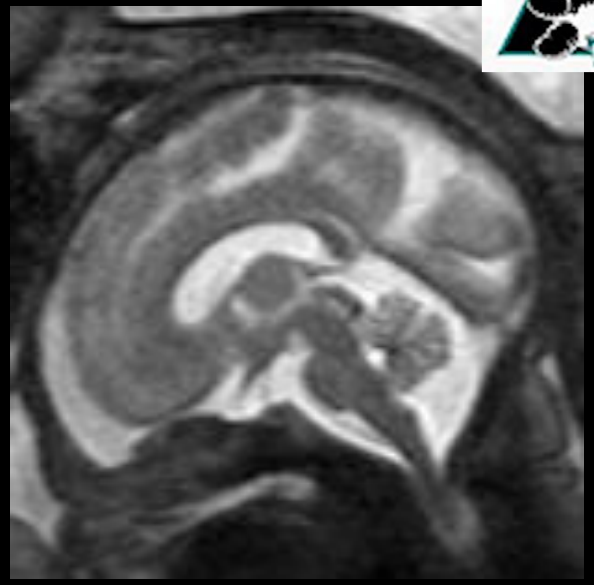
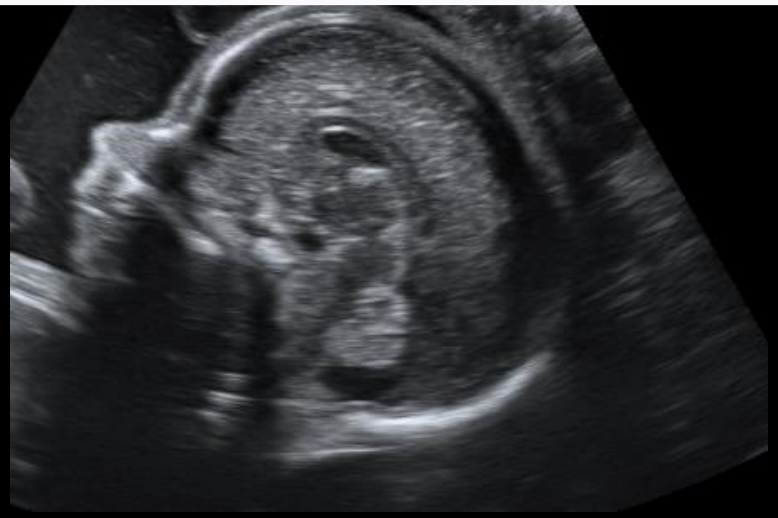
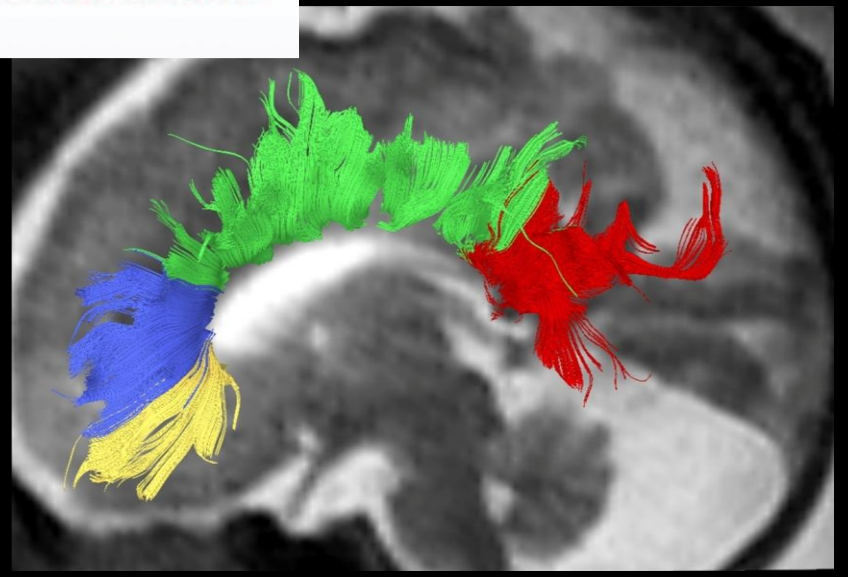
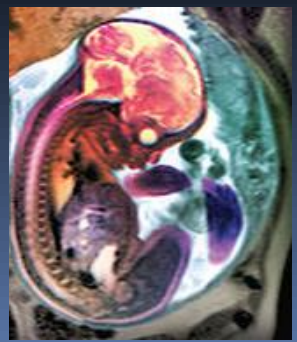
Panda SA
The Paediatric Neurology and Development Association of Southern Africa

Disorders of the Fetal Corpus Callosum

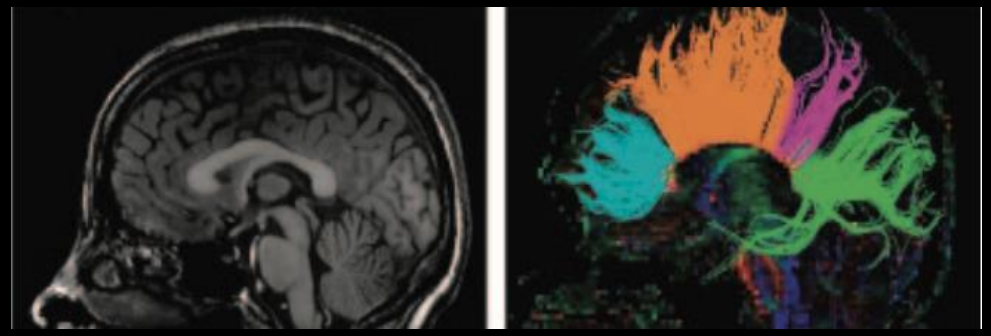
Tally Lerman-Sagie

Fetal Neurology Clinic, Wolfson Medical Center, Israel



Images courtesy of:
Gustavo Malinger, Zvi Leibovitz, Liat Ben-Sira, Catherine Garel, Gregor Kasprian, Efrat Hadi

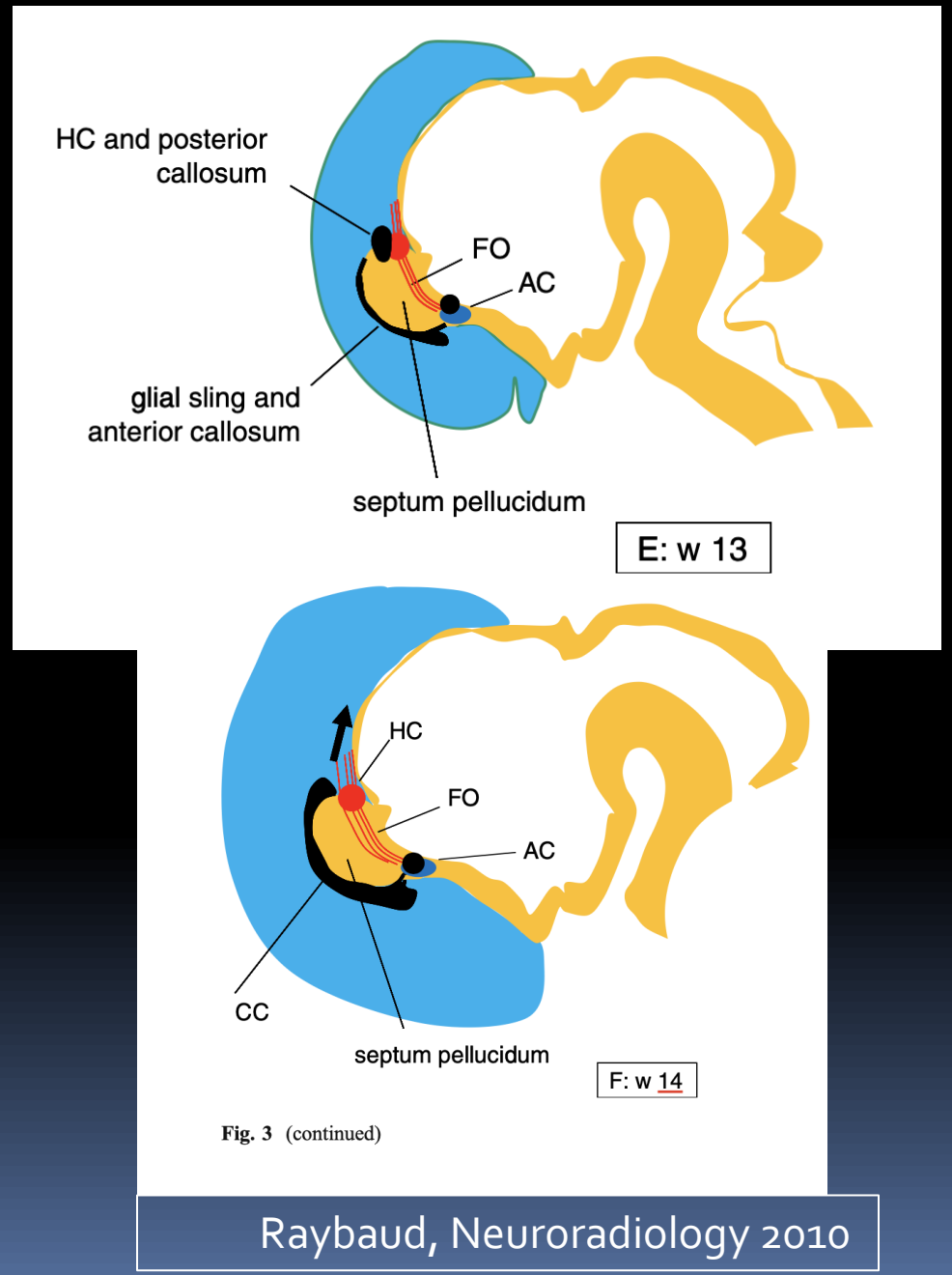
Introduction



- The CC is the largest commissure in the human brain
- Unique to placental mammals (facilitates long-distance integration within large brains)
- ~190 million axons
- Allows interhemispheric integration of sensory, motor and high-order cognitive information such as language and abstract reasoning
- All callosal fibers are present at birth
- Functional connectivity increases as these fibers myelinate from 4 postnatal months into young adulthood

Corpus Callosum Development

- Pioneer fibers that form the anterior CC begin to cross by 14 W GA
- The splenium develops separately from fibers joining and expanding the hippocampal commissure, and later fuses with the anterior CC
- From then on, the anterior CC grows pushing the splenium dorsally
- All structural parts of the human CC are formed by 18 w GA

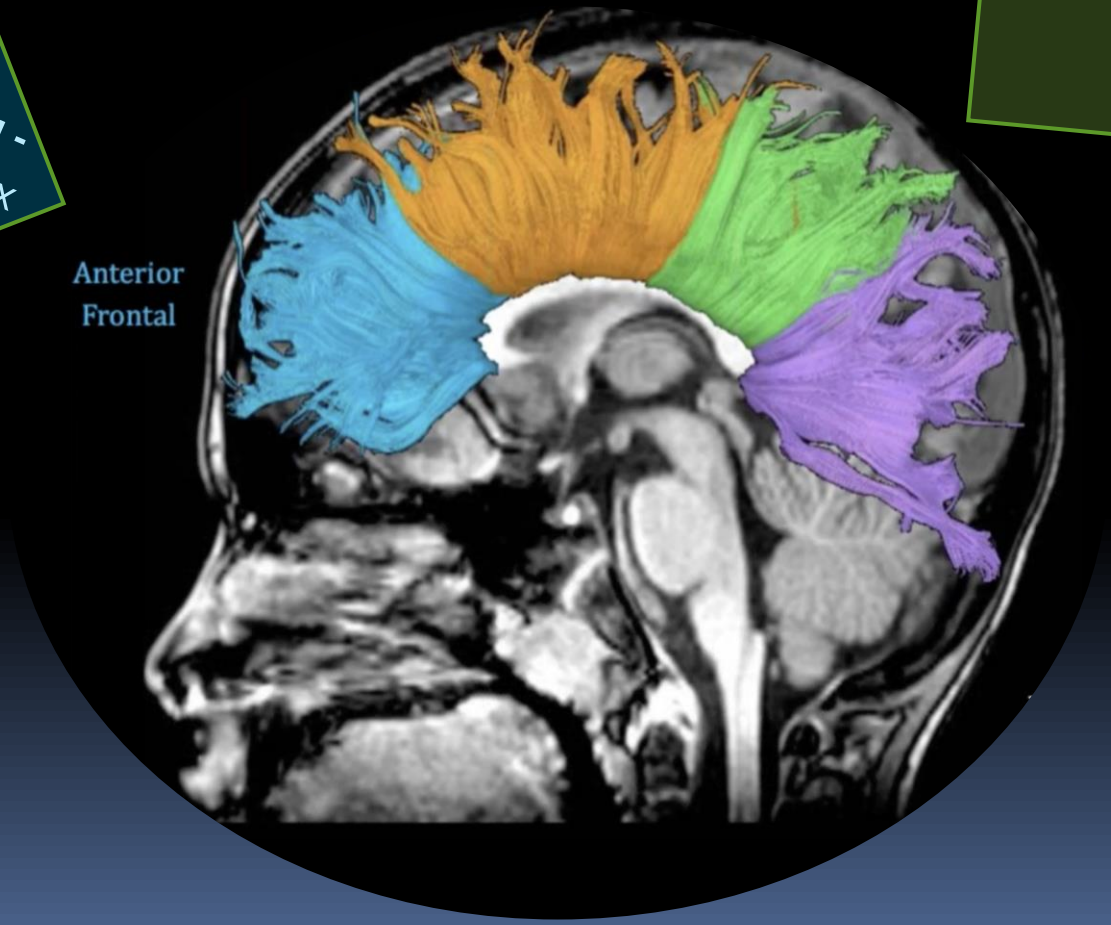


Raybaud, Neuroradiology 2010

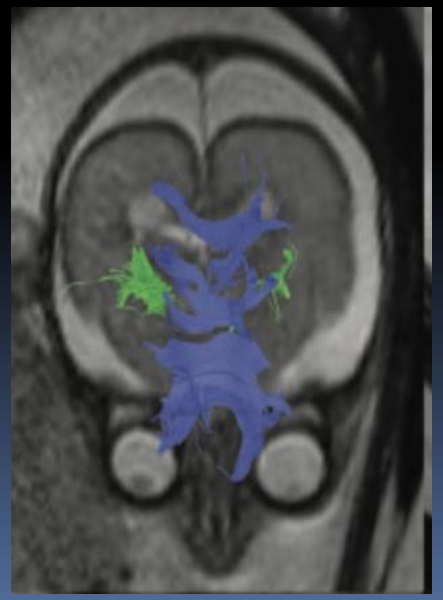
Ant. Body - Premotor
Posterior body -
Primary Motor cortex

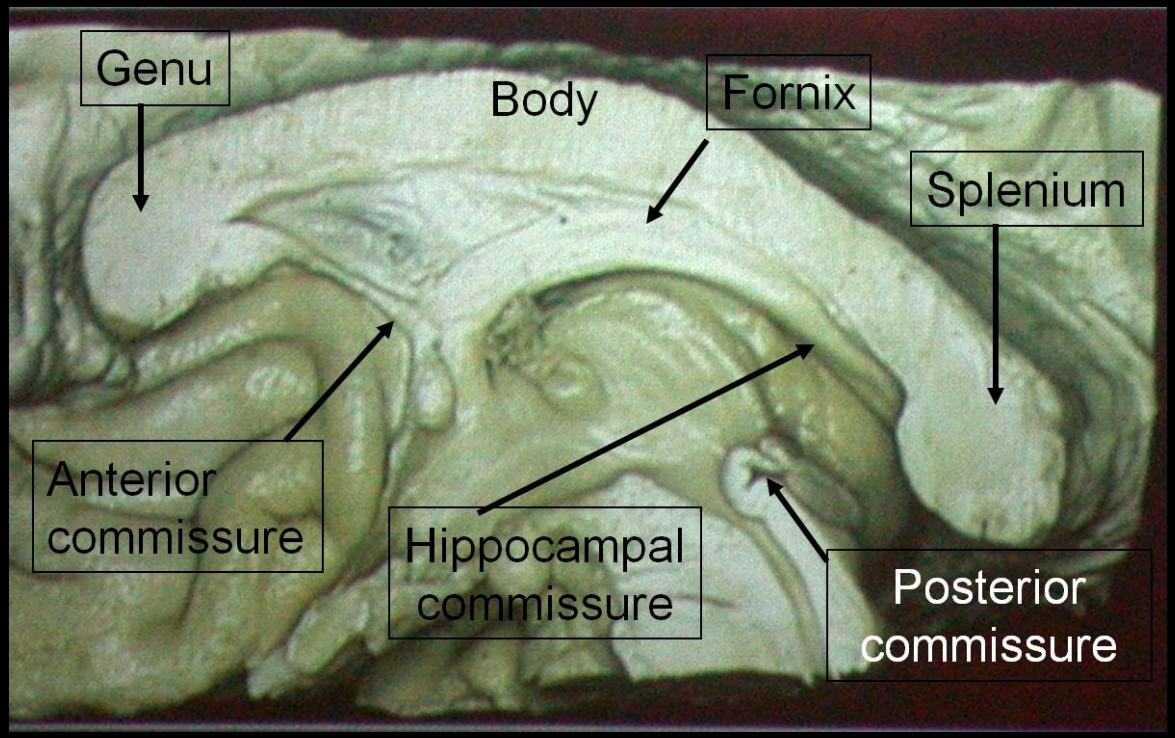
Rostrum & Genu -
Prefrontal cortex

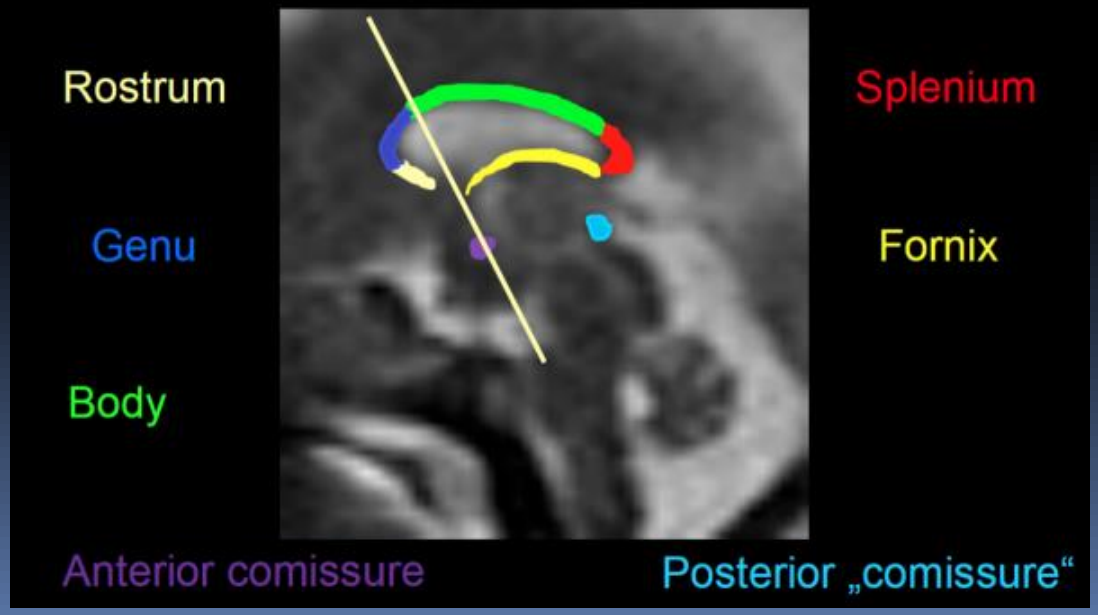
Isthmus -
Sensory, Motor, primary auditory cortex

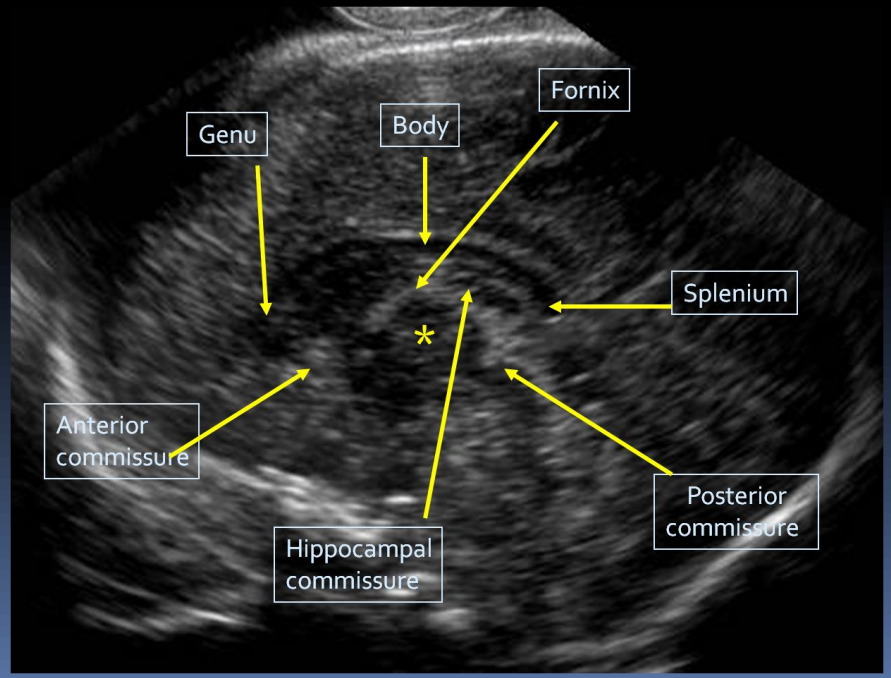


Splenium
primary visual (calcarine) cortex
Parietal, Temporal & occipital lobe



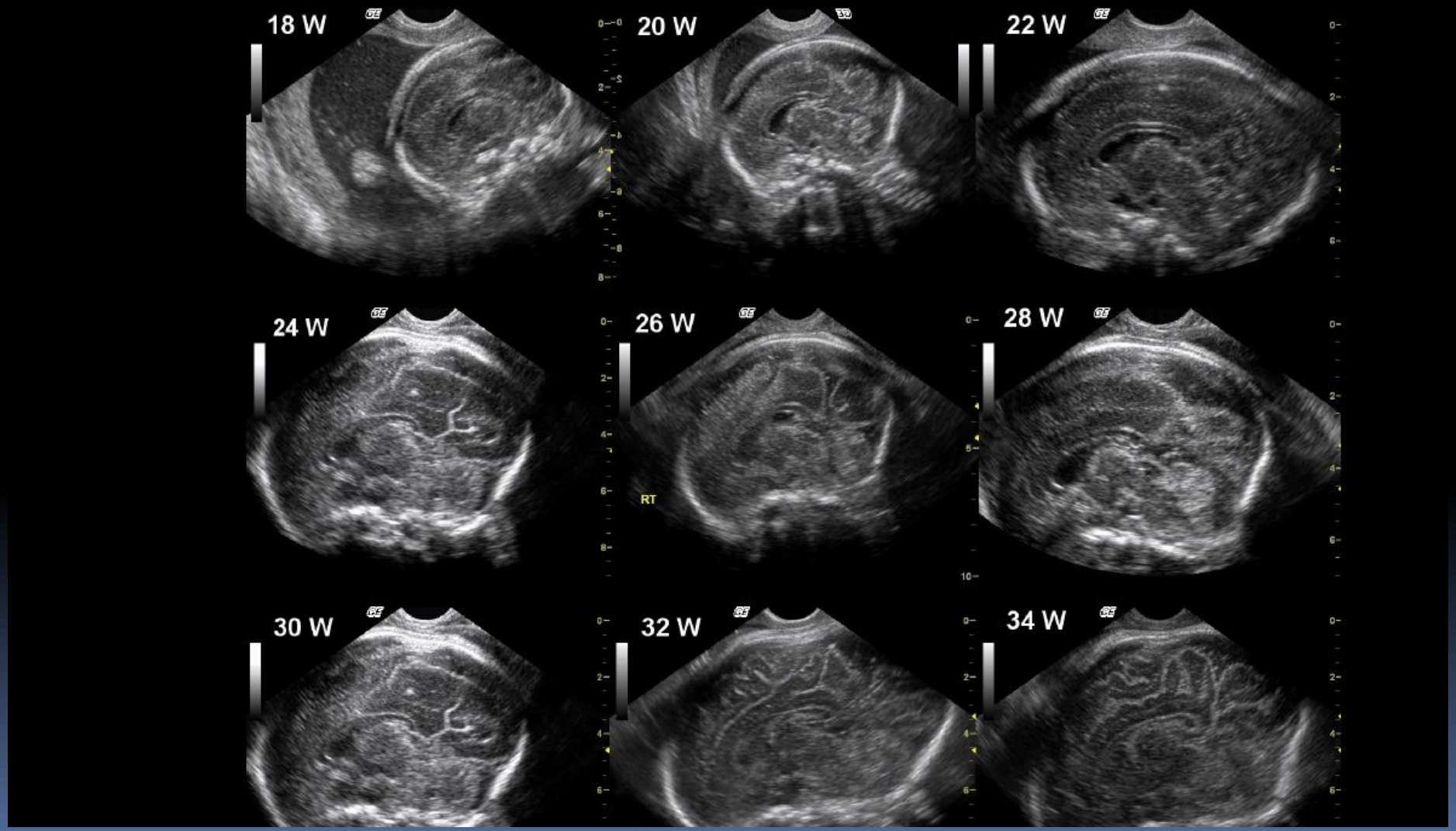

Genu
Body
Fornix
Splenium
Anterior commissure
Hippocampal commissure
Posterior commissure


