Intrauterin Enfeksiyonlarla Karışan Genetik Sendromlar

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Fetus ve enfeksiyon

Intrauterin enfeksiyonlar

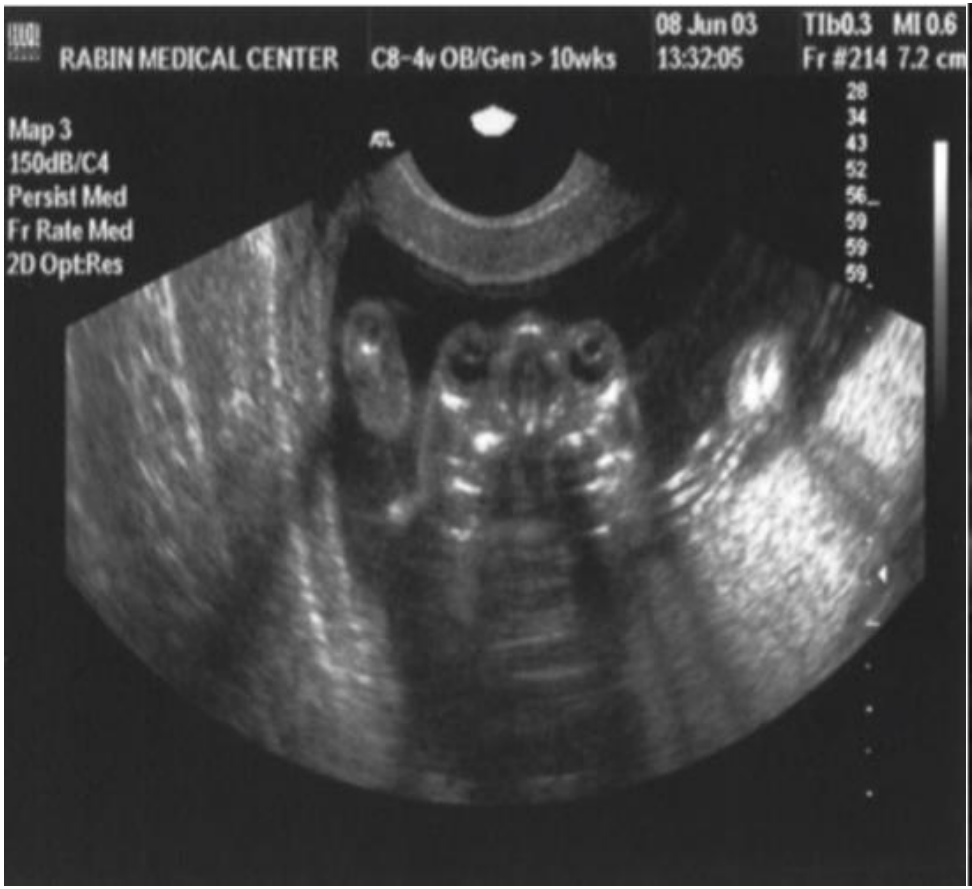
- abort
- konjenital anomaliler
- hidrops
- fetal ölüm
- preterm doğum
- erken membran rüptürü

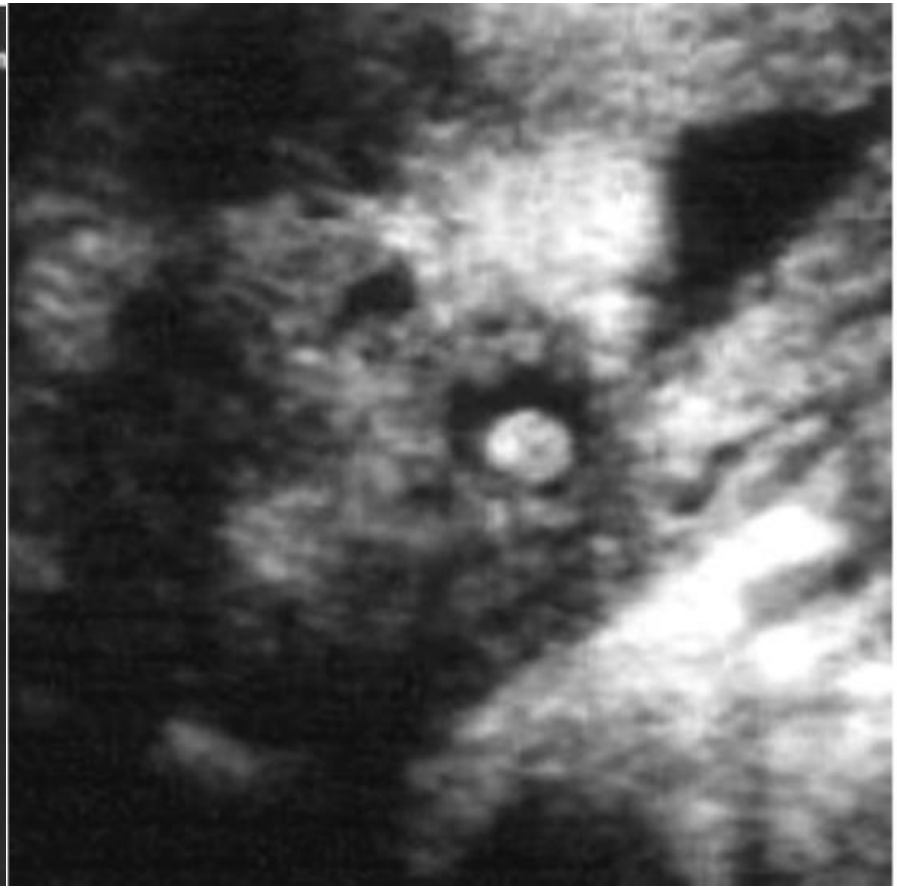
Viral hastalıklar

- **Rubella**
  - *kongenital katarakt, glokom, KKH*, sağırlık, *mikrosefal*i
- **Parvovirus**
  - Hidrops
- **Cytomegalovirus**
  - Mikrosefali
  - IUGR
  - Hepatomegaly, splenomegali
  - *Ventrikulomegali*
  - *Serebral atrofi*
  - Koryoretinit/ Optic atrofi
  - *Intrakranyal kalsifikasyon*
  - Uzun kemiklerde radiolusent alanlar

- **Varicella Zoster**
  - Preterm dogum
  - *Limb hipoplazisi*
  - Missing/hipoplastik digit
  - Mikrosefali, ventrikulomegali
  - Serebral atrofi
  - koryoretinit/ optic disc hypoplasia
  - Katarakt, mikroftalmi
  - Horner's S.
- **Herpes** bilinen konjenital anomali yok
- **Rubeola** bilinen konjnital anomali yok
- **Toxoplazmosis**
  - koryoretinit
  - Ensefalit
  - Sarılık
- **Zika virus** mikrosefali

Katarakt


RABIN MEDICAL CENTER
C8-4v OB/Gen > 10wks
08 Jun 03
13:32:05
TIb0.3 MI 0.6
Fr #214 7.2 cm
Map 3
150dB/C4
Persist Med
Fr Rate Med
2D Opt:Res
28
34
43
52
56
59
59
59



Intrauterin katarakt

Syndrome	Frequency	Genetics and etiology	Principal ultrasonographic findings, in addition to cataract	Diagnosis
Facio-craniostenoses				
Apert syndrome [22–24]	1/160,000	AD; chrom. 10; FGFR2 gene	Acrosyndactyly with mitten hands and syndactyly of the feet; turribrachycephaly; clover leaf skull	US; causal mutation
Polymalformation and complex cranio-facial malformation syndromes				
Smith-Lemli-Opitz syndrome [25, 26]	1/20,000–1/30,000	AR; chrom. 11; DHCR7 gene	Microretrognathism; nasal anteversion; wide forehead; atrioventricular septum defect; renal hypoplasia; postaxial hexadactyly; IUGR affecting mainly the long bones; micropenis	US; maternal plasma with oestriol ↓; normal caryotype; from 13 W, AFP with 7-DHC ↑ and cholesterol ↓
Hallerman Streiff syndrome [27–29]	Rare	Sporadic; etiology unknown	Microcephaly; frontal bossing; micrognathia; bird head; beaky nose; teeth at birth; microphthalmia; small proportional stature	US
Rubinstein Taybi syndrome [30, 31]	1/125,000	AD/neomutation; CBP gene (chrom. 16) or EP300 (chrom. 22)	Large thumbs; large toes; small stature; antimongoloid palpebral fissures	US, difficult since not very specific
Musculoskeletal conditions				
Chondrodysplasia punctata syndrome [32, 33]	1/100,000	AR; PEX gene for peroxin 7; peroxysomal transfer ↓	Short femurs and humerus; proximal epiphyseal punctuations; congenital, early, bilateral, total cataract in almost 50% of the cases	US
Walker-Warburg syndrome [34–36]	1.2/100,000	AR; POMT1, POMT2, FKRP gene	Dandy-Walker malformation; hydrocephaly; lissencephaly; microcephaly; microphthalmia; retinal detachment	US; in utero muscle biopsy; genetic
Roberts syndrome [37, 38]	Very rare	AR probable; etiology unknown	Reductional anomalies of the limbs similar to phocomelia; round face; hypertelorism; microretrognathia; labiopalatine fissure	US; AC: premature centromere separation

