Anemia during Pregnancy

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This guideline has been updated with gender inclusive language.

Summary

- All pregnant patients should have a screening CBC in the first trimester and 24-28 weeks gestation.
- All patients should have a hemoglobin electrophoresis in pregnancy if not yet done.
- Patients diagnosed with anemia should have screening for iron deficiency and/or other causes of anemia based on CBC indices and medical history.
- Screening for micronutrient deficiencies such as B12 and folate deficiencies should be considered for patients at increased risk based on medical/surgical history or dietary limitations.
- Iron deficiency is diagnosed if ferritin < 30 g/dL and/or transferrin saturation < 20%
- We recommend treatment with oral iron, daily or every other day, as a first line treatment for antenatally diagnosed iron deficiency anemia.
    - **More than once daily dosing of oral iron should not be administered.**
- IV Iron should be considered for
    1. **Patients <28 weeks with a Hgb of <9 g/dL or ≥ 28 weeks with a Hgb of < 10 g/dL**
    2. Patients who do not tolerate oral iron therapy.
    3. Patients with malabsorption syndromes (i.e. IBD, gastric bypass).
    4. Patients who are refractory to oral iron after 4 weeks of therapy.
    5. **For postpartum patients with hemoglobin of <9 g/dL (who do not meet criteria for a blood transfusion) and/or 3g/dL drop in hemoglobin.**

Background

Pathologic anemia in pregnancy is exceedingly common, affecting 40% of pregnant patients worldwide and nearly one third of pregnant people in the United States.[1] In a cohort from Baylor College of Medicine, the prevalence of anemia diagnosed by a hemoglobin 11.0 g/dL on admission to labor and delivery was 35%.[2]

Several studies have identified associations between maternal anemia and higher rates of preterm labor, low birth weight neonates, low neonatal 5-minute APGAR, preeclampsia, Cesarean delivery, postpartum hemorrhage, blood transfusion, perinatal death and maternal death.[1-5] Additionally, iron deficiency with or without anemia has been associated with an increased incidence of perinatal depression.

Iron deficiency is the leading cause of pathologic anemia in pregnancy. The Institute of Medicine and ACOG recommend 27mg of ferrous iron daily during pregnancy, an amount which is typically present in prenatal vitamins.[6,7] The goal is to prevent development of or worsening iron deficiency and/or anemia. A 2024 Cochrane review evaluated 57 trials to determine the effect of iron deficiency on pregnancy outcomes.[8] They found that treatment with iron supplementation reduced maternal iron deficiency anemia as well as incidence of having a neonate with low birthweight (weight < 2500g). Evidence is still uncertain about whether treatment of anemia improves other associated outcomes, particularly incidence of perinatal depression. However, it is also important to note that the symptoms associated with anemia and/or iron deficiency (fatigue, restless legs, headache, palpitations, syncope) can adversely affect quality of life.[9] Therefore, it is valuable to screen, treat and monitor anemia and iron deficiency during pregnancy to provide symptomatic benefit alone.

Other micronutrient deficiencies, such as B12 or folate deficiency, are rare and more often seen diagnosed in patients with malabsorptive syndromes, prior bariatric surgery, or specific dietary restrictions (vegan and vegetarian diets).[6,10] These deficiencies have also been associated with adverse perinatal outcomes as well as long term neurocognitive symptoms for the fetus.[10,11] Therefore, it is important to diagnose and treat these conditions although definitive evidence that repletion improves associated outcomes is lacking.[8]

Iron Deficiency
1. Heavy menstrual cycle
2. Dietary
3. Short interpregnancy interval
4. Malabsorption (IBD, IBS, history of gastric surgery, chronic PPI use or metformin use)
5. Malnutrition (inadequate access to food, hyperemesis)

B12 Deficiency
1. Dietary (especially vegan and vegetarian diets)
2. Malabsorption (IBD, history of gastric surgery)
3. Malnutrition (inadequate access to food, hyperemesis)

Folate Deficiency
1. Dietary
2. Malabsorption
3. Malnutrition (inadequate access to food, hyperemesis)

Screening and Work UpACOG recommends screening for anemia for all pregnant people in the first trimester and at the end of the second trimester from 24-28 weeks.[6] **Anemia is diagnosed when hemoglobin levels of 11 g/dL in the first and third trimesters or 10.5 g/dL in the second trimester are noted**.[6] These same criteria should be applied to all pregnant people, regardless of race and/or ethnicity.

