Hydrops fetalis
Cystic hygroma
Abdominal wall defects

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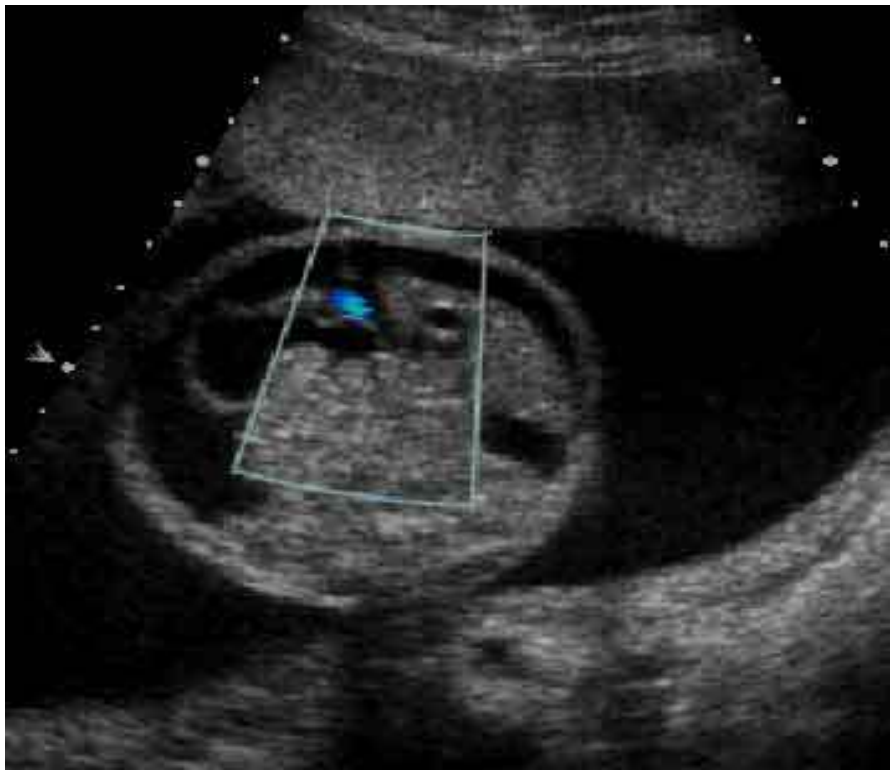
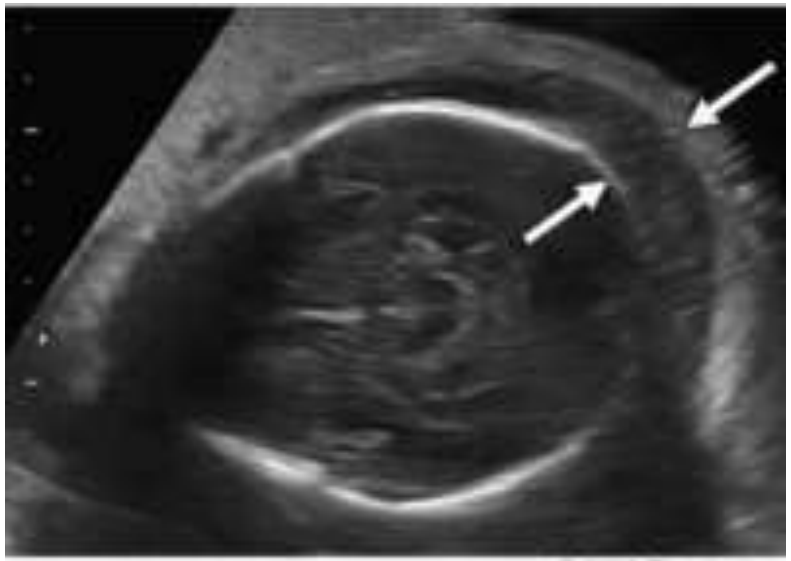
Hydrops fetalis

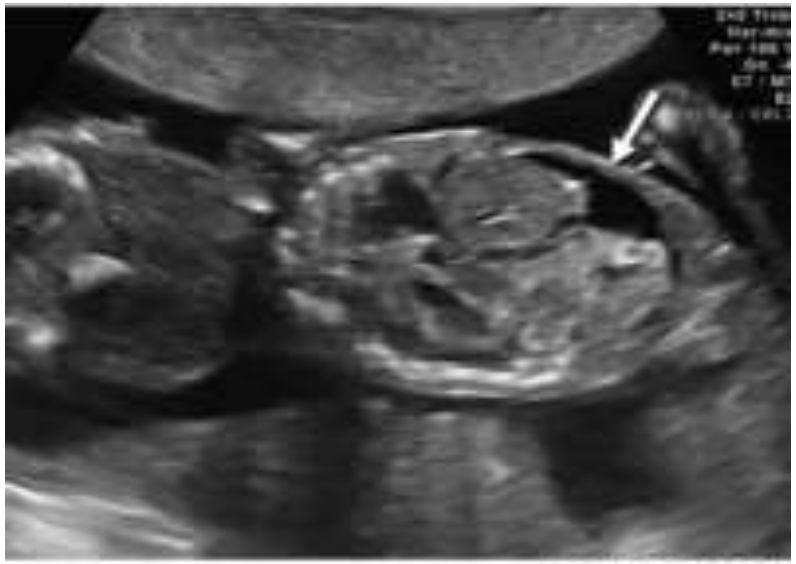
- Excess fluid in 2 or more body compartments:
  - Thorax
  - Abdomen
  - Skin
- Scalp and body wall edema, pericardial effusion, pleural effusion, ascites
- Associated with:
  - Polyhydramnios
  - Placental thickening

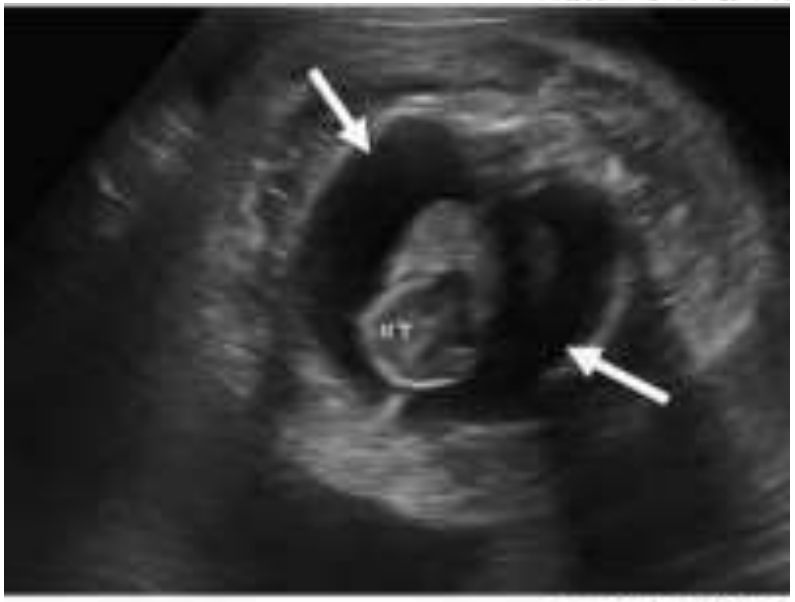
  Incidence:
  - 1/2000 live births
- Prognosis:
  - 80% mortality

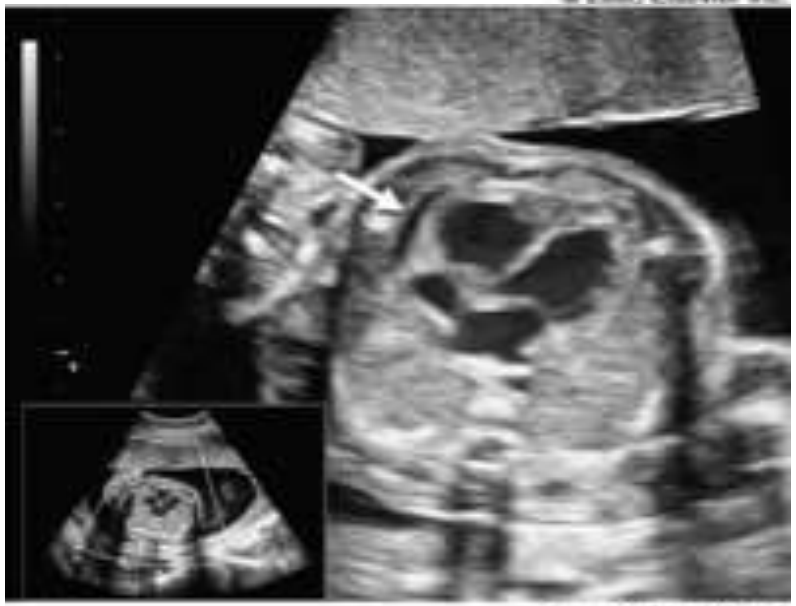


Hydrops fetalis







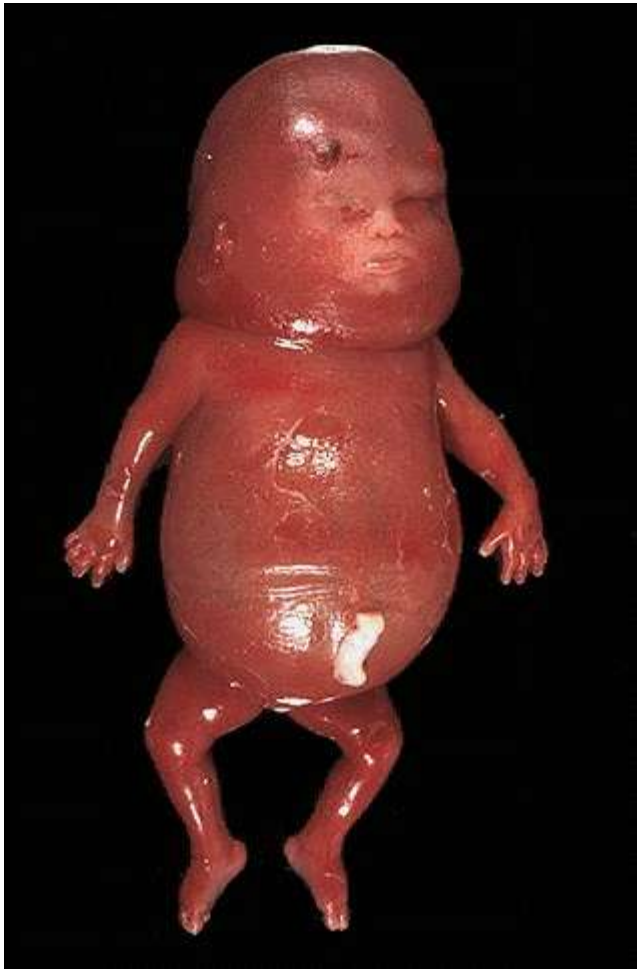


Maternal complications of hydrops fetalis

- Polyhydramnios related:
  - Supine hypotension
  - Preterm labor, PPROM
- Mirror syndrome:
  - Significant placental hydrops
  - Maternal edema, rapid weight gain, mild proteinuria and hypotension
  - Maternal intravscular volume expanded (DD from PET)
  - Hyperplacentosis
  - Usually resolves after resolution of fetal hydrops

Hydrops fetalis

- **Subdivision by etiology:**
- Immune:
  - Related to fetal anemia secondary to maternal alloimmunization to red cell antigens
  - Rarer now (prevention methods)
- Nonimmune:
  - Related to a variety of other causes
  - About 90%



Hydrops fetalis - etiology

Table 29-6. Categories of Disorders Causing Nonimmune Hydrops Fetalis in 5437 Pregnancies

Category	Percent
Cardiovascular	21.7
Chromosomal	13.4
Hematological	10.4
Infections	6.7
Thoracic	6.0
Lymphatic	5.7
Twin-twin transfusion	5.6
Syndromic	4.4
Urinary tract	2.3
Others	6.0
Idiopathic	17.8

Data from Bellini and colleagues, 2009

Immune hydrops fetalis

Hemolytic disease of the fetus and newborn (HDFN)

Immune hydrops fetalis
Hemolytic disease of the fetus and newborn (HDFN)

- **Pathophysiology:**
  - Formation of maternal antibodies (red cell alloimmunization) to more than 40 different red cell antigens
  - Hemolysis
  - Severe fetal anemia
- RhD is the most immunogenic
- RhD positive fetal cells enter fetal circulation following pregnancy related events: miscarriage, delivery

Immune hydrops fetalis

Table 29-5. Atypical Antibodies and Their Relationship to Fetal Hemolytic Disease

Blood Group System	Antigens Related to Hemolytic Disease	Hemolytic Disease Severity	Proposed Management
Lewis	*		
I	*		
Kell	K	Mild to severe†	Fetal assessment
	k, Ko, Kp^a Kp^b, Js^a, Js^b	Mild	Routine obstetric care
Rh (non-D)	E, C, c	Mild to severe†	Fetal assessment
Duffy	Fy^a	Mild to severe†	Fetal assessment
	Fy^b	‡	Routine obstetric care
	By^3	Mild	Routine obstetric care
Kidd	Jk^a	Mild to severe	Fetal assessment
	Jk^b, Jk^3	Mild	Routine obstetric care
MNSs	M, S, s, U	Mild to severe	Fetal assessment
	N	Mild	Routine obstetric care
	Mi^a	Moderate	Fetal assessment
MSSSs	Mt^a	Moderate	Fetal assessment
	Vw, Mur, Hil, Hut	Mild	Routine obstetric care

Immune hydrops fetalis

Lutheran	Lu^a, Lu^b	Mild	Routine obstetric care
Diego	$D1^a$, Di^b	Mild to severe	Fetal assessment
Xg	Xg^a	Mild	Routine obstetric care
P	$PP_{1pk}(Tj^a)$	Mild to severe	Fetal assessment
Public antigens	Yt^a	Moderate to severe	Fetal assessment
	Yt^b, Lan, Ge, Jr^a, CO^{1-b-}	Mild	Routine obstetric care
	En^a	Moderate	Fetal assessment
	Co^a	Severe	Fetal assessment
Private antigens	Batty, Becker, Berrens, Evans, Gonzales, Hunt, Jobbins, Rm, Ven,$Wright^b$	Mild	Routine obstetric care
	Biles, Heibel, Radin, Zd	Moderate	Fetal assessment
	Good, $Wright^a$	Severe	Fetal assessment

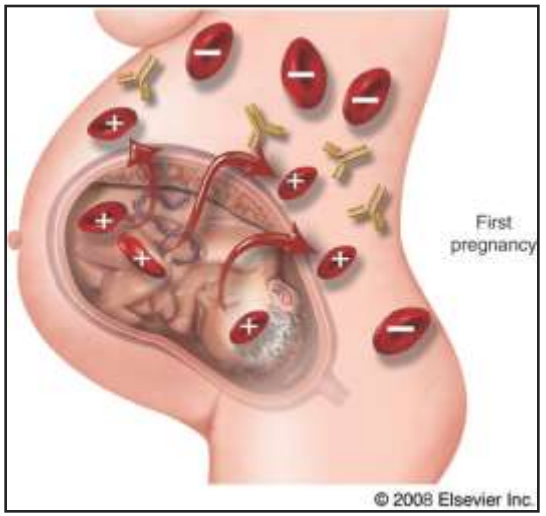
*Not a proven cause of hemolytic disease of the newborn.

