ALLOIMMUNIZATION SECONDARY TO PREGNANCY AND TRANSFUSION IN WOMEN OF CHILD BEARING AGE

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Medical Disorders of Pregnancy Program

Objectives

Overall objective

To appreciate the effect of red cell alloimmunization in women of child bearing age

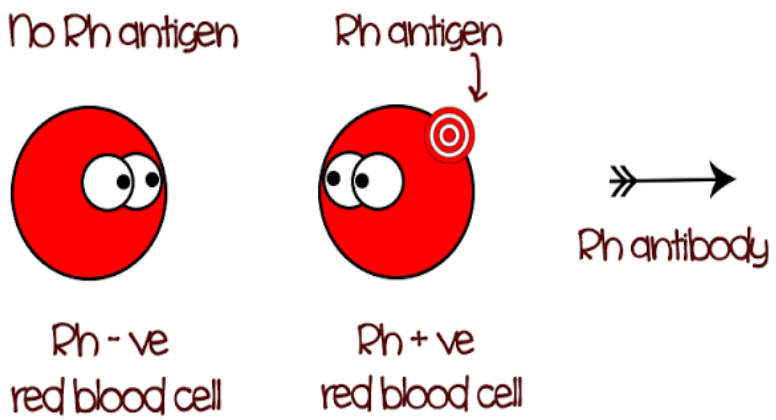
Alloimmunization from paternal exposure

Know the indications for RhIG to prevent D alloimmunization

Alloimmunization from Red Cell Transfusion

Appreciate the changes in hemoglobin levels during pregnancy, indications and alternatives for transfusion peripartum to prevent red cell allommunization

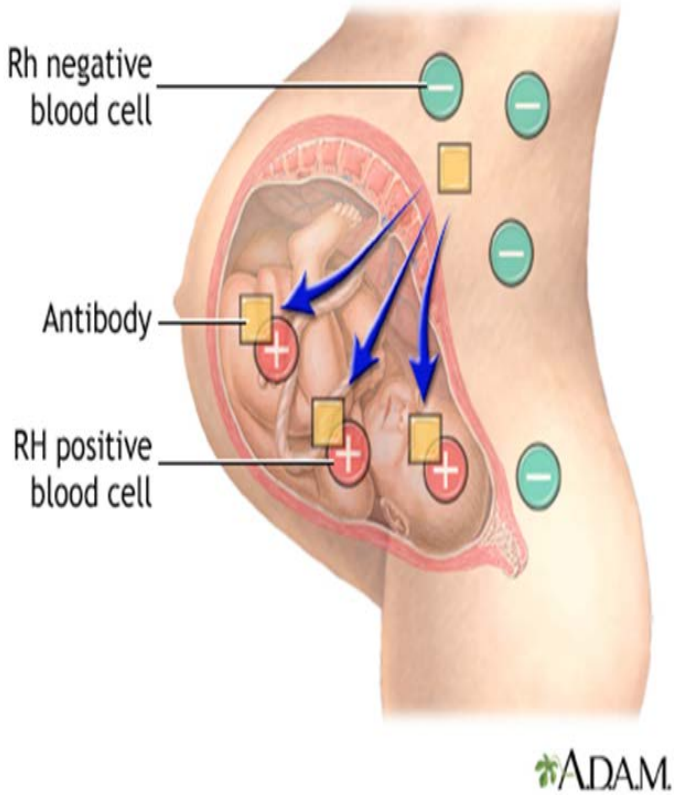
Alloimmunization (development of an alloantibody) occurs following from



1. Exposure to paternal antigens by fetal maternal hemorrhage during pregnancy
2. Exposure by RBCs

IgG maternal alloantibodies traverse the placenta

Can bind to fetal antigens on red cells resulting in destruction of fetal/neonatal red cells=Hemolytic Disease of the Fetus and Newborn (HDFN)



http://www.nlm.nih.gov/medlineplus/ency/presentations/100217_3.htm

The ability to develop an alloantibody depends on

The immunogenicity and embryonic development of the red cell antigen

The volume of red cell antigen exposure

The immune responsiveness of the individual

e.g. alloimmunization following exposure to paternal D antigens occurs in 16% of women

The ability to develop an alloantibody depends on the **red cell antigen**

Immunogenicity of the antigen

Polypeptide antigens give rise to IgG e.g. Rh vs. carbohydrate antigens tend to give rise to IgM-class antibodies (ABO), P, Lewis and I