Intrauterin katarakt

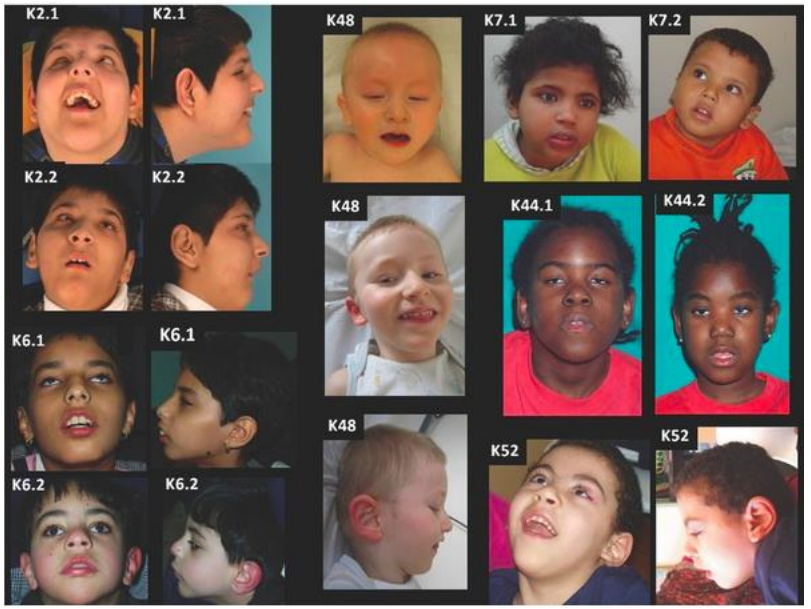
Aneuploidism and chromosomal anomalies				
Trisomy 13 [39]	1/10,000		Holoprosencephaly; Fallot tetralogy; septal defect (VSD, ASD); omphalocele; hydronephrosis; club foot; cystic kidney; microphthalmia	US; fetal caryotype
Trisomy 18 [40]	1/8,000		Low ears; micrognathia; microphthalmia; omphalocele; septal defect (VSD, ASD); IUGR; overlapping fingers	US; fetal caryotype
Trisomy 21 [41, 42]	1/700		Nuchal translucency; mongoloid palpebral fissures; defect of nasal bones; cardiac (Fallot tetralogy), gastroduodenal (duodenal atresia), urinary (pyelectasis) anomalies; 40% has cataracts, but not necessarily in the antenatal period	US; fetal caryotype
Others [9, 41]	Triploidism, monosomy, deletion (5p), duplication			US; fetal caryotype
Cutaneo-dental disorders				
Nance Horan syndrome [43, 44]	Rare	Semi-dominant; chrom. X	In 100% of cases: male sex and congenital bilateral dense, most often total cataract. Also possible: microcornea (<10 mm in diameter); microphthalmia; long face; prognathism; large nose; large protruding ears; dental anomalies	US difficult; to our knowledge, only one publication exists on prenatal diagnosis of Nance-Horan syndrome
Metabolic disorders				
Zellweger syndrome [45–47]	1/50,000	AR	Prominent forehead; hypertelorism; mongoloid palpebral fissures; depressed nasal root; retrognathism; micrognathism; subcortical renal cysts; cardia defect; small stature; nuchal translucency; absent corpus callosum; abnormal neuronal migration (MRI)	US laborious; plasma and amniocytes: LCFA, with (C26:1) ↑ and (C26:0) ↑

Intrauterin katarakt

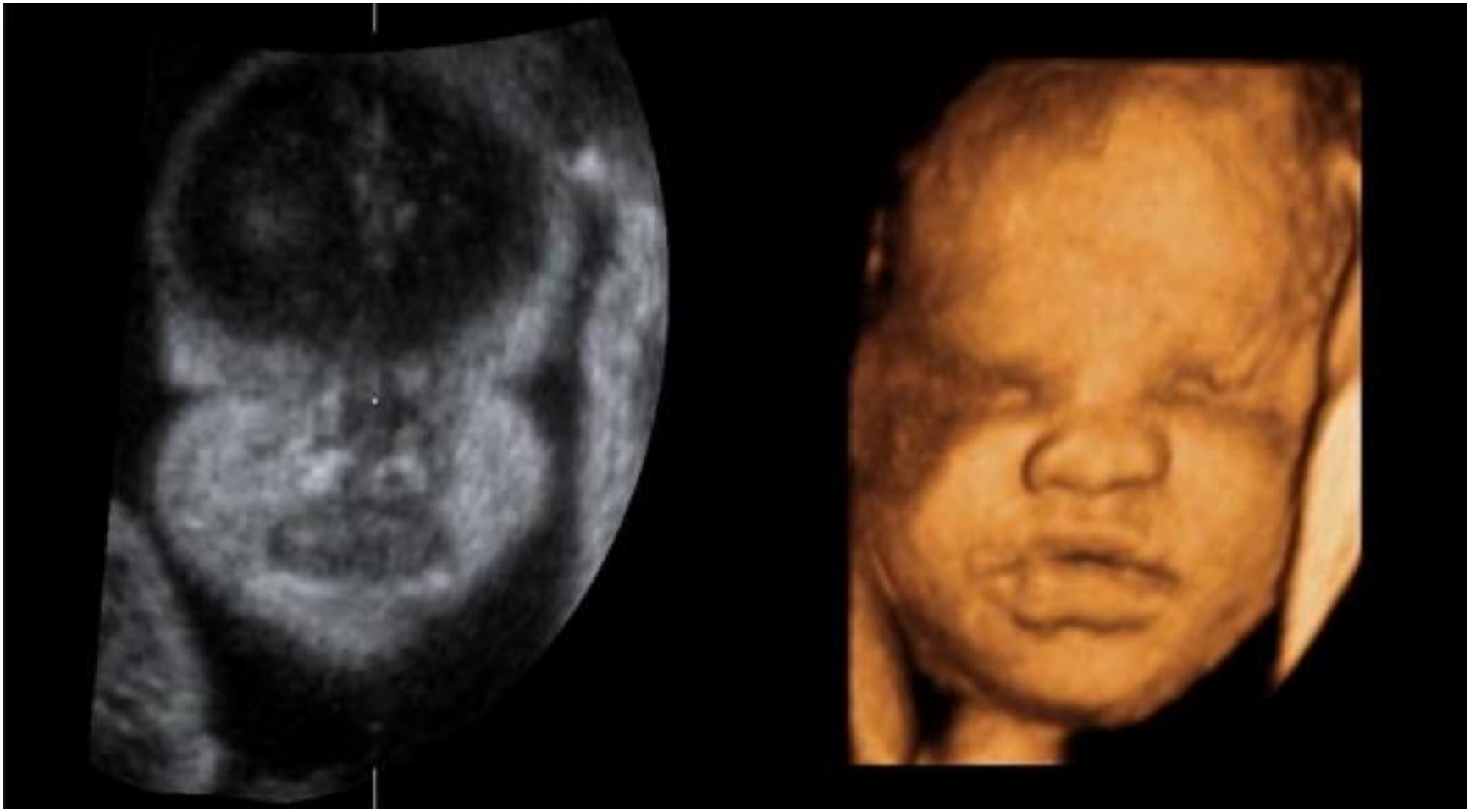
Syndrome	Frequency	Genetics and etiology	Principal ultrasonographic findings, in addition to cataract	Diagnosis
Lowe's Oculo-cerebro-renal syndrome [48–50]	1/500,000	X-linked; recessive; OCRL1 protein gene, coding for Ptdlns(4,5)P2	Early congenital cataract in all patients affected; antenatal diagnosis of cataract is possible and has already been reported	US not very conspicuous; AFP: AC with Ptdlns(4,5)P2 ↓ and abnormal PCR mRNA of OCRL1
Infectious diseases				
Rubella [3, 51, 52]	First cause of congenital cataract	After the 6th W, the lens vesicle is separated, limiting viral access	Cardiac malformations (septal defects, pulmonary artery hypoplasia); microphthalmia; microcephaly; polycystic kidneys; IUGR; splenomegaly; hepatomegaly	US; serology; AFP (culture, PCR)
Varicella [9, 51]			Limb hypoplasia; microphthalmia; positional anomalies of the extremities; intracranial calcifications; polyhydramnios; hydrocephaly; highly echogenic liver	US; serology; AFP (culture, PCR)
CMV [51, 53]	2.3/100–4/100		Hepatosplenomegaly; microcephaly; IUGR; cerebral/hepatic calcifications; highly echogenic intestine; ventriculomegaly	US; serology; AFP (culture, PCR)
Herpes simplex [9, 51]			Microcephaly; microphthalmia; hydranencephaly; multicystic encephalomalacia; ascites; intrahepatic calcifications	US; serology; AFP (culture, PCR)
Toxins Corticosteroids, antipsychotic drugs such as chlorpromazine [54, 55]: harmful effects on lens but no publications of fetal cataract. Coumarin derivatives [56, 57]: punctuated chondrodysplasia, nasal hypoplasia, brachytelephalangic, microphthalmia, reports of cataract.				
Idiopathic Most fetal cataracts are idiopathic, but no accurate data are available on the percentage.				

