THE INCIDENCE, COMPLICATIONS AND TREATMENT OF IRON DEFICIENCY IN PREGNANCY

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OUTLINE

- The Incidence
- Racial and ethnic disparities
- The pathophysiology
- Symptoms
- Complications: maternal, Fetal
- Screening
- Treatment: Oral Iron, Intravenous iron

THE INCIDENCE OF IRON DEFICIENCY IN PREGNANCY

- First trimester: in US 40% (<50μg/L)
- Iron deficiency without anemia: 30–50% by the end of pregnancy
- Anemia by the third trimester
- Serum ferritin, hemoglobin, hematocrit

RACIAL AND ETHNIC DISPARITIES

- The underlying etiology not well understood.

- Mexican American (20.5%) non-Hispanic Black women (19.9%)
- Hispanic (13.5%) non-Hispanic, non-Black women (7.7%)

- The large, cross-sectional Hemochromatosis and Iron Overload Screening Study (HEIRS): higher proportion of Hispanic and black women than white and Asian women

RACIAL AND ETHNIC DISPARITIES

- Different thresholds for Black women in the United Sates: Hgb less than 10.2 g/dL
- The prevalence of anemia in pregnant individuals is two times higher in Black females (35.38/1,000; RR=2) than in white (18.02/1,000) in the United States.
- CDC in 2019: the PRMR of Black women in the United States is 40.8/100,000 births compared to 13/100,000 birth for white females.
- Specifically, Black females constitute 9.7% of deaths attributed to hemorrhage, compared to only 9.1% of white females (despite the racial demographics of the country)
- The American College of Obstetricians and Gynecologists (ACOG) no longer recommends race-based definitions of anemia.

THE PATHOPHYSIOLOGY OF IRON DEFICIENCY AND IRON DEFICIENCY ANEMIA IN PREGNANCY

- Menstruation:
  In 1967 Scott and Pritchard:
  Low iron stores in 58% of healthy 18 year old, non pregnant women
- Pregnancy:
  Physiologically: red blood cell mass expansion 25% while blood volume expands by 50%.
- Total iron loss in pregnancy and lactation(1 gram for an average weight of 55 kg)
- 350 mg for fetal and placental development, 500mg with expansion in red cell mass, and 250mg with blood loss at delivery.
- A typical diet contains 12–18 mg of elemental iron per day.
- The recommended daily intake of ferrous iron during pregnancy is 27 mg and 10 mg during lactation

SYMPTOMS OF IRON DEFICIENCY AND ANEMIA

- Asymptomatic
- Symptomatic:
  fatigue, irritability, dyspnea, headache, hair loss, poor concentration, pica, restless legs syndrome, and reduced physical performance.

  symptoms are often **dismissed** as normal during pregnancy

  Pagophagia, a specific form of pica entailing eating of ice, has a 95% specificity for iron deficiency in women.

MATERNAL COMPLICATIONS OF IRON DEFICIENCY AND IRON DEFICIENCY ANEMIA

- abnormal thyroid function, preterm labor, preterm birth (OR 1.54; 95%CI, 1.36– 1.76), placental abruption, preeclampsia, eclampsia, and cesarean delivery (OR 1.30; 95%CI, 1.13–1.49).
- increased risk of postpartum depression, decreased quality of life, severe postpartum hemorrhage, maternal shock, increased admission to maternal intensive care unit, hysterectomy (OR 7.66; 95%CI 4.57–12.85)
- antenatal and postnatal maternal sepsis, need for blood transfusion (OR 5.48; 95%CI, 4.57–6.58), poor wound healing, cardiac failure, and even maternal death (OR 2.36; 95% CI 1.60–3.48).

FETAL COMPLICATIONS OF MATERNAL IRON DEFICIENCY AND IRON DEFICIENCY ANEMIA

- Animal models: altered brain metabolism, neurotransmission, epigenetics and myelination in offspring that persist into later in life
- The fetal cardiovascular system: reduced circulation, slowed cardiovascular development, and enlarged hearts
- Higher risk for hypertension, obesity, and changes in lipid metabolism (although these results may be confounded by the impact of maternal obesity on fetal iron stores)
- Low birth weight, small size for gestational age, and higher rates of fetal distress
- Intellectual disabilities: offspring are at an increased risk of neurological disorders such as autism spectrum disorder, attention deficit disorder, and other

Neonatal Risks

- Low birth weight
- Small for gestational age
- Fetal distress
- Preterm birth

Offspring Risks

- Memory/processing disorders
- Intellectual disability
- Iron deficiency

In 2019, Wiergersma et al.: a cohort study of over 500,000 infants and nearly 300,000 mothers: a significant association between diagnosis of anemia prior to 30 weeks and **autism spectrum disorder** (OR 1.44; 95% CI 1.13–1.84).

