

ULTRASOUND LECTURE SERIES

— Presented by —

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Chromosomal Anomalies in the Second Trimester

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Objectives

- **To learn the sonographic signs of trisomy 21 in the second trimester and to be able to recognize affected fetuses**
- **To learn the sensitivity, specificity, and likelihood ratios of the sonographic scoring index in detection of second-trimester fetuses with Down syndrome both in high- and low-risk women**
- **To learn how to use the genetic sonogram after the patient has had prior serum and/or first-trimester testing for fetal Down syndrome**

The Second-Trimester Sonographic Detection of Autosomal Trisomies

- Trisomy 21
- Trisomy 18
- Trisomy 13
- Triploidy

Until 1984, the only screen available for Down syndrome (DS) was advanced maternal age or an occasional major fetal anomaly found on ultrasound.

In 1984-1985, two potential methods of screening for DS emerged:

- **The nuchal fold thickening**
- **The low maternal serum α -fetoprotein**

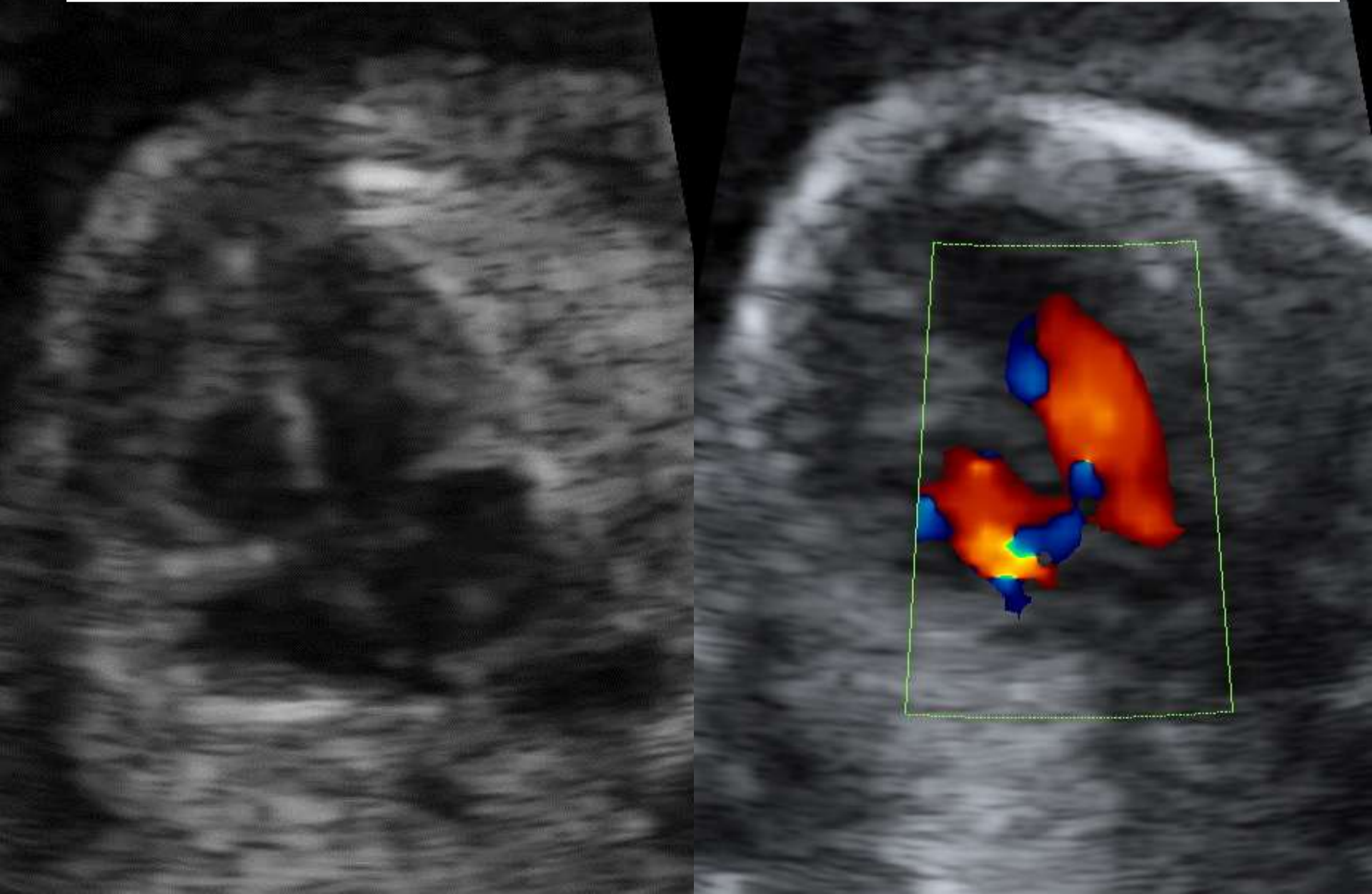
Cuckle et al. Lancet 1984; 1:926-929.

Benacerraf et al. Am J Obstet Gynecol 1985; 151:1078.

Most Common Sonographic Anomalies of Second-Trimester Down Syndrome

- Heart defect (ventricular septal defect [VSD], atrioventricular canal)
- Ventriculomegaly
- Thick nuchal fold ≥ 6 mm; some say 5 mm (considered major marker)
- Cystic hygroma
- Duodenal atresia

DS and VSD seen with color Doppler



Two different fetuses with DS and AV canal
Note the defect is more obvious in diastole than systole.

