

**Fetal Ocular Imaging**

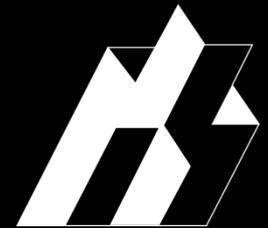
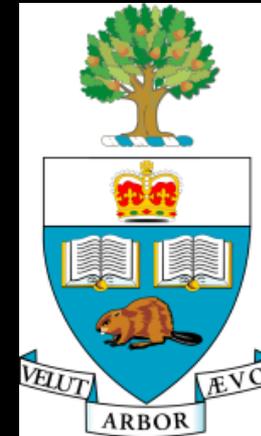
-

**US and MRI**

**Dr. Ashley J. Robinson**

# Acknowledgements

- The Hospital for Sick Children
  - S Blaser - Diagnostic Imaging
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- Mount Sinai Hospital
  - D Chitayat - Prenatal Diagnosis & Medical Genetics
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  - G Ryan - Obstetrics & Gynaecology
- UCSF
  - Ruth Goldstein
- BC Women's Hospital
  - D Pugash, K Lim & A Gagnon & team – Centre for Prenatal Diagnosis and Treatment
- BC Children's Hospital
  - A Byrne - neuroradiology



# Purpose

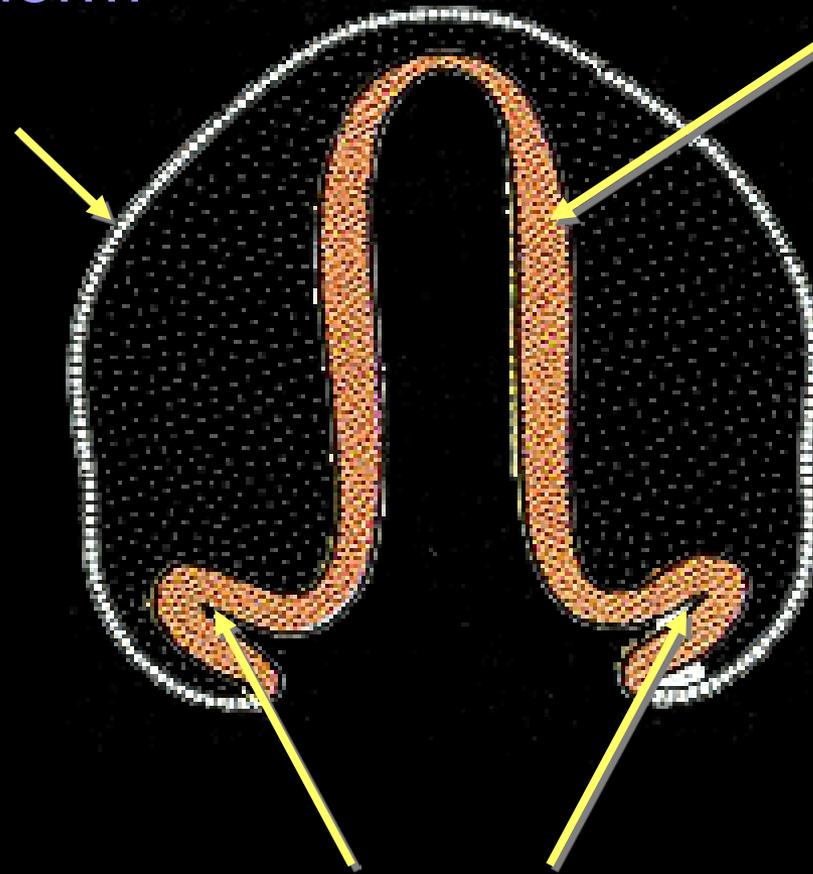
- Evaluation of fetal eyes:
  - US - Not routinely required according to various guidelines (AIUM/ACOG/ACR), RCR
    - Evaluation of eyes is a reasonable expectation in detailed anomaly scan
  - MR – various protocols & guidelines for fetal imaging
    - Evaluation of eyes now included
- Demonstrate that ocular pathologies & syndromes involving the eyes (esp. bilateral & symmetric) can go un-noticed without systematic approach
- Demonstrate that sonographic growth charts cannot be used for assessment by MRI

# Embryology

## 22 days

Surface ectoderm

Wall of forebrain



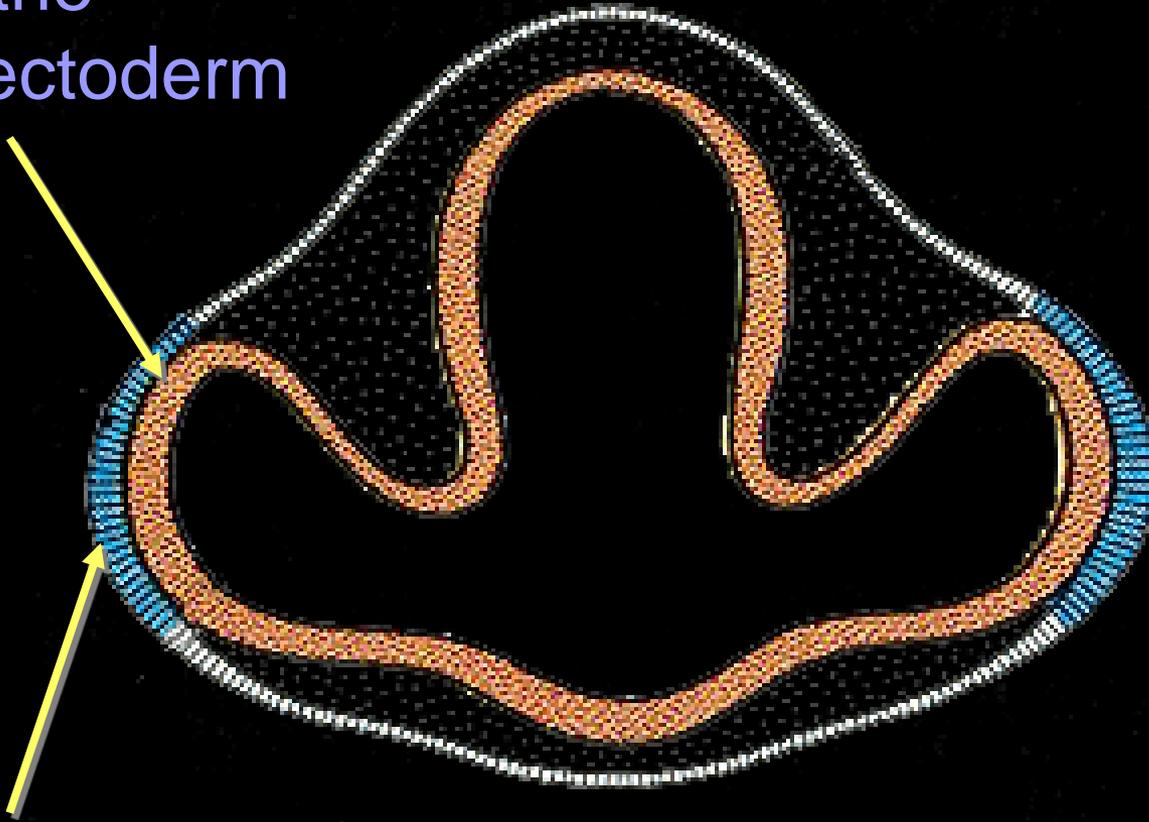
Optic vesicles

Diagrams from "Langmans Essential Human Embryology" 2004.

# Embryology

## 22 days

Contact the  
surface ectoderm



Induce lens  
formation

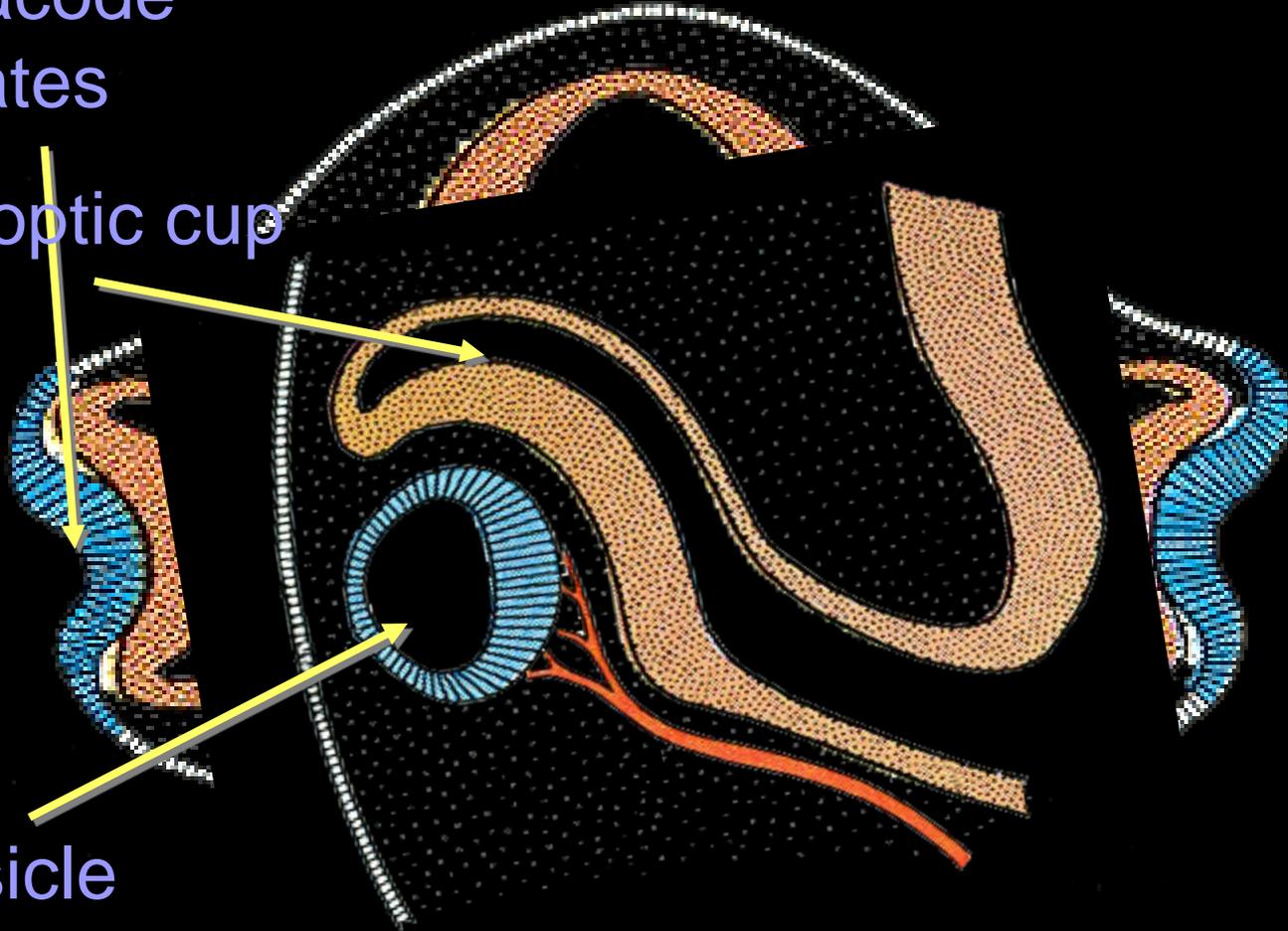
# Embryology

## 5<sup>th</sup> – 7<sup>th</sup> weeks

Lens placode  
invaginates

Forms optic cup

lens vesicle



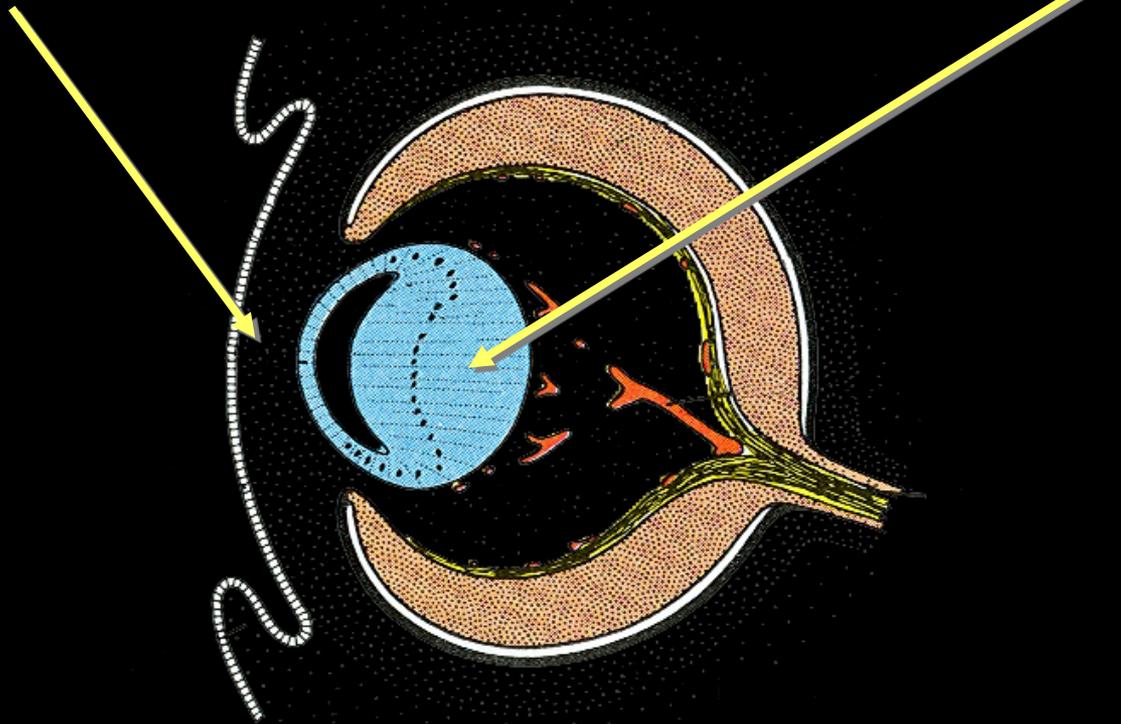
Diagrams from “Langmans Essential  
Human Embryology” 2004.

# Embryology

## 5<sup>th</sup> – 7<sup>th</sup> weeks

Lens vesicle  
loses contact with  
surface ectoderm

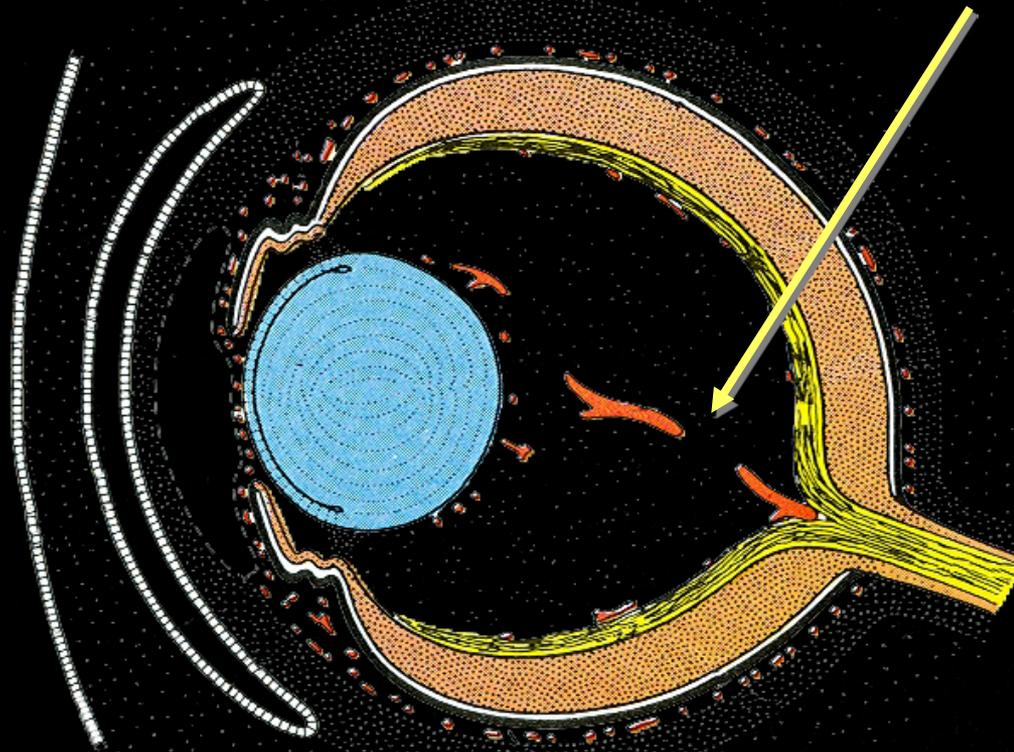
Elongation of lens  
cells fills lumen of  
vesicle



Diagrams from "Langmans Essential Human Embryology" 2004.

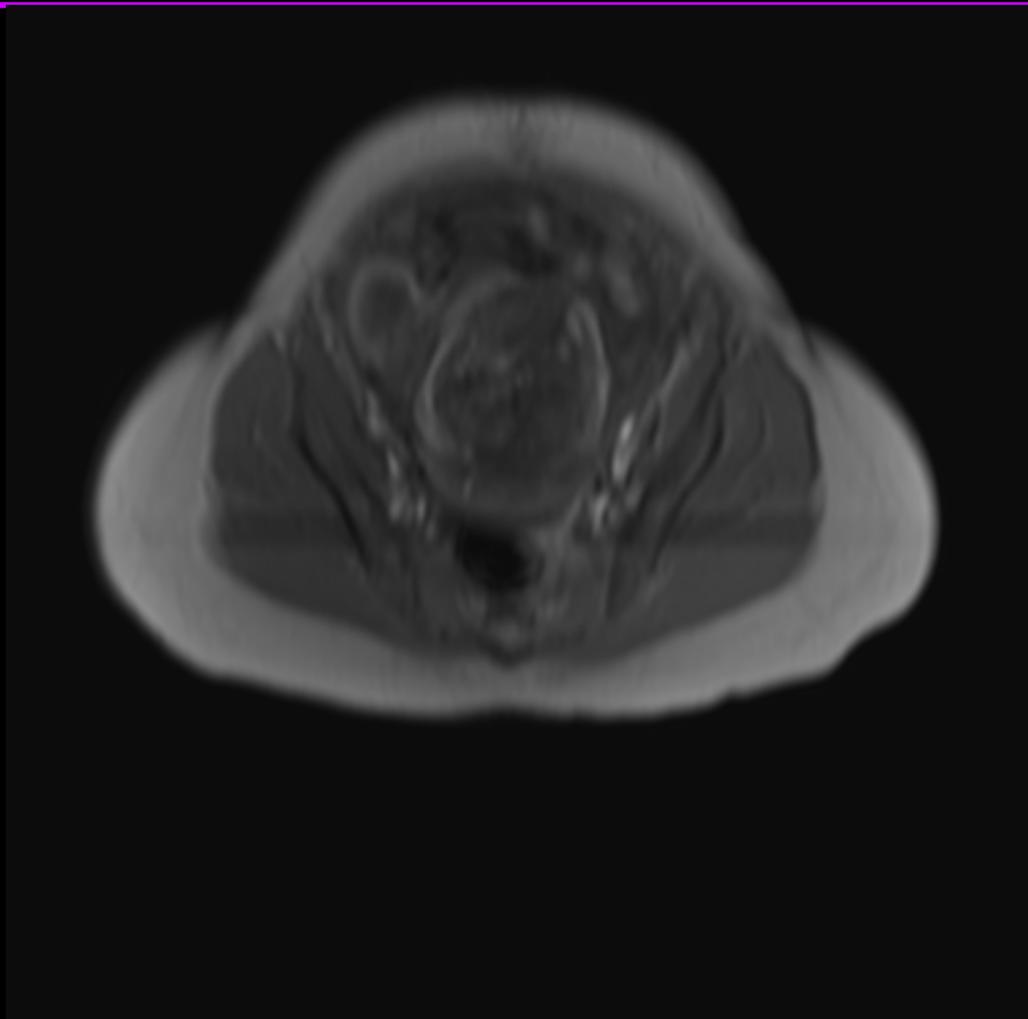
# Embryology by 30 weeks

Obliteration of hyaloid artery completed

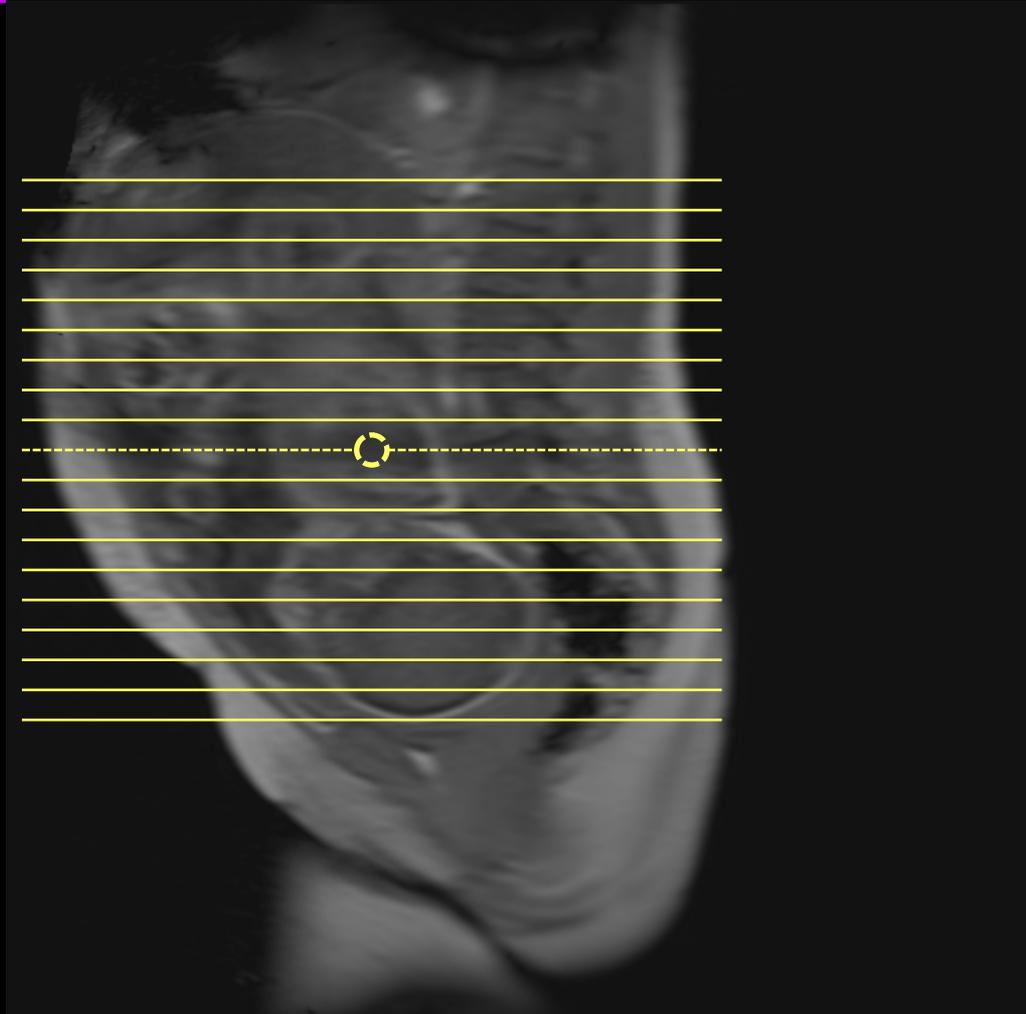


Diagrams from "Langmans Essential Human Embryology" 2004.

