# Anaemia of Pregnancy

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## Disclosures

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**Committees, directorships, associate:**

- WHO strategic committee for Patient Blood Management
- AABB global standards committee
- International Collaborative Transfusion Medicine guidelines group
- International Foundation Patient Blood Management Associate (Africa)
- Non-executive Director, Western Cape Blood Service, Global Transfusion Forum Education subcommittee

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# Introduction

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## Guideline Definitions of Anaemia in Pregnancy

| Guideline | Trimester 1st | Trimester 2nd | Trimester 3rd | Post-partum |
|---|---|---|---|---|
| WHO | <11.0 g/dL | <11.0 g/dL | <11.0 g/dL | < 10 g/dL |
| CDC | <11.0 g/dL | <10.5 g/dL | <11.0 g/dL | |
| ACOG | <11.0 g/dL | <10.5 g/dL | <11.0 g/dL | |

There is no specific Hb value that can distinguish physiologic dilutional anemia from other causes of anemia

James AH. Obstet Gynecol 2021;138:663–74

ACOG, American College of Obstetricians and Gynecologists; CDC, Centers for Disease Control and Prevention; WHO, World Health Organization

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## BUT keep your common-sense hat on…

- Some individuals may have significant decrease from baseline **without crossing** these thresholds, e.g.
  - If baseline Hb 14 g/dL and decreases to 11 g/dL with macrocytosis – check B12 and folate
  - If baseline Hb 14 g/dL and decreases to 11 g/dL and no macrocytosis – check iron, B12 and folate

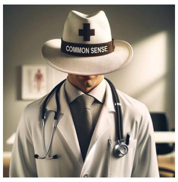


Image:© Vernon J Louw

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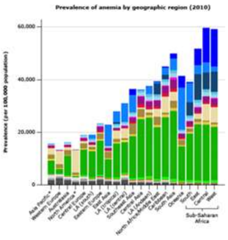
## Prevalence of Anaemia in Pregnancy – Regional Variation

- Southeast Asia 48%
- Africa 46%
- East Mediterranean 37%
- Europe 24%
- Americas 19%




Data Source : Worldbank.org

Kassebaum NJ et al. Blood 2014; 123: 615-624

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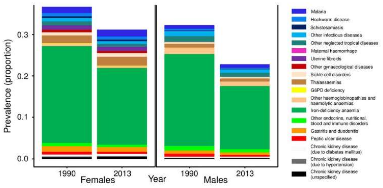
## Background Anaemia Prevalence: Data from 187 countries (1990 – 2010)




≥50%

GBD 2013 Lancet. 2015 Jan 10;385(9963):117-71.

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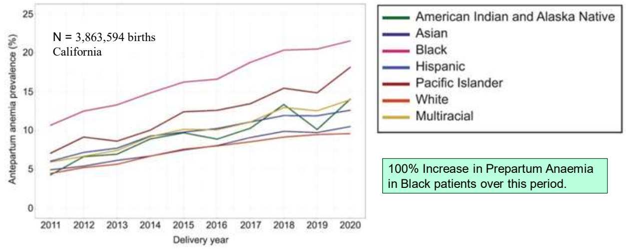
## Trends in Antepartum Anaemia, 2011–2020.




100% Increase in Prepartum Anaemia in Black patients over this period.

Igbinosa I et al. Obstet Gynecol. 2023 Oct 1;142(4):845-854.

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## Etiology

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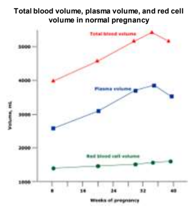
## Physiologic Anaemia of Pregnancy

- Plasma volume increase > RBC mass increase
  - Plasma volume increases by 40-50%
  - RBC mass increases by 15-25%

    Disproportion
    - Greatest disproportion during late 2nd/early 3rd trimester
    - Lowest Hb 28–36 weeks
  - Hb increases near term due to cessation plasma expansion and continuing increase in RBC mass




Shnider SM, Levinson G. Anesthesia for Obstetrics. 3rd ed. 1993: p8

Hb, haemoglobin; RBC, red blood cell.

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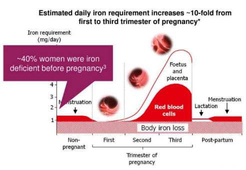
## Red cell mass and plasma volume in pregnancy

- Decrease in haemoglobin concentration
  - RELATIVE ANAEMIA = **PHYSIOLOGICAL ANAEMIA OF PREGNANCY**
  - May become clinically significant if baseline anaemia in early pregnancy
- Increased need for folate, iron and B12




Shnider SM, Levinson G. Anesthesia for Obstetrics. 3rd ed. 1993: p8

Hb, haemoglobin; RBC, red blood cell.

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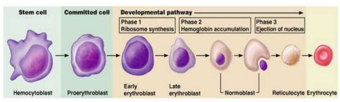
## Shortened lifespan RBCs in pregnancy

- Increase in RBC mass mediated by a 50% increase in **erythropoietin** during pregnancy
  - Supports higher requirement for **oxygen** delivery during pregnancy
  - Due to "emergency erythropoiesis" in response to elevated erythropoietin (EPO) levels

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Lurie S & Mamet Y. Eur J Obs Gyne. 2000 (93):185-192

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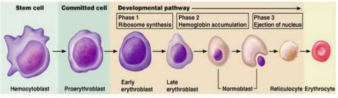
## Shortened lifespan RBCs in pregnancy

- RBCs formed in response to elevated EPO levels have a **shortened lifespan**
  - Erythroid lineage skips the terminal cell division
  - Nucleus expelled one cell division before final maturation
  - Results in younger reticulocytes in circulation
  - These RBCs are larger than usual and removed earlier from circulation than normal RBCs






Lurie S & Mamet Y. Eur J Obs Gyne. 2000 (93):185-192

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## Physiologic anaemia of pregnancy

- Physiologic haemodilution may provide survival benefits during pregnancy and childbirth
  - Expanded plasma volume
    - Less viscous blood improves uterine and intervillous **perfusion**
    - Meets increased metabolic **demands** of the uterus and placenta
    - Facilitates **nutrient delivery** to developing fetus
    - Facilitates **removal of waste**
    - Protects against impaired **venous return** when mother is supine or standing
    - Blood lost during delivery more dilute ("natural form of **normovolaemic haemodilution**"?)
  - Increased red blood cell mass, coupled with increased uterine blood flow, optimises **oxygen transport** to the fetus

Physiologic anaemia of pregnancy and iron deficiency account for the vast majority of causes of anaemia in pregnancy

Constantine MM. Front Pharmacol 2014;5:65.
Cunningham G, et al. Chapter 4 – Maternal Physiology. In: Williams Obstetrics. 24th Ed. 2013

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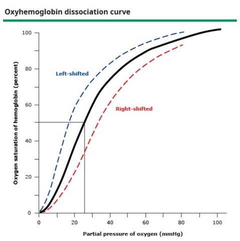
## Physiologic anaemia of pregnancy

2,3-DPG elevated during pregnancy (right-shift curve)

- leads to decreased oxygen affinity of mother's haemoglobin AND
- low pCO2 of maternal blood due to increased minute ventilation
- facilitates transport of oxygen across the placenta and to the foetal RBCs, which have greater oxygen affinity due to foetal haemoglobin






Costantine MM. Frontiers in Pharmacology. 2014

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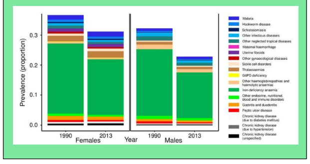
## Causes of Pathological Anaemia in Pregnancy

- Most common cause (by far!)
  - Iron deficiency
    - Heavy Menstrual Bleeding before
    - Previous pregnancies
    - Diet, etc




- Anaemia affects 2.36 billion individuals worldwide.
  - The prevalence of iron-deficiency anaemia alone was 1.46 billion.

**Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015**

GBD 2015 Disease and Injury Incidence and Prevalence Collaborators*

GBD 2015. Lancet. 2016 Oct 8;388(10053):1545-1602. doi: 10.1016/S0140-6736(16)31678-6.