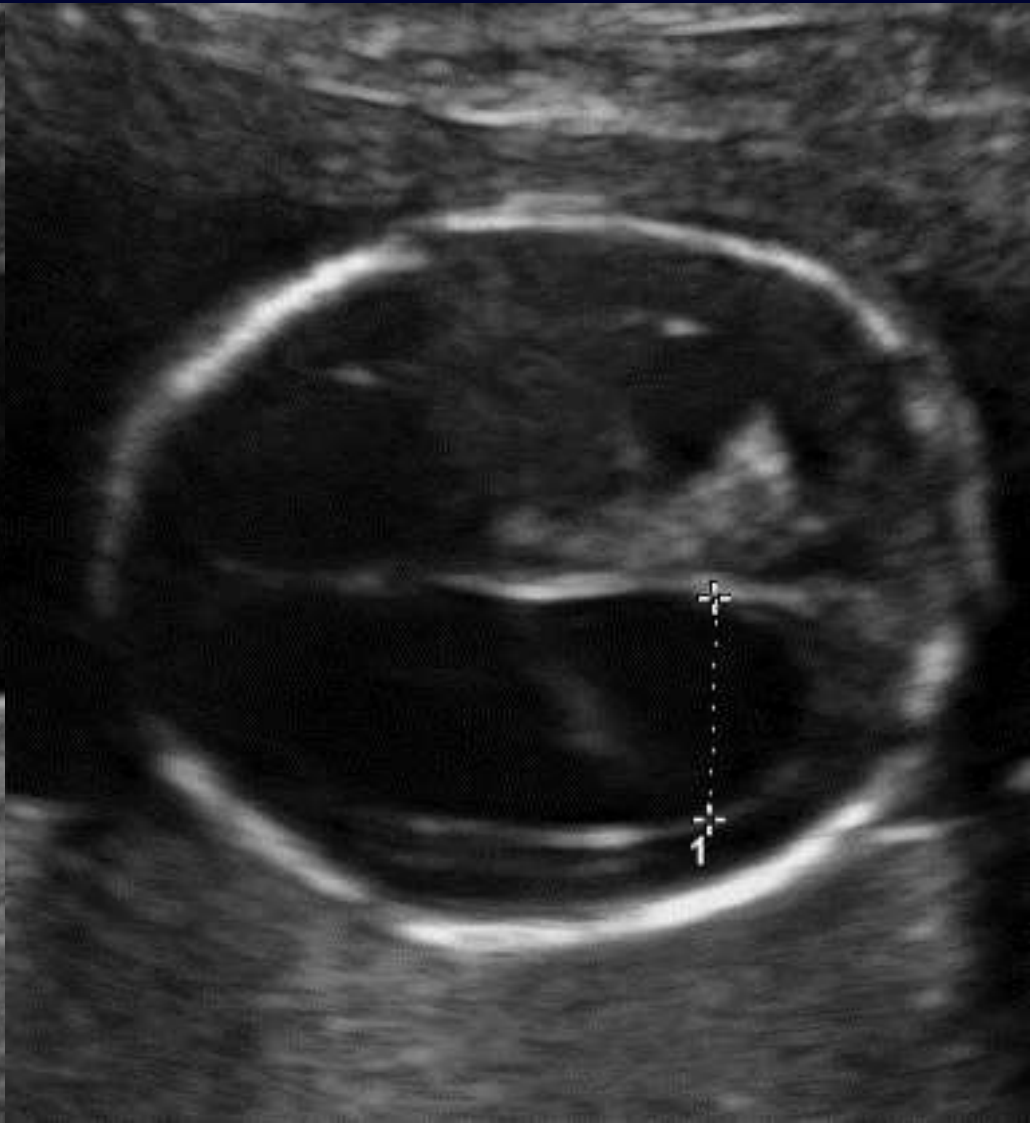
**Diastole: common AV
valve open**



**Systole: note the closed
common AV valve**



**17-week fetus with Down syndrome:
ventriculomegaly**

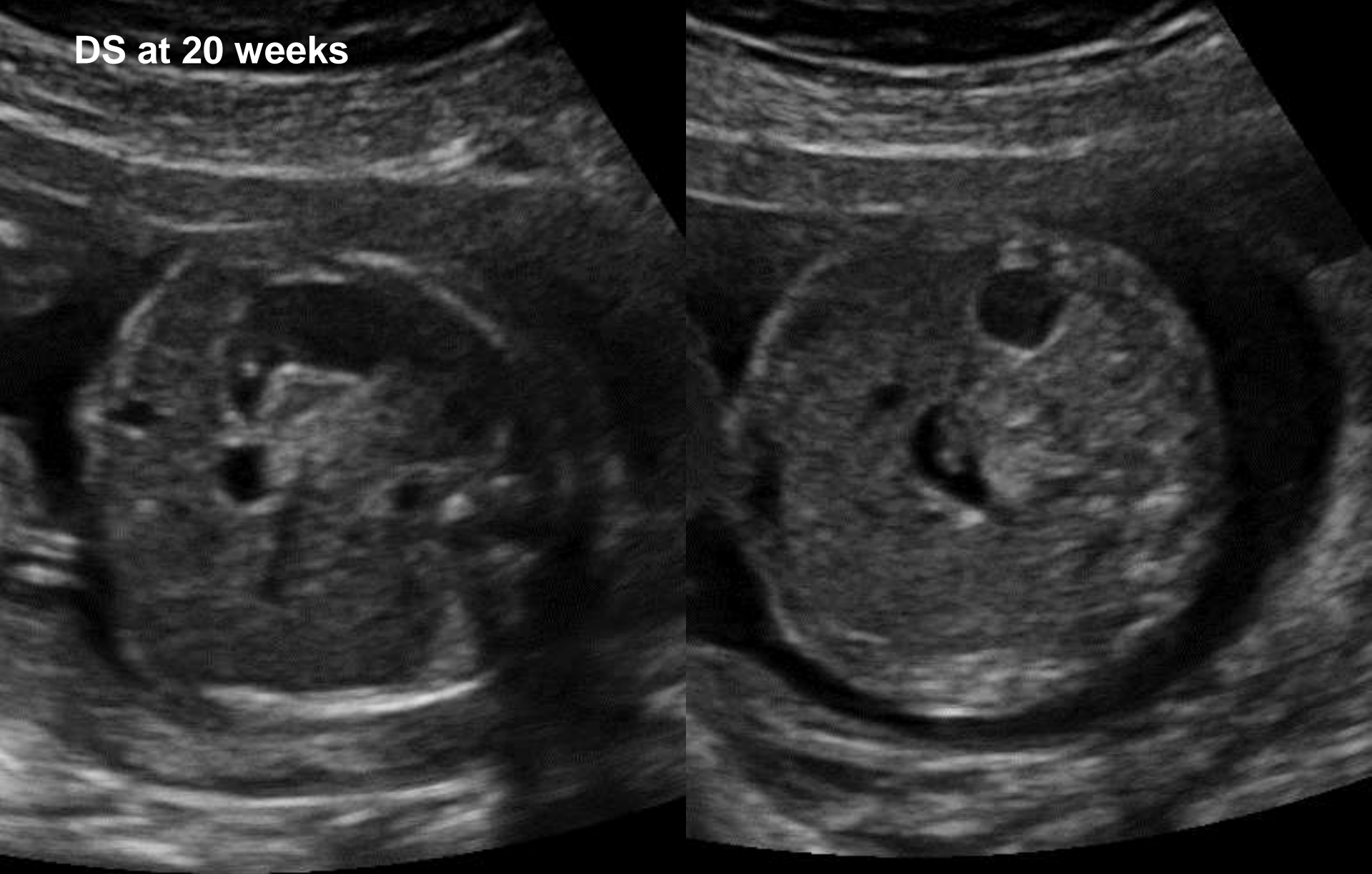


Thickened nuchal fold



Duodenal atresia may be subtle at less than 24 weeks

DS at 20 weeks



Late 2nd trimester

Duodenal atresia

3rd trimester



Additional Sonographic Features of Second-Trimester Fetal Down Syndrome

These are hard to detect accurately sonographically

- **Flat facies**
- **Clinodactyly**
- **Sandal gap foot**
- **Short ear length**
- **Short frontal lobe**
- **Wide iliac angle**

