ULTRASOUND FEATURES OF GENETIC SYNDROMES: WHAT YOU SHOULD KNOW

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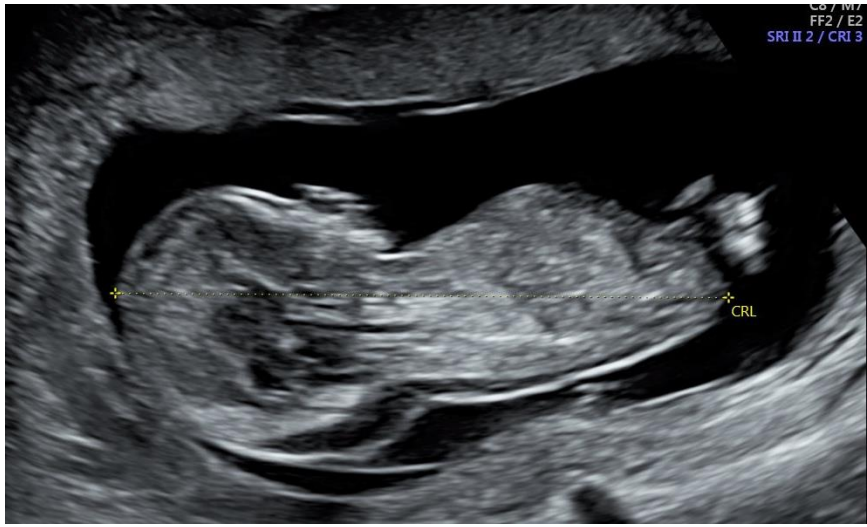

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Disclosures

- None

UCSF

Syndromes, genetic evaluation, and fetal malformations

- Most structural anomalies are isolated, with a more favorable outcome
- Some are associated with genetic syndromes, often with a less favorable outcome
- No one genetic test tells you about all possible genetic disorders
- Suspecting a specific syndrome can guide and optimize testing

Selecting Genetic Testing

Broader coverage

Whole exome or genome sequencing

Chromosomal microarray

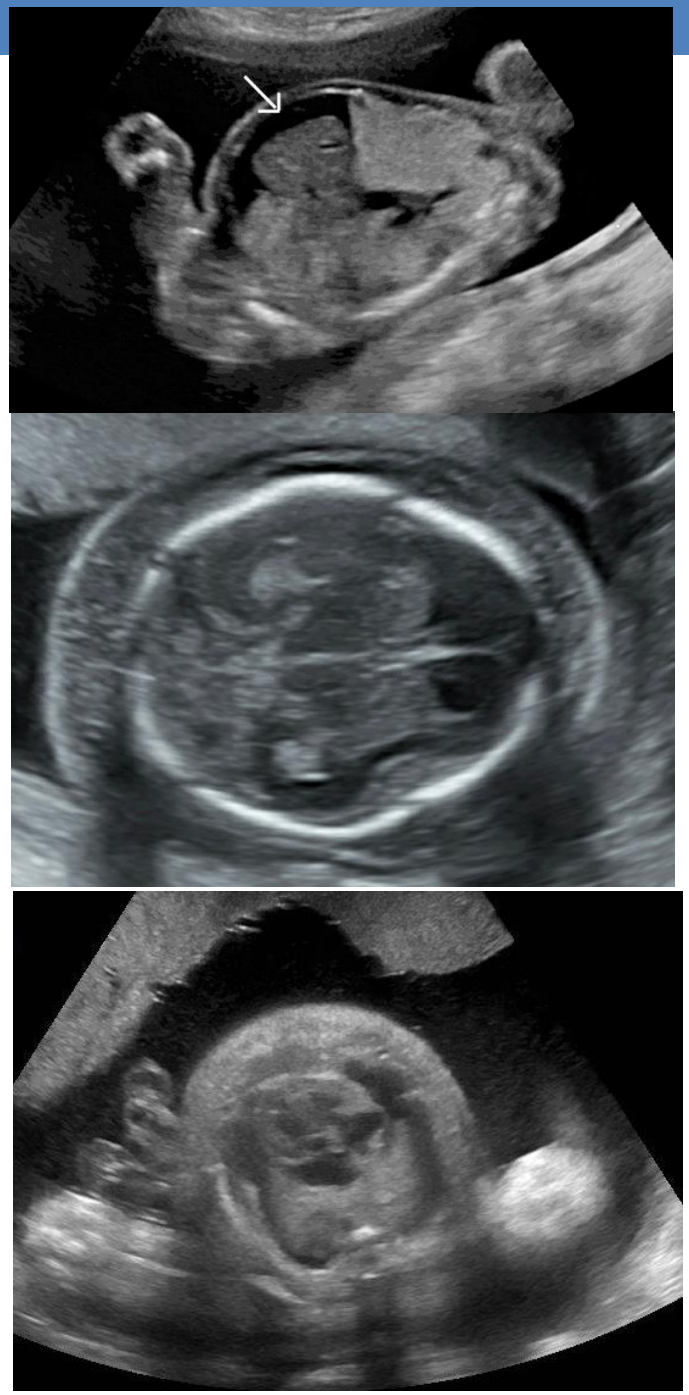
Gene panels

Single gene tests

More specific testing, greater certainty of diagnosis

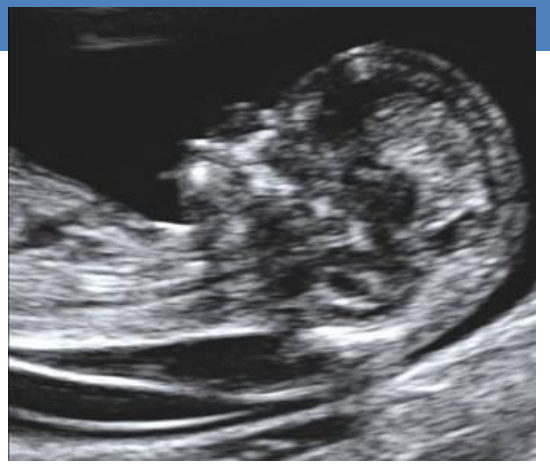
Making a precise diagnosis is important for determining:

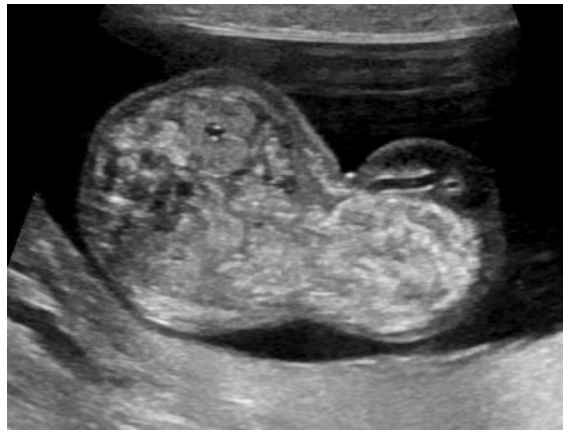
- Etiology
- Prognosis
- Recurrence risk
- Prevention / prenatal diagnosis options in future pregnancies

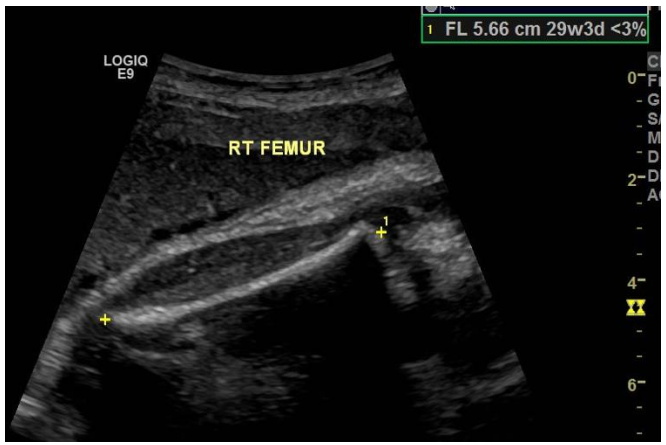


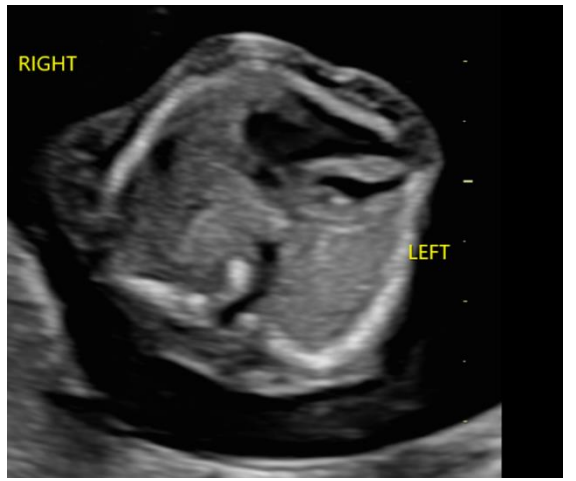
What syndromes to think about (and what to do) when you see…

- Enlarged nuchal translucency
- Ventral wall defects
- Cardiac anomalies
- Short long bones

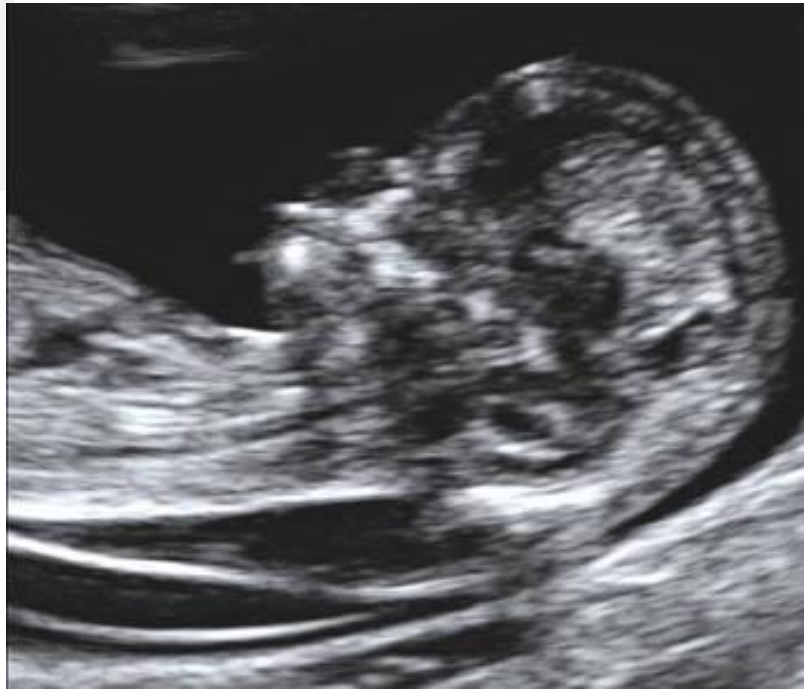






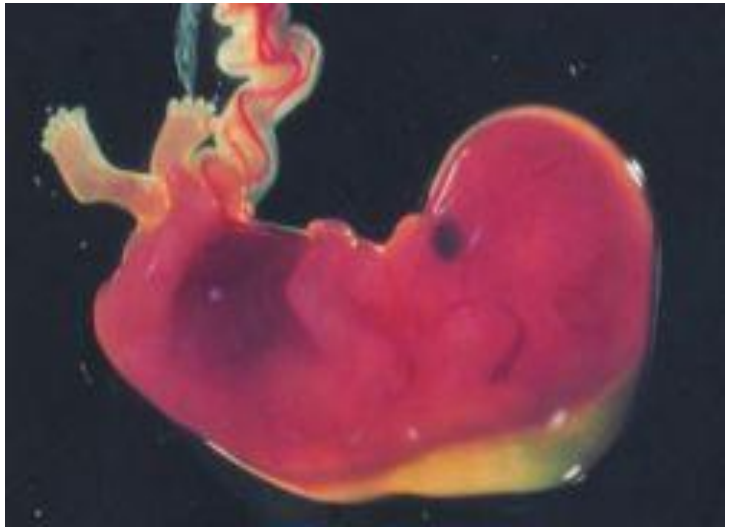


Increased NT is a nonspecific finding



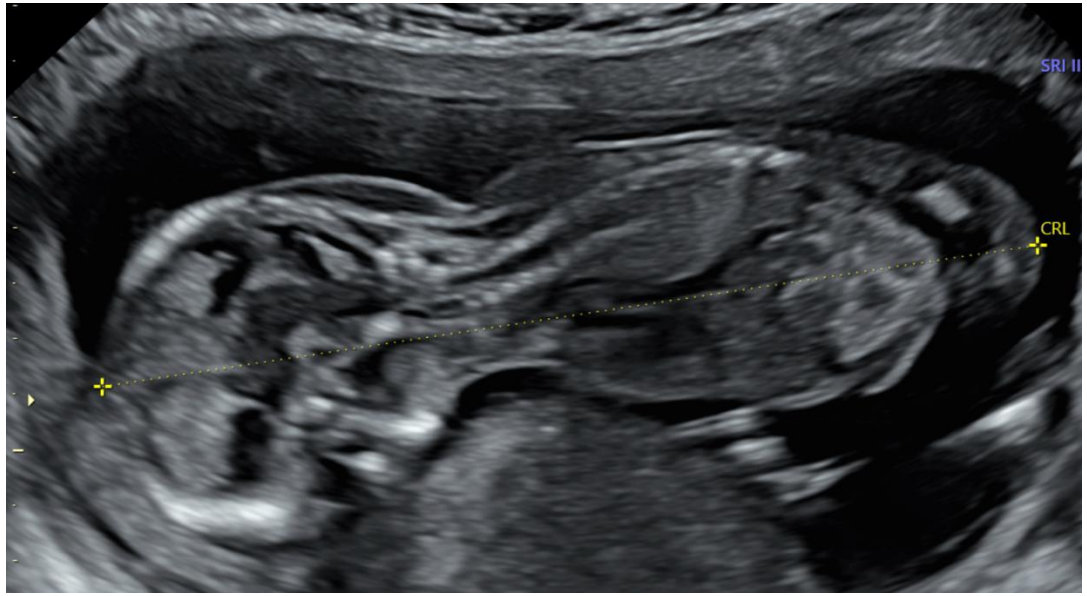
Many mechanisms and many causes

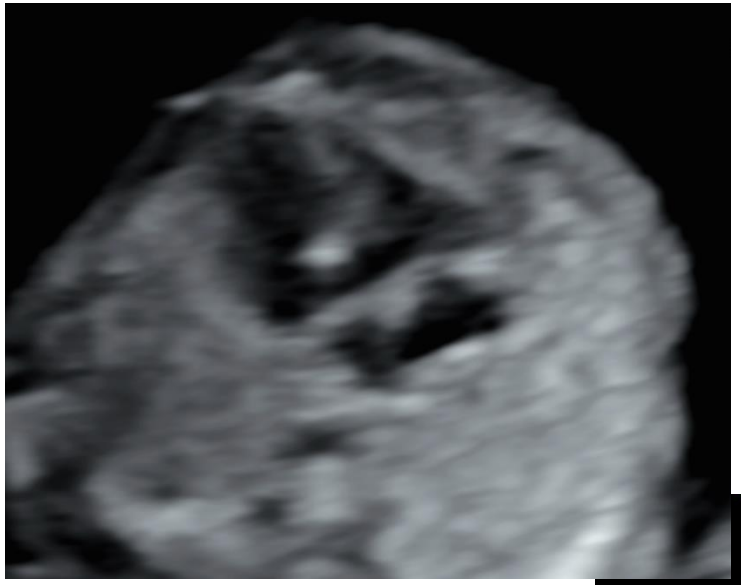
- Aneuploidy (Turner syndrome, Down syndrome)
- Structural anomalies
  - Cardiac abnormalities
  - Others
- Single gene disorders
  - RASopathies (Noonan syndrome)
  - Skeletal dysplasia
  - Other genetic diseases



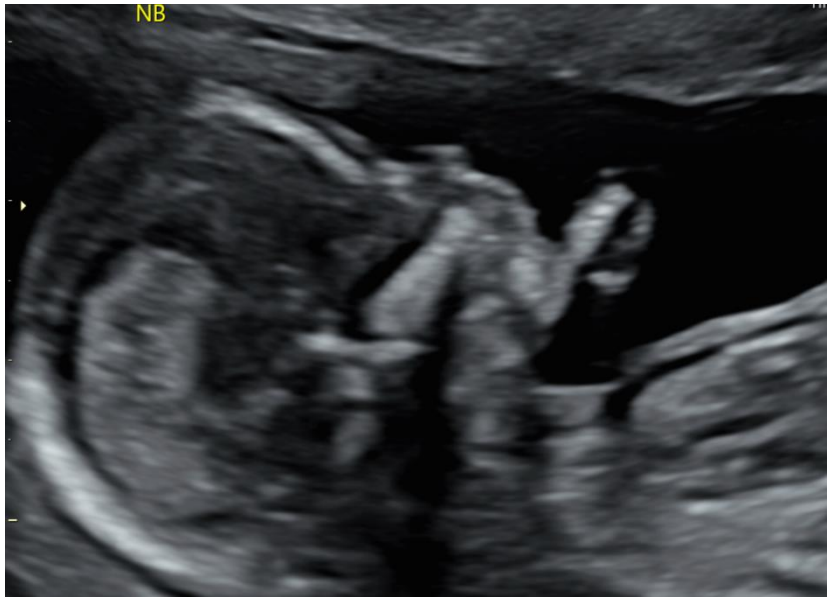
What is the appropriate evaluation for increased NT in the cfDNA era?