Embryonic development of the antigen

D antigen appears as early as 38 days gestation vs. AB antigens postnatally

Geaghan S. Sem Per 2011:35:148, Urbaniak SJ, Greiss MA. BloodRev 2000;14:44–61, Oepkes D et al. Am J Obstet Gynecol 2001;184;1015-20. Kapur R et al. Br J Haematol 2014;166:936-45. Blood. Tormey C, Henrickson JE. 2019;133:1821-1830)

The ability to develop an alloantibody depends on the volume of **red cell antigen exposure**

Transplacental hemorrhage

Is high in each of the trimesters

- 1st: 56% (0.07 ml)
- 2nd : 63% (0.08 ml)

Increases with invasive procedures, trauma, delivery

Transfusion

RhD: Primary immune response: 15% after 1 ml RBCs and 70–90% after 250 ml

Secondary immune response may occur after exposure to as little as 0.03 ml RBCs

Geaghan S. Sem Per 2011:35:148, Urbaniak SJ, Greiss MA. BloodRev 2000;14:44–61, Oepkes D et al. Am J Obstet Gynecol 2001;184;1015-20. Kapur R et al. Br J Haematol 2014;166:936-45

The ability to develop an alloantibody depends on the **immune responsiveness of the individual**

Characteristics of the antibody

- Ability to present the red cell antigen (e.g. HLA genotype)
- Ability to lyse
- Ability to suppress erythropoiesis

ABO incompatibility between mother and fetus, less lysis with ABO incompatibility

Geaghan S. Sem Per 2011:35:148, Urbaniak SJ, Greiss MA. BloodRev 2000;14:44–61, Oepkes D et al. Am J Obstet Gynecol 2001;184;1015-20. Kapur R et al. Br J Haematol 2014;166:936-45. Rydr AB et al. Transfus Med Hemother 2014;41:406–419

Spectrum of HDFN for those who develop an alloantibody

No disease

No fetal destruction of RBCs

Mild disease

Hemolytic disease of the newborn

Severe disease

Hemolytic disease of the fetus requiring intrauterine transfusion

Fetal hydrops

Antigen	Severe Disease in Alloimmunized Pregnancies*
D	20%
K	11-50%
c	17-26%
Duffy	14-16% (Duffy a> b)
E	1%-18%

*Requiring intrauterine transfusion or neonatal exchange transfusion

Hackney DN et al. ObstetGyn 2004;103:24-30, *J.M. Koelewijn, Transfusion* 2008;48:941-952. Grant SR. BJOG 2000;107: 481-485, Joy SD et al. Obstet Gynecol 2005;105:24-8

Prevention of Alloimmunization

Paternal

Rh Immune globulin for exposure to D antigen in D negative mothers

Transfusion

- Transfusion avoidance
- Antigen negative transfusion e.g. D-, K-

Rh immune globulin should be administered within 72 hours in a D negative woman for

A. Abdominal trauma

B. Vaginal spotting at 12 weeks gestation

C. All of the above

D. None of the above

Rh immune globulin is a plasma derived IgG protective for exposure to D antigen

Pooled plasma product derived from donors with high anti-D antibodies

Risk of contracting viruses reduced by the manufacturing process

Mechanism

The antibody coated cells, are destroyed by the spleen before D is seen by antigen-presenting cells

The antibody alters D antigen processing reducing T cell and B cell activation

Bink D, Lazarus AH. Hematology
ASH Education Program 2009;185

Prophylactic RhIG has reduced alloimmunization from 16% - ~ 0.2-1% in D negative women

300 micrograms suppresses the response of up to 15 ml of RBCs

300 micrograms to all D-negative women at 26-28 weeks' gestation, and within 72 hours of delivery (for fetuses that are D+ or D unknown)

Administer RhIg within 72 hours of a sensitizing event: may be given up to 10 days of the event

Prior to 12 weeks gestation (fetoplacental blood volume is 3ml)

120-300 μg

Between 12-20 weeks gestation

300 μg

More than 20 weeks

Minimum dose 300 μg

Rosette/Betke Kleihauer/Flow cytometry to determine presence and volume of a bleed

Postpartum

120-300 μg if the neonate is D+ and BK/flow cytometry to determine presence and volume of a bleed