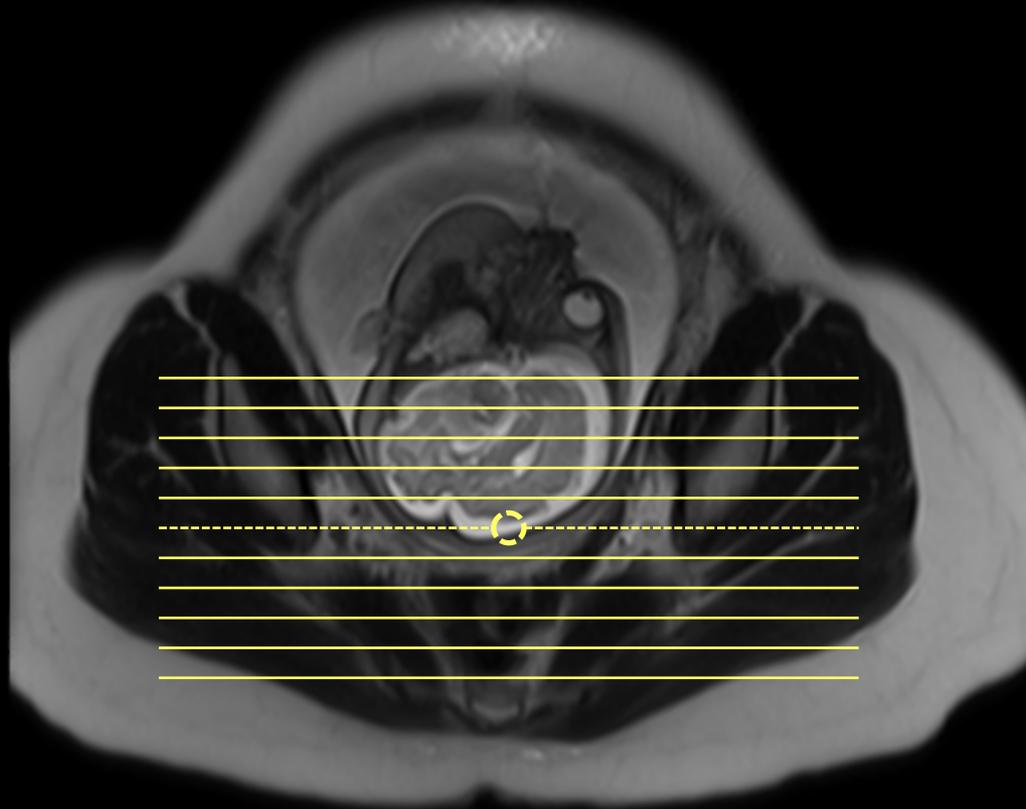
# Technique



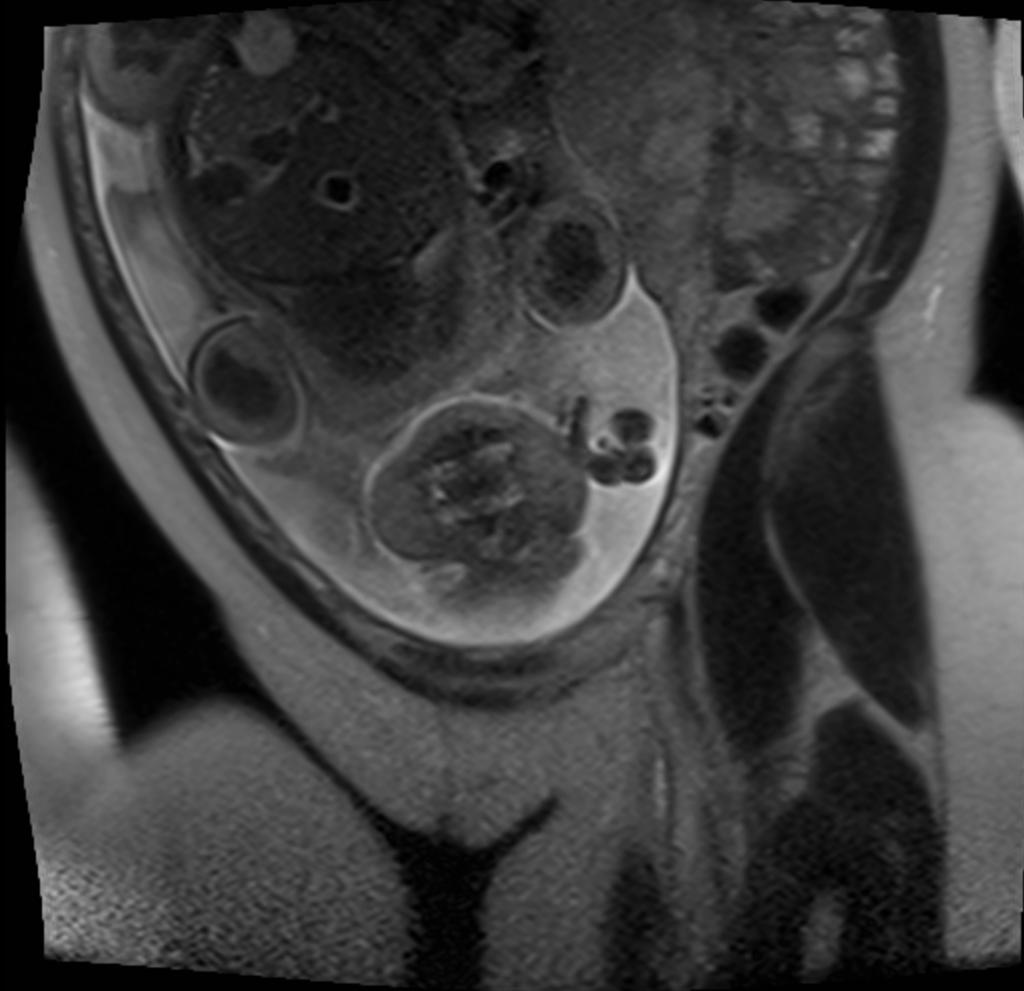
# Technique



# Technique



# Technique



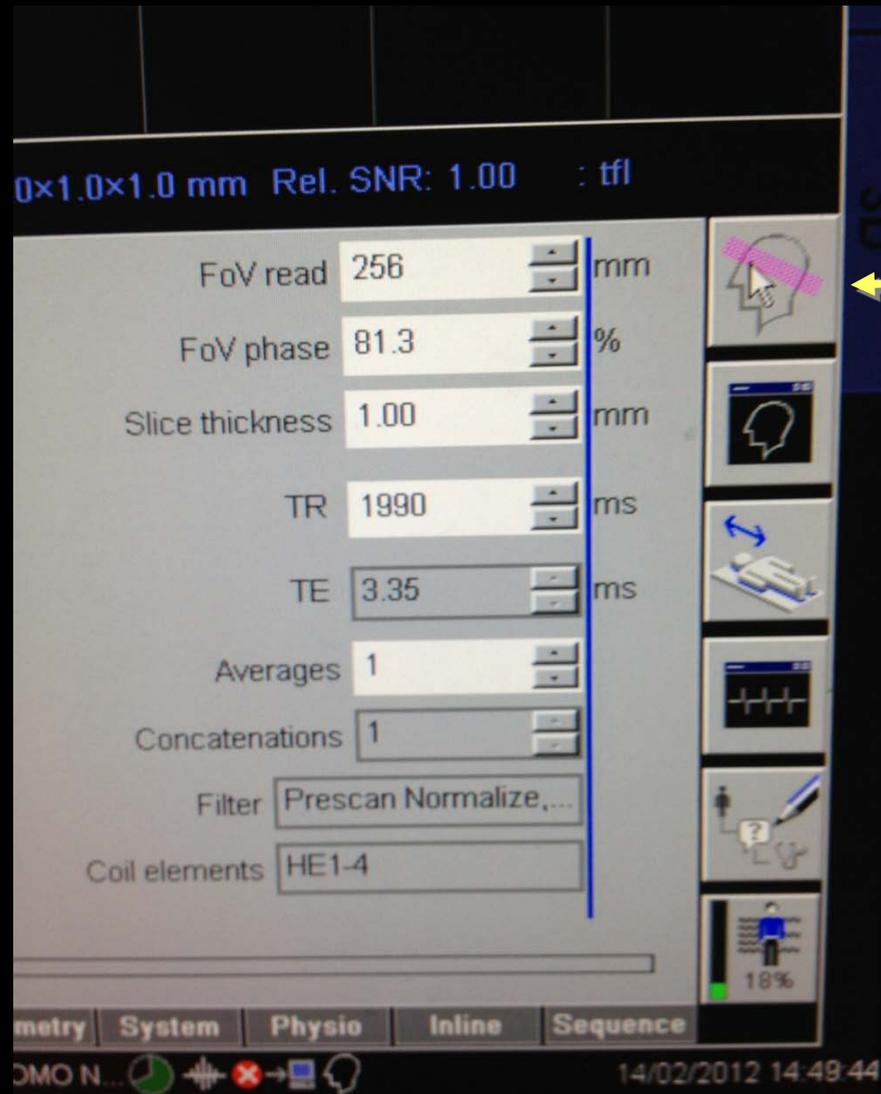
# Technique

0x1.0x1.0 mm Rel. SNR: 1.00 : tfl

FoV read	256	mm
FoV phase	81.3	%
Slice thickness	1.00	mm
TR	1990	ms
TE	3.35	ms
Averages	1	
Concatenations	1	
Filter	Prescan Normalize,...	
Coil elements	HE1-4	

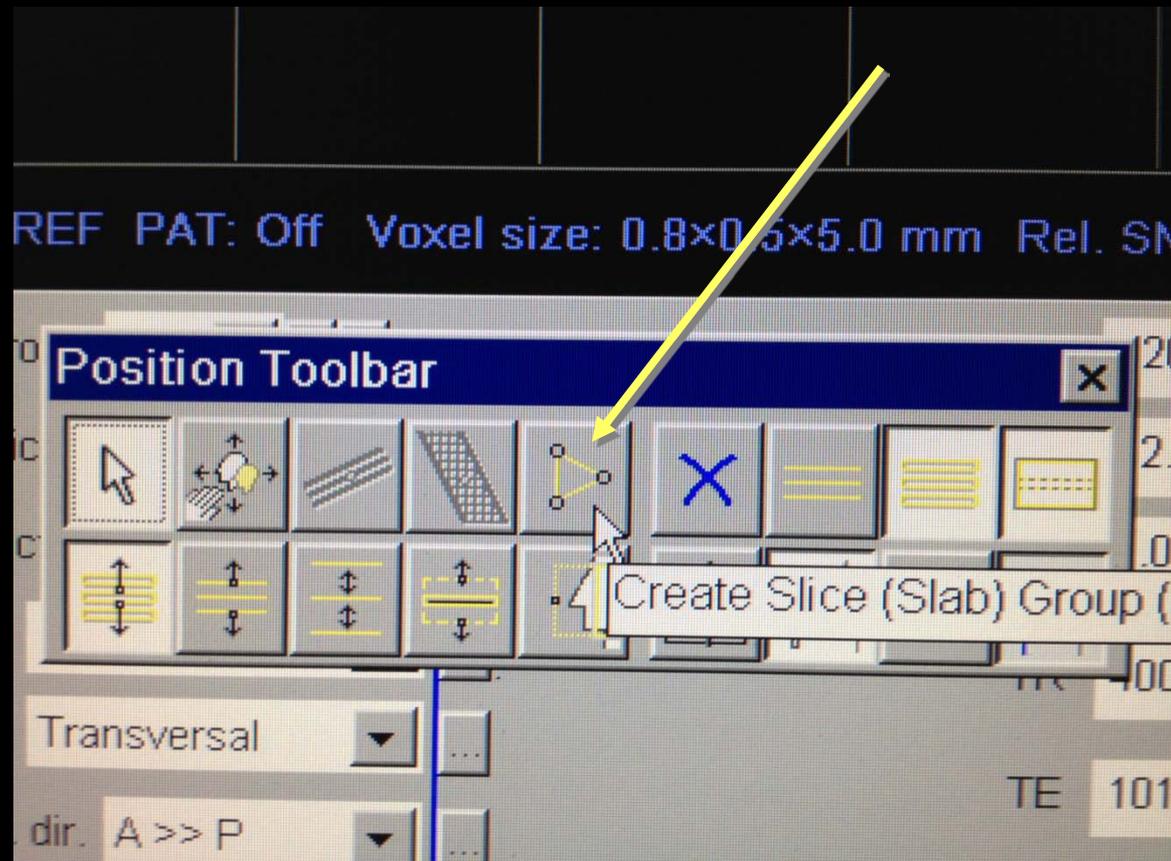
metry System Physio Inline Sequence

14/02/2012 14:49:44

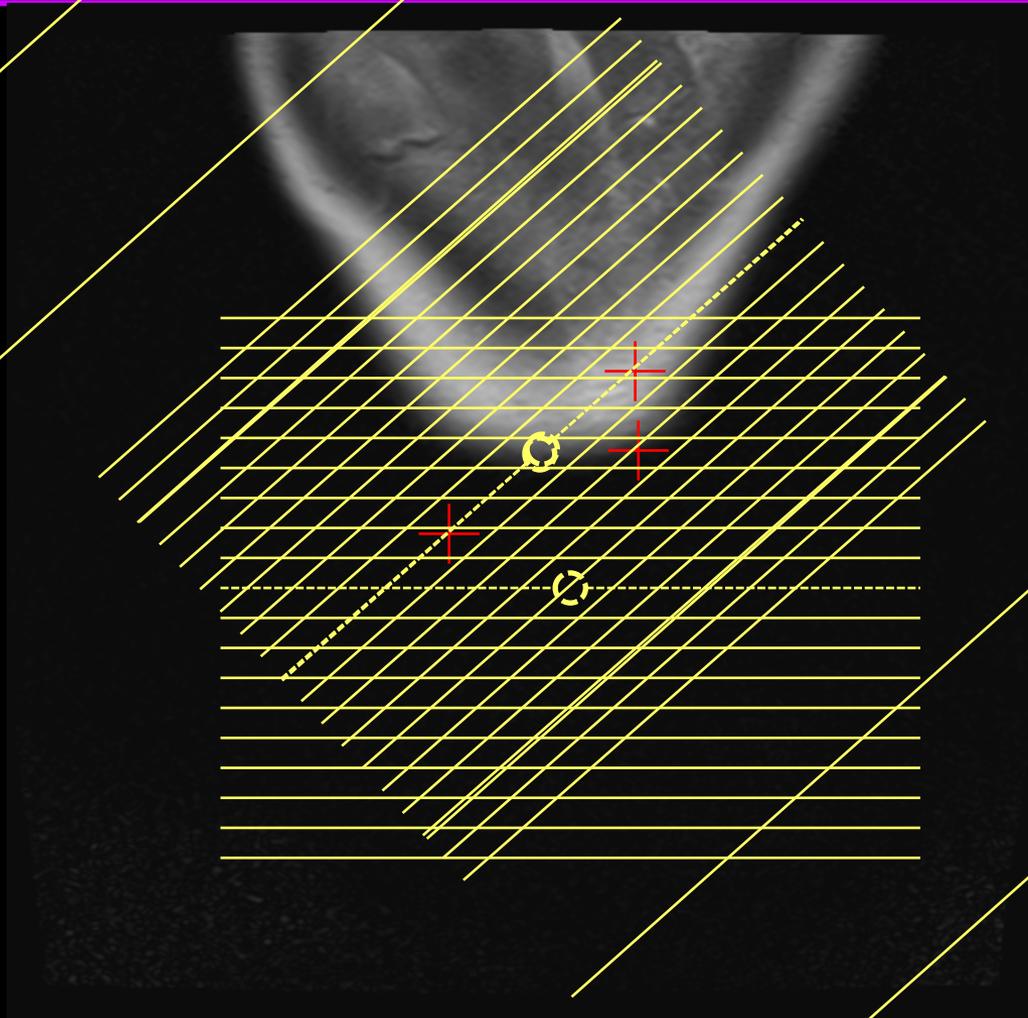


The image shows a screenshot of an MRI software interface. The main window displays technical parameters for a scan, including FoV read (256 mm), FoV phase (81.3%), Slice thickness (1.00 mm), TR (1990 ms), TE (3.35 ms), Averages (1), Concatenations (1), Filter (Prescan Normalize,...), and Coil elements (HE1-4). A vertical toolbar on the right side contains several icons, including a head icon with a hand cursor, a head icon with a brain, a blue double-headed arrow, a waveform icon, a question mark icon, and a person icon with a percentage (18%). A yellow arrow points to the head icon with a hand cursor. The bottom of the screen shows a status bar with the text 'metry System Physio Inline Sequence' and the date and time '14/02/2012 14:49:44'.

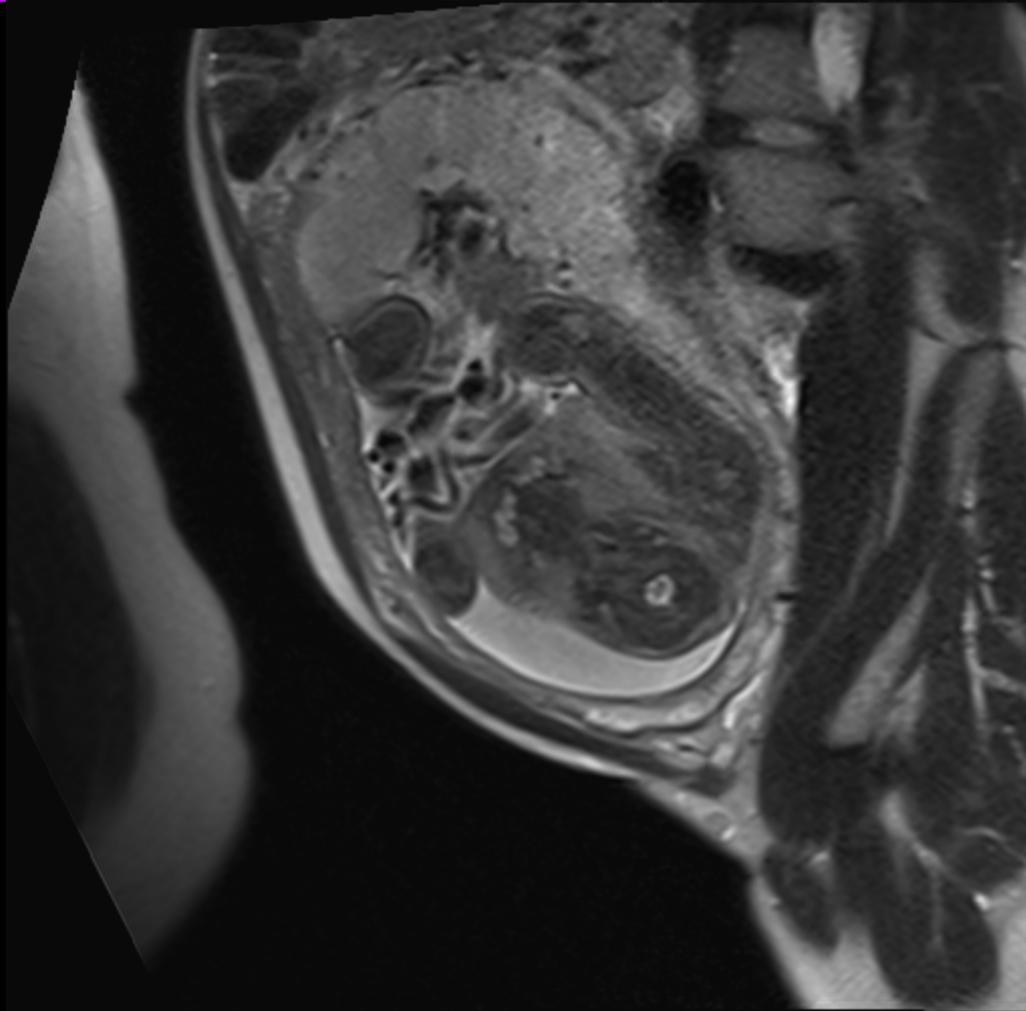
# Technique



# Technique



# Technique



# Method of assessment

- Presence / absence of eyes (microphthalmia/anophthalmia)
- Morphology of lens, vitreous and optic nerve
- Biometry
- Extraocular pathologies

# Anophthalmia / Microphthalmia

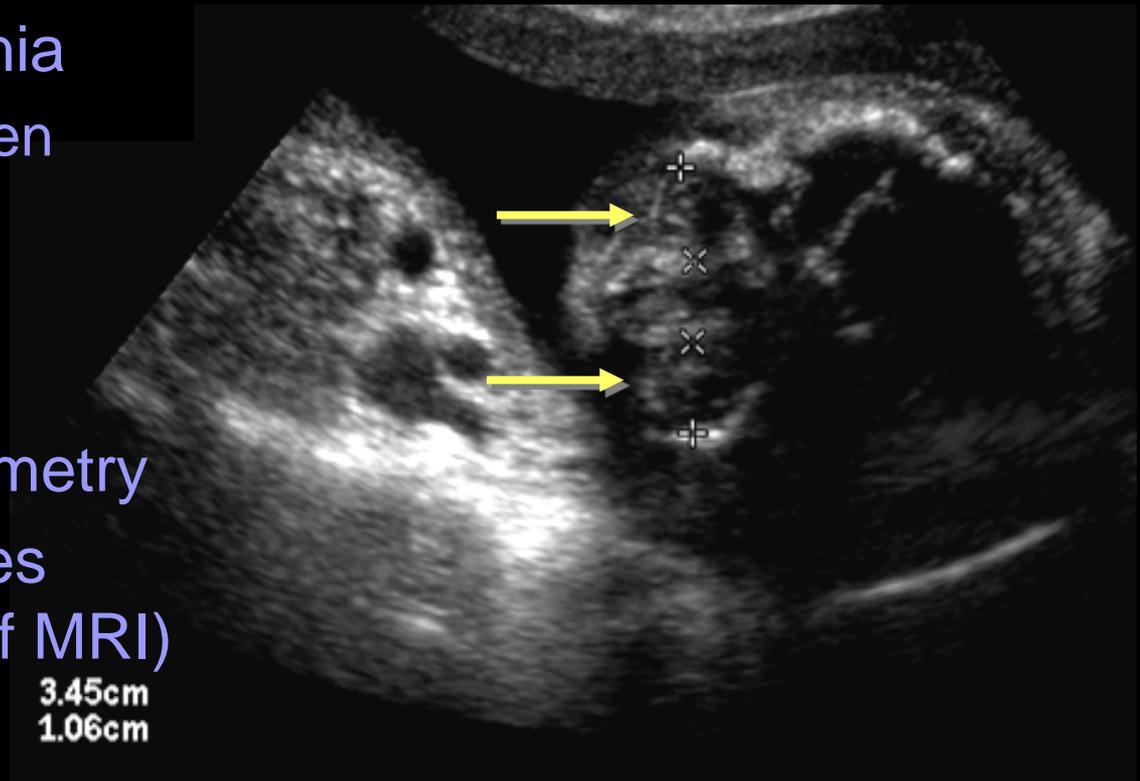
- Anophthalmia is complete absence of the globe in presence of ocular adnexa (eyelids, conjunctiva, lacrimal apparatus)
  - often only be differentiated from microphthalmia pathologically
- 1:2400 pregnancies
- Defined as OD < 5%
- should be differentiated from cytopthalmos
  - Failure of separation of the eyelids – should occur by 24 weeks
  - Usually bilateral
  - When occurs with multiple other abnormalities is known as Fraser syndrome
    - Autosomal recessive inheritance

