Anencephaly, Dandy-Walker, Holoprosencephaly

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Texas Tech Physicians
MATERNAL-FETAL MEDICINE

1

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2

ANENCEPHALY, DANDY-WALKER, HOLOPROSENCEPHALY

- Pathophysiology
- Genetics
- Ultrasound findings
- Antepartum management
- Postpartum outcomes

3

ANENCEPHALY

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4

Exencephaly-anencephaly sequence

- Occurs in 3 per 10K live births
- The most common neural tube defect
- Cause is multifactorial (genetic susceptibility combined with environment)
- Affects females more than males
- Six times more common in Caucasians than African Americans

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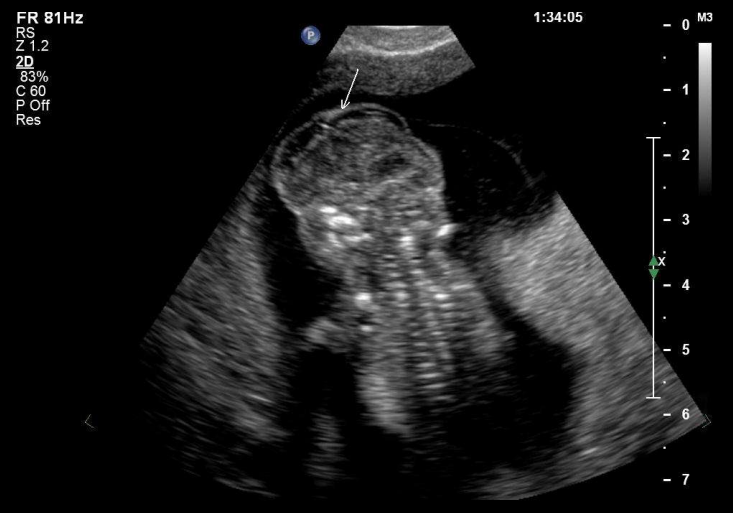
Exencephaly
Step 1: failure of cranial bones to develop



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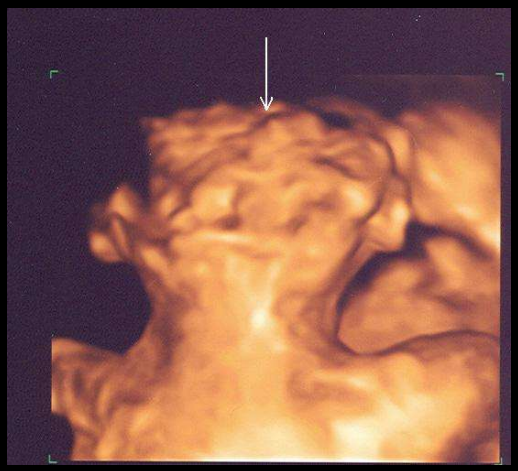
Step 2: exposure to amniotic fluid destroys brain tissue =anencephaly



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Exencephaly - anencephaly

- This sequence is initiated at 18-20d after fertilization
- The neural tube is closed (or not closed) by 28 days

9

Anencephaly : Risk factors

- Use of anticonvulsants that affect folate metabolism
- MTHFR C677T mutation which affects folate metabolism
- NTD’s seem to peak in May and June conceptions ?

10

Anencephaly genetics

- All the trisomies (2,9,13,18 and 21) and triploidy have been associated with anencephaly but the majority of cases are euploid
- If there are additional anomalies the risk of aneuploidy is increased

11

Anencephaly

- Will be detected by an elevated MSAFP
- Alpha fetoprotein is produced by the yolksac, GI tract and liver-any open lesion will cause elevation.

12

Anencephaly (ultrasound findings)

- Easily diagnosed at the 11-14 week scan
- A triangle shaped face
- Absence of the echogenic skull bones
- Brain tissue may sit on the top of the head
- 89% of cases have echogenic amniotic fluid
- An open lesion on the spine may be present
- Look for other anomalies particularly face and heart

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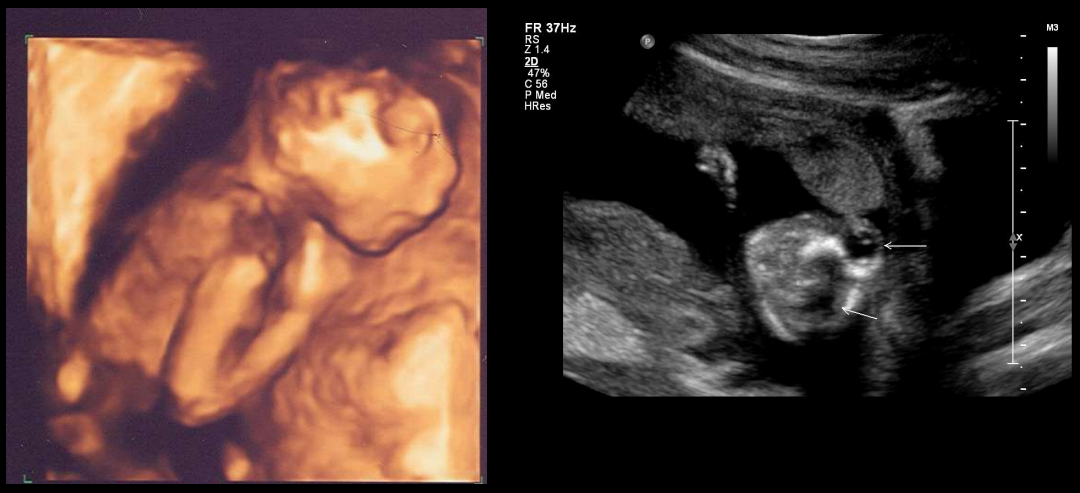

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Anencephaly (antenatal mgmt.)