The cause of anemia should be investigated with additional laboratory evaluation and a detailed patient history. Anemia can be stratified into microcytic (MCV < 80 fL), normocytic (MCV 80-100 fL), and macrocytic (MCV >100 fL), which can help predict potential causes of anemia. **It is important to note, however, that mixed anemias (with more than one cause) can have a falsely normal MCV.** Therefore, review of a patient's medical, surgical and social histories can provide extra insight into potential causes of anemia. Figure 1 describes risk factors for common micronutrient deficiencies.

The BCM OB/Gyn Perinatal Guideline committee recommends screening with a complete blood count to review hemoglobin/hematocrit as well as MCV. Figure 2 illustrates the differential diagnosis based on MCV as well as the recommended work up for anemias. Additionally, per ACOG recommendations, **all** patients should have screening for hemoglobinopathies with a hemoglobin electrophoresis regardless of anemia status (if not done previously).[12]

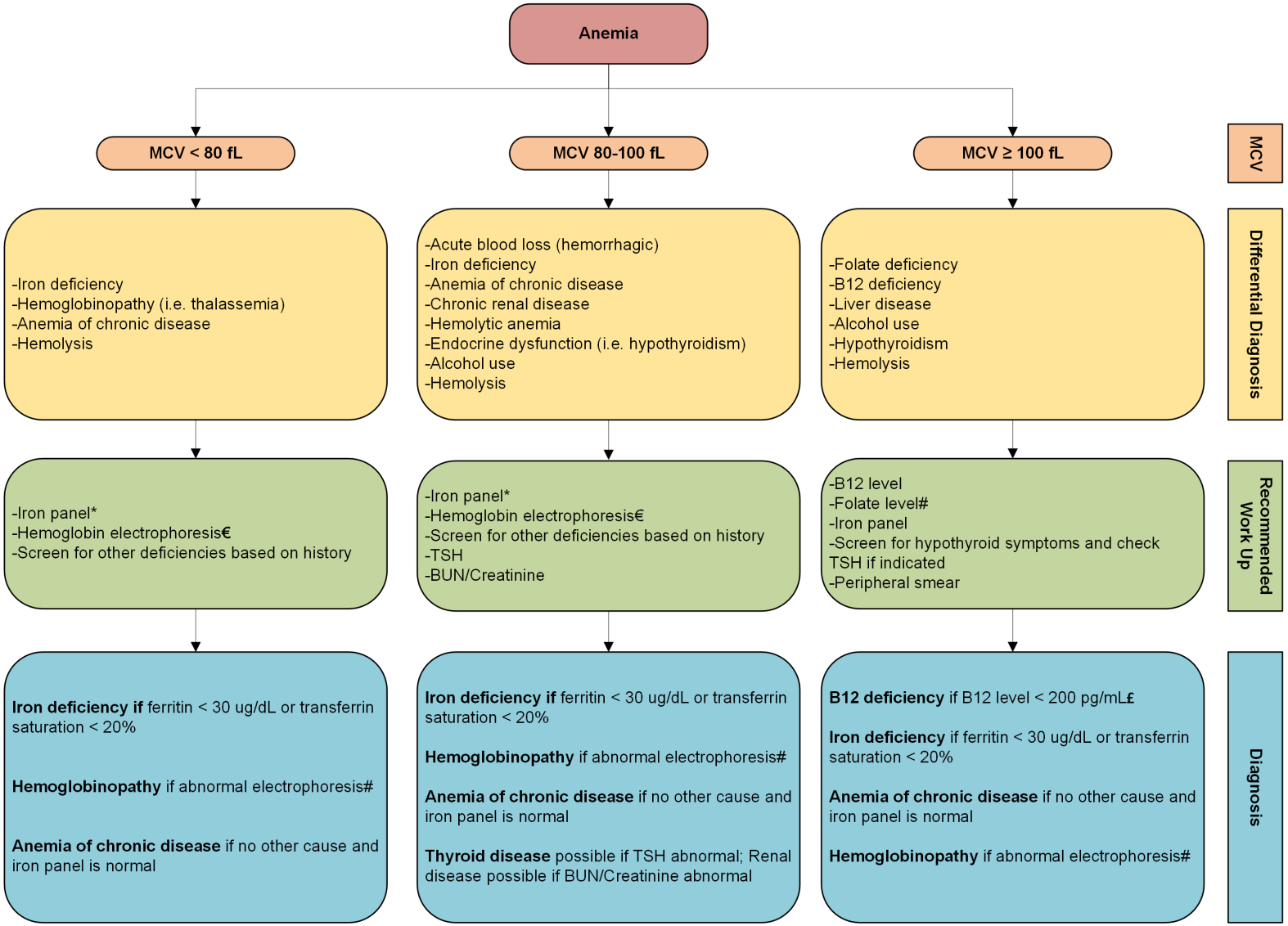

Figure 1. Differential Diagnosis and Work Up for Anemia

*** An Iron Panel should include Ferritin, Iron, TIBC, Transferrin Saturation. At Ben Taub, an iron profile does NOT include a ferritin so it must be added.**
Serum folate levels are an inaccurate measure of true folate stores in patients taking a prenatal vitamin. Those at high risk of folate deficiency can be treated empirically.
€ Hemoglobin electrophoresis will only detect beta hemoglobinopathies (beta thalassemia, sickle cell trait or anemia). It will NOT detect alpha thalassemia. Therefore, if patient has microcytosis that does not resolve with iron supplementation, consider alpha thalassemia genetic testing
