Transfusion Considerations In Obstetrical Patients

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Objectives

1. Review the prevention and management of RBC alloimmunization in pregnancy
2. Discuss the role of optimizing and treating iron deficiency anemia in reducing transfusions
3. Highlight unique considerations when transfusing a pregnant /postpartum patient

Pre- test #1 When should a Maternal Hemmorhage Screen (FMH) be drawn after birth?

a. Immediately after birth
b. Between 30 minutes and 2 hours after birth
c. Within 24 hours after birth
d. Within 72 hours after birth

Pre- test #2 All Red blood cell antibodies can lead to hemolytic disease of the fetus/newborn

- True

Or

- False

Pre- test #3 A RhIg dose of 300 ug will cover up to this much RBC's in maternal blood

a. 5 mL

b. 10 mL

c. 30 mL

d. 60 mL

Pre- test #4 What is the recommended cut off value for diagnosing Iron deficiency Anemia in pregnancy

a. Hgb < 120 g/ L

b. Hgb < 110 g /L

c. Hgb < 100 g/L

d. Hgb < 80 g/L

Pre- test #5 Aggressive management of Iron deficiency anemia with IV iron is important for PPH prevention

True

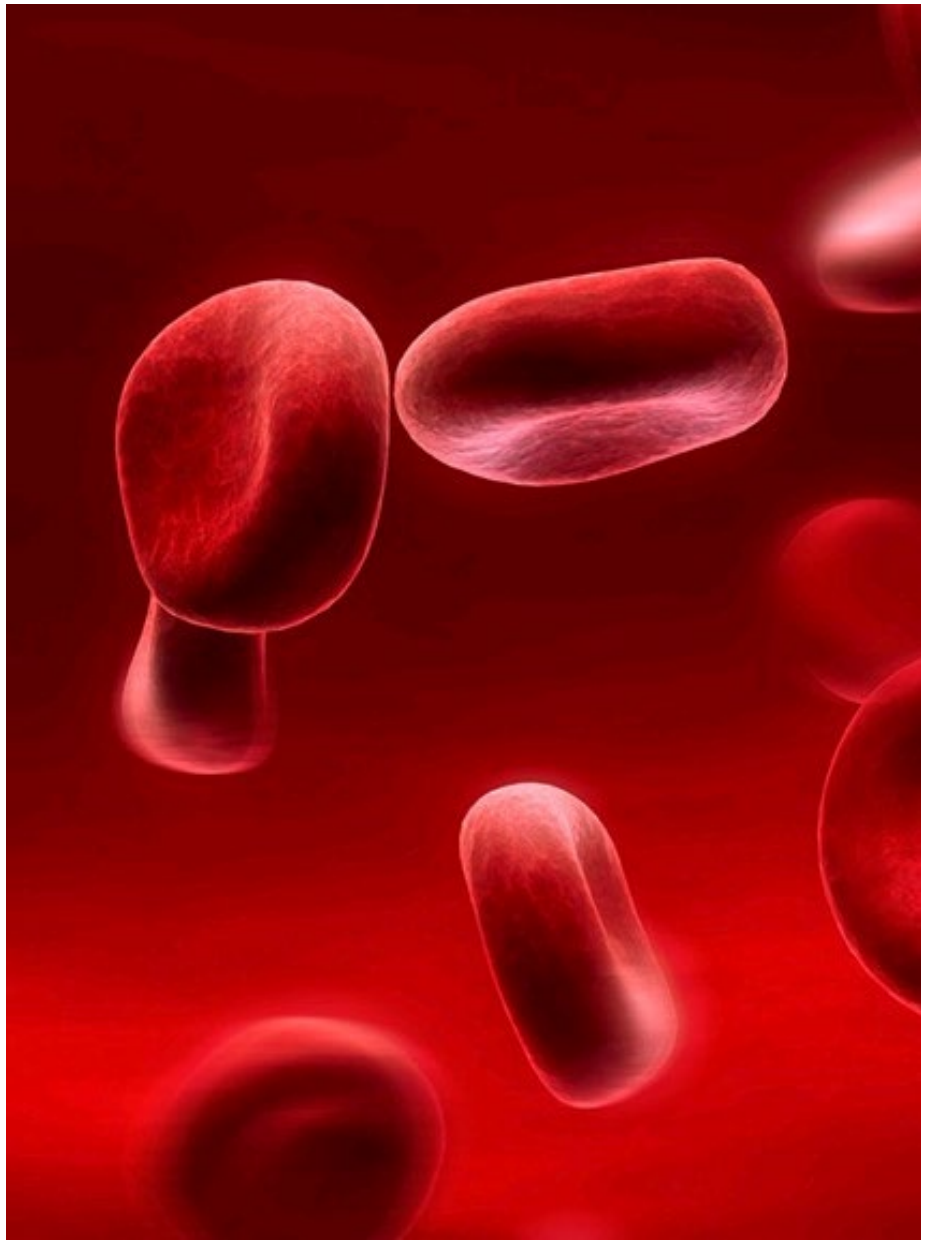
Or

False

The prevention of RBC alloimmunization in pregnancy

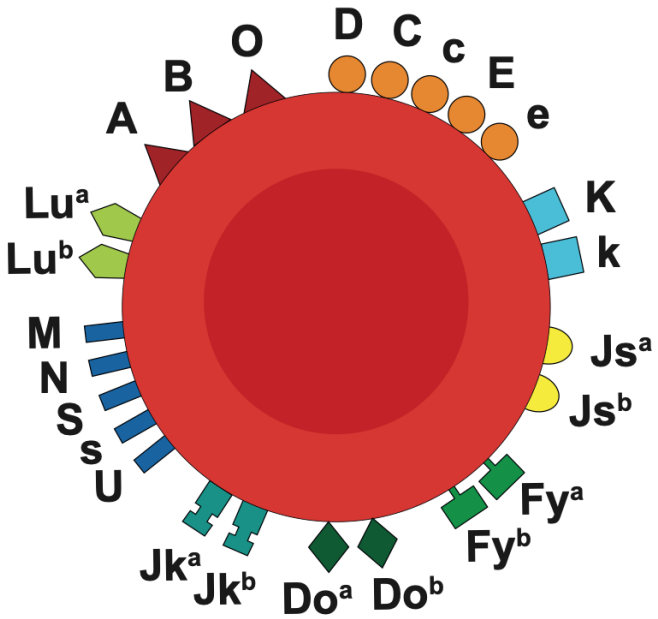
What is the Rh Factor?

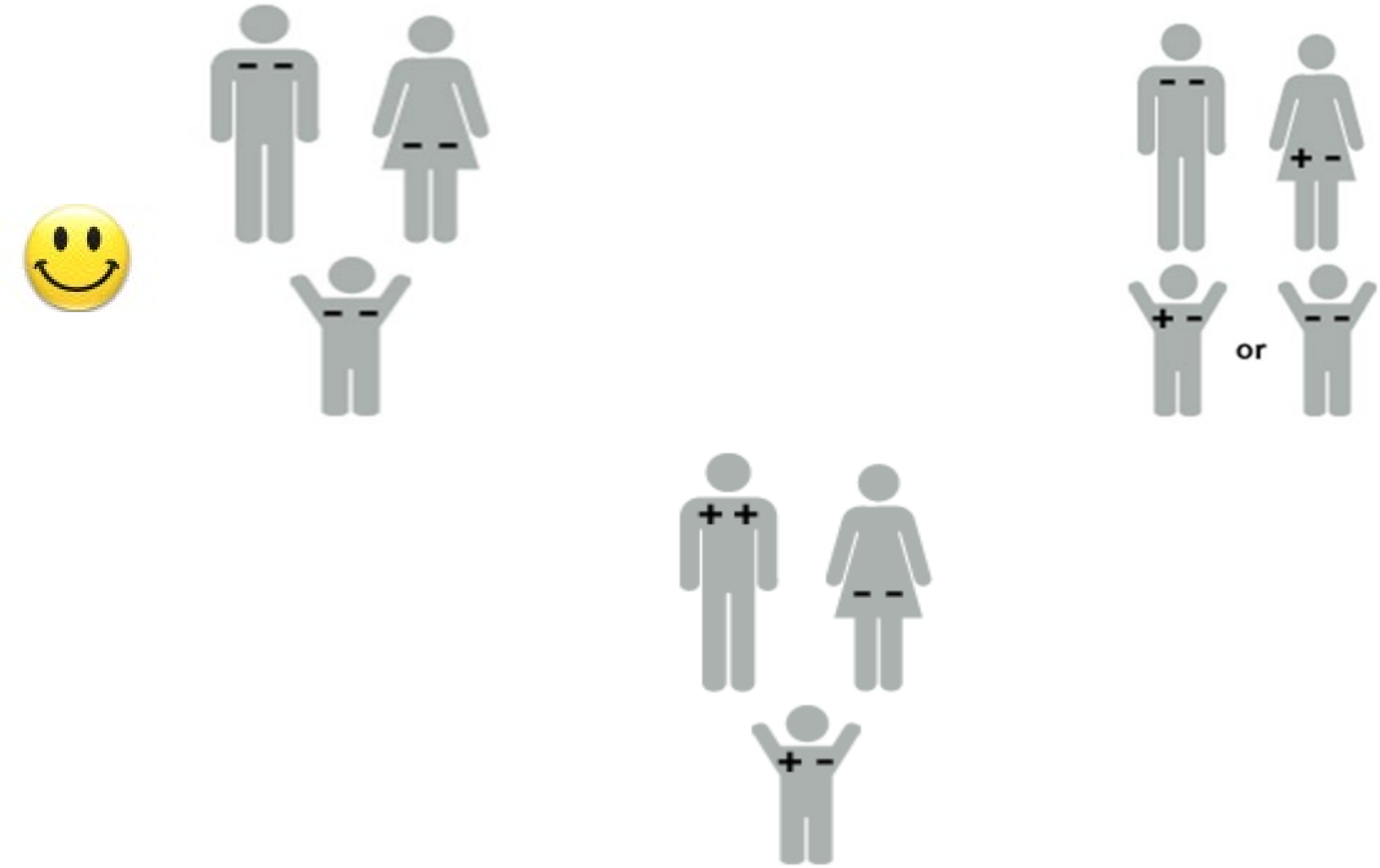
- A group of proteins that occur on the surface of the RBC
- When Rh factor is present in RBC's then patient is Rh "Positive"
- If the Rh factor is absent then patient is Rh "Negative"



