Hydrops Fetalis:
Diagnosis and Evaluation

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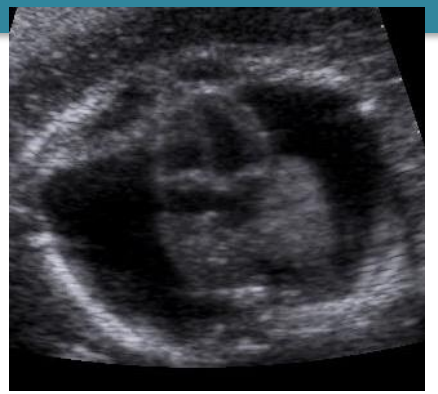
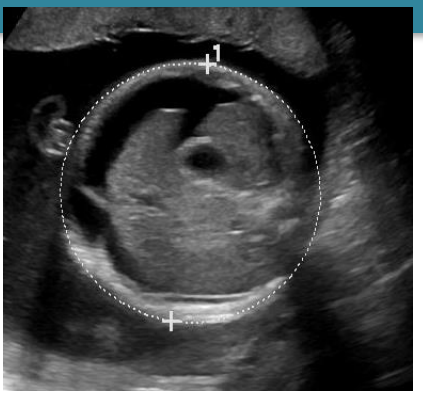
Disclosures

- None
- Research funding from the Fetal Health Foundation

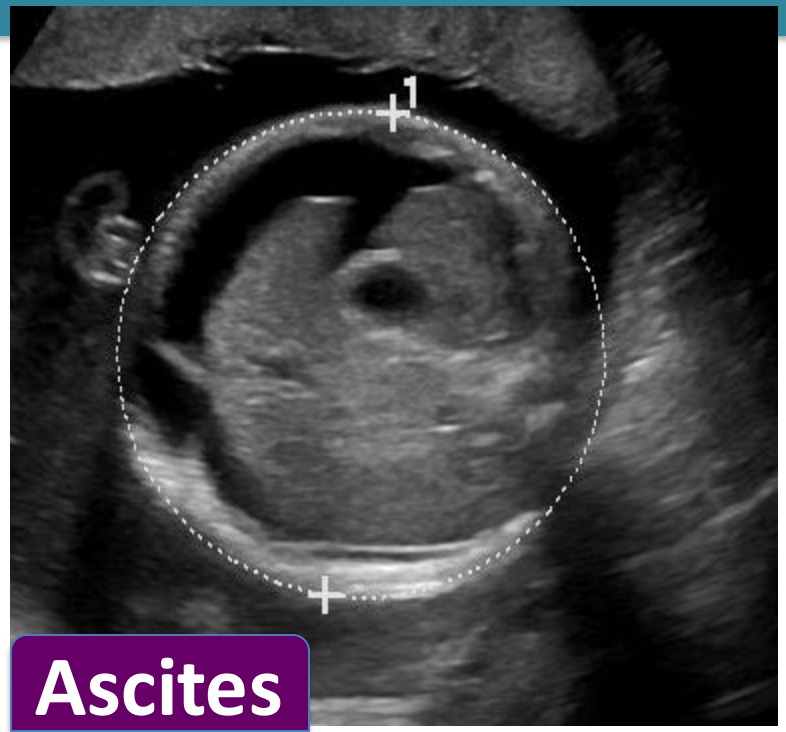
Hydrops Fetalis (ὕδωρ)



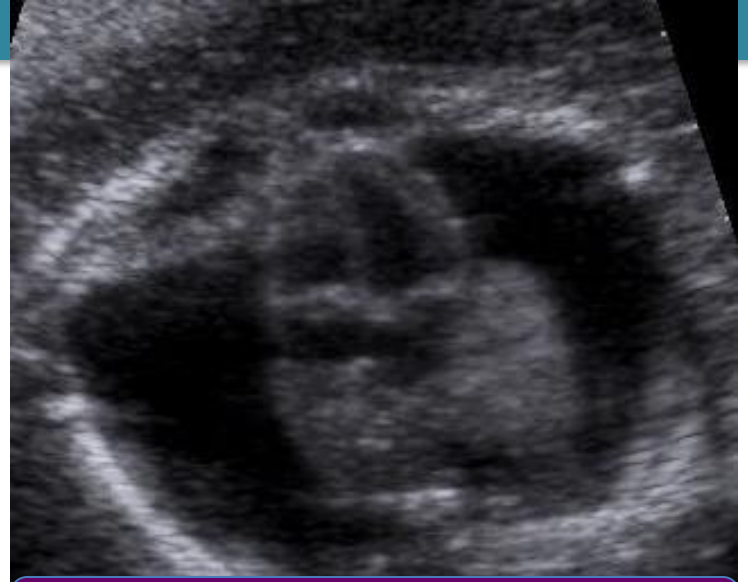


- Pathologic fluid collection in fetal soft tissues and serous cavities
- Two or more abnormal fluid collections
  - Ascites, pleural or pericardial effusions, skin edema (>5mm)
  - May also have placentomegaly (≥4mm in 2nd trimester or ≥6mm in 3d)
  - Polyhydramnios (>8 cm DVP)