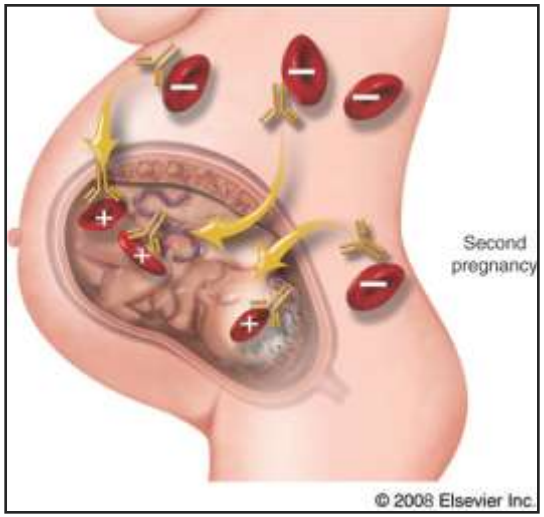
†With hydrops fetalis.

‡Not a cause of hemolytic disease of the newborn.

Pathophysiology of immune hydrops

- Initial pregnancy:
  - the mother is Rh negative and is carrying a fetus that is Rh positive
- At the time of delivery, the fetal Rh positive red blood cells enter the maternal circulation and initiate an antibody response
- In a subsequent pregnancy, antibodies enter the fetal circulation, attaching to the red blood cells and resulting in the sequestration and destruction of these cells





Pathophysiology of immune hydrops

- Severe cases:
  - Progressive anemia
  - Fluid collection in extracellular spaces (hydrops)
  - Death
- Milder cases:
  - Minor anemia
  - Hyperbilirubinemia at birth
  - Kernicterus
- Extramedullary hematopoiesis: liver, spleen enlargement

Pathophysiology of immune hydrops

- Fetal hydrops occurs when HG < 6 SD for age
- Small pericardial effusion
- Followed by ascites and pleural effusions
- Scalp edema – late manifestation
- Trimester 2 – maybe severe anemia w/out hydrops
- Trimester 3 – usually progressess quickly to hydrops
- Less lymphatic flow with advanced gestation

Prevention of alloimmunization

- Administration of RhD immune globulin prevents formation of anti – D antibodies in 99%

Early detection

- Prenatal care
- Early referral to perinatal centers

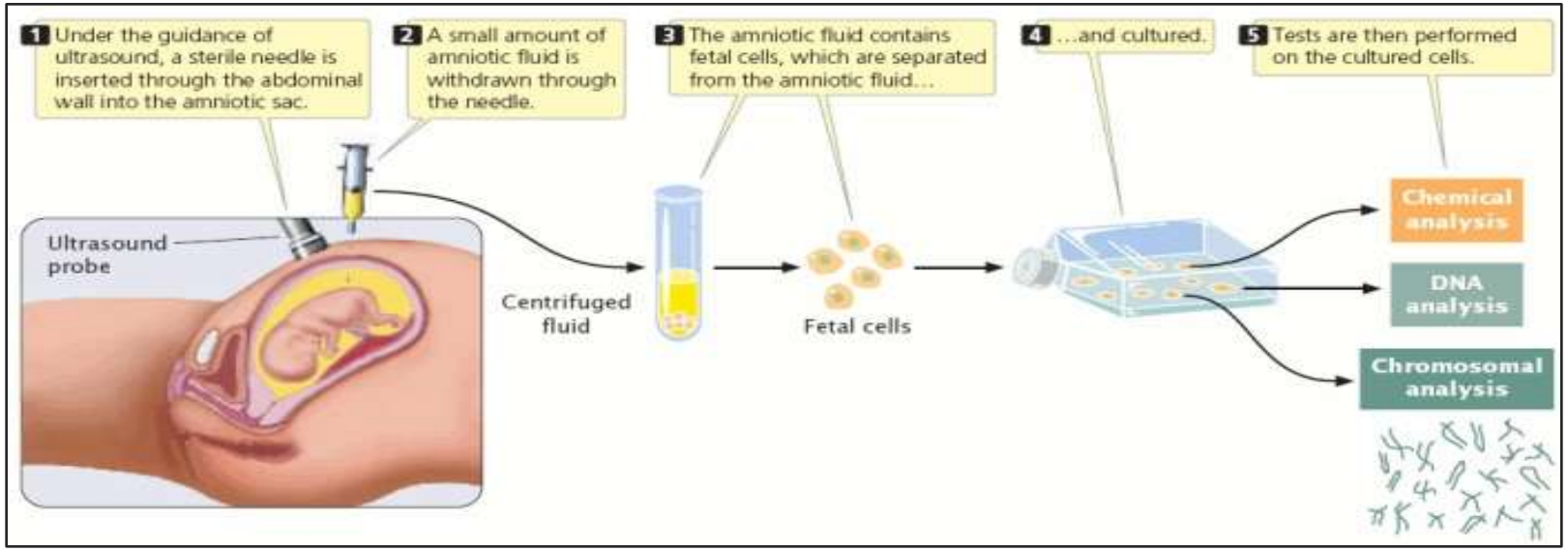
No hydrops or only mild hydrops – 98% perinatal survival
(Van Kamp, 2001)

Maternal antibody measurement

- Positive indirect coombs
- 4 week intervals (1st and 2nd tri) 2 week interval (3rd tri)
- Threshold: 1/8-1/32
- Anti Kell threshold 1/8 (more severe disease along with bone marrow suppression)

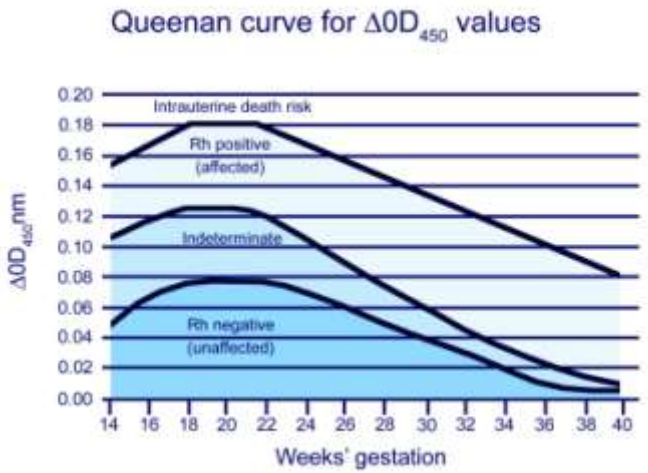
Fetal antigen testing

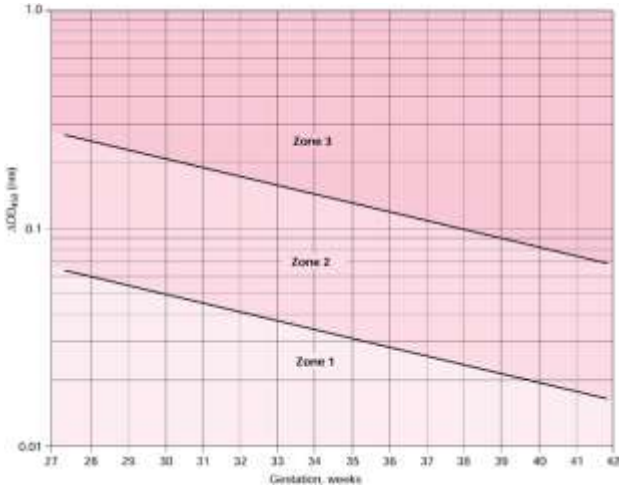
- Paternal evaluation:
  - if negative no further assessment
- If heterozygous: amniocentesis and PCR for fetal blood type (D,C/c, E/e, Kell/cellano, JK, Fy/Fy, M/N, S/s antigens)
  - if negative no further assessment
- If positive: start serial evaluation
- Free DNA RhD typing in maternal blood



Diagnosis of fetal anemia

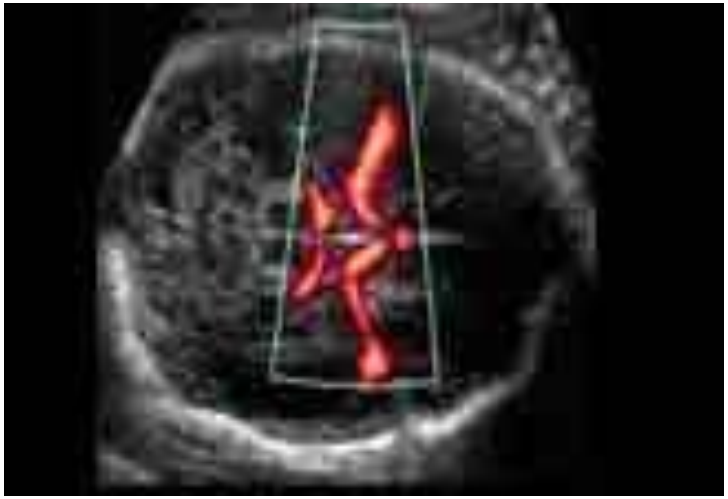
- Traditional:
  - Serial amniocentesis to measure amniotic fluid bilirubin - ΔOD assay
- Spectrophotometry
- Liley curve, Queenan curve
- No longer used

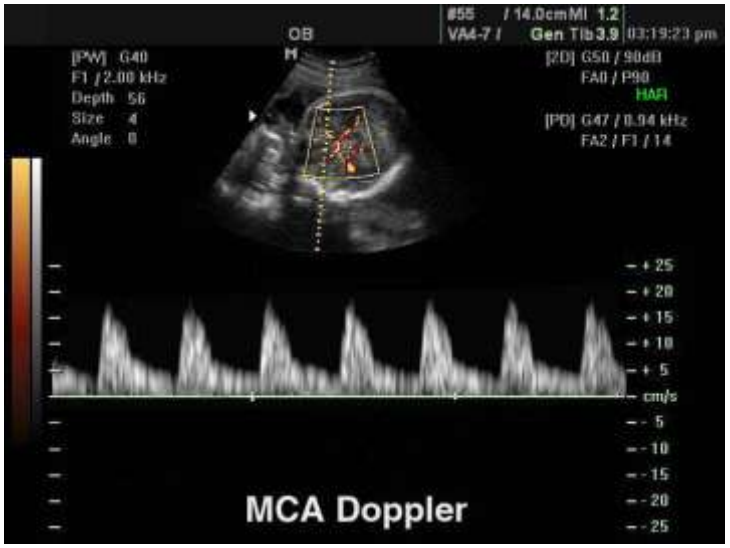




Diagnosis of fetal anemia

- Middle cerebral artery Doppler
  - Peak systolic velocity
  - Fetal blood velocity increases in anemic fetuses (less viscous and fetal tachycardia)
- MOM's because of generalized increase with gestational age
- From 18 weeks gestation
- Repeat every 1-2 weeks





