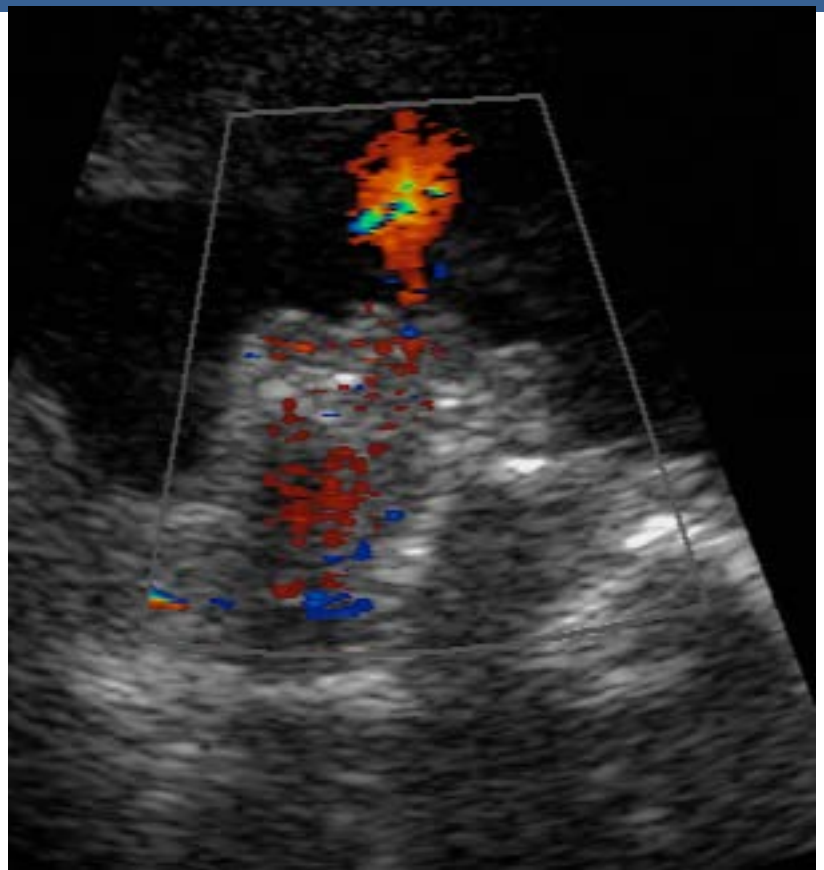
PSEUDO- AND QUASI-ULTRASOUND ABNORMALITIES OF THE FETUS



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61st ANNUAL OB/GYN UPDATE

Park City UT

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Disclosure

- Research support: Natera
- Consultant, Scientific Advisory Board: Invitae

Prenatal Ultrasound

- 3-4% of women will deliver a baby with a major birth defect
- “Pseudo” abnormalities are present in ~15% of pregnancies
- Most often these are normal variants
- Some may be associated with aneuploidy
- Most do not indicate a serious problem
- *Are we doing more harm than good?*

Is ultrasound risk free?

May cause harm by:

- Creating anxiety related to false-positive diagnoses
- Prompting unnecessary interventions
- Falsely reassuring women at high risk
- Dissuading high risk women from undergoing diagnostic procedures

Patient reaction to “soft markers”

Cristafalo et al. J Perinatol, 2006

- Women with isolated CPC report shock, fear, distress, decreased attachment
- Half report negative emotions temporary

Watson et al, Prenat Diagn, 2002

- Women with soft markers have clinically significant levels of anxiety

NICHD Fetal Imaging Workshop December, 2012

Current Commentary

Fetal Imaging

Executive Summary of a Joint *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Society for Maternal-Fetal Medicine, American Institute of Ultrasound in Medicine, American College of Obstetricians and Gynecologists, American College of Radiology, Society for Pediatric Radiology, and Society of Radiologists in Ultrasound Fetal Imaging Workshop

*Uma M. Reddy, MD, MPH, Alfred Z. Abuhamad, MD, Deborah Levine, MD, and George R. Saade, MD, for the Fetal Imaging Workshop Invited Participants**

Follow up of Isolated Soft Markers: NICHD Fetal Imaging Workshop

Marker	Other Considerations and Follow-Up
Echogenic cardiac focus*	None
Pyelectasis*	
≥4 mm up to 20 weeks of gestation	32-week ultrasonography to assess kidneys
≥7 mm at 32 weeks of gestation	Postnatal follow-up
Short humerus length*	Consider third-trimester growth ultrasonography
Short femur length*	Consider third-trimester growth ultrasonography
Nuchal thickening	Genetic counseling
Echogenic bowel	Genetic counseling 32-week ultrasonography to assess growth, bowel
Absent/hypoplastic nasal bone	Genetic counseling

“Soft Markers” for Down syndrome

- First reported in the 1980’s
  - Only screening option for women <35 yo at that time
  - AMA was poor predictor of aneuploidy
    - Women aged 35 have relatively LOW risk of DS
- Compared with cell free DNA, or even serum markers and NT, second trimester ultrasound has very poor predictive value for DS

Lack of consistency in what is considered a “soft sign”

Common: Echogenic intracardiac focus, choroid plexus cyst, mild renal pelviectasis, thick nuchal fold, echogenic bowel, short FL/HL

First trimester: NT, nasal bone

Other findings sometimes included: Mild ventriculomegaly, single umbilical artery, mega-cisterna magna, absent/hypoplastic nasal bone

Esoteric: Clinodactyly, absent middle phalanx 5th finger, sandal gap toe, widened iliac angle, shortened frontal lobe, prefrontal nasal thickness, ear length, transverse cerebellar diameter, flat facies, aberrant right subclavian artery, liver calcification, persistent right umbilical vein

Pseudo- & Quasi- Fetal Abnormalities

Findings with no pathologic significance

- Choroid plexus cysts
- Echogenic intracardiac focus

Findings with possible significance

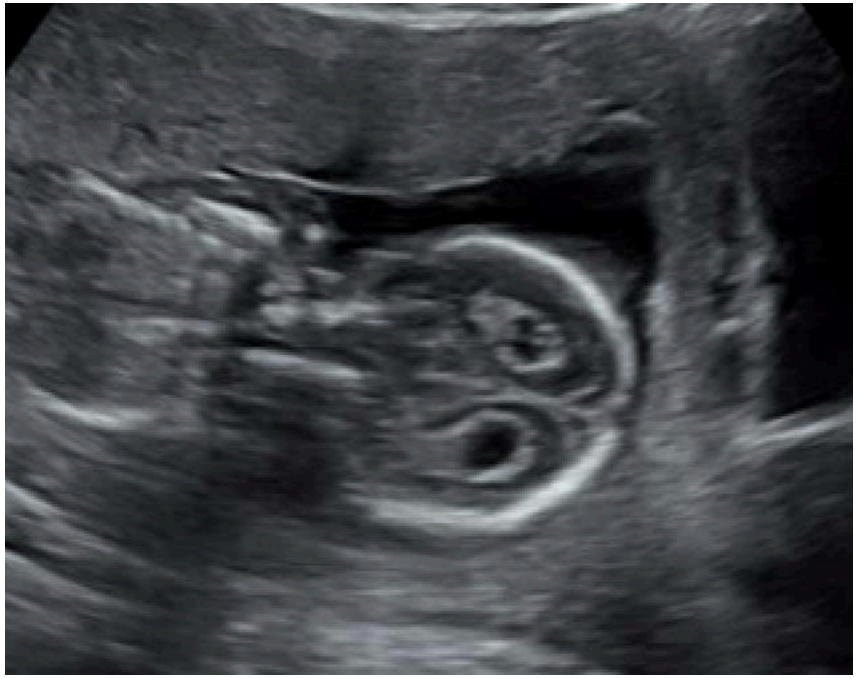
- Short HL/FL
- Renal pelviectasis
- Single umbilical artery

Findings with potential for significant abnormality, but often seen in normal fetuses

- Ventriculomegaly
- Echogenic bowel

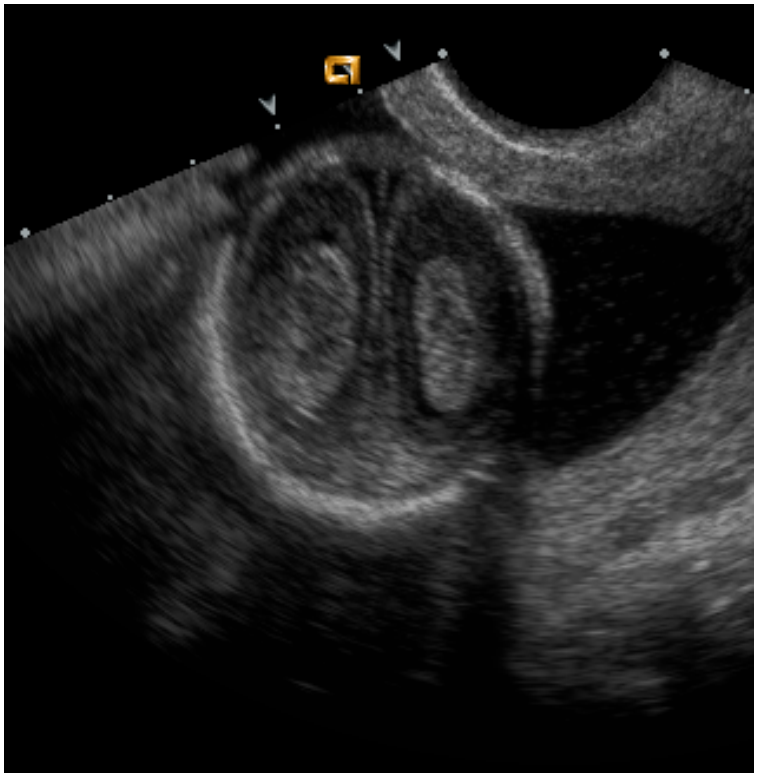
Findings with NO pathologic significance

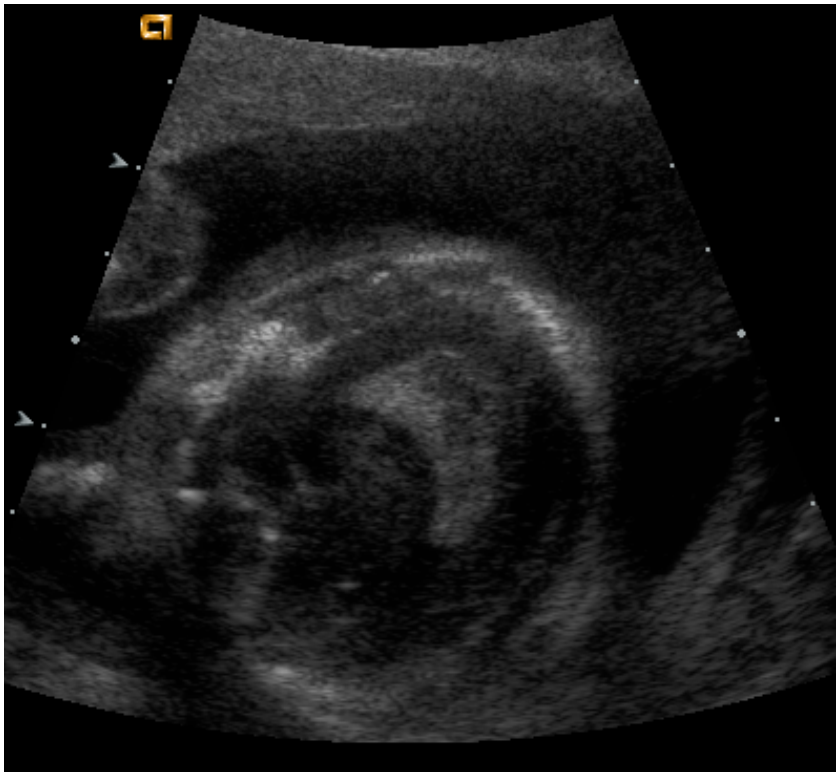
Choroid Plexus Cysts

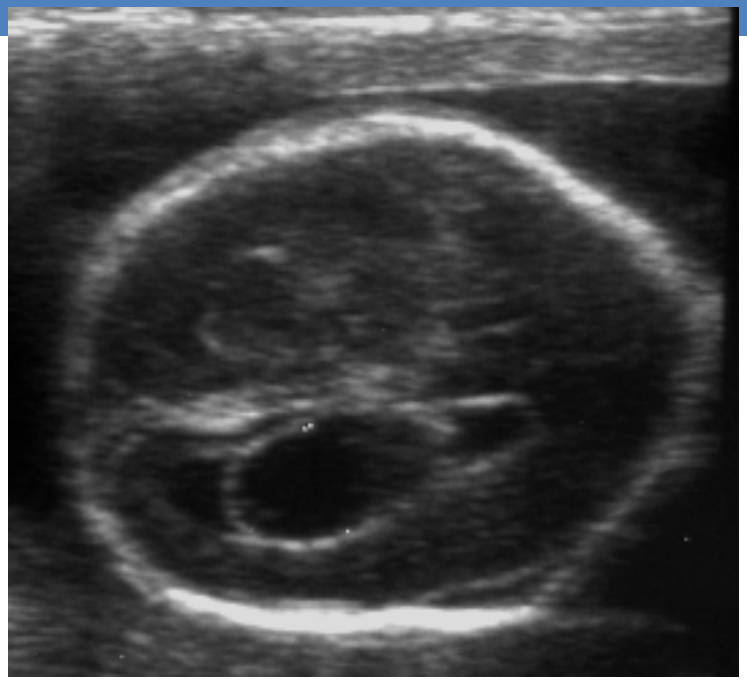


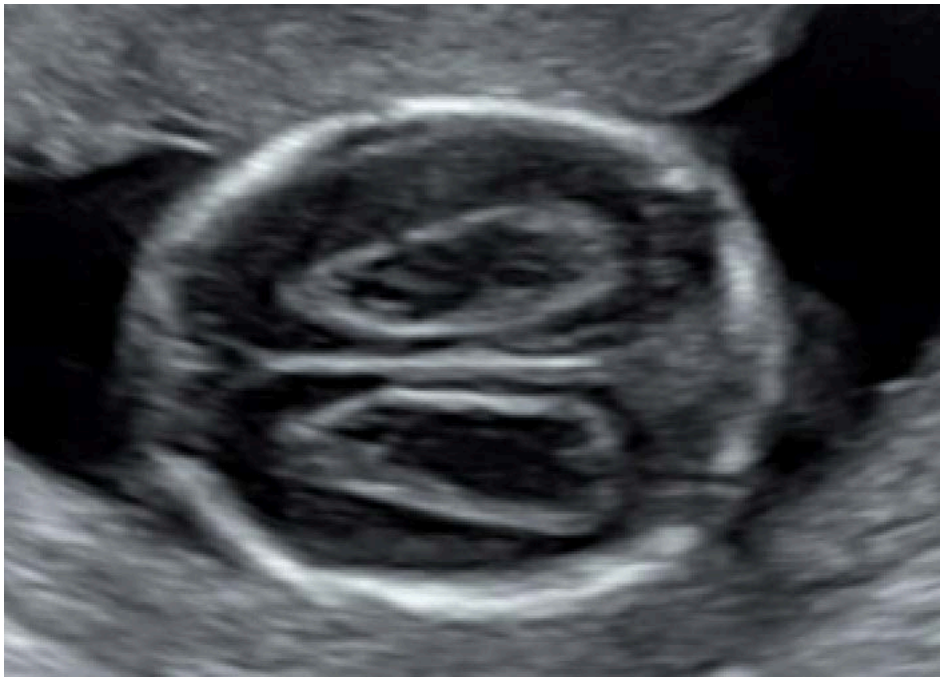
- Cyst in choroid plexus of developing brain
- Common in second trimester (0.3-3%)
- Resolve in essentially all cases
- Associated with trisomy 18, not Down syndrome

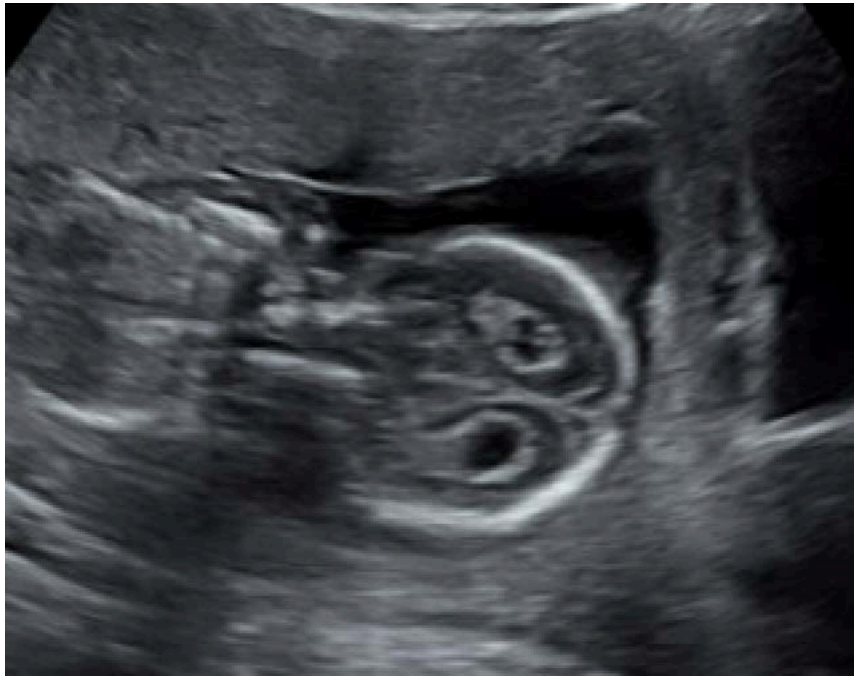
Heterogeneous Choroid









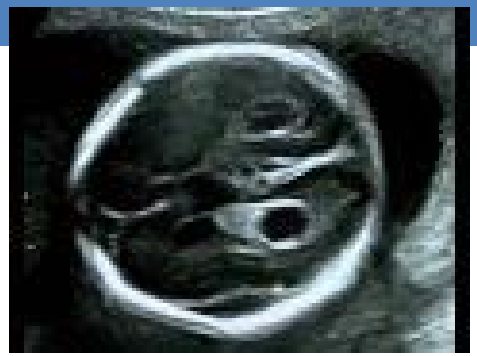


Choroid Plexus Cysts

Demasio et al. Am J Ob Gyn, 2002

- Isolated choroid plexus cysts in women < 35
- Meta-Analysis of studies of CPC
- 8 studies, 1990-2000
- N=106,732 women screened
- 1.0% of fetuses had isolated CPC (n=1017)
- Isolated = no anomalies & normal triple screen
- None had trisomy 18

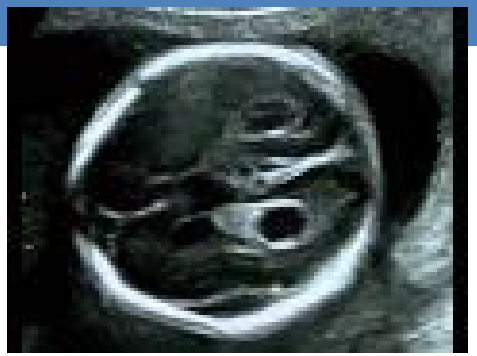
Isolated CPC and T18



- *Coco et al, J Ultrasound Med 2004*
  - n=12,672 unselected exams
  - 366 had isolated CPC – none had T18