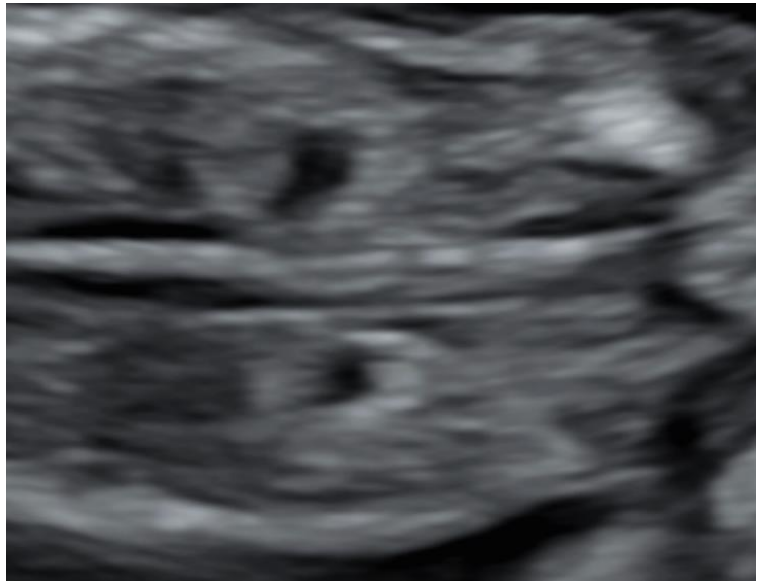
37 y.o. G1P0 at 13 weeks, cfDNA + for Down syndrome

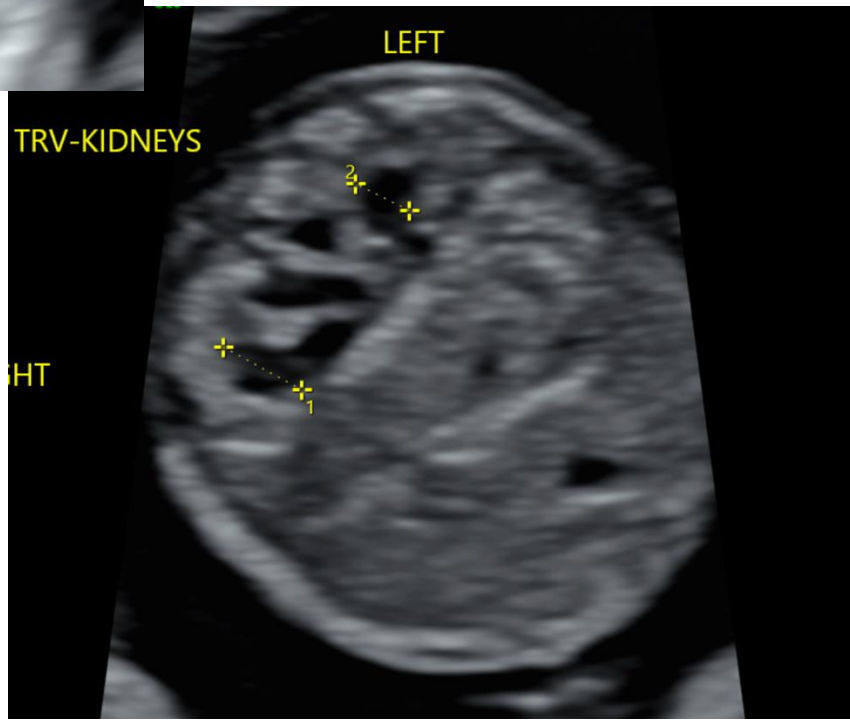




CVS: trisomy 21

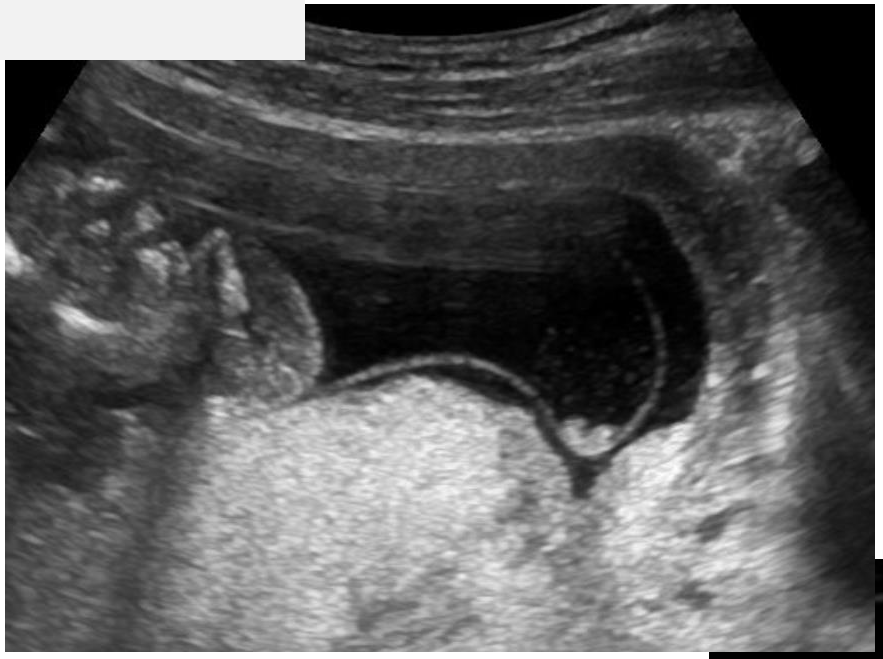


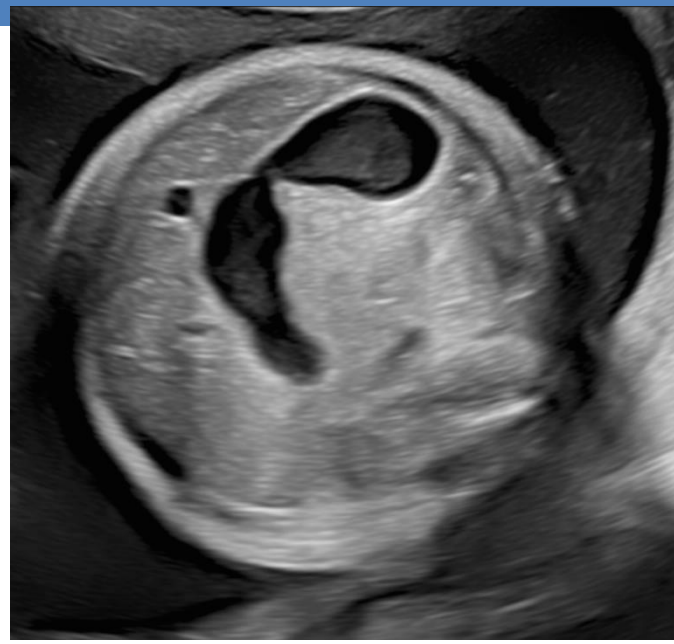


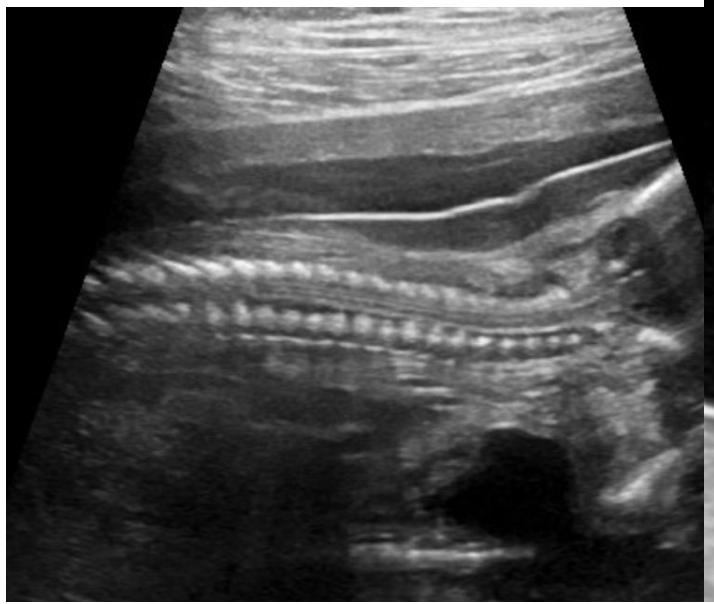


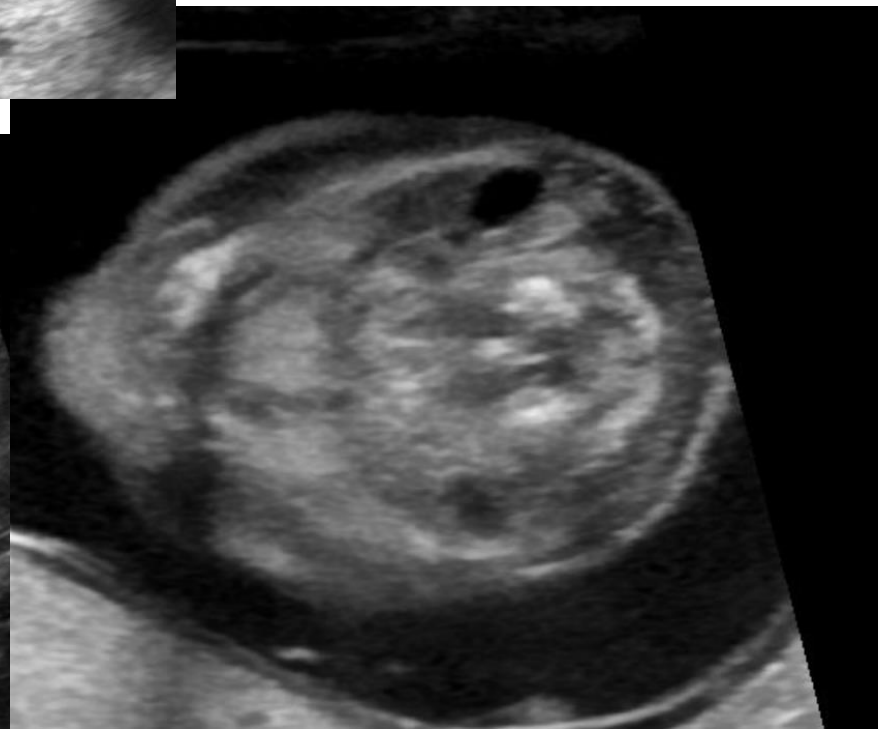
Suspected Down syndrome

- Several tests can make the diagnosis
  - Cell free DNA screening
  - Amniocentesis or CVS
    - Fluorescence in situ hybridization
    - Karyotype (FISH)
    - Chromosomal microarray
- Karyotype is the best option
  - Definitive diagnosis
  - Identifies translocation and recurrence risk
- Cell free DNA
  - Late gestational age, patient declines diagnostic testing
  - High PPV with typical anomalies

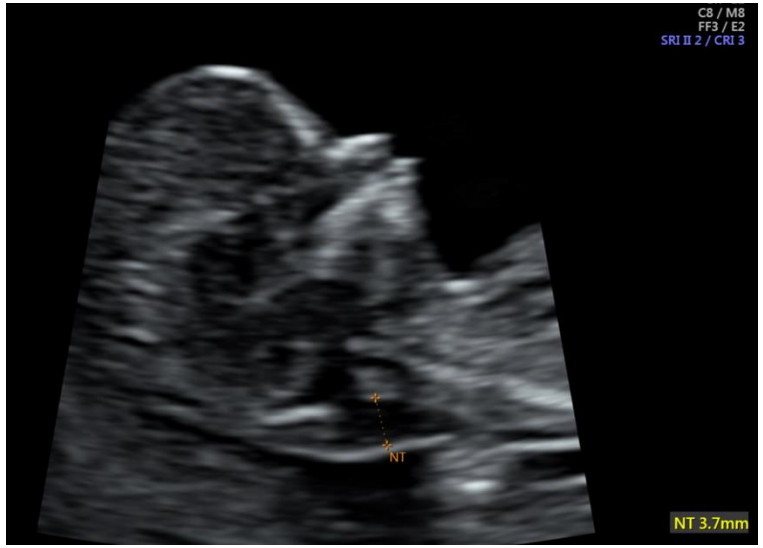


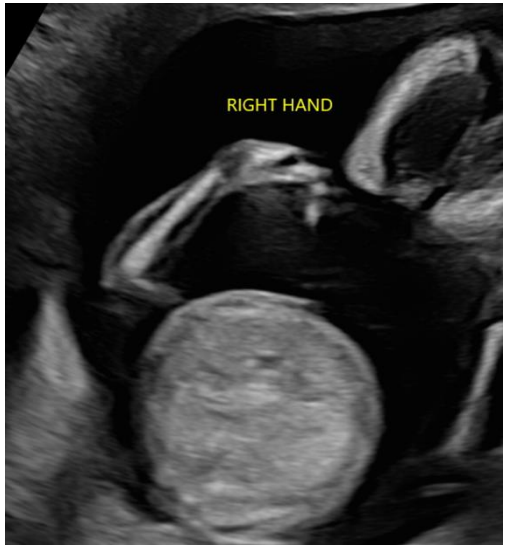


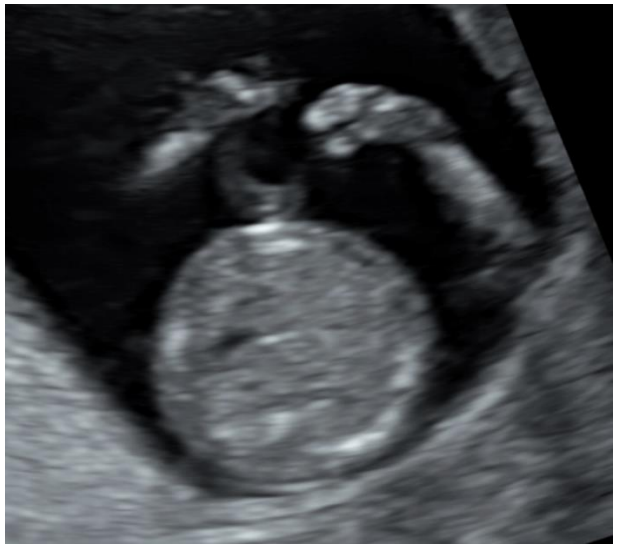




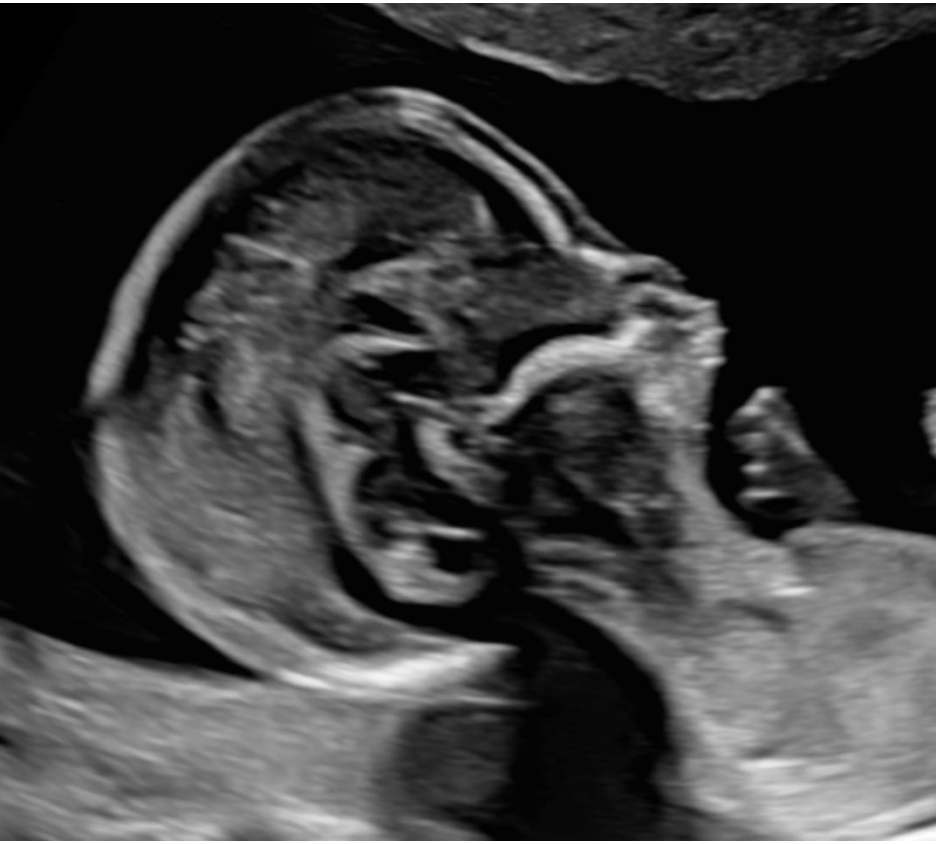
38 yo G2P0 at 13 weeks, cfDNA + for trisomy 18