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## Causes of Anaemia in Pregnancy

- Fertile, non-pregnant women
  - 30% anaemic globally
  - 40% iron deficient (low reserves)
- Pregnant women
  - 35-80% **anaemic** (Africa, Asia and Latin America) compared to 20-45% in high-income countries
    - 75% IDA
    - 25% other
      - Folate
      - B12
      - Haemoglobinopathies, RBC membrane disorders, schistosomiasis, etc.
  - 42% **Non-anaemic iron deficiency** (NAID)
- Post-partum anaemia in 1/3

Other common causes (globally):

- Folate deficiency
- B12 deficiency
- Chronic infections (e.g. HIV, TB, etc.)
- Bone marrow suppression
- Haemolytic diseases (e.g. sickle cell disease and malaria)
- Chronic blood loss (e.g. hookworm infestation)

Auerbach M et al. J Matern Fetal Neonatal Med 2019;3:1-4
Auerbach M et al. J Matern Fetal Neonatal Med. 2021 Mar;34(6):1002-1005.

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## Antepartum anemia and Severe Maternal Morbidity by Race

Table 3. Associations Between Anemia and Severe Maternal Morbidity by Race and Ethnicity, California, 2011–2020 (N=3,863,594)

| Race and Ethnicity | Adjusted RR (95% CI)* | Adjusted Population Attributable Risk Percentage (95% CI)* |
|---|---|---|
| American Indian–Alaska Native | 3.27 (2.46–4.34) | 16.7 (5.2–29.0) |
| Asian | 2.57 (2.43–2.71) | 11.3 (8.9–13.3) |
| Black | 2.81 (2.64–3.00) | 20.9 (18.1–23.4) |
| Hispanic | 3.63 (3.54–3.73) | 20.9 (19.9–22.1) |
| Multiple races | 2.94 (2.59–3.32) | 21.4 (17.5–25.0) |
| Pacific Islander | 3.37 (2.67–4.24) | 16.4 (7.3–26.4) |
| White | 2.96 (2.82–3.09) | 14.7 (13.3–16.0) |

RR, relative risk.
* Adjusted for age, education, payment method, obstetric comorbidity score, parity, and delivery method.

"In our cohort of 3,863,594 births, antepartum anemia was associated with SMM and contributed to nearly **one in five** SMM cases in Black pregnant patients."

Igbinosa II et al. Obstet Gynecol. 2023 Oct 1;142(4):845-854.

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## Causes of Obstetric Death

Table 4: Primary Obstetric cause of Maternal deaths and iMMR for 2021 (UNCORRECTED)

| Primary obstetric problem | Number MDs | % | iMMR |
|---|---|---|---|
| **INDIRECT** | | | |
| Medical and surgical disorders | 188 | 12.6 | 18.5 |
| Non-pregnancy-related infections* | 554 | 37 | 54.5 |
| **DIRECT** | | | |
| Ectopic pregnancy | 33 | 2.2 | 3.2 |
| Miscarriage | 54 | 3.6 | 5.3 |
| Pregnancy-related sepsis | 67 | 4.5 | 6.6 |
| Obstetric haemorrhage | 234 | 15.6 | 23.0 |
| Hypertension | 187 | 12.5 | 18.4 |
| Anaesthetic complications | 17 | 1.1 | 1.7 |
| Adverse drug reactions | 5 | 0.3 | 0.5 |
| Embolism | 43 | 2.9 | 4.2 |
| Acute collapse - cause unknown | 36 | 2.4 | 3.5 |
| Miscellaneous | 3 | 0.2 | 0.3 |
| Unknown | 52 | 3.5 | 5.1 |
| **Total:** | **1473** | **100** | **145.0** |

*Deaths from COVID-19 complications were classified under NPRI/other*

TIME OF COVID

Obstetric haemorrhage most common direct obstetric cause of maternal deaths in S Africa

Saving Mothers Report 2021



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## Risk of haemorrhage during childbirth in women with pre-existing anaemia.

Risk of obstetric haemorrhage

Women in **Ghana** with **moderate–severe anaemia** (Hb <10 g/dL) undergoing **vaginal deliveries**[1]
*"For every unit increase in Hb, the odds of developing primary PPH decreased 0.5791 times (95% CI 0.46–0.73)."*
**OR** 3.14 (1.21–8.14)

**Anaemic** women in **USA** undergoing **vaginal deliveries** (Hb <9 g/dL)[2]
**OR** 2.46 (0.92–6.56)

| **UK births**[3] **(all delivery methods)** | Pre-pregnancy anaemia | During pregnancy and Hb <10.5 g/dL |
|---|---|---|
| PPH ≥1500 mL | OR **1.31** (0.35–4.95) | OR **1.27** (0.84–1.92) |
| PPH ≥500 mL | OR **0.76** (0.24–2.43) | OR **1.15** (0.83–1.60) |

**OR** 6.65 (3.77–11.74)
In **Senegal and Mali**, **severe chronic anaemia** (<7 g/dL) was significantly associated with risk of PPH maternal mortality (**all delivery methods**)[4]

**OR** 2.73 (1.43–5.23)
Women in **Egypt** with **antepartum anaemia** (Hb ≤11 mg/dL) who underwent **vaginal deliveries**[5]

**OR** 1.82 (1.00– 3.32)
**Women from ethnic minority backgrounds in the UK** diagnosed with anaemia during their current pregnancy (**all delivery methods**)[6]

**OR** 0.99 (0.72–1.35)
Women in **rural Uganda** with moderate–severe anaemia during pregnancy (**all delivery methods**)[7]

For PPH ≥500 mL unless otherwise stated

1. Owiredu KL, et al. BMC Preg Childbirth 2016;16:17; 2. Wetta L, et al. Am J Obstet Gynecol 2013;209:51.e1–6; 3. Briley A, et al. BJOG 2014;121:876–88; 4. Tort J, et al. BMC Pregnancy Childbirth 2015;15:235;
5. Prata N, et al. BMC Pregnancy Childbirth 2011;11:97; 6. Nair M, et al. PLoS One 2014;9:e95086;
7. Onongе S, et al. Reprod Health 2016;13:38

CI, confidence interval; Hb, haemoglobin; IDA, iron-deficiency anaemia; OR, odds ratio; PPH, postpartum haemorrhage

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## Risk of iron deficiency anaemia on mother

- The lower the Hb, the closer to the cliff of PPH-related morbidity and mortality[1–3]

1. Frass KA. Alexandria J Med 2015;51:333–7; 2. Villar J, et al. J Nutr 2003;133:1606S–25S;
3. Pavord S, et al. Br J Haematol 2020;188:819–30; 4. Smith C, et al. Obstet Gynecol 2019;134:1234–44;
5. Kumar A, et al. Pediatrics 2008;121:e673–7; 6. Wassef A, et al. J Psychosom Obstet Gynaecol 2019;40:19–28;
7. Kang SY, et al. J Psychiatr Res 2020;122:88–96; 8. Murray-Kolb LE, Beard JL. Am J Clin Nutr 2009;89:946S–50S; 9. Harvey T, et al. Womens Health (Lond) 2016;12:95–102

Hb, haemoglobin; IDA, iron deficiency anaemia; PPH, postpartum haemorrhage

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## Effects of iron deficiency on mother

- The lower the Hb, the closer to the cliff of PPH-related morbidity and mortality[1–3]
- Increased risk pre-eclampsia[11]
- Increased risk caesarian section[12]
- Increased risk of infection[3,4]
- Reduced breast milk iron in severe IDA[5]
- Increased post-natal depression[6,7, 10]
- Decreased bonding mother and baby[6,8]
- Fatigue and forgetfulness[3,9]

1. Frass KA. Alexandria J Med 2015;51:333–7; 2. Villar J, et al. J Nutr 2003;133:1606S–25S;
3. Pavord S, et al. Br J Haematol 2020;188:819–30; 4. Smith C, et al. Obstet Gynecol 2019;134:1234–44;
5. Kumar A, et al. Pediatrics 2008;121:e673–7; 6. Wassef A, et al. J Psychosom Obstet Gynaecol 2019;40:19–28;
7. Kang SY, et al. J Psychiatr Res 2020;122:88–96; 8. Murray-Kolb LE, Beard JL. Am J Clin Nutr 2009;89:946S–50S; 9. Harvey T, et al. Womens Health (Lond) 2016;12:95–102; 10. Ohsuga T, Egawa M, Kii M, Ikeda Y, Ueda A, Chigusa Y, Mogami H, Mandai M. Association between non-anemic iron deficiency in early pregnancy and perinatal mental health: A retrospective pilot study. J Obstet Gynaecol Res. 2022 Nov;48(11):2730-2737. 11. Bone JN et al. BMC Pregnancy Childbirth. 2022 May 13;22(1):407. 12. Drukker L et al. Transfusion. 2015 Dec;55(12):2799-806.