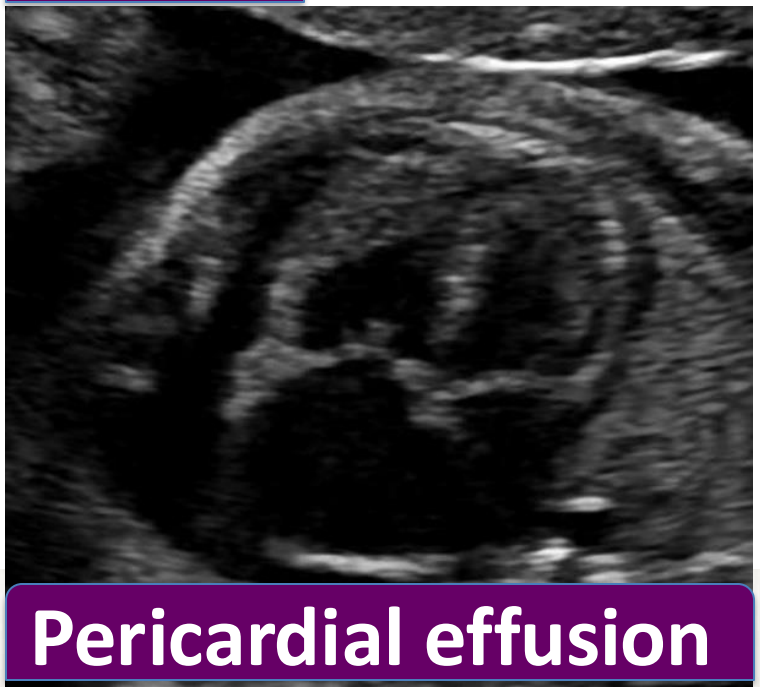
Hydrops: Two or more of these effusions



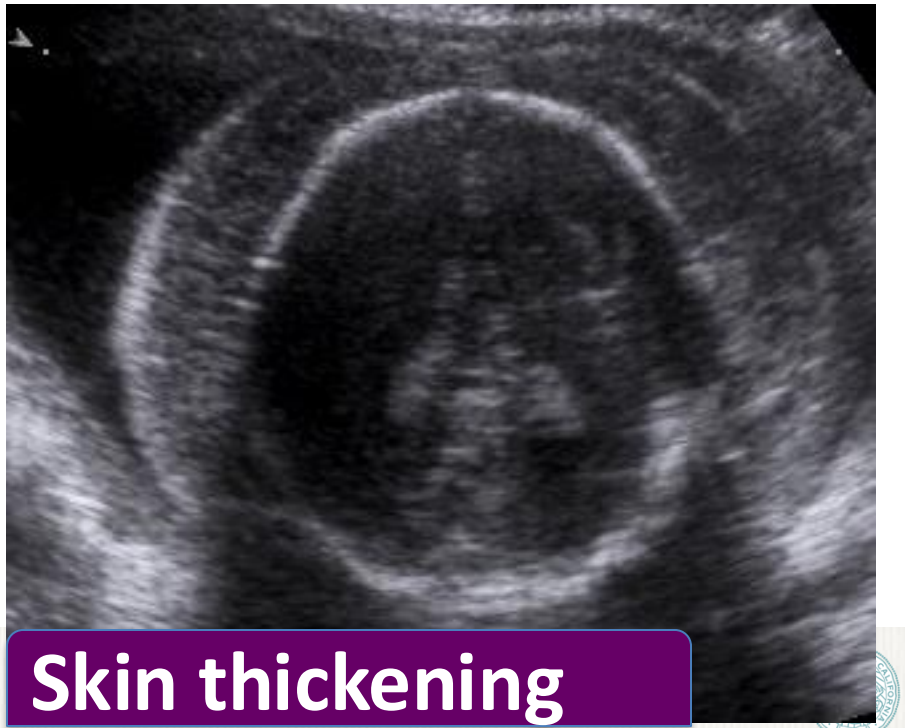
Ascites



Pleural effusion

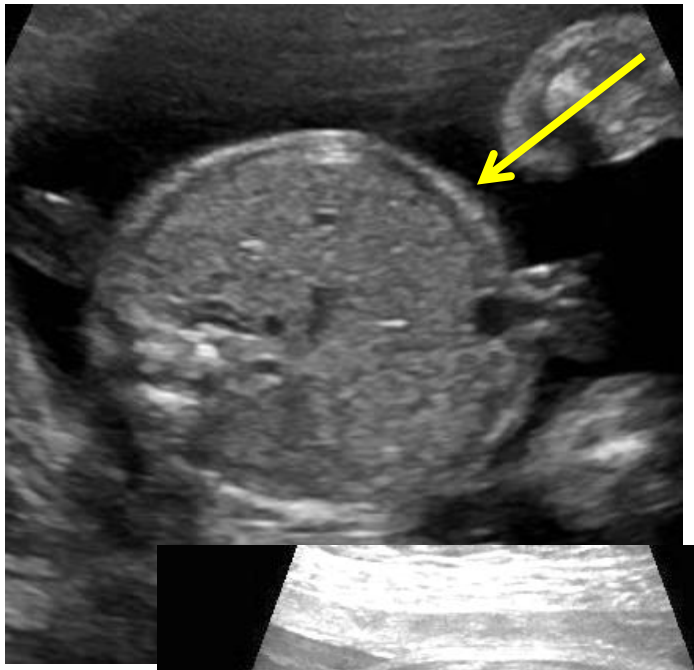


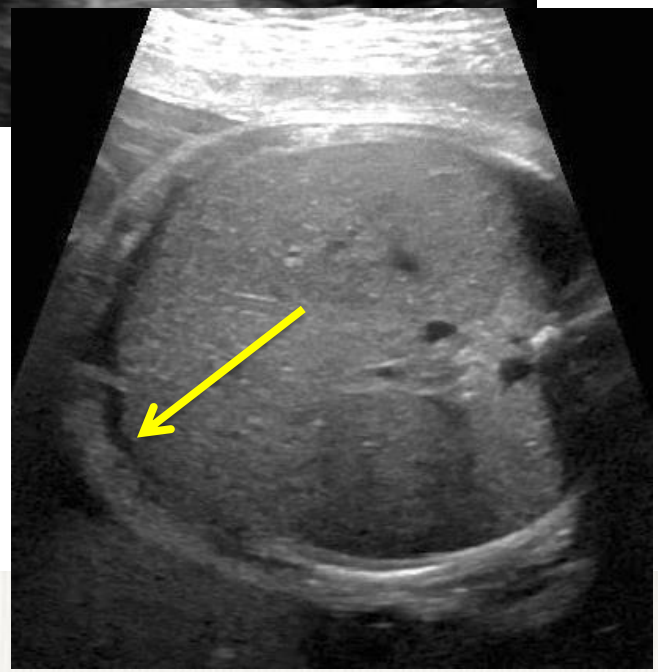
Pericardial effusion

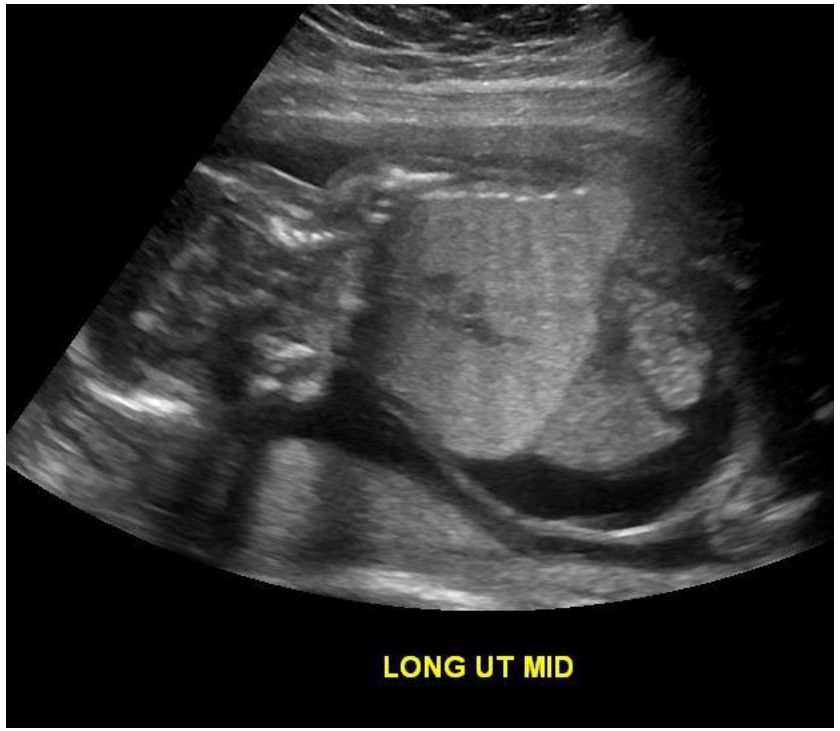


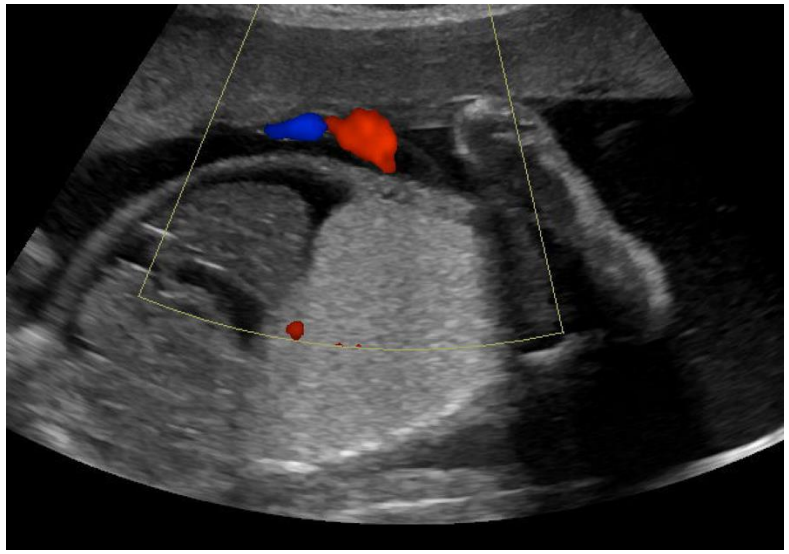
Skin thickening

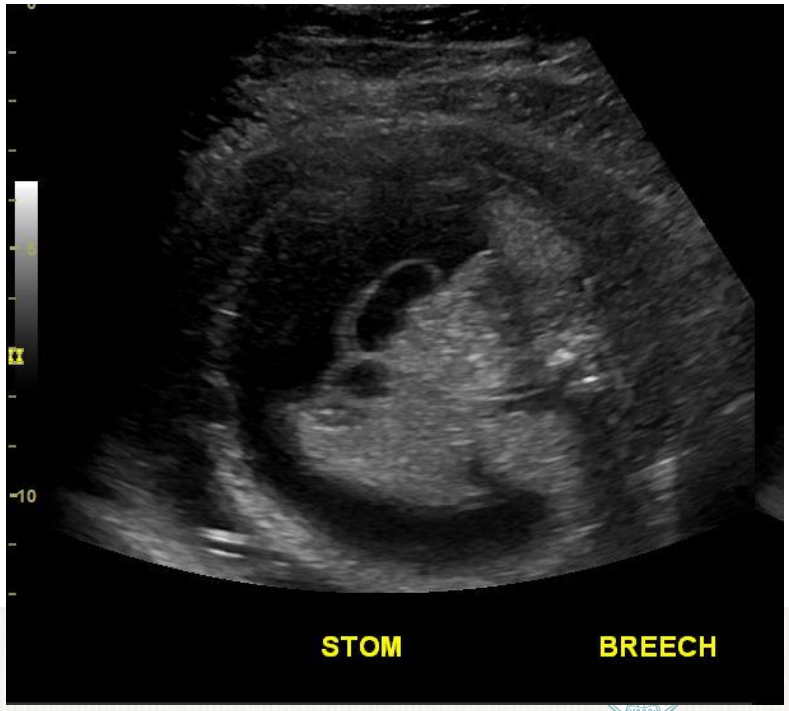
Ascites vs Pseudo-ascites



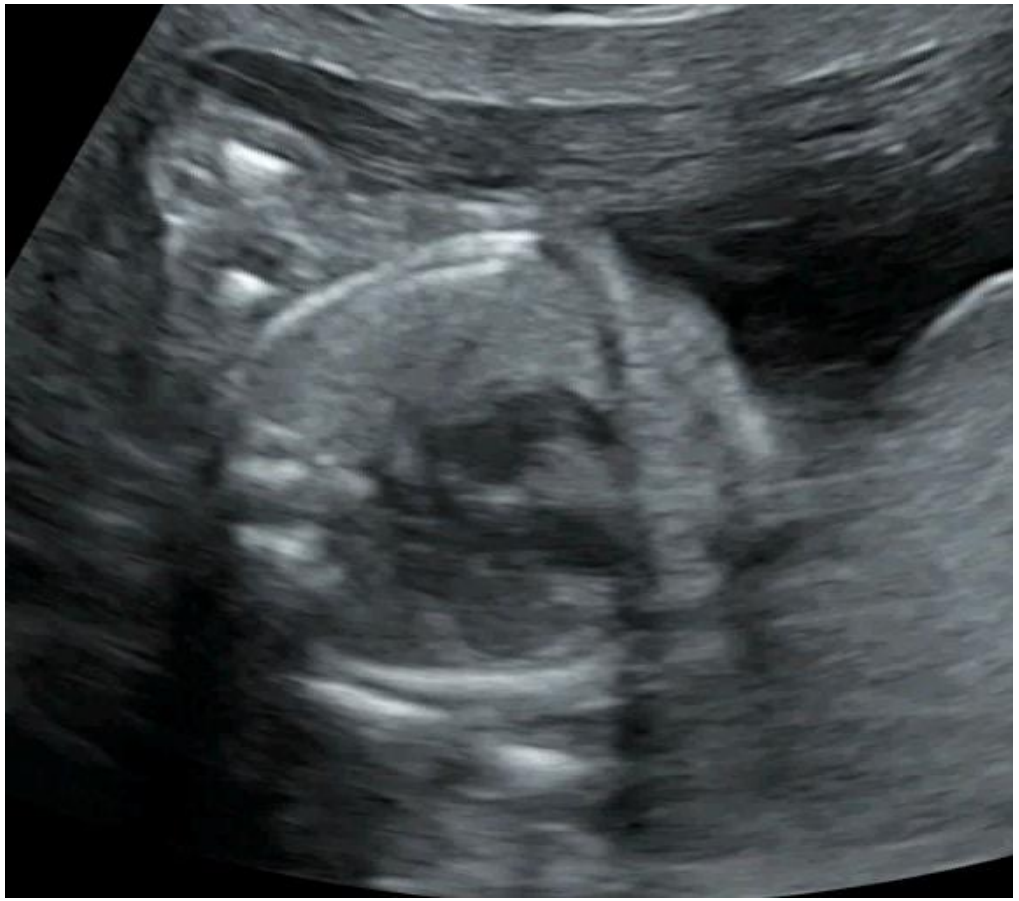