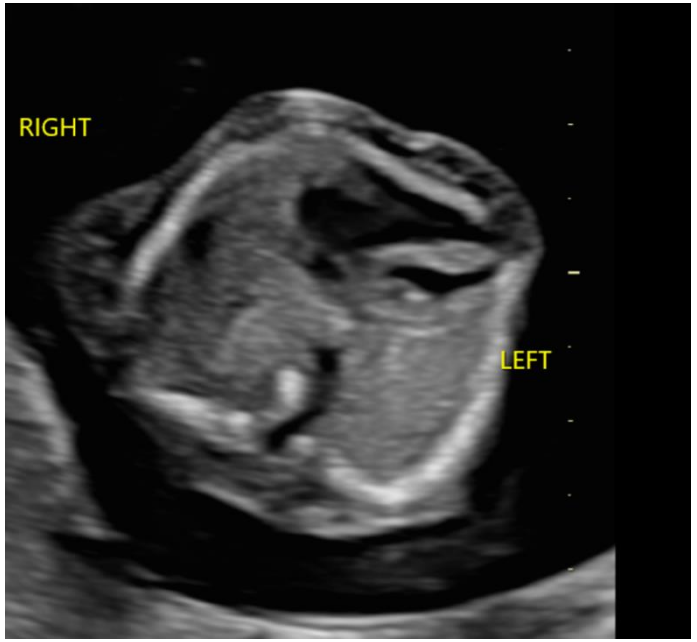


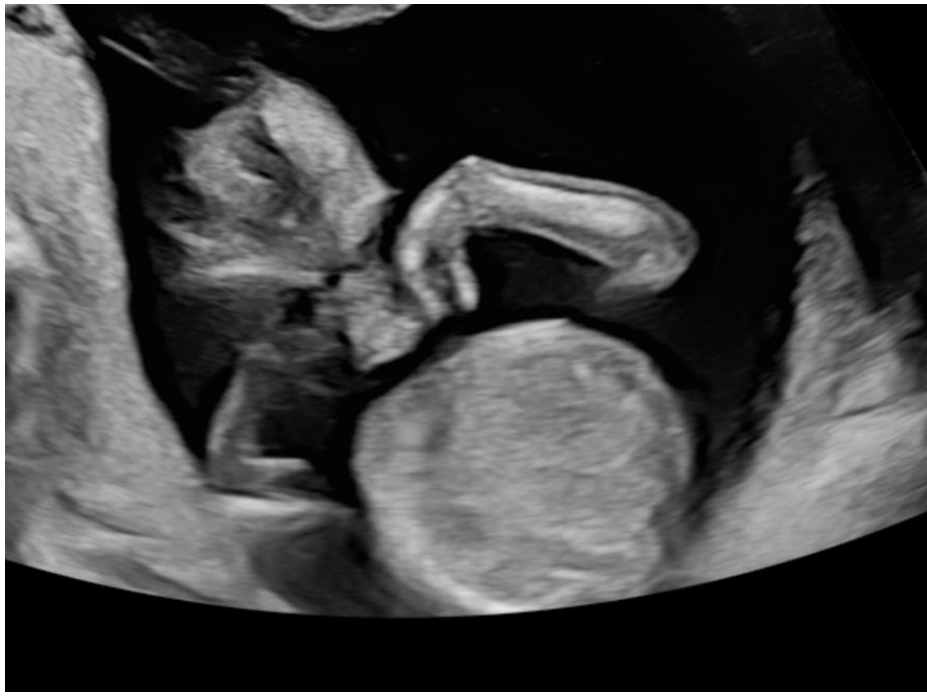




38 yo G2P0 at 16+ weeks, cfDNA + for trisomy 18



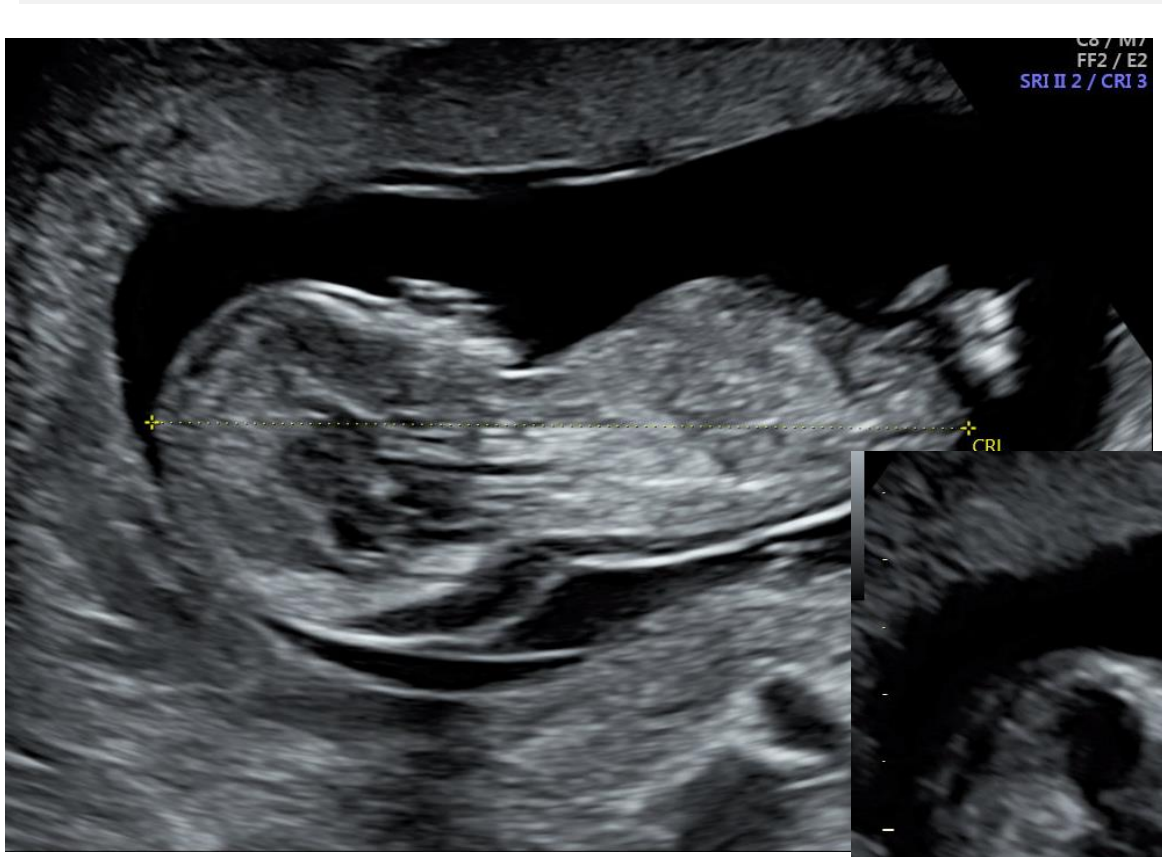


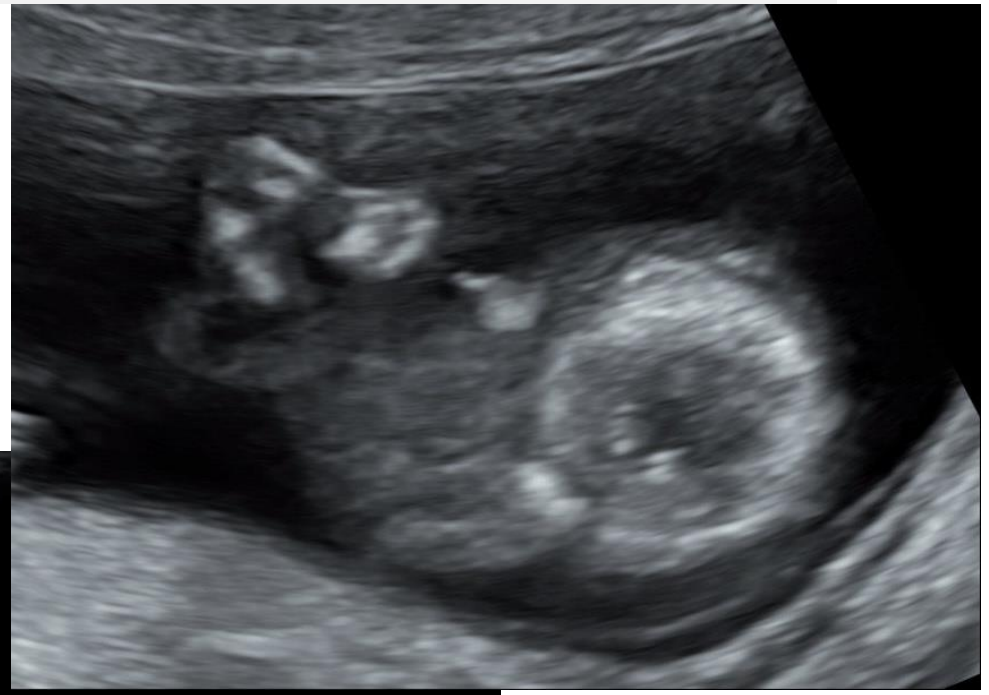


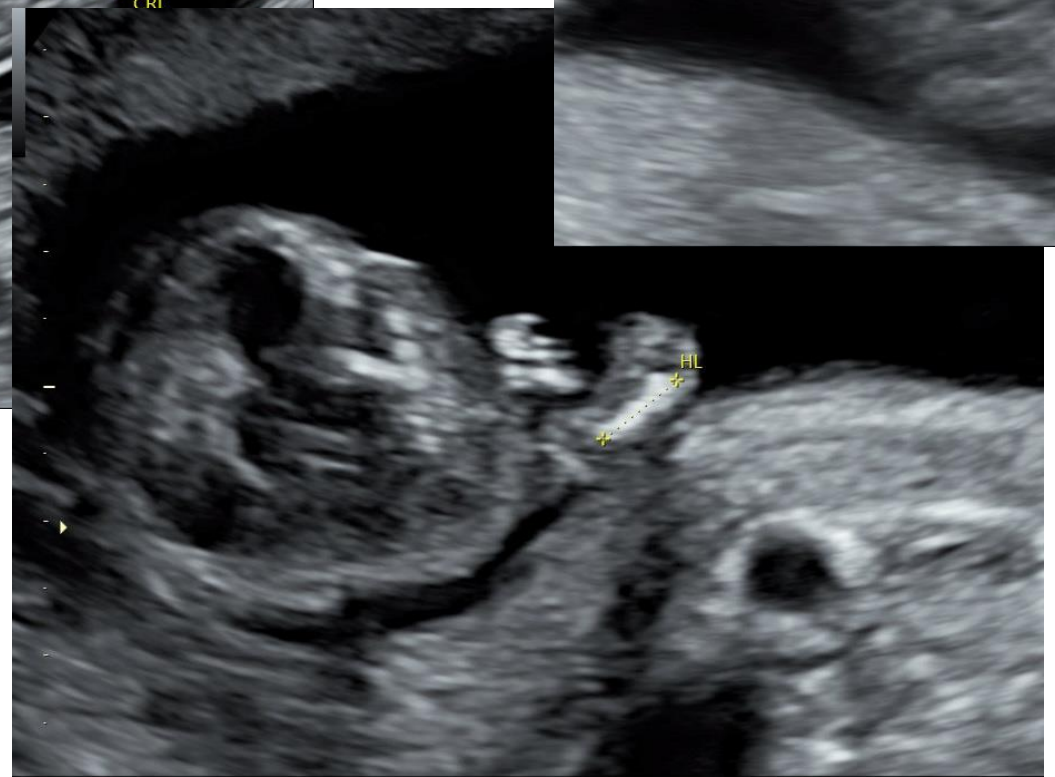
Ultrasound features of common aneuploidies

	Trisomy 21	Trisomy 13	Trisomy 18	45,X (Turner syndrome)
NT	Enlarged	Enlarged	Enlarged	Very enlarged
Cardiac	Common, AV canal defect, TOF, ASD/VSD	HLHS, VSD/ASD	ASD/VSD, TOF	Hypoplastic left heart, coarctation
Facial	Absent nasal bone	CL/CP, microphthalmia, anophthalmia	CL/CP, micrognathia	Usually normal
CNS	Mild ventriculomegaly	Holoprosencephaly, ventriculomegaly, ACC microcephaly, myelomeningocele	CPC, Dandy Walker, myelomeningocele, ventriculomegaly, ACC	Usually normal
GU	Mild pelviectasis	Polycystic kidneys, cystic dysplasia	Bladder outlet obstruction	Horseshoe kidney
GI	Echogenic bowel, duodenal atresia	omphalocele	Esophageal atresia, omphalocele, CDH	Usually normal
Other	Thick nuchal fold, cystic hygroma, hydrops, ARSA, polyhydramnios	Limb reduction defects, polydactyly, radial aplasia, FGR, polyhydramnios	Clenched hands, FGR, rocker bottom feet, polyhydramnios	Hydrops, cystic hygroma, FGR, polyhydramnios

