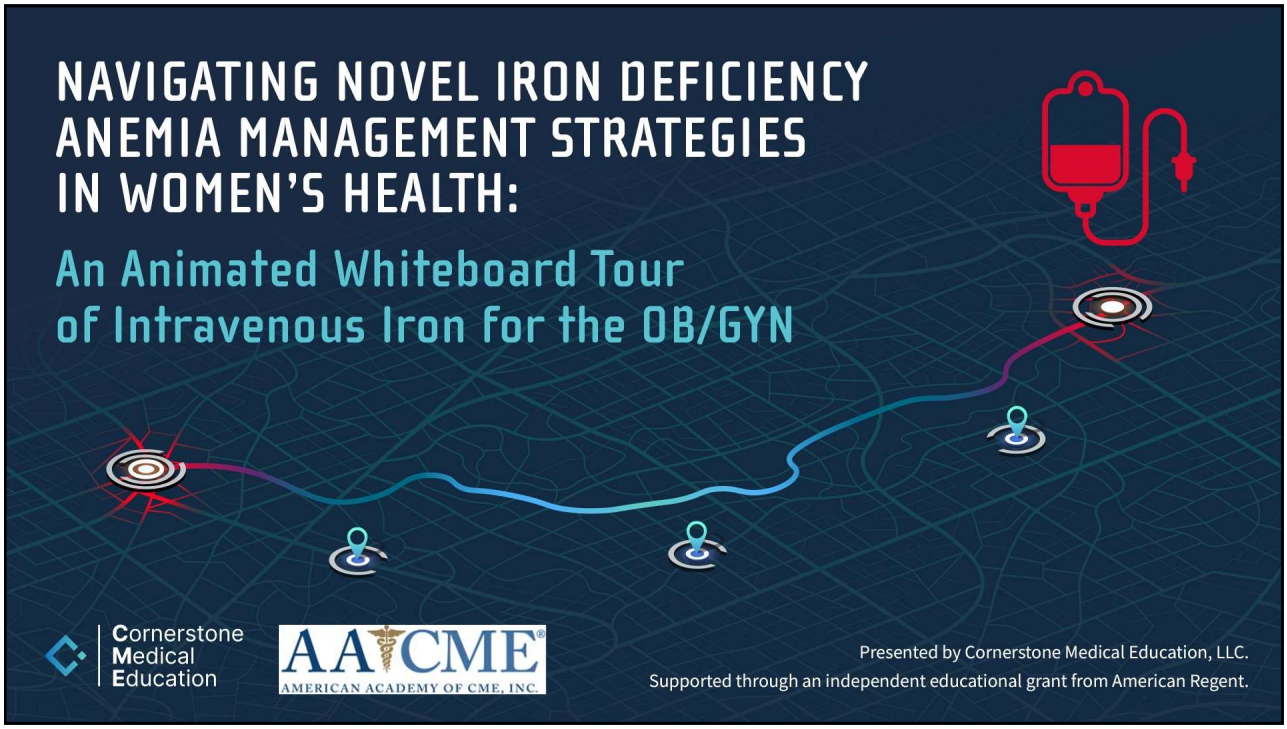


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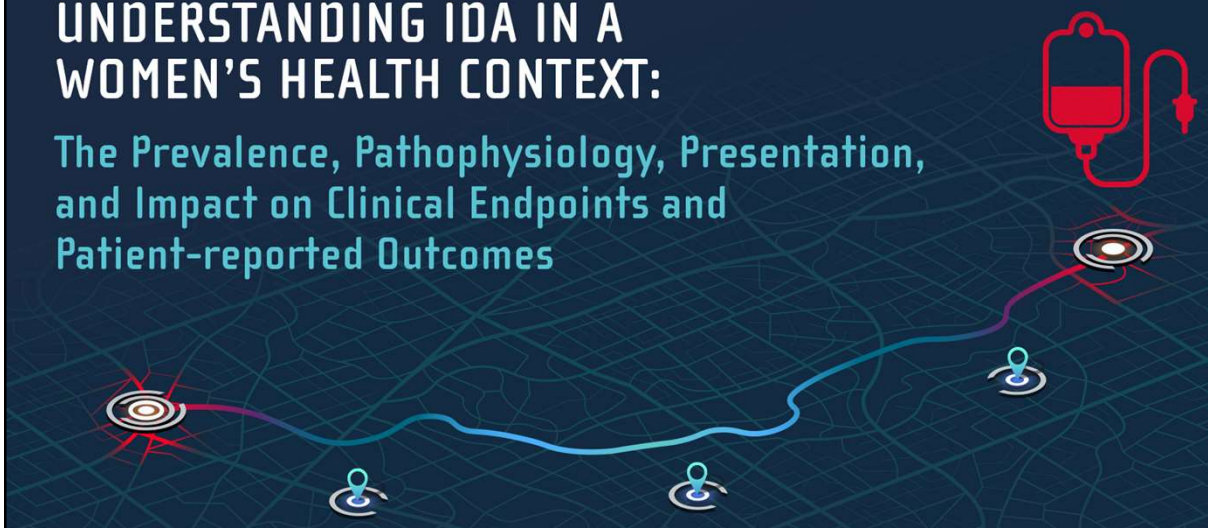
# UNDERSTANDING IDA IN A WOMEN'S HEALTH CONTEXT:

## The Prevalence, Pathophysiology, Presentation, and Impact on Clinical Endpoints and Patient-reported Outcomes



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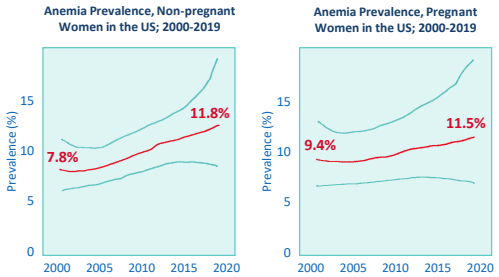
# Iron Deficiency Anemia (IDA)

## *Epidemiology in Women's Health*

- Globally, anemia prevalence in women of reproductive age (15-49) = 29.9%
  - Non-pregnant women = 29.6%
  - Pregnant women = 36.5%
- Anemia prevalence in women of reproductive age in the United States:
  - Non-pregnant women = 11.8%
  - Pregnant women = 11.5%
  - *Latest World Health Organization (WHO) data suggest an increasing prevalence trend (2000-2019) in the U.S.*




WHO. Global anemia estimates. 2021; Stevens GA, et al. *Lancet Glob Health*. 2022; Friedman AJ, et al. *Obstet Gynecol Surv.* 2015; PAHO. Anemia in women and children. 2019.



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# Diagnosing Anemia

## *World Health Organization (WHO) Hemoglobin Thresholds*

- Pregnant women
  - Non-anemic: ≥ 11 g/dL
  - Mild: 10-10.9 g/dL
  - Moderate: 7.0-9.9 g/dL
  - Severe: <7.0 g/dL
- Non-pregnant women of reproductive age (≥ 15 years)
  - Non-anemic: ≥ 12 g/dL
  - Mild: 11-11.9 g/dL
  - Moderate: 8.0-10.9 g/dL
  - Severe: <8.0 g/dL

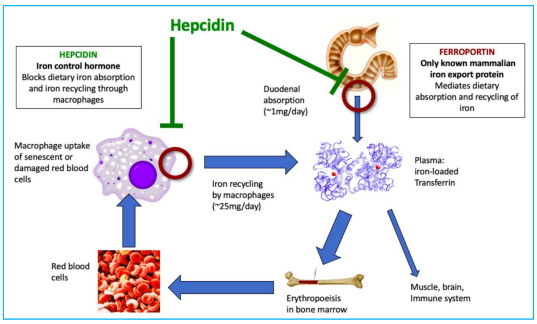
Stevens GA, et al. *Lancet Glob Health*. 2022; WHO. Hemoglobin concentrations for the diagnosis of anemia and assessment of severity. 2011; Percy L, et al. *Best Pract Res Clin Obstet Gynaecol*. 2017.



# A Closer Look at the Fundamental Problem

## *The Elemental Impact of Iron Deficiency (ID)*

- ID is the most common anemia etiology worldwide
  - WHO estimates that ID is implicated in ~50% of all anemia cases
- Independent of anemia, *ID is the leading cause of years lived with disability burden among women*
  - ID in women of reproductive age = 15.7%
  - ID in pregnant women = 18%
  - Note: *these data likely underestimate true prevalence; some estimates range* ***≥ 45%***
- *Identification of cause and subsequent iron repletion strategies are thereby requisite for effective IDA management*




Benson CS, et al. *Anaesthesia*. 2021; Lopez A, et al. *Lancet*. 2016; Stevens GA, et al. *Lancet Glob Health*. 2013; Camaschella C. *Blood*. 2019; Georgieff MK. *J Obstet Gynecol.* 2020.

