Alloimmunization in Pregnancy

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Disclosures

- No financial relationships to disclose.

Objectives

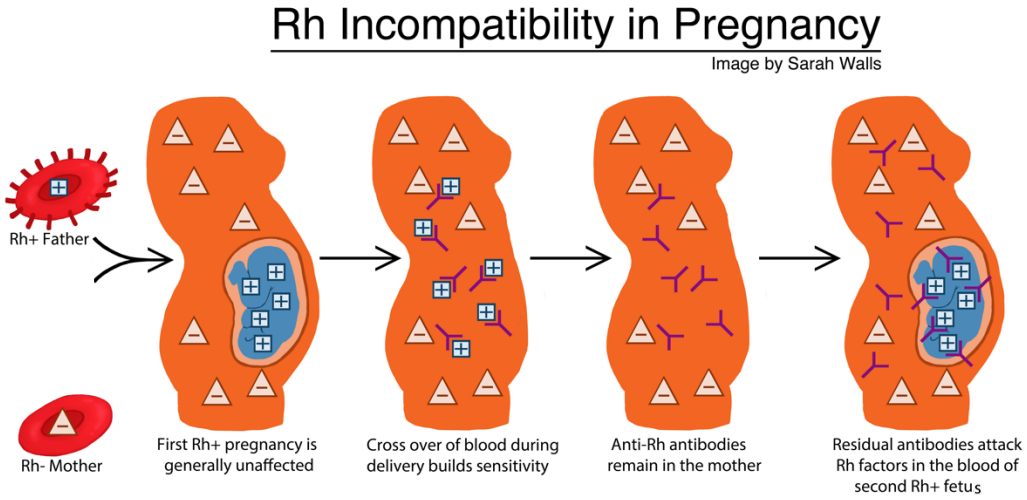
- Explain the causes and potential consequences of alloimmunization in pregnancy
- Review typical monitoring plans for pregnant patients at risk for hemolytic disease of the fetus and newborn (HDFN)
- Identify signs of fetal hydrops on ultrasound
- Discuss interventions for fetal anemia and hydrops

Alloimmunization

- Blood antigen mismatch with significant interaction causing sensitization and immune response

- Sensitization can occur from maternal-fetal hemorrhage, blood transfusion, or other blood exposures

  - Memory B lymphocytes recognize fetal antigen
  - IgG mediated
  - Antibodies cross the placenta and bind to fetal erythrocytes and hemolyzed by fetal spleen
  - Tend to worsen with each subsequent pregnancy
  - Fetal sex may play a role
    - More common in RhD-positive male fetuses compared to females (13x)



Red cell antibodies

- ~15:1000 pregnancies in the US
- Type and screen
  - Most common red cell antibodies associated with HDFN
    - Anti-E
    - Anti-D
    - Anti-Kell
    - Anti-c