34 y.o. G2P0 at 13 weeks, routine screening

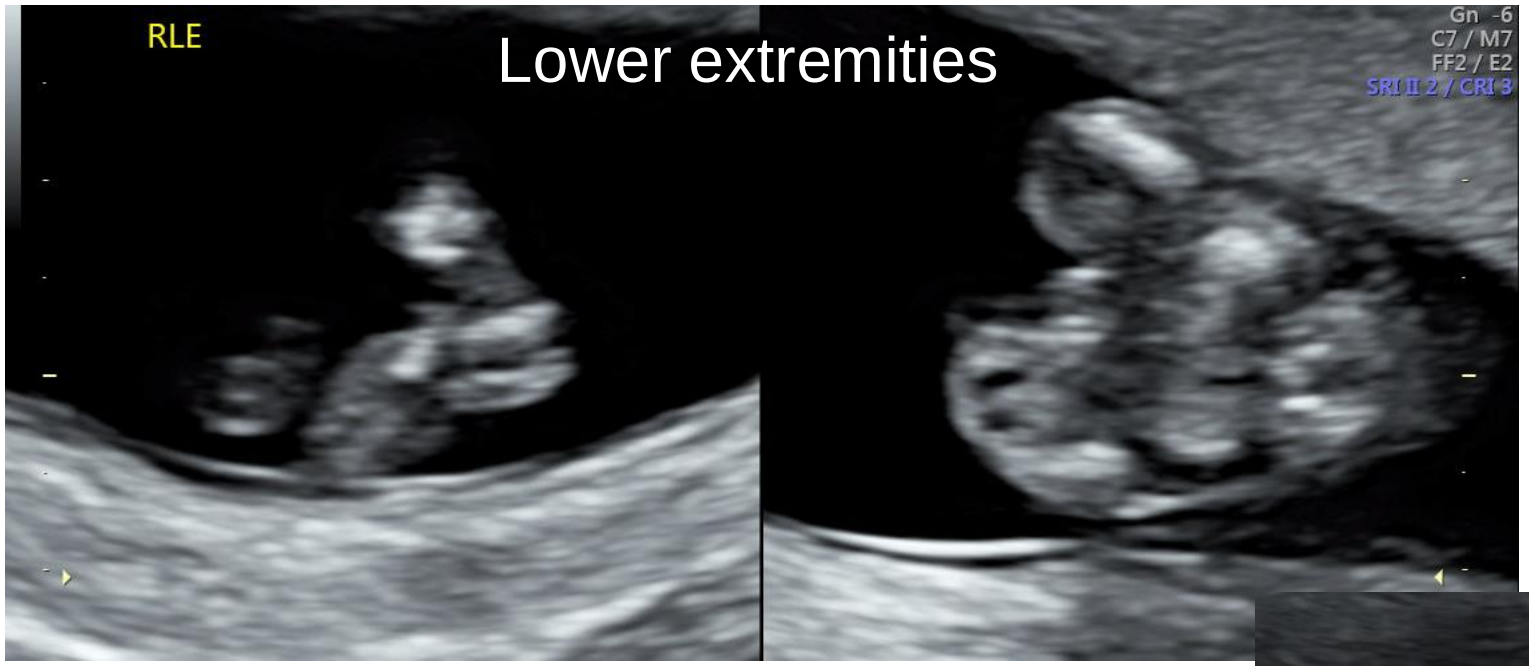


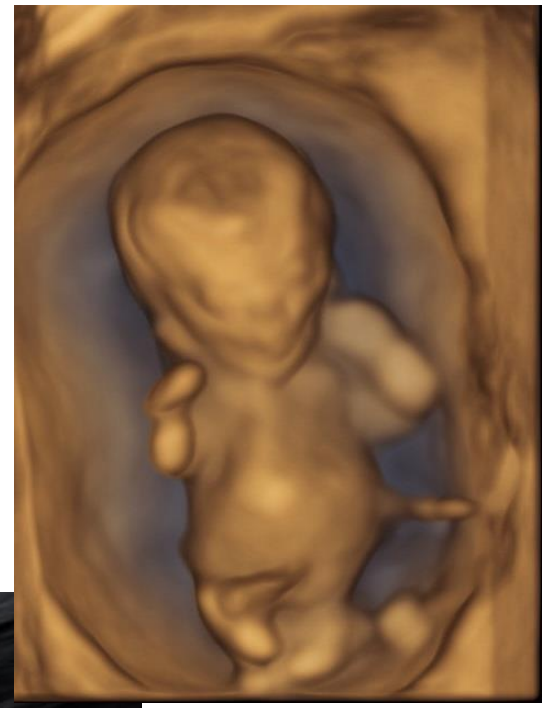


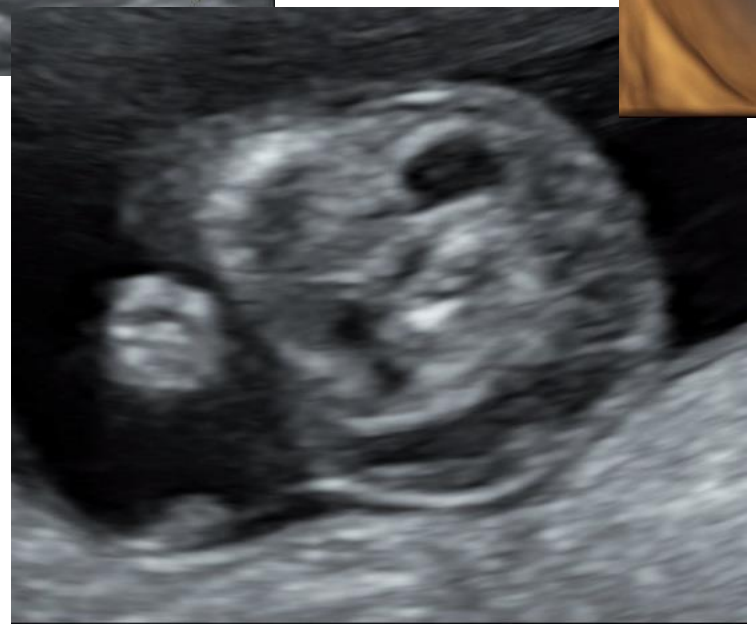


Upper extremities

34 y.o. G2P0 at 13 weeks: thanatophoric dysplasia

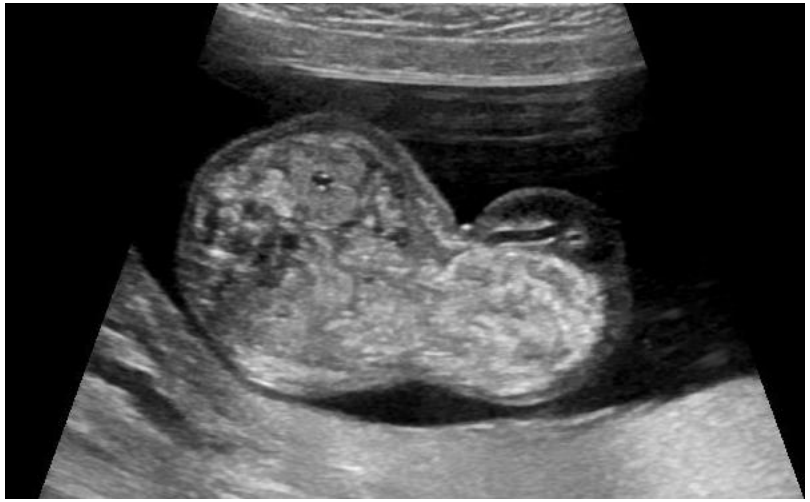






With enlarged NT: do a detailed ultrasound!

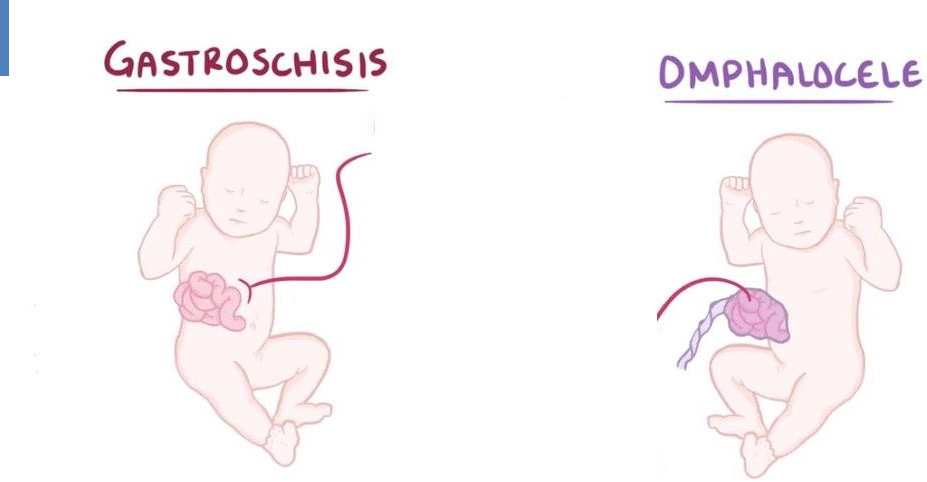
Ventral wall defects

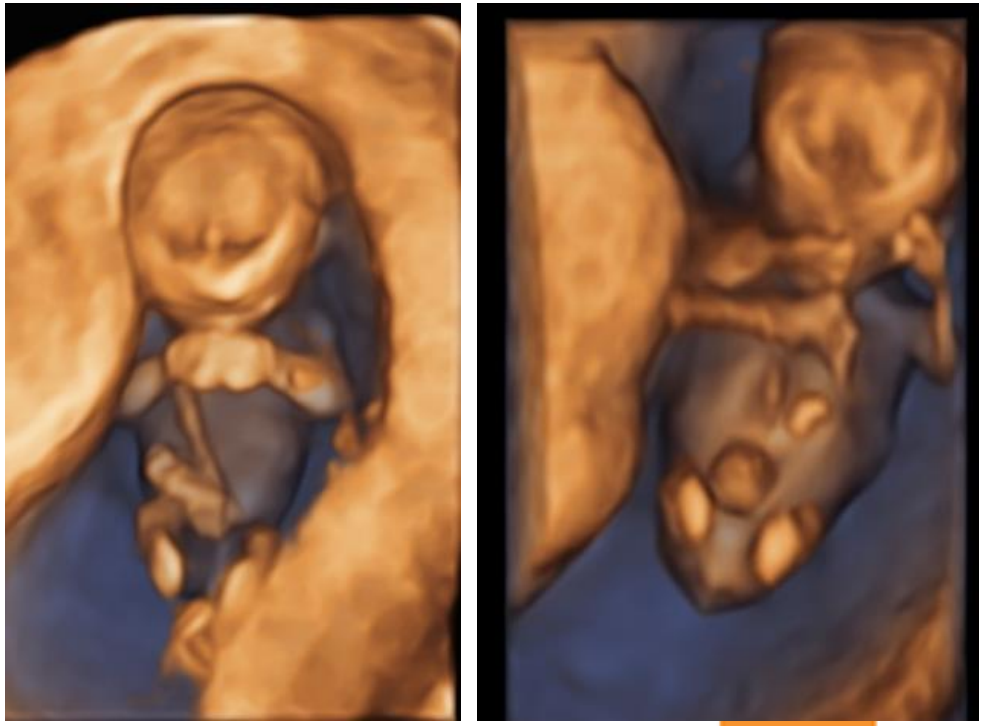


Types of ventral wall defects

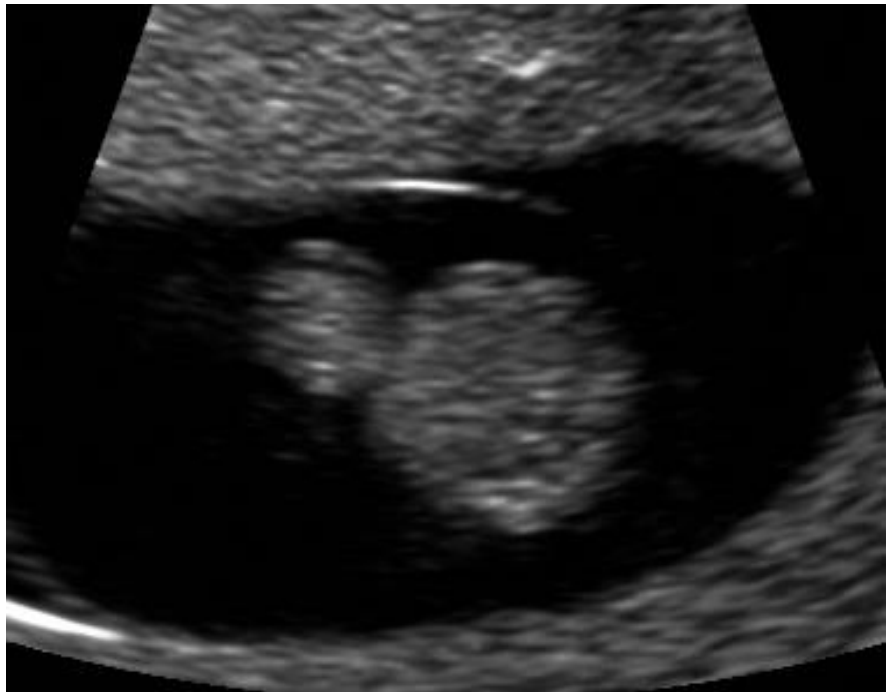
- Omphalocele
  - OEIS (omphalocele, exstrophy of the cloaca, imperforate anus, and spine abnormalities)
  - Pentalogy of Cantrell (heart, pericardium, diaphragm, sternum, ventral wall)
- Gastroschisis
  - Limb-body wall /body stalk anomaly/amniotic band sequence
- Cloacal extrophy
- Bladder extrophy

} OEIS complex

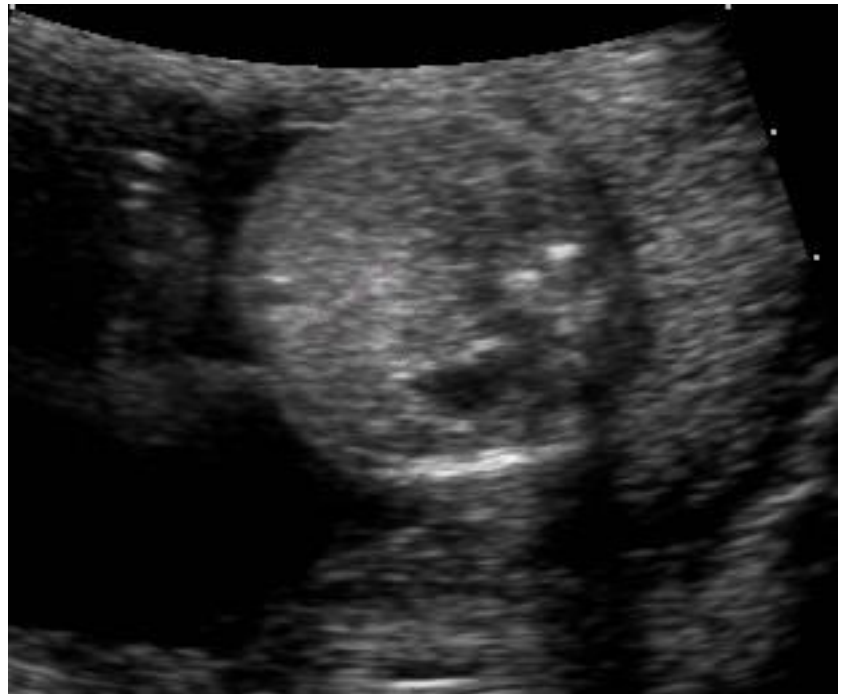




Cord Insertion: Physiologic Herniation in Early Pregnancy



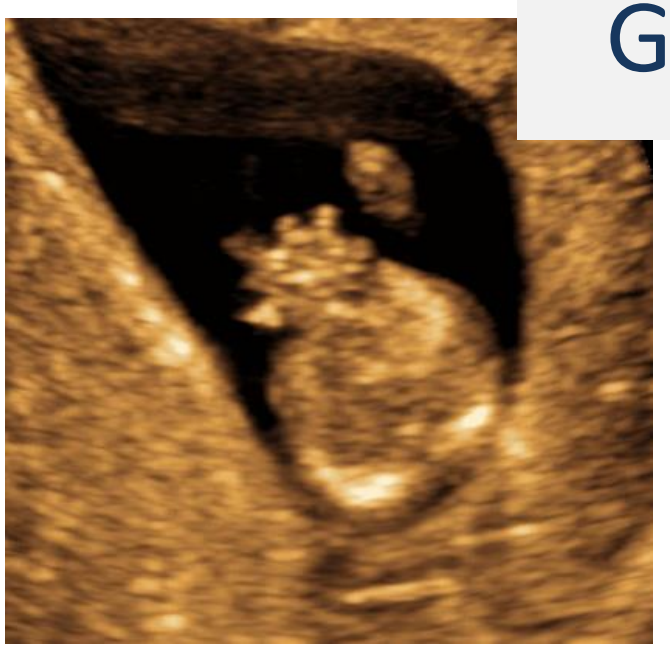
11 weeks

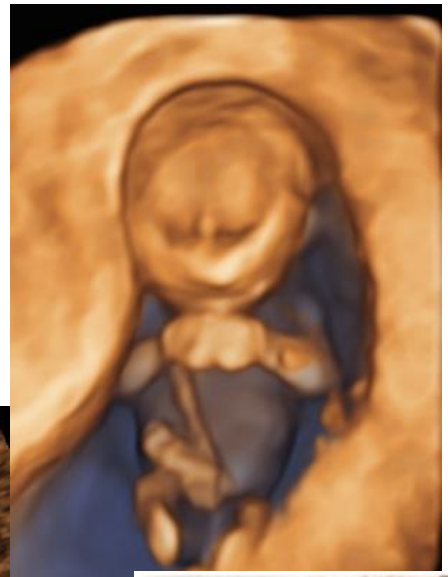


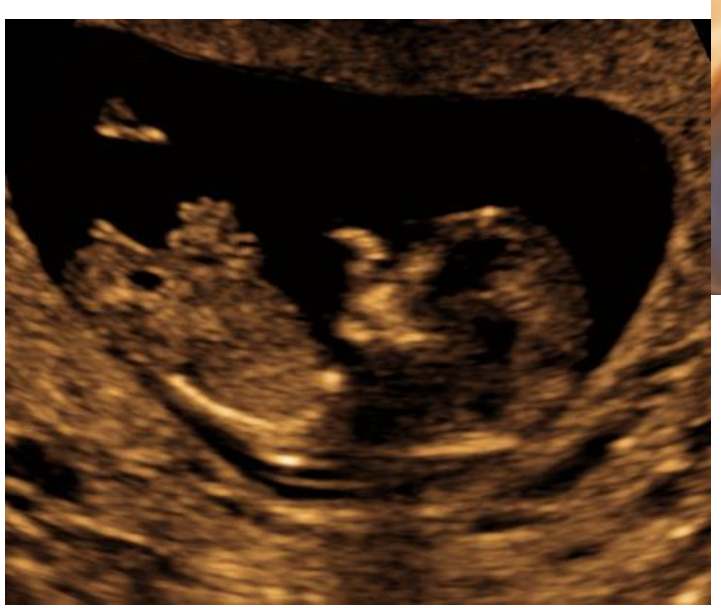
18 weeks

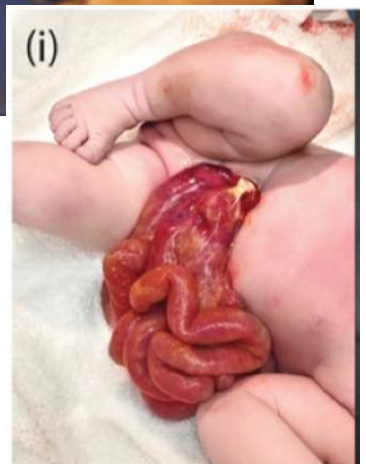
Gastroschisis versus omphalocele

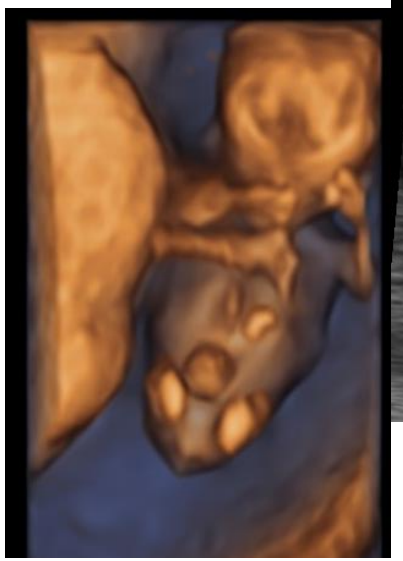
Important to distinguish as they are VERY DIFFERENT

