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Atlas of Ultrasound Findings in Down Syndrome

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Agenda

- Background of Down Syndrome
- Patient Cases
- Menu of Tests
- Full Fetal Ultrasound
- Screening Methods for Down Syndrome
- Ultrasound Findings
- Summary

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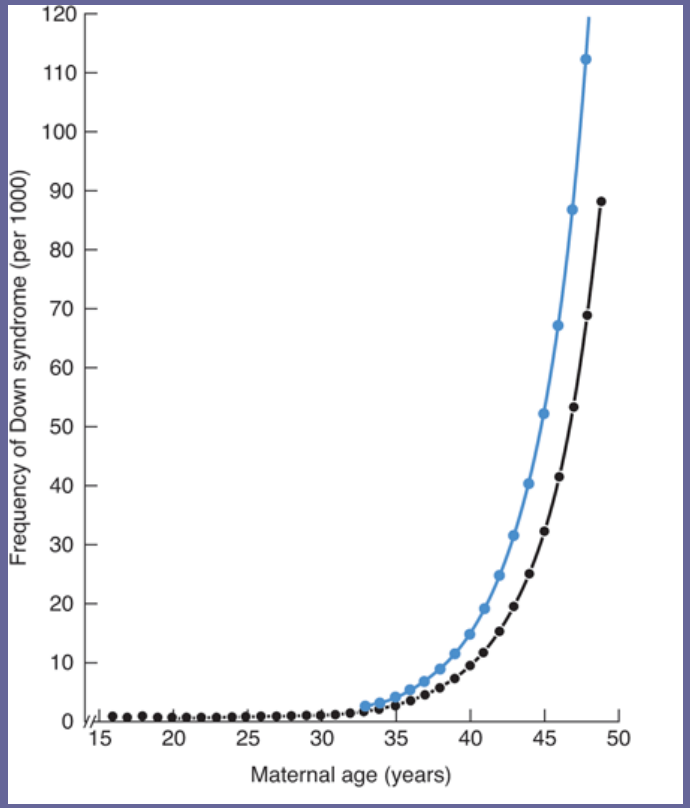
Down Syndrome: Background

- Trisomy 21: Most common chromosomal abnormality among liveborn infants (1/629)
- Caused by chromosomal abberation
  - Most often non-disjunction during maternal meiotic segregation
    - Strong association with increased maternal age
  - Less often via Robertsonian translocation

Frequency of Down Syndrome by Maternal Age



Source: McPhee SJ, Hammer GD: Pathophysiology of Disease: An Introduction to Clinical Medicine, 6th Edition: http://accessmedicine.com

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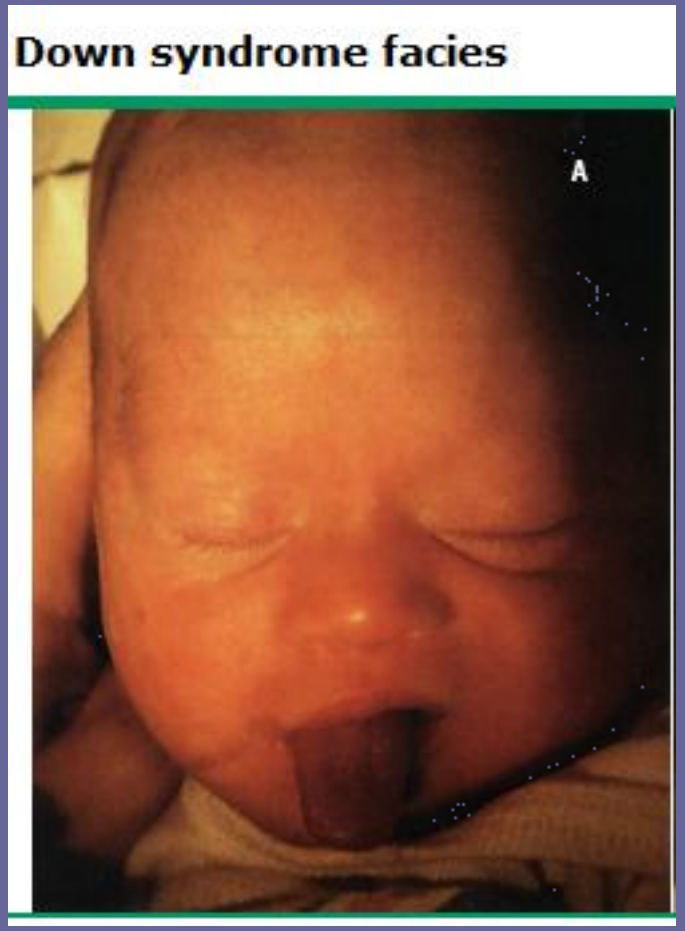
Down Syndrome: Clinical Features

- Mental Retardation
- Congenital heart defects (50%)
- Characteristic facies (90%):
  - upslanting palpebral fissure
  - epicanthal folds
  - flat nasal bridge
  - small ears
  - macroglossia
- Dysmorphic features:
  - transverse palmar crease
  - hypotonia
  - hyperextensible joints
- Increased rates of disease:
  - Alzheimer's disease
  - leukemia
  - infections



