CERPO
Centro de Referencia Perinatal Oriente
Facultad de Medicina, Universidad de Chile

Malformaciones del Desarrollo Cortical

Dr. Pablo Silva Labarca
Programa de especialización Medicina Materno Fetal
Facultad de Medicina
Universidad de Chile

Introducción

- El desarrollo cortical comienza alrededor de las 7 semanas de gestación.

- 3 fases:
  - Proliferación
  - Migración
  - Organización

Barkovich AJ, Kuzniecky RI, Jackson GD, Guerrini R, Dobyns WB. A developmental and genetic classification for malformations of cortical development. Neurology. 2005 Dec 27;65(12):1873-87.

Introducción

- Las malformaciones del desarrollo cortical son un grupo etiológicamente heterogéneo de patologías con distintos fenotipos.

- Etiologías:
  - Enfermedades monogénicas
  - Errores de metabolismo
  - Enfermedades mitocondriales
  - Daño hipóxico
  - Enfermedades maternas
  - Exposición a teratógenos.

- Etiología permanece desconocida en 50% de los casos

Barkovich AJ, Kuzniecky RI, Jackson GD, Guerrini R, Dobyns WB. A developmental and genetic classification for malformations of cortical development. Neurology. 2005 Dec 27;65(12):1873-87.

Introducción

- Manifestaciones clínicas
  - Convulsiones 75%
  - Retraso en el desarrollo 68%
  - Anomalias neurológicas 48%
  - Anomalias extra SNC 18%

Barkovich AJ, Kuzniecky RI, Jackson GD, Guerrini R, Dobyns WB. A developmental and genetic classification for malformations of cortical development. Neurology. 2005 Dec 27;65(12):1873-87.

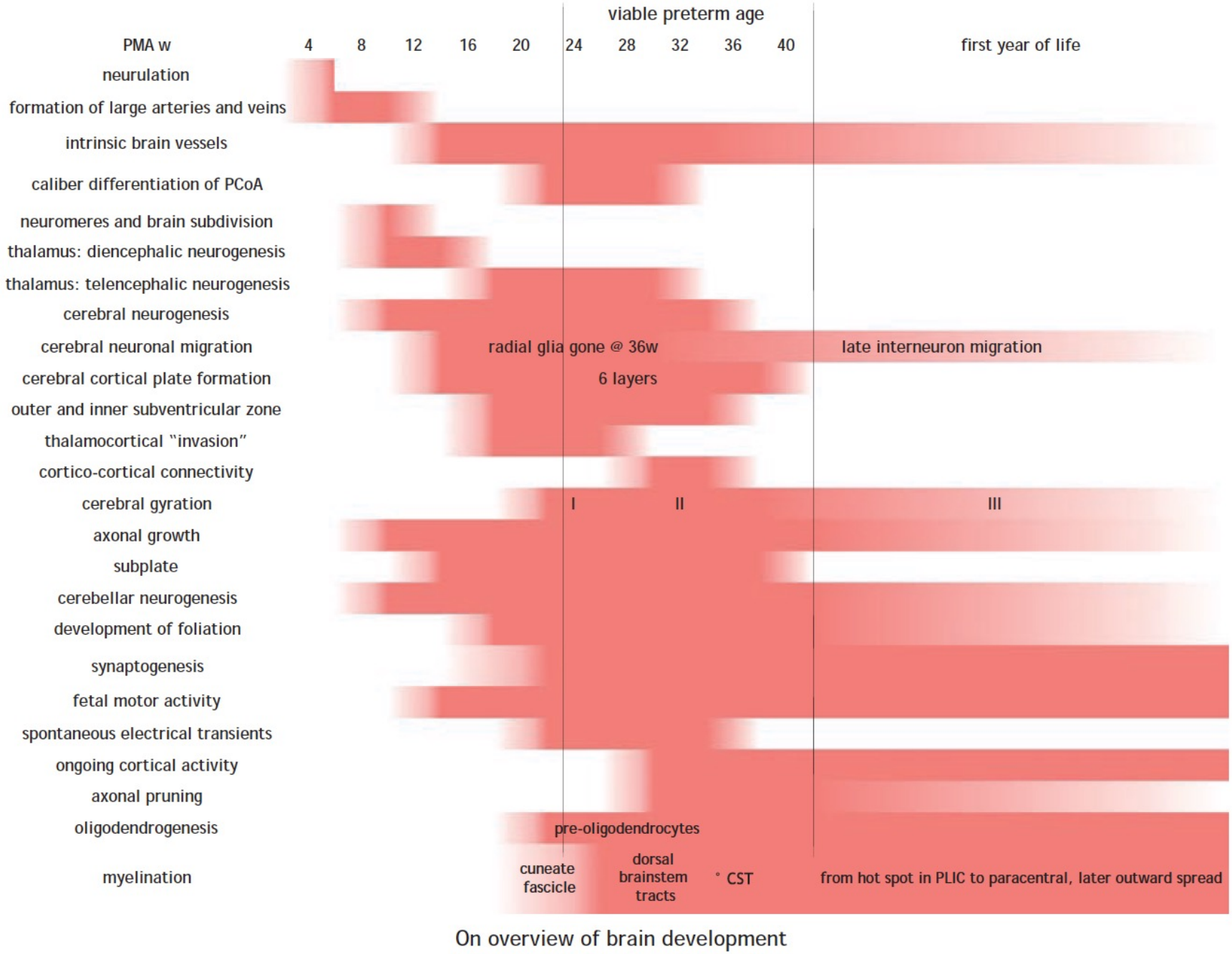

Fig. 14.4. An overview of brain development.

time of appearance at postmortem
GA as postmenstrual weeks.

superolateral convexity	
lateral fissure (fl)	17
central sulcus (sc)	21
precentral sulcus (sprc)	26 ± 3
superior frontal sulcus (sfs)	25 ± 2
inferior frontal sulcus (sfi)	30 ± 3
postcentral sulcus (spoc)	26 ± 3
intraparietal sulcus (sip)	29 ± 2
superior temporal sulcus (sts)	26 ± 3
inferior temporal sulcus (sti)	31 ± 3
inferior cerebral surface	
hippocampal sulcus (sh)	15
rhinal sulcus (sr)	25 ± 2
collateral sulcus (scoll)	24 ± 2
occipitotemporal sulcus (sot)	30 ± 3
medial cerebral surface	
cingulate sulcus (sci)	19
marginal branch of cingulate sulcus (rssci)	30 ± 3
paracentral sulcus (spac)	30 ± 3
subparietal sulcus (ssp)	30 ± 3
calcarine sulcus (scal)	17
parietoccipital sulcus (spo)	17

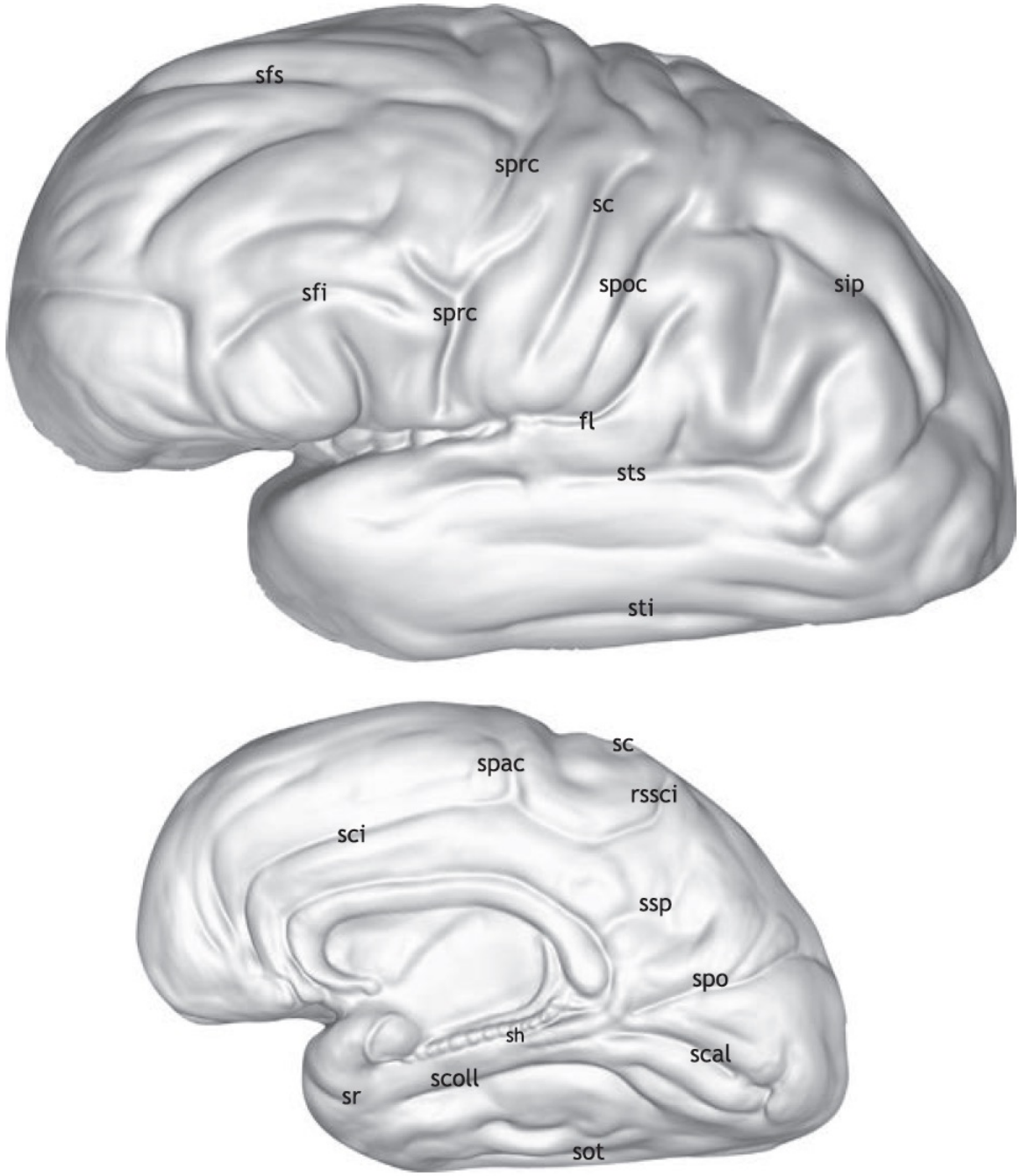

Fig. 14.11. Timelines of primary sulci at postmortem.

Stages of development of central and insular sulci.

Afif et al. (2007, 2014)	Central sulci	Insular sulci
13–17 weeks GA		Stage 1: Appearance of the first sulcus
18–19 weeks GA	Stage 1: Appearance of the inferior part of the central cerebral sulcus	Stage 2: Development of the peri-insular sulci
20–22 weeks GA	Stage 2: Development of the pericentral lateral regions and beginning of opercularization	Stage 3: Central sulci and opercularization of the insula
24–26 weeks GA	Stage 3: Development of parietal and temporal cortices and covering of the postcentral insular region	Stage 4: Covering of the posterior insula
27–28 weeks GA	Stage 4: Maturation of the central cerebral regions	Stage 5: Closure of the posterior sylvian fissure

Govaert P, Triulzi F, Dudink J. The developing brain by trimester. Handb Clin Neurol. 2020;171:245-289.

Table 1 Age (menstrual weeks) when some cerebral sulci appear in normal fetuses at anatomical, magnetic resonance imaging and ultrasound examinations

	Examination type/study									
	Anatomical		*Magnetic resonance imaging*					*Ultrasound*		
	Chi et al.[4] *(1977)*	*Dorovini-Zis and Dolman*[5] *(1977)*	*Lan* et al.[9] *(2000)*	*Girard* et al.[6] *(2001)*	*Ruoss* et al.[10] *(2001)*	*Garel* et al.[8] *(2001)*	*Levine and Barnes*[7] *(1999)*	*Bernard* et al.[11] *(1988)*	*Monteagudo and Timor-Tritsch*[16] *(1997)*	*Present study (2004)*
Fetuses (n)	507	80	25	NA	51	173	40	70	262	50
Age range (weeks)	10–44†	22–41‡	12–38§	NA¶	23–43**	22–38††	14–38‡‡	10–37§§	14–40¶¶	15–29***
Interhemispheric sulcus	8–10					(22–23)	14	12		
Callosal sulcus	14				32–40	(22–23)		21	(14)	
Parieto-occipital fissure	16	(22)	26	20	30–33	(22–23)	18–19	25	18	18.5–20.5
Calcarine sulcus	16	(22)		24	29–38	24–25	18–19	25	18	18.5–21.9
Cingulate sulcus	18	24		27	28–33	24–25	24–25	26	26	23.2–24.3
Central sulcus	20	24	24–26	24	24.5–32	27	26–27			
Superior temporal sulcus	23	28	24–26	28		27	26–27			
Convexity sulci*	20–25	24	24–26	24	24.5–32	27	26–27	25–27		23.2–27.9

The numbers in parentheses indicate the age range at which the sulcus was visible on the youngest brain available, although the sulcus was likely to have been identifiable earlier. *Any sulcus on outer convex hemispheric surface, generally central, postcentral or superior temporal sulcus. †Gestational age determined from last menstrual period (LMP) given by mother. Ages when named sulci were seen in 25–50% of brains. ‡Gestational age as given by mother and microscopic evaluation of fetal kidneys. Renal age derived from histology used in 11 cases with unknown or discrepant dates. §Gestational age estimated from LMP compensated by ultrasound crown–rump length measurement. ¶Gestational age determination technique not described. **Postpartum premature and term infant magnetic resonance imaging (MRI) study. Neonatal gestational age was calculated from LMP as well as early prenatal ultrasound. ††Age when sulci visible in over 75% of fetuses. Gestational age determined by 12-week ultrasound scan. ‡‡Gestational age based on LMP. All fetuses underwent an ultrasound scan on the same day as MRI and the ultrasound scan result correlated with menstrual age within 1 week. §§Gestational age determined from LMP and correlated with postnatal Dubowitz score and dating by ultrasound. ¶¶Patients included if they had known dates in agreement with ultrasound dates. ***Present study: 50 measurements in 46 fetuses at different gestational ages. Fetal age calculated from ultrasound biometry, which was in agreement with menstrual dates and/or first-trimester ultrasound scan. NA, not available.

Toi A, Lister WS, Fong KW. How early are fetal cerebral sulci visible at prenatal ultrasound and what is the normal pattern of early fetal sulcal development? Ultrasound Obstet Gynecol. 2004 Dec;24(7):706-15.