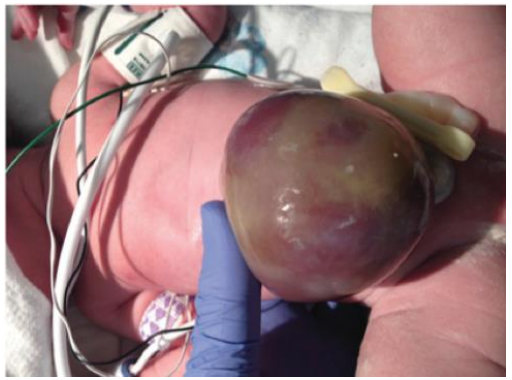


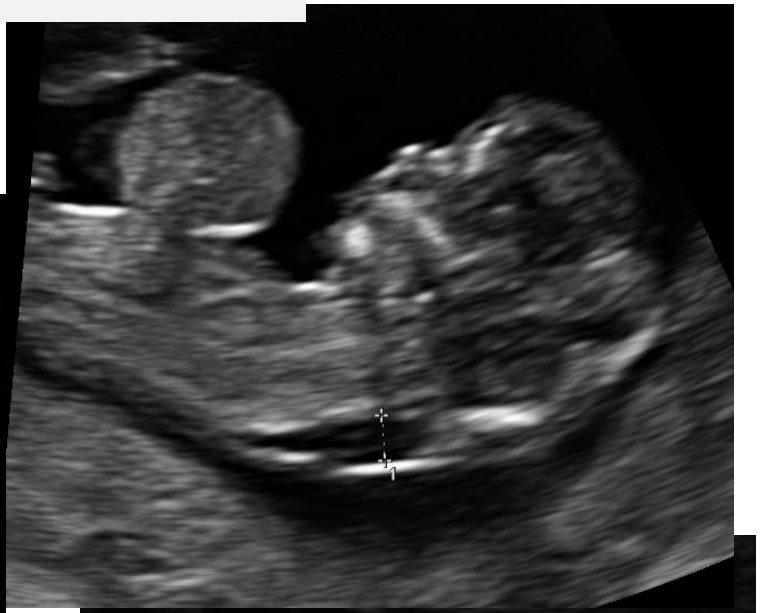


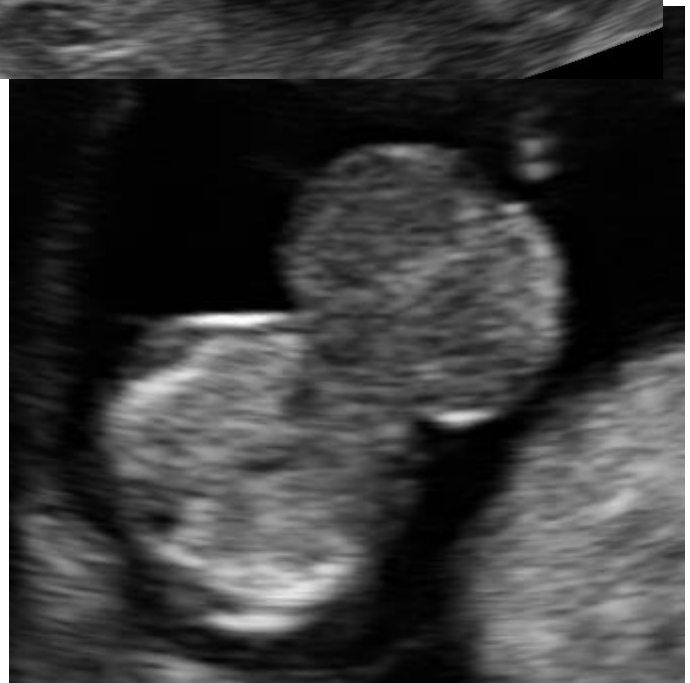












Co-occurring non-omphalocele and non-gastroschisis anomalies among cases with congenital omphalocele and gastroschisis

Claude Stoll | Yves Alembik | Marie-Paule Roth

Omphalocele: much higher rate of associated anomalies than gastroschisis

TABLE 1 Isolated and co-occurring anomalies in 101 cases with omphalocele and 71 cases with gastroschisis

	Omphalocele			Gastroschisis		
	n	%	*p*[a]	*n*	%	*p*[a]
Associated anomalies						
Nonchromosomal						
Recognized conditions[b]	16	15.8		4	5.6	
MCA[c]	31	30.7		11	15.5	
Chromosomal	28	27.7		1	1.4	
Total	75	74.3	1.94	16	22.5	0.41
Isolated malformation	26	25.7	0.67	55	77.5	1.42
All	101		2.61	71		1.83

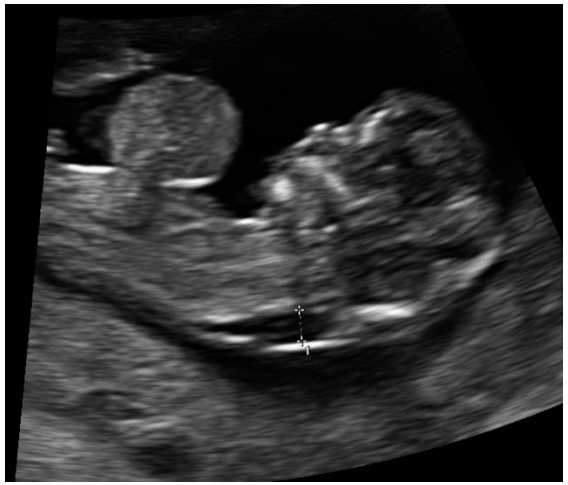
[a]Prevalence per 10,000 births.
[b]Include syndromes, associations, sequences, complexes, and spectrums.
[c]MCA, multiple congenital anomalies, excluding recognized syndromes, associations, sequences, complexes and spectrums.

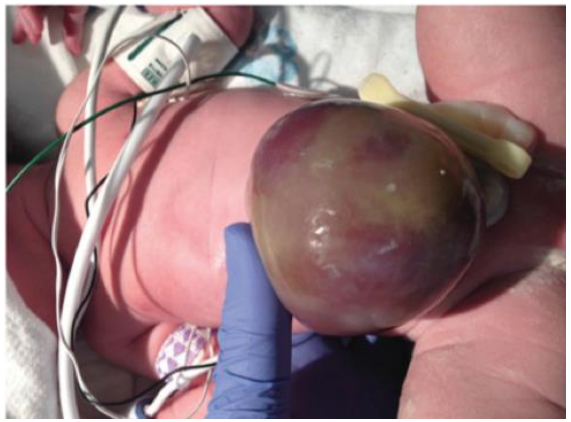
Stoll C et al, Am J Med Genet 2021

Omphalocele

- Failure of abdominal viscera to return to the abdomen
- 1/1000 pregnancies –> 1/4000 to 6000 live births
- 60% to 80% have associated anomalies
  - 50% of these are congenital heart defects
- Clinically recognized disorder: ~60%
- 1/3 have trisomy 18 or another aneuploidy (T13, T21)
  - Lower with isolated

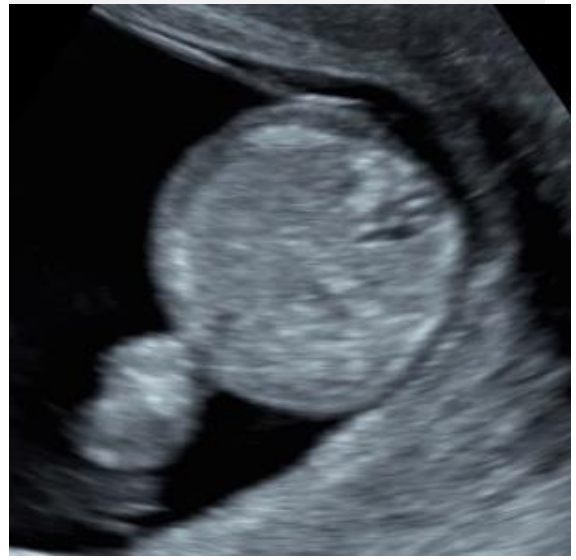
13 wk omphalocele





Omphalocele

13 wk omphalocele: Trisomy 18



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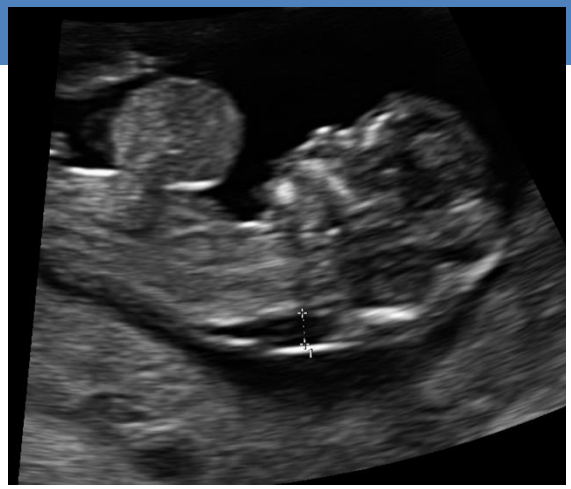
  - Lower with isolated
  - ➢**High risk of aneuploidy with smaller lesions**

Omphalocele associations



Common

- **Aneuploidy (T18)**
- **Beckwith-Weidemann syndrome**
- Pentalogy of Cantrell (heart, pericardium, diaphragm, sternum, ventral wall)
- OEIS sequence (omphalocele, exstrophy of the cloaca, imperforate anus, and spine abnormalities)

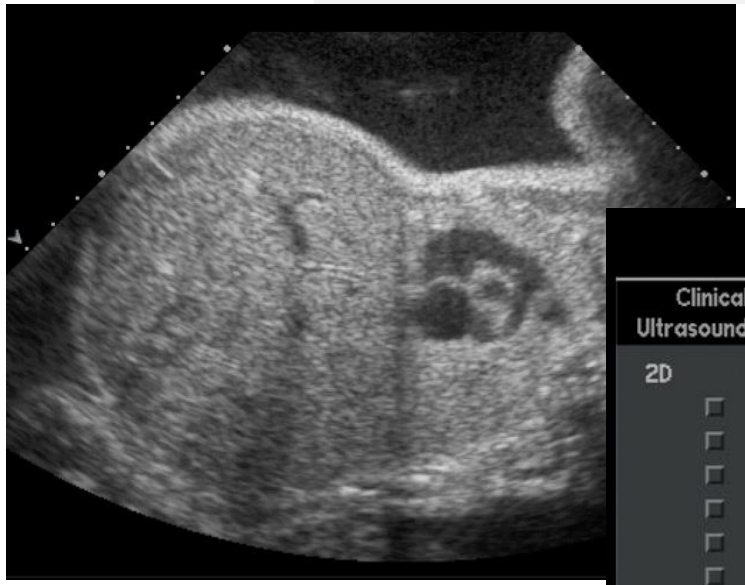
Rare

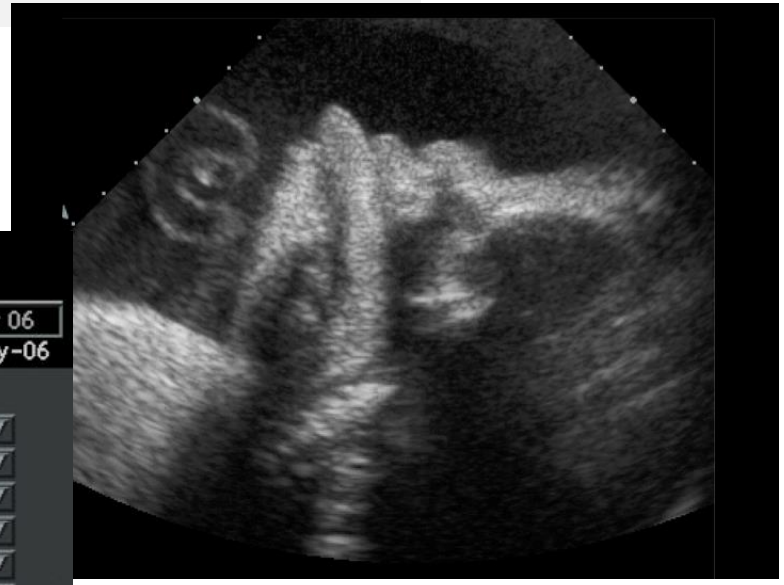
- CHARGE
- Cornelia de Lange
- Focal dermal hypoplasia
- Fryns syndrome
- Fraser syndrome
- Boomerang dysplasia
- Carpenter syndrome
- Shprintzen syndrome
- Fibrochondrogenesis, type 1
- Hydrolethalia
- Pallister-Killian syndrome
- Meckel-Gruber syndrome

Beckwith Weidemann Syndrome (BWS)

- Reported in 5-25% of fetal omphaloceles
  - Higher (37%) after exclusion of aneuploidy
  - Higher chance with IVF pregnancies
- Usually contain only small bowel
- Usually no other structural anomalies but can have overgrowth including macrosomia, organomegaly, macroglossia, polyhydramnios, and placentomegaly
- One recent study, only 33% of cases were diagnosed prenatally