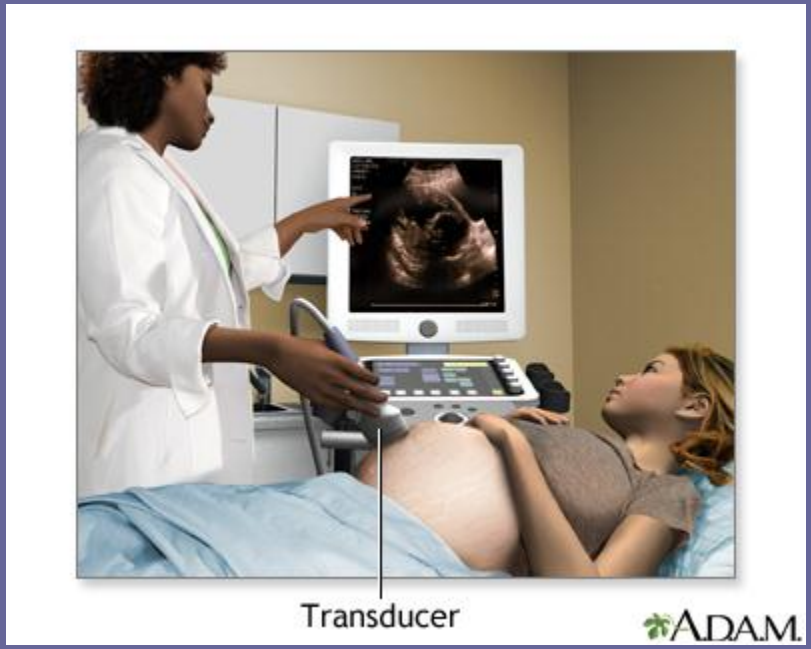
Source: Clark DA. Atlas of Neonatology, WB Saunders, Philadelphia 2000. Copyright © 2000 Elsevier

Our Patient: Presentation

- 32-year-old female G1P0 presenting at 20 weeks 1 day gestational age by dates for routine full fetal survey
  - Declined genetic screening
  - No known history of inherited genetic or chromosomal disorders

Menu of Tests: Ultrasound

- Advantages:
  - Non-invasive
  - Not harmful to fetus
  - Cost-effective
  - Portable
  - Can guide procedures
- Disadvantages
  - Highly operator-dependent

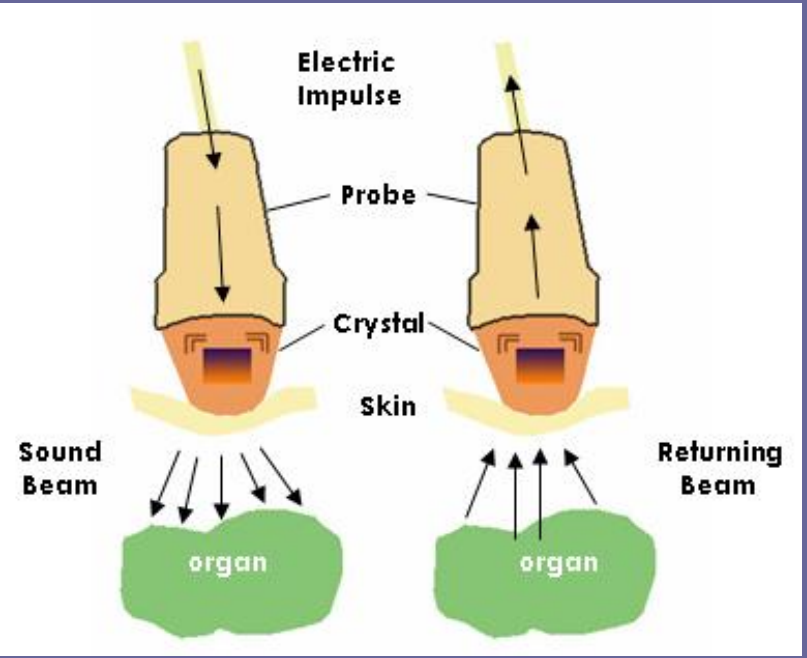


http://www.umm.edu/pregnancy/000233.htm

Ultrasound: Mechanics

- Piezoelectric crystals convert electrical energy into sound waves that are released in synchronized pulses
- Transducer then "listens" for the returning echoes
- Real-time image created from sound waves reflected back from organs, fluids and tissue interfaces of the fetus

http://www.usra.ca/



Grayscale Key:
Black: fluid
Grey: solid organs
White: air, fat, bone

Ultrasound: Safety

www.acr.org

- Should only be performed with valid medical indication and with lowest possible exposure setting to gain necessary information
  - Recent studies show that prolonged ultrasound exposure may affect migration of brain cells in fetal mice (Rakic 2006)
- "Keepsake fetal imaging" is not condoned by FDA or AIUM!
- Routine 2nd trimester full fetal survey is current recommendation

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Routine 2nd Trimester Prenatal Ultrasound

- Purpose is to obtain information to enable provision of optimal antenatal and perinatal care
- Information Obtained:
  - Fetal viability
  - Gestational age, expected date of delivery
  - Number of fetuses
  - Fetal survey to detect congenital anomalies
  - Assessment of amniotic fluid volume
  - Placental location (2nd trimester)
- Performed 18-20 weeks – Why?
  - Optimal balance between visualization of anatomy and time for diagnostic procedures and legal termination

2nd Trimester US Findings of Trisomy 21

1) Major Structural Defects
   - Aneuploidy often associated with anomalies
   - NB: 2-3% of infants are found to have major birth defects, not all with T21
2) "Soft-Signs"
   - Markers which increase risk but alone are of uncertain clinical significance. Previously utilized in 'genetic sonogram" to calculate risk based on quantity of markers found
   - Now, presence of any marker leads to referral for fetal karyotyping
   - The more soft signs evident, the higher the risk