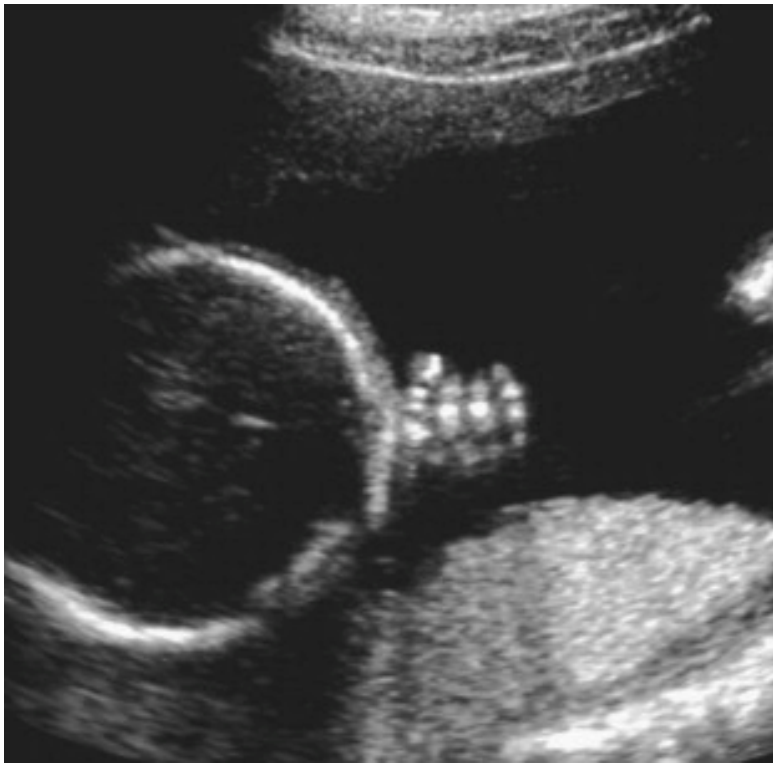
- *Bronsteen et al, J Ultrasound Med 2004*
  - n=49,435 second trimester exams
  - 1060 had isolated CPC-- none had T18

Isolated CPC and T18

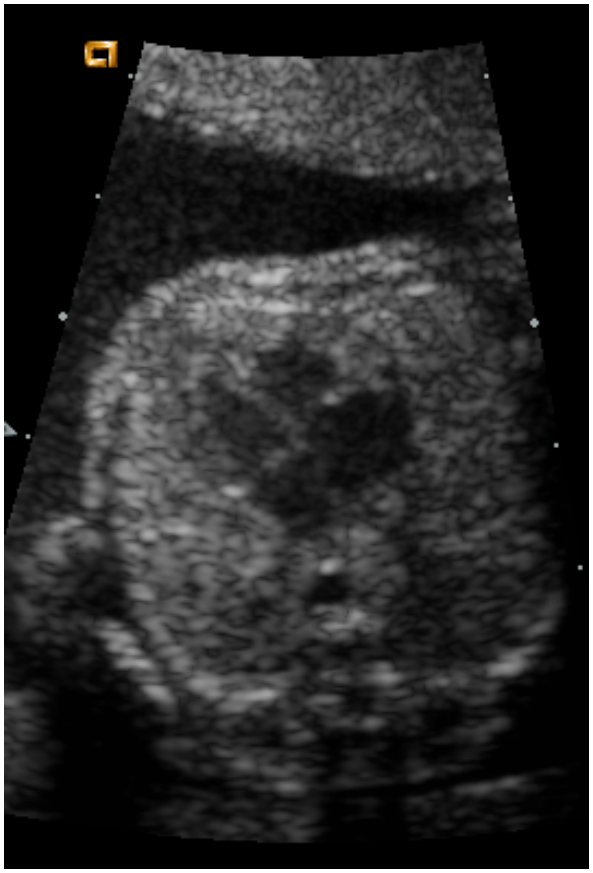


- *Bronsteen et al, J Ultrasound Med 2004*
  - 49 cases of T18
    - All cases of T18 had other anomalies *provided an adequate exam was performed*
  - In some cases clenched hands were the only other anomaly

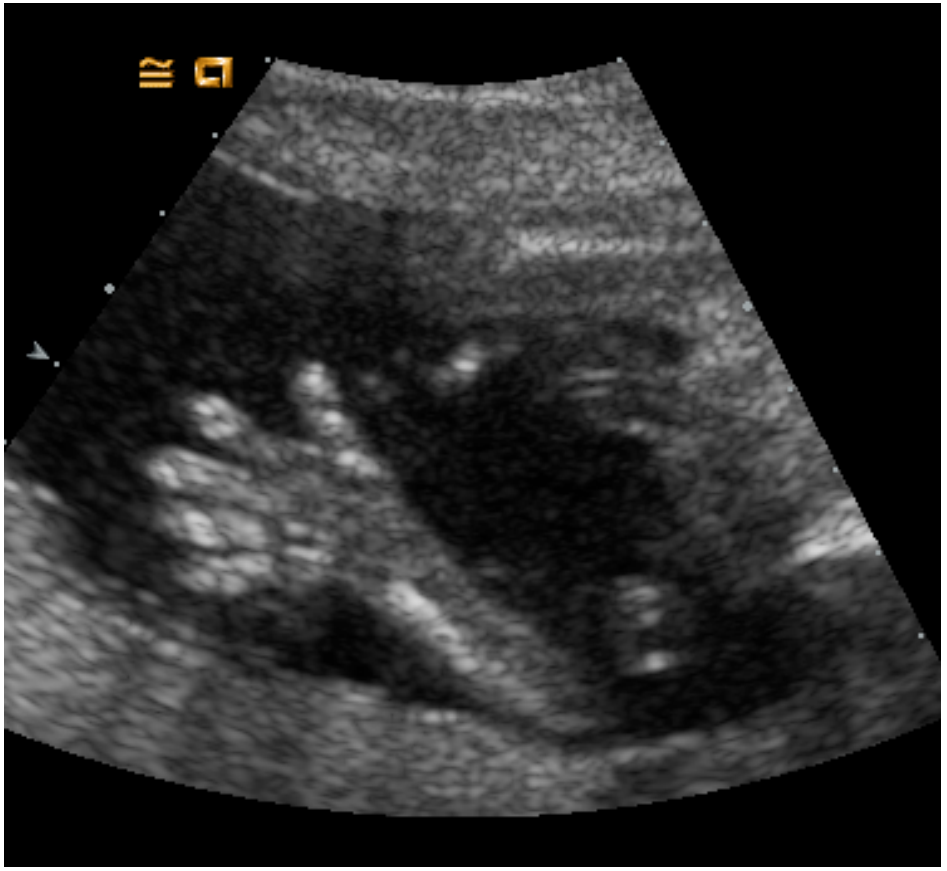
Clenched Hands: Trisomy 18



Choroid Plexus Cyst
Additional US evaluation



Detailed cardiac exam



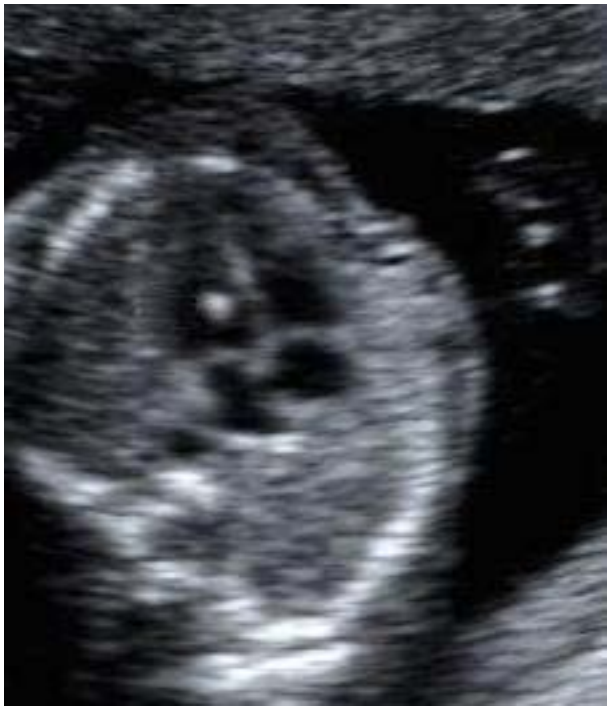
Open hand

Isolated Choroid Plexus Cysts

Recommendations:

- Correlation with screening results
  - If ***isolated*** and T18 risk is low, no further evaluation is required
- No ultrasound follow up is recommended
  - CPCs almost always resolve
  - No prognostic implications if they do not
- Amniocentesis not warranted in absence of other risk factors
- Cell free DNA screening is very accurate for trisomy 18, reasonable to offer if no other screening has been done

Echogenic Intracardiac Focus



- Calcifications of papillary muscle, typically seen in 2nd trimester
- Typically in left ventricle (85%)
- More common in non-Caucasians
- NOT associated with congenital heart defects
- Marginally increased risk of chromosome abnormalities (trisomies 13 and 21)
- Association also seen in first trimester

Echogenic Intracardiac Focus

Recommendations:

- Correlation with other risk factors for chromosome abnormalities (screening results, maternal age)
- Likelihood ratio: 1.8 has been used
- More recent data indicates LR of 0.95 when isolated
- No US follow up or fetal echo warranted
- Cell free DNA can be useful for Down syndrome if borderline risk or no prior screening

Society for Maternal-Fetal Medicine
High-risk pregnancy experts

Society for Maternal-Fetal Medicine (SMFM) Consult Series | #42
smfm.org

The role of ultrasound in women who undergo cell-free DNA screening

Society for Maternal-Fetal Medicine (SMFM) with the assistance of Mary E. Norton, MD; Joseph R. Biggio, MD; Jeffrey A. Kuller, MD; Sean C. Blackwell, MD

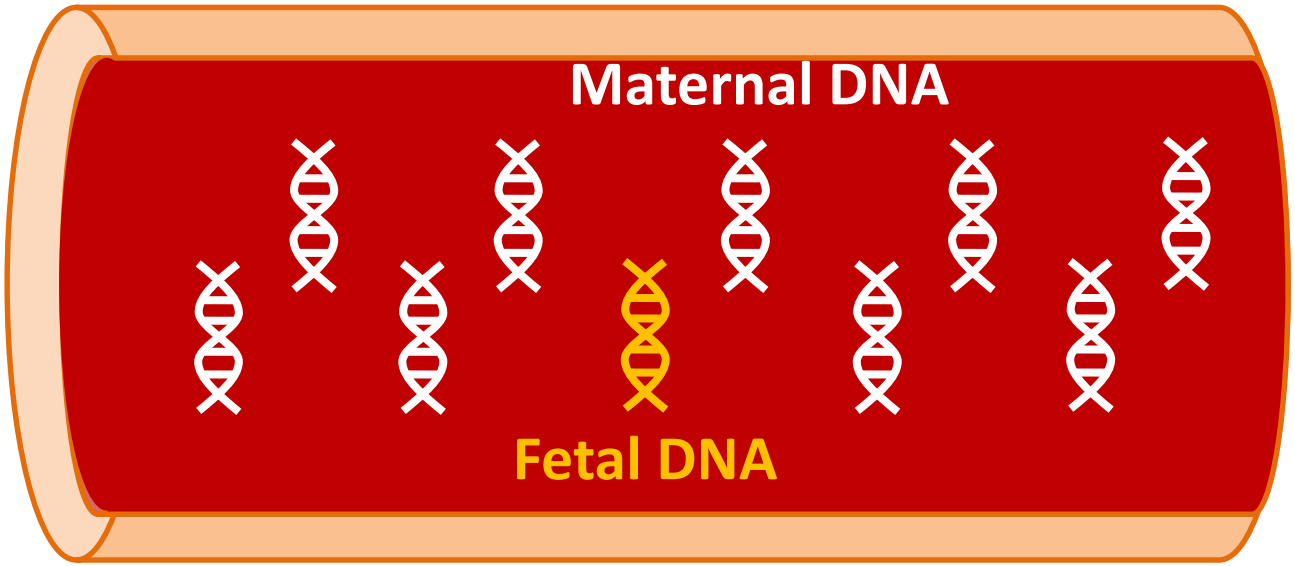
"In women with an isolated soft marker that has no other clinical implications (ie, choroid plexus cyst or echogenic intracardiac focus) and a negative cell-free DNA screen, we recommend describing the finding as not clinically significant or as a normal variant."

Genetic testing: CPC and EIF

- CPC and EIF have no clinical significance in a fetus with a known normal karyotype
- In patient that has had diagnostic testing (amnio or CVS), these are normal variants, no follow up required
- Diagnostic testing should not be recommended in patients solely for the indication of an isolated soft marker in the setting of negative cfDNA

Cell free fetal DNA

- Cell free fetal DNA (cffDNA): short segments of fetal DNA in maternal plasma
- Origin primarily placental



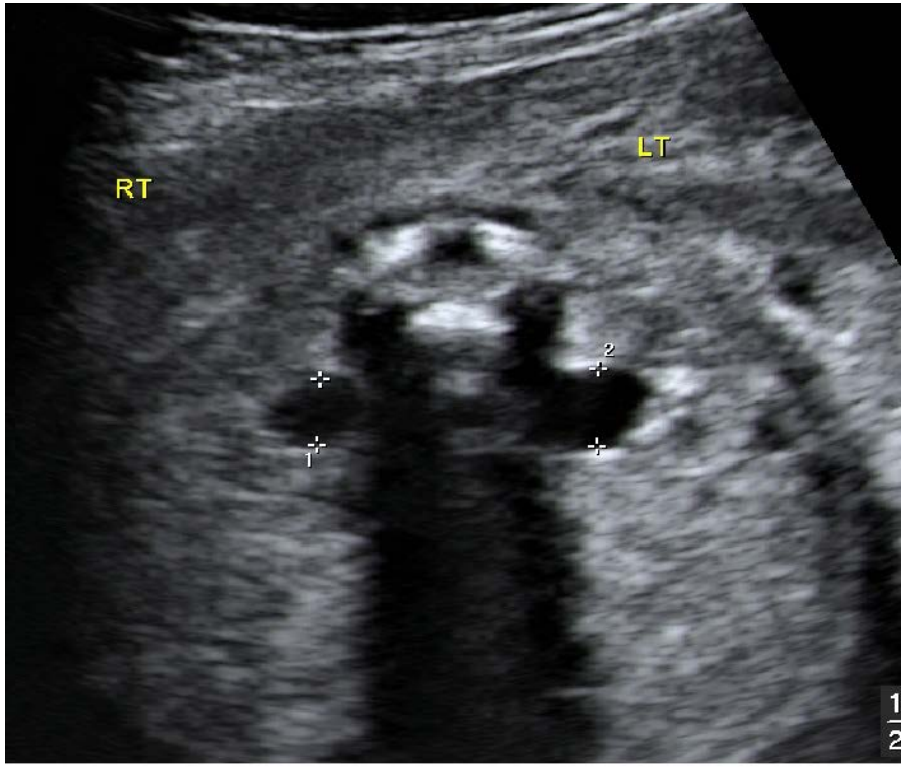
Cell free DNA screening (cfDNA)

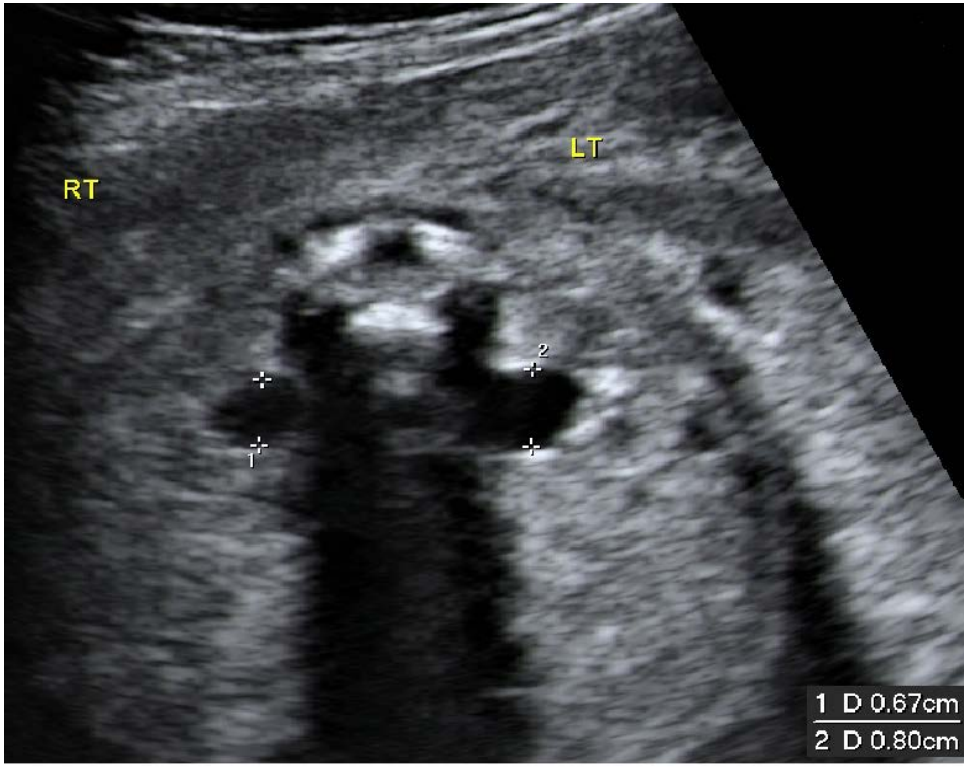
- Outstanding screen for Down syndrome
  - Near diagnostic
- Excellent (not quite as good) for trisomy 18
  - More false positive and false negative results
- cfDNA is a very good alternative in patient with EIF or CPC who wants further testing
  - Especially if no prior screening OR borderline risk

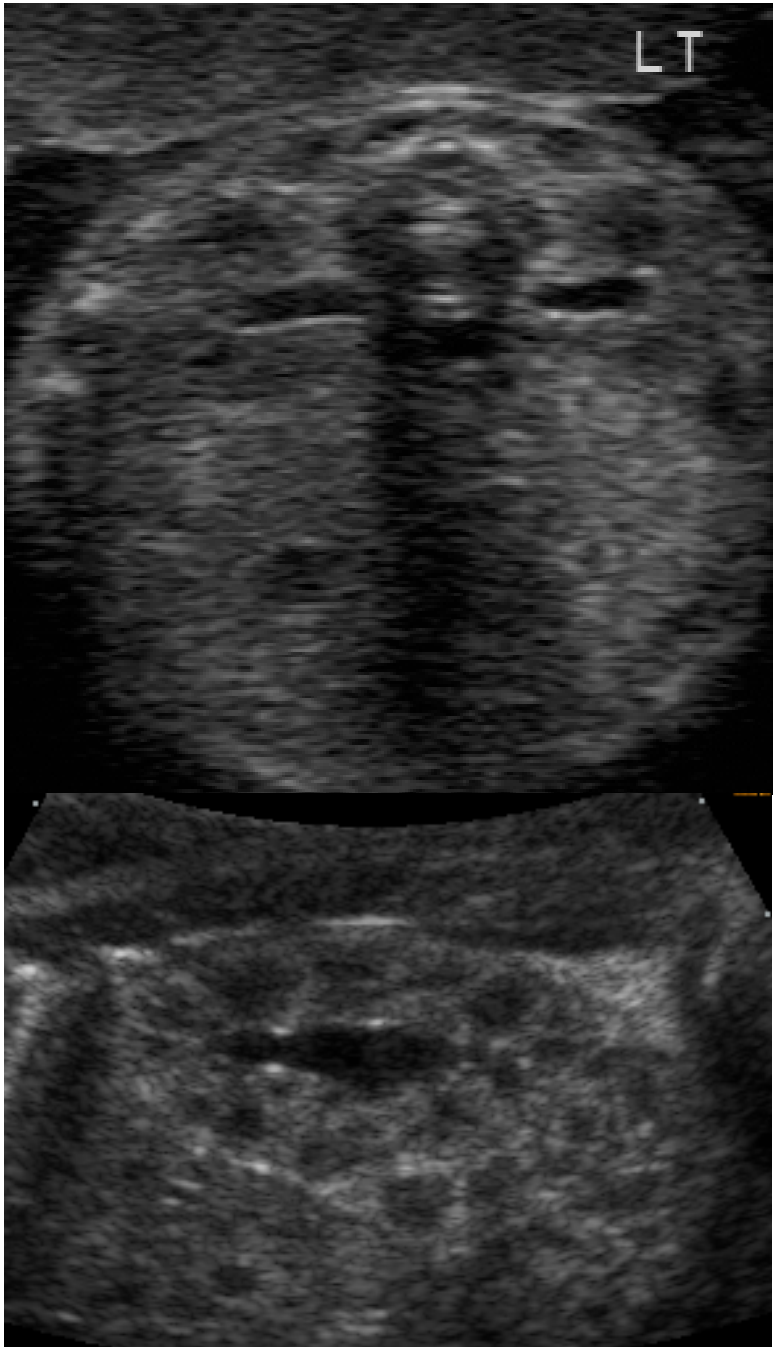
Findings of MINIMAL significance to the fetus