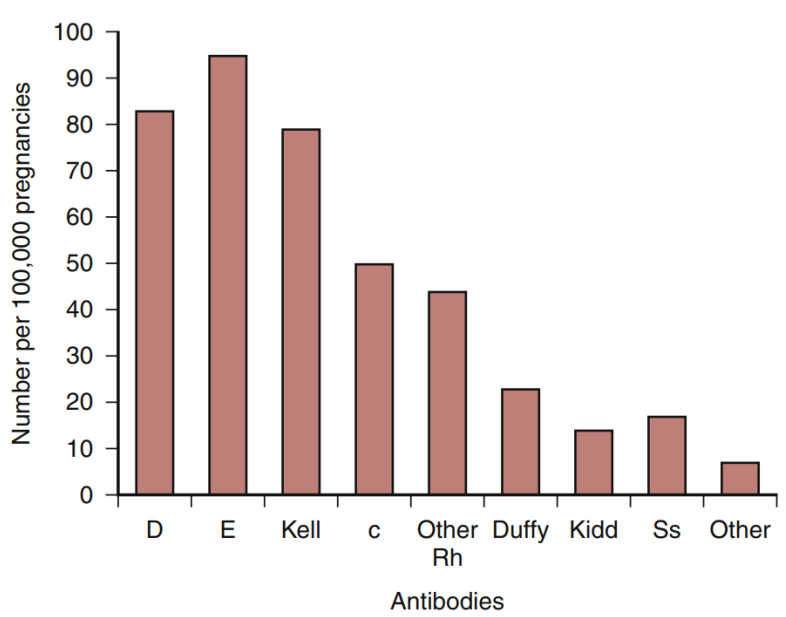


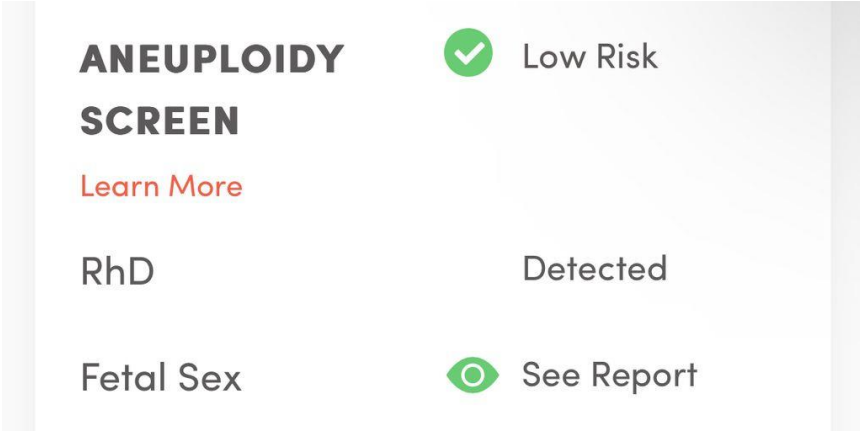
Figure 35.1 Hemolytic disease of the fetus and newborn (HDFN).

Creasy and Resnik, 9e. Chapter 35

Blood Group System	Antigens Related to Hemolytic Disease	Hemolytic Disease Severity	Proposed Management
Lewis	*		
I	*		
Kell	K	Mild to severe†	Fetal assessment
	k	Mild	Routine obstetric care
	Ko	Mild	Routine obstetric care
	Kp^a	Mild	Routine obstetric care
	Kp^b	Mild	Routine obstetric care
	Js^a	Mild	Routine obstetric care
	Js^b	Mild	Routine obstetric care
Rh (non-D)	E	Mild to severe†	Fetal assessment
	C	Mild to severe†	Fetal assessment
	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	Mild	Routine obstetric care
	Jk^3	Mild	Routine obstetric care
MNSs	M	Mild to severe	Fetal assessment
	N	Mild	Routine obstetric care
	S	Mild to severe	Fetal assessment
	s	Mild to severe	Fetal assessment
	U	Mild to severe	Fetal assessment
	Mi^a	Moderate	Fetal assessment
MSSs	Mt^a	Moderate	Fetal assessment
	Vw	Mild	Routine obstetric care
	Mur	Mild	Routine obstetric care
	Hil	Mild	Routine obstetric care
	Hut	Mild	Routine obstetric care
Lutheran	Lu^a	Mild	Routine obstetric care
	Lu^b	Mild	Routine obstetric care
Diego	$D1^a$	Mild to severe	Fetal assessment
	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	Mild	Routine obstetric care
	Lan	Mild	Routine obstetric care
	En^a	Moderate	Fetal assessment
	Ge	Mild	Routine obstetric care
	Jr^a	Mild	Routine obstetric care
	Co^a	Severe	Fetal assessment
	Co^{1-b-}	Mild	Routine obstetric care
Private antigens	Batty	Mild	Routine obstetric care
	Becker	Mild	Routine obstetric care
	Berrens	Mild	Routine obstetric care

