Preventing & Treating Iron Deficiency Anaemia in Pregnant Women

Are we doing our best ?

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Global Burden of Diseases 2010 Study

- Anemia is a highly common and debilitating medical condition
- It is estimated that one third of the world's population suffers from anemia
- The most common cause of anemia is iron deficiency
- Lack of awareness about iron deficiency anemia leads to under-diagnosis and under-treatment

Kasselbaum NJ, et al. Blood 2014; 123:615-24

Children and women have the highest burden

- The global burden of anemia **is higher than** other common disorders such as major depression or chronic respiratory diseases

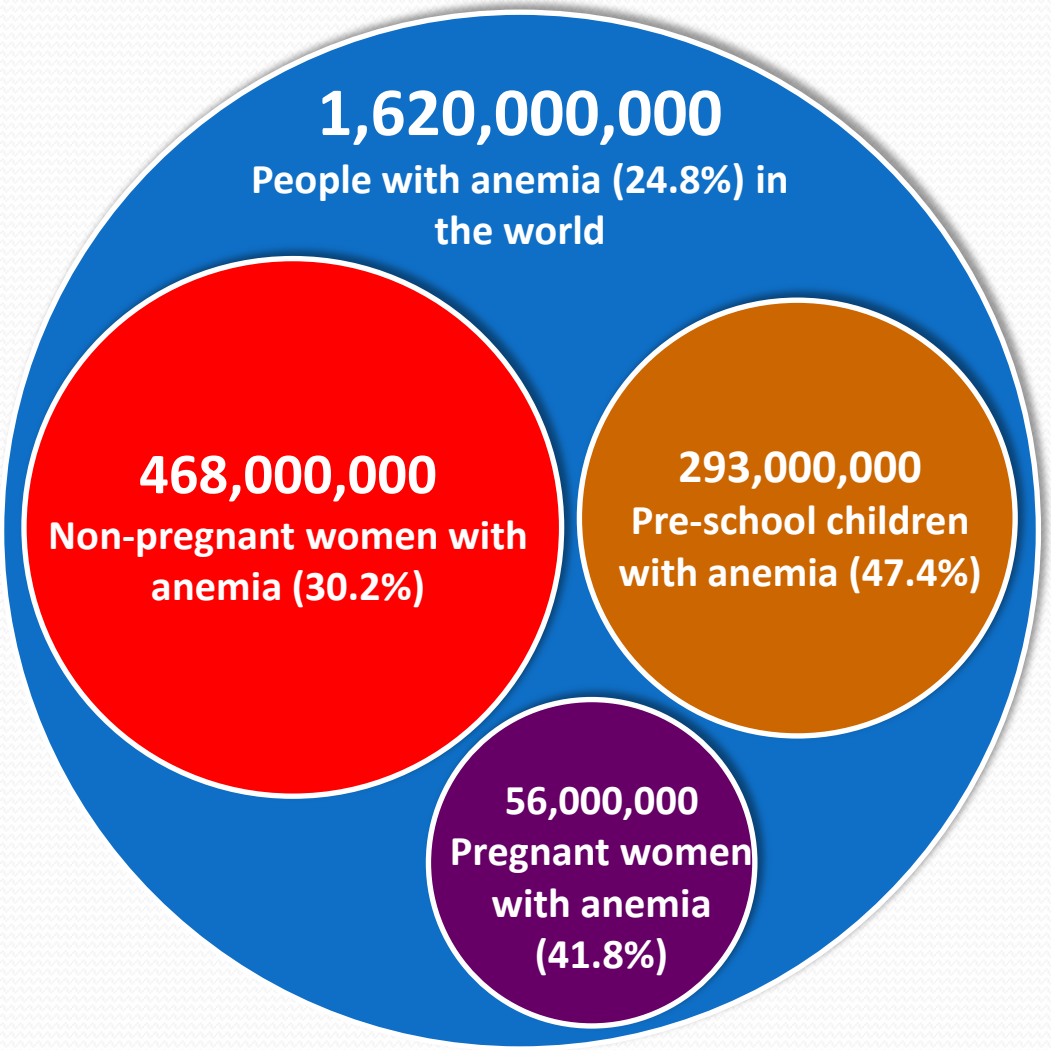
- The most vulnerable age group is children under age 5 years.

Kasselbaum NJ, et al. Blood 2014; 123:615-24

Worldwide prevalence of anemia

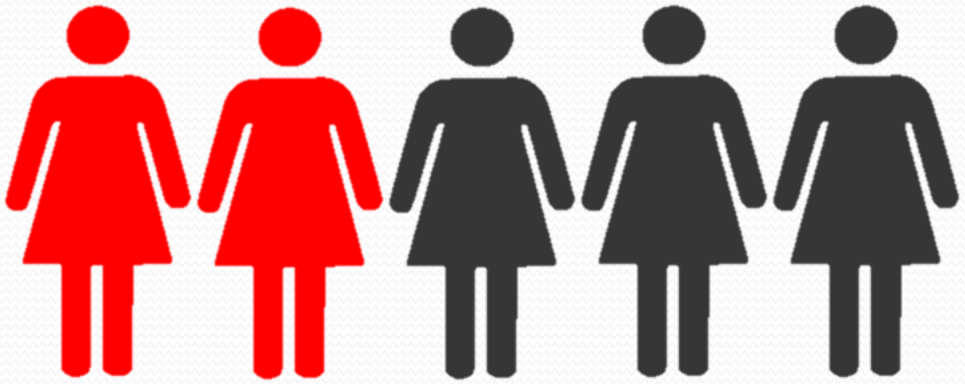
WHO Vitamin and Mineral Nutrition Information System, 1993-2005