£ B12 levels between 200 and 300 pg/mL may still indicate a B12 deficiency. Diagnosis of B12 deficiency can be confirmed with an elevated methylmalonic acid level, although this may not be accurate in pregnancy. For patients with risk factors for B12 deficiency, recommend empiric treatment with B12 supplementation.

Treatment

Iron deficiency anemia

Figure 3 represents the recommended algorithm for iron supplementation during pregnancy.

Iron deficiency is diagnosed if ferritin is < 30 µg/L and/or transferrin saturation is < 20%.

Oral Iron Therapy

Oral iron supplementation is a safe, effective, readily available option for improving iron deficiency anemia. This is considered the first line management for iron deficiency anemia for a majority of patients.[6,13] However, limitations of oral iron include low rate of systemic absorption, slow improvement in parameters, and high incidence of gastrointestinal side effects such as nausea, gastric irritation, metallic taste and constipation. These adverse effects contribute to poor adherence with oral iron. Research suggests that once daily or every other day dosing may be the optimal method for iron supplementation. **More frequent dosing (BID or TID) is NOT recommended and should not be used** as this may reduce iron absorption and increase adverse side effects.[14] **Every other day dosing is as effective as daily dosing and reduces the side effect profile**.[15]

There are multiple different oral iron supplements, but studies suggest they all have similar efficacy and side effect profiles. **The BCM OB/Gyn Perinatal Guidelines Committee recommends ferrous sulfate 325mg daily or every other day x3-4 weeks with an assessment of medication adherence and side effects, as well as repeat lab work after that time.**

Parenteral Iron Therapy

Parenteral Iron is indicated in the setting of inability to tolerate oral iron, lack of improvement despite oral iron supplementation, and in patients with iron malabsorption syndromes (i.e. IBD, history gastric bypass surgery).[6*]