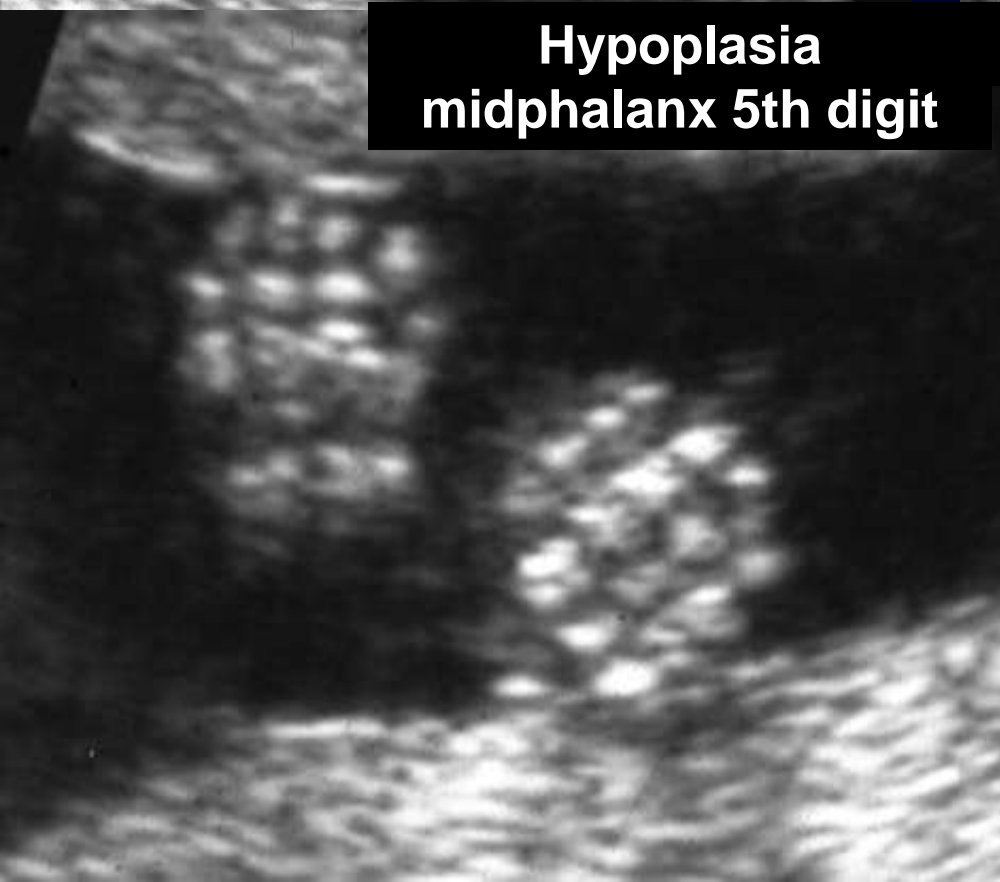
**Sandal gap
toes**



Clinodactyly



**Hypoplasia
midphalanx 5th digit**



Flat profile



Sonographic Markers of Second-Trimester Down Syndrome

- **Nuchal fold ≥ 6 mm (some say 5 mm)**
- **Short femur**
- **Short humerus**
- **Echogenic intracardiac focus**
- **Hyperechoic bowel**
- **Mild pyelectasis**
- **Absent nasal bone ossification**

Nuchal fold: 16-20 weeks

- The nuchal fold is abnormal at ≥ 6 mm (some say ≥ 5 mm).
- 40%-50% of 2nd-trimester DS fetuses have a thickened nuchal fold. False + <1%.
- This is a major marker.

First reports:

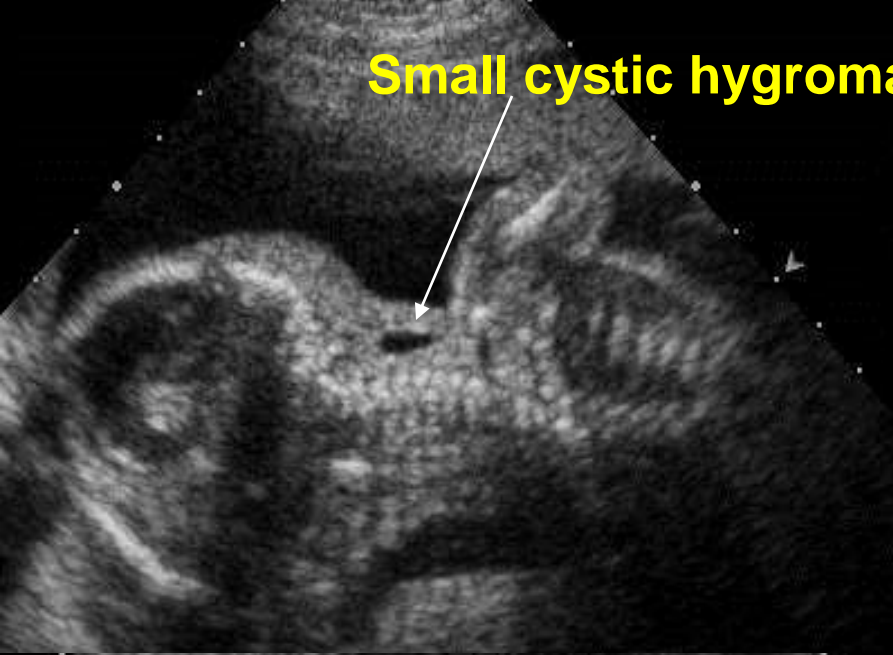
Benacerraf et al. Am J Obstet Gynecol 1985; 151:1078-1079.

Benacerraf et al. Radiology 1987; 163:811-813.

Benacerraf et al. N Engl J Med. 1987; 317:1371-1376.



Small cystic hygroma



The neck



The femur length of fetuses with DS is slightly shorter than normal fetuses

Expected femur length =

$$\mathbf{-9.3105 + 0.9028 \times BPD}$$

- **Criteria used for the femur length for an increased risk of Down syndrome—measured to expected ratio based on biparietal diameter (BPD) (not gestational age): ≤ 0.91**

First report: Benacerraf et al. Radiology 1989; 173:377.

The humeral length of fetuses with DS is shorter than normal fetuses

Expected humeral length =

$$\mathbf{-7.9404 + 0.8492 \times BPD}$$

- **Criteria used for the humeral length for an increased risk of Down syndrome—measured to expected ratio based on BPD (not gestational age): <0.90**

First report: Benacerraf et al. Radiology 1989; 173:377.

The echogenic intracardiac focus

- Discrete “dot” in the cardiac ventricle which is as bright as bone
- Studies suggest a 2× increased risk of DS when isolated



First reports:

Brown et al. *J Ultrasound Med* 1994; 13:613-616.

Lehman et al. *Radiology* 1995; 194:217-222.