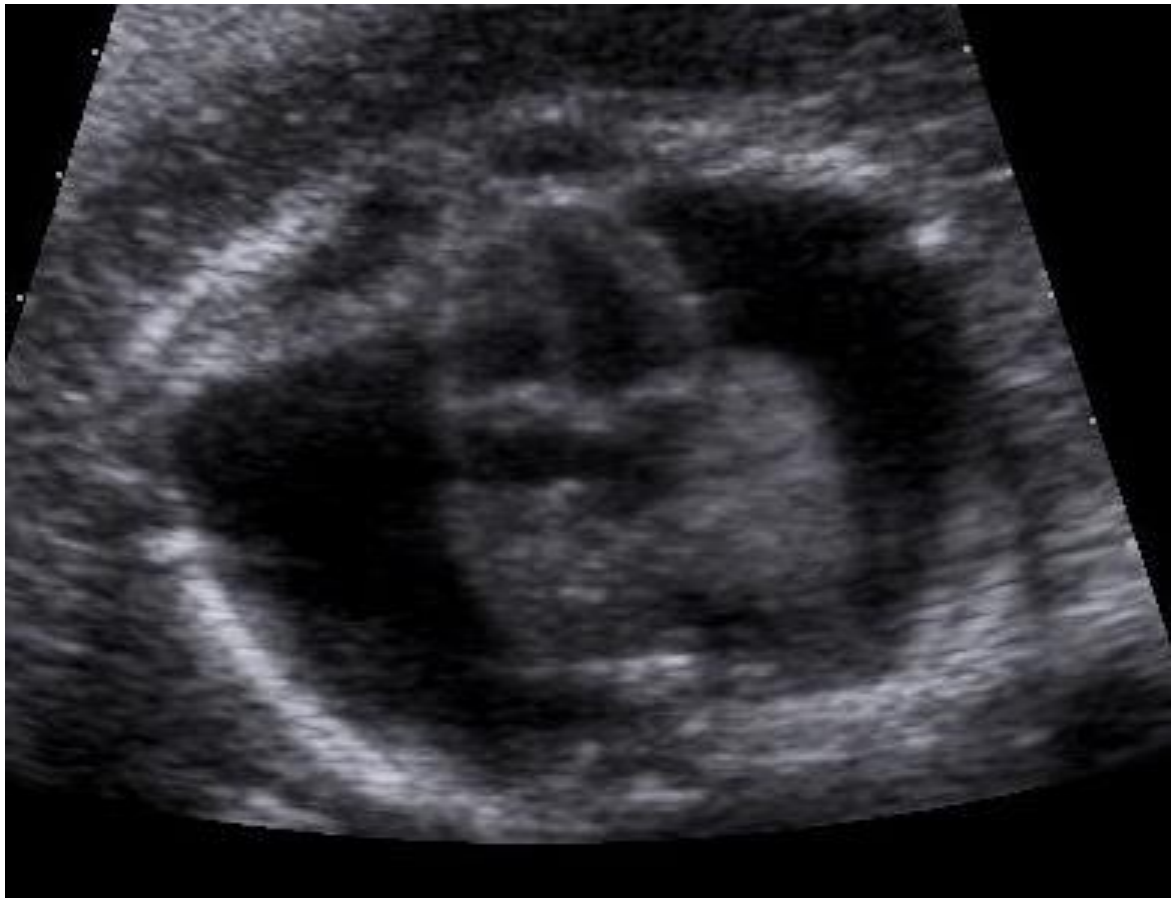






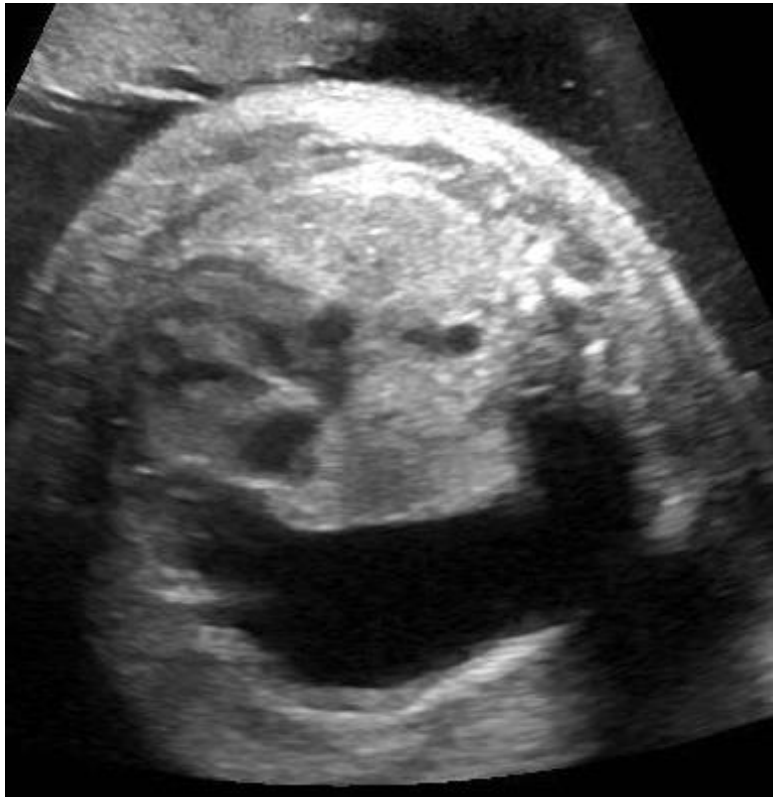
Pericardial and pleural effusions



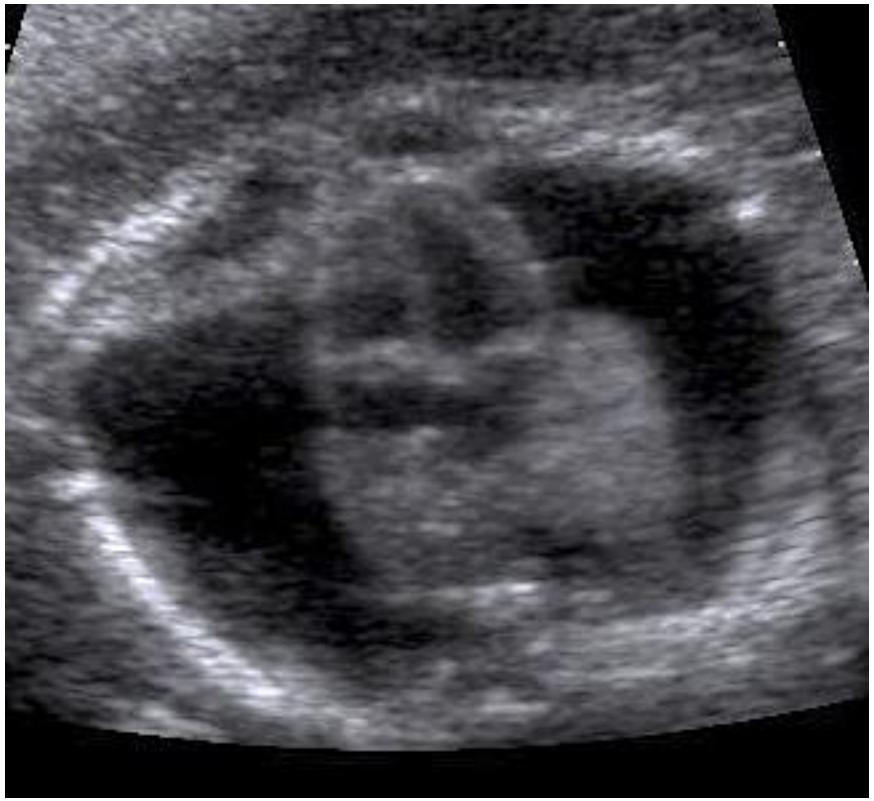


Pleural effusions

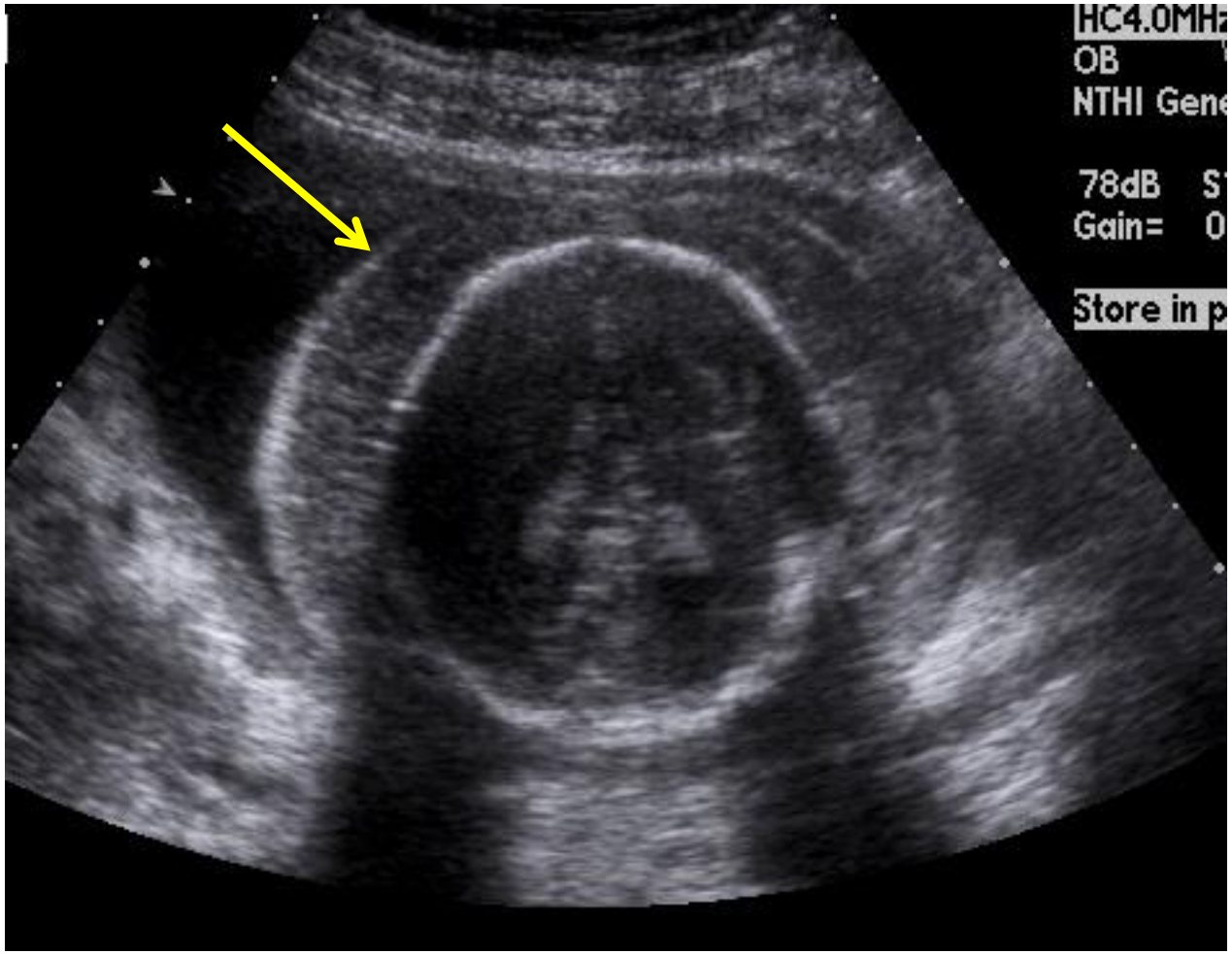
Unilateral

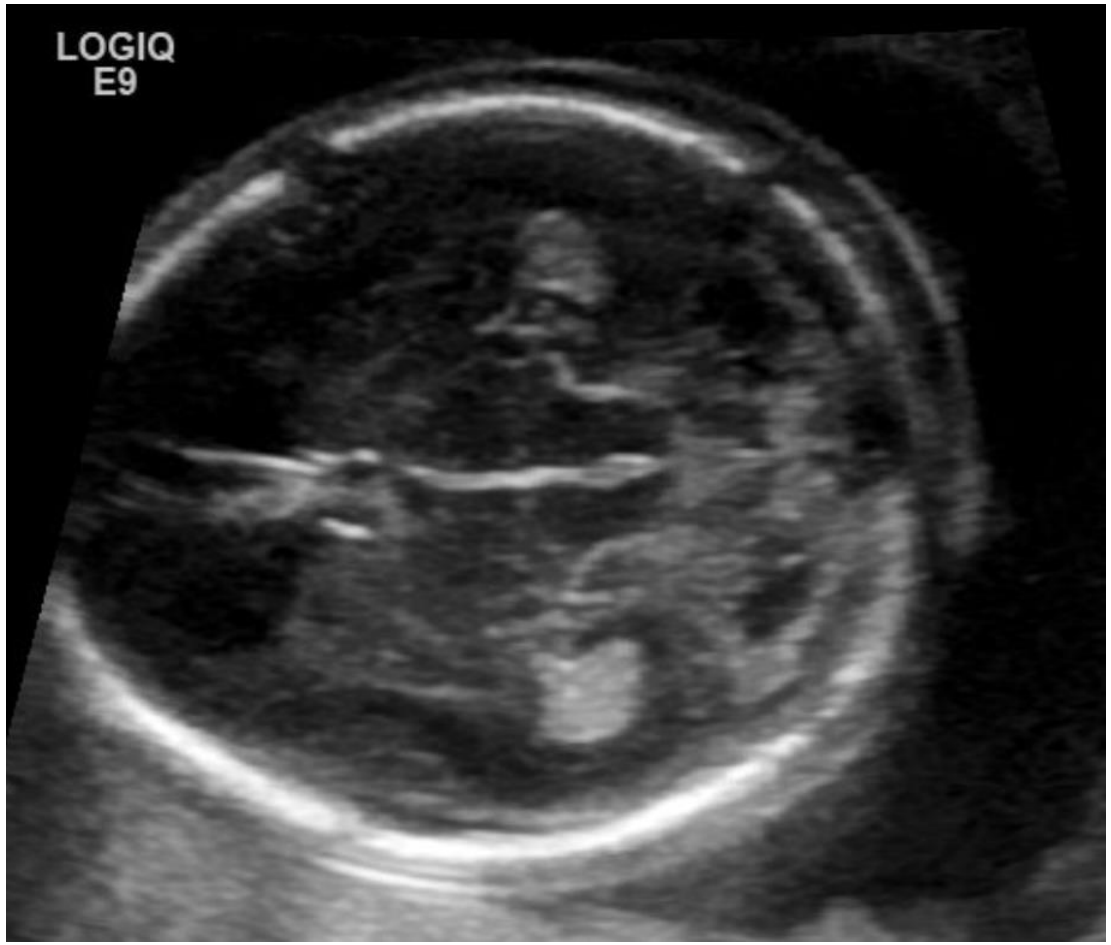


Bilateral

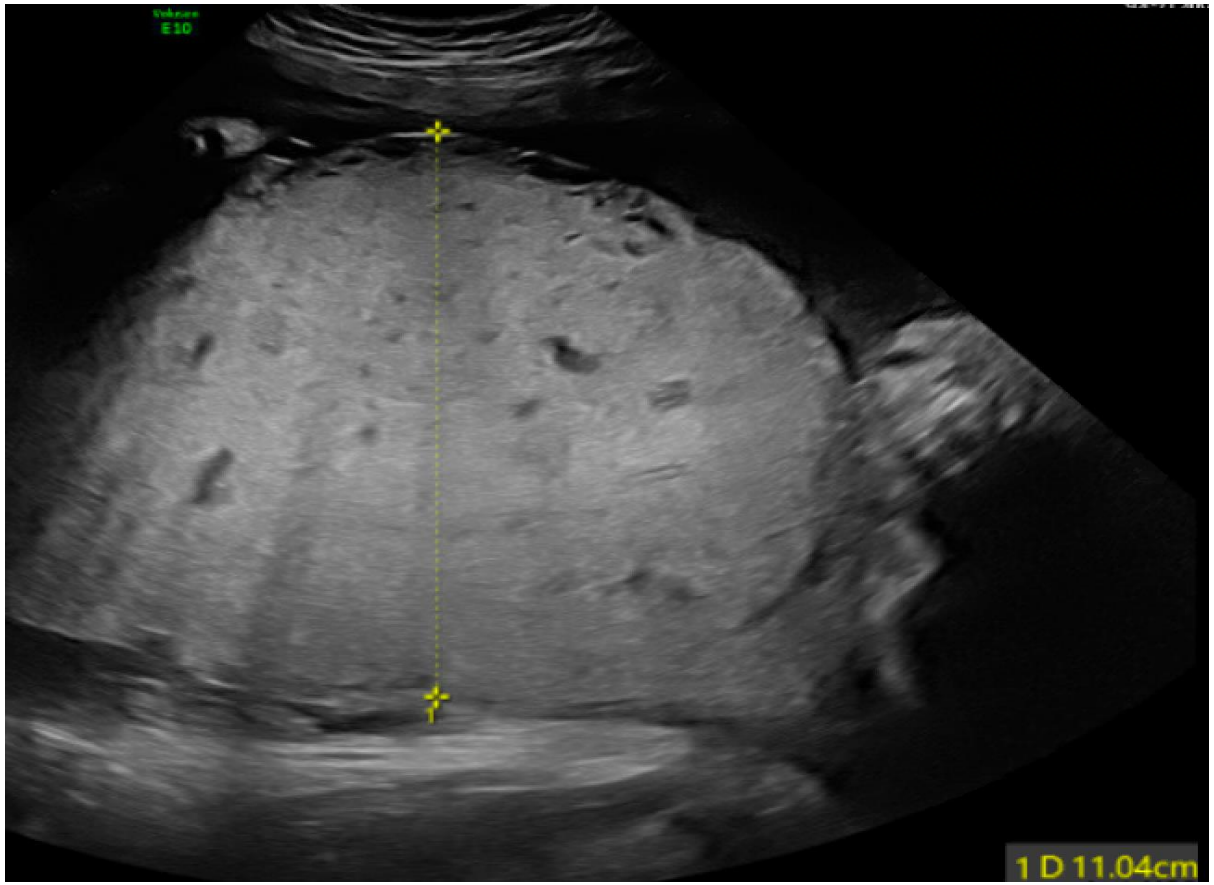


Skin thickening (≥5mm)

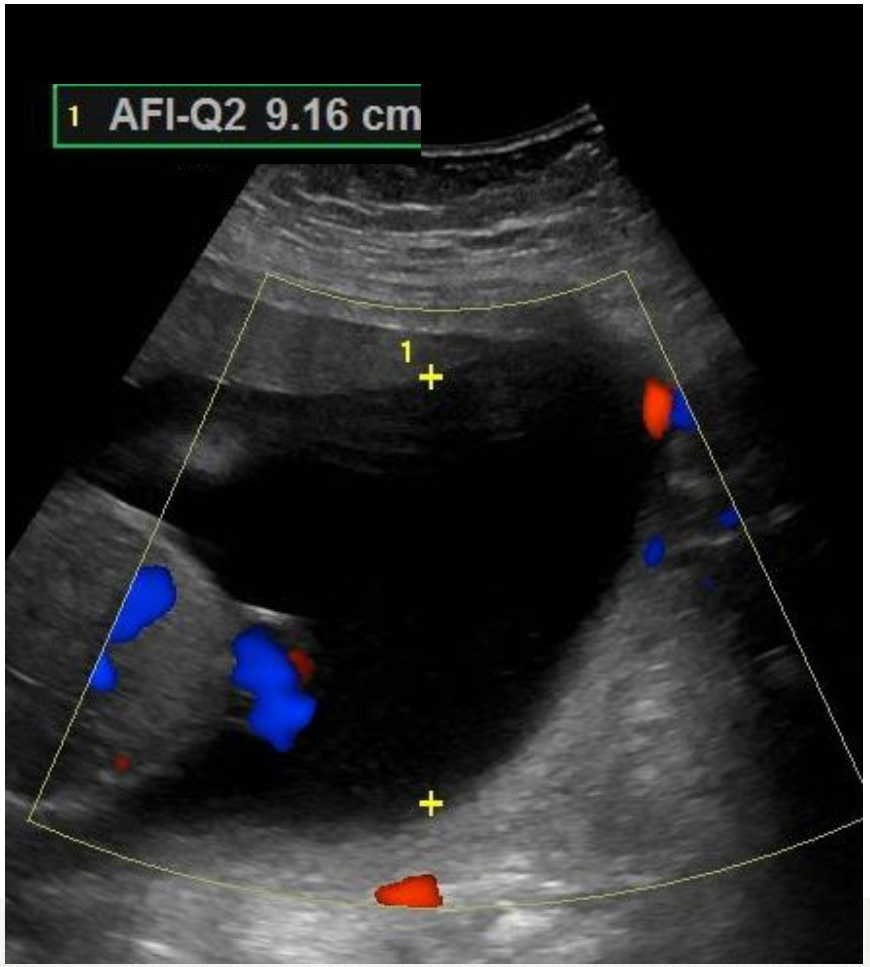




Placental thickening (≥4mm or ≥6 mm)



Polyhydramnios (DVP >8cm or AFI >25cm)