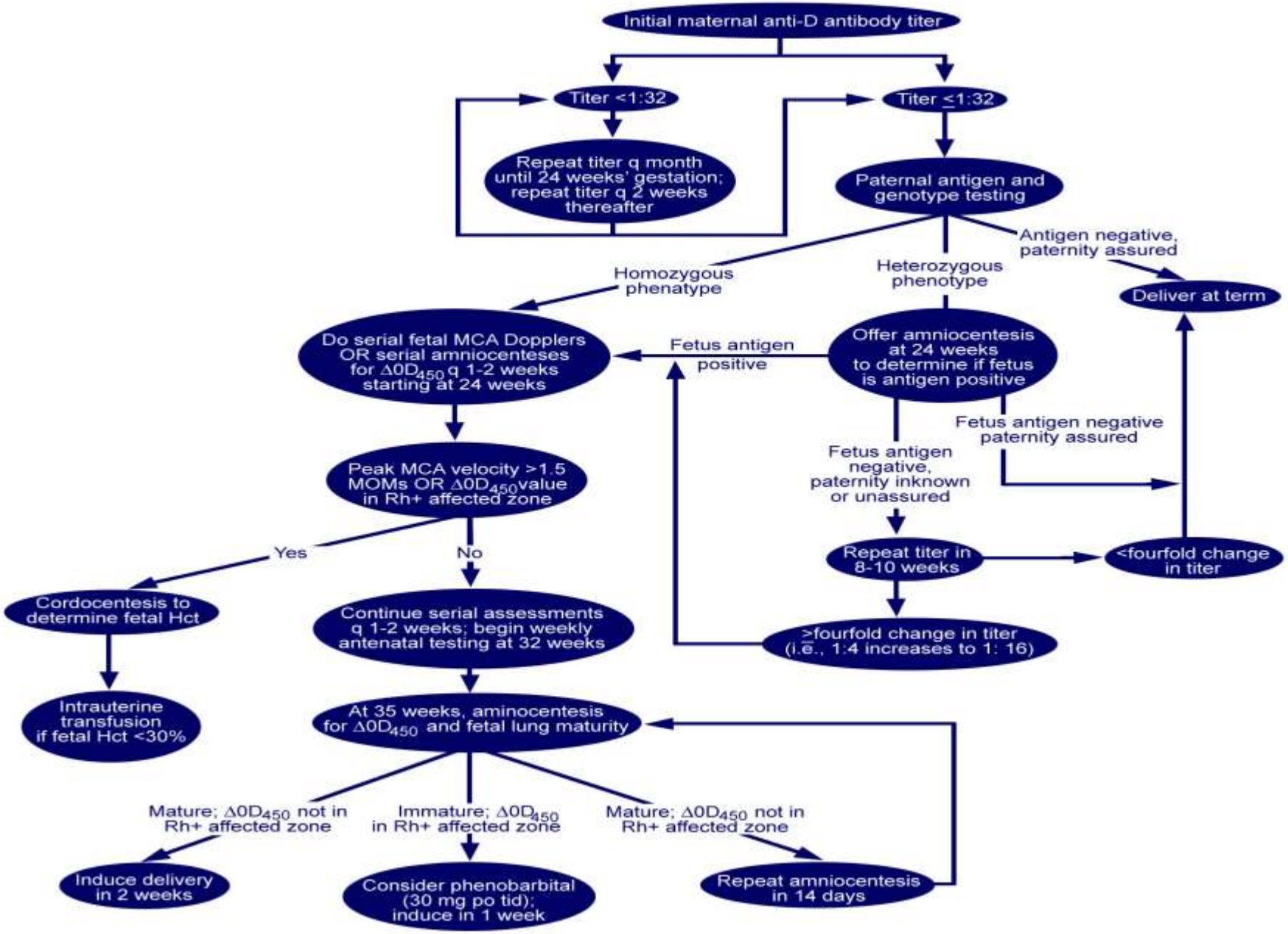
Diagnosis of fetal anemia

Medscape® www.medscape.com

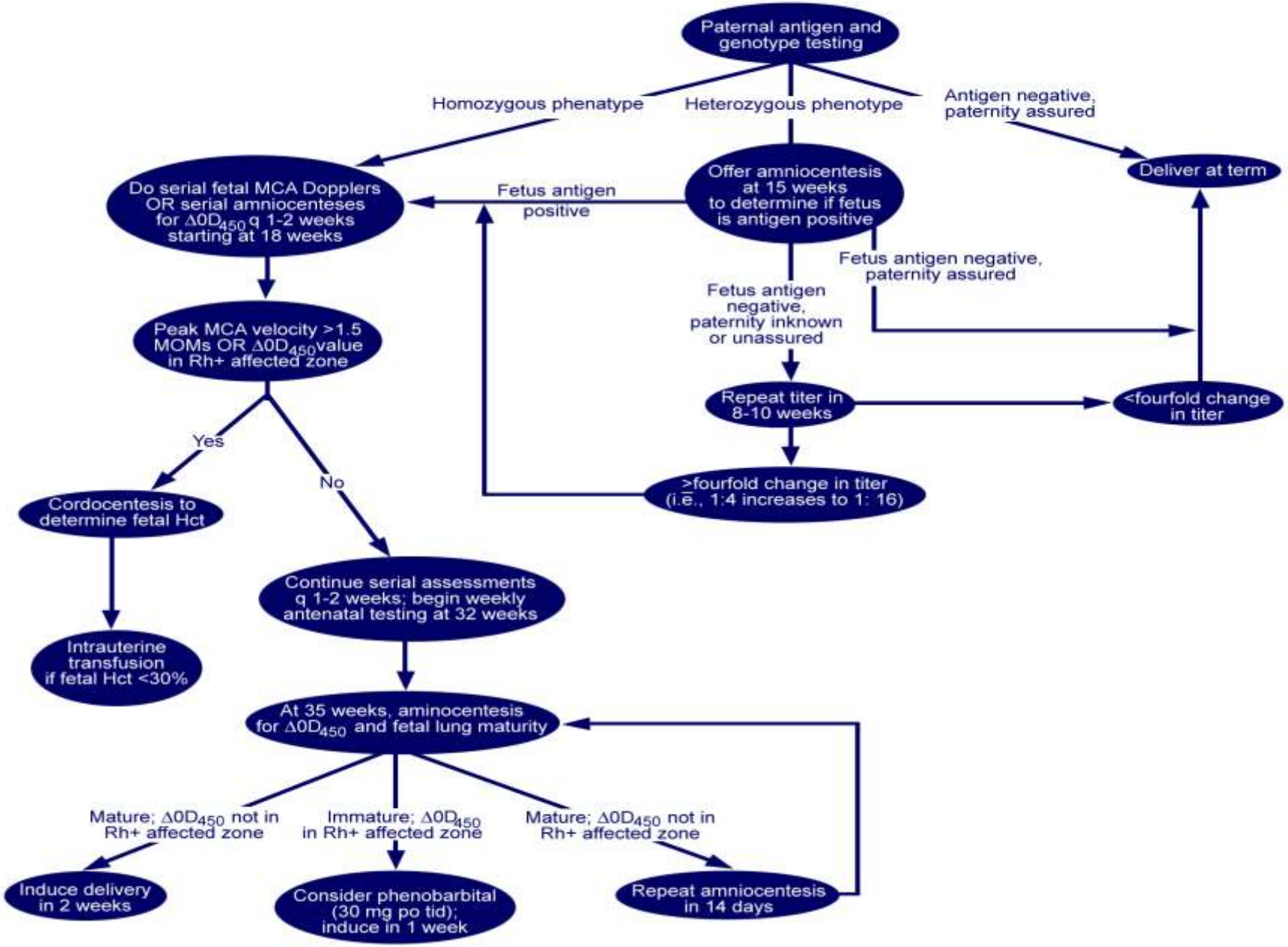
Gestational age (w)	1.00 (median)	1.29	1.50	1.55
18	23.2	29.9	34.8	36.0
20	25.5	32.8	38.2	39.5
22	27.9	36.0	41.9	43.3
24	30.7	39.5	46.0	47.5
26	33.6	43.3	50.4	52.1
28	36.9	47.6	55.4	57.2
30	40.5	52.2	60.7	62.8
32	44.4	57.3	66.6	68.9
34	48.7	62.9	73.1	75.6
36	53.5	69.0	80.2	82.9
38	58.7	75.7	88.0	91.0
40	64.4	83.0	96.6	99.8

*Table created based on data from Mari G, Deter RL, Carpenter RL, et al. Noninvasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization. Collaborative Group for Doppler Assessment of the Blood Velocity in Anemic Fetuses. *N Engl J Med.* 2000 342:9-14.[74]

Managing a first sensitized pregnancy



Managing patients with a previously affected fetus



Overall management

Follow maternal titers every 4 weeks up to 24 weeks' gestation; repeat every 2 weeks thereafter.

If titer 1/ 32; 1/8 for antiKell): serial MCA Doppler (from 18 weeks' gestation.) or amniocentesis every 10 days - 2 weeks for ΔOD_{450} using the Queenan curve.
If heterozygous paternal phenotype - amniocentesis by 24 weeks for fetal antigen status. If -negative - no further testing.
Begin antenatal testing at 32 weeks' gestation, with twice-weekly biophysical profiles.

MCA Doppler > 1.5 MoMs or the ΔOD_{450} in *positive (affected)* zone of Queenan curve - cordocentesis with blood readied for IUT for a fetal hematocrit of less than 30%

If repeat MCA velocities remain less than 1.5 MoMs, consider induction at 37 to 38 weeks' gestation.

If the MCA velocity is greater than 1.5 MoMs at more than 35 weeks' gestation, perform amniocentesis for DOD_{450} and fetal lung maturity. If mature and the ΔOD_{450} value is not in the upper, *Rh positive (affected)* zone, induce delivery in 2 weeks. If the fetal lungs are noted to be immature and the ΔOD_{450} value is in the upper, *Rh positive (affected)* zone, consider administering 7 days of maternal phenobarbital (30 mg PO TID) to enhance fetal hepatic maturity. Induce labor in 1 week. If fetal lung immaturity is noted and the ΔOD_{450} value is not in the upper, *Rh positive (affected)* zone, repeat the amniocentesis in 2 weeks.

If using serial ΔOD_{450} values and these remain below the *Rh positive (affected)* zone, perform the last amniocentesis at 37 weeks. If mature and the ΔOD_{450} value is not in the upper, *Rh positive (affected)* zone, induce delivery in 1 to 2 weeks. If immature lungs and the ΔOD_{450} value is in the upper, *Rh positive (affected)* zone, consider administering 7 days of maternal phenobarbital (30 mg PO TID) to enhance fetal hepatic maturity. Induce labor in 1 week.

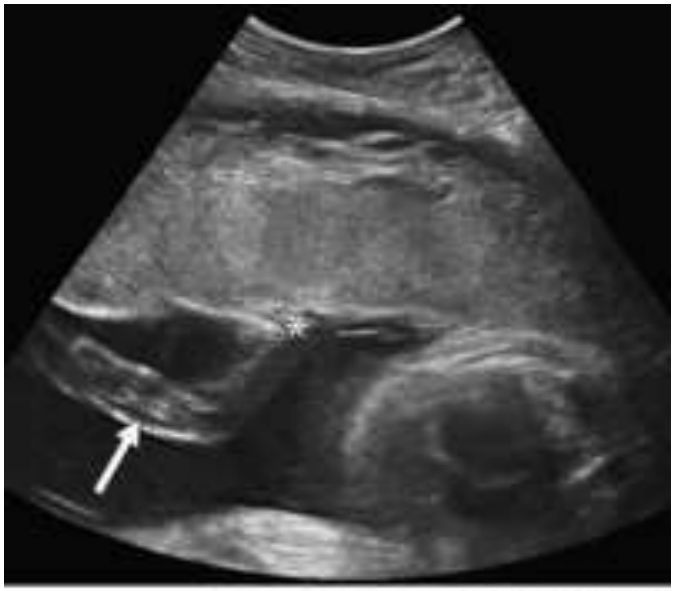
Previously affected fetus or infant (fetus needed IUTs or neonate required exchange transfusions):
Maternal titers are *not* helpful in predicting the onset of fetal anemia after the first affected gestation.

In cases of a heterozygous paternal phenotype, perform amniocentesis at 15 weeks' gestation to determine the fetal RhD status. If an RhD-negative fetus is found, no further testing is warranted.

Begin serial MCA Doppler assessment or amniocenteses for ΔOD_{450} (Queenan curve) at 18 weeks' gestation. Repeat at 1- to 2-week intervals.
Remainder of protocol is similar to the first affected pregnancy.

Intrauterine transfusion

- Ultrasound-directed needle puncture of the umbilical cord at its insertion into the placenta or puncture of the intra-hepatic portion of the umbilical vein
- Tightly packed donor red cells (hematocrit 78% to 80%) are then infused
- Repeat as necessary
- Final IUT as late as 35 weeks' gestation, with delivery anticipated at 37 to 38 weeks
- Bone marrow suppression; follow postpartum



Prognosis

- Cerebral palsy and developmental delay are more common in fetuses with HDFN when compared with unaffected infants
- Normal outcome can be expected in more than 90% of cases
- Mean gestational age at delivery - 33.5 weeks
- 80% of cases - emergency cesarean section
- Sensorineural hearing loss- more frequent (prolonged exposure to elevated levels of bilirubin and its toxic effect on the developing eighth cranial nerve)

Nonimmune hydrops fetalis

Hydrops - pathogenesis

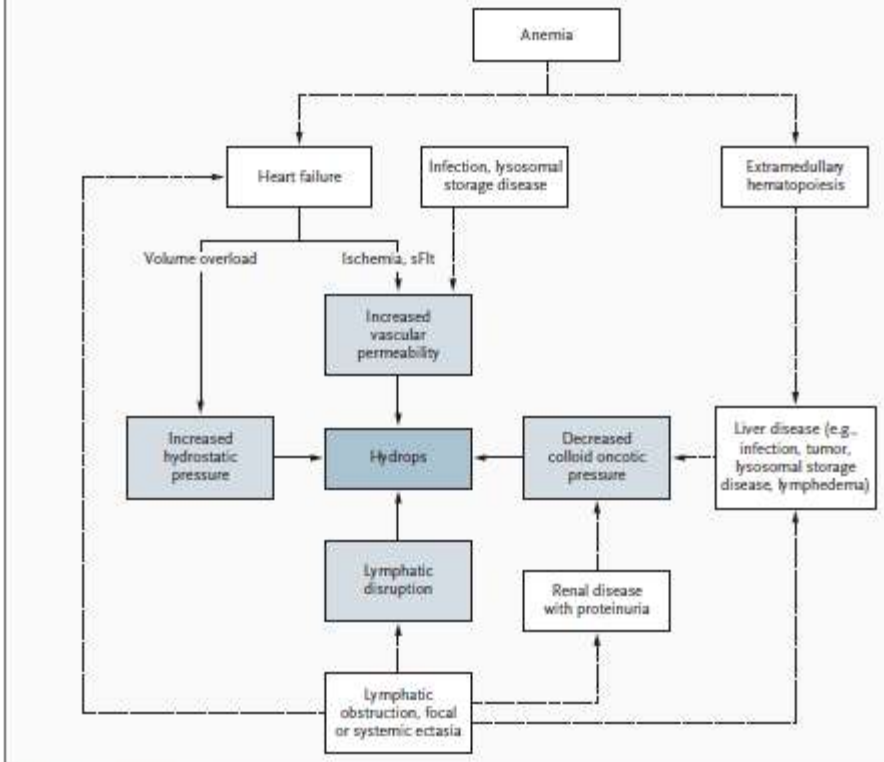


Figure 3. Pathogenesis of Nonimmune Hydrops Fetalis.

The primary pathogenic processes leading to nonimmune hydrops fetalis are increases in hydrostatic pressure, decreases in colloid oncotic pressure, and increases in blood and lymphatic vascular permeability. Multiple diseases can trigger any or all of these primary processes. For example, cardiac failure can lead to volume overload and increased hydrostatic pressure, whereas resultant tissue ischemia can directly increase vascular permeability or indirectly promote this phenomenon by increasing placental synthesis of soluble Fms-like tyrosine kinase-1 (sFlt). Increased vascular permeability can also result from elevated cytokine levels accompanying fetal infections or vascular involvement from lysosomal storage disease. Fetal anemia can lead to high-output cardiac failure or, in many cases, extramedullary hematopoiesis. Extramedullary hematopoiesis can cause the failure of hepatic protein synthesis, thus decreasing colloid oncotic pressure. Other causes of hepatic failure include infections, lysosomal storage disease, tumors, and lymphedema. Renal diseases, such as those caused by congenital nephrosis, lysosomal storage disease, and lymphedema, can decrease colloid oncotic pressure because of proteinuria. Lymphatic disorders contribute to hydrops directly by disruption of lymphatic vessels and secondarily by inducing chylothorax, which — if associated with mediastinal shifts — impairs venous return and induces cardiac tamponade, causing cardiac failure.

Pathophysiology of nonimmune hydrops

- **Three theories:**
- Hypoprotenemia:
  - Hepatic dysfunction, endothelial damage (infection), iron overload
- Inadequat cardiac output and myocardial failure:
  - Regurgitant intracardiac flow (e.g.Ebstein anomaly
  - Obstruction to preload or afterload based on intrathoracic lesions (e.g. chylothorax)
  - Poor myocardial contractility (adenovirus-induced myocarditis)
- Structural lymphatic obstruction:
  - Turner or Noonan syndrome

Nonimmune hydrops

- 1/3000
- > 120 reported causes:
  - Cardiovascular – 25%
  - Chromosomal – 10%
  - Thoracic – 9%
  - TTTS – 8%
  - Infection – 4%
  - Idiopathic – 22%

Table 1. Primary Causes of Nonimmune Hydrops Fetalis (NIHF) and Their Relative Frequency.*

Category	Percentage of All Cases of NIHF
Cardiovascular diseases	24 to 40
Cardiac	
Structural cardiac defects	
Tachyarrhythmias	
Bradyarrhythmias	
Vascular	
Obstruction	
Aneurysms	
Vascular tumors (e.g., large placental chorioangiomas)	
Twin disorders	8 to 9
Twin-to-twin transfusion syndrome	
Twin reversed-arterial-perfusion syndrome	
Infections	6 to 7
Chromosomal abnormalities	8 to 10
Associated with prominent cystic hygromas	2
Associated with profound fetal akinesia	1
Anatomical abnormalities	
Thoracic lesions	4 to 9
Tumors	
Diaphragmatic hernia	
Lethal skeletal dysplasia	
Urinary tract and renal abnormalities	4
Prune belly	
Finnish nephrosis	
Gastrointestinal disorders	1
Fetal hepatic tumors	
Hepatitis	
Volvulus	
Meconium peritonitis causing severe ascites	
Metabolic disorders (e.g., lysosomal storage diseases)	1 to 15
Anemias	
Genetic disorders causing fetal anemia	1
α-Thalassemia	
Diamond–Blackfan anemia	
Red-cell enzyme defects	
Other hematologic abnormalities	1
Fetal-to-maternal hemorrhage	
Intraventricular hemorrhage associated with alloimmune thrombocytopenia	
Primary lymphatic disorders	1
Congenital pulmonary lymphangiectasis leading to chylothorax	
Generalized (systemic) lymphangiectasis syndrome	

* Data are adapted from Warsof et al.,[4] Abrams et al.,[5] Machin,[6] Stevenson et al.,[7] and Wieacker et al.[8]

Nonimmune hydrops fetalis - etiology

Fetal causes	
Anomalies	
Cardiac	Atrial or ventricular septal defect, hypoplastic left heart, pulmonary valve insufficiency, Ebstein subaortic stenosis, dilated hear V canal defect, single ventricle, Fallot tetralogy, premature closure of foramen ovale, subendocardial fibroelastosis
Thoracic	Diaphragmatic hernia, cystic adenomatous malformation, pulmonary hypoplasia, lung hamartoma, mediastinal teratoma, chylothorax
Gastrointestinal	Jejunal atresia, midgut volvulus, intestinal malrotation or duplication, meconium peritonitis
Urological	Urethral stenosis or atresia, posterior bladder neck obstruction, bladder perforation, prune belly, neurogenic bladder, ureterocel
Syndromes	Thanatophoric dwarfism, arthrogryposis multiplex congenita, asphyxiating thoracic dystrophy, hypophosphatasia, osteogenesi imperfecta, achondroplasia, achondrogenesis, recessive cystic hygroma, and Nevakova, SaldinoNoonan, and Pena-Shokeir type I syndromes
Conduction defects	Supraventricular tachycardias, heart block (including with maternal lupus erythematosus)
Miscellaneous	Cystic hygroma, congenital lymphedema, polysplenia syndrome, neuroblastoma, tuberous sclerosis, sacrococcygeal teratoma
Aneuploidies	Trisomy 21 and other trisomies, Turner syndrome, triploidy
Vascular	A-V shunts, large vessel thromboses (cava, portal, or femoral vein), KasabachMerritt syndrome
Infections	Cytomegalovirus, toxoplasmosis, syphilis, listeriosis, hepatitis, rubella, parvovirus, leptospirosis, Chagas disease
Multifetal pregnancy	Twin-twin transfusion syndrome, twin reversearterial perfusion (TRAP) syndrome
Miscellaneous	α_4-thalassemia (Bart hemoglobin), twisted ovarian cyst, fetal trauma, anemia, Gaucher disease, gangliosidosis, sialidosis
Placental causes	Chorioangioma, fetomaternal hemorrhage, AV shunts, placenta trauma with fetal hemorrhage, twin-twin transfusion syndrome
Maternal causes	
Medications	Indomethacin

Cardiovascular

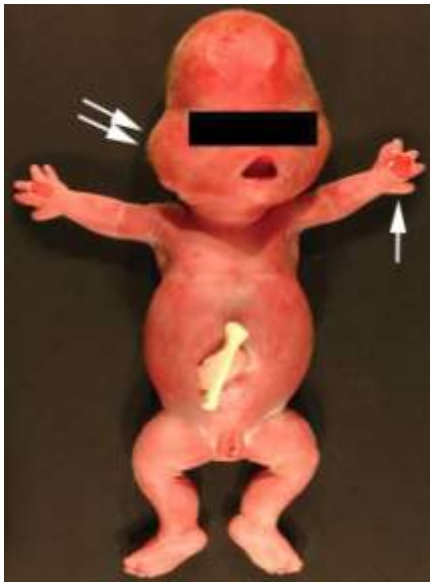
- Tachyarrythmias
- Congenital heart block
- Anatomical defects
  - ASD, VSD, HLHS, PV reg, Ebstein, AV canal, TOF, single ventricle, etc.