Shao et al. : a significant association between maternal ferritin 13.6 μg/L and **fetal iron deficiencies**.

Early onset postnatal iron deficiency: approximately 14% of term infants born to iron-deficient mothers have a serum ferritin concentration 30 μg/L at birth.

Infants born to mothers with mild to moderate iron deficiency anemia who appear to be iron sufficient at birth still carry a risk for iron deficiency through the first year of life.

SCREENING RECOMMENDATIONS

- The United Kingdom : risk-based screening for iron deficiency :
- history of anemia, parity greater than or equal to three, multiple gestation, interpregnancy interval <1 year, poor dietary habits, vegetarian or vegan diet, pregnant teenagers, those at high risk of bleeding during birth, or in individuals who decline blood products
  serum ferritin of less than or equal to 30 µg/L

SCREENING RECOMMENDATIONS

- ACOG:

recommends screening for anemia
implementing universal iron supplementation
assessment of iron stores in previously diagnosed anemia

- Ferritin <30 µg/L by ACOG
  Ferritin <15 µg/L by WHO
  others have suggested thresholds as high as 50 micrograms/L

TREATMENT

- Oral Iron in pregnancy:
- ACOG and CDC recommend that all pregnant individuals receive oral iron supplementation
- daily or every other day
- **Side effects**:
- constipation, abdominal pain, flatulence, nausea, vomiting and diarrhea

TREATMENT

- A meta-analysis of 20 trials: gastrointestinal side effects with oral ferrous sulfate compared to placebo (OR=2.32, 95% CI 1.74–3.08, $p<0.001$).
- reduced compliance with therapy in 30–70% of symptomatic cases.
- oral iron represents the only safe option for repletion during the first trimester of pregnancy
- As such, we reserve intravenous (IV) iron for the second and third trimester

Formulations	Benefits	Complications
Ferrous Iron Salts *	Inexpensive, widely available	Tendency to cause gastrointestinal side effects
Polysaccharide-Iron Complex	Potentially lower risk of gastrointestinal intolerance, better taste profile	Less effective than ferrous salts in at least one randomized clinical trial of children.
Heme Iron	Higher absorption rate	Expensive. Not be a viable option for vegetarian or vegan individuals.
Carbonyl Iron	Inexpensive	No clear efficacy or side effect benefit as compared
Iron Protein Succinylate	Some data to suggest there may be better tolerability and efficacy as compared to ferrous salts.	Unsuitable for individuals with hypersensitivity to milk protein
Iron Amino Acid Chelates **	Less susceptible to dietary interactions.	May be more expensive than ferrous salts

TREATMENT

INTRAVENOUS IRON IN PREGNANCY

- **Iron Sucrose**
- A large phase III trial comparing iron sucrose to oral iron enrolled 2,018 pregnant individuals with iron deficiency anemia, 999 of whom received iron sucrose
- No difference in reducing adverse maternal outcomes.
- While safe, iron sucrose is generally administered at lower doses (generally 200mg per session) requiring multiple visits.

TREATMENT

INTRAVENOUS IRON IN PREGNANCY

- **Low Molecular Weight Iron Dextran (LMWID):**
- LMWID can be offered in a single infusion (1000 mg IV over 1 hour)
- The safety of LMWID has been demonstrated in several clinical trials of pregnant individuals.
- The first prospective study in the United States examined 74 oral iron-intolerant pregnant individuals receiving 1,000mg of LMWID.
- The average pre- and post-hemoglobin concentrations were 9.7 and 10.8 g/dL ($p<0.00001$), transferrin saturations of 11.7% and 22.6% ($p=0.0003$) and ferritin levels of 14.5 and 126.3 ng/mL ($p<0.000001$) respectively.
- Six participants had minor infusion reactions that resolved, and no infants were diagnosed with iron deficiency anemia.