Positive Red Cell Antibody

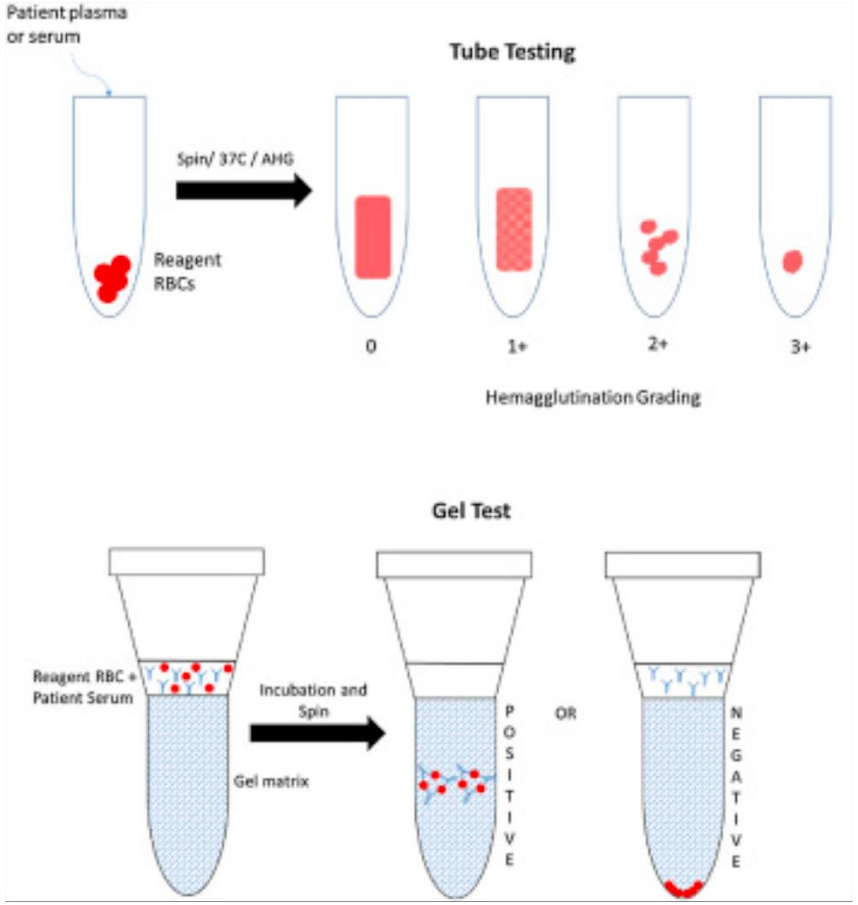
- Determine paternal genotype
  - ~3% misattributed paternity
- Fetal genotype testing
  - Amniocentesis
  - Cell free DNA testing limited to RhD only in US