Bromley et al. *Obstet Gynecol* 1995; 86: 998-1001.

Hyperechoic Bowel

- **Criteria: as bright as bone**
- **Incidence in general population: ~0.5%.**
- **Sensitivity for Down syndrome: 16%-25%**



**Nyberg et al. Obstet Gynecol 1990; 76:370.
Bromley et al. Obstet Gynecol 1994; 83:647-651.**

Renal Pyelectasis

- 2nd-trimester fetal pyelectasis has been associated with DS (AP diameter, ≥ 4 mm).
- 20% of fetuses with DS have fetal pyelectasis (PPV, 3%).



Benacerraf et al. Obstet Gynecol 1990; 76:58.

Markers: Genetic Sonogram

164 DS and 656 Controls

Marker	T21	Controls	Isol.LR
NF 6mm	42.3%	0.5%	12
NF 5mm	47.0%	0.8%	
Anomaly	26.8%	1.2%	3.3
Humerus	48.7%	2.1%	5.8
Femur	53.7%	5.3%	1.2
Bowel	13.0%	0.9%	no isol DS
EIF	34.2%	4.3%	1.4
Pyelectasis	21.3%	2.4%	1.5

Sensitivity and Specificity of Genetic Sonogram: 164 DS

Marker	DS = 164 (%)	NL = 656 (%)	LR
NI scan	32/164 (19.5%)	575/656 (87.7%)	0.2

The absence of any marker conveys an 80% reduction (0.2 times) in DS prior risk.

Number of Markers and LRs: The more markers found, the higher the LR

Markers

LR

0

0.2

1

(use isolated

LR)

2 (any 2 minor)

Bromley et al. J Ultrasound Med 2002; 21:1087-1096.

Sensitivity of Genetic Sonogram for DS in Several Different Studies

Author	# T21	Sens.	Fls +
Benacerraf ('94)	71	73%	4%
Owen ('94)	38	75%	25%
Devore ('94)	15	73%	7.4%
Bromley ('98)	53	75%	5.7%
Nyberg ('98)	142	74%	14.7%
Bahado-Singh '98	24	60%	4.5%
Bahado-Singh '98	31	73.5%	15%
Vergagni ('99)	22	59%	5.3%
Stohl ('99)	55	67%	19.4%
Vintzileos ('99)	34	82%	13%

Likelihood Ratios for DS w/ Isolated Markers

Marker	**Smith-B	*AAURA	•Nyberg	••Bromley
None	-	0.40	0.36	0.22
NF	17	18.6	11	12
H. bowel	6.1	5.5	6.7	-
Humerus	7.5	2.5	5.1	5.8
Femur	2.7	2.2	1.5	1.2
EIF	2.8	2	1.8	1.4
Pyelect.	1.9	1.5	1.5	1.5

*Nyberg. *Ultrasound Obstet Gynecol* 1998; 12:8.
•Nyberg. *J Ultrasound Med* 2001; 20:2053. **Smith-Bindman. *JAMA* 2001; 285:1044. ••Bromley et al. *J Ultrasound Med* 2002; 21:1087-1096.

**Based on Bayes theorem,
calculate a risk adjustment
using likelihood ratios.**

**A priori risk ×
likelihood ratio =
revised risk**

**A priori risk can be based on first-trimester
and/or second-trimester screening or even
maternal age.**

Example 1

The patient has an a priori risk of 1:200 based on prior testing.

She has a negative genetic sonogram (use LR 0.3 to decrease risk, average of reported LR).

$$\text{Revised risk} = 0.005 \times 0.3$$

$$= .0015 \text{ or } 1/666$$

Example 2

The patient has an a priori risk of 1:1000 based on prior testing.

She has a thickened nuchal fold on ultrasound (use LR of 12).

$$\text{Revised risk} = 0.001 \times 12$$

$$= .012 \text{ or } 1/83$$

Example 3

The patient has an a priori risk of 1:2000 based on prior testing.

She has an isolated EIF (use LR of 2).

$$\begin{aligned}\text{Revised risk} &= 0.0005 \times 2 \\ &= .001 \text{ or } 1/1000\end{aligned}$$

Example 4

The patient has an a priori risk of 1:400 based on prior testing.

She has an EIF *and* a short femur (use LR of 6.2 due to 2 markers).

$$\begin{aligned}\text{Revised risk} &= 0.015 \times 6.2 \\ &= .015 \text{ or } 1/67\end{aligned}$$

Ethnic Differences in Marker Prevalence

- *EIF*: Asian mothers are 3.8 times more likely to have an EIF (NL fetuses) than white or black mothers.
- *Femur Length*: Fetuses of Asian mothers have shorter femurs; fetuses of black mothers have longer femurs compared to white mothers. $P = .0007$.

Shipp et al. *Ultrasound Obstet Gynecol* 2000; 15:460-462.
Shipp et al. *J Ultrasound Med* 2001; 20:141-144

Genetic sonography can be an effective sequential screen following first-trimester risk assessment



Can genetic sonography (GS) be used sequentially after nuchal translucency (NT) screen?

First-trimester screen	88.5%	4.2%
GS: 1 marker	96.5%	13.2%
GS (likelihood ratios)	94.5%	5.4%
GS (only for risk 1/300-1/2500)	93.3%	4.9%

Krantz. Ultrasound Obstet Gynecol 2007; 29:666.

14,934 fetuses, of which 51 had Down syndrome

- **Mixed population**
- **41/51 detected in 1st trimester: 79.6% sensitivity and 2.7% screen-positive**
- **5 more detected in 2nd trimester (1 + nuchal fold and 4 heart defects): 89.7% sensitivity and 4.2% screen-positive**

Rozenberg et al. Am J Obstet Gynecol 2006; 195:137.

2nd-trimester nuchal fold after 1st-trimester NT screen

- **224 normal and 19 DS fetuses: sequential screen with NF at 2nd-trimester scan**
- **NT and GS were independent markers for DS**
- **Median NF 1.538 in DS vs 0.99 in NL**
- **If NF replaces 2nd-trimester biochemistry, they predict 91% sensitivity for 5% screen-positive**

Maymon et al. Ultrasound Obstet Gynecol 2008; 32:501.