Rostrum
Genu
Body
Anterior comissure
Splenium
Fornix
Posterior „comissure“


Genu
Body
Fornix
Splenium
*
Anterior commissure
Hippocampal commissure
Posterior commissure

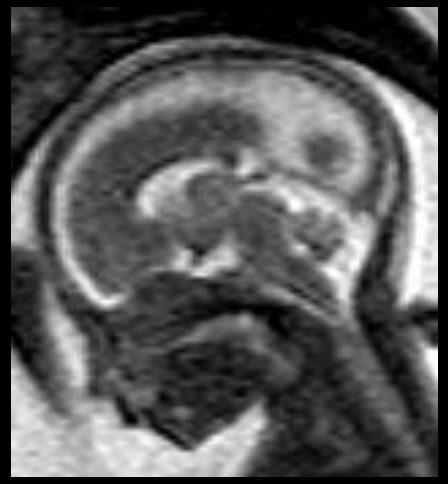
Normal development

US Anatomy

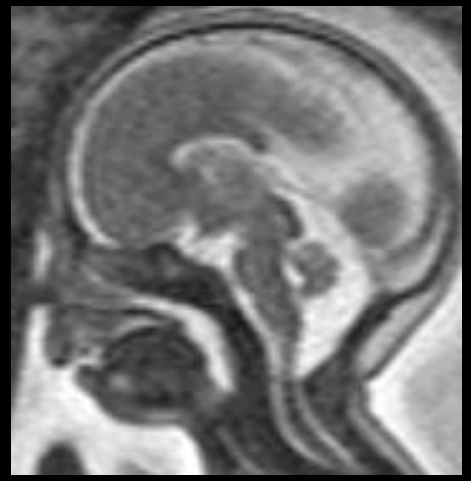


Normal development

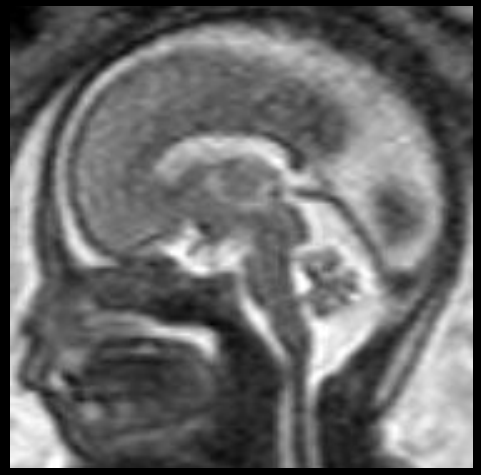
MRI Anatomy



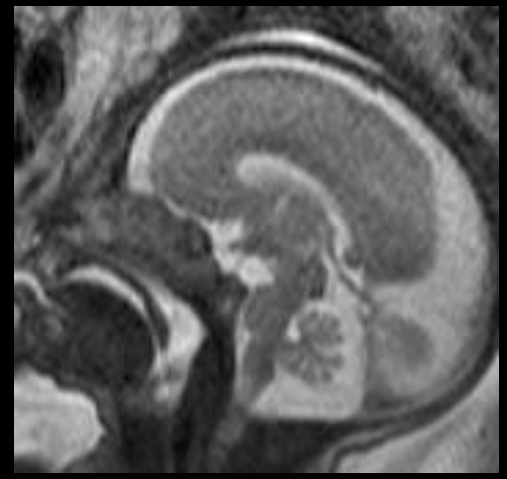
GW 20



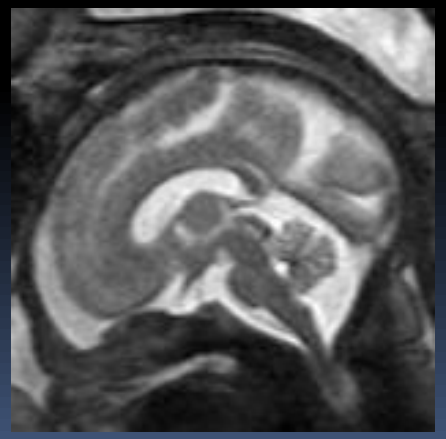
GW 22



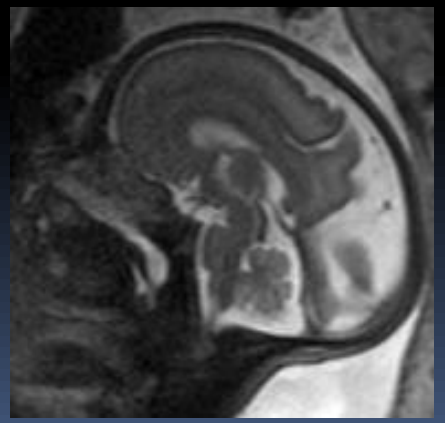
GW 24



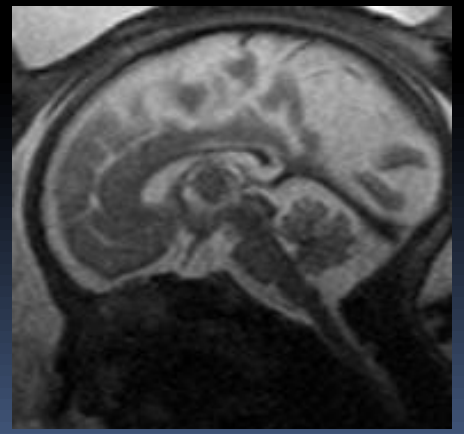
GW 27



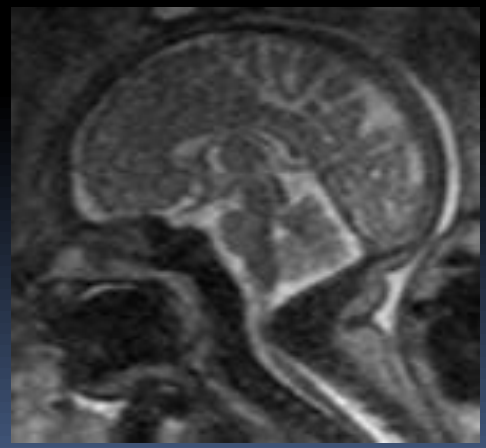
GW 29



GW 32



GW 34



GW 37

Normal Postnatal Development of the Corpus Callosum

- The corpus callosum changes dramatically during childhood and adolescence
- Alternating phases of callosal growth and shrinkage
- During the first month of life the corpus callosum is uniformly thin
- During the second month, a variable spurt of growth occurs in the genu, followed by a similar period of rapid growth in the splenium between 4-6 months of age.
- The corpus callosum has an adult appearance on sagittal scans by about 8 months of age.

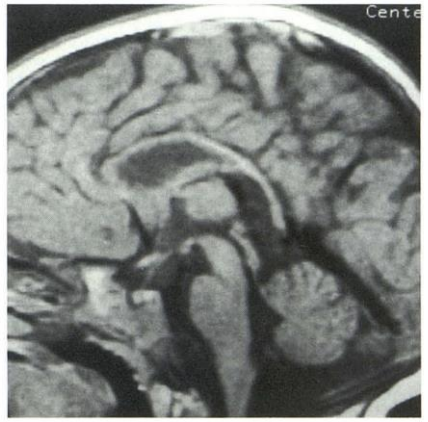


Fig. 3.—Midsagittal spin-echo image, 600/20, in 2-week-old neonate. At this age, the corpus callosum is thin and flat, without the normal bulbous enlargements at the genu and splenium.

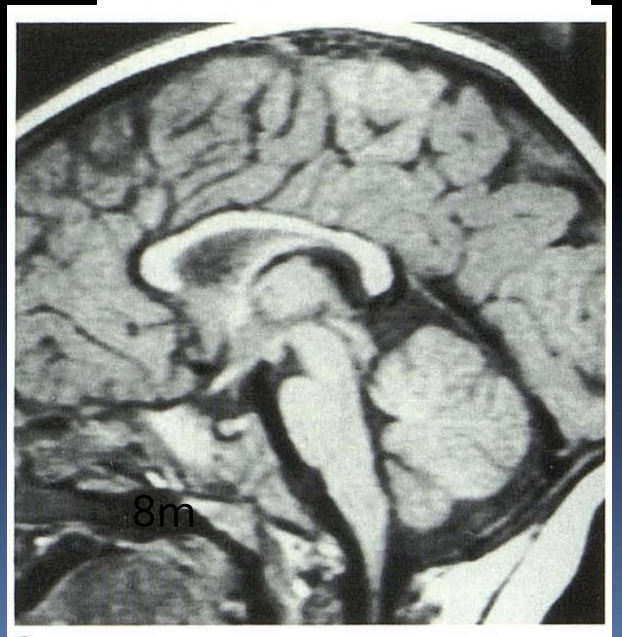


TABLE 1: Measurements of Corpus Callosum in Normal Postnatal Development

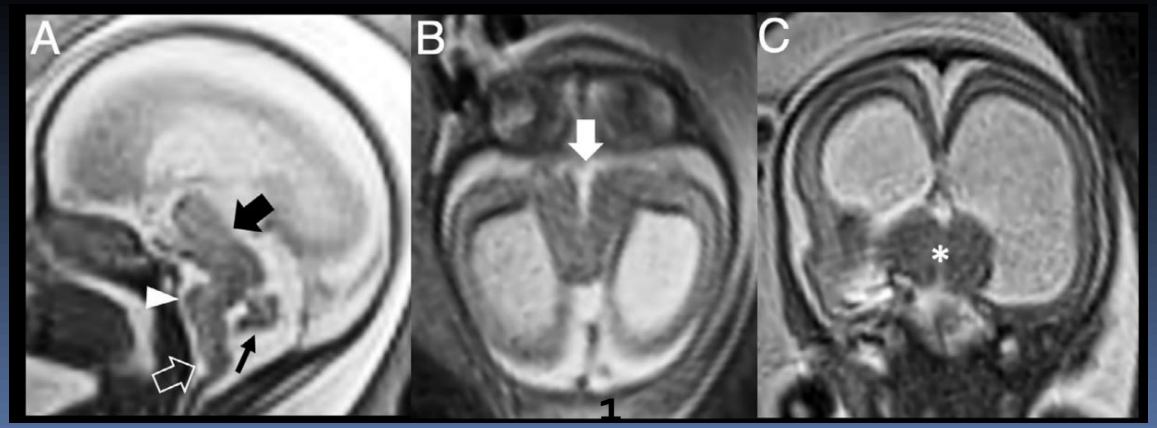
Age (months)	No. of Patients	Mean ± 1 SD (mm)				Callosum:Brain Ratio[b]
		Thickness			Length[a]	
		Genu	Midbody	Splenium		
0–2	12	5.1 ± 1.0	2.3 ± 0.5	3.7 ± 0.6	47.7 ± 2.8	0.395
2–4	18	5.0 ± 1.3	2.5 ± 0.5	4.5 ± 0.9	51.2 ± 4.5	0.398
4–6	7	7.0 ± 1.3	3.0 ± 0.8	5.8 ± 1.3	50.8 ± 3.4	0.394
6–8	7	6.3 ± 1.0	2.8 ± 0.4	6.6 ± 0.6	54.0 ± 0.8	0.400
8–10	8	7.7 ± 1.3	4.2 ± 1.0	7.6 ± 1.6	59.0 ± 8.2	0.388
10–12	11	7.8 ± 1.1	4.2 ± 0.8	8.3 ± 1.2	57.6 ± 4.9	0.392

(Barkovich & Kjos AJNR 1988)

Disorders of the Corpus Callosum

- Among the most common CNS malformations diagnosed during the fetal period
- Often associated with other CNS and extra-CNS anomalies, aneuploidies and genetic syndromes
- Frequently associated with neuronal migration disorders
- Carries a high risk of adverse neurodevelopmental outcome
- The individual outcome in children with isolated DCC is difficult to predict
  → **Difficult parental counseling**

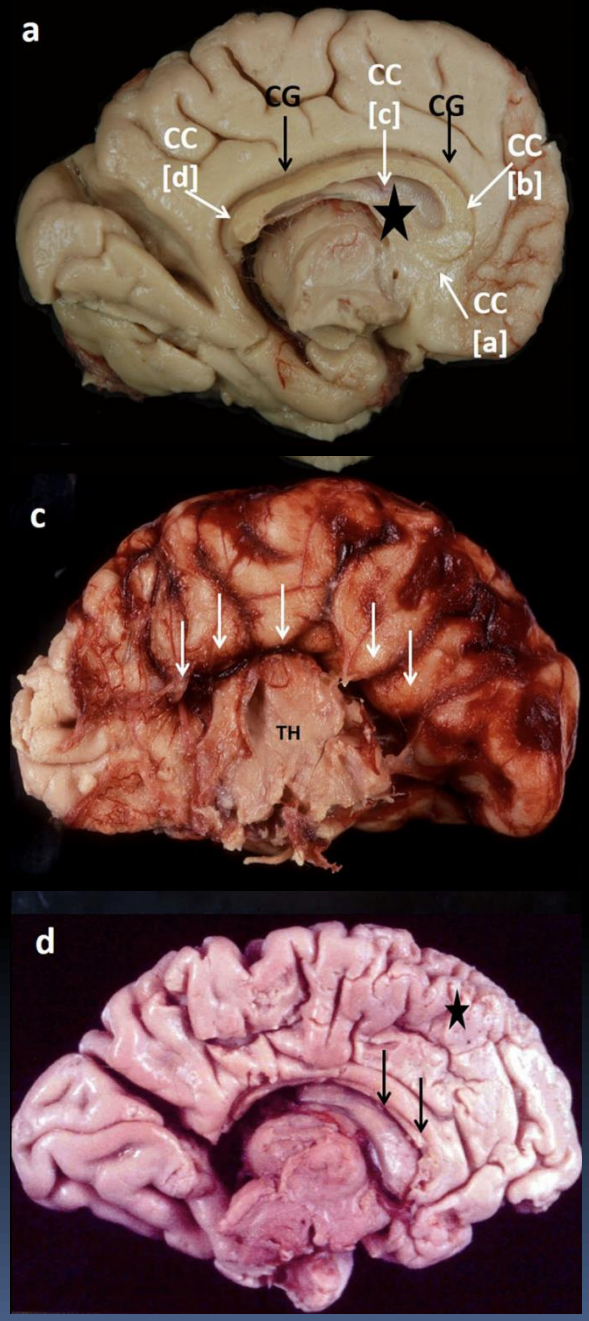
Typical MRI findings in X linked hydrocephalus d/t L1CAM mutation (Accogli 2021)



Definitions

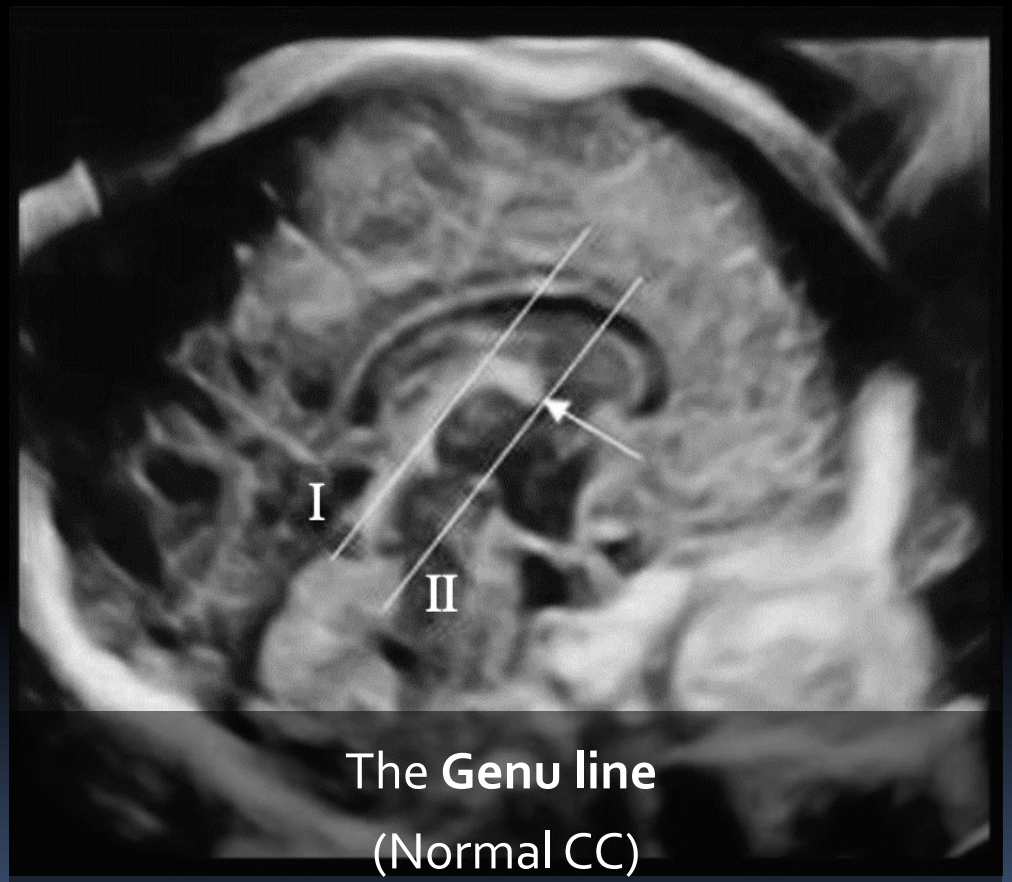
- Disorder of corpus callosum (DCC) any anomaly of the CC
- Complete ACC – Total absence of all 4 parts
- Partial ACC – A part, usually the splenium is absent. The remaining portion may also be abnormal
- Hypoplasia – CC normally formed but thin (short?)
- Dysgenesis – CC abnormally shaped or thick
- Isolated DCC-no associated systemic or CNS anomalies

Mahallati, **Heterogeneity in defining fetal corpus callosal pathology**: systematic review, UOG 2021



Kidron 2016

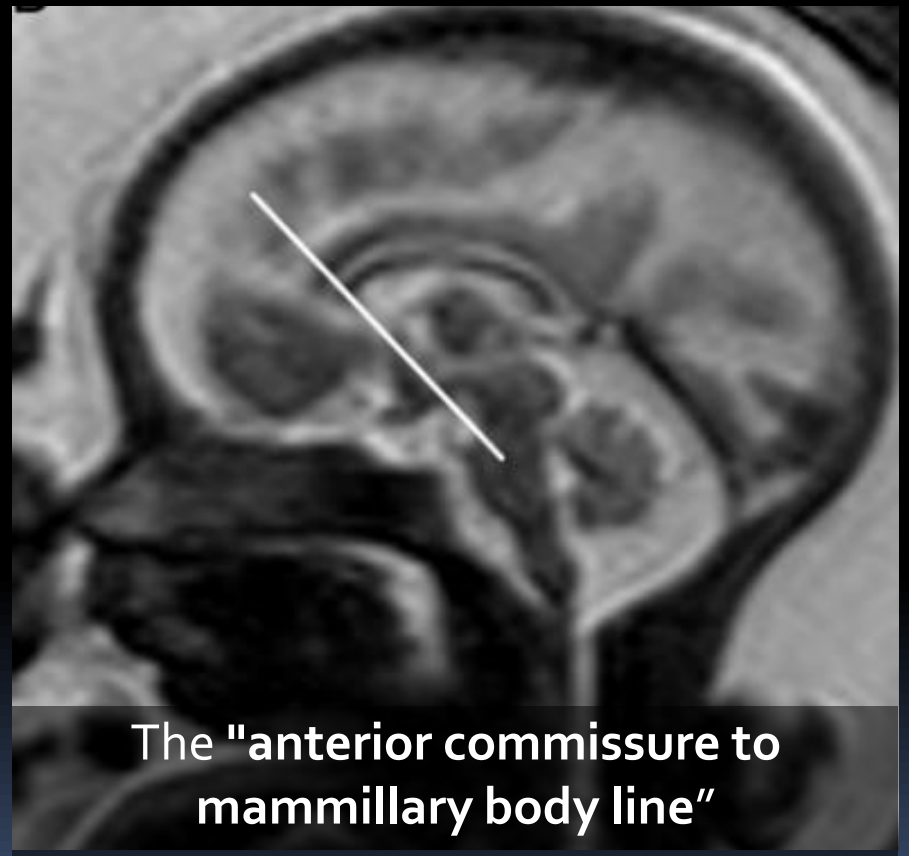
Morphologic Evaluation of the Corpus Callosum



The **Genu line**

(Normal CC)

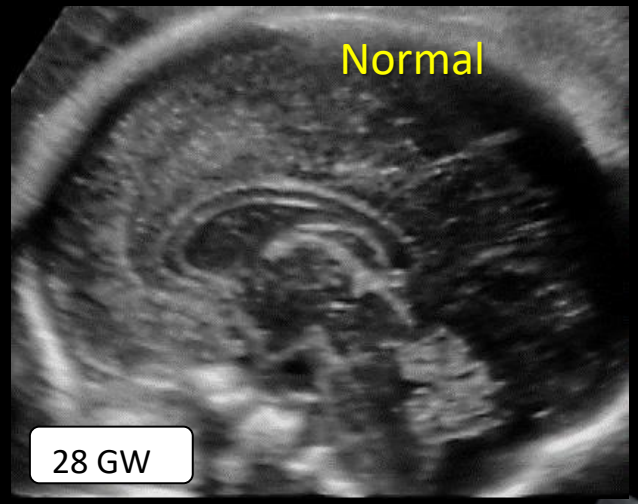
Pashaj 2013

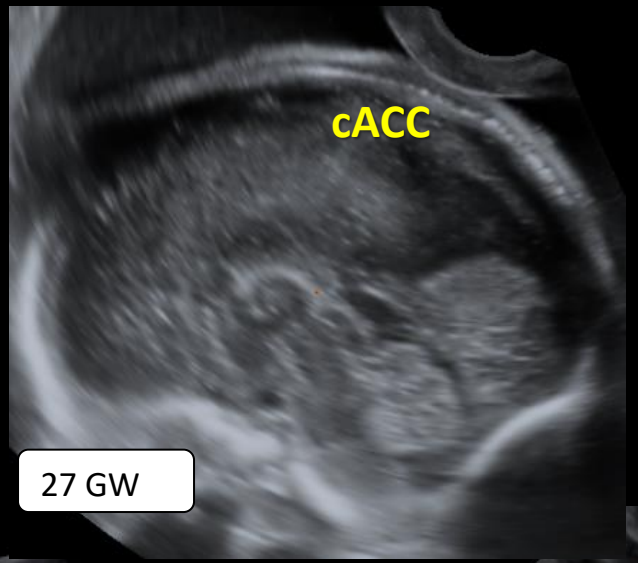


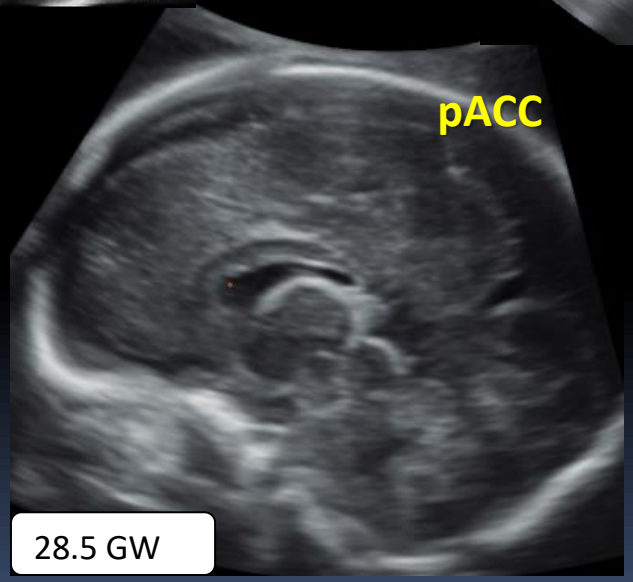
The **"anterior commissure to mammillary body line"**