- It is recommended to offer genetic testing via amniocentesis
- This is for future pregnancies and allows counseling on recurrence risk
- If patient does not want prenatal diagnosis testing can be done after birth

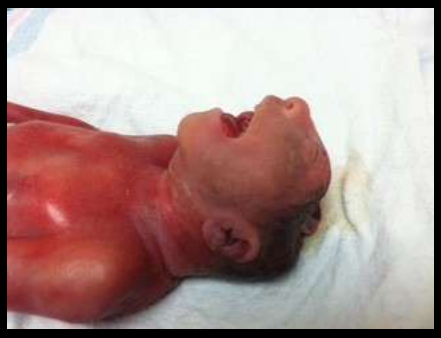
15

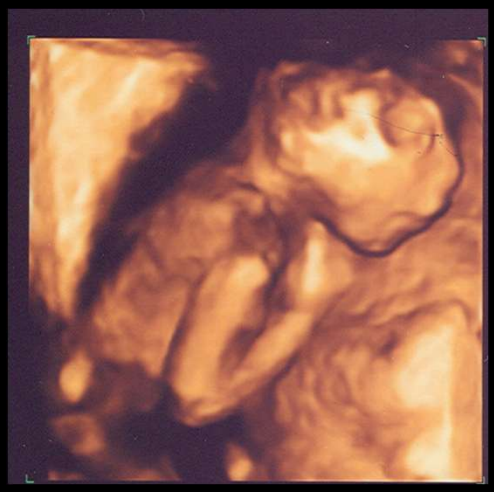
Anencephaly

- Should be considered a lethal anomaly
- Some babies will be born alive if carried to term.
- It is believed that an intact fetal hypothalamic-pituitary axis is required for initiation of spontaneous labor – these babies often don't go into labor and the head is not able to dilate the cervix in the usual way. Though vaginal delivery is recommended.
- According to the national birth defect registry: <50% born alive; 25% live 3-5d. Reports of at least one baby living for months

16

Anencephaly





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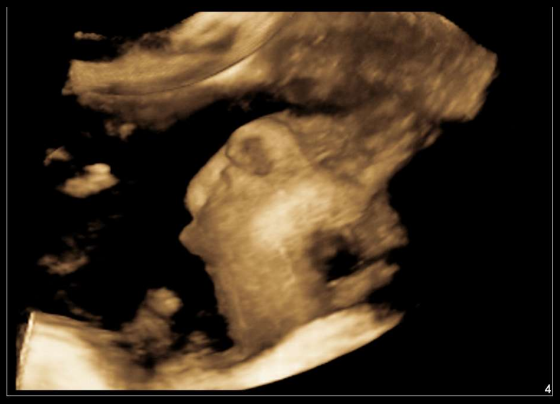

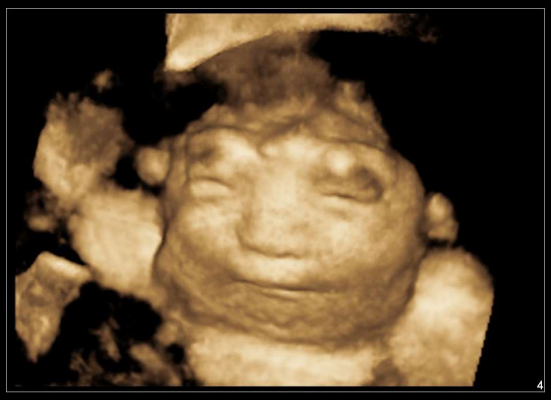

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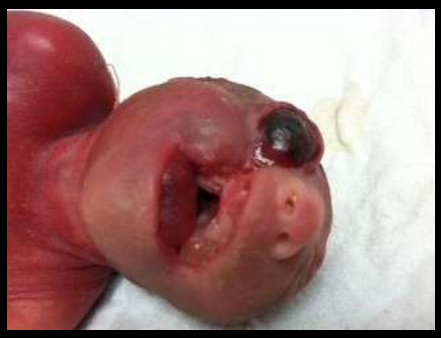

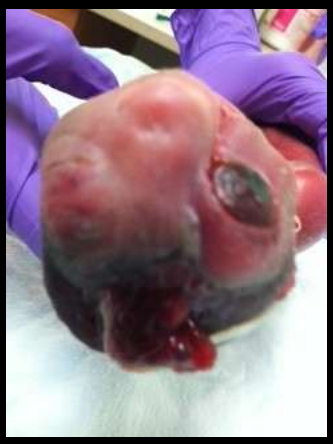

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Anencephaly: early detection

- Patients with a previous affected child should have an 11-14 weeks scan. Acrania /anencephaly is usually readily diagnosed at this time
- Patient should also have MSAFP screening at 15-22 weeks

20

Anencephaly: Recurrence risk

- Sibling of parent: 1.8%
- 1 previous child with anencephaly 3.15%
- 2 previous children with anencephaly 10%

21

Prevention: anencephaly

- All patients with a history of a baby with anencephaly or other NTD should take 4mg of folate daily.
- Ideally this should be started 3 months before becoming pregnant
- After first missed period its too late

22

23

DANDY-WALKER

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24

Dandy-Walker

- Complete malformation consists of vermian agenesis, cystic dilation of the posterior fossa and communication through the vermis to the fourth ventricle causing dilation.
- There are many Dandy-Walker variants: small posterior fossa cyst with a small vermian defect; other degrees of vermian agenesis
- (NOTE use of dandy-walker variant is discouraged)
- Occurs in 1:25000 – 35000 births
- Males to female ratio is 1:3

