Nonimmune hydrops fetalis

Lylach Haizler-Cohen, MD
Maternal Fetal Medicine and Medical Genetics
Fetal Health Center

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UMKC School of Medicine

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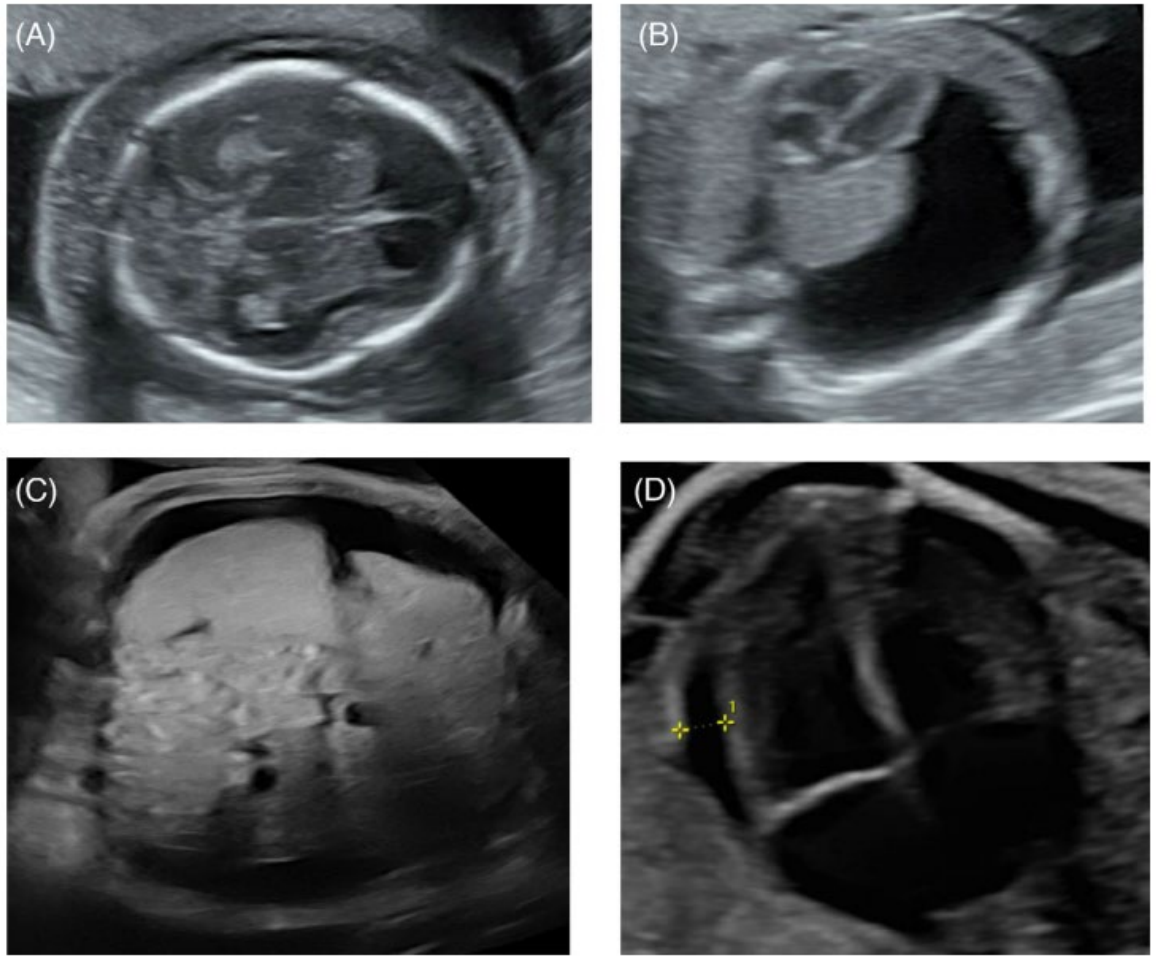
Definition

- Fluid accumulation in at least two fetal compartments:
  - Pleural effusion
  - Pericardial effusion (>3mm)
  - Ascites
  - Skin edema (>5 mm)
- Associated findings but not in formal diagnostic criteria:
  - Placental thickening
  - Polyhydramnios



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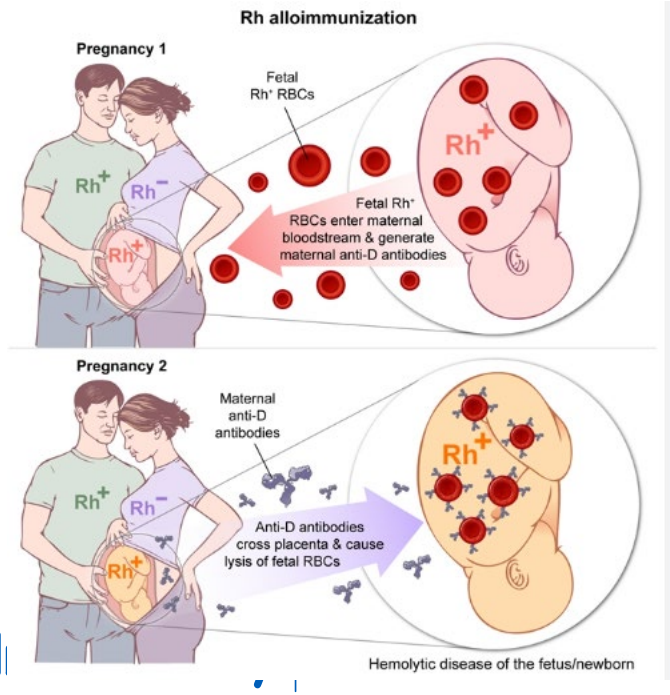
Types of fetal hydrops

Immune hydrops fetalis

Caused by red blood cell alloimmunization



Nonimmune hydrops fetalis (NIHF)

Not caused by red blood cell alloimmunization.

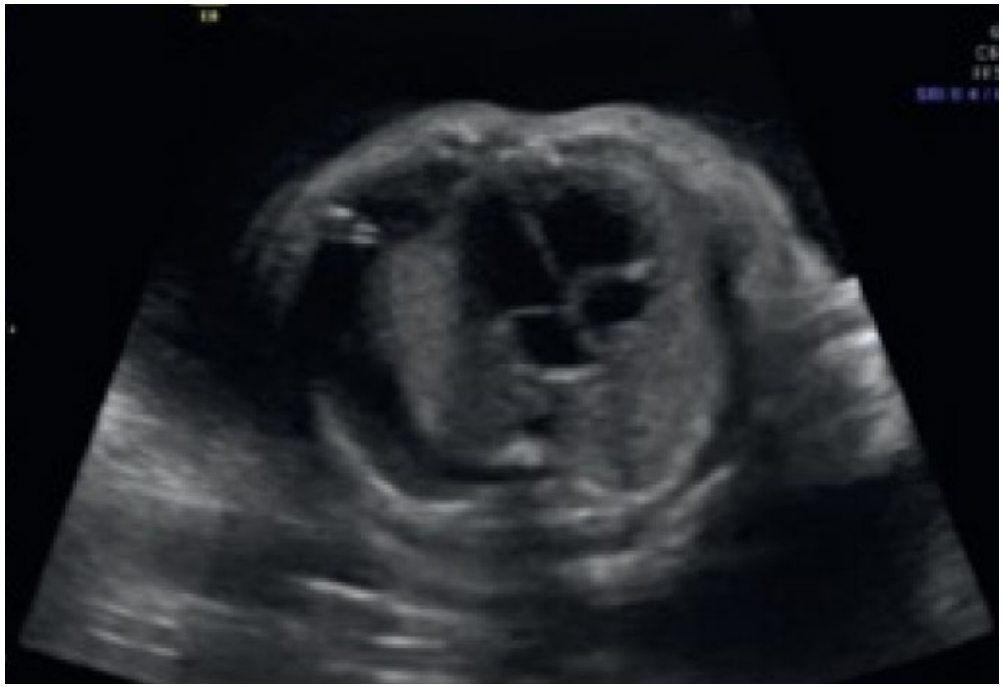
Accounts for **90%** of all fetal hydrops cases

Incidence of NIHF

- 1 in 1700-3000 pregnancies
- 1 in 4000 live births
- Prevalence is likely higher with more advanced sonography

What if there is only one fetal effusion?

- New terminology: **NIHF spectrum**
- Monitor for progression to NIHF
- Underlying causes and diagnostic evaluation is the same as NIHF
- Management, prognosis and outcomes are different among isolated effusion and NIHF
  - varies depending on the underlying etiology, severity of effusion and gestational age at diagnosis and birth



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Pathogenesis of NIHF

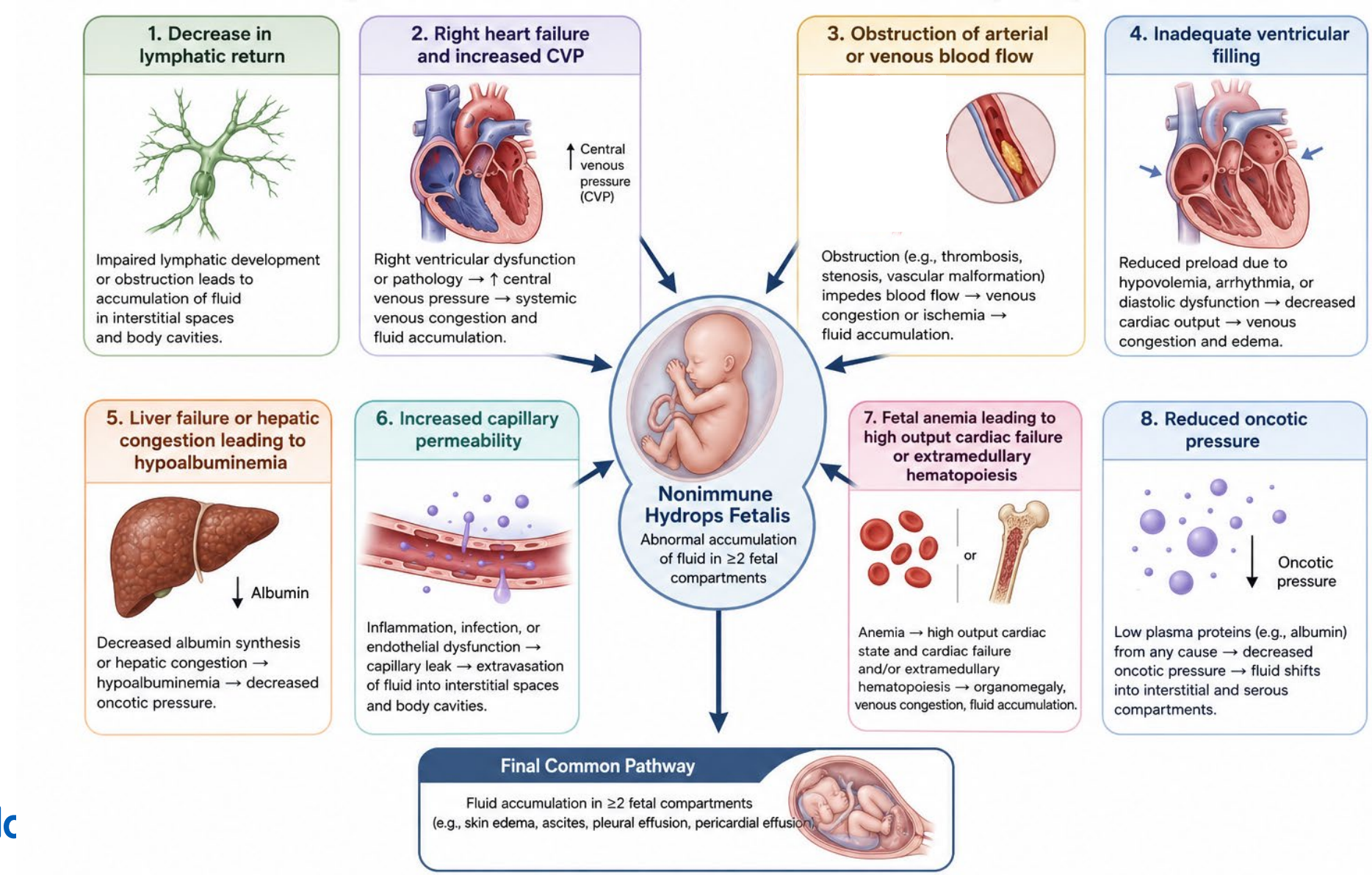

Table 11 Types of hemodynamic derangement caused by fetal conditions

Hemodynamic derangement	Fetal condition	Common abnormalities detected by echocardiography
High–cardiac output lesions[73-75]	• Arteriovenous malformation • Agenesis of ductus venosus • Fetal anemia • TRAP • TTTS • Vascular masses/tumors	• Elevated CCOi • Cardiomegaly (CTAR) • AV valve regurgitation • Abnormal or normal vein Doppler • LV/RV systolic dysfunction • Hydrops
Increased preload (volume overload)[76,77]	• AVSD with severe AV valve regurgitation • Complete AV block • TOF/absent pulmonary valve	• Elevated MPI • Systolic dysfunction • Abnormal venous Doppler • Cardiomegaly (CTAR) • Hydrops
Increased afterload lesions[78,79]	• Bilateral semilunar valve stenosis including truncal valve stenosis • Constriction of the ductus arteriosus • TTTS	• Elevated MPI • AV valve regurgitation • Diastolic dysfunction • Abnormal venous Doppler • Hydrops
Cardiac compression (decreased preload)[75,80-82]	• CDH • CHAOS • CPAM	• Low CCOi • Abnormal tricuspid inflow and/or venous Doppler (CHAOS, CPAM) • Hydrops • Left heart compression, reduced LV stroke volume (CDH)

Causes of NIHF

NIHF is a **fetal phenotype** with a variety of underlying causes.

TABLE 1 Approximate frequency of structural fetal anomalies, placental abnormalities, genetic syndromes, and infections among pregnancies with non-immune hydrops fetalis [24, 27, 30].

Etiology of non-immune hydrops fetalis	Proportion[a]
Multiple anomalies/syndromic/genetic[b]	19%–53%
Cardiovascular anomalies	8%–20%
Lymphatic dysplasia	6%–10%
Infection	7%–8%
Pulmonary/thoracic anomalies	5%–6%
Twin-twin transfusion syndrome	4%–5%
Placental chorioangioma	2%
Hematological condition	0%–10%
Genitourinary anomalies	0%–2%
Gastrointestinal condition	0%–1%
Extra-thoracic tumor	0%–1%

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1. Multiple anomalies/genetic disorders

Not detected with CMA. Exome/genome sequencing (preferably) or gene panels are needed.

TABLE 2 Approximate frequencies of genetic disorders underlying pregnancies with non-immune hydrops fetalis spectrum [16, 24, 26, 27, 29, 40, 41].