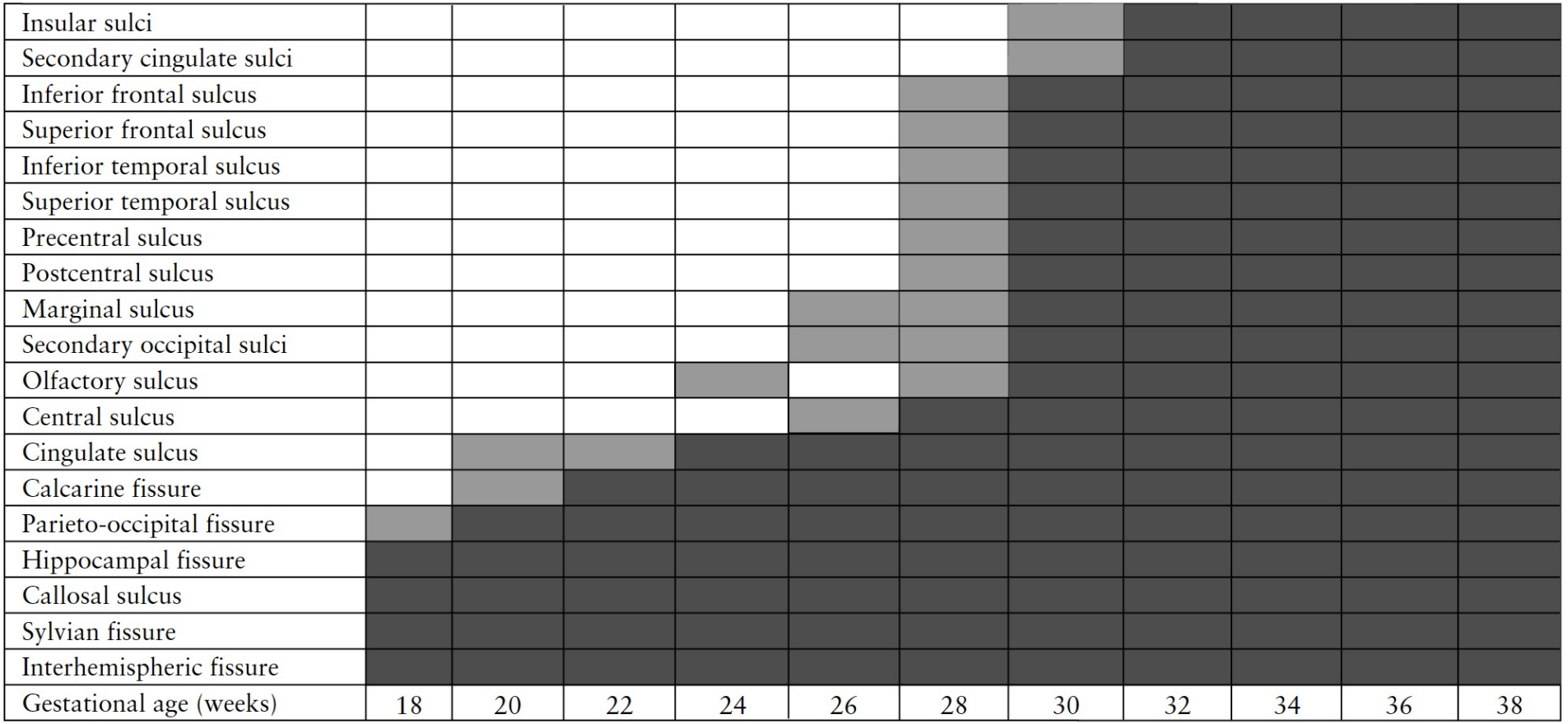

Figure 1 Detectability of sulci and gyri according to gestational age. We considered a particular structure to be present when it was seen in more than 75% of the fetuses (■) detectable if it was observed in 25–75% of the examinations (■) and absent when it was not observed in at least 25% of the examinations (□).

Cohen-Sacher B, Lerman-Sagie T, Lev D, Malinger G. Sonographic developmental milestones of the fetal cerebral cortex: a longitudinal study. Ultrasound Obstet Gynecol. 2006 May;27(5):494-502.

Signos de MDC en US

- Retraso o ausencia de desarrollo de surcos
- Surcos prematuros anormales
- Capa cortical delgada e irregular
- Surcos anormalmente amplios y superdesarrollados
- Surco aislado ampliamente abierto
- Abultamiento nodular hacia los ventrículos laterales
- Hendiduras corticales
- Nódulos ecogénicos intraparenquimatosos

Lerman-Sagie T, Leibovitz Z. Malformations of Cortical Development: From Postnatal to Fetal Imaging. Can J Neurol Sci. 2016 Sep;43(5):611-8.

Signos de MDC en RNM

- Retraso en el desarrollo cortical
- Disgenesia de la cisura de Silvio
- Retraso en aparición de los surcos
- Engrosamiento cortical
- Irregularidad de la pared ventricular
- Ausencia o apariencia anormal de las cisuras
- Giros anormales y asimétricos
- Corteza discontinua

Lerman-Sagie T, Leibovitz Z. Malformations of Cortical Development: From Postnatal to Fetal Imaging. Can J Neurol Sci. 2016 Sep;43(5):611-8.

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A practical approach to prenatal diagnosis of malformations of cortical development

Tally Lerman-Sagie [a, b, c, *], Ivana Pogledic [d], Zvi Leibovitz [a, e, f], Gustavo Malinger [c, g]

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Table 1

Intracranial imaging signs suggestive of fetal MCD.

1. Abnormal development of the Sylvian fissure

1. Abnormal development of the Sylvian fissure
2. Delayed achievement of cortical milestones
3. Premature or aberrant appearance of sulcation
4. Irregular ventricular borders
5. Abnormal cortical thickness (thick, thin)
6. Abnormal shape and orientation of the sulci and gyri
7. Irregular, abnormal, asymmetric, and enlarged hemisphere
8. Simplified cortex
9. Non continuous cortex or cleft
10. Intraparenchymal echogenic nodules.

Lerman-Sagie T, Pogledic I, Leibovitz Z, Malinger G. A practical approach to prenatal diagnosis of malformations of cortical development. Eur J Paediatr Neurol. 2021 Sep;34:50-61.

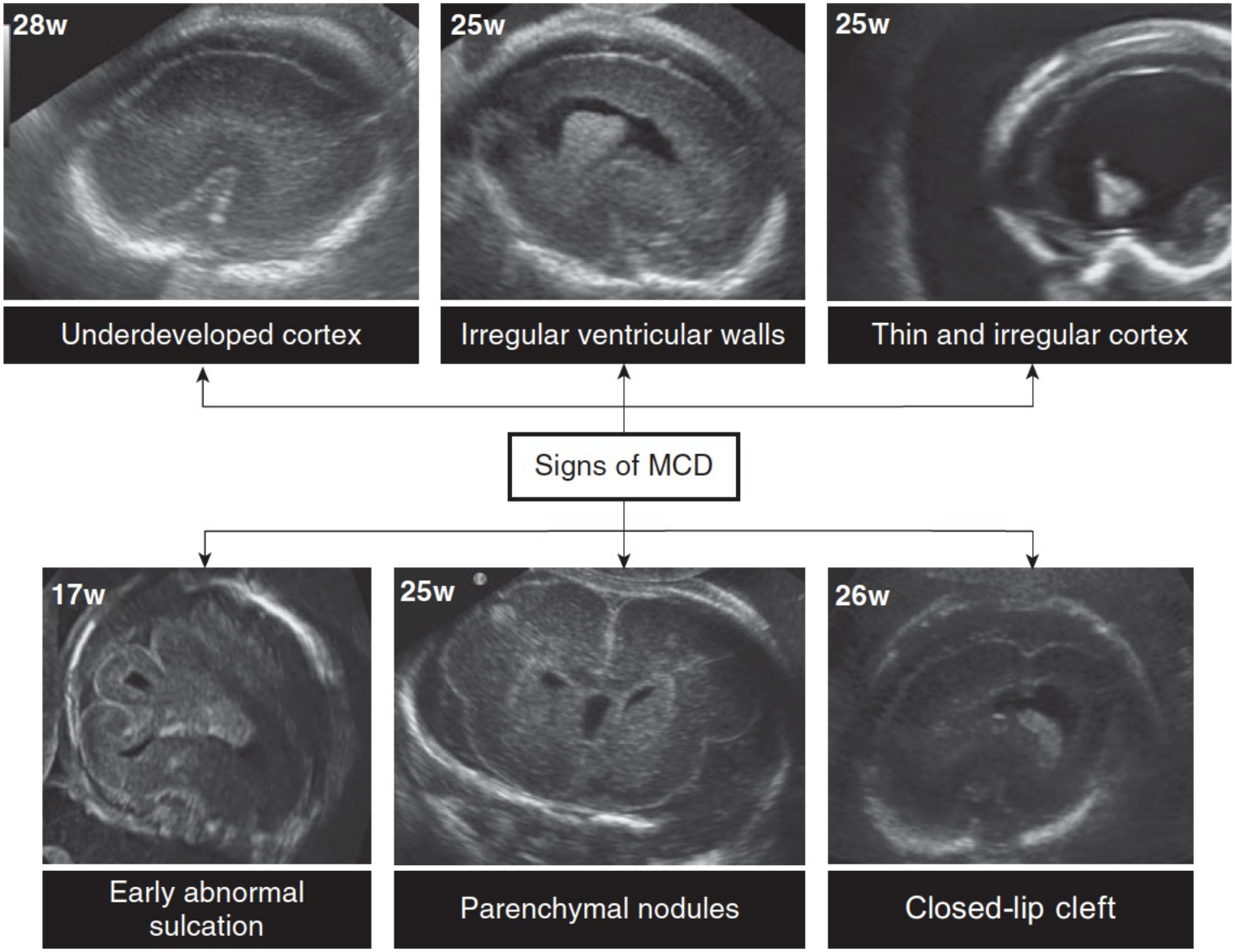

Figure 7–1. Ultrasound signs of malformations of cortical development.

Malformaciones del Desarrollo Cortical

A developmental and genetic classification for malformations of cortical development

A.J. Barkovich, MD; R.I. Kuzniecky, MD; G.D. Jackson, MD; R. Guerrini, MD; and W.B. Dobyns, MD

I. Malformations due to abnormal neuronal and glial proliferation or apoptosis

A. Decreased proliferation/increased apoptosis or increased proliferation/decreased apoptosis—abnormalities of brain size

1. Microcephaly with normal to thin cortex
2. Microlissencephaly (extreme microcephaly with thick cortex)
3. Microcephaly with extensive polymicrogyria
4. Macrocephalies

B. Abnormal proliferation (abnormal cell types)

1. Nonneoplastic
   a. Cortical hamartomas of tuberous sclerosis
   b. Cortical dysplasia with balloon cells
   c. Hemimegalencephaly
2. Neoplastic (associated with disordered cortex)
   a. Dysembryoplastic neuroepithelial tumor
   b. Ganglioglioma
   c. Gangliocytoma

Barkovich AJ, Kuzniecky RI, Jackson GD, Guerrini R, Dobyns WB. A developmental and genetic classification for malformations of cortical development. Neurology. 2005 Dec 27;65(12):1873-87.

A developmental and genetic classification for malformations of cortical development

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II. Malformations due to abnormal neuronal migration

A. Lissencephaly/subcortical band heterotopia spectrum

B. Cobblestone complex/congenital muscular dystrophy syndromes

C. Heterotopia

1. Subependymal (periventricular)

2. Subcortical (other than band heterotopia)

3. Marginal glioneuronal

Barkovich AJ, Kuzniecky RI, Jackson GD, Guerrini R, Dobyns WB. A developmental and genetic classification for malformations of cortical development. Neurology. 2005 Dec 27;65(12):1873-87.

A developmental and genetic classification for malformations of cortical development

A.J. Barkovich, MD; R.I. Kuzniecky, MD; G.D. Jackson, MD; R. Guerrini, MD; and W.B. Dobyns, MD

III. Malformations due to abnormal cortical organization (including late neuronal migration)

A. Polymicrogyria and schizencephaly

1. Bilateral polymicrogyria syndromes

2. Schizencephaly (polymicrogyria with clefts)

3. Polymicrogyria or schizencephaly as part of multiple congenital anomaly/mental retardation syndromes

B. Cortical dysplasia without balloon cells

C. Microdysgenesis

Barkovich AJ, Kuzniecky RI, Jackson GD, Guerrini R, Dobyns WB. A developmental and genetic classification for malformations of cortical development. Neurology. 2005 Dec 27;65(12):1873-87.

A developmental and genetic classification for malformations of cortical development

A.J. Barkovich, MD; R.I. Kuzniecky, MD; G.D. Jackson, MD; R. Guerrini, MD; and W.B. Dobyns, MD

IV. Malformations of cortical development, not otherwise classified

A. Malformations secondary to inborn errors of metabolism

1. Mitochondrial and pyruvate metabolic disorders

2. Peroxisomal disorders

B. Other unclassified malformations

1. Sublobar dysplasia

2. Others

Barkovich AJ, Kuzniecky RI, Jackson GD, Guerrini R, Dobyns WB. A developmental and genetic classification for malformations of cortical development. Neurology. 2005 Dec 27;65(12):1873-87.

Malformaciones del desarrollo cortical

Proliferación

- Microcefalia
  - HC < 2 SD
  - **Corte < 3 SD, sin falsos negativos (Chervenak, 1984)**
  - Corte < 4 SD, sin falsos positivos
  - Incidencia 0,37-0,86 por 10000 nacimientos.
  - Etiología
    - Anomalías cromosómicas
    - Defectos monogénicos
    - Infecciones
    - Factores ambientales

Timor-Tritsch IE, Monteagudo A, Pilu G, Malinger G. eds. *Ultrasonography of the Prenatal Brain, 3e*. McGraw Hill; 2017

Microcefalia

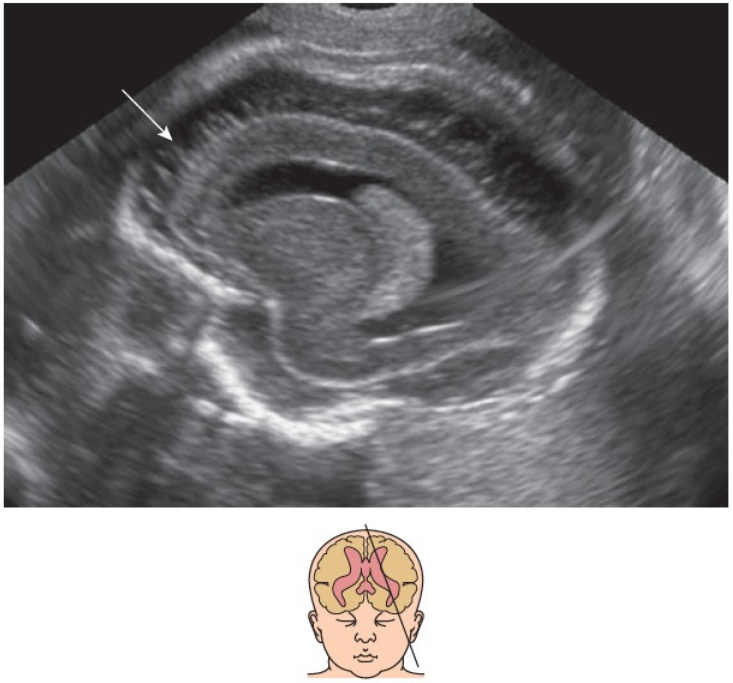


Figure 7–3. Increased amount of subarachnoid fluid due to the presence of a very small brain in a microcephalic fetus at 24 postmenstrual weeks. The abnormal subarachnoid space is particularly evident around the frontal lobe (*arrow*).