Urinary tract dilation

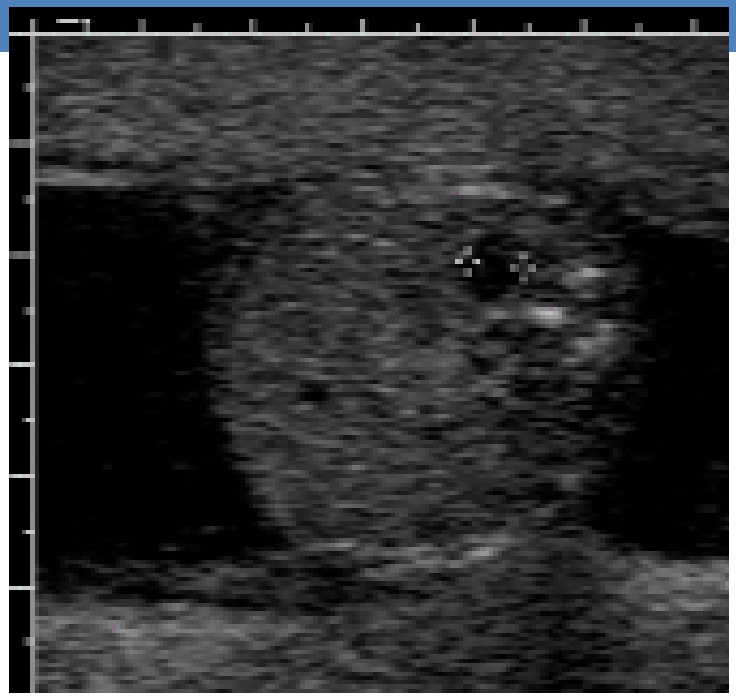
- Dilatation of anteroposterior diameter of renal pelvis without frank hydronephrosis
- In > 90% of cases, is a physiologic response
- In fewer, this represents true pathology, such as UPJ obstruction or reflux

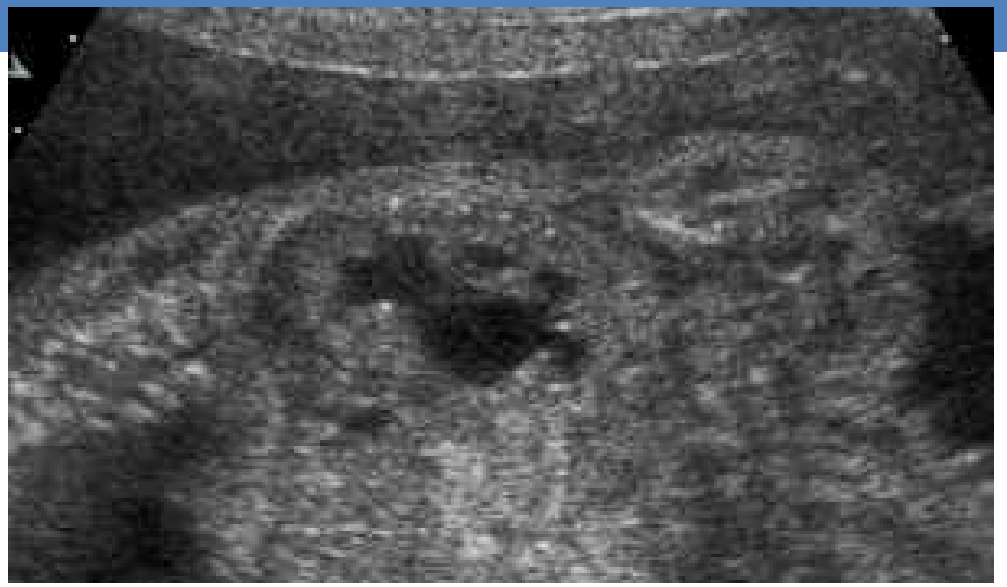




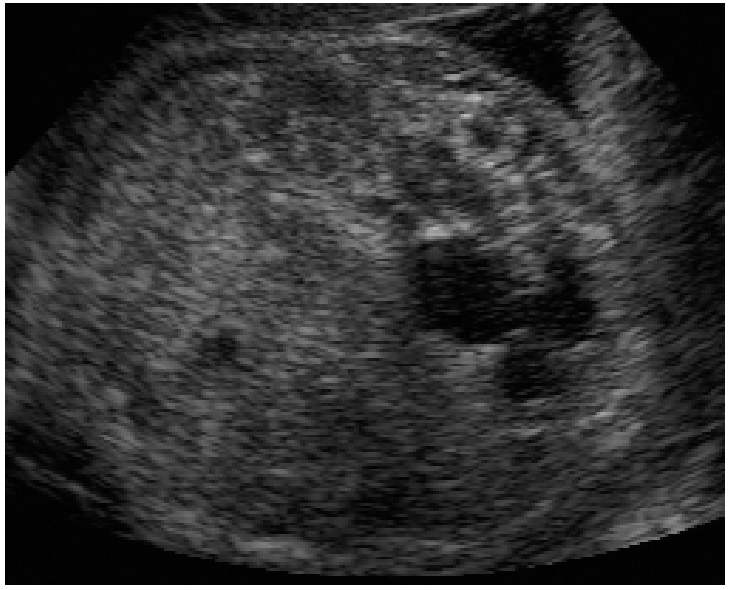


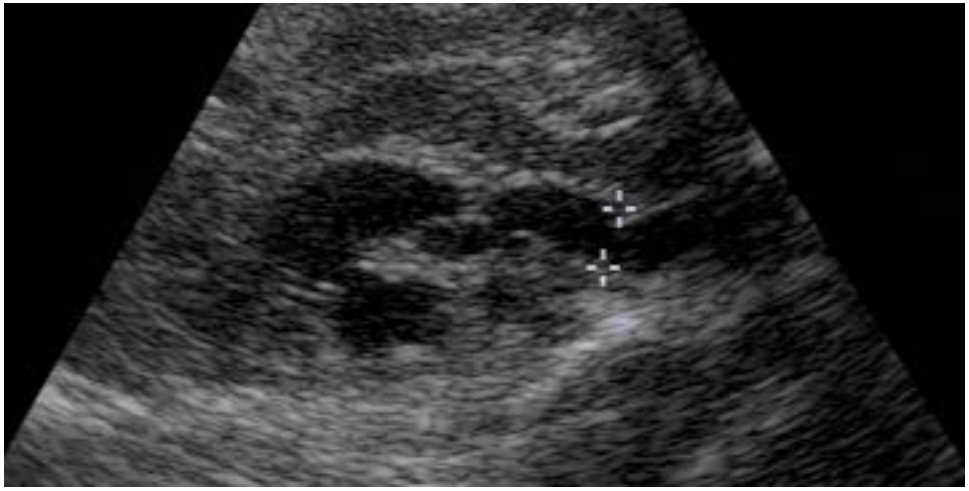
“Physiologic” Pelviectasis



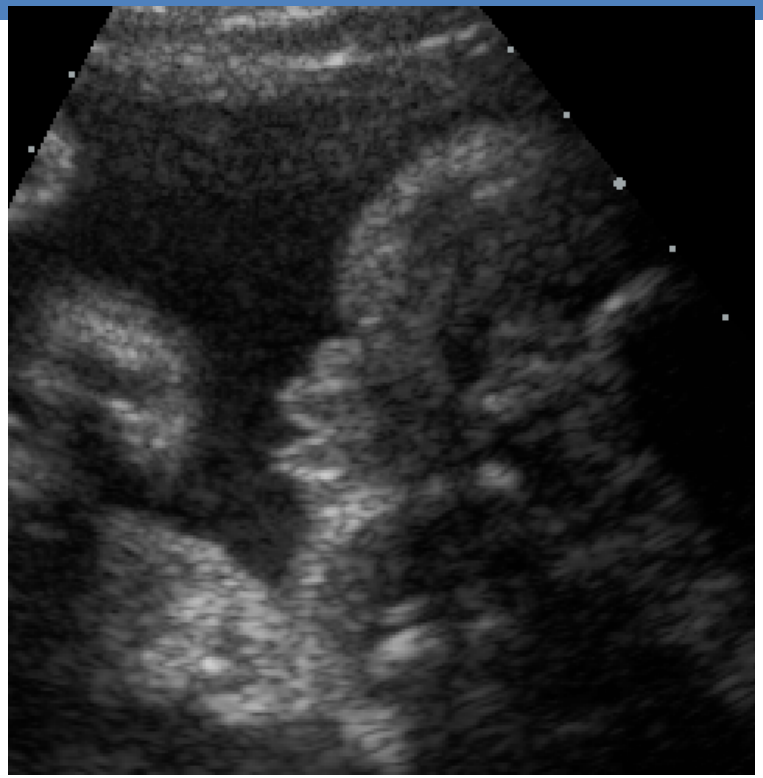


Dilated Calyces -> Hydronephrosis



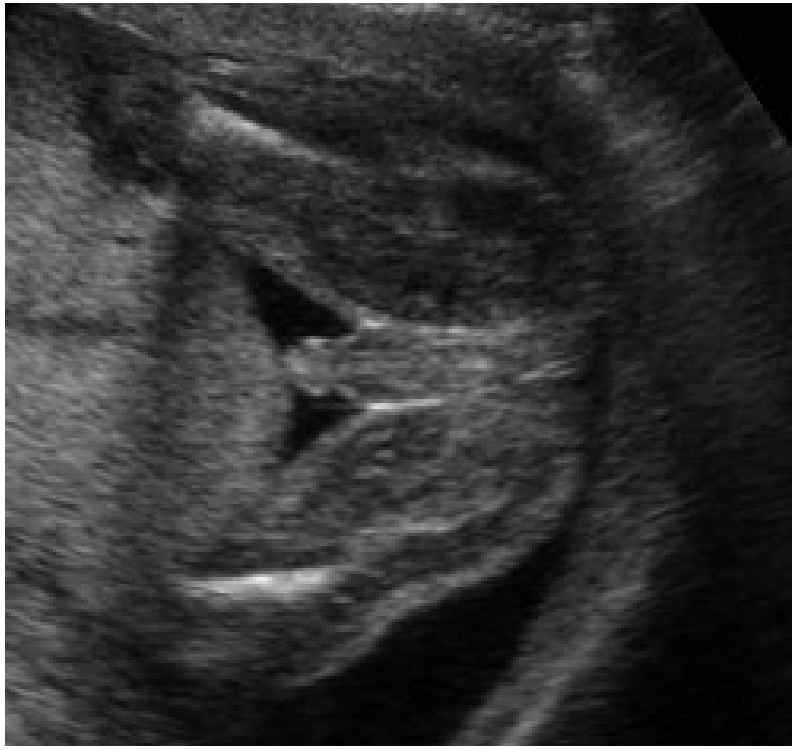


Hydroureter



US evaluation:

- amniotic fluid volume
- urinary bladder
- fetal sex



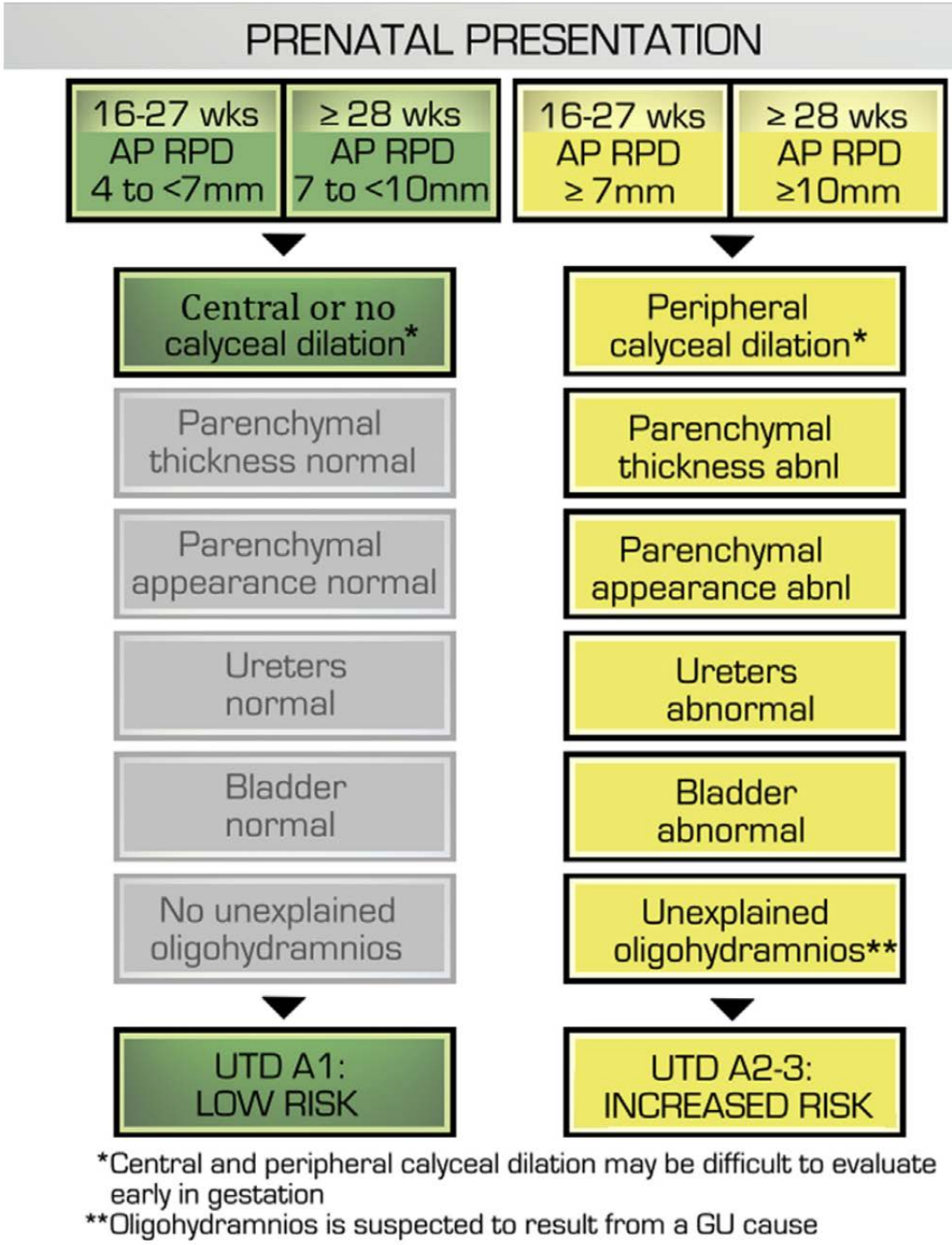
Journal of Pediatric Urology (2014) 10, 982—999

ELSEVIER

Journal of Pediatric urology

Multidisciplinary consensus on the classification of prenatal and postnatal urinary tract dilation (UTD classification system)

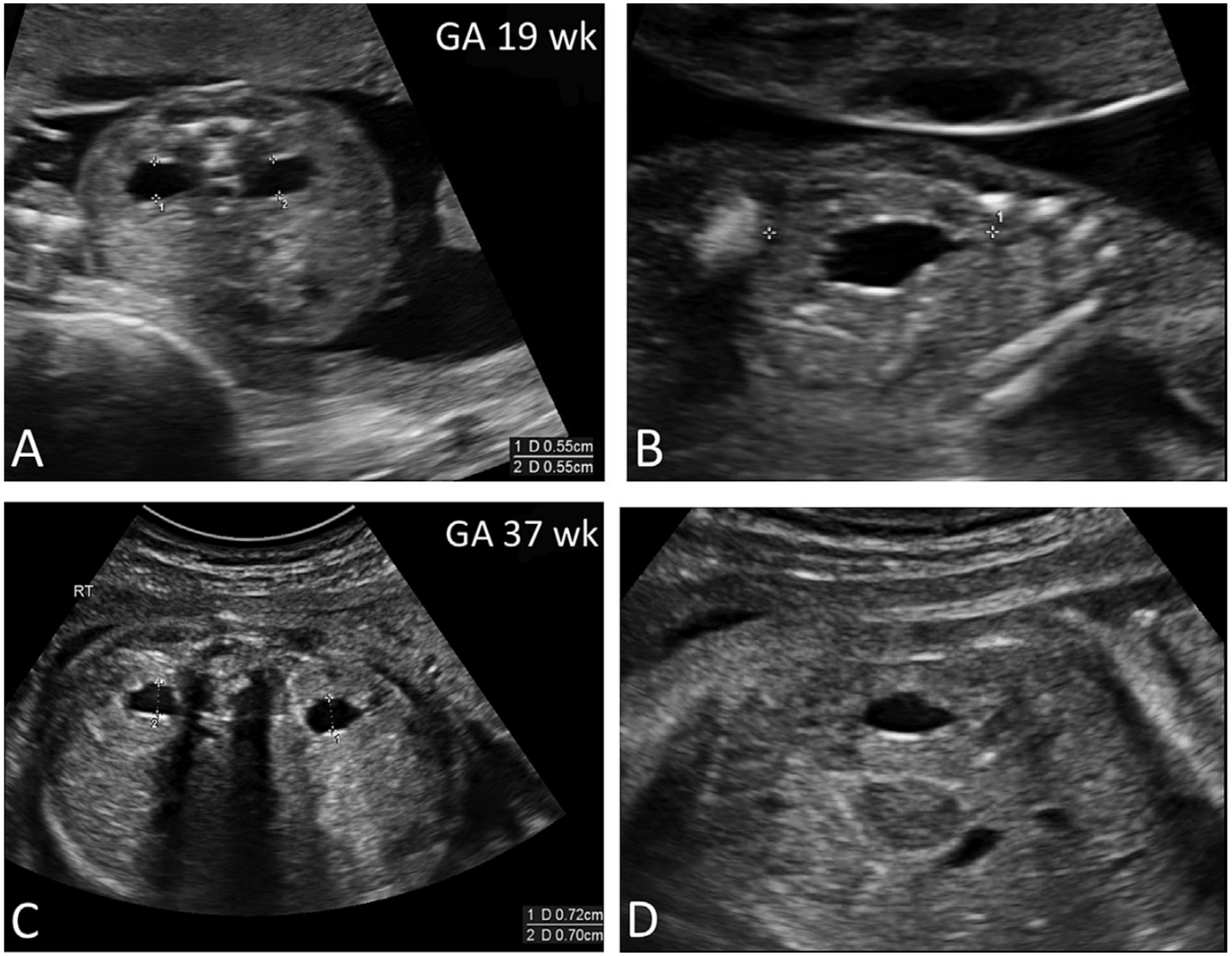
Hiep T. Nguyen [d,f,*], Carol B. Benson [h,a], Bryann Bromley [b], Jeffrey B. Campbell [d,f], Jeanne Chow [g], Beverly Coleman [a,h], Christopher Cooper [d,f], Jude Crino [e], Kassa Darge [g], C.D. Anthony Herndon [d,f], Anthony O. Odibo [e], Michael J.G. Somers [c], Deborah R. Stein [c]



Multidisciplinary classification system for urinary tract dilation (UTD)