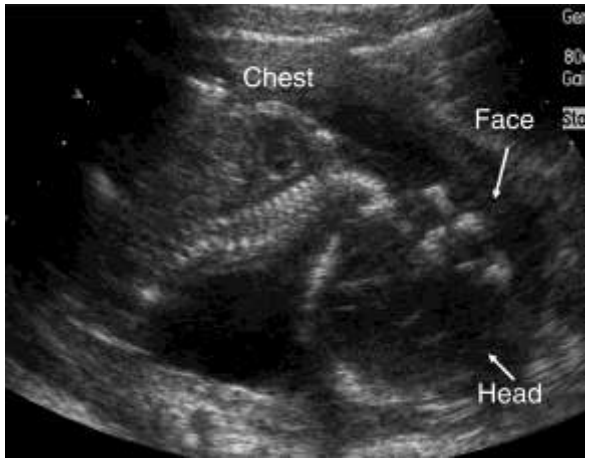
Chromosomal

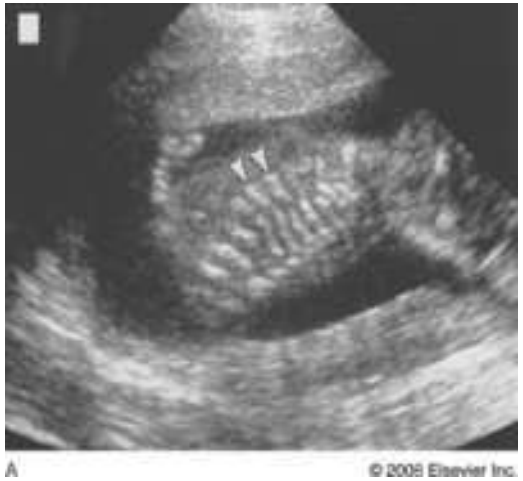
- Down syndrome
- Other trisomies
- Turner syndromes
- Triploidy

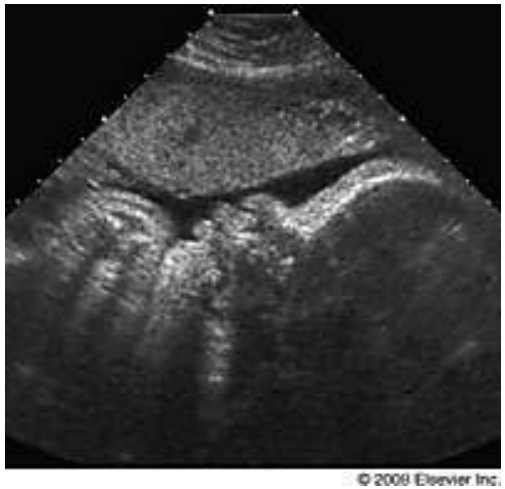
Malformation syndromes

- Thanatophoric dwarfism
- Arthrogryposis
- Osteogenesis Imperfecta
- Achondroplasia









Hematological

- α-Thalassemia

Infections

- **Parvovirus B19:**
- Small single-stranded DNA virus
- Potent inhibitor of hematopoiesis
- The cellular receptor for parvovirus B19 is globoside, which is found on erythrocyte progenitor cells (erythroblasts and megakaryocytes) and also on erythrocytes, synovium, placental tissue, fetal myocardium and endothelial cells
- Causing maternal and fetal signs and symptoms:
  - maternal joints, fetal red blood cells, placenta, and myocardium
- Respiratory droplets (also: blood products, vertical transmission (does not occur if the mother is immune at the time of exposure)

Parvovirus B19

- Viremia in mother - peaks approximately 1 week after infection
- Maternal symptoms - 10 - 14 days after infection in approximately 50% of infected women
- Parvovirus B19 IgM antibodies - detectable in maternal serum 7 - 10 days after infection, peak at 10 -14 days, decrease within 2 - 3 mo.
- IgG antibodies rise more slowly and reach a plateau at 4 weeks after infection
- Associated with profound fetal anemia and hydrops fetalis when maternal infection occurs before 20 weeks' gestation
- Risk for fetal hydrops- 3.9%
- The peak incidence of parvovirus associated hydrops fetalis is between 17 and 24 weeks of gestation

Evaluation

- Careful maternal history:
  - Exposure to parvovirus B19
- Comprehensive ultrasound examination:
  - Special emphasis - cardiac structures and rhythm
  - Fetal echocardiogram
  - Decrease in cardiac output with right atrial overload is likely the primary cause in most cases of early hydrops fetalis
  - Inadequate cardiac output - due to AVSD, cardiomyopathy
- 2 mm or less of pericardial fluid is normal
- Doppler evaluation of the middle cerebral artery

Evaluation cont.

- R/O infectious causes
- Previous obstetric history of stillbirth or a hydropic fetus – consider lysosomal storage diseases
- Consanguineous relationship - consider autosomal-recessive diseases as the etiology

Laboratory tests

- Antibody screen for anti–red cell antibodies
- Rapid test for syphilis
- Kleihauer-Betke test or fetal cell stain by flow cytometry
- Maternal serologies for toxoplasmosis, cytomegalovirus, and parvovirus should be considered but may not be diagnostic particularly with acute onset of fetal hydrops

Amniocentesis

- Cordocentesis – past
- Amniocentesis with fluorescent in situ hybridization for major chromosomal abnormalities, and PCR testing for viral infections have decreased the role of this procedure
- PCR for toxoplasmosis, cytomegalovirus, parvovirus, adenovirus, and enteroviruses
- Amniotic fluid analysis for mucopolysaccharides and neuraminic acid
- Cultured amniocytes should be analyzed for complete karotype as well as enzymatic levels for the more common lysosomal disorders including β-glucuronidase, β-glucosidase, and β-galactosidase
- Other lysosomal diseases if warranted by maternal history: Niemann-Pick types A and C, Wolman, Faber, Mucolipidosis II, and multiple sulfatase deficiency

Treatment

- **Depends on etiology:**
- **Parvovirus:**
  - MCA Doppler to confirm the anemia - systolic velocity > 1.5 MoMs
  - Amniocentesis – PCR - diagnostic in 24 to 48 hours
  - 1/3 of fetal hydrops cases spontaneously resolved within 5 weeks; half of these cases occurred before 23 weeks' gestation
  - IUT of packed red cells was associated with survival in approximately 85% of cases
- **Fetomaternal hemorrhage:**
  - IUT - If a recurrent decline in fetal hematocrit is detected due to a persistent fetomaternal bleed, abandonment of additional transfusions may be warranted
- **Fetal CMV:**
  - Hyperimmune globulin?

Treatment

- Other Infections:
  - Adenovirus - fetal myocarditis; consider maternal administration of digoxin
  - Fetal toxoplasmosis – hydrops resolves after maternal administration of pyrimethamine, sulphadiazine, and folinic acid with good short-term neurologic outcome
  - Syphilis related hydrops - reverse with maternal treatment with penicillin; overall prognosis due to cerebral complications remains high
- Arrhythmias:
  - Ventricular rates of less than 50 bpm due to structural cardiac lesions or inflammation secondary to maternal anti-Ro antibodies are not amenable to therapy
  - The administration of maternal betamimetics has not been successful at increasing the fetal heart rate
  - Attempts at direct fetal pacing have also failed
  - Parenteral administration of digoxin followed by the addition of flecanide or sototol is usually successful in converting tachyarrythmias to sinus rhythum

Treatment

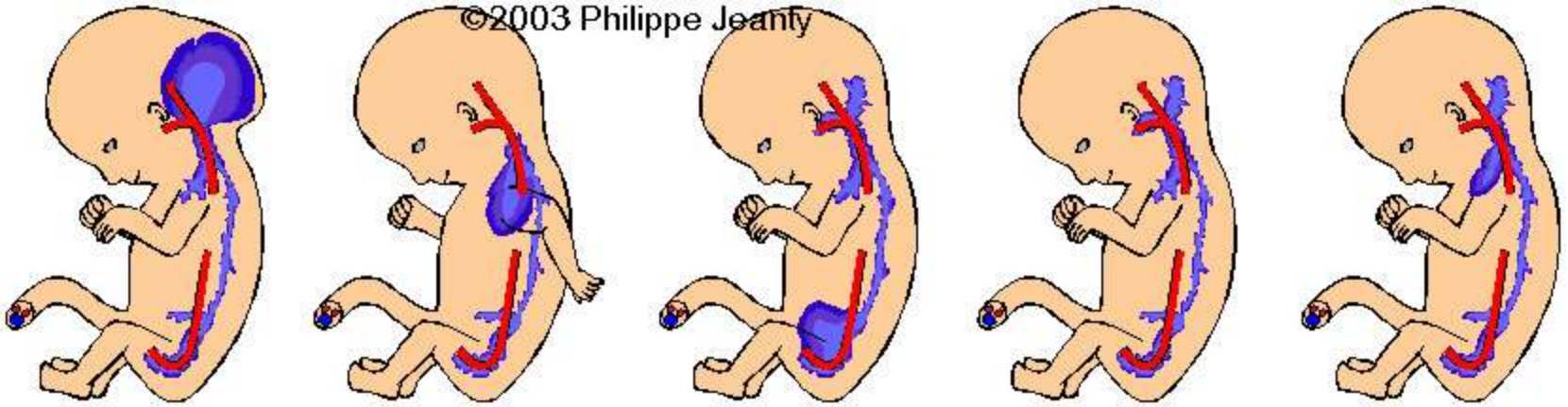
- Solid lesions of the chest and sacrococcygeal teratomas in association with NIHF open fetal surgery with mixed results
  - Referral to a center experienced in open fetal surgery should be considered if NIHF is noted before 26 weeks' gestation
- Unilateral pleural effusions, large macrocystic CCAMS:
  - Thoracoamniotic shunt placement under ultrasound guidance has been successful in decreasing the size of the fluid or cyst resulting in a return of the mediastinum to its midline position
  - Hydrops usually resolves within several weeks.
- Twin-to-twin transfusion:
  - Hydrops fetalis usually occurs in the recipient
  - Serial amnioreduction or septostomy - only marginally improves perinatal survival
  - Fetoscopic-directed laser ablation of the anastomoses between the placental circulations of the twins resulted in an overall perinatal survival of 70%
  - Laser therapy is now considered the standard of care in this condition.

Prognosis

- Etiology of hydrops defines outcome
- Survival rate between 30% and 40%
- Predicting factors:
  - Detection before 24 weeks - survival rate after exclusion of chromosomal abnormalities was 31%
  - Detection after 24 weeks' gestation - 48%
  - Apgar score at 5 minutes of less than 5 – O% survival
  - major pleural effusions – poor survival
  - Fetuses who developed pleural effusions after 29 weeks' gestation and who delivered after 31 weeks' gestation were more likely to survive (related to pulmonary hypoplasia)
- Few studies on long-term outcome in NIHF:
  - One small series of 19 infants that survived to 1 year of age:
    - 15% had severe psychomotor delay
    - An additional 10% exhibited mild mental retardation

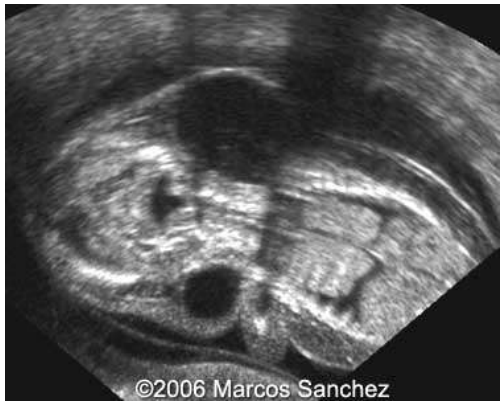
Cystic Hygroma

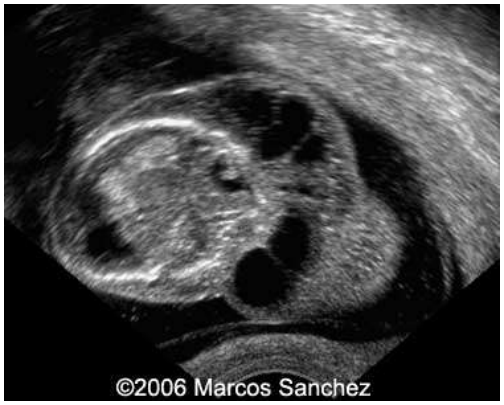
- Septated cystic hygroma – enlarged NT space, covers entire fetus, with septations
- Typically NT>4mm
- Anomaly of the lymphatic system: single or multiple cysts within the soft tissue
- Mostly nuchal: axillary, or anterior neck
- Generalized lymphatic obstruction (drains into jugular lymphatic sac)



Cystic Hygroma

- 1/250 in at 11-14 weeks
- 50% aneuploidy:
  - 1st tri: Trisomies:
    - mostly 21, 18
  - 2nd tri: Turner