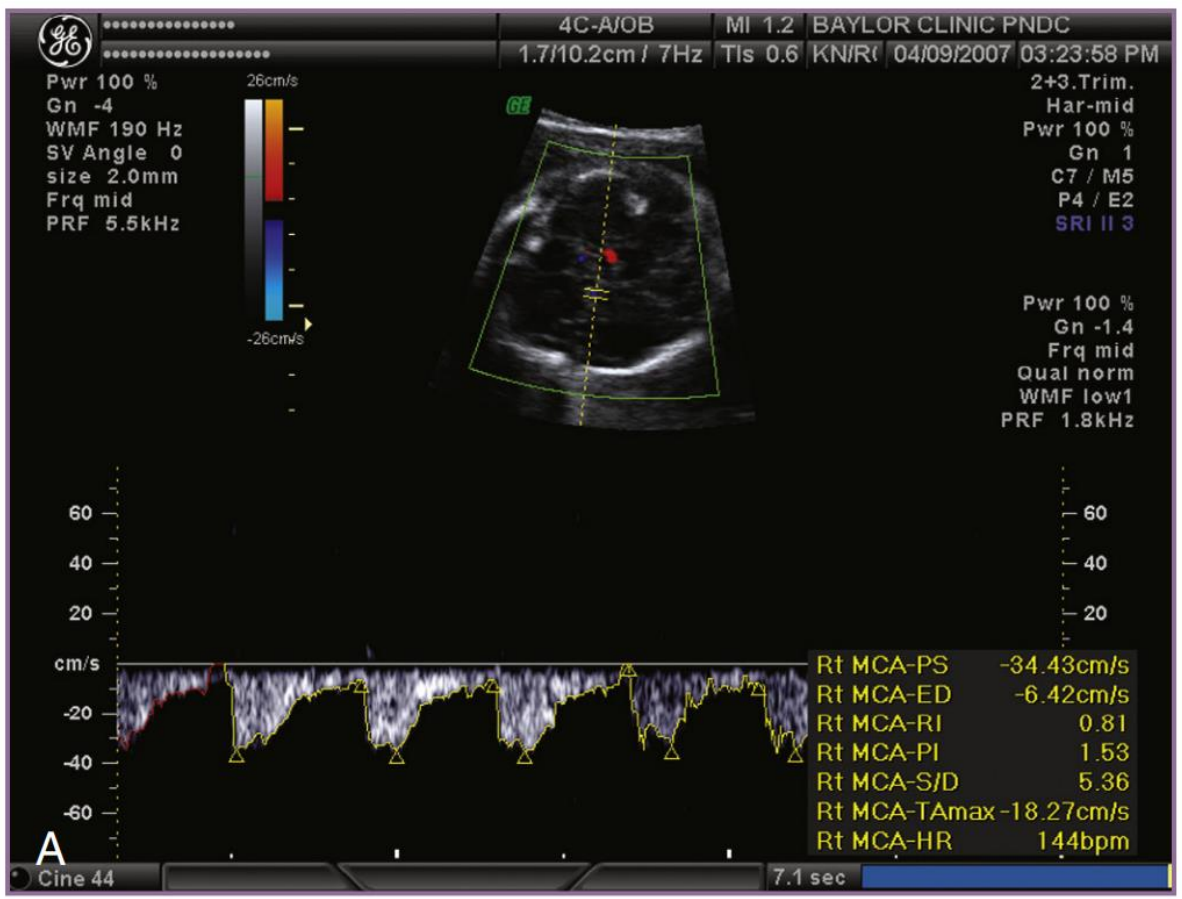
Fetus with potential for HDFN

Check antibody titers (tube)