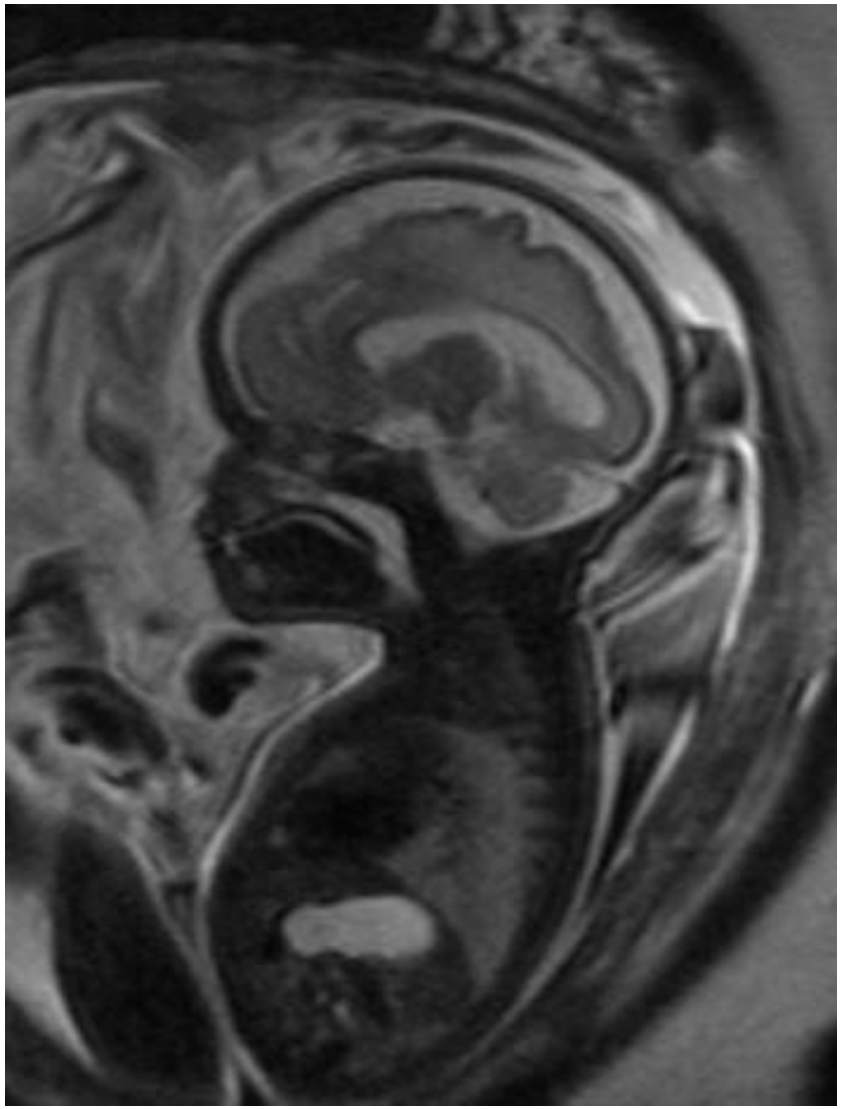
Konjenital katarakt

- Steinert myotonik dıstrofi, Turner sendromu Alport sendromu , Stickler sendromu ve glukoz 6 fosfat dehidrogenaz defekti
- Mikroftalmi ile birlikte
  - **Micro sendrom (**mental gerilik, mikrosefali, hypogenitalya, hiptoni, korpus kallosum anomalileri
  - **Martsolf Sendromu** (mental gerilik, boy kısalığı hypogenitalya, mikrosefali)
  - **Cerebro-oculo-facia-skeletal Sendrom (COFS)** (mikrognati, multiple eklem kontraktürleri ve ‘rockerbottom feet’)
  - **Cockayne S.**



Mikroftalmi -anoftalmi





MRI da Bilateral anoftalmili fetus

Primer anoftalmi 0,6/10000

Coğu zaman eşlik eden diğer konjenital malformasyonlar ile birlikte anaploidilerde ya da bir sendromun parcası olarak

Fraser, Goltz, Goldenhar, Waardenburg

Lenz mikroftalmi.

Microphthalmia/Anophthalmia/Colobo ma Spektrum

Mikroftalmi-anoftalmi spektrumu (MACS)

Kromozom anomalileri

Aneuploidy
- Trisomy 9
- Trisomy 13
- Trisomy 18

Deletion 4 (Wolf-Hirschhorn s.)
- Deletion 7p15.1-p21.1
- 13q-, ring 13
- Deletion 14q22.1-q23.2, 18q-
- Deletion 3q26 (includes *SOX2*)

Duplication
- Duplication 3q syndrome
- Duplication 4p syndrome
- Duplication 10q syndrome

Tek gen hastalıkları

Microphthalmia with linear skin defects **(MIDAS syndrome)** XL
- Sclerocornea, hidrosefali, kardiak & SSS anomalileri, genital anomaliler

HESX1 **Septooptic dysplasia**
- Optic nerve hypoplasia
- Pituiter hipoplasi, CC agenezisi, septum pellucidum yokluğu

IKBKG **Incontinentia pigmenti (mikrosefali,katarakt, hemivertebra)**

PORCN **Focal dermal hypoplasia(Goltz s)**
- kutis aplazi, tırnak anomalileri , notched alae nasi, CL/P

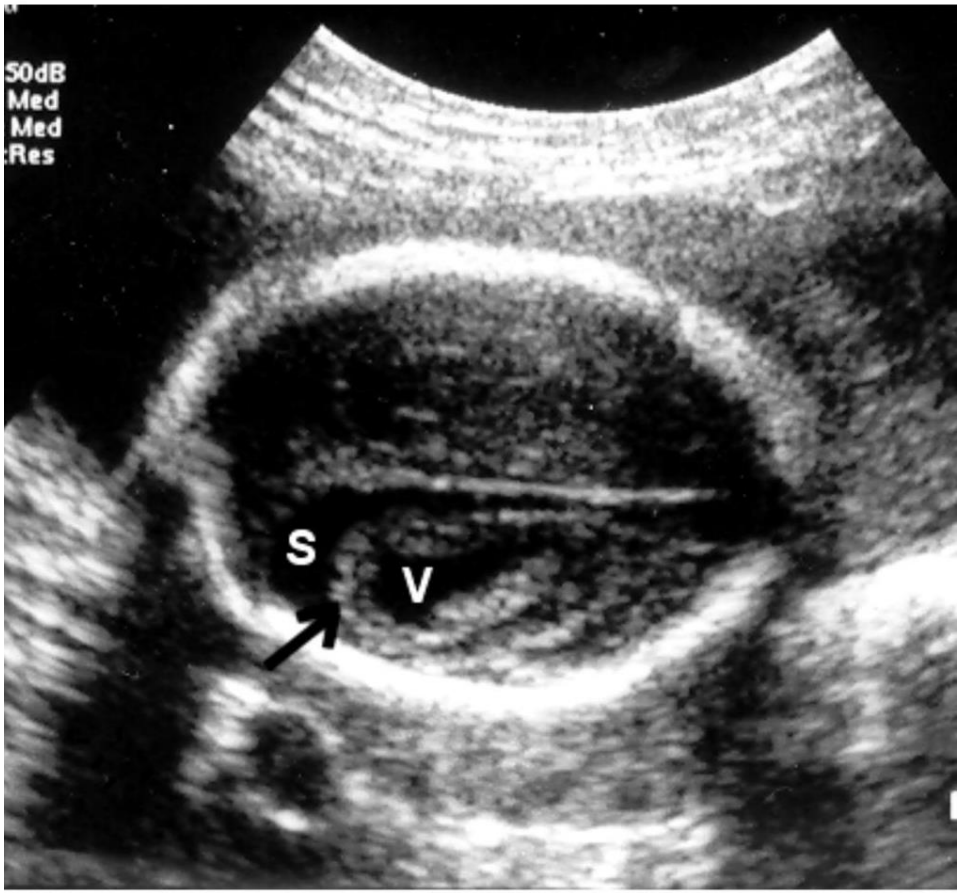
Holoprosencephaly
- Holoprozensefali, CL/P

Waardenburg anophthalmia s
- Oligosyndactyly, distal limb anomalileri

Branchiooculofacial s
- Branchial skin defect,
- cleft lip, upper lip pits, malformed pinnae

Mikrosefali

- Ortalama 28.GH da tespit ediliyor
- %50 den fazlasında IUGR mevcut
- perinatal mortalite oranı %70
- İzole mikrosefali (%16.7)
- Holoprozensefaliye bağlı mikrosefali (%16.7)
- Kromozom anomalileri ile ilişkili mikrosefali (%23.3)
- Genetik bir sendromun parçası (%20.0)
- Multiple anomalilerin bir parçası (%23.3).



Ultrasound Obstet Gynecol 2000; 15: 282±287

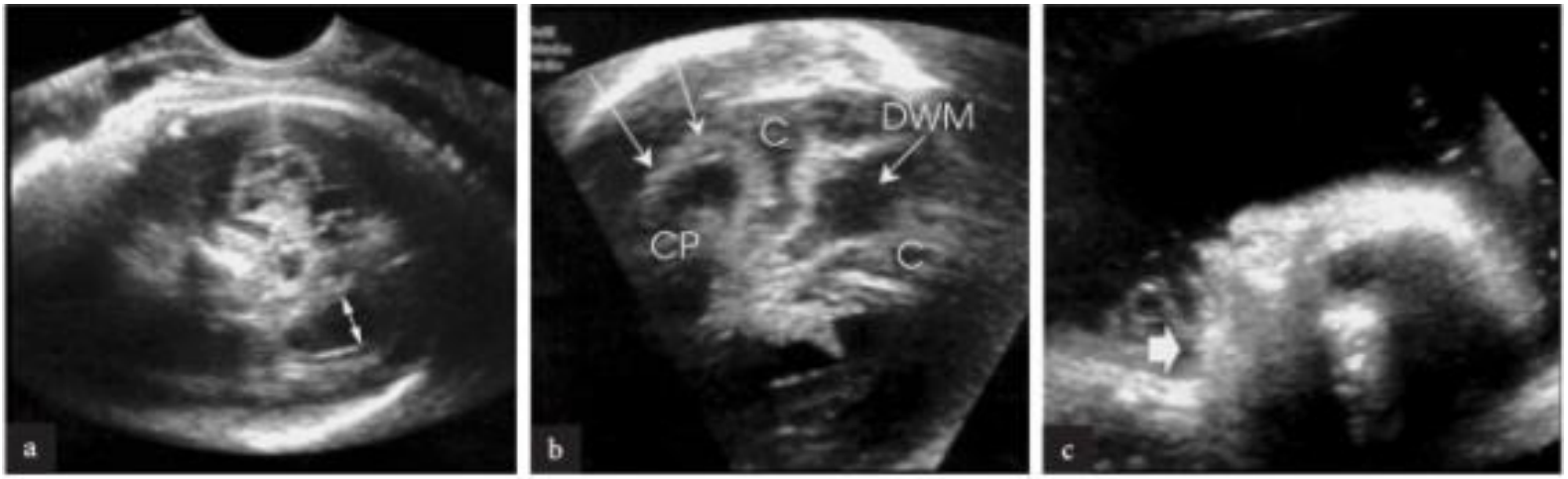


Fig. 37.1a–c. Microlissencephaly, group 5. **a** Prenatal US shows borderline ventriculomegaly (*double arrow*) associated with a very thin cortex (*arrows*) in a microcephalic fetus. **b** Concurrent enlargement of the subarachnoid space and Dandy-Walker malformation (DWM). *Cp*, choroid plexus; *C*, cerebellar hemispheres. **c** Profile of the fetal face shows a sloping forehead and marked micrognathia (*large arrow*)