# The Clinical Gravity of IDA in Women's Health

## *Characterizing the Patient Burden*

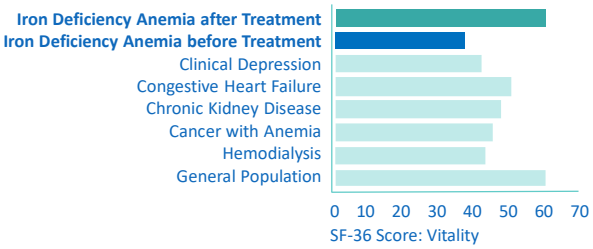
- Multifarious adverse impacts on the health-related quality of life (hrQOL) of women
  - ID, *even without anemia*, associated with diminished physical and emotional well-being
- Increased fatigue
- Brain fog/reduced ability to concentrate
- Impaired exercise capacity and work performance
- Myriad nonhematologic symptoms:
  - Pica, cheilitis, alopecia, restless legs syndrome, brittle nails, ungual alterations
- Adverse reproductive outcomes
  - Maternal/fetal mortality, pre-term birth, low-birth-weight infants, neonatal complications, developmental issues, and disturbance of postpartum maternal-infant interactions

WHO. Global anemia estimates. 2021; Benson CS, et al. *Anaesthesia*. 2021; Percy L, et al. *Best Pract Res Clin Obstet Gynaecol*. 2017; Fernandez-Jimenez MC, et al. *Women's Health Report*. 2020; Petraglia F, et al. *Fertil Steril*. 2022; Daru J, et al. *Lancet Glob Health*. 2018; Means RT. *Nutrients*. 2020; Smith C, et al. *Obstet Gynecol*. 2019.



# The Clinical Gravity of IDA in Women's Health

## *Patient-Reported Outcomes (PROs) – Vitality Score*



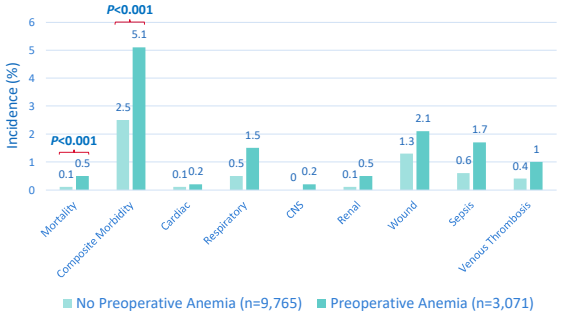

- 36-Item Short Form Health Survey (SF-36) – widely-used PRO comprised of 36 questions in 8 health domains with 2 component summary measures: physical and mental
- SF-36 data in women confirm that *untreated IDA precipitates vitality scores comparable to clinical depression and serious chronic diseases, including cancer-related anemia (CRA)*
  - Importantly, when IDA is effectively treated, vitality scores are restored to normal levels

Strauss WE, et al. *Patient Relat Outcome Meas*. 2018; Friedman AJ, et al. *J Women's Health*. 2012.

# The Clinical Gravity of IDA in Women's Health

## *Obstetrical Morbidity & Mortality*

- In pregnancy, *maternal mortality is directly correlated with the severity of IDA*
  - Also associated with neonatal/perinatal mortality
  - Increased postpartum hospitalization rates
- For women undergoing gynecologic surgery, including elective procedures:
  - *Preoperative anemia independently associated with increased postoperative 30-day mortality* and elevated composite morbidity
- ID and IDA are general indicators of diminished health status and are broadly considered negative prognostic factors across the women's health continuum of care

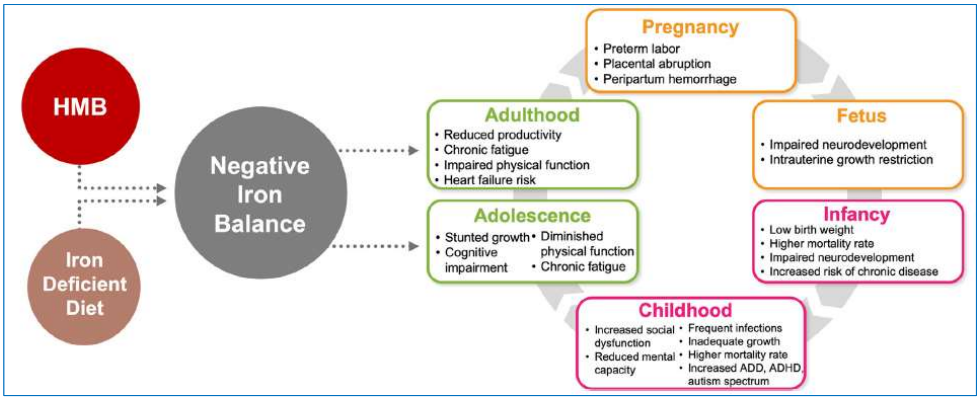



Garzon S, et al. *Oman Med J*. 2020; Smith C, et al. *Obstet Gynecol*. 2019; Friedman AJ, et al. *J Women's Health*. 2012; Richards T, et al. *PLoS One*. 2015.



# The Clinical Gravity of IDA in Women's Health

## *Longitudinal Impact*



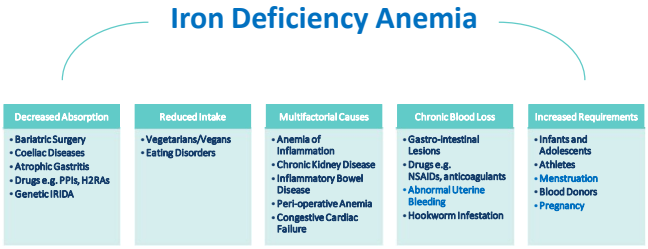

HMB, heavy menstrual bleeding

Munro M, et al. *Am J Obstet Gynecol*. 2023.

# IDA Origins in Women's Health

## *An Overview of Pathophysiology & Etiology*

- ID and IDA etiologies in women's health can be conceptually categorized into 5 buckets:
  - Increased utilization/requirements
  - Decreased absorption
  - Chronic blood loss (+/- acute)
  - Reduced intake
  - Hyperinflammatory disease processes
- The 3 most common ID/IDA etiologies in women:
  - **Dysfunctional uterine bleeding (DUB)/heavy menstrual bleeding (HMB)**
  - **Pregnancy**
  - **Postpartum hemorrhage (PPH)**




Benson CS, et al. *Anaesthesia*. 2021; Miller JL, et al. *Cold Spring Harb Perspect Med*. 2013; Percy L, et al. *Best Pract Res Clin Obstet Gynaecol*. 2017; Petraglia F, et al. *Fertil Steril*. 2022.



# IDA Origins in Women's Health

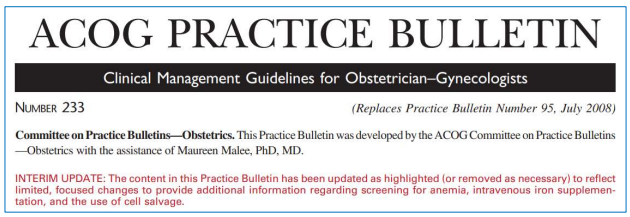
## *Pregnancy*

- Anemia in pregnancy: <11 g/dL (1st & 3rd trimesters); <10.5 g/dL (2nd trimester)
- *Pregnancy onset = clinical case of impending ID*
  - ID is overwhelmingly common in pregnancy, with some estimates topping 50% prevalence in developed nations (≥80% in lower-income regions)
- Empirically, pregnancy is a *physiologic state of increased iron demand*
  - Increase in maternal blood and plasma volume = dilutional effect
  - Heightened iron requirements to meet baby's metabolic needs
  - The placenta is a metabolically active organ with additional iron demands
- All told, pregnancy requires ~1-1.2 grams of additional iron
- Presence of ID, and subsequent IDA, portends myriad harmful consequences

Georgieff MK. *Am J Obstet Gynecol*. 2021; Garzon S, et al. *Oman Med J*. 2020; Percy L, et al. *Best Pract Res Clin Obstet Gynaecol*. 2017; Petraglia F, et al. *Fertil Steril*. 2022.

# IDA Origins in Women's Health

## *Pregnancy*



ACOG PRACTICE BULLETIN

Clinical Management Guidelines for Obstetrician–Gynecologists

NUMBER 233 *(Replaces Practice Bulletin Number 95, July 2008)*

**Committee on Practice Bulletins—Obstetrics.** This Practice Bulletin was developed by the ACOG Committee on Practice Bulletins —Obstetrics with the assistance of Maureen Malee, PhD, MD.

INTERIM UPDATE: The content in this Practice Bulletin has been updated as highlighted (or removed as necessary) to reflect limited, focused changes to provide additional information regarding screening for anemia, intravenous iron supplementation, and the use of cell salvage.

- Summary of current recommendations:
  - Anemia screening: 1st trimester, 24 weeks, 28 weeks
  - Low-dose iron supplementation recommended, starting in 1st trimester
  - IDA in pregnancy should be treated with iron supplementation + prenatal vitamins
  - RBC transfusion should be limited to cases of severe anemia (<7.0 g/dL)
  - After 1st trimester (including postpartum), ***IV iron should be considered if oral iron is intolerable or ineffective, or if ID/IDA is severe***

ACOG Practice Bulletin No. 233. *Obstet Gynecol.* 2021.