G1P0 at 32 weeks' gestation





Clinical Ultrasound

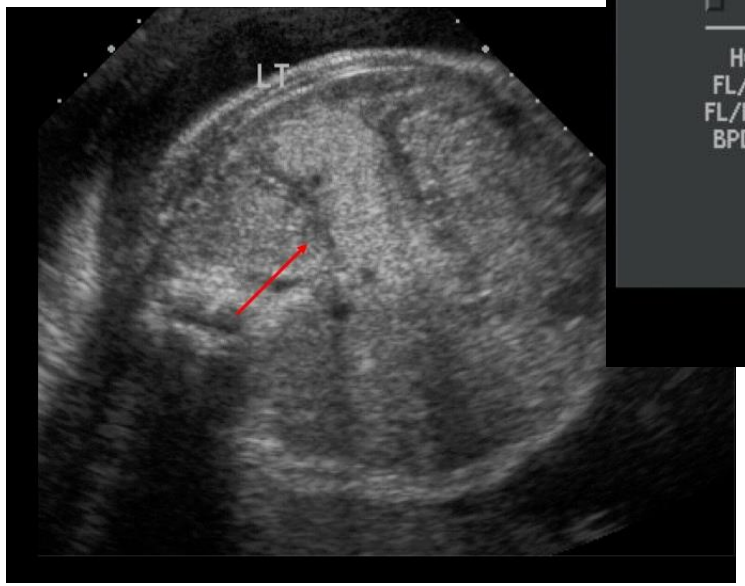
LMP =

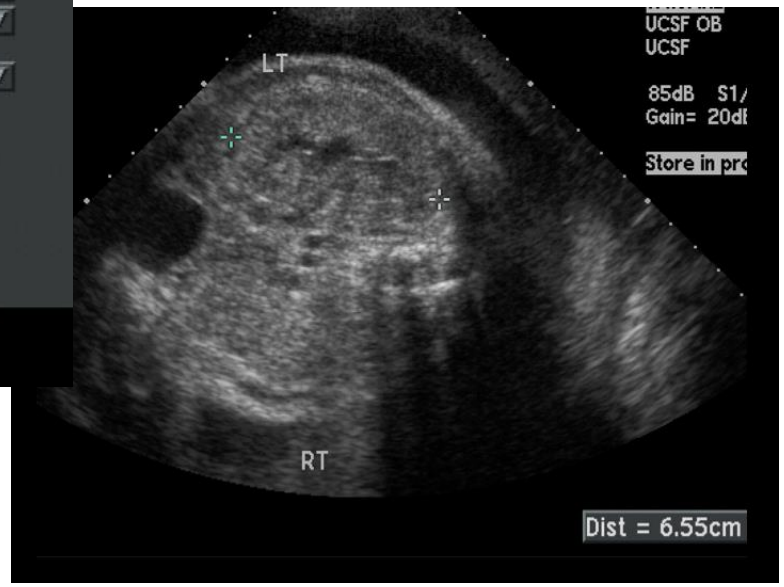
MA = 32w0d
MA = 32w6d±18d

EDD = 17 May 06
EDD = 11-May-06

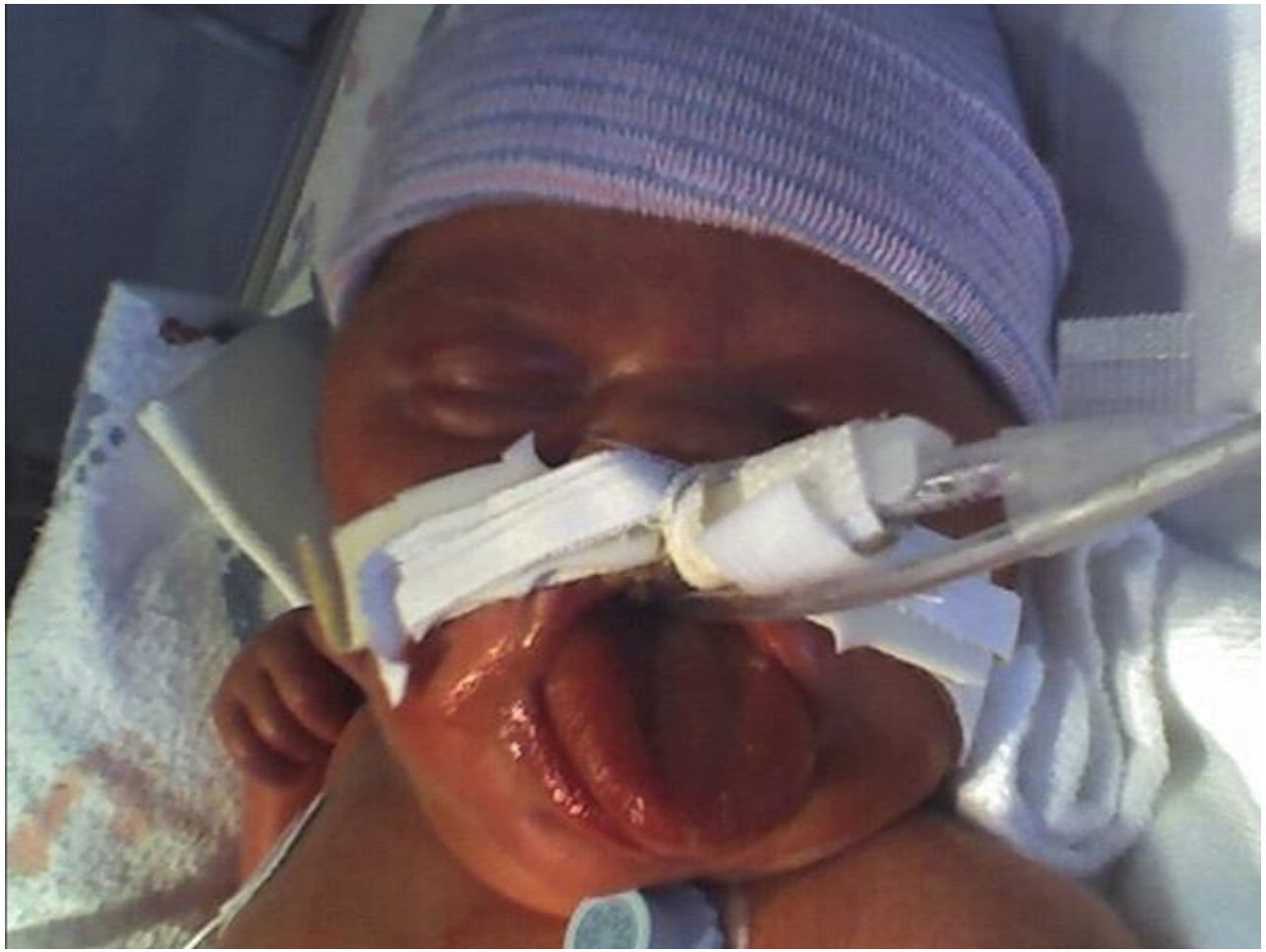
2D		MA	±SD	Mean						
☐	BPD	35w2d	±22d	8.75cm	8.72	8.77				(Hadlock)
☐	HC	34w6d	±21d	31.14cm	31.2	31.0				(Hadlock)
☐	AC			39.90cm	39.7	40.0				(Hadlock)
☐	FL	31w0d	±21d	5.94cm	5.93	5.94				(Hadlock)
☐	CRL									(Hadlock)
☐	GS									(Nyberg)
☐	HUM									(Jeanty)

HC/AC	0.78	(0.95 - 1.14)	Q1	6.32	EFW 3801±441g (Hadlock)
FL/AC%	14.9	(20% - 24%)	Q2	2.26	8lb, 6oz ±16oz
FL/BPD%	67.9	(71% - 87%)	Q3	11.0	LMP% >90%
BPD/TTD			Q4	8.67	
CI	81.2	(70% - 86%)	AFI	28.27cm	



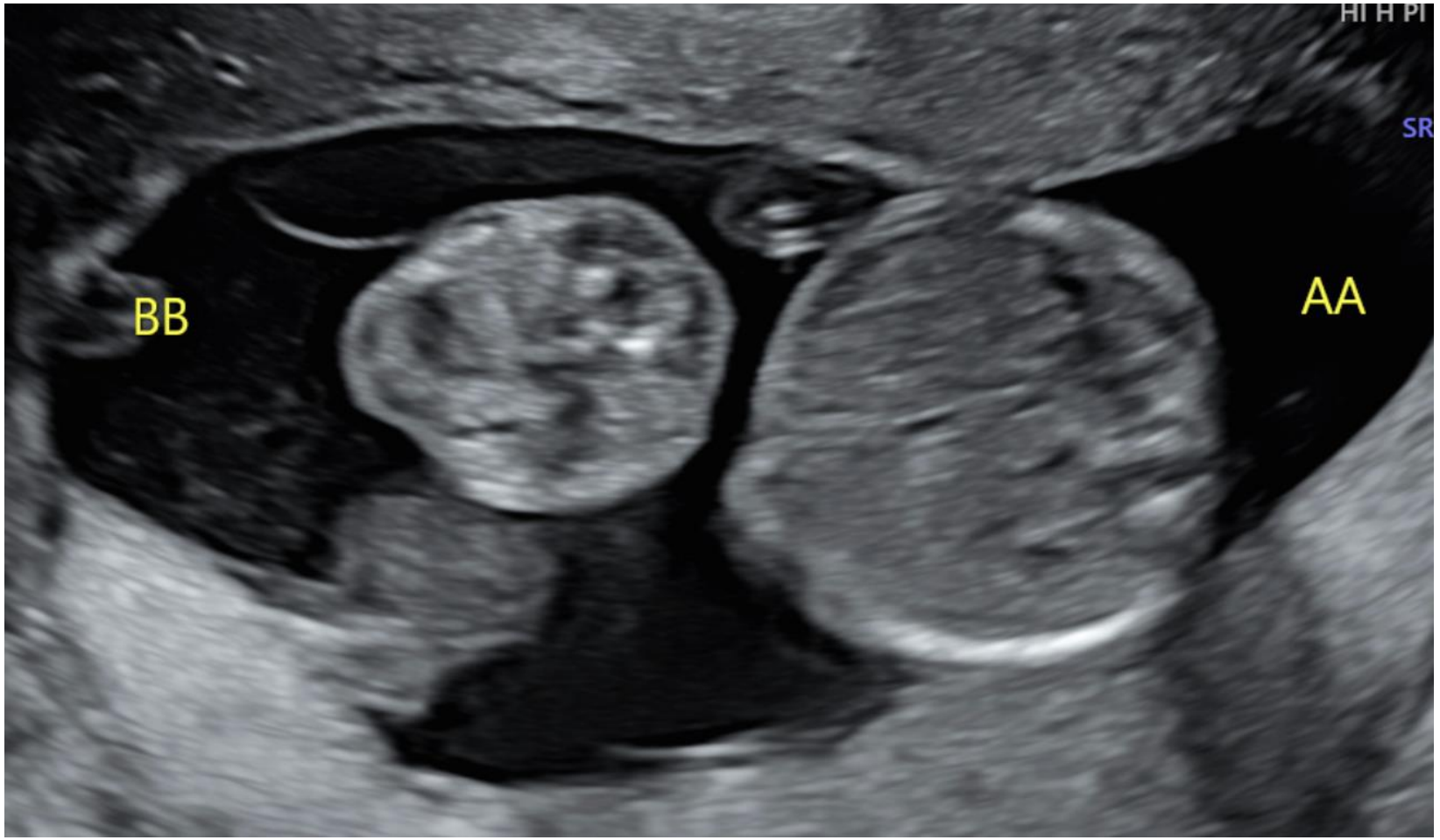


Beckwith Wiedemann Syndrome

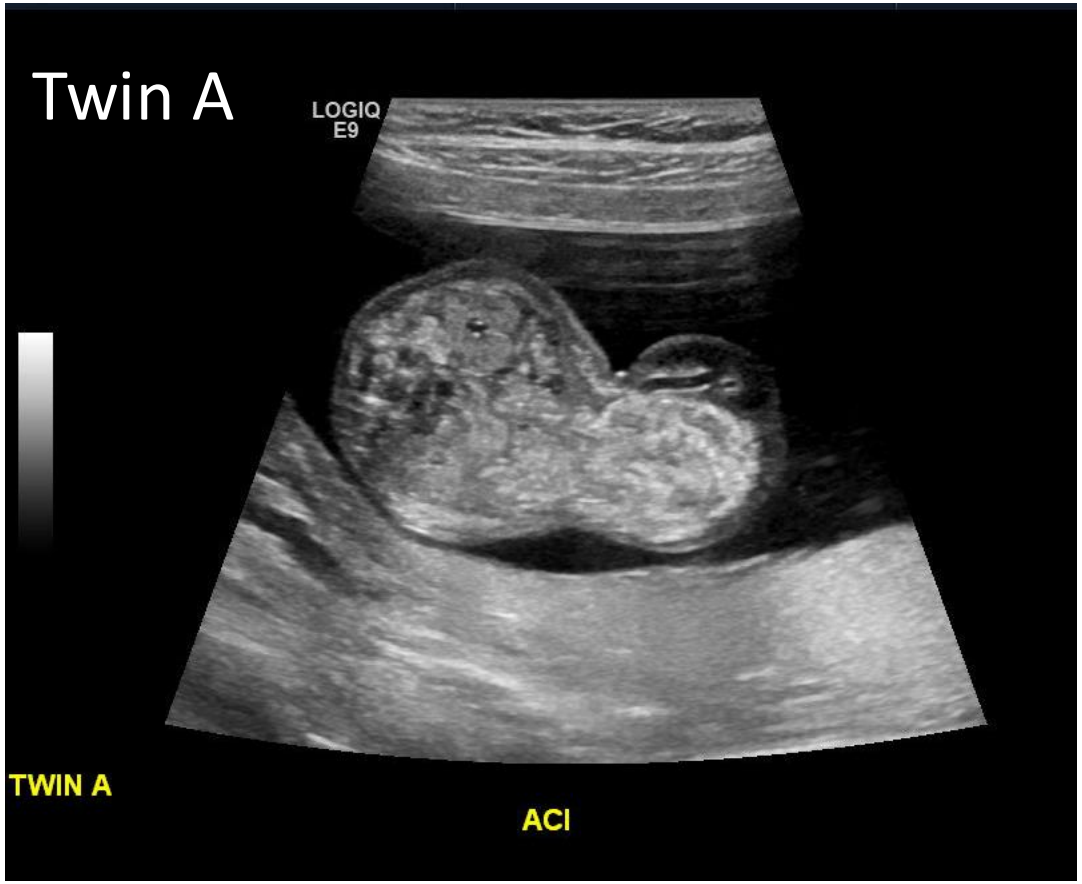


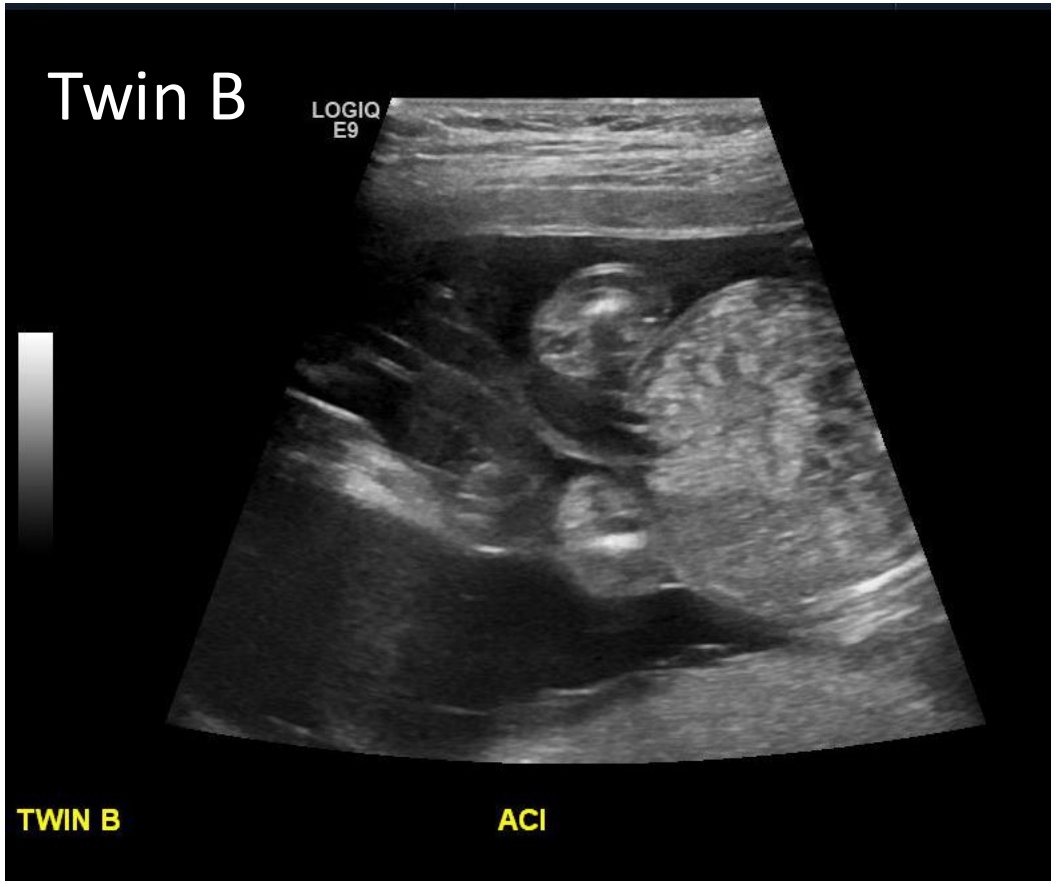
- Molecular studies done on amniotic fluid confirmed BWS.
- Hypomethylation of IC2 gene, the most common genetic cause of BWS.

Monochorionic/diamniotic twins: 16 wks



Monochorionic/diamniotic twins: 16 wks





Methylation Results: IC2 ABNORMAL/IC1 NORMAL

Twin A

Locus	Method	Methylation Index	Normal Range	Result
IC2 (KNCQ1OT1)	msPCR	0.00	0.44 - 0.56	Abnormal
IC2 (KCNQ1OT1)	RD-PCR	0.09	0.42 - 0.58	Abnormal
IC1 (H19)	msPCR	0.43	0.40 - 0.60	Normal
IC1 (H19)	RD-PCR	0.51	0.41 - 0.59	Normal

Hypomethylation of BWS-IC2 critical region, responsible for 50% of BWS cases

Methylation Results: NORMAL

Twin B

Locus	Method	Methylation Index	Normal Range	Result
IC2 (KNCQ1OT1)	msPCR	0.53	0.44 - 0.56	Normal
IC2 (KCNQ1OT1)	RD-PCR	0.44	0.42 - 0.58	Normal
IC1 (H19)	msPCR	0.43	0.40 - 0.60	Normal
IC1 (H19)	RD-PCR	0.52	0.41 - 0.59	Normal

Overrepresentation of pregnancies conceived by artificial reproductive technology in prenatally identified fetuses with Beckwith-Wiedemann syndrome

J Assist Reprod Genet 2018)

John P. Johnson[1] · Linda Beischel[2] · Corbin Schwanke[1] · Katie Styren[1] · Amy Crunk[3] · Jonathan Schoof[1] · Abdallah F. Elias[1]

- N=301 prenatal samples tested for BWS; 40 were positive

Table 1 Prenatal BWS test results of 301 fetuses with omphalocele

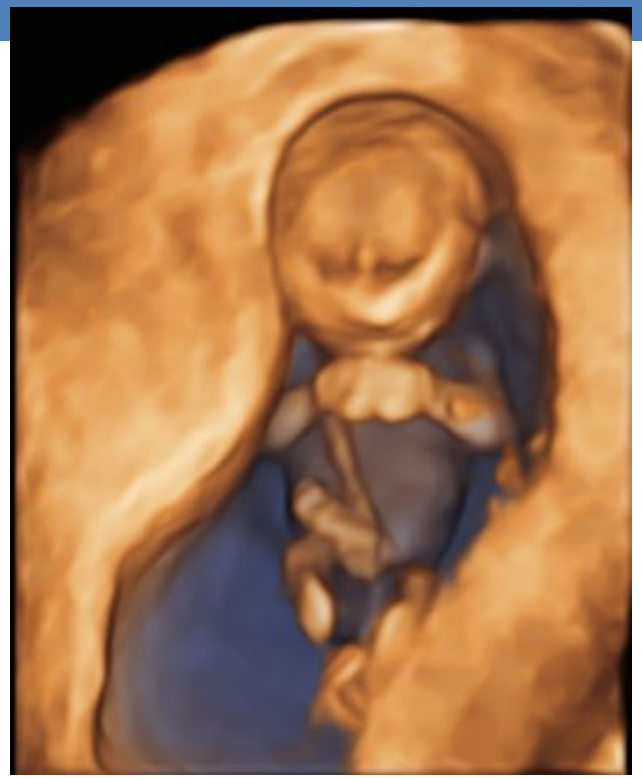
Sample type	Total number	BWS positive[a]	BWS negative[b]
Amniocytes (cultured)	184	32	152
Amniocytes (direct)	1	0	1
CVS (cultured)	101	5	96
CVS (direct)	1	0	1
POC/fetal tissue (cultured)	5	1	4
Extracted DNA (CVS or amniocytes)	9	2	7
Total	301 (100%)	40 (13.3%)	261 (86.7%)