Pediatr Radiol 2015

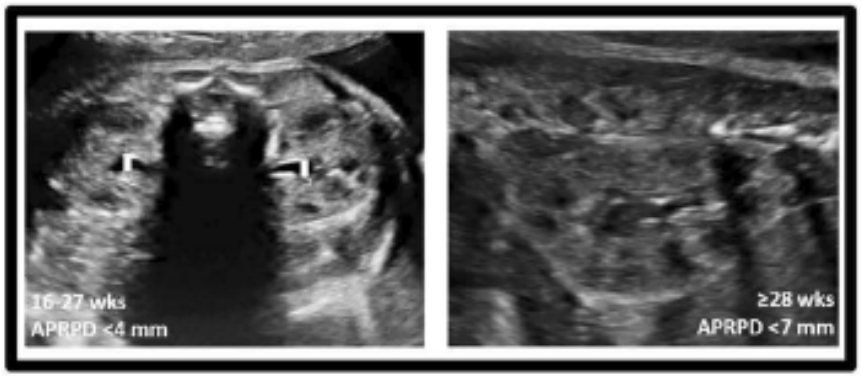
Urinary tract dilation: A1



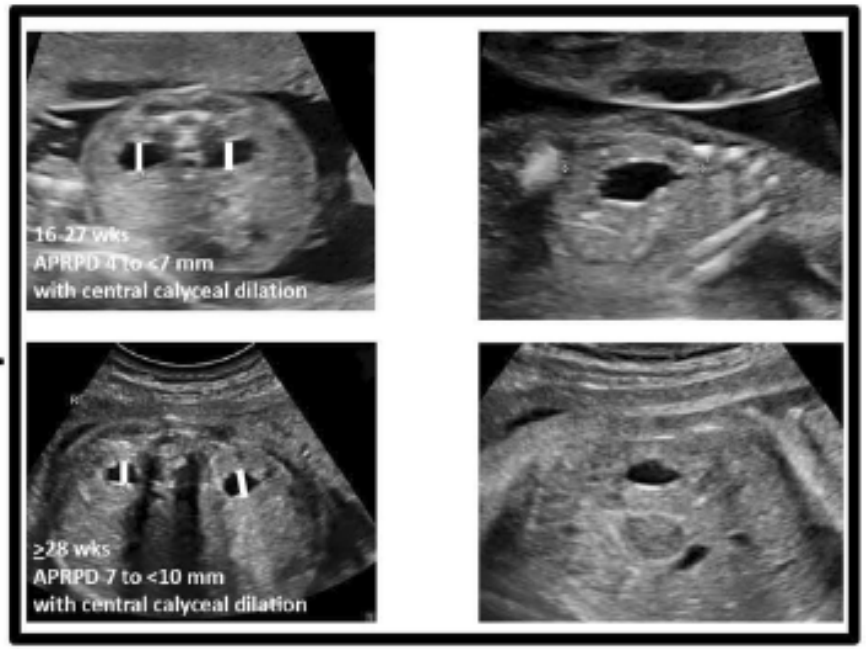
Antenatal Presentation

Transverse View | Sagittal View

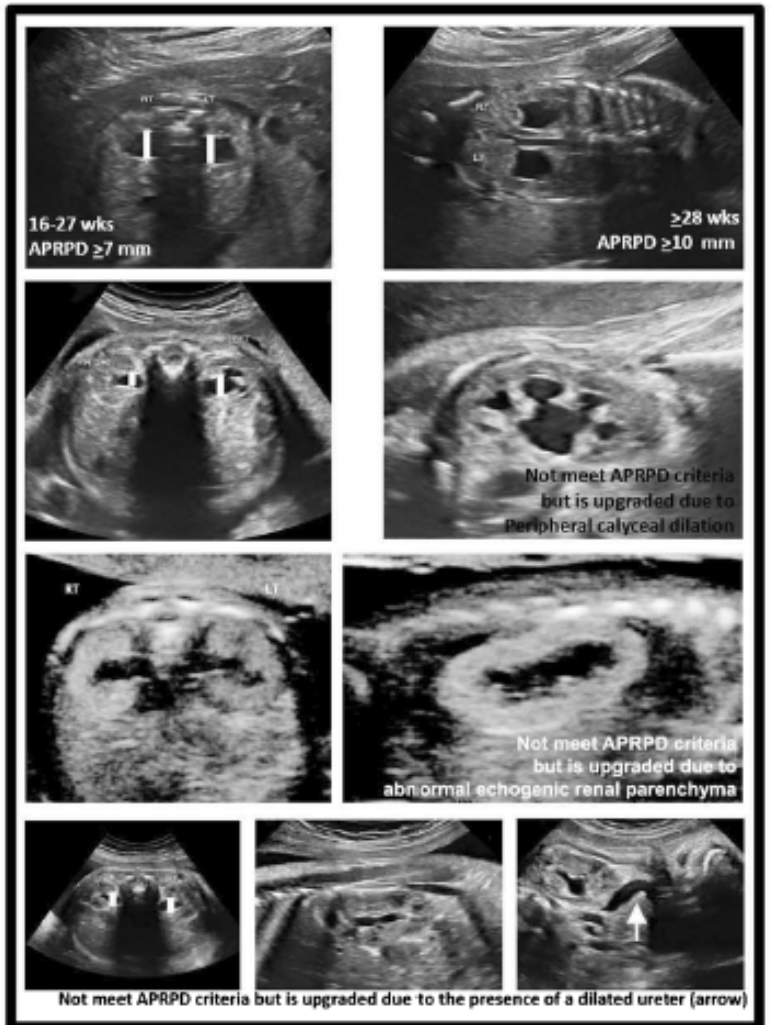
Normal



A1



A2-3



Urinary tract dilation

What warrants follow up?

- ≥4 mm before 28 wks
- ≥7 mm at ≥28 weeks
  - Half will be normal or better
  - 30% unchanged
  - 15% worse

(*Signorelli 2005*)

Postnatal Pathology Reported After Prenatally Detected Mild Pelviectasis

UPJ obstruction	5%
Vesicoureteral reflux	5-10%
Posterior urethral valves	0.2%
Ureteral obstruction	1.2%
Other renal abnormalities	1.2%
Total with any pathology	12%

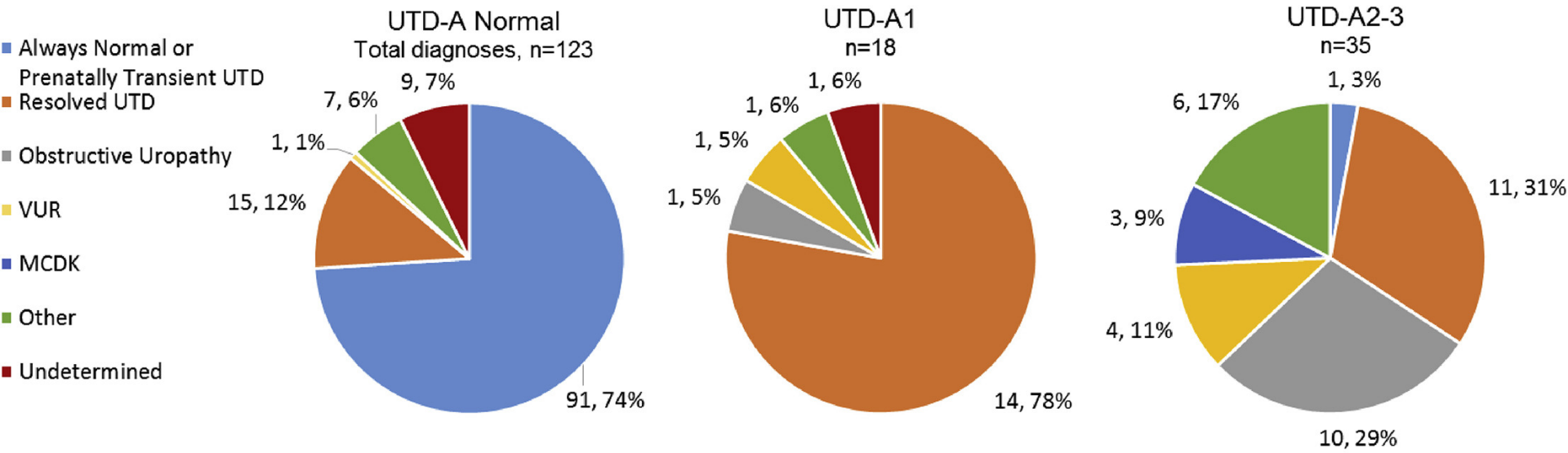
Lee et al, Pediatrics 2006

Outcomes of Prenatally Detected Hydronephrosis

Degree of AH	2nd tri	3d tri	Postnatal Pathology
Mild	≤7mm	≤9	12%
Moderate	7-10 mm	9-15 mm	45%
Severe	≥10mm	≥15 mm	88%

Lee et al, Pediatrics 2006

Antenatal UTD system outcomes



Diagnoses in more detail:

UTD-A Normal	'Other': 1 with renal vein thrombosis, 3 myelomeningocele, 3 pelvic kidney
UTD A1	'Other': 1 duplex collecting system
UTD A2-3	'Other': 3 with cystic dysplasia, 2 duplicated collecting system, 1 bladder rupture in utero
	'Always normal/transient UTD': 1 unexplained oligohydramnios and normal KUT

Kasper et al, J Pedi Urol, 2017

Pelviectasis/mild UTD and Down Syndrome

- Mild pelviectasis is common in Down syndrome
- Risk of DS slightly increased when pelviectasis present
- Approximately double the prior risk based on screening (likelihood ratio = 2)
- Usually not enough to warrant amnio in absence of other risk factors
- cfDNA is a good alternative for the patient who is at borderline risk or very anxious

Pelviectasis/mild UTD

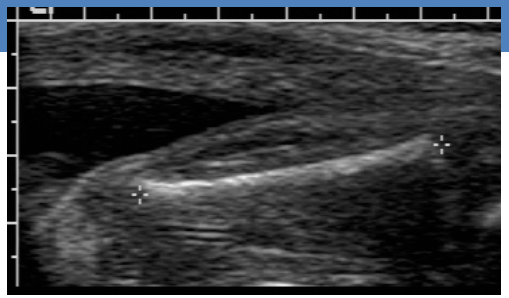
Recommendations:

- Correlation with screening results
  - Offer cfDNA or amniocentesis if patient anxious, or borderline risk for Down syndrome
- Detailed US to rule out pathology, other anomalies
- Repeat US in mid-third trimester to rule out progression and determine need for postnatal F/U

If findings persist in 3rd trimester (>/=7mm)

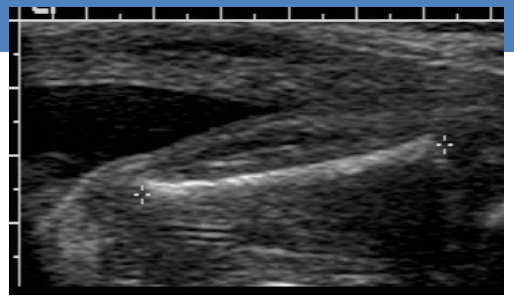
- Postnatal follow up >48h but <1month after birth
- ? Antibiotic prophylaxis until follow up obtained

Shortened long bones (FL and HL)



- FL and HL both shorter in Down syndrome
  - HL shorter than FL
- Definition(s):
  - Observed/expected BPD/FL ratio: ≤0.93, 0.91, 0.90, 0.85
  - <5%ile for GA
  - <0.91 MoM (FL) or 0.89 MoM (HL) for GA
- Length varies with race/ethnicity
- Increased risk for Down syndrome
  - 4-5X for short HL
  - 1.6-4.6X for short FL

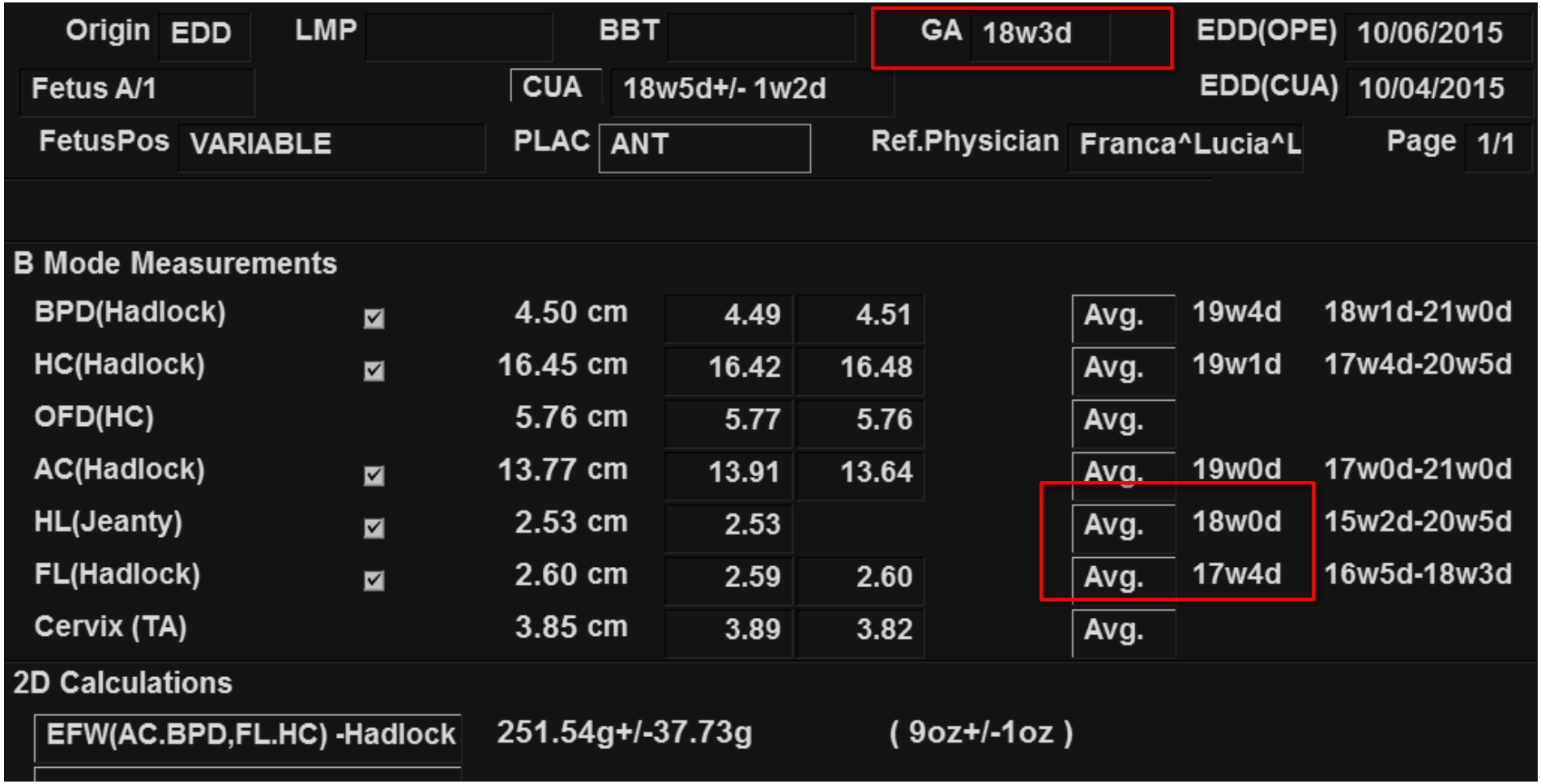
Shortened long bones (FL and HL)



<u>Is there an increased risk of SGA, skeletal dysplasia?</u>

- Slightly increased risk of SGA (OR 2.6; *Weisz 2008)*
- Is there an increased risk of skeletal dysplasia?
  - Severe skeletal dysplasia typically involves more severe shortening and bowing
  - Achondroplasia has normal FL until >25 wks (*Chitty 2011)*
- May be a need for follow up scan(s) to rule out SGA
  - One follow up scan at 32 wks for fetal growth

18+3 wks gestation, routine scan



Origin	EDD	LMP		BBT		GA	18w3d	EDD(OPE) 10/06/2015
Fetus A/1			CUA	18w5d+/- 1w2d				EDD(CUA) 10/04/2015
FetusPos	VARIABLE		PLAC	ANT		Ref.Physician	Franca^Lucia^L	Page 1/1

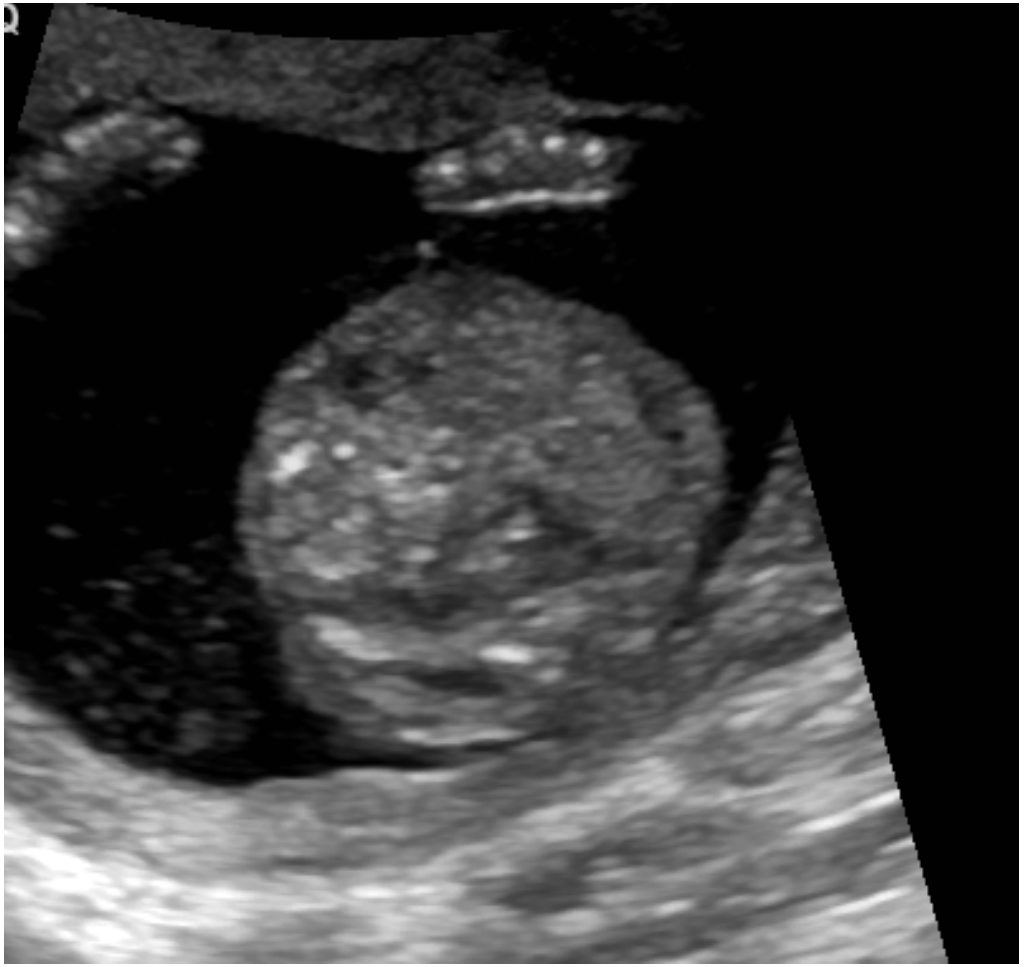
B Mode Measurements

BPD(Hadlock)	☑	4.50 cm	4.49	4.51	Avg.	19w4d	18w1d-21w0d
HC(Hadlock)	☑	16.45 cm	16.42	16.48	Avg.	19w1d	17w4d-20w5d
OFD(HC)		5.76 cm	5.77	5.76	Avg.		
AC(Hadlock)	☑	13.77 cm	13.91	13.64	Avg.	19w0d	17w0d-21w0d
HL(Jeanty)	☑	2.53 cm	2.53		Avg.	18w0d	15w2d-20w5d
FL(Hadlock)	☑	2.60 cm	2.59	2.60	Avg.	17w4d	16w5d-18w3d
Cervix (TA)		3.85 cm	3.89	3.82	Avg.		