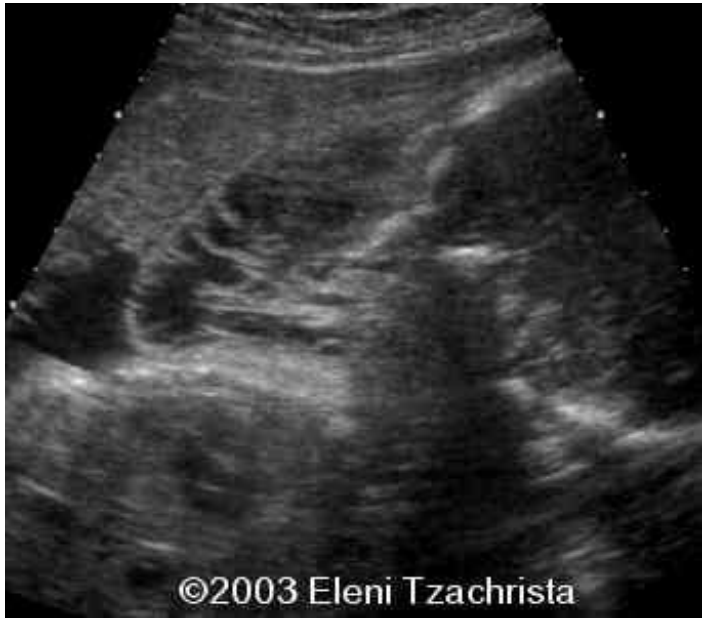




- Euploid
  - AR trait
  - Genetic and nongenetic syndromes: Noonan, familial pterygium colli, fetal alcohol syndrome
  - 50% associated major malformation, mostly cardiac or skeletal dysplasias
- Septated vs. increased NT: *5 aneuploidy, *12 cardiac defects, *6 fetal or neonatal demise

Cystic hygroma - DD

– Anterior:
  - Thyroglossal duct cyst, branchial cleft cyst, bronchogenic cyst, hamartomas
– Posterior:
  - Encephalocele, meningocele

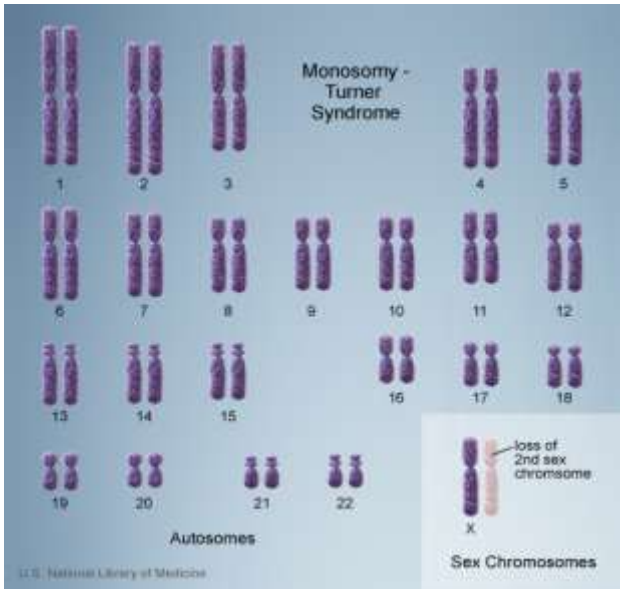


Cystic Hygroma

- Prognosis:
  - depends on age, associated anomalies or hydrops
- Diagnosis at 11-14 weeks:
  - 17% intact survival only
- Diagnosis at midtrimester:
  - Mortality almost 100%
- Counselling:
  - Karyotype (CVS or amnio)
  - If normal:
    - detailed anomaly scan
    - Fetal echo at 18-20 weeks
  - Counsel similarly if NT > 3mm

Turner syndrome

- 45 XO, Monosomy X
- 5/10000 live born females
- ¼ of spontaneous abortions caused by chromosomal abnormalities
- Etiology:
  - Absence of paternal chromosome
  - 8-16% - mosaic
- Dilatation of the jugular lymphatic sacs
- Spont remission of cyst leads to webbed neck

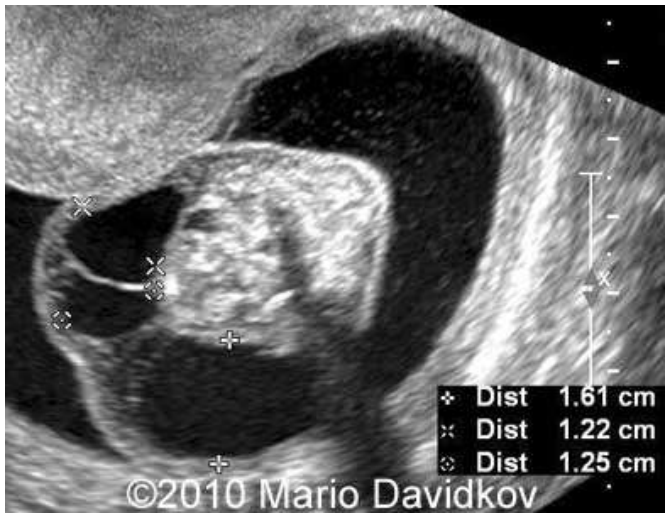


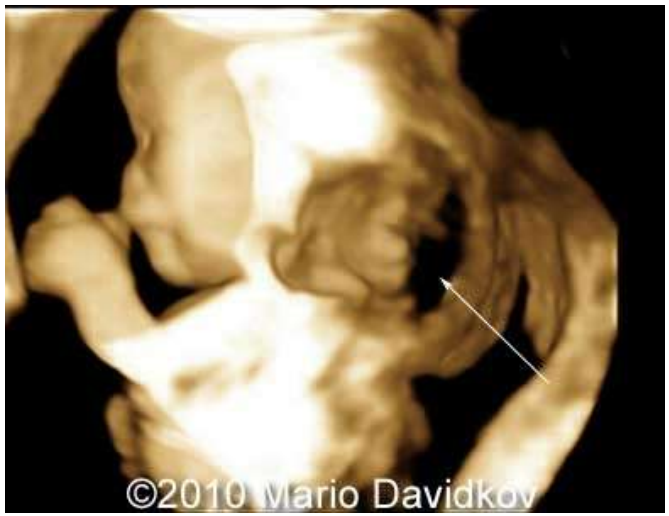
Turner syndrome

- Lymphedema (hands and feet), anasarca, hydrops, short cervical spine, IUGR, short neck, prominent auricles, horseshoe kidney, heart defects (coarctation (44%) and bicuspid aortic valve), tachycardia, bone dysplasia, short stature
- 90% - Ovarian dysgenesis – causing infertility
- Mental and developmental retardation - variable

Turner syndrome

- Prognosis:
  - IUFD (hydrops)
  - Mosaicism – better prognosis
  - May remain undiagnosed if discrete
- Sporadic
- Karyotype and decide



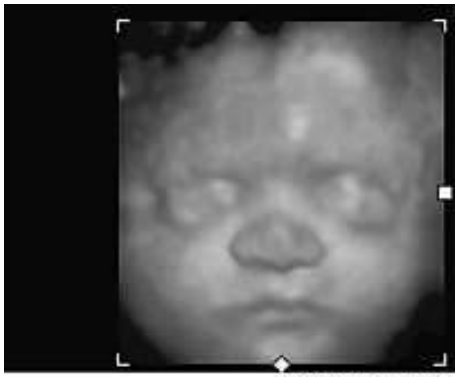


Noonan syndrome

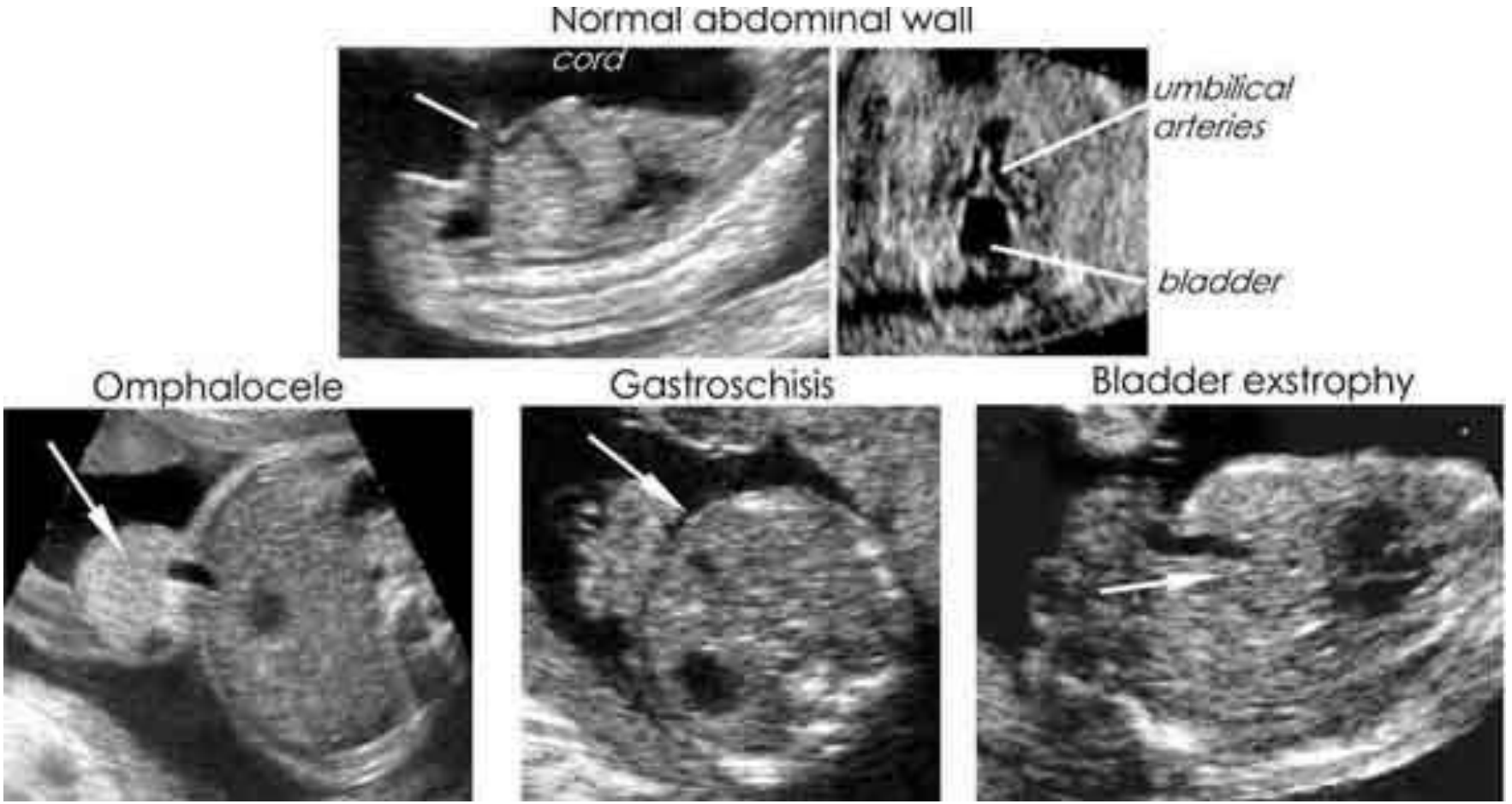
- “Turner synd with normal karyotype”
- 4-10/10000
- AD, sporadic new mutations
- Posterior nuchal cystic hygroma – first finding
  - May regress later
- 50% can be detected genetically: chr 12 long arm, PTPN11 gene
- Strong family history
- 5% recurrence when parents normal
- Diagnosis may lead to TOP

Noonan syndrome

- Cystic hygroma – 42%, Increased NT and hydrops – 33%
- Facial features:
  - Low-set ears, depresses nasal bridge, large head, broad webbed neck
- Congenital heart disease: 60%
  - PS (19%), hypertrophic cardiomyopathy (25%), ASD (10%)
  - Cardiac and cervical abnormalities
  - Pers. RUV, ductal agenesis with iliac connection
- Pleural effusions
- Renal abnormalities
- Polyhydramnios – 58%
- Short stature, borderline femurs

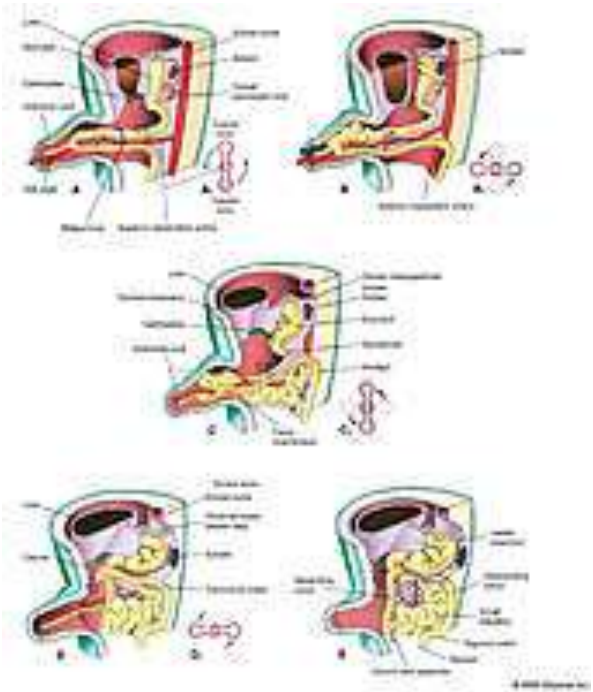


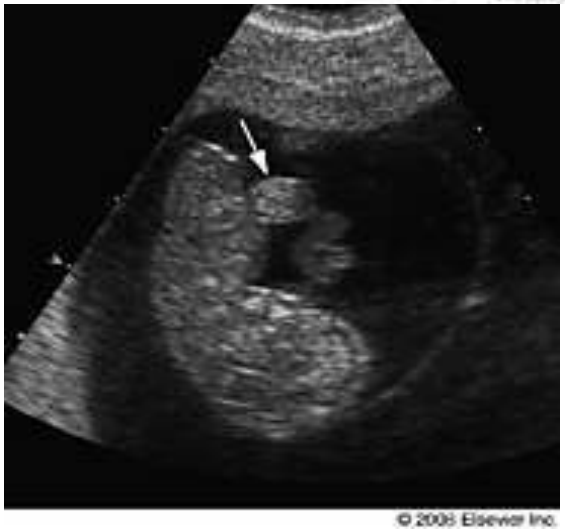
Abdominal wall defects



Physiologic midgut herniation

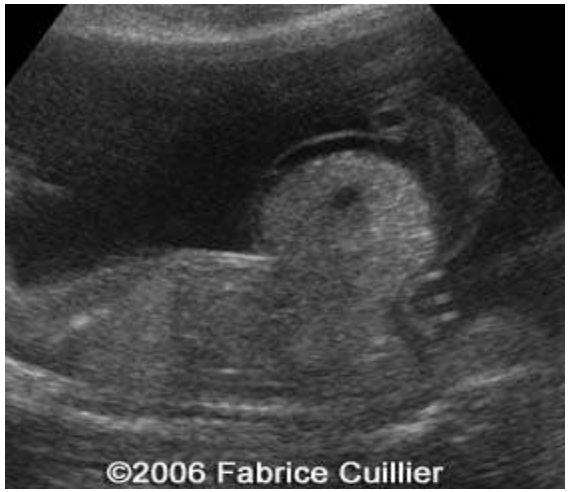
- Rapid elongation of the gut and its mesentery
- Simultaneous marked growth and expansion of the liver occurs
- Intestinal loops enter the extra-embryonic coelom in the umbilical cord
- Physiologic midgut herniation takes place during the 6th week of development
- Reduction of the midgut hernia - intestine returns into the abdominal cavity - 10th week
- Is completed by week 12





Omphalocele

- Defect in the ventral abdominal wall
- Herniated intra-abdominal content covered by a membrane consisting of peritoneum and amnion
- Herniated viscera: Most common - small bowel; Less common - liver, spleen, stomach, and large bowel
- Moderate to large omphaloceles - liver usually present
- 1/5800