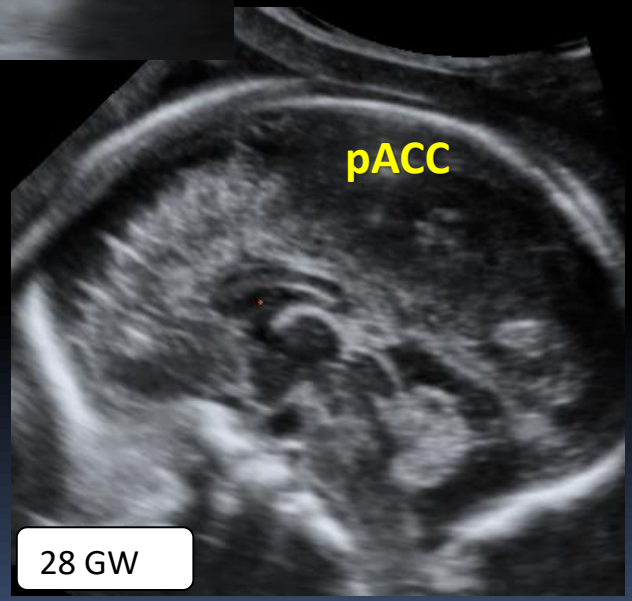
(Short CC, Missing anterior part)

Bartholmot 2021


Normal
28 GW

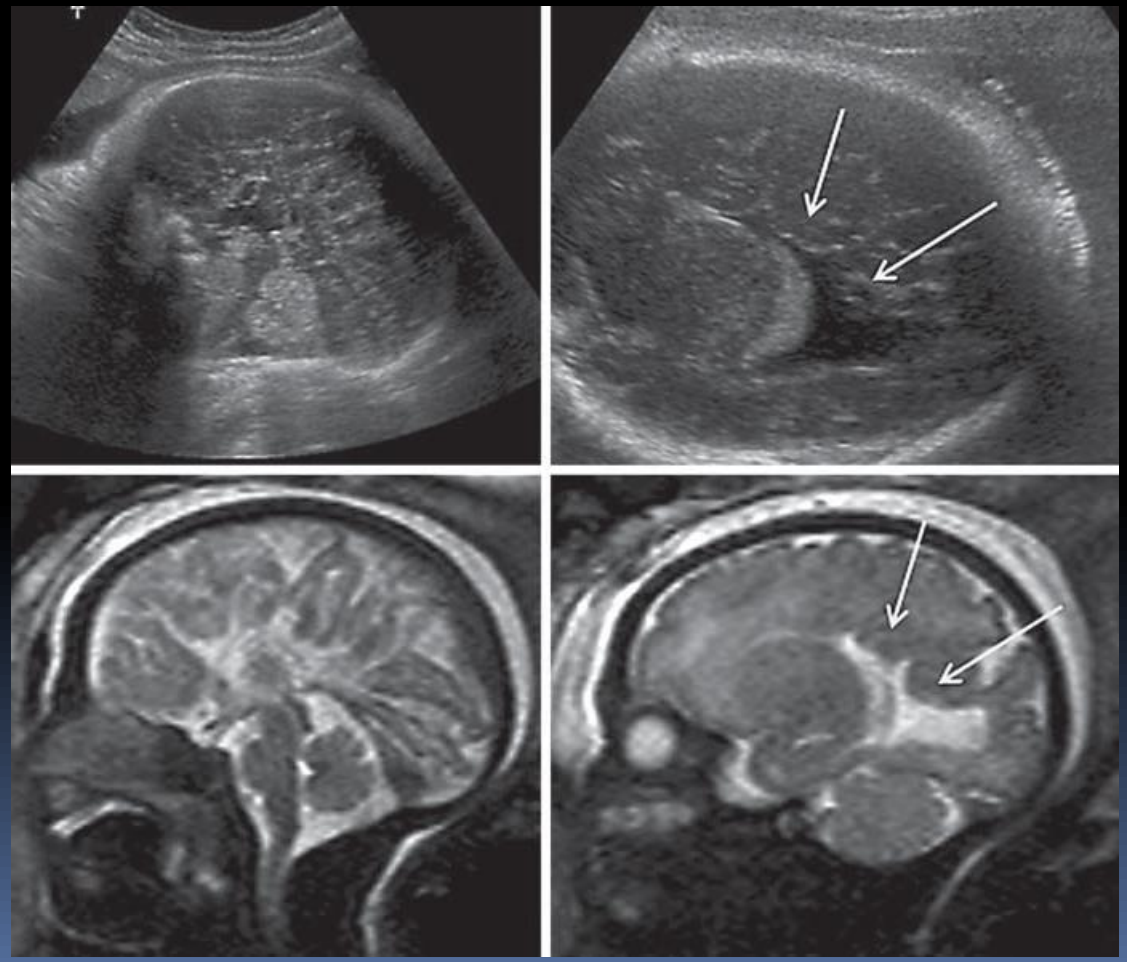

cACC
27 GW


pACC
28.5 GW


pACC
28 GW

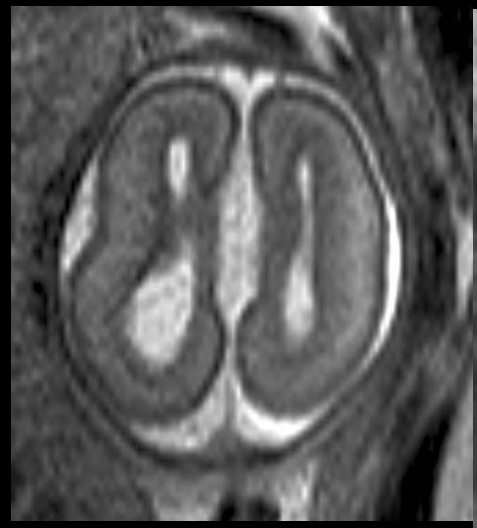
Diagnosis of Agenesis of the Corpus Callosum

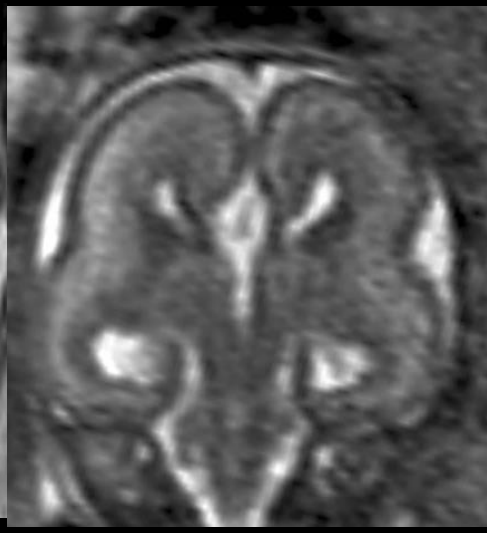
- Direct sign-No visualization of CC in the midline

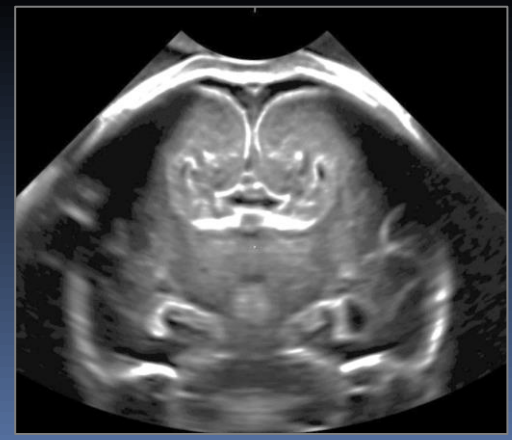


Diagnosis of Agenesis of the Corpus Callosum

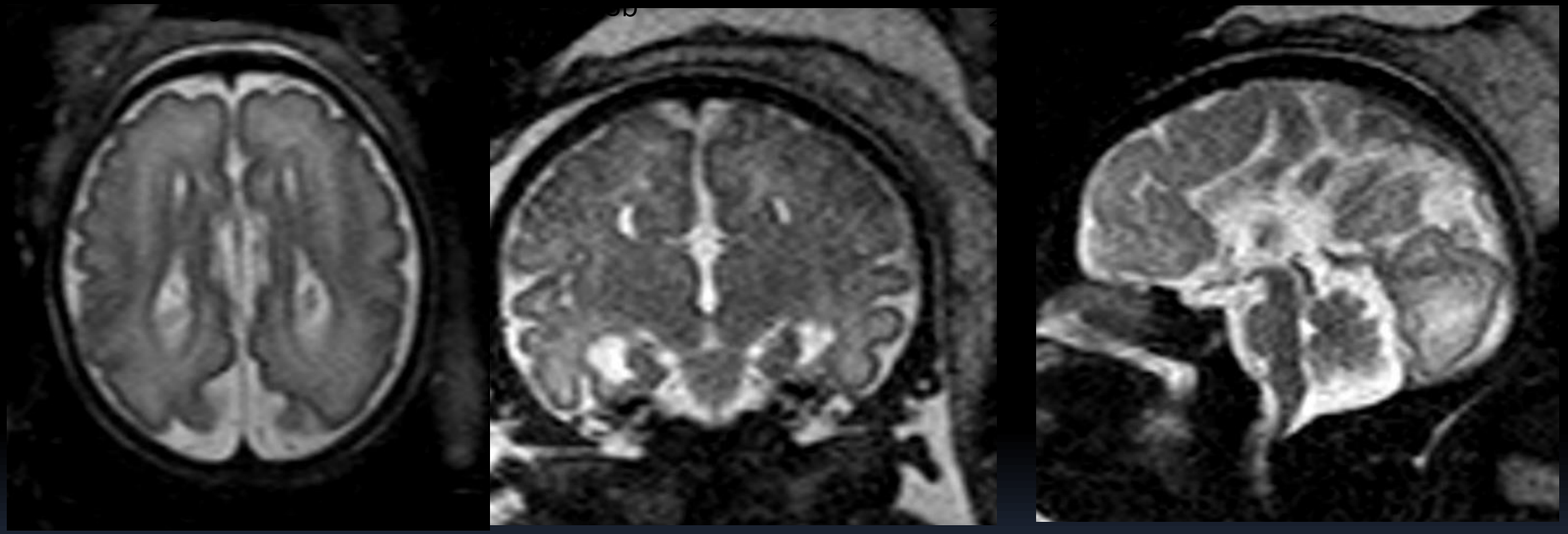
- Indirect findings:
  - Absent CSP
  - Upward displacement of the third ventricle
  - Lateral displacement of the lateral ventricles
  - Comma-shaped or “buffalo horn” appearance of the frontal horns
  - Parallel ventricles with drop like appearance-colpocephaly
  - Radial sulci on the internal aspect of the hemispheres





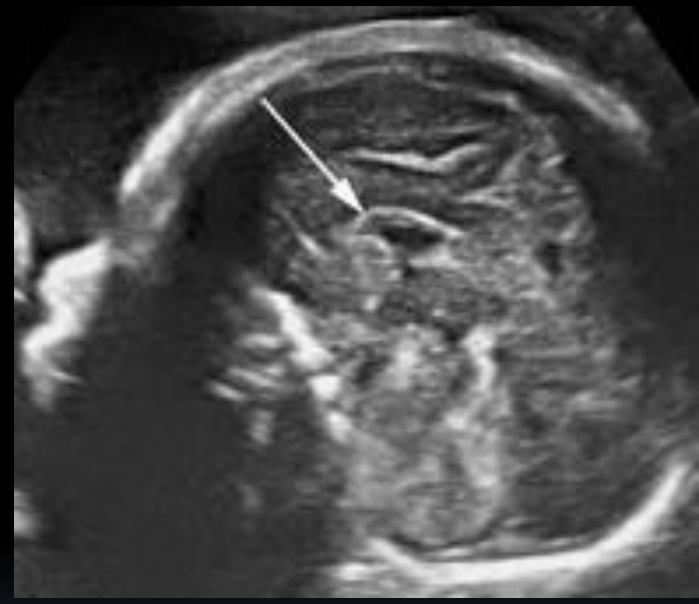


Complete Agenesis of CC

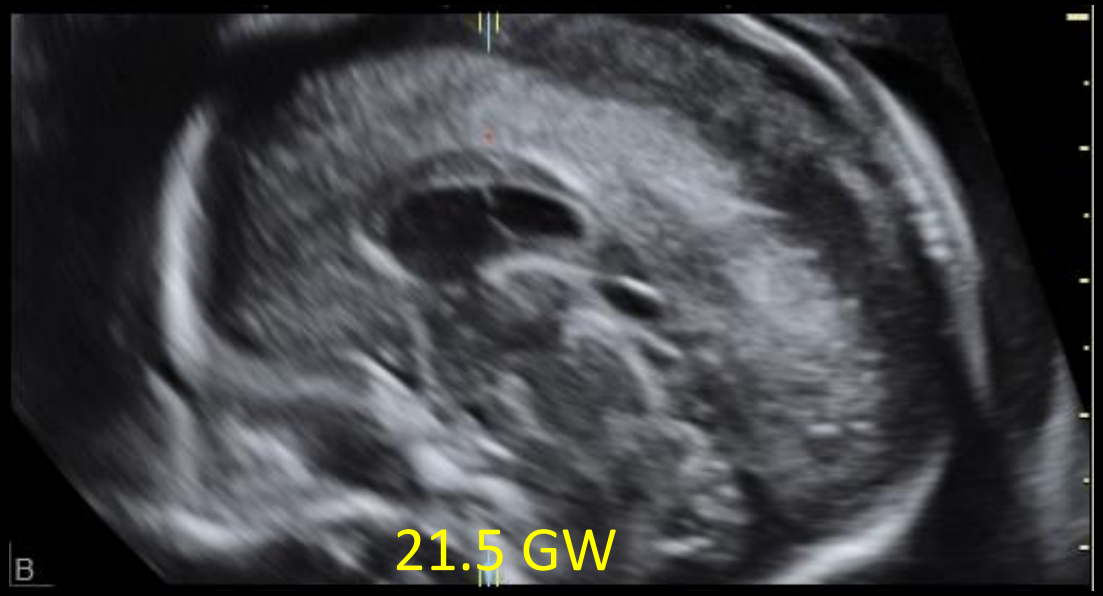


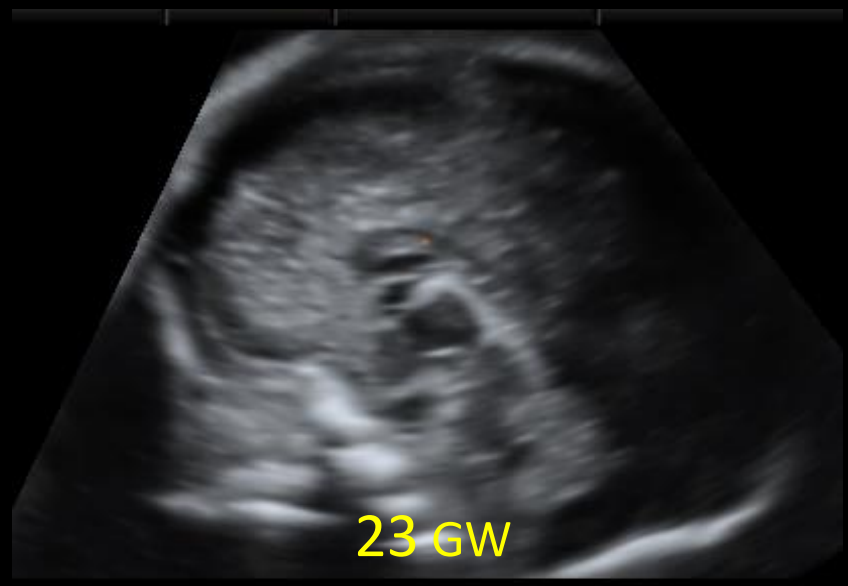
Partial Agenesis of CC

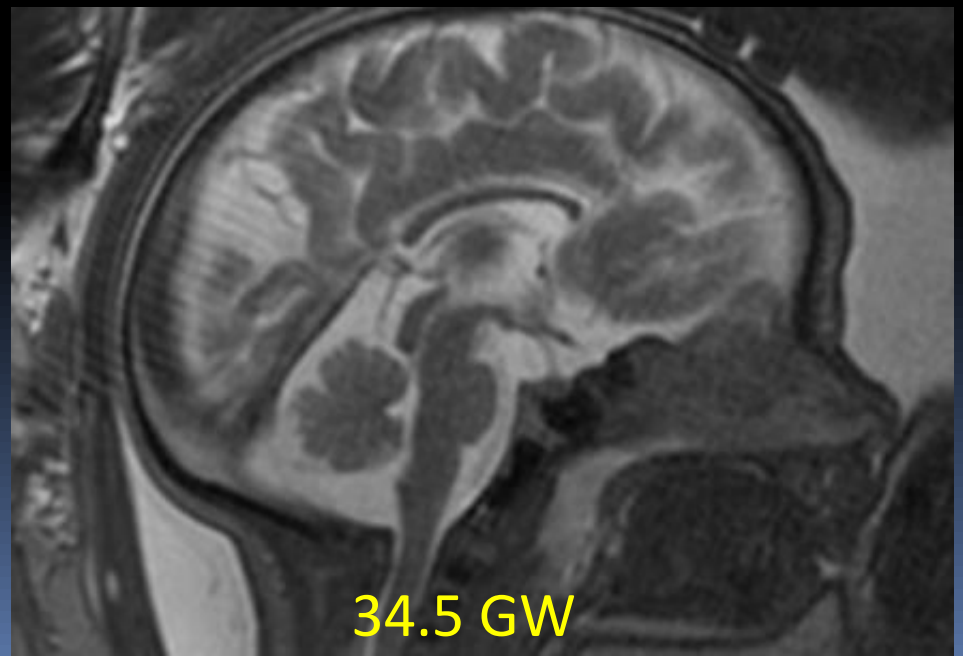
- A part of the CC is missing
- Indirect signs are seen only when the agenesis is extensive
- Different parts may be missing
- Most frequently lack of the splenium
- Can be associated with agenesis of genu and rostrum



Partial Agenesis CC







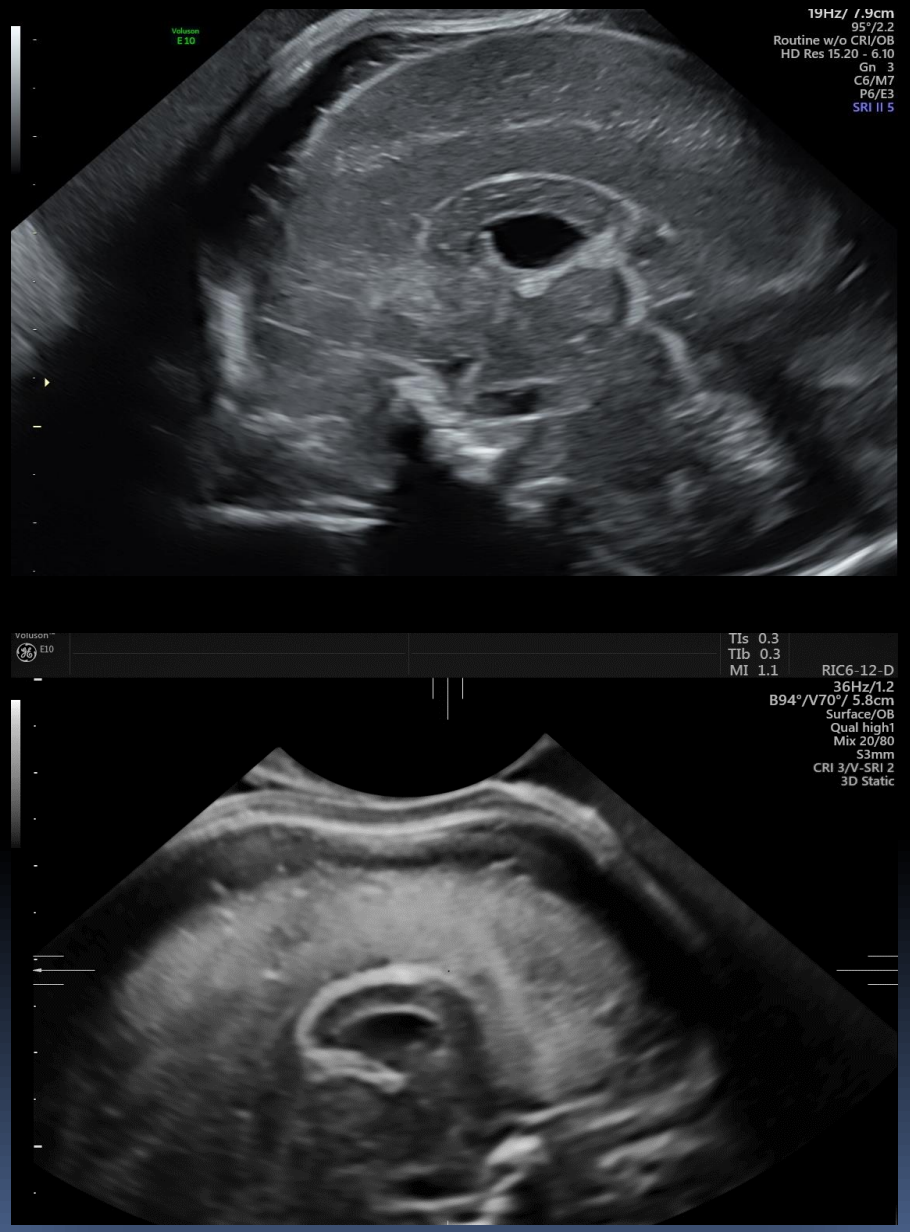
Dysgenesis of Corpus callosum

- Thick CC
- Lipoma of CC
- Interhemispheric cyst

Thick Corpus Callosum

- Mostly related to genetic syndromes with associated cortical malformation:
  - Megalencephaly (e.g neurofibromatosis or macrocephaly capillary malformation syndrome, MPPH-macrocephaly, polymicrogyria, polydactyly, hydrocephalus)
  - Microcephaly (Cohen syndrome)

Poor prognosis in 8 fetuses with associated CNS malformations

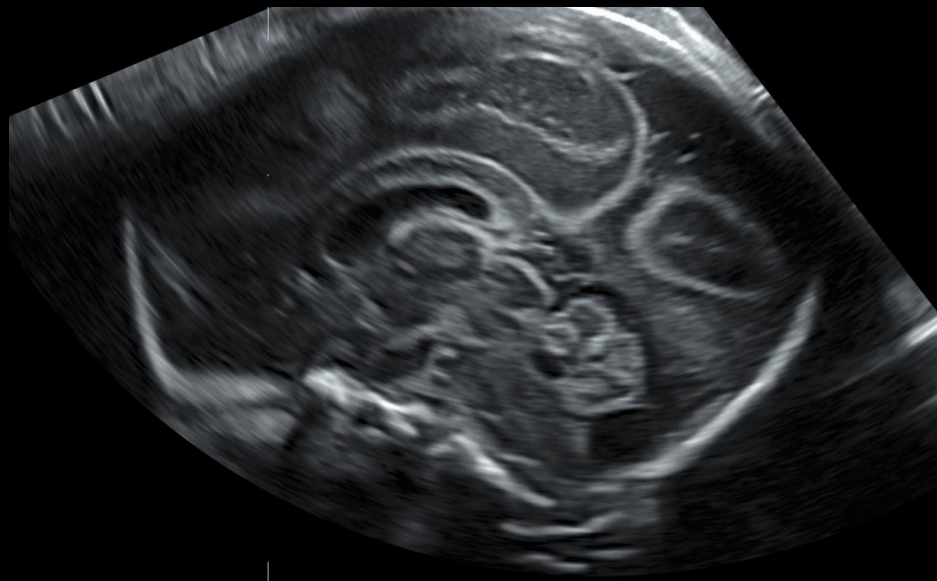


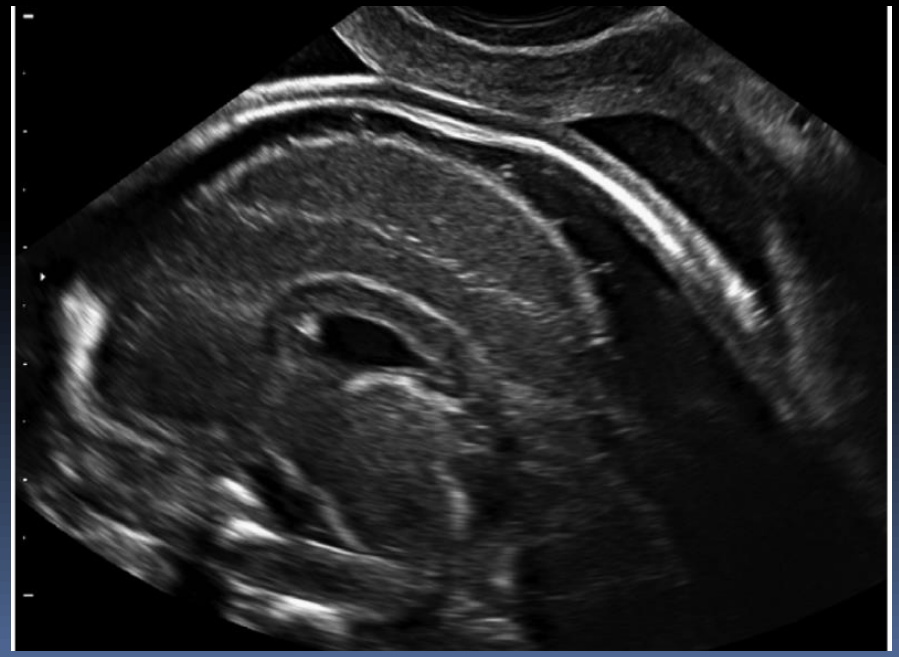
Lerman-Sagie, UOG 2009

Thick Corpus Callosum

- 9 isolated cases with generalized/ focal thickness
- In 6 short CC
- In 3 thickness asymmetry
- In 6 cases with complete follow up thickness normalized during the third trimester (4) or after birth (2)
- Normal ND at short term follow up