# Anophthalmia / Microphthalmia

- Primary (eyes never form)
- usually associated with:
  - Chromosomal abnormality e.g. trisomy 13
  - Syndromic (>180 syndromes)
  - Genetic: *SIX3*, *HESX1*, *BCOR*, *SHH*, *PAX6*, *RAX*, *SIX6*
    - *HOX10* (Chr 14) – *MCOP1* & *MCOP2* – isolated AR
    - *CHD7* (CHARGE syndrome)
    - *IKBK*G (incontinentia pigmenti)
    - *NDP* (Norrie disease)
    - *SOX2* (SOX2-related eye disorders)
    - *POMT1* (Walker-Warburg syndrome)
- Secondary (insult during development)
  - Infection e.g. TORCH, syphilis, EBV, parvo
  - Vascular event e.g. Goldenhar (Oculo-auriculo-vertebral spectrum)
  - Toxic / metabolic event (e.g. low Vitamin A, ethanol, retinoic acid)

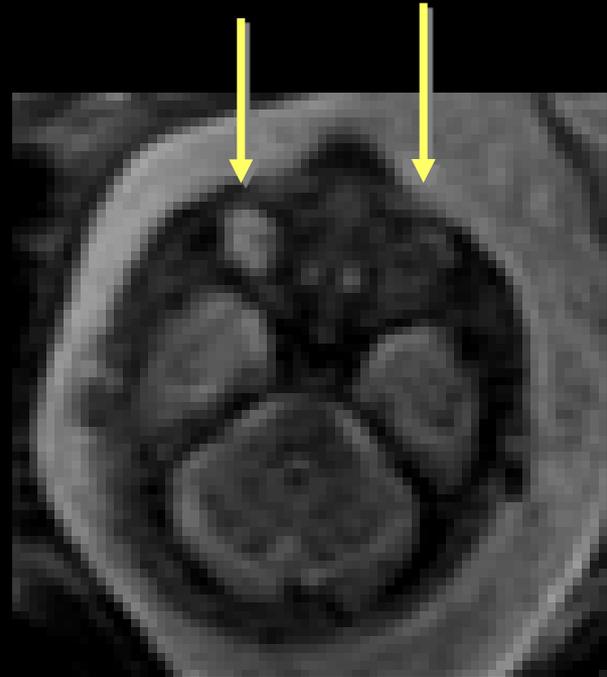
# 25 weeks gestation US findings

- Diaphragmatic hernia
  - Diaphragm only seen anteriorly
  - Stomach up
- Cataracts
- Delayed ocular biometry
- & Cardiac anomalies (unknown at time of MRI)



# 30 weeks gestation additional MR findings

- Normal brain
- Microphthalmia
- & Anophthalmia



# Matthew-Wood Syndrome

- Died at birth
- Unilobated lungs, pulmonary hypoplasia
- Diaphragmatic hernia
- Hypoplastic heart
- & Absent globes with hypoplastic optic nerves



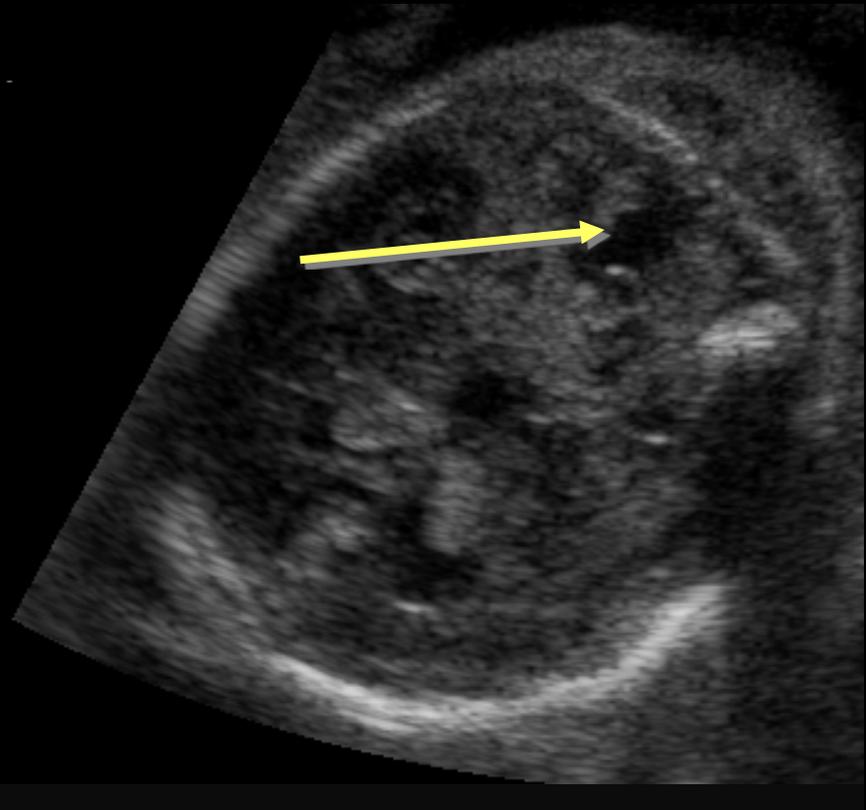
# Matthew-Wood Syndrome

- A.K.A.:
  - Spear
    - Pulmonary hypoplasia
    - Microphthalmia
    - Diaphragmatic hernia
  - PMD
    - Pulmonary hypoplasia
    - Diaphragmatic hernia
    - Anophthalmia
    - Cardiac anomaly



# 29 weeks US findings

- Unilateral ventriculomegaly
- & Vermian defect
  - “?Dandy-Walker variant”



# 29 weeks MR findings

- Thickened cortex
- Cortical defect
- Callosal dysgenesis
- Pontine hypogenesis with dorsal kink
- Vermian hypogenesis
- Occipital cephalocoele
- & Ocular asymmetry



# Congenital Muscular Dystrophy

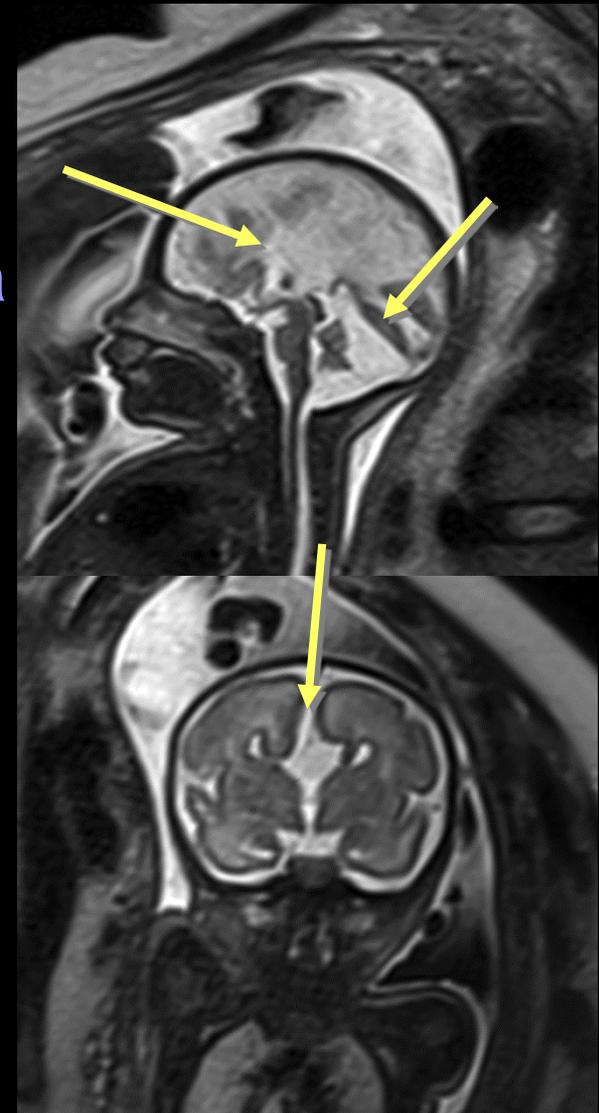
- Comprises a typical pattern of:
  - cobblestone lissencephaly (overmigration)
  - Primitive Z-shaped brainstem (retains early embryonic form)
  - & vermian hypoplasia
- Main types:
  - Fukuyama (Japanese) - normal eyes (typically)
  - Muscle-eye brain (Finnish) – mild ocular abnormalities
  - Walker-Warburg - More marked ocular abnormalities
    - occipital cephalocele (not always)

# Congenital Muscular Dystrophy Walker-Warburg phenotype

- Patient survived into early childhood
  - Developmental delay & hypotonia
  - Had Fukutin genotype (rare)
    - Different allele on same gene

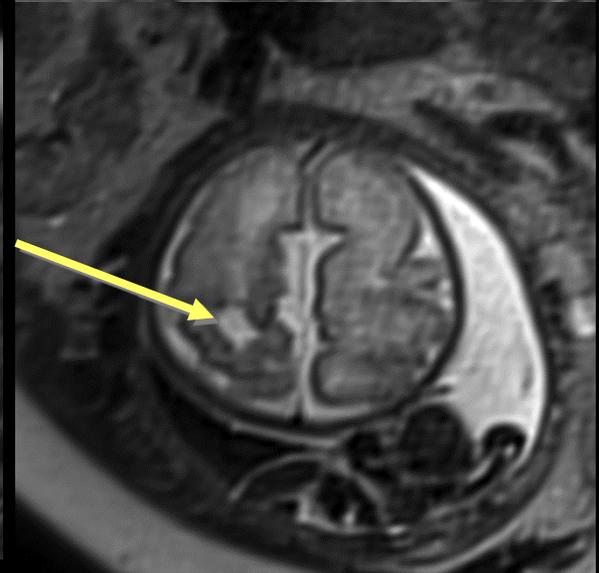
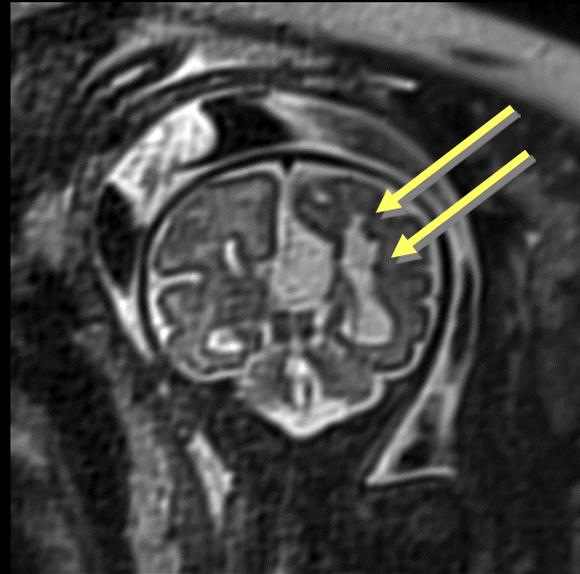
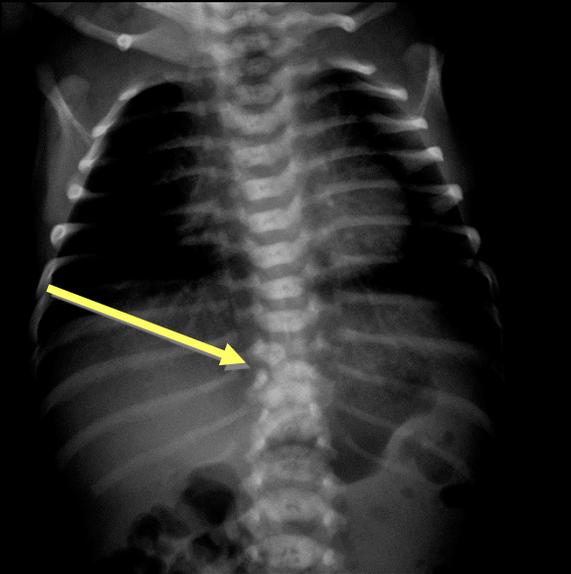
# 31 week fetus MRI findings

- callosal dysgenesis
- Cystic malformation of posterior fossa
- female
- (guess the diagnosis?)



# Aicardi syndrome

- microphthalmia
- Porencephalic cyst
- heterotopias
- & vertebral segmentation anomaly

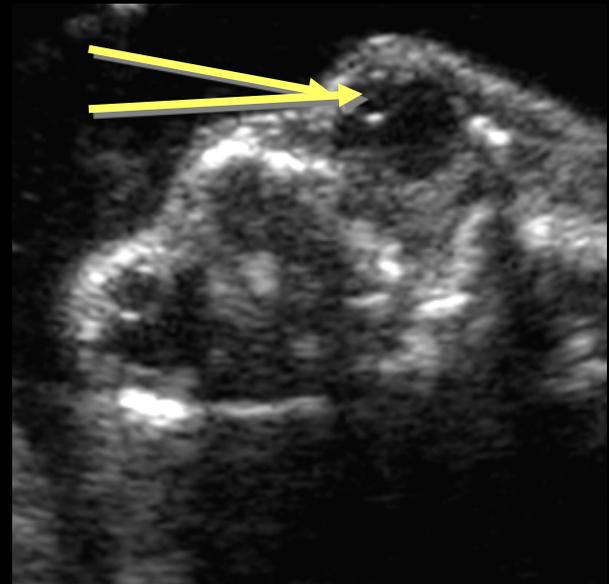


# Method of assessment

- Presence / absence of eyes (microphthalmia/anophthalmia)
- Morphology of lens, vitreous and optic nerve
- Biometry
- Extraocular pathologies

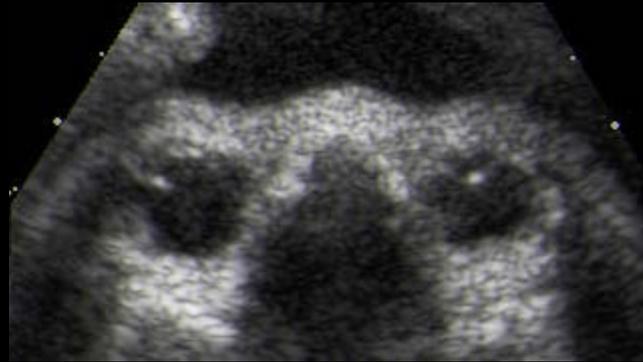
# Normal Morphology US

- on EV-US lens visible by 14 weeks
  - thin echogenic rim
  - Anechoic centre



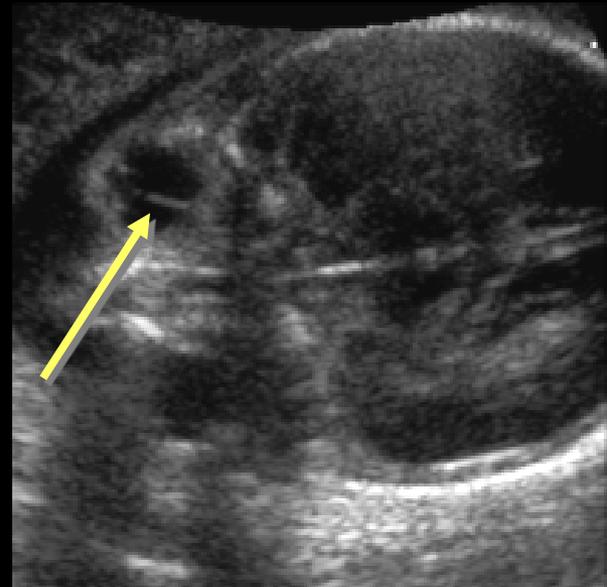
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# Normal Morphology US

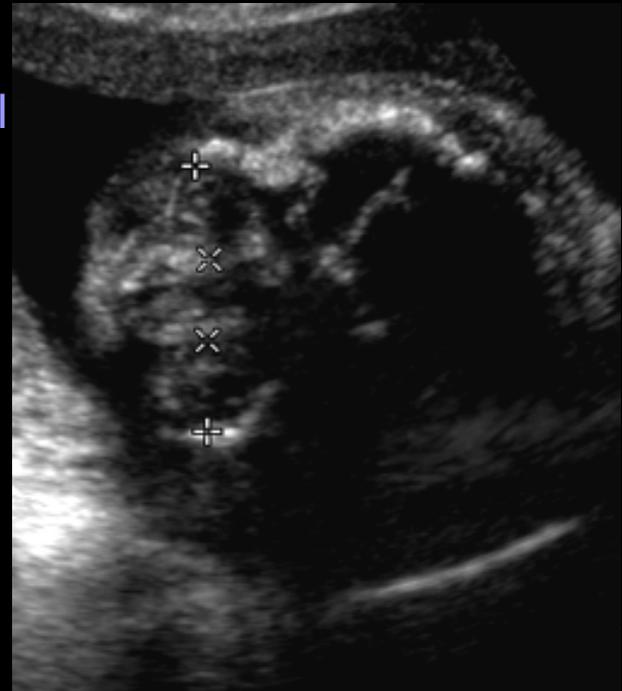
- on EV-US lens visible by 14 weeks
  - thin echogenic rim
  - Anechoic centre
- Hyaloid artery
  - echogenic line bisecting vitreous
  - Gradually becomes beaded
  - Involutes by 30 weeks MA
  - Remnant channel = Cloquet's canal
  - & Failure of involution = persistent hyperplastic primary vitreous
    - Frequently seen in trisomy syndromes and other brain anomalies



# Abnormal Morphology

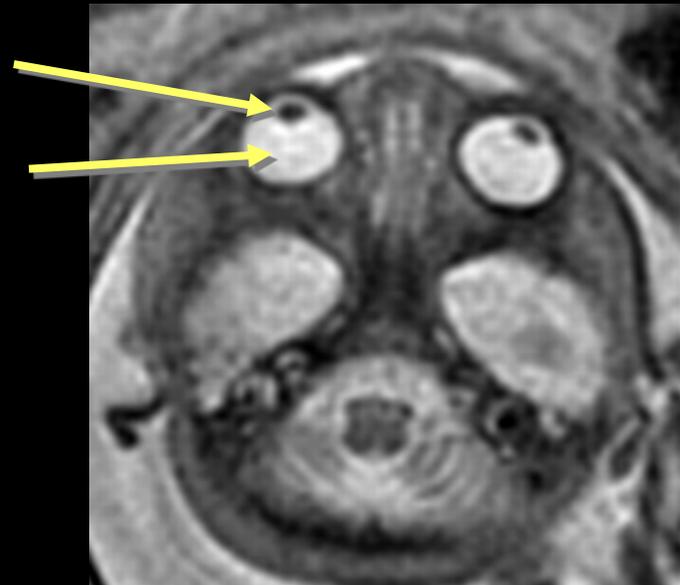
## US

- Cataracts
- Causes:
  - Metabolic / infectious / genetic / chromosomal
    - Idiopathic
    - toxoplasmosis
    - X-rays
    - IVF
    - PHPV
    - Nance-Horan syndrome
    - Adams-Oliver syndrome
    - Walker-Warburg syndrome
    - Neu-Laxova syndrome
    - Lowe syndrome
    - rhizomelic chondrodysplasia punctata
    - trisomy 17 mosaicism
    - trisomy 21



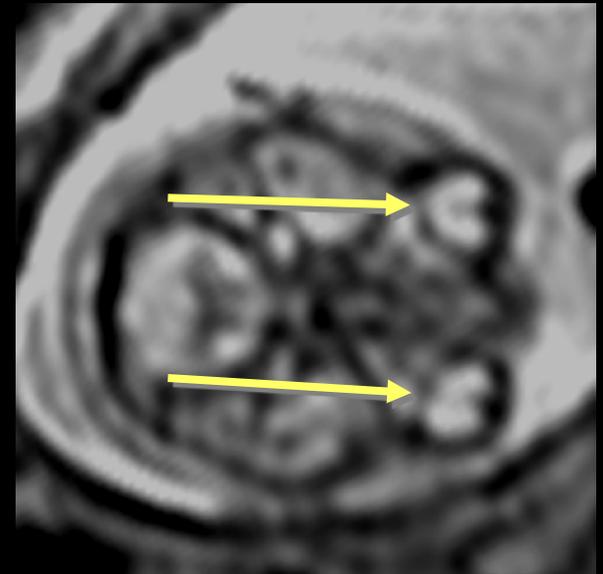
# Normal Morphology MR

- Lens
  - low signal on SSFSE
- Vitreous & anterior chamber
  - high signal on SSFSE
- Neither hyaloid artery nor Cloquet's canal normally visible



# Abnormal Morphology MR

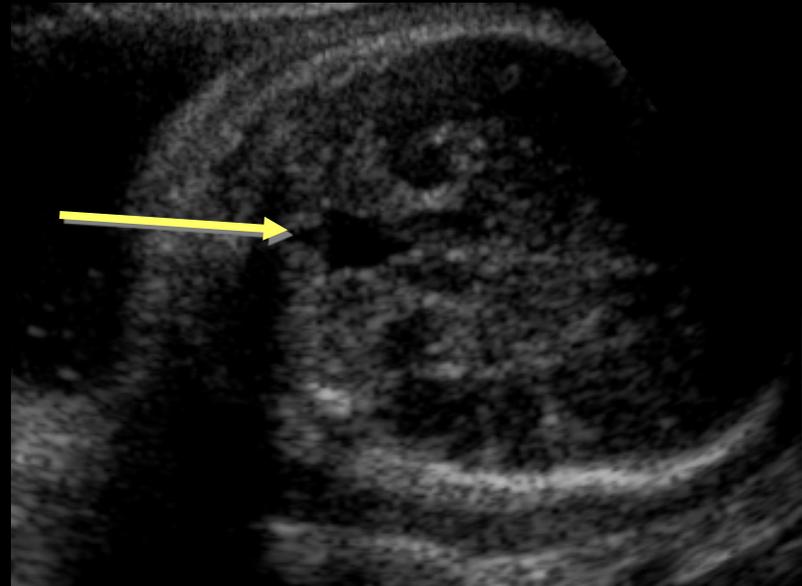
- Occasionally low signal is seen in position of Cloquet's canal
- often is artifactual and not seen on all sequences
- 2 fetuses @ 20 weeks gestation
- Low signal seen on all sequences
  - Fetus 1
    - mass at torcula herophili
    - Normal female karyotype
  - Fetus 2
    - Callosal agenesis & horseshoe kidney
    - Normal male karyotype
- & considered pathologic finding