Several randomized trials have been conducted to compare oral versus intravenous iron use for maternal anemia, addressing clinical, hematologic parameters and adverse effects as outcomes. A systematic review and meta-analysis from 2019 included 20 of these randomized trials and revealed higher hemoglobin levels at delivery with intravenous iron, but fewer medical reactions and no difference in blood transfusion with this route compared to oral iron.[16] Similar comparisons have been made for postpartum anemia.[17,18] It should be noted that patients with hemochromatosis, thalassemia, porphyria or some infectious intestinal diseases may not be candidates for iron supplementation.

There are three main types of **reactions** to iron infusions, minor, moderate and severe (anaphylaxis), Minor infusion reactions to IV iron are due to labile iron and not to hypersensitivity.[19] **These minor reactions include chest and back pressure, flushing, itching and/or urticaria.** Notably, they are without accompanying hypotension, tachypnea, tachycardia, wheezing, and stridor or periorbital edema. Hypotensive reactions may occur, in particular with rapid infusions due to the labile iron content of IV iron formulations. Rarely (<1:250,000) iron infusion can be severe/life-threatening when it is a hypersensitivity reaction which can lead to anaphylaxis.[19] A recommended management algorithm for reactions during intravenous iron can be seen in Figure 4.

One study found that extravasation and skin staining occurred in approximately 1% of patients. This can be minimized by ensuring a patent IV prior to initiating the infusion, using an IV at a non-flexural site.[20]

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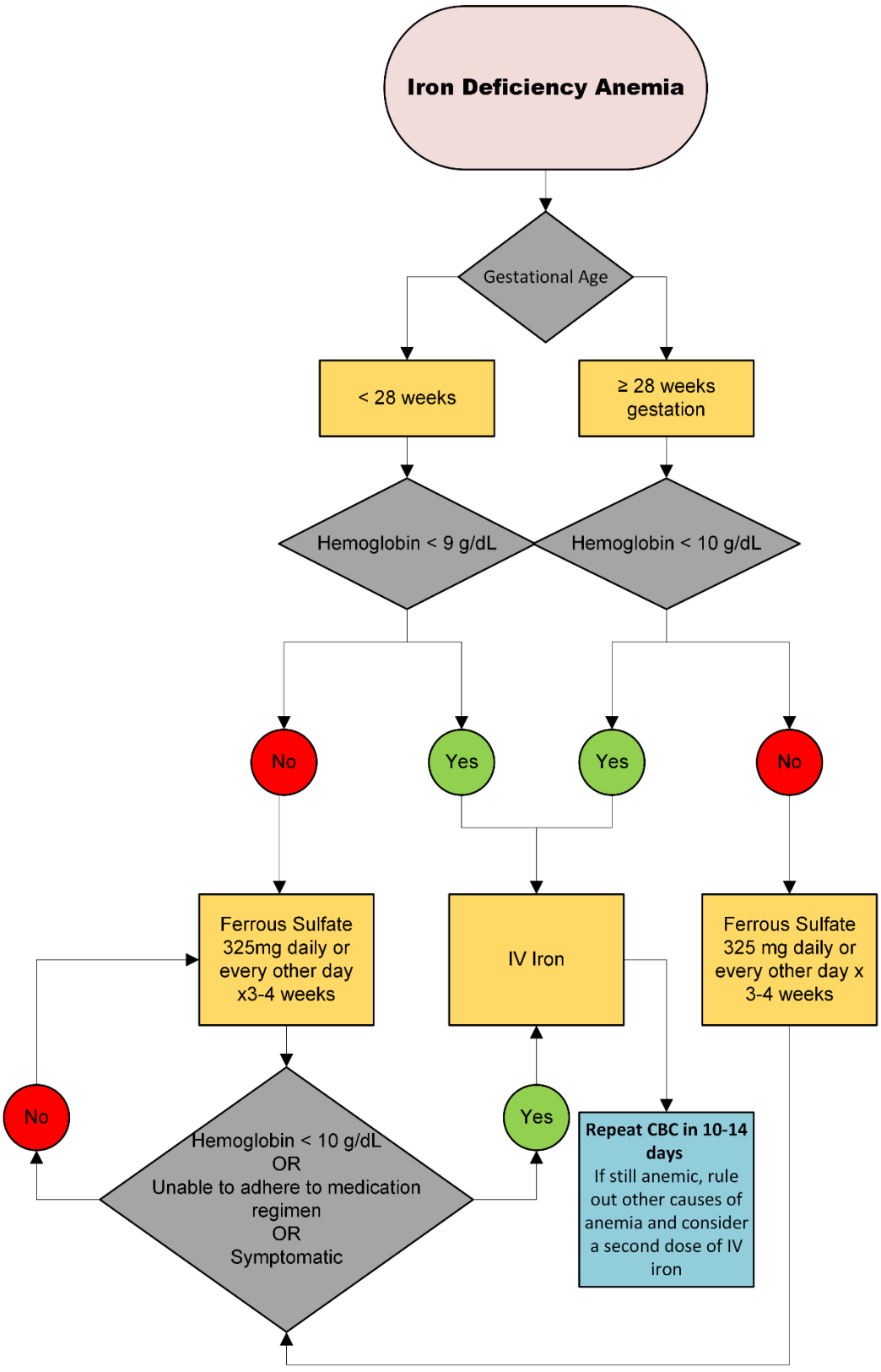
* There is increasing evidence of safety and efficacy to suggest encouraging its use more readily in cases of severe iron deficiency and when more rapid replenishment is necessary. Intravenous iron administration carries a risk of transfusion reaction, with an incidence of anaphylaxis of approximately 1% with iron dextran; newer formulations such as iron sucrose have been suggested to have an improved side effect profile (18). Given overall safety profile with newer parenteral formulations, some authors have called for more liberal use of intravenous iron particularly in the third trimester of pregnancy (19).