Hb, haemoglobin; IDA, iron deficiency anaemia; PPH, postpartum haemorrhage

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JAMA Network | Open

Original Investigation | Obstetrics and Gynecology

### Severity of Anemia During Pregnancy and Adverse Maternal and Fetal Outcomes

Huifeng Shi, PhD; Lian Chen, MD; Yuanyuan Wang, PhD; Mengxing Sun, MBBS; Yijie Guo, BS; Shang Ma, BS; Xiaoli Wang, PhD; Hai Jiang, MM; Xiaoxia Wang, BS; Jie Lu, MD; Lin Ge, MD; Shu Dong, MM; Yu Zhuang, MM; Yangyu Zhao, MD; Yuan Wei, MD; Xudong Ma, MD; Jie Qiao, MD

18 948 443 pregnant females (15 to 49 years)
1508 hospitals
17.8% anaemic; 70% iron deficiency
Iron supplementation not routine

Shi H et al.. JAMA Netw Open. 2022 Feb 1;5(2):e2147046.

23

201X-XX vX.0

23

## Examples of significant maternal findings

- Abruptio placentae (aOR)
  - 1.36 with **mild** anemia
  - 1.98 with **moderate** anemia
  - 3.35 with **severe** anemia
- Preterm birth (aOR)
  - 1.08 with **mild** anemia
  - 1.18 with **moderate** anemia
  - 1.36 with **severe** anemia
- Severe postpartum hemorrhage (aOR)
  - 1.45 with **mild** anemia
  - 3.53 with **moderate** anemia
  - 15.65 with **severe** anemia
- Maternal shock (aOR)
  - 1.50 for **moderate** anemia,
  - 14.98 for **severe** anemia
- Maternal intensive care unit (ICU) admission
  - 1.08 with **moderate** anemia
  - 2.88 for **severe** anemia

Shi H et al.. JAMA Netw Open. 2022 Feb 1;5(2):e2147046.

201X-XX vX.0

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## Effects of Iron Deficiency on Baby

Increased risk of:
- Fetal death[1]
- Low birth weight[1,2,7]
- Intra-uterine growth restriction[2,7]
- Small for gestational age[7]
- Preterm birth[1,2]
- NICU admission[8]
- Lower cord Hb levels compared with controls[3]
- Poor bonding with mother[4]
- Hearing development[5,6]

1. Harvey T, et al. Womens Health (Lond) 2016;12:95–102;
2. Ganju S. Int J Clin Obstet Gynaecol 2020;4:152–5;
3. Timilsina S, et al. BMC Pregnancy Childbirth 2018;18:70;
4. Murray-Kolb LE, Beard JL. Am J Clin Nutr 2009;89:946S–50S
5. Amin SB, et al. J Pediatr 2010;156:377–81
6. Amin SB, et al. J Pediatr 2013;163:1267–71
7. Yang J et al. Br J Nutr. 2017 Mar;117(6):862-871.
8. Lin L et al. BMC Pregnancy Childbirth. 2018 Apr 23;18(1):111.

Hb, haemoglobin

Image: © Vernon J Louw

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BJOG An International Journal of Obstetrics and Gynaecology

DOI: 10.1111/1471-0528.14263
www.bjog.org

Epidemiology

### The effect of maternal haematocrit on offspring IQ at 4 and 7 years of age: a secondary analysis

D Drassinower,[a] JA Lavery,[b] AM Friedman,[a] HI Levin,[a] SG Običan,[a] CV Ananth[b,c]

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*Correspondence:* D Drassinower, MD, Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University, 622 West 168th Street, New York, NY 10032, USA. Email daphniedrassinower@yahoo.com

*Accepted 13 July 2016. Published Online 17 August 2016.*

n= 35959

Drassinower D, et al. BJOG 2016;123(13):2087-2093.

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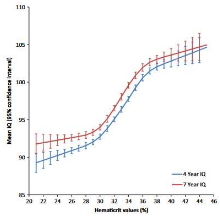


**Figure 1.** Lowest maternal haematocrit and offspring mean IQ at 4 and 7 years of age adjusted for parity, maternal education, marital status, race, tobacco use, alcohol use, drug use, socio-economic index, BMI, chronic hypertension, pre-eclampsia, infant gender, and gestational age at delivery. The association between mean IQ at 4 and 7 years (as a continuous variable) in relation to maternal haematocrit (also as a continuous variable) was analysed by fitting a log-linear regression model with log-link function and a binomial error structure to adjust for possible confounders. Maternal haematocrit values were modelled using restricted cubic splines.

- Mean IQ at 4 and 7 years significantly lower in MODERATE and MILD anaemia patients compared to normal.
- Mean IQ at 4 years:
  - High: 104.5
  - Normal: 100.6
  - Mild: 94.7
  - Moderate: 92.3
- Mean IQ at 7 years:
  - High: 103.2
  - Normal: 99.1
  - Mild: 93.4
  - Moderate: 90.2

$p<0.01$

Drassinower D, et al. BJOG 2016;123(13):2087-2093.

Hct Mild:22-26, Moderate 27-32; Normal 33-38; High 39+

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## Neurocognitive consequences of iron deficiency

Effects seen at **age 4–6 years old** in formerly iron deficient (FID) infants:
- Slower perceptual speed
- Poorer motor proficiency
- Impaired language abilities
- Increased fearfulness, unhappiness and wariness
- Increased fatigue and lower activity
- Increased proximity to the mother during free play, developmental testing and at home
- Behavioural problems

Algarín C, et al. Pediatr Res 2003;53:217–23;
Lozoff B, et al. Nutr Rev 2006;64:S34–91;
Lozoff B, et al. J Nutr 2007;137:683–9
McCarthy EK et al. Am J Clin Nutr. 2021 Apr 6;113(4):1032-1041.

These effects were demonstrated in multiple studies that used standardised educational tests and global tests of infant development in children aged 4–6 years

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## Screening

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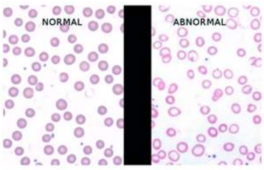
## Classic lab findings – the traditional ("old") approach




- ↓ MCV (<80 fL) = microcytic
- ↓ MCH = hypochromic
- ↓ ferritin
- ↓ BM iron stores

**= ADVANCED IRON DEFICIENCY ANAEMIA**

Image courtesy of S Bhimji under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/)
Warner MJ, Kamran MT. Iron Deficiency Anemia. Available at: https://www.ncbi.nlm.nih.gov/books/NBK448065/figure/article-23767.image.f4/ (accessed October 2021);
Firkin F, Rush B. Aust Prescr 1997;20:74−6
ASH 2021. Available at: https://www.hematology.org/education/patients/anemia/iron-deficiency (accessed October 2021);
Sarma PR. In: Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd edition. Walker HK, Hall WD, Hurst JW, editors. Boston: Butterworths; 1990; Munoz M, et al. Blood Transfus 2017;15:422−37

MCV, mean corpuscular volume; MCH, mean corpuscular haemoglobin; BM, bone marrow

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## Stages of iron deficiency

| Progressive iron depletion and deficiency | | |
|---|---|---|
| **Stage I:**<br>**Iron depletion**<br>**(NAID)** | Serum iron – can be low<br>Serum ferritin – low<br>Iron stores – low or absent | Not anaemic<br>No morphologic changes |
| **Stage II:**<br>**Early iron deficiency** | Serum iron – can be low<br>Serum ferritin – low<br>Iron stores – absent | Normocytic anaemia<br>No morphologic changes |
| **Stage III:**<br>**Advanced iron deficiency** | Serum iron – can be low<br>Serum ferritin – low<br>Iron stores – absent | Increased RDW<br>Microcytic hypochromic anaemia<br>Tissue changes – glossitis, stomatitis, koilonychias, oesophageal webbing |

Table adapted from: Barragán-Ibañez G, et al. Rev Med Hosp Gen Mex 2016;79:88−97 and Soppi ET. Clin Case Rep 2018;6:1082–6

NAID, non-anaemic iron deficiency; RDW, red blood cell distribution width

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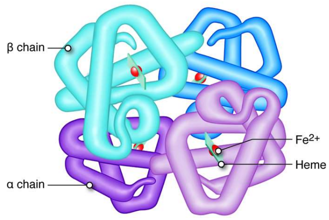
## Diagnostic tests

- Haemoglobin
  - If used in isolation, **<u>many iron deficient patients will be missed</u>**




Auerbach M, et al. J Matern Fetal Neonatal Med 2021;34:1002–5;
Pasricha S-R, et al. Lancet 2021;397:233−48; Firkin F, Rush B. Aust Prescr 1997;20:74−6
Abbaspour N, et al. J Res Med Sci 2014;19:164−74; Muckenthaler MU, et al. Cell 2017;168:344−61; EBM Consult. Available at: https://www.ebmconsult.com/articles/lab-test-ferritin-level (accessed October 2021)

*This number is based on one example however the number could vary depending on setting/region.