- Monthly
- Critical value 1:16 or 1:4 for anti-Kell



Ultrasound Screening – MCA Doppler



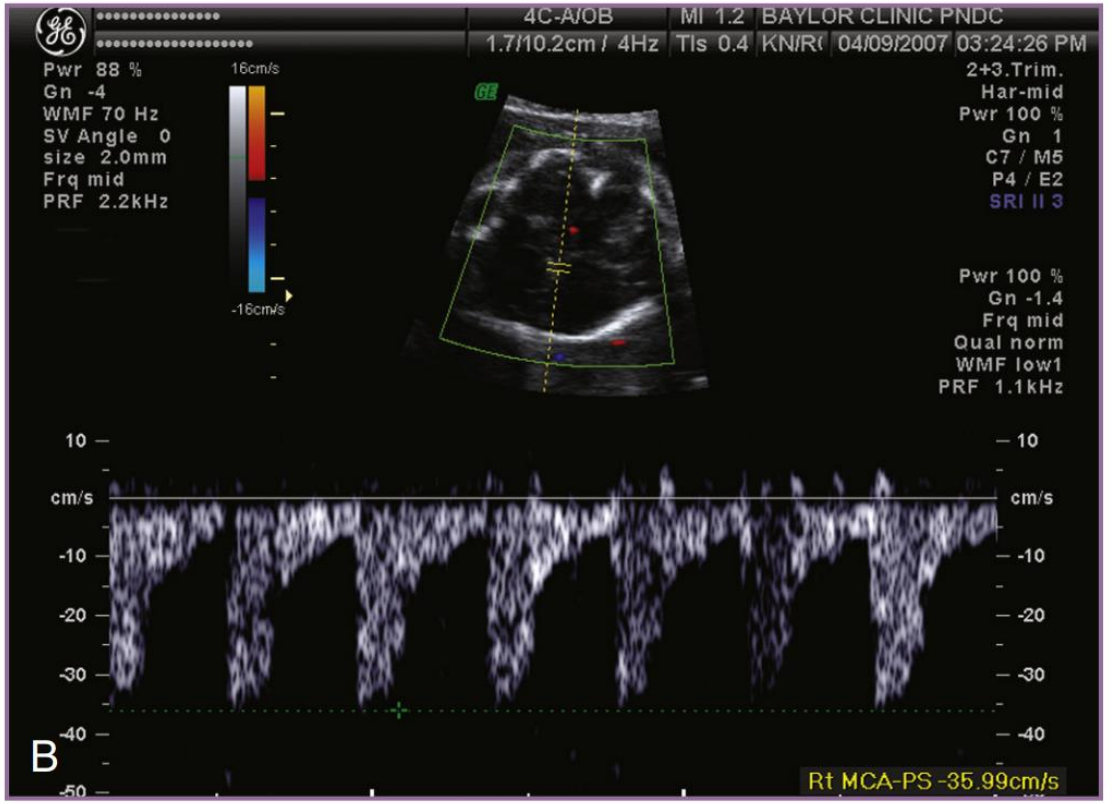


Figure 35.6 Optimization of Doppler parameters. (A) Baseline and pulse repetition frequency *(PRF)* not optimized; automated software is used to measure a peak velocity of 34 cm/s. (B) Doppler baseline changed to 10 cm/s, PRF optimized; manual caliper is used to measure a peak velocity of 36 cm/s.

Ultrasound Screening – MCA Doppler

- Initiate by 16-18 weeks gestation or at time of critical titer diagnosis if later.
  - Perform every 1-2 weeks
- MCA Peak Systolic Value (PSV) of >1.5 MoM can indicate moderate to severe fetal anemia.
  - Values can be falsely elevated (~10%) from fetal motion, fetal heart rate accelerations, or previous fetal transfusions

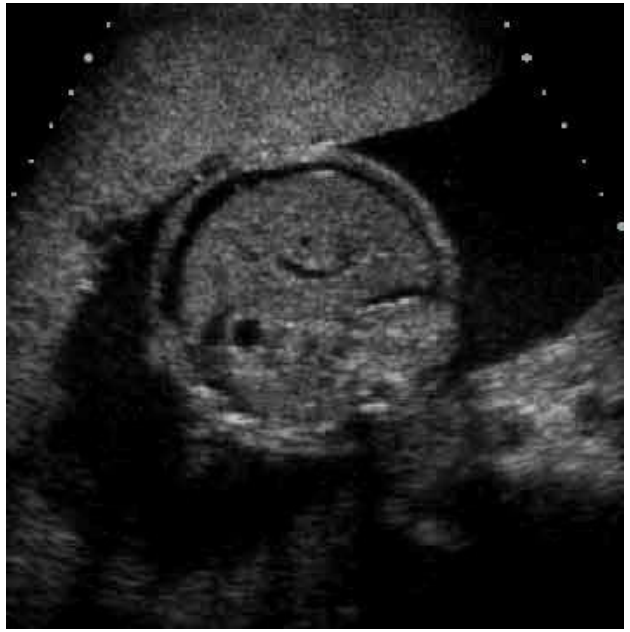
GA (weeks)	FETAL MCA PSV (cm/s)		
	Present study		
	Median	1.29 MoM	1.50 MoM
25	32.05	41.3	48
26	33.11	42.7	49.6
27	35.19	45.3	52.8
28	37.19	48	55.8
29	38.74	50	58.1
30	40.05	51.6	60
31	42.13	54.3	63.2
32	44.87	57.8	67.3
33	46.59	60.1	69.9
34	48.25	62.2	72.4
35	50.35	64.9	75.5
36	52.15	67.3	78.2
37	54.80	70.7	82.2
38	57.40	74	86.1
39	60.45	78	90.7
40	62.05	80	93