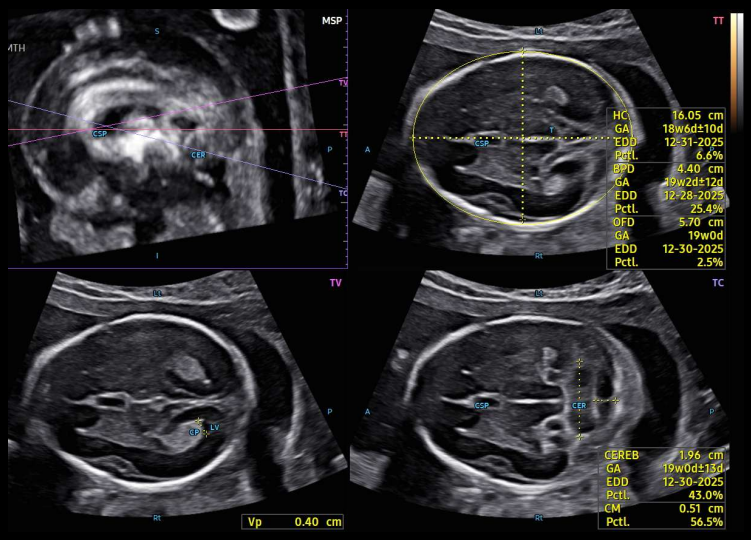
25

Dandy-Walker

- Shares an embryologic etiology with several abnormalities of the cerebellum including:
- Mega cisterna magna
- Blakes pouch cysts
- 80% of true cases will develop hydrocephalus

26

Dandy-Walker ultrasound



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Dandy-Walker : Ultrasound

- Ultrasound is the most effective way to diagnose prenatally
- A defect in the vermis allowing the 4th ventricle to communicate with the posterior fossa is diagnostic
- Caution before 18 weeks because cerebellar vermis grows from top to bottom prior to that time.

- 57% of cases have other structural anomalies: CNS most common followed by cardiac

28

Dandy-Walker : ultrasound

1) The transcerebellar view (sub-occipito-bregmatic)

Should include the two cerebellar hemispheres joining in the midline by the vermis. The cisterna magna is also visualized at this point

2) Visualize the 4th ventricle as a small anechoic area between the cerebral peduncles

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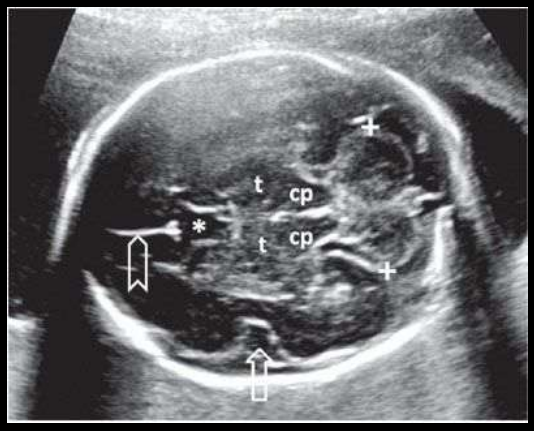
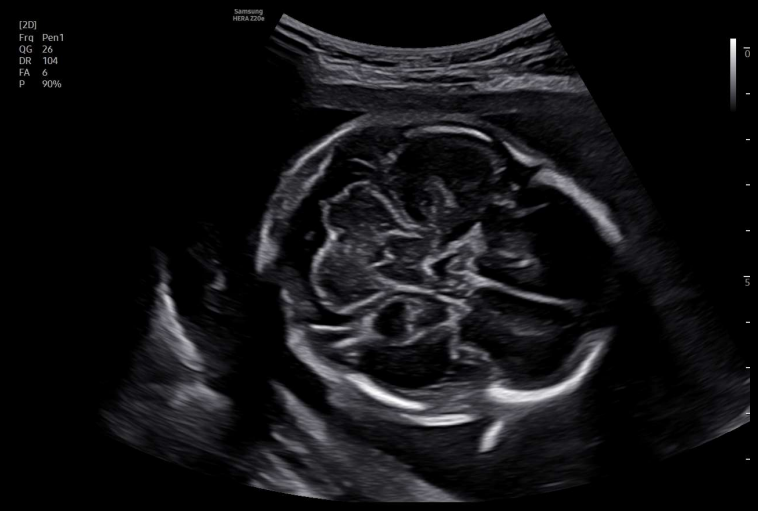


30

Dandy-Walker : the fourth ventricle



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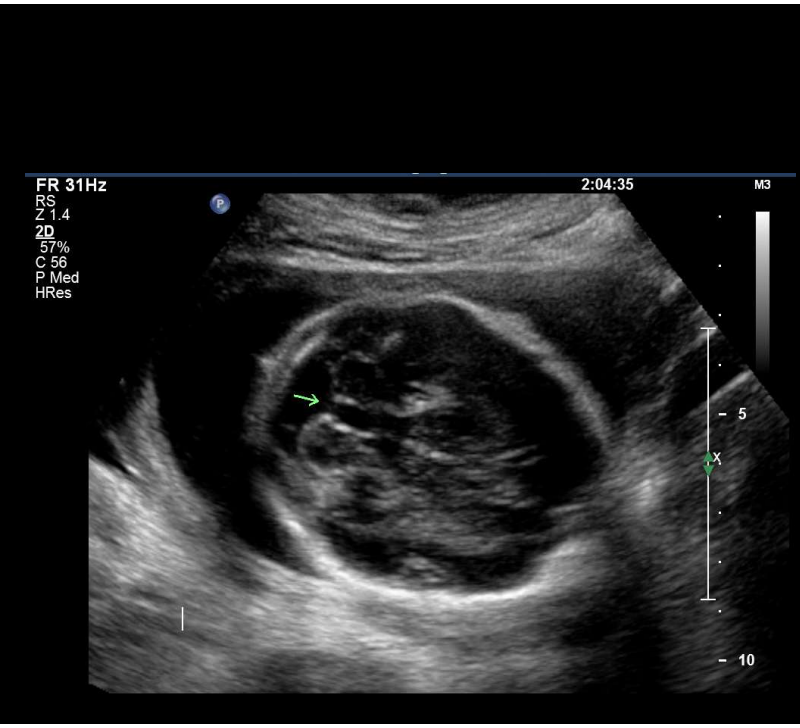