Table 4 Pregnancies conceived by ART among BWS-positive and BWS-negative prenatal cases

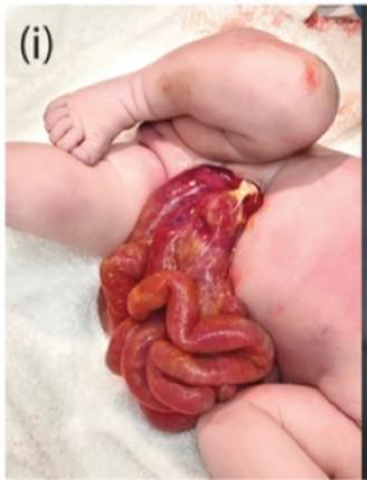
Sample type	ART pregnancies	
	BWS-positive samples ($n = 40$)	BWS-negative samples ($n = 261$)
Amniocytes	12	2
CVS	4	6
POC/fetal tissue	0	0
Total	16 (40.0%)	8 (3.1%)

ART assisted reproductive technology, *BWS* Beckwith-Wiedemann syndrome

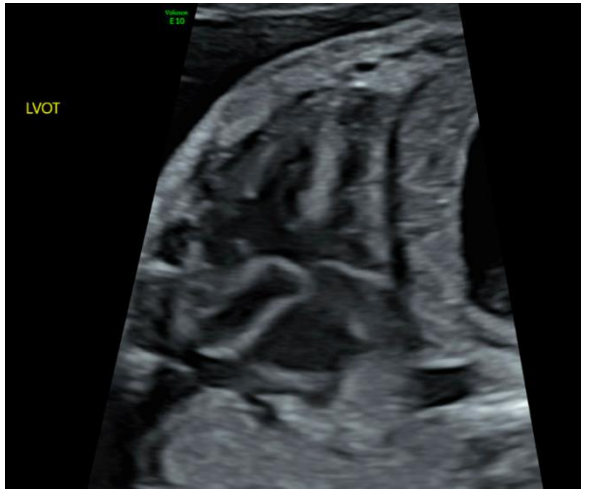
Gastroschisis



- Defect right of the umbilical cord
- Not covered by a membrane
- Usually isolated
  - Associated anomalies are often related to bowel injury
  - Chromosome abnormalities are rare
- Risk factors: young maternal age, low BMI, nulliparity, rural birth, cigarette and alcohol use, some over-the-counter medications
- 2-5 per 10,000 live births, rate increasing in many studies



Genetic causes of CHD



CONGENITAL HEART DISEASE: PREVALENCE AT LIVEBIRTH

THE BALTIMORE-WASHINGTON INFANT STUDY

CHARLOTTE FERENCZ,[1] JUDITH D. RUBIN,[1] ROBERT J. McCARTER,[1] JOEL I. BRENNER,[2] CATHERINE A. NEILL,[3] LOWELL W. PERRY,[4] SEYMOUR I. HEPNER[5] AND JOHN W. DOWNING[6]

Am J Epidem 1985

- 25% of children with CHD had extracardiac malformations
- 1/3 of these had known genetic disorders

RESEARCH ARTICLE

Prevalence of associated extracardiac anomalies in prenatally diagnosed congenital heart diseases

Chi-Son Chang[1], Sir-yeon Hong[1], Seo-yeon Kim[1], Yoo-min Kim[2], Ji-Hee Sung[1], Suk-Joo Choi[1]*, Soo-young Oh[1], Cheong-Rae Roh[1], Jinyoung Song[3], June Huh[3], I-Seok Kang[3]

N=791 cases of prenatal CHD

- 25% had extracardiac malformations
- 12% chromosomal abnormalities
- 5% 22q11.2 deletion syndrome

PLoS ONE, 2021

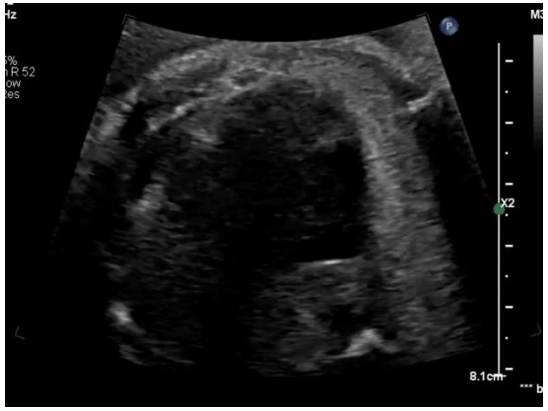
Rate of syndromic associations and other extracardiac malformations varies with type of CHD

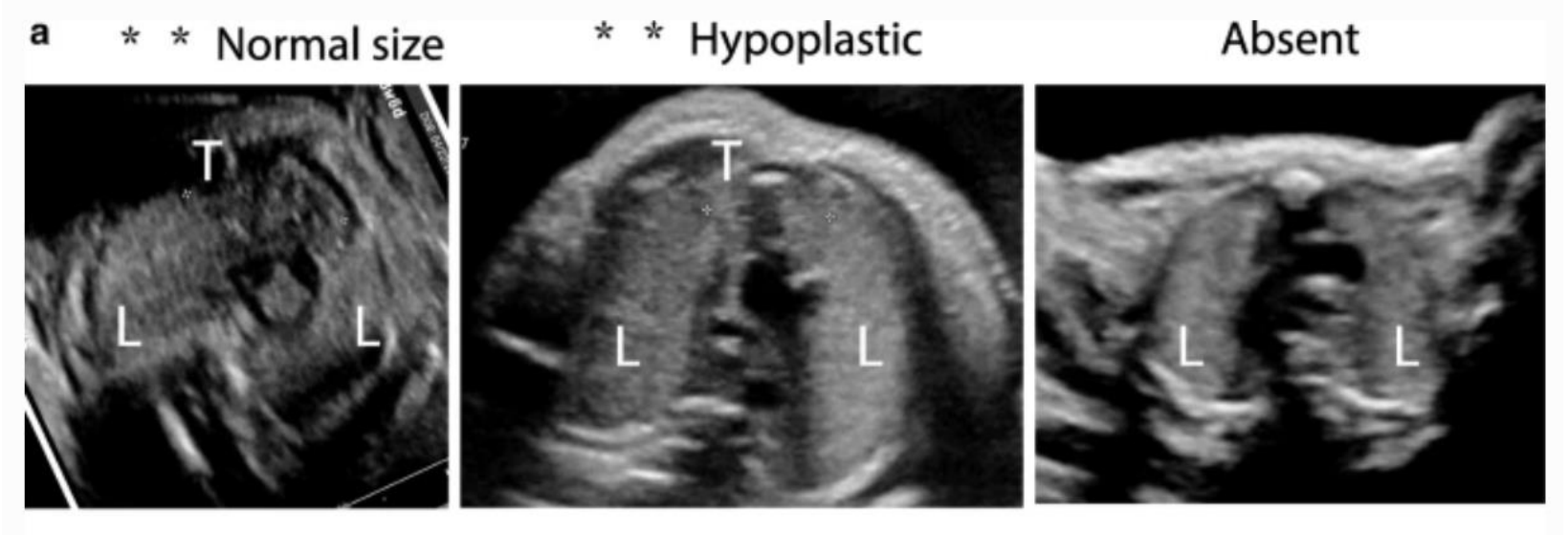
- Atrioventricular septal defect: 75% (mostly trisomy 21)
- Tetralogy of Fallot: 25% (many are 22q11.2 deletion)
- Transposition of great arteries: Rare

- Genetic causes affect:
  - Associated anomalies
  - Outcomes of syndromic versus non-syndromic cases
  - Recurrence risk
  - Test options in future pregnancies

Ultrasound features of 22q11.2 deletion syndrome

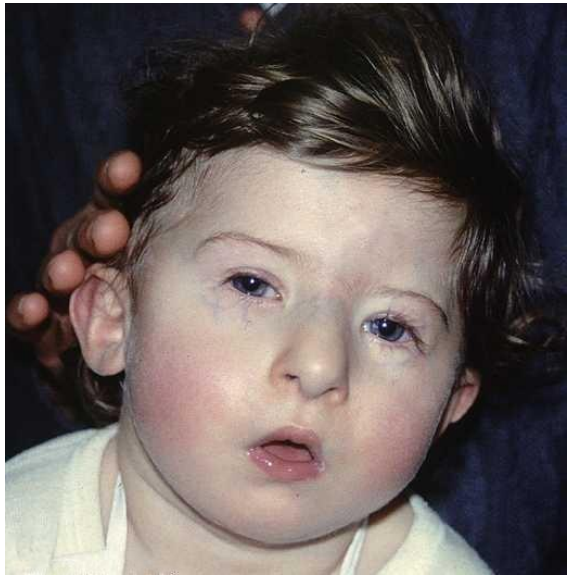
- Conotruncal heart defects
  - Truncus arteriosus, tetralogy of Fallot, interrupted aortic arch type B, DORV, pulmonary atresia
- Absent thymus
- Cleft palate
- Renal anomalies
- Growth restriction
- Wide CSP





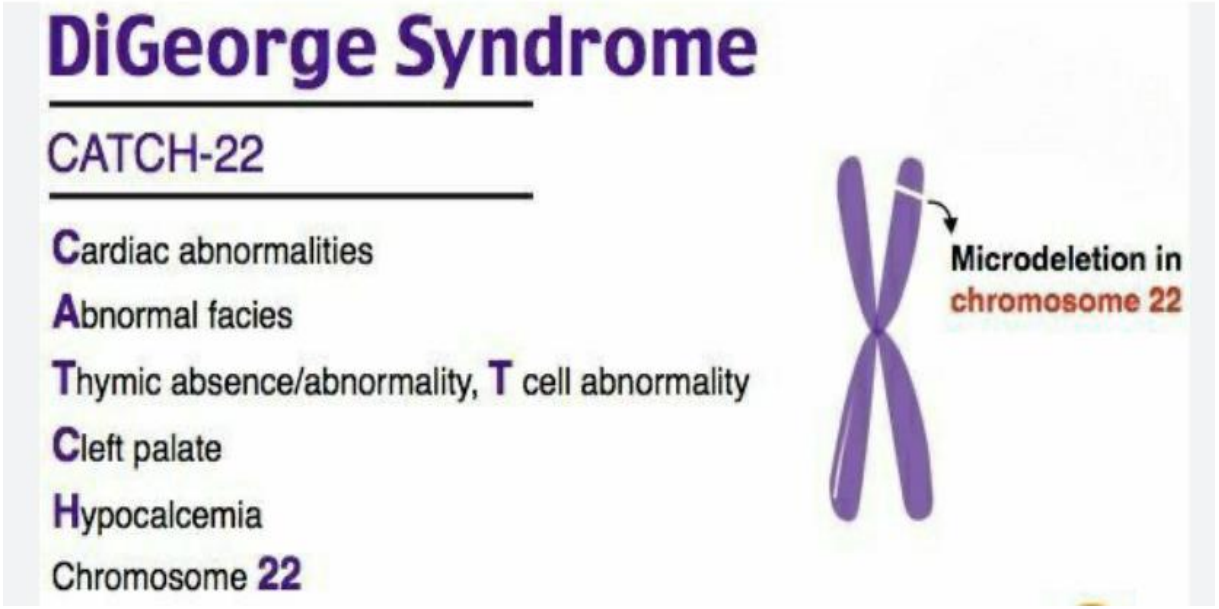
*Dou, Y. et al. J Clin Immunol **40**, 783–785 (2020)*

22q11.2 deletion syndrome (DiGeorge)



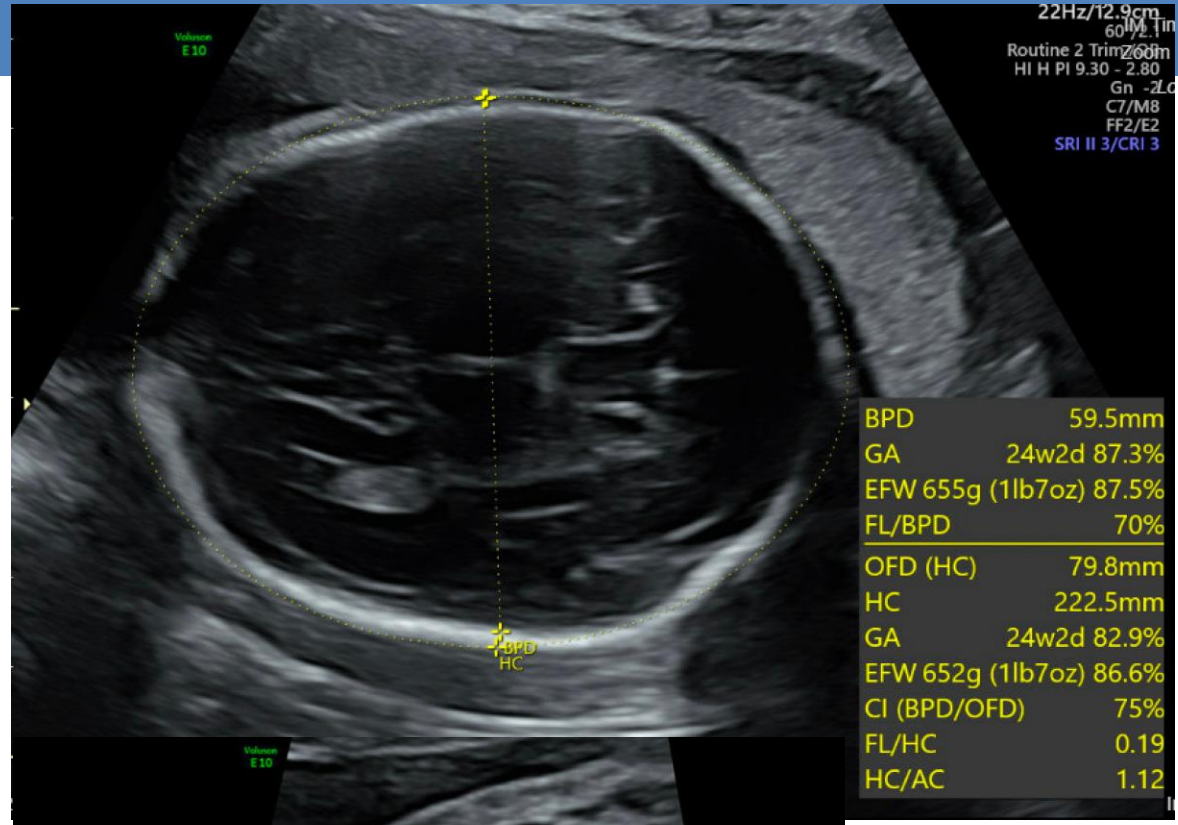
Important prognostic implications:

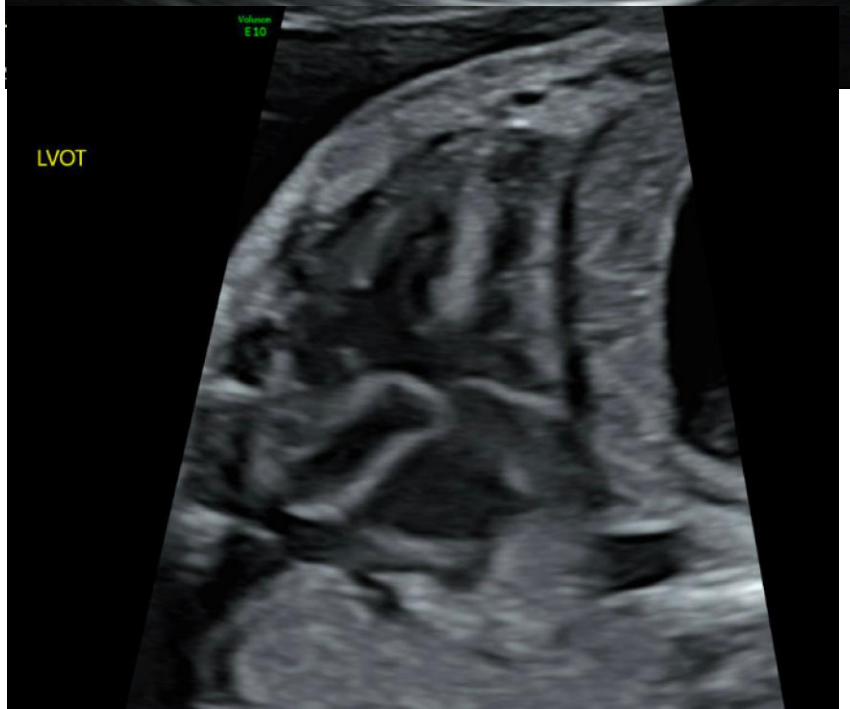
- Many associated anomalies, including cleft palate, developmental delay and psychiatric disorders
- About 5% of cases inherited from apparently normal parent
- If so, recurrence risk is 50% (vs 2-3% for isolated heart defect)
- Prenatal diagnosis very accurate



36 yo G4P0 at 24 weeks’