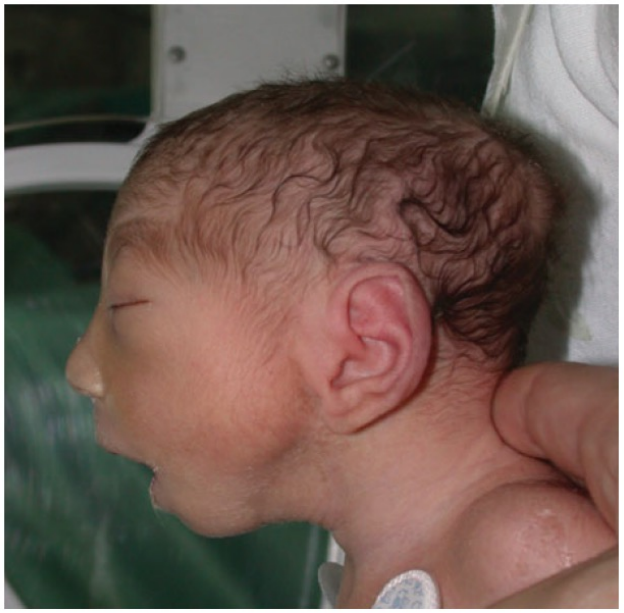


Figure 7–2. Newborn with severe microcephaly showing sloping forehead. The size of the ear is normal but when compared with the small head gives the impression as being big.

Timor-Tritsch IE, Monteagudo A, Pilu G, Malinger G. eds. *Ultrasonography of the Prenatal Brain, 3e*. McGraw Hill; 2017

Malformaciones del desarrollo cortical

Proliferación

- Microcefalia
  - Anomalías asociadas
    - Asociación directa al tamaño cerebral pequeño
    - Asociación a migración anormal
    - Otras anomalías cerebrales
    - Anomalías extra-SNC

Timor-Tritsch IE, Monteagudo A, Pilu G, Malinger G. eds. *Ultrasonography of the Prenatal Brain, 3e*. McGraw Hill; 2017

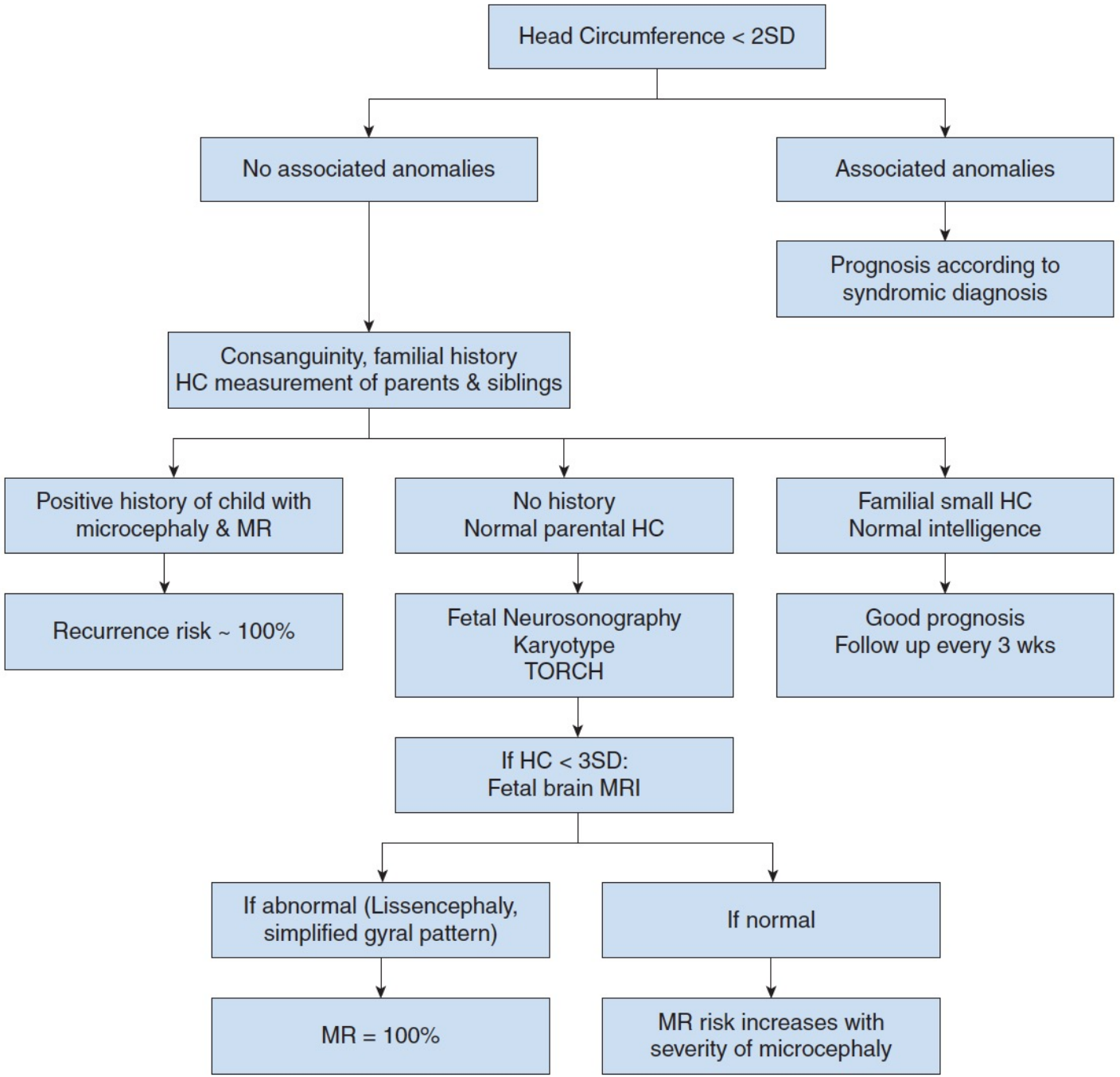


Figure 7–7. Proposed flowchart for the diagnosis of microcephaly.

Malformaciones del desarrollo cortical

Proliferación

- Macrocefalia
  - HC > 2 SD
  - Excluye el aumento de la circunferencia craneana por causas secundarias.
  - Incidencia variable según población seleccionada.
  - Aislada o sindromática

Timor-Tritsch IE, Monteagudo A, Pilu G, Malinger G. eds. *Ultrasonography of the Prenatal Brain, 3e*. McGraw Hill; 2017

Malformaciones del desarrollo cortical

Proliferación

- Macrocefalia
  - Anomalías asociadas
    - Relacionadas al tamaño cerebral
    - Asociadas con malformaciones del desarrollo cortical
    - Otras anomalías cerebrales
    - Anomalías extra SNC

- Pronóstico
  - HC < 2 SD tienen niveles de inteligencia mas bajos pero no retardo mental (OR 1,32; CI 1,11-1,38)
  - Riesgo retardo mental 7 a 10%

Timor-Tritsch IE, Monteagudo A, Pilu G, Malinger G. eds. *Ultrasonography of the Prenatal Brain, 3e*. McGraw Hill; 2017

Macrocefalia

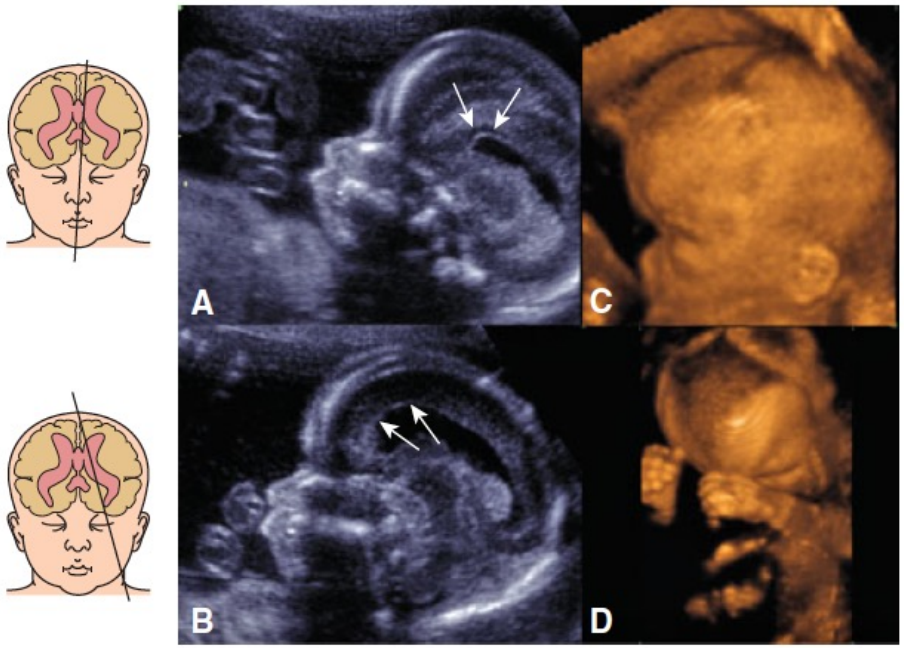


Figure 7–10. Macrocephaly (HC = +2 SD) in a fetus at 20 postmenstrual weeks with chromosome 3q deletion. **(A)** Median section of the brain shows dysgenesis of the corpus callosum (*arrows*). **(B)** Paramedian section shows ventriculomegaly; note the irregular ventricular wall (*arrow*). **(C, D)** Three-dimensional (3D) imaging of the fetal profile shows frontal bossing (C) and wide open anterior fontanelle (D).

Timor-Tritsch IE, Monteagudo A, Pilu G, Malinger G. eds. *Ultrasonography of the Prenatal Brain, 3e*. McGraw Hill; 2017

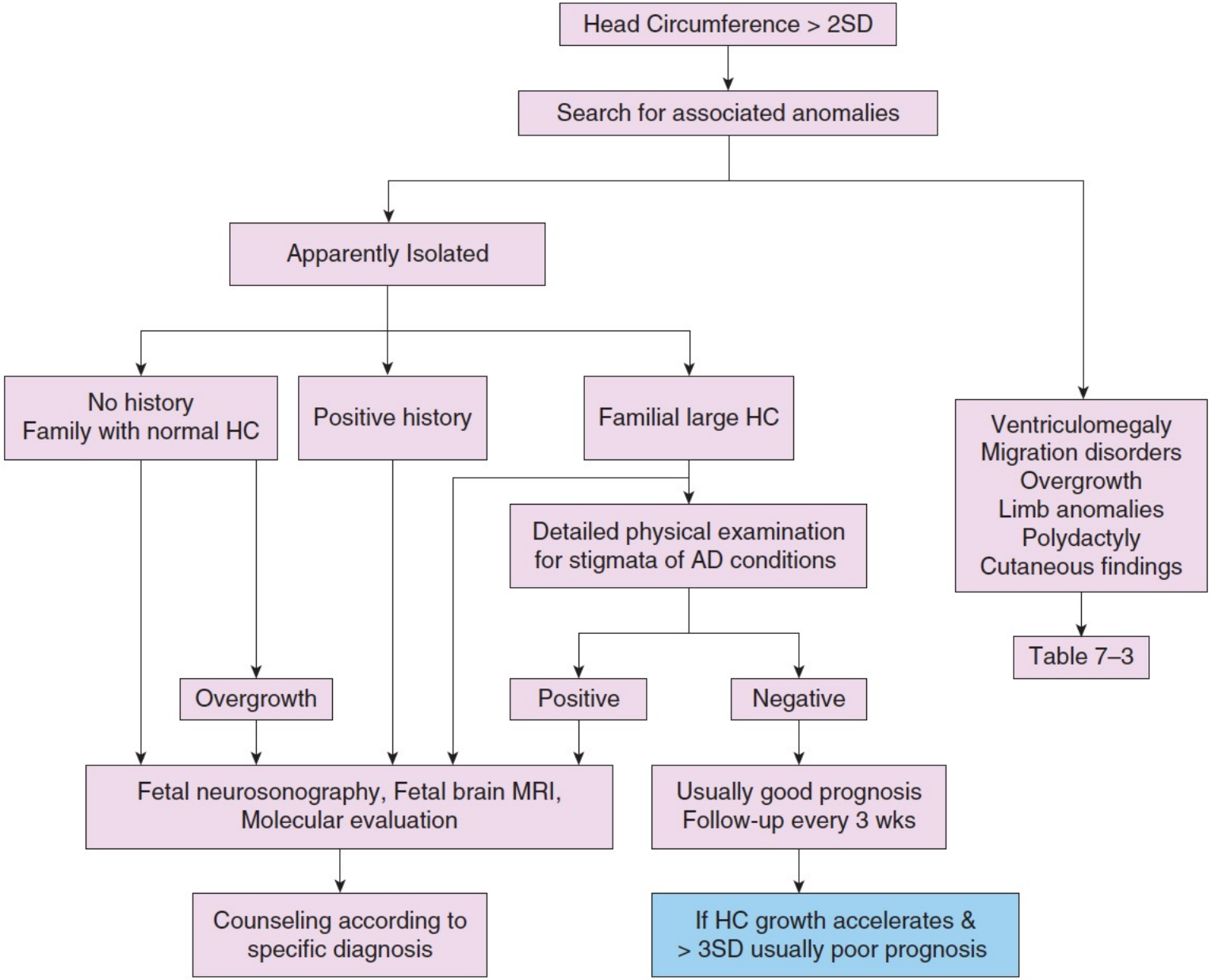


Figure 7–13. Proposed flowchart for the diagnosis of macrocephaly.

Malformaciones del desarrollo cortical

Proliferación

- Complejo Esclerosis Tuberosa
  - Proliferacion anormal de neuronas y glia en forma de hamartoma o tumores de bajo grado acompañado de anomalías de migración y diferenciación.
  - Prevalencia 7-12 por cada 100000 nacidos vivos.
  - Trastorno autosómico dominante.
    - Mutaciones en TSC1 (cromosoma 9) o TSC2 (cromosoma 16).
  - Retardo mental en 50 a 80% de los casos.