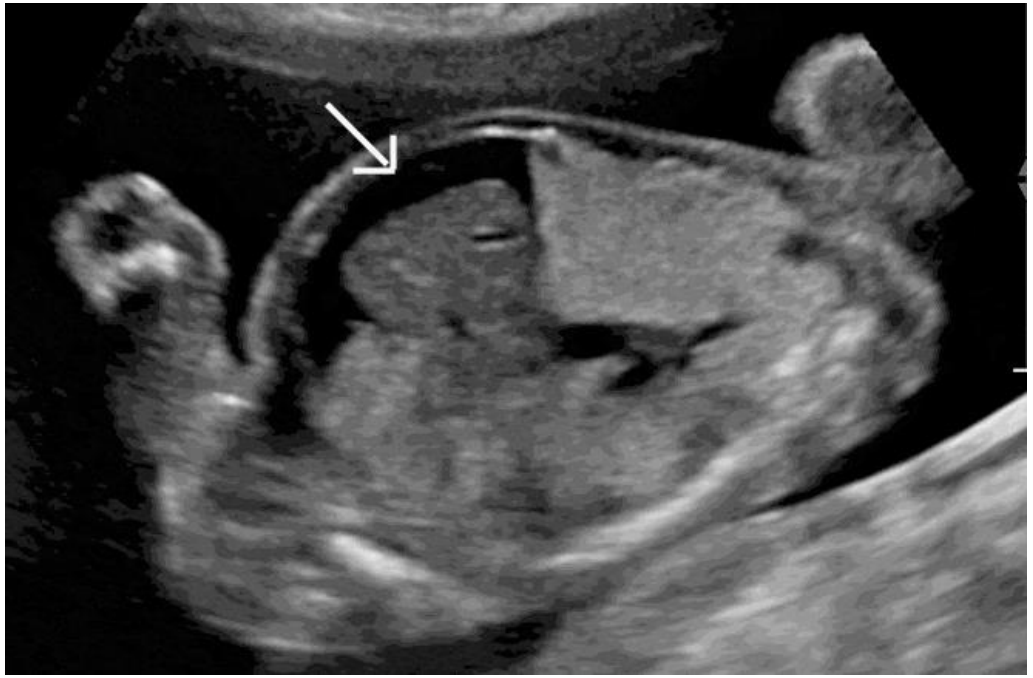


Hydrops Fetalis (ὕδωρ)

1/3000 pregnancies

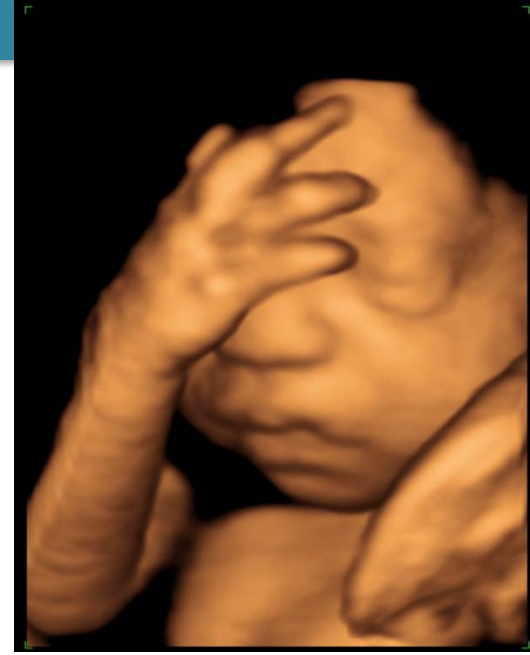
10% immune

90% non-immune



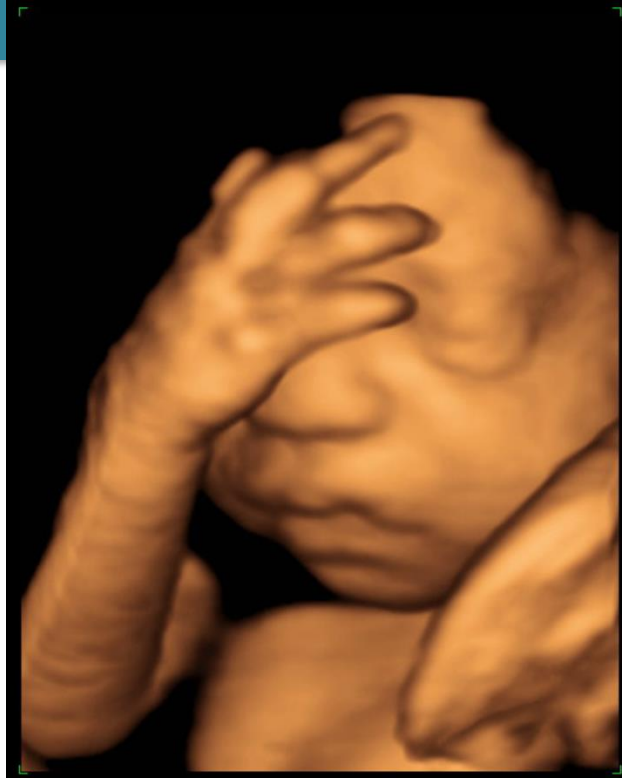
- Extensive differential diagnosis
- Historically, diagnosis has been made in <50% of cases

There are many causes of nonimmune hydrops: Final common pathway of many conditions



○ Cardiovascular	17-35%	○ GI	0.5-4%
○ Chromosomal	7-16%	○ Lymphatic dysplasia	5-6%
○ Hematologic	4-12%	○ Tumors	2-3%
○ Genetic	5-10%	○ Skeletal dysplasia	3-4%
○ Infectious	5-7%	○ Syndromic	3-4%
○ Thoracic	6%	○ Inborn errors	1-2%
○ TTTS	3-10%	○ Miscellaneous	3-15%
○ Urinary Tract	2-3%	○ Unknown	15-25%

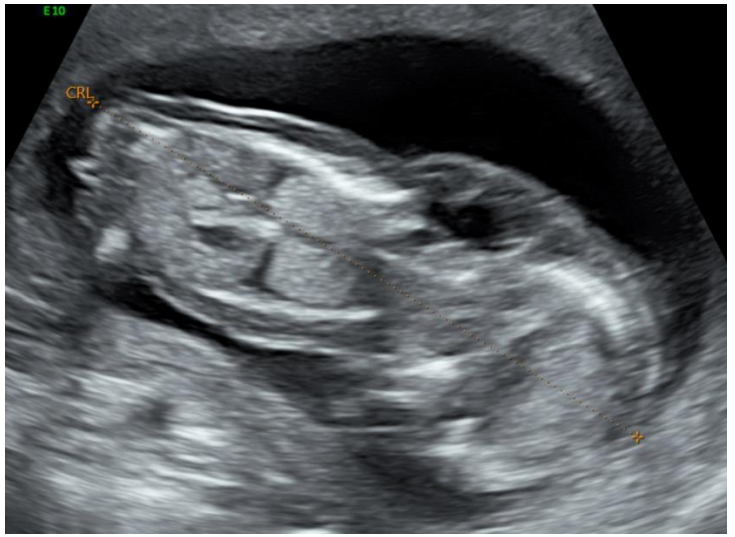
Causes of nonimmune hydrops

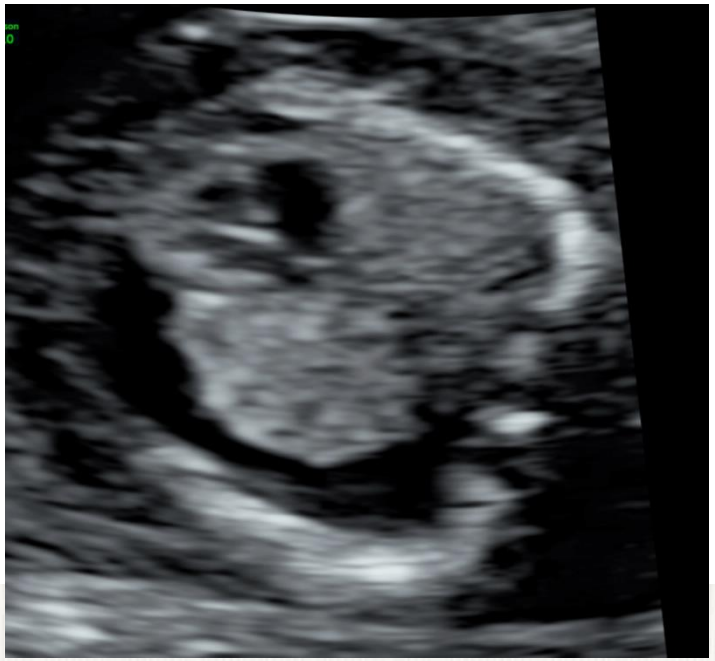


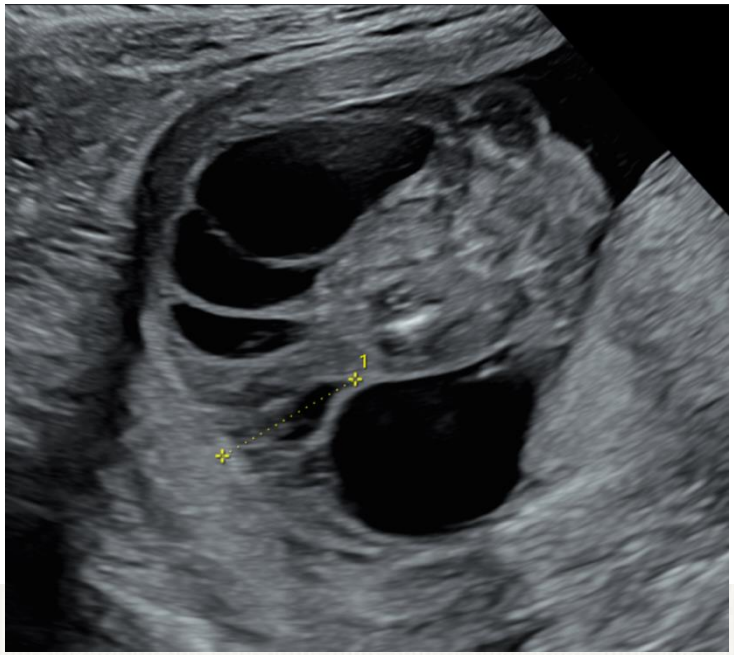
- Chromosomal
  - 45,X (Turner syndrome); Trisomy 21 (Down syndrome)
  - ➢ Most common cause early in pregnancy
- Cardiovascular
  - Arrhythmias, structural, cardiomyopathies, tumors, vascular
- Genetic
  - Noonan syndrome, inborn errors of metabolism
- Hematologic
  - Anemia (acquired or inherited)
  - ➢ Many are treatable
- Infectious
  - Parvovirus, CMV, syphilis, toxoplasmosis

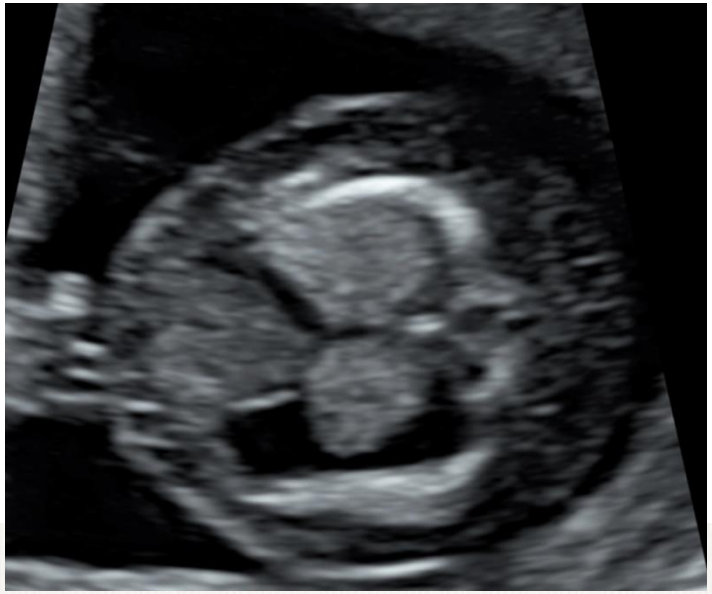
Chromosomal abnormalities associated with hydrops

- 45,X (Turner syndrome)
- 47,+21 (Down syndrome)
- Trisomies 13 and 18
- Triploidy