Fetal genetic disorder	Proportion[a]
Aneuploidy	13%–30%
RASopathies	7%–8%
Inborn errors of metabolism	1%–5%
Other congenital lymphatic anomalies	2%–4%
Akinesia/neurologic disorders	2%
Musculoskeletal disorders	1%–3%
Hereditary anemias	1%–2%
Cardiovascular disorders	1%
Mitochondrial disorders	<1%
Immunologic disorders	<1%
Ciliopathies	<1%
Other	2%–4%

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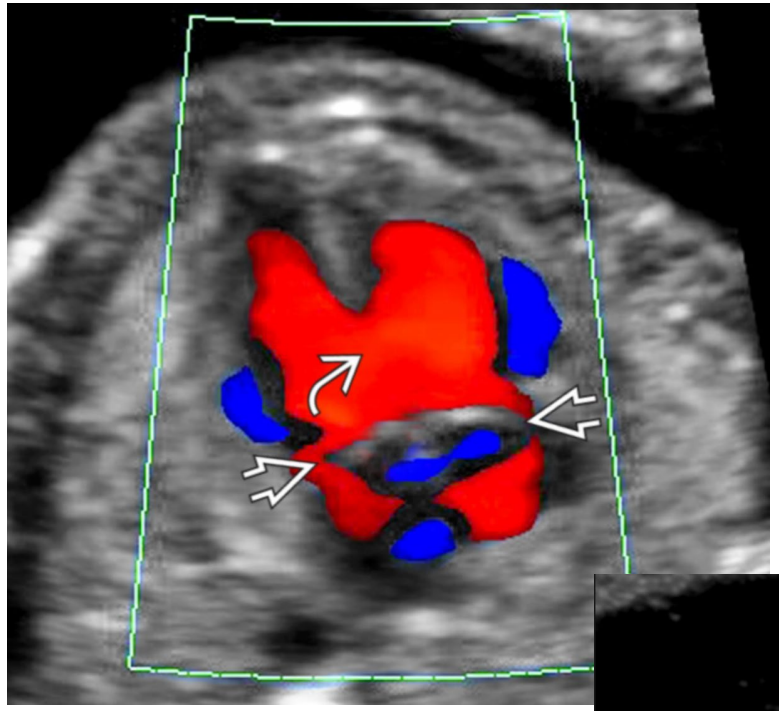
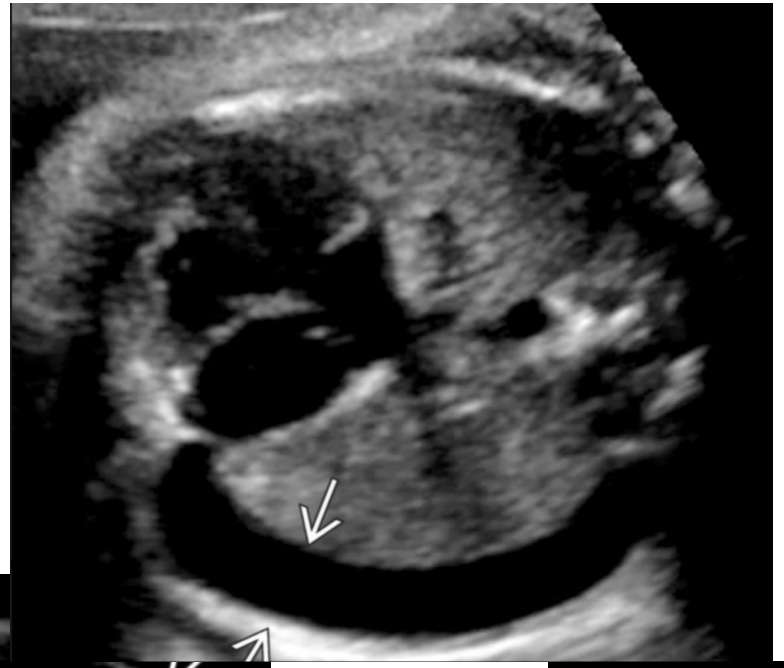
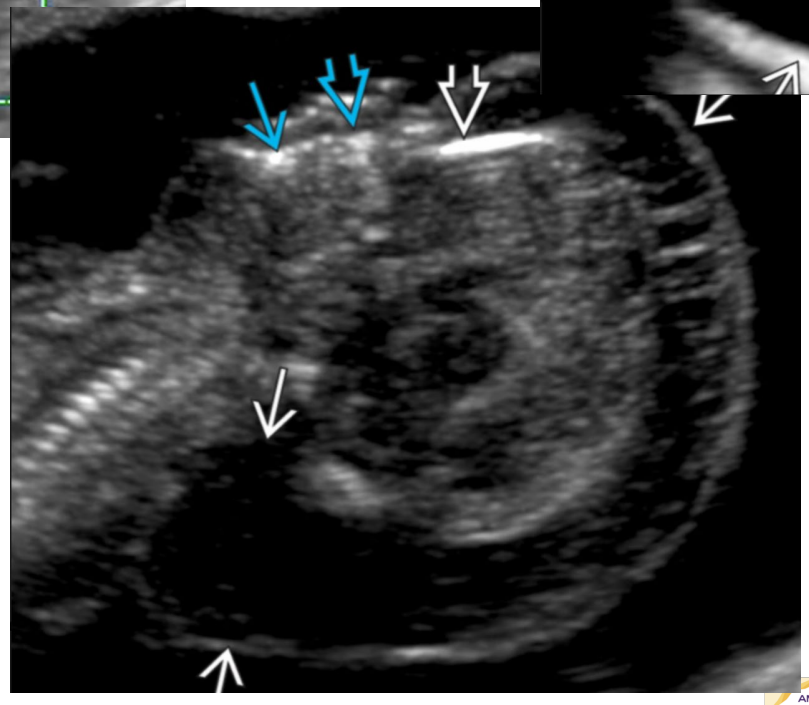
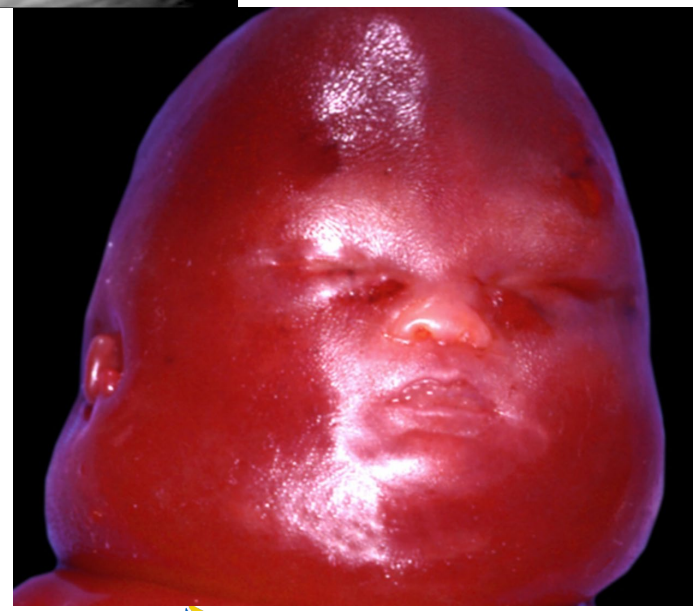
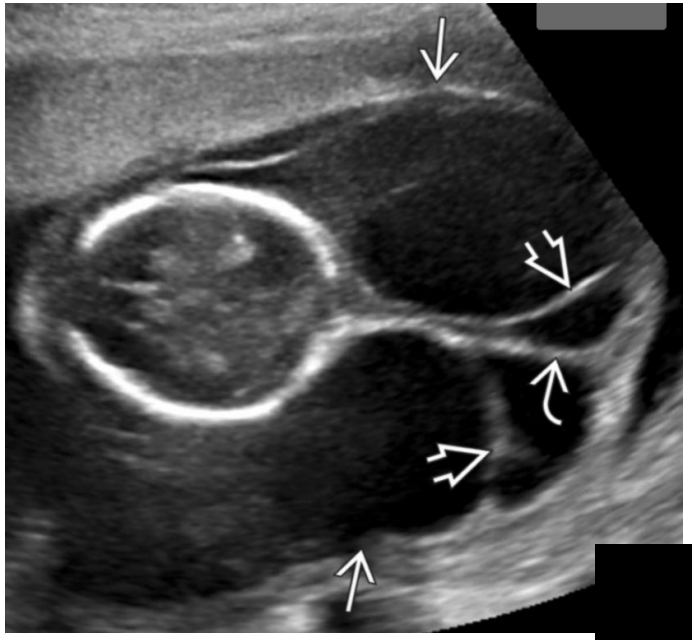