One trial treated 100 pregnant individuals with iron deficiency anemia with LMWID, comparing their outcomes to 50 matched controls receiving oral iron supplementation (ferrous sulfate 200 mg three times a day).
The mean increase of hemoglobin in the intervention group was 2.43 gm/dl (95% CI 2.4 – 3.8) and for the control group it was 0.7 gm/dl (95% CI 0.6–2.3).
Flushing and palpitations were observed in 4% of the intervention group and none in the control group. No significant adverse reactions were observed in either group.

Another study evaluated 189 consecutives, unselected second and third trimester gravidas refractory to oral iron.
All received a test dose of 25 mg LMWID and were monitored for adverse events during the 60-min infusion.
No serious adverse events occurred, but approximately 2% of participants experienced transient infusion reactions.
Hemoglobin improved by 1–1.9 g/dL in 82% and ≥2 g/dL in 24%. Second trimester treatment was not associated with a greater hemoglobin improvement than third trimester treatment.

TREATMENT

INTRAVENOUS IRON IN PREGNANCY

- **Ferric Carboxymaltose (FCM)**
- FCM: two doses of 750 mg at least 7 days apart.
- While effective, it carries a higher rate of hypophosphatemia but short-lived
- A prospective observational study analyzed data from 863 pregnant individuals:
  significantly increased hemoglobin in individuals with mild, moderate, and severe iron deficiency anemia and individuals with isolated iron deficiency at 3- and 6-week post-infusion ($p<0.01$ for all).
  No serious adverse events were recorded, with minor temporary side effects (including local skin irritation, nausea, and headache) occurring in 11% of individuals. No adverse fetal or neonatal outcomes were observed.

TREATMENT

INTRAVENOUS IRON IN PREGNANCY

- **Ferumoxytol**
- Ferumoxytol can be given as two 510 mg doses approximately a week apart. Several studies also report the use of a single 1,020 mg dose.
- One study recently reported the outcomes of 131 iron-deficient second- and third-trimester pregnant individuals who received either 510 mg of IV ferumoxytol twice or 1,020 mg once. Among all infusions of 1,020 mg or 510 mg, minor infusion reactions were observed in 19 (14%), of which 11 occurred with the 510 mg infusion, and 8 with the 1,020 mg infusion. All reactions were self-limited with resolution within minutes, and all but one (patient had refused) received the full intended dose. There were no serious adverse events, episodes of hypotension or hospitalizations