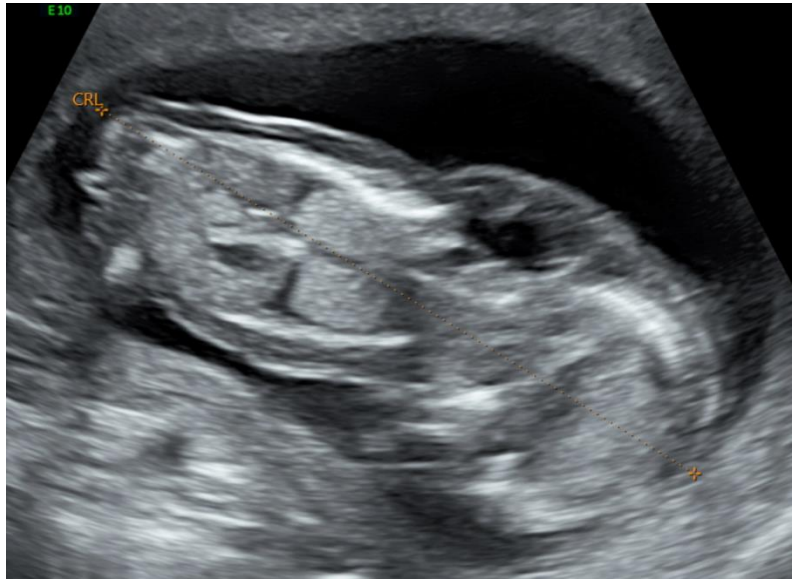


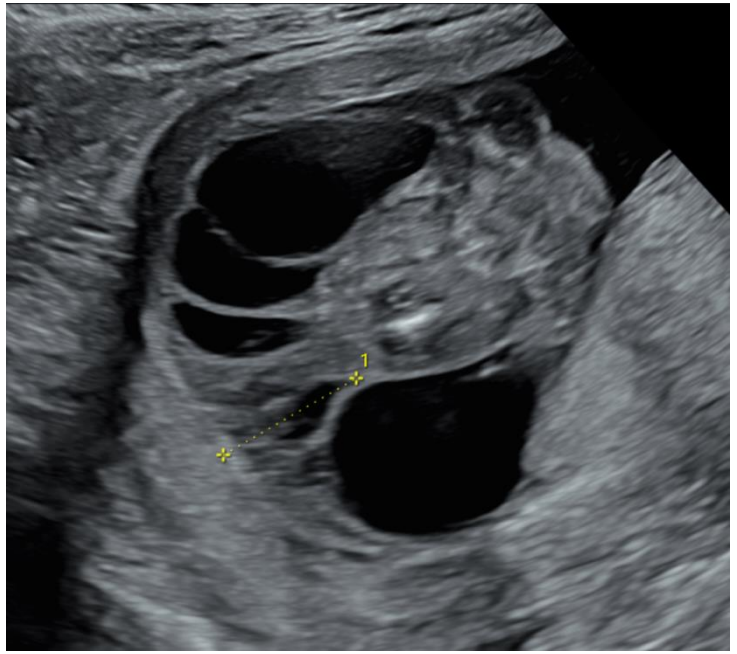


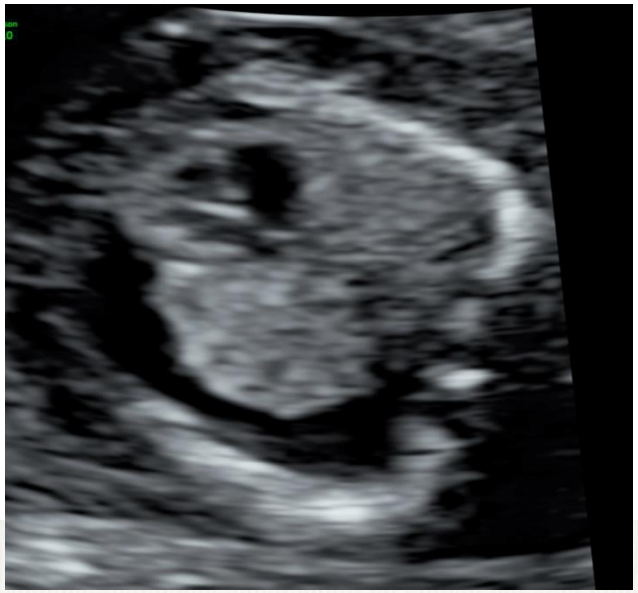


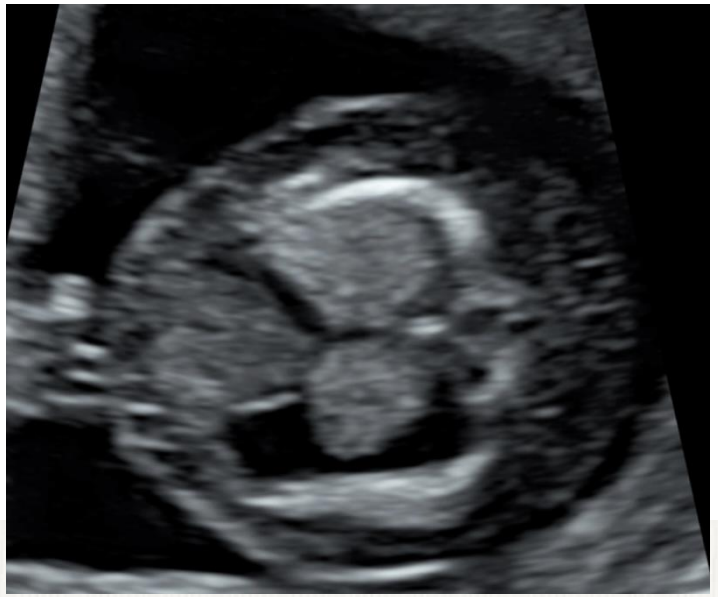
Turner syndrome (45,X or monosomy X)

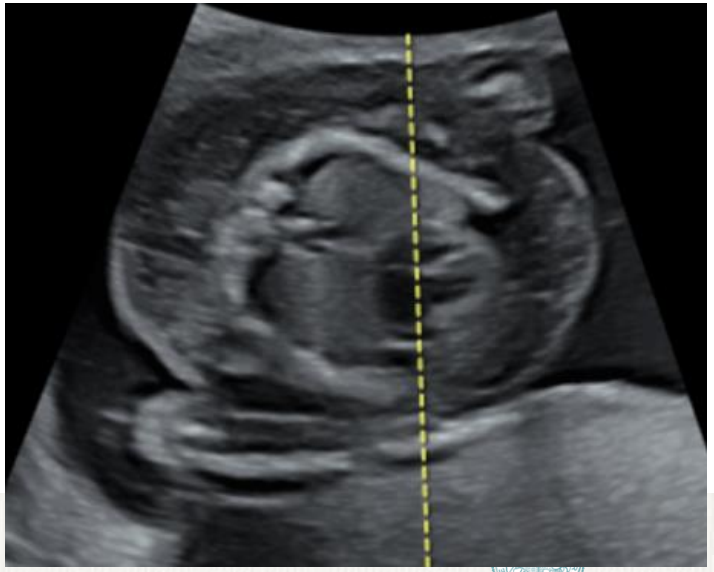
- Cystic hygroma
- Skin edema
- Generalized hydrops
- Left-sided heart defects





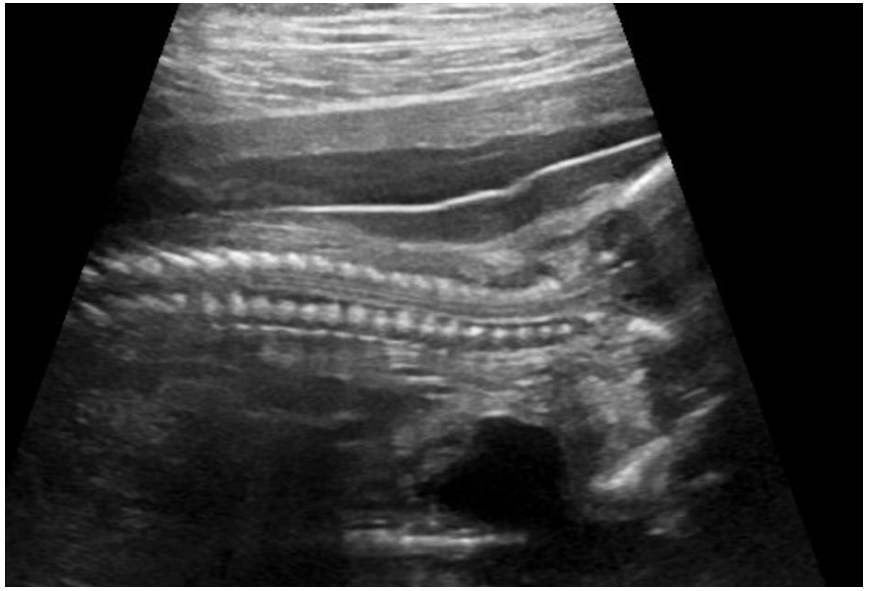


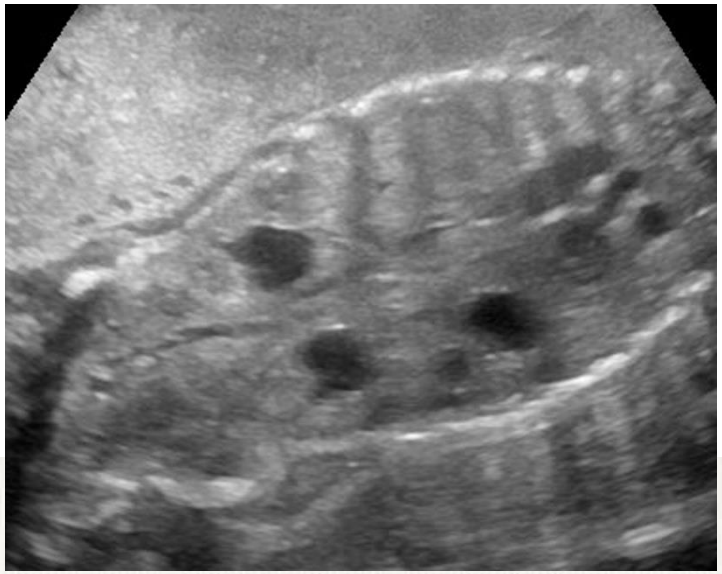


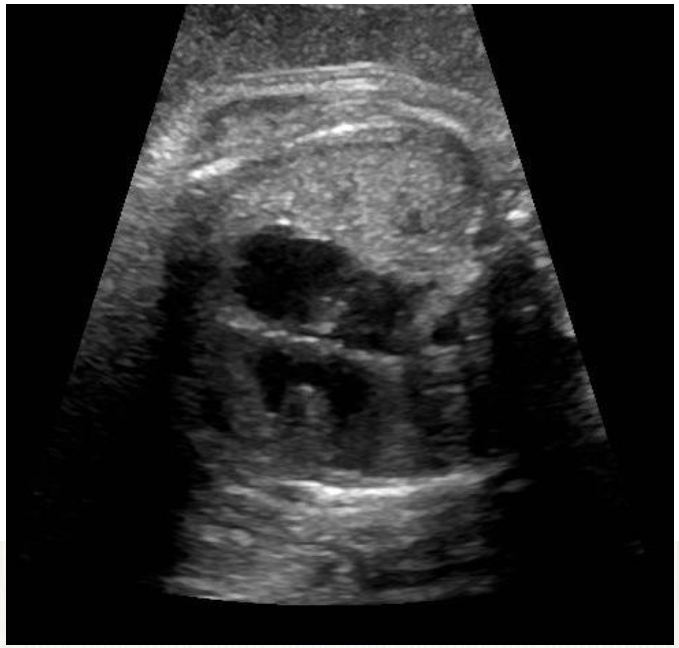


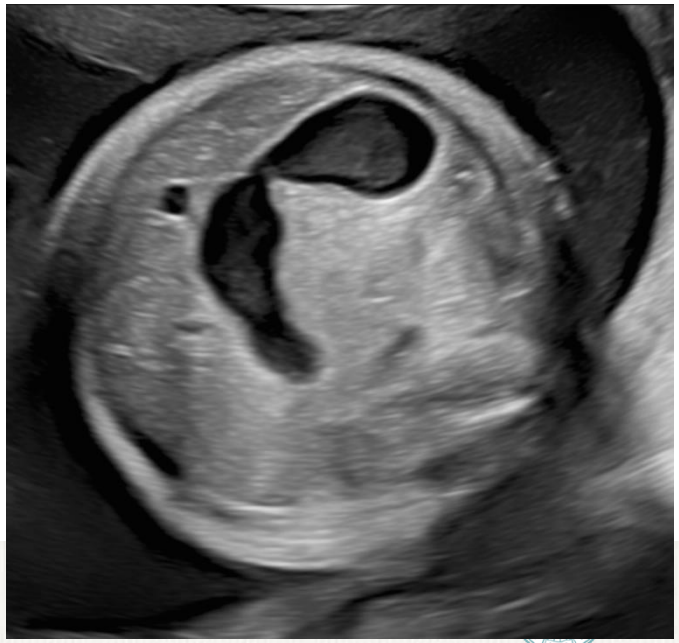
Down syndrome (trisomy 21)

- Enlarged nuchal translucency
- Cardiac anomalies (atrioventricular septal defects)
- Duodenal atresia
- Hydronephrosis

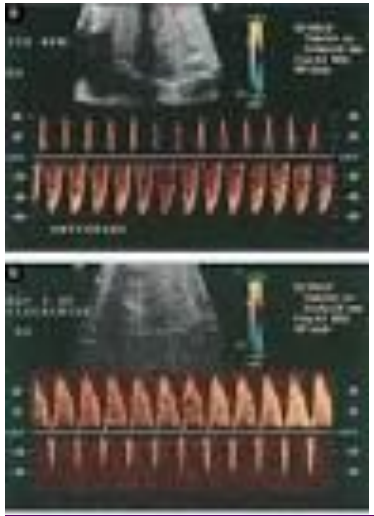




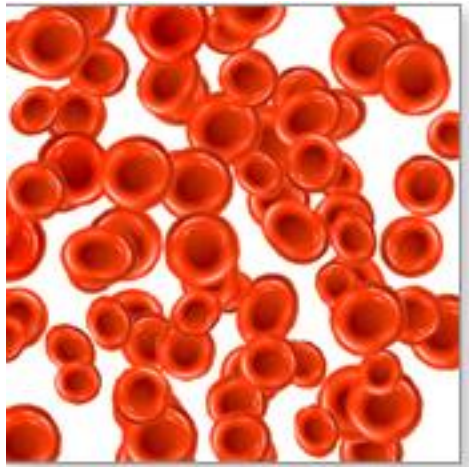


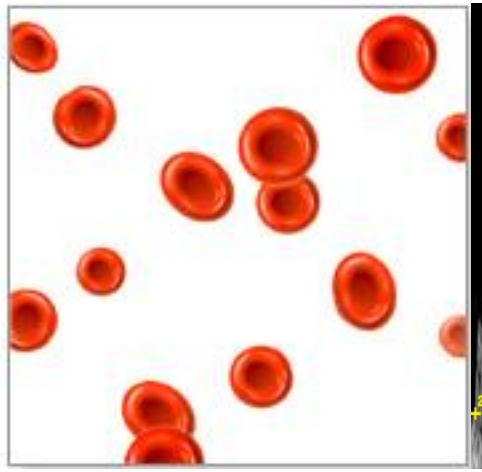


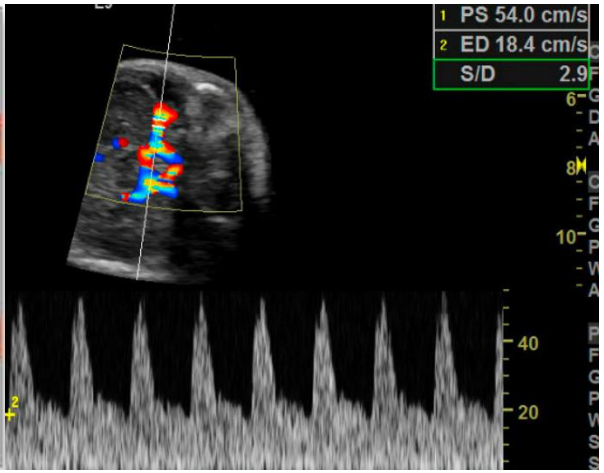
There are a few treatable causes of NIHF