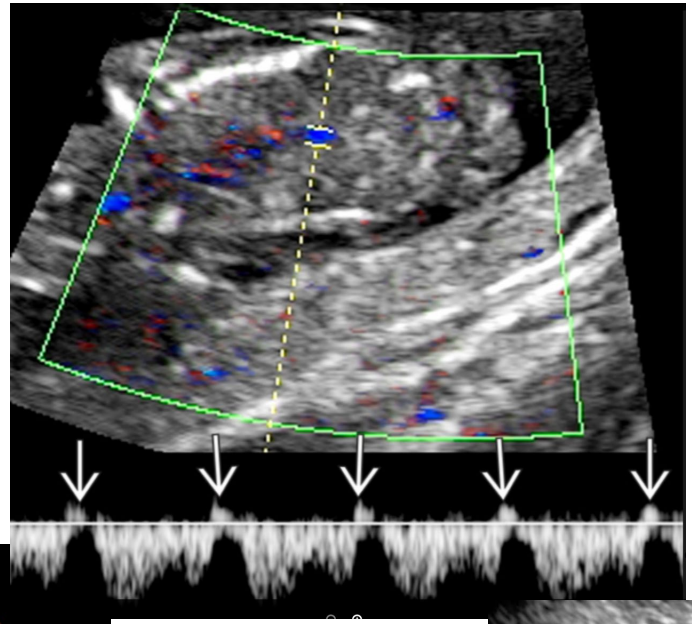


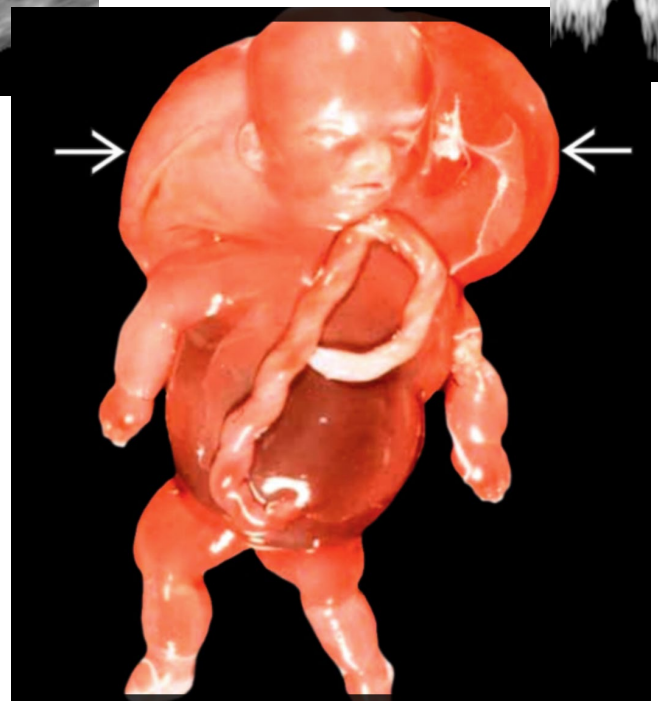


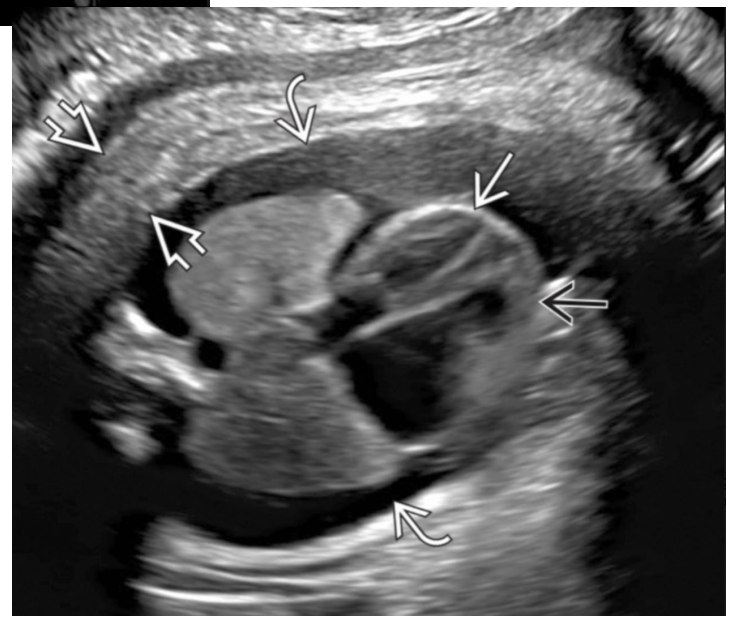


Trisomy 21









Turner syndrome

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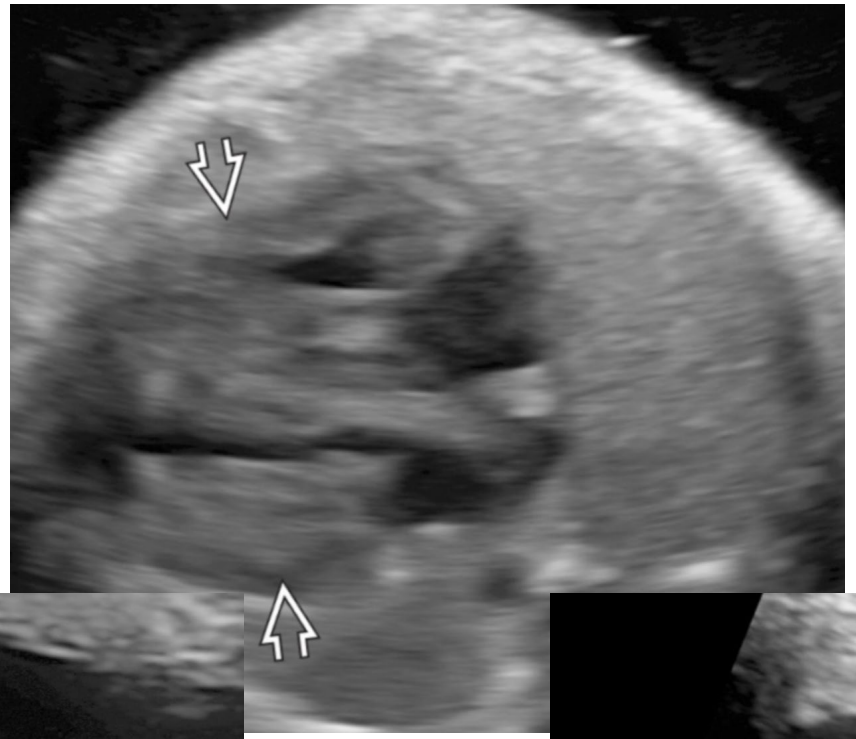
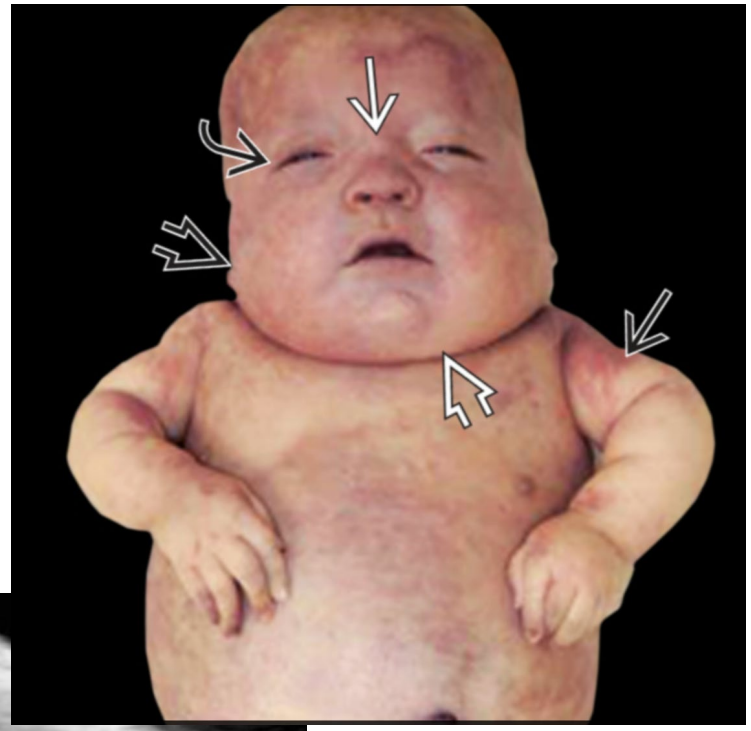
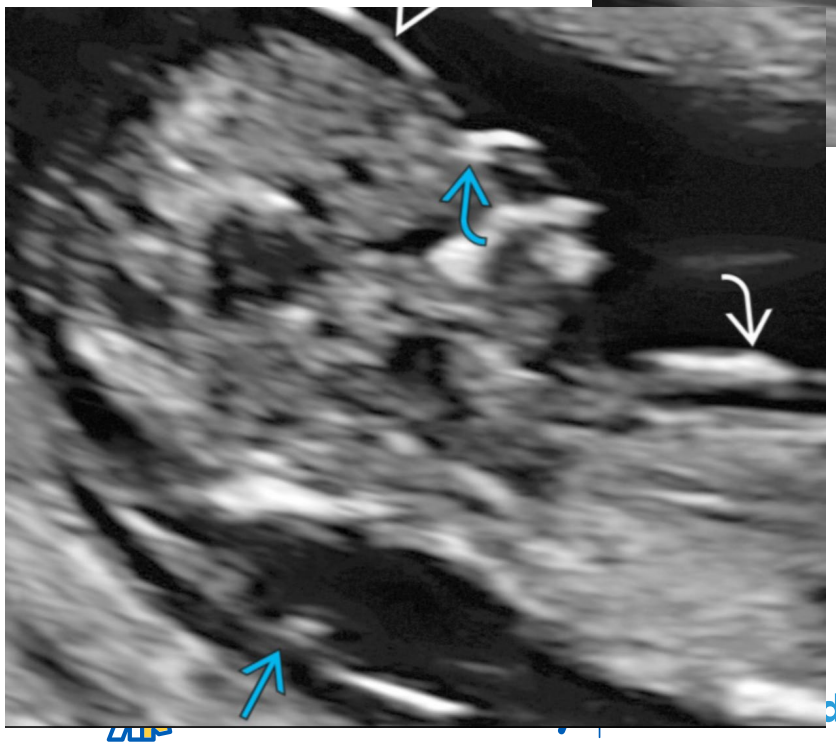
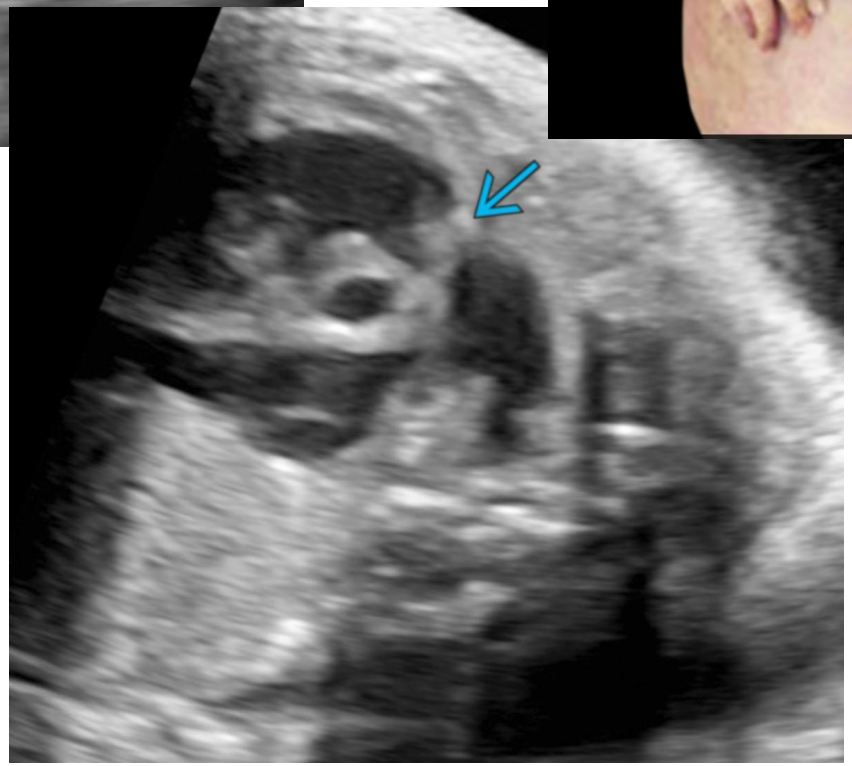
RASopathies









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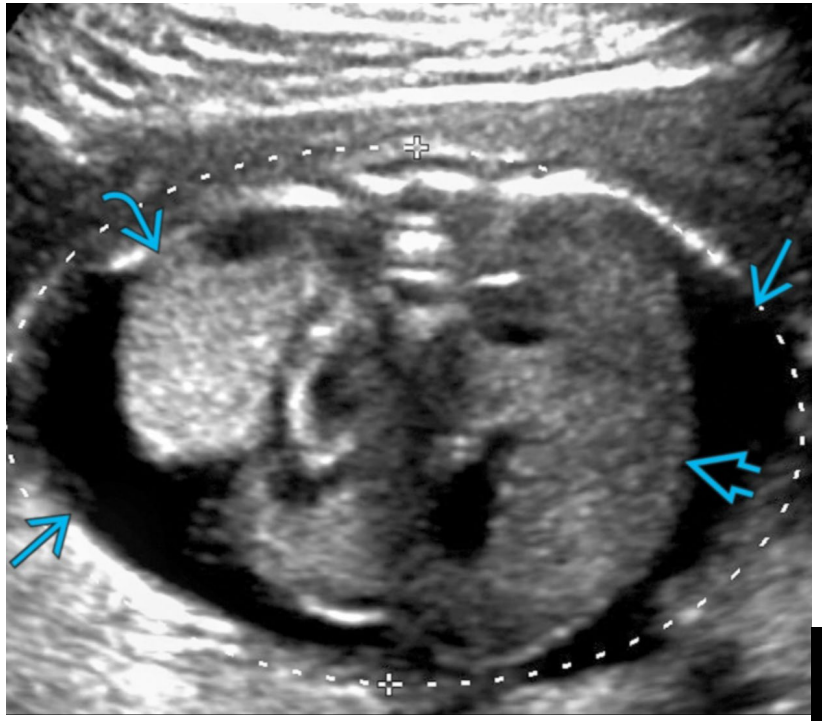
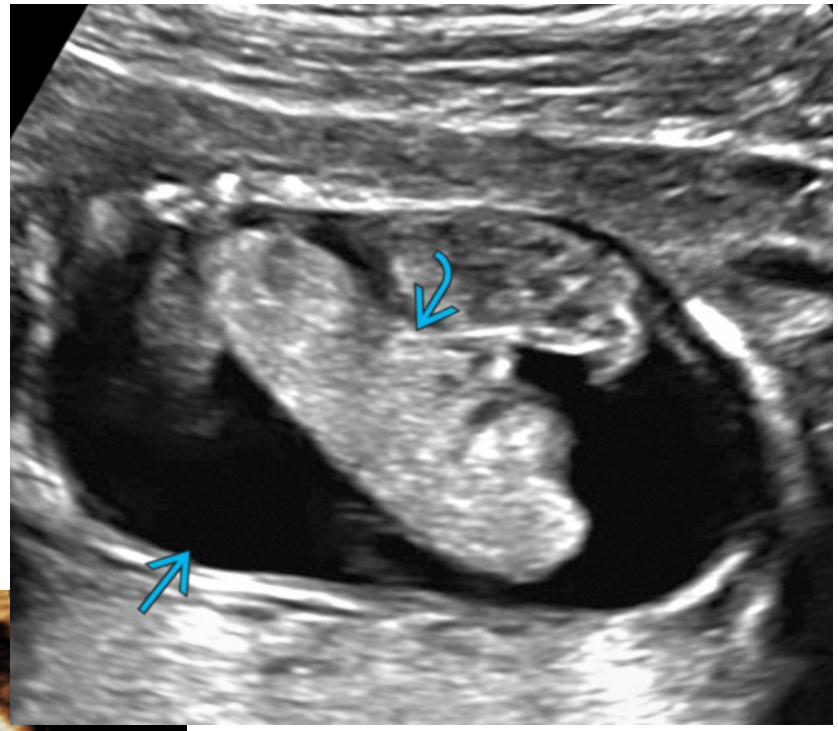
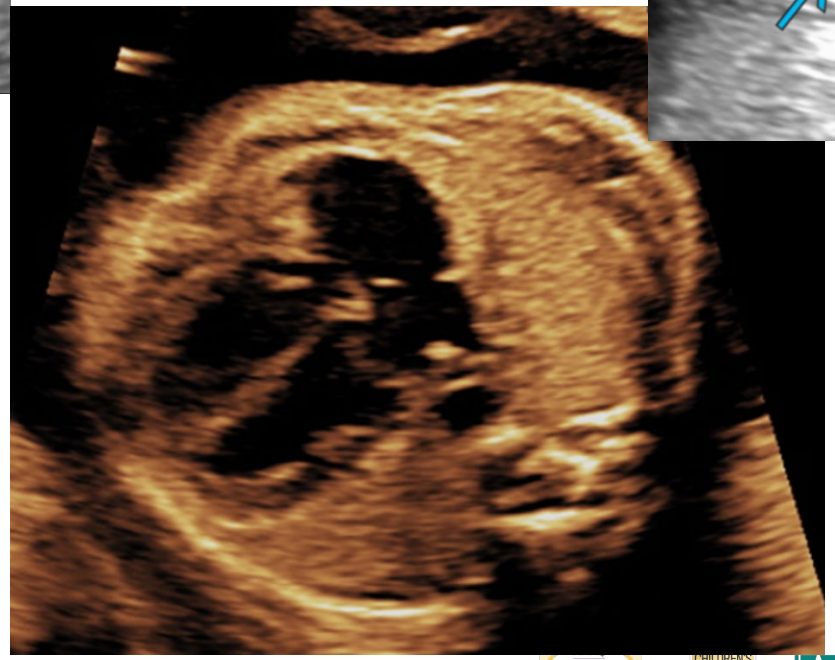


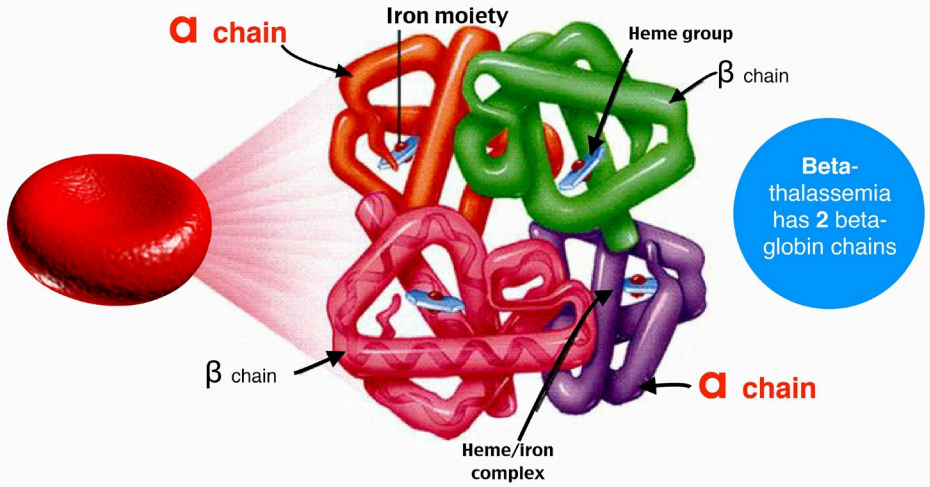




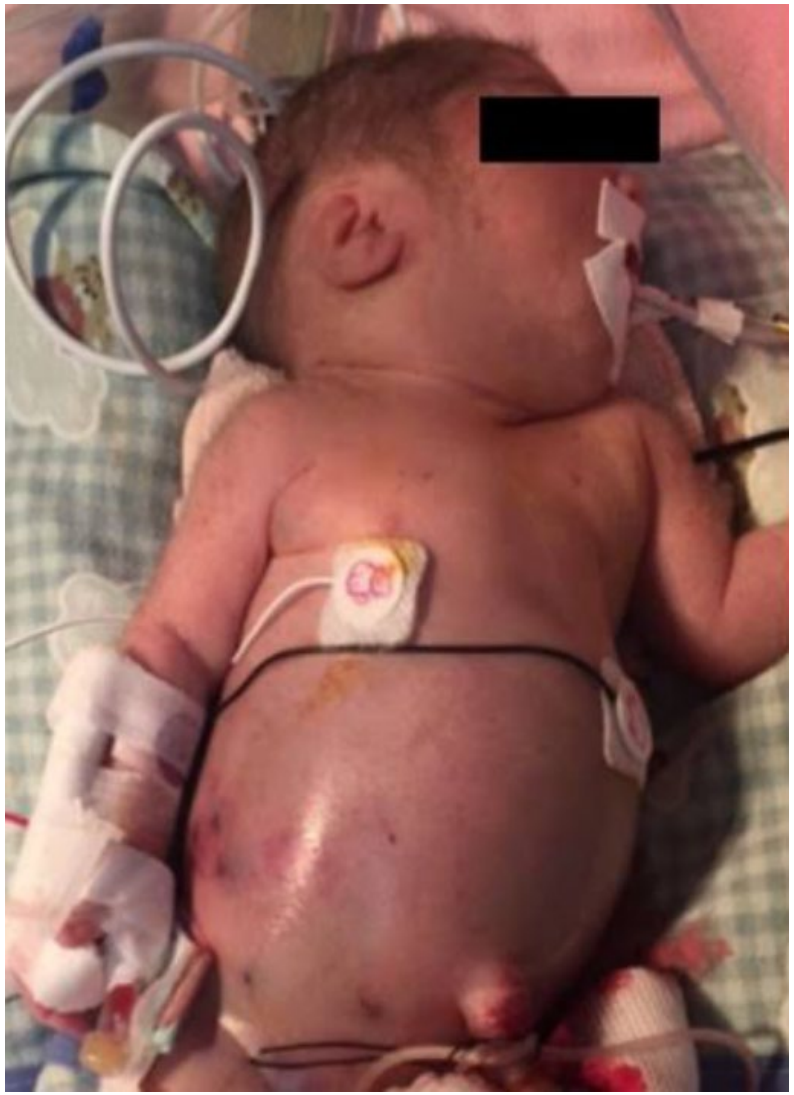
Inherited disorders of metabolism

Alpha-Thalassemia

Occurs when **one or more** of the **four** **alpha-globin chain** genes fails to function



Normal	α α / α α	**Normal:** No deletions
Carrier	α α / α α	**No abnormalities:** 1 deletion
Minor	α α / α α or α α / α α	**Alpha-thalassemia minor: 2 deletions** • Usually asymptomatic • Mild microcytic anemia
Hb H disease	α α / α α	**Hemoglobin H Disease: 3 deletions** • Splenomegaly, hemolytic, & microcytic anemia • Avoid oxidative drugs
Hydrops fetalis	α α / α α	**Hydrops fetalis: 4 deletions** • Fetal demise • Total body edema



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2. Structural abnormalities - cardiovascular

Anatomic

Most common:

- Right heart lesions
- Cardiomyopathy
- Hypoplastic left heart syndrome

Functional

Most common:

- Tachyarrythmias: SVT and arial flutter
- Bradyarrythmias: congenital heart block

Both may be related to structural differences such as **heterotaxy**.

Genes related to conduction system *(SCN5A, GATA4, HRAS*).