32

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## Diagnostic Tests Iron Deficiency

- Serum ferritin
  - Reflects iron stores – best screening test
  - Serious problems with "normal" reference ranges
    - Based on populations where iron deficiency without anaemia was not fully excluded
- Transferrin saturation (test fasting)
  - Reflects iron available for erythropoiesis and other tissues
    - Low if <20%
  - Very useful if serum ferritin is normal or high

Auerbach M, et al. J Matern Fetal Neonatal Med 2021;34:1002–5;
Pasricha S-R, et al. Lancet 2021;397:233−48; Firkin F, Rush B. Aust Prescr 1997;20:74−6
Abbaspour N, et al. J Res Med Sci 2014;19:164−74; Muckenthaler MU, et al. Cell 2017;168:344−61; EBM Consult. Available at: https://www.ebmconsult.com/articles/lab-test-ferritin-level (accessed October 2021)
Muñoz M *et al*. Blood Transfus. 2017 Sep;15(5):422-437.

*This number is based on one example however the number could vary depending on setting/region.

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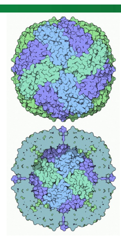
## Clinical application of Serum Ferritin

**Good measure of iron stores in healthy person**

- 1 ng/mL ferritin ~ 10 mg of total iron stores
  - Serum ferritin 30 ng/mL ~ 300 mg of iron stores
  - Serum ferritin 200-250 ng/mL
    - ~ 2000-2500 mg iron stores (normal female)
  - Serum ferritin 350-400 ng/mL
    - ~ 3500-4000 mg iron stores (normal male)
- Adult female:
  - Needs **<u>1000 mg extra</u>** iron for every pregnancy
    - ~ Serum ferritin of 100 ng/mL



Abbaspour N, et al. J Res Med Sci 2014;19:164−74;
Muckenthaler MU, et al. Cell 2017;168:344−61;
EBM Consult. Available at: https://www.ebmconsult.com/articles/lab-test-ferritin-level. (accessed October 2021); Munoz M, et al. Blood Transfus 2017;15:422−37

Image molecular structure: https://pdb101.rcsb.org/motm/35
Image tin: Prof Vernon J Louw Inc ©

34

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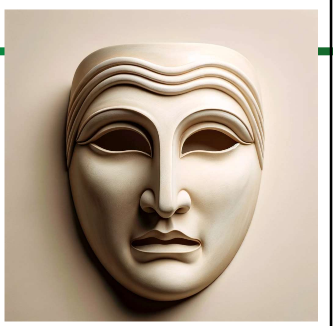
## Clinical relevance of ferritin

- Measure of iron stores
  - If LOW, easy = Iron Deficiency
    - No other known cause for low ferritin
  - If NORMAL or HIGH
    - Iron deficiency may be masked
- Acute phase protein – HIGH in:
  - Infection, Inflammation, Cancer, Obesity, Heart failure; Renal failure
- Liver disease
- Iron overload



EBM Consult. Available at: https://www.ebmconsult.com/articles/lab-test-ferritin-level. (accessed October 2021); Kowdley KV, et al. Hepatology 2012;55:77−85

Image tin: Prof Vernon J Louw Inc ©

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## Serum ferritin and TSAT

- Intracellular iron storage protein which correlates well with body's iron stores in the absence of inflammation
- **Ferritin ≤15 µg/L (Severe iron deficiency)** – sensitivity 57%, specificity 99%
  - **<u>You will miss 43% of cases</u>**

Do not use lab reference ranges for serum ferritin – these are often based on old and incorrect datasets

Adapted from a slide by Dr Perry Loebenberg. Daru J, et al. Am J Clin Nutr 2017;106:1634S–9S;
Pasricha S-R, et al. Lancet 2021;397:233−48; Dignass A, et al. Int J Chron Dis 2018;9394060;
Cappellini MD, et al. J Int Med 2019; doi:10.1111/joim.13004

TSAT, transferrin saturation

36

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## Serum ferritin and TSAT

- Intracellular iron storage protein which correlates well with body's iron stores in the absence of inflammation
- **Ferritin ≤15 µg/L (Severe iron deficiency)** – sensitivity 57%, specificity 99%
  - **You will miss 43% of cases**
- **Ferritin ≤30 µg/L (Iron deficiency)** – sensitivity 92%, specificity 98%
  - **You will miss only 8% of cases**
    - These can be diagnosed if transferrin saturation (%) is added

Do not use lab reference ranges for serum ferritin – these are often based on old and incorrect datasets

Adapted from a slide by Dr Perry Loebenberg. Daru J, et al. Am J Clin Nutr 2017;106:1634S–9S; Pasricha S-R, et al. Lancet 2021;397:233−48; Dignass A, et al. Int J Chron Dis 2018;9394060; Cappellini MD, et al. J Int Med 2019; doi:10.1111/joim.13004
Milman N et al. Dan Med Bull. 1983 Mar;30(2):115-20.

TSAT, transferrin saturation

37

37

## Serum ferritin and TSAT

- Intracellular iron storage protein which correlates well with body's iron stores in the absence of inflammation
- **Ferritin ≤15 µg/L (Severe iron deficiency)** – sensitivity 57%, specificity 99%
  - **You will miss 43% of cases**
- **Ferritin ≤30 µg/L (Iron deficiency)** – sensitivity 92%, specificity 98%
  - **You will miss only 8% of cases**
    - These can be diagnosed if transferrin saturation (%) is added
- **Ferritin 30–100 µg/L and transferrin saturation <20% (Iron deficiency)**
  = Iron deficiency

Do not use lab reference ranges for serum ferritin – these are often based on old and incorrect datasets

Adapted from a slide by Dr Perry Loebenberg. Daru J, et al. Am J Clin Nutr 2017;106:1634S–9S; Pasricha S-R, et al. Lancet 2021;397:233−48; Dignass A, et al. Int J Chron Dis 2018;9394060; Cappellini MD, et al. J Int Med 2019; doi:10.1111/joim.13004

TSAT, transferrin saturation

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Haemoglobin **AND** serum ferritin

Artwork © Vernon Louw
Algorithm based on Dignass A, et al. Int J Chron Dis 2018;9394060 and Cappellini MD, et al. J Int Med 2019; doi:10.1111/joim.13004

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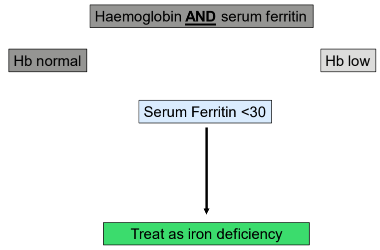


© Vernon Louw
Algorithm based on Dignass A, et al. Int J Chron Dis 2018;9394060 and Cappellini MD, et al. J Int Med 2019; doi:10.1111/joim.13004

Hb, haemoglobin; SF, serum ferritin

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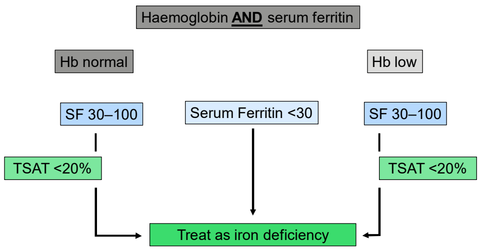


© Vernon Louw
Algorithm based on Dignass A, et al. Int J Chron Dis 2018;9394060 and Cappellini MD, et al. J Int Med 2019; doi:10.1111/joim.13004

Hb, haemoglobin; SF, serum ferritin; TSAT, transferrin saturation

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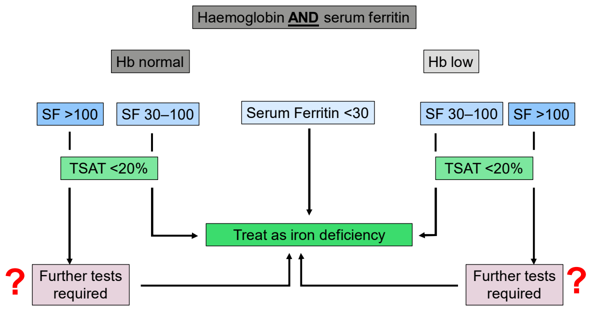