# 37 weeks gestation US findings

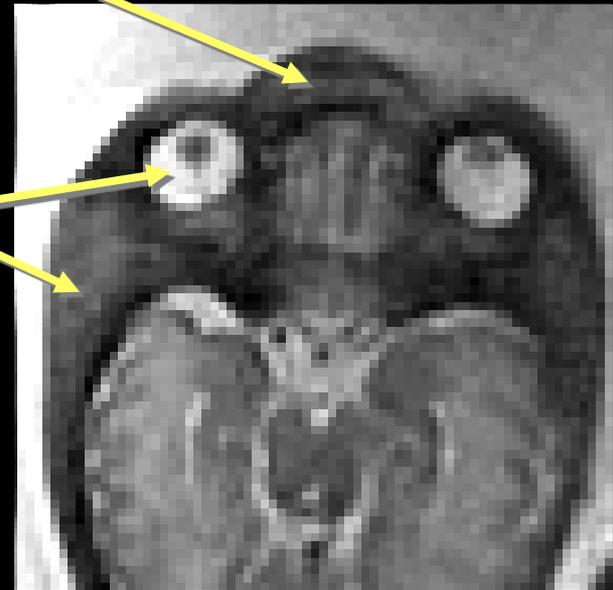
- Cleft lip & palate
- IUGR
- Hypertelorism
- Mild asymmetry & echogenicity
- & Vermian defect
  - “?Dandy-Walker variant”

+	2.74cm
×	5.67cm



# 37 weeks gestation MR findings

- CLAP
- microtia
- Microphthalmia
- & triangular lens distortion with persistent hyaloid artery = Persistent Hyperplastic Primary Vitreous



# Complete Trisomy 22

- Pathology:
  - cleft palate/lip
  - abnormal ears
  - preauricular pits/tags
  - & growth retardation

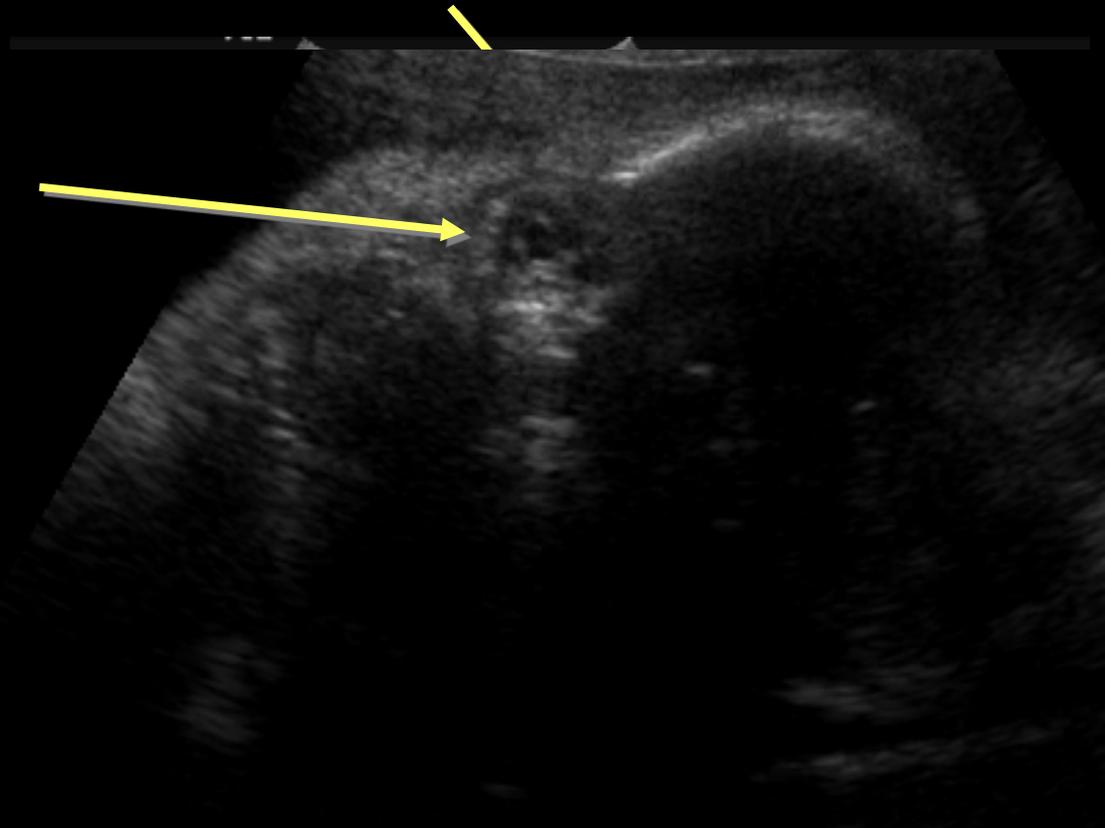


# Excavations of the optic disc

- Coloboma
- Morning glory disc
- Peripapillary staphyloma
  
- all can significantly impair visual function

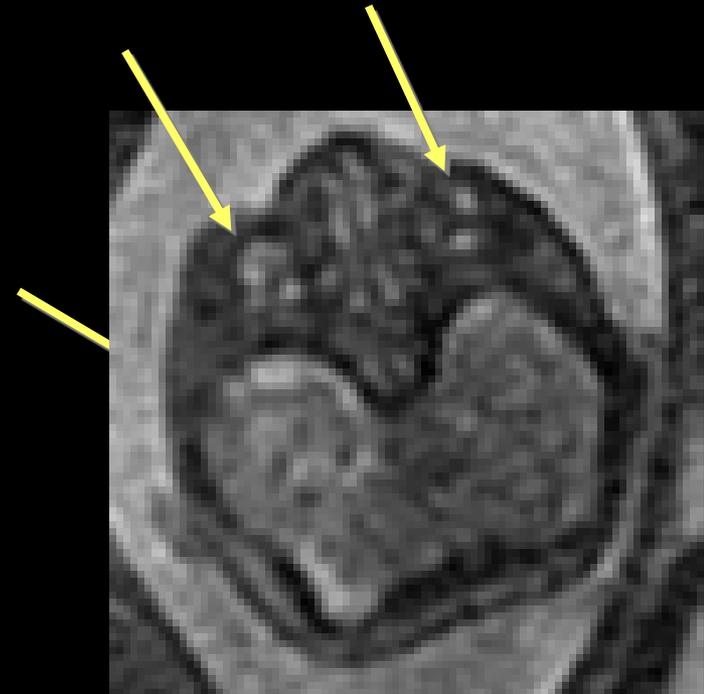
# 32 weeks gestation US findings

- Angulated keel-shaped occiput
- Cataract?



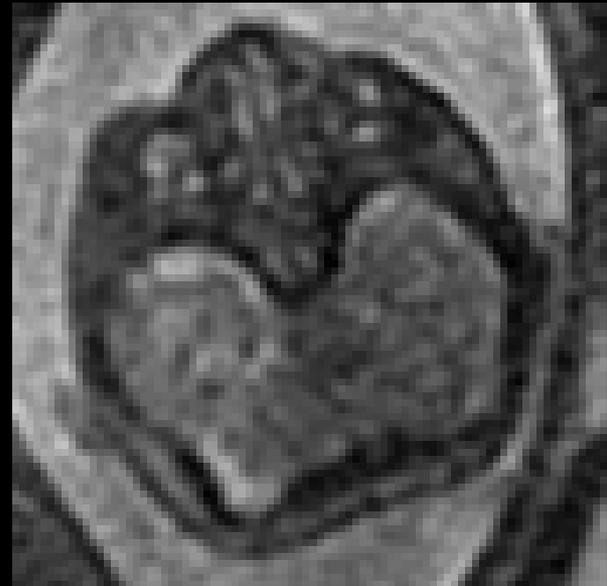
# 32 weeks gestation MR findings

- Angulated occiput
- Broad glabella
- & Abnormal eyes
  - Missed because bilateral and symmetric abnormality
  - Not routinely assessing eyes at that time
  - read by non-neuroradiologist not routinely doing fetal MRI



# Partial trisomy 22 = “Cat eye” syndrome

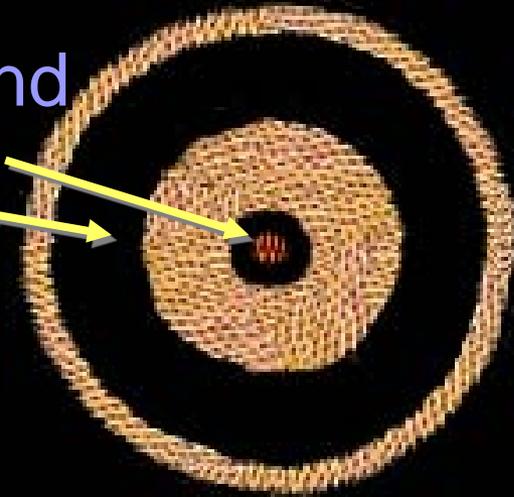
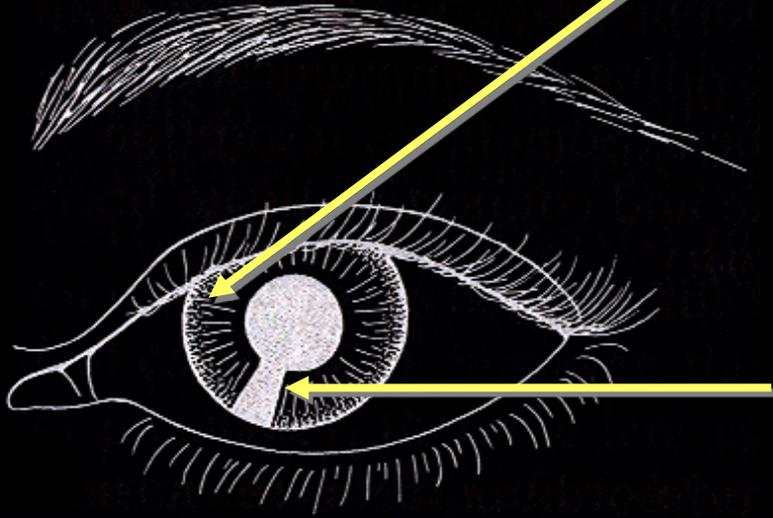
- Hypertelorism
- Inferior vertical iridal & choroidal coloboma (cat eye)
- & Auricular / GI / GU abnormalities
  
- Genetics
  - Supernumerary fragment of Ch22 & Ch16
  - Inherited from maternal translocation t(16;22)



# Coloboma

## 7 weeks

Invagination of optic cup  
Choroidal fissure should surround  
hyaloid artery  
Choroid fissure stays open  
Coloboma (cat eye)



# Optic nerve hypoplasia

- Usually looking for in context of absent cavum septi pellucidi
- Absent CSP can be:
  - a normal variant
  - the only obvious prenatal finding in SOD
- Hormonal abnormalities undetectable until neonatal period
  - Hypo-pituitarism
  - diabetes insipidus
  - Hypoglycaemia
  - isolated growth hormone deficiency may only manifest even later

# Absent Cavum Septi Pellucidi

–Look for associated abnormalities

–Malformative:

- dysgenesis of corpus callosum
- Holoprosencephaly spectrum
- Chiari II

–Acquired:

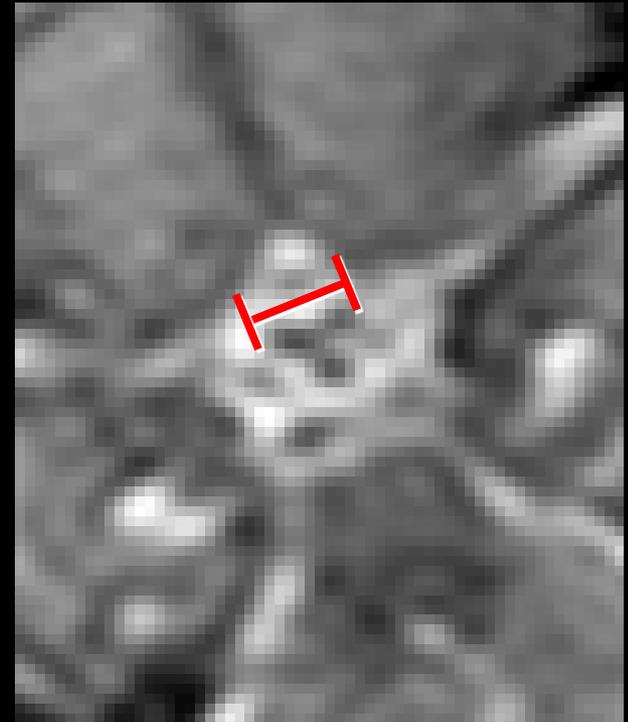
- Hemorrhage / hypoxic-Ischemic
  - Hydranencephaly
  - Porencephaly
  - Schizencephaly

–If it appears isolated, is problematic.....

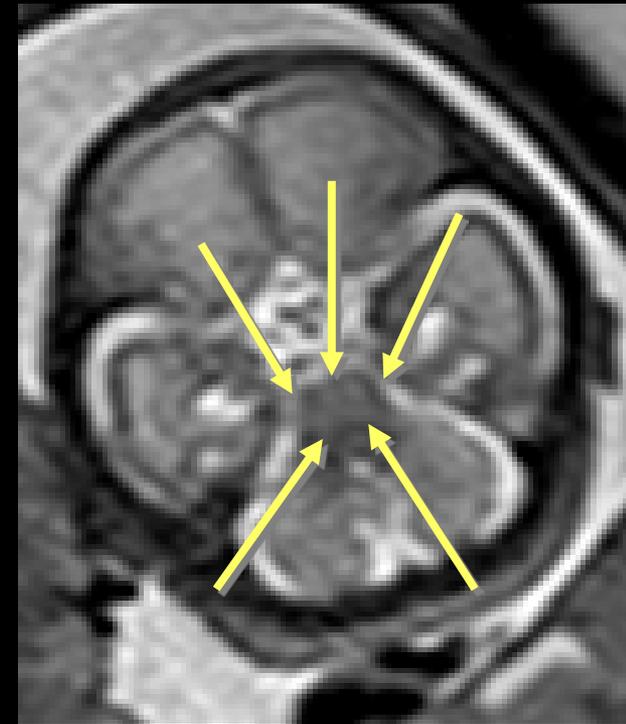
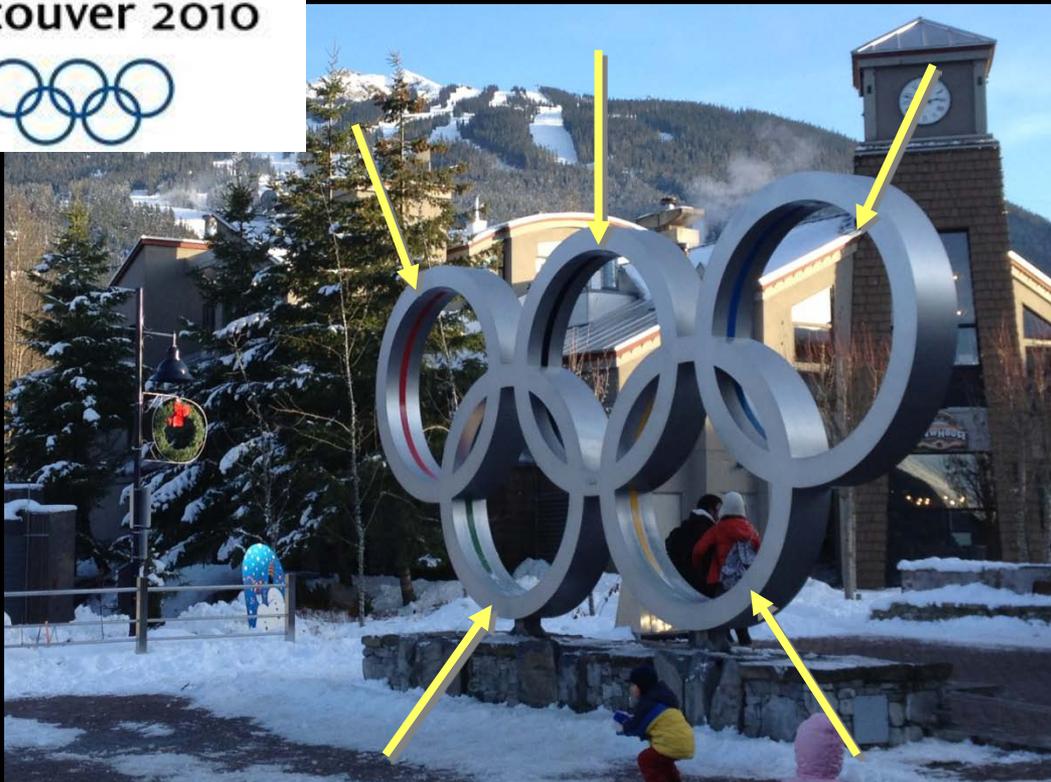


# Absent Cavum Septi Pellucidi ?septo-optic dysplasia

- Hypoplasia/dysplasia of optic nerve can be assessed by both US and MRI
- Look for the optic chiasm
- Normal growth of transverse diameter of optic chiasm has been described by US
  - Role of three-dimensional ultrasound measurement of the optic tract in fetuses with agenesis of the septum pellucidum **Ultrasound in Obstetrics & Gynecology 2011; 37: 570-5** J. P. Bault, L. J. Salomon, L. Guibaud and R. Achiron
- 23 with absent CSP, 13 with f/u
- 9 normal measurements
  - 8 normal vision
- 4 Z-score <-3 all abnormal



# Absent Cavum Septi Pellucidi ?septo-optic dysplasia



# Method of assessment

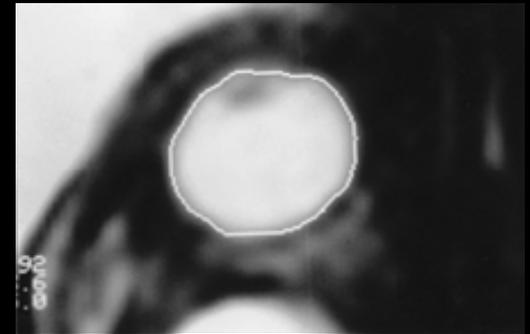
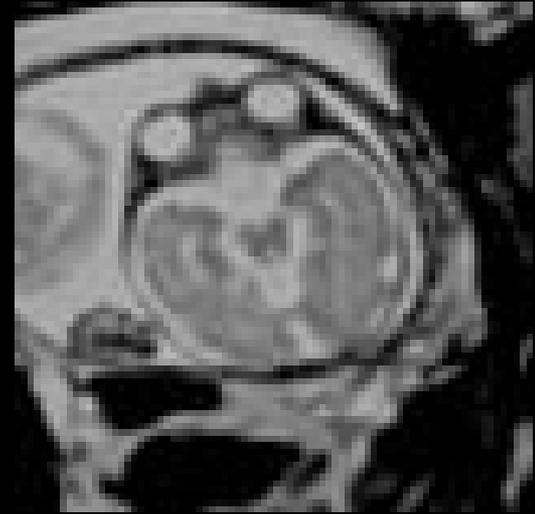
- Presence / absence of eyes (microphthalmia/anophthalmia)
- Morphology of lens, vitreous and optic nerve
- Biometry
- Extraocular pathologies

# Biometry

- Previously measurements of binocular and intraocular distances were defined by ultrasound
  - measured according to the bony landmarks of the medial and lateral orbital walls
  - these bony landmarks cannot be seen on fetal MR
  - However vitreous is well-defined and easy to measure

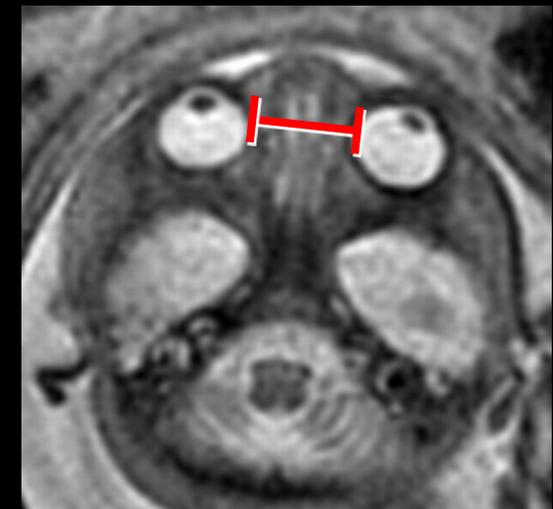
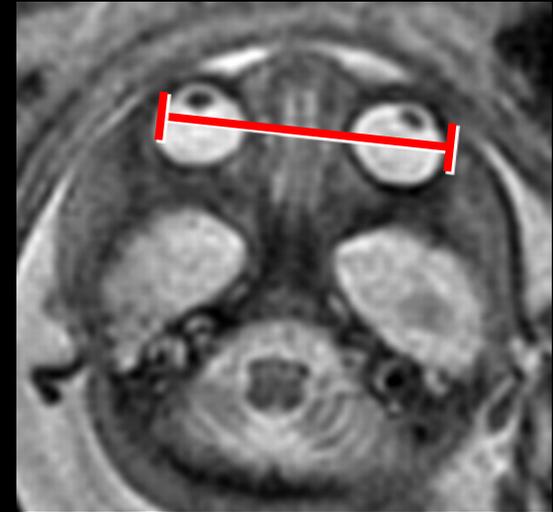
# Bremond-Gignac 1997

- 35 fetuses
- 0.5T
- 4mm / 1mm
- 256x256
- FOV not given
- Axial through lens/nerve
- surface area of this equatorial section
- Linear regression model



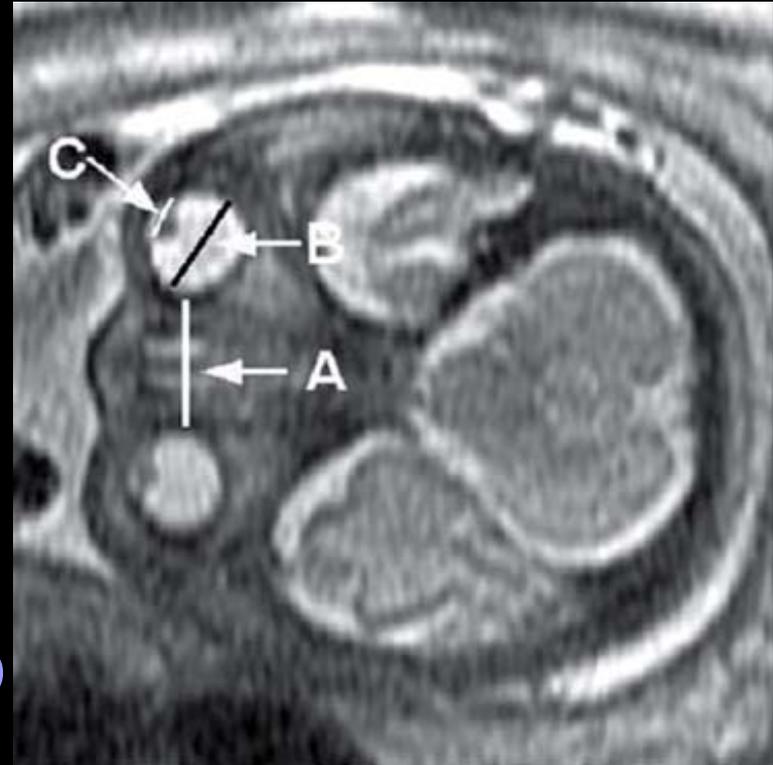
# Robinson / Ryan 2008

- 198 fetuses
- 3mm / 1.5mm or 4mm / 0mm
- 256x256
- 350mm FOV
- 158 normals
  - 111 suitable images for measurements
- Logarithmic regression model