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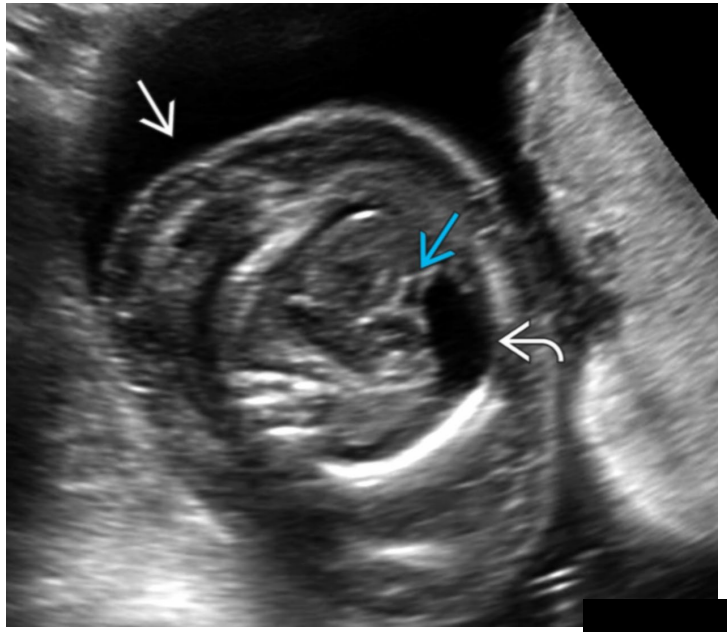

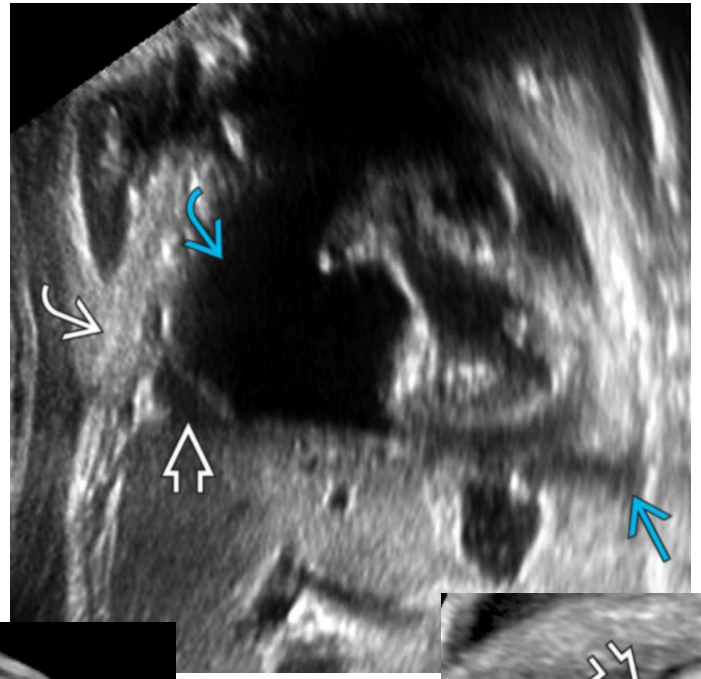

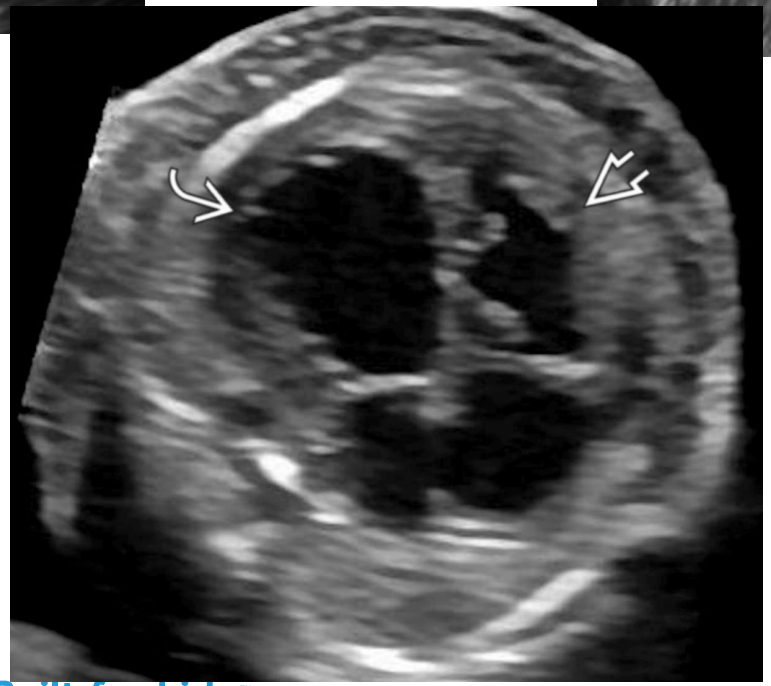

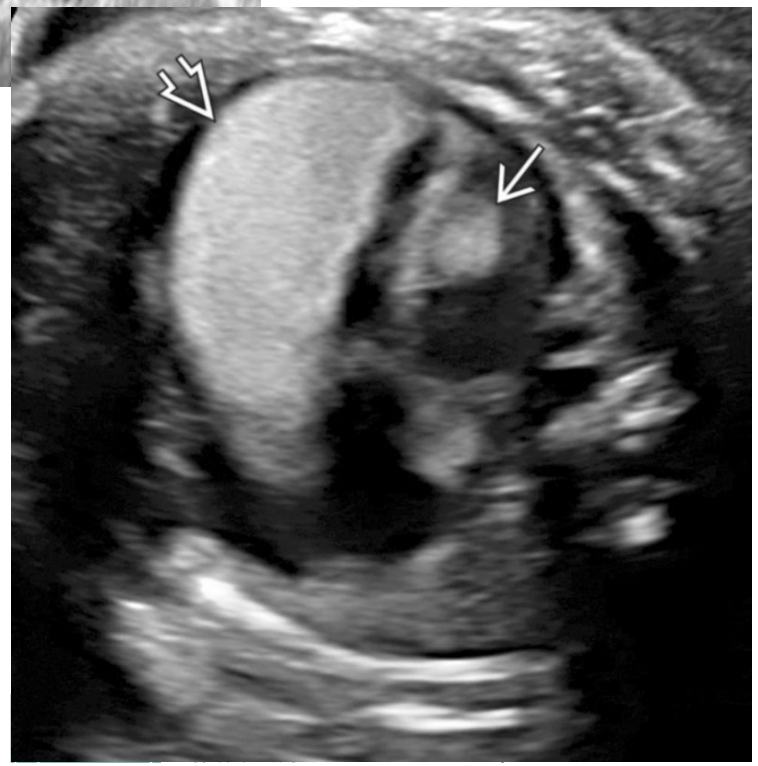

Cardiac anatomic abnormalities

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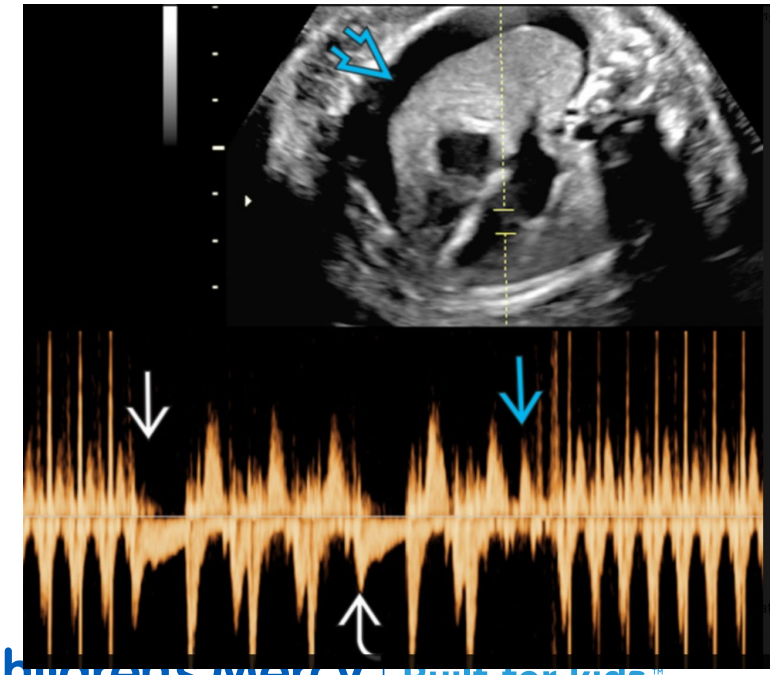
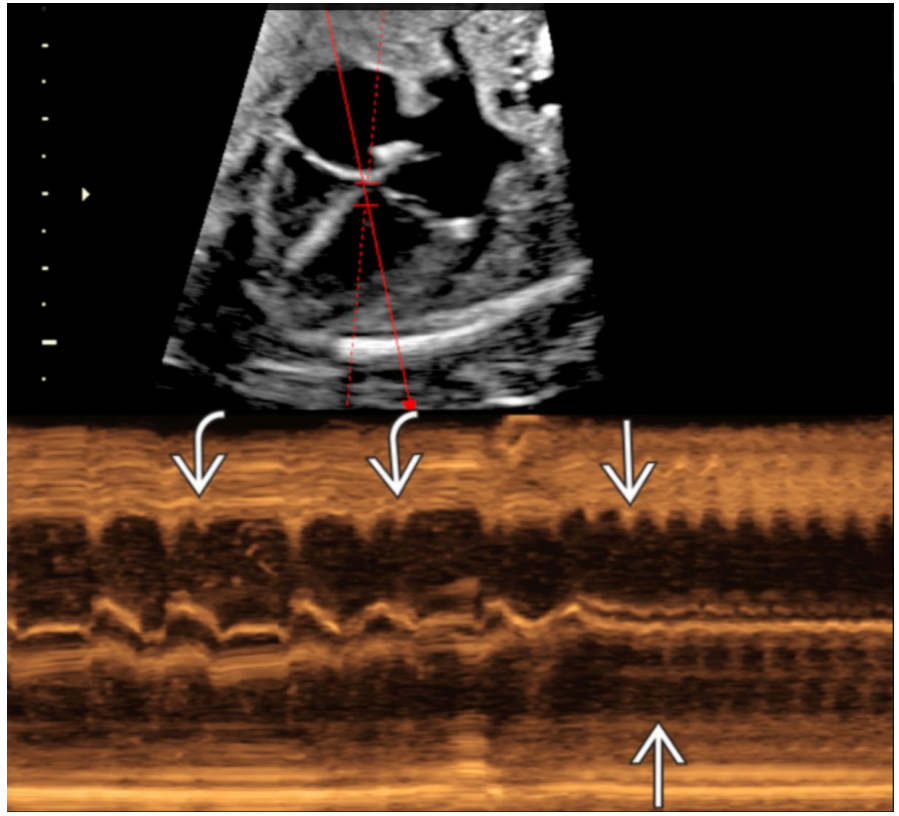
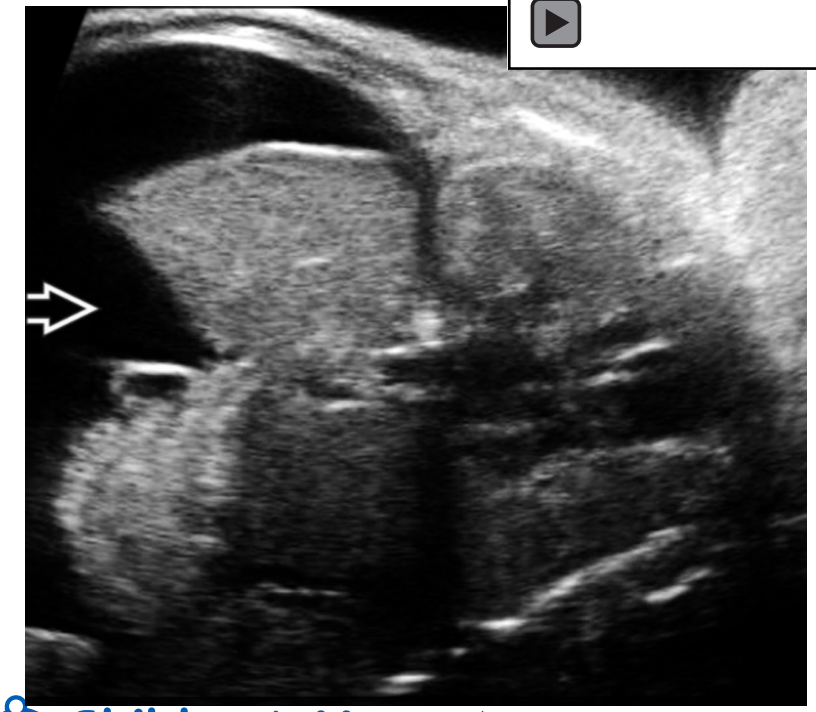
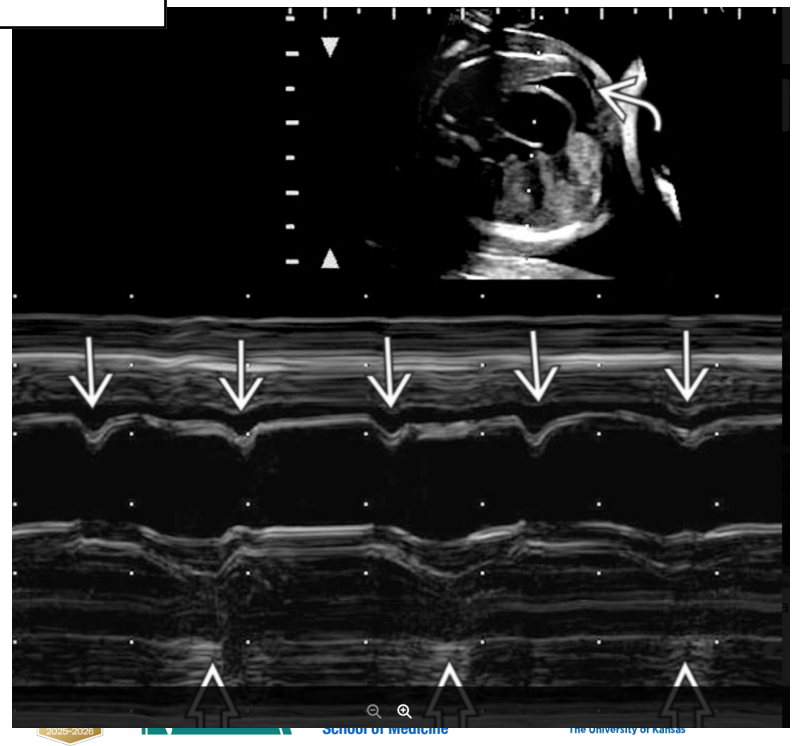
Tachyarrythmias