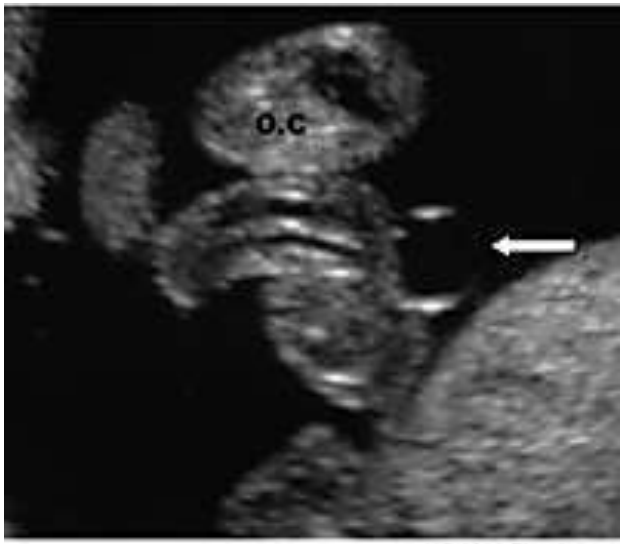


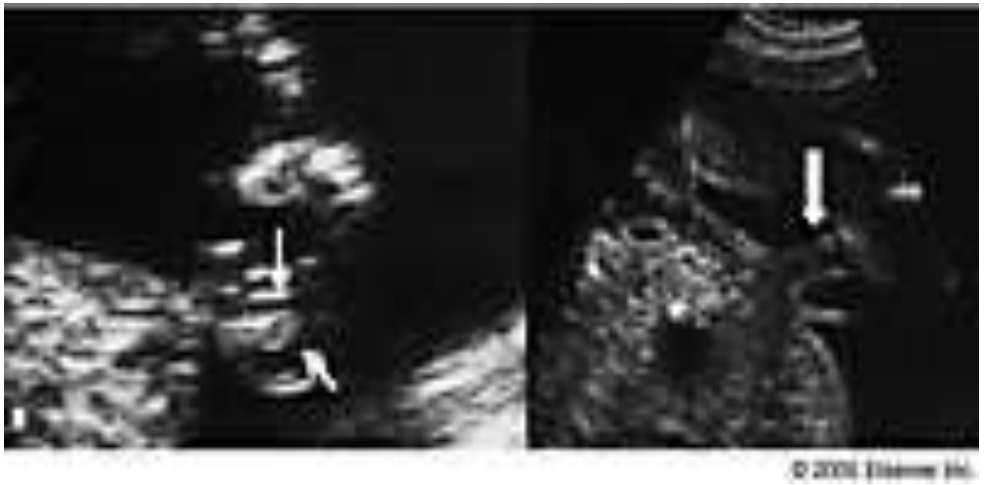
Omphalocele

- **Associated anomalies:**
- 67-88%
- Cardiac – 50%
- GI – 40%
- Chromosomal (13,18,21, sex chr) – 30-40%
- Karyotype abnormalities more common in bowel omphalocele
- 58 different syndromes:
  - Pentalogy of Cantrell
  - Beckwith - Wiedemann
- Most cases - sporadic

Omphalocele

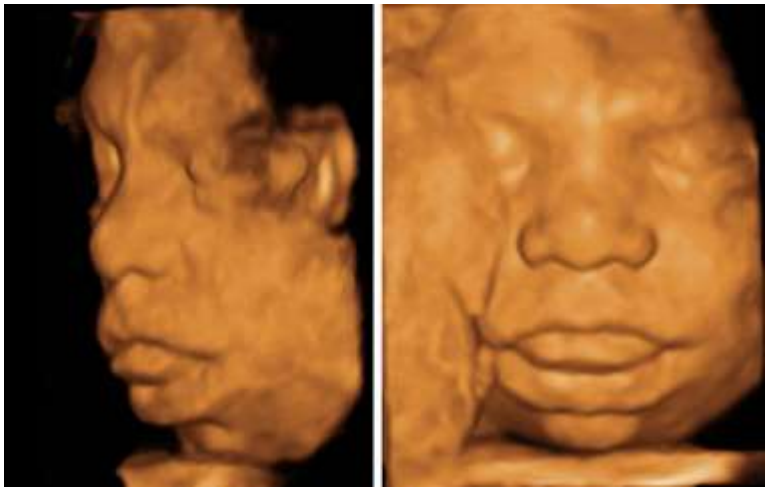
- **Prognosis:**
- Associated structural and chromosomal anomalies
- Nonisolated omphalocele – poor prognosis
- Isolated omphalocele – good prognosis with normal quality of life

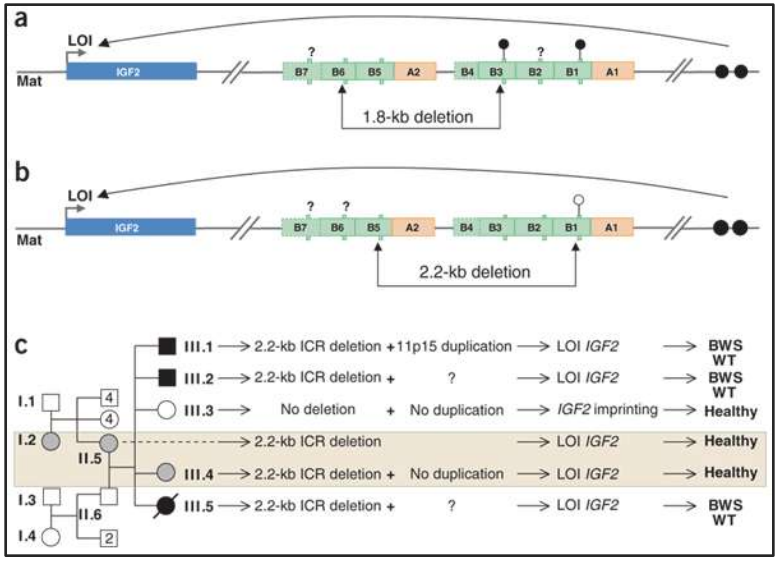




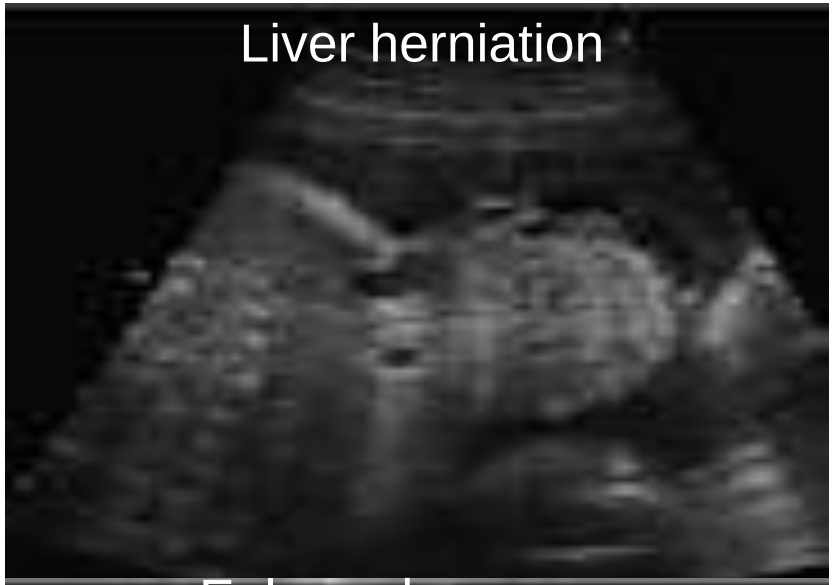
Omphalocele and Beckwith-Wiedemann Syndrome

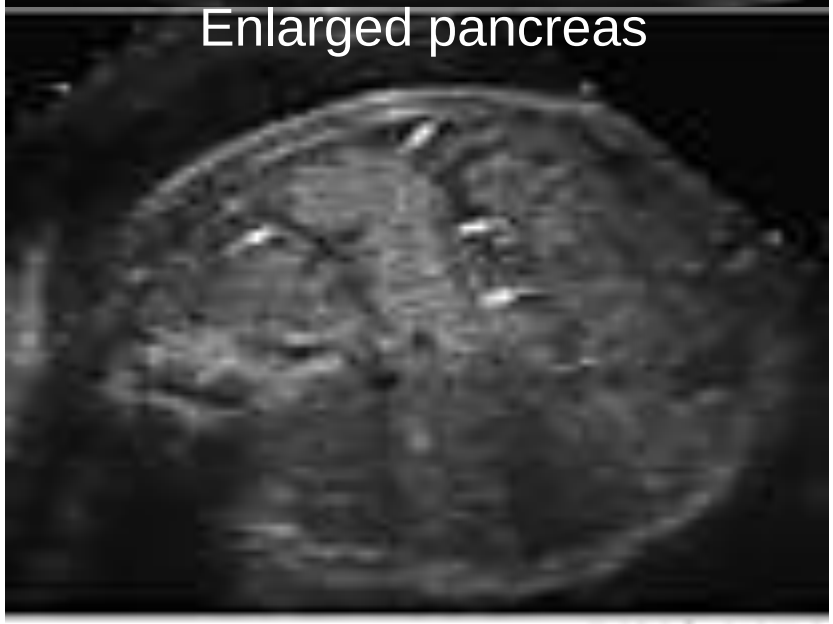
- 10% to 22% of isolated cases
- Macroglossia, organomegaly, cystic enlarged pancreas, abnormal kidneys, macrosomia, microcephaly, placental dysplasia
- Can manifest after delivery
- Careful ultrasound follow-up throughout gestation
- Follow up fetuses with omphalocele after birth (ultrasound of kidneys and adrenals) - to exclude Wilms' tumor and adrenal tumors

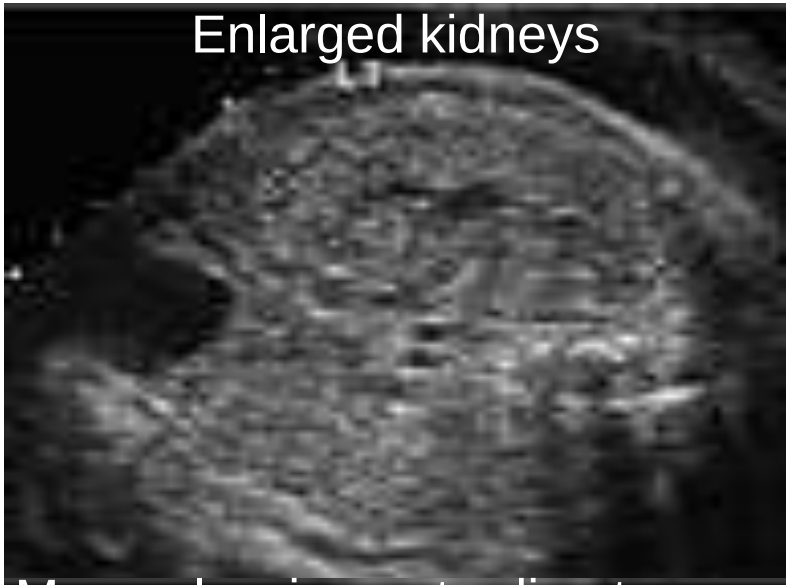




Omphalocele and Beckwith-Wiedemann Syndrome







Differential Diagnosis of Omphalocele

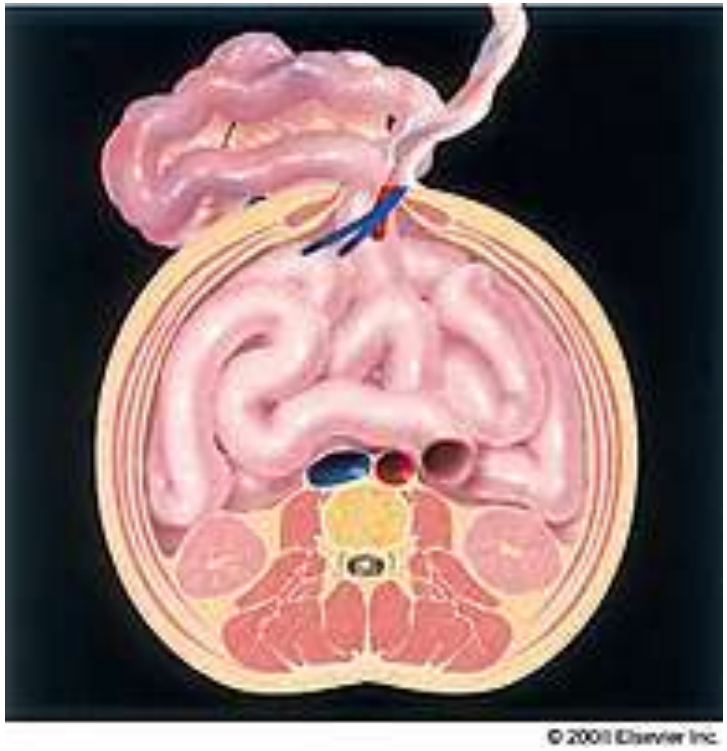
- 1. Gastroschisis
- 2. Midline disruption sequence
- 3. Physiological midgut herniation. Only omphaloceles containing liver may be diagnosed in the first trimester
- 4. Umbilical cord cyst, edema, lymphangioma, or calcified Wharton jelly
- 5. Umbilical hernia

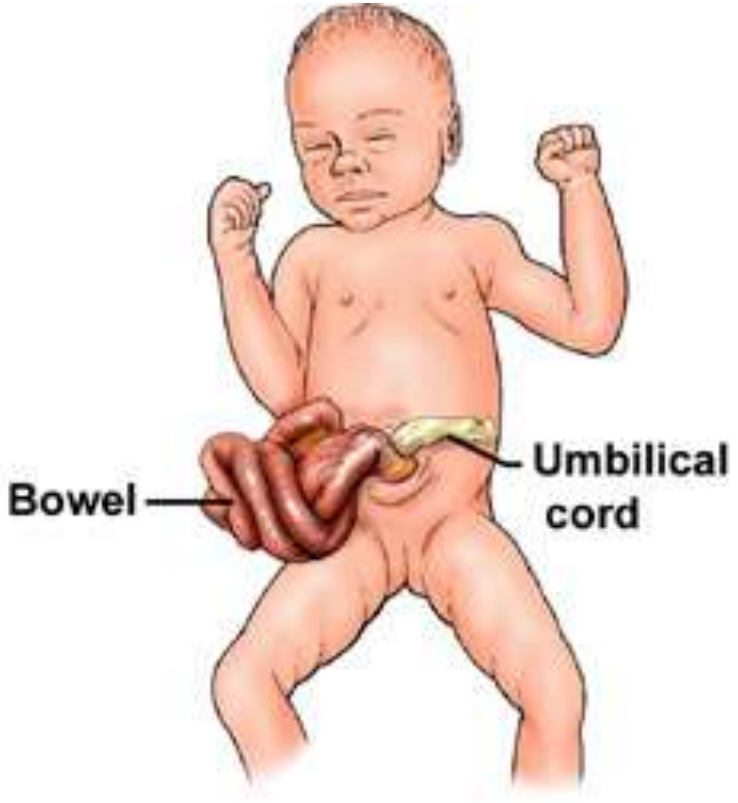
Gastroschisis

- Paraumbilical defect
- Right sided (left-sided rare)
- Small bowel (occasionally stomach, rarely - liver, spleen)
- No covering membrane
- Direct exposure to amniotic fluid (peritonitis)