# IDA Origins in Women's Health

## *Postpartum Hemorrhage (PPH)*

- Postpartum anemia:
  - <11 g/dL at 1 week
  - <12 g/dL at 8 weeks
- PPH = *"cumulative blood loss ≥ 1000 mL or blood loss accompanied by signs or symptoms of hypovolemia within 24 hours after birth"*
- Prevalence of PPH = ~5-6% of deliveries
  - Healthy peripartum blood loss = ~300 mL
- 24-48 hours post-delivery, anemia prevalence = ~50%
- Clinical ramifications:
  - Diminished hrQoL, impaired cognition, emotional instability, clinical depression

Milman N. *Ann Hematol.* 2011; ACOG Practice Bulletin No. 183. *Obstet Gynecol.* 2017.

# IDA Origins in Women's Health

## *DUB/HMB*

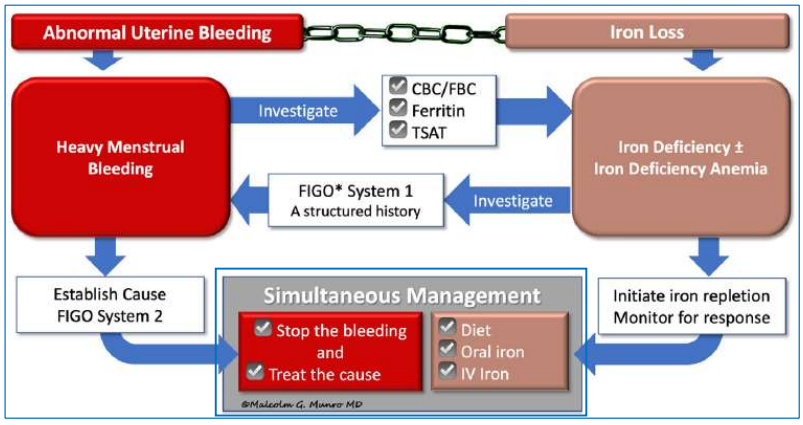
ANIMATED WHITEBOARD VIDEO

Jain V, et al. *Nat Rev Endocrinol*. 2022; Petraglia F, et al. *Fertil Steril*. 2022; Fraser I, et al. *Int J Gynaecol Obstet*. 2015; Percy L, et al. *Best Pract Res Clin Obstet Gynaecol.* 2017; Deloughery TG. *Med Clin North Am.* 2017; McDonagh T, et al. *Eur J Heart Failure.* 2015. Chodankar R, et al. *Obstet Gynaecol Reprod Med*. 2018; Schoep M, et al. *Am J Obstet Gynecol.* 2019; Munro MG, et al. *Int J Gynaecol Obstet*. 2018.



# IDA Origins in Women's Health

## *DUB/HMB – The Close Interrelationship with ID/IDA*




FIGO, International Federation of Gynecology and Obstetrics

Munro M, et al. *Am J Obstet Gynecol*. 2023.

# Optimizing Management of HMB-associated IDA

## *Bridging Prominent Gaps in Care*

- HMB is the leading cause of IDA among reproductive age females in the U.S.
  - A recent survey of ~43,000 women discovered HMB prevalence = 53.7%
- *And yet, HMB remains woefully under-reported, under-diagnosed, and under-treated*
  - 46% of women never report symptoms
    - Of those who do, ~54% are not treated
  - 56% of women never diagnosed
  - Discordant – or non-existent – guideline recommendations for HMB-associated ID/IDA screening and repletion protocols
  - "It's time to ***open the societal dialogue*** and ***educate clinicians*** and patients alike."

**Prevalence and parameters of specific menstruation-related symptoms**

| | Prevalence: number (percentage) | Number of days | Pain or intensity score[b] | Maximum pain or intensity score > 4,[b] number (percentage) | Impact on daily activities[c] |
|---|---|---|---|---|---|
| Abdominal pain during period | 36,079 (85.4%) | 2.9 ± 1.7 | 6.0 ± 2.1 | 26,754 (77.6%) | 4.4 ± 2.4 |
| Heavy bleeding | 21,375 (53.7%) | 2.9 ± 1.4 | 6.9 ± 3.9[d] | N/A | 4.1 ± 2.4 |
| Headache | 21,903 (56.2%) | 2.7 ± 1.9 | 5.2 ± 2.3 | 13,313 (62,7%) | 4.2 ± 2.6 |
| Back pain | 22,244 (59.2%) | 3.0 ± 1.8 | 5.1 ± 2.2 | 13,347 (61.4%) | 3.8 ± 2.6 |
| Tiredness | 27,154 (70.7%) | 3.9 ± 1.9 | 5.7 ± 2.2 | 18,834 (71.9%) | 4.1 ± 2.2 |
| Perimenstrual psychological complaints | 28,392 (77.3%) | 4.3 ± 2.3 | 5.7 ± 2.3 | 19,804 (71.3%) | 3.5 ± 2.4 |

Percy L, et al. *Best Pract Res Clin Obstet Gynaecol*. 2017; Chodankar R, et al. *Obstet Gynaecol Reprod Med*. 2018; Schoep M, et al. *Am J Obstet Gynecol.* 2019. Fraser I, et al. *Int J Gynaecol Obstet*. 2015; Mansour D, et at. *Adv Ther*. 2021.



# Optimizing Management of HMB-associated IDA

## *Bridging Prominent Gaps in Care*

- **Step 1 - Identify the chasm(s)**
  - Societal normalization and stigma
    - Widely-held misperception that heavy bleeding is normal, and thus, a personal/private matter
    - Clinical ramification: *under-reporting*
  - Lack of screening and patient-clinician discussion of menstrual experience
    - Patient reticence + clinician unawareness/deprioritization
    - Clinical ramification: *under-diagnosis*
  - Even when HMB is diagnosed and managed, ID and IDA often neglected in women's health clinic
    - OB/GYN overreliance on primary care to manage concomitant ID/IDA + paucity of expert consensus guidelines
    - Clinical ramification: *under-treatment*

Percy L, et al. *Best Pract Res Clin Obstet Gynaecol*. 2017; Chodankar R, et al. *Obstet Gynaecol Reprod Med*. 2018; Schoep M, et al. *Am J Obstet Gynecol.* 2019. Frick KD, et al. *Women's Health Issues*. 2009; Schoep M, et al. *BMJ Open*. 2019; Fraser I, et al. *Int J Gynaecol Obstet*. 2015.

# Optimizing Management of HMB-associated IDA

## *Bridging Prominent Gaps in Care*

- **Step 2 - Build the bridge(s)**
  - Debunk stigma and de-normalize HMB via proactive clinical conversations
    - Ask questions about volume, duration, pain, impacts on hrQoL
  - Screen for ID and anemia in all women with HMB
    - ID = serum ferritin, TSAT
    - Anemia = Hb
  - *Concurrently* integrate ID and IDA treatment strategies into HMB management plans
    - For optimal outcomes – diagnose and manage ID early, before onset of IDA
    - Oral iron is traditional first line repletion modality
    - Consider IV iron > oral iron if ID/IDA is severe, HMB remains uncontrolled, or rapid repletion is required

Munro M, et al. *Am J Obstet Gynecol.* 2023.
Percy L, et al. *Best Pract Res Clin Obstet Gynaecol.* 2017; Chodankar R, et al. *Obstet Gynaecol Reprod Med.* 2018; Schoep M, et al. *Am J Obstet Gynecol.* 2019.
Frick KD, et al. *Women's Health Issues.* 2009; Schoep M, et al. *BMJ Open.* 2019; Fraser I, et al. *Int J Gynaecol Obstet.* 2015.