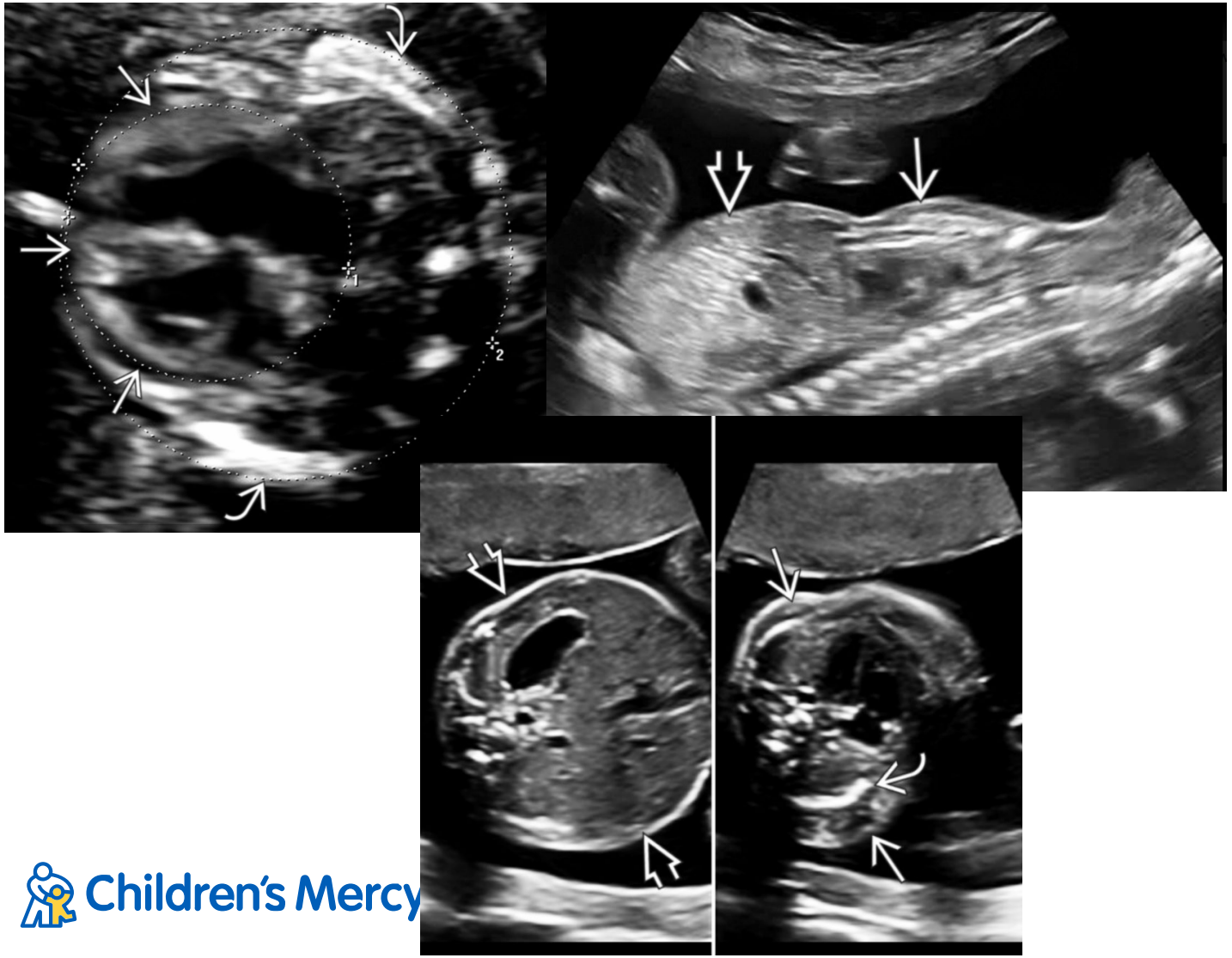


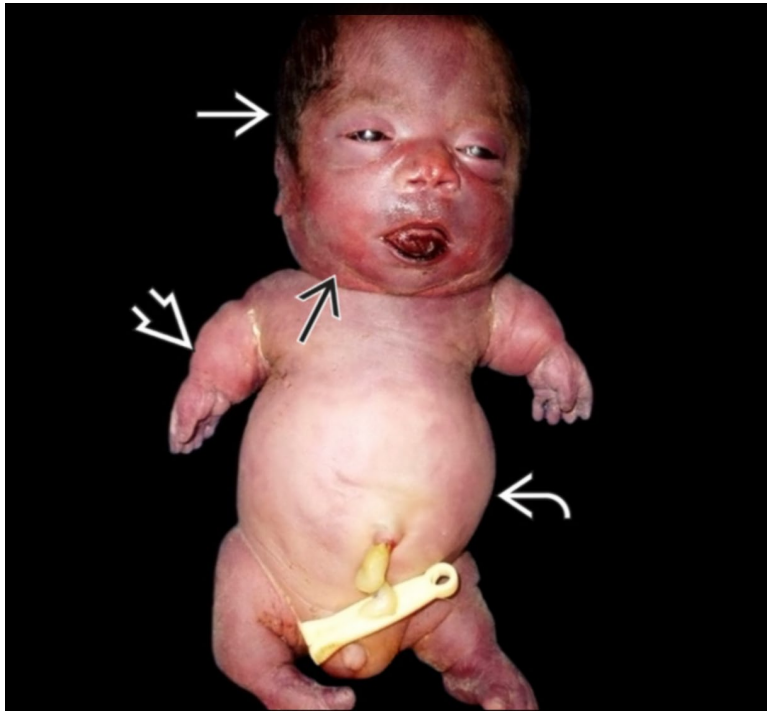
Bradyarrythmias





2. Structural abnormalities - Skeletal





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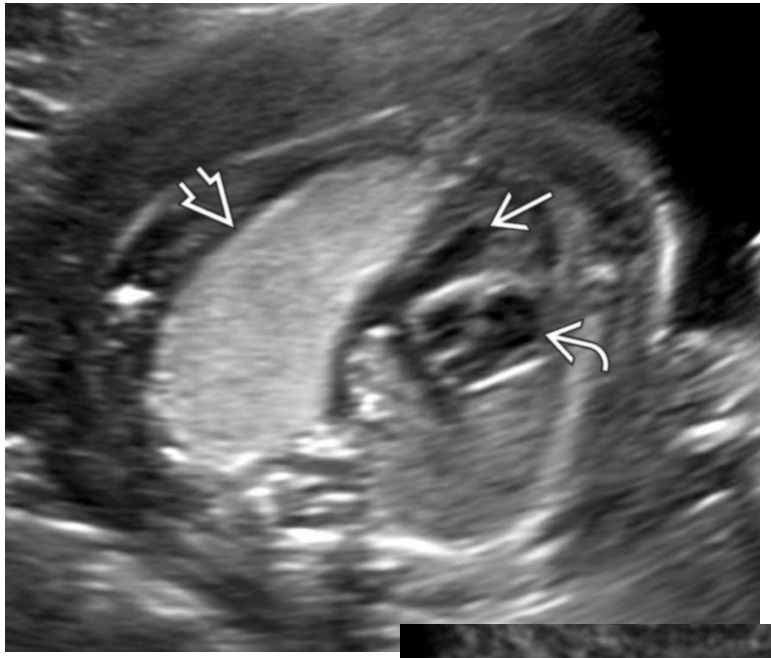
2. Structural abnormalities - Masses

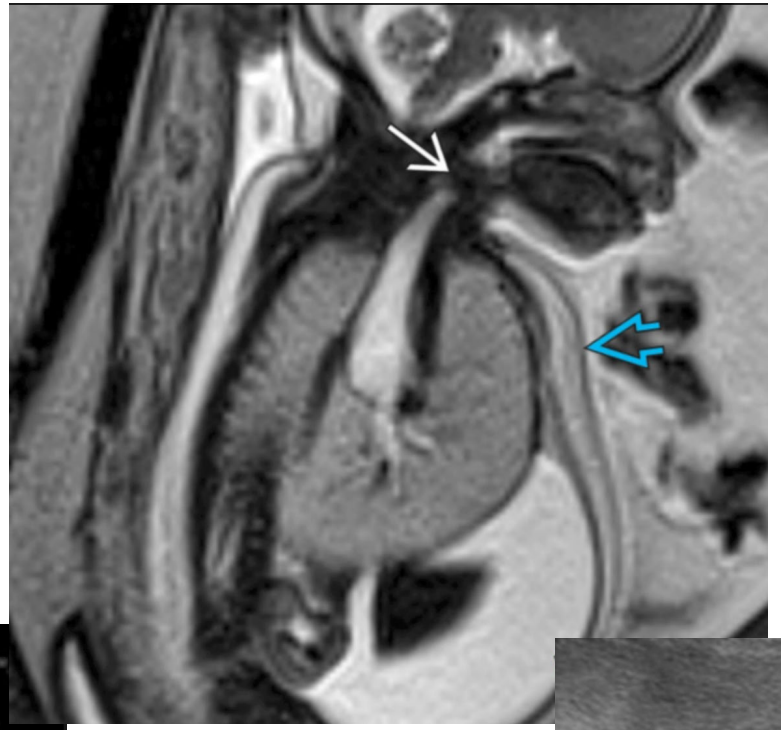
Mass effect

- Congenital pulmonary airway malformation
- Bronchopulmonary sequestration
- Congenital high airway obstruction syndrome
- Rhabdomyomas
- Hepatoblastoma, neuroblastoma

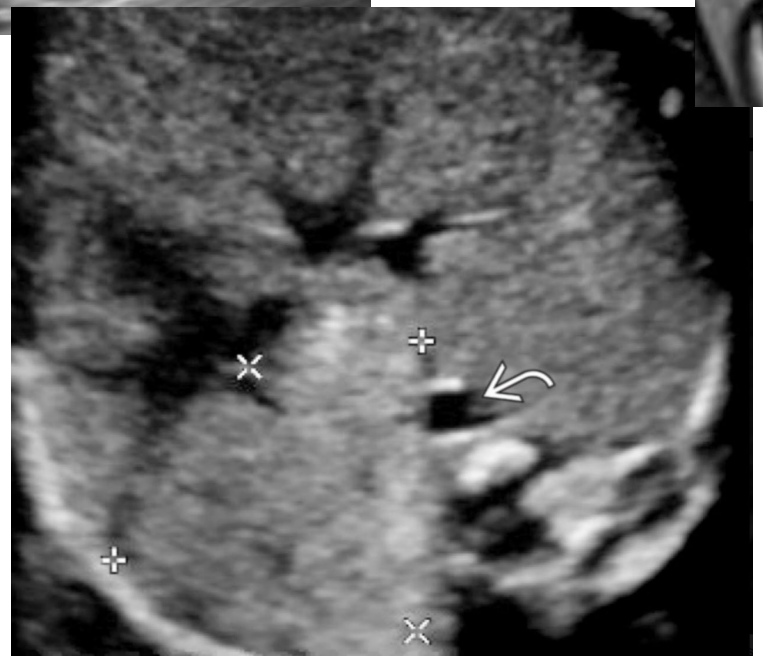
Vascular lesions

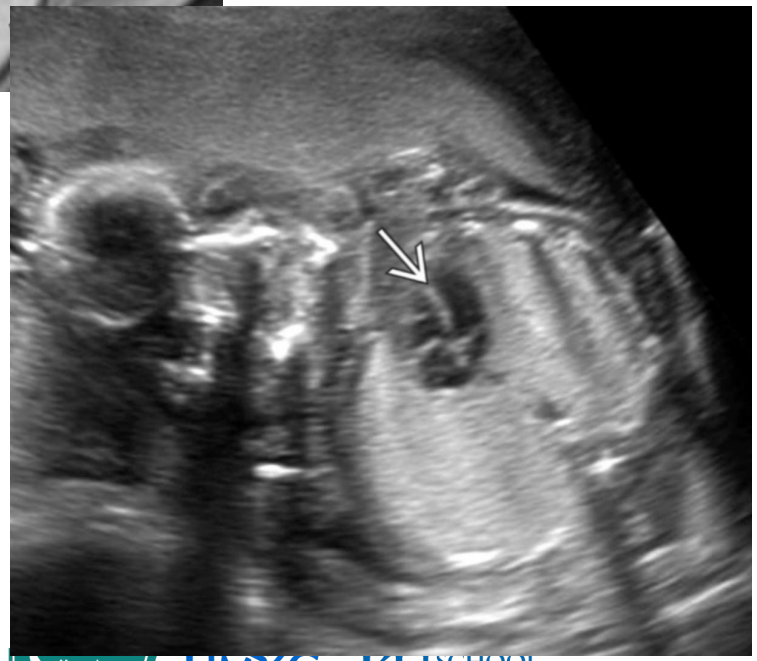
- Sacrococcygeal teratoma
- Vein of Gallen