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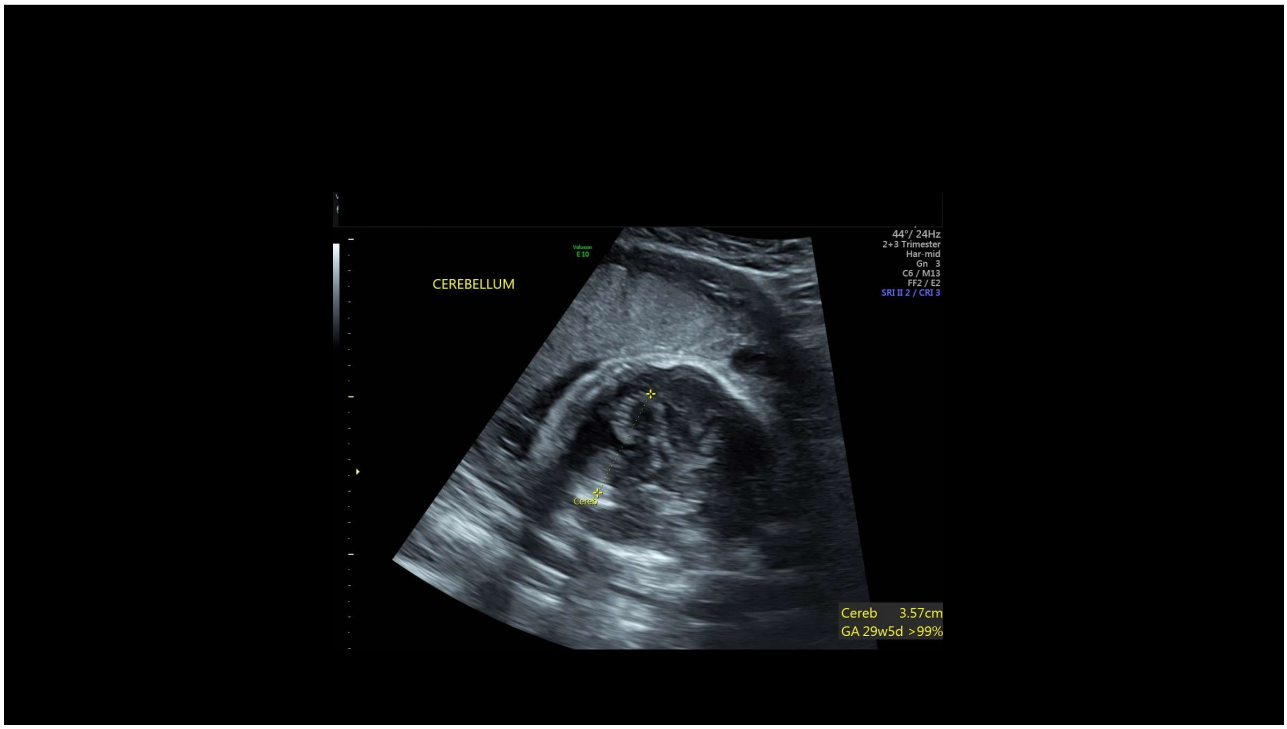