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Algorithm based on Dignass A, et al. Int J Chron Dis 2018;9394060 and Cappellini MD, et al. J Int Med 2019; doi:10.1111/joim.13004

Hb, haemoglobin; LLN, lower limit of normal; SF, serum ferritin; TSAT, transferrin saturation

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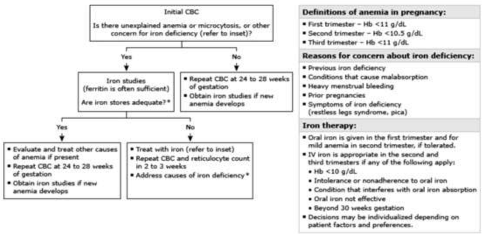
## Minimum Testing Algorithm



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## Screen ALL gravidas at high risk for iron deficiency

- Previous diagnosis of iron deficiency
- Diabetes
- Smoking
- HIV infection
- Inflammatory bowel disease
- Multiparas, especially those with an interpregnancy interval <6 months
- History of abnormal uterine bleeding
- Body mass index (BMI) above or below the normal range
- Vegetarian or vegan diet
- Symptoms such as restless legs syndrome or pica, especially pagophagia (ice craving)
- Decreased access to health care, which may correlate with decreased screening for heavy menstrual bleeding and infections and reduced access to healthy foods

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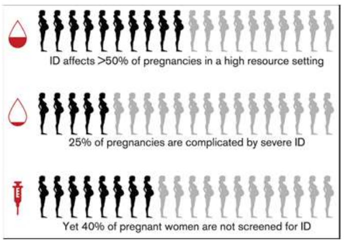
## Prevalence of Ferritin testing

N= 44552




Teichman J et al. Blood Adv. 2021 Nov 23;5(22):4666-4673.

blood advances

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## Ferritin testing in Anaemic Patients

N= 44552

| Hemoglobin level | No. of pregnant patients (% of all patients with a CBC test) | No. of pregnant patients with subsequent ferritin (% of anemia severity category) |
|---|---|---|
| 100-104 g/L | 2014 (5.92) | 447 (22.19) |
| 90-99 g/L | 1046 (3.07) | 365 (34.89) |
| 80-89 g/L | 176 (0.52) | 68 (38.64) |
| 70-79 g/L | 26 (0.08) | 11 (42.31) |
| <70 g/L | 6 (0.02) | 4 (66.67) |

Teichman J et al. Blood Adv. 2021 Nov 23;5(22):4666-4673.

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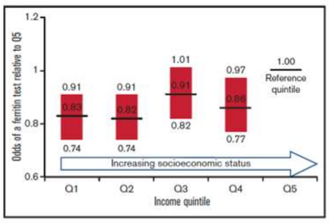
## Odds of Ferritin test and Socio-Economic Status[1]

N= 44552




Women from lower socio-economic status less likely to receive iron supplementation[2] and more likely to receive a blood transfusion[3]

1.Teichman J et al. Blood Adv. 2021 Nov 23;5(22):4666-4673.
2. Cogswell ME et al. J Nutr. 2003 Jun;133(6):1974S-1977S.
3. VanderMeulen H et al. BMC Pregnancy Childbirth. 2020 Apr 6;20(1):196.

blood advances

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FIGO the global voice for women's health

- It is to be recognised that **anaemia is a late sign** of ID.
- Consequently, **Hb testing should not be relied on** to assess iron status.
- Ideally, all reproductive-aged girls and women should be regularly tested for ID starting from menarche and throughout their life, preferably by measuring serum ferritin and/or, where chronic inflammation is known or suspected, transferrin saturation (TSAT).
- When ID or IDA are identified in nonpregnant women and girls of reproductive age, the symptom of HMB should be suspected and, if identified, appropriately investigated and treated.
- **Before planned pregnancy, all reproductive-aged females should have their Hb and iron status assessed** and, if deficient, appropriately treated before attempting conception.

https://www.figo.org/resources/figo-statements/iron-deficiency-and-anaemia-women-and-girls

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## Features suggesting other common causes of anaemia

- MCV < 80 and normal iron studies
  - suggestive of thalassemia
- MCV >100 fL
  - suggestive of B12 or folate deficiency or reticulocytosis due to hemolysis
    - note that macrocytosis can be masked if concomitant iron deficiency
- Other cytopenias such as thrombocytopenia or neutropenia
  - Suggests problem in bone marrow
- Abnormally high white blood cell (WBC) count or platelet count
- Abnormal RBC or WBC morphologies
- Failure of the anemia to correct with iron supplementation
  - note that 50% of patients on oral iron supplements do not respond adequately and may need IV iron

Peripheral blood smear VERY useful in most

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## Prevention

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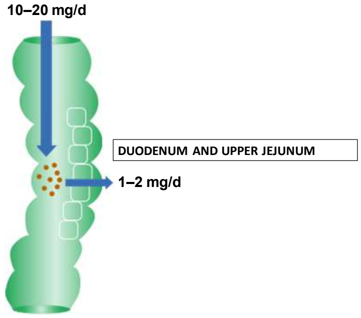
## Absorption

- Western diet: 10–20 mg of iron/day
- Heme iron (meat, poultry, fish)
  – **well absorbed (30%)**
- Inorganic iron (meat, vegetables)
  – **poorly absorbed (<10%)**




Sweeten MK, et al. J Food Qual 1986;9:263–75; Ems T, et al. StatPearls 2021; Abbaspour N, et al. J Res Med Sci 2014;19:164–74

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## Spinach

- 2.6 mg Fe/100 gram
  - 1.7% absorbed
    = 0.044 mg
- Daily needs = 1–2 mg
- Daily spinach intake to meet daily needs = **2.25–4.5 kg**

The chemistry of spinach: the iron myth and 'spinach teeth'. Available at: https://www.compoundchem.com/2018/07/17/spinach/ (accessed April 2022)

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## Factors affecting absorption of iron

**Food**

- Poor absorption when iron is taken with food for most products
  - Cereal (phosphates, tannates, phytates)
  - Calcium-containing foods and beverages (milk) and supplements
  - Eggs (phosvitin in egg yolk)
  - Tea (tannins), coffee (polyphenols, etc.)
    - Does not affect absorption of heme iron
    - Rooibos tea does not inhibit iron absorption
- Take on empty stomach or use formulation that can be taken with food
- Orange juice increases iron absorption

Munoz M, et al. Blood Transfus 2017;15:422−37; Zijp IM, et al. Crit Rev Food Sci Nutr 2000;40:371−98;
Tan V. HealthLine.com. Available at: https://www.healthline.com/nutrition/increase-iron-absorption (accessed April 2022);
Sweeten MK, et al. J Food Qual 1986;9:263−75; Abbaspour N, et al. J Res Med Sci 2014;19:164−74

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14 April 1979 SA MEDIESE TYDSKRIF 631

**Die Effek van Rooibostee op Ysterabsorpsie**

P. B. HESSELING, J. F. KLOPPER, P. D. R. VAN HEERDEN

Iron absorption after 14 days

TABEL II. % YSTERABSORPSIE NA 14 DAE

| Proefpersone | Groep A (rooibostee) | Groep B (gewone tee) | Groep C (water) |
|---|---|---|---|
| 1 | 1,68 | 0,82 | 2,98 |
| 2 | 2,22 | 0,87 | 3,17 |
| 3 | 2,96 | 1,00 | 6,67 |
| 4 | 4,95 | 1,02 | 7,27 |
| 5 | 7,54 | 1,15 | 7,33 |
| 6 | 7,70 | 1,52 | 8,05 |
| 7 | 9,14 | 1,56 | 11,44 |
| 8 | 9,64 | 1,58 | 12,30 |
| 9 | 12,03 | 1,86 | 15,30 |
| 10 | 14,60 | 5,64 | 18,91 |
| Gemiddeld | 7,25 | 1,70 | 9,34 |
| Standaard-afwyking | ± 4,30 | ± 1,43 | ± 5,12 |

Hesseling PB, Klopper JF, van Heerden PD. S Afr Med J. 1979 Apr 14;55(16):631-2. Afrikaans. PMID: 462276.

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## Maternal iron intake

British Journal of Nutrition (2017), 117, 862–871
© The Authors 2017
doi:10.1017/S0007114517000691

Maternal iron intake during pregnancy and birth outcomes: a cross-sectional study in Northwest China

Jiaomei Yang[1], Yue Cheng[2], Leilei Pei[1], Yufen Jiang[1,3], Fangliang Lei[1], Lingxia Zeng[1], Quanli Wang[1], Qiang Li[1], Yijun Kang[1], Yuan Shen[1], Shaonong Dang[1]* and Hong Yan[1,*]


Yang J et al. Br J Nutr. 2017 Mar;117(6):862-871.