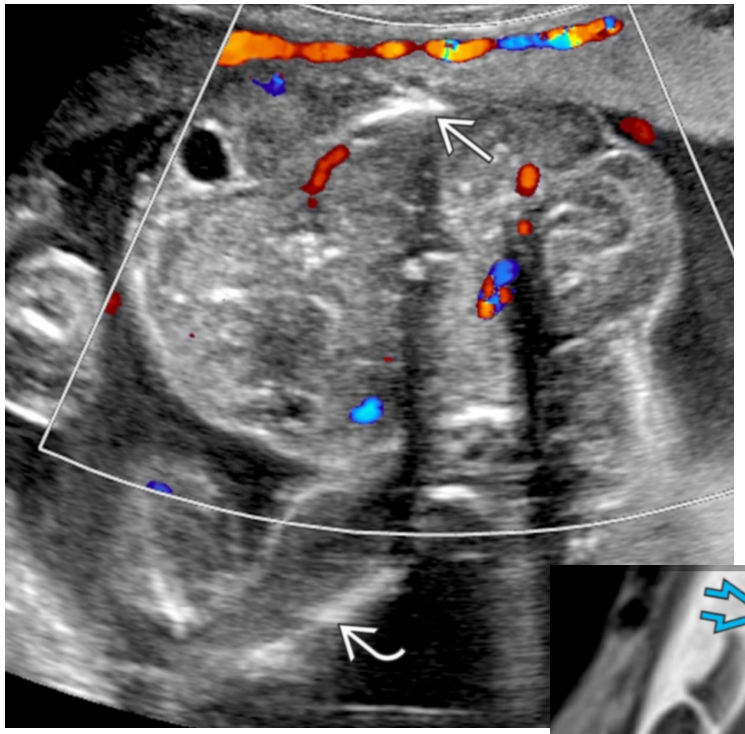


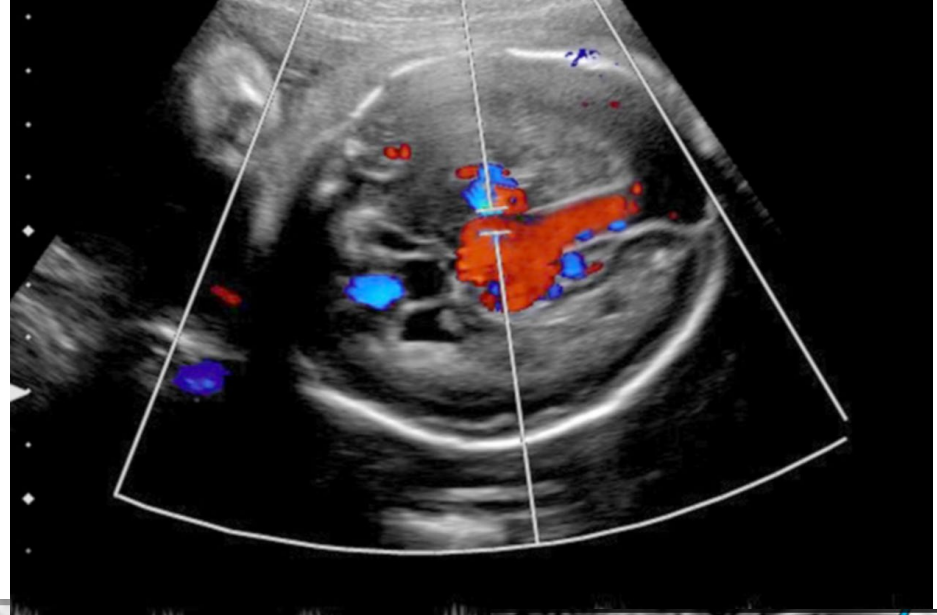


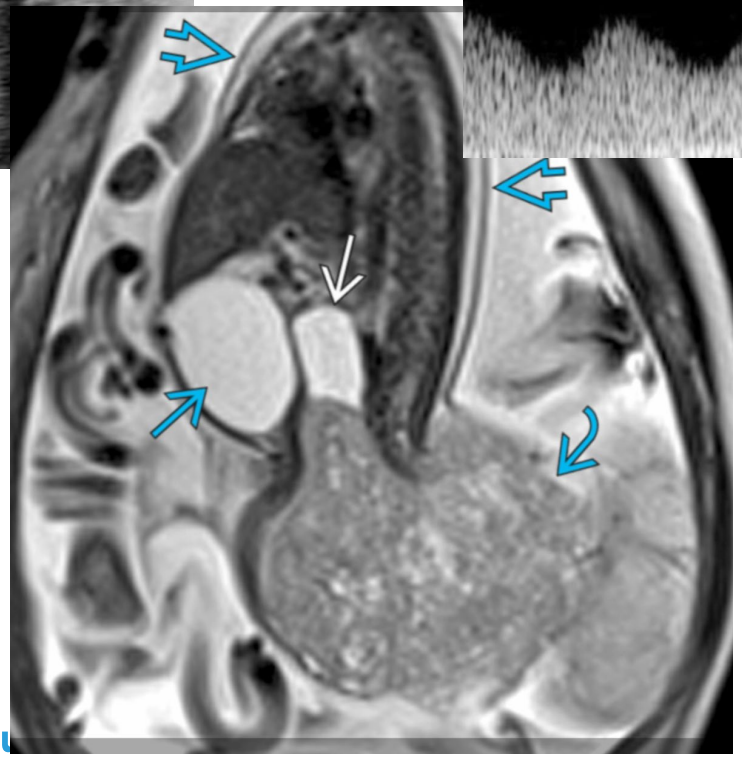
Mass effect

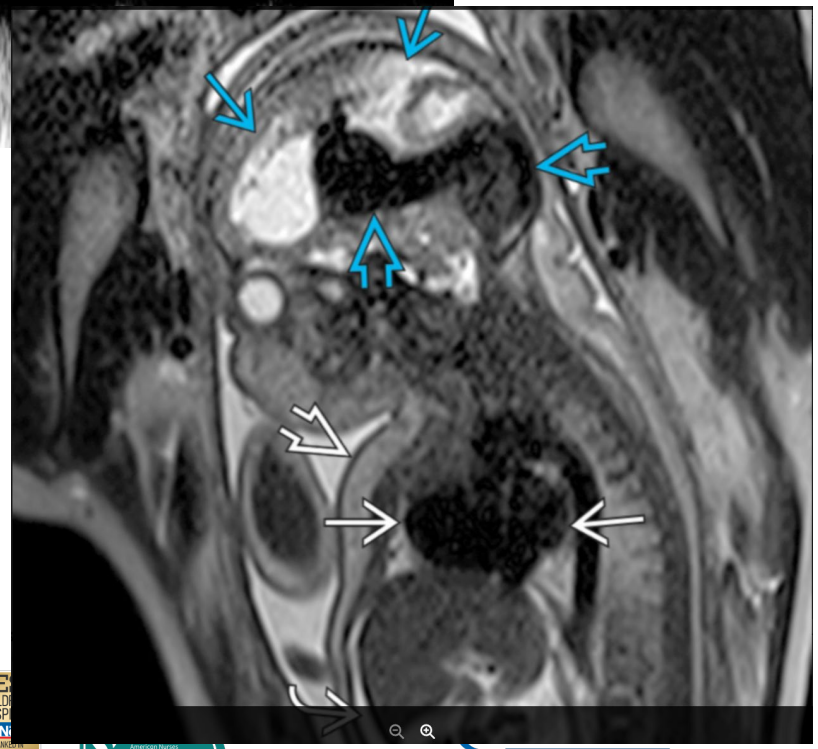






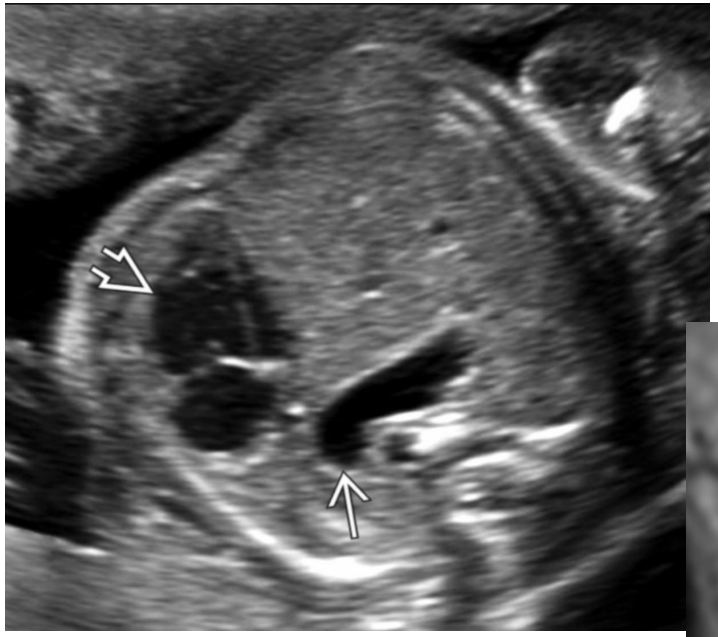


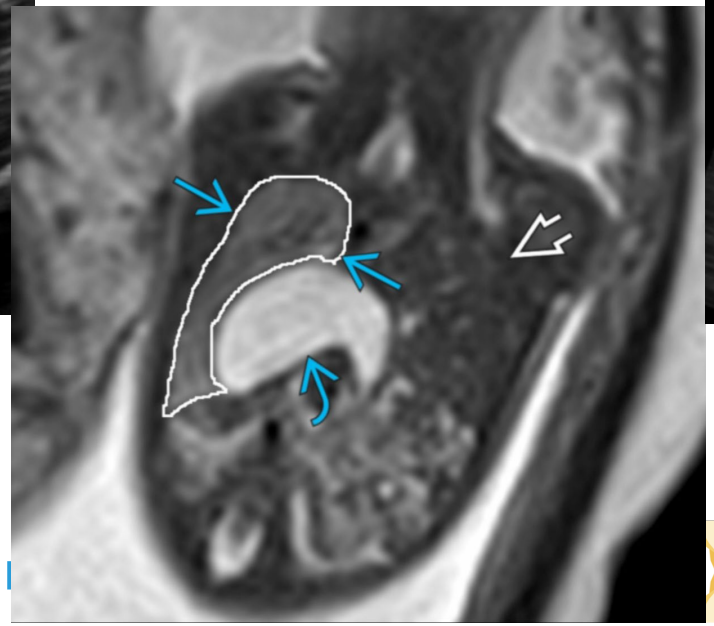


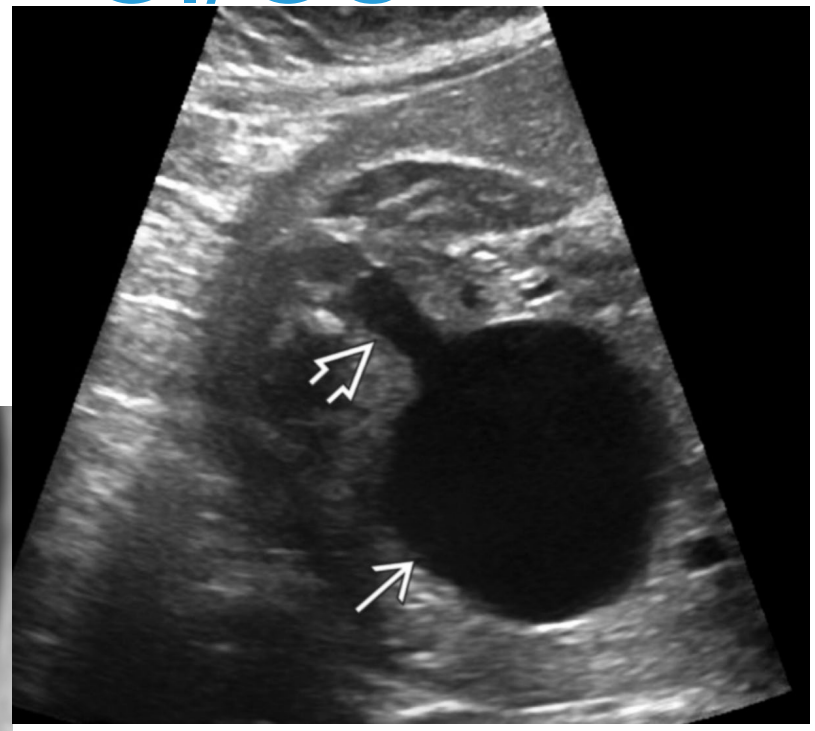


Vascular lesions

Structural abnormalities – GI/GU

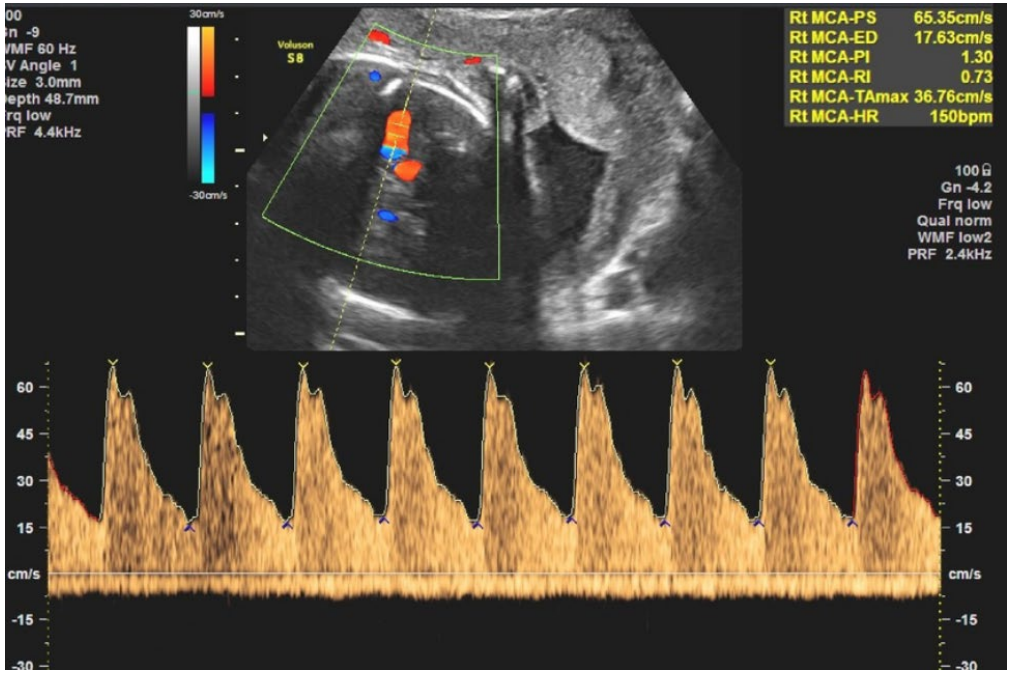






3. Fetal anemias

- Hereditary: alpha thalassemia
- Fetal-maternal hemorrhage
- Infections: Parvovirus
- Detected with MCA dopplers: Elevation considered PSV >1.5 MoM.
- Treatable with PUBS and IUT if fetus is anemic.



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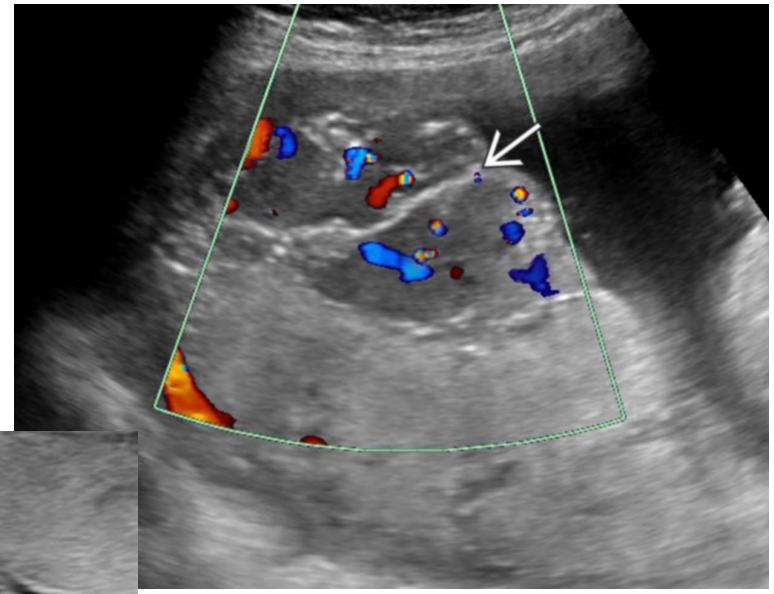
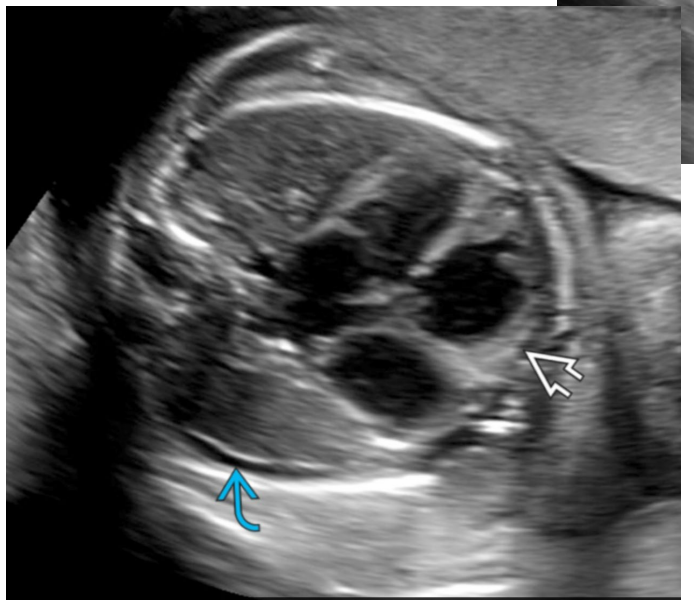
4. Structural abnormalities in the placenta or cord

- Large chorioangiomas >4-5 cm
- High volume arterio-venous shunts leading to high output cardiac failure





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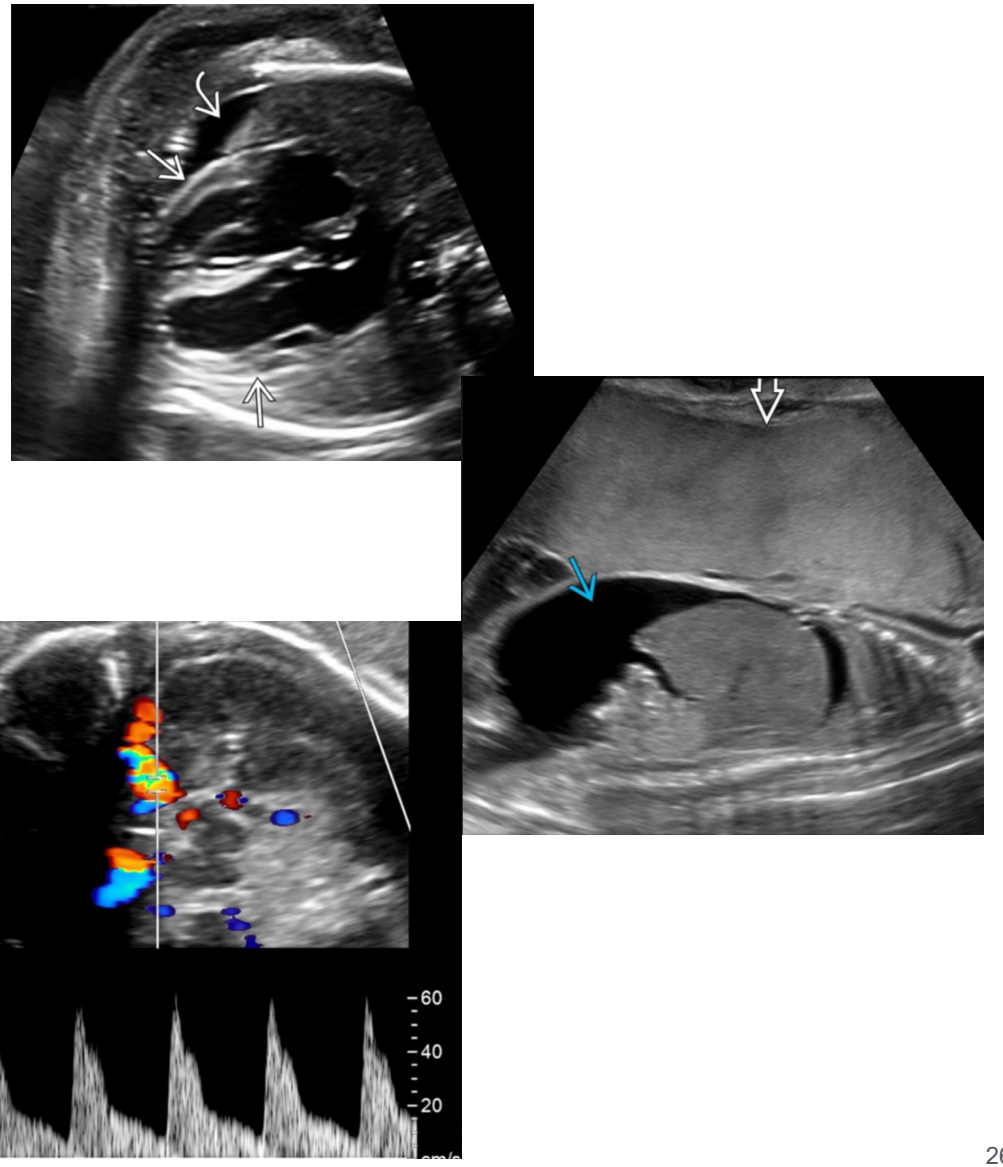
5. Infectious etiologies