# Summary of Key Teaching Points

## *IDA in Women's Health*

- ID and IDA are highly prevalent in women and are associated with clinical gravity
  - *ID* is the leading cause of years lived with disability among women
- Most common IDA etiologies in women are HMB, pregnancy, and PPH
  - HMB is the leading cause of IDA among reproductive age women in the U.S.
- HMB-associated ID and IDA are vastly under-diagnosed and under-treated
- ***OB/GYNs and interprofessional team must take the lead in diagnosing (via open patient-centric dialogue) and initiating treatment for ID/IDA concurrently with HMB management***
- Expanding clinical rationale for IV iron in women's health
  - Particularly in cases of uncontrolled bleeding (HMB), prior to scheduled surgeries, and late in pregnancy

# PILLARS OF CHANGE:

## An Expert Appraisal of Evidence-driven Approaches for Diagnosing, Evaluating, and Treating IDA in the OB/GYN Clinic

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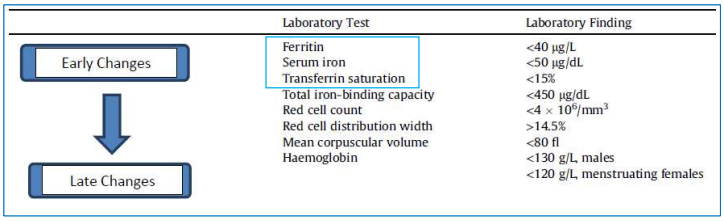
# Diagnosing IDA in Women's Health

## *First Thing's First – Focusing on ID*

- ID can occur with – *or without* – concurrent anemia
  - Hb concentration has low specificity and sensitivity for predicting ID
  - *CBC alone is insufficient to diagnose ID*
- Progressive iron depletion is the most common cause of anemia
  - *ID typically precedes anemia*
- Earliest laboratory changes in IDA development are iron indices
  - Keystone diagnostic utility of *serum ferritin* and *TSAT*
- Recognizing and treating ID *before* onset of IDA = improved outcomes




| Laboratory Test | Laboratory Finding |
|---|---|
| Ferritin | <40 µg/L |
| Serum iron | <50 µg/dL |
| Transferrin saturation | <15% |
| Total iron-binding capacity | <450 µg/dL |
| Red cell count | <4 × $10^6$/mm$^3$ |
| Red cell distribution width | >14.5% |
| Mean corpuscular volume | <80 fl |
| Haemoglobin | <130 g/L, males<br><120 g/L, menstruating females |

Generally accepted criteria for ID diagnosis:

- *Absolute ID:* serum ferritin < 30 ng/mL + TSAT < 20%
- *Functional ID:* serum ferritin 100-299 ng/mL + TSAT < 20%

Petraglia F, et al. *Fertil Steril.* 2022; Percy L, et al. *Best Pract Res Clin Obstet Gynaecol.* 2017; Kassebaum NJ, et al. *Blood.* 2014; Johnson-Wimbley TD, et al. *Ther Adv Gastroenterol.* 2011.



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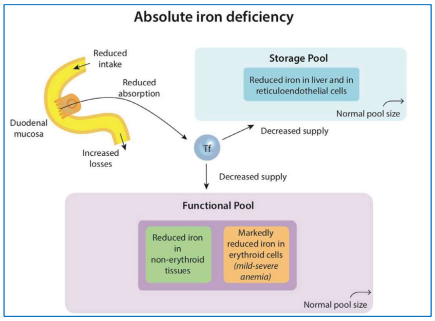
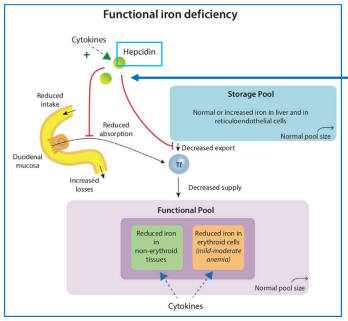
# Diagnosing IDA in Women's Health

## *Absolute vs. Functional ID*

*Absolute ID* = total body iron is decreased, *impacting both storage and functional pools*

*Functional ID* = total body iron is normal or increased; *only functional pool is diminished*




Hepcidin-induced pathologic sequestration into macrophages and hepatocytes (iron maldistribution) = ***reductions in functional pool***

Percy L, et al. *Best Pract Res Clin Obstet Gynaecol*. 2017; Anand I, et al. *Circulation*. 2018.



# Screening for IDA in Women's Health

## *The Critical Role of the OB/GYN & the Interprofessional Team*

- Discordance in expert guidelines = discordance in clinical practice patterns
  - A recent survey of OB/GYNs revealed:
    - Only 38% screen non-pregnant patients for IDA regularly based on risk factors
    - Only 50% screen pregnant patients for IDA at initial visit
  - >50% of current guidelines do not address ID (without anemia) screening, iron repletion strategies, or IV vs. oral considerations
- Centers for Disease Control (CDC)
  - Screen all non-pregnant women every 5-10 years; *annual screening for women with risk factors (DUB/HMB, prior IDA, low iron diet, etc.)*
- American College of Obstetricians and Gynecologists (ACOG)
  - Screen all pregnant women for IDA in first trimester, at week 24, and week 28; no recommendation for non-pregnant screening
- US Preventive Services Task Force (USPSTF)
  - Current recommendation (update pending) states insufficient evidence on cost/benefit ratio for IDA screening in pregnancy
- Actionable takeaway: *OB/GYNs and members of their interprofessional team are ideally placed to provide IDA screening for women, and despite current guideline discordance, annual IDA screening for most non-pregnant women is reasonable*

Mansour D, et al. *Adv Ther*. 2021; Marcewicz LH, et al. *Matern Child Health J*. 2017; CDC. Recommendations to prevent and control iron deficiency in the United States. *MMWR*. 1998; ACOG Practice Bulletin No. 233. *Obstet Gynecol.* 2021; uspreventiveservicestaskforce.org.

# Treating IDA in Women's Health

## *Oral Iron – Benefits & Shortcomings*

### Practical benefits

- Affordability
- Accessibility (including availability as OTC products)
- Effective for IDA management with appropriate patient selection

### Therapeutic shortcomings

- Absorption is limited (~5-10%), leading to modest bioavailability
- GI side effects – nausea, constipation, diarrhea, cramping – dramatically limit compliance (~50% non-adherence rates)
- Clinical response is slow, achieving only ~2 g/dL Hb increase in 4-8 weeks
- Vastly diminished benefit in presence of chronic inflammation (i.e., hepcidin)

### Clinical scenarios of particular utility

- Mild ID/IDA
- First trimester of pregnancy
- No scheduled surgery or impending procedure ≤ 6 weeks
- Absence of IBD, gastric bypass, or other barriers to absorption

Friedman AJ, et al. *Obstet Gynecol Surv*. 2015; Jimenez K, et al. *Gastroenterol Hepatol*. 2015; Deloughery TG. *Med Clin North Am*. 2015; Percy L, et al. *Best Pract Res Clin Obstet Gynaecol*. 2017; Munoz M, et al. *Anaesthesia*. 2017; Mansour D, et al. *Adv Ther*. 2021.



# Treating IDA in Women's Health

## *Oral Iron – Clinical Pearls*

- Advise patients to take on an empty stomach
  - 1 hour prior to meals or at least 2 hours after
  - Though taking with food ameliorates GI side effects, it further diminishes absorption
  - Consider combining with vitamin C to improve absorption
- For absorption, *ferrous formulations > ferric formulations*
  - Newer oral agents (i.e., ferric maltol) offer improved absorption and tolerability profiles
- Oral iron dose = acute ↑ hepcidin = ↓ iron bioavailability
  - Potential rationale for alternate day dosing
- Laboratory response to oral iron (Hb, serum ferritin, TSAT) should be conducted within 4 weeks of initiation
  - ≥ 2 g/dL Hb increase is typically considered an effective treatment response with oral iron
- *Educate patients on risk of GI toxicity and empower shared decision-making*
  - Incidence of GI adverse effects as high as ~70% of patients (with traditional agents)
  - **The earlier intolerance is recognized and reported, the quicker alternative options – namely IV iron – can be started**

Friedman AJ, et al. *Obstet Gynecol Surv*. 2015; Jimenez K, et al. *Gastroenterol Hepatol*. 2015; Moretti D, et al. *Blood*. 2015; Schmidt C, et al. *J Clin Med*. 2021; Percy L, et al. *Best Pract Res Clin Obstet Gynaecol*. 2017; DeLoughery TG. *Acta Haematol*. 2019.

# Treating IDA in Women's Health

## *The Evolving Utility of Intravenous Iron*

- IV iron safety stigma is unsubstantiated, particularly for next-gen products
  - Systematic review and meta-analysis of 103 trials (~10,000 patients receiving IV iron vs. ~4,000 receiving oral iron vs. ~1,000 receiving no iron)
    - *No increased risk of severe adverse events with IV iron (RR, 1.04)*
  - *<1 life-threatening adverse event per 200,000 doses administered (including anaphylaxis) with next-generation agents*
- Traditionally used in 2nd line setting for IDA, when oral iron ineffective or intolerable
  - Emerging evidence increasingly suggestive of front-line utility in specific circumstances
- Clinical scenarios in which to consider IV iron for first-line IDA management
  - ***Severe cases of ID/IDA***
  - ***When time is of the essence***
    - Before scheduled surgeries (particularly if ≤ 6 weeks)
    - Late pregnancy (ACOG Guidelines suggest IV iron > oral iron in specific scenarios after 1st trimester)
  - ***When ongoing bleeding is expected***
    - HMB/DUB

| IV Iron Agent | Anaphylactoid Reactions (%) |
|---|---|
| Ferric carboxymaltose | 0.1% |
| Ferumoxytol | 0.2% |
| Ferric derisomaltose | 0.3% |

Avni T, et al. *Mayo Clin Proc*. 2015; DeLoughery TG. *Acta Haematol*. 2019; Friedman AJ, et al. *Obstet Gynecol Surv*. 2015; Percy L, et al. *Best Pract Res Clin Obstet Gynaecol*. 2017; Munoz M, et al. *Anaesthesia*. 2017; ACOG Practice Bulletin No. 233. *Obstet Gynecol.* 2021; Mansour D, et al. *Adv Ther*. 2021; FDA Prescribing Information.