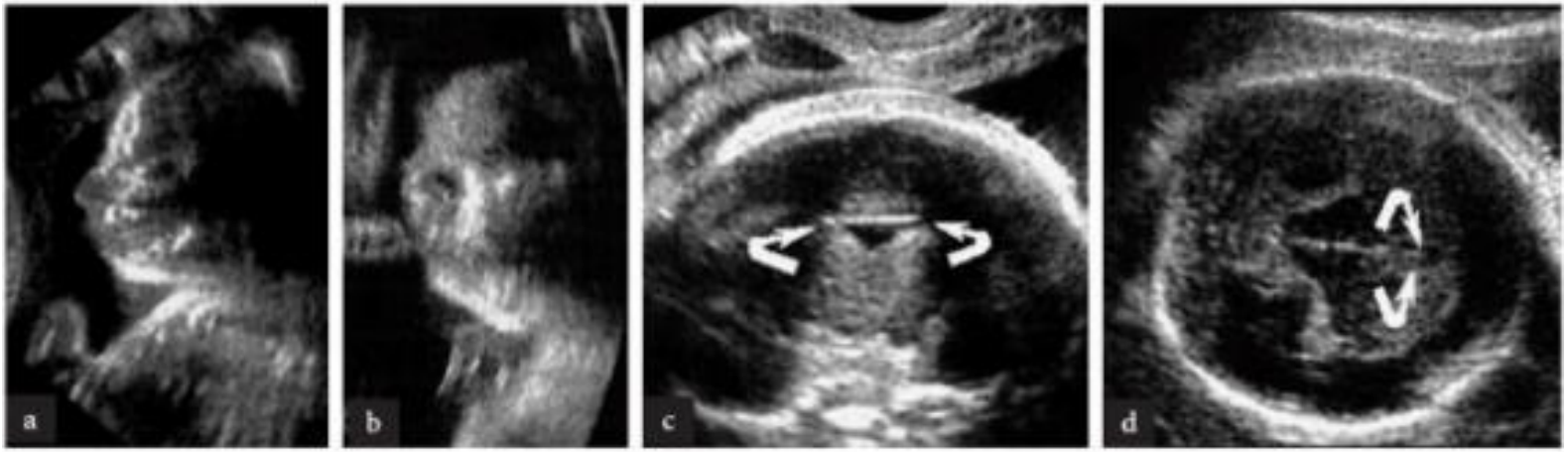
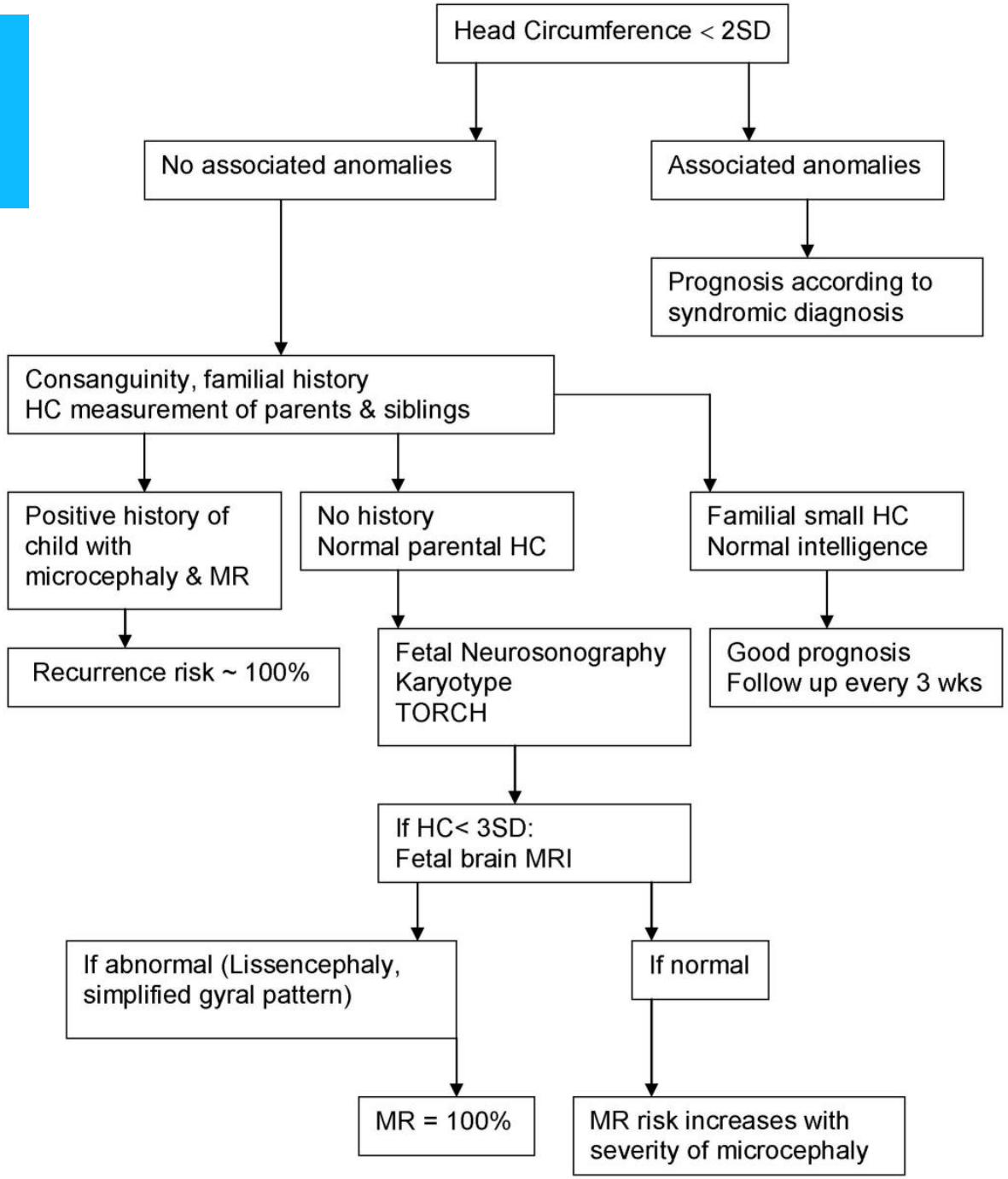


Fig. 37.2a–d. Microcephaly and semilobar holoprosencephaly. **a, b** Sagittal views of microcephalic fetal head show an abnormal shape of the head with a sloping forehead. **c** Coronal scan shows partially fused thalami and a single ventricle (*curved arrows*). **d** Axial scan reveals the frontal lobes are not separated in the midline (*curved arrows*). There is absence of the septum pellucidum and enlargement of the subarachnoid spaces

Mikrosefalide morbidite



Mikrosefali, genetik nedenleri

Ilişkili malformasyonlar ile birlikte

- Kromozom anomalileri
- Tek gen hastalıkları
  - Kromozom instabilite sendromları (Bloom, Cockayne, Fanconi, Roberts)
  - Lissensefali S
  - Seckel, Dubowitz
  - SLOS
  - Cornelia de lange
  - Walker Warburg S. (mikroftalmi glokom, katarakt optik sinir hipoplazisi persistan hyaloid arter, dandy walker, hidrosefali)

    ensefalosel, CC agenezisi
  - Rubinstein taybi

- Izole mikrosefali
  - Primer mikrosefali
  - Paine S (mikrosefali,spastik dipleji)
  - Alper hastalıgı (mt DNA deplesyon sendromu)
  - Metabolik hastalıklar
  - Folik asit metabolizması bozuklukları
  - Metilmalonik asidemi
  - PKU

Diğer SSS anomalileri

- Intrakranyal kalsifikasyon
- Serebral atrofi
- Ventrikulomegali

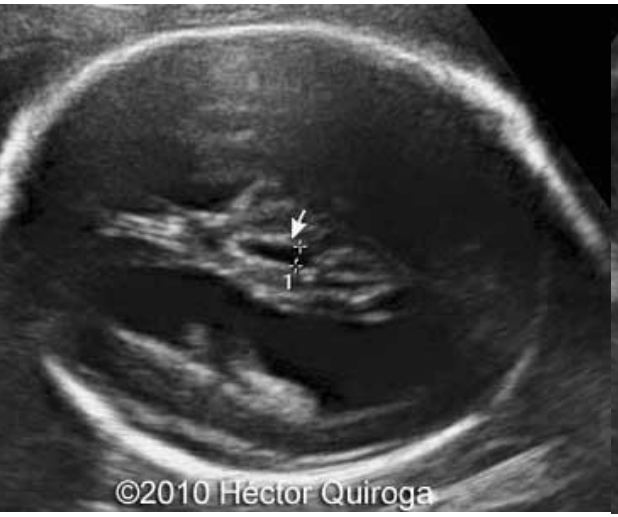
Izole ventrikulomegali

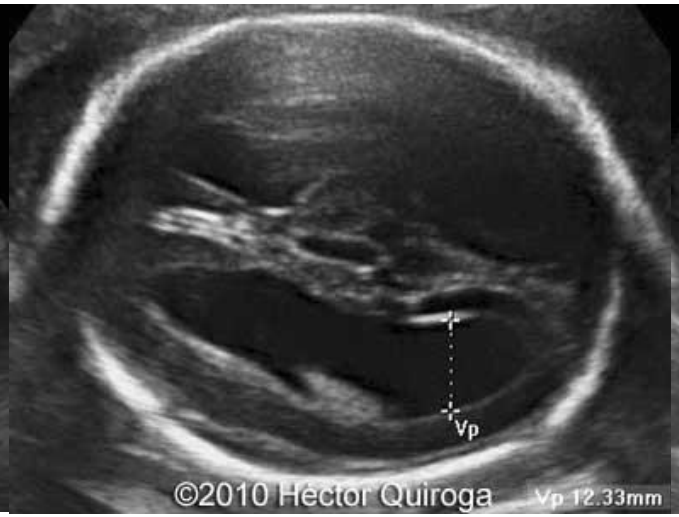
TANIMLAR

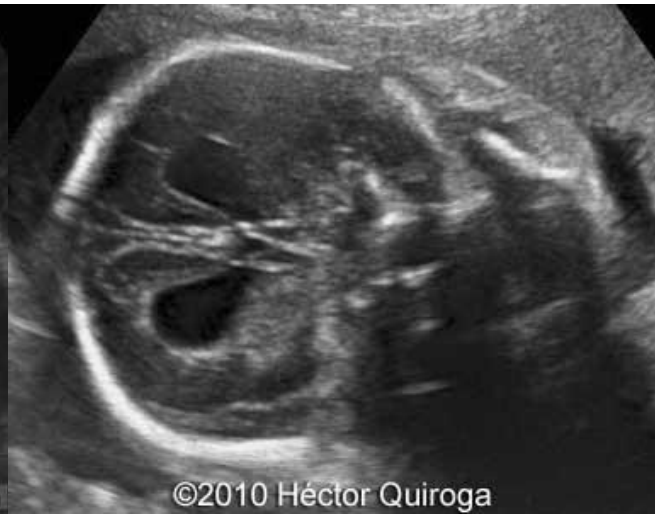
Atrial mesafenin 10-14mm ölçülmesi- sınırda ventrikülomegali