Major Structural Defects
associated with aneuploidy

- CNS:
  - Ventriculomegaly
  - Dysgenesis of corpus callosum
  - Abnormal posterior fossa
- MSK:
  - Syndactyly
  - Clinodactyly
- Face:
  - Cleft palate
  - Low set/small ears
  - Macroglossia
  - Micrognathia
- Cardiac:
  - VSD
  - Endocardial cushion defect
  - Hypoplastic left heart syndrome
  - Tetralogy of Fallot
- GI:
  - Esophageal/duodenal atresia
  - Diaphragmatic hernia,
  - Ompalocele
- GU
  - Hydronephrosis
  - Renal Agenesis

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2nd Trimester Sonographic Markers Aka "Soft Signs"

- Nuchal fold
- Absent/hypoplastic nasal bone
- Short femur
- Short humerus
- Echogenic bowel
- Echogenic intracardiac focus
- Pyelectasis
- Heart defect
- Mild ventriculomegaly
- Hypoplasia of fifth digit
- Wide iliac angle
- Ear length
- Frontothalamic distance

Back to our Patient

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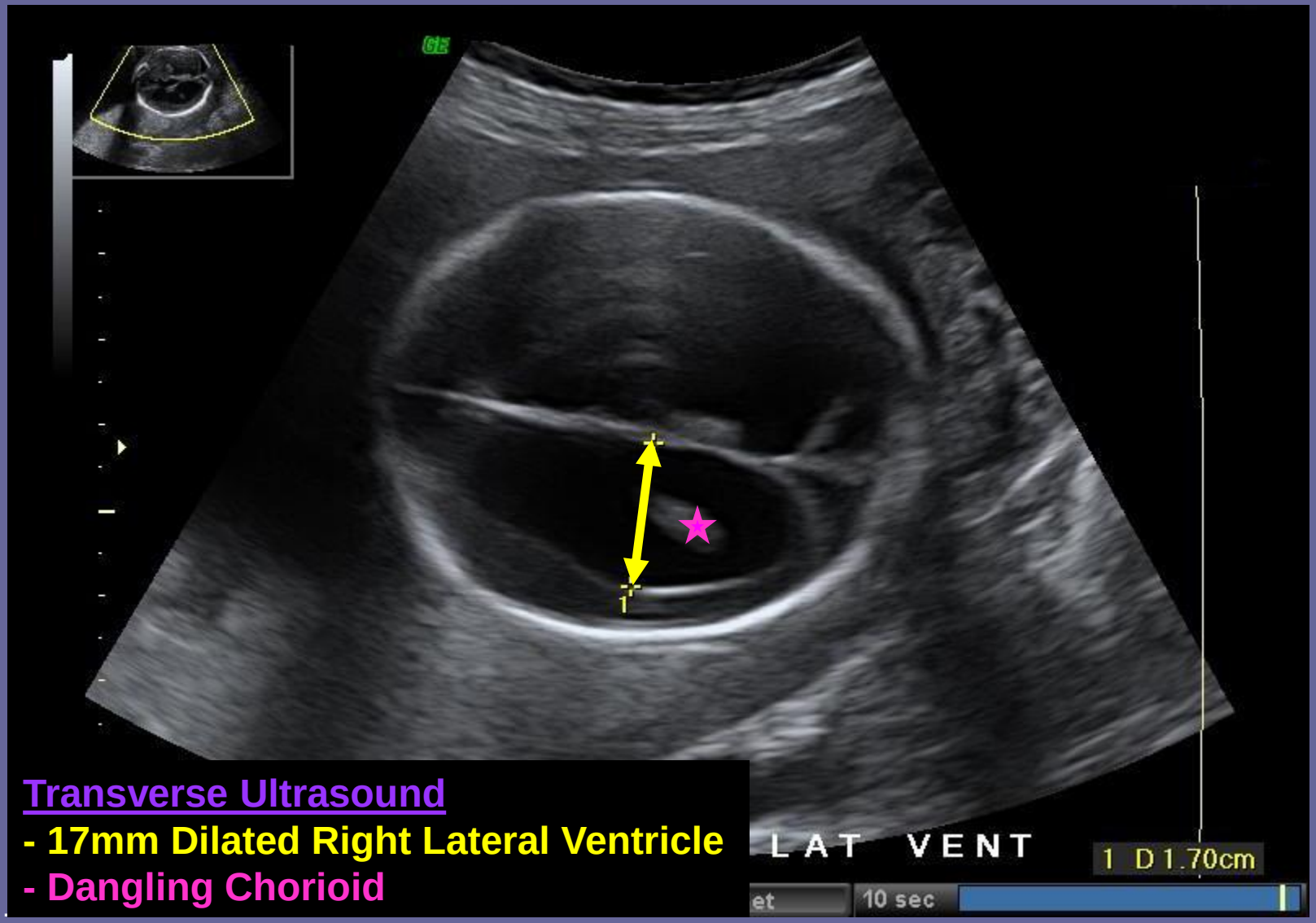
Our Patient: Fetal Ventriculomegaly on 20w US



Transverse Ultrasound

- 17mm Dilated Right Lateral Ventricle

- Dangling Chorioid

PACS, BIDMC

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Ventriculomegaly

- Enlargement of cerebral ventricles which represents abnormal brain development
- Measurement taken at atrium of lateral ventricle; portion where body, posterior horn and temporal horn converge
  - Ventriculomegaly >10 mm width
    - Severe ventriculomegaly >15mm width
  - Dangling choroid plexus characteristic in severe cases
- DDx: Wide variety genetic and environmental causes
  - T21, 18, 13 (5-25% risk of aneuploidy)
  - CMV and Toxoplasmosis