# Treating IDA in Women's Health

## *IV Iron Mechanism, Safety, & Nanocolloidal Design*

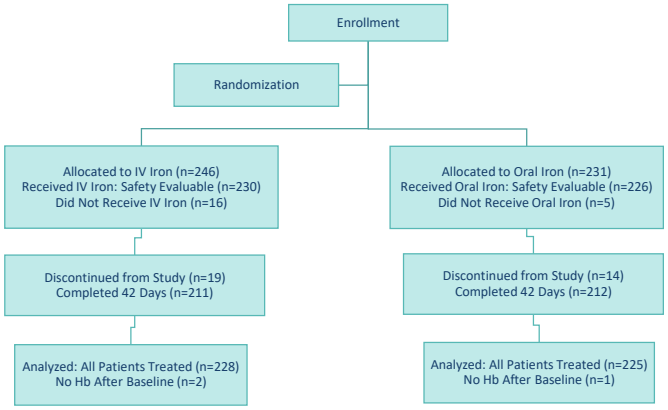
ANIMATED WHITEBOARD VIDEO

Nikravesh N, et al. *Nanomedicine*. 2020; Friedman AJ, et al. *Obstet Gynecol Surv*. 2015; Percy L, et al. *Best Pract Res Clin Obstet Gynaecol*. 2017 Avni T, et al. *Mayo Clin Proc*. 2015; DeLoughery TG. *Acta Haematol*. 2019; FDA Prescribing Information.

# Treating IDA in Women's Health

## *IV Iron Evidentiary Base – DUB/HMB*

- 477 women with HMB-associated IDA randomized to either:
  - IV ferric carboxymaltose (FCM) ≤ 1,000 mg, repeated weekly as needed to achieve a total calculated iron replacement dose
  - Oral ferrous sulfate 325 mg PO TID
  - Study period = 6 weeks (42 days)
- Primary efficacy endpoint:
  - Hb increase ≥ 2 g/dL from baseline
- Secondary efficacy endpoints:
  - Hb increase ≥ 3 g/dL from baseline
  - Anemia correction (Hb ≥ 12g/dL)
  - PROs – vitality, physical function, fatigue (SF-36, LASA)
- Safety analysis:
  - Drug-related adverse events
  - Analysis of treatment discontinuations



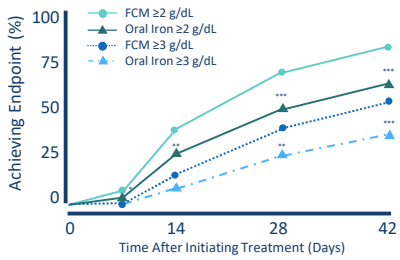

Van Wyck DB, et al. *Transfusion*. 2009.



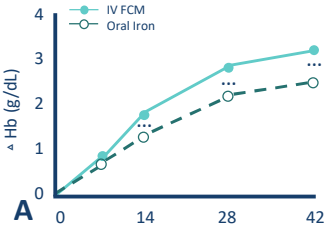
# Treating IDA in Women's Health

## *IV Iron Evidentiary Base – DUB/HMB*

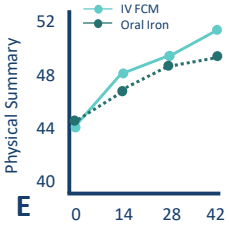
****P*<0.001; ***P*<0.01; **P*<0.05




IV FCM achieved a greater proportion of Hb increases ≥ 2 g/dL (82% vs. 62%) and ≥ 3 g/dL (53% vs. 36%) vs. oral iron




IV FCM attained greater anemia correction (73% vs. 50%) vs. oral iron




IV FCM prompted greater improvements in physical function, vitality, and fatigue scores vs. oral iron

Van Wyck DB, et al. *Transfusion*. 2009.



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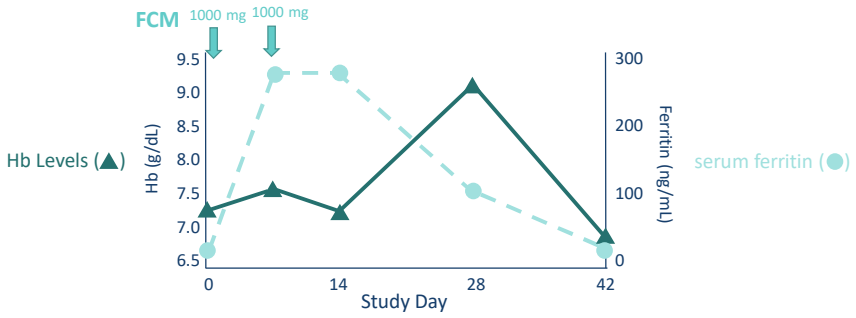
# Treating IDA in Women's Health

## *IV Iron Evidentiary Base – DUB/HMB*




**Study conclusion:**

***IV FCM is more effective than oral ferrous sulfate for repleting iron stores, correcting anemia, and improving health-related quality of life in patients with HMB-associated IDA, with fewer drug-related adverse events.***

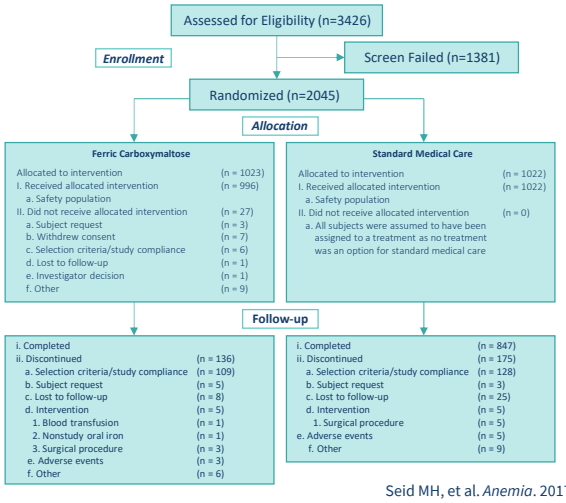
Van Wyck DB, et al. *Transfusion*. 2009.



# Treating IDA in Women's Health

## *IV Iron Evidentiary Base – DUB/HMB +/- PPH*

- 2,045 women with HMB- or postpartum-associated IDA randomized to either:
  - IV FCM 15 mg/kg (max dose = 1,000 mg)
  - Standard medical care (SMC) - investigator-determined
    - 93% of SMC patients received oral ferrous sulfate
- Study definition of post-partum-associated IDA:
  - Hb ≤ 11 g/dL within 18 hours of delivery
- Study definition of HMB-associated IDA:
  - Hb ≤ 11 g/dL or ≤ 11.5 g/dL at point-of-care
  - HMB = 1 or more of the following in last 6 months:
    - Insufficiency of tampons alone
    - >12 pads per period or 4 tampons per day
    - Passage of clots
    - Period duration > 7 days
- Primary endpoint = safety
- Secondary endpoint = impact on mean Hb levels

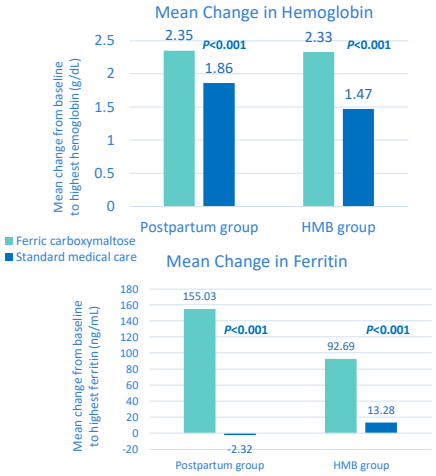



Seid MH, et al. *Anemia*. 2017.

# Treating IDA in Women's Health

## *IV Iron Evidentiary Base – DUB/HMB +/- PPH*

- Safety
  - Total incidence of drug-related adverse events (AEs) was similar between the two treatment arms (FCM = 27.3% vs. SMC = 26.9%; *P*=0.841)
  - However, rate of treatment discontinuation due to AEs was higher in the SMC arm (2.2%) vs. the FCM arm (0.7%)
  - *Incidence of serious AEs higher with SMC vs. FCM (2.2% vs. 0.6%; P=0.004)*
- Efficacy
  - FCM achieved *increases in Hb* and *serum ferritin* that were clinically meaningful and statistically significant vs. SMC
- Study conclusion:
  - ***FCM is a safe and effective treatment option for women with HMB- or postpartum-associated IDA that meaningfully improves upon established approaches to medical care***



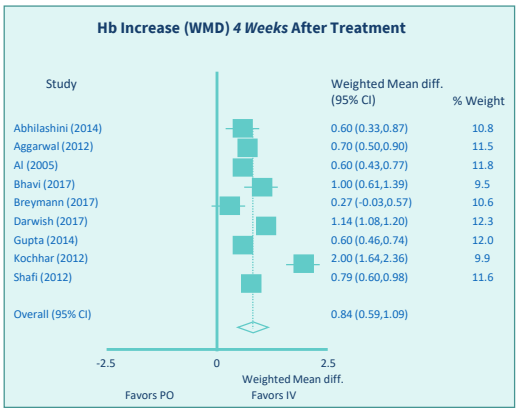

Seid MH, et al. *Anemia*. 2017.