Genetics

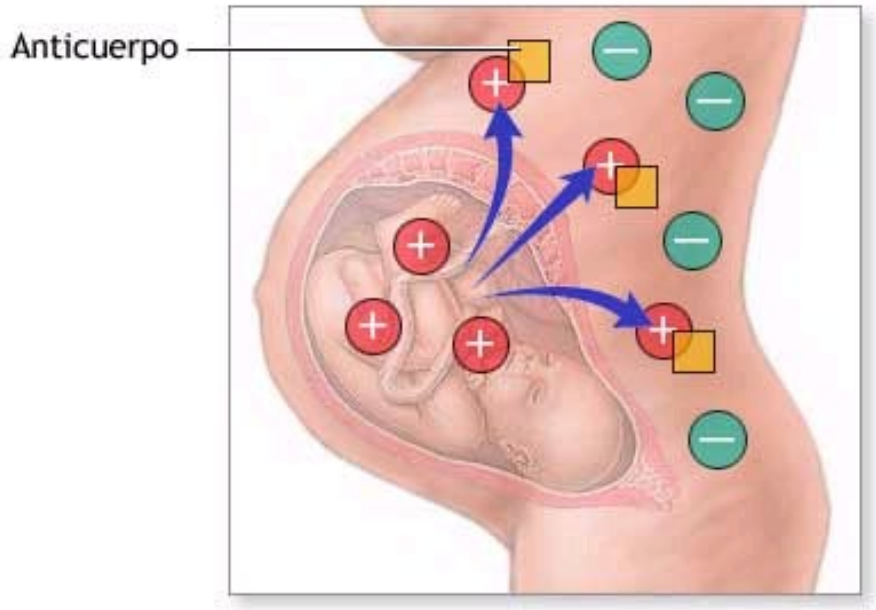
- A number of known RBC antigens are involved in the Rh system
- Individuals who are homozygous for the D antigen (DD) or heterozygous (Dd) are Rh + because the D antigen is dominant
- Individuals who are homozygous (dd) recessive antigen are Rh -




or

Rh Sensitization

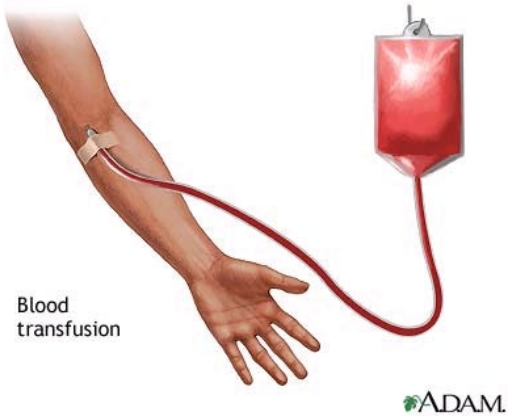
- During normal pregnancy small amounts of fetal blood (< 0.5 ml) may cross the placenta
- If fetus is Rh pos, pregnant persons can develop anti-D antibodies in response to this exposure

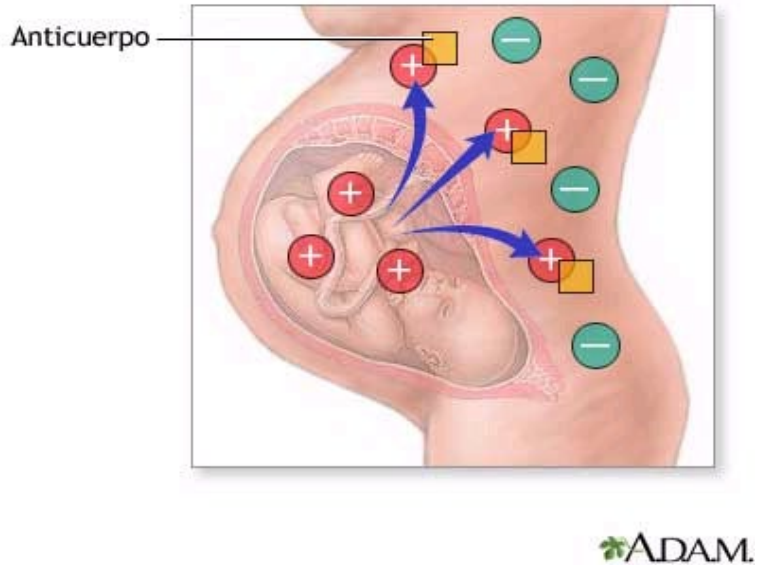


A.D.A.M.

Causes of Rh Sensitization

- Rh - person carries a Rh + fetus
- Rh - person has a Rh + pregnancy which is spontaneously or planned terminated
- Rh - person has a Rh + ectopic pregnancy
- Rh - person receives a Rh + blood transfusion





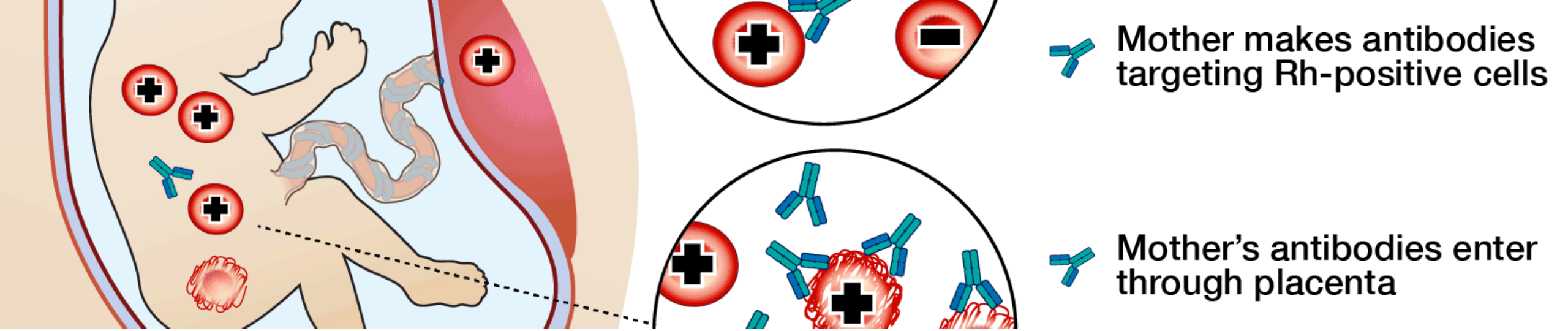
Rh Sensitization Response

Primary:

- Gamma M immunoglobin (**IgM**)
- Develops slowly (weeks or months)
- Large and do not cross the placenta

Secondary:

- Gamma G Immunoglobulin (**IgG**)
- “anti-D antibody” develops very quickly
- Can cross the placenta and coat the fetal Rh (D) pos RBC causing hemolysis



Rh Sensitization

If there is a second exposure to even a very small amount of Rh(D) + cells, either in the current pregnancy or future pregnancy this produces a rapid secondary immune response

- **Tranfusion Testing during Routine Pregnancies**

Antenatal Testing

- **Testing for ABO RhD and antibody screen is recommended after 8+0 weeks (11 and 14 weeks)**
    - Eg. K is expressed on fetal RBC at 10 weeks
  - to identify RhD negative pregnancies that require RhIg prophylaxis
  - To Identify pregnancies with clinically significant alloantibodies (thus requiring monitoring)

SOGC Group and screens and RhIG is not required prior to 8 weeks

Antenatal Testing

- **Routine Testing <u>may not be necessary</u> at 28 weeks gestation**
  - Repeat testing is of very low value as only 0.01- 0.43% of pregnancies with a Neg first trimester antibody screen develop a new alloantibody later in pregnancy
  - In those that do- severe HDFN is exceptionally rare (< 0.01 %)

Antenatal Testing

- **Antibody testing is suggested for all pregnancies (RhD + and RhD -) following a sensitizing event or after maternal RBC transfusion**
  - To detect any clinically significant alloantibodies requiring additional monitoring

Antenatal Testing

- **ABO, RhD and antibody screen at time of labour/birth is <u>only</u> recommended when**
  - No prior testing is available during that pregnancy and/or
  - There is a clinically significant antibody and/or
  - The risk of maternal transfusion is increased, and/or
  - The risk of neonatal transfusion is increased

Polling Question #1 Is the practice at your centre/hospital to always draw a GSO on admission for labour and birth?