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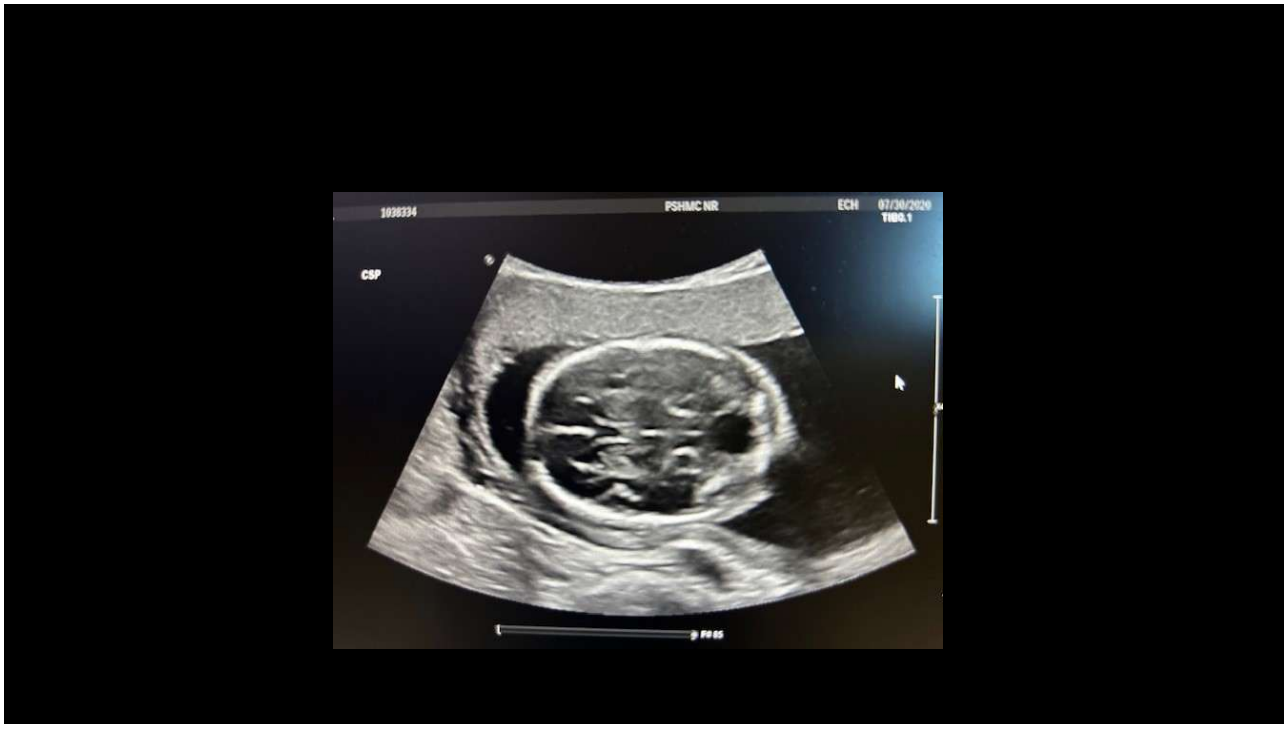
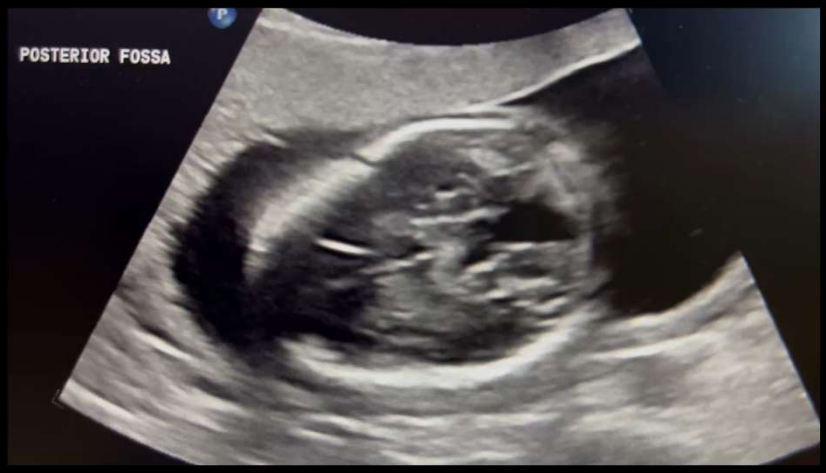


34

Dandy- Walker???



35

Blakes pouch cyst (on the DWM spectrum)

- Infravermian cyst that bulges into +/- communicate with the 4th ventricle
- Upward displacement of the vermis
- Usually has a keyhole appearance

- Blakes pouch is usually transient regressing by 12 weeks
- Controversial whether on the dandy-walker continuum

36

Mega cisterna Magna (DWM spectrum)

- Normal vermis and cerebellum
- Enlarged posterior fossa (>1.0cm)
- No hydrocephalus

37

Dandy-Walker: genetics

- Dandy – Walker is considered multi-factorial
- Approximately 40% have a chromosome abnormality

-- sometimes aneuploidy

-- but also abnormal copy number variations which require a microarray

The risk of aneuploidy increases with the presence of other anomalies.

38

Dandy-Walker : antenatal care

- Offer amnio for microarray
- Look for other anomalies especially CNS and heart
- Monthly growth
- Anticipate vaginal delivery

39

Dandy-Walker : postnatal

- 80% develop hydrocephalus by 3 months of age
- In contrast patients with mega cisterna magna are often asymptomatic with no issues
- All babies with the diagnosis should have an MRI for detailed evaluation of the brain

40

Dandy-Walker : prognosis

- The prognosis is uncertain
- In two large studies MR defined as IQ below 80 was between 40-70%
- (Pilu et al 1992)

One study found most affected children had some degree of MR and psychomotor delay

On the plus side there are reports of children with no associated anomalies and normal karyotype with no identified concerns

The best that can be said is that outcomes are on a spectrum

41

Dandy-Walker: prognosis

- Two distinct categories
- 1) those with varying degrees of vermian agenesis and otherwise normal brain –
- 2) those with significant dysplasia of the vermis and midline brain abnormalities

42

Dandy-walker: recurrence risk

- In isolated (non-syndromic cases) 1-5%
- Believed to be due to a de novo mutation
- If part of a syndrome – can be as high as 25% if associated with a known genetic cause

43

Dandy-Walker: prevention

- No identified cause which can be avoided
- Consideration of family history

44

HOLOPROSENCEPHALY

45

holoprosencephaly

- A continuum of structural anomalies of the prosencephalon (forebrain)
- Occurs within the third and fourth week of gestation
- Affects 1:250 conceptions but 1:8000-16000 live births
- Key takeaway : affected individuals range from lethal anomalies to mild developmental delay with no visible defects

46

Holoprosencephaly

- Development of the prosencephalon occurs in 3 stages
- Formation : the prosencephalic vesicle is established by 22-24 days
- Cleavage: cells in the midline undergo programmed death leading to splitting of the telencephalon
- Midline development :cerebral hemsphers and thalami develop