- Parvovirus
  - Erythroid progenitor cells
  - Highest risk when infection before 20-24 weeks
  - Anemia often transient. IUT can support baby through aplastic anemia crisis.
- Cytomegalovirus – ascites most common
- Toxoplasma
- Syphilis



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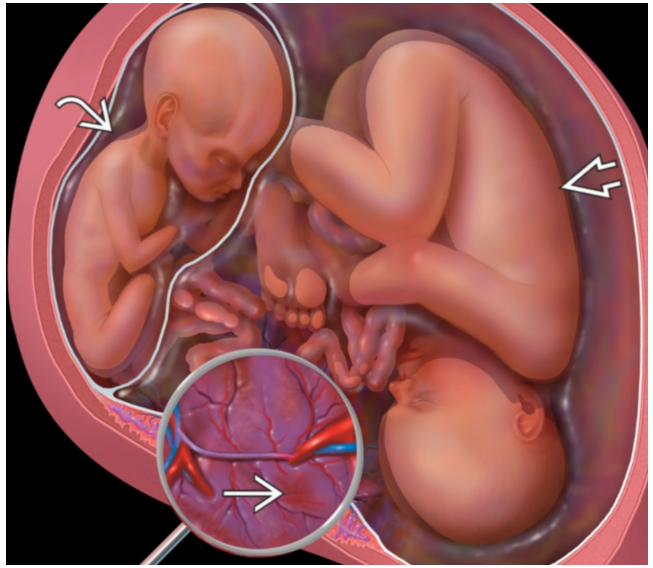
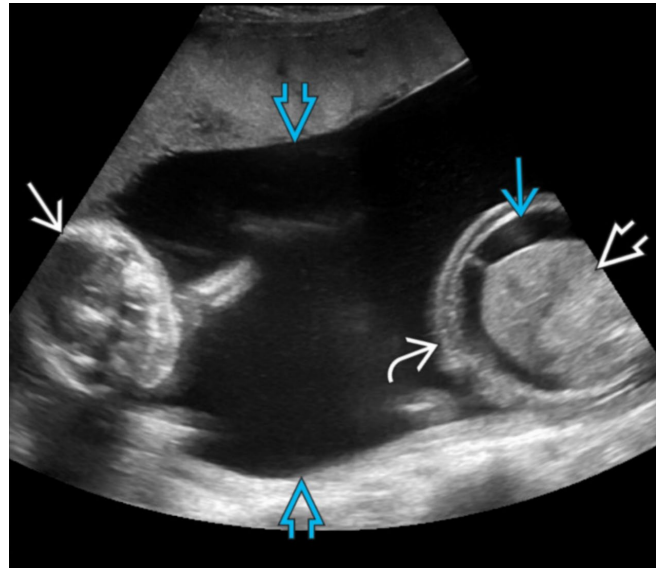
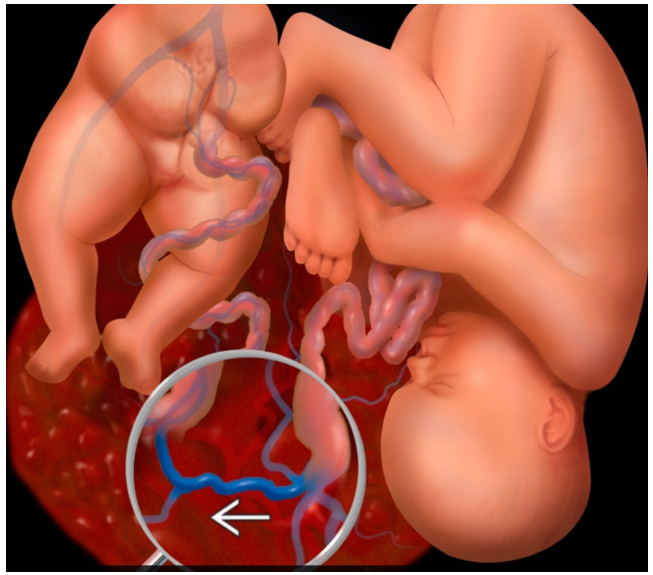
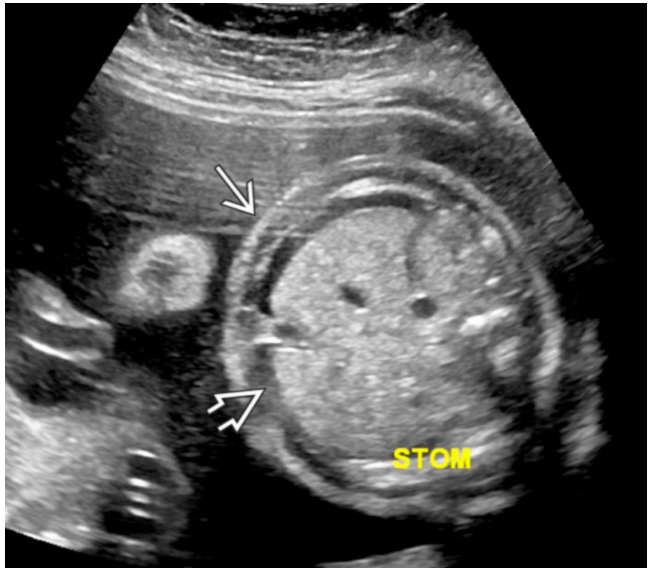
6. Complications of monochorionic twins

- Twin to twin transfusion syndrome
  - Especially the recipient twin
  - Hydrops considered stage IV
  - Fetal echocardiogram used to stratify TTTS cases for fetal intervention
- Twin reversed arterial perfusion sequence









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Evaluation of NIHF

1. Family, medical and obstetric history
2. Complete anatomical survey of the fetus, placenta and umbilical cord
   - Fetal growth, amniotic fluid
   - MCA dopplers to search for fetal anemia
3. **Fetal echocardiogram**
4. Blood work: Type and screen, CBC and hemoglobin electrophoresis, syphilis, serology for CMV/Toxo/Parvo, KB
5. Genetic testing:
   - CMA first line although exome and genome sequencing higher yield.
   - PCR for CMV, Toxoplasma and Parvo
6. Placental pathology, fetal autopsy

Table 1 Potential indications for fetal echocardiography

	ASE 2023 recommendation	AIUM 2020[4]	AHA 2014[2*]
Maternal factors (absolute risk)[†]			
Pre–gestational diabetes (3%-5%)	Is indicated	Is indicated	I (indicated)
Gestational diabetes diagnosed after second trimester (<1%)	Not indicated	Not indicated	III (no benefit)
Phenylketonuria (12%-14%)	Is indicated	Is indicated	I (indicated)
Autoimmune disease: SSA/SSB positive (1%-5%)[‡]	Is indicated	Is indicated	IIa (probably indicated)
In vitro fertilization (1.1%-3.3%)	May be considered[§]	Is indicated	IIa (Probably indicated)
Maternal infection: rubella (3%-4%)	Is indicated	Is indicated	I (indicated)
Family history of CHD: first-degree relative (3%-20%)[¶]	Is indicated	Is indicated	I (indicated)
Family history of CHD: second-degree or more distant relative (<2%)[‖]	Not indicated	May be indicated	IIb (may be indicated)
Obesity (BMI > 30 kg/m^2) (1-2%)	Not indicated	Not indicated	—
Retinoids (8%-20%)	Is indicated	Is indicated	I (indicated)
ACE inhibitors (3%)	May be considered[§]	May be indicated	IIa (probably indicated)
Paroxetine (3%)	May be considered[§]	May be indicated	IIb (may be indicated)
Other selective serotonin reuptake inhibitors (1%-2%)[6,7]	Not indicated	Not indicated	III (no benefit)
Anticonvulsants (1%-2%)	Not indicated	May be indicated	IIb (may be indicated)
Lithium (1%-2%)	Not indicated	May be indicated	IIb (may be indicated)
Warfarin (<1%)[8]	Not indicated	Not indicated	III (no benefit)
Fetal factors identified during screening (absolute risk)			
Fetal hydrops (15%-20%)[9]	Is indicated	Is indicated	I (indicated)
Extracardiac anomaly (20%-45%)[10,11]	Is indicated	Is indicated	I (indicated)
Chromosomal abnormalities (10%-90%)	Is indicated	Is indicated	I (indicated)
Monochorionic twinning (2%-10%)	Is indicated	Is indicated	I (indicated)
Nuchal translucency 3.0-3.4 mm (~3%)	May be considered[§]	May be indicated	IIa (probably indicated)
Nuchal translucency ≥3.5 mm (6%-60%)	Is indicated	Is indicated	I (indicated)
Single umbilical artery in isolation (1.2%-1.8%)[12]	Not indicated	Not indicated	IIb (may be indicated)

FETAL ECHOCARDIOGRAPHY FOR EVALUATION OF IN UTERO CONGESTIVE HEART FAILURE

A Technique for Study of Nonimmune Fetal Hydrops

CHARLES S. KLEINMAN, M.D., RICHARD L. DONNERSTEIN, M.D., GREGGORY R. DEVORE, M.D., C. CARL JAFFE, M.D., DIANA C. LYNCH, R.N., RICHARD L. BERKOWITZ, M.D., NORMAN S. TALNER, M.D., AND JOHN C. HOBBINS, M.D.

Abstract Thirteen fetuses with nonimmune hydrops (22 to 39 weeks of gestation) were evaluated with two-dimensional and M-mode echocardiography. Ten fetuses had cardiovascular abnormalities resulting in heart failure, and three had noncardiac causes of hydrops. In three cases, hydrops was caused by supraventricular tachycardia. One of these fetuses responded to cardioversion at birth, another responded to transplacental digoxin therapy, and the third died with ätrial flutter and high-grade atrioventricular block before delivery. There were no cases of "idiopathic" hydrops. Our results show that fetal echocardiography is useful in determining cardiac causes of in utero heart failure resulting in hydrops fetalis. The fetal echocardiogram may also be used in monitoring transplacental therapy of heart failure. (N Engl J Med. 1982; 306:568-75.)

Why is cardiac function assessment important?

- Determining need and timing of potential intervention
- Predicting outcome
- Delivery planning and timing
- Follow up assessment after fetal intervention

Components of cardiac function assessment

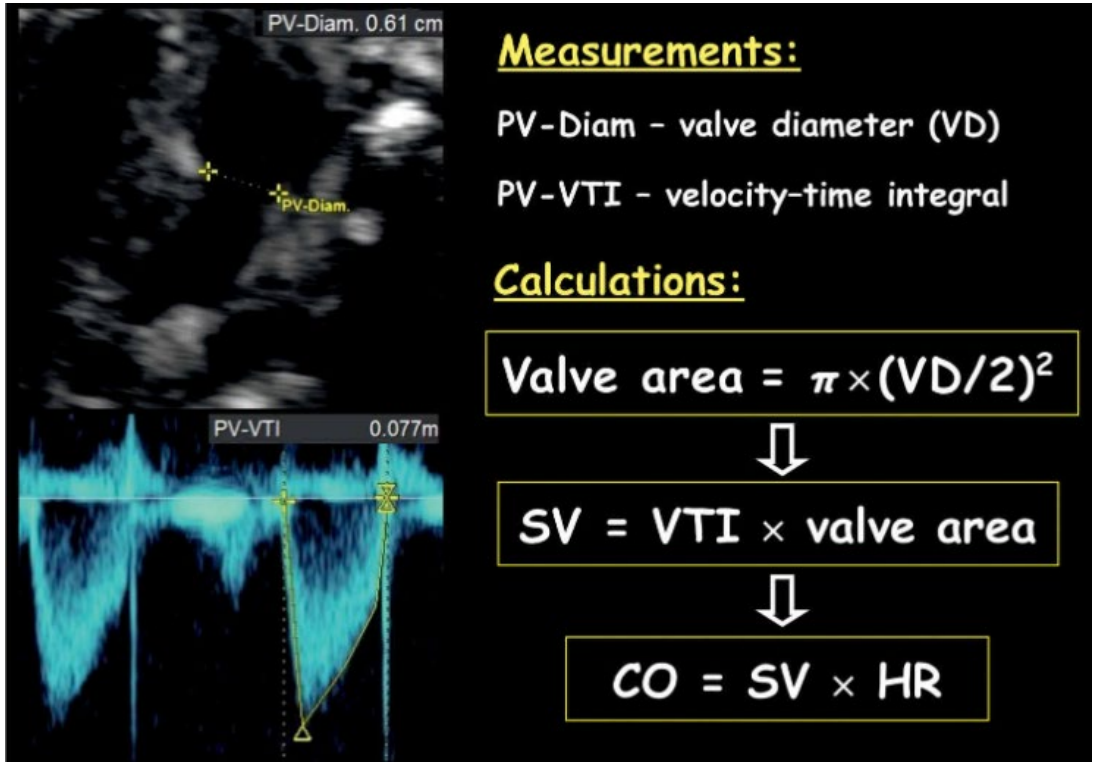
- Assess for fetal hydrops
- Cardiac size (cardiothoracic ratio)
- Cardiac chamber size and ventricular function
- AV valve regurgitation
- Myocardial performance index
- Combined cardiac output
- Venous dopplers (ductus venosus)

Fetal cardiac function assessment

Table 10 Recommendations for components of a comprehensive fetal cardiac functional assessment