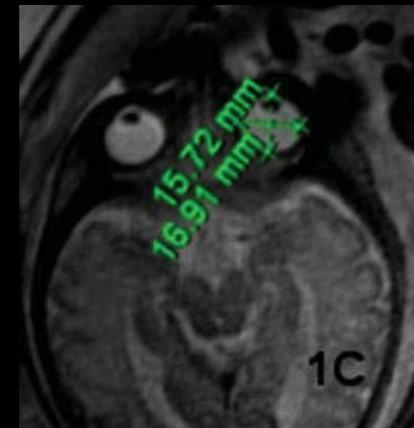
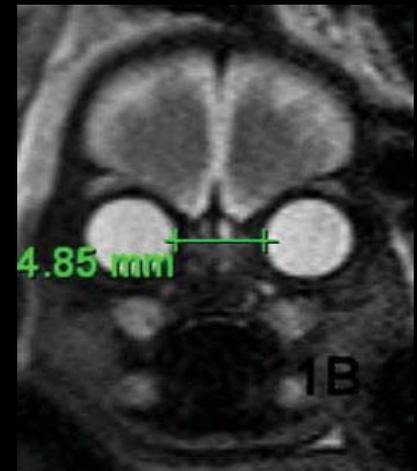
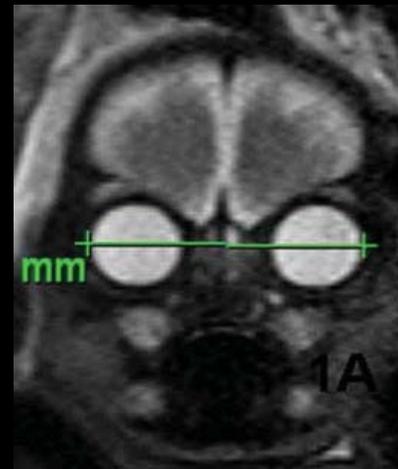
# Paquette/Panigrahy 2009

- 127 fetuses
- 1.5T & body coil
- 3mm / 0mm
- Matrix 128/320
- FOV not given
- Axial occ. Coronal
- OD (trans), Lens transverse, IOD
- Quadratic regression model
- IOD < Robinson
- OD > Robinson



# Li / Kasprian / Prayer 2010

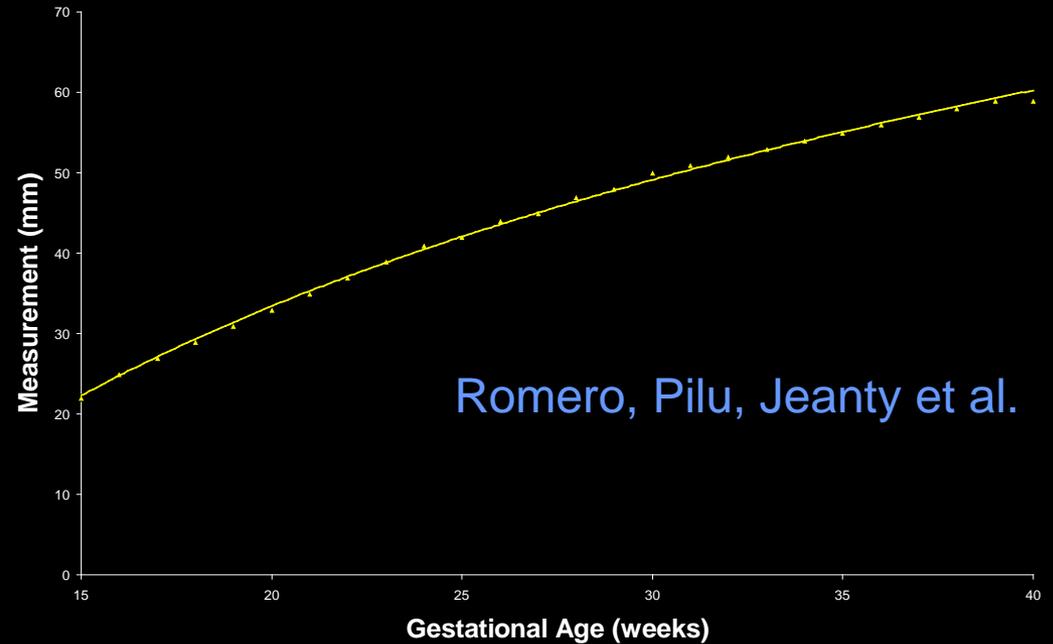
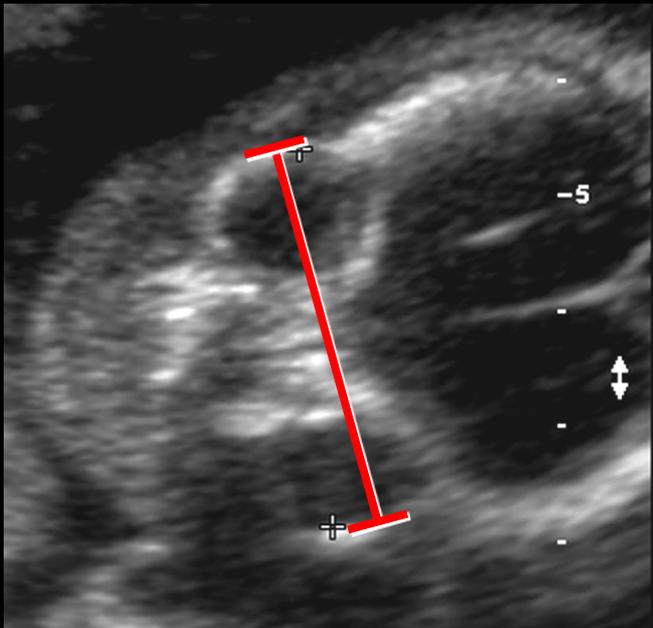
- 216 fetuses
- 1.5T 5-element cardiac coil
- 4mm
- 256/256
- 180mm – 230mm FOV
- IOD coronal
- BOD coronal
- OD (trans)
- OD (axial)
- IOD/BOD < Robinson
- OD > Robinson



# Li / Kasprian / Prayer 2010

- Differences due to:
  - Patient selection (Europeans only)
  - Sample sizes
  - Plane of measurement
  - Method of measurement
  - Resolution (matrix size, FOV)
- Quadratic (best) > logarithmic (very close) > linear
- Globe is ellipsoid possibly due to hyaloid artery
  - Becomes more spherical in later gestation

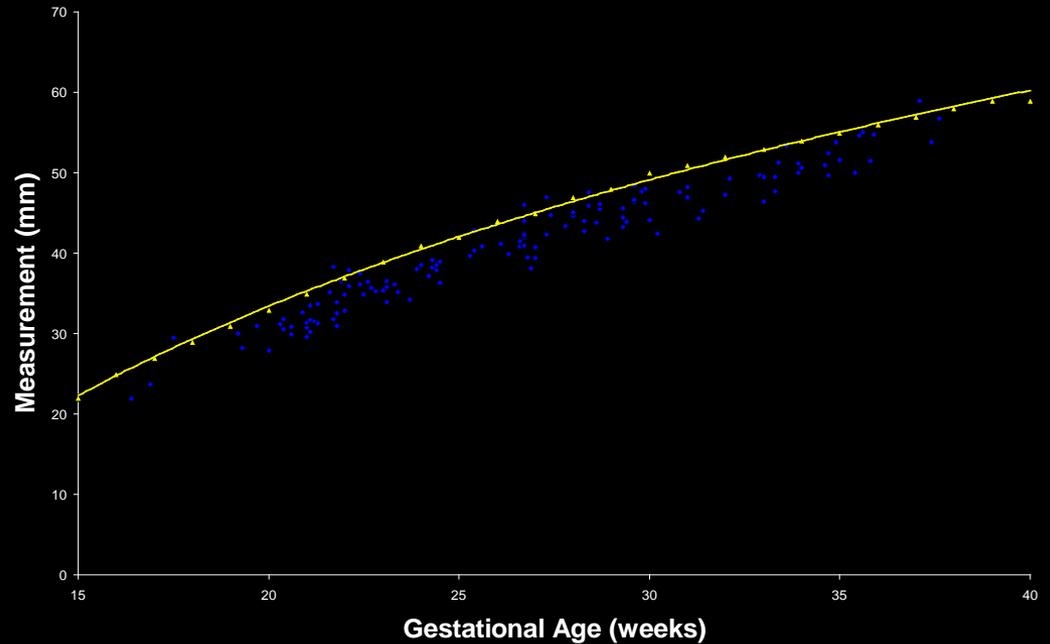
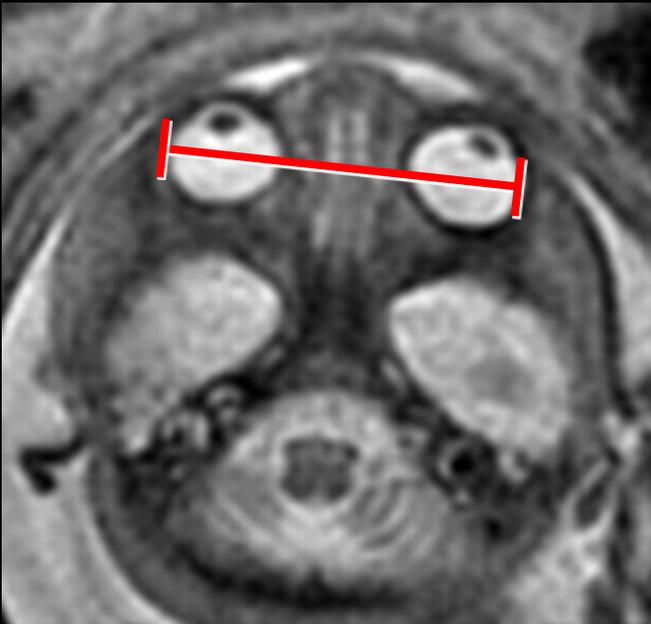
# Measurements by US Binocular distance



Measured between  
lateral orbital margins

# Measurements by MR

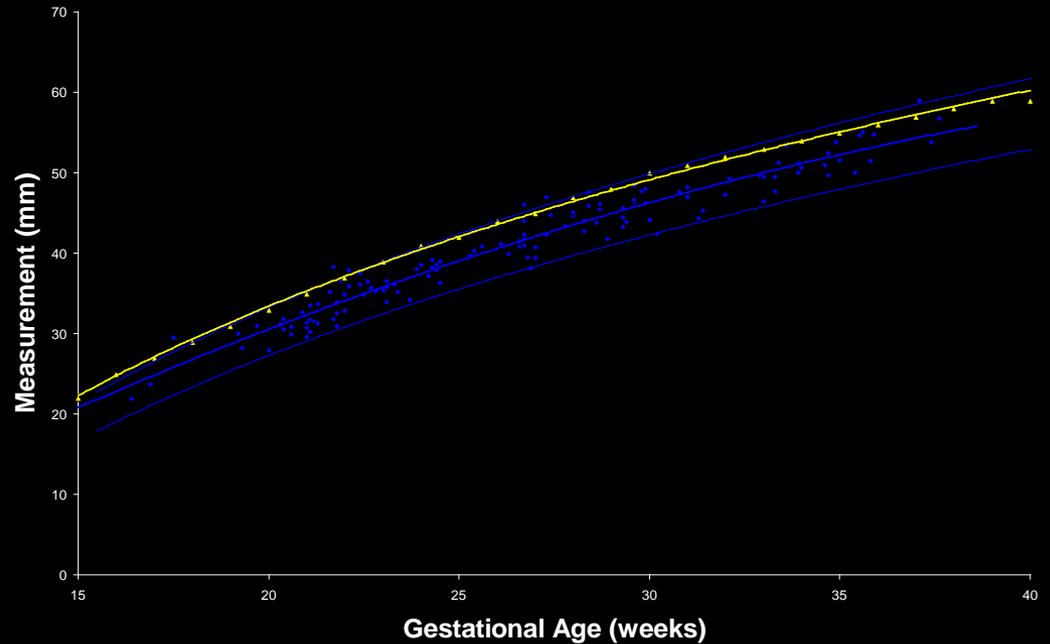
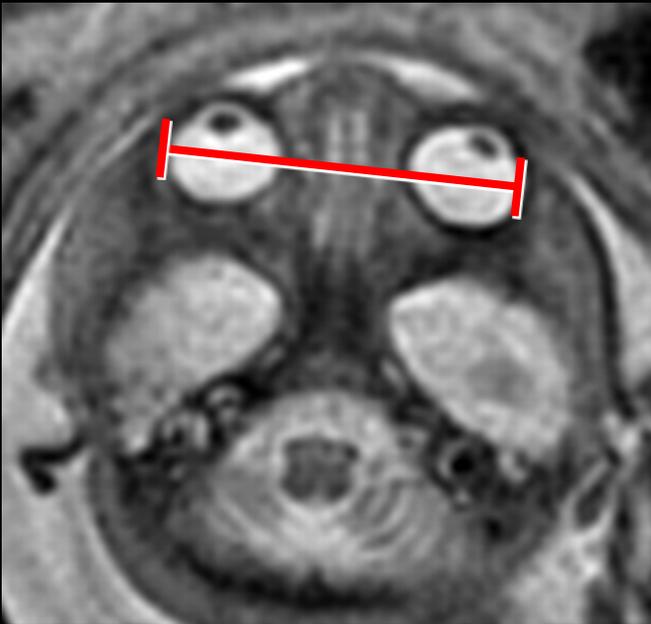
## Binocular distance



Measured between  
lateral margins of vitreous

# Measurements by MR

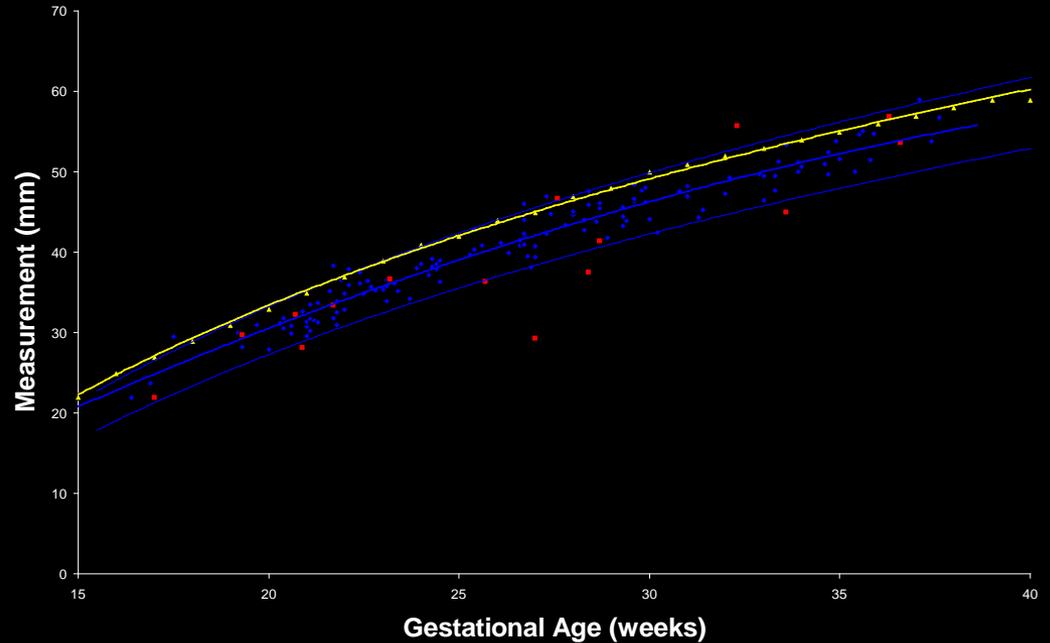
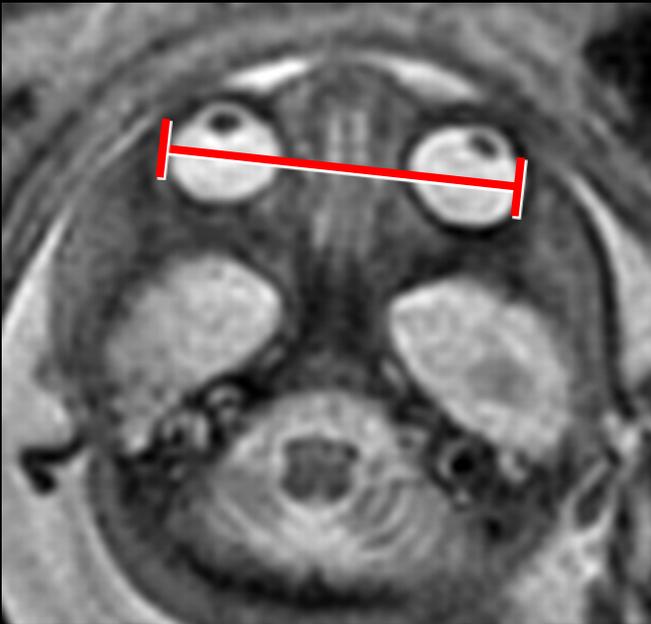
## Binocular distance



Measured between  
lateral margins of vitreous

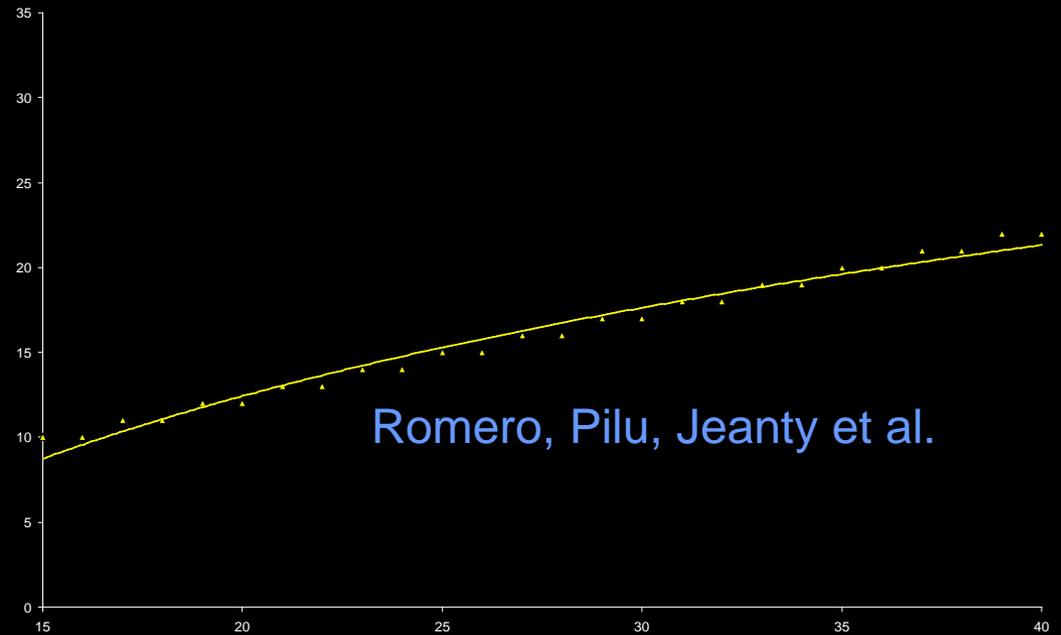
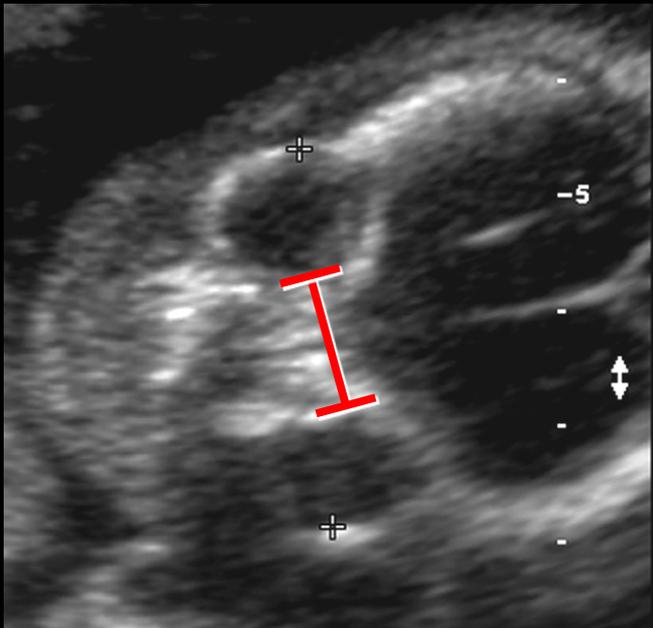
# Measurements by MR

## Binocular distance



Measured between  
lateral margins of vitreous

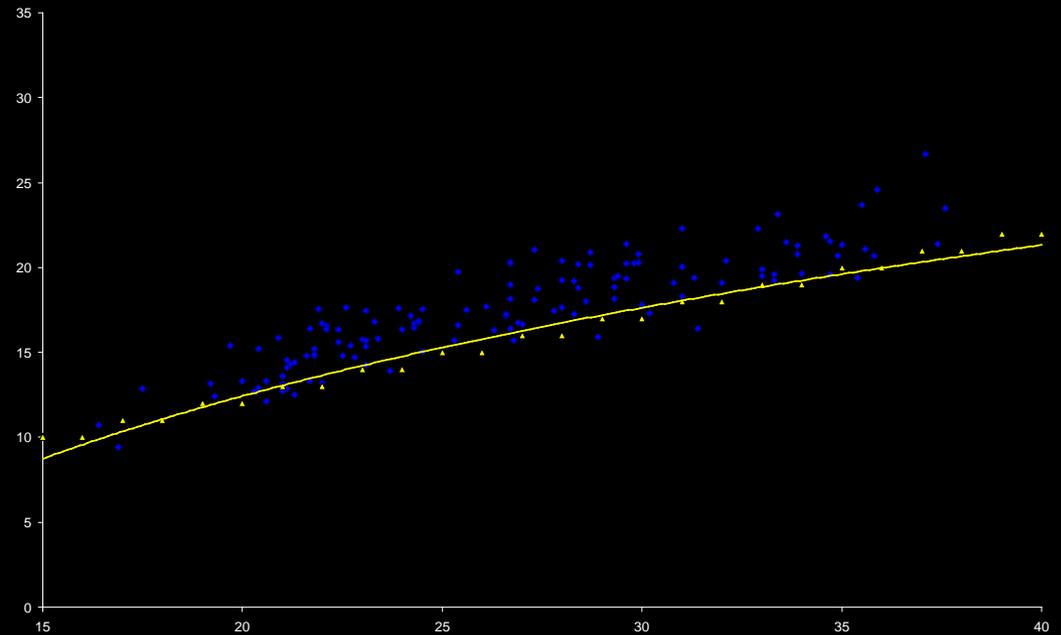
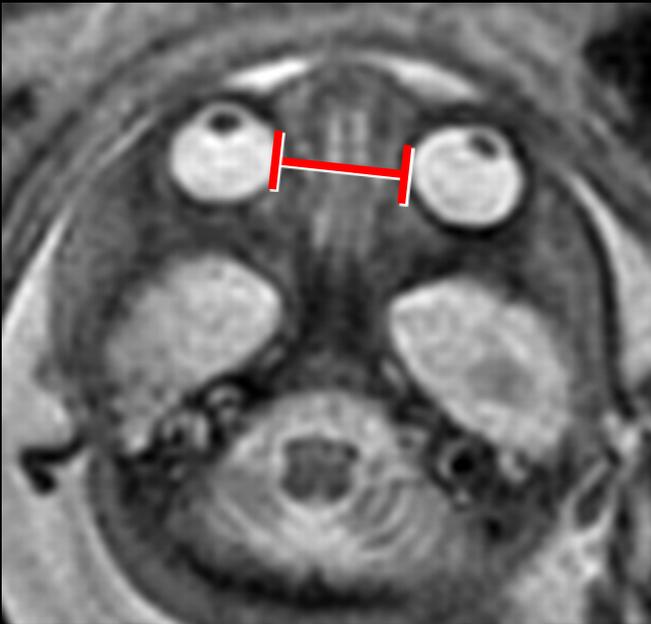
# Measurements by US Inter-ocular distance