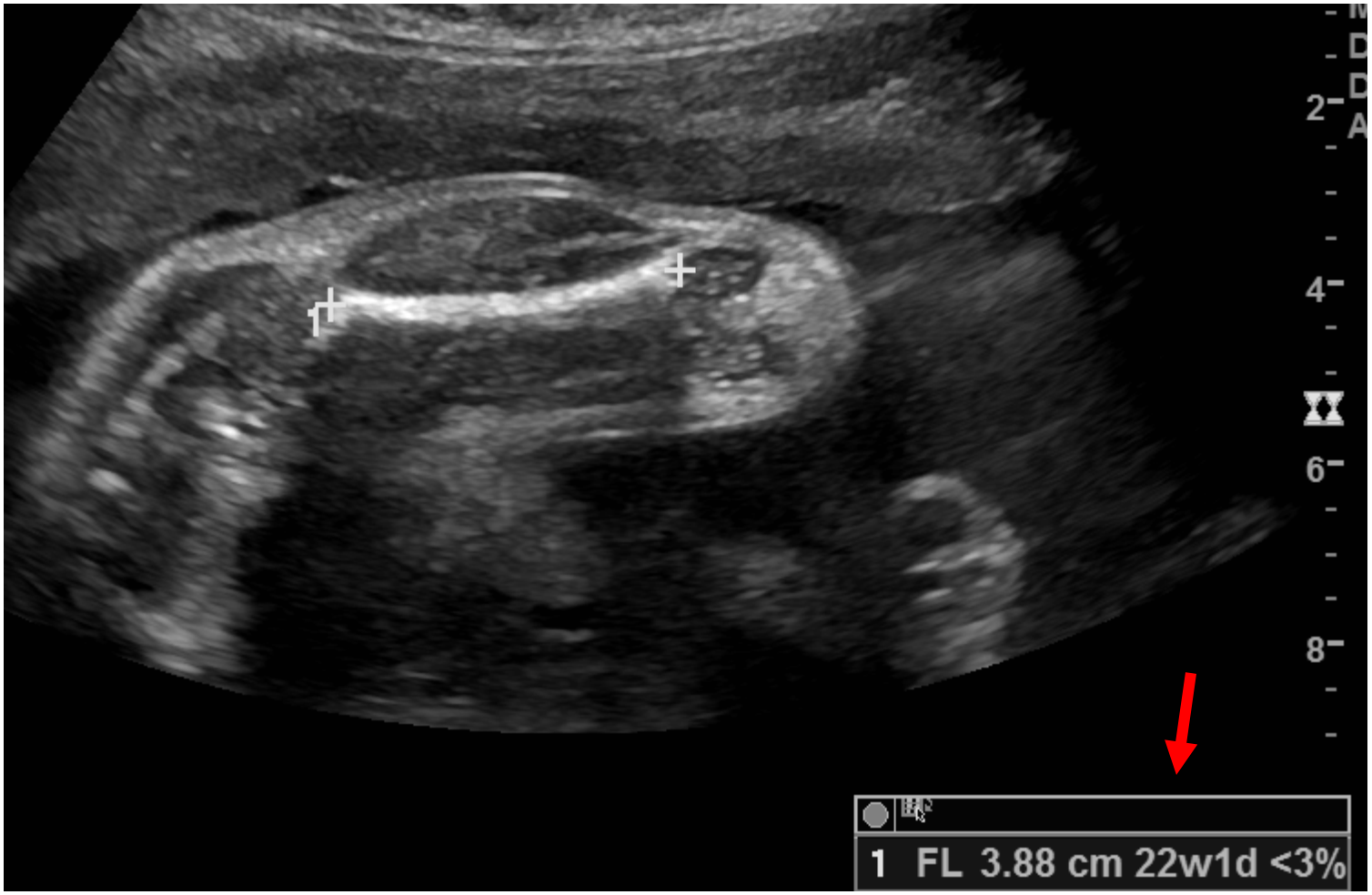
2D Calculations

EFW(AC.BPD,FL.HC) -Hadlock	251.54g+/-37.73g	(9oz+/-1oz)

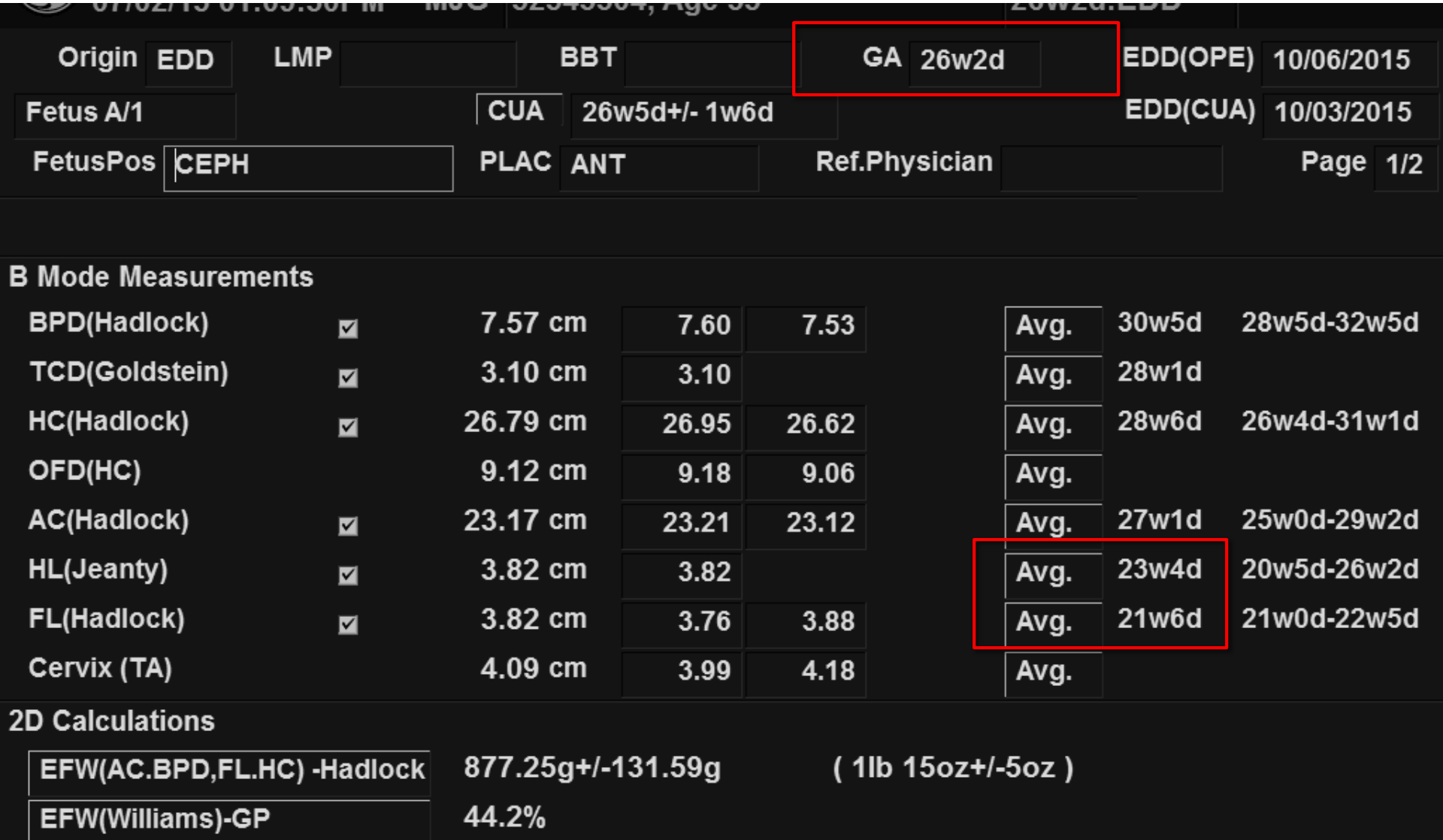
18+3 wks gestation, routine scan



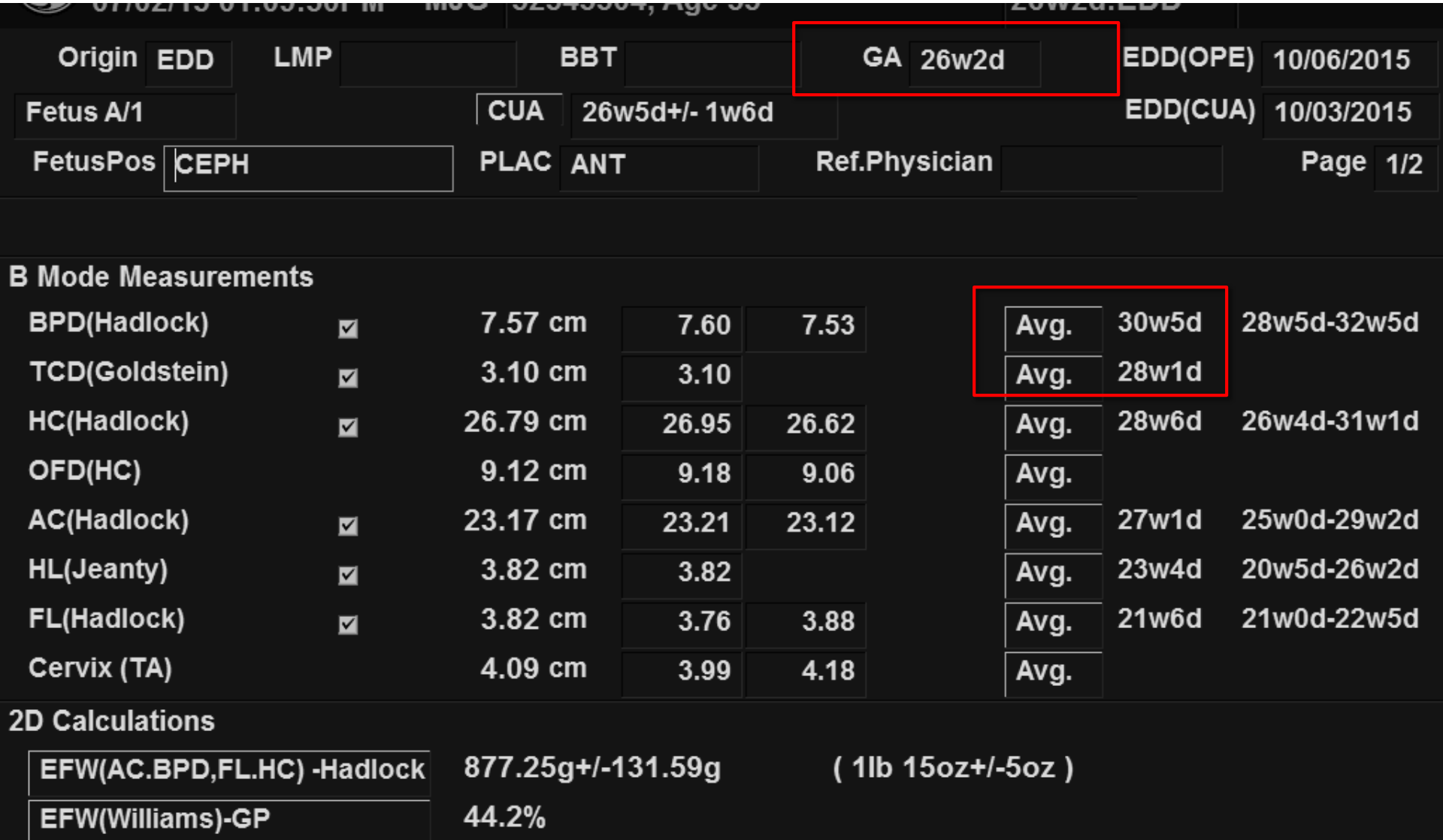
26+5 wks, follow up scan



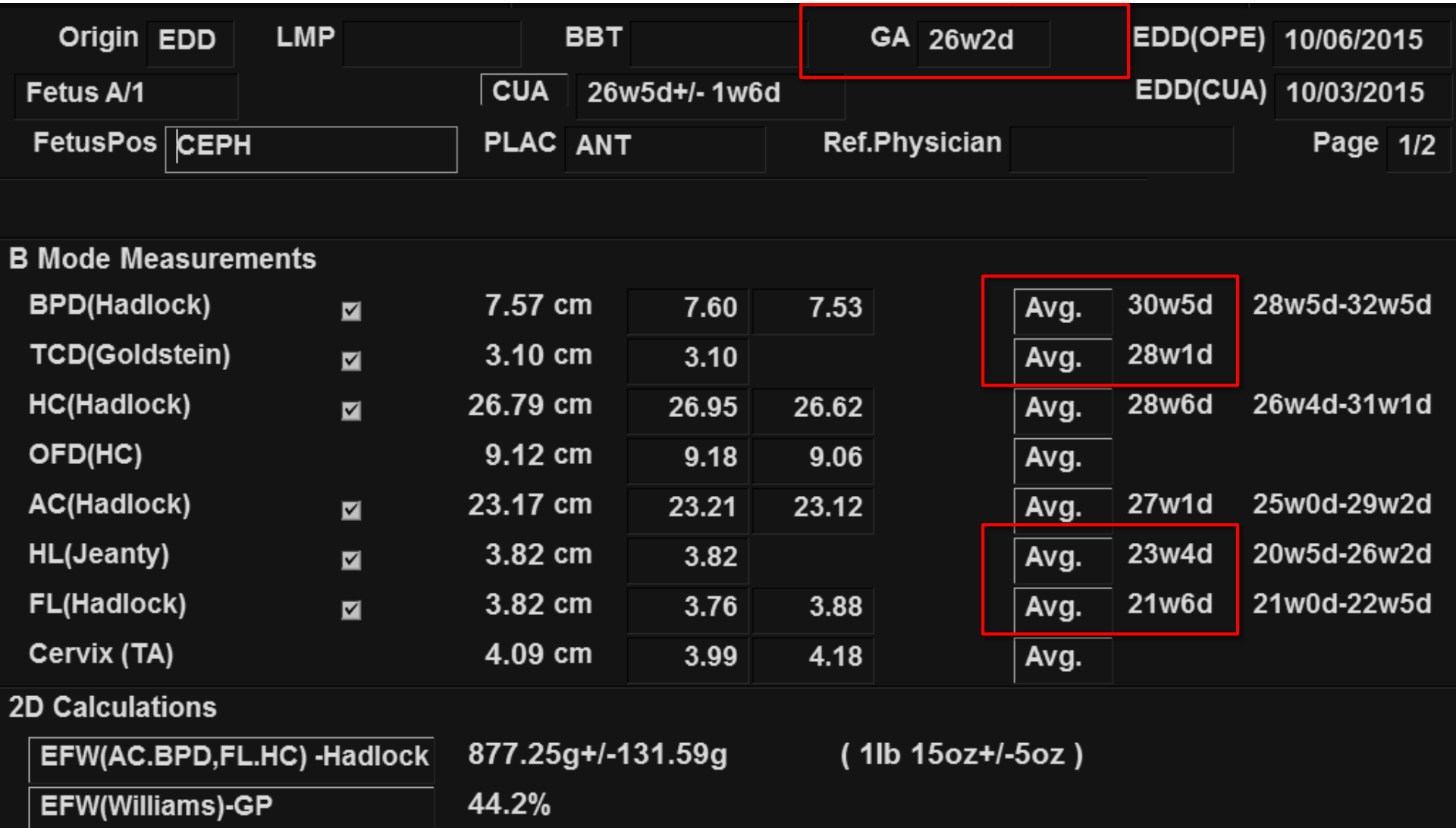
26+2 wks, follow up scan



26+2 wks, follow up scan



26+5 wks, diagnosis→ achondroplasia



Origin	EDD	LMP		BBT		GA	26w2d	EDD(OPE) 10/06/2015
Fetus A/1			CUA	26w5d+/- 1w6d				EDD(CUA) 10/03/2015
FetusPos	CEPH		PLAC	ANT		Ref.Physician		Page 1/2

B Mode Measurements

BPD(Hadlock)	☑	7.57 cm	7.60	7.53	Avg.	30w5d	28w5d-32w5d
TCD(Goldstein)	☑	3.10 cm	3.10		Avg.	28w1d	
HC(Hadlock)	☑	26.79 cm	26.95	26.62	Avg.	28w6d	26w4d-31w1d
OFD(HC)		9.12 cm	9.18	9.06	Avg.		
AC(Hadlock)	☑	23.17 cm	23.21	23.12	Avg.	27w1d	25w0d-29w2d
HL(Jeanty)	☑	3.82 cm	3.82		Avg.	23w4d	20w5d-26w2d
FL(Hadlock)	☑	3.82 cm	3.76	3.88	Avg.	21w6d	21w0d-22w5d
Cervix (TA)		4.09 cm	3.99	4.18	Avg.		

2D Calculations

EFW(AC.BPD,FL.HC) -Hadlock	877.25g+/-131.59g	(1lb 15oz+/-5oz)
EFW(Williams)-GP	44.2%	

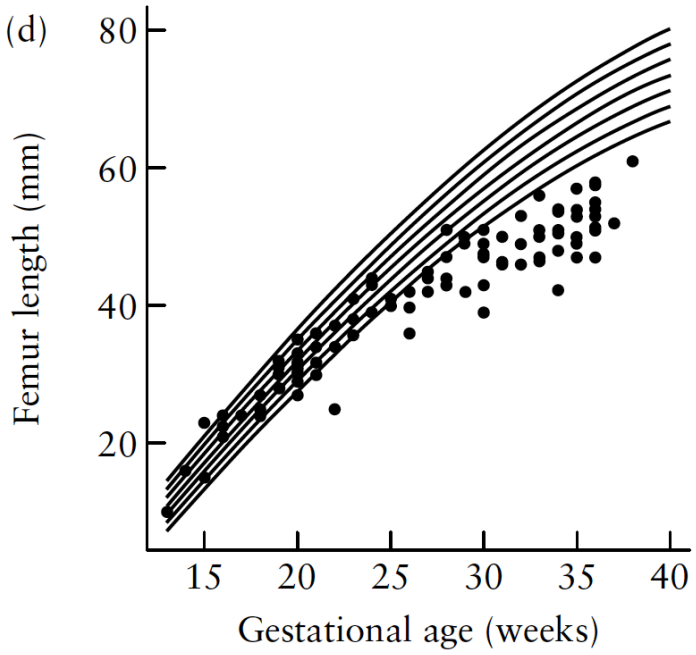
Ultrasound Obstet Gynecol 2011; **37**: 283–289
Published online 1 February 2011 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.8893

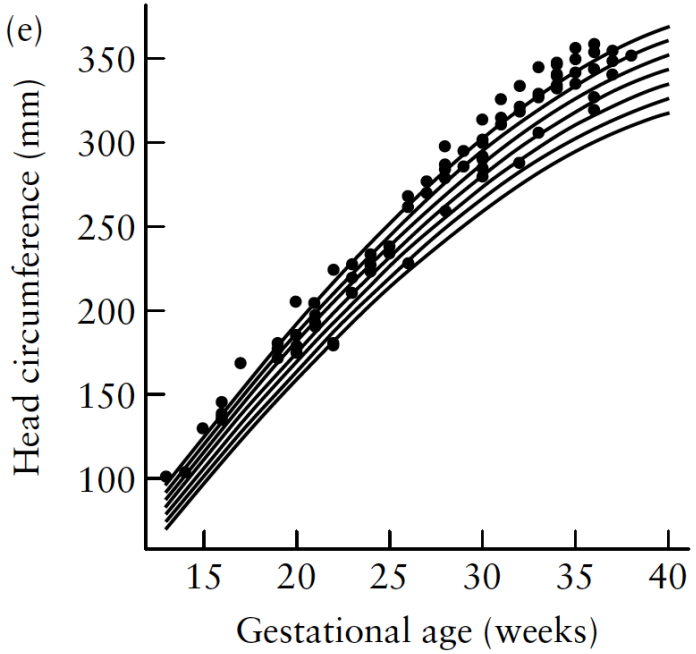
New aids for the non-invasive prenatal diagnosis of achondroplasia: dysmorphic features, charts of fetal size and molecular confirmation using cell-free fetal DNA in maternal plasma

L. S. CHITTY*†, D. R. GRIFFIN‡, C. MEANEY§, A. BARRETT§, A. KHALIL†, E. PAJKRT¶ and T. J. COLE**

**Clinical and Molecular Genetics Unit, University College London Institute of Child Health, London, UK; †Fetal Medicine Unit, University College London Hospitals NHS Foundation Trust, London, UK; ‡Department of Obstetrics and Gynaecology, West Herts Hospital, Watford, UK; §North East Thames Regional Genetics Laboratory, Great Ormond Street Hospital, London, UK; ¶Fetal Medicine Unit, Academic Medical Centre, Amsterdam, The Netherlands; **Medical Research Council Centre of Epidemiology for Child Health, University College London Institute of Child Health, London, UK*

FL and HC in achondroplasia





DOI: 10.1002/pd.4583

ORIGINAL ARTICLE

Non-invasive prenatal diagnosis of achondroplasia and thanatophoric dysplasia: next-generation sequencing allows for a safer, more accurate, and comprehensive approach

Lyn S. Chitty[1,2]*, Sarah Mason[3], Angela N. Barrett[3], Fiona McKay[3], Nicholas Lench[3], Rebecca Daley[2] and Lucy A. Jenkins[3]

- N=47 cases
- Correct in 46 (96.2%)
- Useful tool in 3rd trimester to distinguish IUGR from achondroplasia

Chitty LS, et al. *Prenat Diagn* 35:656, 2015

PreSeek Non-invasive Prenatal Gene Sequencing Screen

PreSeek is a cell-free fetal DNA non-invasive prenatal multi-gene screen that assesses for fetal disorders using maternal blood. PreSeek screens for genetic disorders that can cause skeletal dysplasias, cardiac defects, multiple congenital anomalies and/or intellectual defects due to variants in the genes included. PreSeek will report only pathogenic and likely pathogenic variants and will not report variants of uncertain significance or benign variants. PreSeek detects predominantly de novo variants (a gene variant that is not inherited). The rate of de novo variants has been shown to increase as paternal age advances. Both biological parental samples are required for this screen to be performed.