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## Maternal iron intake

Shaanxi Province, Northwest China (n=7375)

Highest tertile compared to lowest tertile of maternal **haem iron** intake associated with lower risk of:

- Low birth weight
  - OR 0.68 [95% CI 0.49,0.94]
- Small for gestational age
  - OR 0,76 [95% CI 0.62, 0.94]
- Birth defects
  - OR 0.55 [95% CI 0.32, 0.89]
- Intra-uterine growth retardation
  - OR 0.76 [95% CI 0.59, 0.93]

Yang J et al. Br J Nutr. 2017 Mar;117(6):862-871.

Hb, haemoglobin

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## Maternal iron intake

Odds ratio of Low Birth Weight associated with **iron supplement** use during pregnancy:

- 1st Trimester 0·72 [95 % CI 0·50, 0·95]
- 2nd Trimester 0·67 [95 % CI 0·42, 0·98]
- 3rd Trimester 0·47 [95 % CI 0·24, 0·93]

No associations of total Fe, dietary total Fe or non-haem Fe intake with birth outcomes in this study.

Yang J et al. Br J Nutr. 2017 Mar;117(6):862-871.

Hb, haemoglobin

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## Prevention of Iron Deficiency

- Increase dietary iron intake of iron
- All pregnant women should receive supplemental oral iron
- Start with 27-30 mg/d PO at first prenatal visit
  - usually part of pregnancy multivitamin/iron combination
- If intolerant to prenatal vitamin combination, take prenatal vitamin WITHOUT iron and give 60 mg elemental iron separately on alternate days (Monday, Wednesday, Friday)

Note that only a small proportion of iron in supplements are absorbed, thus the need to take a higher total dose to match increased requirements.

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The Journal of Nutrition
Nutrient Requirements and Optimal Nutrition

See corresponding editorial on page 2184.

### Iron-Deficiency Prevalence and Supplementation Practices Among Pregnant Women: A Secondary Data Analysis From a Clinical Trial in Vancouver, Canada

Kelsey M Cochrane,[1,2] Jennifer A Hutcheon,[2,3] and Crystal D Karakochuk[1,2]

[1]Food Nutrition and Health Faculty of Land and Food Systems University of British Columbia, Vancouver, Canada; [2]BC Children's Hospital Research Institute University of British Columbia, Vancouver, Canada; and [3]Obstetrics and Gynaecology Faculty of Medicine University of British Columbia, Vancouver, Canada

- Despite almost all patients achieving 100% RDA of iron intake with iron supplement (27 mg) and diet, **28% of women were iron-deficient at baseline (8-21 weeks) and 81% at endline (24-38 weeks)**

Cochrane KM *et al.* J Nutr. 2022 Oct 6;152(10):2238-2244.

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Open Access | Research

BMJ Open

# Is selective prenatal iron prophylaxis better than routine prophylaxis: final results of a trial (PROFEG) in Maputo, Mozambique

Elina Hemminki,[1] Bright I Nwaru,[2,3] Graca Salomé,[4] Saara Parkkali,[1] Fatima Abacassamo,[5] Orvalho Augusto,[5] Julie Cliff,[5] Elena Regushevskaya,[1] Martinho Dgedge,[6] Cesar Sousa,[5] Baltazar Chilundo[5]

High Malaria and HIV endemic area – concerns about increased infection risk with iron supplementation

Hemminki E et al. BMJ Open. 2016 Jun 13;6(6):e011280.

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## Trial Design and Rationale

- **Design**: A pragmatic randomised controlled clinical trial.
- **Setting**: 2 health centres in Maputo, Mozambique.
- **Participants**: Pregnant women (≥18 years old; non-high-risk pregnancy) were randomly allocated to routine iron (n=2184) and selective iron (n=2142) groups.
- **Interventions**:
  - **Routine group:** 60 mg ferrous sulfate plus 400 µg folic acid/d
  - **Selective group:** 1 mg of folic acid daily and haemoglobin (Hb) screening at each visit; with low Hb (cut-off 9 g/dL) treatment (120 mg+800 µg of folic acid daily) for a month.
- **Outcome measures:**
  - **Primary outcomes:** preterm birth, low birth weight
  - **Secondary outcomes:** self-reported malaria, labour complications, caesarean section, perinatal death, woman's death.

Hemminki E et al. BMJ Open. 2016 Jun 13;6(6):e011280.

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| Birth outcomes | Original+traced birth data (n=3301) Selective iron (n=1642) | Routine iron (n=1659) | p Value |
|---|---|---|---|
| (% of recruited) | (76.7) | (76.0) | |
| Duration of gestation*, n (%) | | | |
| <37 weeks | 445 (27.1) | 419 (25.3) | |
| ≥37 weeks | 1197 (72.9) | 1240 (74.7) | 0.193 |
| Duration of gestation*, mean (SD) weeks | 38.9 (5.7) | 39.1 (5.8) | 0.302 |
| Birth weight (g), n (%) grams | | | 0.072 |
| <2500 | 181 (11.0) | 189 (11.7) | |
| 2500–2999 | 421 (25.6) | 416 (25.0) | |
| 3000–3499 | 552 (33.6) | 513 (30.9) | |
| 3500–3999 | 183 (11.1) | 198 (11.9) | |
| ≥4000 | 45 (2.7) | 29 (1.7) | |
| No information | 260 (15.8) | 314 (18.8) | |
| Birth weight, mean (SD) grams | 2993.1 (514.2) | 2977.6 (534.3) | 0.462 |
| Mode of delivery, n (%) | | | 0.775 |
| Normal | 1115 (67.9) | 1130 (68.1) | |
| Caesarean section | 66 (4.0) | 74 (4.5) | |
| No information | 461 (28.1) | 455 (27.4) | |
| Perinatal deaths†, n (%) | 39 (2.4) | 40 (2.4) | 0.946 |

*Calculated using dates of conception and birth (or admission if date of birth is missing); see Methods.
†As available in birth records, a likely underestimation.

Hemminki E et al. BMJ Open. 2016 Jun 13;6(6):e011280.

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blood advances

## The Lucky Iron Fish: a simple solution for iron deficiency

Gavin R. Armstrong

Armstrong GR. The Lucky Iron Fish: a simple solution for iron deficiency. Blood Adv. 2017 Jan 24;1(5):330.

blood advances

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# Treatment – Oral or IV?

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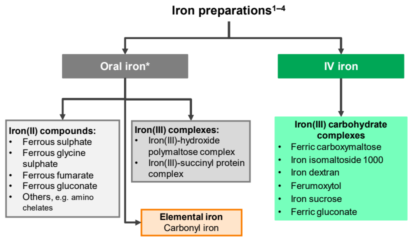
## Treatment of iron deficiency




1. Fehr J, et al. Praxis 2009;98:1445–51; 2. Gordeuk VR, et al. Am J Clin Nutr 1987;46:1029–34; 3. Aapro M, et al. Ann Oncol 2012;23:1954–62; 4. Auerbach M, et al. Hematology Am Soc Hematol Educ Program 2010;2010:338–47

*With/without folic acid
IV, intravenous

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## Treatment with oral iron: benefits and limitations

**Advantages**

- Convenient[1]
- Inexpensive, but frequent dosing can increase cost[1,2]
- In general, oral irons are well tolerated[3]

**Limitations**

- Non-compliance[1]
- Gastrointestinal side effects[1]
- Low intestinal absorption of iron[1] (absorption is lower if patient has inflammation)
- Treatment duration (3–6 months) [1]
- Interactions with food and medicine[1,4]
- Patient's history (ongoing bleeding, bowel issues, infection or coeliac disease)[4]

1. Percy L, et al. Best Pract Res Clin Obstet Gynaecol 2017;40:55–67;
2. Macdougall IC. Curr Med Res Opin 2010;26:473–82;
3. Yasa B, et al. Int J Pediatr 2011;2011:524520;
4. DeLoughery TG. Med Clin N Am 2017;101(2):319–32

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## CHALLENGES <u>ORAL</u> IRON

- pH
  - Iron best absorbed in mildly acidic medium
  - Medications that decrease gastric acidity may impair absorption
    - Antacids, proton pump inhibitor
    - Iron to be take 2 hours BEFORE or 4 hours AFTER antacids
  - Add Vit C 250 mg or 1/5th of a glass of orange juice 30 minutes before breakfast
  - Oral iron completely ineffective in patients who had gastrectomy