The nasal bone as a marker for Down syndrome in the 2nd trimester

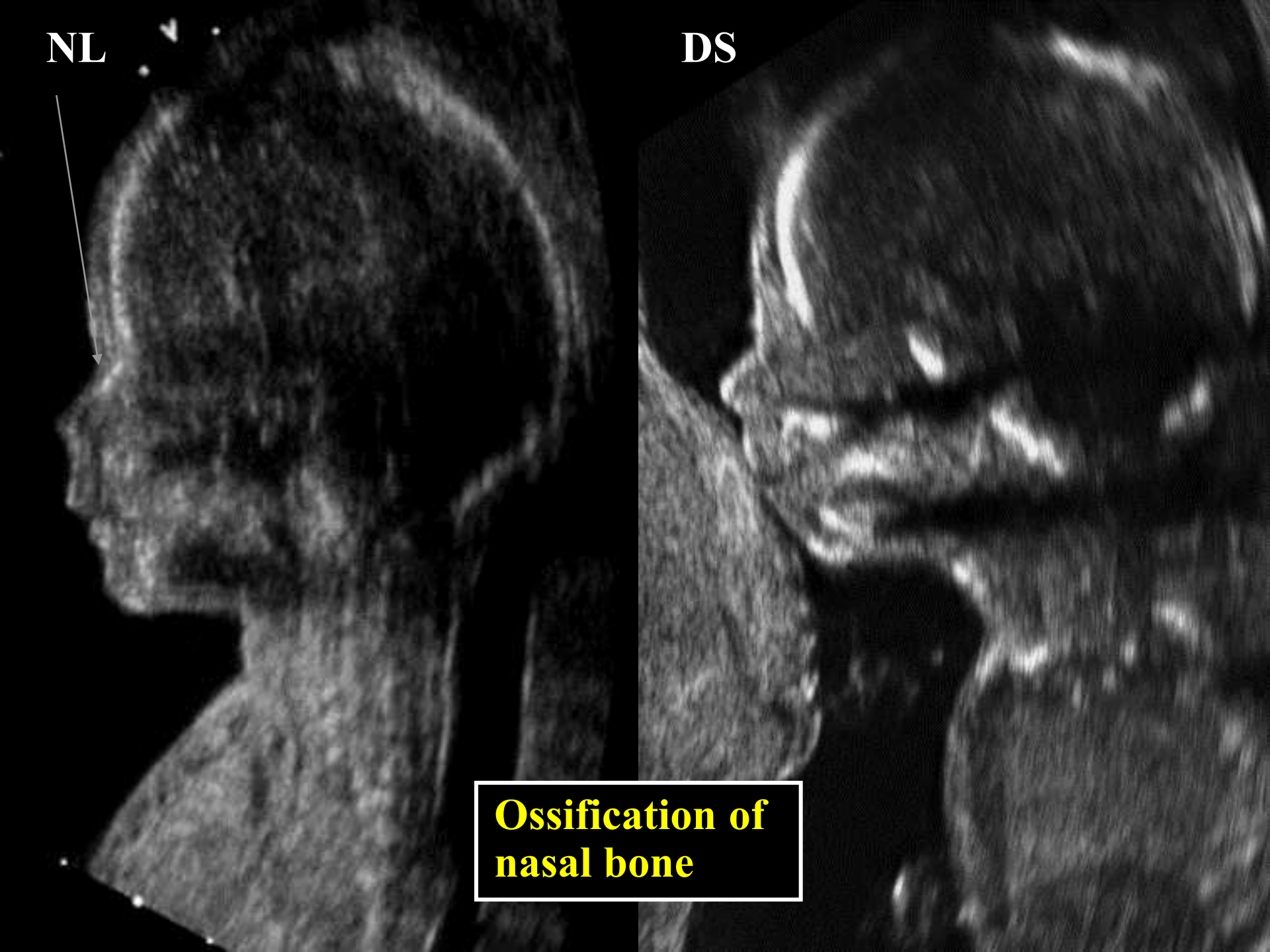
- **Absence of ossification of the nasal bone or even a short nasal bone is associated with a high risk of fetal DS.**



NL

DS

**Ossification of
nasal bone**



Postmortem radiologic and pathological series showed that 23%-30% of DS fetuses do not have an identifiable nasal bone ossification DS.

Keeling et al. Am J Med Genet 1997

Stempfle et al. Pediatr Radiol 1999

Tuxen et al. Ultrasound Obstet Gynecol 2003

Fetal Nasal Bone: A Marker for DS in the 2nd Trimester

Study # Criteria Sens. Scr+

Bromley 2002	16	Absent	37%	0.5%
		BD/NB ≥ 11	69%	5%
Cicero 2003	34	<2.5 mm	62%	8.8%
Bunduki 2003	22	<5th %ile	59%	5.1%
Vintzileos 2003	29	Absent	41%	0%
Odibo 2006	22	Absent	23%	1%
		BD/NB	41%	7%

Trisomy 18

- **Fisted hands**
- **Clubfeet**
- **Heart defects**
- **Omphalocele**
- **Diaphragmatic hernia**
- **Abnormal facial profile**
- **Prominent cisterna magna**
- **Single umbilical artery**
- **Choroid plexus (CP) cysts**
- **Cystic hygroma**