Clinical	*Research*	*Prenatal*	*Carrier*
✓		✓	

GENETests™

SIGN IN

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PreSeek Non-invasive Prenatal Gene Sequencing Screen

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North East Thames
Regional Genetics Service

Great Ormond Street Hospital for Children NHS
NHS Foundation Trust

Implementing Non-Invasive Prenatal Diagnosis (NIPD) of monogenic diseases in a National Health Service Laboratory

Fiona McKay
Principal Clinical Scientist, NE Thames Regional Genetics Service
8th June 2017

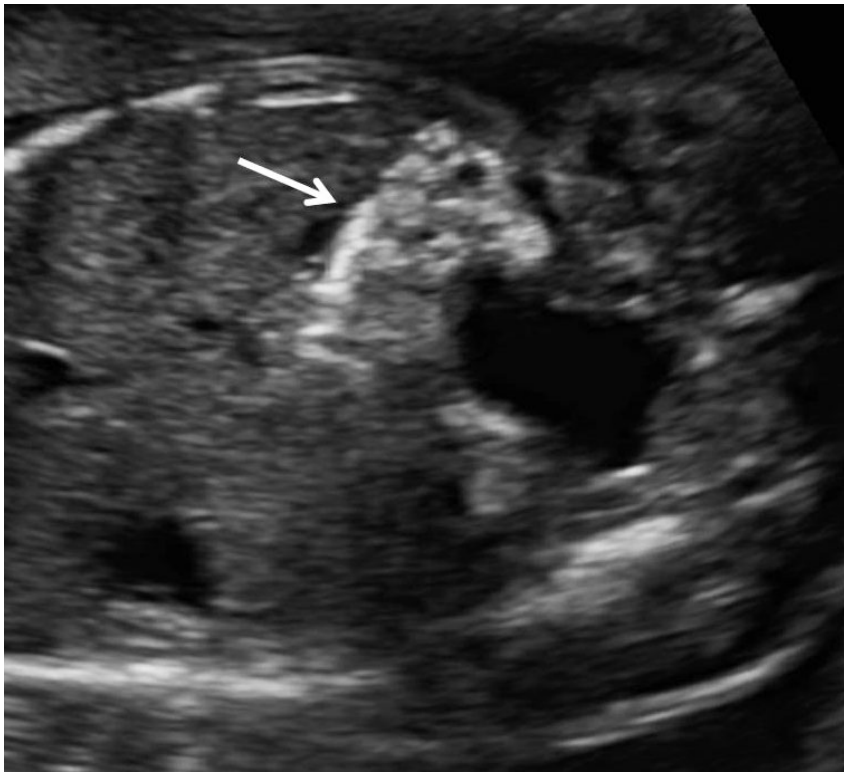
Routine cell free DNA for shortened HL and FL?

- Poor markers for DS
- Not associated with other aneuploidies
- If truly shortened, may be other pathologies
  - Amnio/cfDNA address only DS, risk is only marginally increased
  - Does not address most of the likely pathologies
- cfDNA is a reasonable alternative to amnio for patient who wants additional testing, or if DS risk borderline by screening

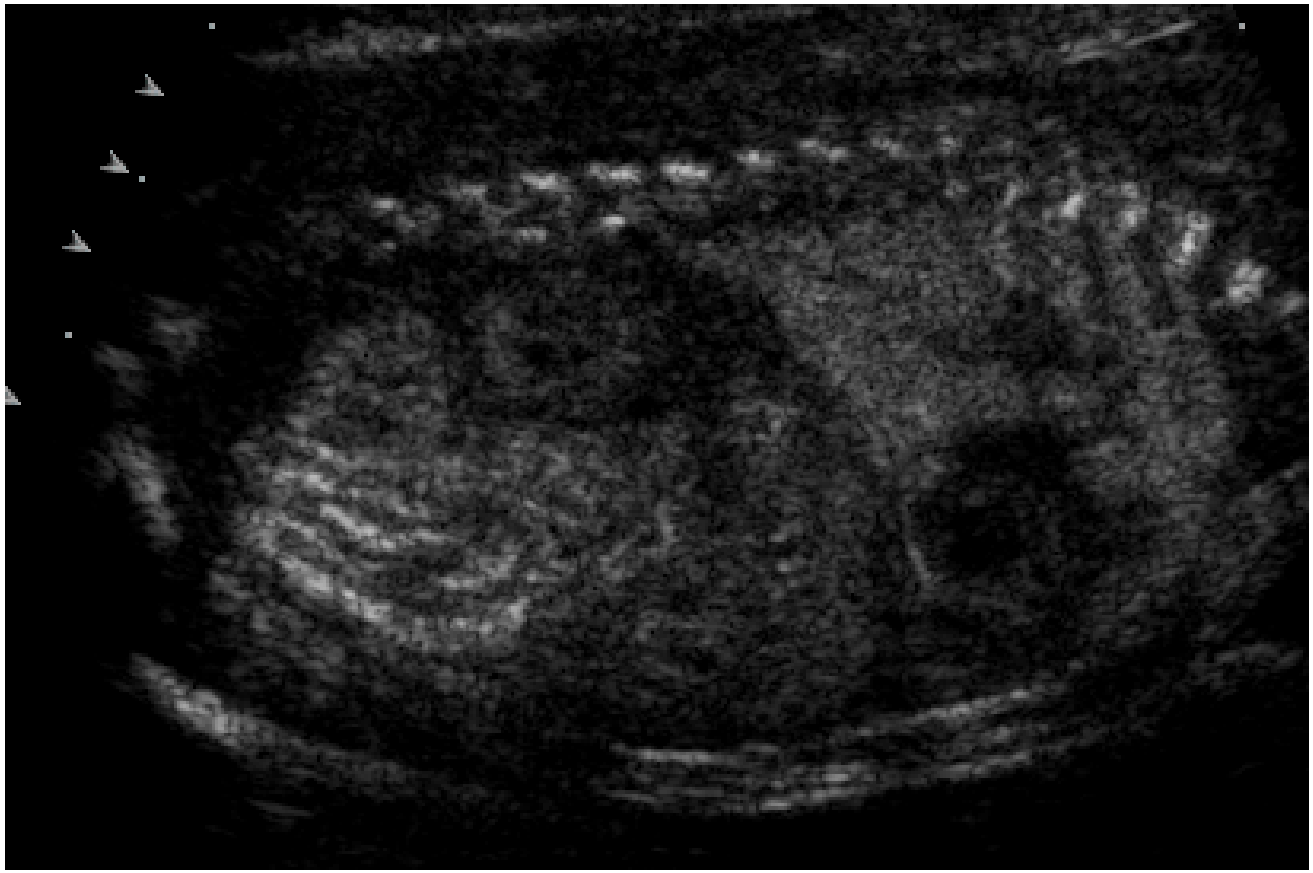
Findings with potential for significant abnormality, but often seen in normal fetuses

Echogenic Bowel

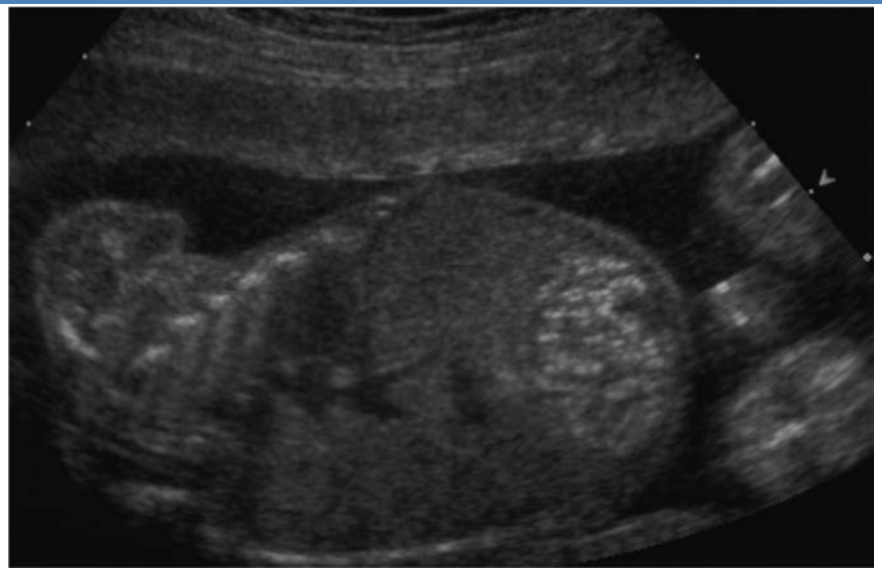
- Diffuse, multifocal bright bowel (as bright as bone)
- Discrete intra-hepatic or intra-abdominal calcifications
- Meconium peritonitis, small bowel atresia, volvulus or meconium ileus

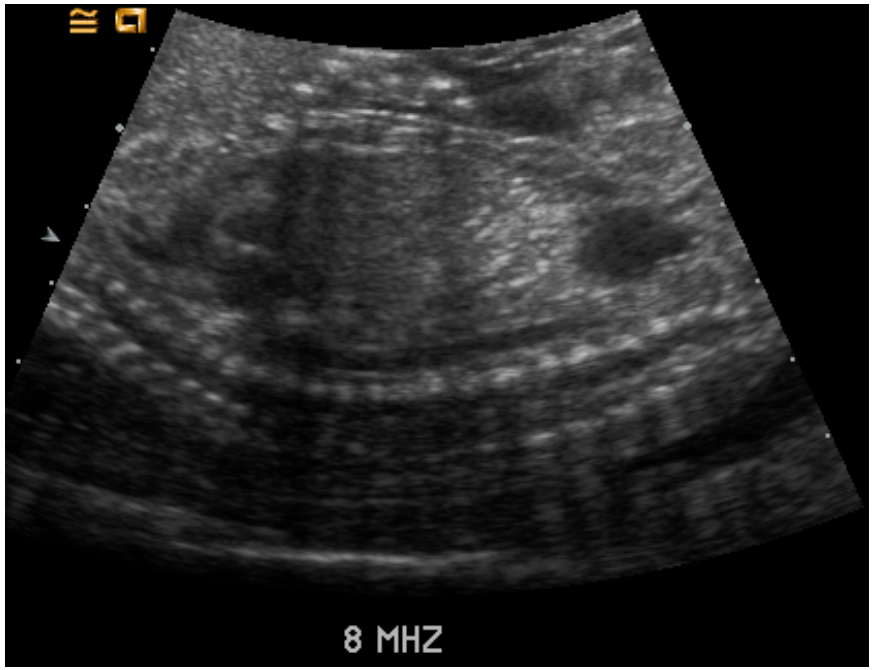


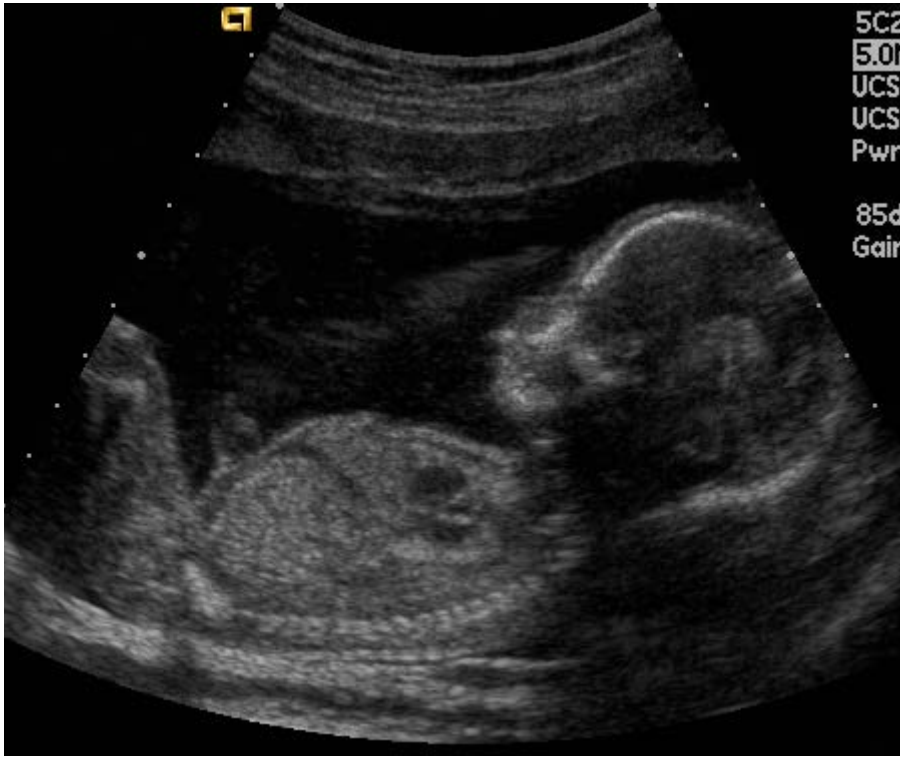
? Echogenic Bowel



Vincoff N, Callen P, et al. Effect of ultrasound transducer frequency on the appearance of the fetal bowel. J Ultrasound Med 18:799-803, 1999



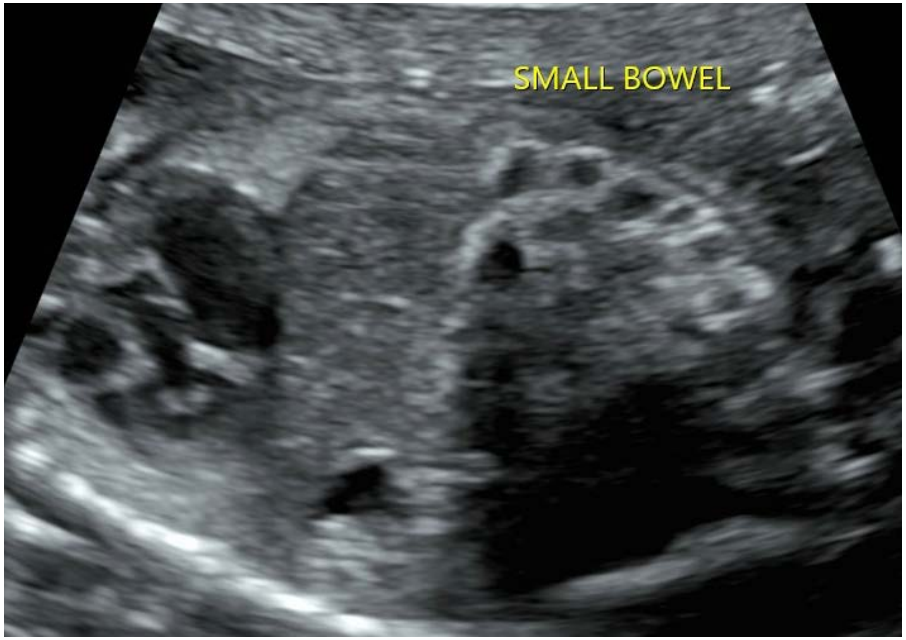


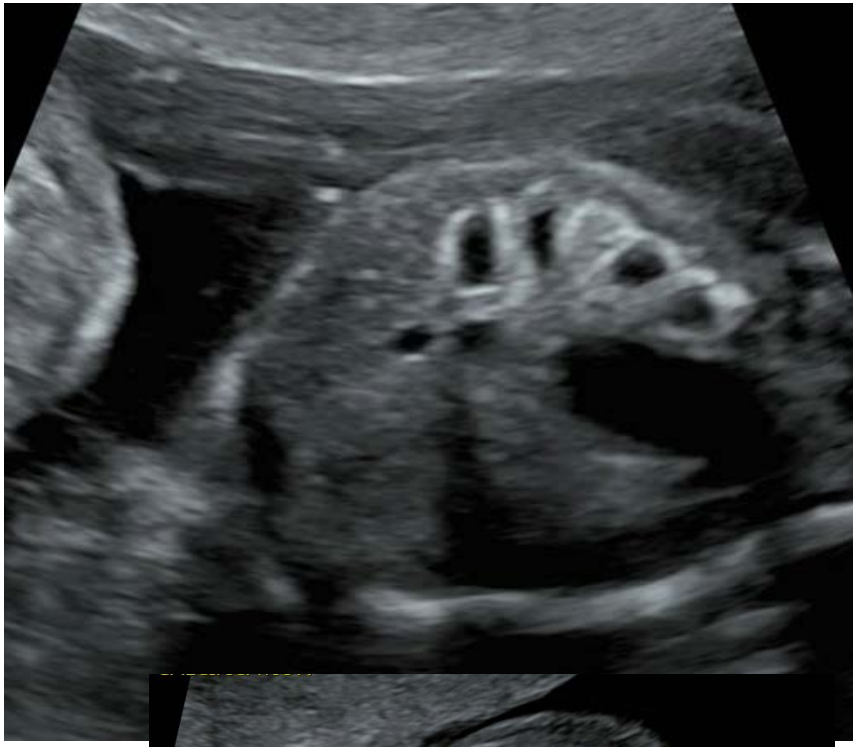


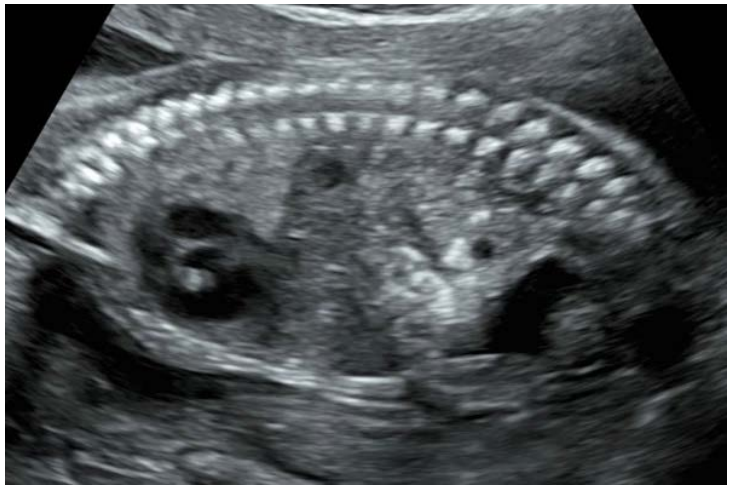
Ultrasound Technique

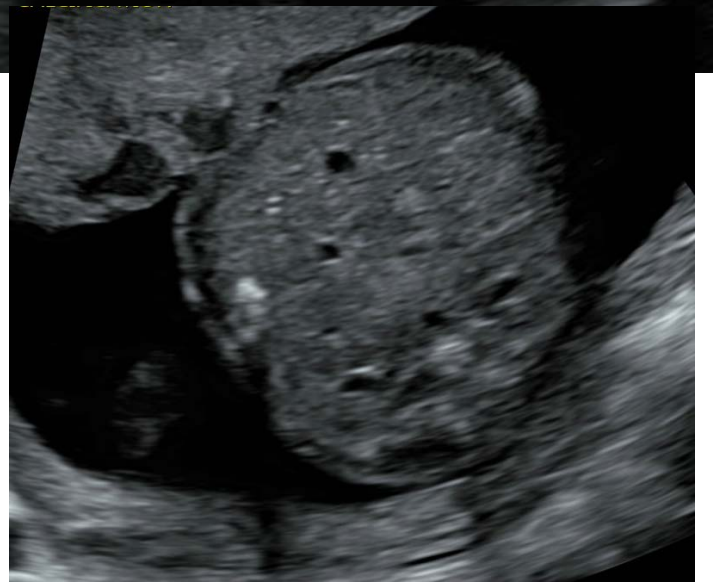
- transducer
- frequency
- harmonics
- settings

