

# ULTRASOUND LECTURE SERIES

— Presented by —

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# **Ultrasound Evaluation of Abnormal Midtrimester Serum Screen**

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# Objectives

**At the conclusion of this learning activity, participants will be able to discuss:**

- Evaluation for high  $\alpha$ -fetoprotein (AFP)
- Evaluation for increased Down syndrome and other aneuploidy
- Counseling for unexplained elevated maternal serum AFP (MSAFP) and accuracy of ultrasound in Down syndrome detection
- Pregnancy follow-up for unexplained high MSAFP and increased Down syndrome risk

# Brief Overview

- AFP first used in the late 1970s as a marker for neural tube defects (NTD)
- Mid-1980s AFP found to be low in Down syndrome
- Eventually other markers (human chorionic gonadotropin [hCG], unconjugated estriol [uE3], and dimeric inhibin A) added as aneuploidy markers

# MSAFP

- AFP, an oncofetal protein
- Yolk sac production in early pregnancy
- Fetal liver production after yolk sac involution
- Amniotic fluid AFP is about 10,000 × MSAFP
- Amniotic fluid AFP peaks in midtrimester

# High MSAFP

- Common definitions of high MSAFP:  $>2$  or 2.5 multiples of the median (MoM)
- Sensitivity of 65%-90% and specificity of 1%-5% depending on threshold used
- MSAFP increased in 100% of open NTD
- About 20% of NTD are closed, with normal MSAFP
  - 82% encephaloceles are skin covered
    - *Haddow JE. Semin Perinatol 1990; 14:488.*

# High MSAFP

- MSAFP levels usually adjusted for:
  - Gestational age
  - Maternal weight
  - Maternal race
  - Insulin-dependent diabetes mellitus status
  - Multiple gestation
  - Impact of smoking and in vitro fertilization appears minimal
    - *Palomaki et al. Obstet Gynecol 1993*
    - *Lambert-Messerlian et al. Prenat Diagn 2006*

# Anatomy Survey for High MSAFP

- Cranial anatomy for:
  - Anencephaly
  - Encephaloceles
  - Spina bifida markers