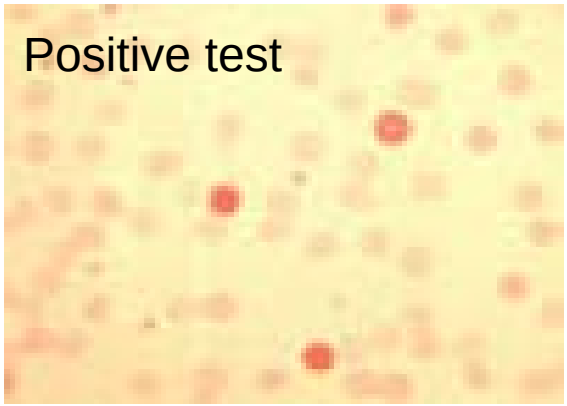
The Betke Kleihauer acid elution test detects Hemoglobin F

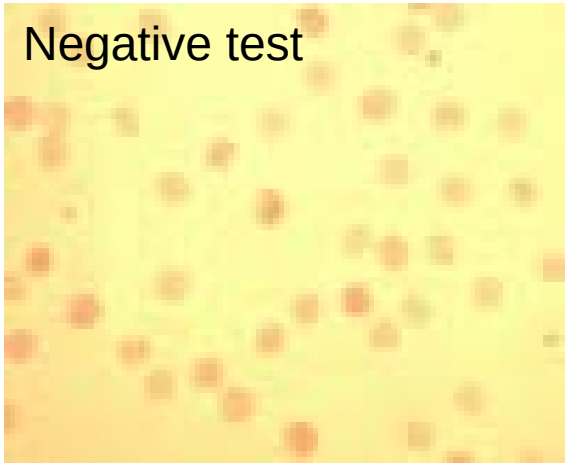
Fetus: Hemoglobin F is the predominant hemoglobin of the fetus, is more acid-resistant than other hemoglobins (fetal cells appear as dark reddish/pink cells)

Adult: Hemoglobin F usually < 1% in adults, concentrated in F cells

Predominant HbA is denatured by acid and eluted=ghost cells

ml bleed=% fetal cells (#fetal/#counted) x 5L (BV)





Flow cytometry has better accuracy: can differentiate fetal cells from adult F cells

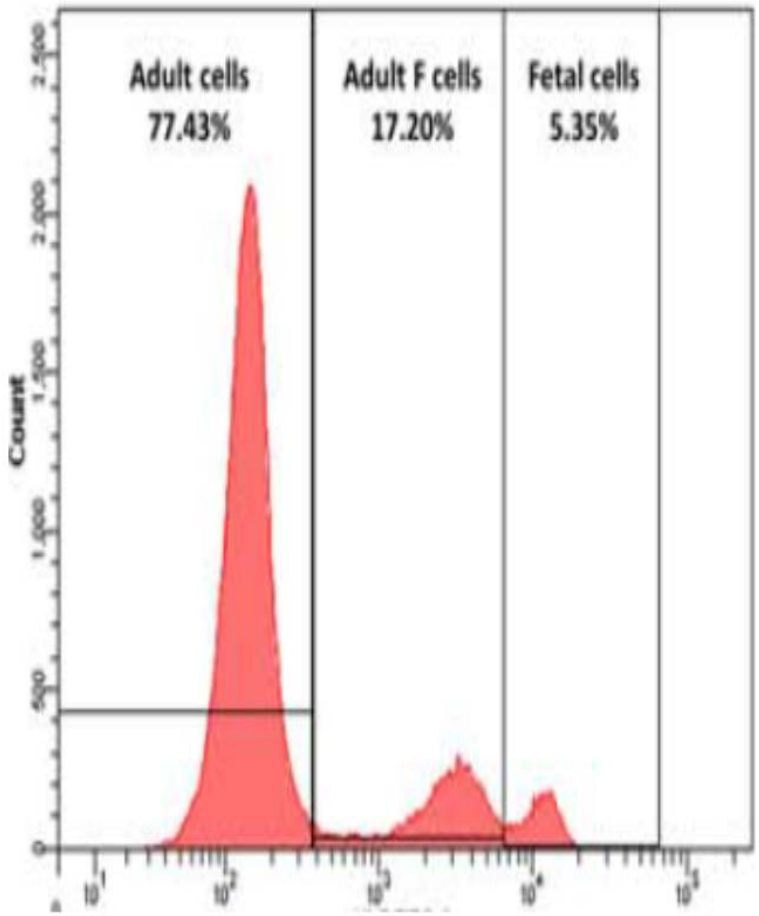
F cells contain 20-25% HbF in an adult

F cells increases during pregnancy

Can be as high as 7% by 32 wks

F cells increased with hemoglobin disorders

Better accuracy in estimating volume of FMH



Othman J et al. Cyt 2018:94B

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Would you transfuse RBCs?