Iron deficiency is the most contributing factor for anaemia



World Health Organization and Centers for Disease Control and Prevention. 2008

Iron Deficiency (ID) is underdiagnosed



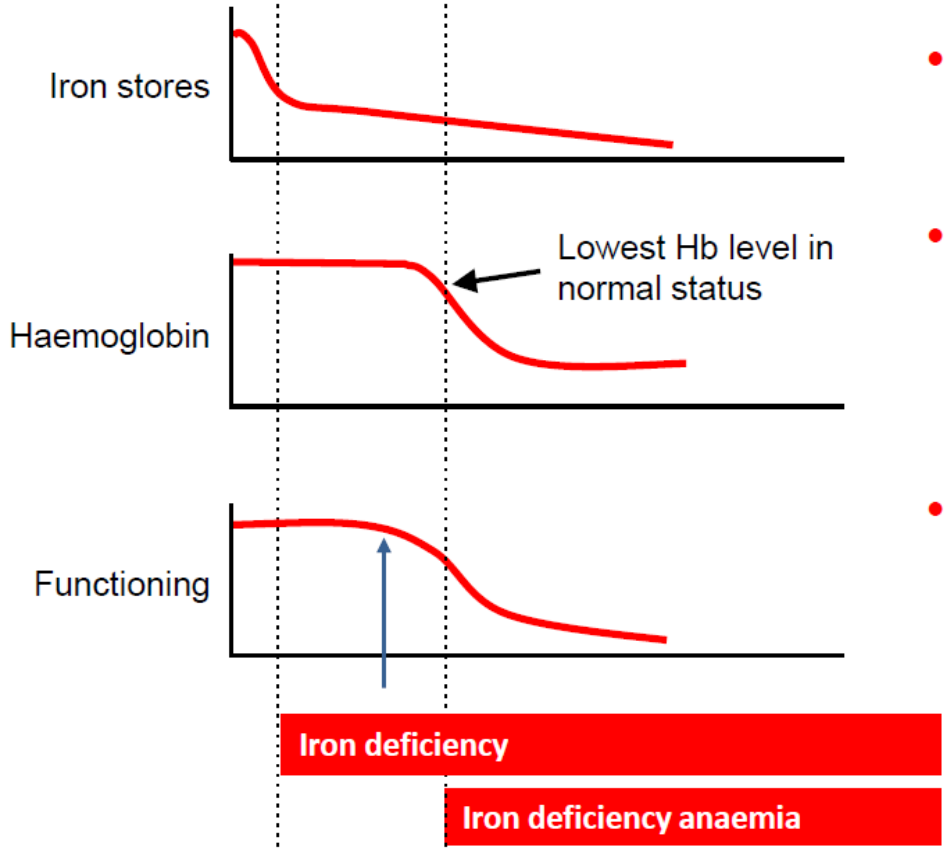
2 in 5

healthy women have **iron deficiency***

1/3 with anaemia**

**Anaemia : Hb < 12g/dL ; *iron deficiency : ferritin <30ng/mL
Interim result from the survey conducted by SATA CommHealth Singapore of 778 women

From Iron Deficiency to Iron Defiency Anaemia



- Iron stores decline well before any reduction in Hb
- Iron-deficiency erythropoiesis occurs once:
  - ↓ ferritin
  - ↓ TSAT
- Declines in immunological, exercise and neural functioning start before ↓Hb

Adapted from Beard JL. *J Nutr* 2001;131(2S-2):568S–79S

Sign and symptoms of Iron deficiency

Brittle & Spoon-Shaped Nails

Shortness of Breath

Cognitive impairment

Cold Hand & Feet

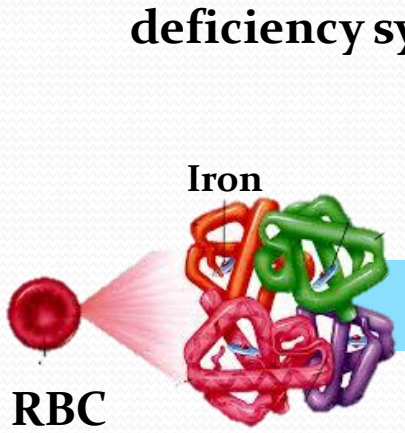
Fatigue

Hair Loss

Iron works in cellular level

carrying oxygen (Hb) and utilizing oxygen (cell)

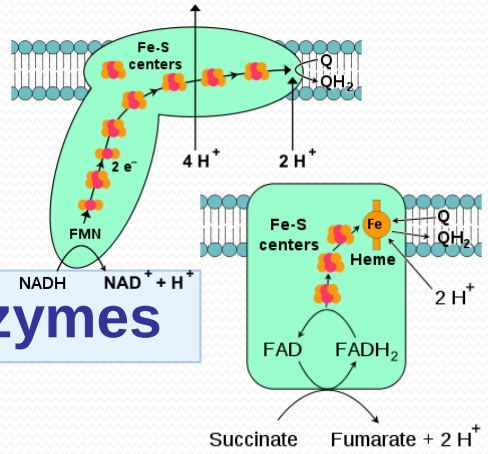
- **Iron essential for respiratory chain processes**
- **Low iron levels, even without anaemia, increases fatigue and other iron deficiency symptoms**