Measured between  
medial orbital margins

# Measurements by MR

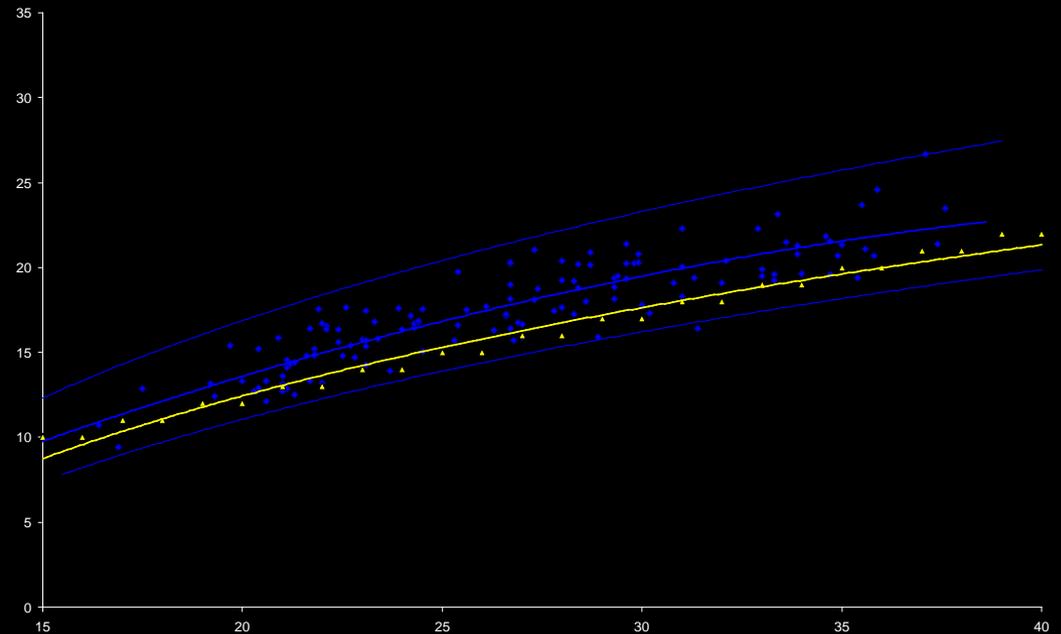
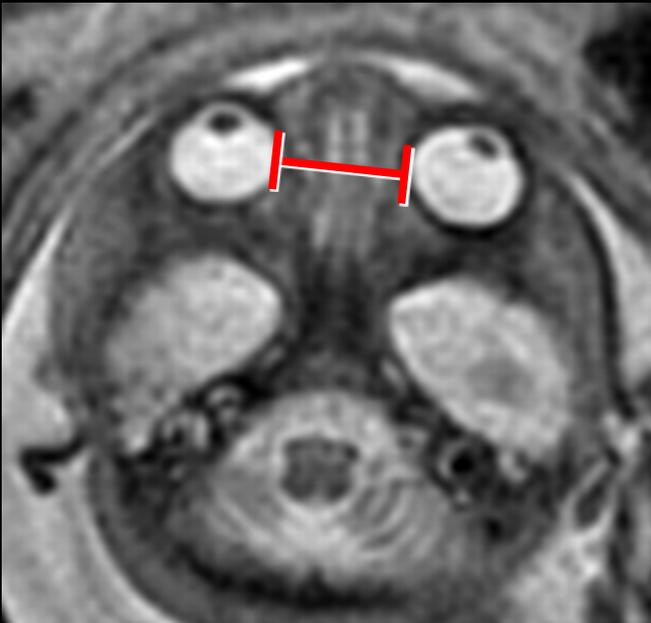
## Inter-ocular distance



Measured between  
nasal margins of vitreous

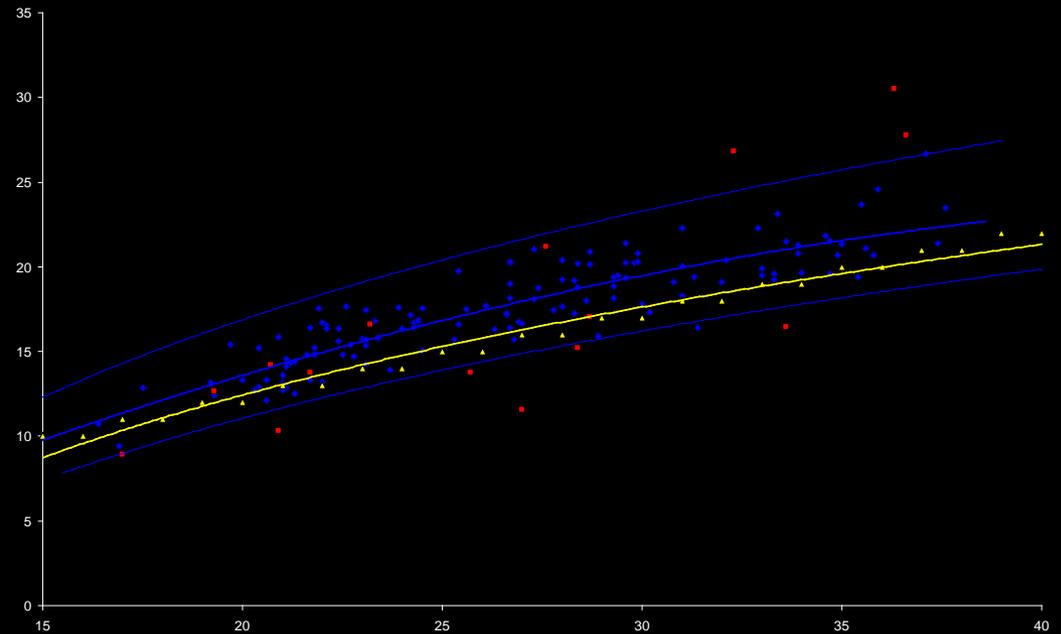
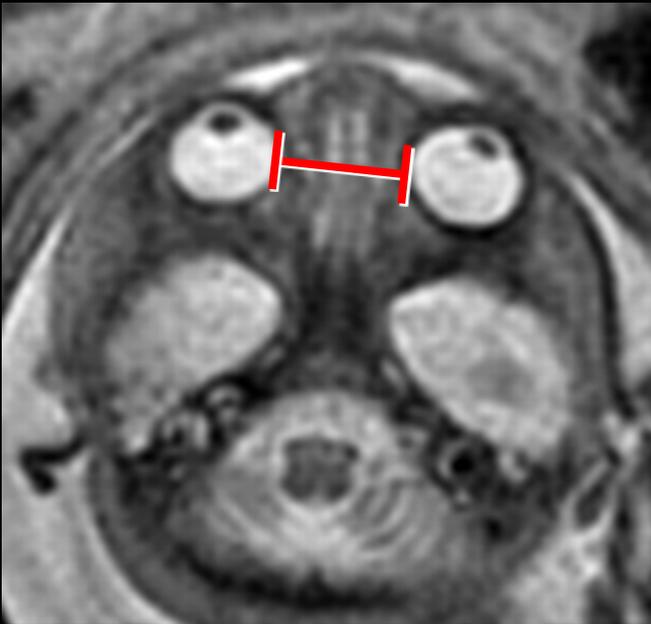
# Measurements by MR

## Inter-ocular distance



Measured between  
nasal margins of vitreous

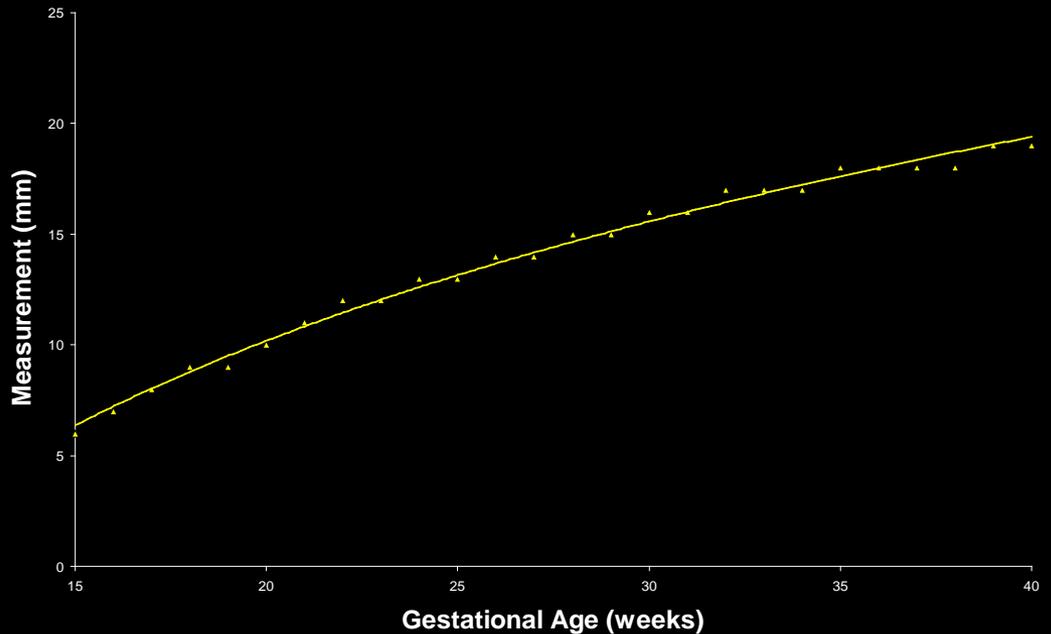
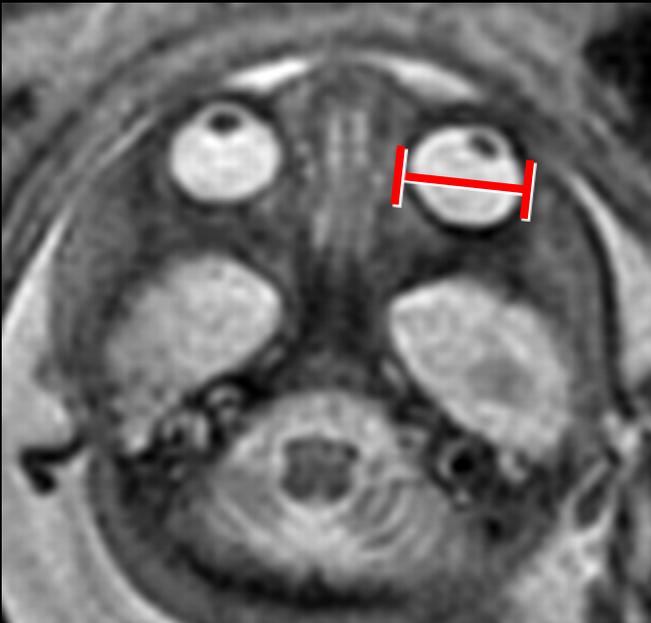
# Measurements by MR Inter-ocular distance



Measured between  
nasal margins of vitreous

# Measurements by MR

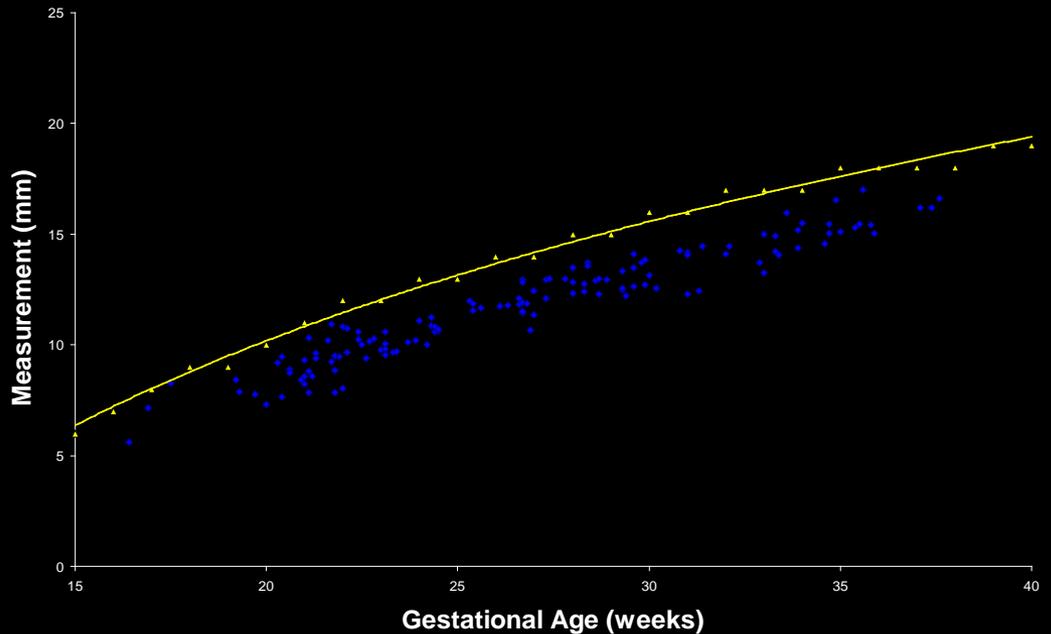
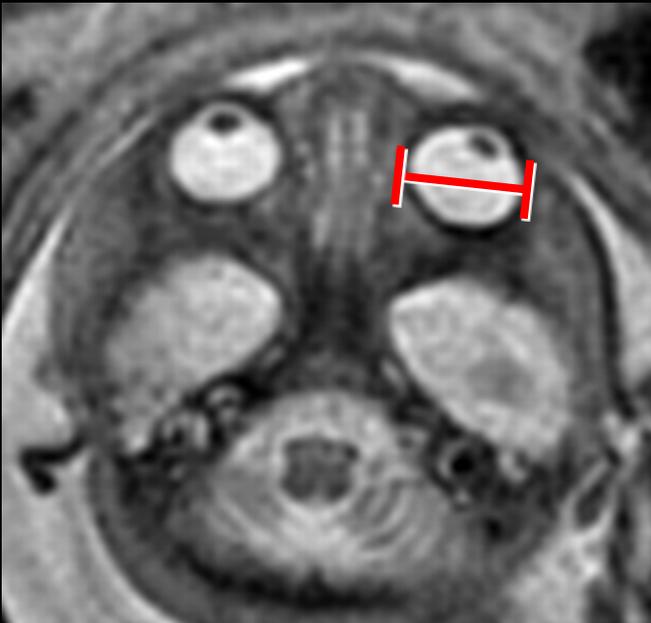
## Ocular diameter



Usually calculated  
 $OD = (BOD - IOD) / 2$

# Measurements by MR

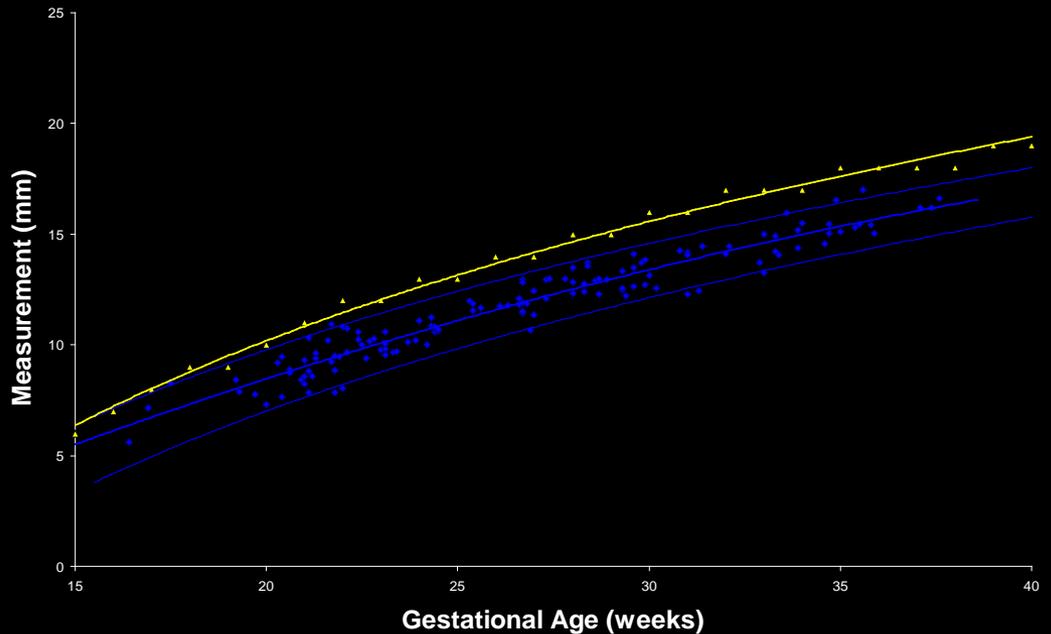
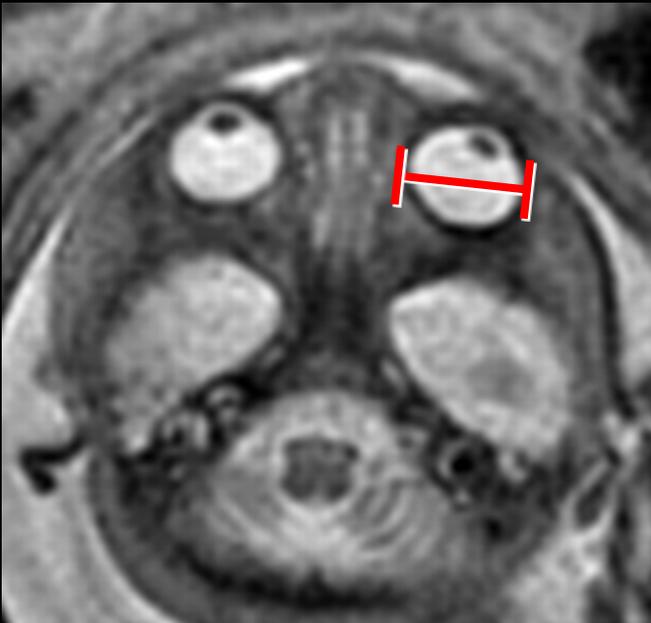
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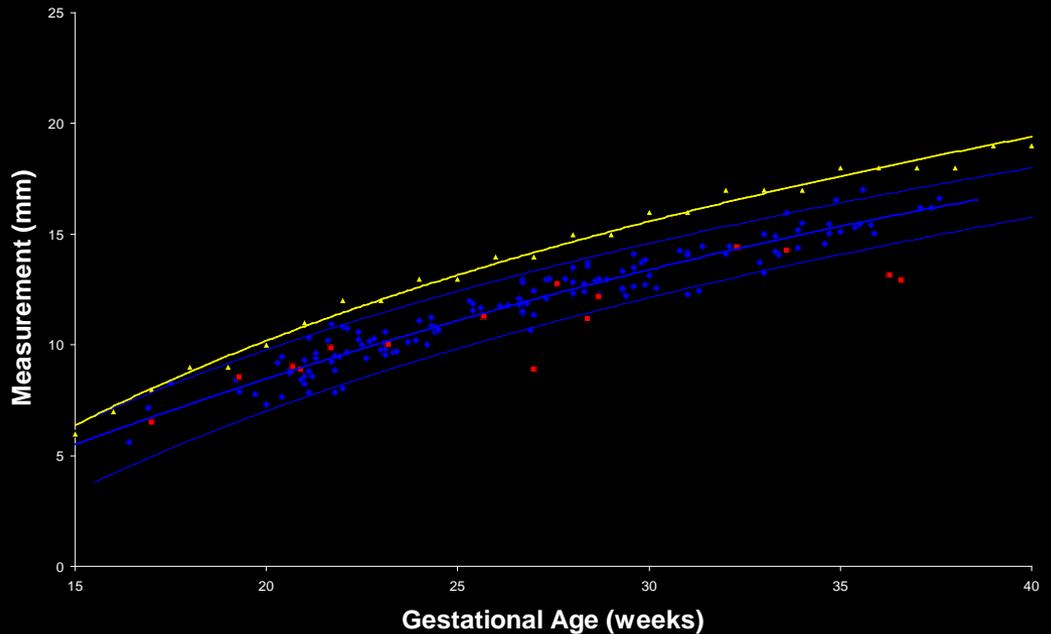
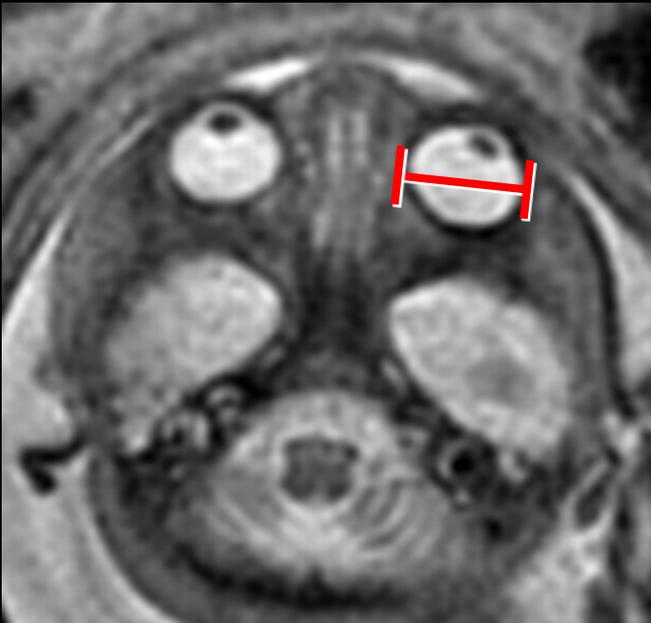
## Ocular diameter



Usually calculated  
 $OD = (BOD - IOD) / 2$

# Measurements by MR

## Ocular diameter



Usually calculated  
 $OD = (BOD - IOD) / 2$

# Hypotelorism

- IOD/BOD < 5%
- Primary (more common)
  - Usually seen with holoprosencephaly
- Secondary

# Hypotelorism - primary Embryology craniofacial skeleton

- From both mesoderm and neural crest cells of mesencephalon
- Intimately related to forebrain development with similar induction mechanism
- Facial skeletal abnormalities are often associated with underlying cerebral malformations
  - “The face predicts the brain”
- Craniofacial abnormalities are actually due to more caudal expression of abnormal genetic gradient
  - “The brain predicts the face”

# Hypotelorism - primary Embryology

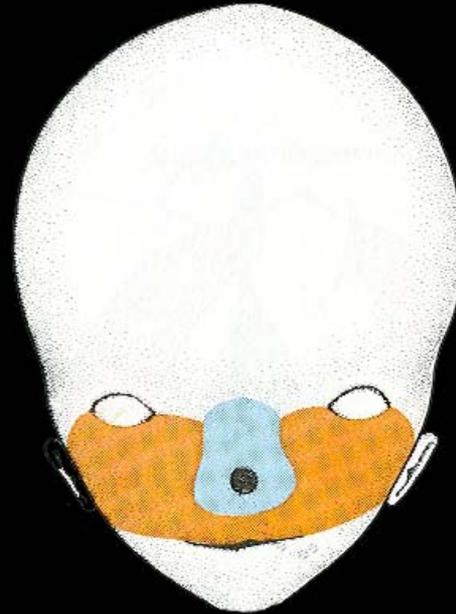
Nose forms from  
paired nasal  
swellings

Migrate medially  
and inferiorly

Fuse in midline

Deficient mesial migration

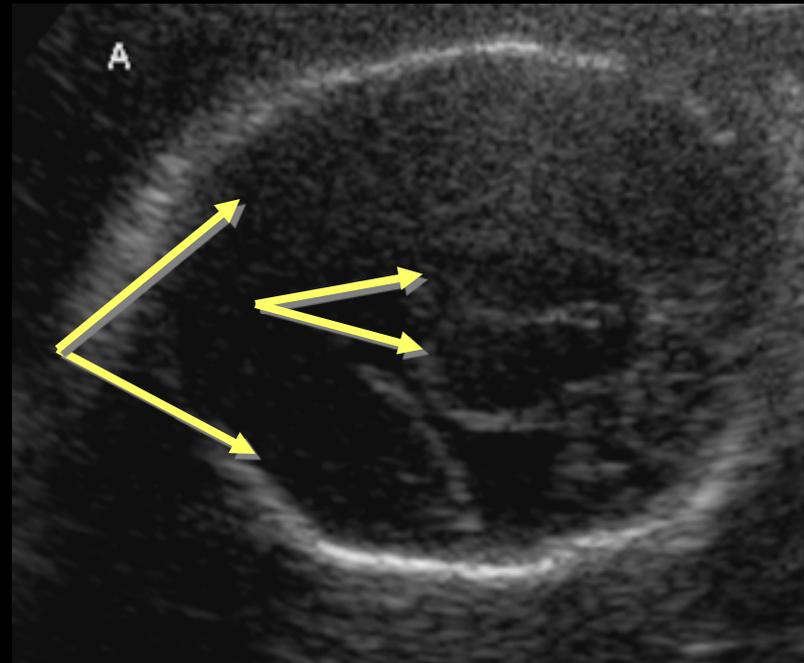
Halves of face &  
brain too close  
together



Diagrams from "Langmans Essential  
Human Embryology" 2004.