25 year old female G1P0 at 27 weeks gestation with perivaginal spotting, Hb 65 g/L

1. Yes
2. No

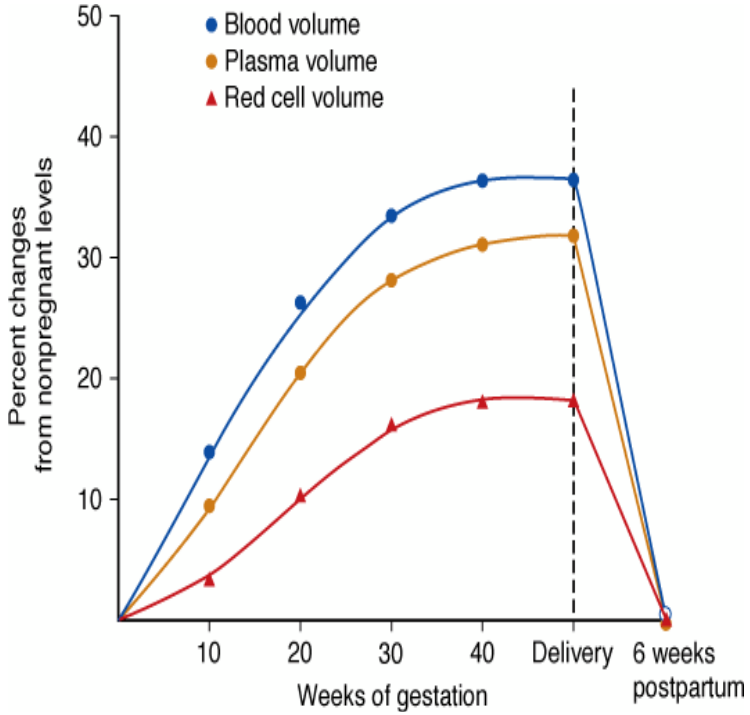
Are the benefits worth the risk of exposure to red cell antigens?

Is the mother compromised by the anemia?

Is the fetus compromised by maternal anemia?

Are there alternatives?

Physiological changes during pregnancy result in a lower Hb level



Cunning FE et al. Williams Obstet 23 ed.