TREATMENT

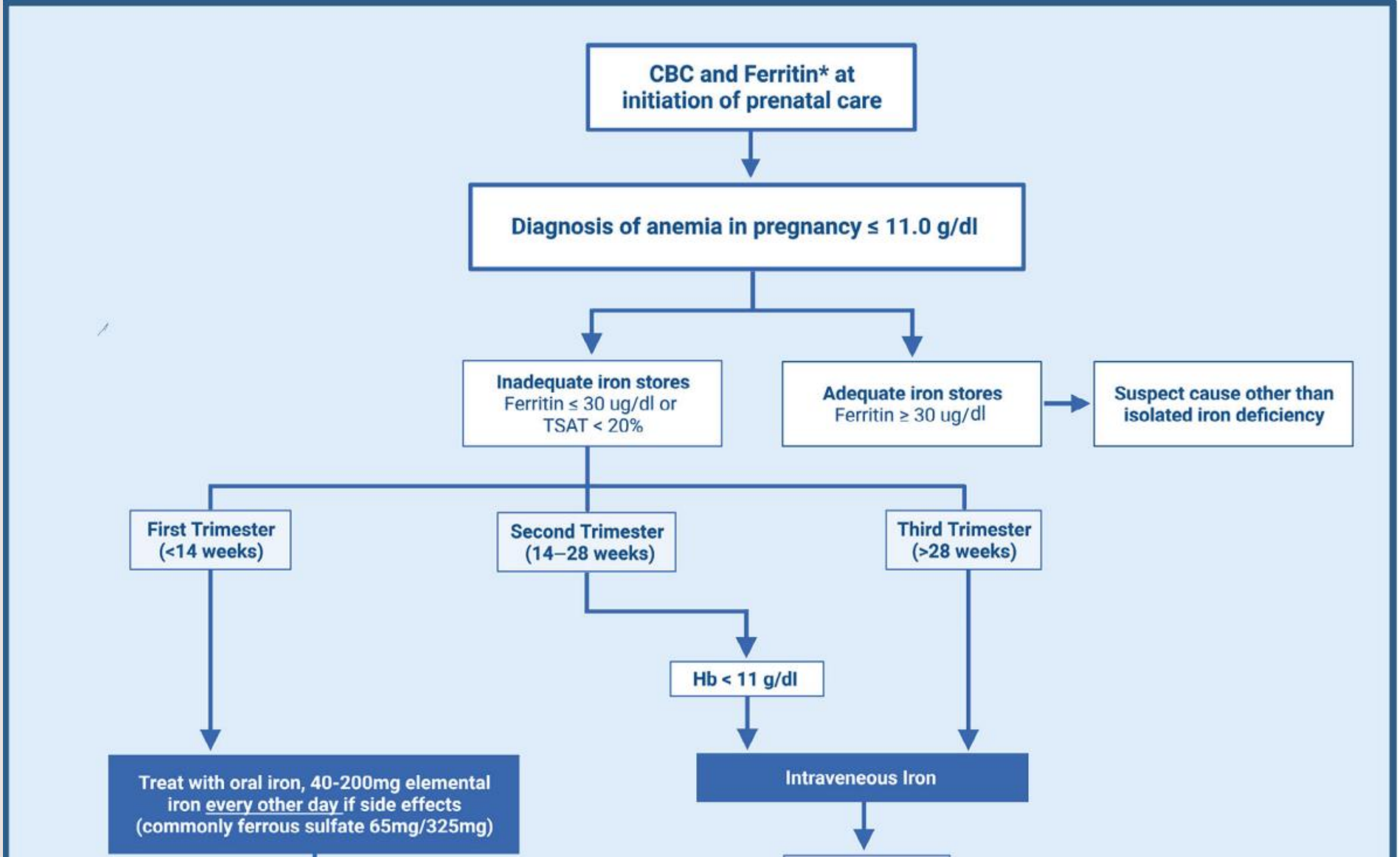
INTRAVENOUS IRON IN PREGNANCY

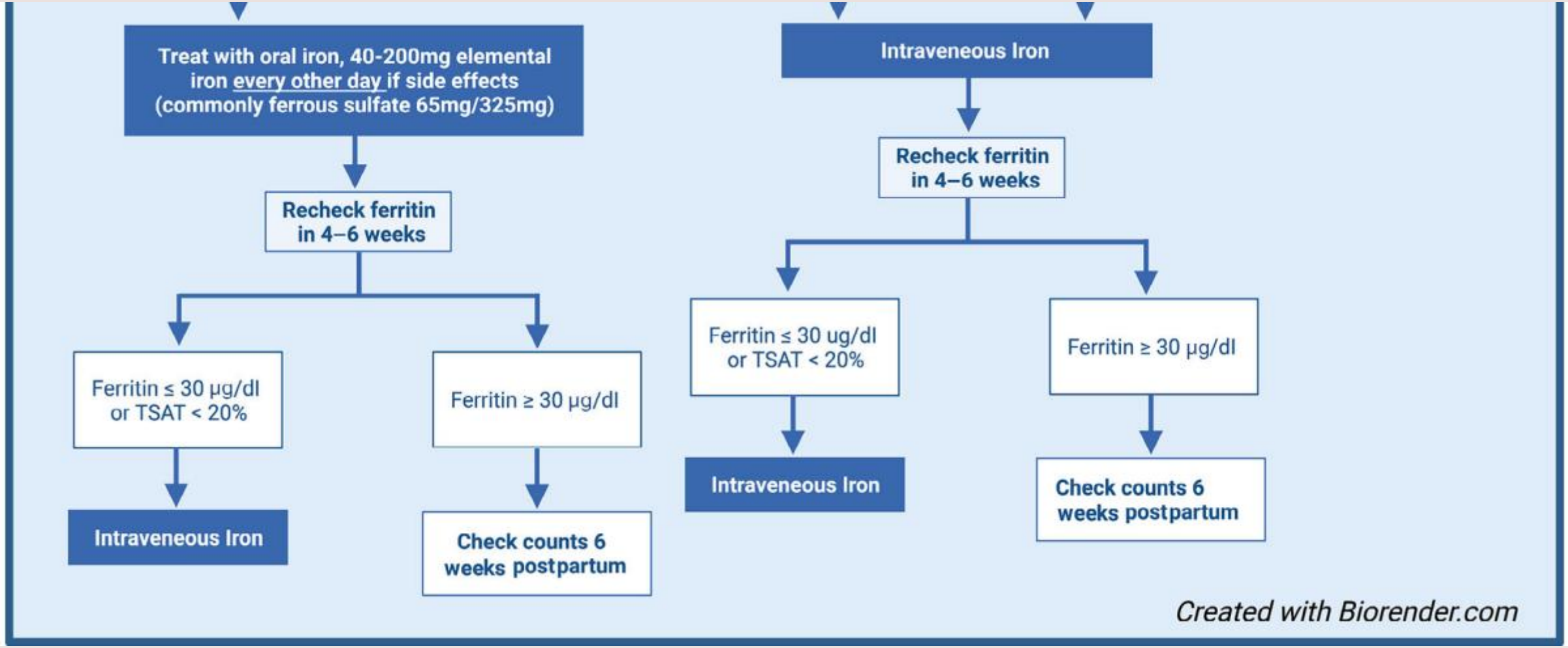
- **Ferric derisomaltose**
- Although recently approved in the United States to be given as a single 1,000 mg dose over 15–20 minutes, pregnancy specific data has yet to be published.
- Recently, a single-center, open-label, randomized controlled trial demonstrated superiority of IV ferric derisomaltose over oral iron for the treatment of persistent iron deficiency anemia (ferritin<30μg/L) in early second trimester (14–21 weeks) resulting in treatment of anemia in addition to improved fatigue and quality of life.
- A study outlining the safety of ferric derisomaltose in pregnancy as compared to iron sucrose is currently ongoing