- Yes
- No

Antenatal Testing

- **RHD genotyping is recommended in any pregnant person with weak or variably reactive RhD typing**
  - Up to 1 % of the population RhD serologic typing may be weak, indeterminate, or discrepant with historical results
  - This may represent a variant RH D allele which may or may not have the potential for anti- D formation
  - While genotype results are pending, people should be considered Rh D negative.

Antenatal Testing

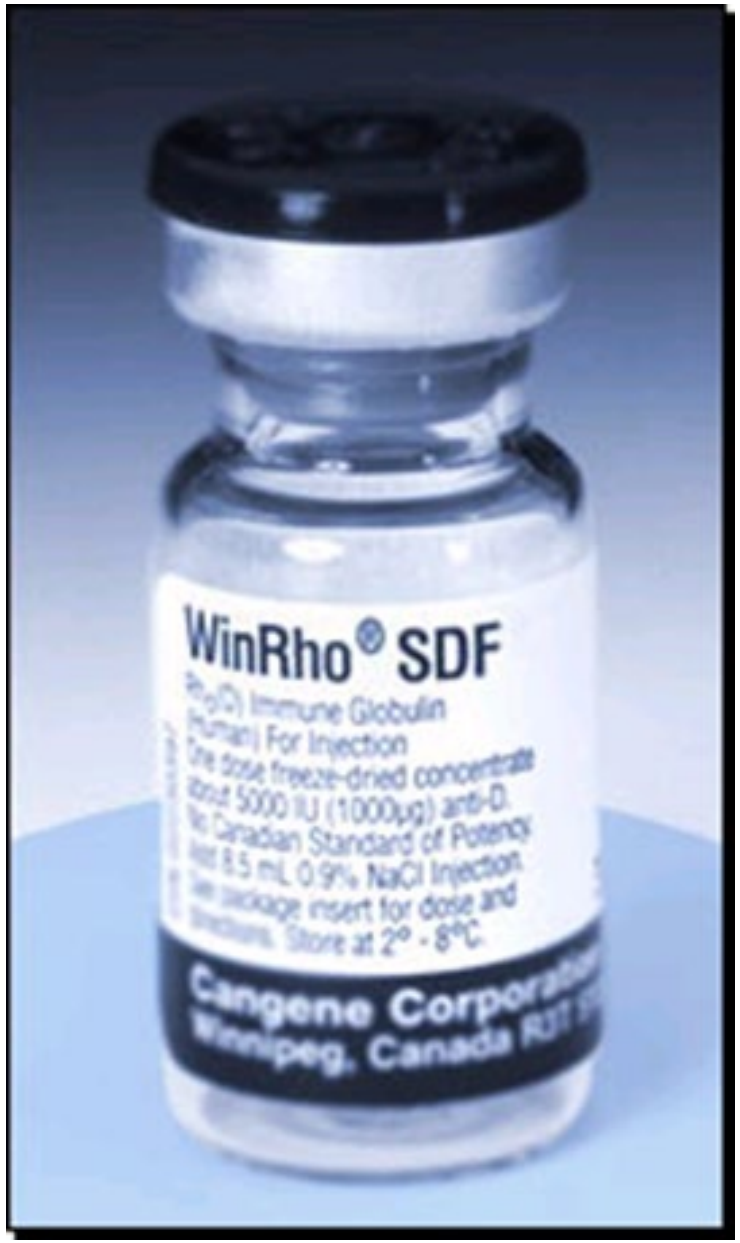
< 12 week GA (threatened, spontaneous or therapeutic abortions) screening and RhIg is not required

- FMH testing by flow cytometry suggests that the amount of FMH prior to 12 weeks GA is insufficient to cause RhD alloimmunization
- Several guidelines allow for exclusion of RhIg prior to 12 +0 weeks GA due to barriers in accessing care

*** If dating is uncertain, RhIG should be administered**

Rho (D) Immune Globulin

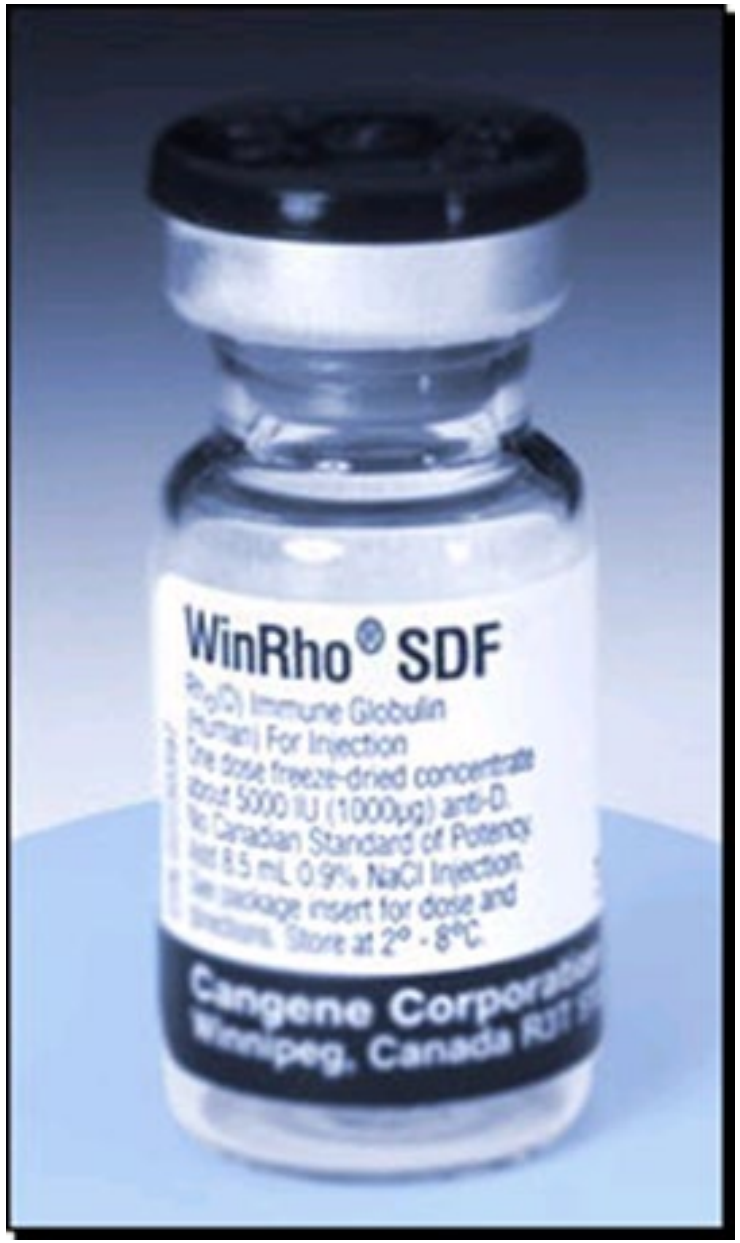
- Derived from human blood containing a high titre of antibody to RhD antigens of RBC's
- Available in Canada under the brand name WinRho SDF in doses of 300ug or 120ug
- Each 300 ug dose will last approx. 12 weeks
- The 300 ug dose should cover approx15 - 30 ml of Rh pos whole blood



Rho (D) Immune Globulin

How does it work?