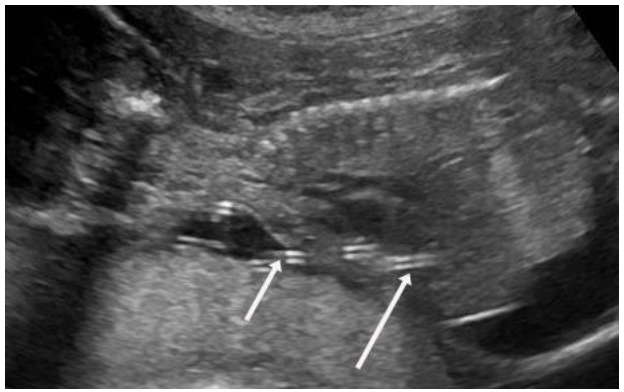
Tachycardia



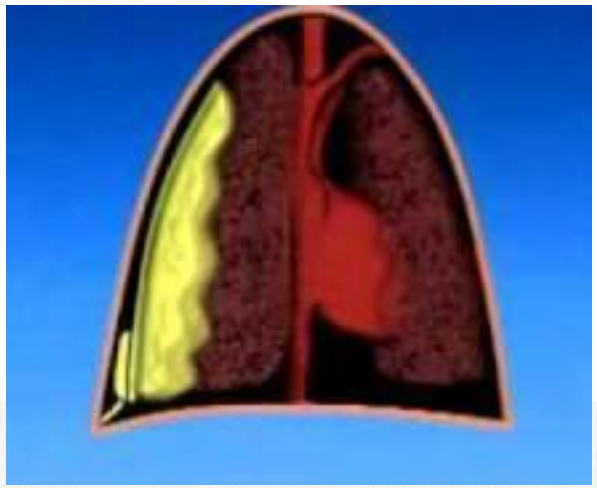




Anemia



Pleural Effusion

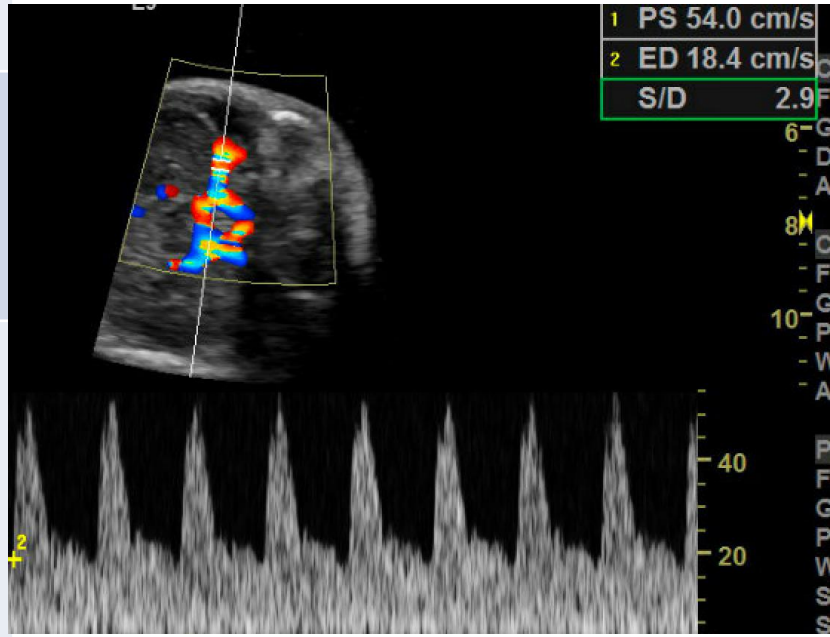


Chest mass

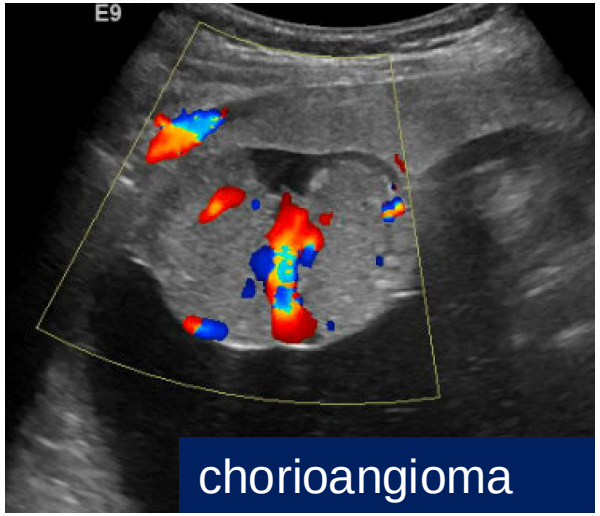
Causes of Fetal Anemia

Categories	Cause
Immune	Red blood cell alloimmunization Rh Atypical antigens
Infectious	Parvovirus CMV Toxoplasmosis Syphilis
Genetic	Metaboic diseases (e.g. Mucopolysaccharidosis type VII, Niemann-Pick disease, Gaucher disease) Blackfan-Diamond anemia Fanconi anemia Alpha-thalassemia Pyruvate kinase deficiency G-6-PD deficiency
Other	Aneuploidy TTTS; Twin anemia-polycythemia sequence Fetomaternal hemorrhage Maternal acquired red cell aplasia

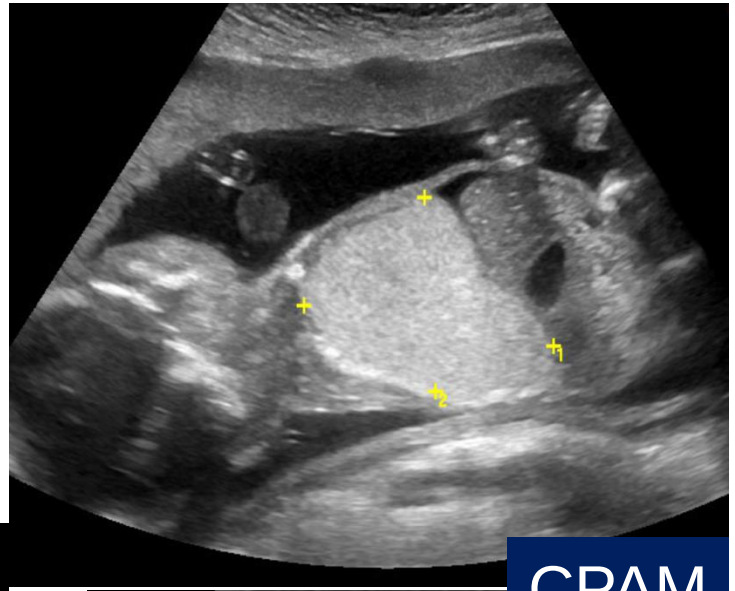
Fetal anemia can be treated



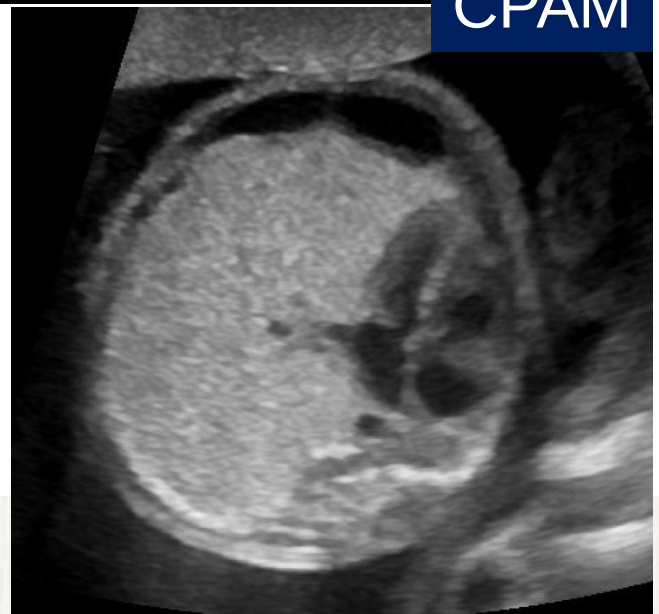
Large masses can cause hydrops

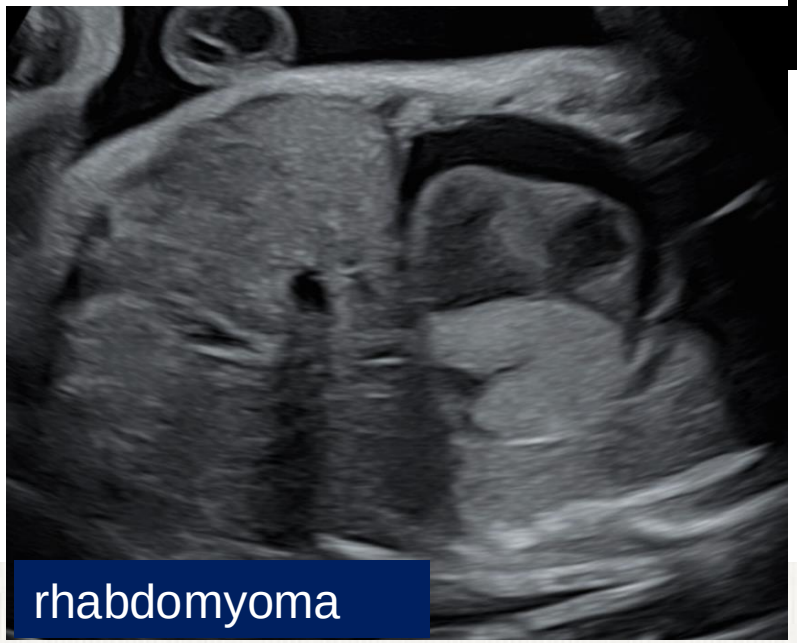


chorioangioma

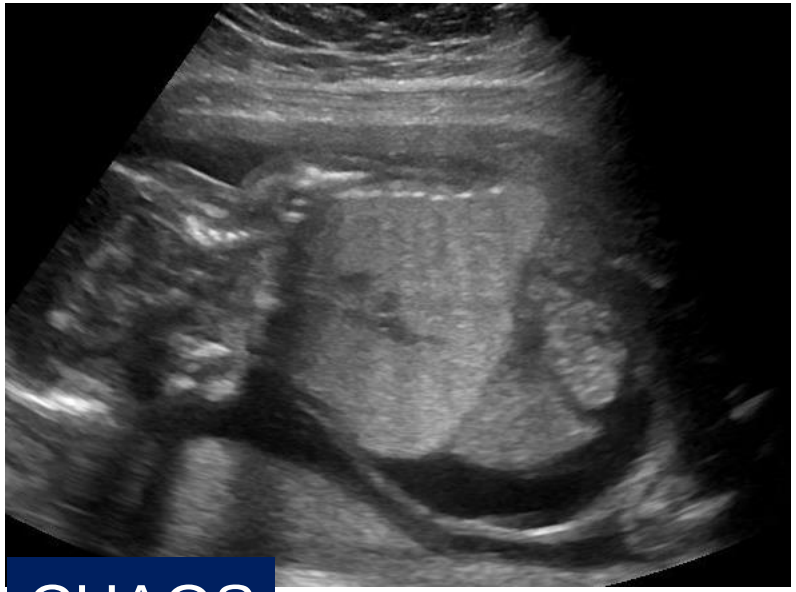


CPAM

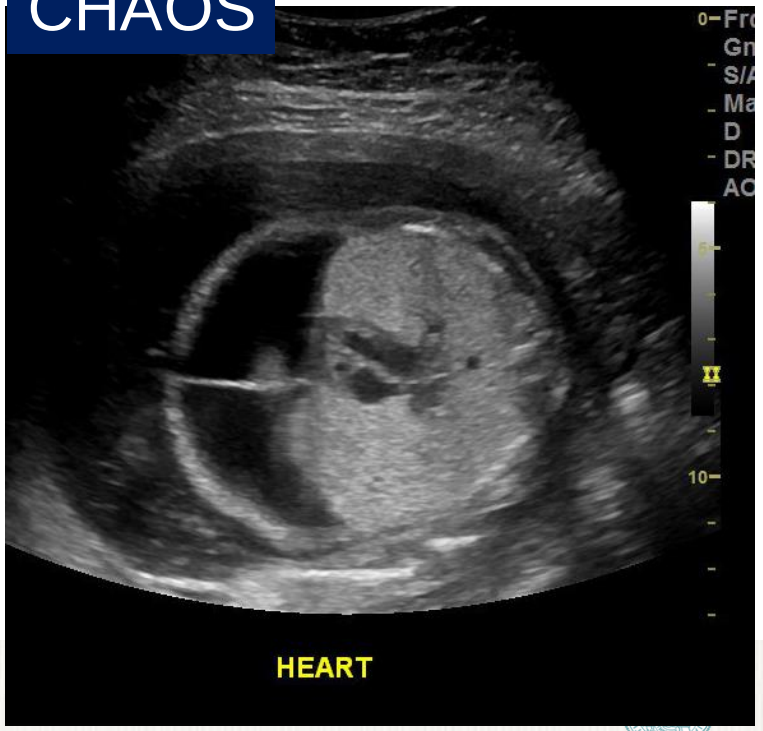




rhabdomyoma



CHAOS



Evaluation of non-immune hydrops

Review family, medical, and obstetric history including genetic diseases and viral exposures

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Maternal labs: indirect Coombs, Kleihauer-Betke, cfDNA
Risk factors for alpha thalassemia (MCV, ancestry)

→ Send molecular testing for alpha thalassemia if MCV <80 fL or high-risk ancestry

↓

Detailed ultrasound including fetal echo, MCA Dopplers, and evaluation of placenta (chorioangioma)