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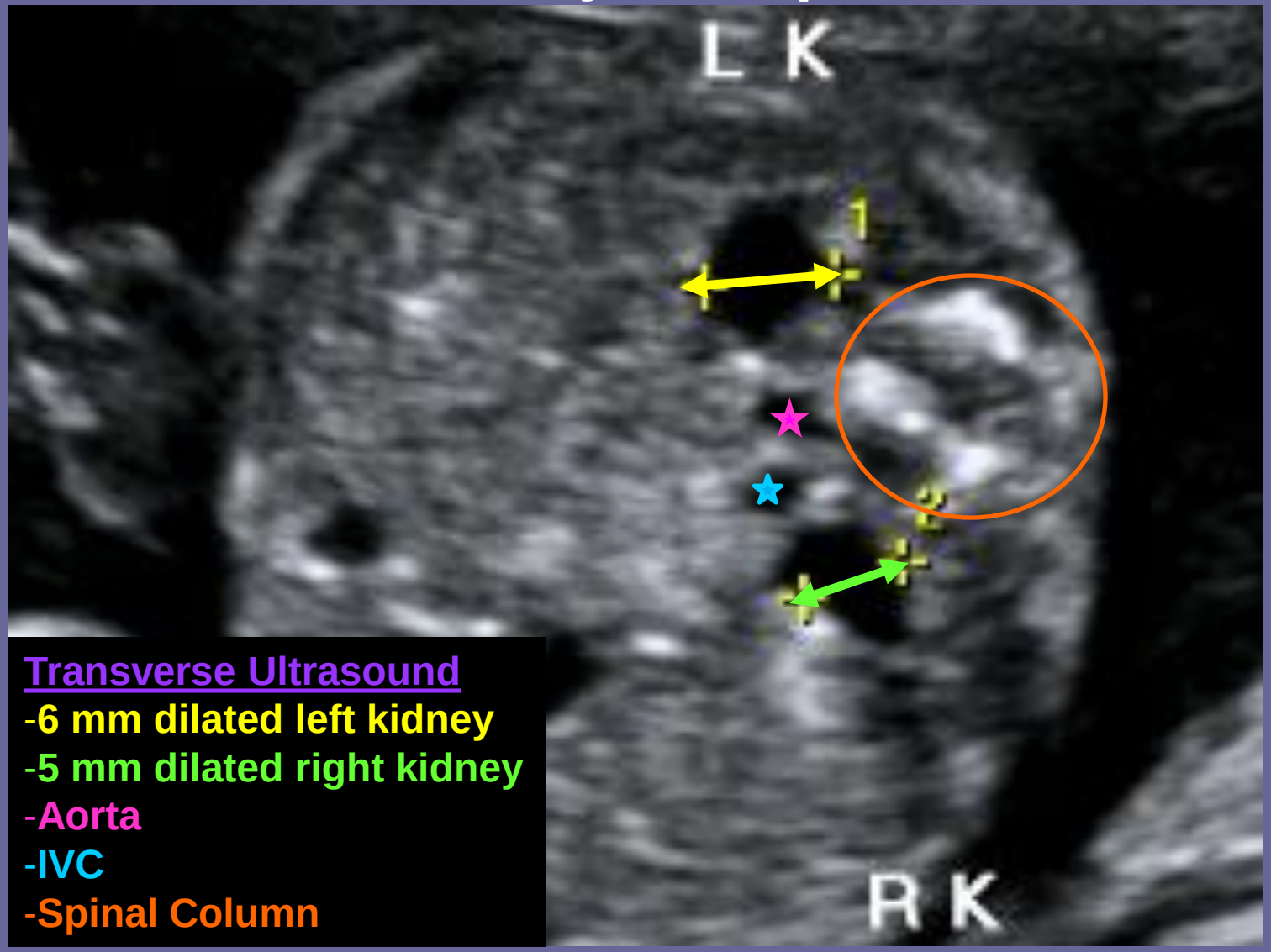
Our Patient: Bilateral hydronephrosis on 20w US



Courtesy of Dr. Olga Brook

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Renal Pyelectasis

- Enlargement of the fluid-filled renal pelvis (>4mm)
- DDx:
  - Commonly seen in normal fetuses (2-3%)
    - May be related to maternal hydration, fetal bladder distention
    - Look for flow at the bladder, reimage kidneys because enlargement may be dynamic
  - GU malformation
    - Fetal VUJ obstruction
    - Posterior urethral valves
    - Vesicoureteric reflux
    - Duplex kidney
  - Down Syndrome - soft sign (17%)

Companion Patient #1

- 33-year-old female G1P0 presenting at 16 weeks 2 days gestational age by dates for fetal survey after abnormal quadruple screen result
  - Abnormal quadruple screen revealed
    1 in 13 risk of T21
    - Age-related risk was 1 in 625

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Let's continue to discuss screening

Aneuploidy Screening Basics

www.acog.org

- ACOG 2007 Practice Guidelines:
  - All women should be offered aneuploidy screening before 20 weeks gestation
  - All women should have the option of invasive testing, regardless of maternal age

- Purpose of screening is to identify highest risk pregnancies for invasive diagnostic procedure

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Aneuploidy Screening Options

- First trimester combined test
- Full integrated test
- Quadruple test
- Cell-free fetal DNA test

Screening: 1st Trimester Combined Test

- Consists of:
  - Ultrasound Measurements: 10-13 weeks GA
    - Nuchal Translucency (NT) and gestational age (GA) by crown-rump length
  - Serum Assay: 9-13 weeks GA
    - Pregnancy-associated plasma protein-A (PAPP-A)
    - Beta human chorionic gonadotropin (β-hCG)
- Pros:
  - risk assessment available early
- Cons:
  - follow-up test is chorionic villus sampling (CVS) with higher risk of procedure-related pregnancy loss compared to amniocentesis