Atrial mesafenin >15mm ölçülmesi-hidrosefali

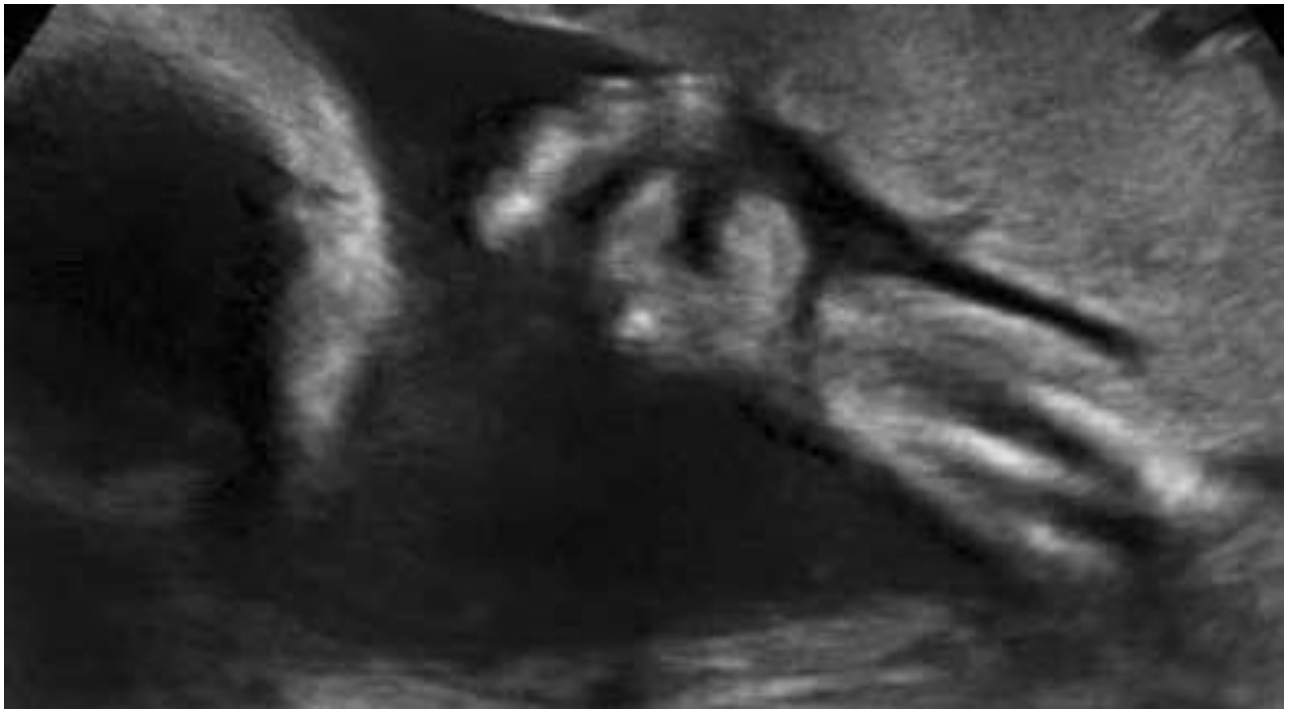
X'e bağlı hidrosefali izole VM nin %5 inin sebebi
L1CAM geni
Bunun dışındakiler multifaktöryel
Izole VM saptanan bir ailede tekrarlama riski %4







Izole VM



Adducted thumb ve erkek fetus ise ***X linked hidrosefaliden*** şüphelen !!