Cystic hygroma

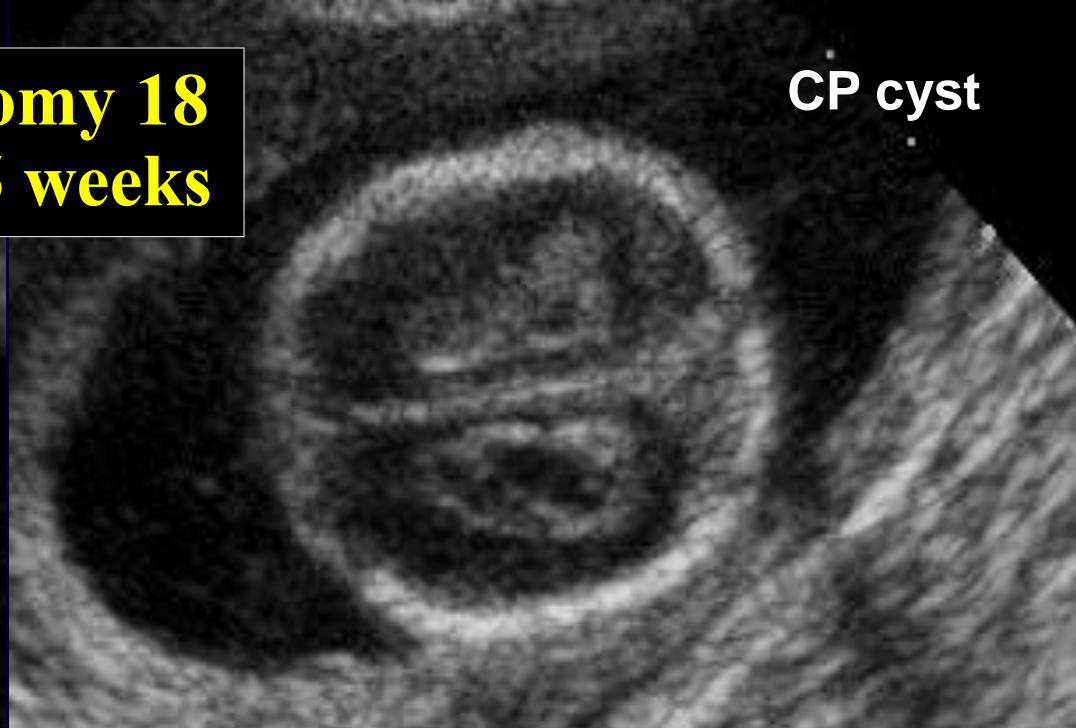
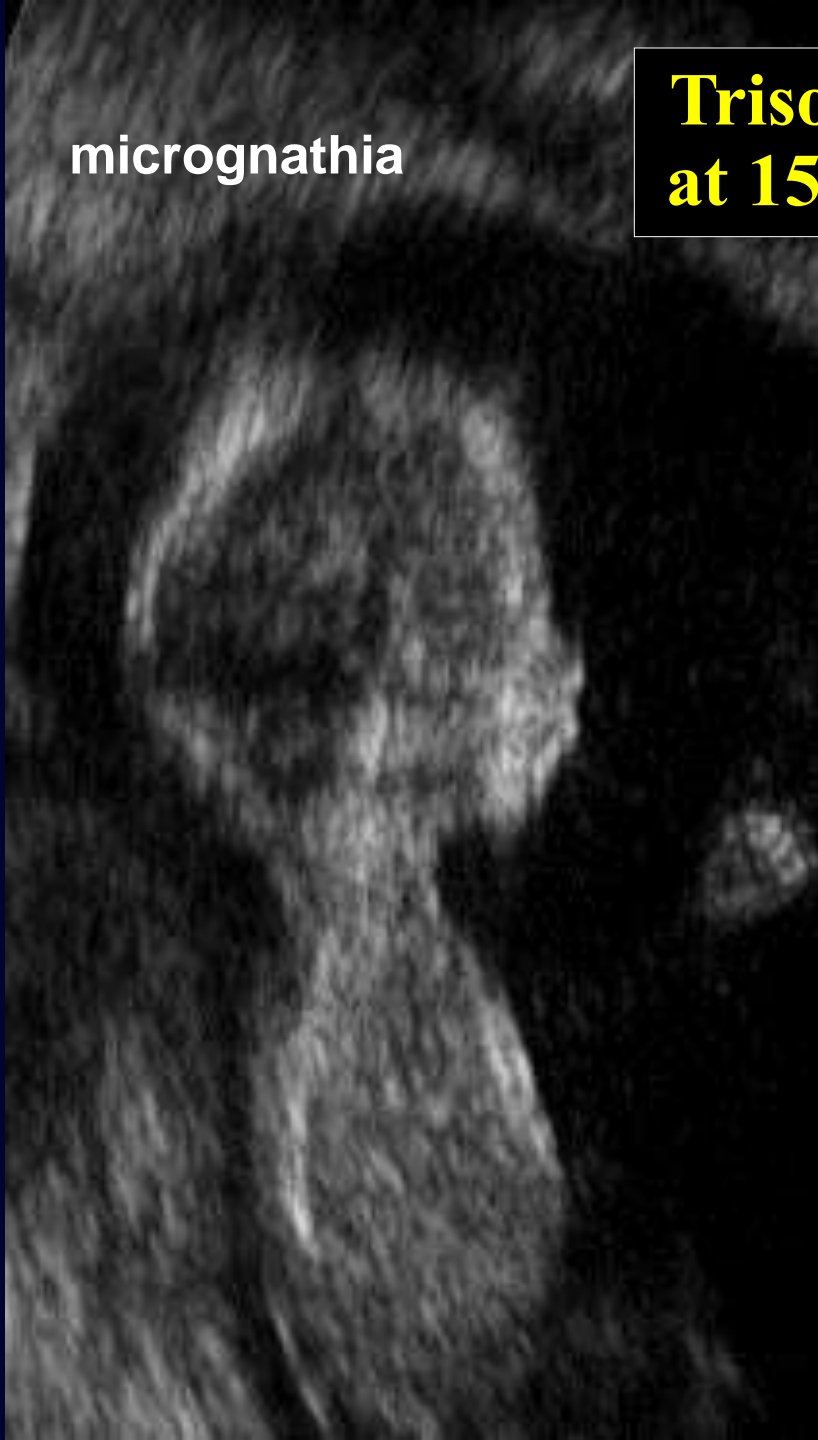


