomy 18, 30 percent of fetuses with trisomies 13, and 37.5 percent of fetuses with Turner syndrome.

STRUCTURAL ANOMALIES

- The frequency of **chromosomal abnormalities** is **increased** in fetuses with sonographic evidence of **structural anomalies**. an abnormal karyotype in these fetuses was 11 percent versus only 0.5 percent in normal liveborn.
- The magnitude of risk for chromosomal abnormality is highly dependent upon the specific malformation.

FETAL GROWTH RESTRICTION

- Although the most **common etiologies** for small fetal size are **uteroplacental insufficiency** and **constitutional** factors, **aneuploidy** has been detected in **20 percent** of pregnancies referred for further evaluation of a small .

- However, almost all small fetuses with karyotypic abnormalities **also have structural defects**: only 2 percent of fetuses with isolated growth restriction have abnormal chromosomes.

- When the **crown-rump length** was **shorter** than expected (ie, observed/expected CRL ≤0.86) the risk of any aneuploidy was significantly increased.

SINGLE UMBILICAL ARTERY

- There is a well documented association between single umbilical artery (SUA) and an increased risk of aneuploidy **when additional fetal malformations** are detected.

- The rate of aneuploidy with isolated SUA is not known, but most experts **do not recommend routine chromosomal analysis** if there are **no other** .

Likelihood ratio of Down syndrome based on the presence of an isolated soft marker (pooled results)

Finding	Sensitivity Down syndrome, percent	False positive rate (ie, marker detected in euploid karyotype), percent	Positive likelihood ratio if the marker is isolated, percent*
Absent or hypoplastic nasal bone	48.9 to 69.9	1.9 to 4.0	6.58
Aberrant right subclavian artery	17.9 to 47.4	1.0 to 2.1	3.94
Ventriculomegaly•	4.2 to 12.9	0.1 to 0.4	3.81
Increased nuchal fold$^{\Delta}$	20.3 to 32.9	0.5 to 1.9	3.79
Hyperechoic bowel$^{\diamond}$	13.4 to 20.7	0.8 to 1.5	1.65
Pyelectasis§	11.2 to 17.2	1.4 to 2.0	1.08
Echogenic intracardiac focus	20.9 to 28.2	3.4 to 4.5	0.95
Short humerus	17.1 to 47.9	2.8 to 7.4	0.78
Short femur	19.3 to 38.1	4.7 to 8.8	0.61

Results from meta-analysis of data pooled from 48 studies of low and high risk populations. Gestational age at ultrasound 14 to 24 weeks. Most studies involved women at increased risk.

The authors concluded that if a systematic ultrasound examination is performed by expert sonologists and all of these markers are absent, the risk of Down syndrome is the mother's a priori risk based on maternal serum screening multiplied by 0.13.

* Derived by multiplying the positive likelihood ratio for the marker by the negative likelihood ratio for each of the other markers.

• Diameter of lateral cerebral ventricle ≥10 mm.

Δ Thickness ≥6 mm.

◇ Echogenicity the same as bone.

§ Anteroposterior diameter 3 to 5 mm.

Data from: Agathokleous M, Chaveeva P, Poon LCY, et al. Meta-analysis of second trimester markers for trisomy 21. Ultrasound Obstet Gynecol 2013; 41:247.