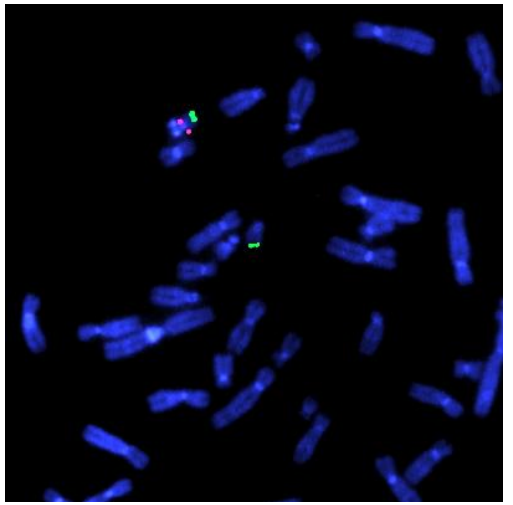
- Ultrasound: wide CSP, complex CHD including VSD with malalignment, interrupted aortic arch
- Findings suspicious for 22q11.2 deletion syndrome
- Prognosis for isolated CHD and 22q11.2DS are much different



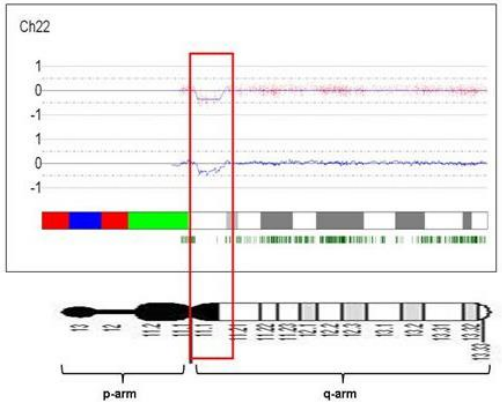


Suspected 22q11.2 deletion syndrome

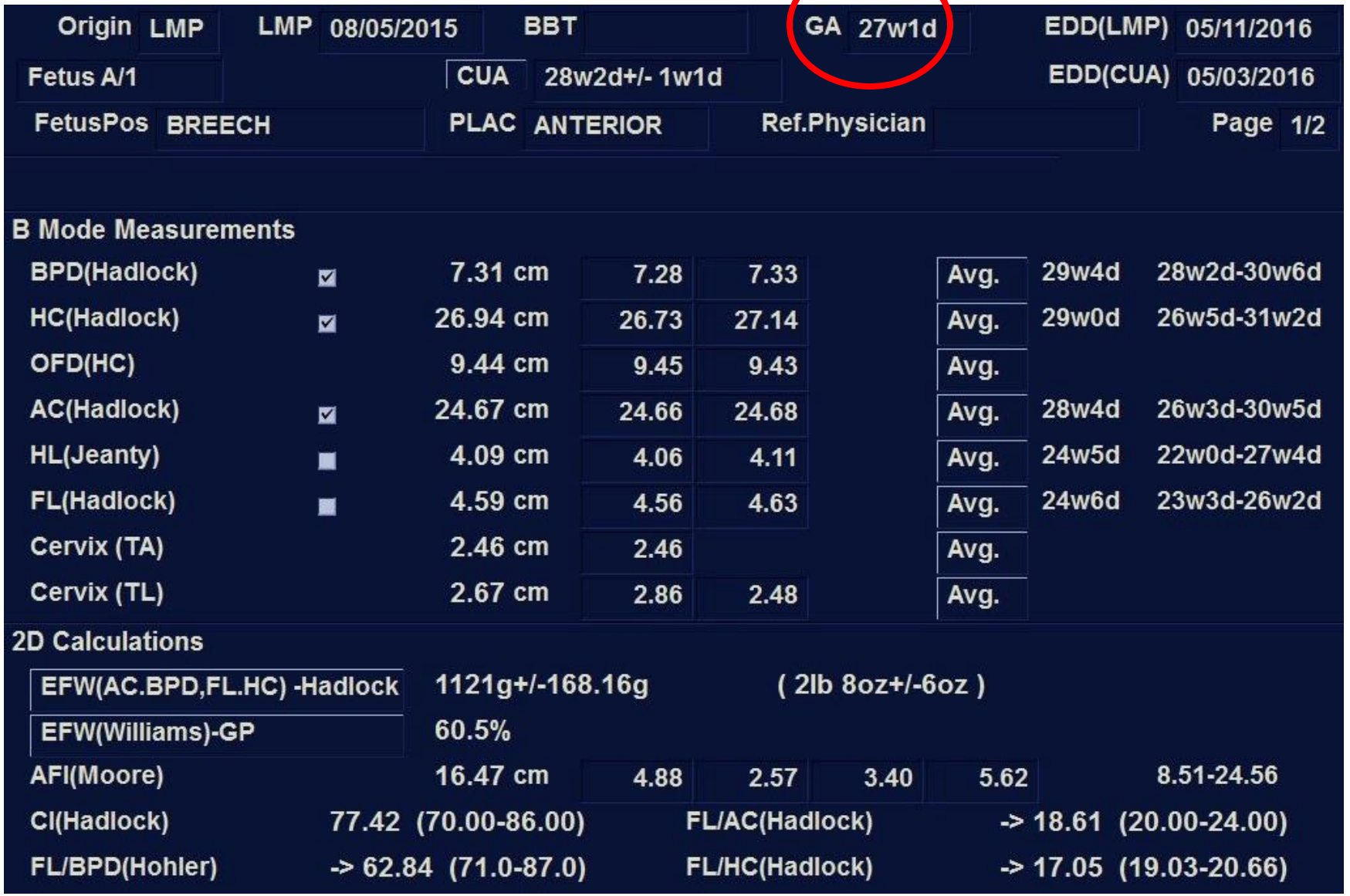
- Several tests can make the diagnosis
  - Cell free DNA screening including 22q11.2DS
  - Amniocentesis or CVS:
    - Chromosomal microarray
    - Karyotype with FISH for 22q11.2
- Chromosomal microarray is the best option
  - Definitive diagnosis
  - Detects other CNV as well
- Cell free DNA
  - Late gestational age, patient declines diagnostic testing
  - Accuracy varies by laboratory; sensitivity varies widely but lower than CMA
  - PPV with typical heart defect much higher than with normal ultrasound



FISH



G1P0 at 27 weeks with short long bones



Origin	LMP	LMP	08/05/2015	BBT		GA	27w1d	EDD(LMP) 05/11/2016
Fetus A/1		CUA	28w2d+/- 1w1d					EDD(CUA) 05/03/2016
FetusPos	BREECH	PLAC	ANTERIOR	Ref.Physician				Page 1/2

B Mode Measurements

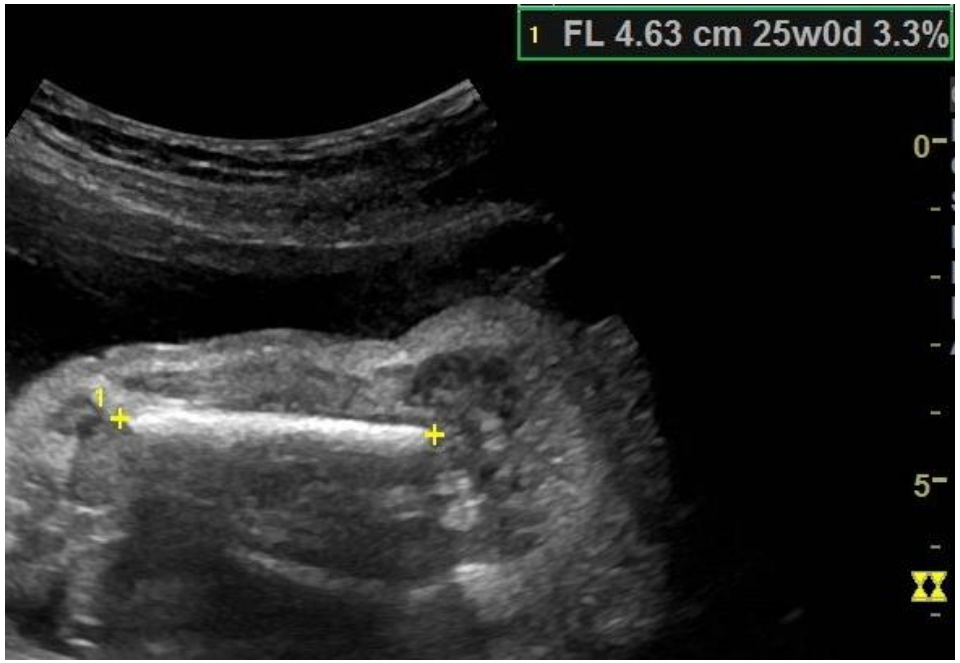
BPD(Hadlock)	☑	7.31 cm	7.28	7.33	Avg.	29w4d	28w2d-30w6d
HC(Hadlock)	☑	26.94 cm	26.73	27.14	Avg.	29w0d	26w5d-31w2d
OFD(HC)		9.44 cm	9.45	9.43	Avg.		
AC(Hadlock)	☑	24.67 cm	24.66	24.68	Avg.	28w4d	26w3d-30w5d
HL(Jeanty)	☐	4.09 cm	4.06	4.11	Avg.	24w5d	22w0d-27w4d
FL(Hadlock)	☐	4.59 cm	4.56	4.63	Avg.	24w6d	23w3d-26w2d
Cervix (TA)		2.46 cm	2.46		Avg.		
Cervix (TL)		2.67 cm	2.86	2.48	Avg.		

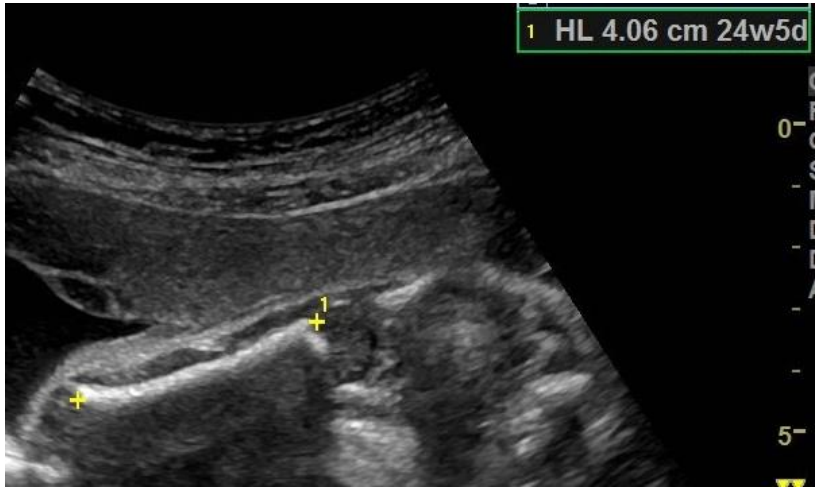
2D Calculations

EFW(AC.BPD,FL.HC) -Hadlock	1121g+/-168.16g	(2lb 8oz+/-6oz)				
EFW(Williams)-GP	60.5%					
AFI(Moore)	16.47 cm	4.88	2.57	3.40	5.62	8.51-24.56

CI(Hadlock)	77.42 (70.00-86.00)	FL/AC(Hadlock)	-> 18.61 (20.00-24.00)
FL/BPD(Hohler)	-> 62.84 (71.0-87.0)	FL/HC(Hadlock)	-> 17.05 (19.03-20.66)

G1P0 at 27 weeks with short long bones: normal bone morphology





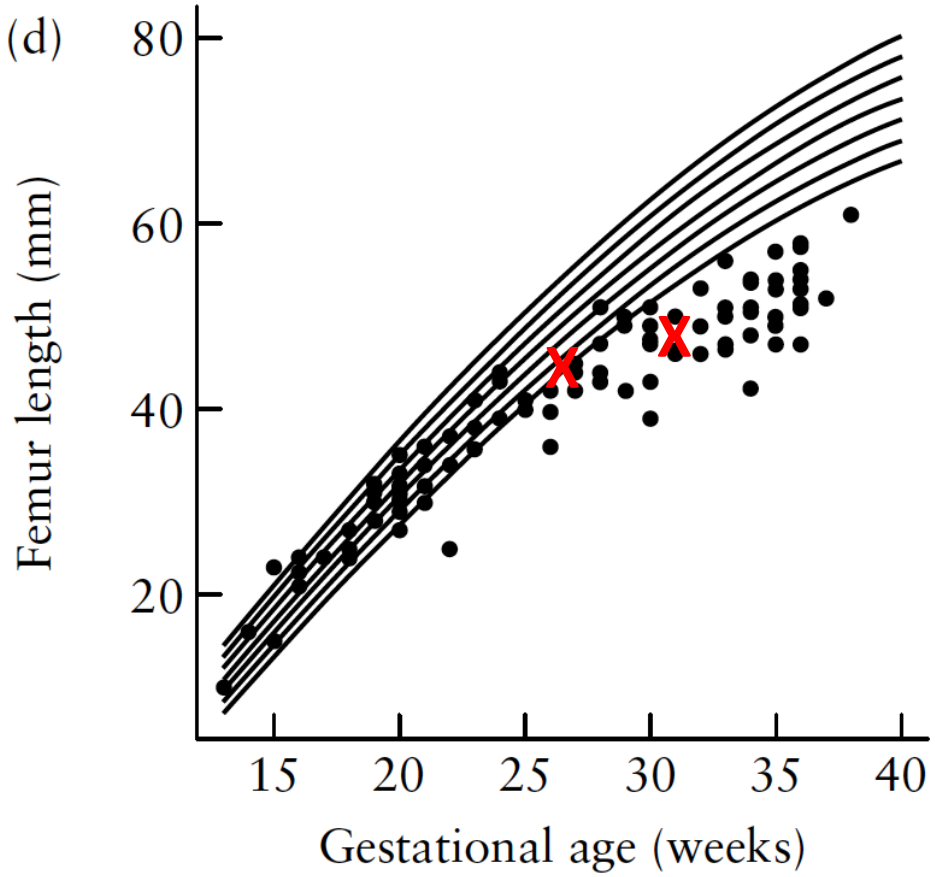
Ultrasound Obstet Gynecol 2011; **37**: 283–289
Published online 1 February 2011 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.8893

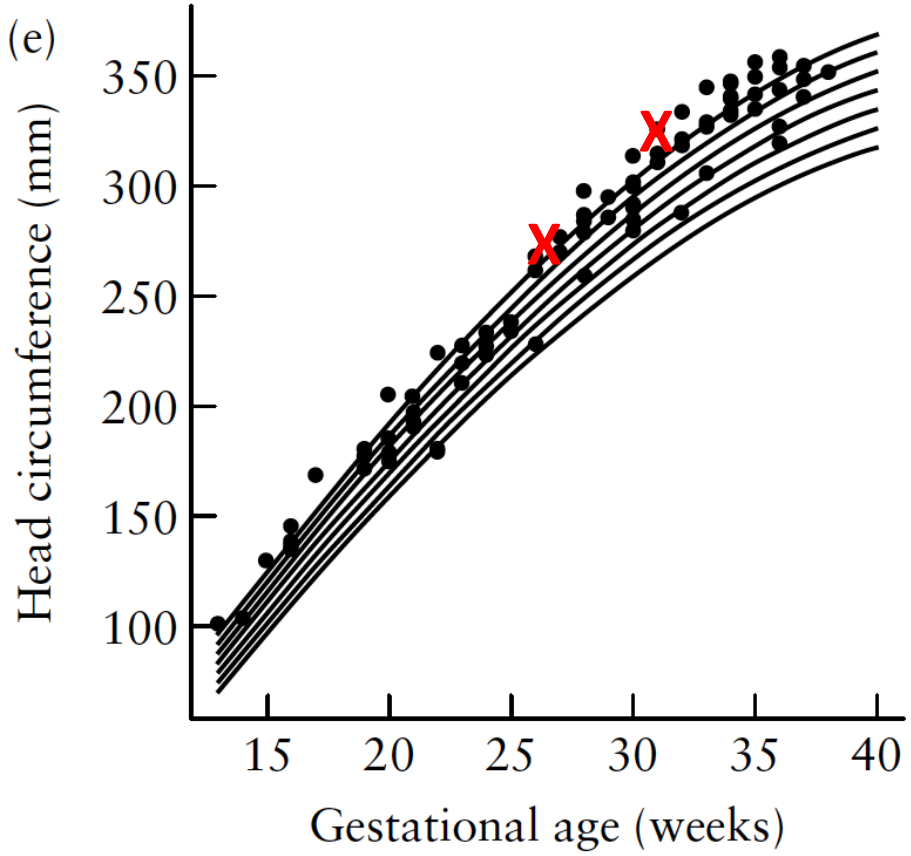
New aids for the non-invasive prenatal diagnosis of achondroplasia: dysmorphic features, charts of fetal size and molecular confirmation using cell-free fetal DNA in maternal plasma

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 PRENATAL DIAGNOSIS

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 FGR from achondroplasia

Conclusions

- Even if US anomaly is felt to be lethal, full evaluation is important.
  - Prognosis
  - Recurrence
- Value of detailed imaging evaluation, careful history, and genetic consultation and testing.
- Range of testing options depending on certainty that disorder is genetic, suspicion of diagnosis


Thank you!
UCSF Medical Center