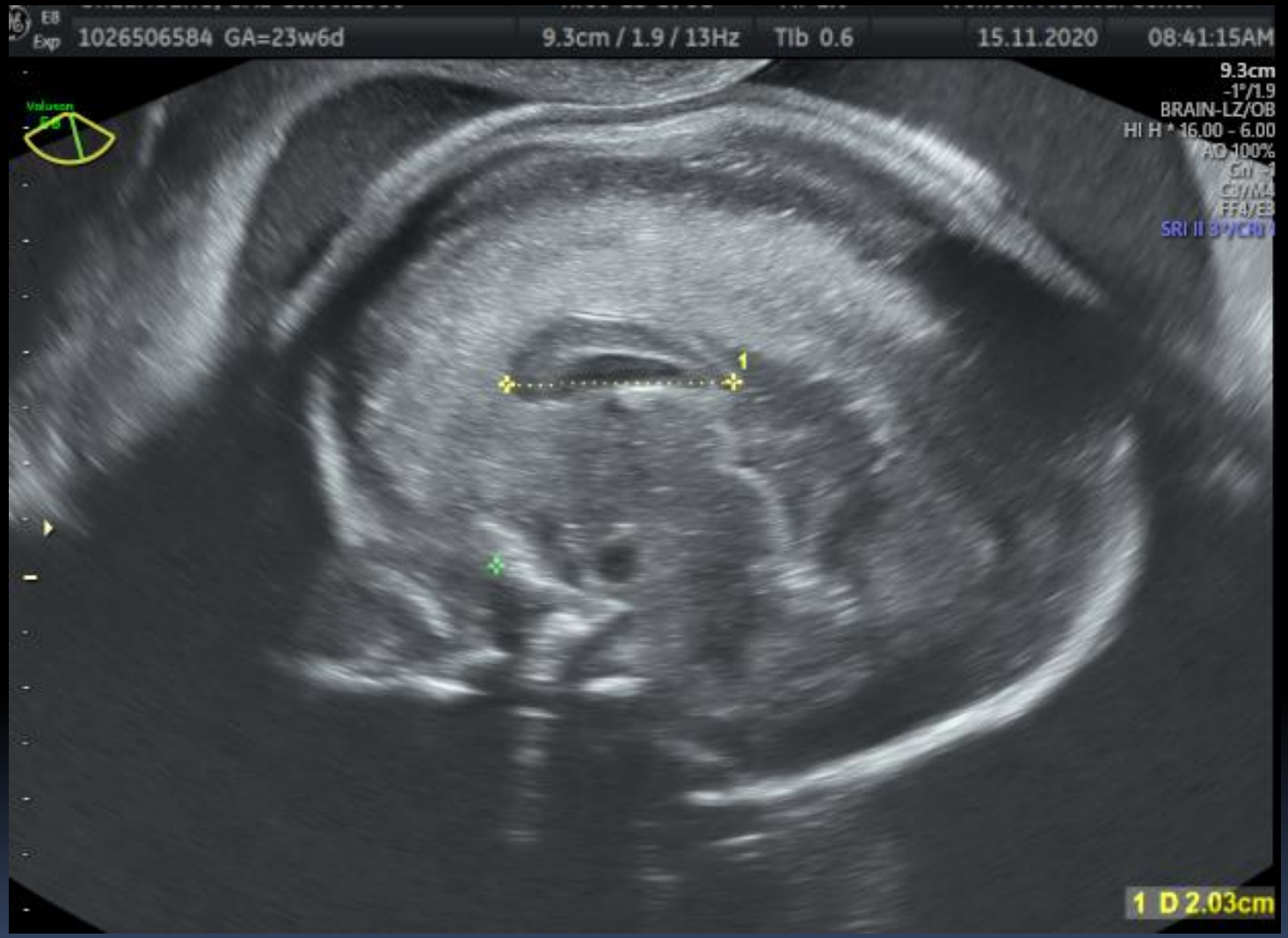
Thick CC in the second trimester can be a transient finding with normal ND outcome





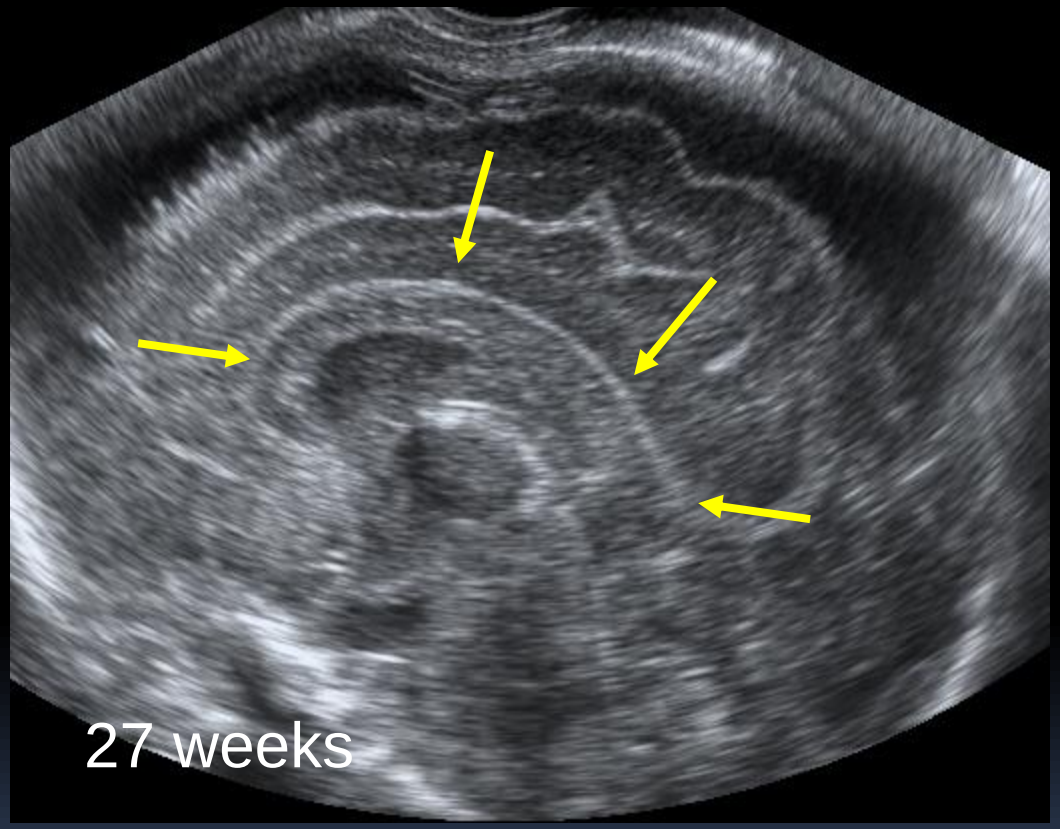
Shinar S, UOG 2016

Thick Corpus Callosum



24 GW short, thick, no rostrum, ARID1B
Coffin-Siris Syndrome

Thick, echogenic CC and macrocephaly

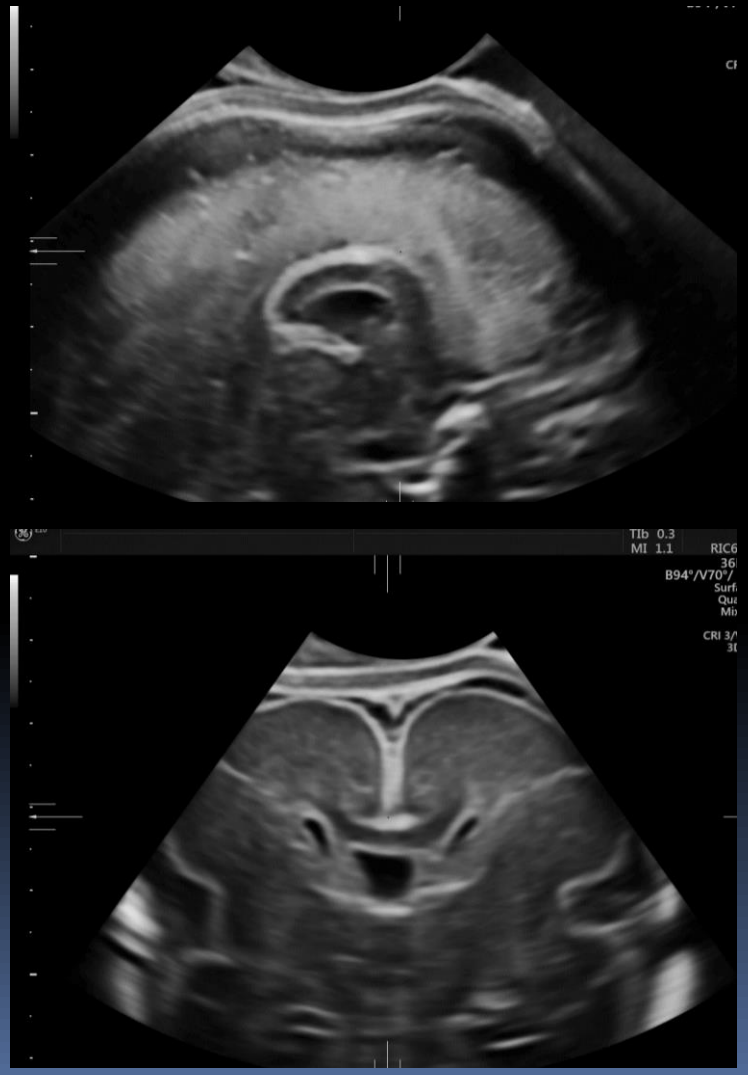


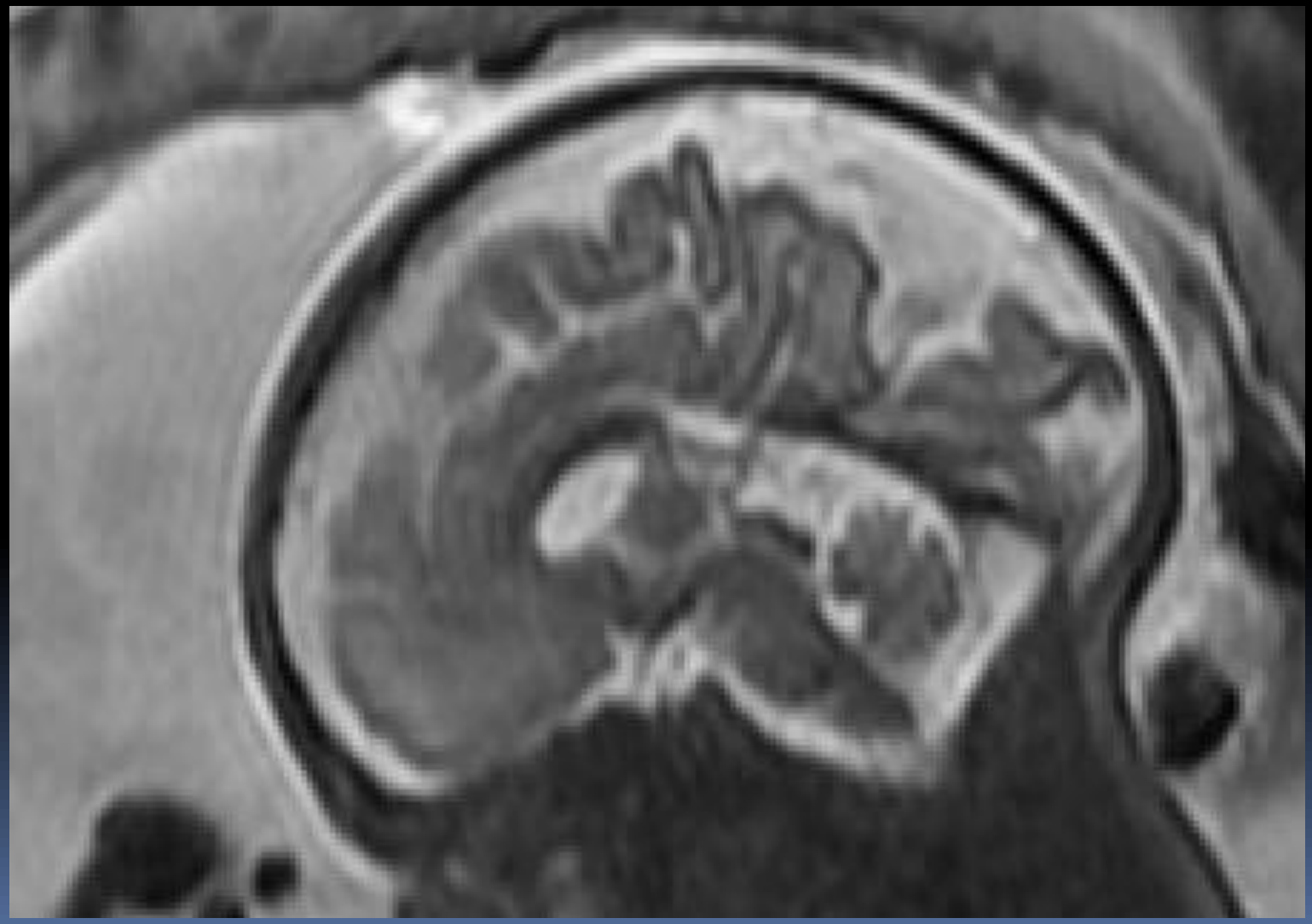
Macrocephaly Capillary Malformation Syndrome

Etiology of Thick CC

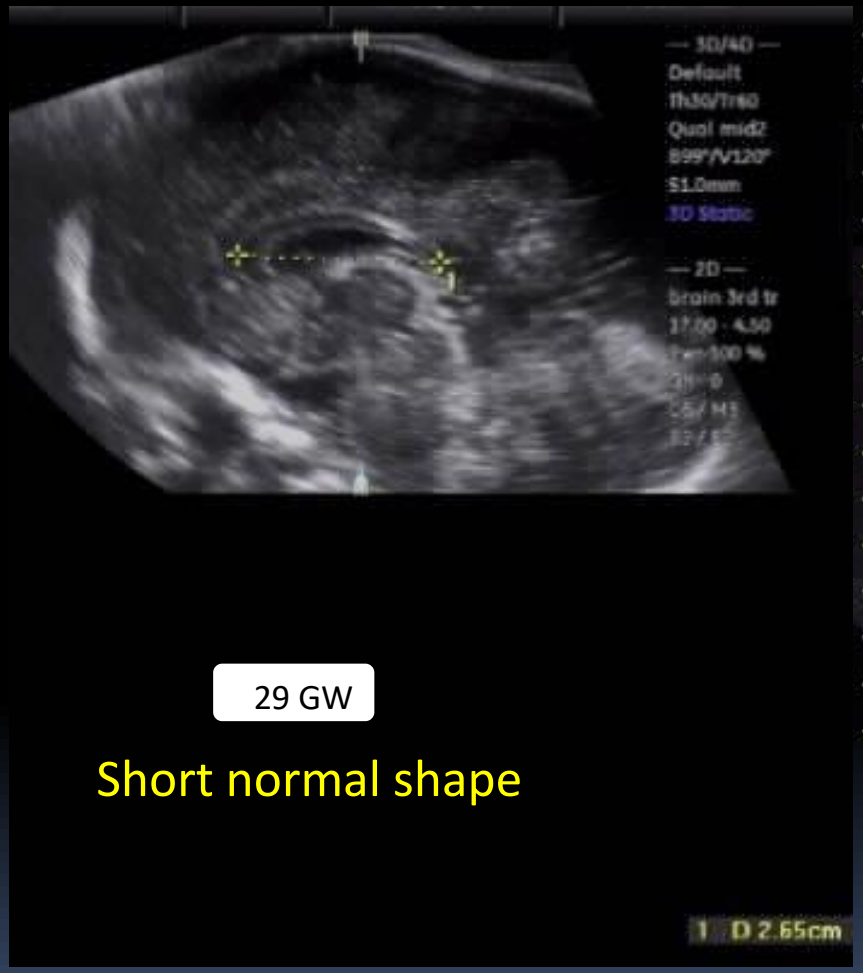
- Increased CC fibers
- Indusium Grisium overlying CC
- Hyperplastic fornix dorsalis -supracallosal longitudinal bundle
- Aberrant cingulate