micrognathia

**Trisomy 18
at 15 weeks**

CP cyst

**Clenched
hand**



Large VSD: large aortic root



Omphalocele & acrania



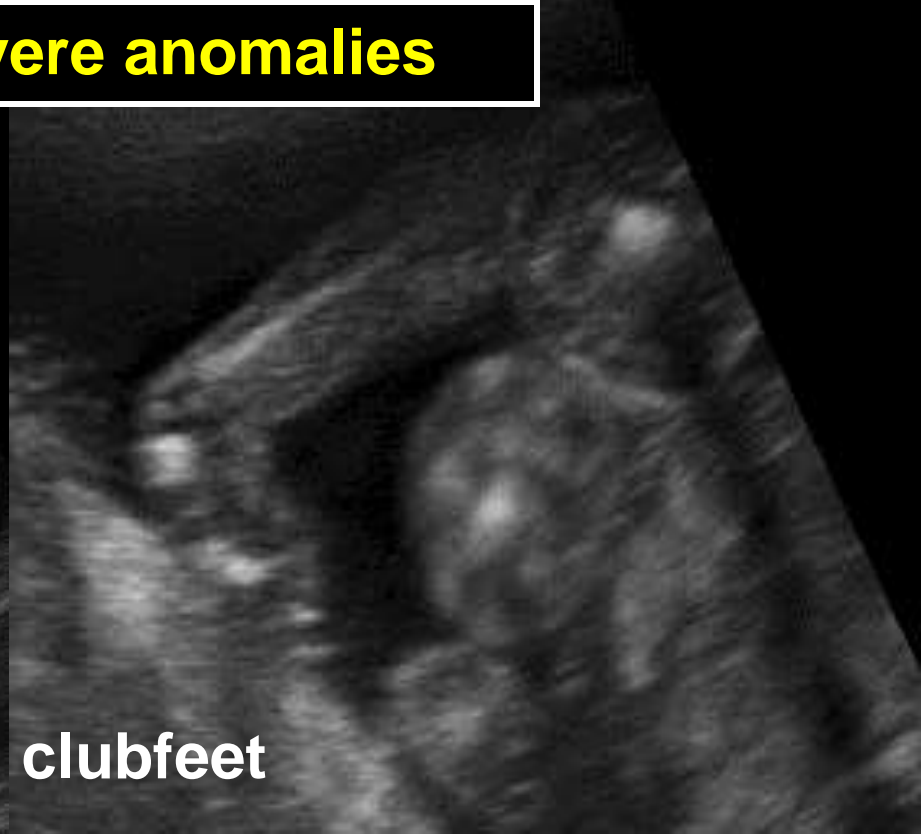
Absent radius



T18 with severe anomalies



Bilateral clubfeet



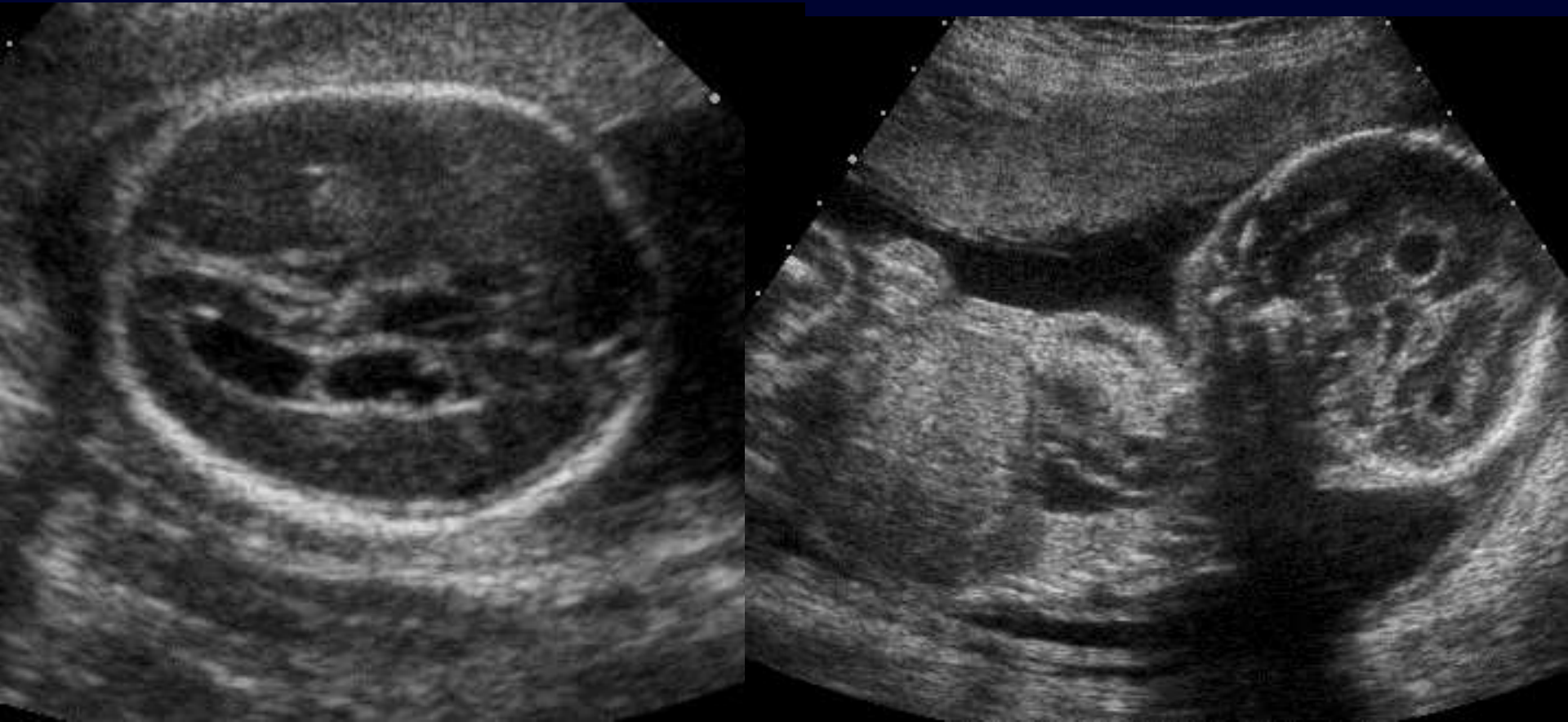
Bilateral clenched hands



Trisomy 18: micrognathia and omphalocele



**Choroid plexus cysts
in a patient with trisomy 18**



12,672 unselected patients, of which 366 (2.9%) had CP cysts

- **33% of T18 fetuses had CP cysts.**
- **12 cases with CP cysts with major anomalies, 2 with T18.**
- **43 cases with CP cysts with no/or minor findings, none with T18.**
- **Isolated CP cysts are not an indication for invasive testing.**

Meta-analysis on Isolated CP Cysts and T18

- 13 studies showed 0.27% incidence of T18 in fetuses with isolated CP cysts, and does not warrant invasive testing.
- Risk of Down syndrome is not increased with isolated CP cysts.

Gross. *Obstet Gynecol* 1995; 172:83-87.

Gupta. *Lancet* 1995; 346:724-729.

Bromley. *Ultrasound Obstet Gynecol* 1996; 8:232-235

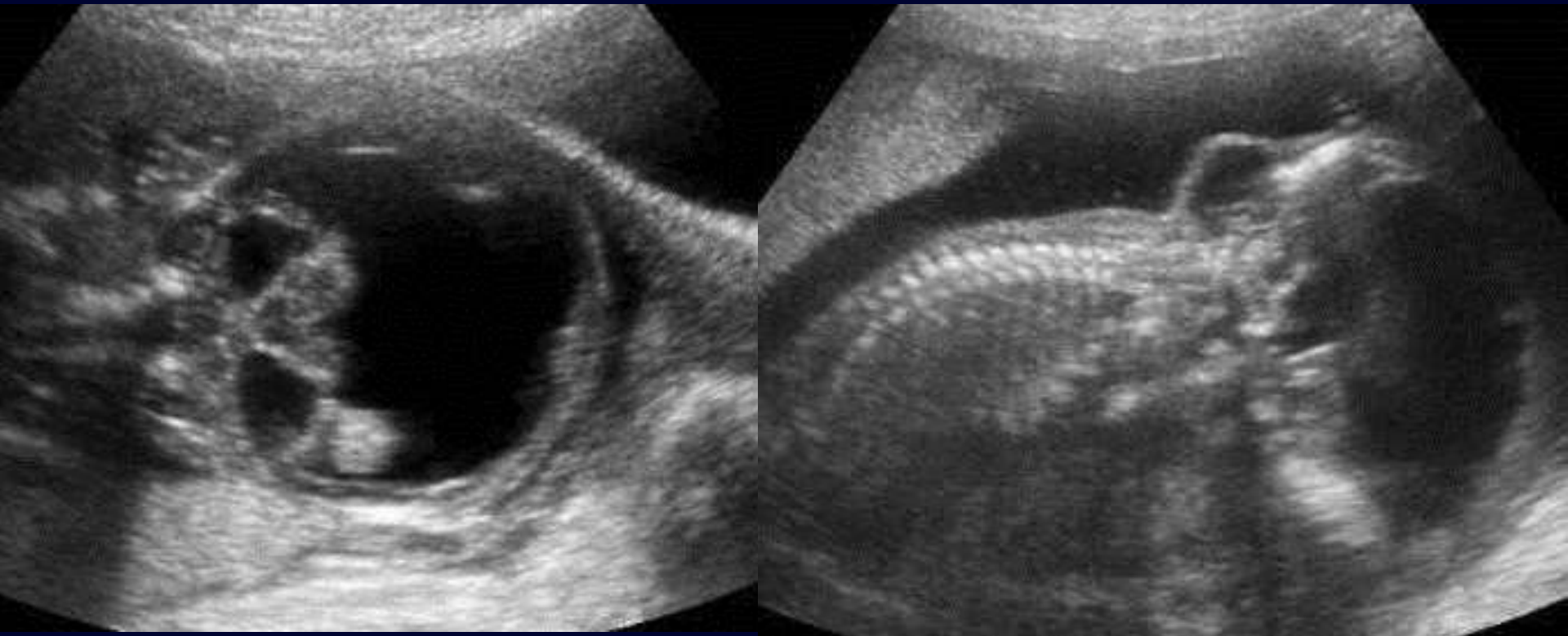
Recommendations for Patients With CP Cysts