- Blocks maternal antibody production
  - Destroys fetal cells in the maternal circulation before sensitization occurs
- Immune suppression appears to be effective as long as it occurs **before** the development of IgG antibodies (Secondary response)



RhIG Administration

- **Informed consent must be obtained and documented prior to administration of RhIG**
- For RhD negative pregnancies, determination of fetal RhD status by non-invasive prenatal testing (cffDNA testing of maternal plasma) is suggested to avoid unnecessary RhIG administration
- The need for RhIg prophylaxis is eliminated if a fetus is confirmed RhD-negative (not universally available in Canada yet)

RhIG Administration

- **Routine antenatal RhIG (300 ug 1500 IU) is recommended for all RhD- negative pregnant people at approximately 28 weeks gestation**
  - All RhD negative people should receive antepartum RhIG prophylaxis if the fetus is RhD pos, indeterminate or unknown.
  - The biggest risk of sensitization is at birth the RhIg dose further reduces the risk from 1% to 0.2%.

RhIG Administration

- **FMH testing is required postpartum for RhD – neg pregnancies with an RhD- pos neonate**
  - If Neonate is pos or unknown, postpartum RhIG and FMH testing are required for RhIg eligible people
  - Maternal samples are collected between 30 min and 2 hours from birth*
  - If neonate is RhD Neg (including weak testing) FMH testing is NOT req'd

RhIG Administration

- Flow cytometry is recommended for confirmation of diagnosis and quantification of FMH, where feasible
  - Assessing FMH starts with screening test (rosette or Betke-Kleihauer)
  - Positive tests should then be confirmed and quantified using flow cytometry method
  - *Pnts with beta thal, sickle cell or hereditary persistence of fetal hgb consider directly going to flow cytometry

Management of Pregnancies with maternal alloimmunization

Alloimmunization

Identification of clinically significant antibody

Step 1 – paternal testing

Step 2 – cffDNA testing if required

Step 3 - Fetal Anemia studies

Step 4 - Intrauterine transfusions if required

CffDNA

Application for out of country testing

Maternal sample collected on a Mon/Tues processed and then shipped to the UK

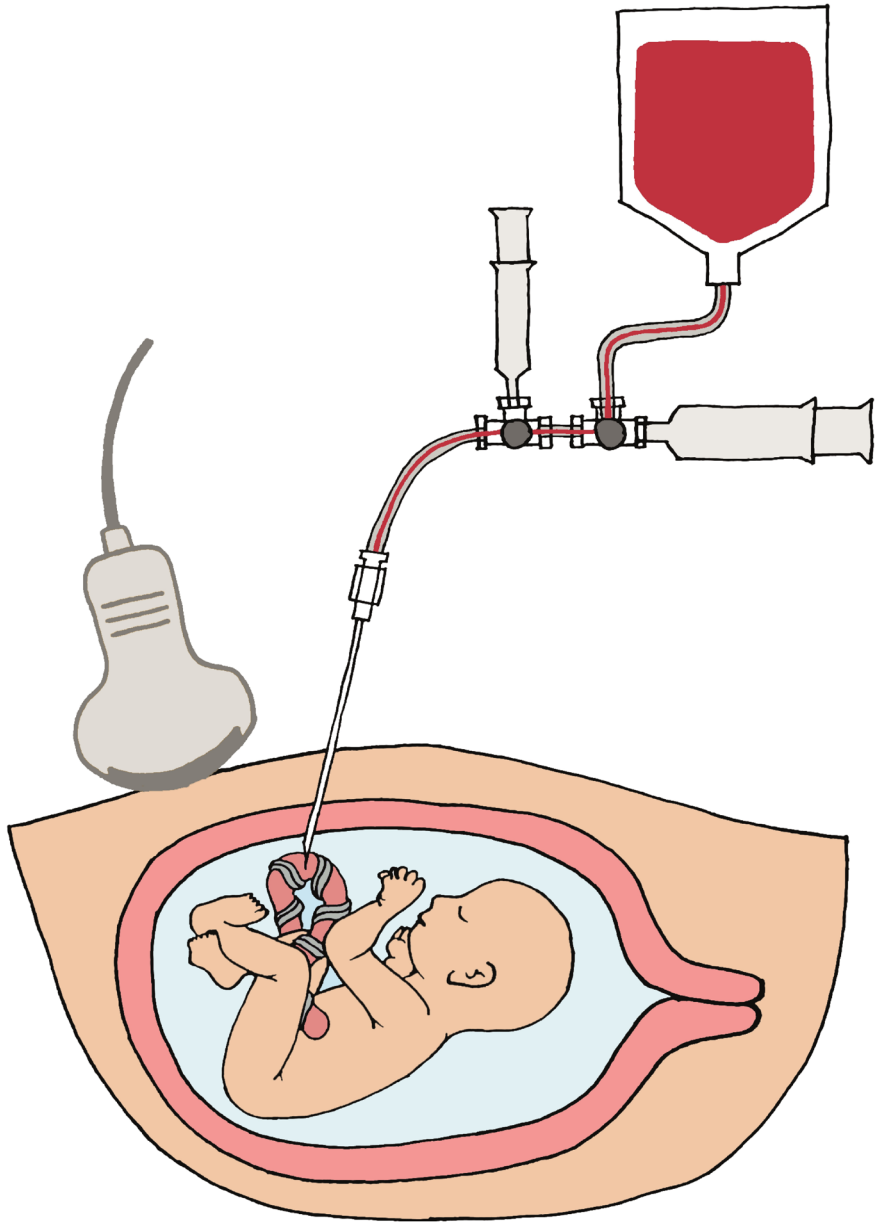
Get result about 2 weeks later

Samples for K need to be after 20 weeks and repeated after 28 weeks

Intrauterine Blood Transfusion (IUT)

the effectiveness of the in-utero transfusions (with O neg blood) is that it increases the fetus's hemoglobin and suppresses the bone marrow which then prevents further formation of blood cells

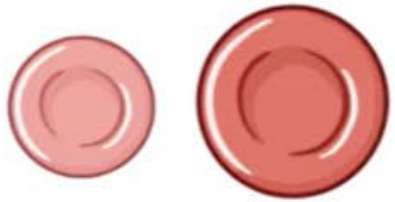
Babys blood will test showing donor blood (if neg could take months for the blood to test as Rh positive)
BLOOD BANK NEEDS TO KNOW ABOUT THESE CASES!
Cord Blood and NICU admission and long term f/u



Prevention and Treatment of Iron Deficiency Anemia in Pregnancy and Postpartum

IRON DEFICIENCY ANEMIA

MICROCYTIC HYPOCHROMIC



NORMAL

- ↓BODY's IRON STORES, caused by:
  - * ↓INTAKE
    - ~ INFANTS
    - ~ VEGETARIANS
  - * ↑DEMAND
    - ~ CHILDREN
    - ~ ADOLESCENTS
    - ~ PREGNANCY
  - * ↓ABSORPTION
    - ~ ↓HYDROCHLORIC ACID
    - ~ DUODENAL DISORDER
  - * ↑LOSS
    - ~ ♀ w/ FREQUENT or HEAVY MENSTRUATION
    - ~ BLEEDING GASTRIC ULCERS
    - ~ COLON CANCER

TREATMENT

- * ORAL
- * INTRAVENOUS
- * BLOOD TRANSFUSION

https://www.osmosis.org/learn/Iron_deficiency_anemia

Prevalence

- Anemia affects 32 million (36%) pregnant women globally.
- Every year, it contributes to more than 115 000 maternal deaths and 591 000 perinatal deaths worldwide
- WHO 1995 set a target for maternal anemia by 2025 to be reduced from 43 % to 15% by 2025 (> 50% reduction)
- *Currently more than double that* target - FIGO