Blood volume increases by 1.5 L

Plasma volume increases by 50%

Red blood cell mass increases by 25%

Lower hemoglobin levels occur

because plasma volume increases>

red cell volume

Anemia is defined as a hemoglobin level…

Non pregnant : <120 g/L

1st trimester : <110 g/L

2nd and 3rd trimester : < 105 g/L

Postpartum : < 100 g/L

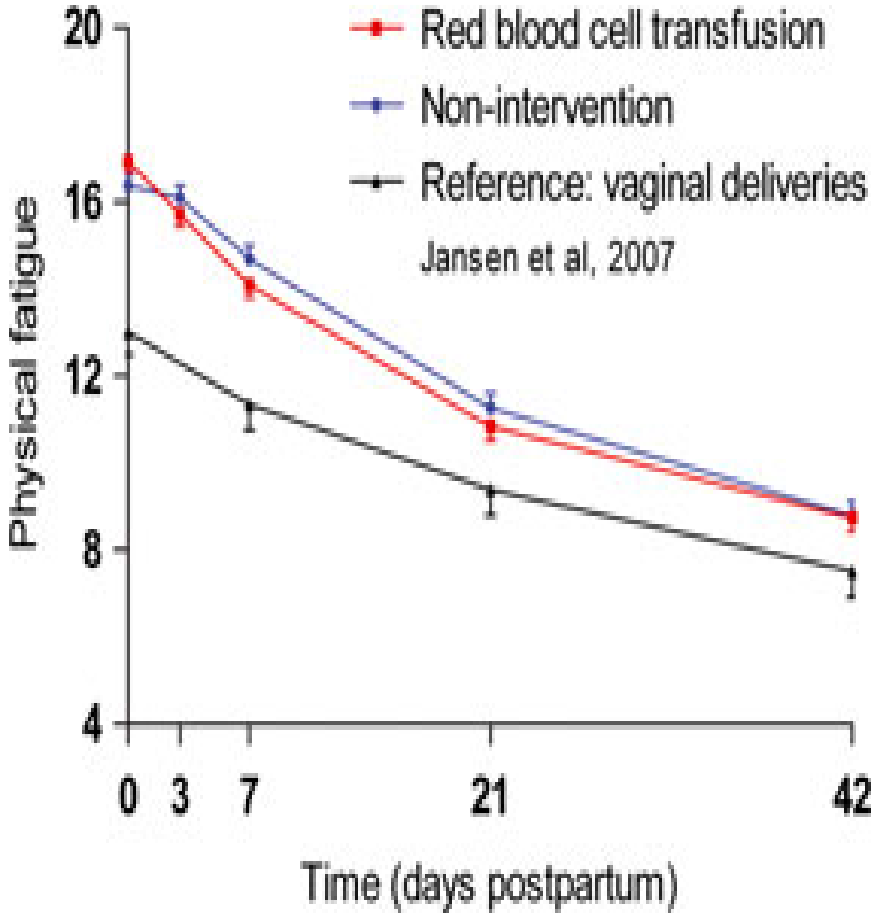
Pavord S et al. Br J Haematol 2019; epub,
Pasricha SR. Lancet Haem. 2018;5: e60

Postpartum: Women can tolerate a reduction to 50% of their hemoglobin concentration

Patients: Postpartum with Hb 48- 79 g/l 12–24 hours after delivery (mean age 31 yrs) and **hemodynamically stable**

Randomized to RBC vs no RBC

Fatigue was increased after 7 days but was the same after 42 days



Prick BW et al. BJOG Jul;121(8):1005-14.

The most common cause of anemia in pregnancy is iron deficiency: in 18%

Marked increase in iron demands in pregnancy

27-30 mg elemental iron in a prenatal vitamin/total iron requirement-1.2 g

during the entire pregnancy

Higher frequency with iron deficiency in a prior pregnancy, multiparty, low

SES, brief intervals between pregnancy, poor nutritional status, PPH

Diagnosed by ferritin <30 µg/L or fasting iron saturation <15%

https://www.rcog.org.uk/globalassets/documents/guidelines/consultation-documents/gtg47-draft.pdf , Mei Z et al. Am J of Clin Nut 93 (6):1312-1320. doi:10.3945/ajcn.110.007195, Breymann C, Auerbach, M. ASH 2017

Iron preparations

Preparation	Elemental iron (mg)
Oral formulations	
Prenatal vitamin (Ferrous fumarate)	27-35mg/tablet
Ferrous gluconate	35/tablet
Ferrous sulfate	65/tablet
Ferrous fumarate	100/tablet
Polysaccharide-iron Complex	150/capsule
Heme-iron polypeptide	11mg/tablet
Intravenous formulation	
Iron sucrose	20 mg/ml*

* The dose is calculated as (prepregnancy weight (kg) x[(target hemoglobin-actual hemoglobin g/L)/10]) x 2.4 +500. Maximum dose/infusion/day is 300 mg. Doses higher than 300mg need to be administered as divided doses.

Response to IV Iron faster than oral

Response to oral iron

- Hb rise by 1 g/L per day after starting iron
- Return to normal hemoglobin by 6-8 weeks
- Iron stores replenished by 3-6 months

Response to iv iron is 2x as fast

- Well tolerated, no hypersensitivity reactions in 599 patients in a systematic review
- Indications: moderate to severe anemia, no response to oral, side effects to oral iron, limited time to delivery

Govindappagari S, Burwick RM Am J Perinat. 2019, 36:366. Herschco et al. Blood 2014;123:326Breymann C, Auerbach M. ASH 2017

What is the role of erythropoiesis stimulating agents (e.g. erythropoietin)?