# 27 weeks gestation US findings

- Fused thalami
- Anterior cortical mantle



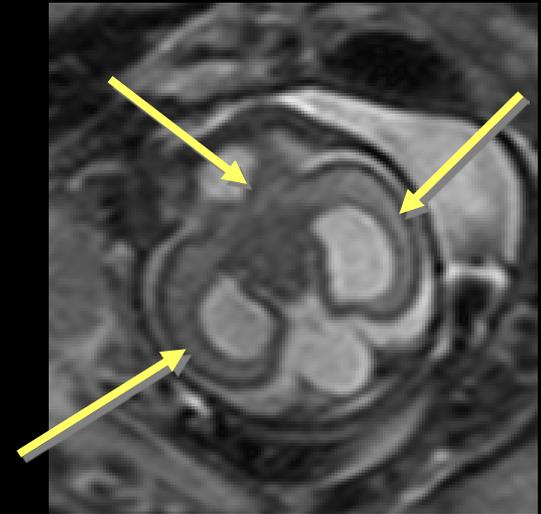
# Alobar holoprosencephaly

- Anterior cortical mantle
- Monoventricle
- Dorsal cyst
- Cyclopia



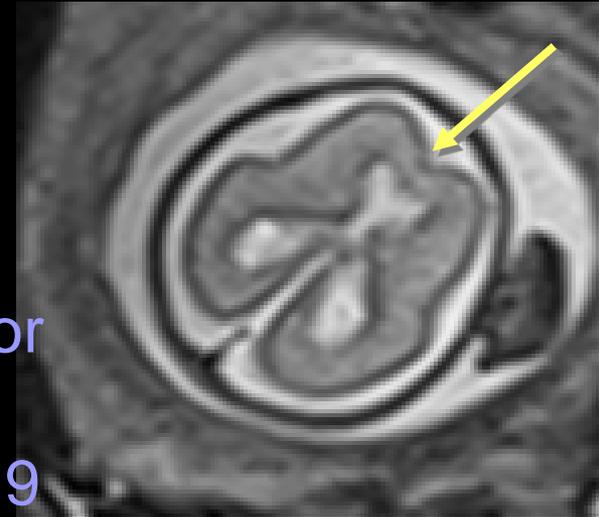
# Semi-lobar holoprosencephaly

- cortical mantle crossing midline
- Ventricle more divided
- Moderate hypotelorism



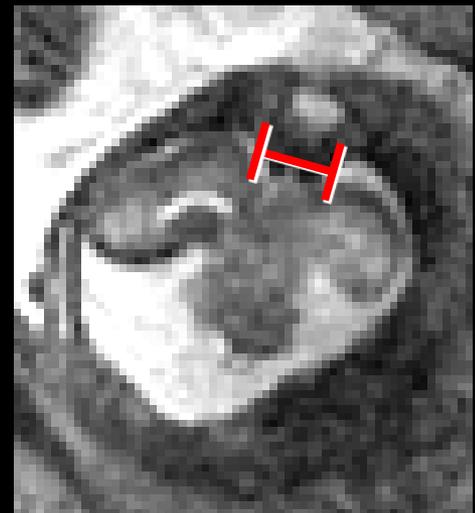
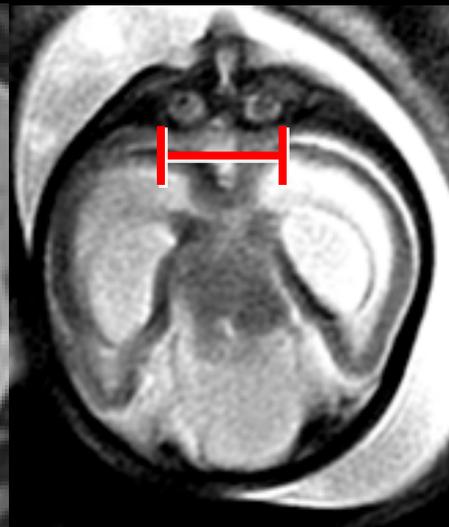
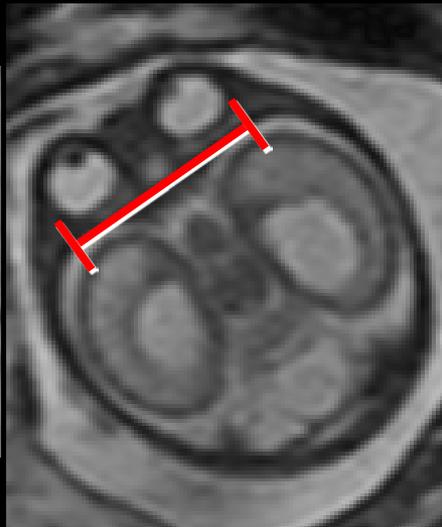
# Lobar holoprosencephaly

- cortical mantle crossing midline
- Ventricles non-divided anteriorly
- IOD/BOD low but within normal range for 23+1 weeks
  - BOD 34.4mm (22.1 weeks) 32.4-38.9
  - IOD 13.4mm (20 weeks) 12.8-19.1
  - OD 10.5mm (24 weeks) 8.8-11.4



# Hypotelorism – Primary spectrum

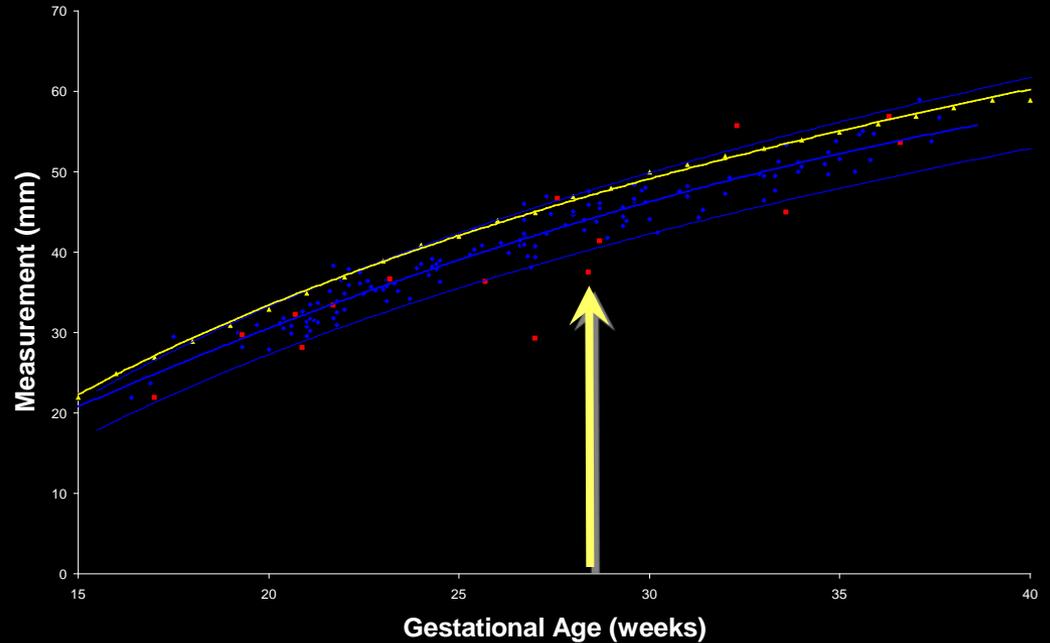
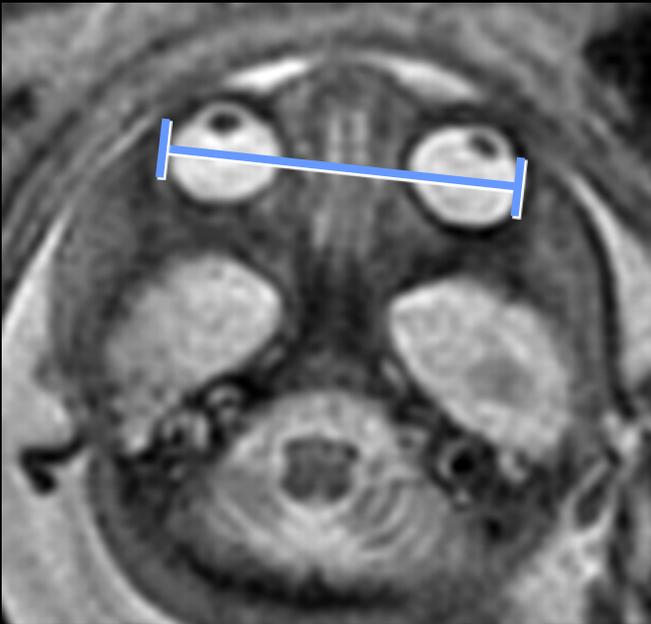
- Septo-optic dysplasia
- (absent /mild hypotelorism)
- Lobar holoprosencephaly
- Semi-lobar holoprosencephaly
- Alobar holoprosencephaly
- cyclopia
- hypotelorism depends on genetic gradients



# Hypotelorism

- IOD/BOD < 5%
- Primary (more common)
  - Usually seen with holoprosencephaly
- Secondary
  - Microcephaly
  - Trigonocephaly
  - Meckel-Gruber
  - & others

# Hypotelorism – secondary



Measured between  
malar margins of vitreous

# 25 weeks gestation US findings

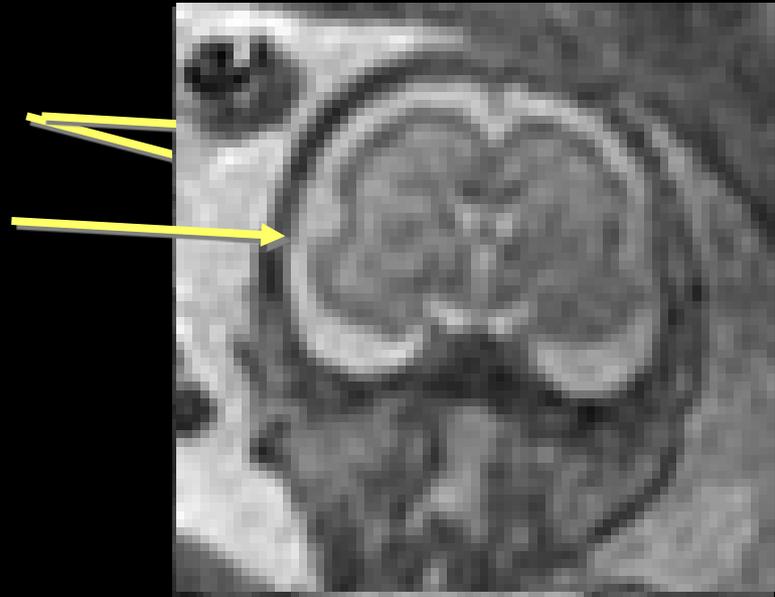
- Microcephaly
- Delayed ocular biometry
- & Bulging eyes

3.81 cm  
1.25 cm



# 29 weeks gestation MR findings

- Microcephaly
  - sloping forehead
- Mild hypotelorism
- & small cerebrum with large extra-axial CSF spaces



# Micrencephaly

- Proptosis
- Dysmorphic features
- & normal karyotype



# Hypertelorism

- IOD > 95%
- BOD often at upper limit of range
- Primary (less common)
  - Deficient migration of neural crest cells in the lamina terminalis of the prosencephalon
  - Deficient formation of medial canthal ligament
  - Eyes stay on the side of the head (lesser mammals, fish, birds)
  - Commonly associated with deficient formation of corpus callosum
  - median facial cleft syndrome (frontonasal dysplasia)
- Secondary

# Hypertelorism - Primary Embryology

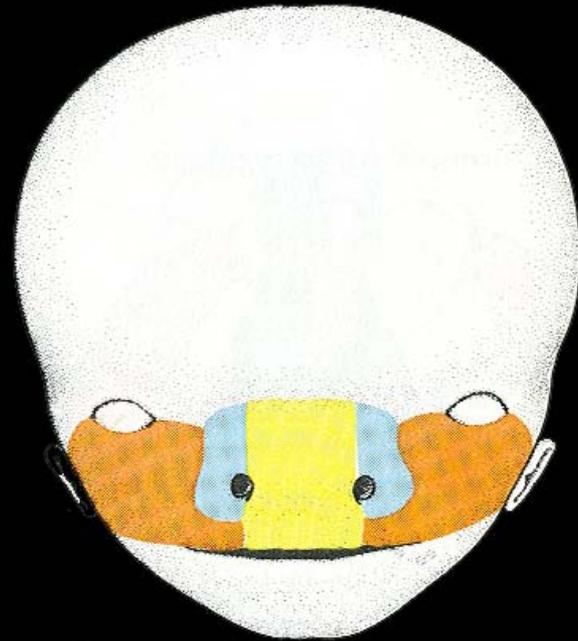
Nose forms from paired nasal swellings

Migrate medially and inferiorly

Deficient medial canthal ligament

Eyes too far apart

Corpus callosum does not form

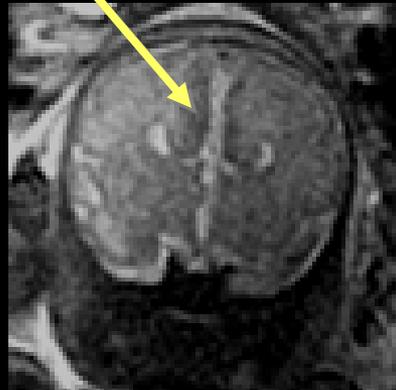
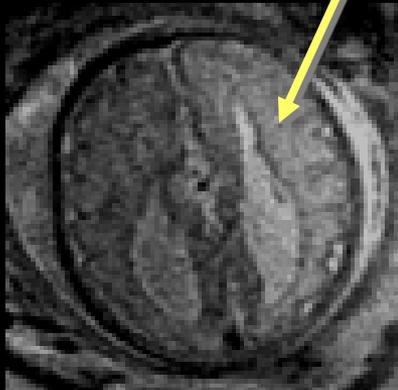


Diagrams from "Langmans Essential Human Embryology" 2004.

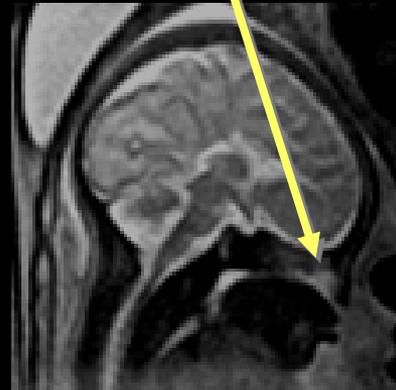
# Median facial cleft syndrome (Frontonasal dysplasia)

Comprises:

Callosal agenesis



Facial clefting



Hypertelorism



# Hypertelorism

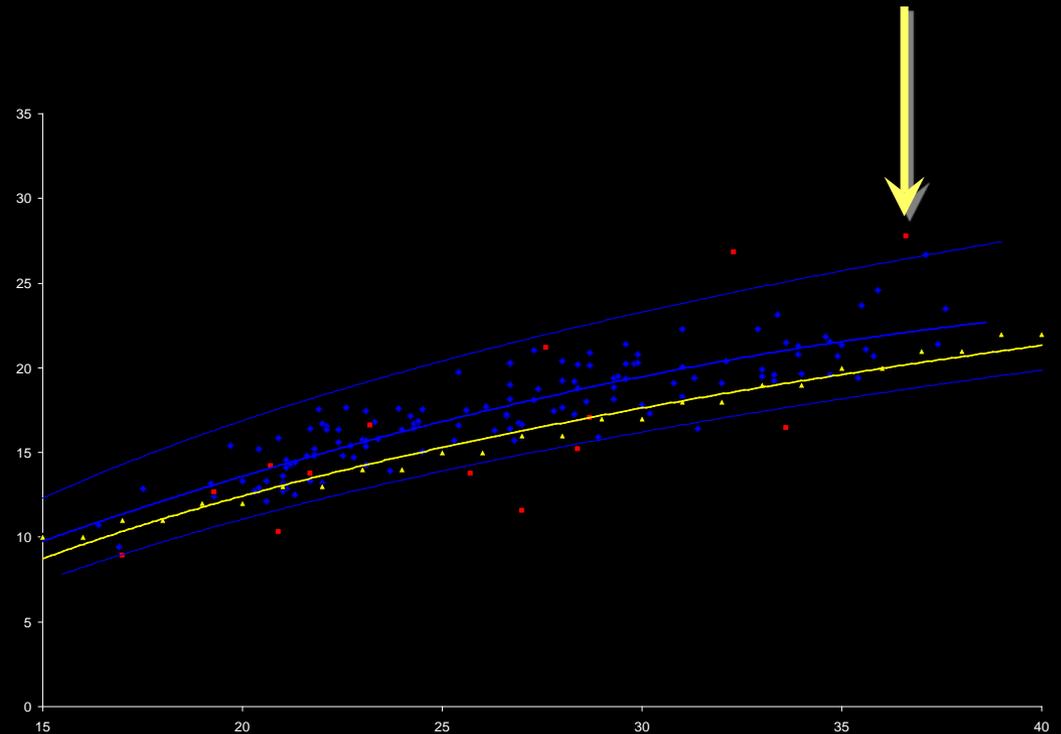
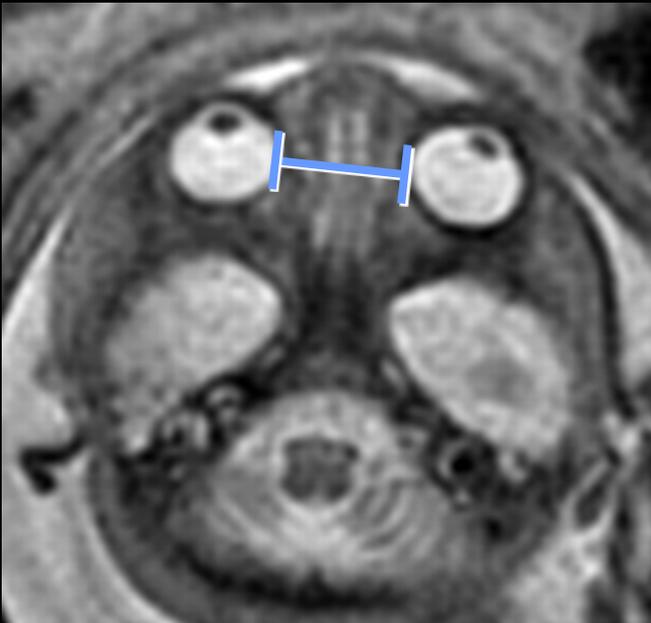
- IOD > 95%
- BOD often at upper limit of range
- Primary (less common)
  - Deficient migration of neural crest cells in the lamina terminalis of the prosencephalon
  - Deficient formation of medial canthal ligament
  - Eyes stay on the side of the head (lesser mammals, fish, birds)
  - Deficient formation of corpus callosum
  - median facial cleft syndrome (frontonasal dysplasia)
- Secondary
  - Anterior cephalocele most common cause
  - Craniosynostoses

# Hypertelorism - Secondary Anterior encephalocele

- Focal defect in skull allows internal structures to herniate
- Protrude into various different locations
- Commonest in south-east Asia
  - esp. children of tea garden workers in Assam