# Anencephaly



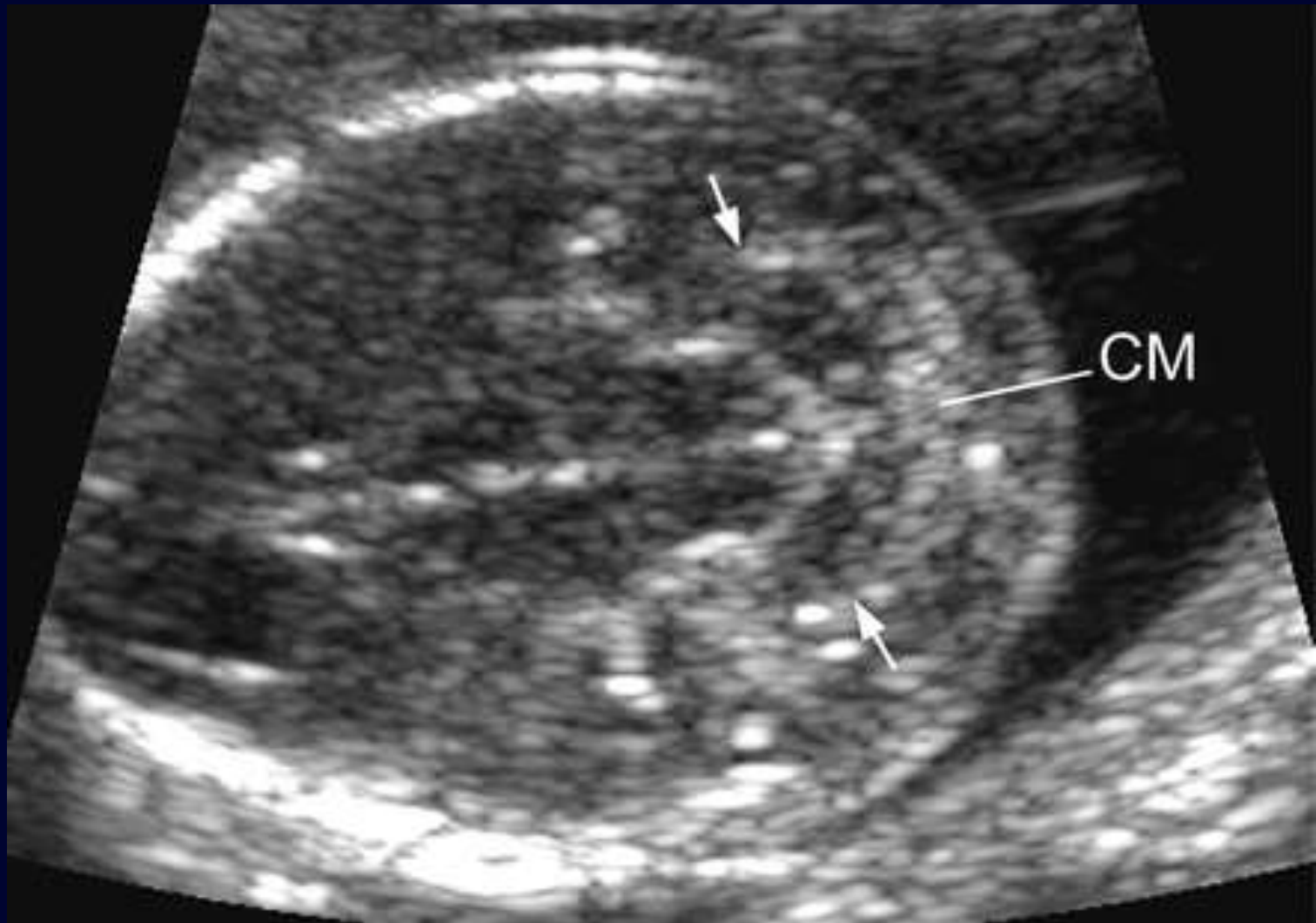
# Encephalocele



# Cranial Signs of Spina Bifida: Lemon-Shaped Cranium



# Cranial Signs of Spina Bifida: Banana Sign



# Spina Bifida



# Other Causes of High MSAFP

- Wrong dates
- Multiple gestations
- Open abdominal wall defects
- Fetal demise or fetomaternal bleeding
- Congenital nephrosis
- Placental abnormalities

# Pregnancy Risk for Unexplained High MSAFP/hCG

## Complications

Intrauterine growth restriction (IUGR)

Abruption

Stillbirth or miscarriage

Preterm birth

Preeclampsia

*Spencer K. Prenatal Diagn 2000; 20:652.*

# Other Evaluations for Elevated MSAFP/hCG

- Evaluation of placenta
  - Lakes, grading
  - ? Role of 4D volume and vascular indices: VI, FI, and VFI
- Uterine artery Doppler
  - Mean pulsatility index
  - Bilateral diastolic notch