Screening: Full Integrated Test

- Consists of:
  - Ultrasound Measurements: 10-13 weeks GA
    - Nuchal Translucency (NT)
  - Serum Assay:
    - PAPP-A: 10-13 weeks
    - β-hCG, alpha fetoprotein (AFP), unconjugated estriol (uE3), inhibin A: 15-18 weeks
- Pros:
  - highest detection rate, lowest positive screen rate
- Cons:
  - risk estimate not available until 2nd trimester

Screening: Quadruple Test

- Consists of:
  - Serum Assay: 15-18 weeks GA
    - AFP, β-hCG, uE3, inhibin A
- Pro:
  - option for women presenting in 2nd trimester for prenatal care
    - Can be performed as late as 22 weeks
- Con:
  - risk estimate not available until 2nd trimester

Screening: cell-free fetal DNA

- Consists of :
  - Maternal plasma-based test to detect trisomy 21, 18, 13 after 10 weeks of gestation.
- Pro:
  - >98% detection rate, false positive rate <0.5%
  - early detection
- Con:
  - expensive; not covered by all insurance
  - not universally recommended as of yet

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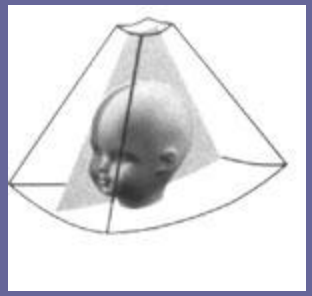
T21 Screening Method Comparison

	Consists of	Gestational Age	Detection Rate (%)	False Positive Rate (%)
First Trimester Combined	• NT • PAPP-A • Beta-hCG	9-13 weeks	85%	4.8%
			95%	21%
Full Integrated	• 10wks: NT, PAPP-A, AFP • 15 wks: uE3, hCG, inhibin A	10-13 weeks + 15-18 weeks	85%	4.4%
			95%	17%
Quadruple	• AFP, uE3, hCG, inhibin A	15-18 weeks	85%	7.3%
			95%	22%
Cell-free fetal DNA	• Genomic sequencing	> 10 weeks	>98%	<0.5%

Data per FASTER and SURUSS trials
Table adapted from: Wald NJ, Rodeck C, Hackshaw AK, et al. Health Technol Assess 2003; 7:1

Nuchal Translucency (NT)



http://www.gehealthcare.com/usen/ultrasound

- NT = increased sonolucent area at back of fetal neck representing fluid between skin and soft tissue (>3mm)
- Criteria:
  1) Crown-rump length (35-84mm at 11-13 wks)
  2) Mid-sagittal plane
  3) Fetus in neutral position without chin flexed
  4) Fetus occupies 75% of image
  5) Distinguish between fetal skin and amnion

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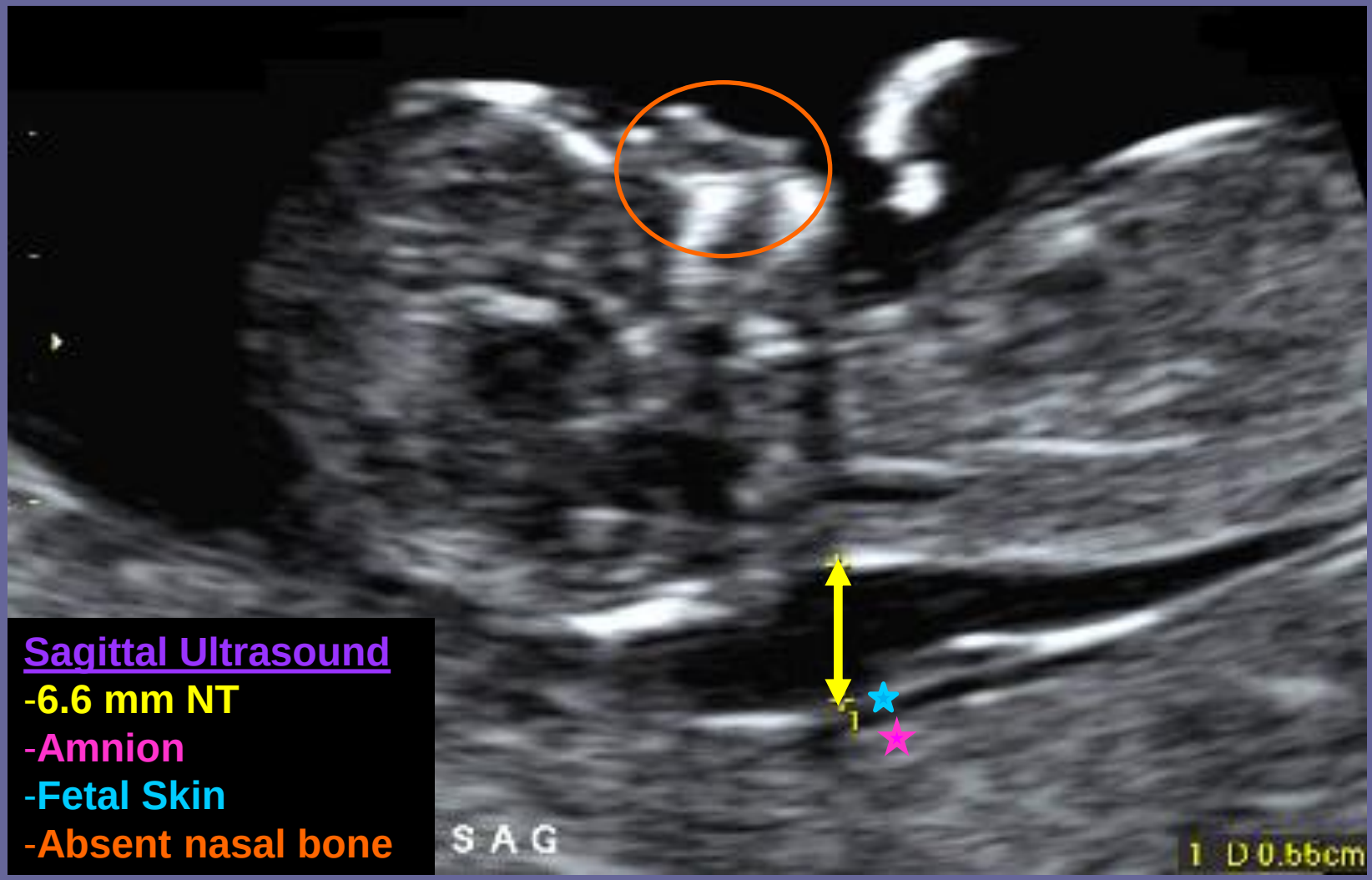
Companion # 2: NT Measurement on US