Figure 3. Algorithm for IV vs. PO iron administration



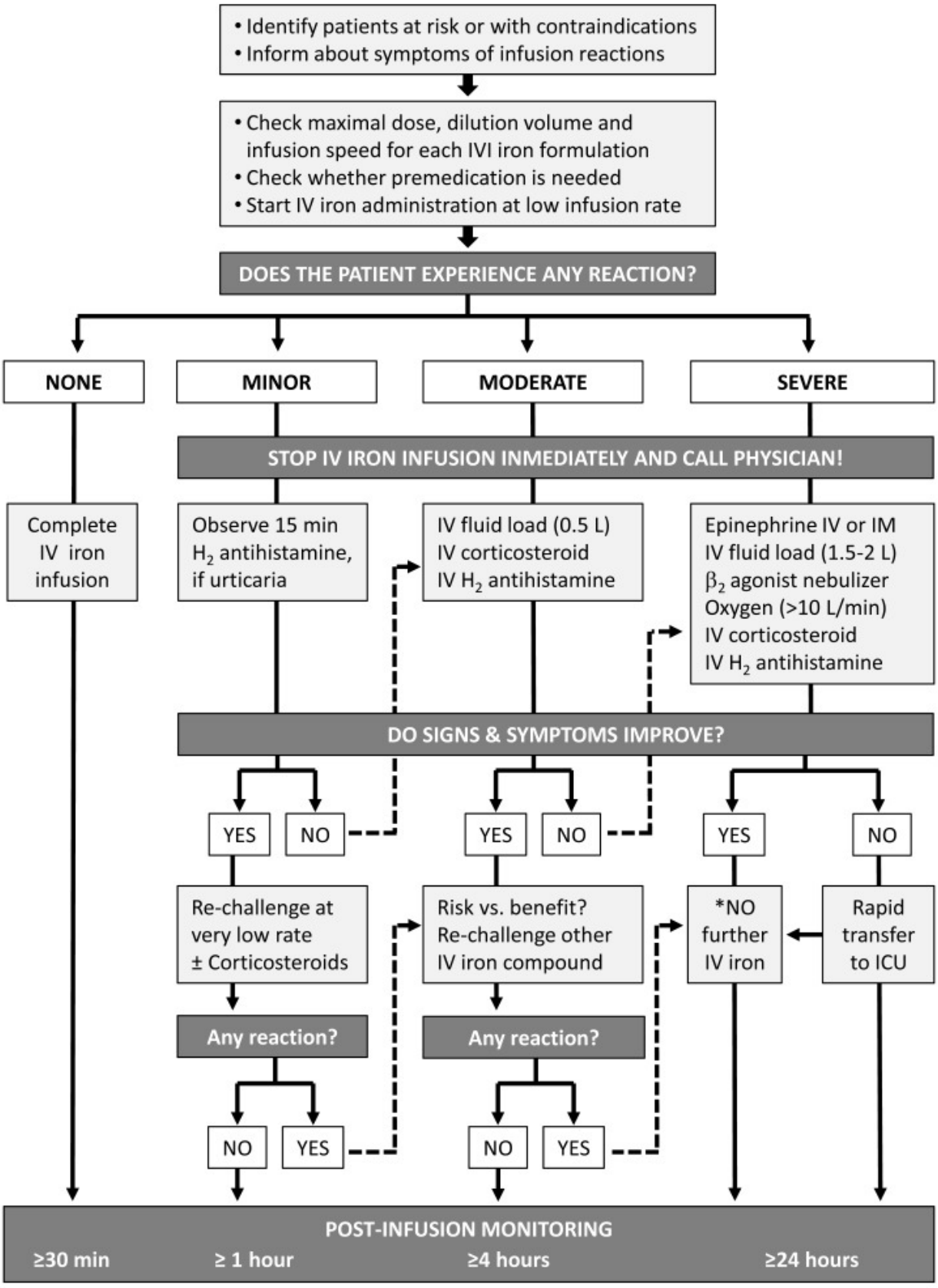
IV Iron Protocols

Ben Taub
The patient is admitted to antepartum for observation with administration as follows:

1. Admit to Ante for Obs
2. Administer Iron dextran 25mg test dose
3. Iron dextran 975mg IV over 6-8 hours
4. Recommend NST for the first dose of IV iron (including test dose) for all pregnancies >24 weeks' gestation.

Pavilion for Women
The patient is scheduled in the PFW Infusion Center and the recommended administration for IV iron is iron sucrose 300mg IV for 3 total doses (separated, daily, every other day or weekly).

Figure 4. Management of reactions during IV iron administration[19]



Other Treatments

There are limited and conflicting data regarding the use of erythropoietin (EPO) either as an adjunct or as therapy for antepartum anemia.[21] However, studies have shown that EPO is unlikely to cross the placenta due to its large molecular size and previous studies have used this with success in pregnancy.[22] EPO is also often used as an adjunct in patients with chronic kidney disease in pregnancy. **The use of EPO should be individualized.**

Blood transfusion has been recommended for severe anemia with Hgb levels less than 6g/dL.[6] This is based on evidence of associated poor fetal outcomes; a 2003 prospective observational study associated Hgb levels less than 6 g/dL with fetal outcomes such as non-reassuring fetal heart rate, low amniotic fluid index, abnormal fetal oxygenation and fetal death.[23] **Blood transfusion should also be considered in symptomatically anemic patients even at Hg levels greater than 6g/dL**.

Treatment Monitoring

Patients should have repeat CBC with consideration for a reticulocyte count within 3-4 weeks of oral iron therapy initiation. Providers should also assess side effects and medication adherence. For patients with an inadequate response, should consider IV Iron as listed in the Figure 3 algorithm. It is also important to reevaluate for other causes of anemia (other micronutrient deficiencies, hemolytic anemia, continued blood loss, etc) if the response has been less than adequate or the anemia has worsened.