Timor-Tritsch IE, Monteagudo A, Pilu G, Malinger G. eds. *Ultrasonography of the Prenatal Brain, 3e*. McGraw Hill; 2017

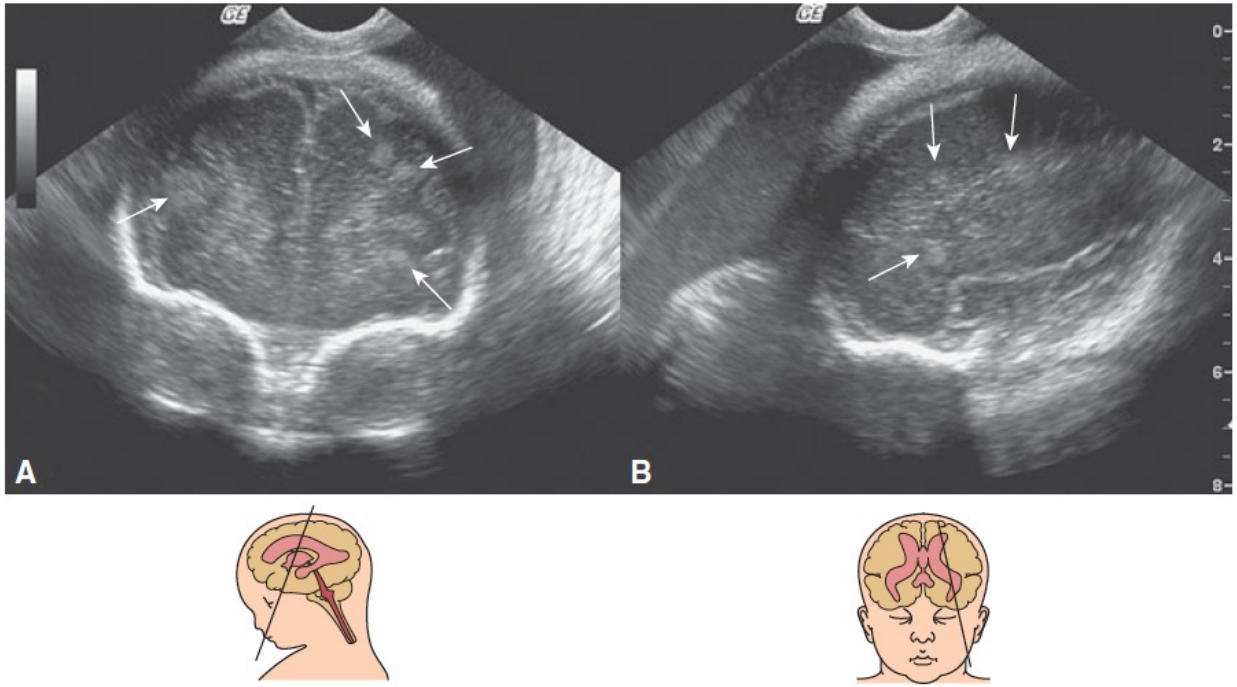


Figure 7–16. Brain transvaginal sonography (TVS) images in a fetus with tuberous sclerosis at 28 postmenstrual weeks (same patient as in Figure 7–14) show multiple parenchymal echogenic nodules (*arrows*). (**A**) Coronal section at the level of the frontal horns. (**B**) Paramedian section lateral to the lateral ventricle.

Timor-Tritsch IE, Monteagudo A, Pilu G, Malinger G. eds. *Ultrasonography of the Prenatal Brain, 3e*. McGraw Hill; 2017

Malformaciones del desarrollo cortical

Proliferación

- Hemimegalencefalia
  - Proliferacion hamartomatosa de un solo hemisferio.
  - La mayoría de los casos son esporádicos.
  - Etiologia desconocida.
  - US
    - Aumento de volumen hemisferio
    - Dilatación ventricular
    - Textura anormal
    - Calcificaciones
    - Características anormales en hemisferio mas pequeño.

Timor-Tritsch IE, Monteagudo A, Pilu G, Malinger G. eds. *Ultrasonography of the Prenatal Brain, 3e*. McGraw Hill; 2017

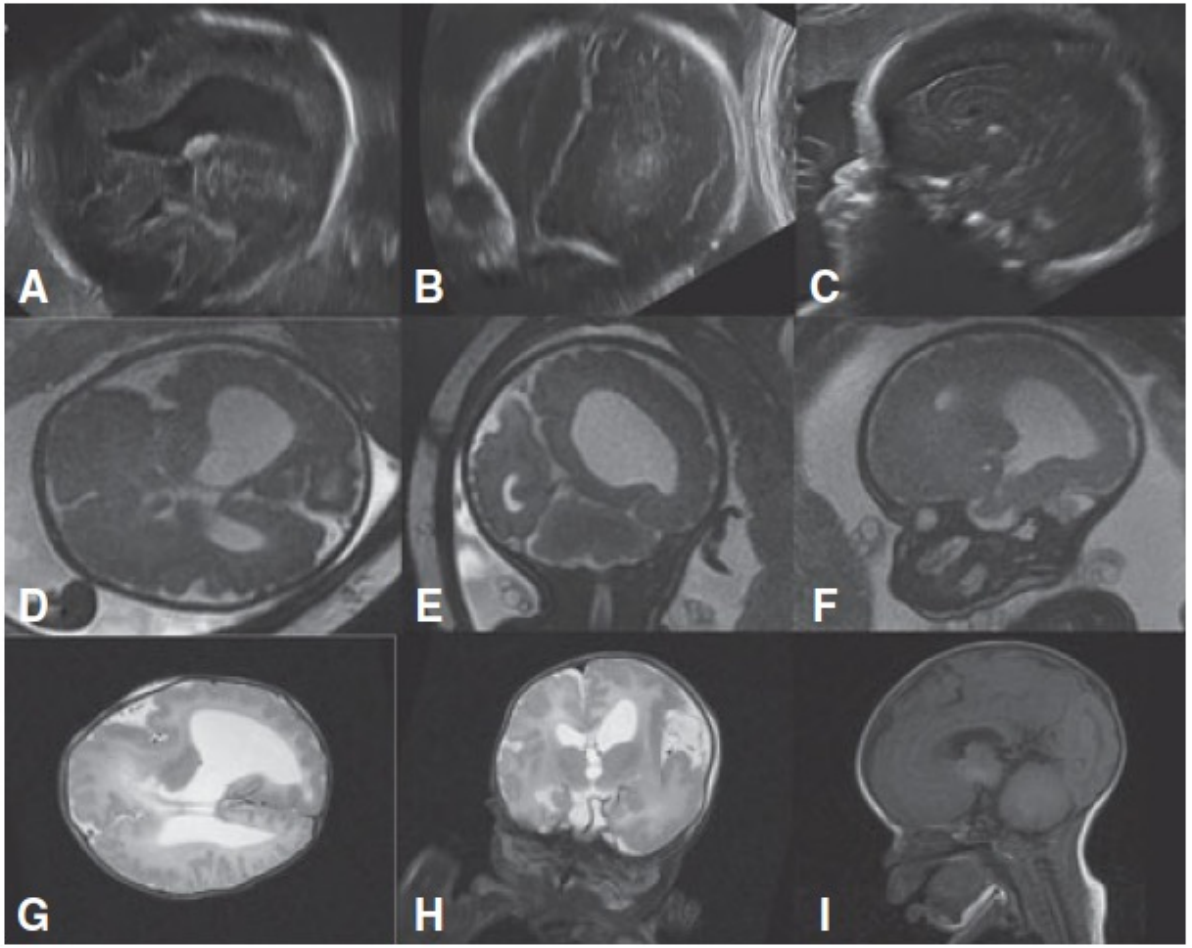


Figure 7–14. Hemimegalencephaly diagnosed by US at 28 postmenstrual weeks of gestation (**A–C**) with MRI confirmation at 29 weeks of gestation (**D–F**) and following delivery (**G–I**). The clinical course was complicated by refractory epilepsy. Note the difference in the size of the cerebral hemispheres and lateral ventricles. The corpus callosum is thick (C, I), and the vermis not observed in the midline (E, I). Abnormal sulcation in the left hemisphere is suggested on fetal images and clearly depicted in both hemispheres on postnatal MRI (G, H). (Courtesy of Dr. Mauricio Herrera, Bogotá, Colombia.)

Malformaciones del desarrollo cortical

Migración

- Lisencefalia/Espectro Heterotopia en banda subcortical
  - Smooth brain
  - Falla en la migración neuronal en alcanzar la superficie cortical
  - Falla total o parcial en formar los surcos y circunvoluciones.
  - La heterotopia en banda subcortical es un fenotipo menos severo que resulta en una corteza delgada con surcos anormales y una segunda capa/banda de neuronas subyacente.

Timor-Tritsch IE, Monteagudo A, Pilu G, Malinger G. eds. *Ultrasonography of the Prenatal Brain, 3e*. McGraw Hill; 2017

Malformaciones del desarrollo cortical

Migración

- Lisencefalia/Espectro Heterotopia en banda subcortical

- Etiologia
  - Autosomica dominante o ligada al X
  - Mutaciones de novo (Recurrencia 1%)
  - 4 tipos genéticos
    - **Mutaciones LIS1 (deficiencia PAFAH)**
    - Mutaciones DCX
    - Mutaciones ARX
    - Mutaciones RELN

Timor-Tritsch IE, Monteagudo A, Pilu G, Malinger G. eds. *Ultrasonography of the Prenatal Brain, 3e*. McGraw Hill; 2017

Malformaciones del desarrollo cortical

Migración

- Lisencefalia/Espectro Heterotopia en banda subcortical
- Peso cerebral normal o bajo
- Cerebro con forma de 9
  - Cisura de Silvio abierta (Falla del frontal y el opérculo temporal en crecer sobre la insula)
- Agiria/Paquigiria
  - Grado 1: Agiria completa
  - Grado 2: Agiria extendida con escasos surcos en frontal y temporal.
  - Grado 3: Extensas áreas de agiria (posterior) y paquigiria (frontal).
  - Grado 4: Paquigiria extendida sin áreas de agiria.

Timor-Tritsch IE, Monteagudo A, Pilu G, Malinger G. eds. *Ultrasonography of the Prenatal Brain, 3e*. McGraw Hill; 2017

Malformaciones del desarrollo cortical

Migración

- Lisencefalia/Espectro Heterotopia en banda subcortical

- Anomalias asociadas
  - Disgenesia de cuerpo calloso
  - Hipoplasia cerebelar
  - CSP amplio
  - Anomalias faciales
    - Frente prominente
    - Nariz corta
    - Labio superior prominente
    - Mandibula pequeña

- Malformaciones extra SNC
  - Cardiacas 20-25%
  - Genitales (en hombres) 70%
  - Extremidades (dedos) 40-45%

Timor-Tritsch IE, Monteagudo A, Pilu G, Malinger G. eds. *Ultrasonography of the Prenatal Brain, 3e*. McGraw Hill; 2017

Malformaciones del desarrollo cortical

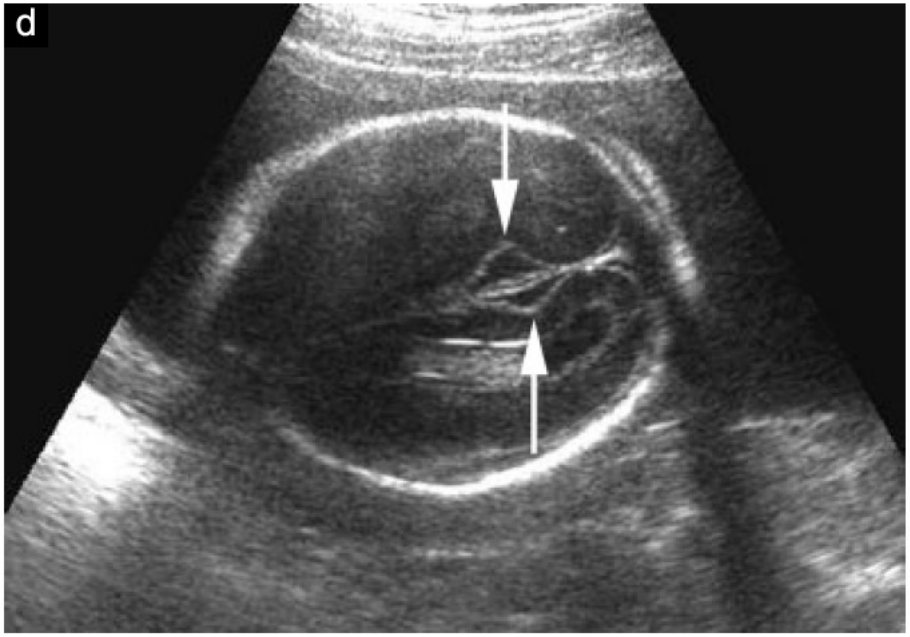
Migración

- Lisencefalia/Espectro Heterotopia en banda subcortical

- Diagnóstico US:
  - Patron de surcos anormales (usualmente simétrico)
    - Cisura de Silvio y cisura parieto-occipital en 2do trimestre
  - Ventriculomegalia leve

- Pronóstico
  - Retardo mental profundo
  - LIS1 aislado no se asocia a otras malformaciones
  - Sindrome Miller-Dieker es siempre severo

Timor-Tritsch IE, Monteagudo A, Pilu G, Malinger G. eds. *Ultrasonography of the Prenatal Brain, 3e*. McGraw Hill; 2017