- 1.75-2.5/10000 live births, sporadic, males>females
- Associations:
  - Low socio-economic status
  - Maternal age < in omphalocele
  - Substance abuse, smoking, chemicals
  - Geographical (UK>Hawaii>Japan)
- Increased incidence recent years
- Rare familial clusters: autosomal inheritance, variable expression (3.5%)

Gastroschisis





Herniation to the right of the cord

Gastroschisis

- **Pathogenesis:**

- 1. Disruption right terminal branch SMA (extraembryonic coelom of body stalk) → ischemia and necrosis → secondary paraumbilical defect

- 2. Failure right UV to involute (28-32 days gestation - 42-47 LMP → vessel compromise, para-umbilical necrosis of mesoderm and ectoderm

Gastroschisis

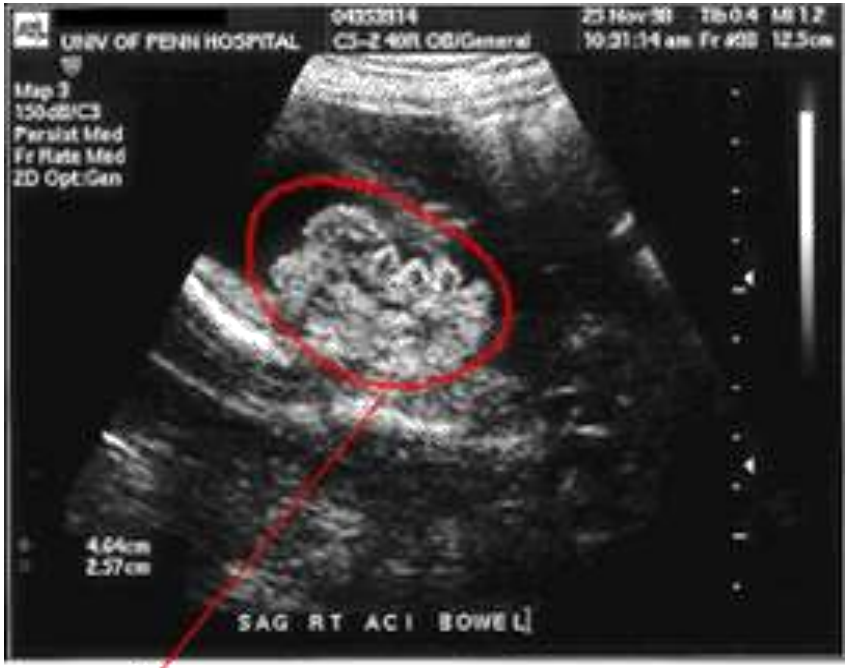
- Rare associated anomalies:
  - **Related to bowel herniation:** hypoperistalsis, malrotation, ischemia, atresia (10-20%), intussusception and volvulus
  - **Not related:** anencephaly, cleft lip/palate, ASD, ectopia cordis, CDH, scoliosis, syndactyly, amniotic band
- Chromosomal – 0-3%
- France>Japan>UK

Gastroschisis

- **Prognosis:**
- Good because no other anomalies
- Survival (tertiary center) 80-90%
- Mortality < 10% (weight>2500)
- 10% - hypoperistalsis syndrome
- Prognostic factors:
  - Prematurity
  - Degree of bowel inflammation

Gastroschisis

- **Prenatal diagnosis:**
- Increased MSAFP
- Routine anomaly scan (from 12 weeks)
  - Detection rate – 76-90% (100%)
- Normal cord insertion
- Not covered
- Oligohydramnion > polyhydramnion
- IUGR – 60%
- Cauliflower-like intestinal loops floating freely in the amniotic fluid



Fetal ultrasound showing bowel protruding from abdominal wall defect.

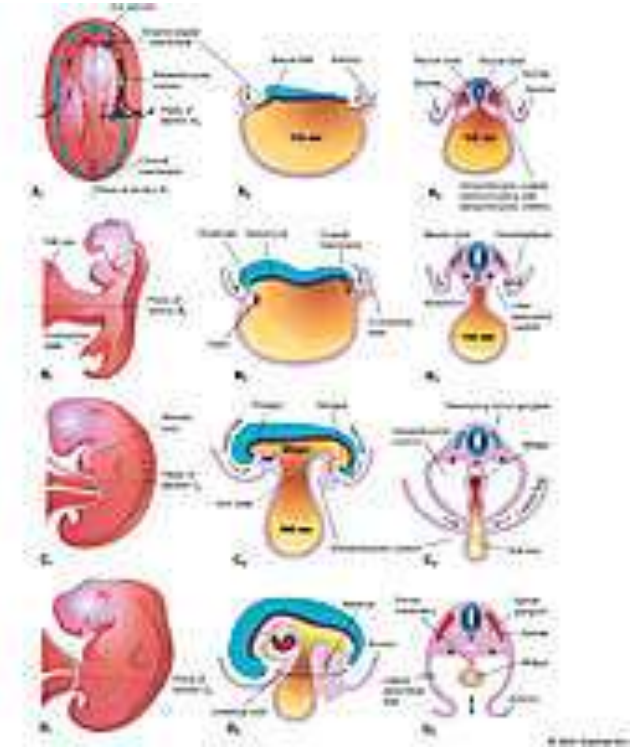
Gastroschisis

- Fibrous coating may develop
- Amniotic fluid > 30 weeks – decreased osmolality, decreased Na concent (potassium, urea, creatinine increase)
- Ischemia and atresia, edema and dilatation, short bowel syndrome
- Variable degree of bowel thickening and intraluminal meconium

- Polyhydramnios (bowel perforation), usually oligohydramnion (cord compression)
- Follow-up:
  - Bowel complications
  - Fetal well-being
  - Plan delivery/prematurity
  - Consult pediatric surgeon
- Mode of delivery – controversial (AJOG 1996;174:540-6)

Midline Disruption Sequence

- 4th week of gestation- folding from a flat germ disc into a three-dimensional structure
- Cephalic, lateral, and caudal edges are brought together along the ventral midline
- Endodermal, mesodermal and ectodermal layers fuse to the corresponding layer on the opposite side
- The of the amnion, amniotic sac encircles the fetus

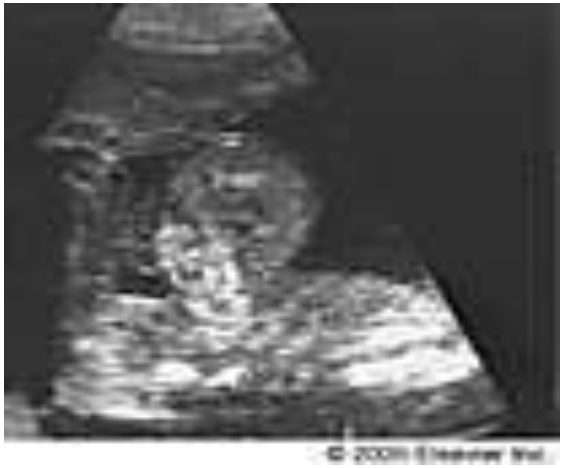


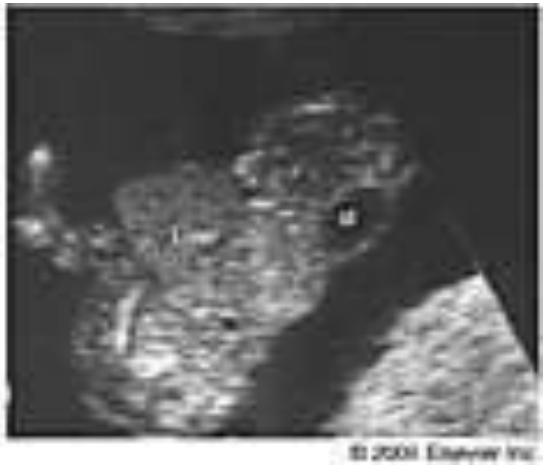
Midline Disruption Sequence

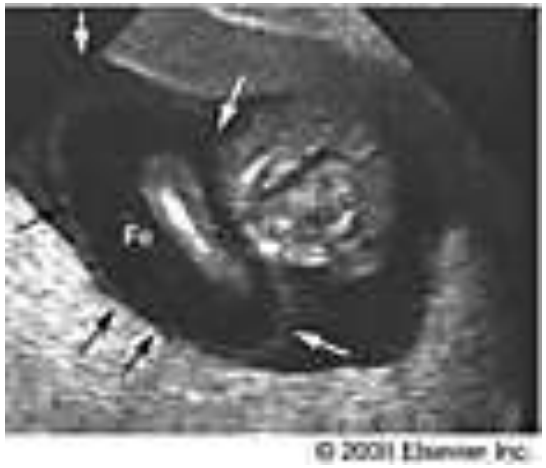
- A defect in these embryologic processes results in fetal anomalies
- Extent of malformation depends on the time of insult and size of damaged embryonic zone
- Evisceration of many abdominal organs is expected if large abdominal wall defect
- Improper closing of the amnion, part of the eviscerated organs will be located outside the amniotic sac
- Malformations observed in other structures may involve the limbs, lower urinary system, cloaca, and external genitalia.

Midline disruption sequence

Pentalogy of Cantrell
Thoracoabdominal eventration
Thoracoabdominal syndrome
Limb body-wall complex
Limb body-wall deficiency syndrome
Body wall defects with limb-reduction anomalies
Body stalk anomaly
Fissure of the abdominal wall with eventration of the abdominal organs
Dysplasia umbilicofetalis



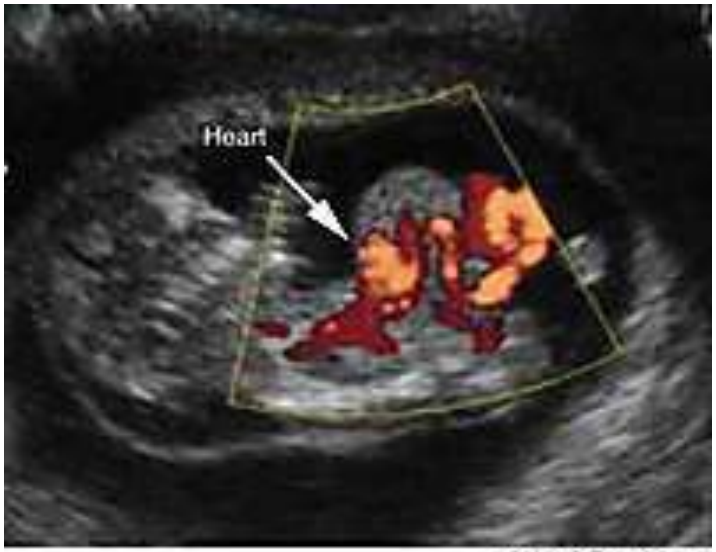


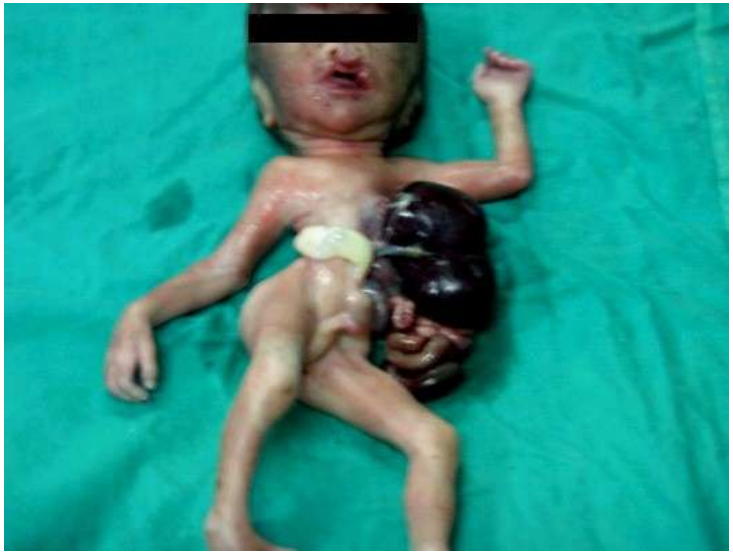


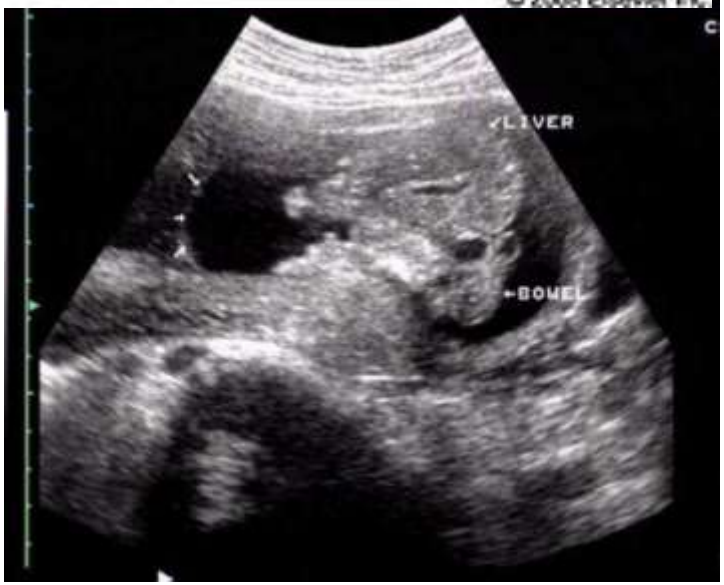
Pentalogy of Cantrell

- Consists of:
  - Midline, supraumbilical abdominal wall defect
  - Defect of the lower sternum
  - Deficiency of the anterior diaphragm
  - Defect in the diaphragmatic pericardium
  - Cardiac anomalies – ectopia cordis
- Prevalence: 0.1-0.5/10000 live births
- Abnormalities in the differentiation of the intraembryonic mesoderm at approximately 14 to 18 days after conception