Iron deficiency

anaemia

↓Aerobic enzymes



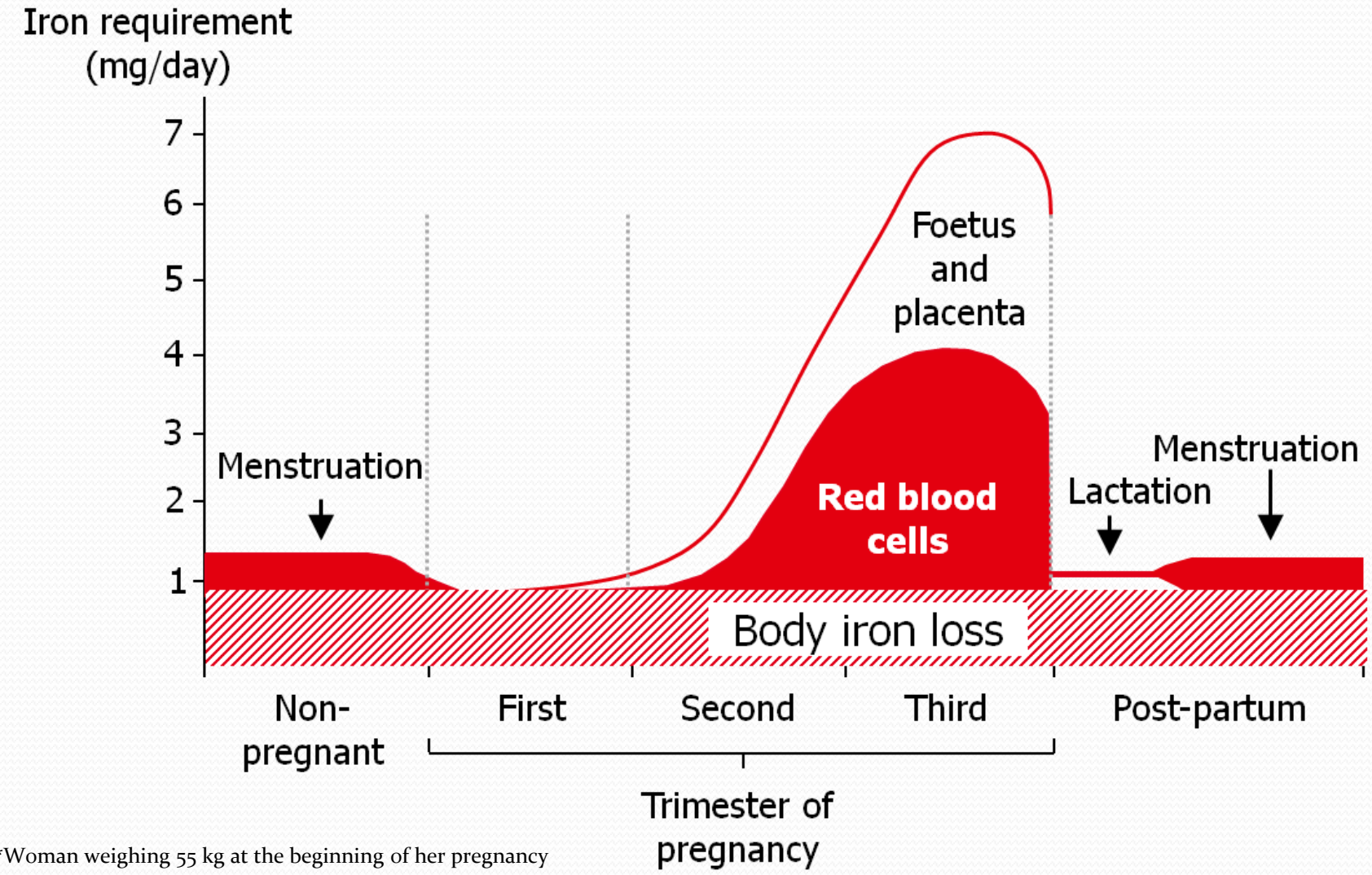
↓O_2 delivery

↓O_2 utilization

reduced exercise capacity

Haas JD & Brownlie T. J Nutr 2001;131(2 suppl 2):676S–690S; Dallman PR. J Intern Med 1989;226:367–372; Willis WT & Dallman PR. Am J Physiol 1989;257:C1080–1085; Figure adapted from: Anker et al. EJHF 2009

Iron deficiency may occur throughout women's health cycle



*Woman weighing 55 kg at the beginning of her pregnancy

Bothwell TH. *Am J Clin Nutr* 2000;72:257S–64S

Consequences of IDA for pregnant mother

Cognitive function[1]

- Lower cognitive performance

Cardiac function[2]

- Increased risk of cardiac failure in severe anaemia

Immune function[3]

- Lowered resistance to infection
- Impaired wound healing

Blood transfusions[4]

- Increased risk

Milk production[4]

- Reduced milk production (insufficient milk syndrome)
- Shorter lactation periods
- Increased supplementary feeding

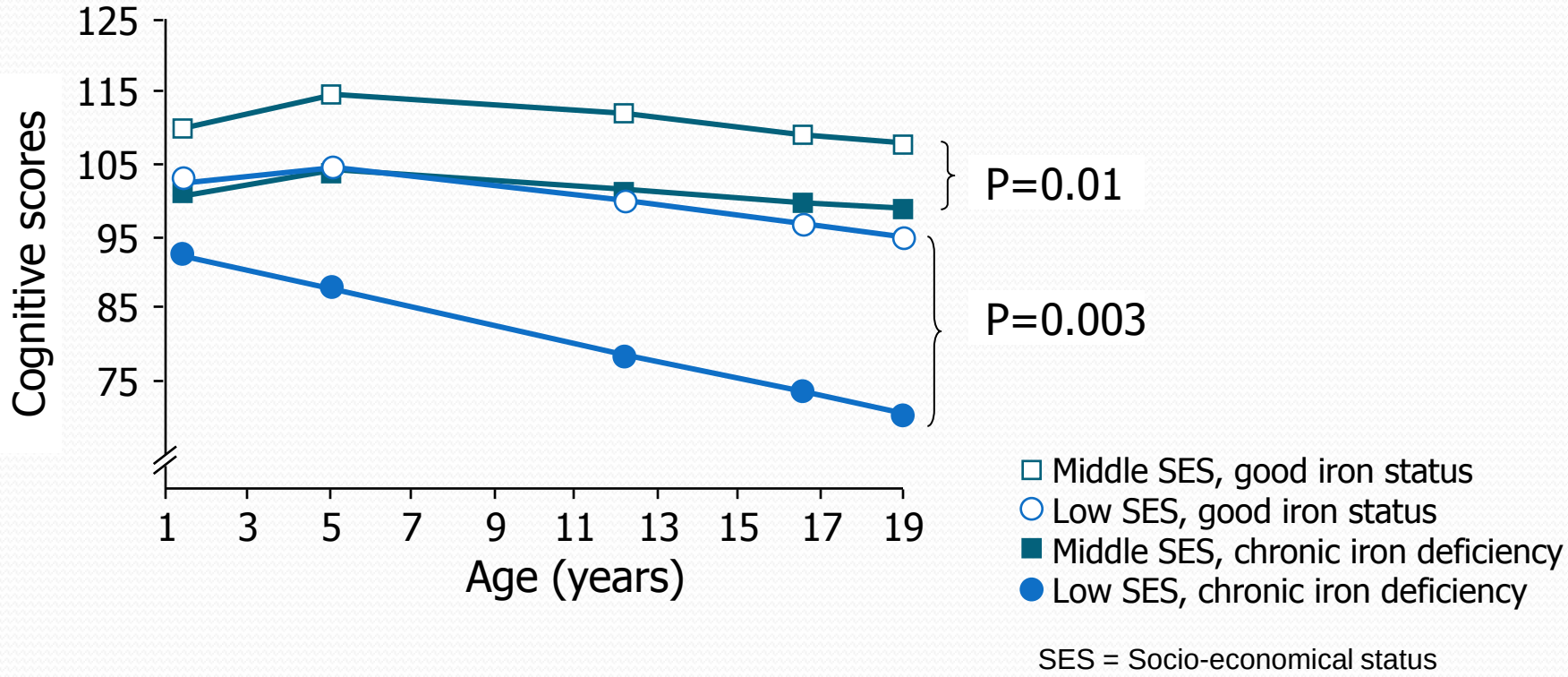
Psychological[5]

- Feeling of not enjoying motherhood
- Apathy
- Emotional instability
- Stress
- Irritability
- Altered thyroid hormone metabolism

1. Beard JL et al. *J Nutr* 2005;135:267–272; 2. Reveiz L et al. Cochrane Database of Systematic Reviews 2007, Issue 2. Art No: CD003094. DOI: 10.1002/14651858.CD003094.pub2; 3. Harrison KA. *Clin Obstet Gynaecol* 1982;9:445–777; 4. Breymann C & Huch R. Anaemia in pregnancy and the puerperium. 2008 UNI-MED; 5. Corwin EJ et al. *J Nutr* 2003;133:4139–4142

Impact on Cognitive Performance

Cognitive scores to age 19 in 185 individuals with or without chronic iron deficiency in infancy