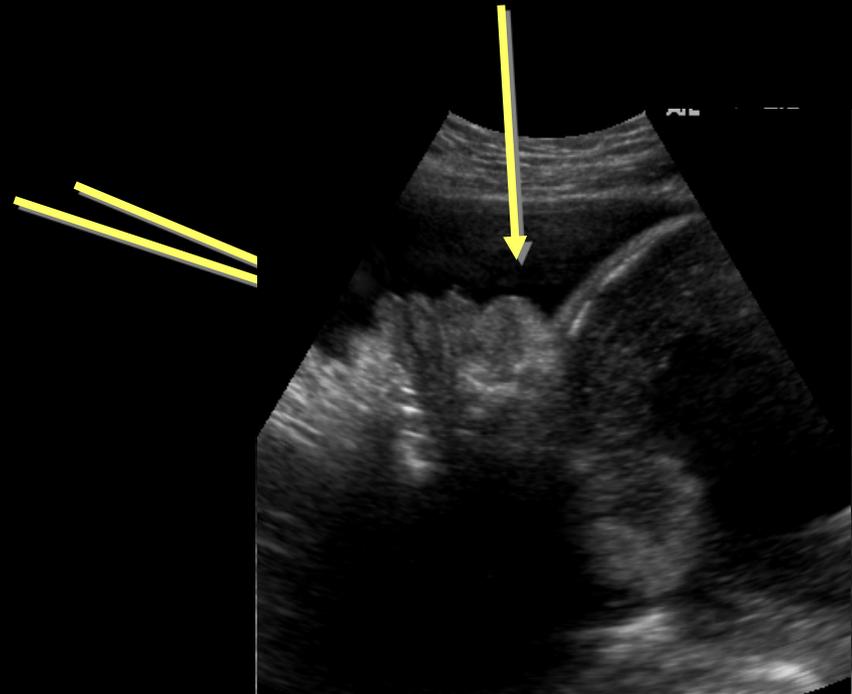
# Hypertelorism – Secondary



Measured between  
nasal margins of vitreous

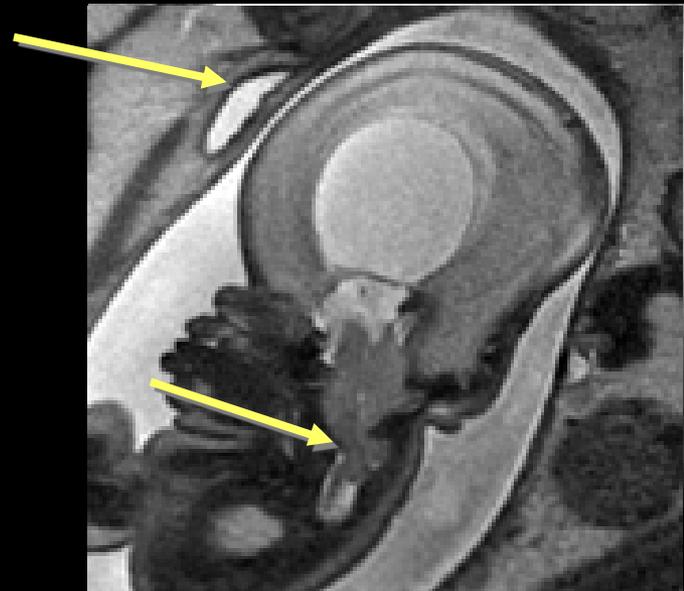
# 36 weeks gestation US findings

- Cloverleaf skull
- Hydrocephalus
- Bulging eyes / hypertelorism
- & midface hypoplasia



# 36 weeks gestation MR findings

- Hypertelorism
- Proptosis
- Hydrocephalus
- & Chiari I malformation



# Acrocephalosyndactyly Pfeiffer type

- Midface hypoplasia
- Acrocephaly
- Broad thumbs
- Soft tissue syndactyly
- & elbow & knee ankylosis
- DD – Antley-Bixler syndrome



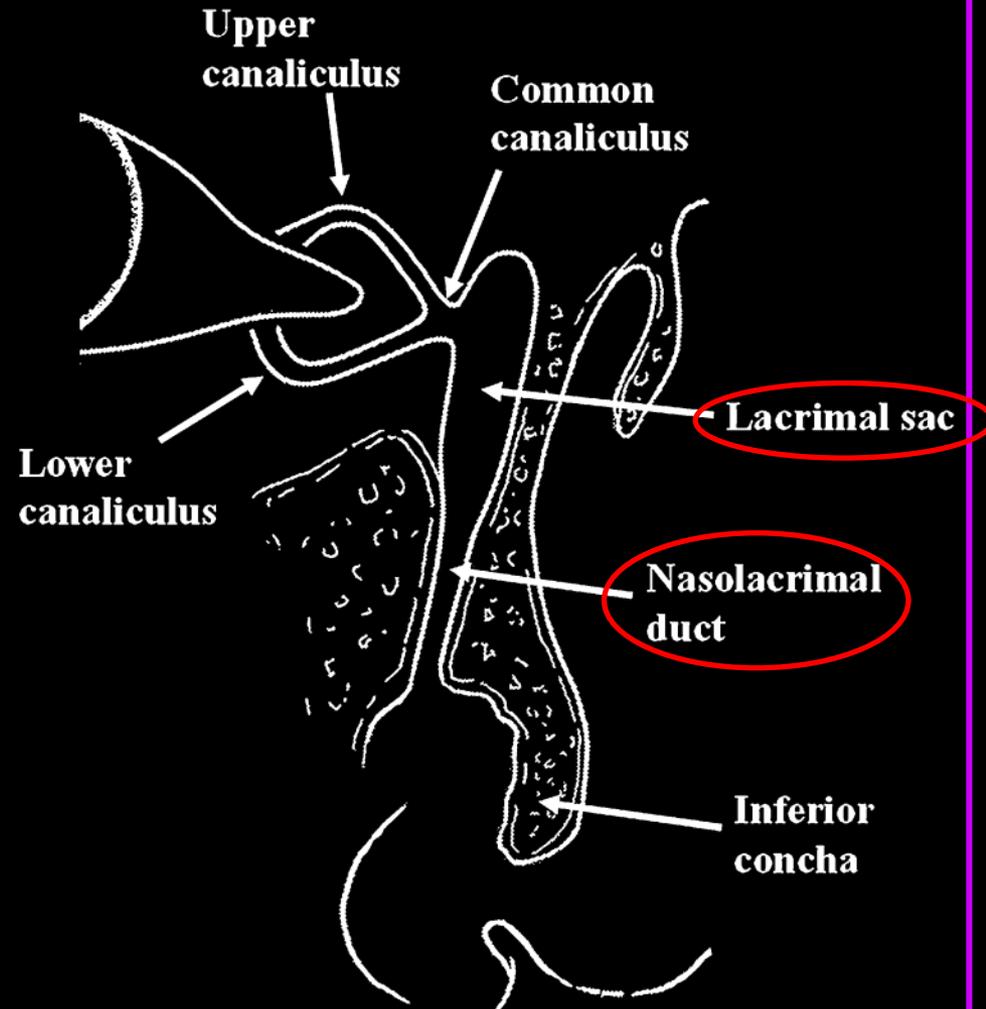
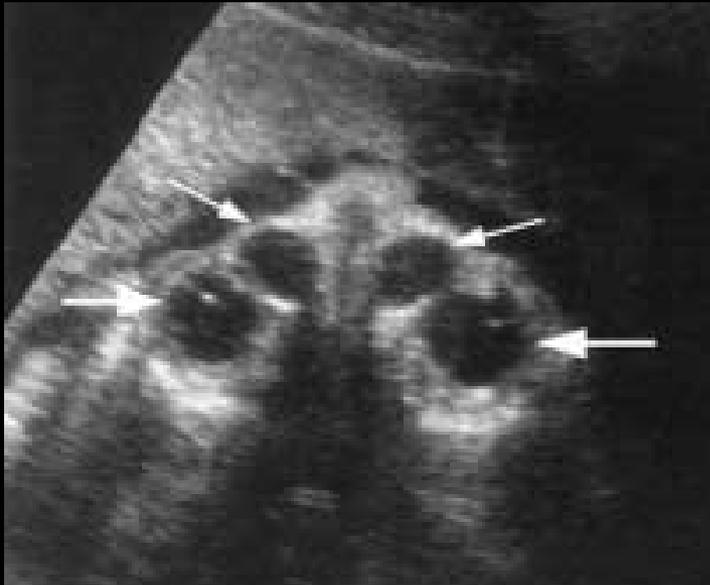
# Method of assessment

- Presence / absence of eyes (microphthalmia/anophthalmia)
- Morphology of lens, vitreous and optic nerve
- Biometry
- Extraocular pathologies
  - Dacrocystoceles
  - tumours

# Dacrocystoceles

(Goldberg, Sebire, Holwell, Hill)

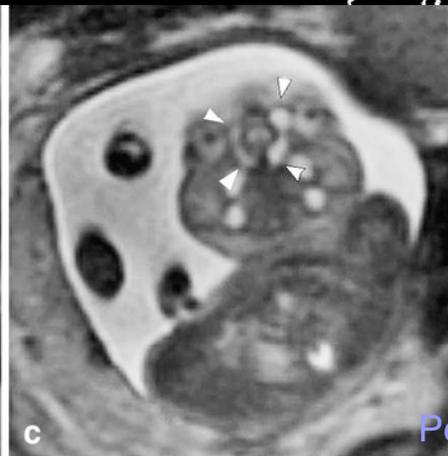
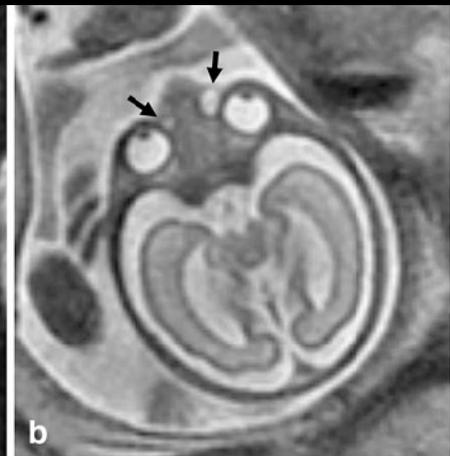
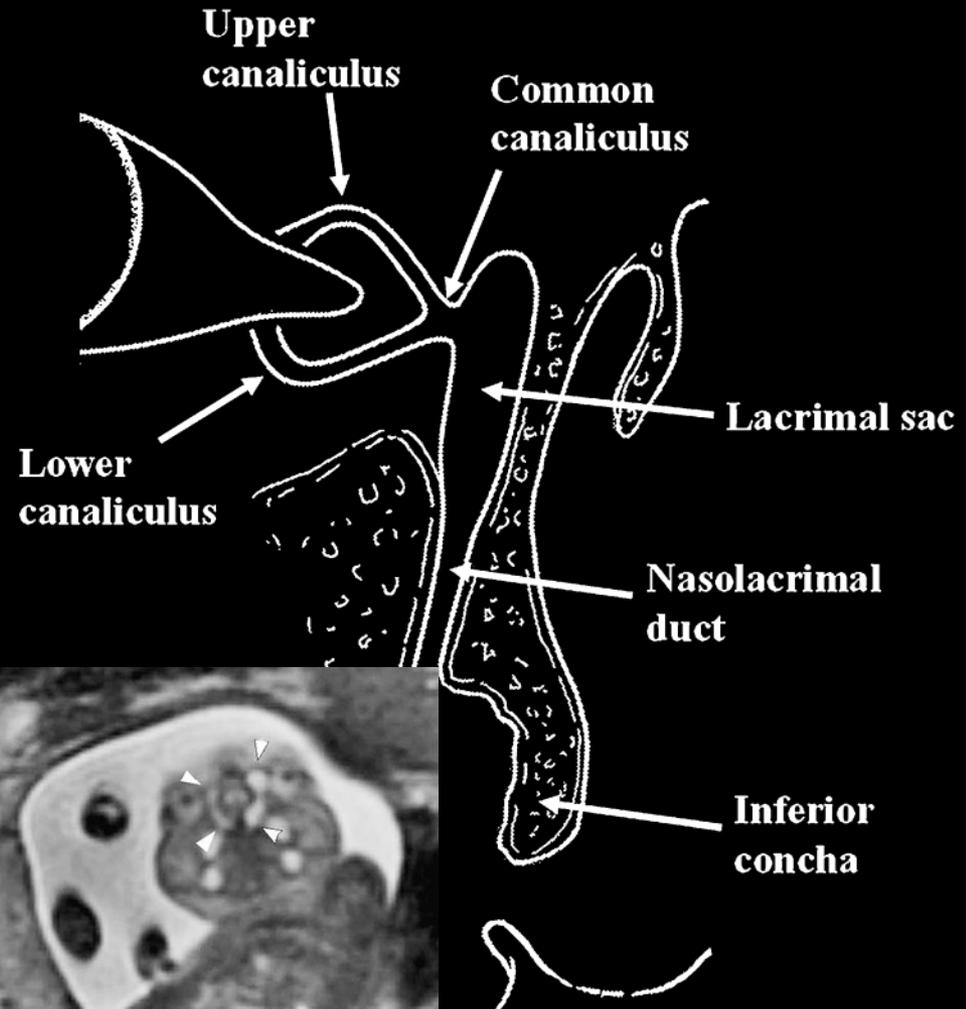
Enlargement of lacrimal sac  
Obstruction of nasolacrimal duct  
Often with intranasal cyst  
Latter two being within bone  
more easily seen with MRI



# Dacrocystoceles

(Yazici, Kline-Fath, Linam, Yazici, Rubio, Calvo-Garcia)

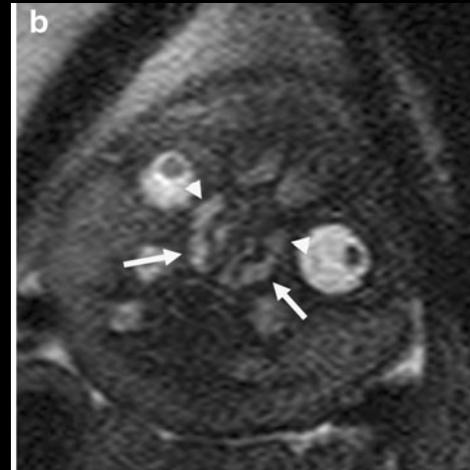
- Due to failure of canalization  
–should complete by 24 weeks
- Incidence 0.7% of fetal MRI studies
- Bilateral in half
- Half with f/u had no symptoms
- often resolve spontaneously



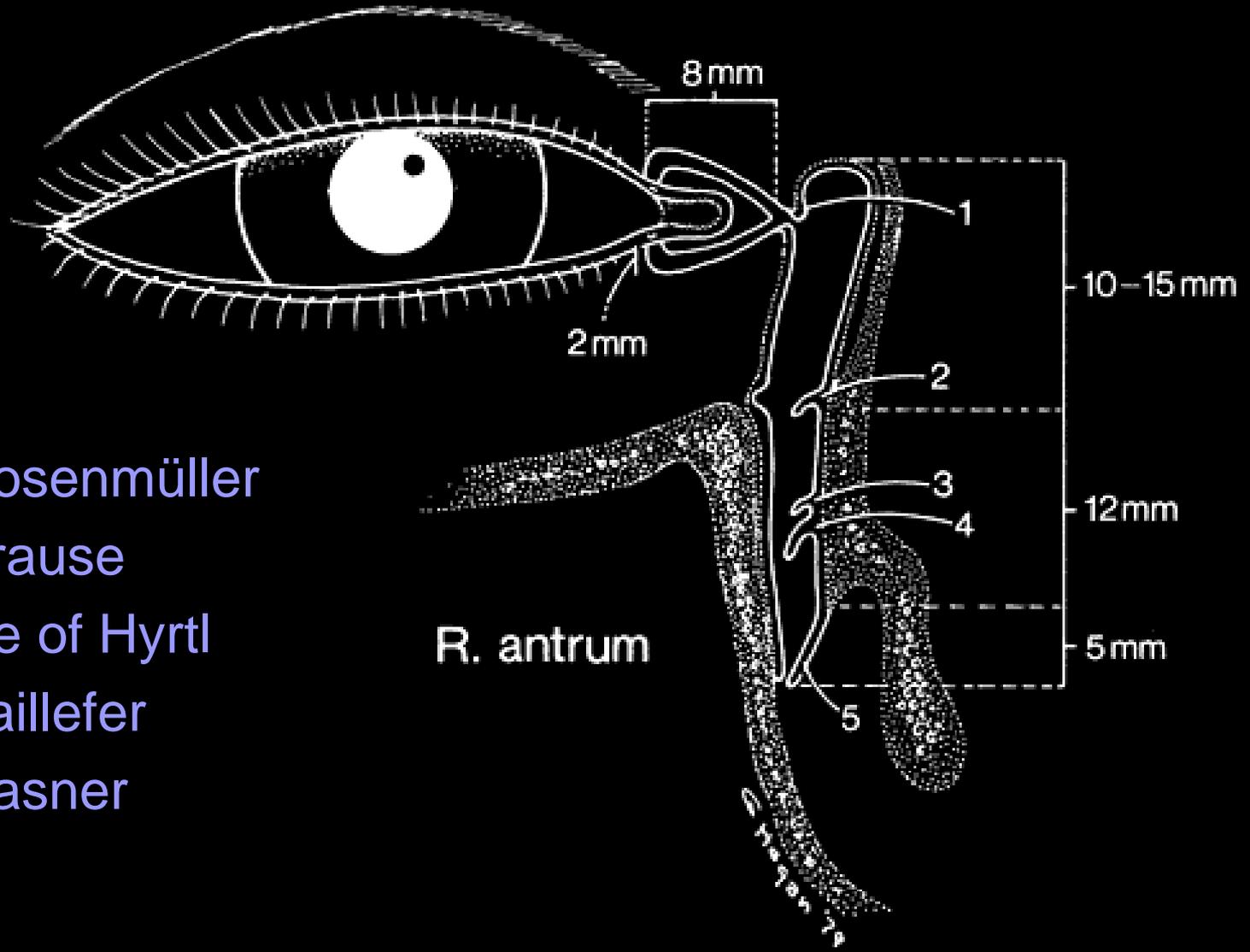
# Dacrocystoceles

(Brugger, Weber, Prayer)

- Fluid filled lachrymal pathways seen in 31.7%
- 49.4% bilateral
- Visibility increased from 24 to 32 weeks then decreased
- Sacs > 5mm = pathologic
- Due to timing of:
  - canalization
  - Eyelid opening
  - Hasner's valve opening



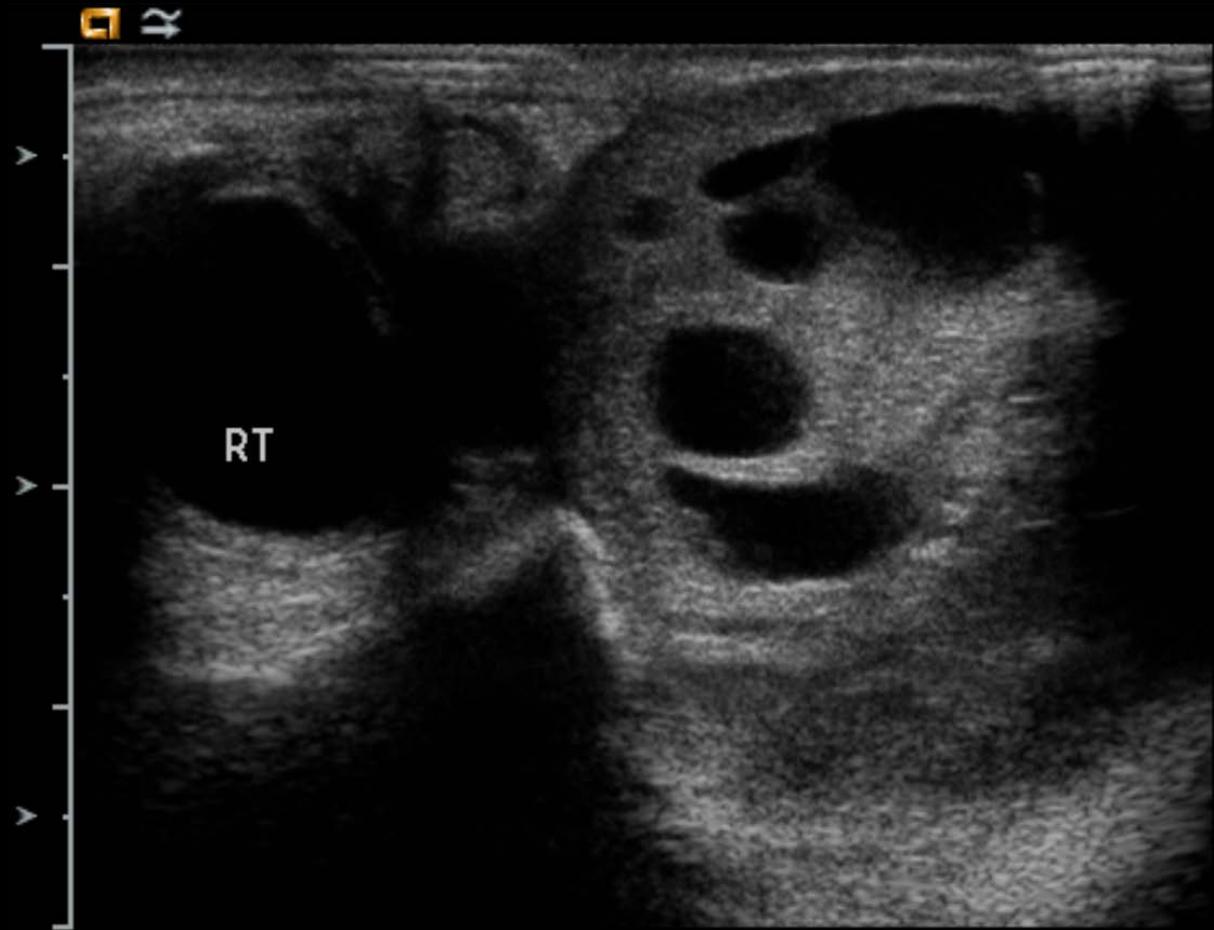
# Dacrocystoceles



- 1 valve of Rosenmüller
- 2 valve of Krause
- 3 spiral valve of Hyrtl
- 4 valve of Taillefer
- 5 valve of Hasner

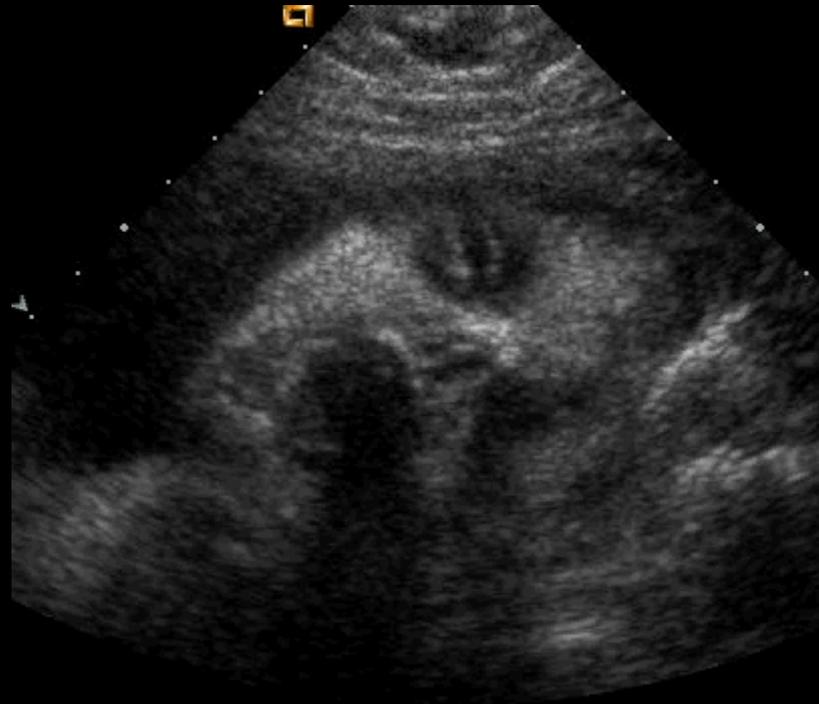
# Extraocular pathologies

- Tumours  
–e.g. Teratoma



# Summary

- Demonstrated:
  - The necessity for knowledge of ocular pathologies
  - That syndromes involving the eyes can go unrecognized without focused approach
  - Ocular abnormalities can sometimes help with diagnosis
- Demonstrated an approach to assessment including:
  - Presence / absence of the eyes
  - Morphology of the lens & vitreous
  - Ocular biometry
- Demonstrated:
  - Existing sonographic growth charts cannot be used for MRI



....The End!