Prevalence

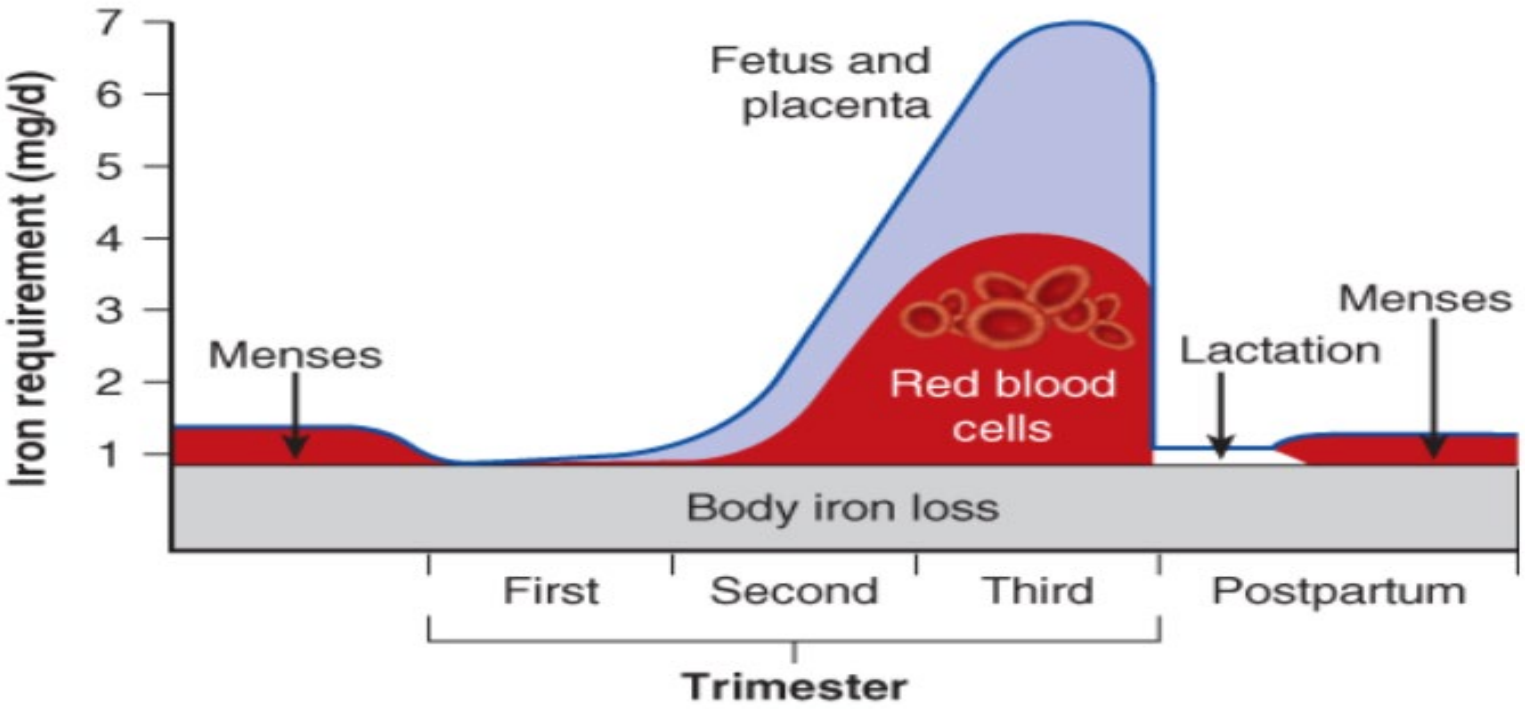
The prevalence of IDA in pregnancy is estimated at 41%, with higher rates in lower socioeconomic populations (SOGC)

- A study, conducted in Toronto of pregnant women screened for IDA found that 91% of participants were iron deficient (ferritin < 50 mg/L with most having severe deficiency ferritin < 20 mg/L despite only 25% of participants having a hemoglobin level < 110 g/L

Tang et al. Prevalence of Iron Deficiency and Iron Deficiency Anemia during Pregnancy: A Single Centre Canadian Study, Blood, Volume 134, Supplement 1, 2019, Page 3389,

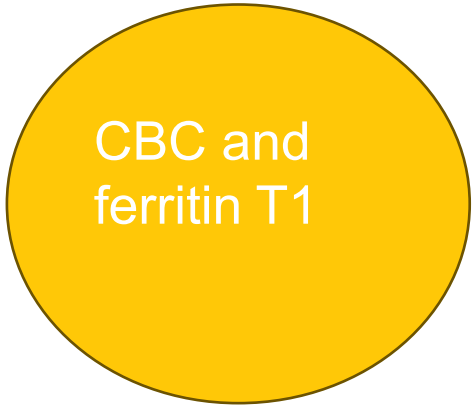
Pathophysiology

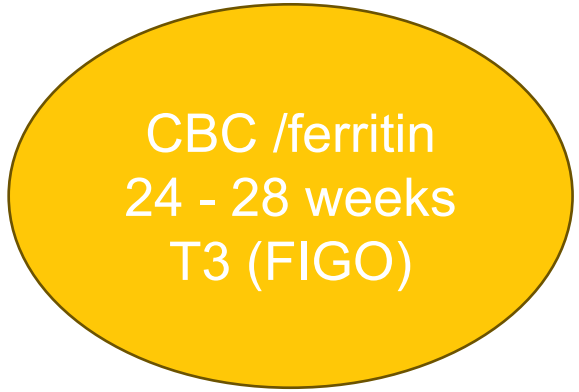
Estimated daily iron requirements during pregnancy in a 55-kg woman. (Modified from Koenig, 2014.)

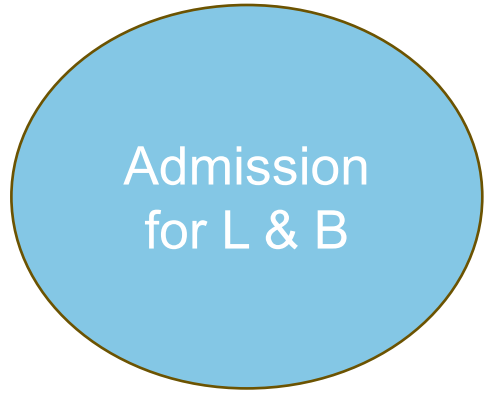


Leveno, K et al. Williams obstetrics. Vol 7. New York: McGraw-Hill Medical, 2014

When to screen for anemia?



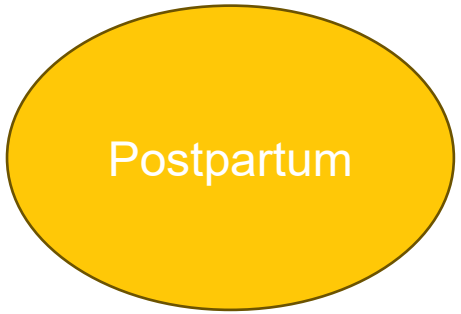




Antenatal: Hb < 110g/L (WHO, UK, FIGO)

Postpartum: Hb <100 g/L (UK) ; Hb < 110 g/L FIGO

Both antenatal and postnatal anemia should be identified and treated aggressively (strong, high).



DIAGNOSIS - Iron Deficiency

** **Ferritin** - protein that stores iron, found in many cells (liver, bone marrow)

- Most cost effective, practical, non-invasive marker
- Acute phase reactant

- **Transferrin -** iron carrier protein. Measured as a % saturation
- **Total iron-binding capacity -** blood's ability to bind to iron
- **Plasma iron -** amount of iron in the blood

Pavord S, Daru J, Prasannan N, et al. UK guidelines on the management of iron deficiency in pregnancy. Br J Haematol 2020;188:819-30.

DIAGNOSIS

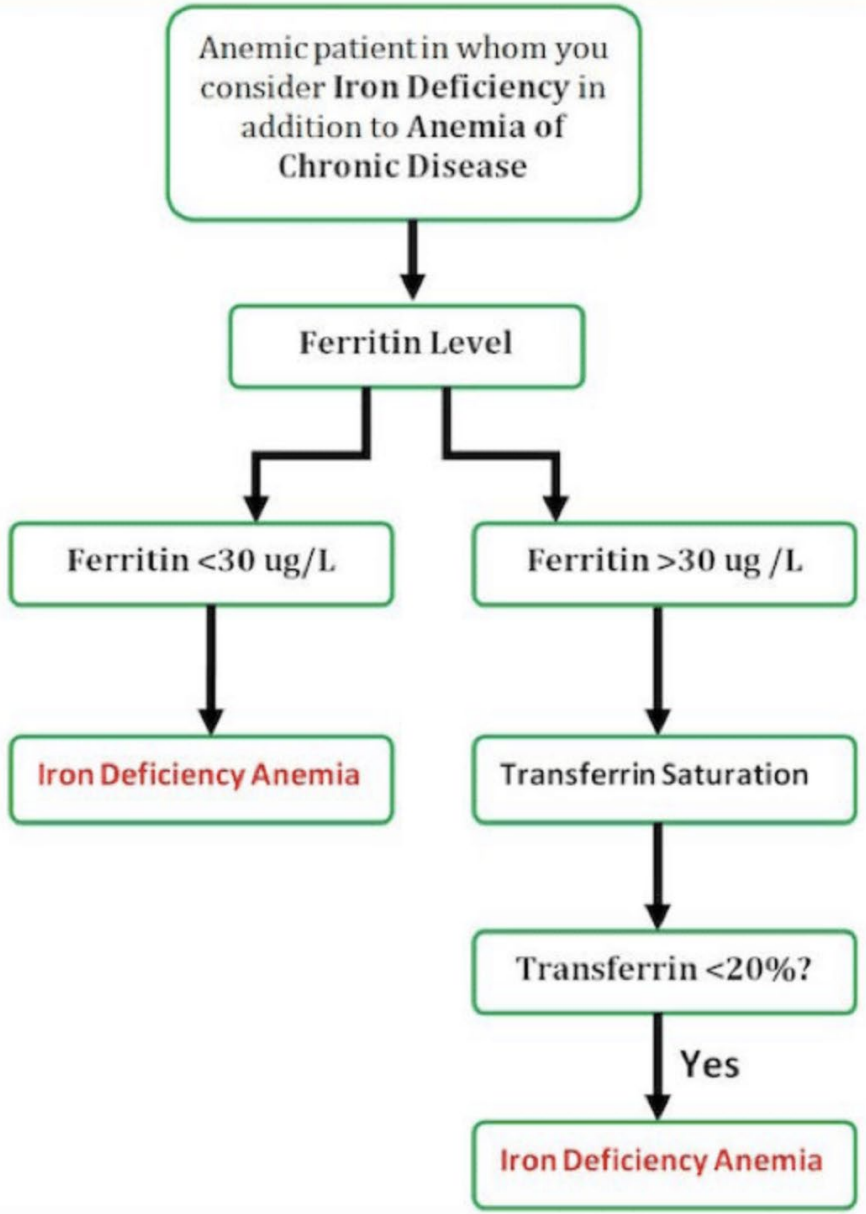
Ferritin < 30 ug/L (UK, ACOG)