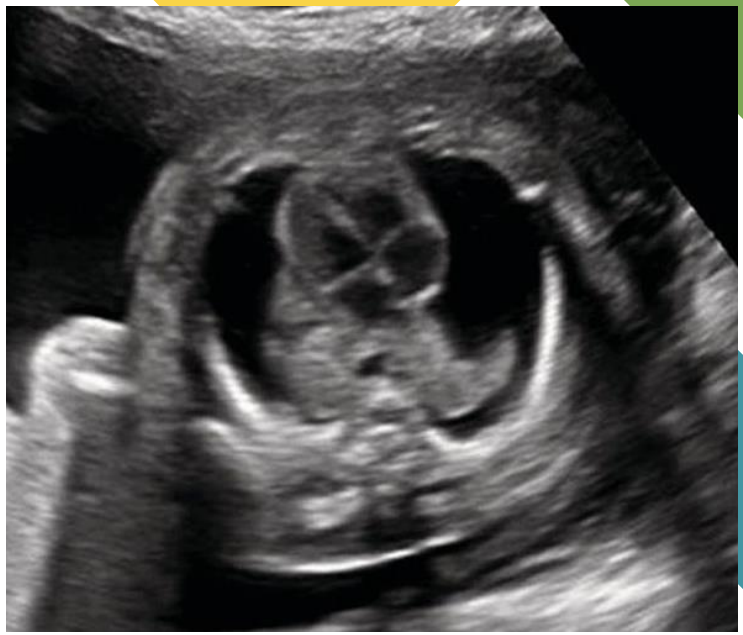
Hydrops fetalis

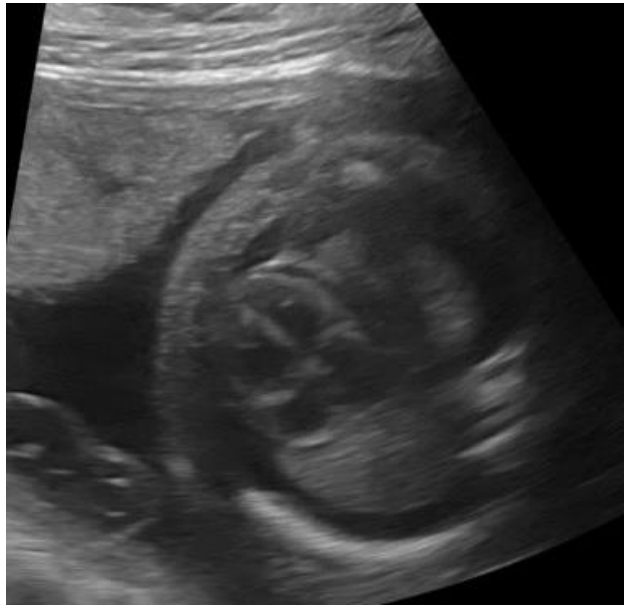
Collection of fluid in at least two compartments

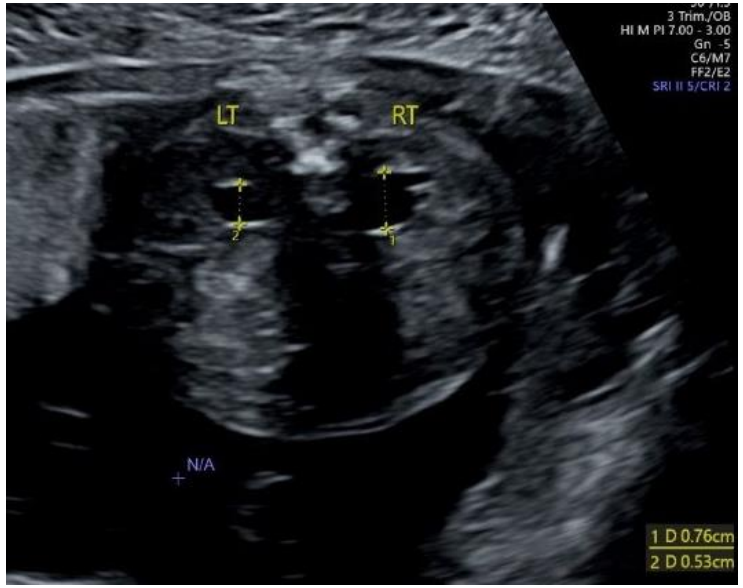
- Ascites
- Pleural effusion
- Skin/scalp edema
- Polyhydramnios
- Placentomegaly