Thick short CC-Pericallosal Lipoma



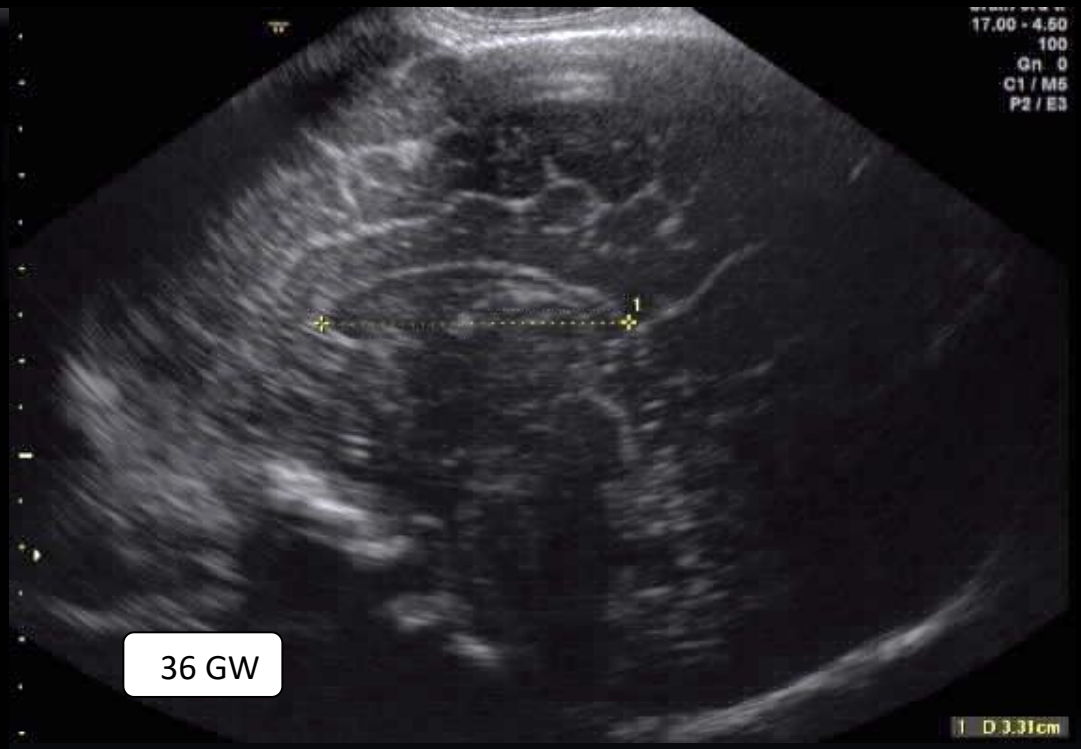


Pericallosal Lipoma



29 GW

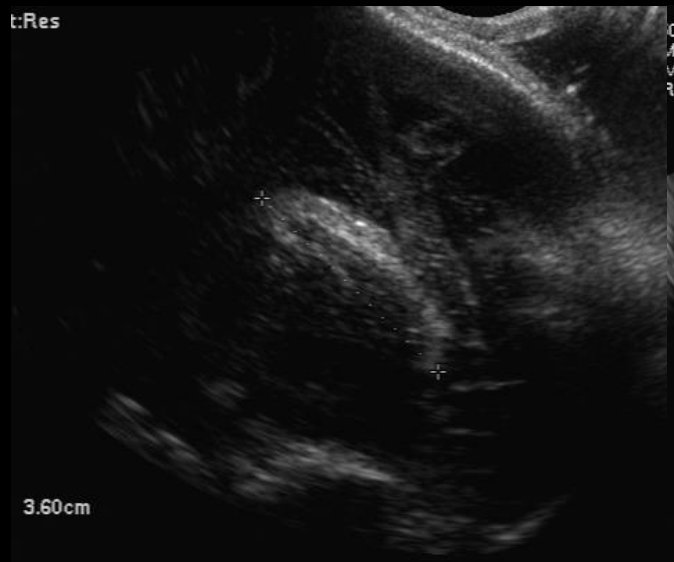
Short normal shape

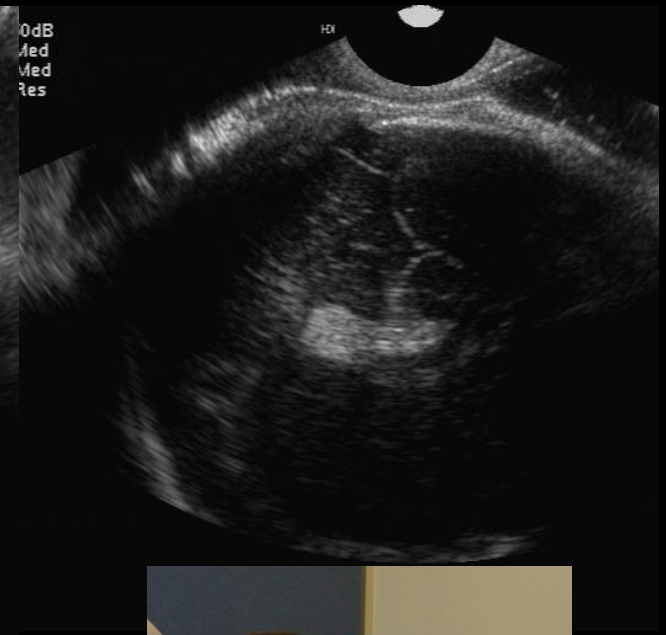


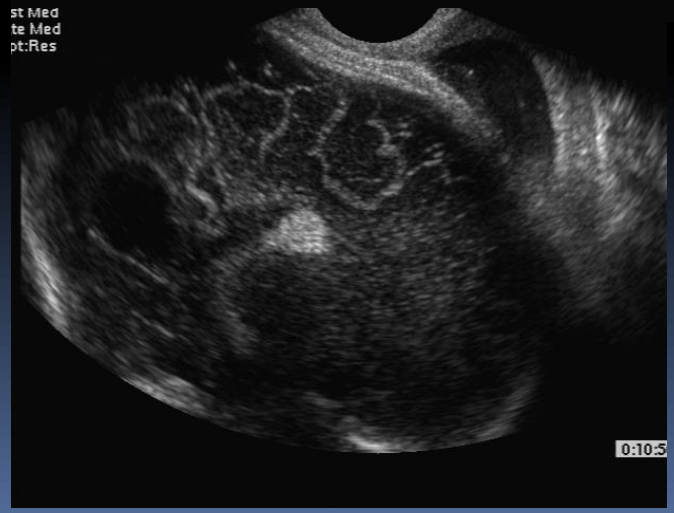
36 GW

Short and thin - complete CC. Normal development, father with short CC

CC lipoma with extension into the choroid plexus

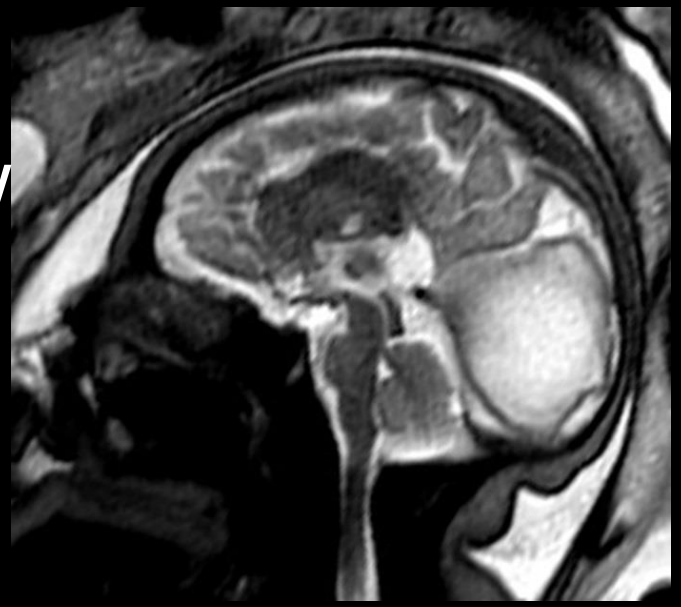




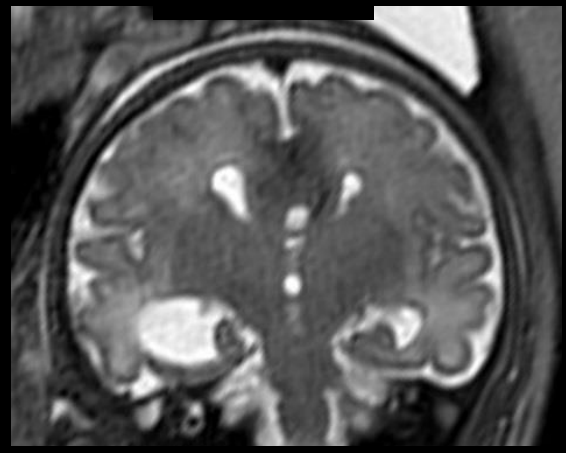


Interhemispheric/pericallosal lipoma

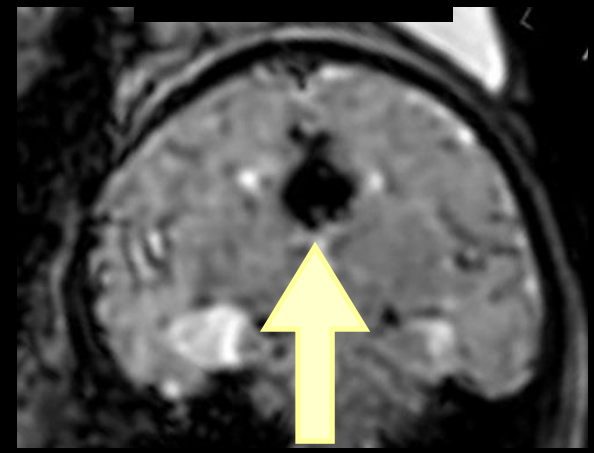
36GW

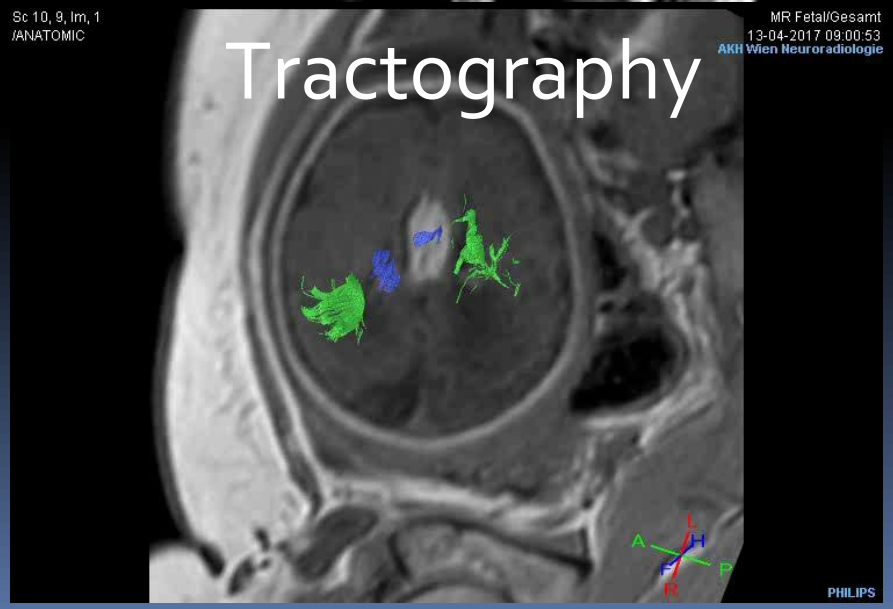


T2-w

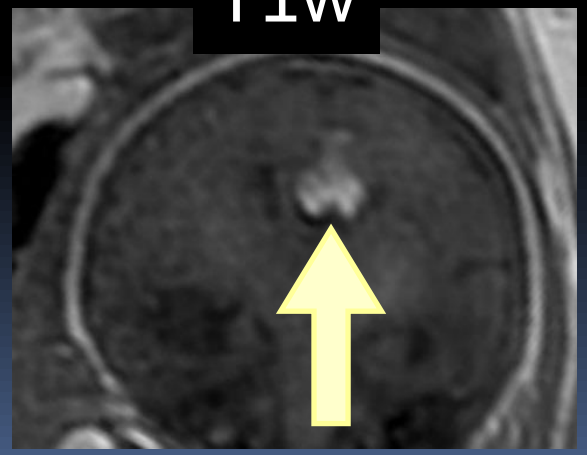


EPI/T2*

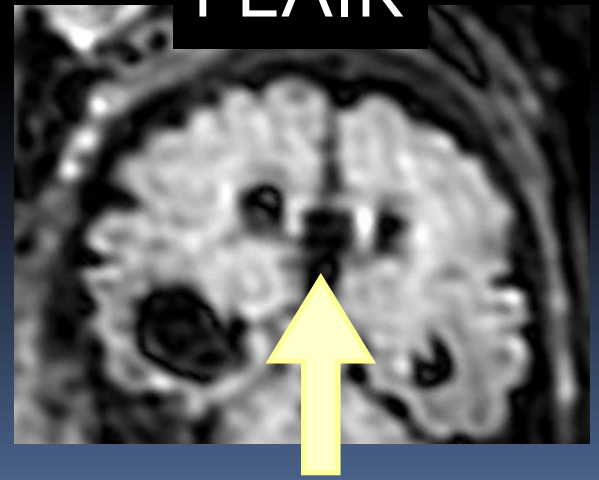




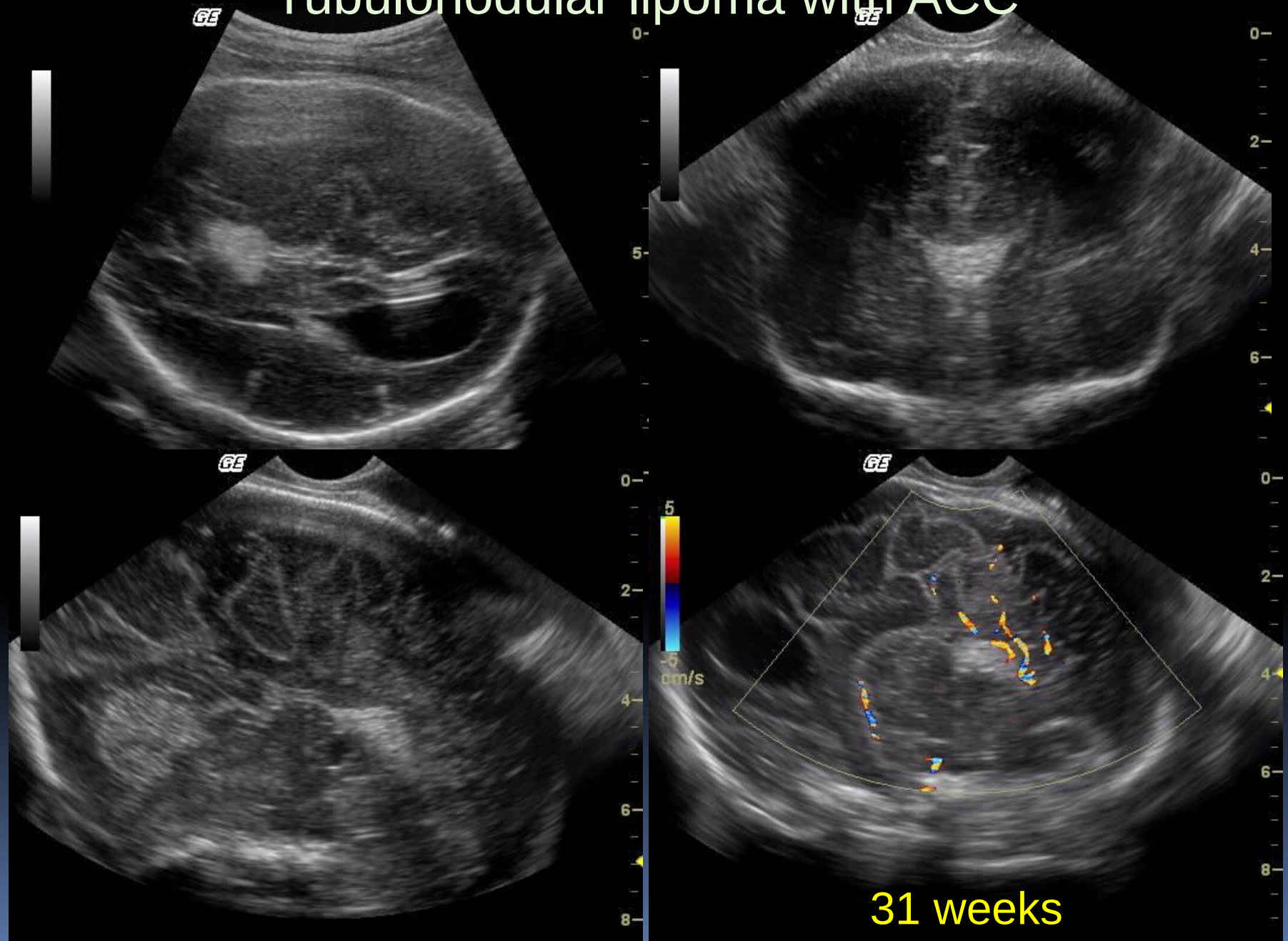
T1w



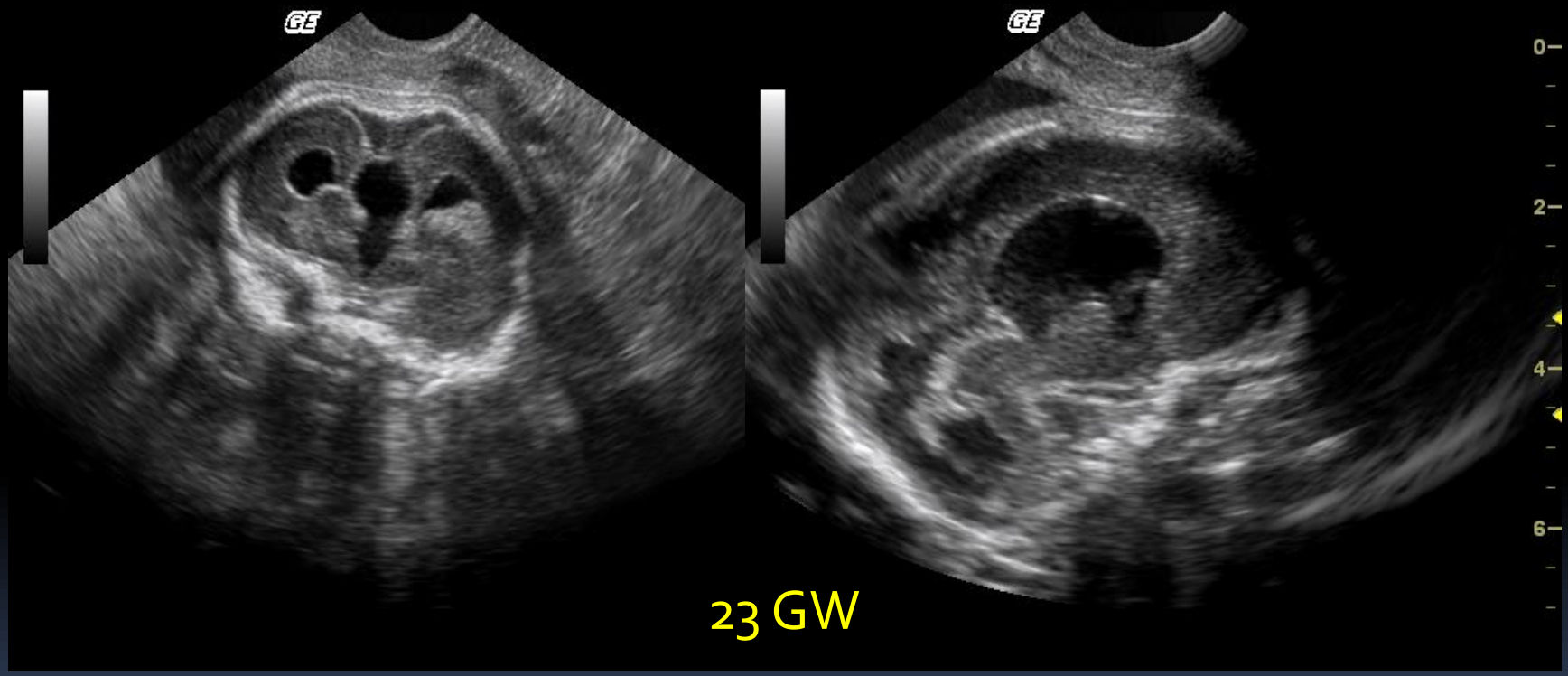
FLAIR



Tubulonodular lipoma with ACC

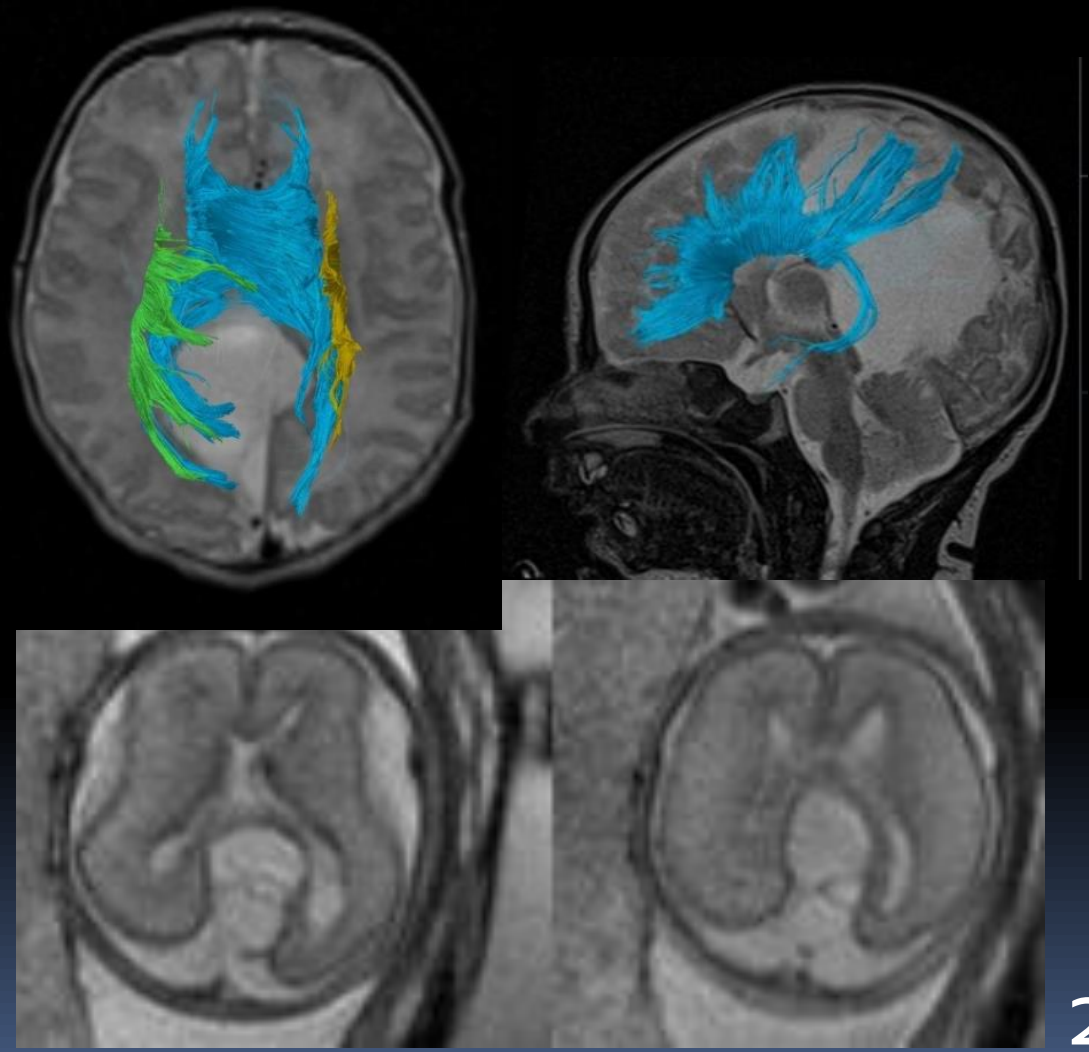