Postpartum Management of iron deficiency or acute blood loss anemia

Management of anemia postpartum is mostly based on expert clinical opinion and there is no established threshold for repletion Iron repletion is effective by either oral or IV formulations. Multiple studies have shown that IV iron produces higher hemoglobin concentration postpartum compared with oral iron.[24,25] However, due to limited resources (i.e. staffing, hospital capacity, availability of IV formulations) this may not always be feasible.

Data indicate that maternal hemoglobin levels six weeks postpartum were approximately 1.0 g/dl higher in people who received intravenous iron compared to those who took oral iron as well as fewer gastrointestinal side effects in these patients.[18] The use of IV iron was also associated with an improvement in fatigue and reduction of anemia in postpartum patients.[26] Several studies have suggested an association between postpartum anemia and postpartum depression.[18,27] Erythropoietin (EPO) has also been studies in postpartum anemia. A randomized trial found that the combination of EPO and iron did not provide any additional benefits compared to iron alone.[28] However, some studies suggest benefit in EPO use in non-responders to IV Iron repletion.

Coadministration of IV iron and blood transfusion has not been studied. It is estimated that there is approximately 250mg of elemental iron in each unit of pRBCs. Therefore, a patient receiving > 3 units of pRBCs receives a typical dose of IV iron from the blood transfusions alone.[29] It is reasonable to consider IV iron for patients who receive ≤ 3 u pRBCs if they meet criteria based on postpartum hemoglobin.

BCM OB/Gyn Perinatal Guidelines Committee recommends offering IV Iron postpartum for patients with a hemoglobin of 6-9 g/dL and/or a 3g/dL drop in hemoglobin. Patients with Hemoglobin between 6 and 7 g/dL should be screened for anemia symptoms as transfused if symptomatic. IV iron should not be used in lieu of a blood transfusion if the patient meets criteria unless they do not accept the transfusion. If they do decline a transfusion, the timing of expected improvement in clinical symptoms (several weeks to months) should be discussed with the patient. IV iron is an option for patients who received 1-2 units of pRBCs, but we recommend against IV iron for patients who receive ≥3 units pRBCs. Oral supplementation should be offered to patients with hemoglobin of 9-11 g/dL.

B12 and/or Folate deficiencies

If folate deficiency is suspected based on risk factors (i.e. malabsorption, malnutrition), folate should be supplemented 1 gram daily.[6] These deficiencies are classically associated with macrocytosis; **however, an elevated MCV should *not* be considered diagnostic criteria for B12 deficiency**, Many patients with this deficiency have a normal MCV especially with concomitant iron deficiency.[30]

Patients with B12 deficiency due to prior bariatric surgery (i.e. Roux-en-Y) or due to pernicious anemia should have lifelong B12 supplementation. Reversible causes of these deficiencies should be treated and have lab monitoring to determine the need for re-treatment. **It is therefore important to determine the cause of the B12 deficiency as this can have a long-term impact.**[31] B12 deficiency can be treated with oral or intramuscular administration. Symptomatic patients, those with severe anemia, and those with malabsorptive syndromes may benefit from IM administration. In general, the treatment regimen is either:

IM 1,000 weekly x4 weeks, monthly x4 months **– OR -**
PO 1,000 daily

A repeat CBC and B12 level (or Folate if deficient) should be reevaluated 4-8 weeks after initiation of the supplementation.

For less common micronutrient deficiencies, it is reasonable and recommended to consult Hematology for treatment planning.

Hemoglobinopathies

Treatment and management of hemoglobinopathies are outside the scope of this guideline. **BCM OB/Gyn Perinatal Guidelines Committee recommends treatment of coexisting micronutrient deficiencies and referral to Hematology if not already done**. Please refer to ACOG Practice Bulletin[32] and Practice Advisory[12] for further information on management of hemoglobinopathies.

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