# Treating IDA in Women's Health

## *IV Iron Evidentiary Base – Pregnancy*

- Systematic review and meta-analysis of 11 studies evaluating IV iron vs. oral iron for IDA management in pregnancy
- Identified 3 fundamental advantages for IV iron > oral iron:
  1. *IV iron achieved target Hb level more often vs. oral iron* (pooled OR, 2.66; 95% CI, 1.71-4.15; *P*<0.001)
  2. *IV iron increased Hb more quickly vs. oral iron*, achieving higher levels at 4 weeks (pooled WMD, 0.84 g/dL; 95% CI, 0.59-1.09; *P*<0.001)
  3. *IV iron boasts superior tolerability vs. oral iron*, with significantly fewer adverse reactions (pooled OR, 0.35; 95% CI, 0.18-0.67; *P*=0.001)
- Real-world applications:
  - IV iron should be used preferentially in pregnancy, especially when:
    - **Anemia is moderate or severe**
    - **Second and third trimester, with increasing preference closer to delivery**
    - **There is a high risk for postpartum hemorrhage**




WMD, weighted mean difference

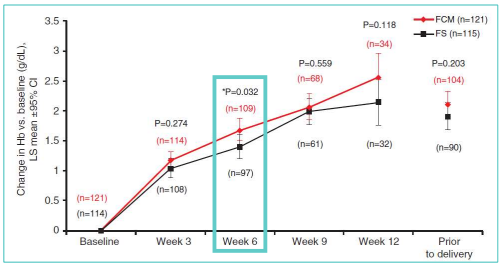
Govindappagari S, et al. *Am J Perinatol*. 2019.

# Treating IDA in Women's Health

## *IV Iron Evidentiary Base – Pregnancy*

- 252 pregnant women – all in 2nd trimester or later – randomized to either:
  - IV FCM – 1,000-1,500 mg
  - Oral ferrous sulfate (FS) – 200 mg elemental iron daily
  - Study period = 12 weeks
- FCM achieved anemia correction more frequently than oral FS (84% vs. 70%; OR, 2.06; 95% CI, 1.07-3.97; *P*=0.031)
- Critically, anemia correction was *faster* with FCM vs. FS
  - 3.4 weeks vs. 4.3 weeks
- FCM also significantly improved PROs vs. FS
  - *Vitality scores (P=0.025)*
  - *Social functioning (P=0.049)*
- Practical implications for pregnancy:
  - **FCM more appropriate than FS for IDA in late-stage pregnancy due to rapidity of response**
  - **Additional studies have also confirmed this benefit in ID alone (without anemia)**

**Change in Hb from Baseline, FCM vs. Ferrous Sulfate**




Breymann C, et al. *J Perinat Med*. 2017; Froessler B, et al. *Arch Gynecol Obstet*. 2018.

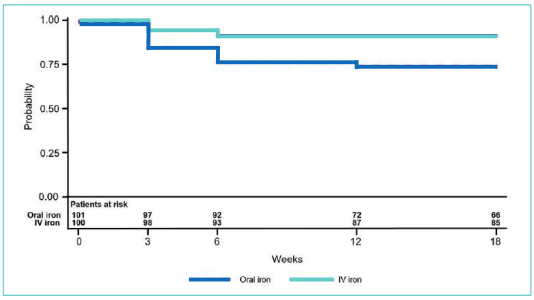


# Treating IDA in Women's Health

## *IV Iron Evidentiary Base – Pregnancy*

- 201 pregnant women – all 14-21 weeks gestation – with persistent ID despite prior oral iron treatment, randomized to either:
  - IV ferric derisomaltose (FDM) 1,000 mg
  - Oral ferrous fumarate (FF) 100 mg elemental iron daily
  - Study period = 18 weeks
- *FDM prevented anemia better than FF*
  - 91% non-anemic on FDM vs. 73% non-anemic on FF throughout follow-up (*P*<0.001)
- Mean Hb increase was significantly higher with FDM vs. FF
  - Week 6 – *P*<0.001
  - Week 12 – *P*<0.001
  - Week 18 – *P*=0.01
- PRO benefits were seen with FDM vs. FF at study weeks 3 and 6
  - Quality of life and fatigue scores
- Practical implications for pregnancy:
  - **FDM is a safe, effective treatment option for preventing anemia onset in pregnant women with ID, especially those for whom prior oral iron was ineffective**

**Product Limit Estimates - Probability of Avoiding Anemia**




Hansen R, et al. *Arch Gynecol Obstet*. 2022.



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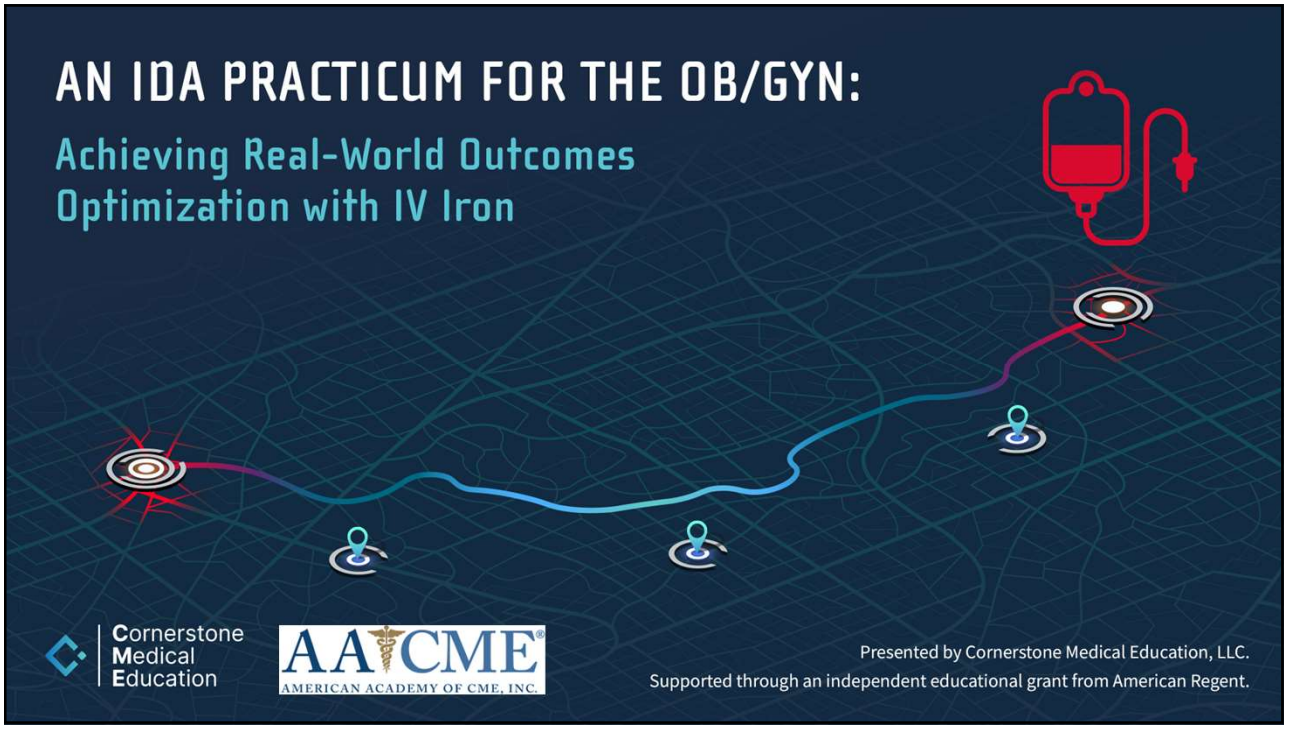
# Summary of Key Teaching Points

## *IDA Diagnosis, Screening, and Treatment in Women*

- ID most often precedes onset of anemia – identifying and treating ID early improves care
  - CBC orders alone are insufficient; must also order serum ferritin and TSAT
- Despite guideline inconsistencies, IDA screening should be regular and rigorous
  - Annually for non-pregnant women of reproductive age (especially if risk factors present)
  - First trimester, week 24, and week 28 for pregnant women
- Nanocolloidal design of next-gen IV iron products dramatically improves safety profiles
- Oral iron has an important, but limited, clinical utility
  - First-line in: mild ID/IDA, first trimester of pregnancy, no scheduled surgery, absence of GI disease
- IV iron has been demonstrated to be a safe and effective therapeutic option for IDA associated with HMB, pregnancy, and/or PPH
  - First-line in: severe ID/IDA, ongoing bleeding (HMB) or high-risk for PPH, late-stage pregnancy, or scheduled surgery ≤ 6 weeks