ACC with interhemispheric cyst



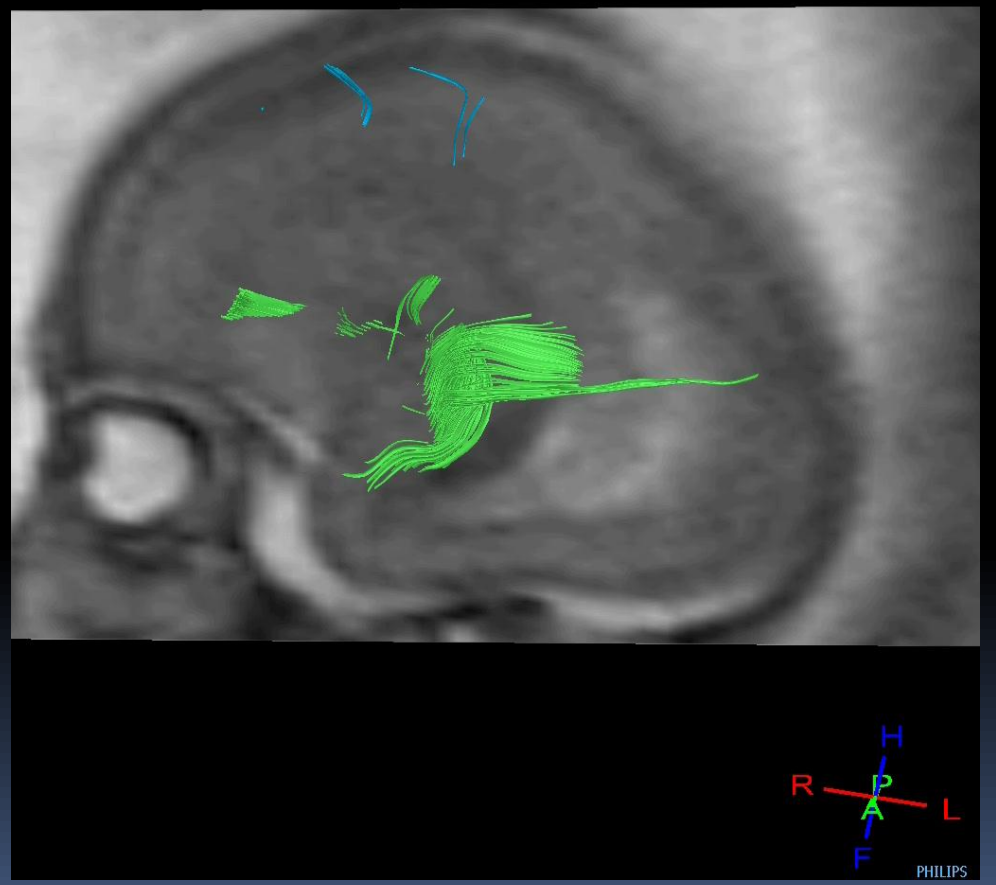
23 GW

ACC with interhemispheric cyst

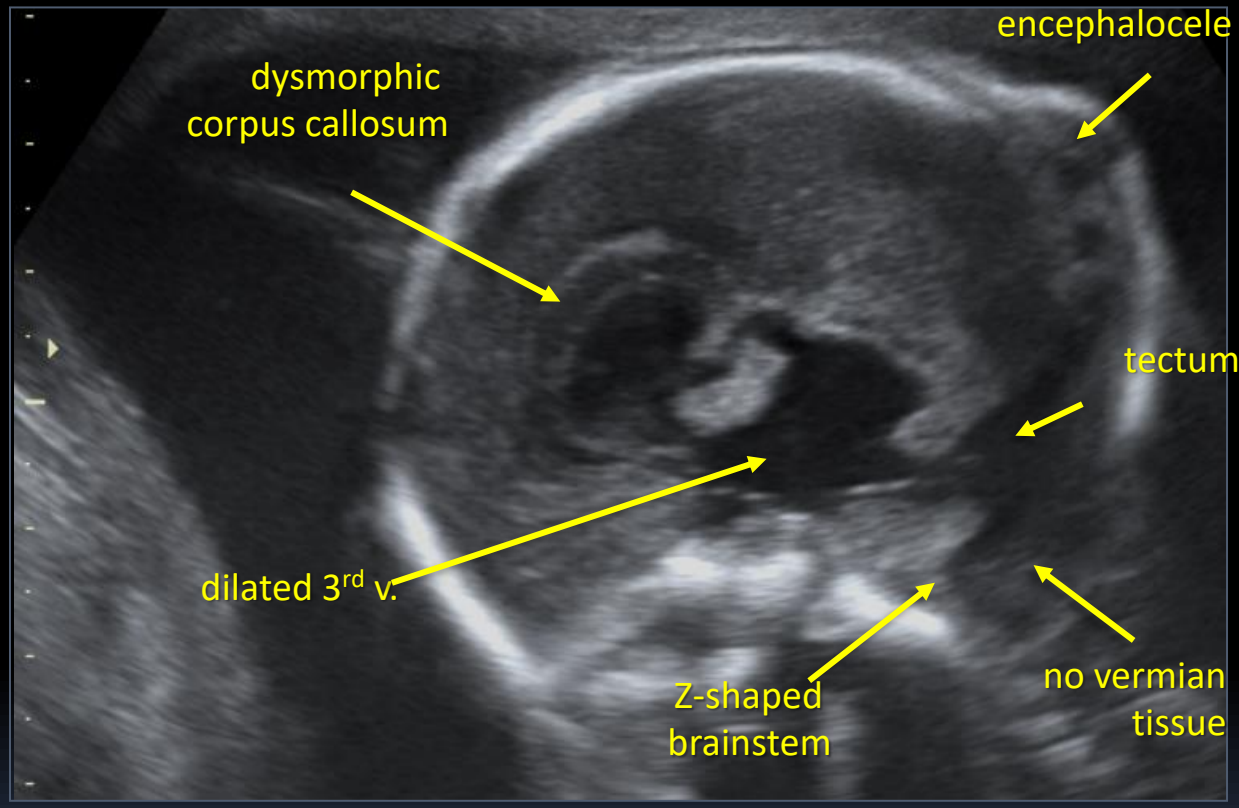


22GW

Callosal dysgenesis? → Deformation/Cyst

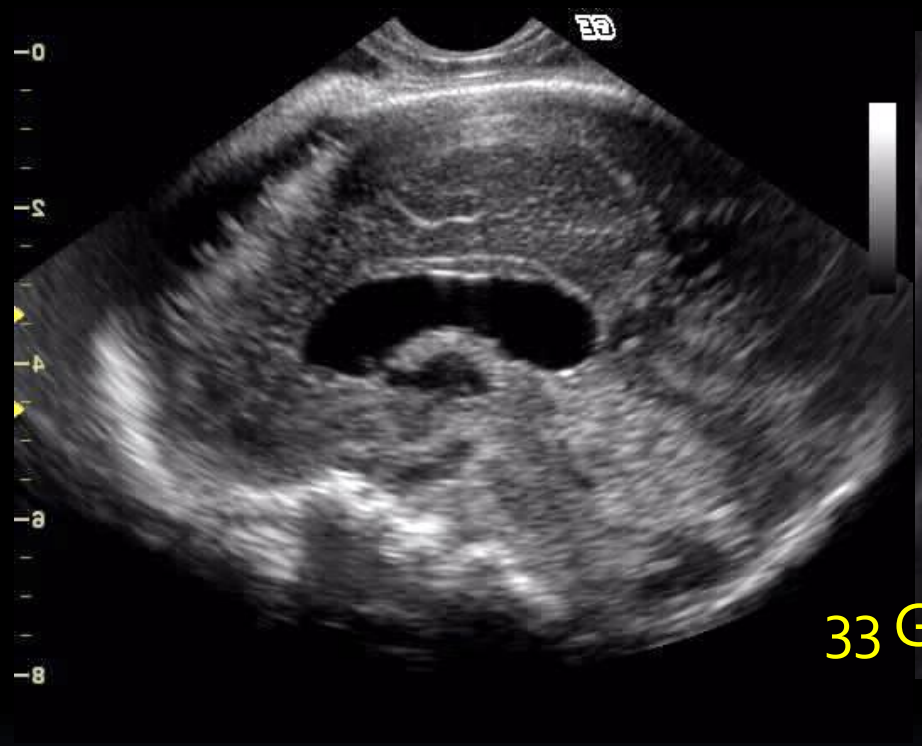


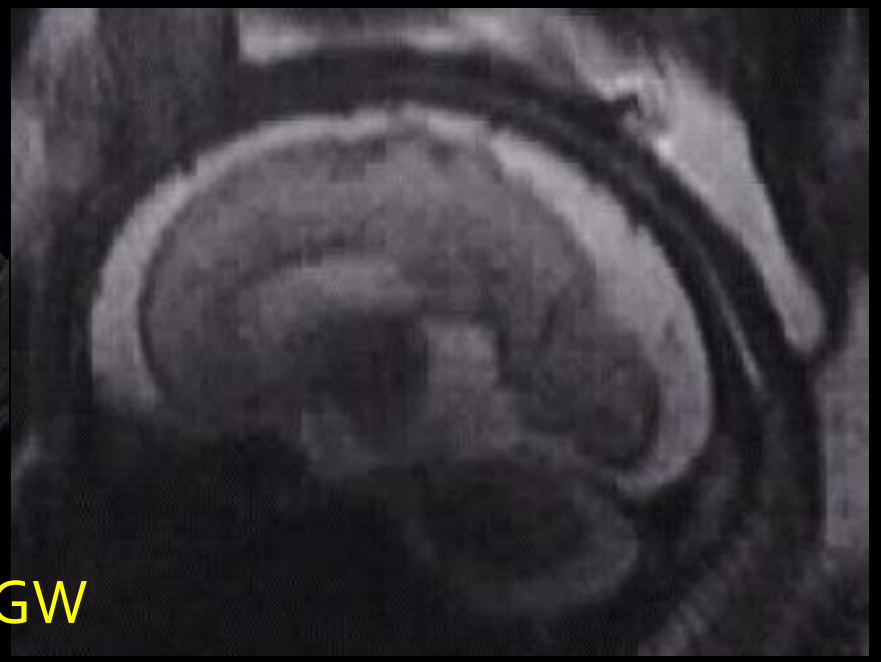
DCC with associated brain anomalies



Cobblestone Malformation Due to DAG1 mutation

DCC and Associated Brain Anomalies

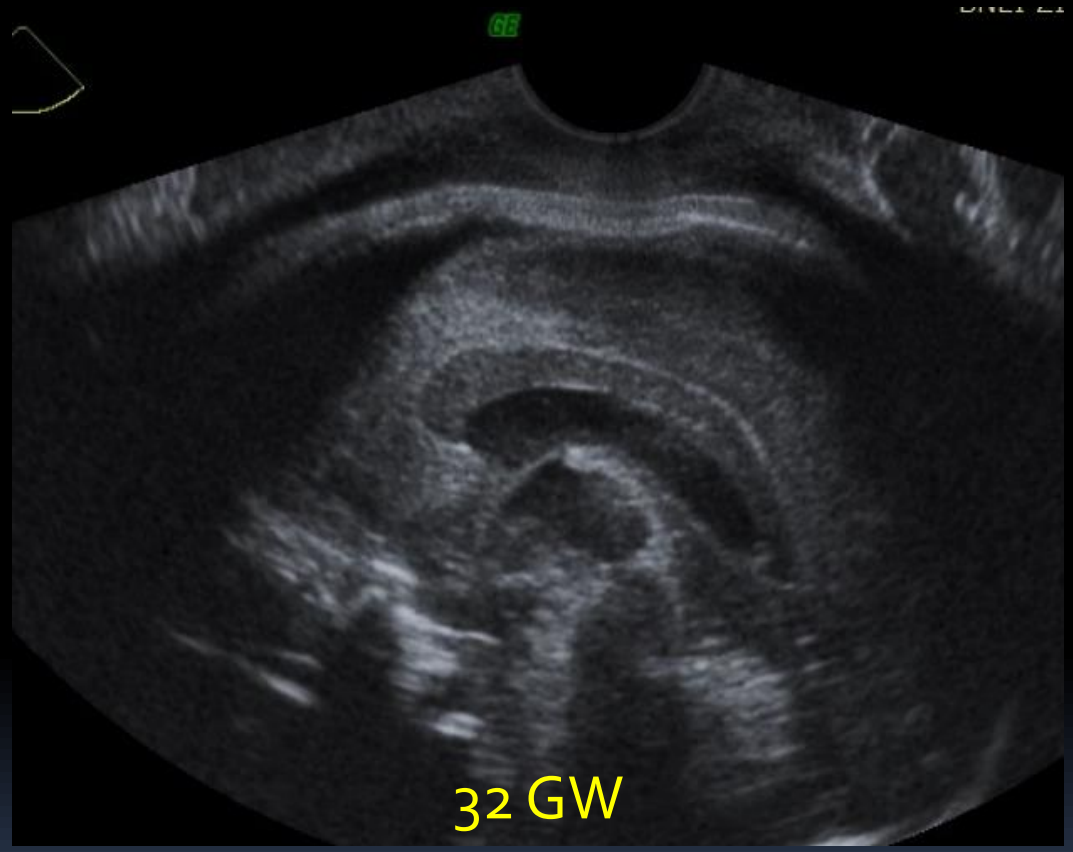




33 GW

Thinning of CC
Lissencephaly & Cerebellar hypoplasia

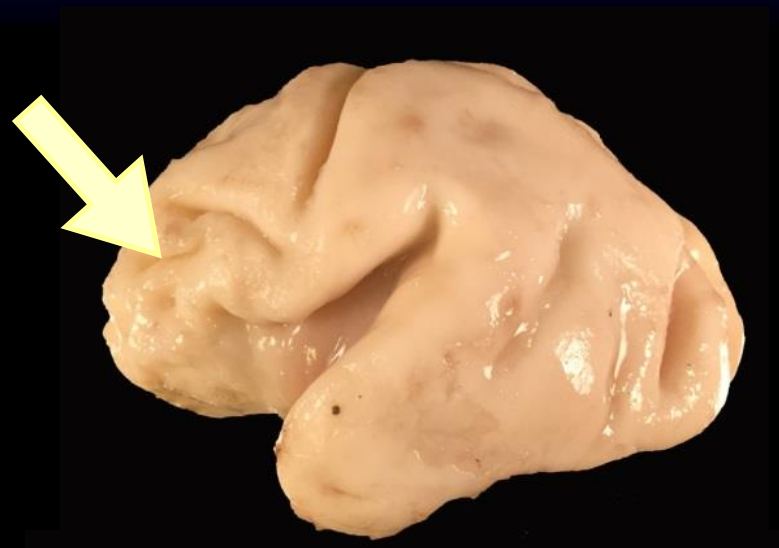
DCC and Associated Brain Anomalies

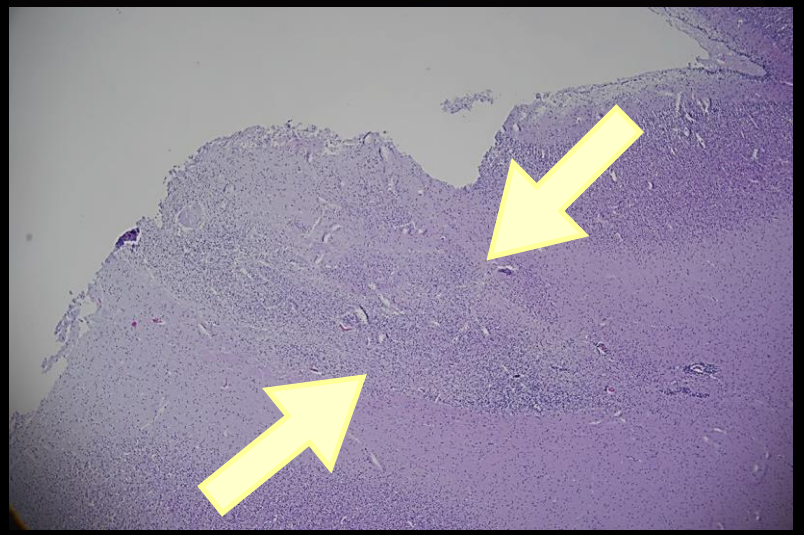


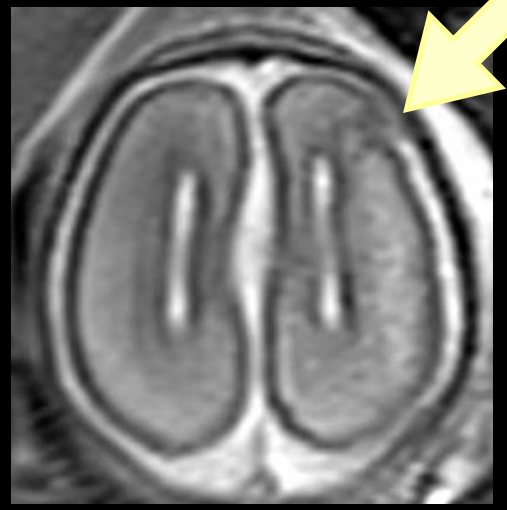
Absent rostrum, thick CC

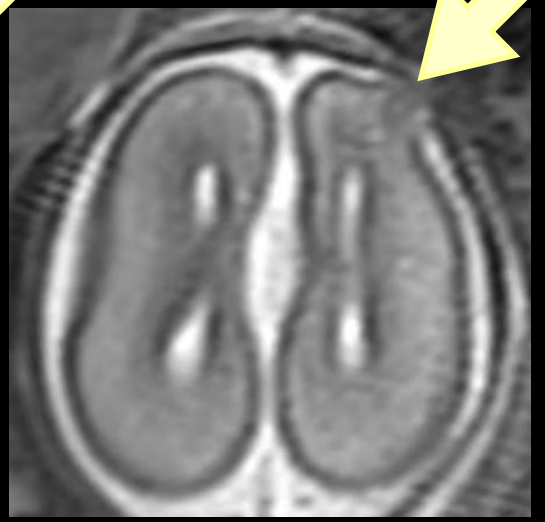
Lissencephaly due to DCX mutation in male fetus

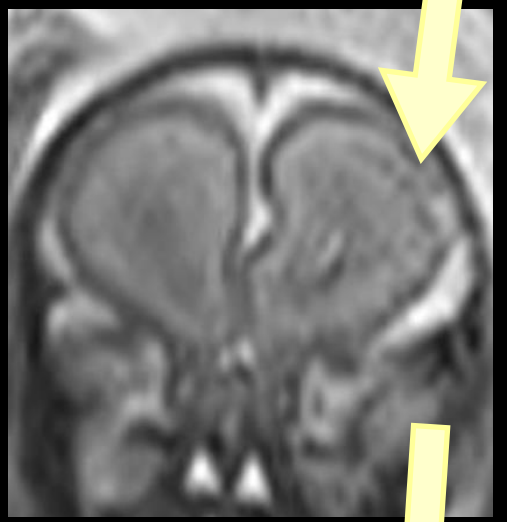
Callosal Agenesis – associated?