Image by Midnightcomm - Own work, CC BY 2.5, https://commons.wikimedia.org/w/index.php?curid=1349743

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## Challenges Oral Iron

- If well absorbed and tolerated, usually restores **<u>HAEMOGLOBIN</u>** within 6-8 weeks, BUT
- Has to be taken for 3-6 months AT LEAST, sometimes up to 12 months to fully replenish **<u>IRON STORES</u>** AFTER normalisation of haemoglobin
- **<u>TOTAL COSTS</u>** may be higher than giving intravenous iron

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THE LANCET
Haematology

ARTICLES | VOLUME 4, ISSUE 11, PE524-E533, NOVEMBER 01, 2017

Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomised controlled trials

Nicole U Stoffel, MSc • Colin I Cercamondi, PhD • Prof Gary Brittenham, MD • Christophe Zeder, MSc • Anneke J Geurts-Moespot, BSc • Prof Dorine W Swinkels, PhD • et al. Show all authors • Show footnotes

Published: October 09, 2017 • DOI: https://doi.org/10.1016/S2352-3026(17)30182-5 • Check for updates

- Every 2nd day (Mon, Wed, Friday)
  - Better response
  - Less side-effects
- Dosing
  - Ferrous sulfate 1-3 tablets every 2nd day
  - Iron polymaltose 200 mg every 2nd day

**Hepcidin increases with oral iron**

Stoffel NU *et al.* Lancet Haematol 2017; 4: 524–33

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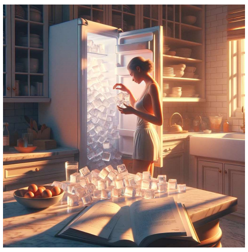
## WHAT CAN YOU EXPECT

- Pagophagia will disappear almost immediately
- General well-being improves within a few days
- Reticulocytosis
  - within 7-10 days if moderate to severe anaemia
  - little or no reticulocytosis if mild anaemia
- Haemoglobin will increase:
  - by about 2 g/dL in 3 weeks



Artwork ©Vernon Louw

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## Time needed to target with **oral** iron

| Starting Hb (g/dL) | Weeks required | Target Hb (g/dL) |
|---|---|---|
| 12 | 1,5 | 13 |
| 11 | 3 | 13 |
| 10 | 4,5 | 13 |
| 9 | 6 | 13 |
| 8 | 7,5 | 13 |
| 7 | 9 | 13 |

- If well absorbed and tolerated, usually restores **HAEMOGLOBIN** within 6-8 weeks, BUT
- Has to be taken for 3-6 months AT LEAST, sometimes up to 12 months to fully replenish **IRON STORES** **<u>AFTER</u> normalisation of haemoglobin**

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# Treatment – Oral or IV?


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## When to switch to IV iron?

- Inadequate response to oral iron
  - Poor absorption (genetic or high hepcidin states)
    - PPIs, Coffee, Tea, Milk, Dietary factors, etc.
    - Inflammation, cancer, heart failure, renal failure
- Oral iron not tolerated
- Inadequate time to wait for effect of oral iron
  - 2nd/3rd trimester pregnancy
  - Preoperative anaemia
- Inability to absorb oral iron
  - Gastrectomy
  - Bariatric surgery
  - Inflammatory bowel disease
- With EPO in renal failure, etc.


Image ©Vernon Louw

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Journal of Perinatology (2019) 39:519–532
https://doi.org/10.1038/s41372-019-0320-2

REVIEW ARTICLE

### Intravenous compared with oral iron for the treatment of iron-deficiency anemia in pregnancy: a systematic review and meta-analysis

Adam K. Lewkowitz[1] · Anjlie Gupta[2] · Laura Simon[3] · Bethany A. Sabol[1] · Carrie Stoll[2] · Emily Cooke[4] · Roxanne A. Rampersad[1] · Methodius G. Tuuli[5]

Received: 10 September 2018 / Revised: 14 December 2018 / Accepted: 3 January 2019 / Published online: 28 January 2019


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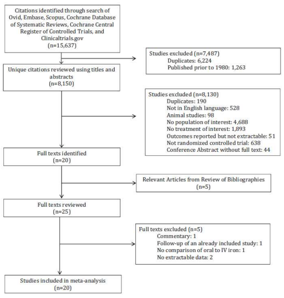


Only RCTs included

Lewkowitz AK et al. Journal of Perinatology 2019 (39):519-532

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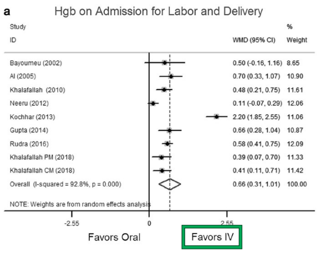
## Haemoglobin on Admission for Labor and Delivery




Lewkowitz AK et al. Journal of Perinatology 2019 (39):519-532

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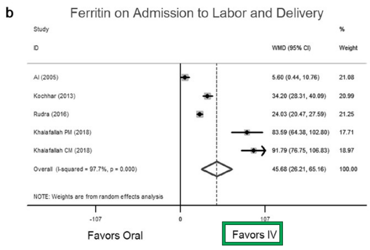
## Ferritin on Admission to Labour and Delivery




Lewkowitz AK et al. Journal of Perinatology 2019 (39):519-532

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## Conclusion

- No severe adverse reactions
  - Overall mild adverse reactions lower with IV iron vs oral iron
- Effect size greatest in:
  - studies from developing countries
  - higher quality studies
  - Studies with pretreatment Hb <= 9 g/dL
- Statistically significant improvement in mean Hb with IV iron that extended 2-6 weeks after treatment
  - Different from previous meta-analyses, as only RCTs and no observational studies included
- Higher neonatal birthweight and neonatal ferritin in IV iron group

Lewkowitz AK et al. Journal of Perinatology 2019 (39):519-532

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Treatment of Iron Deficiency Anemia in Pregnancy with Intravenous versus Oral Iron: Systematic Review and Meta-Analysis

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Am J Perinatol 2019;36:366–376.

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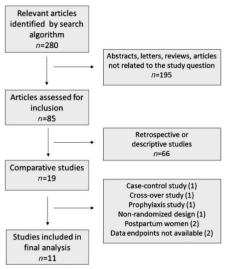
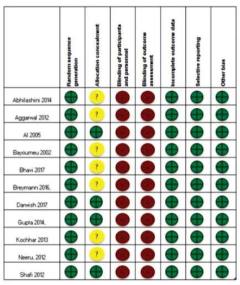



**Fig. 1** Search strategy with flow diagram for study inclusion in meta-analysis.




Govindappagari S et al. Am J Perinatol 2019:36:366-376

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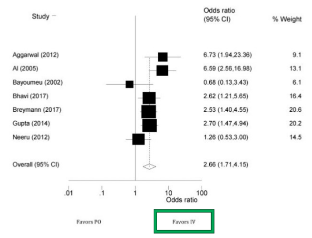
## Achieving target Hb (11-12 g/dL) within 4 weeks

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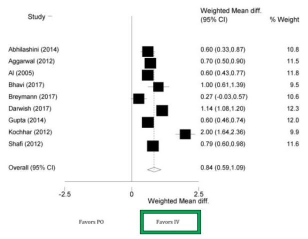
## Difference in Hb increase after 4 weeks

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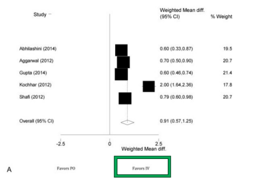
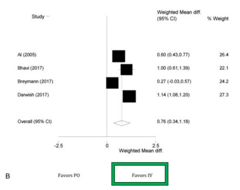
## Difference in Hb increase after 4 weeks depending on starting Hb




Starting Hb < 8 g/dL




Starting Hb > 8 g/dL

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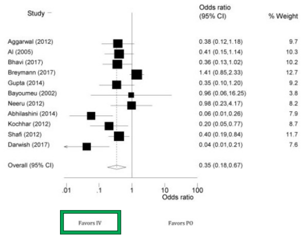
## Adverse events IV vs oral iron




Govindappagari S et al. Am J Perinatol 2019:36:366-376

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### Conclusion

We conclude that IV iron is more efficacious, acts more quickly, and has fewer side effects, when compared with oral iron for treatment of iron deficiency anemia in pregnancy. Most notably, more women treated with IV iron achieve target hemoglobin levels within 4 weeks of treatment. IV iron should be offered to pregnant women with moderate to severe anemia, especially in later gestational age, close to delivery. Furthermore, IV iron should be strongly considered for pregnant women with persistent iron-deficiency anemia near delivery, particularly those at high risk for postpartum hemorrhage or objections to blood products.