# Uterine Artery Doppler

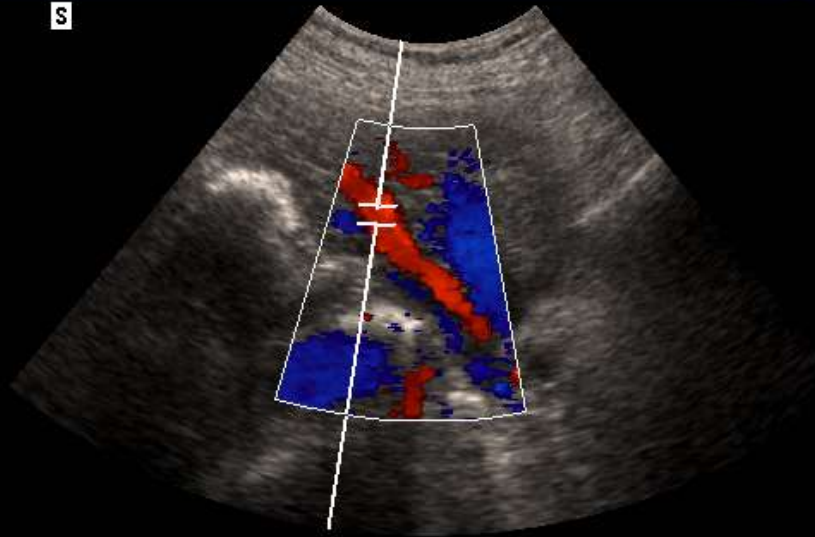
SIEMENS

11585755 CTR. WOMEN'S WELLNESS  
11.17.50 03/15/04 JMZ

32  
32

MAT LT\_

S

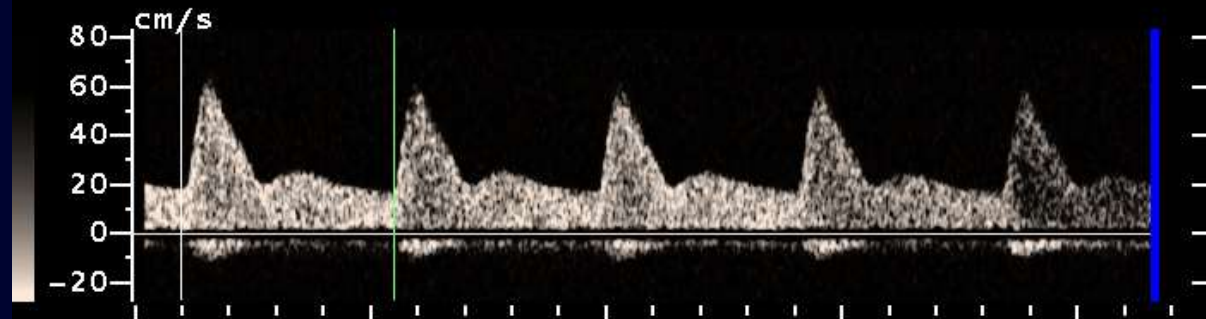


TIB 1.4  
(TIS 0.4)  
3.5C40H/4.0  
OB  
63%  
36dB RS3  
12.0cm 11fps

CF2.8MHz  
PRF2286Hz  
F-Med  
70dB RS3

DF2.8MHz  
PRF3989Hz  
62dB  
GD43 GS5.0  
F50Hz  
 $\theta$  0°

Measure  
0:40:40



PS=      cm/s ED=      cm/s TAMx=      cm/s PI=  
Place marker at end of heart cycle, then press SET.

# Serum Screening for Down Syndrome Risk

- Most centers use the triple screen or quadruple screen
  - AFP, uE3, hCG, and dimeric inhibin-A
- Detection rate of Down syndrome is influenced by:
  - Method of dating
  - Determining risk cutoff based on a fixed false-positive rate
    - *Knight G, Palomaki G. Clin Lab Med 2003.*

# Screening for Trisomy 18

- Levels of AFP, uE3, and hCG are all low in trisomy 18
- Dimeric inhibin A is not associated with trisomy 18
- For a low FPR of 0.5%, the screening detects 80% of trisomy 18 fetuses

– *Palomaki G, et al. Prenat Diagn 1991*

# Evaluation for Increased Down Syndrome Risk

- Fetal biometry: IUGR
- Structural abnormality
- Soft markers

# Structural Abnormalities and Down Syndrome

## Structural Abnormality

Cardiac defects: atrioventricular (AV) canal, ventricular septal defect, tetralogy of Fallot