47

Holoprosencephaly

- Normal face and brain development are paired due to the use of the same signaling molecules:
- Bone morphogenic proteins in the dorsal
- Wingless integrated proteins in the rostral
- Sonic hedgehog genes in the ventral midline

- Sonic hedgehog mediates development of the face
- Hence the face predicts the severity of holoprosencephaly

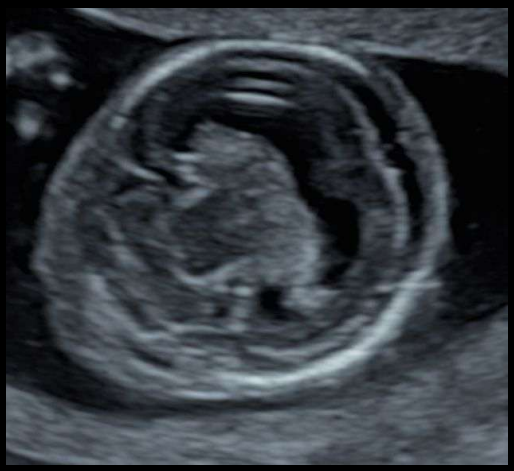
48

Holoprosencephaly

- DeMyer proposed a classification dividing holoprosencephaly into three subcategories
- Alobar – lack of separation of the cerebral hemispheres and monoventricle
- Semi-lobar- only the anterior lobes fail to separate
- Lobar –only the most rostral-inferior parts of the frontal lobes are fused.

49

Alobar holoprosencephaly



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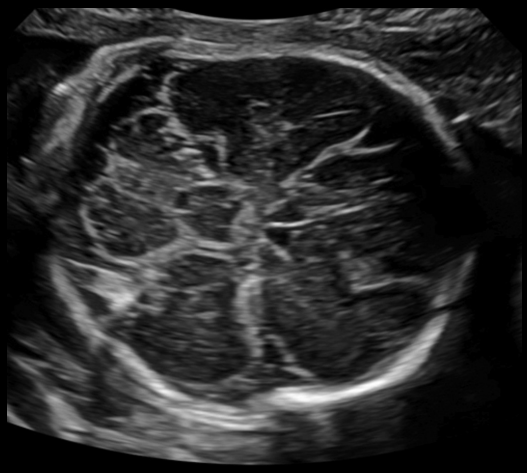
Lobar holoprosencephaly



51

holoprosencephaly

- Other identified categories include
- Middle hemispheric variant : fusion of only the posterior frontal and parietal lobes

- Septo-optic dysplasia is believed to be a variant
- Only facial features (hypotelorism, single central incisor)

- Developmental delay is present in all individuals within the spectrum

52

Holoprosencephaly (Genetics)

- 25-50% have a chromosomal abnormality (aneuploidy or structural)
- Most common is T13 followed by T18
- Structural chromosomal defects (copy number variants) occur in 10-14 % of affected individuals
- 18-25% have a single gene defect (to date all known genes are involved or indirectly in regulation of Sonic Hedge Hog

53

Holoprosencephaly (genetics)

- There are several syndromic single gene disorders associated with HPE
- Smith-Lemli-Opitz (erroring cholesterol biosynthesis)
- Steinfeld syndrome (holoprosencephaly, radial limb defects, organ defects)
- FGFR1 related syndromes (ectrodactyly, kallman syndrome e.g.)

54

Holoprosencephaly (nongenetic factors)

- Maternal diabetes. Pregestational diabetes requiring insulin has a 10x increased risk
- Alcohol exposure (dose dependent) more drinks per week = more risk
- Anything that disrupts the sonic hedgehog pathway(retinoic acid, food borne mycotoxins, drugs that interfere with cholesterol biosynthesis

55

Holoprosencephaly(ultrasound findings)

- Alobar and semilobar HPE is easily diagnosed by Ultrasound
- Complete or partial absence falx (interhemispheric fissure)
- Distorted choroid
- Fused thalami
- Facial abnormalities

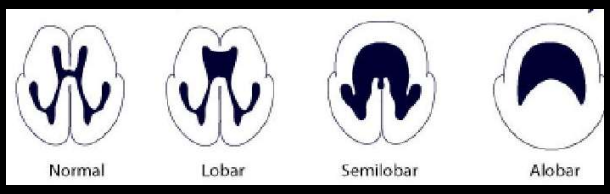
56

Holoprosencephaly (ultrasound)

- Lobar and mild forms of semilobar may indicate some form of cerebral anomaly but the diagnosis is unclear by US especially with a normal face
- MRI is the choice for further evaluation

57

types of holoprosencephaly



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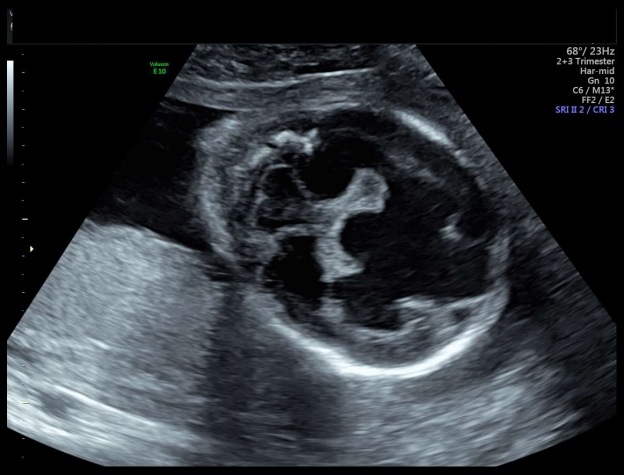
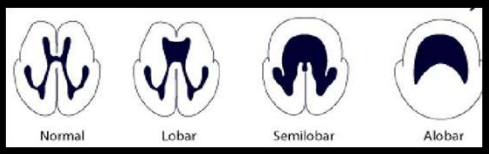
semilobar