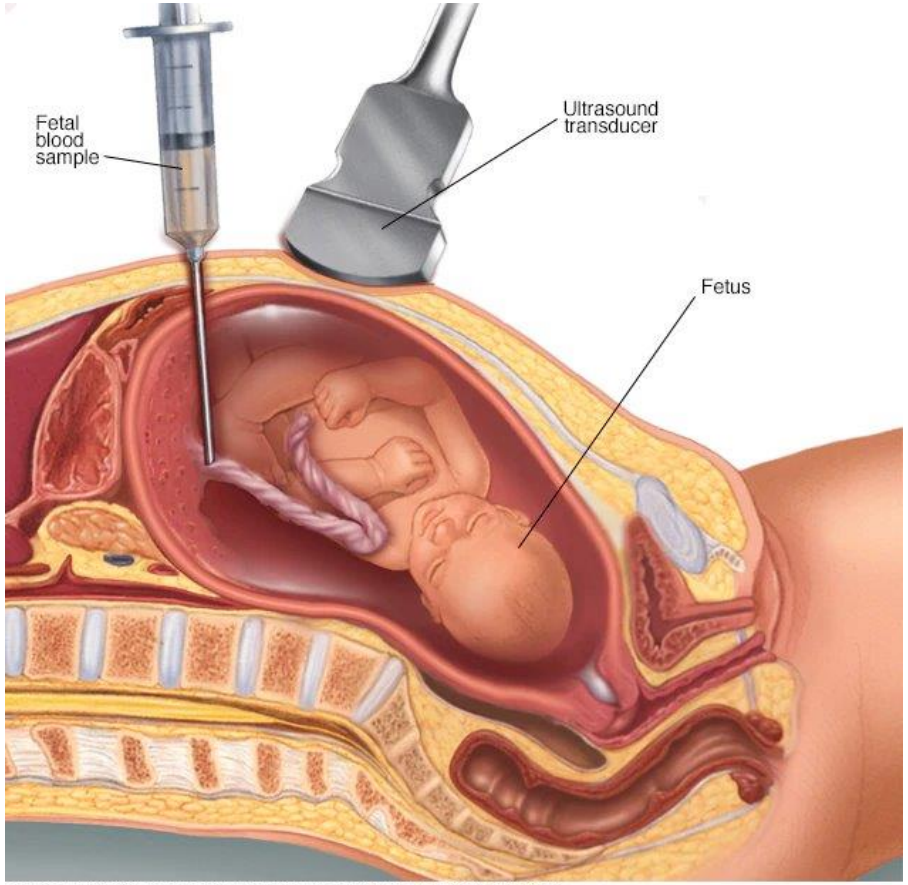
End-stage disease (Hgb deficit >7g/dL)











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Intravascular Fetal Transfusion

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Procedure:

- The abdomen is aseptically prepped.
- A 20-guage,5-inch spinal needle is then guided into the umbilical vein at the placental insertion under ultrasound guidance.
- Fetal blood is aspirated for immediate hematocrit, CBC, blood type and Rh factor.
- Prior to transfusion pancuronium bromide may be administered as an IV bolus.
- Transfusion is performed using type O, Rh-negative, CMV-negative, washed irradiated packed cells, cross-matched against maternal blood.
- The volume of donor blood to transfuse may estimated using the calculator below.