SES = Socio-economical status

Lozoff B et al. *Arch Pediatr Adolesc Med* 2006;160:1108–1113

Diagnosis of iron deficiency

Iron Panel (serum):
- Ferritin
- Iron
- Total iron binding capacity (TIBC)
- Transferrin saturation (TSAT) or Iron saturation*

$$^{*}\,TSAT = \frac{serum\ iron}{serum\ TIBC} \times 100\%$$

Parameter	Description[1]	ID	IDA
Haemoglobin (Hb) (g/dL)	Marker of erythrocyte iron	–	(WHO) Female <12.0 g/dl Male <13 g/dl
Serum ferritin (SF) (ng/mL)	Marker of iron stores; highly sensitive	**<30[5]** **<100 (Inflammation)**	
Transferrin saturation (TSAT) (%)	Measure of mobilised (functional) iron available for red cell production; highly specific	**<20[2]**	

1. Breymann C & Huch R. *UNI-MED* 2008:13–96;
2. Guyatt GH *et al. Journal of General Internal Medicine* 1992;7:145–153;
3. Skikne BS *Am J Hematol* 2002;76:213-218(Table I); 4. Bothwell TH. *Am J Clin Nutr* 2000;72:257S–264S;
5. Pavord et al. British Journal of Haematology, 2012, 156, 588–600

↑ above normal value
ID= Iron deficiency
IDA= Iron deficiency anaemia

WHO to supplement?

Population	Indication for supplementation	Dosage schedule	Duration
Pregnant women	All women	60 mg iron/day*	6 months in pregnancy
Postpartum women	Areas where anemia prevalence is ≥40%	60 mg iron/day	3 months postpartum
Children 6-24 months of age	All children	12.5 mg iron/day	6-12 months of age#
	Areas where anemia prevalence is ≥40%	12.5 mg iron/day	6-24 months of age#

*) Daily oral iron + folic acid supplementation of 400 µg is recommended by the WHO to reduce the risk of low birth weight, maternal anaemia and ID

*) if 6 month duration cannot be achieved in pregnancy, continue to supplement during postpartum or increase the dose to 120mg in pregnanc

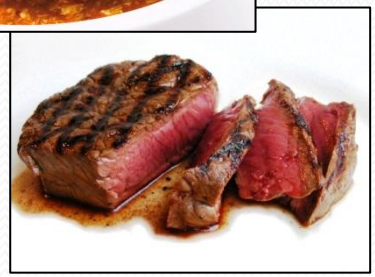
#) 2-24 months if low birth weight (<2500 g)

World Health Organization (2001). WHO Guidelines for the Use of Iron Supplements to Prevent and Treat Iron Deficiency Anemia WHO/NHD/01.3.
http://www.who.int/nutrition/publications/micronutrients/guidelines_for_Iron_supplementation.pdf

Dietary Advice for Iron-rich Food

Haem-iron containing food

Iron from meat, poultry and fish ('heme iron') is **2-3 times more absorbable** than non-heme iron



Vitamin C **enhances non-haem iron absorption**

✓

Iron absorption

✖

Inhibitors of non-haem iron absorption:

Tannins, Caffeine (Tea, coffee)

Calcium (dairy products)

Polyphenols (certain vegetables)

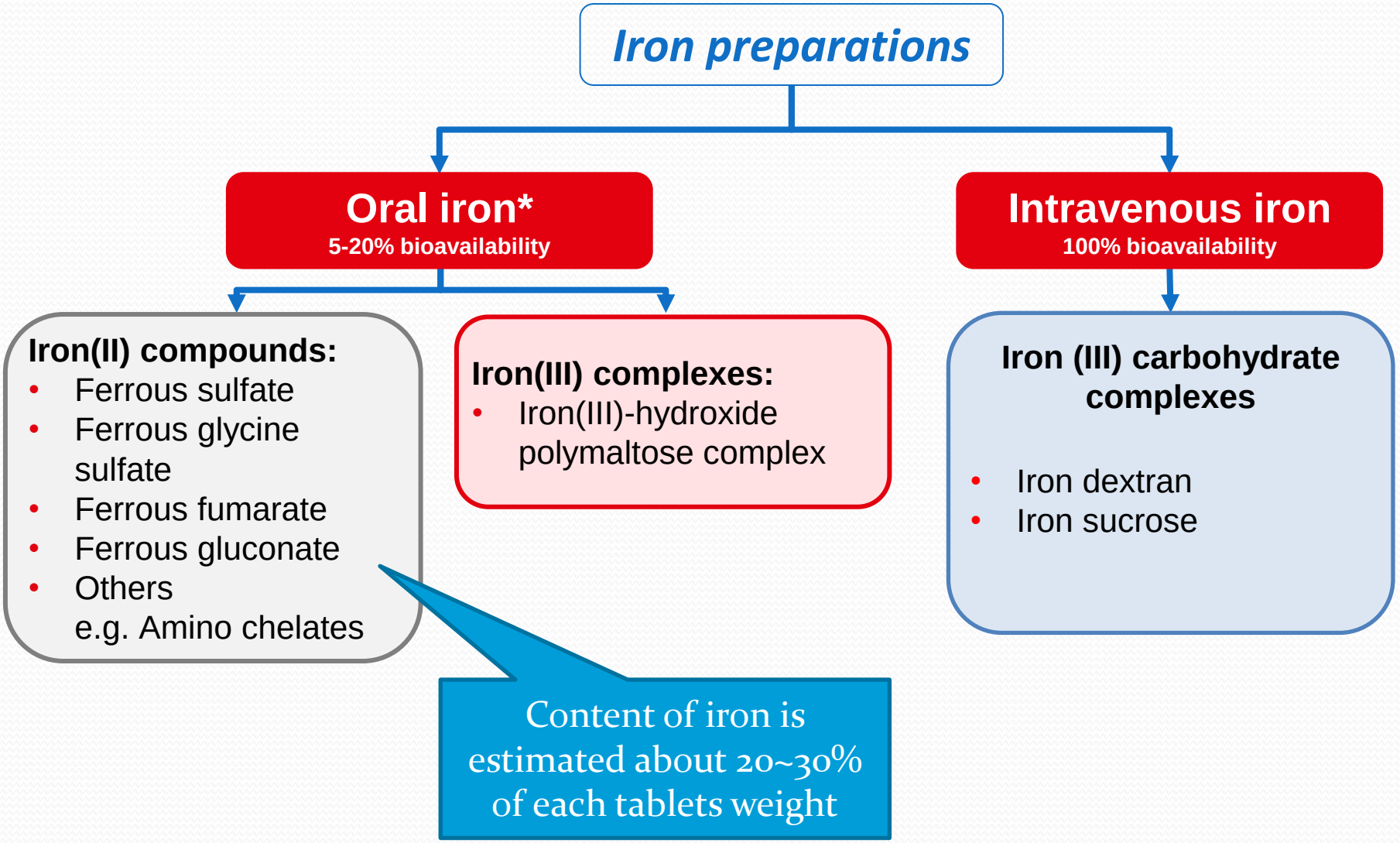
Non haem-iron containing food

Plant-based food Absorption influenced by the presence of enhancing and inhibiting factors