Courtesy of Dr. Olga Brook

Back to Companion Pt #1

- 33-year-old female G1P0 presenting at 16 weeks 2 days gestational age by dates for fetal survey after abnormal quadruple screen result
  - Abnormal quadruple screen revealed 1 in 13 risk of T21
    - Age-related risk was 1 in 625

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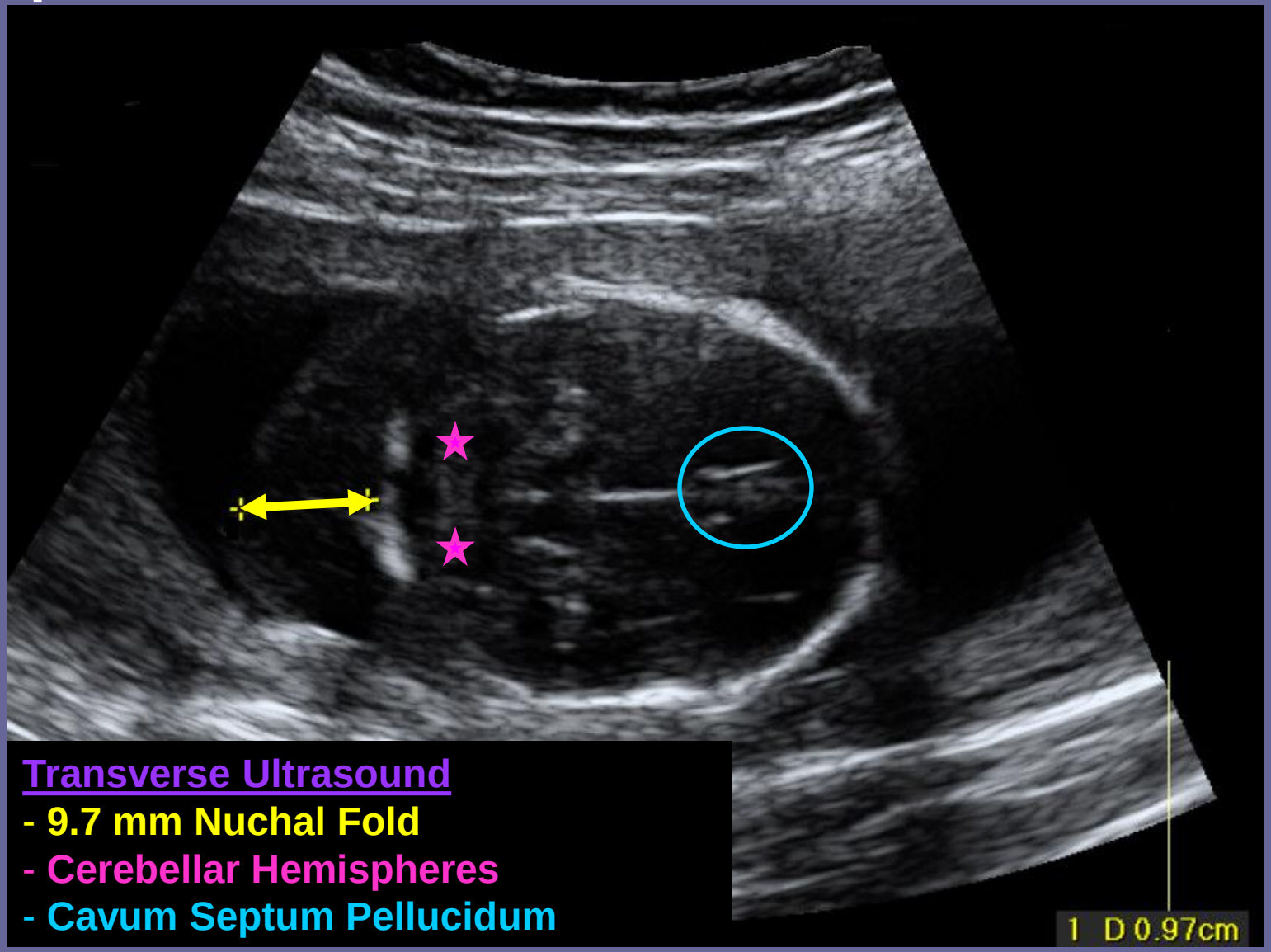
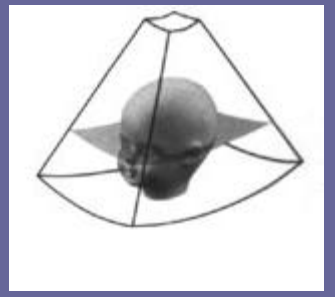
Companion Pt #1: Increased Nuchal Fold on 16w US