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# Implementing IV Iron in Women's Health

## *Currently-Available Products*

| Iron Product | Dosing and Administration | Approved Indications | Common Adverse Drug Effects | Warnings |
|---|---|---|---|---|
| **Low-molecular-weight iron dextran** | • 100 mg daily via IV push over at least 2 minutes<br>• Total dose is calculated based on iron deficit<br>• May repeat daily | Iron deficiency (ID) in adult and pediatric patients 4 months of age and older for whom oral therapy is unsatisfactory or intolerable | Pruritis, abdominal pain, nausea, vomiting, diarrhea | **Black box**: fatal and serious hypersensitivity reactions, including anaphylaxis |
| **Ferumoxytol** | • 510 mg via IV infusion over at least 15 minutes<br>• 2nd (510 mg) dose 3–8 days later | Iron deficiency anemia (IDA) in adult patients who have intolerance or unsatisfactory response to oral iron, or who have a diagnosis of CKD | Dizziness, hypotension, constipation, nausea | **Black box**: fatal and serious hypersensitivity reactions, including anaphylaxis |
| **Sodium ferric gluconate** | • 125 mg (adults) via IV infusion over 1 hour, per dialysis<br>• 1.5 mg/kg in peds<br>• Repeated weekly for up to 8 weeks | IDA in patients 6 years old and older who are receiving hemodialysis and supplemental EPO therapy for CKD | Chest pain, leg cramps, dizziness, dyspnea, nausea, vomiting, diarrhea | Hypersensitivity reactions, hypotension, iron overload, benzyl alcohol toxicity |

FDA Prescribing Information.



# Implementing IV Iron in Women's Health

## *Currently-Available Products*

| Iron Product | Dosing and Administration | Approved Indications | Common Adverse Drug Effects | Warnings |
|---|---|---|---|---|
| **Iron sucrose** | • 100–400 mg, by setting<br>• Doses may be repeated based on clinical response and iron indices | IDA in adult and pediatric patients (2 years of age and older) with CKD | Diarrhea, nausea, vomiting, headache, hypotension, pruritus | Hypersensitivity reactions, hypotension, iron overload |
| **Ferric carboxymaltose** | • For patients weighing ≥50 kg, may give 15 mg/kg up to 1,000 mg (*single-dose TDI*) or 750 mg infusion<br>• If 750 mg is given, may be repeated in 7 days, for a total dosage per course of 1,500 mg<br>• For patients weighing <50 kg, give 15 mg/kg in 2 doses, separated by at least 7 days | IDA in patients 1 yo and older who have intolerance or unsatisfactory response to oral iron, and in adults who have non–dialysis dependent CKD (NDD-CKD)<br><br>ID in adult patients with heart failure and NYHA class II/III to improve exercise capacity | Nausea, hypertension, hypophosphatemia, flushing | Hypersensitivity reactions, symptomatic hypophosphatemia, hypertension |
| **Ferric derisomaltose** | • For patient weighing ≥ 50 kg, give 1,000 mg (*single dose TDI*)<br>• For patients weighing <50 kg, give 20 mg/kg in a single dose | IDA in adult patients who have intolerance or unsatisfactory response to oral iron, or who have non–hemodialysis dependent CKD | Nausea, injection site reactions, rash, hypotension | Hypersensitivity reactions, iron overload |

FDA Prescribing Information.

# Implementing IV Iron in Women's Health

## *Practical Pearls & Product-Specific Considerations*

| Iron Product | Concentration of Elemental Iron (mg/mL) | Total Dose Infusion (TDI) Capacity *On-Label* | Test Dose Required? | Infusion Time |
|---|---|---|---|---|
| **Iron sucrose** | 20 | No | No | ≥15 minutes |
| **Sodium ferric gluconate** | 12.5 | No | No | 1 hour |
| **Low–molecular-weight iron dextran** | 50 | No | **Yes** | 1 hour (not to exceed 50 mg/min) |
| **Ferumoxytol** | 30 | No | No | ≥15 minutes |
| **Ferric carboxymaltose** | 50 | **Yes** | No | ≥15 minutes |
| **Ferric derisomaltose** | 100 | **Yes** | No | ≥20 minutes |

Auerbach M, et al. *Lancet Haematol.* 2020; FDA Prescribing Information.



# Implementing IV Iron in Women's Health

## *A Closer Look at TDI Capacity – On-label vs. In-practice*

| Iron Product | TDI *on the Label* | TDI *in the Clinic* |
|---|---|---|
| **Low-molecular-weight iron dextran** | • No<br>• Label: max of 100 mg (2 mL) daily via IV push over at least 2 minutes | • Yes<br>• Routinely given in practice as up to 1,000 mg administered over 1 hour |
| **Ferumoxytol** | • No<br>• Label: 510 mg via IV infusion over at least 15 minutes; repeat in 3–8 days | • Yes<br>• Trial data support 1,020 mg TDI |
| **Ferric carboxymaltose** | • **Yes**<br>• For patients weighing ≥50 kg, may give either 1,000 mg TDI over at least 15 minutes or 750 mg x 2 doses, at least 7 days apart | • Yes<br>• **Per label** |
| **Ferric derisomaltose** | • **Yes**<br>• For patients weighing ≥50 kg, 1,000 mg given over at least 20 minutes; <50 kg, 20 mg/kg | • Yes<br>• **Per label** |

FDA Prescribing Information; ClinicalTrials.gov.

# Implementing IV Iron in Women's Health

## *Adverse Event Mitigation & Management*

- Life-threatening anaphylaxis/severe hypersensitivity is *very rare* with next-gen IV iron products
  - <1 event per 200,000 doses administered
- It is, however, essential to clinically differentiate minor acute reactions to IV iron from true anaphylaxis ⟶ lack of differentiation = major source of *erroneous stigma*
  - Critical role of *pharmacy* and *nursing* interprofessional team members
- Most common acute infusion reactions to IV iron are *Fishbane* and *complement activation-related pseudo-allergy (CARPA)* reactions
  - Clinical manifestations include: facial flushing, chest tightness, arthralgia/myalgia, itching, mild dyspnea
- **Though these reactions may seem to mimic onset of anaphylaxis, they are *NOT* anaphylaxis**
  - Often self-resolving
  - Typically don't recur – and thus allow for re-initiation of same IV iron product, albeit at slower rate (~50% reduction)
    - Document in patient medical record
  - "Wait and watch" approach, requiring at least a 15-30 minute infusion pause

Avni T, et al. *Mayo Clin Proc*. 2015; DeLoughery TG. *Acta Haematol*. 2019; Rampton D, et al. *Haematologica*. 2014; MacDougall IC, et al. *Am J Nephrol*. 2017; Steveling-Klein EH, et al. *J Allergy Clin Immunol Pract*. 2021; Caimmi S, et al. *Children (Basel)*. 2022.



# Optimizing Real-World IDA Management

## *Patient Case - JC*

- During a routine OB/GYN appointment, JC, a 34-yo female, reports feelingly increasingly fatigued over the past few months and says she's been "foggy" at work
- You inquire about potential causes, including her menstrual experience:
  - JC indicates that "her periods have been heavy since high school, but have gotten a lot heavier in her thirties"
    - Several friends her age have told her it's "normal" and "nothing to be concerned about"
    - Thus, she never thought to mention it to you or to her PCP
  - Bleed-throughs are relatively common, necessitating 7-8 tampons per day (on average)
  - Her periods typically last about 9 days on a 30-32 day cycle
  - She has a 4-yo daughter, but has contended with infertility for nearly 2 years
- Subsequent uterine exam reveals a significant intramural fibroid (2.7 cm diameter)

**As a member of the OB/GYN women's health care team, *what next steps do you recommend for diagnosing, evaluating, and treating JC?***

# Optimizing Real-World IDA Management

## *Patient Case - JC*

ANIMATED WHITEBOARD VIDEO

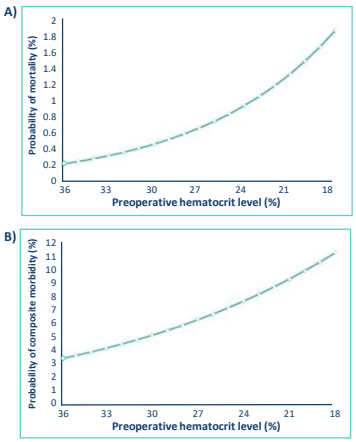
Munro M, et al. *Am J Obstet Gynecol*. 2023; Jain V, et al. *Nat Rev Endocrinol*. 2022; Munoz M, et al. *Anaesthesia*. 2017; Percy L, et al. *Best Practice Res Clin Ob Gyn*. 2017; Richards T, et al. *PLoS One*. 2015.