Echogenic Bowel

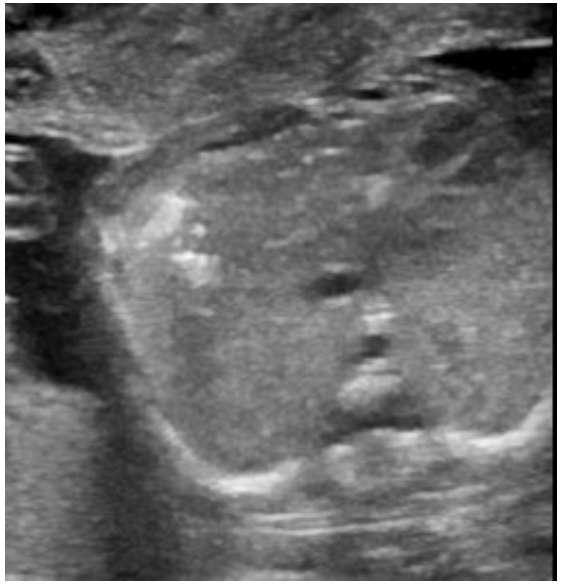


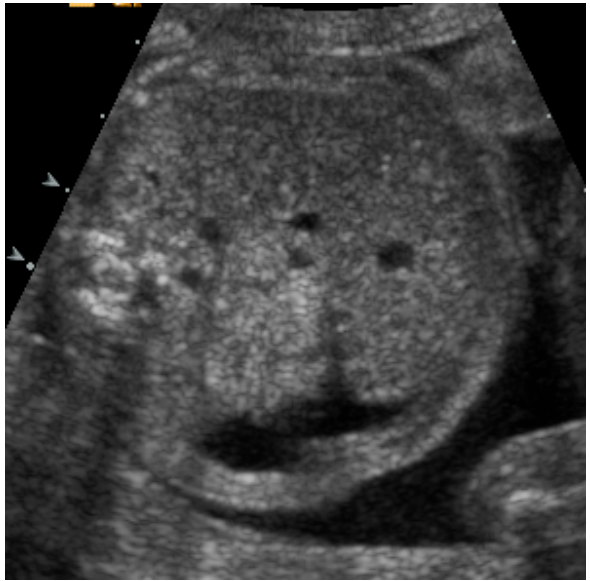


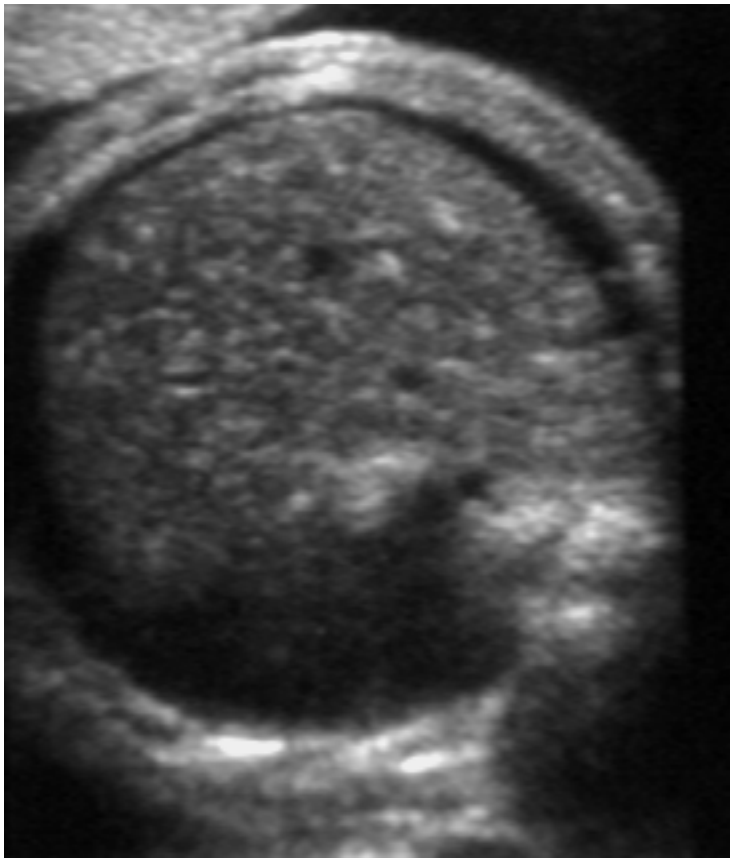


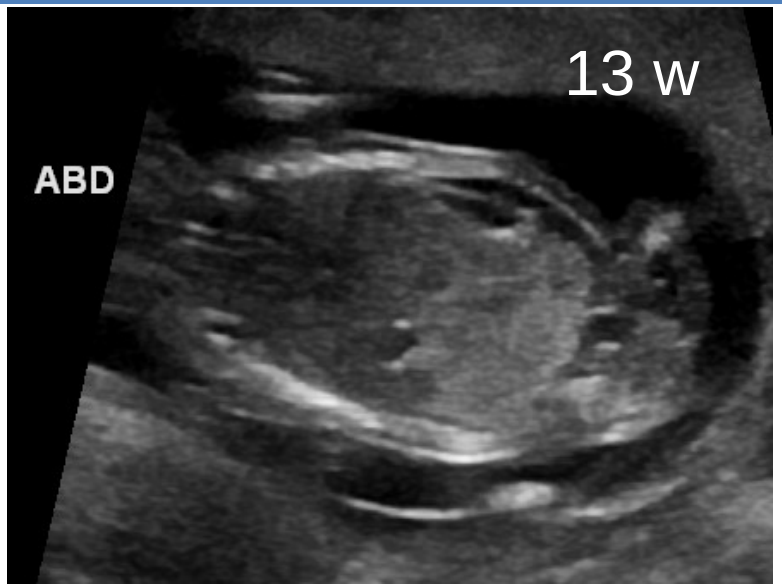


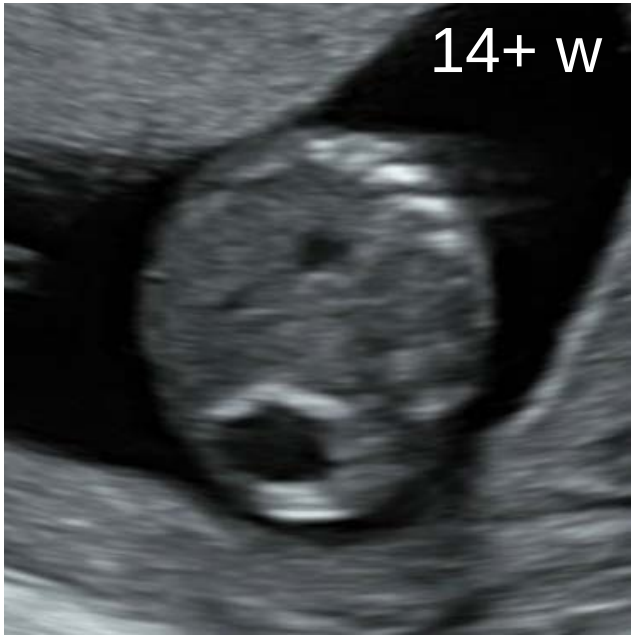
Peritoneal Calcifications +/- Ascites

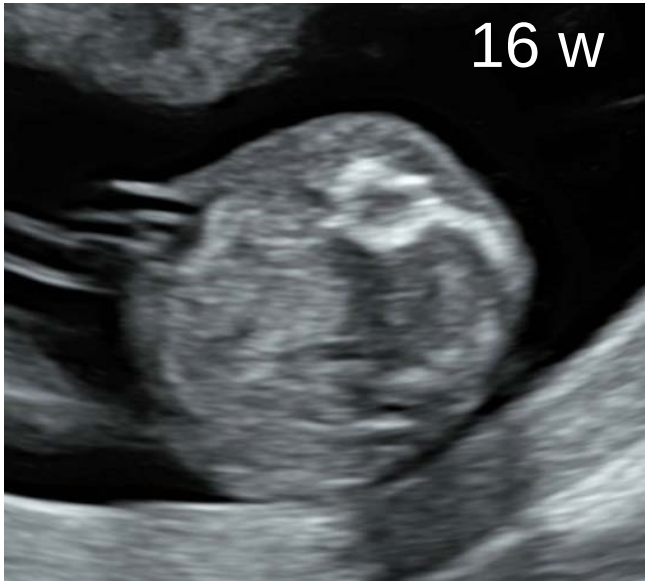


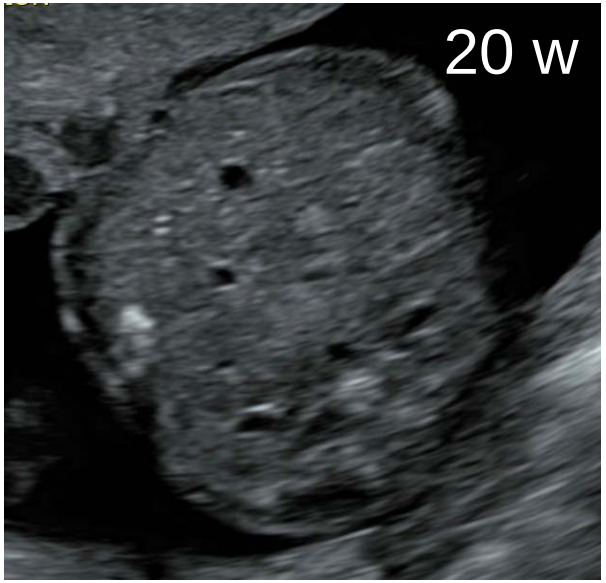




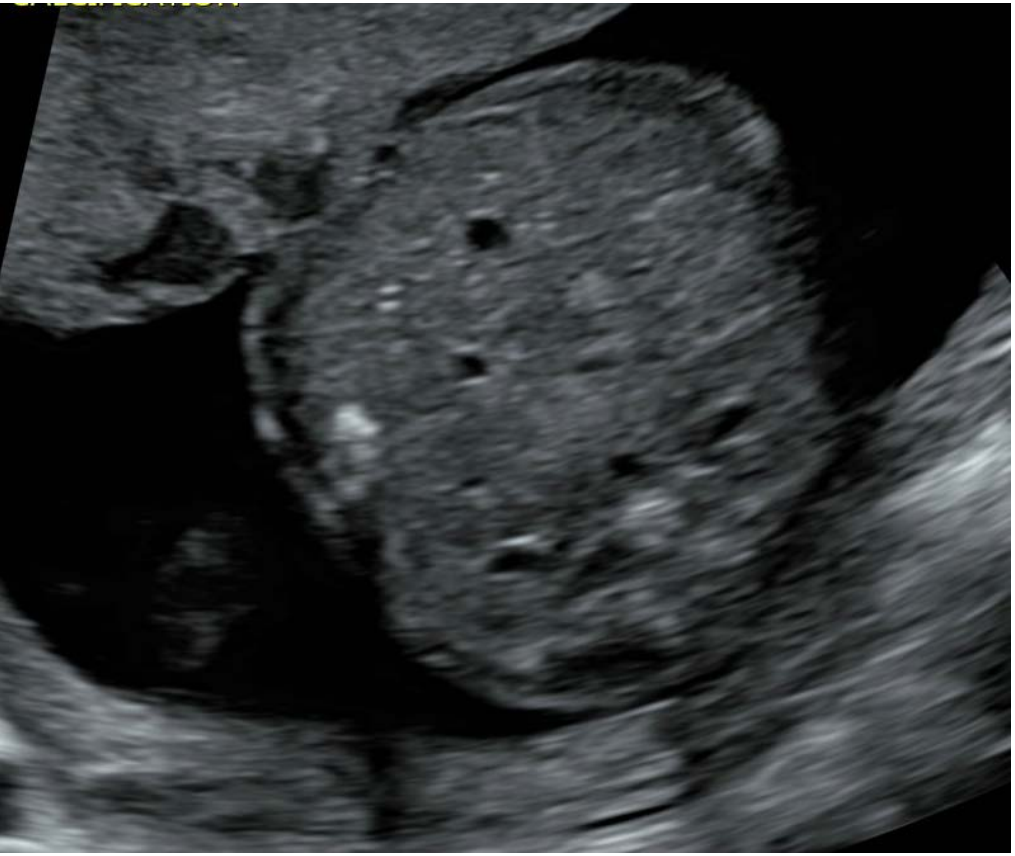

13 w
ABD

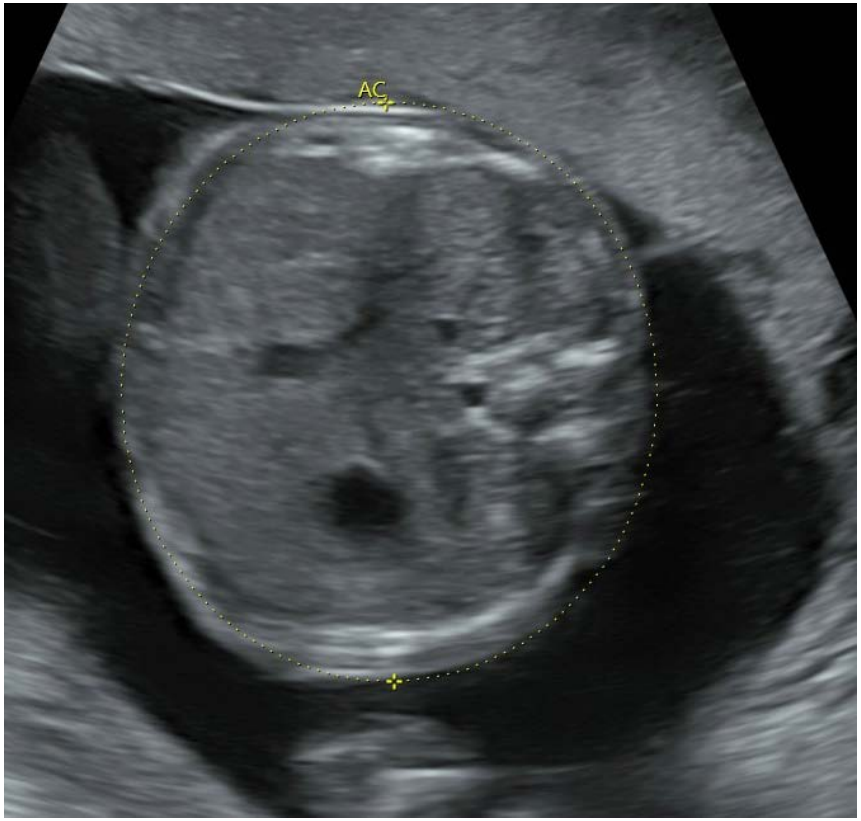

14+ w


16 w


20 w

20 weeks gestation





Echogenic Bowel

- Associated with trisomies, cystic fibrosis, viral infection, FGR, fetal demise
- Aneuploidy cases tend to present with diffuse, echogenic bowel, while CMV tends to present with calcifications
- Cystic fibrosis: classic triad is echogenic bowel, loop dilatation and absent gall bladder

Clinical Significance of Echogenic Bowel

Mailath-Pokorny et al, Prenat Diagn 2012

97 cases over 14 years (nl karyotype)

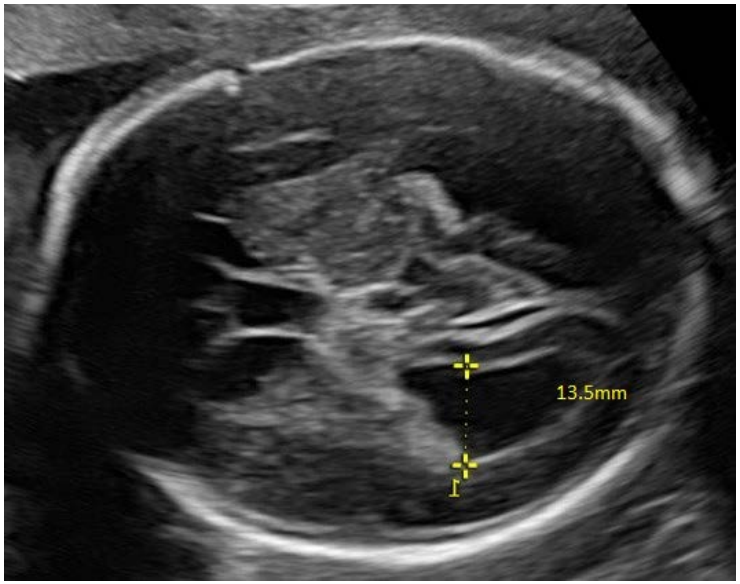
- Congenital infection: 6.2%
- CF: 4.4%
- FGR: 9.9 %
- IUFD: 8.9%
- Normal outcome: 82.5%

Echogenic Bowel

Recommendations

- CF screening
- Maternal or fetal testing for CMV, possibly toxoplasmosis
- Offer amniocentesis or cfDNA
  - Not clear that association is only or largely with Down syndrome
- Follow up ultrasound for bowel & growth in 3rd trimester (32 wks)

Mild Ventriculomegaly

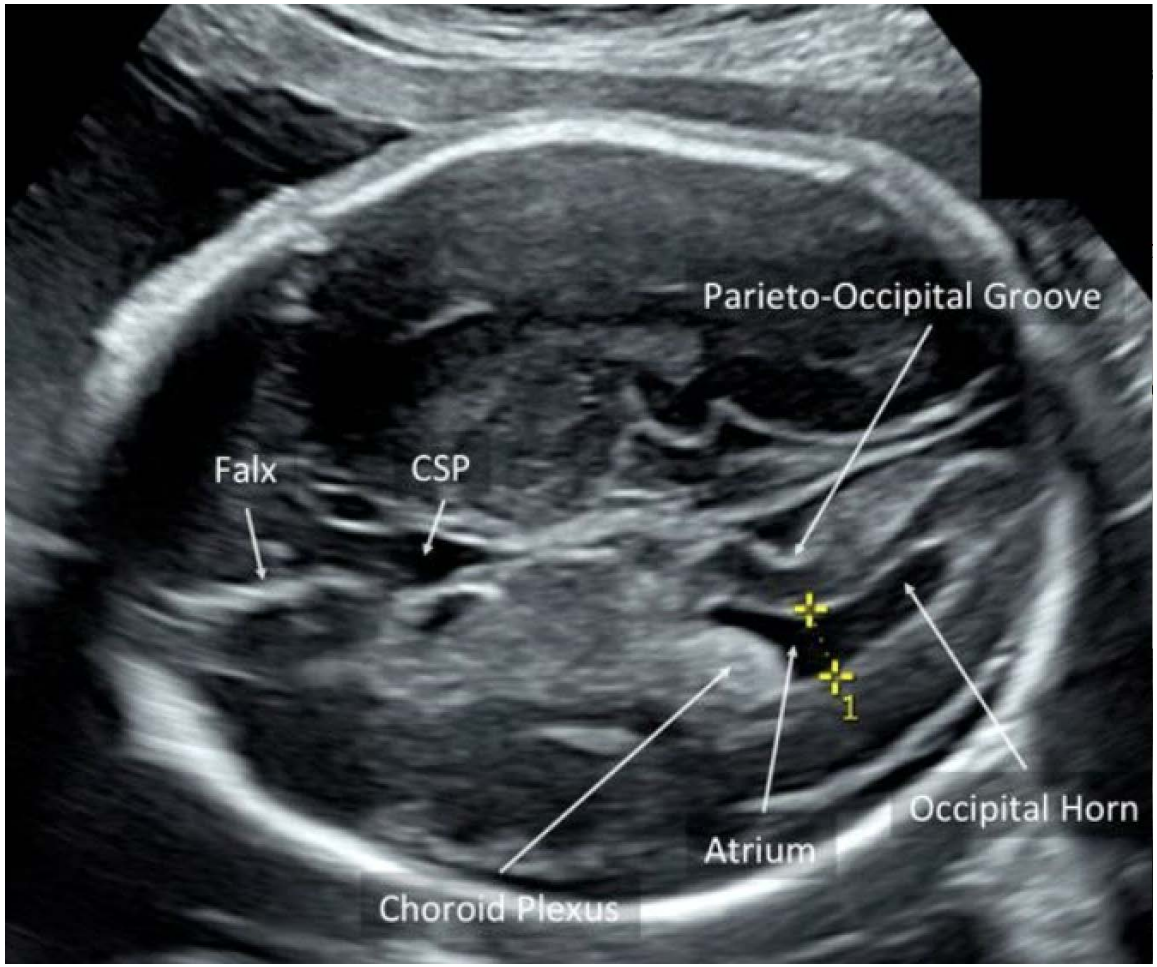


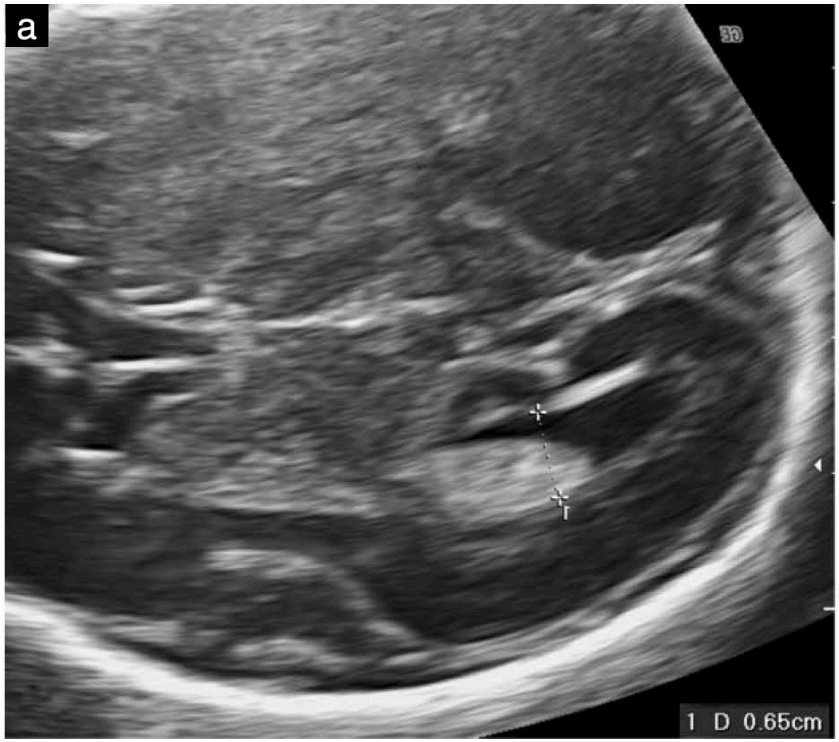
- Ventricles typically 7 mm
- Mild VM: 10-15 mm
- Usually normal outcome when isolated, esp in males, with vents≤12 mm
- Associated with an increased risk of both CNS and non-CNS anomalies