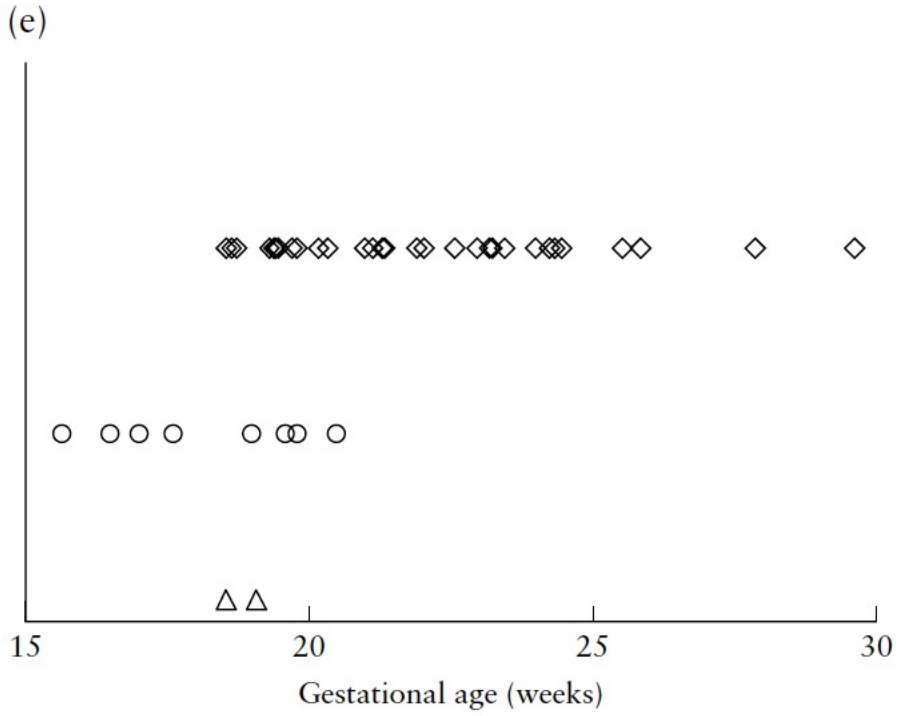
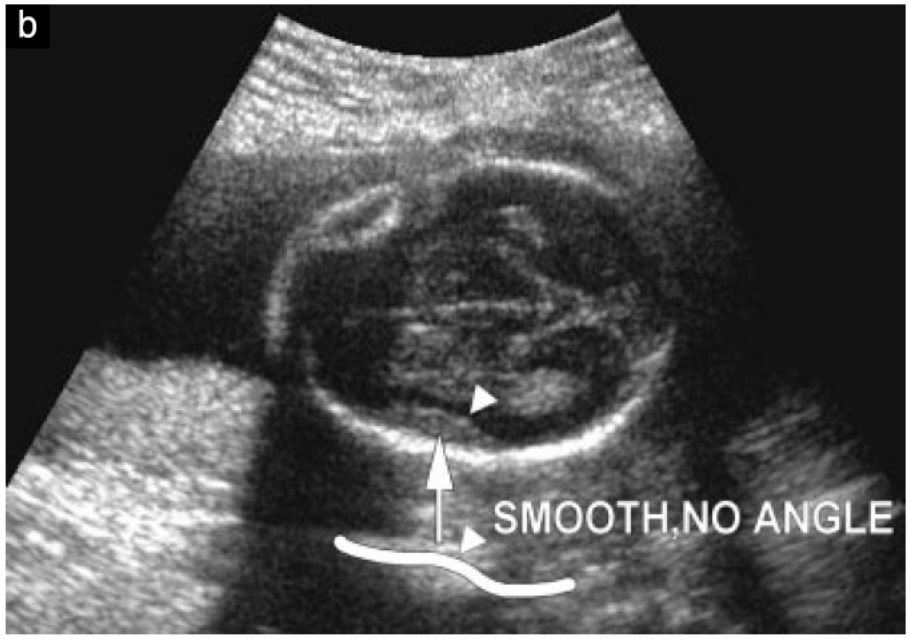
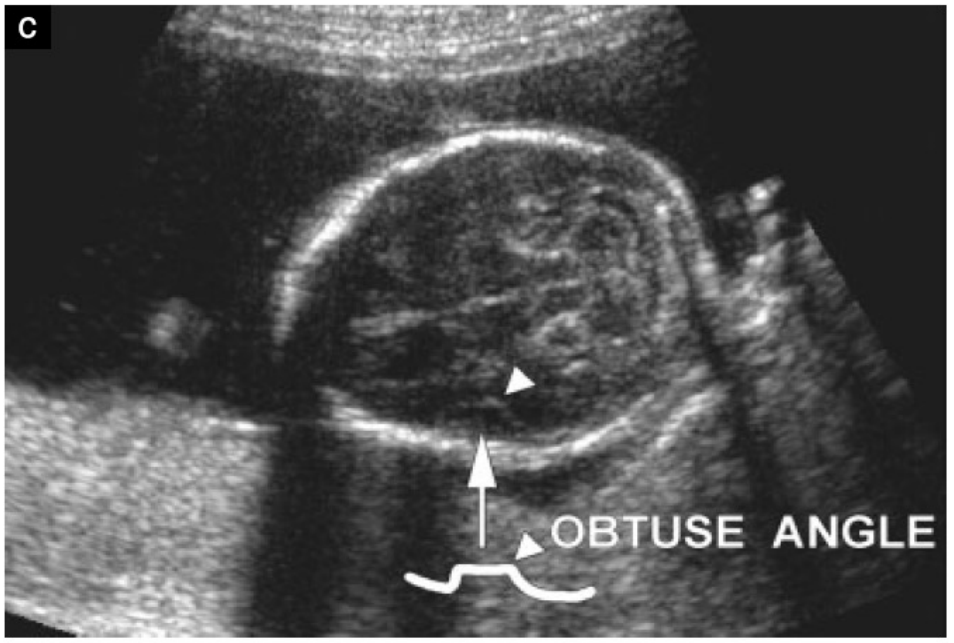
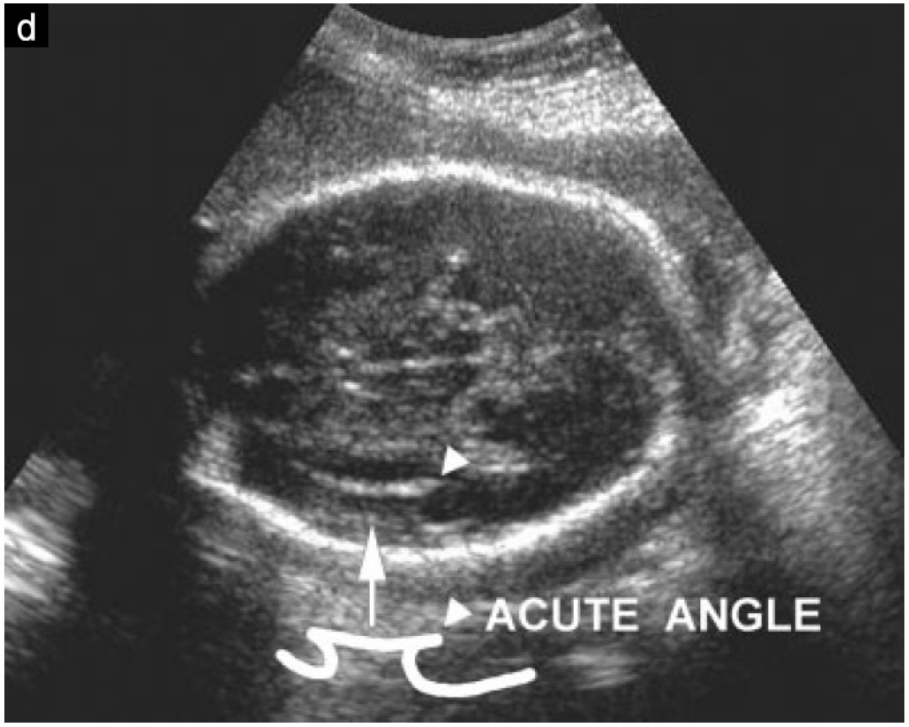


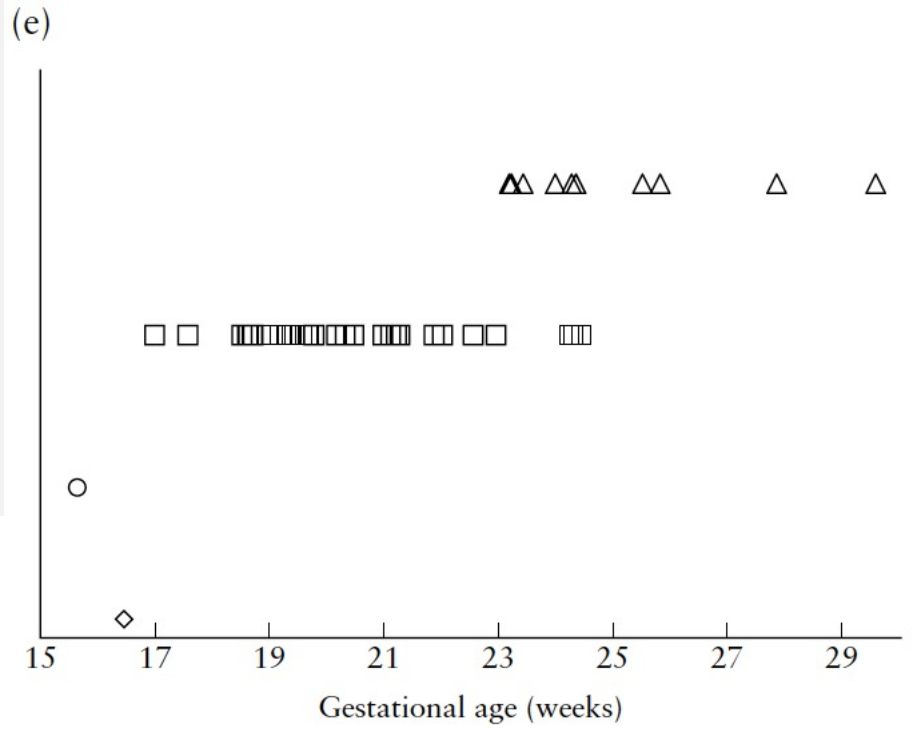
Figure 2 Parieto-occipital fissure. (a) Optimal axial plane of section through brain to show parieto-occipital fissure. (b) Ultrasound image of a 17-week fetus showing smooth medial hemispheric brain surface (arrow) before formation of the parieto-occipital fissure. (c) Ultrasound image of an 18.7-week fetus showing earliest indication of the parieto-occipital fissure as a small dot on the near and far hemispheric surface (arrow). (d) Ultrasound image of a 24.3-week fetus with more advanced fissure development (arrows) giving a diamond shape. (e) Graph illustrating the visibility of the parieto-occipital fissure in individual fetuses at different gestational ages. ◇, visible; ○, not visible; △, unable to assess.

Toi A, Lister WS, Fong KW. How early are fetal cerebral sulci visible at prenatal ultrasound and what is the normal pattern of early fetal sulcal development? Ultrasound Obstet Gynecol. 2004 Dec;24(7):706-15.


b
SMOOTH,NO ANGLE


c
OBTUSE ANGLE


d
ACUTE ANGLE


(e)
15
17
19
21
23
25
27
29
Gestational age (weeks)

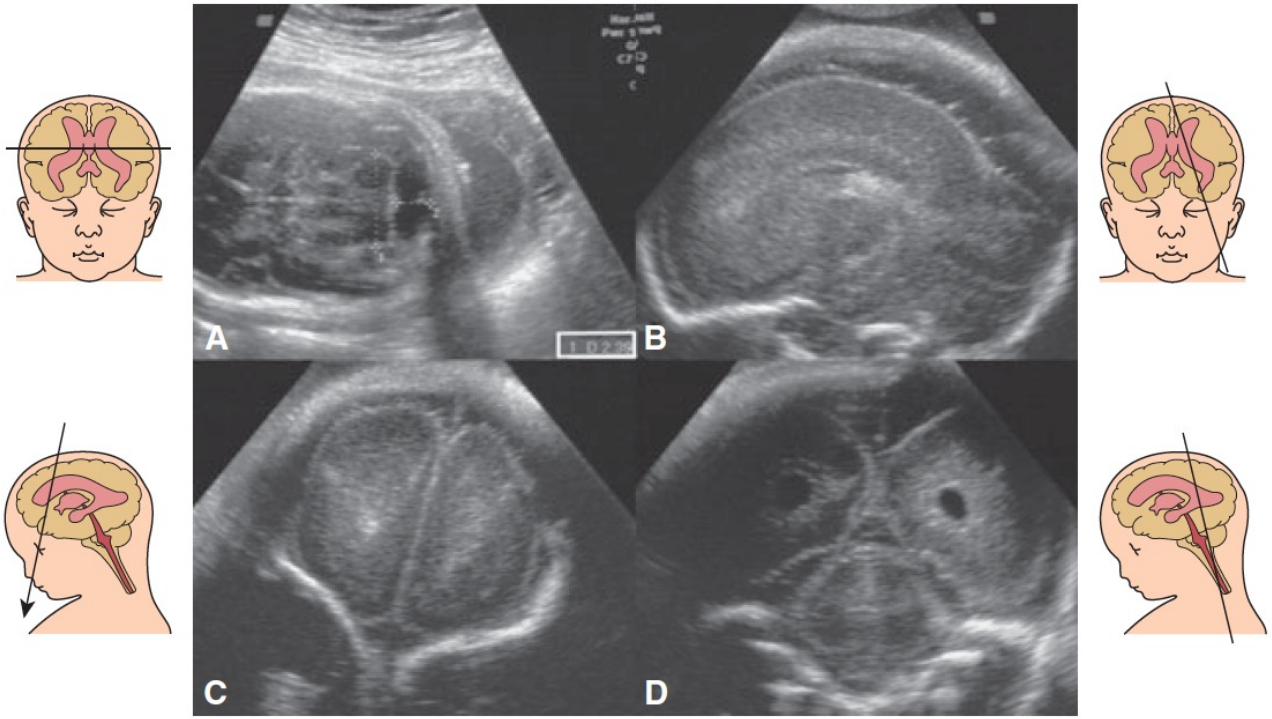


Figure 7–20. Lissencephaly with cerebellar hypoplasia at 28 postmenstrual weeks. **(A)** The transverse cerebellar diameter is well below the fifth percentile. Median **(B)** and coronal **(C, D)** planes showing the lack of sulcation. Note the abnormal shape and small size of the cerebellum **(D)**.

Timor-Tritsch IE, Monteagudo A, Pilu G, Malinger G. eds. *Ultrasonography of the Prenatal Brain, 3e*. McGraw Hill; 2017

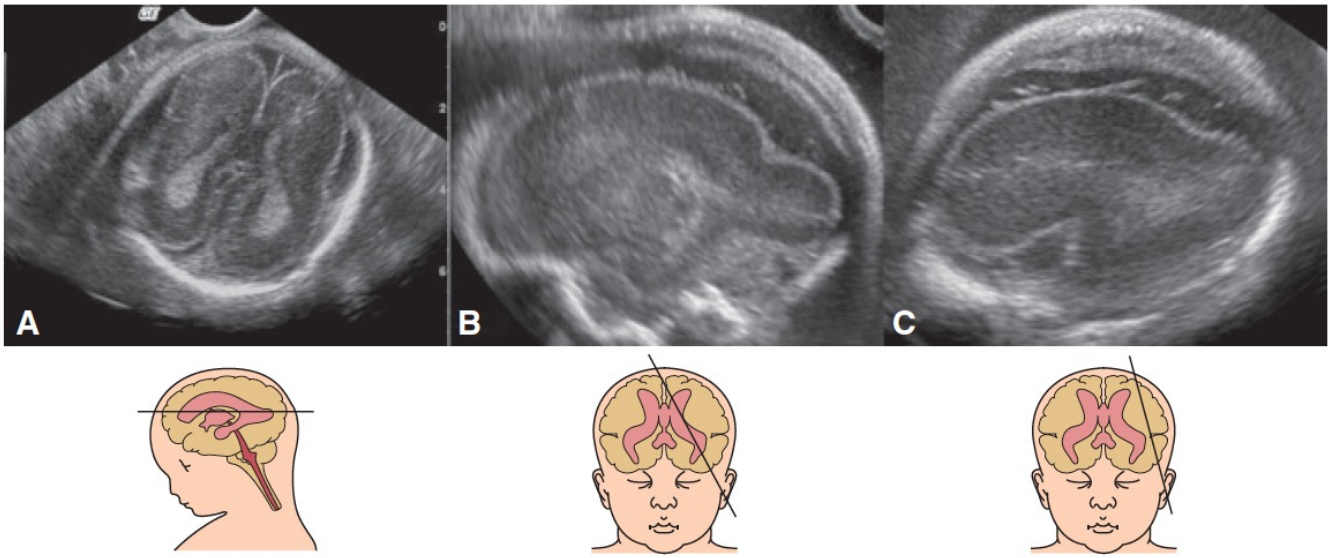


Figure 7–21. Autosomal recessive lissencephaly at 22 **(A, B)** and 25 **(C, D)** postmenstrual weeks of gestation. Two previous children were born with agyria and multiple malformations. At 22 weeks of gestation, the sylvian fissure is absent, and the shape of the brain is abnormal, but only at 25 weeks is the abnormal sulcation evident.