Structurally normal	MCA Dopplers >1.5 MoM[a]	Structurally abnormal
Diagnostic genetic testing with CMA or karyotype; PCR for parvovirus, CMV, and toxoplasmosis; review syphilis testing[b]	Diagnostic genetic testing with CMA or karyotype; offer PCR for parvovirus, CMV, and toxoplasmosis; review syphilis testing[b]	Diagnostic genetic testing with CMA or karyotype
↓	↓	↓
If prior evaluations non-diagnostic, offer gene panel[c] or exome sequencing	If prior evaluations non-diagnostic, offer gene panel[c] or exome sequencing	If prior evaluations non-diagnostic, offer gene panel[c] or exome sequencing

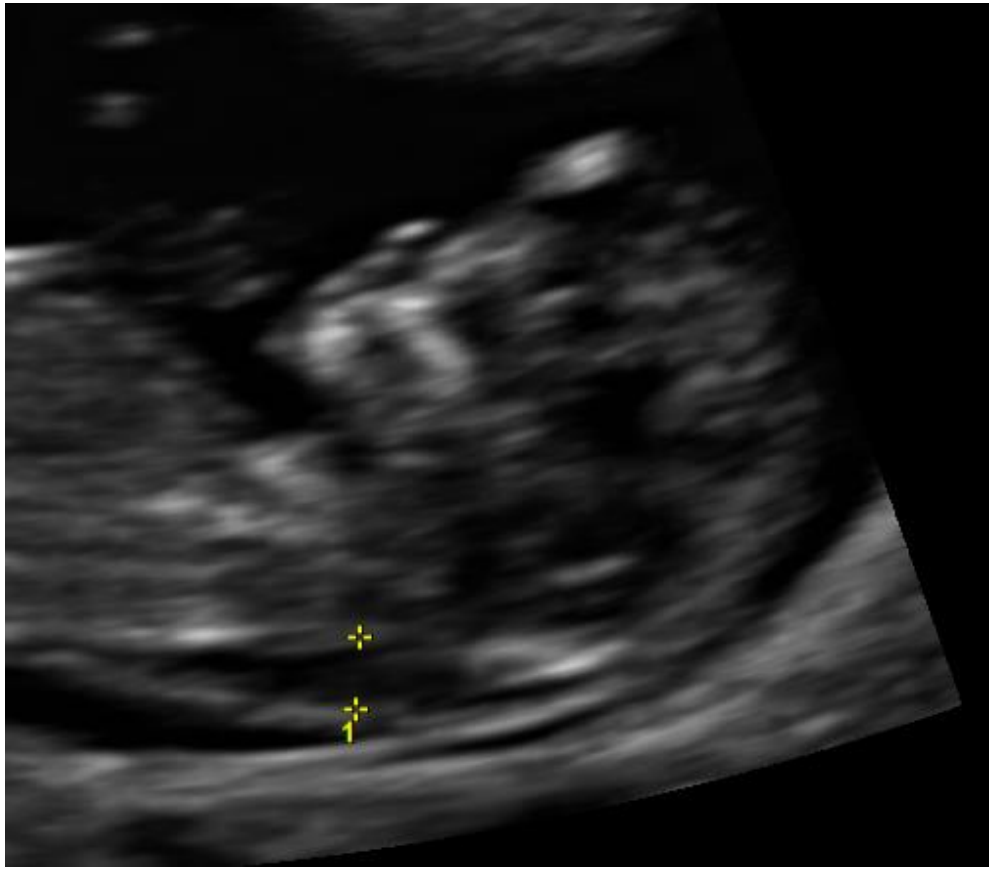
Prognosis and Recurrence of Hydrops by Cause

Cause	Prognosis	Recurrence risk
Chromosomal	Poor	About 0.5-1%
Cardiac	Poor	2-3%
Other structural	Usually poor	Varies
Pleural effusion	Good with treatment	Low
CPAM	Good with treatment	Low
Hematologic (thalassemia)	Poor	25%
Anemia from alloimmunization	Good with treatment	50-100%
Metabolic	Poor	25%
Parvovirus	Usually good	0%

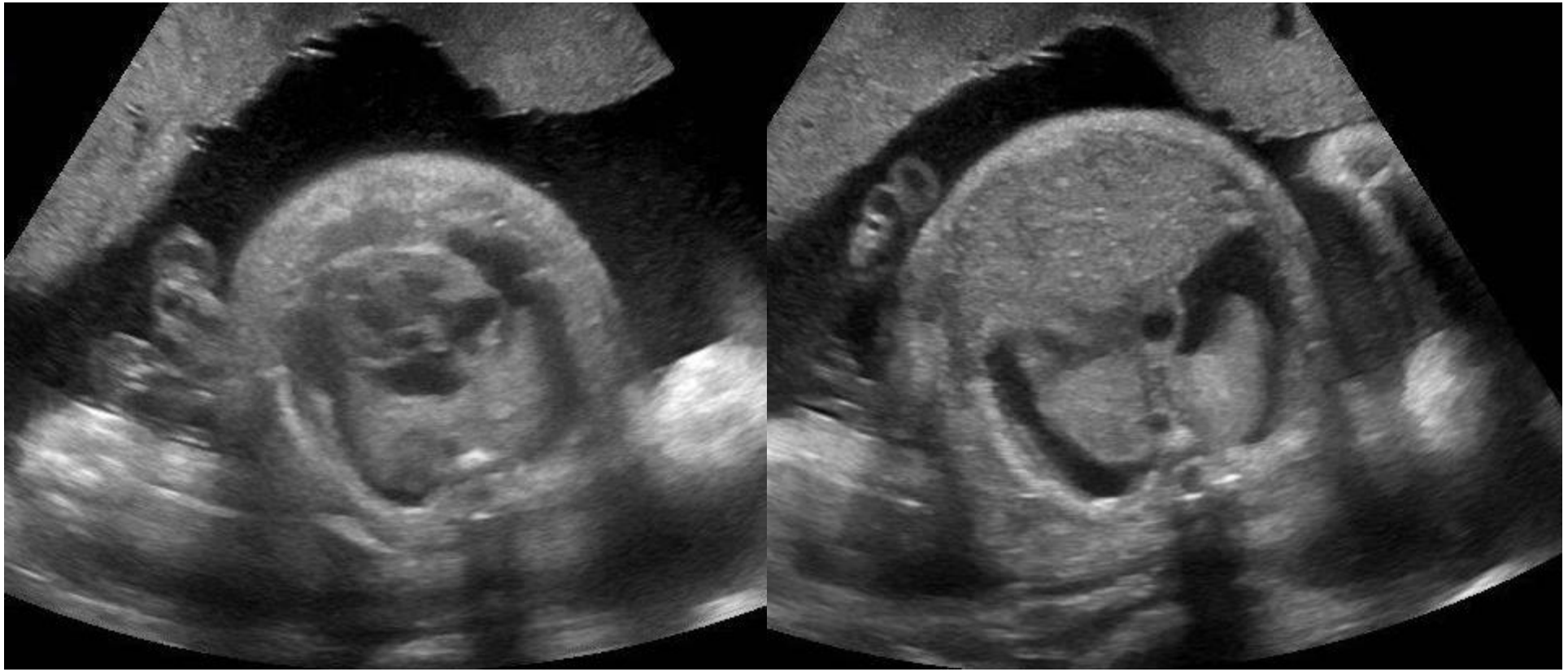
38 y.o. G2P1

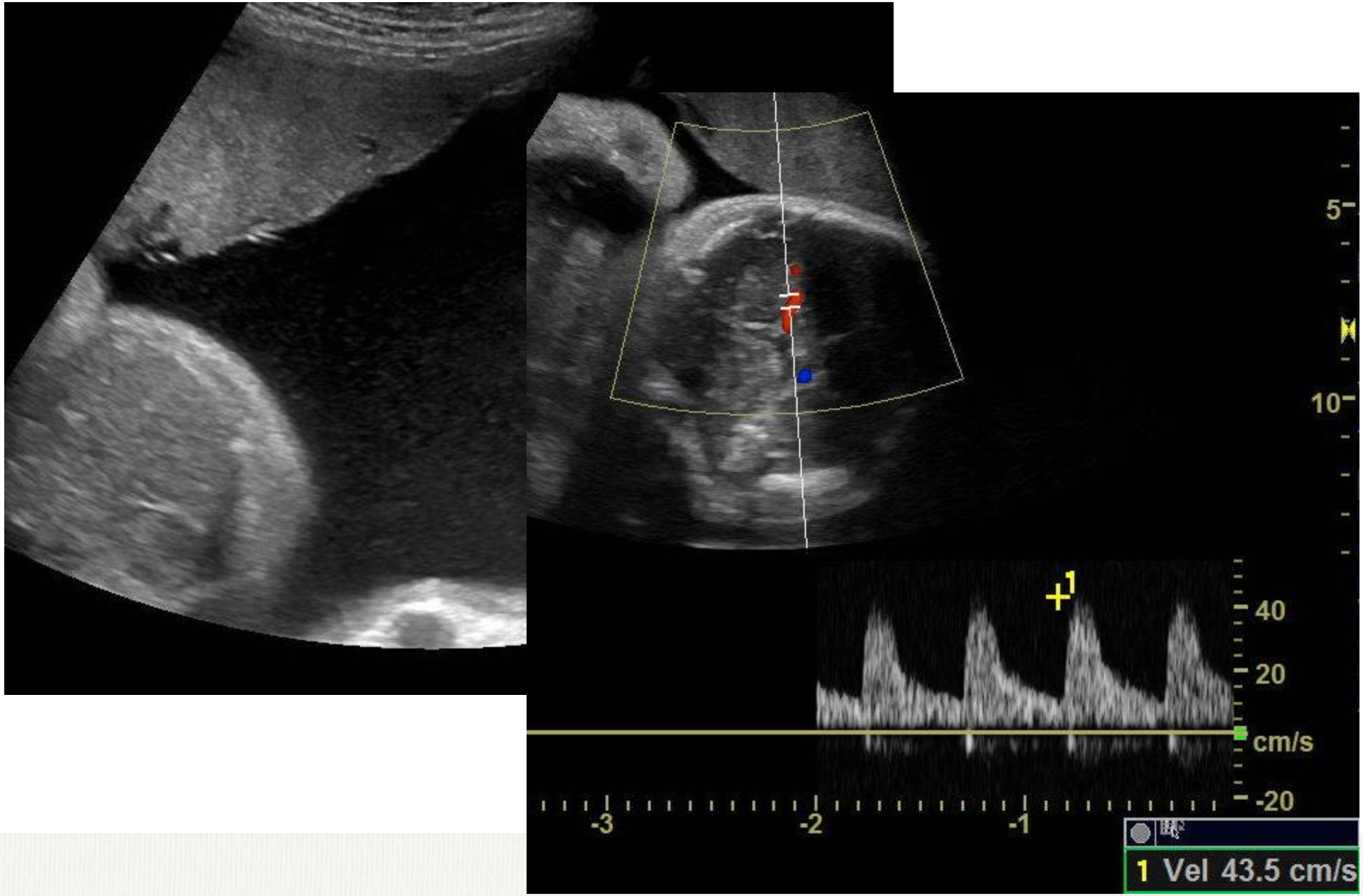
- Seen for CVS at 11 wks
- NT 3 mm

- 46XX
- Normal microarray
- Normal 20 week scan



32 wks: US for size greater than dates




5
10
40
20
cm/s
-20
-3
-2
-1
1 Vel 43.5 cm/s

Admitted for observation

- Delivered after corticosteroids
- Baby critically ill at birth with pulmonary hypertension
- Died at 5 days of age
- PTPN11 testing positive, consistent with a diagnosis of Noonan Syndrome
- Parent's testing negative

European Journal of Human Genetics (2013) 21, 936–942

www.nature.com/ejhg

ARTICLE

Prenatal diagnostic testing of the Noonan syndrome genes in fetuses with abnormal ultrasound findings

Ellen A Croonen[1], Willy M Nillesen[2], Kyra E Stuurman[3], Gretel Oudesluijs[4], Ingrid MBM van de Laar[4], Liesbeth Martens[2], Charlotte Ockeloen[2], Inge B Mathijssen[5], Marga Schepens[2], Martina Ruiterkamp-Versteeg[2], Hans Scheffer[2], Brigitte HW Faas[2], Ineke van der Burgt[2] and Helger G Yntema*[,2]

- 17% of fetuses with enlarged NT and/or hydrops features had variants in one of Noonan genes

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Exome Sequencing for Prenatal Diagnosis in Nonimmune Hydrops Fetalis

T.N. Sparks, B.R. Lianoglou, R.R. Adami, I.D. Pluym, K. Holliman, J. Duffy, S.L. Downum, S. Patel, A. Faubel, N.M. Boe, N.T. Field, A. Murphy, L.C. Laurent, J. Jolley, C. Uy, A.M. Slavotinek, P. Devine, U. Hodoglugil, J. Van Ziffle, S.J. Sanders, T.C. MacKenzie, and M.E. Norton, for the University of California Fetal–Maternal Consortium and the University of California, San Francisco Center for Maternal–Fetal Precision Medicine*