Health Promotion Board Singapore. Accessed from http://www.hpb.gov.sg/HOPPortal/health-article/2652 on 5-Nov-2015

Centers for Disease Control and Prevention.MMWR Recomm Rep 1998;47(RR-3):1–29

Iron replacement therapy



Fehr J *et al. Praxis* 2009;98:1445–1451; Gordeuk VR *et al. Am J Clin Nutr* 1987;46:1029–1034; Aapro M *et al. Ann Oncol* 2012;23:1954–1962

Oral Iron Therapy Options

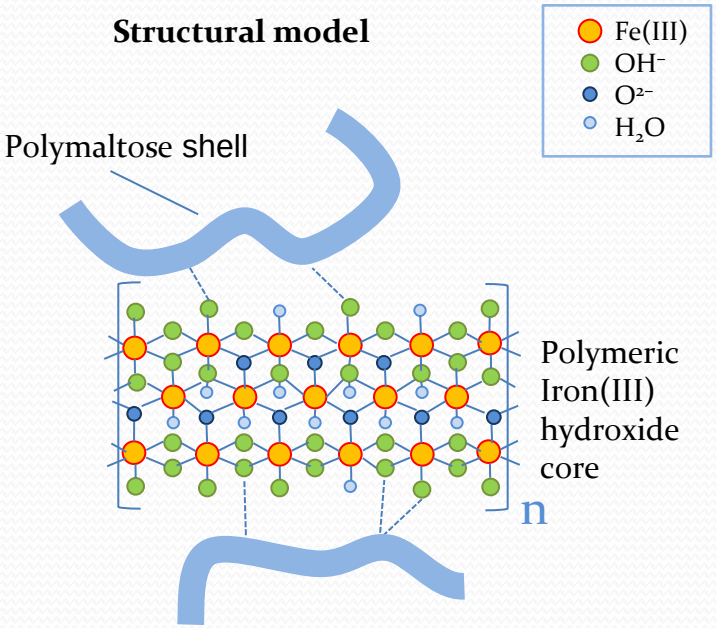
Iron Product	Form	Content (mg)	Elemental Iron (mg)	Absorbed Iron (mg)	
Maltofer Fol (IPC)	Chewable Tablet	-	100	10-15%	~12.5
Maltofer (IPC)	Syrup	10mg/ml	10mg/ml		~0.1
	Drops	50mg/ml	50mg/ml		~6.3
Ferrous fumarate (FF)	Tablet	200	~65		~7.8
Iberet Folic (FS)	Tablet	525	~105		~12.7
Sangobion (FG)	Tablet	250	~30		~7.3
Obimin (FF)	Tablet	90	~30		~3.6
Ferric Ammonium Citrate	Mixture	80mg/ml	~16mg/ml		~1.6

1. Alleyne et al. Am J Med. 2008 November ; 121(11): 943–948.
2. Beguin et al. Expert Opin. Pharmacother. (2014) 15(14):2087-2103
3. MIMS Malaysia 2014
4. Ferrum Hausmann® Summary of Product Characteristic

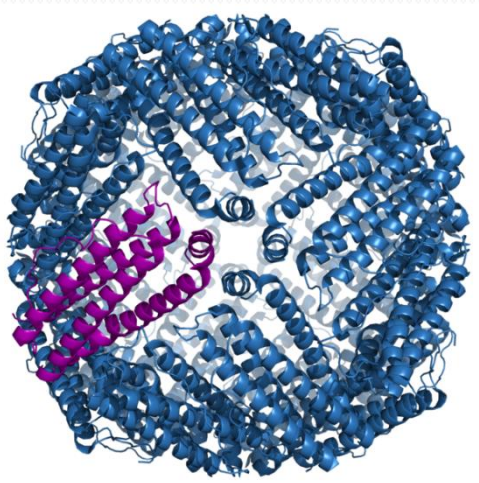
Maltofer®

Iron(III)-hydroxide polymaltose complex (IPC)

The structure of IPC's iron core resembles that of the iron storage protein ferritin



IPC has an iron(III)-hydroxide core with a polymaltose shell



Ferritin has an iron(III)-hydroxide-phosphate core and a protein shell

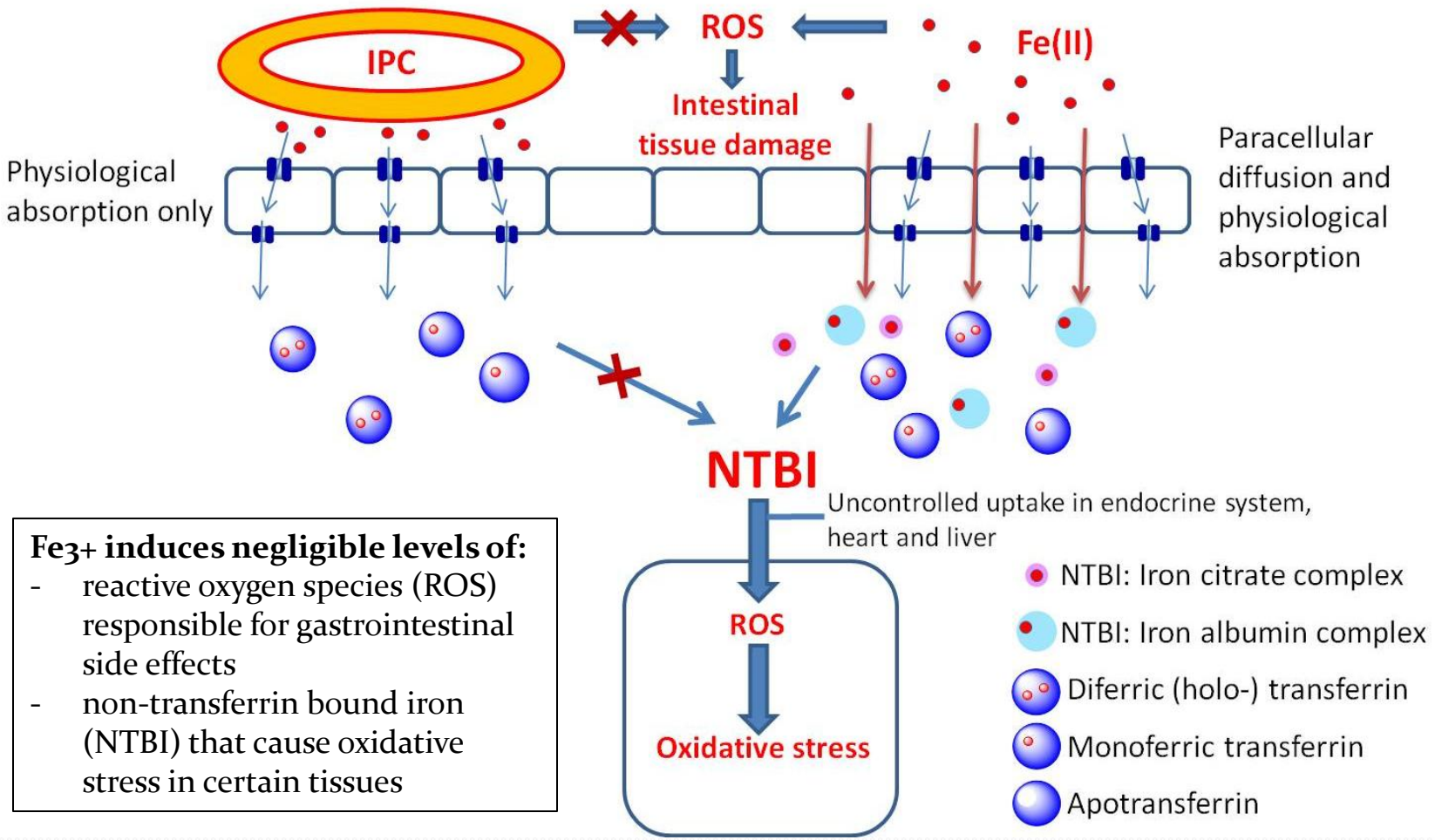
Geisser P. *Arzneimittelforschung* 2007;57:439–452