Duodenal atresia

Brachycephaly

Hydrocephalus

Cystic hygroma

Fetal hydrops

# Cardiac Defects

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WASH UNIV GENETICS

13.01.45 02/20/04 KH

MI 0.5

S

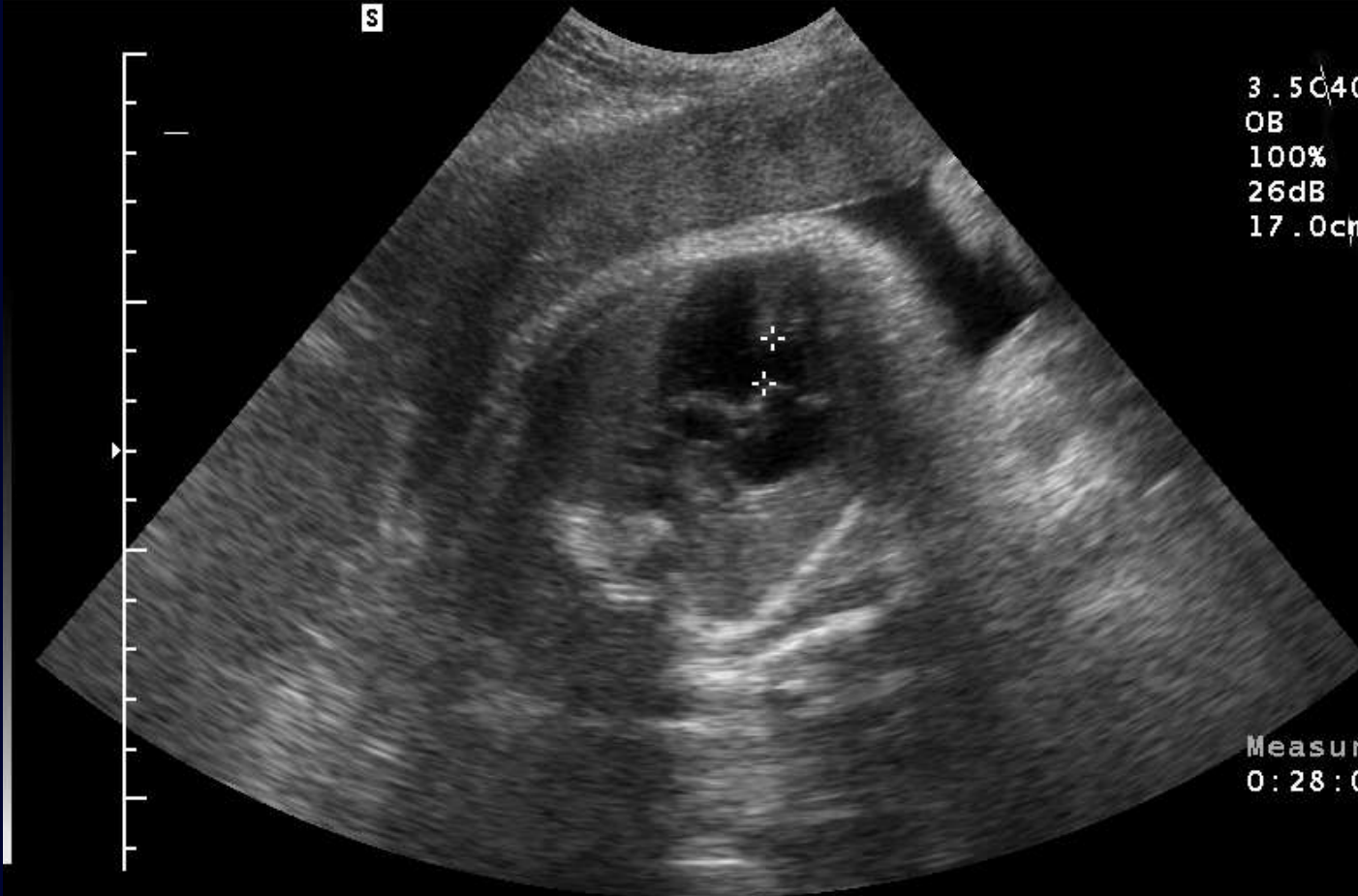
3.5C40H/4.0

OB

100%

26dB RS3

17.0cm 16fps



Measure  
0:28:00

-+ D= 9.2mm

# Cystic Hygroma/Hydrops



# LR for Structural Malformations and Down Syndrome

<b>Study</b>	<b>No. of Down Syndrome</b>	<b>LR</b>	<b>95% CI</b>
Vergani et al, 1999	22	30	15-65
Nyberg and Souter, 2001	186	28	15-64
Bromley et al, 2002	164	22	11-46