Timor-Tritsch IE, Monteagudo A, Pilu G, Malinger G. eds. *Ultrasonography of the Prenatal Brain, 3e*. McGraw Hill; 2017

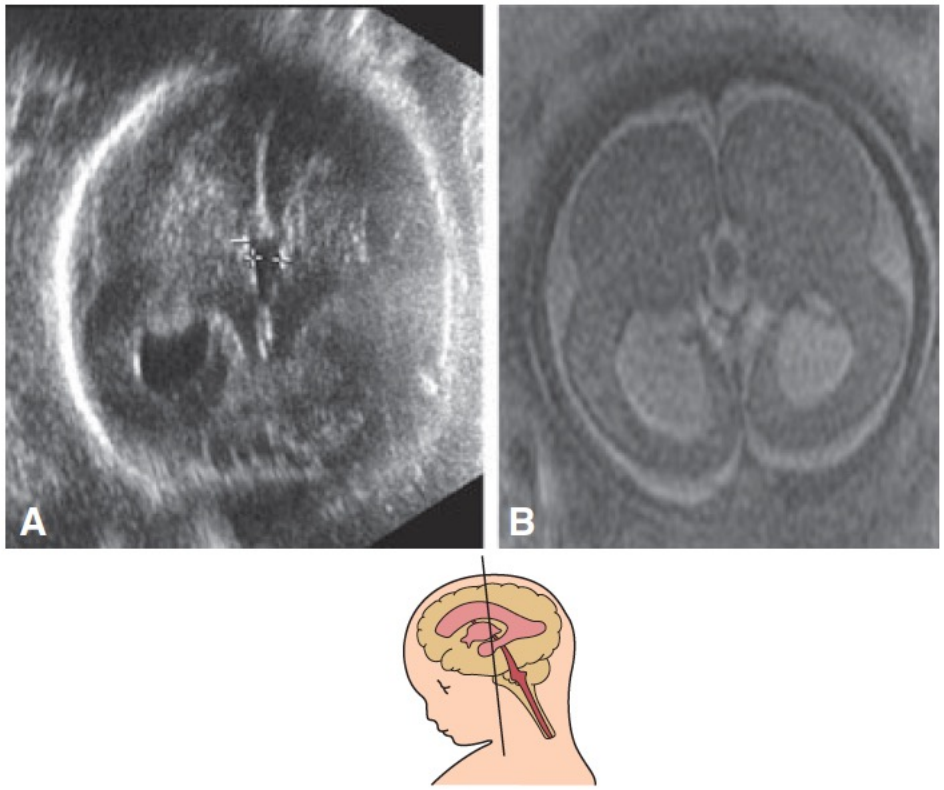


Figure 7–22. Lissencephaly at 33 postmenstrual weeks. Transabdominal US **(A)** and MRI **(B)** axial planes show the lack of sulcation colpocephaly with thick cortex and mild ventriculomegaly. Note the "figure eight" configuration in the MRI.

Timor-Tritsch IE, Monteagudo A, Pilu G, Malinger G. eds. *Ultrasonography of the Prenatal Brain, 3e*. McGraw Hill; 2017

Malformaciones del desarrollo cortical

Migración

- Complejo Cobblestone
  - Migracion anormal de las neuronas a través de la pia y en las meninges.
  - Las capas de la corteza no se desarrollan normalmente y se puede encontrar tejido heterotopico entre la sustancia blanca y la pia.
  - La migración neuronal invade el espacio subaracnoideo resultando en un cerebro predominantemente liso pero con modularidad sutil y vasos que están enterrados en la superficie cerebral.
  - El mas común es el Sindrome Walker-Walburg

Timor-Tritsch IE, Monteagudo A, Pilu G, Malinger G. eds. *Ultrasonography of the Prenatal Brain, 3e*. McGraw Hill; 2017

Malformaciones del desarrollo cortical

Migración

- Complejo Cobblestone / Sindrome Walker-Walburg
  - Autosomico recesivo
  - Distrofia muscular congénita / Lisencefalia / Malformaciones oculares
  - Mutaciones en 6 genes (**POMT1**, POMT2, POMGNT1, FCMD, FKRP, LARGE).

Timor-Tritsch IE, Monteagudo A, Pilu G, Malinger G. eds. *Ultrasonography of the Prenatal Brain, 3e*. McGraw Hill; 2017

Malformaciones del desarrollo cortical

Migración

- Complejo Cobblestone / Sindrome Walker-Walburg

- Anomalías asociadas
  - Ventriculomegalia / Hidrocefalia
  - Macrocefalia
  - Malformación Dandy-Walker
  - Cefalocele
  - Extra SNC
    - Microftalmia
    - Colobomas
    - Cataratas congénitas
    - Fisura labiopalatina
    - Anomalias genitales (hombres)

Timor-Tritsch IE, Monteagudo A, Pilu G, Malinger G. eds. *Ultrasonography of the Prenatal Brain, 3e*. McGraw Hill; 2017

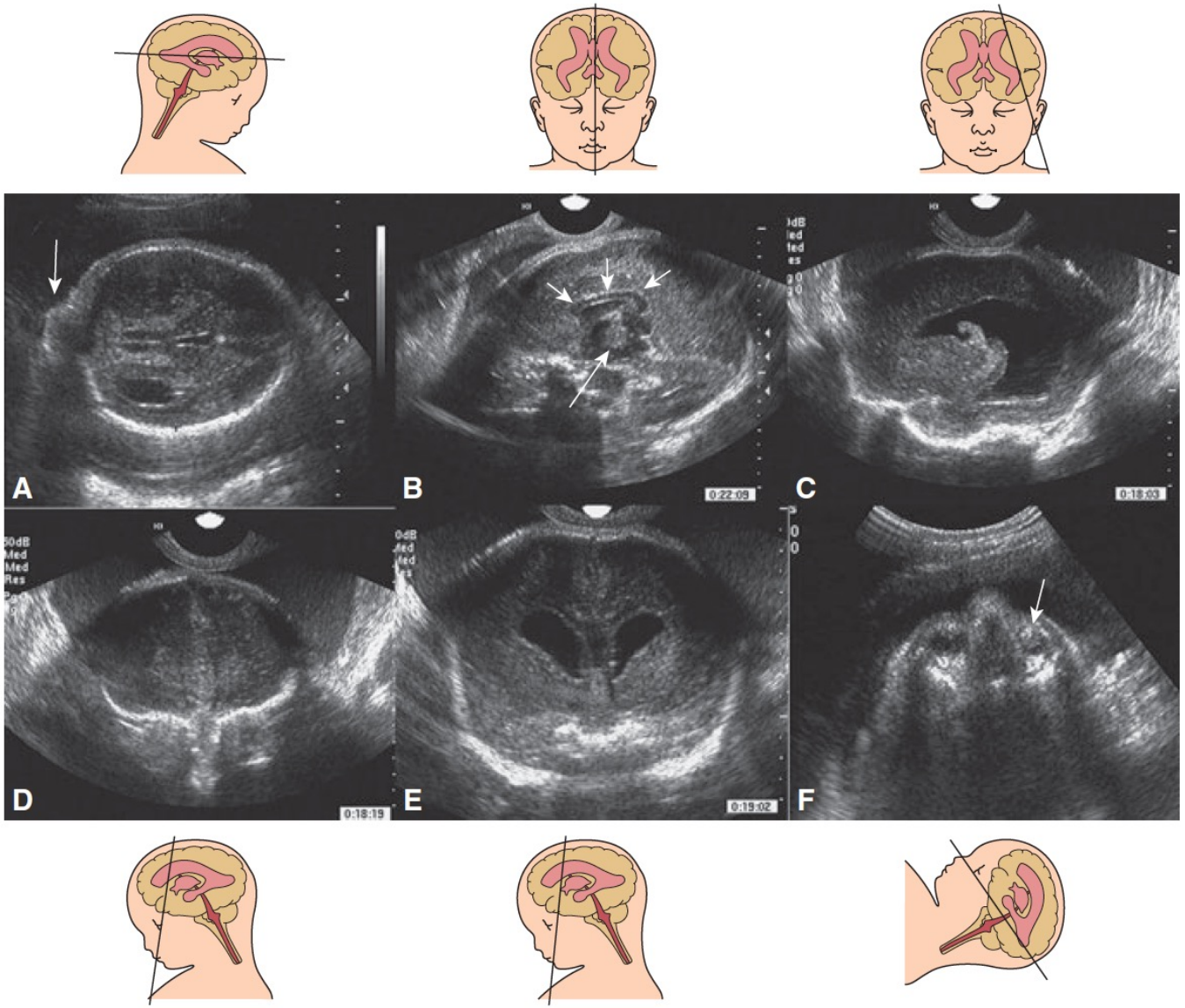
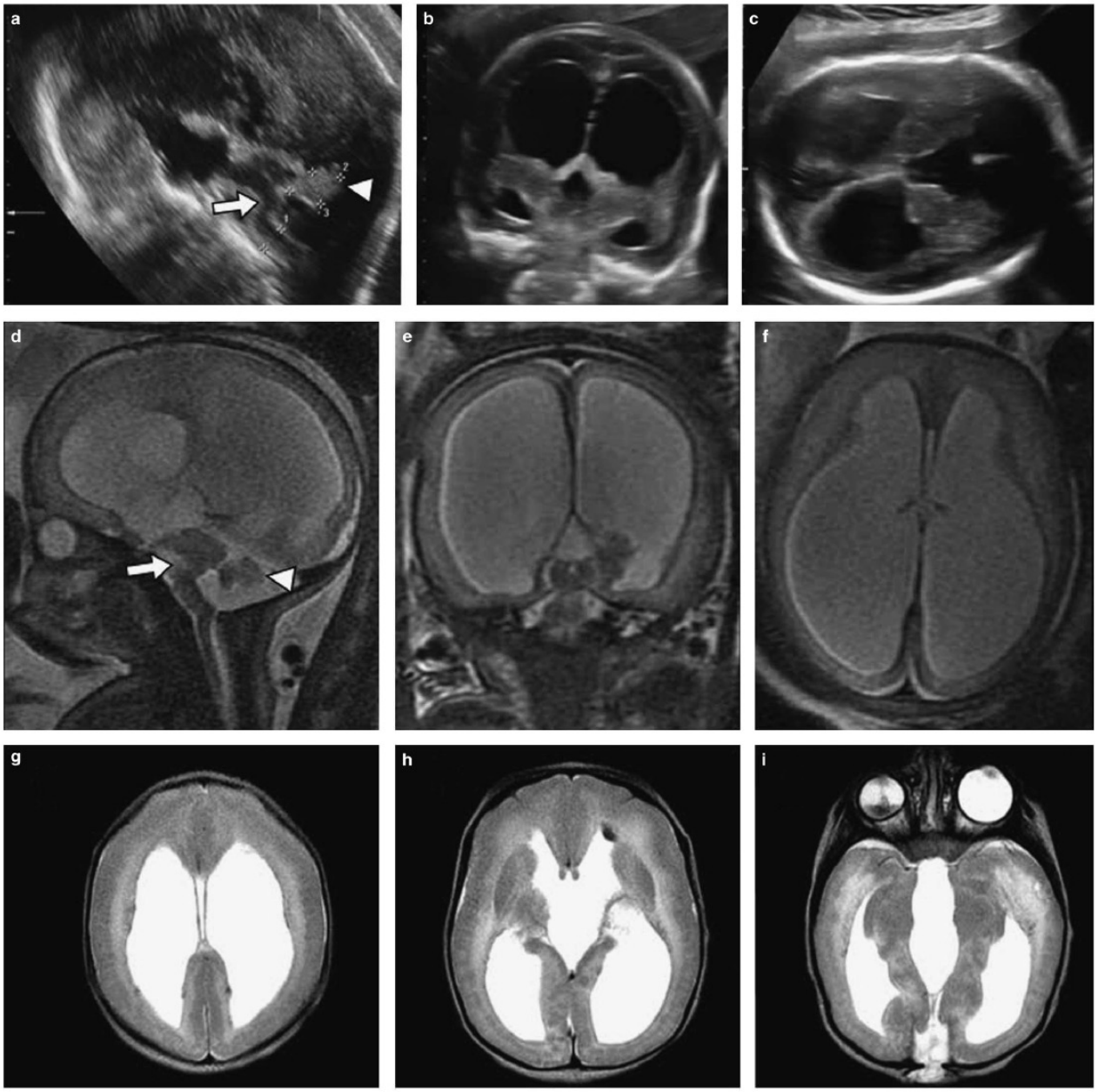


Figure 7–24. Walker-Warburg syndrome (WWS) in a fetus at 34 postmenstrual weeks referred because of ventriculomegaly. **(A)** Transabdominal axial plane shows the presence of a small occipital encephalocele (*arrow*). Note the apparently normal size of the distal lateral ventricle and the lack of sulcation on the same side. **(B)** Transvaginal median plane shows dysgenesis of the corpus callosum. The corpus callosum is shorter than usual, and the genu and splenium are poorly developed (*small arrows*). Note the clear visualization of the intrathalamic adhesion due to dilation of the third ventricle (*large arrow*). **(C)** Paramedian plane shows lateral ventricle dilation and lissencephalic cortex. **(D)** Frontal coronal plane shows almost a complete lack of sulcation. **(E)** Transcaudate coronal plane shows the dilated lateral ventricles and no sulci and gyri. **(F)** Left eye cataract (*arrow*). (With permission from Monteagudo A, 2001.[142])



CERPO

Figure 3: *Cobblestone malformation, prenatal and postnatal imaging (three different cases). (A-C) Ultrasound images at 26 gestational weeks (sagittal, coronal, and axial). Note severe ventriculomegaly, absence of the Sylvian fissures, no primary sulcation, "Z"-shaped (kinked) brainstem (arrow), and hypoplastic vermis (arrowhead). (D-F) Fetal MRI, sagittal, coronal, and axial images at 34 weeks demonstrate "Z"-shaped (kinked) brainstem (arrow), hypoplastic vermis (arrowhead), severe ventricular dilatation, and abnormal sulcation with thin cortex (courtesy of Dr. Chen Hoffman). (G-I) Neonatal MRI, sequential axial images. Note triventricular hydrocephalus, thick irregular cortex with a cobblestone appearance, increased T2 signal from white matter with no interdigitation, retinal detachment, phthisis bulbi of the right eye, and posterior encephalocele. (In addition, small intraventricular blood clots in G and H).*

Malformaciones del desarrollo cortical

Migración

- Heterotopias
- Presencia de trazados o nódulos de neuronas normales en localizaciones anormales por falla en la migrecion desde la matriz germinal periventricular a la corteza
- Tipos (según RNM)
  - **Periventricular nodular**: Nodulos en la región subependimaria de los ventrículos.
  - Focal subcortical: Nodulos en la sustancia blanca.
  - En banda: Sindrome de doble corteza (lisencefalia)

Timor-Tritsch IE, Monteagudo A, Pilu G, Malinger G. eds. *Ultrasonography of the Prenatal Brain, 3e*. McGraw Hill; 2017

Malformaciones del desarrollo cortical

Migración

- Heterotopias
  - Defectos en Filamina A (FLNA)
  - El mas frecuente es el periventricular nodular.
    - Autosomico dominante ligado al X
    - Letal en hombres
  - Anomalias asociadas
    - Microcefalia
    - Polimicrogiria
    - Hipoplasia cerebelar
    - Ventriculomegalia
    - Agenesia cuerpo calloso
    - Lisencefalia
    - Extra SNC: valvulopatia aortica, DAP, aneurisma aórtico, displasia frontonasal, anomalías extremidades, genitales ambiguos.