N=127 cases after non-diagnostic karyotype or microarray

Genetic causes of hydrops in cases with normal karyotype

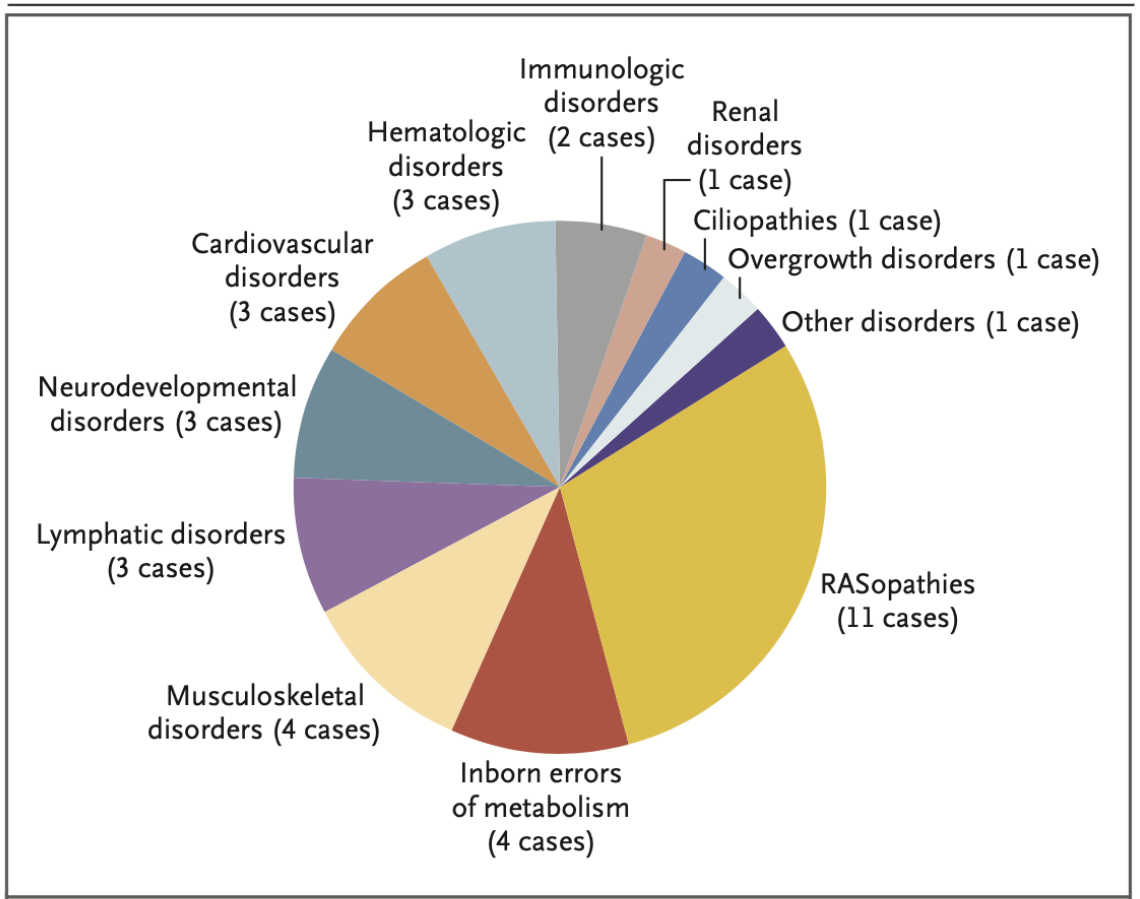


Figure 2. Categories of Genetic Disorders Detected through Exome Sequencing in Cases of NIHF.

RASopathies were defined as disorders affecting the RAS–MAPK cell-signaling pathway.

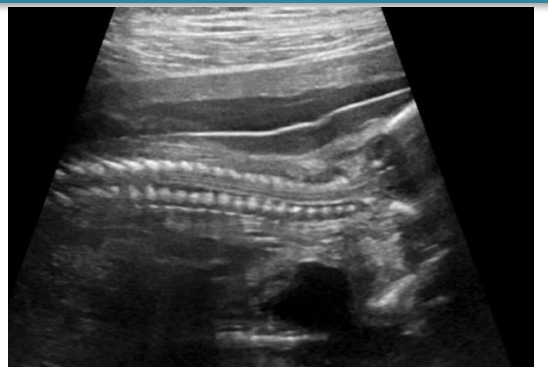
- Diagnostic variant in 29% (37/127)
- Among diagnostic variants:
  - 30% RASopathies (e.g.Noonan)
  - 11% each inborn errors and musculoskeletal
  - 8% each lymphatic, neurodevelopmental, cardiovascular, hematologic
  - Many others

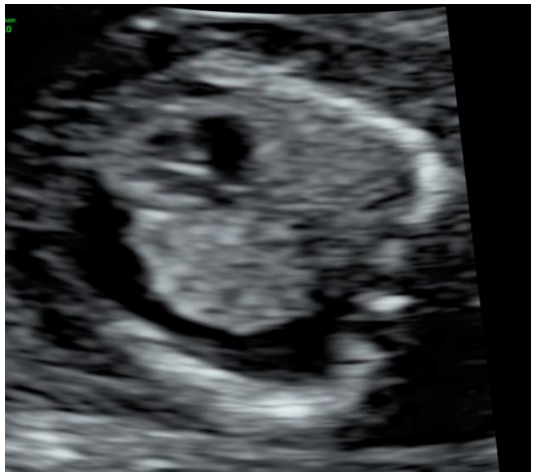
Sparks et al. NEJM 2020

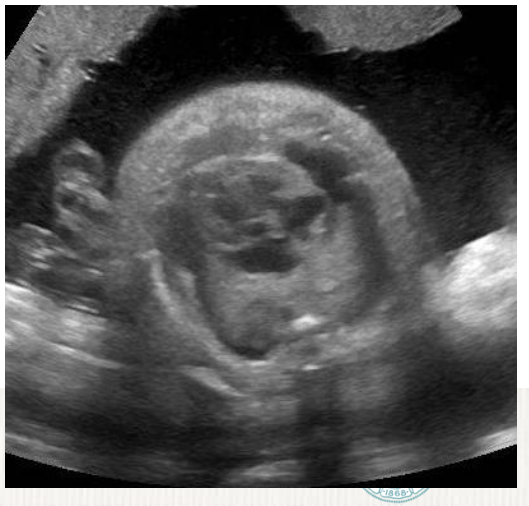
Exome sequencing for NIHF

Diagnostic yield by NIHF phenotypes:

- Isolated enlarged NT: 7%
- Single abnormal fetal fluid collection: 10%
- ≥2 abnormal fluid collections: 34%







Sparks et al. NEJM 2020.

Review > Ultrasound Obstet Gynecol. 2021 Apr 13. doi: 10.1002/uog.23652.
Online ahead of print.

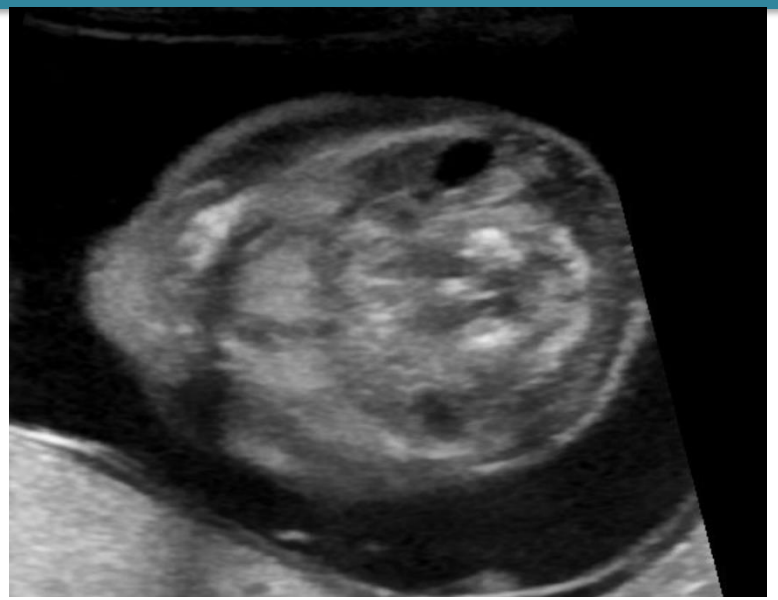
Fetal hydrops and the Incremental yield of Next generation sequencing over standard prenatal Diagnostic testing (FIND) study: prospective cohort study and meta-analysis

F Mone [1 2], R Y Eberhardt [3], M E Hurles [3], D J McMullan [4], E R Maher [5], J Lord [3], L S Chitty [6], E Dempsey [7], T Homfray [8], J L Giordano [9], R J Wapner [9], L Sun [10], T N Sparks [11], M E Norton [11], M D Kilby [1 2]

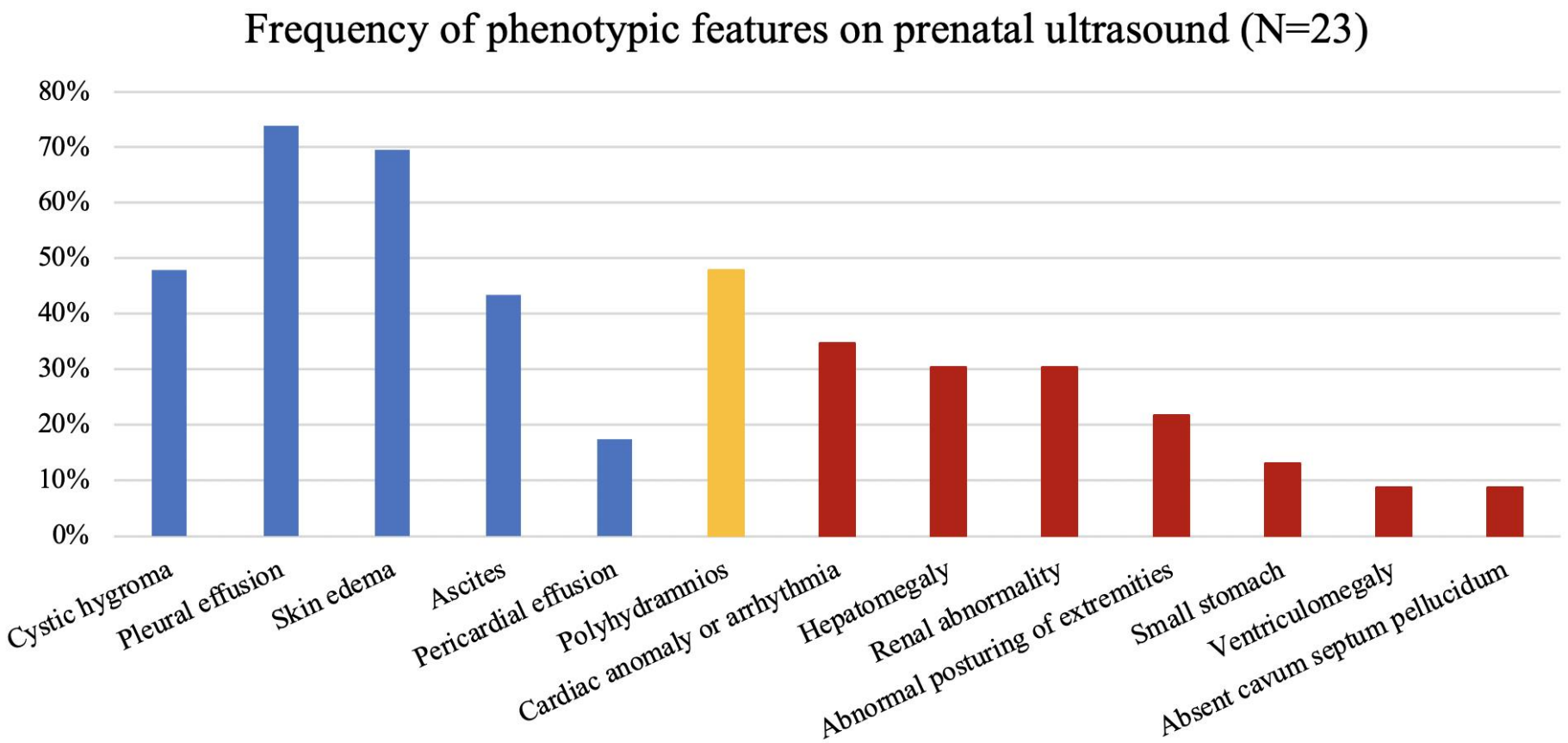
- N=306 cases
- Incremental yield:
  - 29% for all NIHF
    - 30% were RASopathies (Noonan, etc)
  - 24% for isolated NIHF
  - 38% for NIHF+structural anomalies

RASopathies

- Family of disorders with shared genetic basis and clinical features
- Noonan, Costello, cardiofaciocutaneous syndrome, neurofibromatosis
  - **Prenatal:** Polyhydramnios, lymphatic dysplasia, macrosomia, macrocephaly, cardiac and renal anomalies, big NT, NIHF, jugular sacs, hypertrophic cardiomyopathy
  - **Postnatal:** Dysmorphic features, short stature, cardiac anomalies or arrhythmias, developmental delays, coagulation defects, pectus carinatum/excavatum, malignancy, hypertrophic cardiomyopathy



Fetal phenotypes of RASopathies



Blue = abnormal fetal fluid

Yellow = abnormal amniotic fluid

Red = fetal structural abnormalities

Sparks et al. NEJM 2020.

Treatable Causes of NIHF

- Cardiac tachyarrhythmias
  - Anti-arrhythmics
- Fetal anemia due to parvovirus, FMH
  - In utero transfusion
- Large unilateral pleural effusion
  - Drainage, shunting
- Fetal CPAM (cystic pulmonary adenomatoid malformation)
  - Corticosteroids
- Twin twin transfusion syndrome
  - Laser ablation
- Twin reversed arterial perfusion (acardiac/acephalic)
  - Radio-frequency ablation

Follow up of fetal transplantation for alpha thalassemia

Eliana at 3 weeks…

… at 2 years

- Serial fetal transfusions
- Normal neonatal course + postnatal development

The future: Fetal molecular therapies

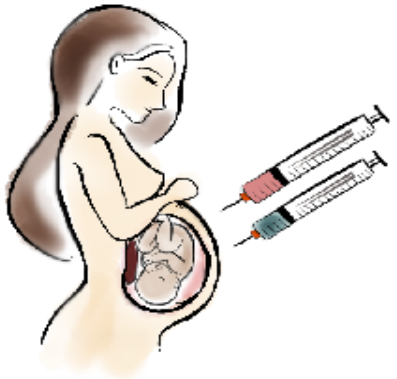
2017-2020 | 2020-2023 | 2023

Stem Cell Transplant

Alpha Thalassemia Major

Beta Thal Major/Sickle Cell/ Fanconi Anemia

Others



In Utero ERT: LSDs

In Utero Gene Therapy: Hemophilia, SMA, LSDs

Summary

- Hydrops is the common end stage of many different conditions
- Some have poor prognosis -- for others there is effective treatment
- Many are genetic disorders with high recurrence risk

➢ Particularly important to diagnose those that are treatable and those that are genetic

Thank you!