# Optimizing Real-World IDA Management

## *The Perioperative Clinical Gravity of IDA*

- Preoperative anemia is common (prevalence = ~≥25%) and associated with deleterious perioperative outcomes in women undergoing gynecologic surgery
  - Increased 30-day mortality (OR, 2.40) and composite morbidity (OR, 1.80)
  - Predictor of perioperative RBC transfusion burden
    - RBC transfusion requirement significantly associated with postoperative complications
    - Major contributor to 30-day mortality (61%) and composite morbidity (16%)
  - Risk factor for increased postoperative hospitalization length of stay
- Laparoscopic myomectomy (vs. hysterectomy) reduces – *but does not eliminate* – the negative prognostic impacts of preoperative anemia
  - Increased perioperative RBC transfusion requirement ($P$<0.01)
  - Higher rate of hospital readmission ($P$=0.01)
  - Increased risk for minor postoperative complications ($P$<0.01)
  - However, no increased risk for "major" 30-day postoperative complications (in contrast to hysterectomy data)




Richards T, et al. *PLoS One*. 2015; Munoz M, et al. *Anaesthesia*. 2017; Thakrar SJ, et al. *BJA Education*. 2017; Musallam KM, et al. *Lancet*. 2011; Tyan P, et al. *J Minim Invasive Gynecol*. 2020; Siewertsz van Reesema LL, et al. *Am J Obst Gynecol*. 2022.



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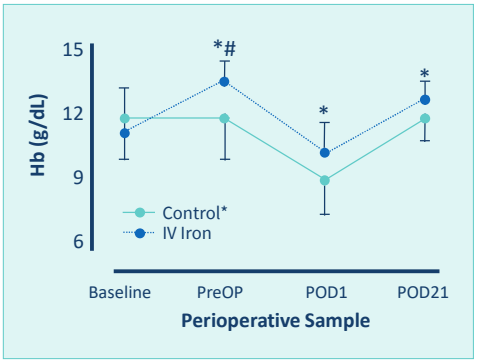
# Optimizing Real-World IDA Management

## *The Perioperative Clinical Utility of IV Iron*

- Systematic reviews and prospective studies have both demonstrated substantive clinical efficacy for IV iron in the gynecologic perioperative setting (vs. oral iron)
  - Increased preoperative Hb levels (*P*<0.001)
  - Reduced transfusion burden (*P*<0.001)
  - Diminished 21-day post-op anemia rates (*P*<0.01)
- Some studies noted an increased risk of infection (RR, 1.33)
- Current perioperative IDA management guidelines suggest *first-line IV iron* in the following clinical scenarios:
  - Patient unresponsive to or intolerant of oral iron
  - **Surgery scheduled <6 weeks after ID/IDA diagnosis**




*Control = oral iron; POD, post-op day

Litton E, et al. *BMJ*. 2013; Diez-Lobo AI, et al. *Transfus Altern Transfus Med*. 2007; Munoz M, et al. *Anaesthesia*. 2017.



# Optimizing Real-World IDA Management

## *IV Iron for Preoperative HMB-associated IDA*

### IV Iron Sucrose vs. Oral Iron

- Study conducted *3 weeks* prior to scheduled surgery
- 76 women, with baseline Hb <9.0 g/dL, randomized:
  - IV iron sucrose administered three times weekly
  - Oral iron – 80 mg/daily
- Results:
  - Greater Hb increase with IV iron (*P*<0.0001)
  - Greater increase in serum ferritin with IV iron (*P*<0.0001)
  - Achievement of target preoperative Hb (≥ 10 g/dL) higher with IV iron (*P*<0.0001)
- Conclusions:
  - ***IV iron is more effective than oral iron – and equally safe – in the management of preoperative HMB-associated anemia***

### IV Ferric Carboxymaltose (FCM) vs. IV Iron Sucrose

- Primary study endpoint = achieving target preoperative Hb (≥ 10 g/dL) within *2 weeks*
- 101 women (average baseline Hb = 8.4 g/dL) randomized:
  - IV FCM 1,000 mg total dose infusion (TDI)
  - Multiple doses of IV iron sucrose (IS)
- Results:
  - FCM and IS similarly effective in achieving primary endpoint (78.8% with FCM vs. 72.3% with IS, *P*=0.452)
  - FCM achieved target Hb significantly faster than IS (7.7 days with FCM vs. 10.5 days with IS, *P*=0.013)
- Conclusions:
  - ***IV FCM improves preoperative HMB-associated anemia to a similar extent as IV IS, but much faster, thereby allowing for earlier surgical scheduling***

Kim YH, et al. *Acta Haematol.* 2009; Lee S, et al. *J Obstet Gynaecol Res*. 2019.

# Optimizing Real-World IDA Management

## *Patient Case - JC*

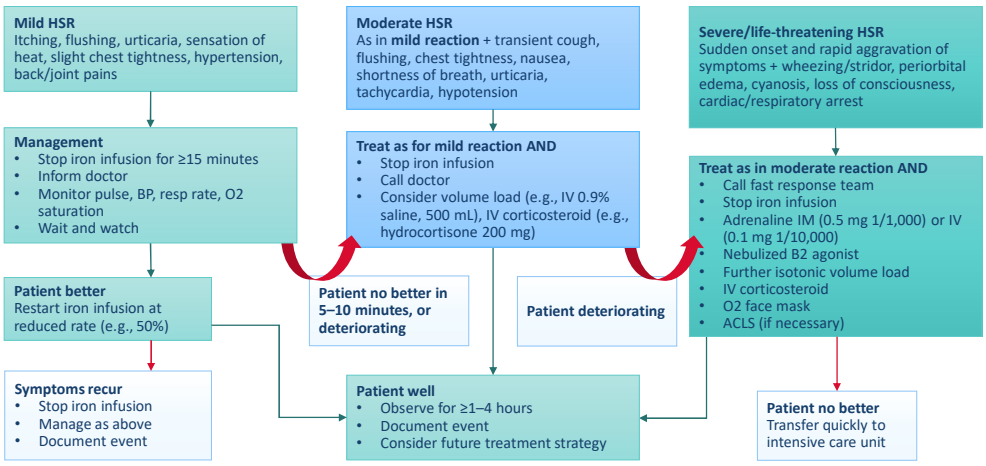
- At JC's 3-week follow-up:
  - Hb = 8.5 g/dL
  - Serum ferritin = 42 ng/mL
  - TSAT = 19%
- Her IDA is still symptomatic (fatigue, brain fog) and she reports intolerance to the oral ferrous sulfate you prescribed (constipation and cramping) that precipitated treatment non-adherence
- It is now just 5 weeks prior to her scheduled myomectomy procedure
- **Decision point** – based on the totality of the evidence (and the fact that JC weighs 68 kg), a single dose IV ferric carboxymaltose 1,000 mg is ordered to be administered during this visit

**About 10 minutes into the infusion, JC experiences acute facial flushing and intense itching on her chest and abdomen. She and your staff are both very alarmed.** ***What do you recommend?***



# Optimizing Real-World IDA Management

## *Evaluation & Management of Acute Hypersensitivity*




Rampton D, et al. *Haematologica*. 2014.

# Optimizing Real-World IDA Management

## *Patient Case - JC*

- You quickly recognize the facial flushing and itching as symptoms of a CARPA reaction
- Per evidence-based protocols, you and your team stop the IV FCM infusion for 30 minutes and observe JC's pulse, BP, respiratory rate, and symptoms
  - Within 5 minutes, the flushing and itching abate and JC's demeanor returns to normal
- **Decision point** – nurse restarts the IV FCM infusion at half the initial rate (now administering over 30 minutes as opposed to 15) and observes for any recurrence of symptoms during and after the infusion. After monitoring JC in the clinic for an hour post-infusion, you send her home
- JC returns to clinic 2 weeks later (3 weeks prior to surgery) and her fatigue and fogginess have fully resolved, as have the GI symptoms. Labs reveal:
  - Hb = 11.2 g/dL
  - Serum ferritin = 301 ng/mL
  - TSAT = 26%

**3 weeks later, JC proceeds to laparoscopic myomectomy with *full resolution of ID/IDA*, and consequently, is medically positioned for an optimal outcome.**



# Summary of Key Teaching Points

## *Practical Women's Health Perspectives on IV Iron*

- There are currently 6 FDA-approved IV iron products
  - Low-molecular-weight iron dextran, sodium ferric gluconate, iron sucrose, ferumoxytol, ferric carboxymaltose (FCM), and ferric derisomaltose
  - TDI capacity on-label: only FCM and ferric derisomaltose
- Imperative to differentiate Fishbane and CARPA reactions from true anaphylaxis
  - Often self-resolve and are a leading cause of misplaced IV iron safety stigma
  - A crucial function of pharmacist and nurse interprofessional team members (one of many)
- Preoperative anemia is a negative prognostic factor for postoperative outcomes
- IV iron is superior to oral iron in achieving target preoperative Hb levels vs. oral iron for women with HMB-associated IDA
  - Appropriate to use IV iron in first-line preoperatively *when interval to surgery is <6 weeks*
- Single-dose IV FCM (TDI) corrects preoperative anemia *faster* than iron sucrose