Timor-Tritsch IE, Monteagudo A, Pilu G, Malinger G. eds. *Ultrasonography of the Prenatal Brain, 3e*. McGraw Hill; 2017

Malformaciones del desarrollo cortical

Migración

- Heterotopias
- Diagnostico US
  - Pared del ventrículo lateral con irregularidad variable e indentaciones de los nódulos heterotopicos.
- Diagnostico diferencial
  - Esclerosis tuberosa
  - Hemorragia periventricular
  - Infecciones

Timor-Tritsch IE, Monteagudo A, Pilu G, Malinger G. eds. *Ultrasonography of the Prenatal Brain, 3e*. McGraw Hill; 2017

Heterotopia nodular periventricular

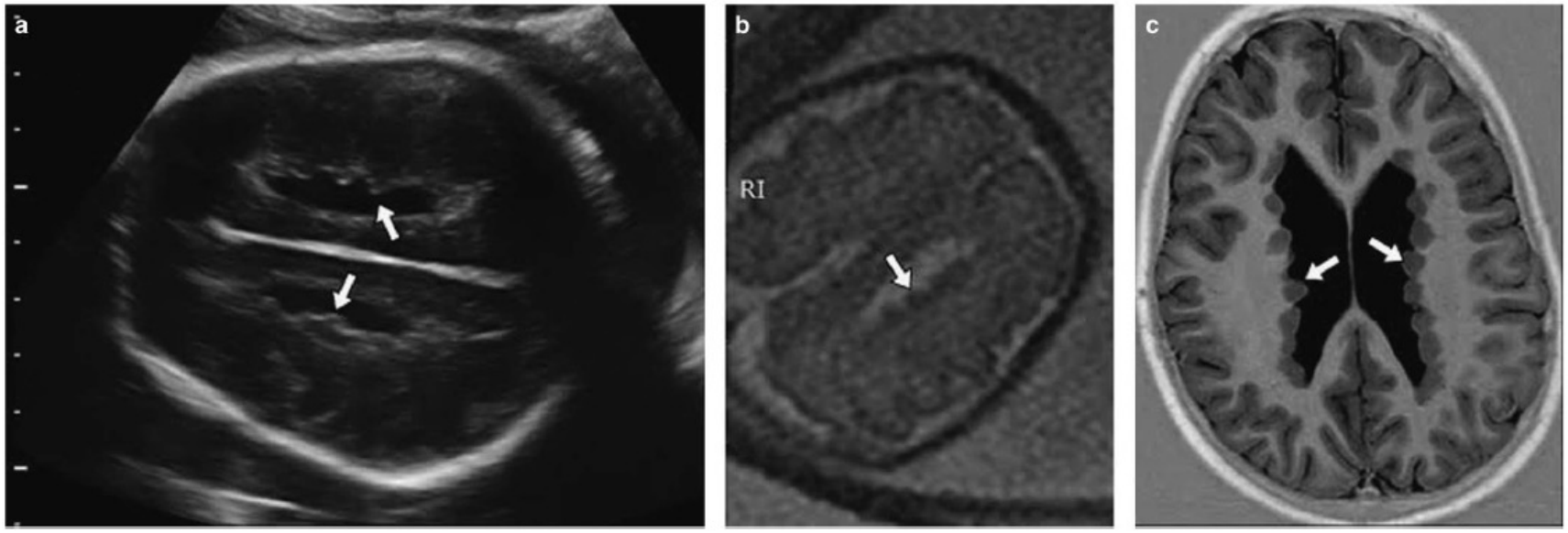


Figure 4: *Periventricular nodular heterotopia, prenatal and postnatal imaging. (A) Ultrasound axial image at 32 gestational weeks. (B) MRI of the same fetus at 33 weeks. Note nodular bulging into the ventricles (arrows). (C) Adult MRI (axial image) showing classical periventricular nodular heterotopia (arrows) with a "string of pearls" appearance.*

Lerman-Sagie T, Leibovitz Z. Malformations of Cortical Development: From Postnatal to Fetal Imaging. Can J Neurol Sci. 2016 Sep;43(5):611-8.

Heterotopia nodular periventricular

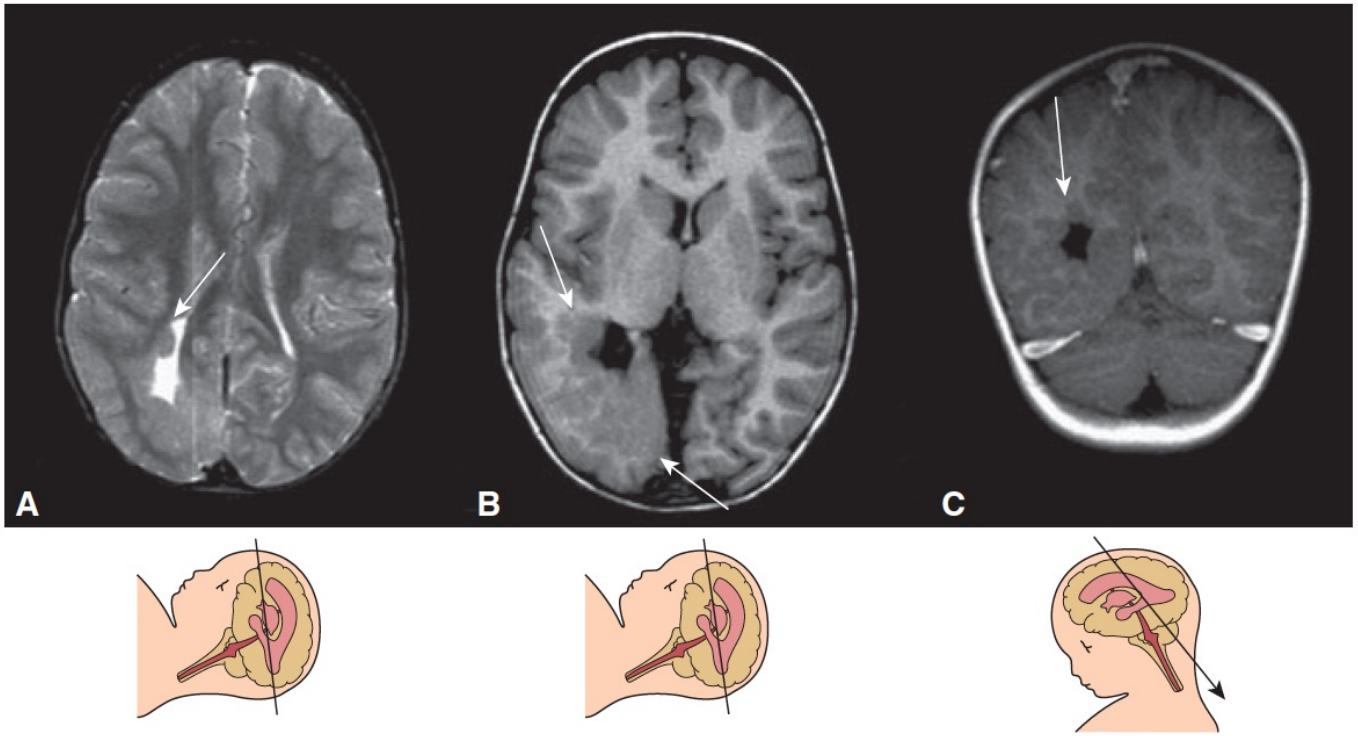


Figure 7–29. Periventricular nodular heterotopia initially evaluated due to fetal asymmetric ventriculomegaly and suspected white matter echogenicity. The girl developed complex partial seizures by the age of 2 years. The MRI was performed at the age of 5 years following the first episode of generalized seizures.T2 axial **(A),** T1 axial **(B),** and T1 coronal **(C)** images demonstrate periventricular heterotopia surrounding and protruding into the occipital horn and associated abnormal overlying cortex.

Timor-Tritsch IE, Monteagudo A, Pilu G, Malinger G. eds. *Ultrasonography of the Prenatal Brain, 3e*. McGraw Hill; 2017

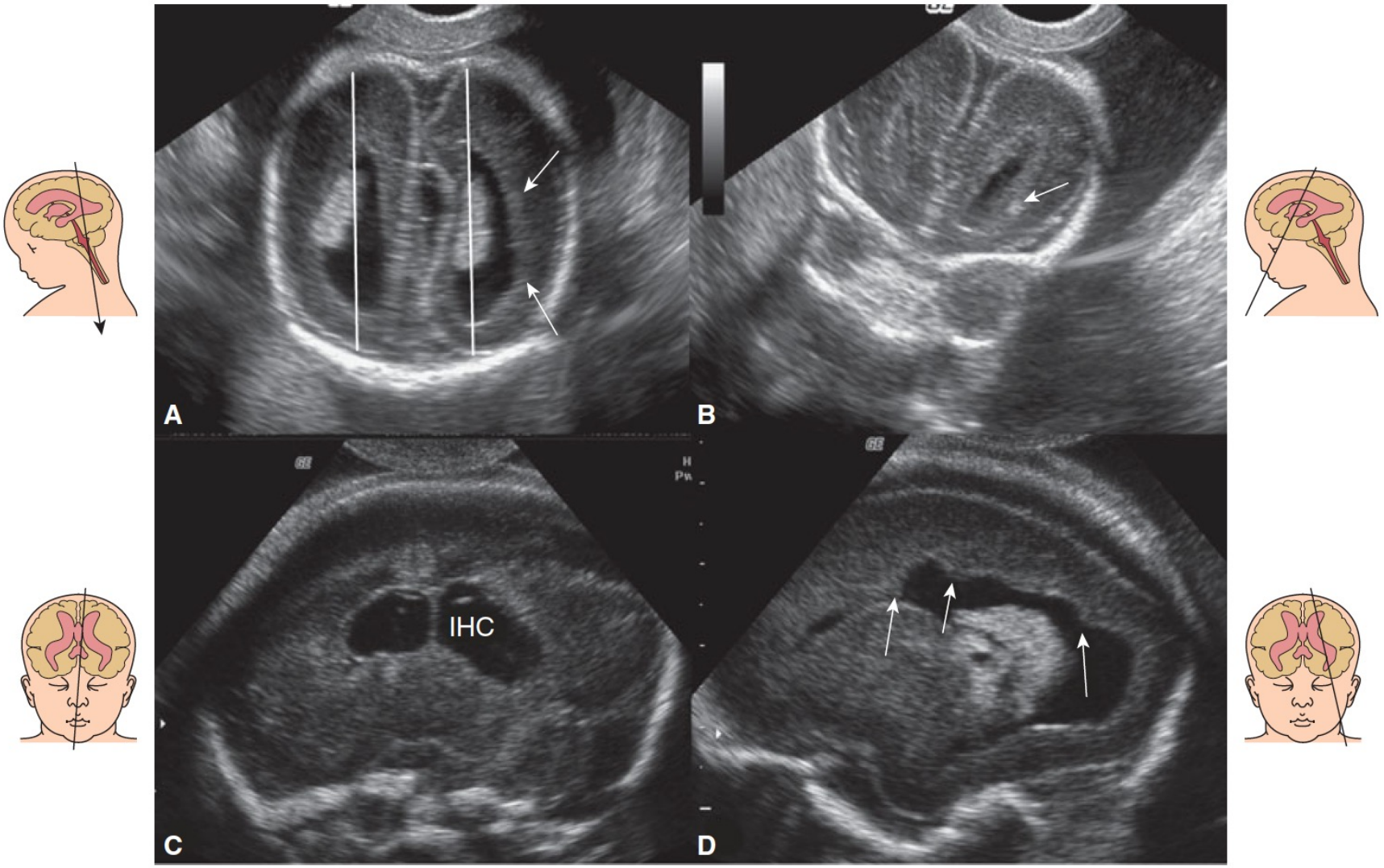


Figure 7–30. Histologically confirmed periventricular nodular heterotopia with agenesis of the corpus callosum in a female fetus at 22 postmenstrual weeks of gestation. Transvaginal technique. **(A)** Modified axial plane shows parallel colpocephalic lateral ventricles. Note the increase in echogenicity at the periventricular zone (*arrows*). **(B)** Frontal coronal plane shows a single hyperechogenic nodule. **(C)** Median plane fails to show the corpus callosum that has been replaced by large intrahemispheric cysts (IHC). **(D)** Paramedian plane at the level of the lateral ventricle shows the irregular ventricular wall with nodules protruding into the ventricle (*arrows*).

Malformaciones del desarrollo cortical

Organización

- Polimicrogiria

- Interrupción en el desarrollo cortical en la fase de migración neuronal tardía o desarrollo post migración.
- Surcos excesivos.
- Desorganización de las 6 capas de laminación de la corteza

- Focal, multifocal o difusa.
- Unilateral/Bilateral
- Simétrica/Asimétrica

- Localización mas común en el aspecto posterior de la cisura de Silvio (60-70% de los casos).

Lerman-Sagie T, Leibovitz Z. Malformations of Cortical Development: From Postnatal to Fetal Imaging. Can J Neurol Sci. 2016 Sep;43(5):611-8.

Malformaciones del desarrollo cortical

Organización

- Polimicrogiria

- Etiología
  - Infecciones congénitas (CMV)
  - Isquemia
  - Trastornos genéticos

- Diagnostico US:
  - Ausencia de surcos normales con múltiples plegamientos anormales en la corteza afectada.
  - Aparición de surcos no esperados para la edad gestacional
  - Desarrollo opercular anormal
  - Superficie cerebral irregular

Table 1 Genes associated with polymicrogyria.

Gene	Location
SRPX2	Xq21.33-q23
RAB3GAP1	2q21.3
EOMES	3p21.3-p21.2
TUBB2B	6p25
KIAA1279	10q22.1
PAX6	11p13
COL18A1	21q22.3
Multiple genes	22q11.2

Lerman-Sagie T, Leibovitz Z. Malformations of Cortical Development: From Postnatal to Fetal Imaging. Can J Neurol Sci. 2016 Sep;43(5):611-8.