VENTRİKÜLOMEGALİ

PROGNOSTİK FAKTÖRLER

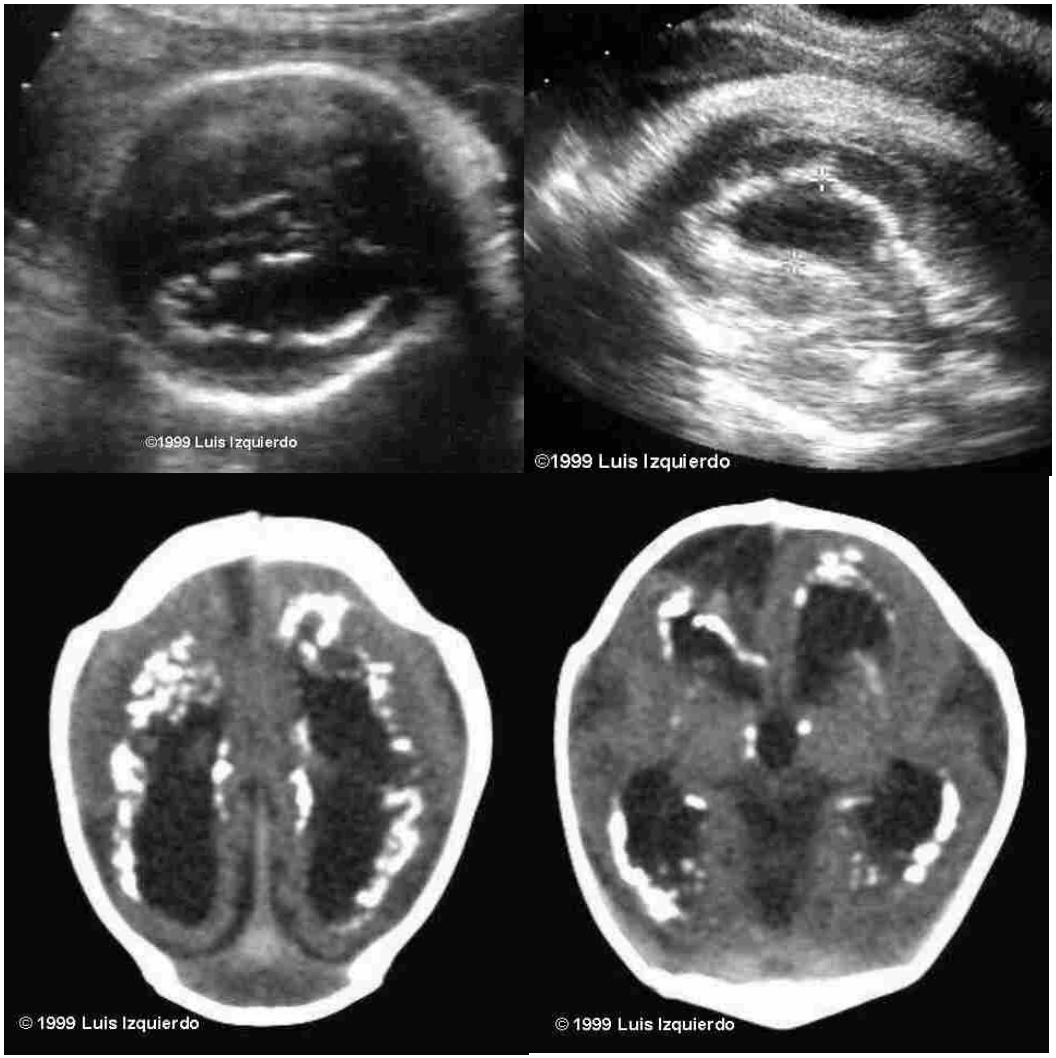
Ek anomali olması

Ventrikül çapının progresyon göstermesi

İZLEM

Antenatal-amninosentez/karyotip, viral seroloji, MRG

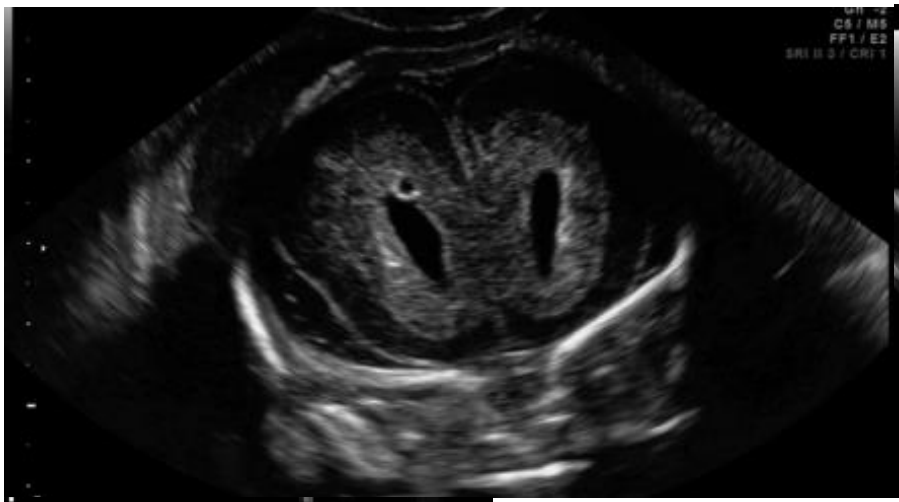
Periventriküler ekojenite artışı

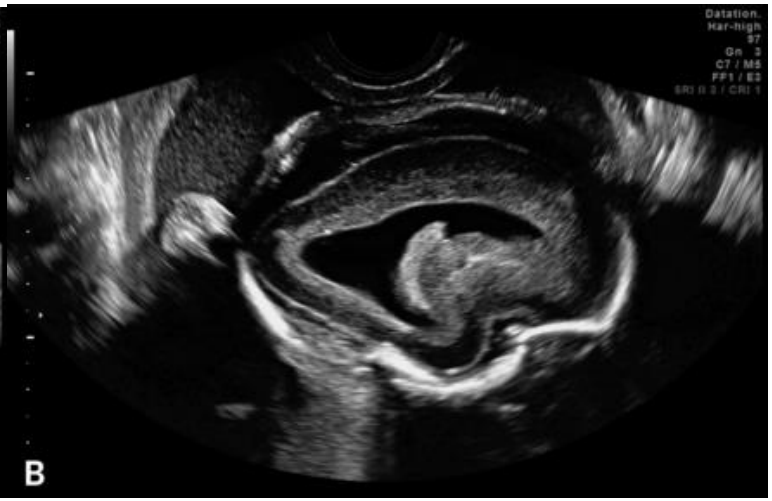


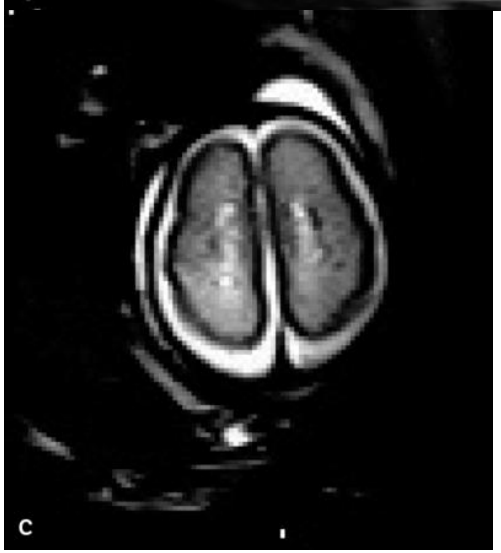
- Familial mitokondrial ensefalopati
- 3-OH Butirik asiduri
- Moebius S.
- Fahr"s S.
- Aircardi Goutiers

(bilateral simetrik özellikle bazal ganglion ve periventriküler)

Aicardi Goutiers S.





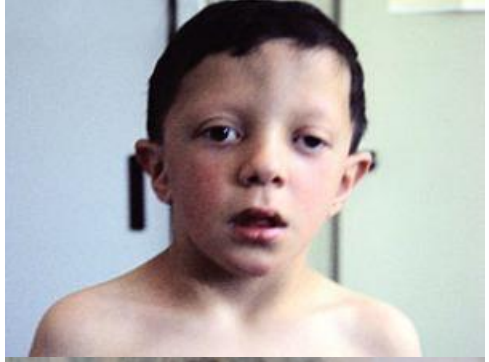


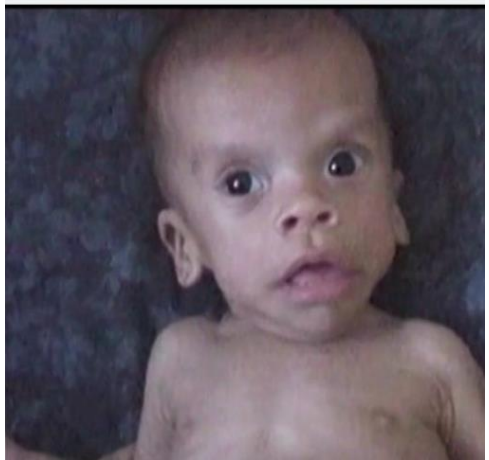
Images from a fetus with AGS. Bilateral periventricular cavitations (A)
inside a bilateral periventricular halo (A and B),
major lissencephaly, periventricular calcifications,
and supraventricular microcystic cavities (C)
were found during second-trimester sonographic and MRI examinations at 26 and 28 weeks of pregnancy, respectively.

Konjenital kardiyak defektler

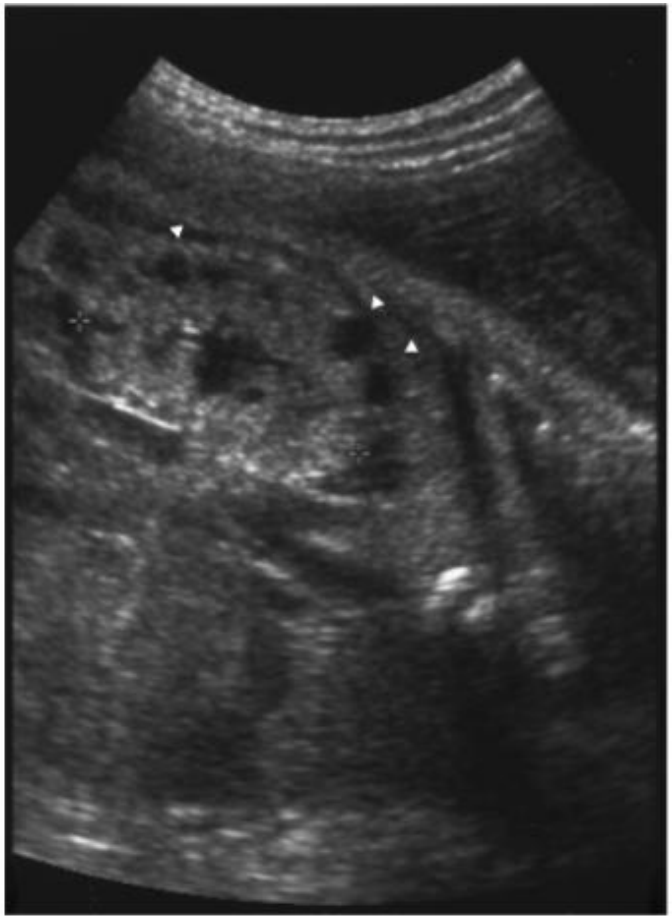
Pulmoner stenoz

- Noonan-CFC-Costello spektrum
  - NT yüksekliği, yele boyun
  - IUGR
  - Mikrognati
  - Düşük kulaklar
  - Asağı eğimli göz kenarları
  - Derin girintili filtrum
  - Pectus carinatum superior
  - Pectus excavatum inferior
  - Klino-brakidaktili
  - Vertebra anomalileri





Hiperekojen böbrekler



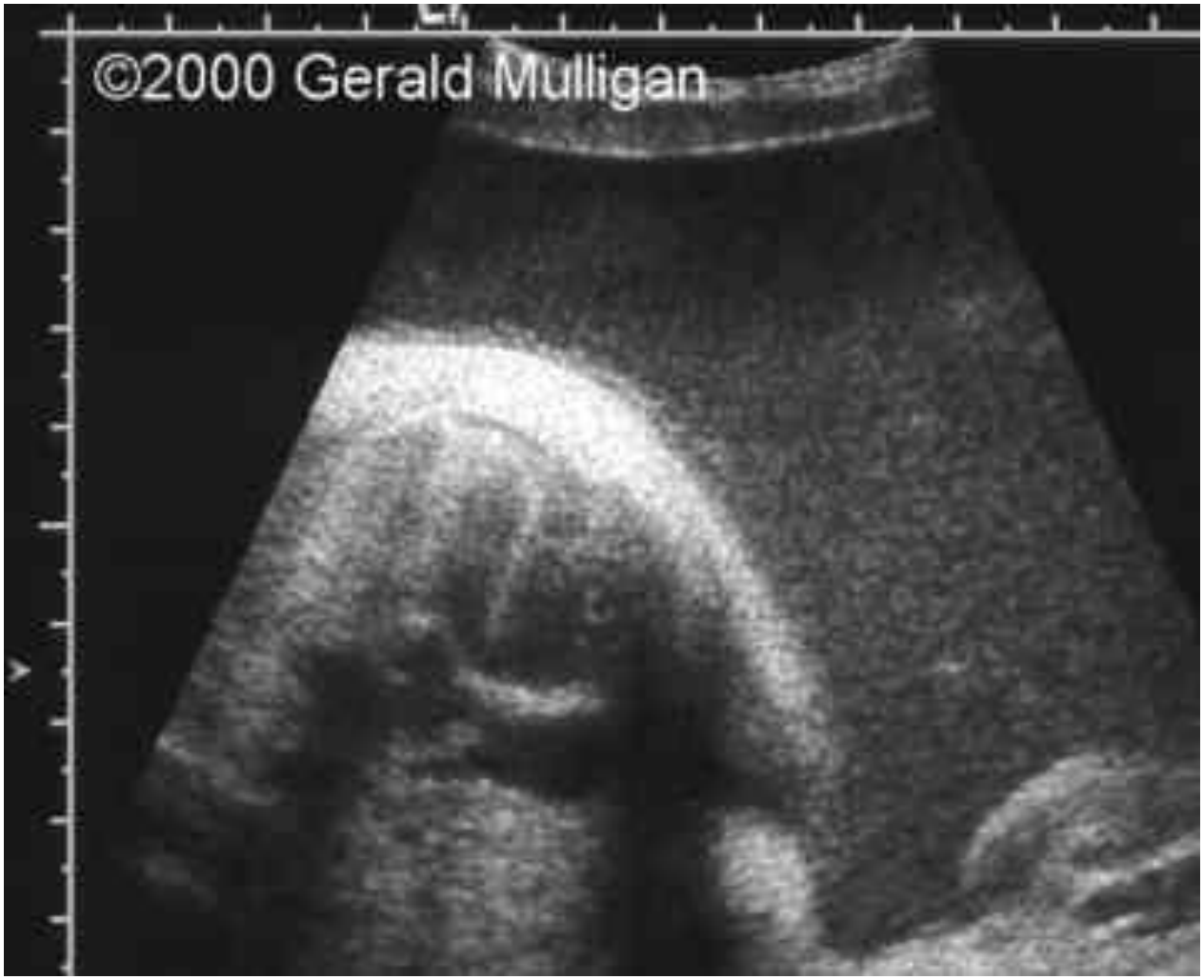
- ODPKB
- ORPKB (HSM eşlik eder)
- Multikistik displazi
- Perlman s (RENAL HAMARTOMAS, NEPHROBLASTOMATOSIS, AND FETAL GIGANTISM, NEPHROBLASTOMATOSIS, FETAL ASCITES, MACROSOMIA, AND WILMS TUMOR)
- Beckwith – Wiedemann s,
- Bardet – Biedl s,
- Meckel s

Polidaktili ve serebellar hipoplaziye dikkat !!