Harrison PM *J of Inorganic Biochemistry* 1986;27:287-293

Knowing the Differences

Ferrous salt (Fe2+) vs Ferric Complex (Fe3+)

The controlled iron uptake from Maltofer® results in **good tolerability** and **low risk for intoxication** or iron overload in cases of acute or chronic overdose



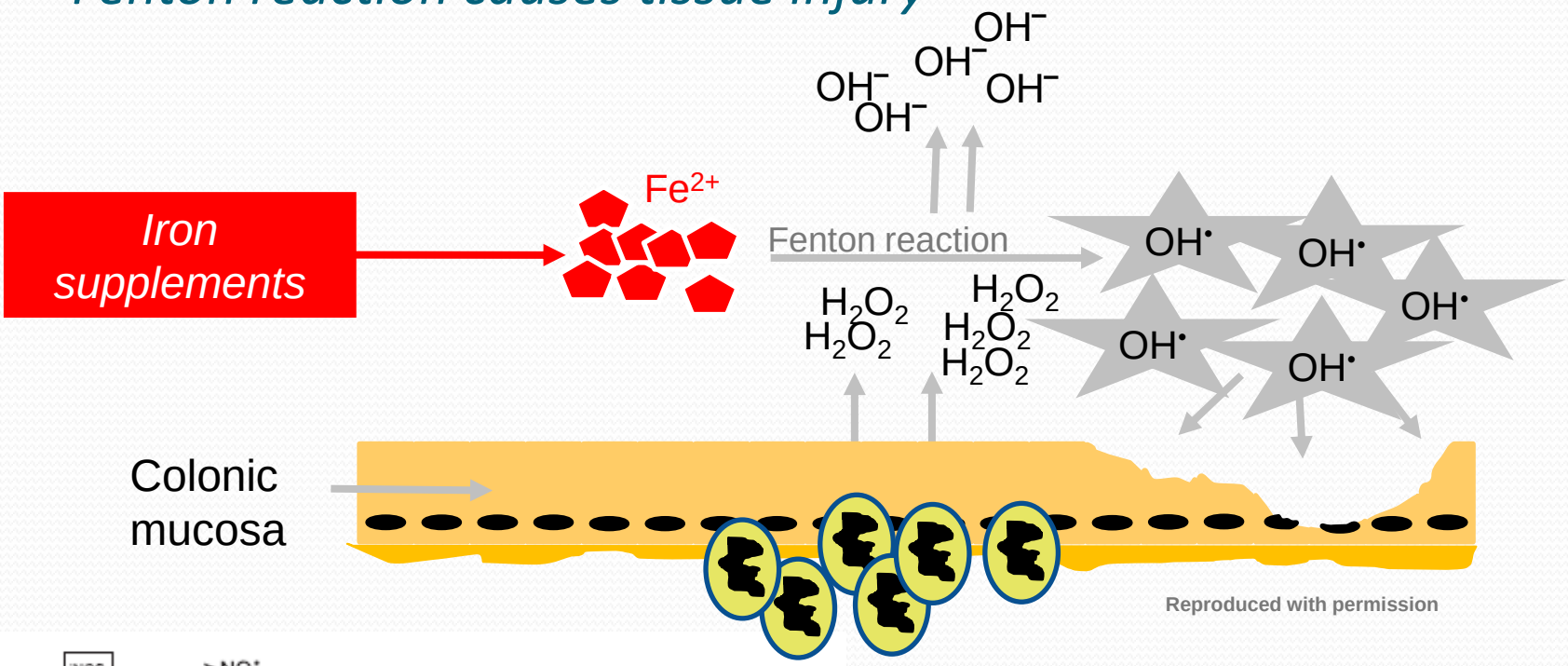
Fe3+ induces negligible levels of:

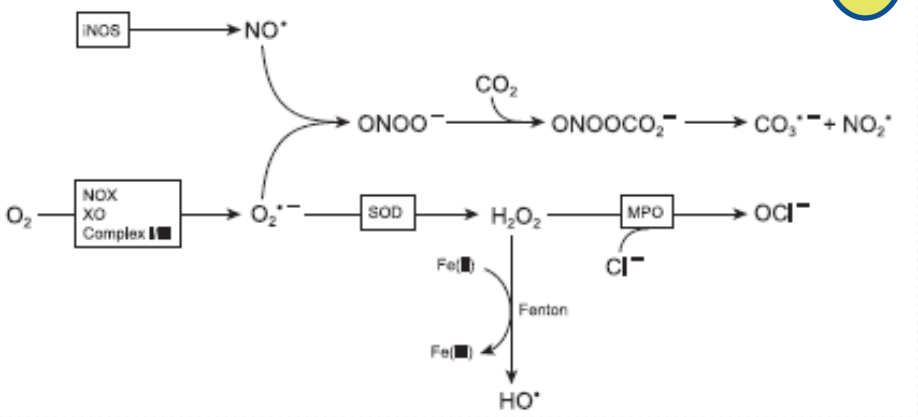
- reactive oxygen species (ROS) responsible for gastrointestinal side effects
- non-transferrin bound iron (NTBI) that cause oxidative stress in certain tissues