Donor hematocrit (75%)
Initial fetal hematocrit
Final fetal hematocrit (~45%)
EFW (grams)

Calculate | Clear Form

Volume RBCs to transfuse **(mL)**

(Typical transfusion volume is 30 to 100 ml)

Percutaneous umbilical cord blood sampling/Intrauterine transfusion (PUBS/IUT)

Transfusions and Delivery

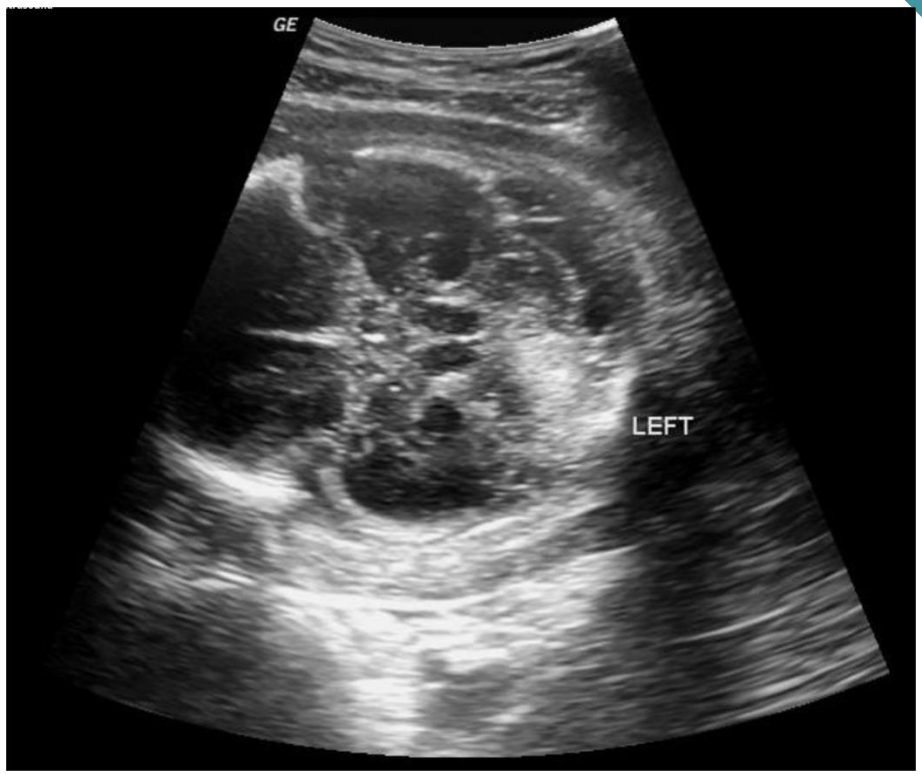
- No critical titer level
  - routine pregnancy management
- Critical titer levels without need for intervention
  - Recommend delivery in the 37-38th week of gestation.
- Patients with transfusion history or evidence of fetal anemia
  - Target final transfusion to be ~2-3 weeks before delivery
    - e.g. 30-32 weeks for delivery at 32-34 weeks

Prevention

- RhIG (Rhogam, Rhophylac, etc.)
  - Standard dose (300 mcg) expected to last for ~12 weeks
  - Covers 15mL of fetal red cells or 30mL of whole fetal blood
  - Not indicated for patients who are already sensitized to RhD
- Consider IVIG for early onset HDFN, patients with subsequent alloimmunized pregnancies, or extremely high titers.

A quick aside: Fetal and Neonatal Alloimmune Thrombocytopenia

- Estimated to affect up to 1:1000 pregnancies
- Maternal and fetal differences in expression of Human Platelet Antigen (HPA)
- Antibodies cross the placenta and bind to fetal platelets which are destroyed by fetal spleen
- Can occur during an initial pregnancy without prior exposure.
- Fetus or newborn with severe thrombocytopenia, ecchymoses, petechiae, or intracerebral hemorrhage
- Treatment: IVIG or intrauterine platelet transfusions



Questions?

References

- Creasy and Resnik, 9th edition. Chapter 35 – Hemolytic Disease of the Fetus and Newborn.
- American College of Obstetricians and Gynecologists, Practice Bulletin 192 – Management of Alloimmunization During Pregnancy.
- Perinatology.com
  - MCA Doppler PSV MoM Calculator
  - Intravascular Fetal Transfusion Calculator