- Ferritin > 100ug/L suggests adequate iron stores (Likelihood ratio 0.8, CI 0.07-0.09)

Transferrin < 20%

Total iron-binding capacity - HIGH

Plasma iron - IRRELEVANT



Pavord S, Daru J, Prasannan N, et al. UK guidelines on the management of iron deficiency in pregnancy. Br J Haematol 2020;188:819-30.

Consequences

- **Maternal consequences**
  - Postpartum hemorrhage
  - Requirement for transfusion
  - Pre-eclampsia
  - Depression*
  - Poor lactation*
  - Impaired bonding*

- **Fetal consequences**
  - SGA
  - Preterm birth

- Uterine atony
  - Less O2 to myometrial cell
  - Cofactor for ATP - myometrial cells have less energy

Tang G et al. Prevalence of iron deficiency and iron deficiency anemia during pregnancy: a single centre Canadian study. Blood 2019;134(Suppl 1):3389.
Young, M.F. et al. 2019., Maternal hemoglobin concentrations across pregnancy and maternal and child health: a systematic review and meta-analysis. Ann. N.Y. Acad.

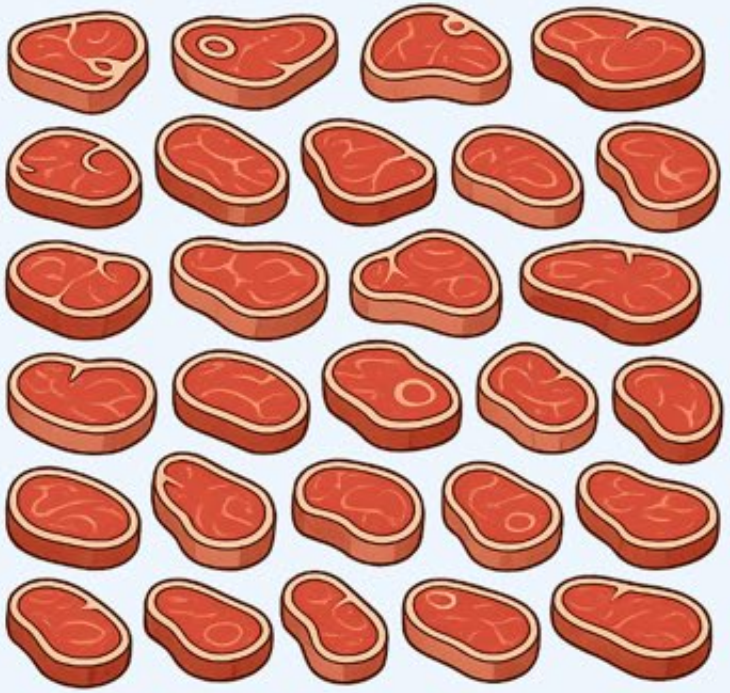
Ryan et al. No. 431: Postpartum Hemorrhage and Hemorrhagic Shock. JOGC. V44, Issue 12, 1293 - 1310.e1

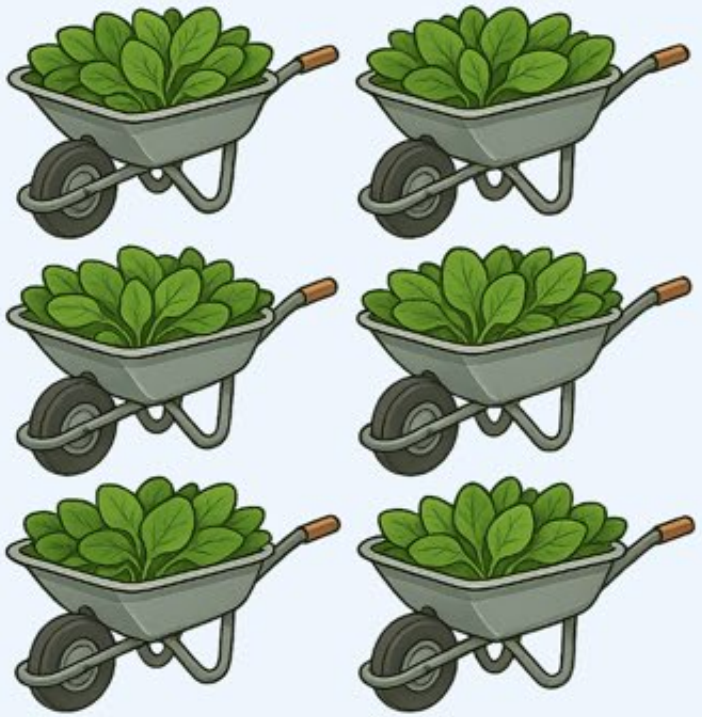
DIAGNOSIS - Trial of po iron

Expect Hb to increase by 10g/L after 2 weeks of adequate po supplementation (or 20g/L in 4 weeks)

Pavord S, Daru J, Prasannan N, et al. UK guidelines on the management of iron deficiency in pregnancy. Br J Haematol 2020;188:819-30.
CMAJ 2021 July 26;193:E1137-8. doi: 10.1503/cmaj.210007

DIETARY IRON





32 steaks per day or 6 wheelbarrows full of spinach per day!

Oral supplementation

Who should start oral iron supplementation in pregnancy (if not anemic)?

- CDC - All patients at first prenatal visit
- ACOG - All patients in first trimester
- UK - “not enough evidence” to recommend routine supplementation
- **FIGO- all pregnant women should receive a daily oral iron supplementation of 30–60 mg* of elemental iron (strong, high) 2025**

- **Intermittent supplementation** - 120 mg of elemental iron weekly (strong, high).

Who should start oral iron postpartum?

- Patients with Hb < 100 g/l within 48 h of birth, who are hemodynamically stable and asymptomatic (or mildly symptomatic), should be offered oral iron **40 – 80 mg daily** for at least 3 months (UK)

ORAL IRON - Prevention

30 – 60 mg daily

- **Rule of thumb - start every other day for compliance, then increase to daily**

Pavord S, Daru J, Prasannan N, et al. UK guidelines on the management of iron deficiency in pregnancy. Br J Haematol 2020;188:819-30.
CMAJ 2021 July 26;193:E1137-8. doi: 10.1503/cmaj.210007

ORAL IRON - Treatment

60 - 120 mg daily

- Continue until Hgb reaches 110 g/L then reduce to 30-60 mg
- Then continue for 3 months or until 6 weeks postpartum whichever is longer

ORAL SUPPLEMENTATION

Table 1: Oral and parenteral iron preparations*

Generic name	Brand name	Daily or alternate day dosing	Dose, mg	Elemental iron, mg/tab	Daily estimated cost, $†
Oral iron					
Ferrous gluconate	Floradix, Floravit	1 to 2 tabs	300	35	0.10
Ferrous sulfate	Ferodan, Ferrotrate	1 tab	300	60	0.20
Ferrous fumarate	Palafer, EuroFer	1 tab	300	100	0.25
Ferrous bisglycinate	Ferrochel, CanPrev	1 tab	25	25	0.30
Polysaccharide iron complex	Feramax	1 tab	150	150	0.75
Heme iron polypeptide	OptiFerA, Proferrin	2 to 3 tabs	398	11	2.40

CMAJ 2021 July 26;193:E1137-8. doi: 10.1503/cmaj.210007

Starting IV iron

- Absolute non-compliance/ intolerance of oral supplementation
- Poor response - **hemoglobin increase of < 10 g/L 2 wk after starting treatment (SOGC)**
- Rapid response required
  - Patients who present after 34 weeks' gestation Hgb of < 100 g/L (UK)
  - Postpartum - Hb < 80g/L (SOGC)
  - Anemia with upcoming urgent surgery
- Special populations
  - Those who can't absorb po iron - **gastric bypass,** end stage renal disease, **celiac disease**
  - **Moderate to Severe Anemia (FIGO, 2025)**
  - Childbirth anticipated within 4 - 6 weeks