TREATMENT

- **Postpartum iron deficiency**
- caused by blood loss or inadequate dietary iron intake/uptake
- symptoms such as fatigue, dyspnea and light-headedness
- A recent meta-analysis evaluated use of intravenous iron as compared to oral iron for the treatment of IDA in the postpartum period. The study included 15 trials including more than 2000 postpartum individuals. Use of IV iron resulted in hemoglobin concentrations that were higher at 6 weeks postpartum with fewer GI side effects. Overall the safety profile was reassuring with an anaphylaxis rate of 0.6%

Drug	Trade name	Maximum approved dose (mg)	# of doses	Duration (min)	Benefit	Side Effect
Low Molecular Weight Iron Dextran	INFeD	1000	1	60	Total dose infusion; cost effective	Although initially there were concerns for a slightly higher risk of anaphylaxis, more recent data has shown a similar safety profile to other common products.
Ferric gluconate	Ferrlecit	125	8	60	Safe in history of dextran induced anaphylaxis	Hypotension, flushing, headache
Iron sucrose	Venofer	200–300 per dose, 1000 mg total	3–5	15	Safe in history of dextran induced anaphylaxis	Diarrhea, headache, nausea, dizziness, hypotension
Ferumoxytol	Feraheme	510	2	15	Total dose in 2 infusions	interferes with certain MRIs. Diarrhea, headache, nausea, dizziness, hypotension
Iron isolamtoside	Monoferric	1000	1	15	Total dose infusion; no test dose required	Appears similar to other commonly used products
Ferric carboxymaltose	Ferinject or Injectafer	750	2	15	Multiple clinical trials in pregnancy	May have higher rates of hypophosphatemia then other products.


CBC and Ferritin* at initiation of prenatal care
Diagnosis of anemia in pregnancy ≤ 11.0 g/dl
Inadequate iron stores
Ferritin ≤ 30 ug/dl or
TSAT < 20%
Adequate iron stores
Ferritin ≥ 30 ug/dl
Suspect cause other than isolated iron deficiency
First Trimester (<14 weeks)
Second Trimester (14–28 weeks)
Third Trimester (>28 weeks)
Hb < 11 g/dl
Treat with oral iron, 40-200mg elemental iron every other day if side effects (commonly ferrous sulfate 65mg/325mg)
Intraveneous Iron


Treat with oral iron, 40-200mg elemental iron every other day if side effects (commonly ferrous sulfate 65mg/325mg)
Recheck ferritin in 4–6 weeks
Ferritin ≤ 30 µg/dl or TSAT < 20%
Intraveneous Iron
Ferritin ≥ 30 µg/dl
Check counts 6 weeks postpartum
Intraveneous Iron
Recheck ferritin in 4–6 weeks
Ferritin ≤ 30 ug/dl or TSAT < 20%
Intraveneous Iron
Ferritin ≥ 30 µg/dl
Check counts 6 weeks postpartum
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THE END

- Thank you for your attention