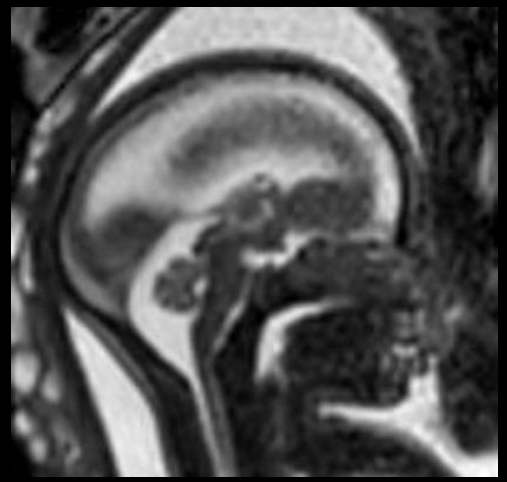


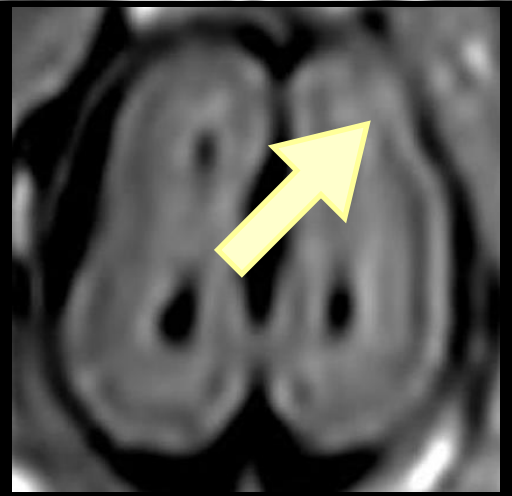


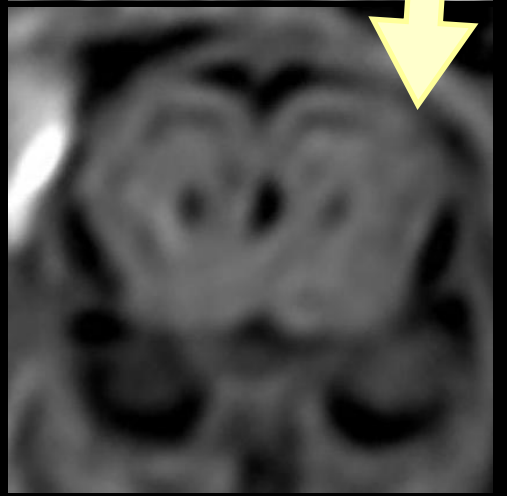










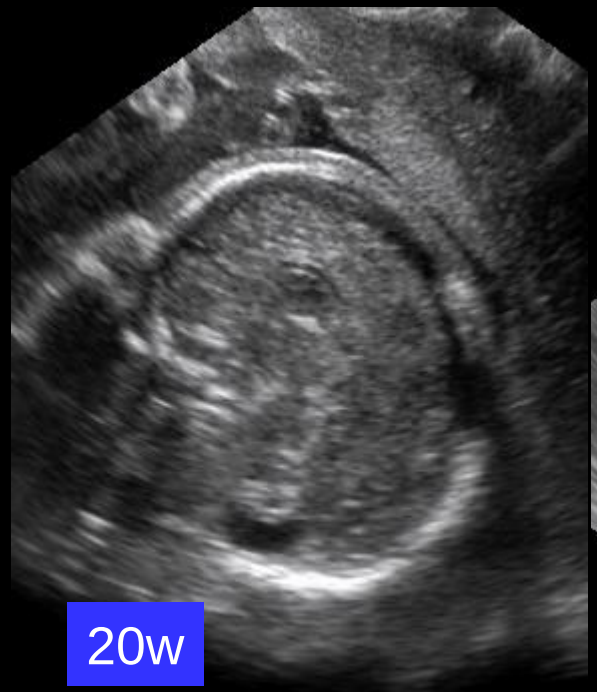


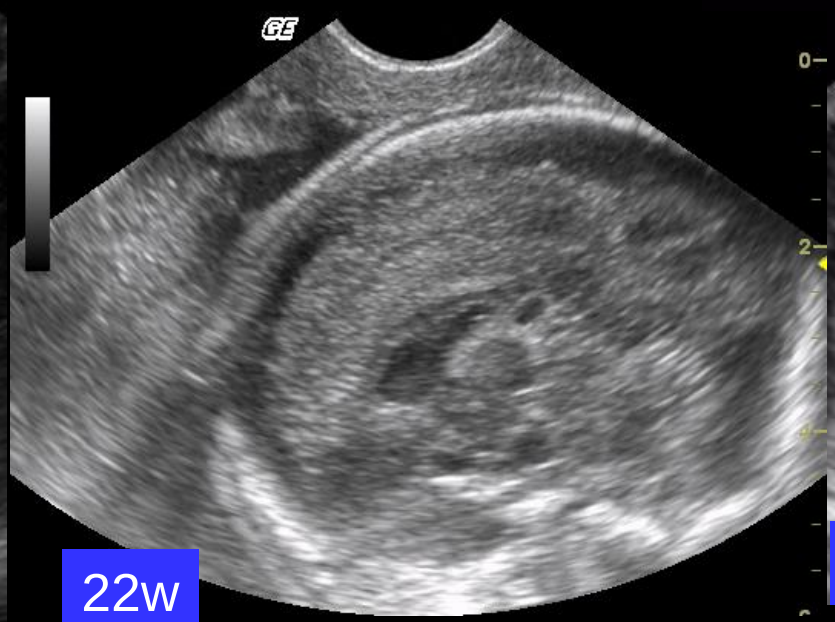
MEDICAL UNIVERSITY OF VIENNA

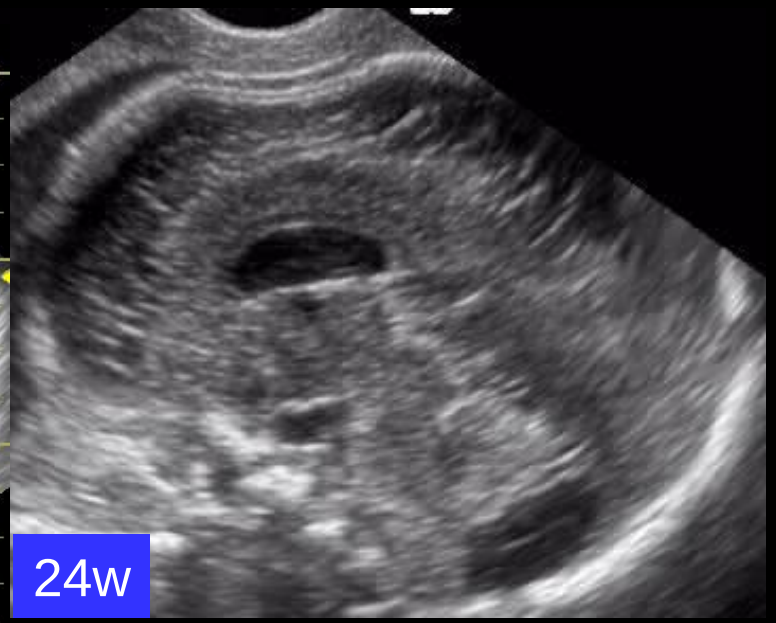
Vienna General Hospital

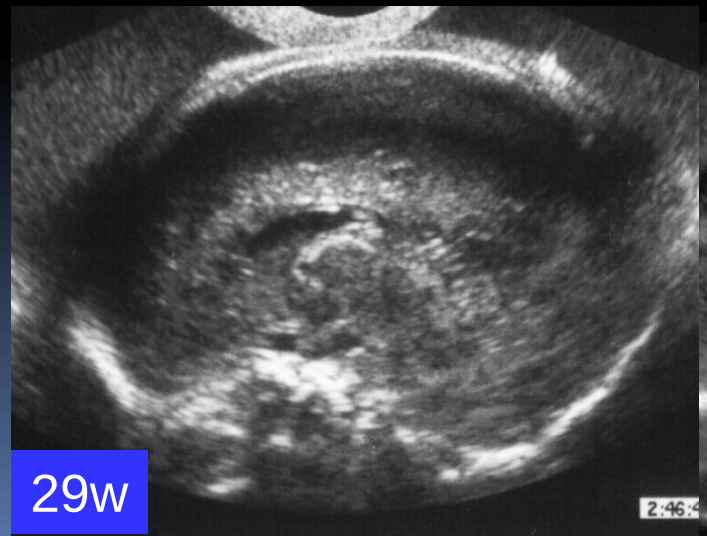
24GW

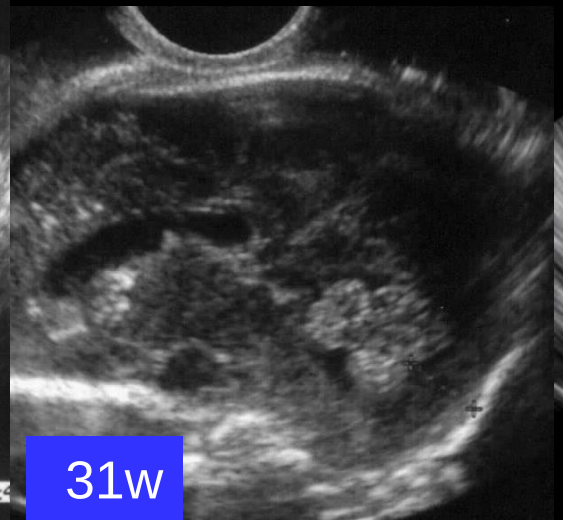
Dysgenesis of CC in CMV

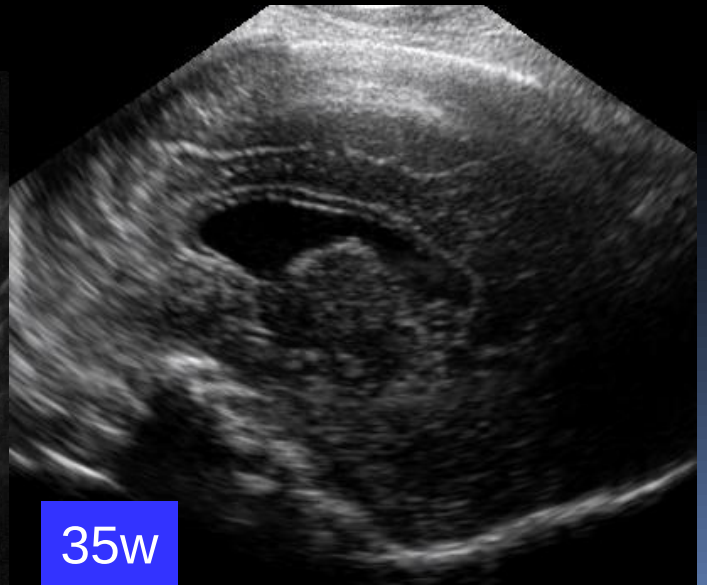








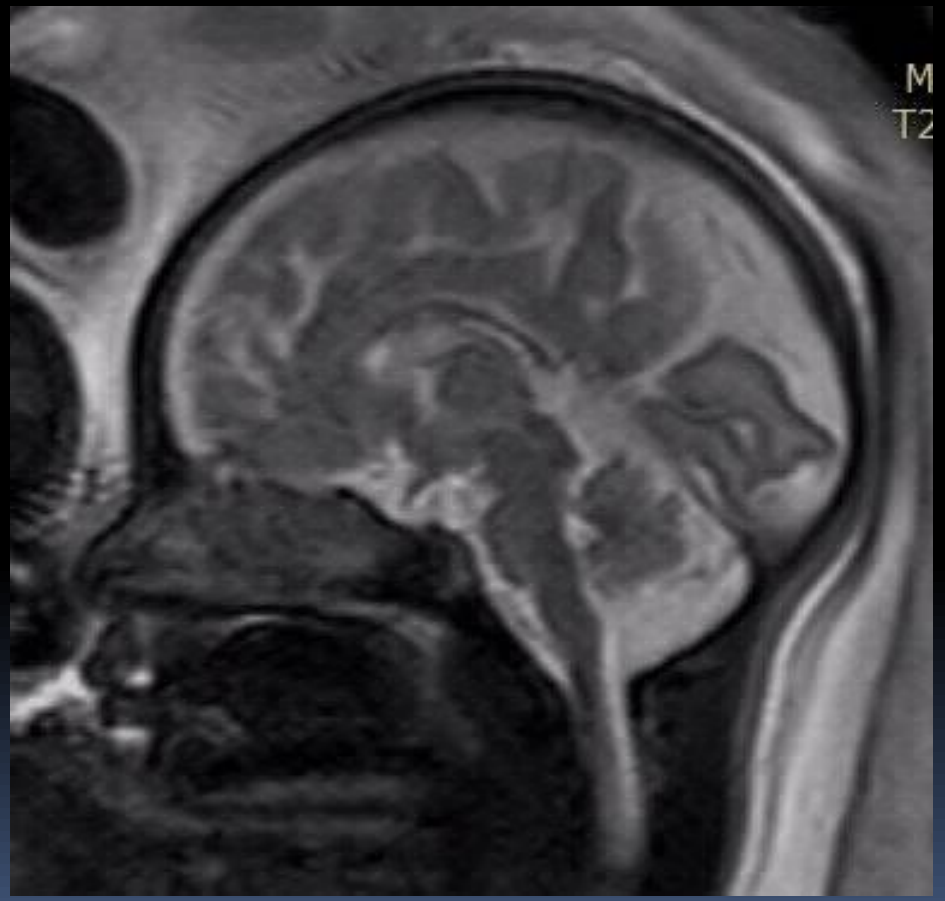




Incompletely answered questions

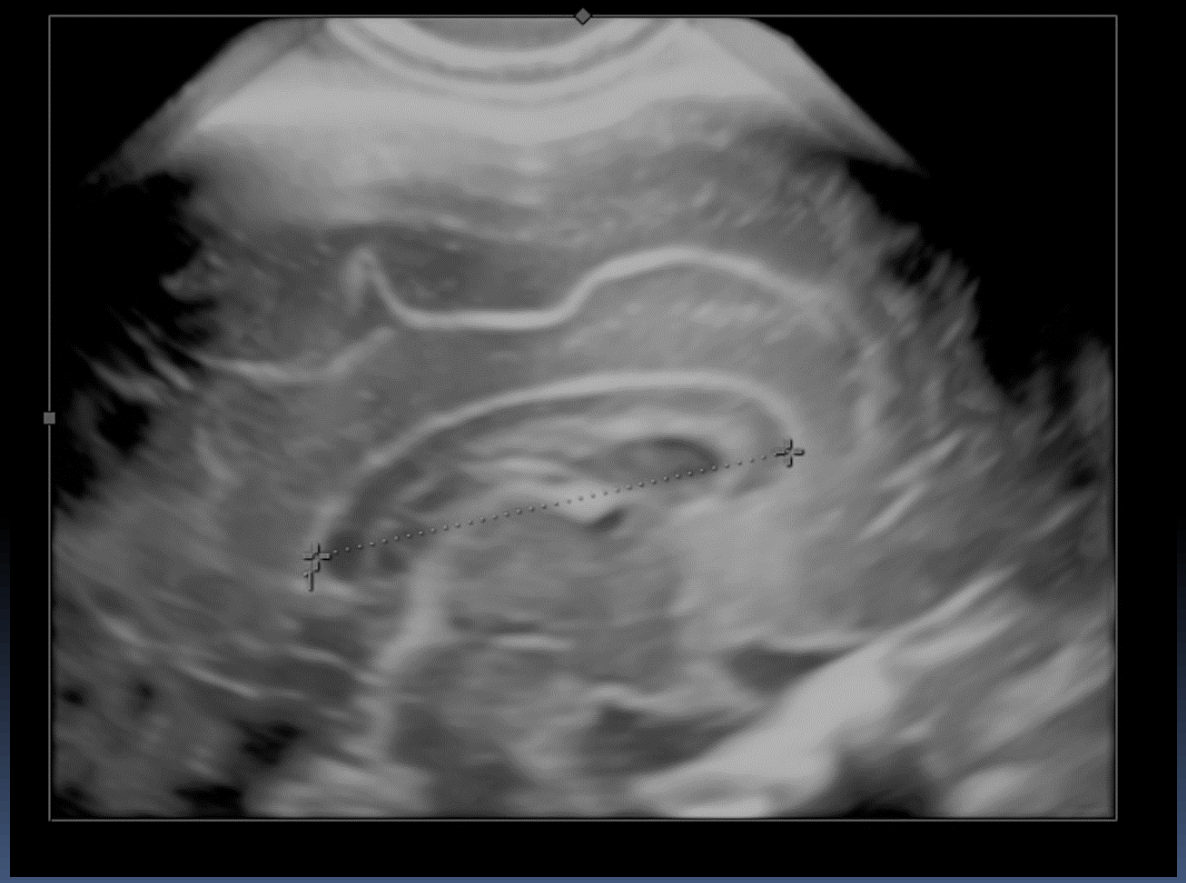
- Does a short CC signify partial agenesis of splenium?
- Does hypoplasia in utero mean a short CC?
- Can a short CC be normal variant?
- Does agenesis of different segments change the prognosis or possibility of a genetic syndrome?
- Do specific syndromes have specific shapes of partial agenesis?
- What is the significance of asymmetry of CC?
- What is the significance of a thick CC?

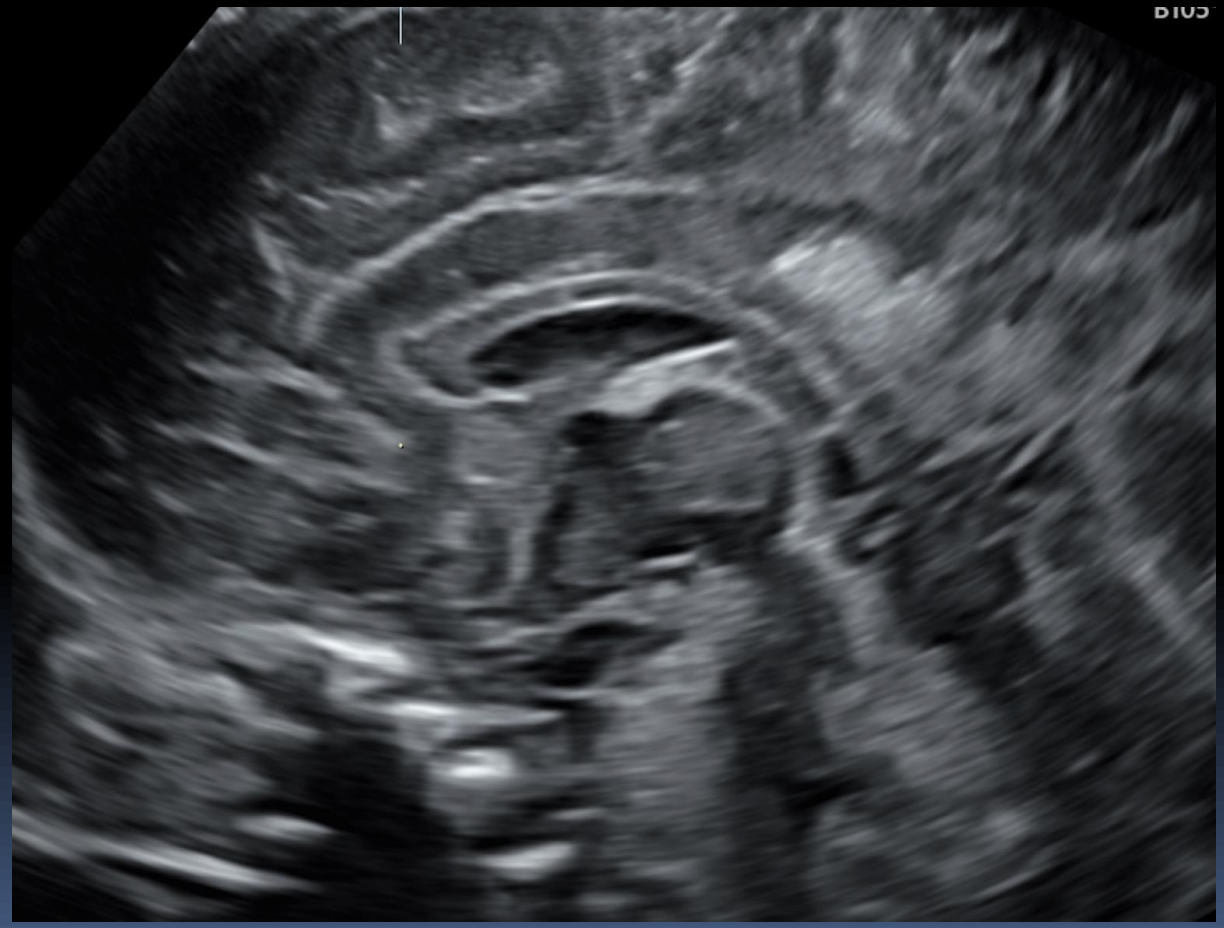
Is this hypoplasia or partial agenesis of CC?



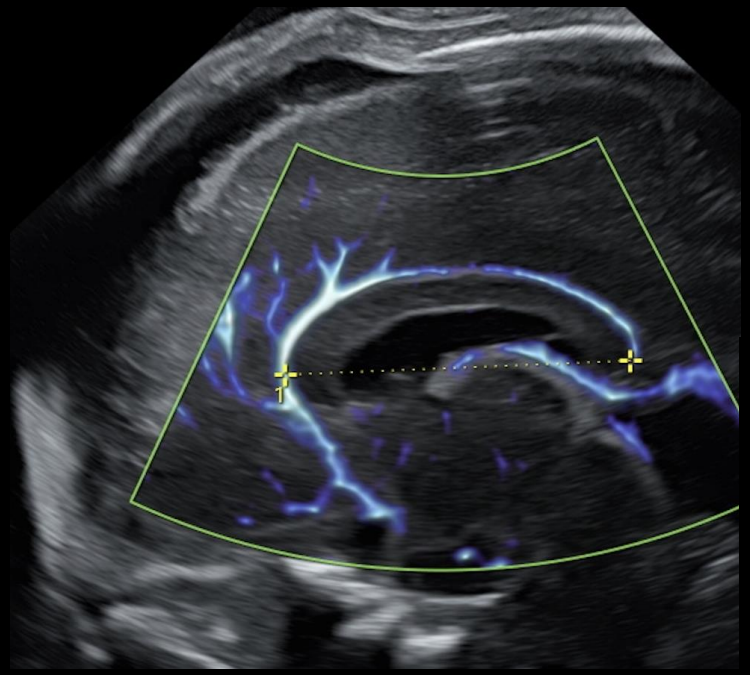
32.5 weeks

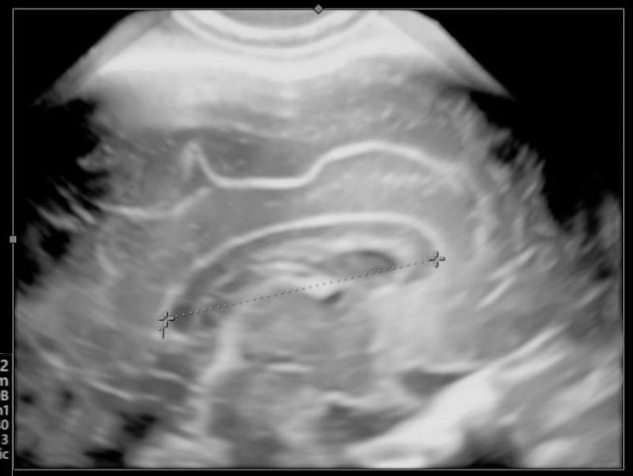
Is this short corpus callosum normal?



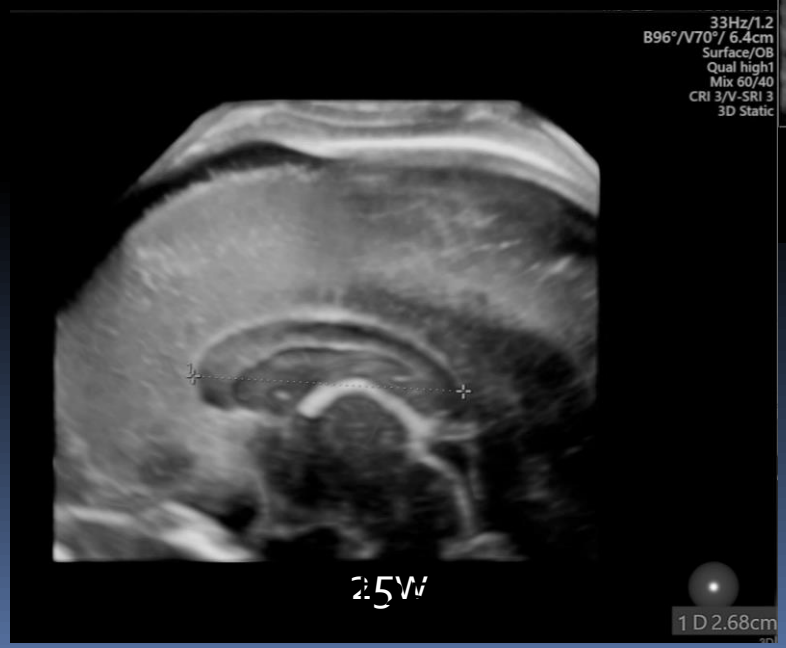


Normal shape but short CC





31W



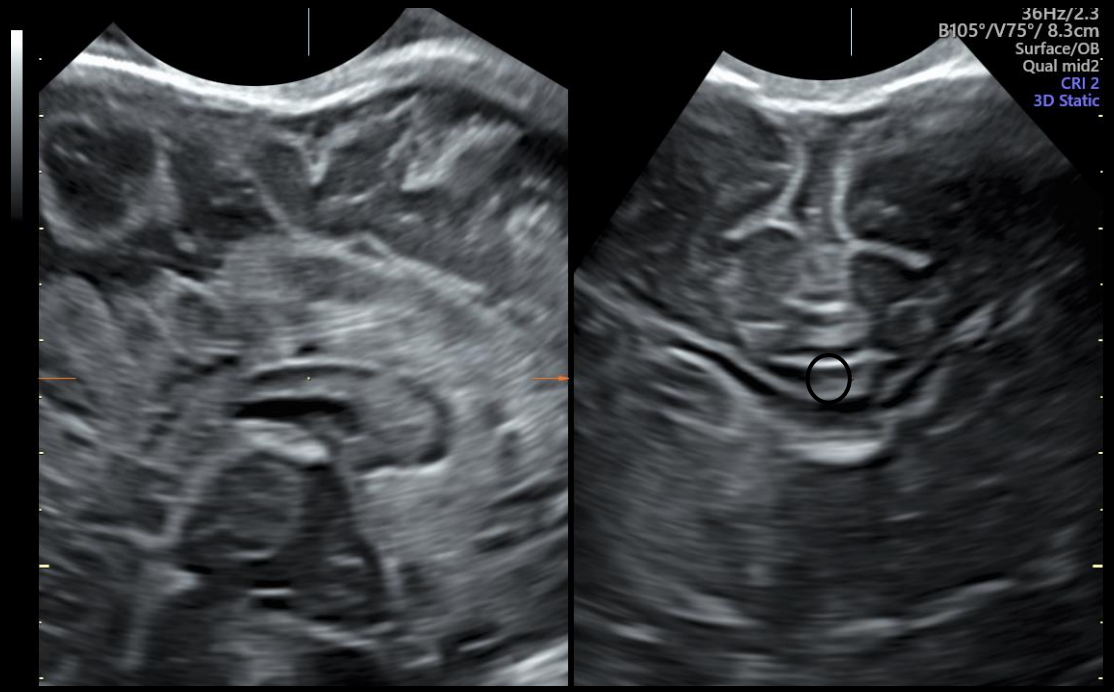
25W

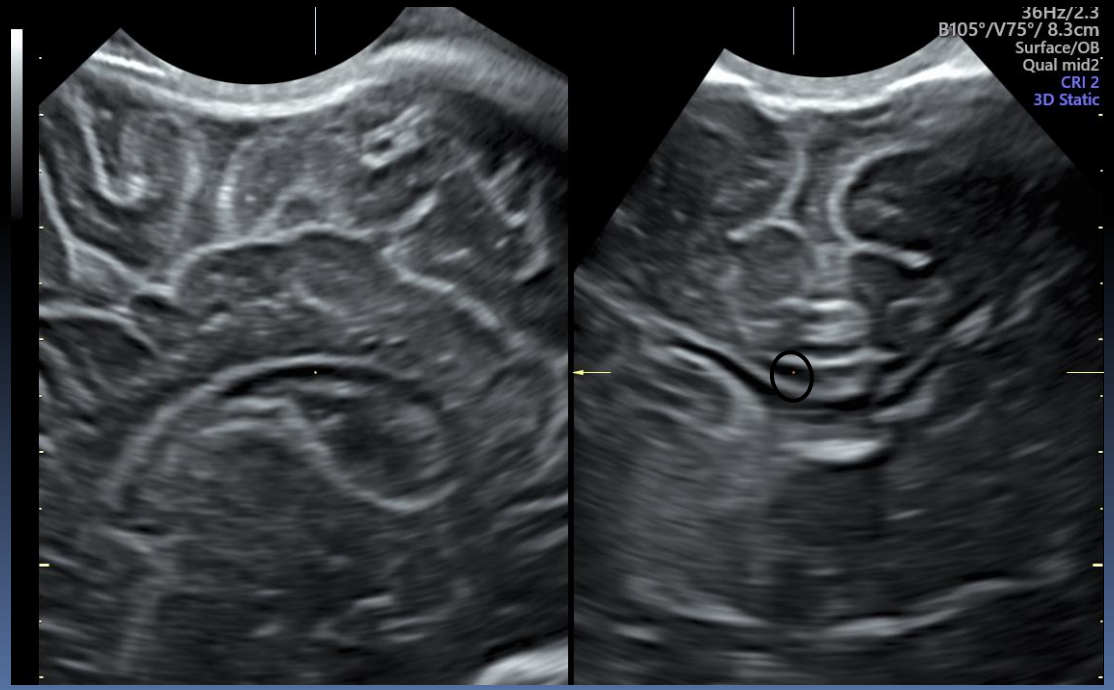
Table 1. Fetal Corpus Callosum Length (mm) by GA

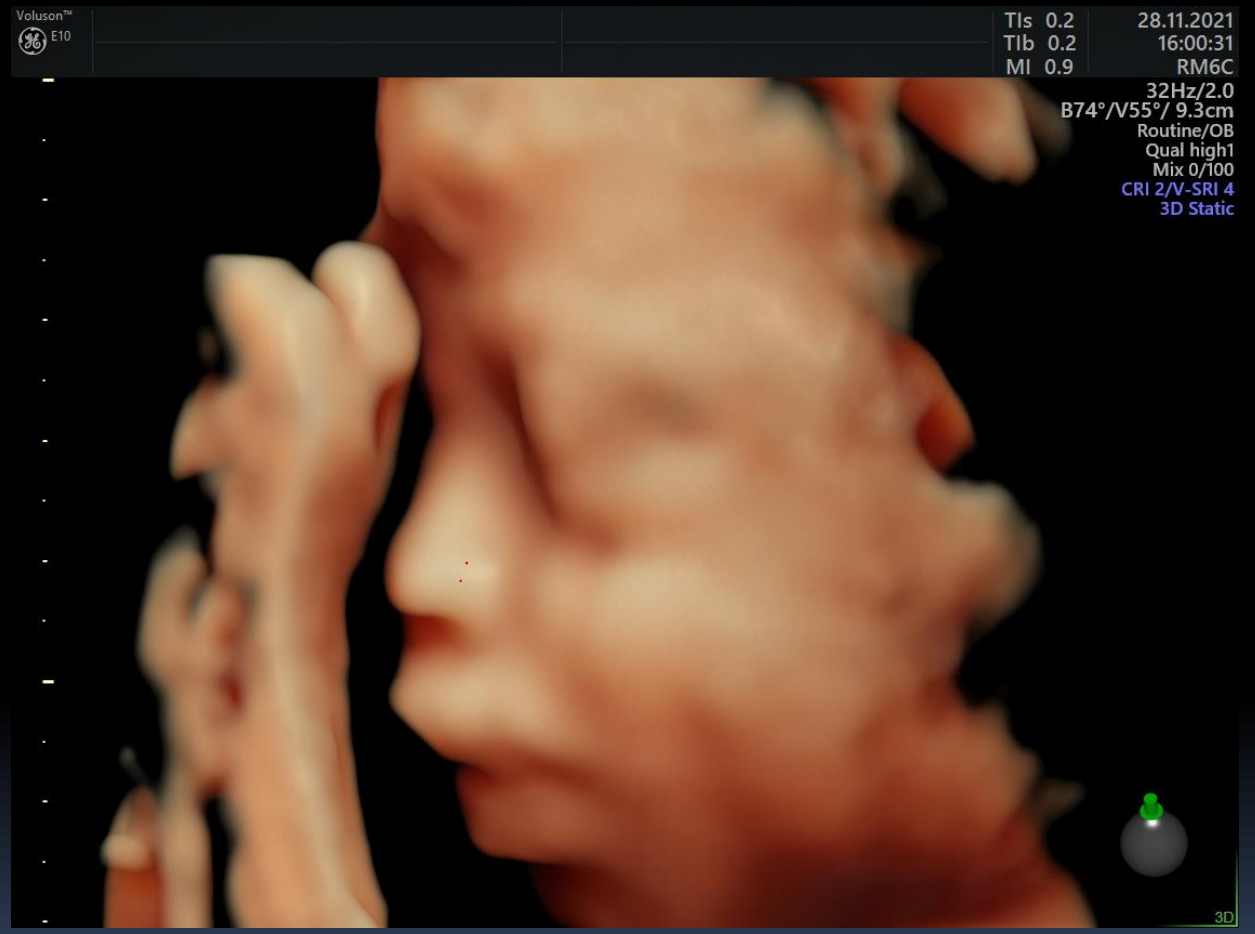
GA, wk+d	n	Mean	SD	95% CI
19+0–19+6	7	18.78	1.33	17.45–20.10
20+0–20+6	75	21.02	1.43	19.59–22.46
21+0–21+6	1002	23.20	1.54	21.66–24.74
22+0–22+6	1322	25.30	1.65	23.65–26.94
23+0–23+6	217	27.31	1.76	25.56–29.07
24+0–24+6	31	29.24	1.86	27.38–31.10
25+0–25+6	34	31.07	1.97	29.10–33.04
26+0–26+6	26	32.81	2.08	30.73–34.89
27+0–27+6	29	34.45	2.18	32.26–36.63
28+0–28+6	24	35.97	2.29	33.68–38.26
29+0–29+6	33	37.38	2.40	34.98–39.78
30+0–30+6	33	38.68	2.51	36.17–41.18
31+0–31+6	43	39.85	2.61	37.23–42.46
32+0–32+6	38	40.89	2.72	38.17–43.61
33+0–33+6	20	41.80	2.83	38.97–44.62
34+0–34+6	6	42.56	2.94	39.63–45.50
35+0–35+6	4	43.19	3.04	40.14–46.23
36+0–36+6	3	43.66	3.15	40.51–46.81
37+0–37+6	3	43.98	3.26	40.72–47.24