    Iron infusions not recommended in T1 (FIGO, 2025)

Ryan et al. No. 431: Postpartum Hemorrhage and Hemorrhagic Shock. JOGC. V44, Issue 12, 1293 - 1310.e1

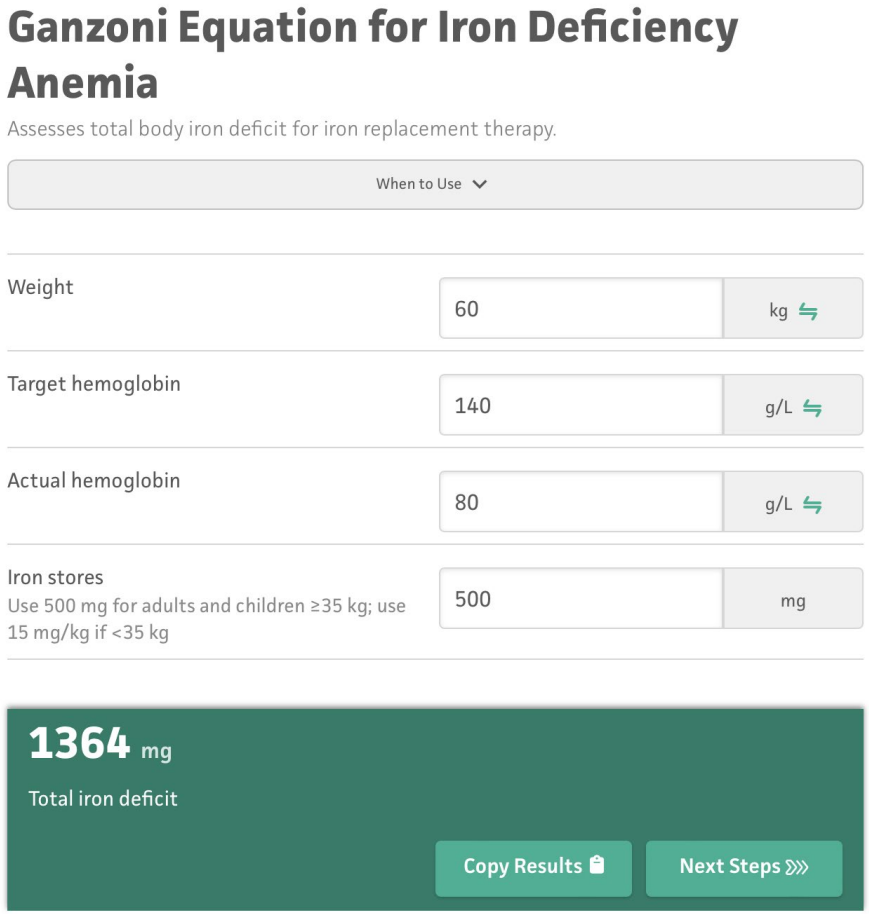
IV Iron - Formulations

Parenteral iron				
Iron sucrose	Venofer	200–300 mg in a single dose over 2 h§	—	375
Ferric derisomaltose‡	Monoferric	500–1500 mg in a single dose over 30 to 60 min§	—	450–900

Chandler, et al. Intravenous iron sucrose: Establishing a safe dose. American Journal of Kidney Diseases, Volume 38, Issue 5, 988 - 991

CMAJ 2021 July 26;193:E1137-8. doi: 10.1503/cmaj.210007

IV Iron - Dose



Wong L et al. Safety and efficacy of rapid (1,000 mg in 1 hr) intravenous iron dextran for treatment of maternal iron deficient anemia of pregnancy. Am J Hematol. 2016;91(6):590-593.

Auerbach M, Deloughery T. Single-dose intravenous iron for iron deficiency: a new paradigm. Hematology Am Soc Hematol Educ Program. 2016 Dec 2;2016(1):57-66. doi: 10.1182/asheducation-2016.1.57. PMID: 27913463; PMCID: PMC6142502.

IV Iron - Dose

		Body Weight	
		<70 kg	≥70 kg
Hb	≥100 g/L	1000 mg	1500 mg
	<100 g/L	1500 mg	2000 mg

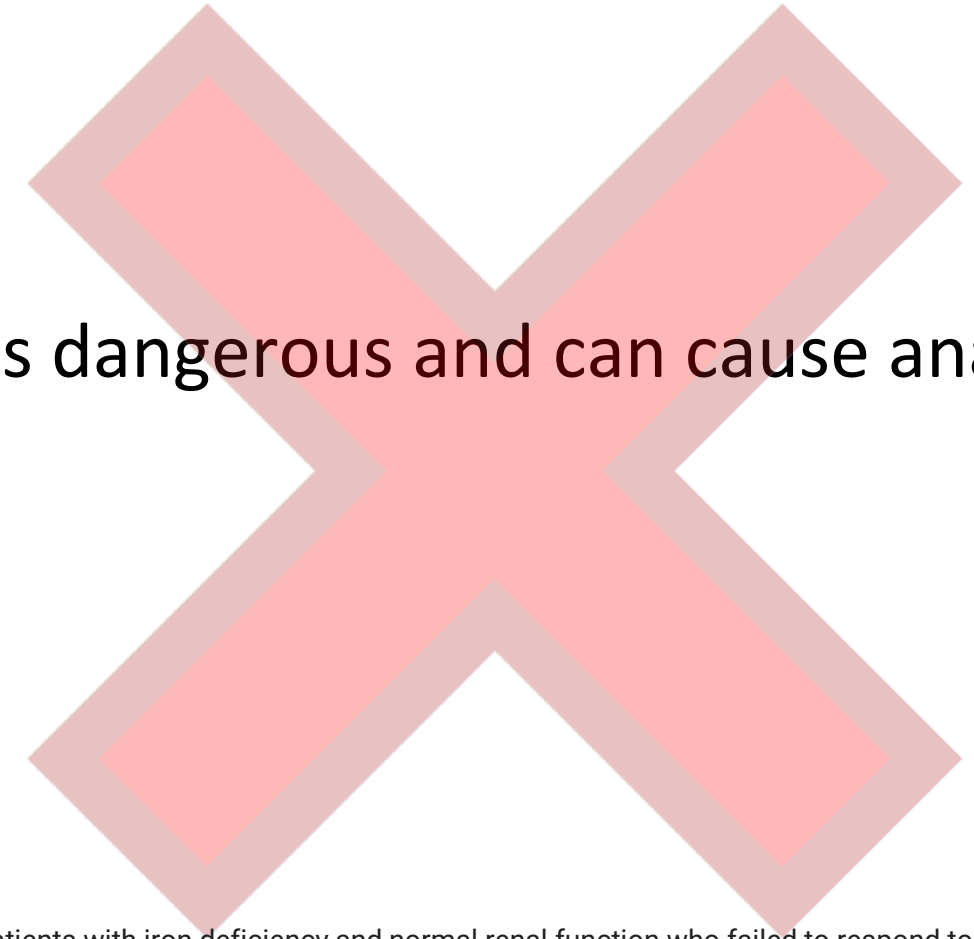
IV Iron - Monoferric

Treatment: Blood Transfusion

- Severe anemia, especially when it is close to EDB/childbirth
- Acute severe bleeding or where there is a risk of further bleeding
- Significant symptomatic anemia with features of hemodynamic or cardiac compromise

	VENOFER	MONOFERRIC
Drug	$140 x 3 doses = $420 for 900mg total Funded by EAP if eligible	$477 for 1000mg Funded by ODB with LU code
Supplies	$11 x 3 visits = $33	$11
Chair/Nursing Time	2-3 hours per visit	30 minutes- 1 hour
Patient Costs	Parking x 3 hours x 3 visits Lost income x 3 visits or Childcare x 3 visits	Parking x 1 hour Lost income x 1 visit or Childcare x 1 visit