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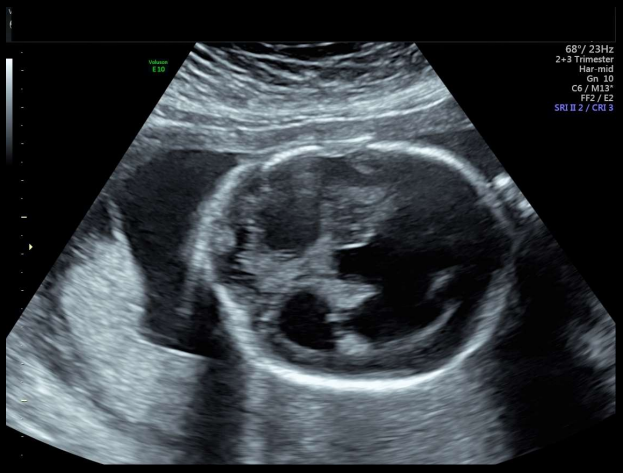
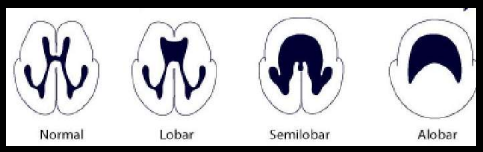
Between lobar and semilobar





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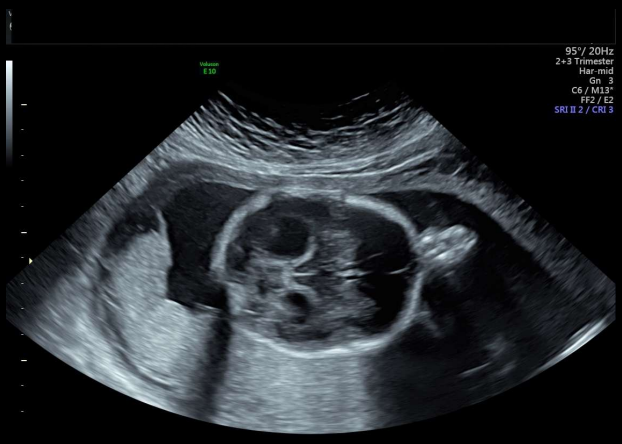
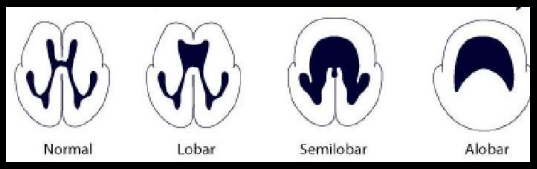
lobar





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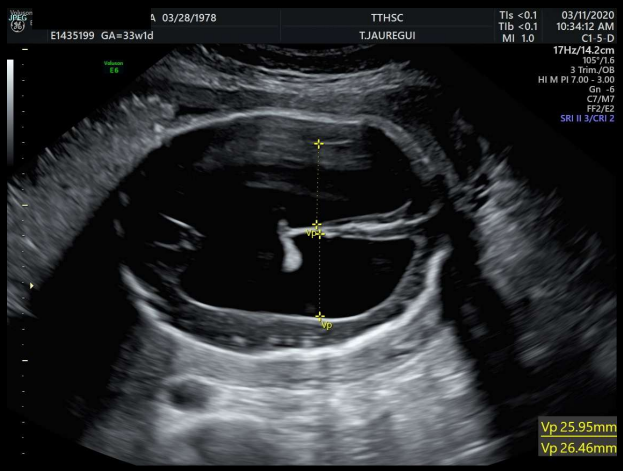
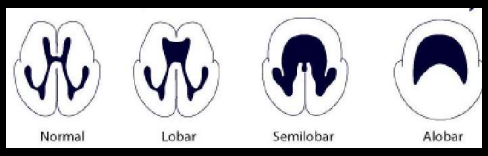
alobar





62

Septo-optic dysplasia (DeMorsier syndrome)

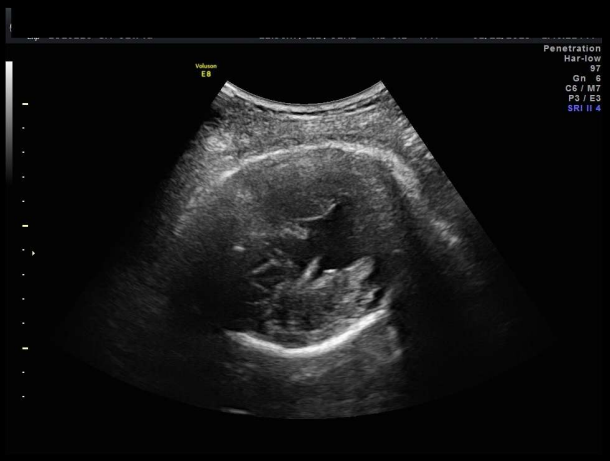
- May be a variant of holoprosencephaly

- Optic nerve hypoplasia
- Midline brain defects (absence of the septum pellucidum)
- Pituitary gland dysfunction