Transverse Ultrasound
- 9.7 mm Nuchal Fold
- Cerebellar Hemispheres
- Cavum Septum Pellucidum

PACS, BIDMC

Nuchal Fold



http://www.gehealthcare.com/usen/ultrasound

- Measurement:
  - Second trimester (versus NT in first trimester)
    - ≥6mm between 15-20 weeks is abnormal
  - Distance between outer edge of occipital bone to outer margin of skin
  - Taken in transverse plane (vs NT in sagittal plane)
- DDx:
  - Down Syndrome - soft sign
    - Most sensitive (40-50% and specific (99%) single ultrasound marker for DS in second trimester
  - Other aneuploidy
  - Normal fetus (0.5%)

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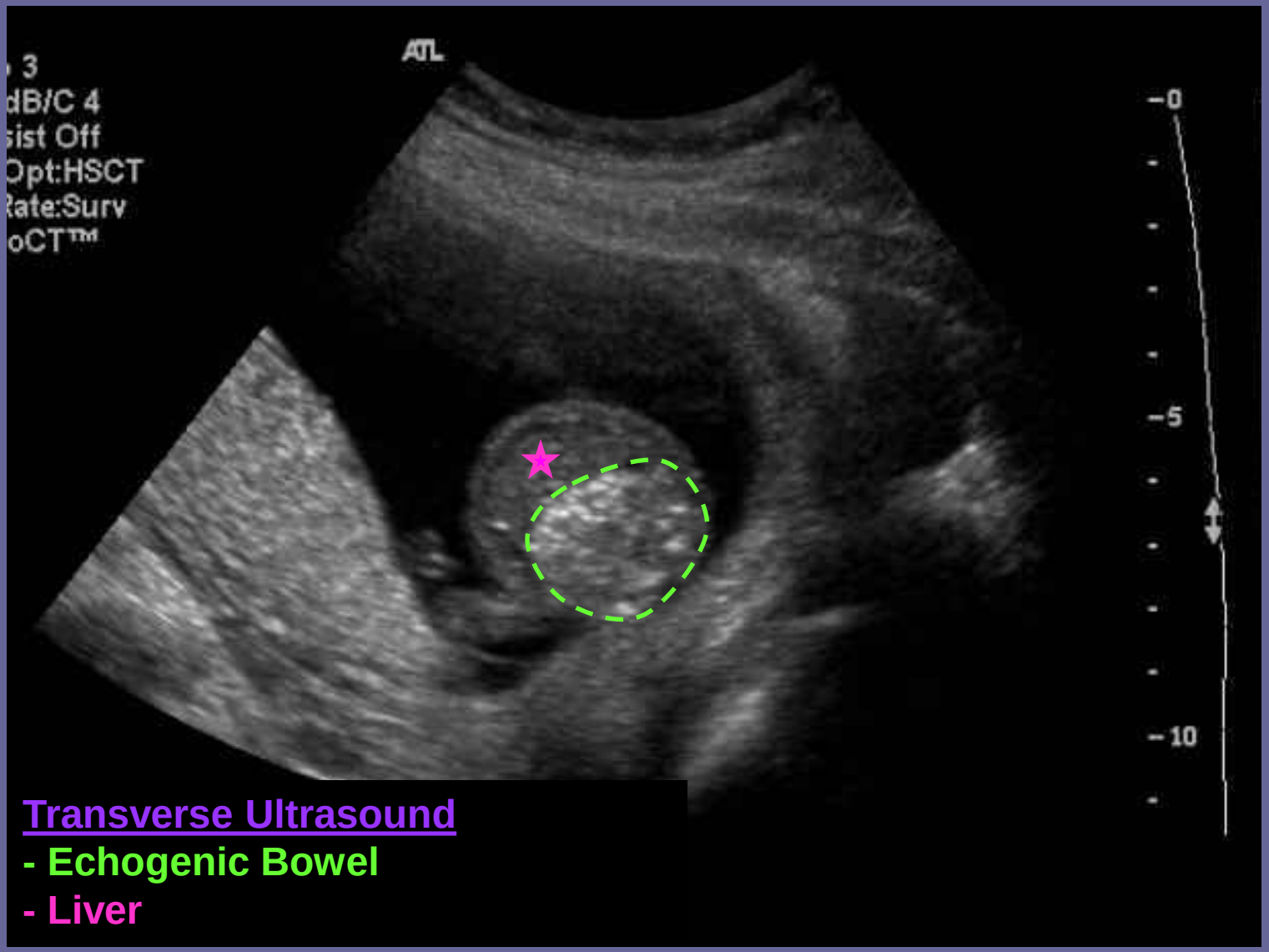
Companion Pt #1: Echogenic Bowel on 16w US



Courtesy of Dr. Olga Brook

Echogenic Bowel

- Defined as bowel echogenicitiy similar or greater than adjacent bone (i.e. iliac crest)
  - Note that a higher frequency transducer can lead to overdiagnosis
- Ddx:
  - Normal variant (0.5% normal fetuses)
  - Swallowed intra-amniotic blood
  - Down Syndrome – soft sign (LR of 6.5)
  - Cystic fibrosis
  - Congenital infection
  - Gastrointestinal malformation