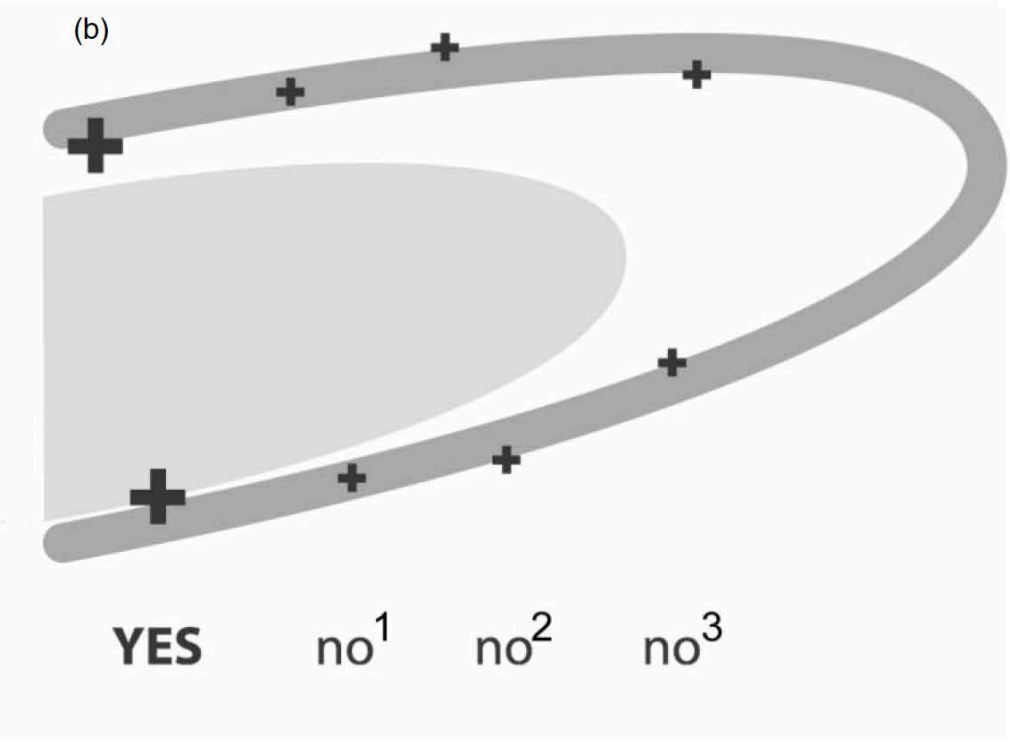
Ventriculomegaly

- Fetal cerebral ventricles of 10 – 15 mm
- Most cases are normal variants
- Can be marker for other underlying CNS pathology
- More common in male fetuses
- When isolated, outcome usually normal
- When associated with other CNS or non-CNS findings, outcome much worse

Mild Ventriculomegaly




a
1 D 0.65cm


(b)
YES
no1
no2
no3

Society for Maternal-Fetal Medicine
High-risk pregnancy experts

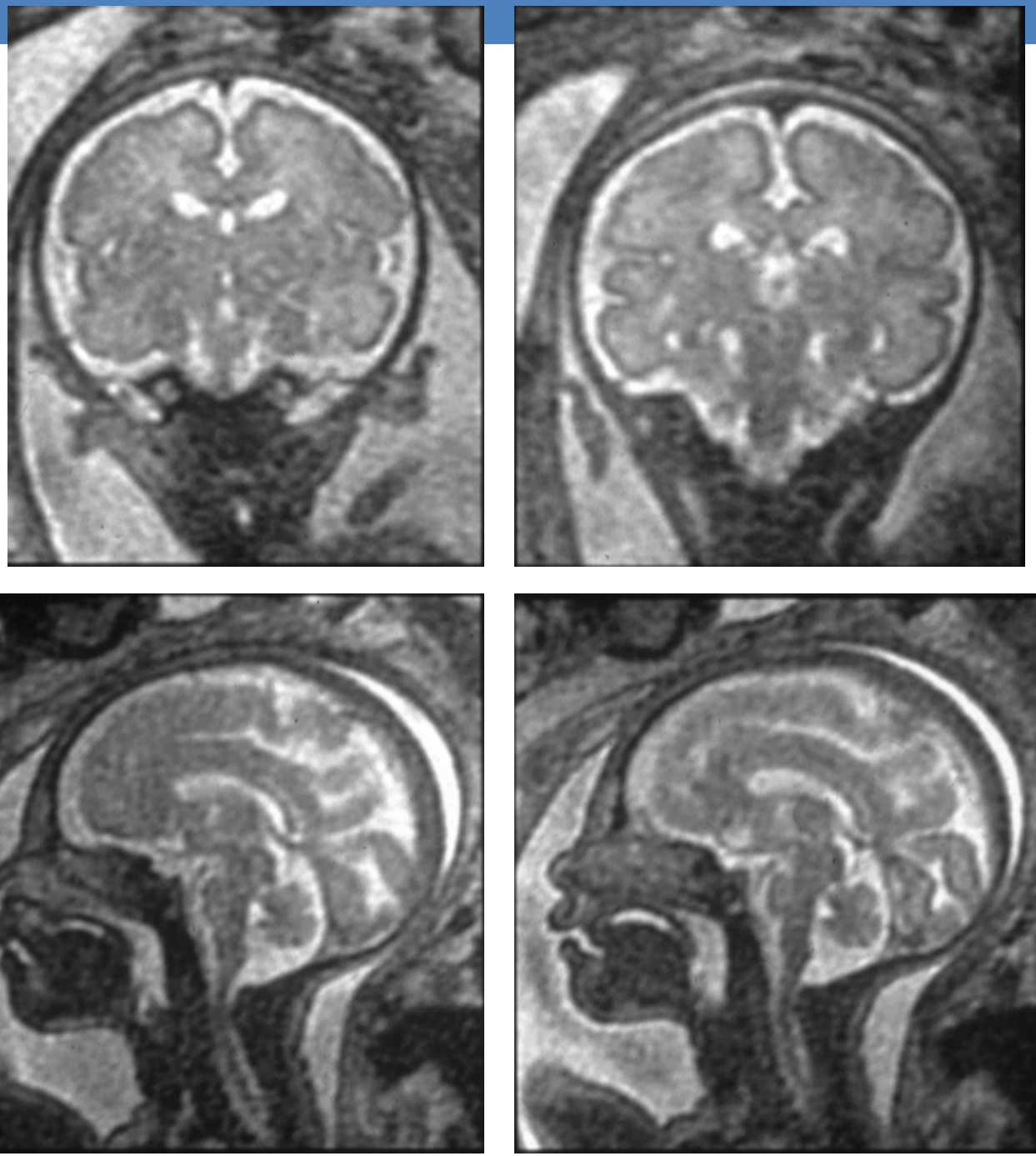
Society for Maternal-Fetal Medicine (SMFM) Consult Series | #45
smfm.org

Mild fetal ventriculomegaly: diagnosis, evaluation, and management

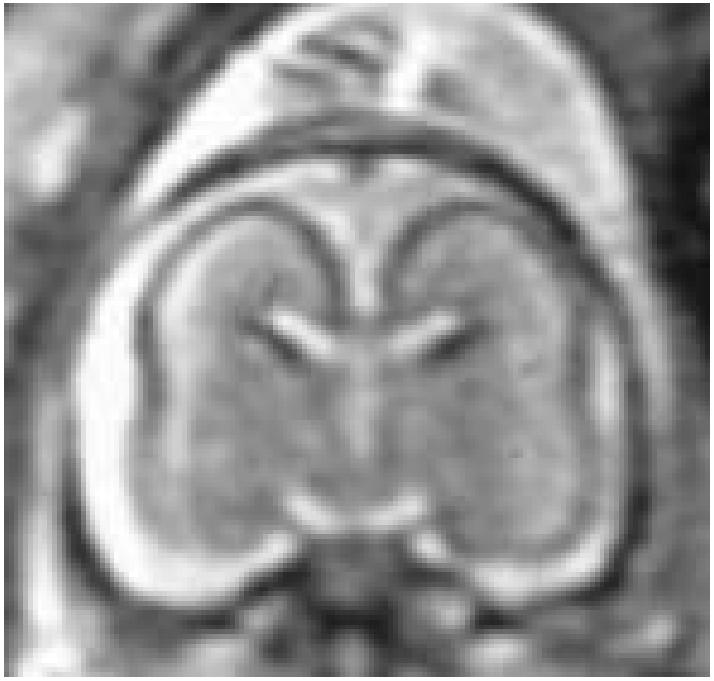
Check for updates

Society for Maternal-Fetal Medicine (SMFM); Nathan S. Fox, MD; Ana Monteagudo, MD; Jeffrey A. Kuller, MD; Sabrina Craigo, MD; and Mary E. Norton, MD

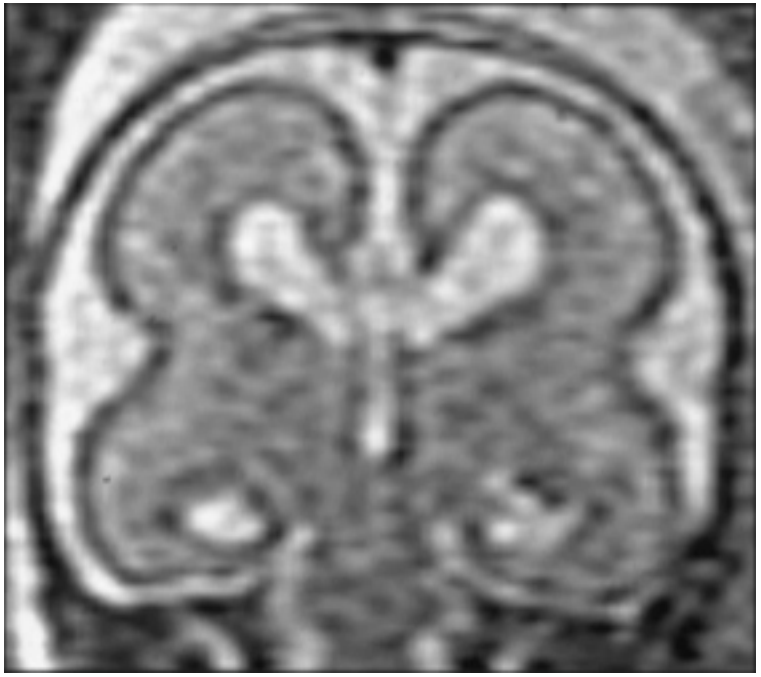
- Detailed ultrasound
- Fetal MRI or expert neurosonography
- Amniocentesis for karyotype/microarray and CMV/Toxoplasmosis testing



Corpus Callosum

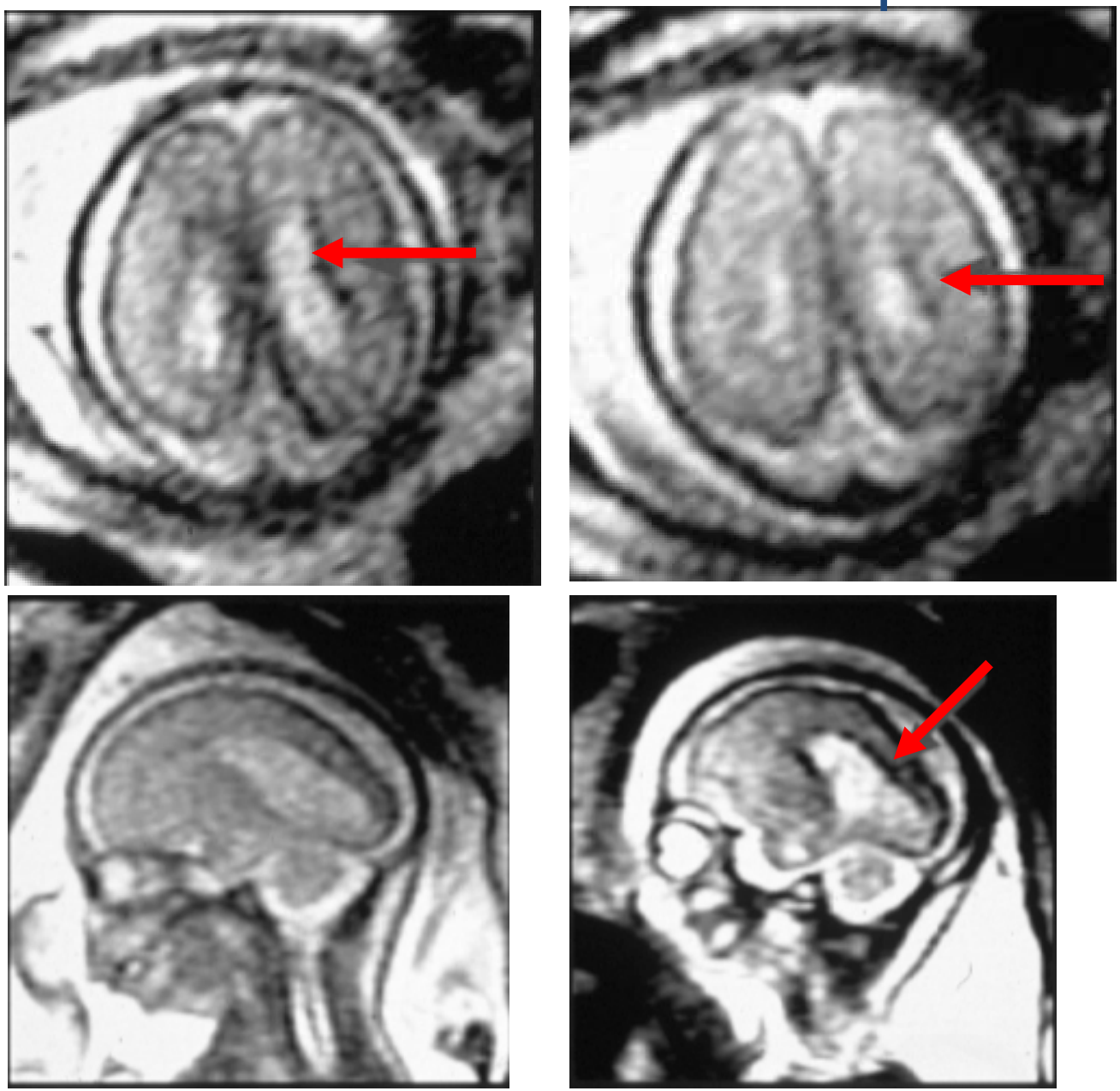


Normal



Agenesis

Periventricular Heterotopia



Outcomes of mild ventriculomegaly

- 10-12mm: Usually a normal variant; >90% normal outcome
- 13-15mm: Moderate ventriculomegaly; most have a good outcome (75-93% normal)

➢ Depends on quality of initial ultrasound → 7-8% have additional anomalies identified after birth

Should we still be using “soft markers” to adjust Down syndrome risk?

Second trimester US markers

- Most studies carried out before current era of serum and NT screening
- Ongoing use should be re-evaluated in light of widespread use of effective screening
- Implications for use of ultrasound and medical resources

Benacerraf, Prenat Diagn, 2010

Should we just do cfDNA in all patients with soft markers?

- Avoids the risk of unnecessary amniocentesis
- Still contributes to significant patient anxiety
- Incurs substantial costs
- Will have some false positive results

Should cfDNA be offered with soft markers?

- **EIF:** Risk of T21 low, but only association is DS
  - US of limited value in ruling out DS
- **CPC:** Risk of T18 low if isolated
- **Pelviectasis:** Risk of T21 low
- **Short FL/HL:** Risk for T21 low
  - Other risks may be higher
- **Echogenic bowel:** Other risks may be higher
- **Thick nuchal fold:** Risk primarily of T21

Professional Society Opinions

Australian Association of Obstetrical and Gynaecological Ultrasonologists Consensus Statement (2007)

- Recent studies have cast doubt on significance of some ultrasound findings as markers for chromosome abnormalities, including CPC, EIF, pelviectasis
- The detection of one of these markers in a routine mid-trimester ultrasound is a warning sign to ***ensure that the ultrasound is of sufficient quality***
- If one of these markers is found in isolation ***in an otherwise low risk patient then it may be considered to be a normal variant and does not necessitate further discussion or investigation.***
- Mild renal pelvis dilatation should be reported due to its association with pediatric renal problems.

NHS Fetal Anomaly Screening Program (UK): 2009

- An established Down's syndrome screening test result should not be recalculated.
- **The term "Down's soft marker" should no longer be used**
- Low risk women should not be referred for further assessment when the following normal variants are found: CPC, dilated cisterna magna, EIF, 2 vessel cord
- The following should be reported and the women referred:
  - Nuchal fold >6mm, ventriculomegaly, echogenic bowel, renal pelvis >7mm, measurements <5%ile

Follow up of Isolated Soft Markers: NICHD Fetal Imaging Workshop

Marker	Other Considerations and Follow-Up
Echogenic cardiac focus*	None
Pyelectasis*	
≥4 mm up to 20 weeks of gestation	32-week ultrasonography to assess kidneys
≥7 mm at 32 weeks of gestation	Postnatal follow-up
Short humerus length*	Consider third-trimester growth ultrasonography
Short femur length*	Consider third-trimester growth ultrasonography
Nuchal thickening	Genetic counseling
Echogenic bowel	Genetic counseling 32-week ultrasonography to assess growth, bowel
Absent/hypoplastic nasal bone	Genetic counseling

Follow up of Isolated Soft Markers: NICHD Fetal Imaging Workshop

Marker	Other Considerations and Follow-Up
Echogenic cardiac	None

* If there is an isolated finding and no aneuploidy screening is performed, recommend cell-free fetal DNA testing or quad screen. If aneuploidy screening is performed and is low-risk, then no further risk assessment is needed. If more than one marker is identified, then genetic counseling is recommended.

Short femur length*	Consider third-trimester growth ultrasonography
Nuchal thickening	Genetic counseling
Echogenic bowel	Genetic counseling 32-week ultrasonography to assess growth, bowel
Absent/hypoplastic nasal bone	Genetic counseling

Society for Maternal-Fetal Medicine
High-risk pregnancy experts

Society for Maternal-Fetal Medicine (SMFM) Consult Series | #42
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The role of ultrasound in women who undergo cell-free DNA screening

CrossMark

Society for Maternal-Fetal Medicine (SMFM) with the assistance of Mary E. Norton, MD; Joseph R. Biggio, MD; Jeffrey A. Kuller, MD; Sean C. Blackwell, MD

- "Diagnostic testing should not be recommended solely for the indication of an isolated soft marker in the setting of a negative cfDNA screen"
- "In women with an isolated soft marker without other clinical implications (ie CPC or echogenic intracardiac focus) and a negative cfDNA screen, we recommend describing the finding as not clinically significant or as a normal variant"

2017

Summary

- “Pseudo” abnormalities are common
- Important to understand implications
- Consider carefully how to report “abnormal” results
- Cell free DNA can be useful if findings specifically suggest trisomy 13, 18 or Down syndrome
- *“The era of ultrasound markers as a screen for fetal aneuploidy is coming to a close.” Winter and Rose, AJR, 2018*