Most of the use is in patients with renal failure during pregnancy

It is a large molecule and it is not thought to cross the placenta

Royal College of Obstetrics and Gynecology advises against

The routine use of erythropoiesis stimulating agents

Exceptions

- Patients who do not have blood readily available
- Patients with renal failure

Complications because of iron deficiency anemia

Mother:

Fatigue

Anemia may result in increased transfusion rates

- Iron supplementation results in a lower incidence of Hb<100 g/L at delivery vs placebo (7% vs. 16%; RR, 0.45 [CI, 0.25 to 0.82])

Fetus:

Controversial

Obstetrical ultrasound detects fetal compromise by maternal anemia

Carless G et al. *AJOG* 2003;188:794-9
Breymann C, Auerbach, M. ASH 2017

When should patients be transfused in the antepartum setting?

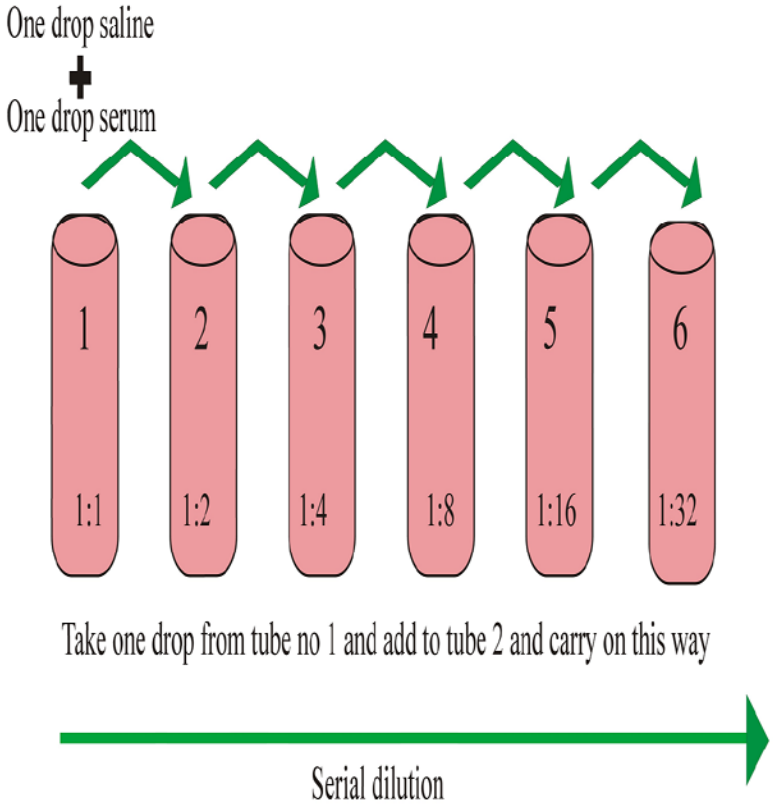
RCOG suggests “There are no firm criteria for initiating red cell transfusion. The decision to provide blood transfusion should be made on clinical and hematological grounds.” In the absence of hemorrhage or hemodynamic instability RBC transfusion is almost always required when the Hb is< 60 g/l and is rarely required when the Hb >100 g/l.”

ACOG suggests “Maternal transfusion should be considered for fetal indications”

RCOG May 2015:47
ACOG 2013: http://www.guideline.gov/content.aspx?id=13320#Section432

If an alloantibody is detected…

- The father's phenotype for the antigen and zygosity
- If the fetus is potentially affected
  - Serial antibody titres: a method to determine strength of the antibody
  - Antibody titre: greatest dilution with a positive agglutination reaction



The alloantibody titre should be monitored

D, c

In a primagravida

Every 4 wks in the 1st and 2nd trimester or every 2 wks if there is a rise and in the 3rd trimester

Referral to high risk centers if

For a first pregnancy

When the alloantibody >1:16-32, D, c, E

At any alloantibody titre for K as titres may not correlate with the severity of anemia: K alloantibodies also suppresses fetal erythropoiesis

Subsequent alloimmunized pregnancy where the first had HDFN

Once pregnancy is confirmed

Summary

Overall objective

To appreciate the effect of red cell alloimmunization in women of child bearing age

Alloimmunization leads to risk of HDFN

Alloimmunization from paternal exposure

Know the indications for RhIG to prevent D alloimmunization

RhIg for any potential FMH within 72 hours

Alloimmunization from RBC transfusion

Appreciate the changes in hemoglobin levels during pregnancy, indications and alternatives for transfusion peripartum to prevent red cell allommunization

Transfuse if symptomatic mother or fetus appears to be compromised e.g. fetal tachycardia, K negative RBC if transfusion needed

QUESTIONS?