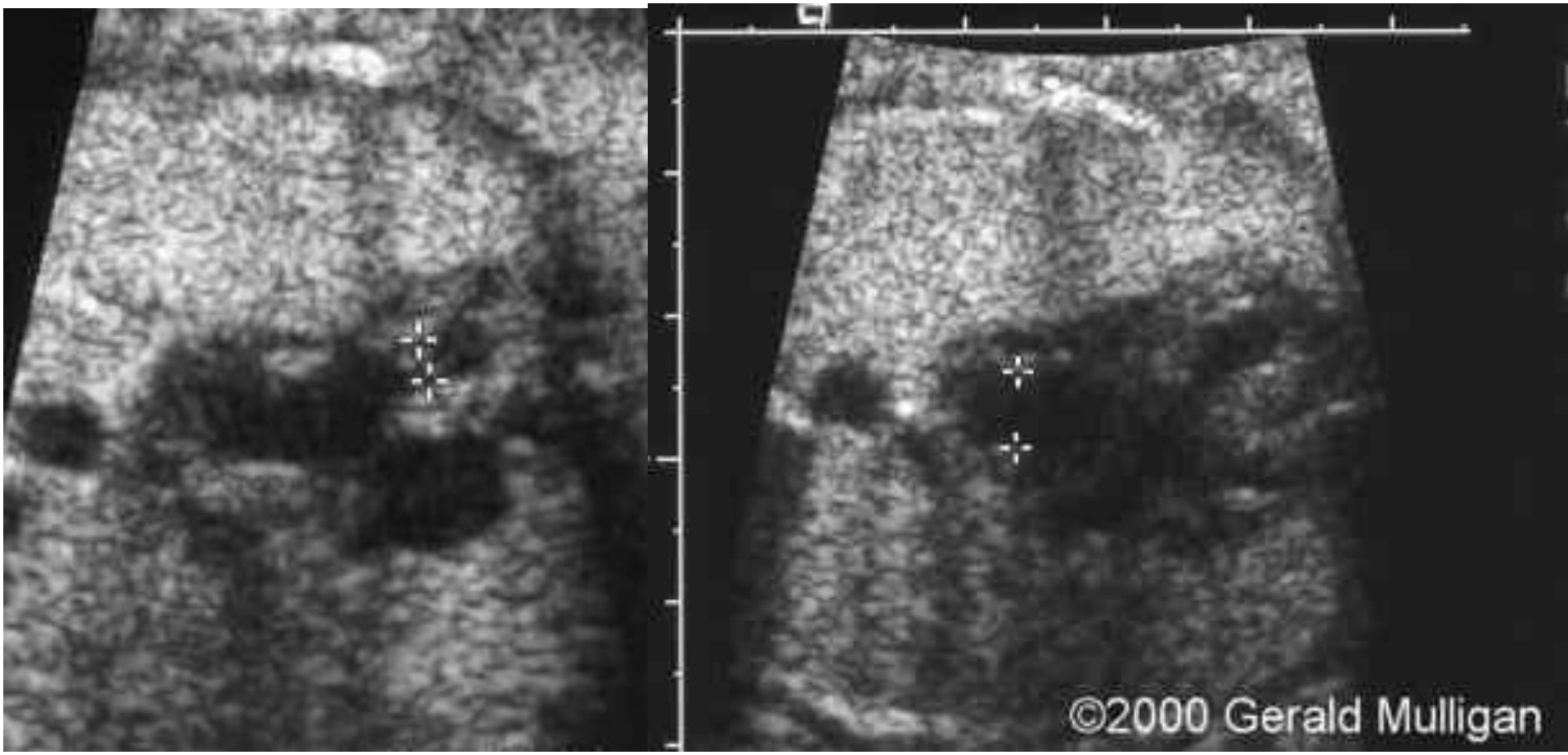
Bir olgu:

32 yaş saglıklı anne G5P4 saglıklı cocuklar 27 GH da *mikrosefali* saptanması nedeniyle perinatolojiye yönlendirildi.