# Soft Markers for Down Syndrome

Soft Marker	LR and 95% CI
Nuchal fold thickening >6 mm	11 (6-22)
Nasal hypoplasia	7.8 (4-15)
Mild ventriculomegaly	7 (6-8)
Short femur	1.5 (0.8-3)
Short humerus	5.1 (2-17)
Echogenic bowel	6.7 (3-17)
Echogenic intracardiac focus	1.8 (1-3)
Pyelectasis	1.5 (0.6-4)
Sandal gap toes	-

*Nyberg et al. J Ultrasound Med 2001.  
 Odibo et al. Am J Obstet Gynecol 2008.  
 Goetzinger et al. Am J Obstet Gynecol 2008.*

# Nuchal Edema



# Nasal Bone and Down Syndrome



# Adjusting Down Syndrome Risk Based on Ultrasound Markers

- Three approaches have been used:
  - Nyberg et al introduced adjusting risk with positive LR only.
  - Nicolaides uses both positive and negative LR (requires software).
  - Bahado-Singh et al use the risk from the serum screen as a priori risk.
- Results of the above approaches are similar but limited by the wide confidence intervals of available LR.

# Example of the Use of LR

Age	Pre-Ultrasound Down Syndrome Risk	Ultrasound Marker	Post-Ultrasound Down Syndrome Risk
35	1:274	NF	1:18
40	1:78	NF	1:5

# Counseling: Accuracy of Ultrasound for Down Syndrome Detection

- Major anomalies are seen in 45%-65% of Down syndrome.
- Little attention has been devoted to the screening efficiency of major structural abnormalities for Down syndrome.
- DeVore et al showed that detailed echocardiography can improve the Down syndrome (DS) detection rate from 65%-91%; FPR may be as high as 13%.
- Finding an AV canal defect should justify amniocentesis.
  - *Khoury and Erikson, 1992; Paladini et al, 2000; Stoll et al, 1998; DeVore, 2001. Ultrasound Obstet Gynecol.*

# Counseling: Accuracy of Ultrasound for Down Syndrome Detection

- Accuracy of soft markers will vary by isolated versus multiple soft markers.
- Many authors do not make the above clarification.
- Sensitivity will decrease with multiple markers, but FPR will also decrease.
- For example, Nyberg et al report a detection rate of 15% with FPR of 0.1% with  $\geq 3$  markers.

# Accuracy of Ultrasound for Down Syndrome Detection Using Either Major Defects or Soft Markers

<b>Study</b>	<b>Sensitivity</b>	<b>FPR</b>
Benacerraf et al, 1994	73%	4%
DeVore and Alfi, 1995	87%	7.4%
Bahado-Singh et al, 1996	71%	14%
Vintzileos et al,	82%	13%
Smith-Bindman, 2001	69%	8%
Nyberg, 2001	69%	14%
Bromley et al, 2002	81%	12%

# Follow-up for Increased DS Risk if Amniocentesis Is Declined

- Need for further evaluation is controversial.
- If DS risk is elevated due to high hCG, may have risk for adverse outcomes, eg, IUGR or preeclampsia.
- May need fetal echocardiography if cystic hygroma or hydrops.
- Management recommendations should be individualized.

# Pregnancy Follow-up for High Unexplained MSAFP

- The threshold level for unexplained high MSAFP requiring follow-up is controversial.
- Risk for adverse outcomes increases from 19% for levels between 2.5-2.9 MoM to 67% when  $>6.0$  MoM.
- Risk may be greater if both AFP and hCG are abnormal.
- The optimal timing and frequency for future ultrasounds are also uncertain.
- Evaluations on subsequent follow-up include growth  $\pm$  uterine and umbilical artery Dopplers.
  - *Robinson et al. Obstet Gynecol 1989.*
  - *Spencer K. Prenat Diagn 2000.*

# Conclusions

- Ultrasound evaluation is important for an abnormal serum screen.
- Optimal follow-up for unexplained MSAFP and DS risk is yet to be determined.
- Referral to tertiary centers for detailed evaluation is key to effective management.

**THANK YOU!**