Govindappagari S et al. Am J Perinatol 2019:36:366-376

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**HHS Public Access**

Author manuscript

*Am J Obstet Gynecol.* Author manuscript; available in PMC 2020 July 01.

Published in final edited form as:

*Am J Obstet Gynecol.* 2019 July ; 221(1): 19–29.e3. doi:10.1016/j.ajog.2018.12.016.

**Oral versus intravenous iron therapy for postpartum anemia: A systematic review and meta-analysis**

**P Sultan[1], S Bampoe[1], R Shah[2], N Guo[3], J Estes[4], C. Stave[5], L Goodnough[6], S Halpern[7], AJ Butwick[8]**

Sultan P et al. Am J Obstet Gynecol. 2019 Jul;221(1):19-29.e3.

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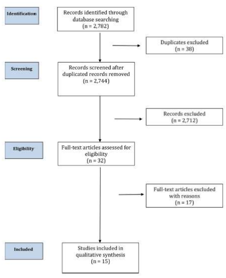


**Figure 1. Prisma flowchart for studies identified and excluded (included studies18–22, 32–41)**

Sultan P et al. Am J Obstet Gynecol. 2019 Jul;221(1):19-29.e3.

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| | Intravenous | | | Oral | | | | Mean Difference |
|---|---|---|---|---|---|---|---|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI |
| Bhandal 2006 | 11.5 | 1.3 | 22 | 11.2 | 1.2 | 21 | 19.0% | 0.30 [-0.45, 1.05] |
| Damineni 2016 | 11.9 | 0.87 | 45 | 11.2 | 0.74 | 45 | 30.8% | 0.70 [0.37, 1.03] |
| El Khouly 2017 | 11.5 | 0.74 | 162 | 10.2 | 0.6 | 54 | 34.3% | 1.30 [1.10, 1.50] |
| Rathod 2015 | 11.4 | 1.2 | 22 | 10.4 | 1.4 | 14 | 15.9% | 1.00 [0.11, 1.89] |
| **Total (95% CI)** | | | **251** | | | **134** | **100.0%** | **0.88 [0.41, 1.35]** |

Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 13.95$, df = 3 (P = 0.003); $I^2 = 78\%$

Test for overall effect: Z = 3.65 (P = 0.0003)

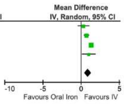


**Figure 3. Forest plot for the mean difference in hemoglobin at 6 weeks postpartum**

CI, confidence intervals; IV, inverse variance; random, random effects model; SD, standard deviation

**Condensation:**

Women with postpartum anemia treated with intravenous iron have postpartum week 6 hemoglobin concentrations nearly 1 g/dL higher than those treated with oral iron.

Sultan P et al. Am J Obstet Gynecol. 2019 Jul;221(1):19-29.e3.

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nature portfolio

www.nature.com/scientificreports

**scientific** reports

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## Clinical outcome post treatment of anemia in pregnancy with intravenous versus oral iron therapy: a systematic review and meta-analysis

Anuj Kumar Pandey[1,2,3], Diksha Gautam[1,3], Himanshu Tolani[1] & Sutapa Bandyopadhyay Neogi[1]

Pandey AK, et al. Sci Rep. 2024 Jan 2;14(1):179.

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## PRISMA Flow Diagram of Studies

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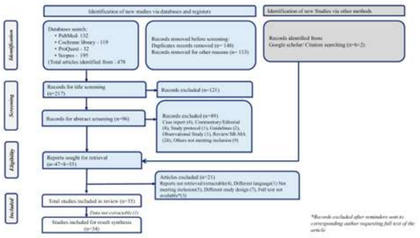

Pandey AK, et al. Sci Rep. 2024 Jan 2;14(1):179.

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## Summary Risk of Bias in Studies

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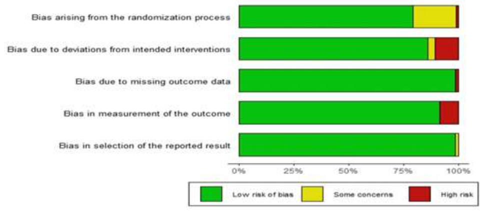


Pandey AK, et al. Sci Rep. 2024 Jan 2;14(1):179.

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## Pooled Maternal Outcomes

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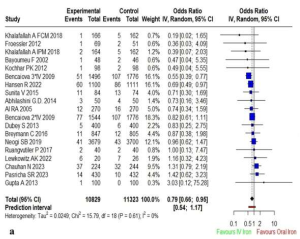

**Maternal outcomes**

- Need for blood transfusion
- Post-partum haemorrhage
- Caesarian section and assisted delivery
- Hypertensive disorders

Pandey AK, et al. Sci Rep. 2024 Jan 2;14(1):179.

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## Neonatal Outcomes

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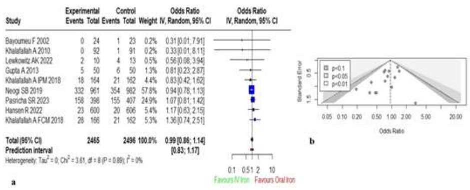

Pandey AK, et al. Sci Rep. 2024 Jan 2;14(1):179.

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## Adverse Events

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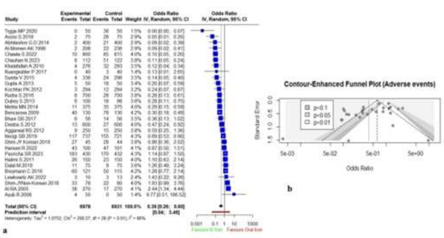

Pandey AK, et al. Sci Rep. 2024 Jan 2;14(1):179.

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## Change in Mean Haemoglobin from Baseline

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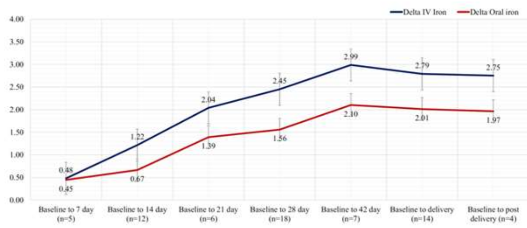


Pandey AK, et al. Sci Rep. 2024 Jan 2;14(1):179.

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## Avoid the following IV iron preparations in pregnancy

- Formulations that contain benzyl alcohol as a preservative due to potential risk to foetus[1]
  - E.g, the ferric gluconate preparation (Ferrlecit), especially since multiple vials are required;
- Iron sucrose[2]
  - Can be used if no alternative
  - Multiple visits required and less effective than other infusions
  - More adverse events compared to ferric carboxymaltose

1. Hiller JL et al. Pediatrics. 1986 Apr;77(4):500-6.
2. Srimathi G et al. Indian J Med Res. 2024 Jan 1;159(1):62-70.

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## Treatment of iron deficiency in pregnancy

IV Iron not used in first trimester due to lack of safety data

| | | | |
|---|---|---|---|
| 1st trimester | Iron deficiency only | Oral iron | Sensitive |
| | Iron deficiency anaemia (Hb <11 g/dL) | Oral iron | Sensitive |
| 2nd trimester | Iron deficiency only | Oral iron | Sensitive |
| | Iron deficiency anaemia (Hb <10.5 g/dL) | IV iron | Sensitive |
| 3rd trimester | Iron deficiency only | IV iron | Critical |
| | Iron deficiency anaemia (Hb <11 g/dL) | IV iron | Critical |
| 6–24 months of infancy | Iron deficiency | Oral iron | Critical |

If severe anaemia, poor response to oral iron or intolerance, treat with intravenous iron

IV iron treatment in pregnancy should be confined to the 2nd and 3rd trimester if the benefit is judged to outweigh the potential risk for both the mother and the foetus. A careful risk/benefit evaluation is required before use during pregnancy, and IV iron should not be used during pregnancy unless clearly necessary.
Hb, haemoglobin; IV, intravenous

Breymann C, et al. J Perinat Med 2011;39:113–21;
Auerbach M. Reprod Health 2018;15 (Suppl 1):96;
Ferinject SmPC, February 2022

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## Summary

- Iron deficiency is the most common cause of anaemia
- Iron deficiency can cause problems independent of anaemia
- Expectations with oral iron supplements should be managed
  - Efficacy
  - Adverse events
- IV iron good alternative for oral iron if needed

**Anaemia in pregnancy one of the best examples of prevention being better than cure!**

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## Questions



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