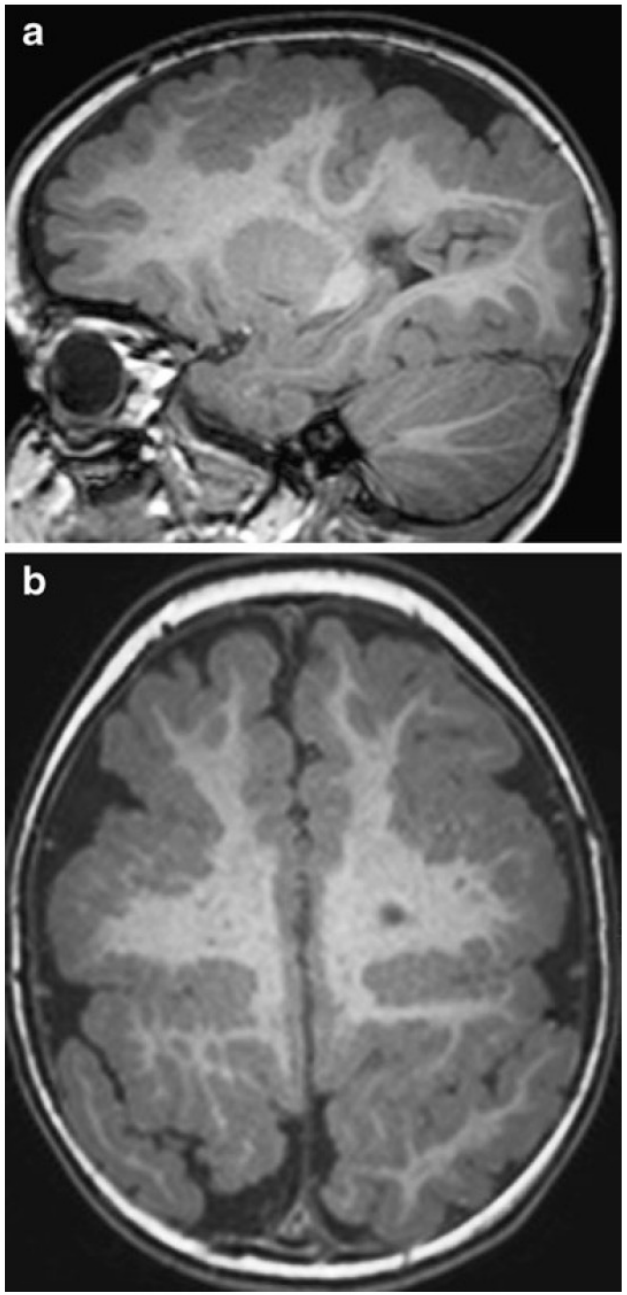


Fig. 7 Grade 2 perisylvian PMG. Parasagittal (**a**) and axial (**b**) images show coarse perisylvian polymicrogyria sparing the anterior frontal lobes and the occipital lobes

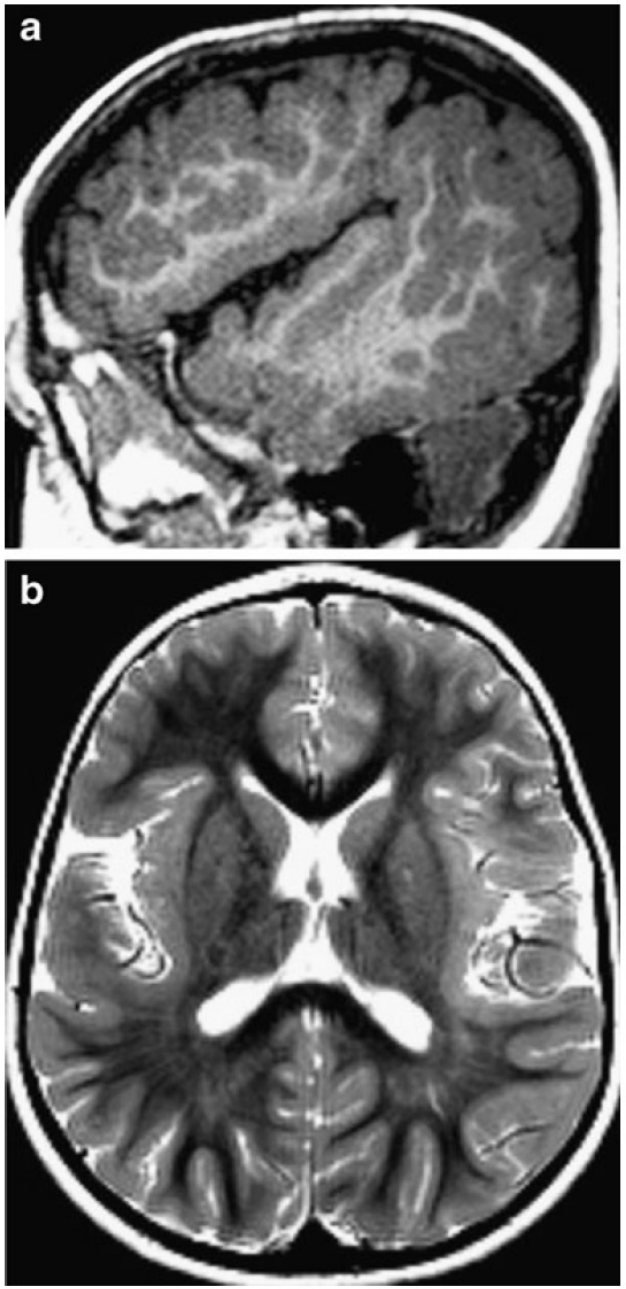


Fig. 8 Grade 3 perisylvian PMG. Parasagittal T1-weighted images (**a**) and axial T2-weighted images (**b**) show polymicrogyria limited to the insulae and operculae

Malformaciones del desarrollo cortical

Organización

- Esquizencefalia
  - Trastorno caracterizado por la presencia de una hendidura en el cerebro, delineada por materia gris anormal y conectando la superficie meníngea con el ventrículo lateral.
  - Tipos:
    - Tipo I (labio cerrado): las paredes del defecto están en contacto.
    - Tipo II (labio abierto): Defecto abierto amplio en que los bordes de la hendidura están separados.

Timor-Tritsch IE, Monteagudo A, Pilu G, Malinger G. eds. *Ultrasonography of the Prenatal Brain, 3e*. McGraw Hill; 2017

Malformaciones del desarrollo cortical

Organización

- Esquizencefalia
  - Prevalencia 1,54 por 100000.
  - Mecanismo patogénico no claro.
  - Generalmente se asocia a polimicrogiria.
  - Etiologia
    - Genetica
    - Infecciones congénitas
    - Exposicion a teratógenos
    - Trauma

Timor-Tritsch IE, Monteagudo A, Pilu G, Malinger G. eds. *Ultrasonography of the Prenatal Brain, 3e*. McGraw Hill; 2017

Malformaciones del desarrollo cortical

Organización

- Esquizencefalia
  - Anomalias asociadas
    - Ausencia de septum pellucidum
    - Displasia focal cortical
    - Disgenesia de cuerpo calloso
    - Megacisterna magna
    - Hidrocefalia
    - Malformaciones de surcos/cisuras
    - Hipoplasia nervio óptico
  - Pronóstico
    - Retraso de desarrollo psicomotor (57-80%)
    - Paralisis cerebral (80-85%)
    - Epilepsia (34-65%)

Timor-Tritsch IE, Monteagudo A, Pilu G, Malinger G. eds. *Ultrasonography of the Prenatal Brain, 3e*. McGraw Hill; 2017

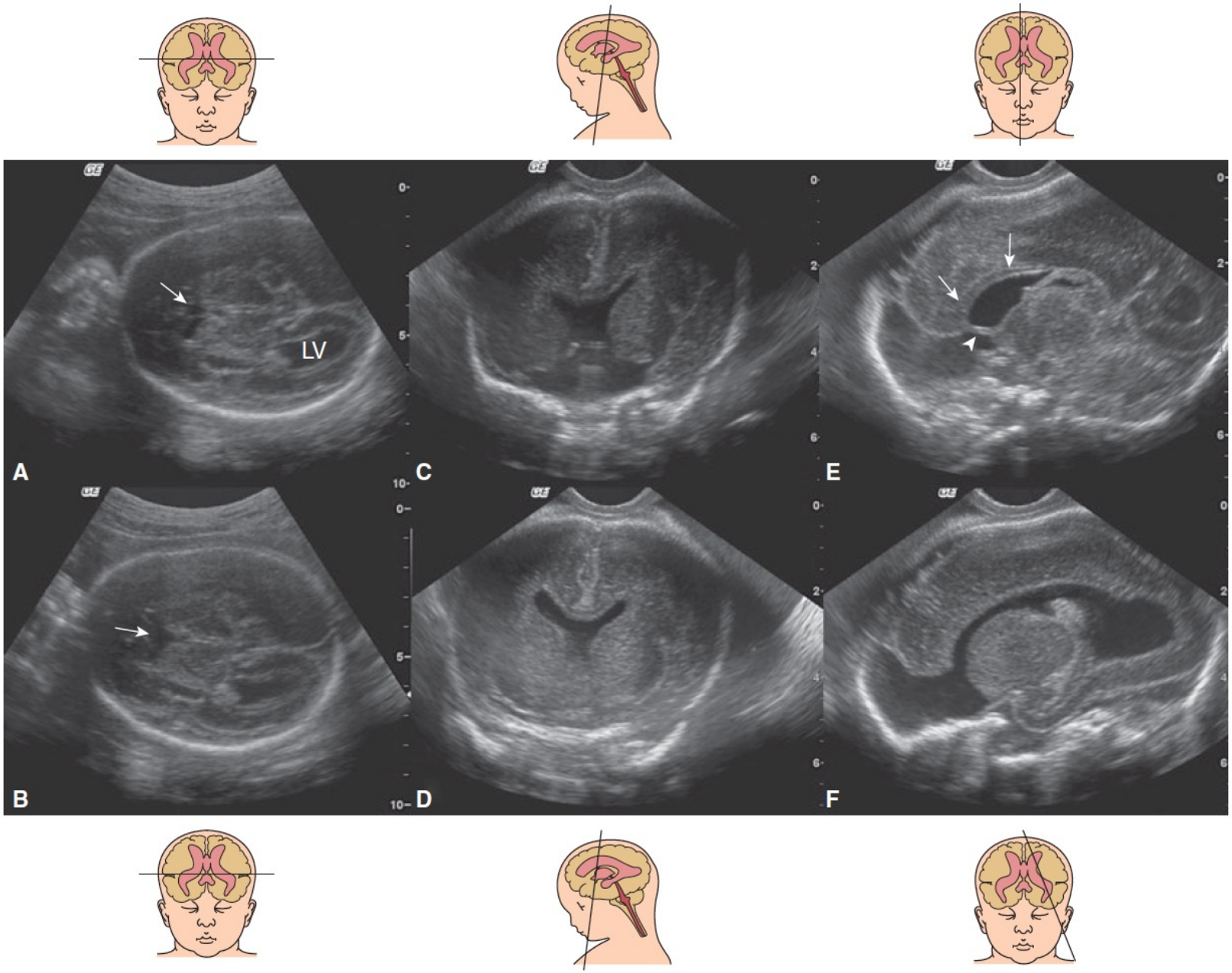


Figure 7–32. Transabdominal axial (**A, B**) and transvaginal coronal (**C, D**) and sagittal (**E, F**) US images in the same fetus as in Figure 7–30. Although the agenesis of the septi pellucidi may be suspected in **B** (*arrow*), these axial planes may be misinterpreted as normal. Note the apparent presence of the septi pellucidi in **A** (*arrow*) and the normal size of the lateral ventricle (LV). The diagnosis is evident in the coronal and axial planes. The corpus callosum is present and apparently normal (*arrows* in **E**).

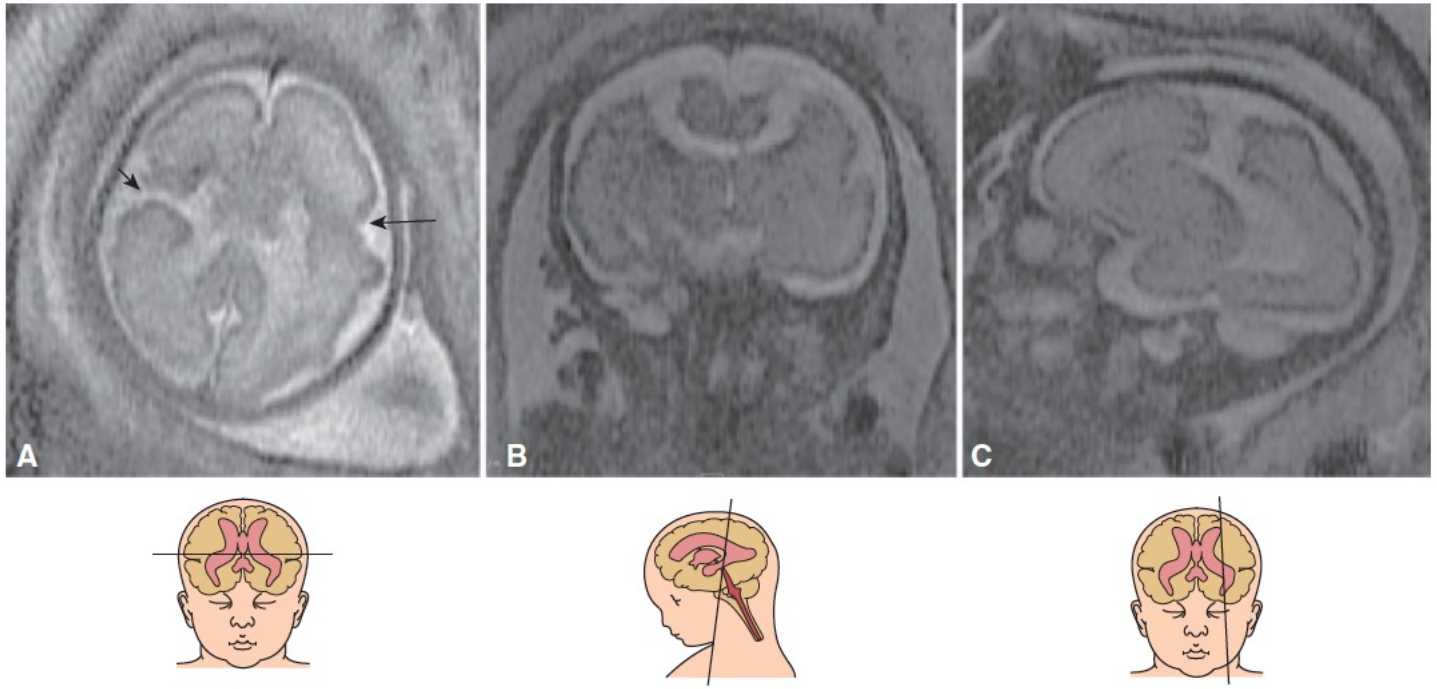


Figure 7–33. T2-weighted MRI at 28 postmenstrual weeks shows bilateral schizencephaly with multiple clefts lined by abnormal gray matter. (**A**) The axial section demonstrates the presence of an open lip (*arrowhead*) and a closed lip (*arrow*). Coronal (**B**) and sagittal (**C**) planes show open-lip defects lined with gray matter.

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Centro de Referencia Perinatal Oriente
Facultad de Medicina, Universidad de Chile

Malformaciones del Desarrollo Cortical

Dr. Pablo Silva Labarca
Becado Medicina Materno Fetal
Universidad de Chile