- Two or more must be present for the dx
- 30% of patients have all 3

63

Septo-optic dysplasia



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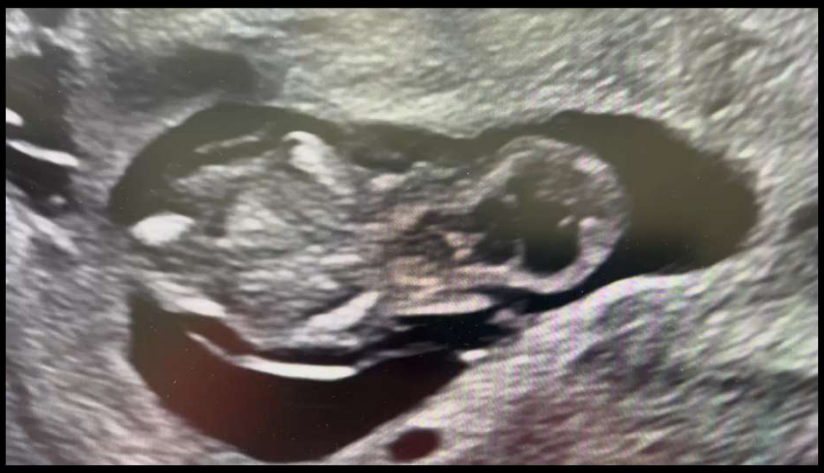

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Holoprosencephaly (management)

- Chromosomal microarray
- Can test for a known panel of HPE genes or do whole exome sequencing (expensive)

- Once a gene is identified in the baby parents should be tested
- Recurrence risk as high as 50% for parents carrying a mutation with incomplete penetrance
- With a clinical diagnosis but no identified genetic cause it is impossible to define recurrence risk

66

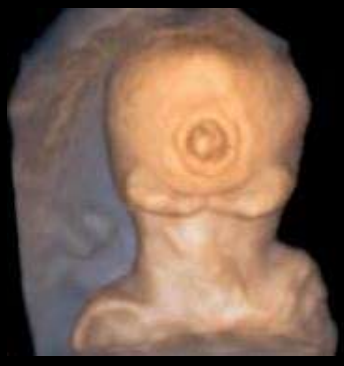
Holoprosencephaly (facial anomalies)

Four main types

1) Cyclopia = single eye with or without proboscis
2) Ethmocephaly = ocular hypotelorism and a proboscis
3) Cebocephaly = ocular hypotelorism and single nostril nose
4) Medial cleft lip and palate and ocular hypotelorism

67

cyclopia



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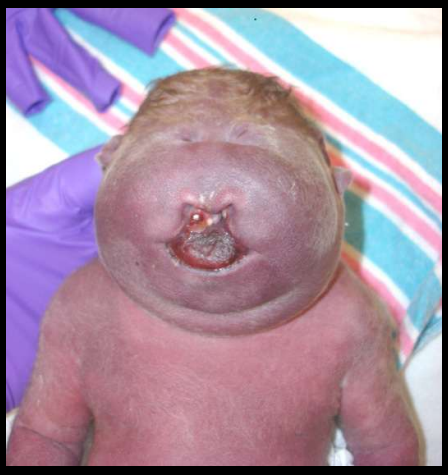
Cleft lip palate, hypotelorism



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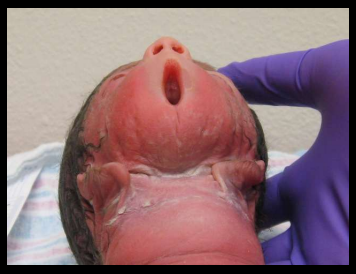

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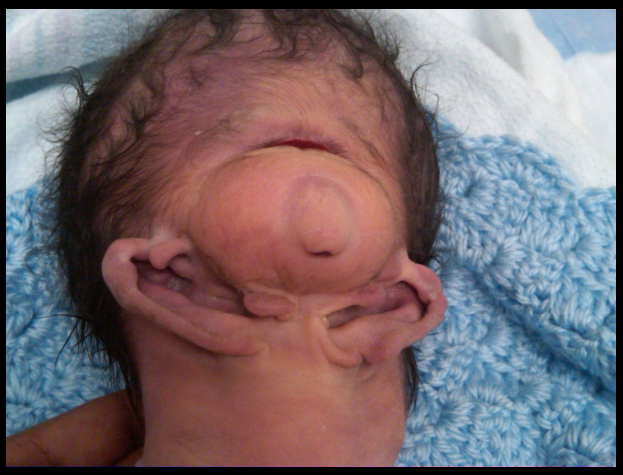

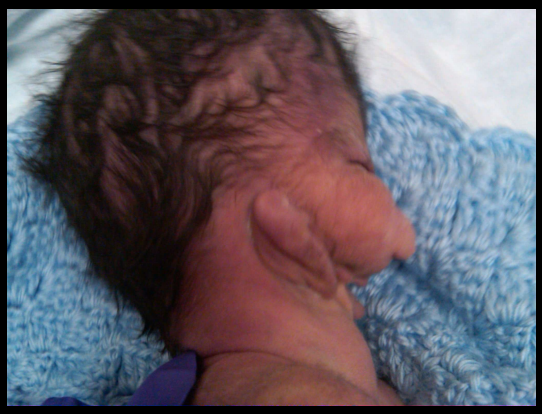

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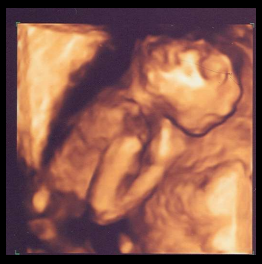
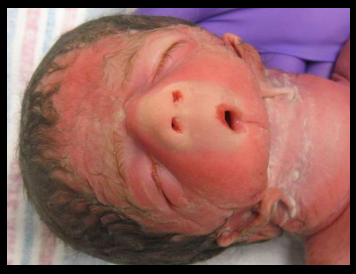
72

QUESTIONS?





73

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74