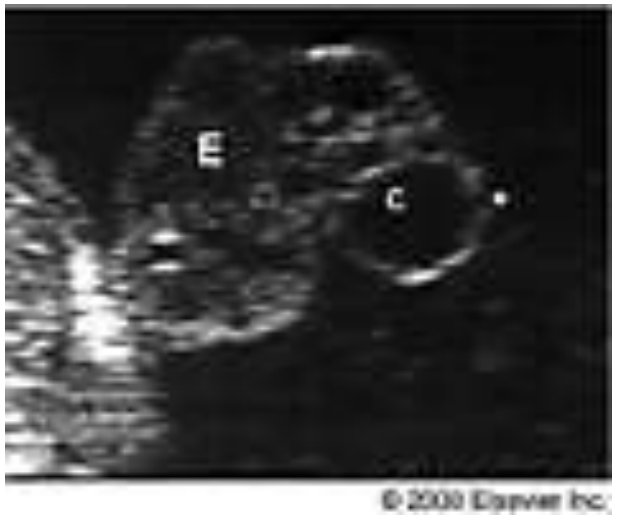
Pentalogy of Cantrell



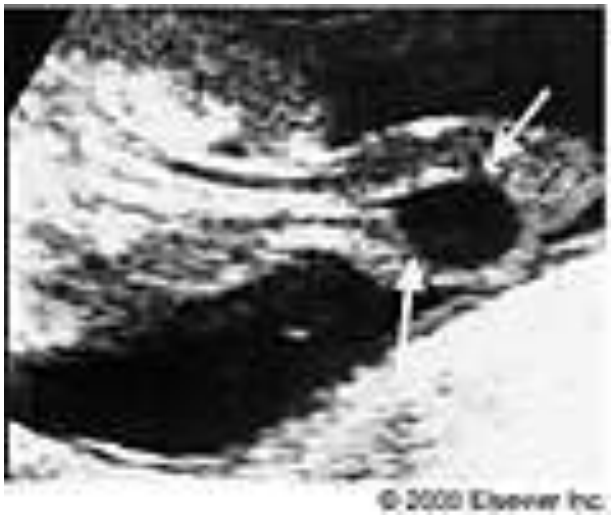




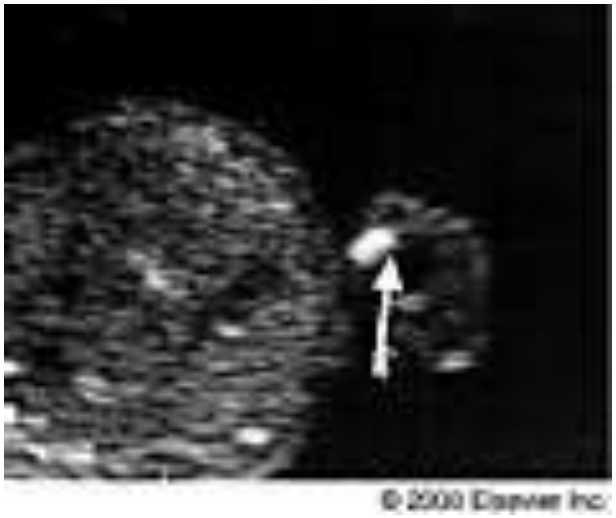
Umbilical cord



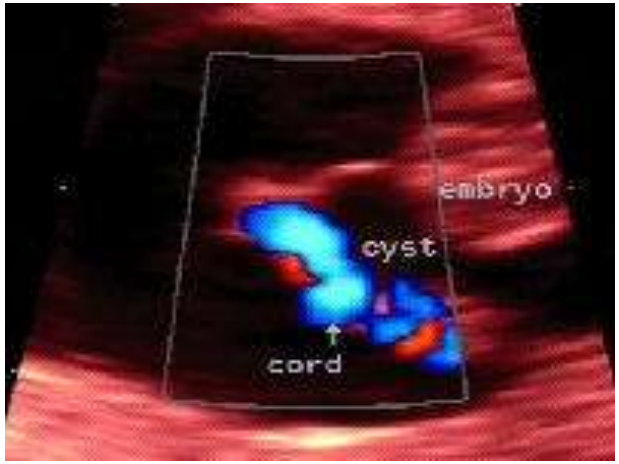
Edematous cord with cyst



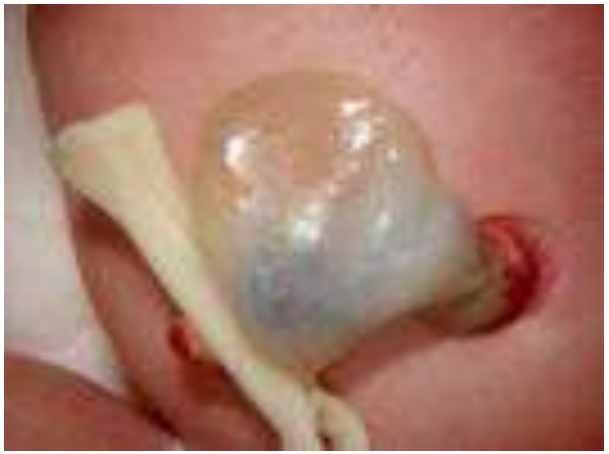
Umbilical cyst



Cyst with calcified focus



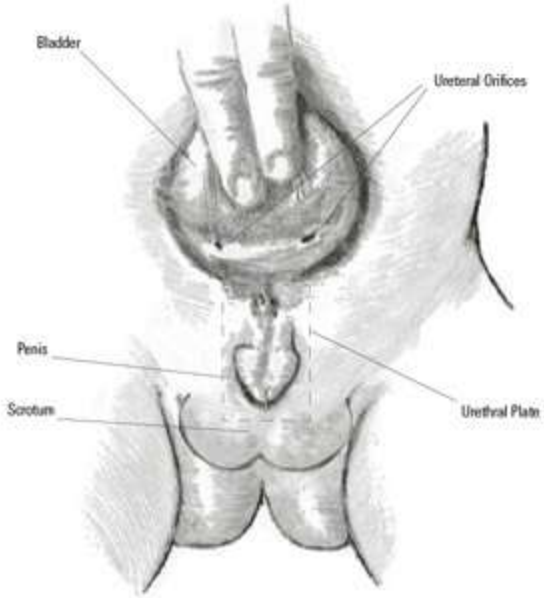
Umbilical cyst

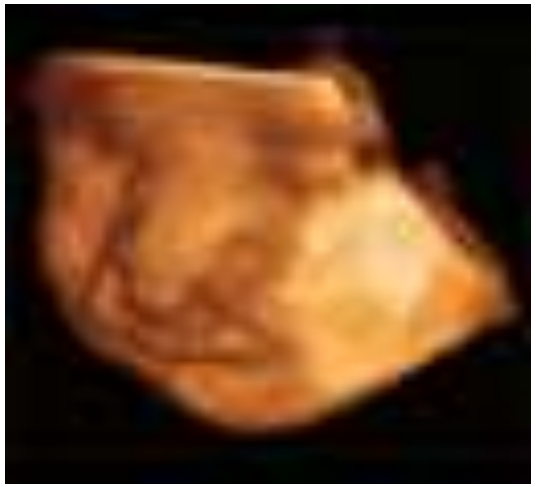


Wharton’s jelly cyst

Bladder exstrophy

- Absent anterior bladder wall
- Posterior bladder wall exposed externally into the amniotic cavity
- Incomplete closure of the anterior lower abdominal wall
- Incidence: 0.25-0.5 to 10,000 births
- Males 2:1 female
- Associated anomalies:
  - partial agenesis of pubic bones
  - pubic bones diastasis
  - Epispadia
  - absence of the urethra, clitoris
  - deformities of the vagina or uterus.





Bladder exstrophy

- Etiology: genetic and environmental factors
- Management: surgical
- DD:
  - Other anterior abdominal wall defects, such as gastroschisis, omphalocele and cloacal exstrophy
  - Gastroschisis and omphalocele have both present urinary bladder which fills normall
  - When bladder is not visualized (without oligohydramnios or other renal abnormalities) consider bladder extrophy

Ultrasound findings

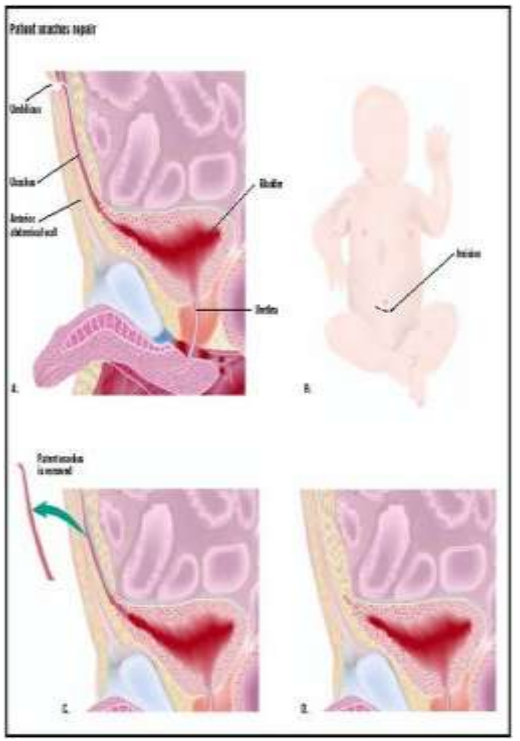
Lower abdominal wall defect with protruding abdominal mass
Absence of the normally filled urinary bladder
No sign of oligohydramnios or other gross renal abnormalities
Color Doppler shows umbilical arteries alongside the abdominal wall mass
External genitalia malformation

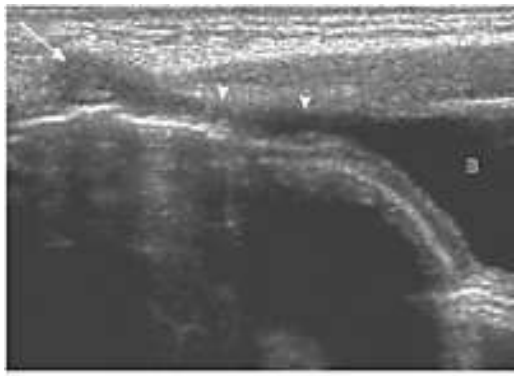
Cloacal Exstrophy Sequence

- OEIS complex:
  - Omphalocele
  - Extrophy of bladder
  - Imperforate anus
  - Spinal anomalies
- Sonographic findings:
  - Nonvisualization of the bladder
  - Anterior abdominal wall defect or cystic mass protruding from the anterior abdominal wall
  - Omphalocele
  - Skeletal anomalies
  - Abnormal genitalia

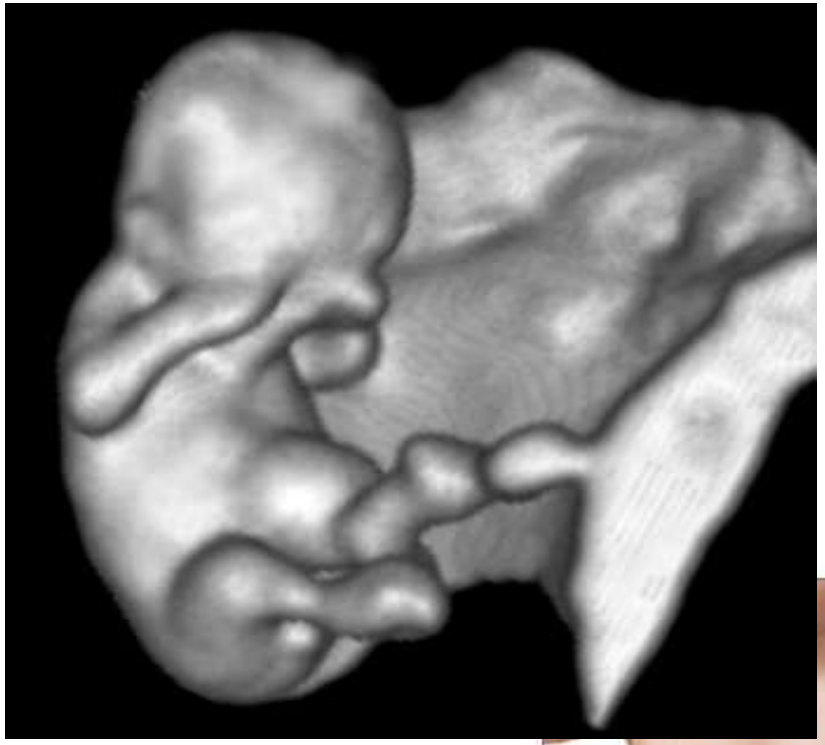
Vesicoallantoic Cyst/Patent Urachus

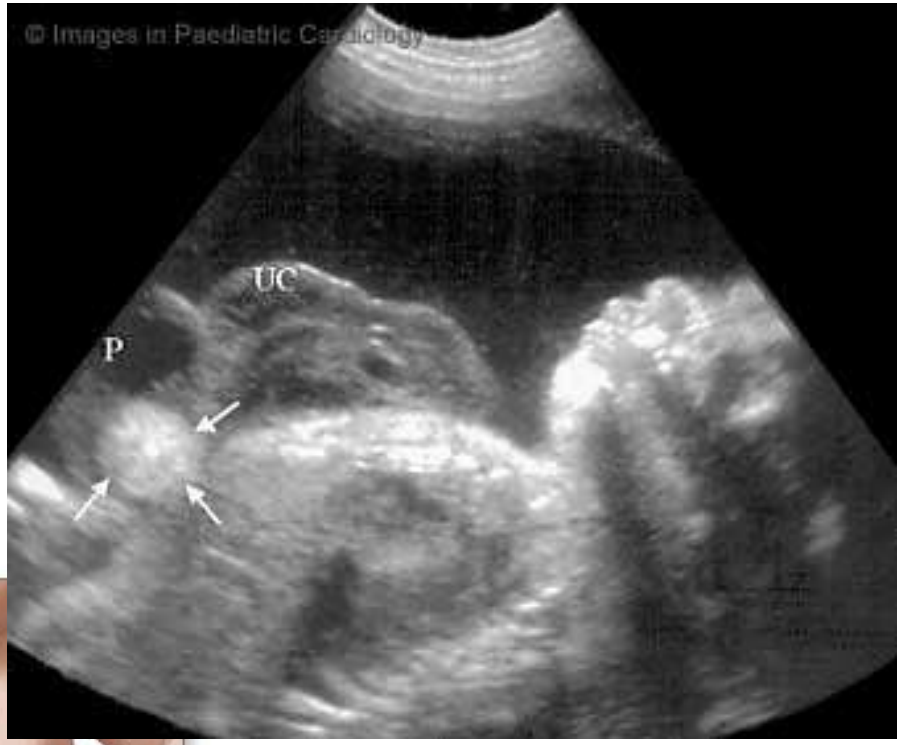
- Cystic structure connecting to the fetal urinary bladder
  - Allantois - diverticulum from the yolk sac
  - Becomes incorporated into the embryo, connecting the ventral aspect of the urogenital sinus to the external portion of the umbilicus
  - Urachus - remnant of the allantois
  - The lumen of the allantois obliterates and the urachus closes to form the median umbilical ligament
- Incidence of 1- 2.5/100,000
- Presence of a fluid-filled mass in direct communication with the fetal urinary bladder, as well as the absence of bowel contents, allows one to discriminate between the two
- Prognosis: Better than omphalocele

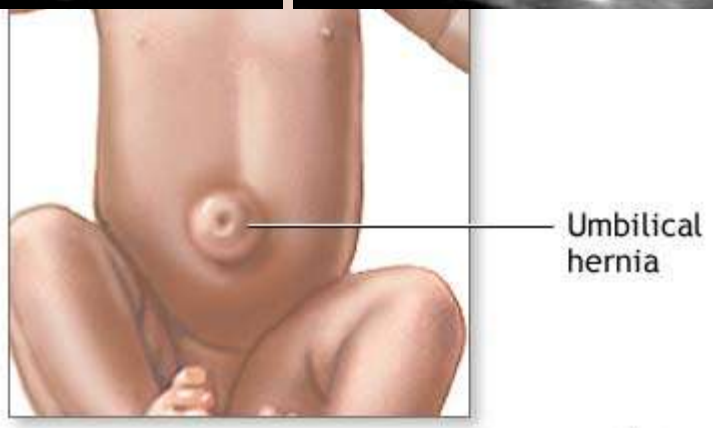




Umbilical hernia







DD – abdominal wall defects

I. Bowel involved		
A. Contained in sac	→	Omphalocele, unless
1. Large defect, no separate cord, fetal scoliosis	→	Body stalk anomaly
2. Bladder persistently not seen, neural tube defect present	→	Cloacal exstrophy
B. Not contained in sac—cord to left side	→	Gastroschisis, unless
1. Liver involved	→	Probable ruptured omphalocele
2. Malformations other than bowel	→	Probable ruptured omphalocele
(Dilated bowel loops are consistent with obstruction and imply gastroschisis.)		
II. Solid mass		
A. Smooth border		
1. Large	→	Probably omphalocele with liver
2. Relatively small with umbilical vessels, no bowel	→	Umbilical cord
B. Irregular border, below umbilicus	→	Bladder exstrophy
III. Large septate cystic mass in lower abdomen or pelvis; neural tube defect present	→	Cloacal exstrophy

תודה רבה

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