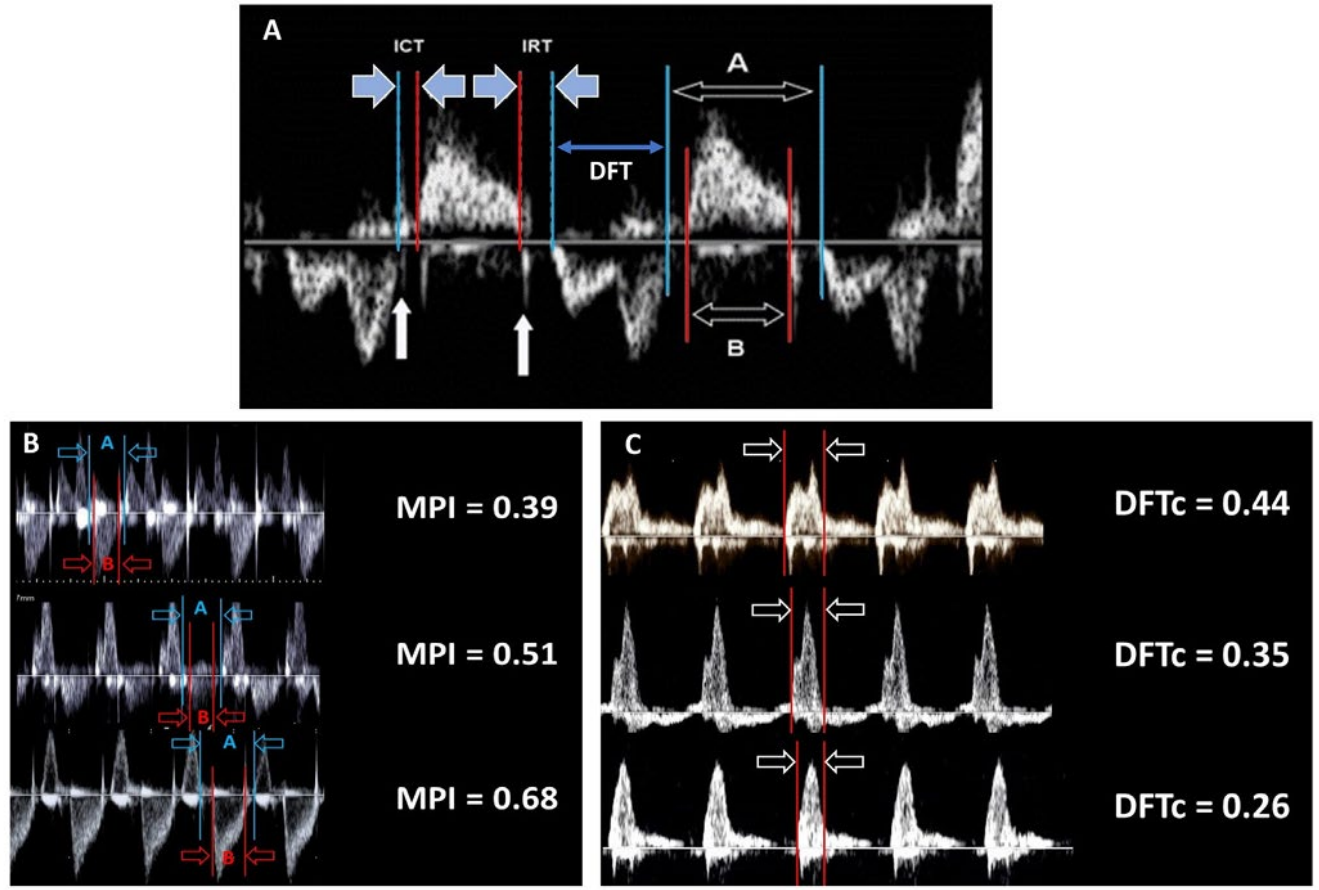
	Function index	Modality
Systolic function	• **LV and RV qualitative assessment or** measured shortening fraction • TAPSE, MAPSE • Myocardial performance (Tei) index (global function)	• 2D, M-mode • M-mode • PW or tissue Doppler
Diastolic function	• **AV valve inflow profile** (E/A velocity, E/A ratio, presence of monophasic inflow pattern) • DFTc • Myocardial performance index (MPI, Tei; global function) • **IVC or hepatic venous flow** (ratio of A-wave VTI/forward flow VTI) • **Ductus venosus flow (presence/absence of A-wave reversal**, pulsatility index**)** • **Umbilical venous flow (presence/absence of venous pulsation)**	• PW Doppler • PW or tissue Doppler • PW Doppler • PW Doppler • PW Doppler • PW Doppler
Valve function	• **Presence/absence of AV valve regurgitation**	• Color flow Doppler
Cardiac output	• Cardiothoracic ratio • Combined cardiac output, indexed to EFW	• 2D • 2D and PW Doppler
Cardiovascular profile score (see Table 13)	• Composite score of overall cardiac function	• 2D, M-mode, PW Doppler

Combined cardiac output

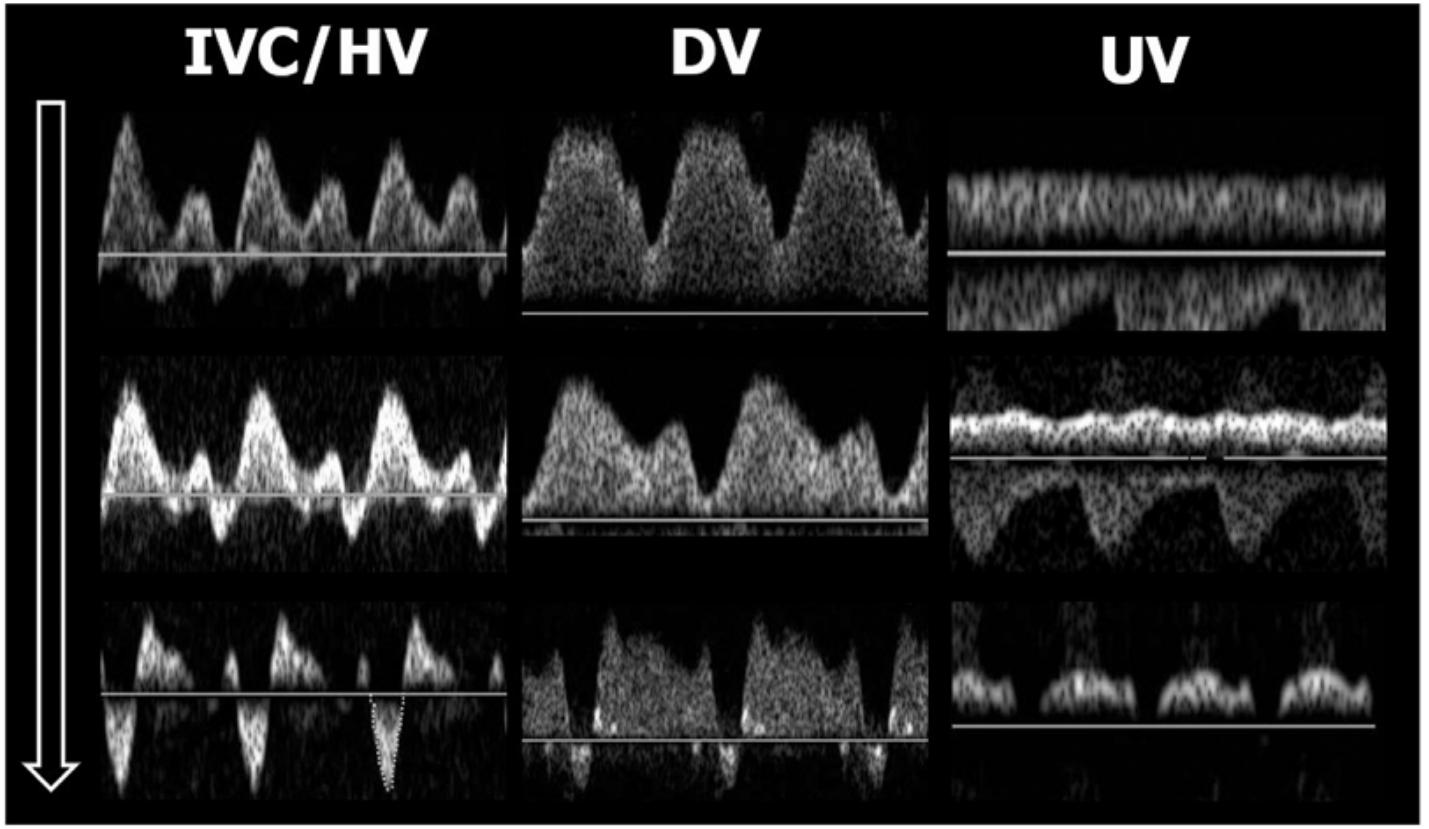


- Normal CCO = 425 mL/min/kg
- Ranges from 225-625 mL/min/kg based on gestational age.
- Predicts outcomes in high output states

Myocardial performance index



Venous doppler flows



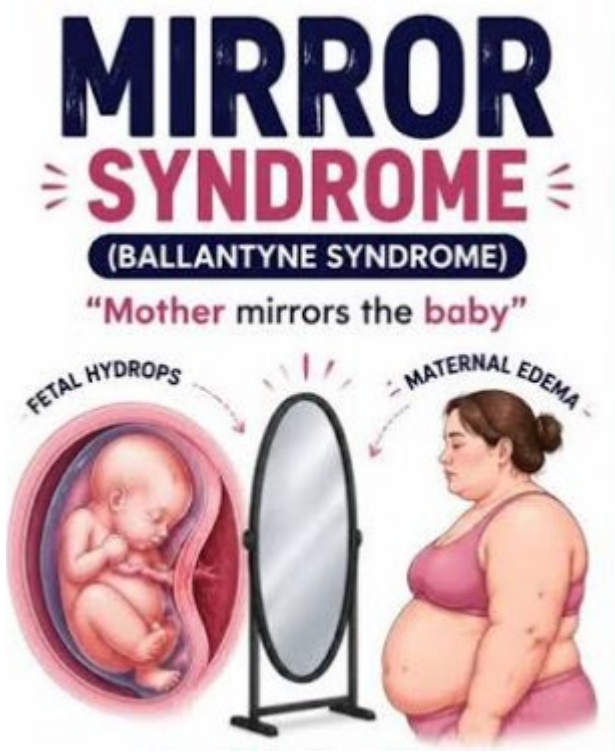
Cardiovascular profile score

Table 12 Cardiovascular profile score*

Category	Subscale points		
	2	1	0
Hydrops	None	Ascites or pleural or pericardial effusion	Skin edema
Heart size (CA/TA ratio)	0.20-0.35	0.35-0.50	>0.50 or <0.20
Cardiac function	Normal biphasic AV inflow, RV and LV SF > 0.28	Holosystolic TR or RV/LV SF < 0.28	Holosystolic MR or TR dP/dt < 400 or monophasic AV inflow
Venous Doppler	Nonpulsatile UV and normal DV	Nonpulsatile UV and negative A wave in DV	Pulsatile UV
Arterial Doppler	Forward diastolic flow in UA	Absent end-diastolic flow in UA	Retrograde end-diastolic flow in UA

Maternal risks

- **Mirror syndrome**
  - Form of preeclampsia, **8-38% pregnancies** with NIHF
  - Common findings: Edema, hypertension, proteinuria
  - Other: headache, visual changes, oliguria, abnormal laboratories
  - Major morbidities**: pulmonary edema**, postpartum hemorrhage, ICU admission
  - Resolution necessitates delivery or abortion care, expectant management in rare circumstances.
- Polyhydramnios
- Preterm delivery
- Cesarean delivery



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Prognosis

- 15-21% spontaneous abortion or stillbirth
- 48% neurologic impairment
- 39% major morbidity
- Prognosis depends on presence of other anomalies or genetic diagnosis, number and type of effusions, response to in utero interventions, gestational age at detection and at delivery, birth weight, resuscitation at birth.
- Poorer outcomes for NIHF secondary to cardiac anomalies

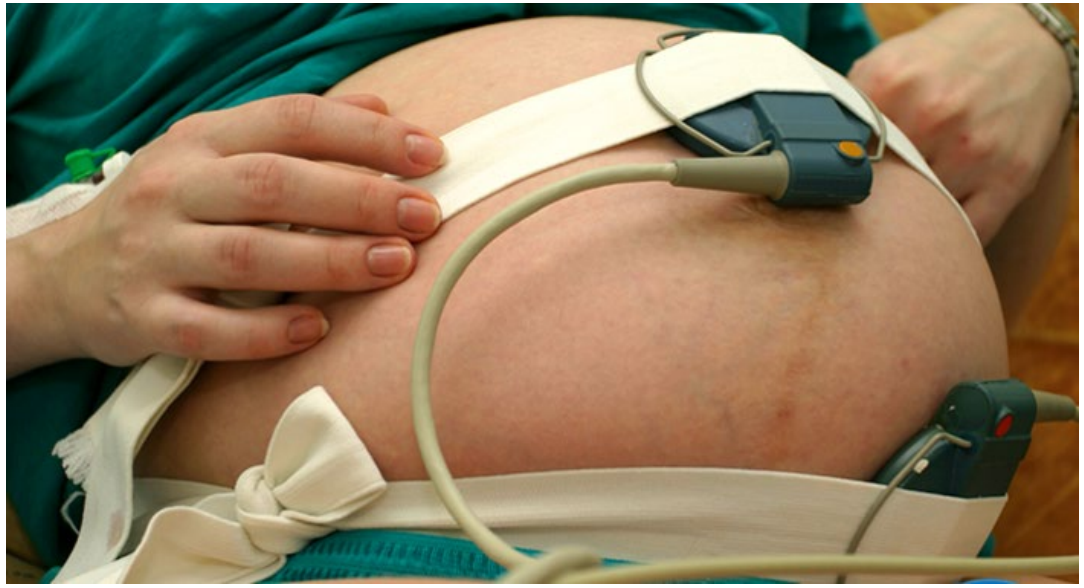
Interventions for NIHF

TABLE 3 Example of therapies for selected etiologies of non-immune hydrops fetalis and single fetal effusions in continuing pregnancies.

Etiology	Therapy[a]	Additional considerations
Fetal tachyarrhythmia, supraventricular tachycardia, atrial flutter, or atrial fibrillation	Maternal administration of antiarrhythmic medication(s)	Treatment with antiarrhythmic medication unless risks associated with delivery are considered less than those of continuing the pregnancy or the medication, or unless there is maternal or obstetrical contraindication
Fetal anemia due to infection, fetomaternal hemorrhage, hereditary anemia, or other	Fetal blood sampling followed by intrauterine transfusion if indicated	Intrauterine transfusion if anemia is confirmed, unless risks associated with delivery are considered less than those with the procedure
Fetal hydrothorax, chylothorax, or large pleural effusion(s)	Needle drainage of fetal effusion or placement of thoracoamniotic shunt	Consider drainage or thoracoamniotic shunt placement when the goal is prolongation of pregnancy or if drainage might confer benefit prior to delivery
Fetal CPAM	Maternal administration of corticosteroids for larger CPAMs, surgical interventions such as cyst aspiration or thoracoamniotic shunt for large cysts	Corticosteroids are most efficacious for microcystic lesions, and a repeat course of corticosteroids can be considered for larger lesions
Twin-reversed arterial perfusion sequence	Percutaneous radiofrequency or microwave ablation	Offer percutaneous radiofrequency or microwave ablation of the acardiac twin

Antepartum fetal surveillance

- Not shown to improve perinatal outcomes
- Reasonable to offer at a gestational age at which neonatal interventions would be offered and desired by the patient



Delivery timing

- No great data
- **86%** of pregnancies with NIHF delivered early secondary to preterm labor or maternal/fetal indications
- In the setting of new or worsening NIHF -> delivery at **34 weeks** to balance risk of IUFD and prematurity
- Preterm delivery should be reserved for obstetric indications

Delivery considerations

- **85%** delivered by **cesarean** section
- Vaginal delivery appropriate if no acute fetal deterioration or if decision was made for palliative care
- Consider draining fetal effusion before delivery to prevent dystocia or improve the efficacy of neonatal resuscitative efforts
- Cesarean delivery should be reserved for standard obstetric indications when postnatal resuscitation is planned.
- Delivery at level III or IV NICU

Key take home messages

- NIHF is a **phenotype** rather than a diagnosis, requiring systemic evaluation
- **Cardiovascular dysfunction** is a common pathway for many causes of NIHF
- **Fetal echocardiography** is central to identifying structural/functional cardiac causes or cardiac dysfunction consequences
- Reversible causes, including fetal anemia and tachyarrhythmia, can have good outcomes with intervention.
- Prognosis depends on the underlying etiology
- Successful management requires a multidisciplinary team

Questions?