Cignini 2014

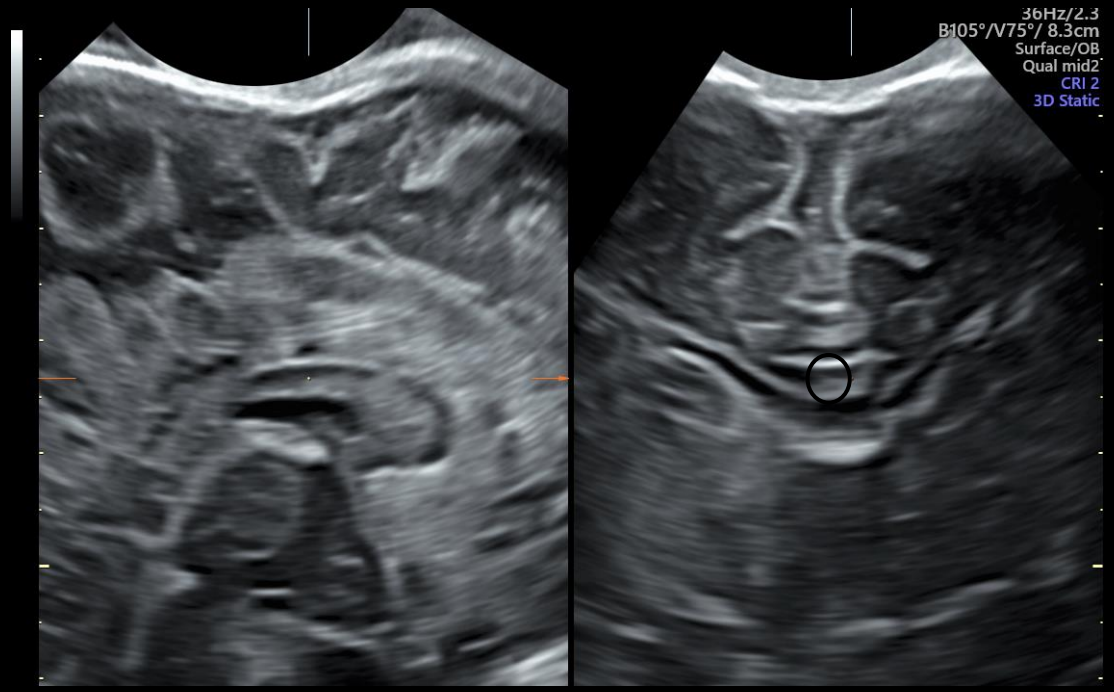
Short Corpus Callosum

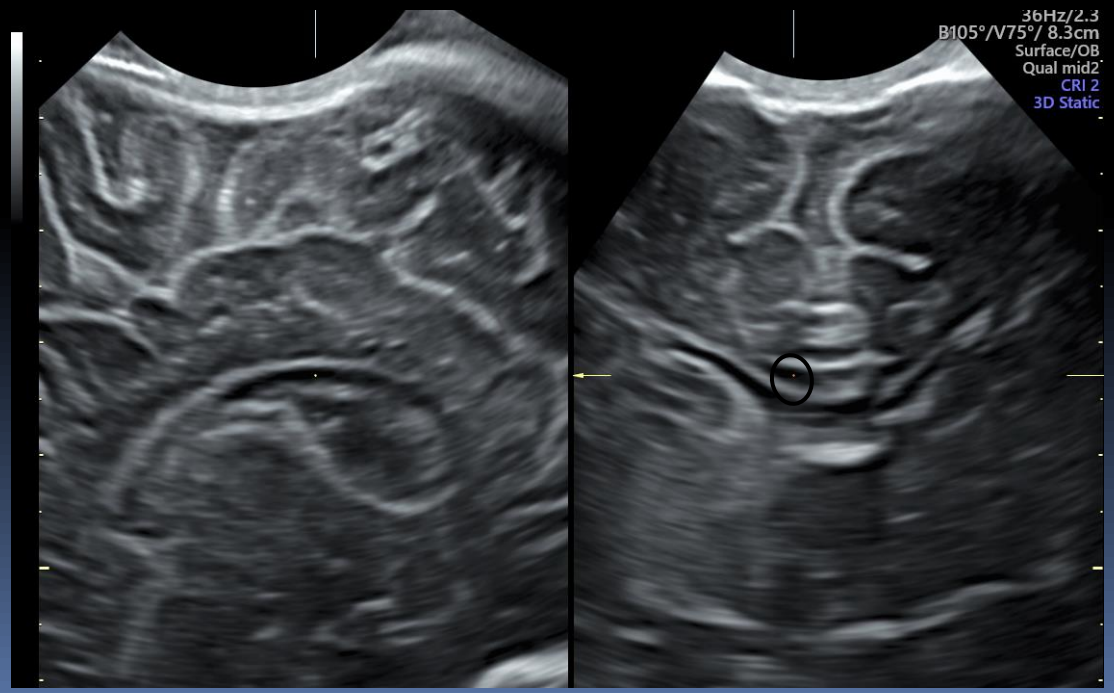




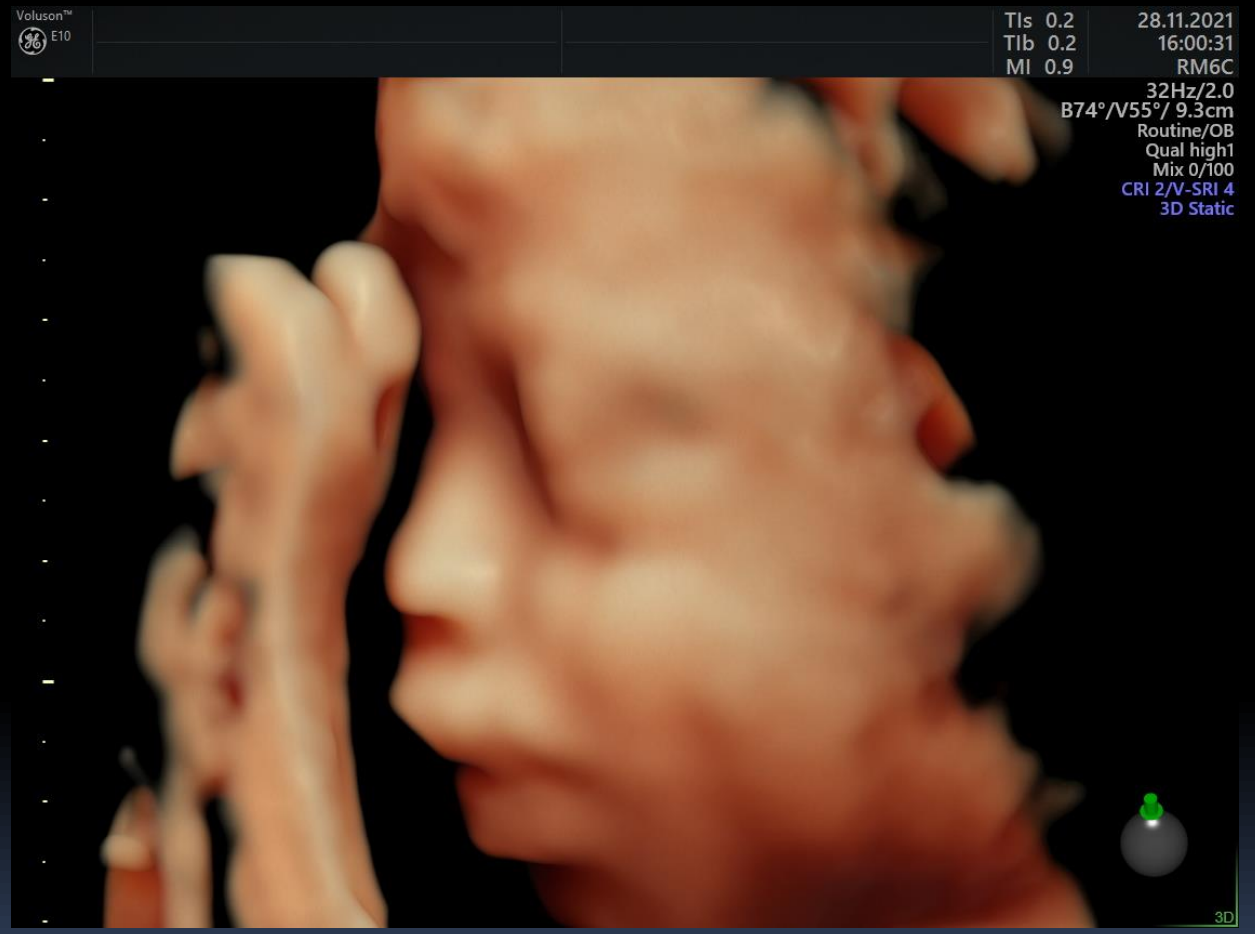


No growth of CC, IUGR, Dysmorphic features





Short Corpus Callosum



Post natal WES: De novo mutation in SMARCB1
Coffin-Siris Syndrome

COUNSELLING

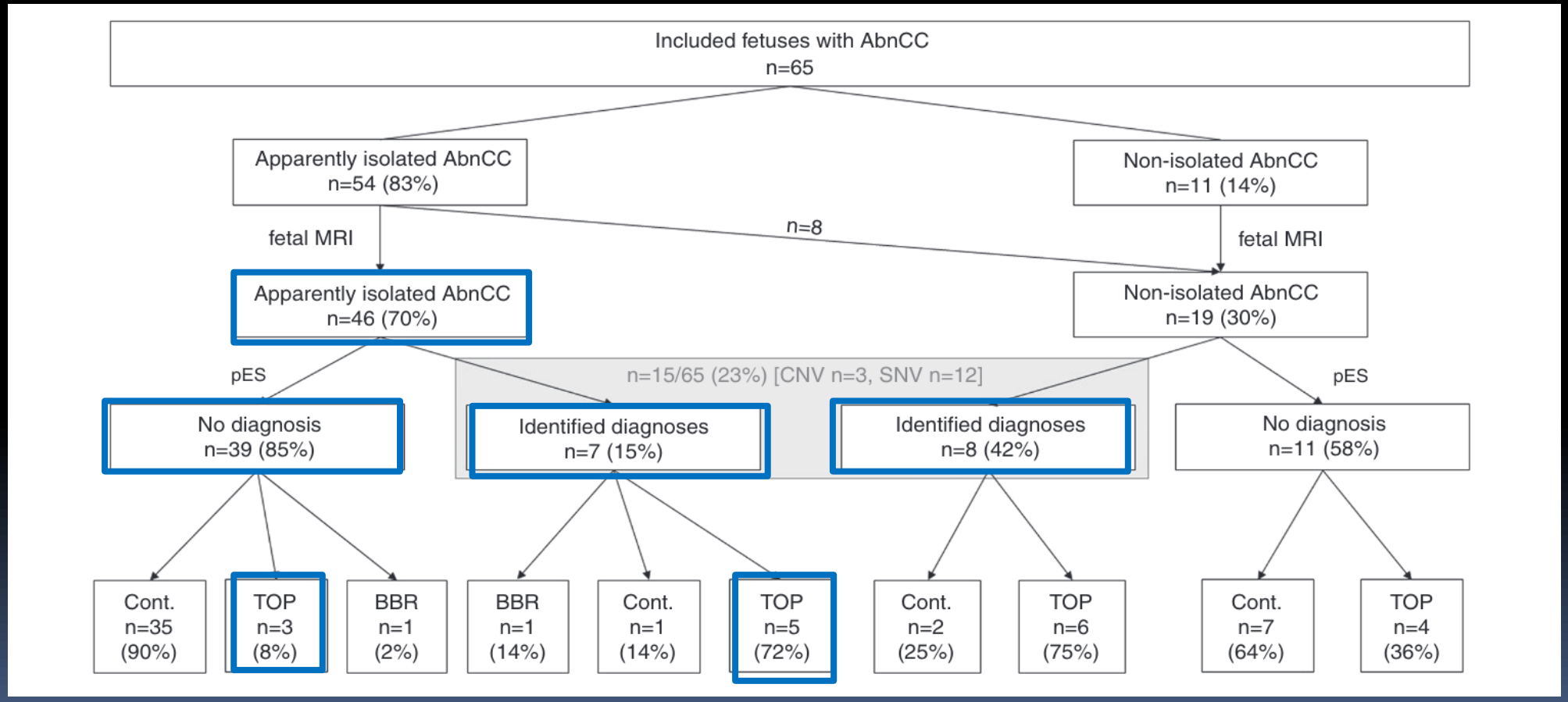
Outcome in Isolated DCC

- Cases with hypoplasia/dysplasia excluded
- Only one study reported CMA results – Abnormal in 5.7% fetuses with C/PACC and normal karyotype
- Abnormal ND performance included: Gross & fine motor control, epilepsy, cognitive status, language, ocular control, coordination
- Normal ND in 76% of cACC and 71% of pACC
- Severe ND in 8% of cACC and 12.5% of pACC
- Chromosomal anomalies 4.8% of cACC and 7.5% of pACC
- Additional structural anomalies diagnosed after birth 5.4% of cACC and 14.5% of pACC

Systematic Review of 27 studies (D'Antonio, Pediatrics 2016)

Prenatal exome sequencing in 65 fetuses with abnormality of the corpus callosum

(Heide, GENETICS in MEDICINE 2020)



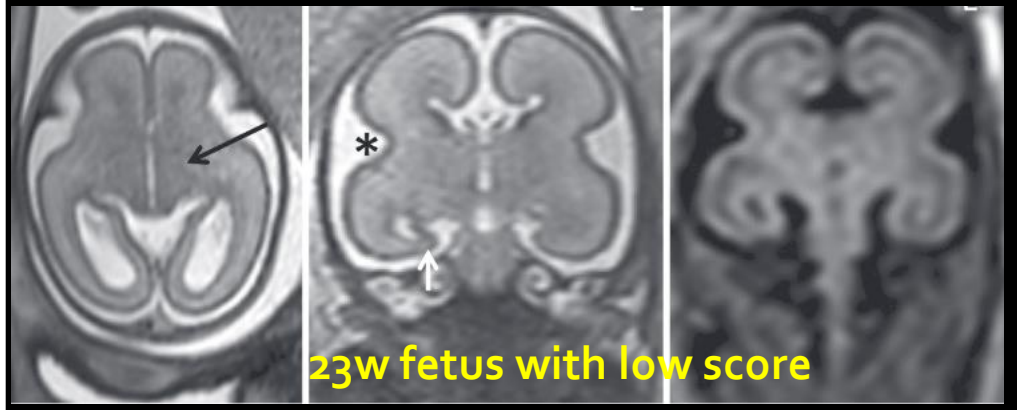
Improved neurodevelopmental prognostication in isolated corpus callosal agenesis: fetal magnetic resonance imaging-based scoring system

(Diogo, Ultrasound Obstet Gynecol 2021)

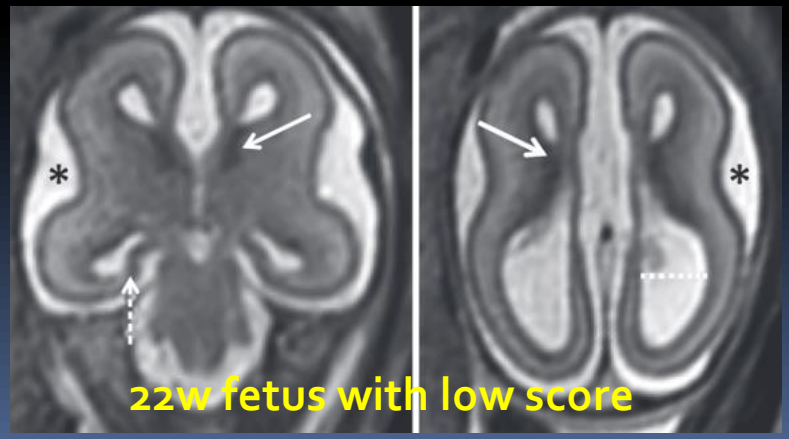
Table 1 Magnetic resonance imaging scoring system for fetuses with corpus callosal agenesis

	Score (points)		
Parameter	*0*	*1*	*2*
Gyration	Normal	Mildly delayed (≤ 2 weeks)	Delayed (> 2 weeks)
Opercularization	Normal	Delayed	—
Temporal lobe asymmetry*	Asymmetrical (R > L)	Symmetrical (R = L) or inverted (L > R)	—
Hippocampi	Normal	Malrotation (mild to moderate and/or unilateral)	Verticalization (bilateral), reduced volume
Lamination	Normal	—	Abnormal
Basal ganglia	Normal	Abnormal	—
Ventricular size†	Normal (< 10 mm)	10–14.9 mm	≥ 15 mm

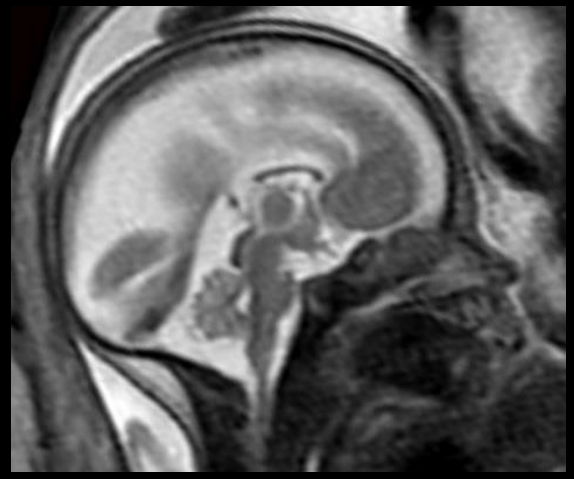
*Temporal lobe asymmetry described according to Kasprian *et al.*[24]; if not assessable (i.e. at later gestational ages (> 32 weeks)), a score of 0 should be given. †Measured at level of atrium; if ventricular size is asymmetrical, larger ventricle should be assessed. L, left; R, right.

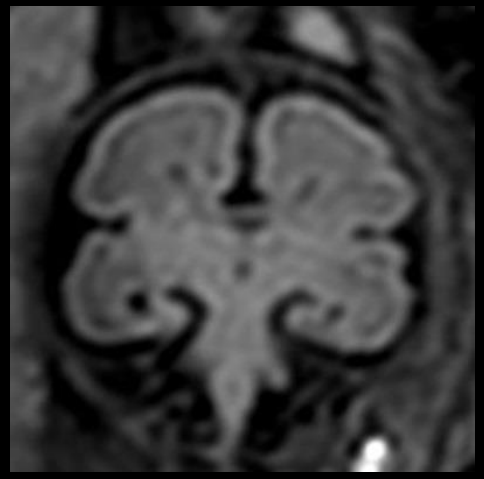


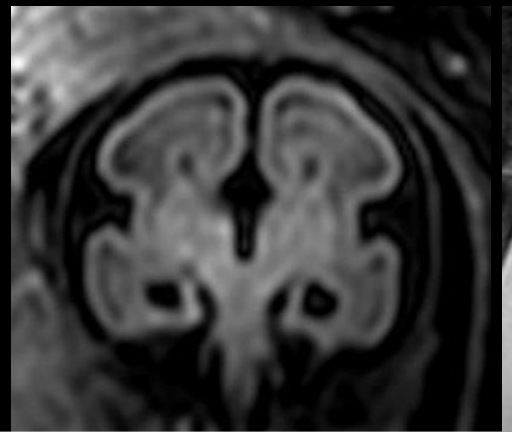
- Score of ≤ 3 points had average / above average ND outcome in cognitive, motor and language outcome
- Score of ≥ 4 points had below average on at least the cognitive or language evaluation.

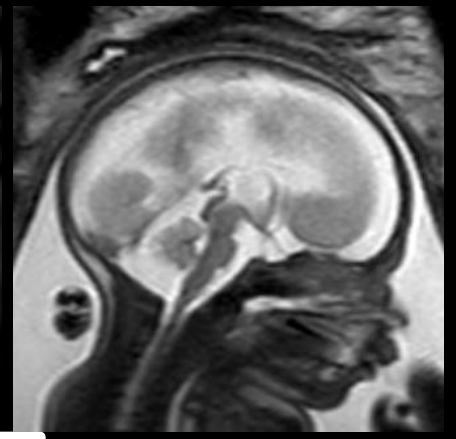


Fetal MRI Score in Callosal Agenesis

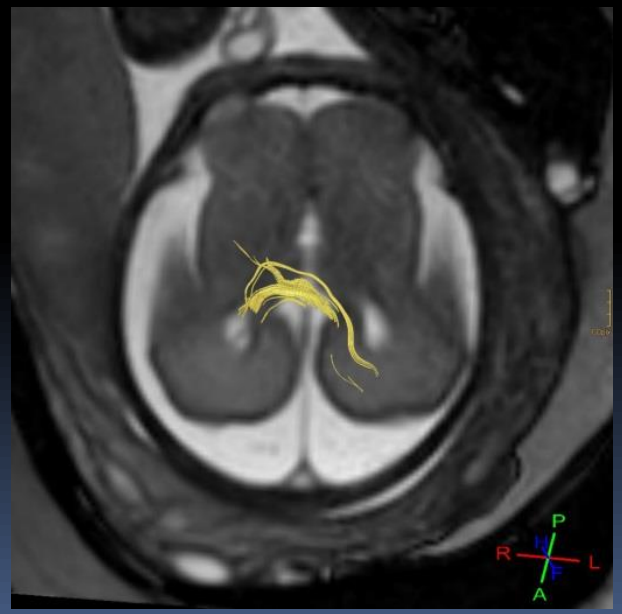




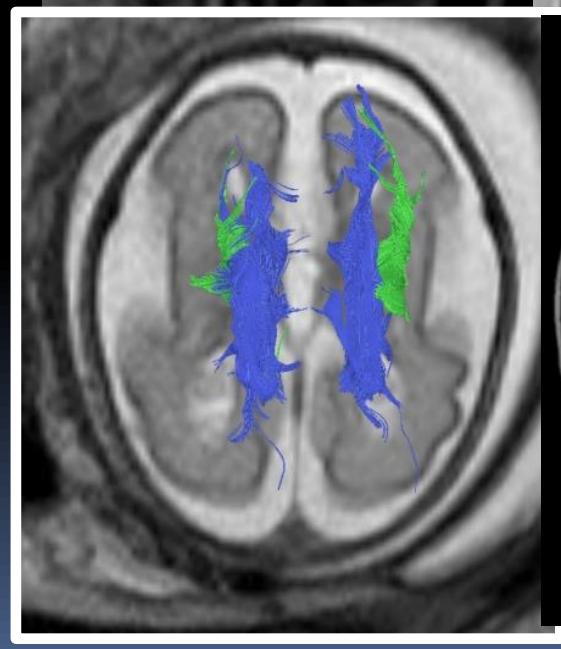


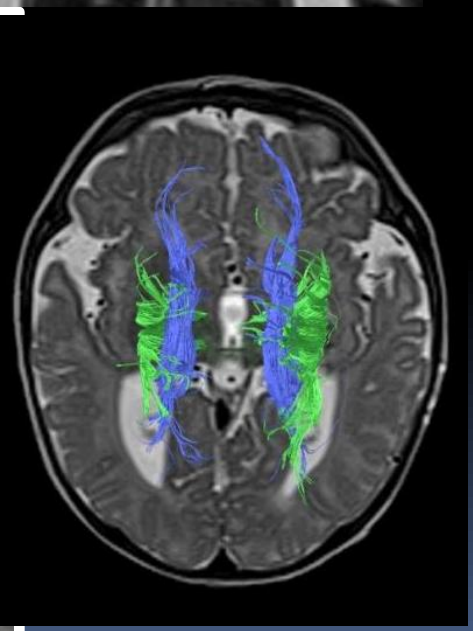


Sarah,
29GW



Bruce,
28GW





Probst bundle — sensorimotor

What should be counselled in callosal dysgenesis?

- The outcome of prenatally detected ACC is mainly dependent on the presence or absence of associated anomalies
- The full assessment of fetal ACC mandates MRI, CMA, WES and a search for more subtle ultrasound features of certain genetic syndromes
- The outcome of isolated ACC is reported to be favorable in ~75% of case
- At least 25-36% of cases with isolated ACC exhibit significant developmental delay (equal distribution between moderate and severe disability

Counselling in callosal dysgenesis

- Ventriculomegaly is part of the ACC malformation and should not be considered an associated finding that worsens the prognosis
- A severe and progressive ventricular dilatation is abnormal and particularly in a male fetus, with adducted thumbs, should raise the diagnosis of L1CAM
- The outcome of isolated PACC is not better than that of complete agenesis of the corpus callosum
- Most of the cases of isolated ACC are sporadic
- It might justify systematic MRI assessment of the parents' CC

Counselling in callosal dysgenesis

- Children with primary ACC may develop a decline in cognitive abilities with age and demonstrate specific neuropsychological and psychiatric abnormalities
- Children with a corpus callosum lipoma usually have a good prognosis, they may develop epilepsy
- A thick corpus callosum is usually associated with other anomalies and carries a poor prognosis
- A thin corpus callosum is a non specific finding seen in children with mental retardation. The prognosis of isolated thin CC identified in utero is not known

Counselling in callosal dysgenesis

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- The full assessment of fetal ACC mandates CMA, WES, MRI and a search for more subtle ultrasound features of certain genetic syndromes
- The outcome of isolated ACC is reported to be favorable in ~75% of case
- At least 25-36% of cases with isolated ACC exhibit significant developmental delay (equal distribution between moderate and severe disability
- We still don´t know how CMA and WES affect prognosis

Counselling in callosal dysgenesis

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- A severe and progressive ventricular dilatation is abnormal and particularly in a male fetus, with adducted thumbs, it should raise the diagnosis of L1CAM
- The outcome of isolated PACC is not better than that of complete agenesis of the corpus callosum
- Most of the cases of isolated ACC, are sporadic
- An autosomal recessive or dominant transmission is rare (~ 3%)
- It might justify systematic MRI assessment of the parents' CC

Counselling in callosal dysgenesis

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