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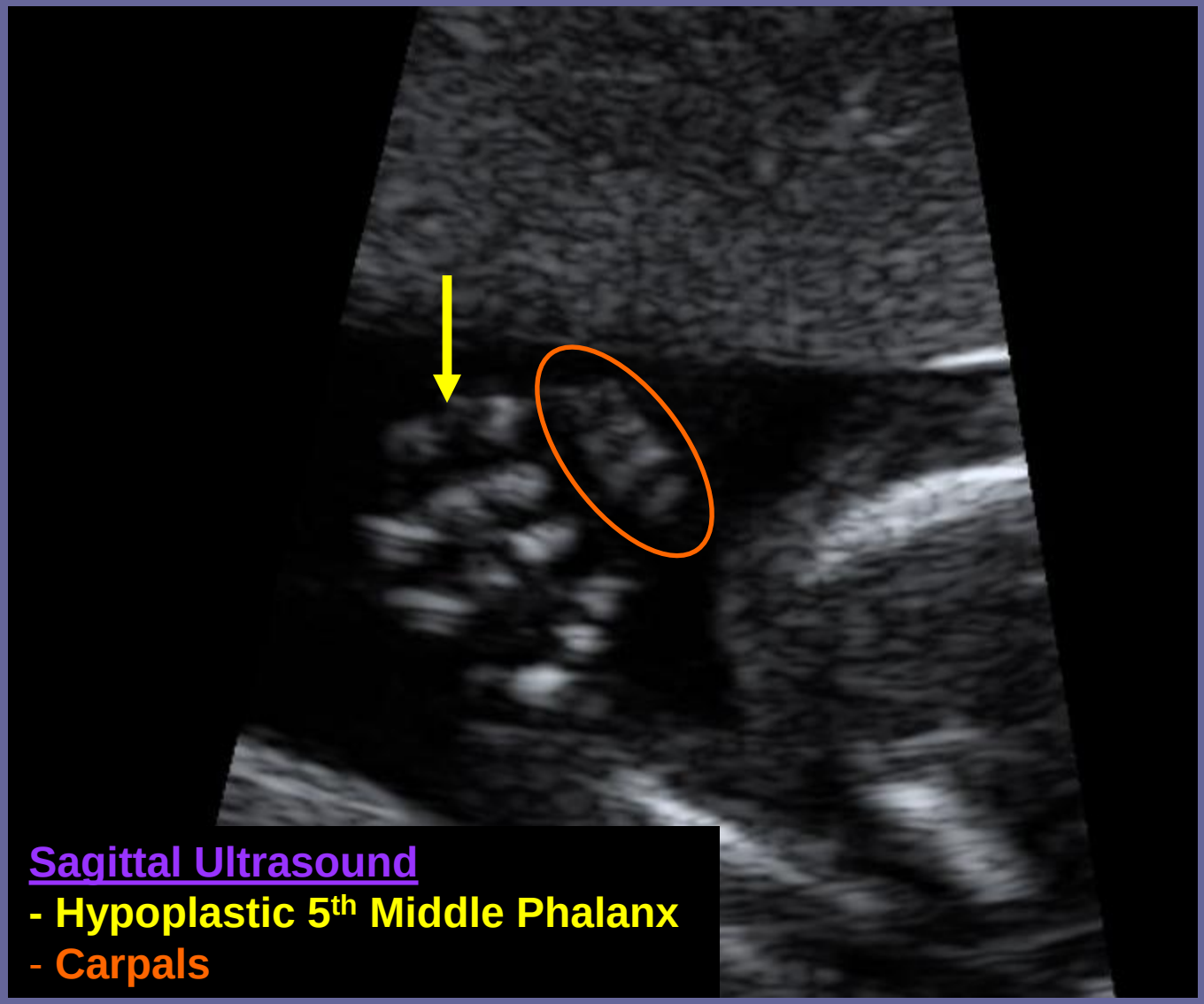
Companion Pt #1: Hypoplastic 5th Digit on 16w US



Courtesy of Dr. Olga Brook

Hypoplastic Fifth Digit

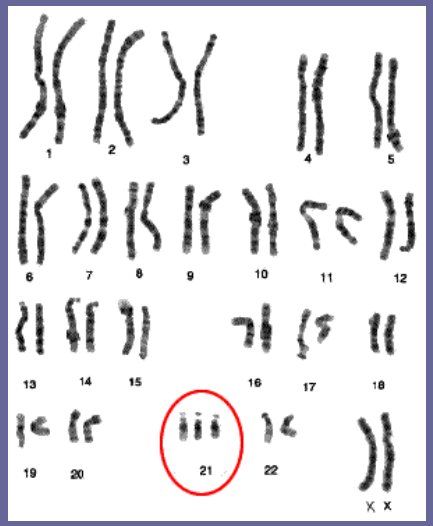
- 60% of T21 infants have hypoplasia of middle phalanx of 5th digit
  - Associated with clinodactyly, curvature of fifth finger toward adjacent fourth finger

https://www.pediatriccareonline.org

- DDx:
  - Down Syndrome - soft sign
  - Trisomy 18
  - Normal variant (3% normal patients)
  - Dwarfism
  - Brachydactylic syndromes

Our Patients' Follow Up

- Both patients underwent amniocentesis for fetal karyotyping, both demonstrating trisomy 21
- Both patients decided to terminate their pregnancies
  - 87-95% of pregnancies prenatally diagnosed with Down Syndrome are terminated



www,click4biology.info

- Both patients went on to subsequently deliver euploidic infants.
  - Risk for subsequent aneuploidic fetus is double the age-associated risk

Summary

- Down syndrome, the most common chromosomal abnormality in liveborn infants
- There are many screening options; serum assay +/- nuchal translucency, cell-free fetal DNA
  - Goal of identifying highest risk patients for diagnostic testing
- Down Syndrome is associated with multiple findings on ultrasound; none are 100% sensitive and specific for T21
  - major structural defects (i.e. ventriculomegaly)
  - ‘soft signs’ (i.e. pyelectasis, EIF, echogenic bowel, nuchal fold, hypoplastic phalanx of fifth digit)

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