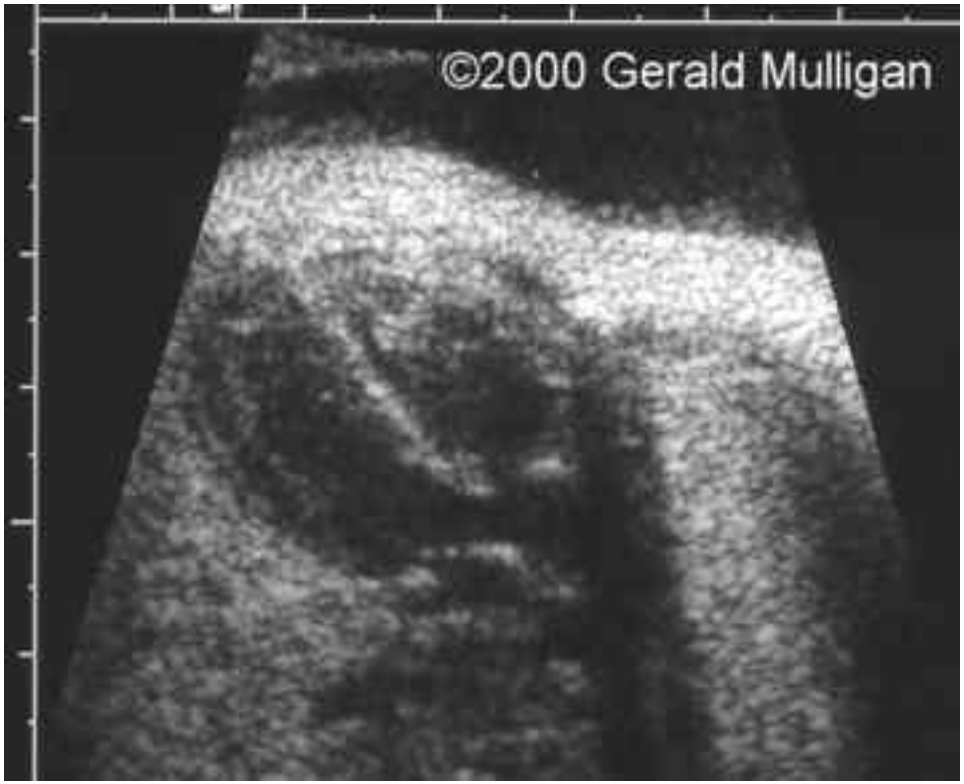
Axial chest



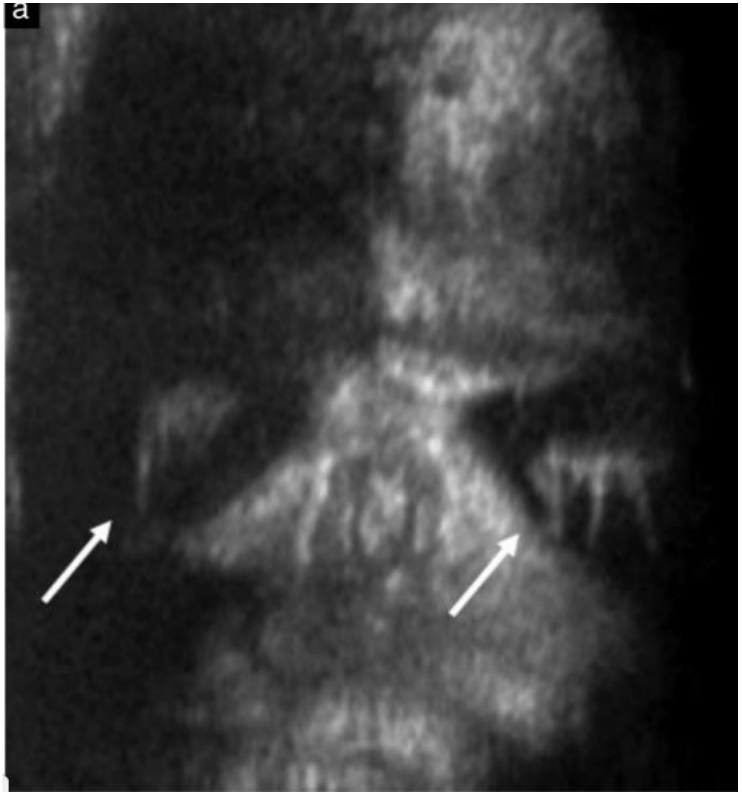
Pulmoner arter Inen aorta



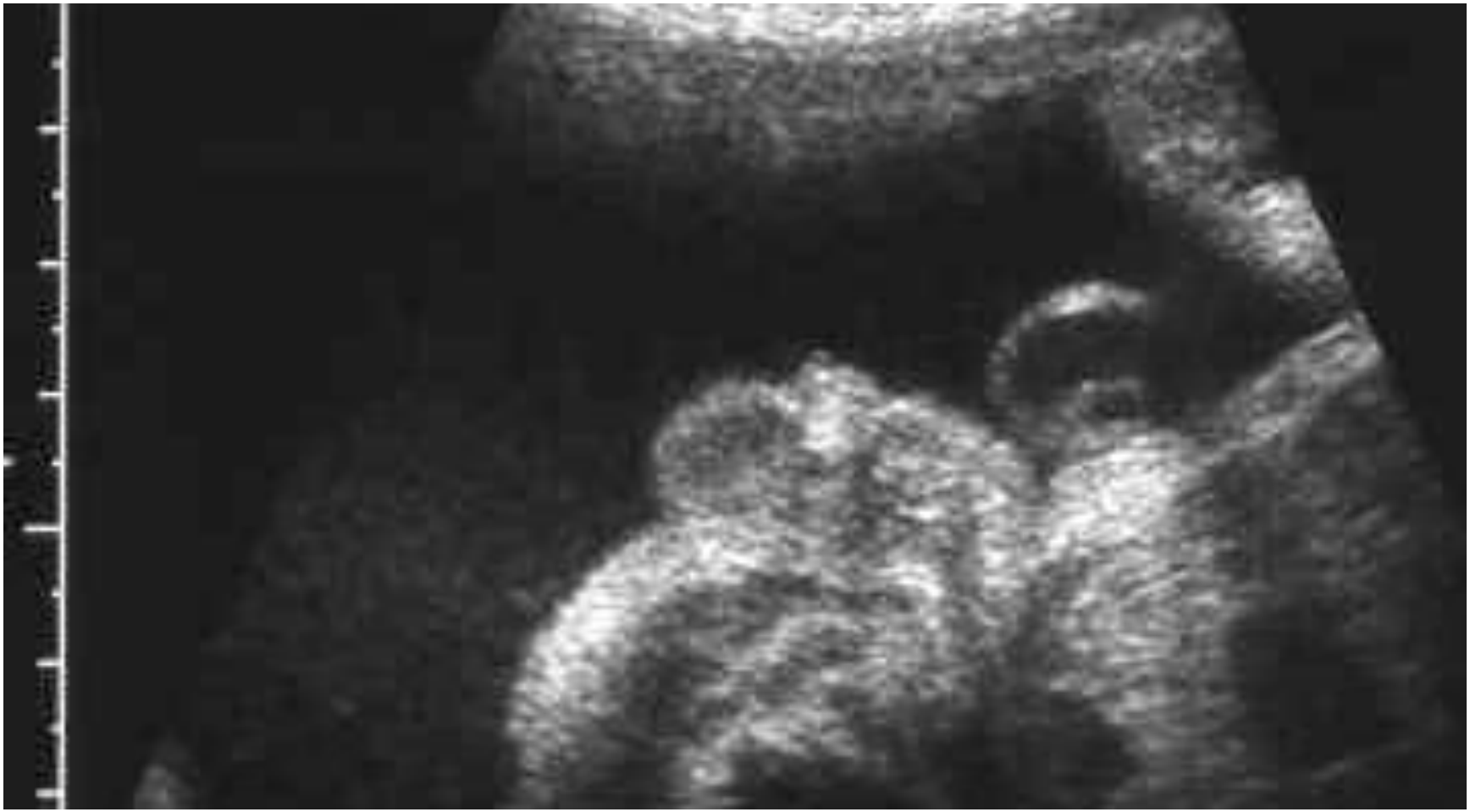
Kardiyak ventrikuller



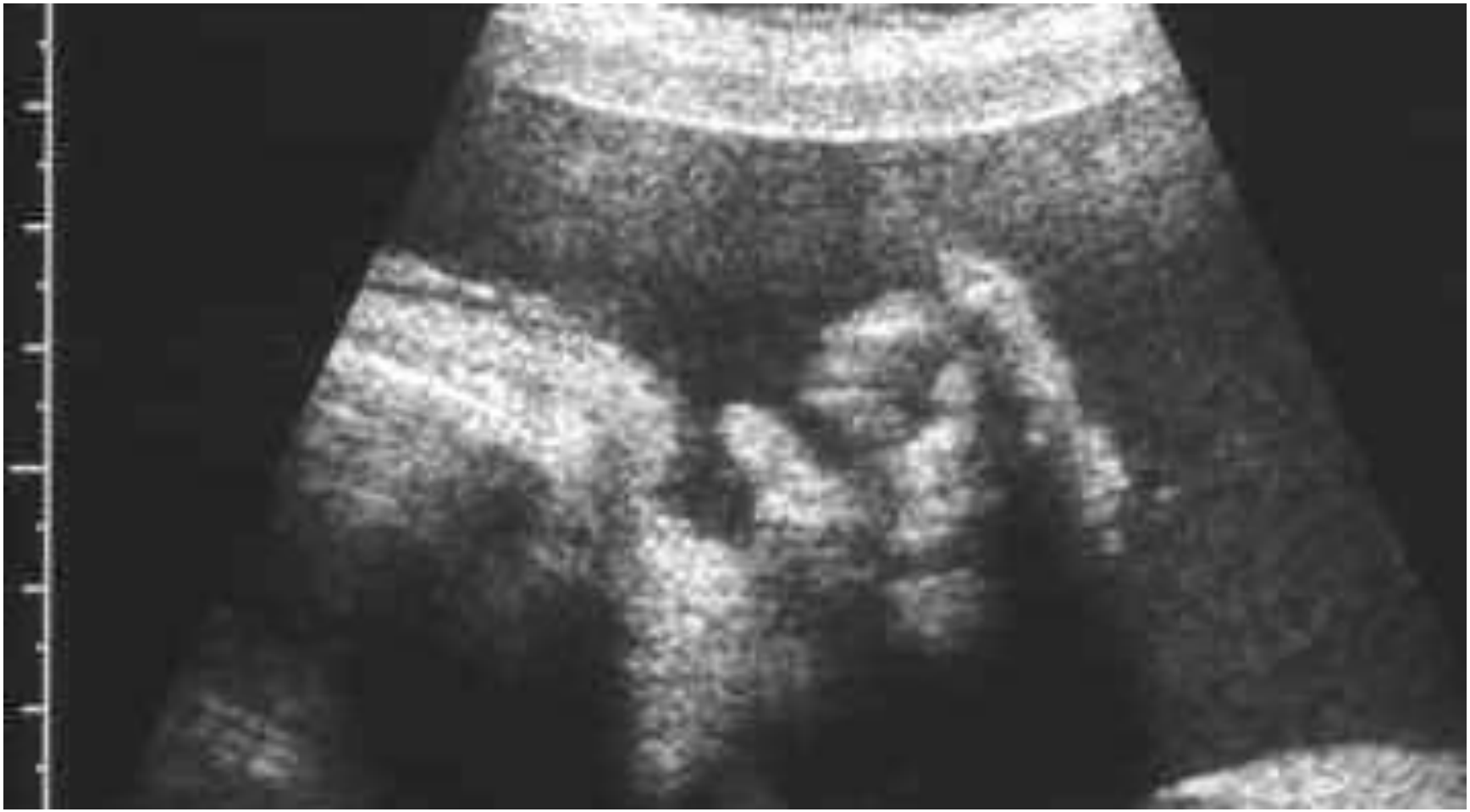
Axial yüz



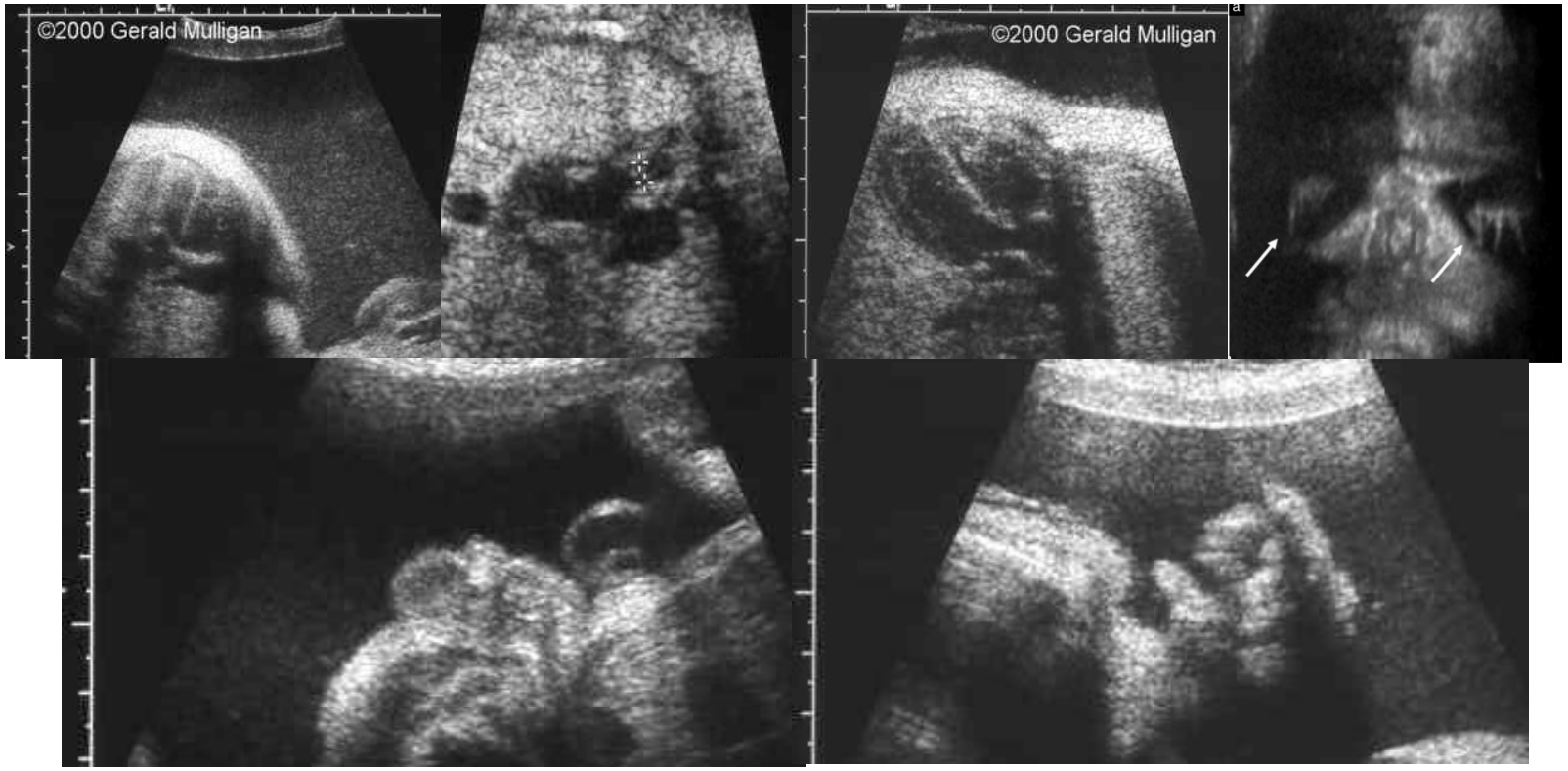
Axial genitalya



El



Pozitif bulgular



- Gövedede hirsutizm
- Pulmoner stenoz
- Fallot tetralojisi

- Uzun kirpikler
- Hipoplastik genitalya
- 3-4 sindaktili
- Mikrosefali

Cornelia de lange S.