Modified from Geisser P & Burckhardt S. *Pharmaceutics* 2011;3:12–33

Ferrous (Fe2+) iron and gastrointestinal events

Fenton reaction causes tissue injury



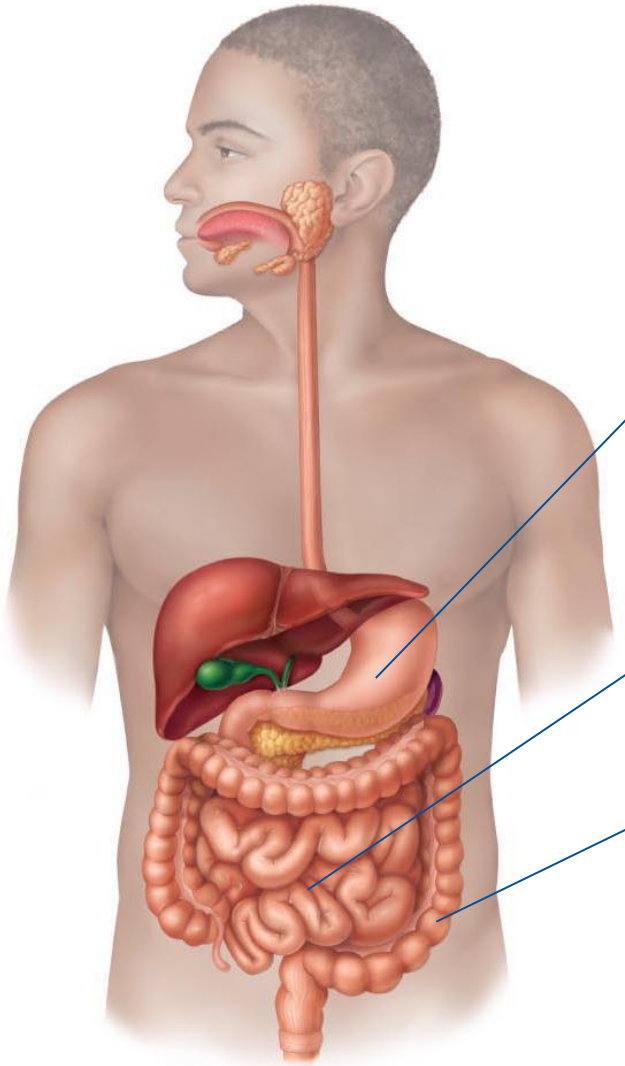


Fe2+ reacts with neutrophil-produced H_2O_2 yielding hydroxyl radical OH causes tissue damage and ulcers

Gasche C *et al*. *Anemia in inflammatory bowel diseases.* UNI-MED Verlag, 2008
Koskenkorva-Frank et al. Free Radic Biol Med. 2013 Dec;65:1174-94.

Gastrointestinal adverse events

Direct effect Fe2+ mucosal irritation



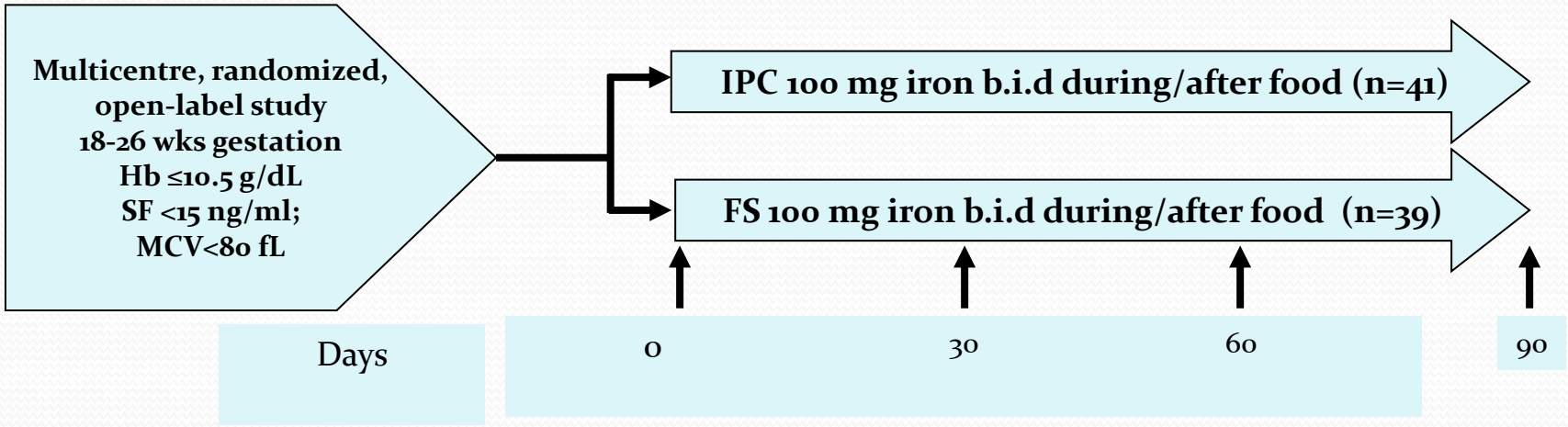
- Nausea
- Diarrhoea
- Constipation

Mechanisms of Diarrhoea in Kumar and Clark's Clinical Medicine 8th ed.
Chassany et al. Drug Saf. 2000 Jan;22(1):53-72.
Ratnaike et al. Aust J Hosp Pharm 2000; 30: 210-13.

Iron polymaltose complex in pregnancy

Objective:

- To evaluate the efficacy and safety of IPC (Maltofer®) vs. ferrous sulfate (FS) in pregnant women with IDA



Primary endpoint:

- Change in Hb from baseline to Days 60 and 90

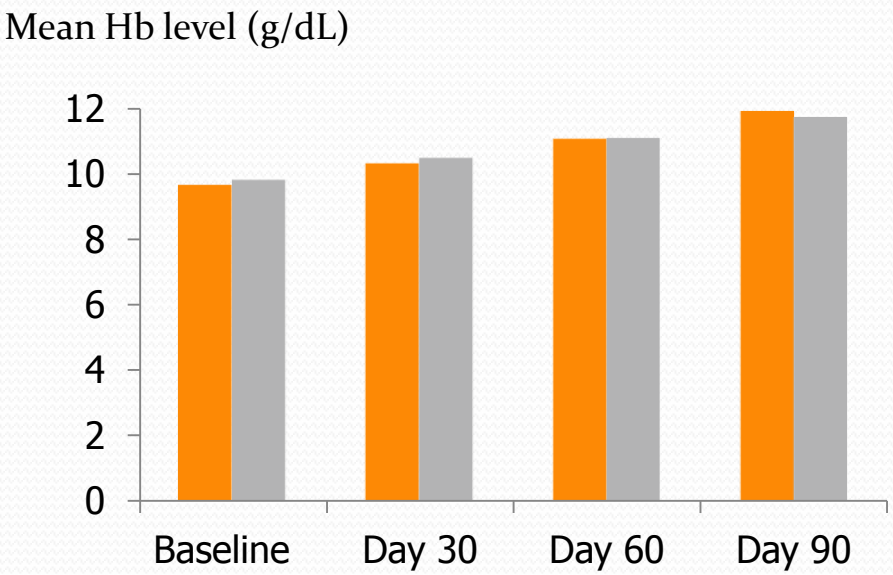
Secondary endpoint:

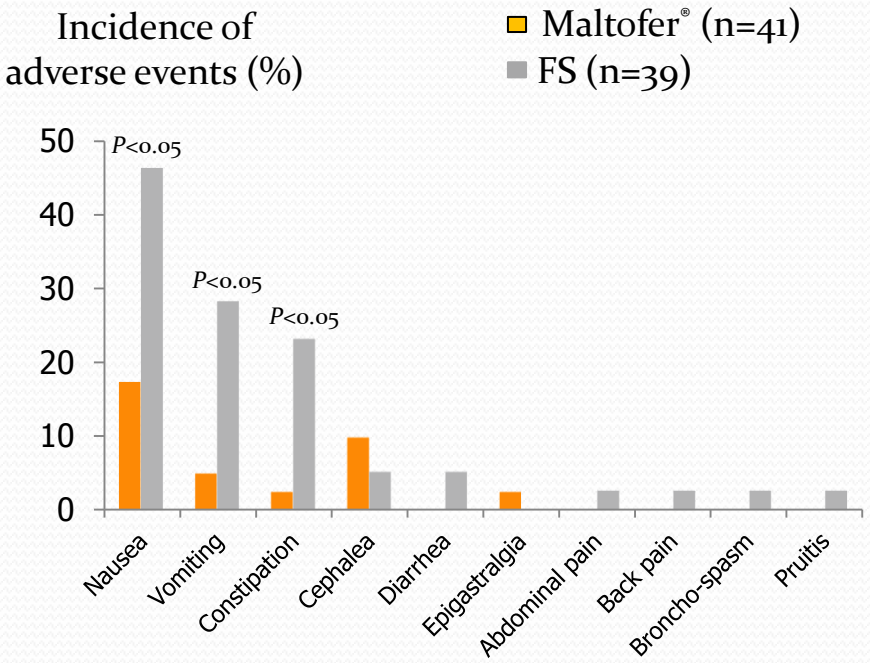
- Hb from baseline to Days 30, 60 and 90, change in serum ferritin, TSAT, serum iron, hemoatocrit, MCH and MCHC

FS, ferrous sulfate; Hb, Haemoglobin; MCH, mean corpuscular haemoglobin; MCHC mean corpuscular haemoglobin concentration; TSAT, transferrin saturation; hct hematocrit; b.i.d, twice daily

Ortiz R *et al. J Matern Fetal Neonatal Med* 2011;24:1347–52

Iron polymaltose complex in pregnancy





- Maltofer® was as effective as FS at correcting Hb levels
- With a lower incidence of most adverse events, Maltofer® showed a favourable tolerability profile versus FS

Modified from Ortiz R *et al. J Matern Fetal Neonatal Med* 2011;24:1347–1352

Oral Iron: Ferrous vs Ferric

Feature	Ferrous (Fe^{2+}) compounds	Ferric (Fe^{3+}) complex
Preparation	FS, FGS, FF	IPC
Mechanism of iron absorption	Active and passive (paracellular) diffusion[1]	Active, controlled iron uptake[2]
Elemental iron	30% from preparation	Preparation contain known amount of iron
Characteristics	In comparison with ferrous compounds, ferric complex is associated with: • Lower risk of intoxication in case of overdose[4] • Reduced oxidative stress[5] • Fewer gastrointestinal side effects[3] • Better tolerability[3] • Higher compliance[6]	

1. Heinrich HC *et al. Z Naturforschg* 1969;24b:1301–1310;
2. Geisser P & Burckhardt S. *Pharmaceutics* 2011;3:12–33;
3. Toblli JE & Brignoli R. *Drug Res* 2007;57:431–438;
4. Jacobs P *et al. S Afr Med J* 1979;55:1065–1072;
5. Dresow B *et al. Biometals* 2008;21:273–276;
6. Jaber L *et al. J Pediatr Hematol Oncol* 2010;32:585–588

Maltofer can be taken with or without food

Maltofer® has no detrimental interactions with a number of common food components and other drugs

Co-medications[1]	Food components[1]
In rat studies, no interactions shown with: • Tetracycline • Aluminium hydroxide • Acetylsalicylate • Sulphasalazine • Calcium carbonate, calcium acetate and calcium phosphate plus vitamin D3 • Bromazepam • Magnesium aspartate • D-penicillamine • Methyldopa • Paracetamol • Auranofin	In *in vitro* studies, no interactions shown with: • Phytic acid • Oxalic acid • Sodium alginate • Vitamin D3 and vitamin E • Soya oil and soya flour • Choline and choline salts • Tannin • Vitamin A
In humans, the following was observed: •No reduction in IPC absorption by aluminium hydroxide and tetracycline •No decline in plasma tetracycline level	Increased iron absorption with vitamin C[2]

1. Maltofer® 2010 Core Summary of Product Characteristics (SmPC)
2. Lundqvist *et al. Arzneimittelforschung* 2007;57:401–16

World Health Organisation

"All women of reproductive age are at risk of iron deficiency. "

"... IDA has been associated with increased risks of low birth weight, prematurity and maternal morbidity."

"Iron deficiency and anaemia reduce the work capacity of individuals and entire populations, bringing serious economic consequences and obstacles to national development."

WHO. *Worldwide prevalence of anaemia,1993–2005*. 2008. http://whqlibdoc.who.int/publications/2008/9789241596657_eng.pdf
WHO. *Guideline: Daily iron and folic acid supplementation in pregnant women*. 2012. http://apps.who.int/iris/bitstream/10665/77770/1/9789241501996_eng.pdf
WHO. *Micronutrient deficiencies*. 2013. http://www.who.int/nutrition/topics/ida/en/

Summary

- Iron deficiency (ID) is highly prevalent among women even in developed nation
  - iron requirement is significantly increased during pregnancy
- Early diagnosis of iron deficiency and anaemia is crucial
  - Anaemia is defined as Hb<11g/dl in pregnancy (WHO)
  - A **ferritin level<30ng/ml** should prompt iron replacement therapy
- Heam iron is the best absorbed but are often insufficient for pregnant mothers
- Not all oral iron is the same, iron polymaltose complex (IPC) has demonstrated efficacy in the prevention and treatment of IDA in pregnant mothers
- Maltofer® has no detrimental interaction with common food and drugs hence co-administration with such component does not reduce the iron absorption

Thank you for your attention