COMMON MISCONCEPTION



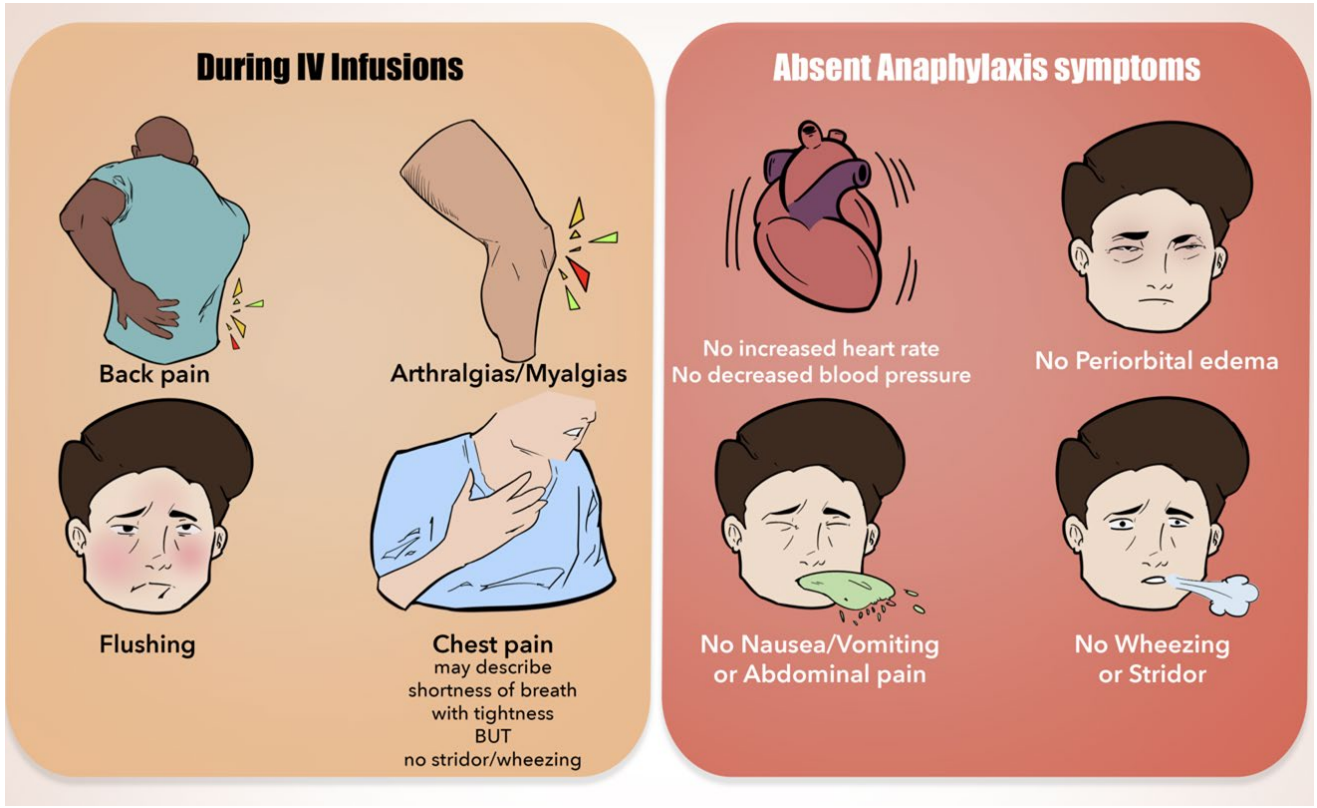
IV Iron is dangerous and can cause anaphylaxis

Barton JC et al. . Intravenous iron dextran therapy in patients with iron deficiency and normal renal function who failed to respond to or did not tolerate oral iron supplementation. Am J Med. 2000 Jul;109(1):27-32

Auerbach M, Macdougall IC. Safety of intravenous iron formulations: facts and folklore. Blood Transfus. 2014 Jul;12(3):296-300. doi: 10.2450/2014.0094-14. PMID: 25074787; PMCID: PMC4111808.

Arastu AH, Elstrott BK, Martens KL, et al. Analysis of Adverse Events and Intravenous Iron Infusion Formulations in Adults With and Without Prior Infusion Reactions. *JAMA Netw Open.* 2022;5(3):e224488

IV Iron - Fishbane Reaction



Fishbane S, The safety of intravenous iron dextran in hemodialysis patients. Am J Kidney Dis. 1996 Oct;28(4):529-34

IV Iron vs. PRBC

- Choi et al 2024 - *A Propensity-Matched Cohort Study of Intravenous Iron versus Red Cell Transfusions for Preoperative Iron-Deficiency Anemia*
  - 154,358 with IDA randomized to pre-op IV iron or pRBC
    - Pre-op iron group had **decreased mortality** (RR 0.63) (p = 0.001), **higher post op Hb** (p = 0.001), **reduced incidence of post-op transfusion** (RR 0.3)

- Holm et al 2017 - *Single-dose IV iron infusion vs. RBC transfusion for treatment of severe postpartum anemia: RCT*
  - 13 patients with anemia (56-81dg/L) got Monoferric vs. pRBC
    - IV iron - **higher reticulocytes week 1, iron weeks 3-12**
    - pRBC - higher Hb day 1, lower retics week 1, lower iron levels

Choi et al.. A Propensity-Matched Cohort Study of Intravenous Iron versus Red Cell Transfusions for Preoperative Iron-Deficiency Anemia. Anesth Analg. 2024 Nov 1;139(5):969-977

Holm C, Thomsen LL, Norgaard A, Langhoff-Roos J. Single-dose intravenous iron infusion versus red blood cell transfusion for the treatment of severe postpartum anaemia: a randomized controlled pilot study. Vox Sang. 2017 Feb;112(2):122-131.

Comparison of anemia therapies

Intervention	Dose	Cost	Duration of therapy	Peak effect	Total acquisition cost	Additional costs - nursing, lab, testing, chair time (may vary)	Change in hemoglobin (g/L)	Cost/g/L increase	Relative Cost per g/L increase in hemoglobin compared to 1 unit RBC	Cost comparator to 1 unit RBC (acquisition + additional costs)
red blood cells	1 unit	$446.00	120min x 1	end of infusion; shorter 1/2 life than endogenous cells	$446.00	$328.30	10	$77.43	1.00	1.00
oral iron salts	100mg elemental daily	$0.28	13-26 weeks	13-26 weeks	$39.20	$28.47	28	$2.42	0.03	0.09
iron sucrose	300mg	$112.50	90min x 4	5-8 weeks	$450.00	$623.15	39	$27.52	0.36	1.39
iron isomaltoside	1200mg	$540.00	60 min x 1	5-8 weeks	$540.00	$64.72	39	$15.51	0.20	0.78

Lett et al. NAC Statement on PBM 2022 June

Key Points

- Every pregnant person needs to be
    1. screened for IDA
    2. Iron supplementation for the prevention of IDA (30 – 60 mg/ day)
- Antenatal - Hb 110g/L/ Postpartum - Hb 100g/L or 110 as per FIGO
- **Ferritin < 30ug/L**
- IDA causes adverse events in pregnancy (fetal, maternal)
- Oral treatment for IDA
    - 60 -120 mg po daily (or every other day) on an empty stomach, with or without Vit C
    - Positive response - increase in Hb 10g/L in 2 weeks or 20 g/L in 4 weeks

- IV treatment for IDA
    - Give it earlier than you think
    - Likely need 1g or more (Ganzoni equation)
    - Adverse reaction - slow the transfusion rate, DON’T give Benadryl

Pre- test #1 When should a Maternal Hemmorhage Screen (FMH) be drawn after birth?

a. Immediately after birth
b. Between 30 minutes and 2 hours after birth
c. Within 24 hours after birth
d. Within 72 hours after birth

Pre- test #2 All Red blood cell antibodies can lead to hemolytic disease of the fetus/newborn

- True

Or

- False

Pre- test #3 A RhIg dose of 300 ug will cover up to this much RBC's in maternal blood

a. 5 mL

b. 10 mL

c. 30 mL

d. 60 mL

Pre- test #4 What is the recommended cut off value for diagnosing Iron deficiency Anemia in pregnancy

a. Hgb < 120 g/ L

b. Hgb < 110 g /L

c. Hgb < 100 g/L

d. Hgb < 80 g/L

Pre- test #5 Aggressive management of Iron deficiency anemia with IV iron is important for PPH prevention

True

Or

False

Unique Considerations when transfusing a pregnant or postpartum patient

Unique Considerations

- Pregnant patients should receive compatible blood that has been screened for Kell antigen
- If a clinically significant antibody is present then should receive blood that has been screened for those antigens
- CMV neg blood should be provided to prevent congenital CMV infections

Unique Considerations

- If Rh + blood is given to a patient in an emergency then RhIg should be administered
- If a patient receives a RBC transfusion during pregnancy they should be screened for antibodies
- Collaboration with Blood transfusion lab (accreta, antibodies, fetal intrauterine transfusions etc.)

Unique Considerations

- Cryoprecipitate should be administered early in a major PPH then guided by fibrinogen levels
- 4 units RBC’s should be given prior to other blood products in an actively bleeding patient who is approaching the maximum allowable blood loss, unless the patient has a coagulation defect
- Fibrinogen levels should be measured in every moderate to severe case of postpartum hemorrhage, and if < 2 g replaced accordingly

Unique Considerations

- A massive hemorrhage protocol with ratios of red blood cells to fresh frozen plasma to platelets of 1:1:1: or 2:1:1 can be used in the absence of timely lab results

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