- Correlation with early risk assessment or quad screen (prior risk).
- Detailed sonogram including heart, face, extremities (an open hand).
- Detection rate of trisomy by second-trimester ultrasound is 80%-90%.
- Amniocentesis is not recommended for isolated CP cysts in a low-risk patient with a normal sonogram.

Trisomy 13

- **Holoprosencephaly**
- **Facial anomalies**
- **Polydactyly**
- **Omphalocele**
- **Heart defects**
- **Echogenic intracardiac foci**
- **Polycystic kidneys**
- **Neural tube defect**

**Fetus with trisomy 13:
holoprosencephaly and
encephalocele**



**2nd-trimester fetus with trisomy 13:
cleft lip/palate and omphalocele**



**2nd-trimester fetus
with trisomy 13: facial
anomaly with cyclopia
and proboscis**



Single
ventricle



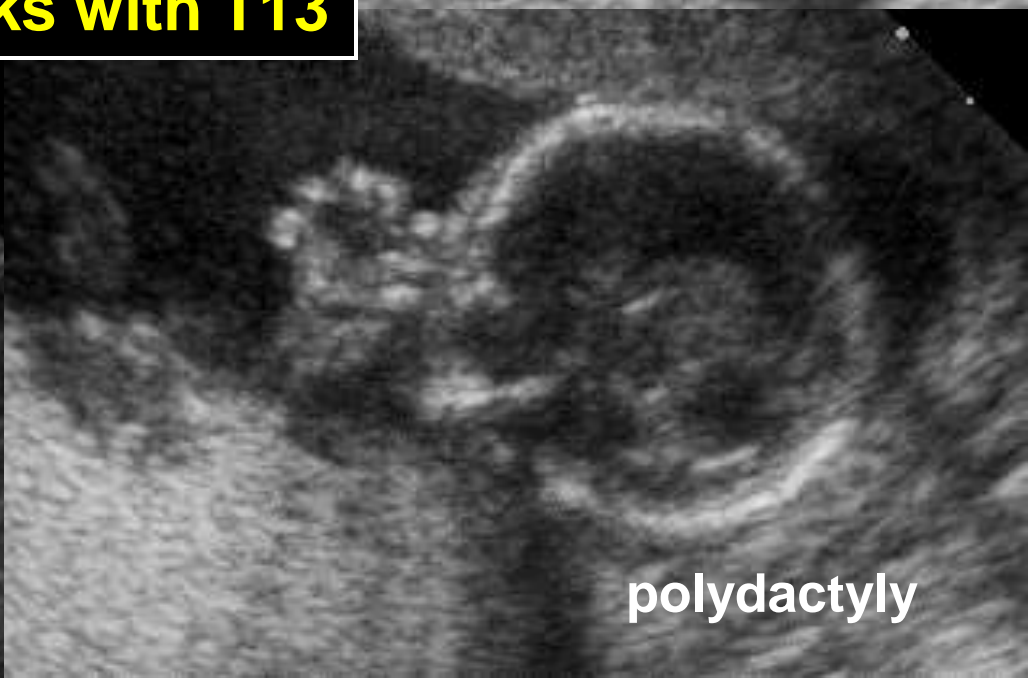
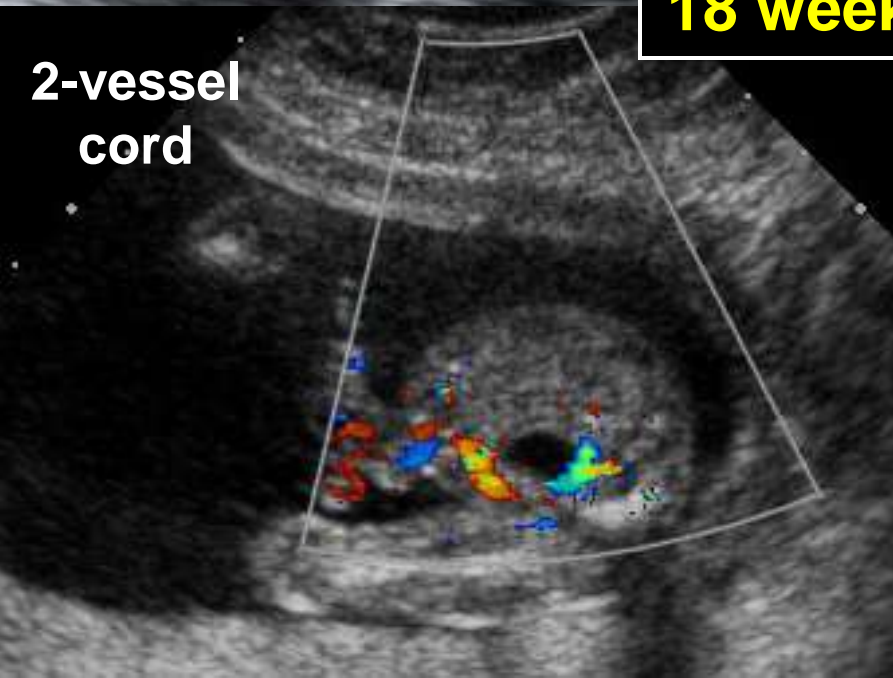
Ha
Pwr
C8
P
S

Dandy-
Walker cyst



18 weeks with T13


2-vessel
cord



polydactyly



polydactyly



Axial view
face: cleft and
microoph-
thalmia

**Trisomy 13:
2nd trimester**



Heart defect



Facial cleft

**Third-trimester fetus with
trisomy 13 and cleft lip/palate**



Conclusions

- **Ultrasound can detect 60%-80% of fetal Down syndrome in the second trimester, based on fetal malformations and markers.**
- **The genetic sonogram is used in conjunction with serum screening and early risk assessment for best accuracy.**
- **Ultrasound can identify 80%-90% of fetuses with trisomies 18 and 13 in the second trimester.**

THANK YOU.