Anaemia in Pregnancy

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Prevalence of anaemia

- **Non-pregnant women**: 28.7-31.6%
- **Pregnant women**: 39.9-43.8%
- **Children <5 years**: 45.7-49.1%
- **Children ≥5 years**: 19.9-30.9%

*95% CI

Anaemia during pregnancy is a global problem

<table>
<thead>
<tr>
<th>WHO region</th>
<th>Prevalence of anaemia (%) in pregnant women [95% CI]</th>
<th>Number of pregnant women affected (millions) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>57.1 [52.8-61.3]</td>
<td>17.2 [15.9-18.5]</td>
</tr>
<tr>
<td>Americas</td>
<td>24.1 [17.3-30.8]</td>
<td>3.9 [2.8-5.0]</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>48.2 [43.9-52.5]</td>
<td>18.1 [16.4-19.7]</td>
</tr>
<tr>
<td>Europe</td>
<td>25.1 [18.6-31.6]</td>
<td>2.6 [2.0-3.3]</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>44.2 [38.2-50.3]</td>
<td>7.1 [6.1-8.0]</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>30.7 [28.8-32.7]</td>
<td>7.6 [7.1-8.1]</td>
</tr>
<tr>
<td>Global</td>
<td>41.8 [39.9-43.8]</td>
<td>56.4 [53.8-59.1]</td>
</tr>
</tbody>
</table>

Anaemia in Pregnancy

- Iron deficiency – 90% of all anaemias in pregnancy
- B12 and Folate
- Affects 20% of the world’s population
- It is poorly managed
- Significant cause of morbidity & mortality
Anaemia Prevalence

Booking

28/238 (11.8%)

28 Weeks

43/227 (18.9%)
Dietary iron intake compared to recommendations

Pregnancy increases iron requirements

- **Non-pregnant**
  - Average dietary intake (mg/day): 10

- **Pregnant**
  - Average dietary intake (mg/day): 20

**RDA** = Recommended daily allowance

1. Non-pregnant women www.hoptechno.com;
2. Institute of Medicine, Food and Nutrition Board 2001:1–28
## Iron Requirements

<table>
<thead>
<tr>
<th>Source of increased iron requirement</th>
<th>Iron demand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in red cell mass</td>
<td>450mg</td>
</tr>
<tr>
<td>Foetus &amp; Placenta</td>
<td>300mg</td>
</tr>
<tr>
<td>Increase in basal maternal requirements</td>
<td>240mg</td>
</tr>
<tr>
<td>Blood loss at delivery (NVD)</td>
<td>250mg</td>
</tr>
<tr>
<td><strong>Iron requirements for pregnancy, labour and delivery</strong></td>
<td><strong>1240mg</strong></td>
</tr>
</tbody>
</table>

- Only 10% of dietary iron is absorbed
- Increased in pregnancy and triples from 1\textsuperscript{st} to 3\textsuperscript{rd} trimester, peaking at 30w
Iron deficit during pregnancy

Difference between iron requirements and iron absorption has to be covered by iron mobilisation from stores or by iron supplementation.
Haemodilution affects Hb cut-off levels in pregnancy

Disproportionate increase in plasma volume relative to RBC volume

Blood, plasma and erythrocyte volumes (L)


With permission from UNI-Med science
Iron delivery to the foetus

- In pregnancy, iron is transferred from the mother to the developing foetus via the placenta.
- When the maternal iron status is poor, the number of placental transferrin receptors increases to increase iron uptake.
- If the mother is iron deficient, the capacity of this system may be inadequate to maintain iron transfer to foetus.

Most iron transfer to the foetus occurs after week 30 of gestation.

Breymann C & Huch R. Anaemia in pregnancy and the puerperium. 2008 UNI-MED
Iron in pregnancy

- Typical western diet contains 15mg/d of iron
- RDA of iron in pregnancy is 30mg/d

- Iron requirements in pregnancy rise from 1-2mg/d in 1\textsuperscript{st} trimester to 4mg/d in 2\textsuperscript{nd} trimester and peaking to 6mg/d in 3\textsuperscript{rd} trimester
- Lactation requires 0.5-1.0mg/d of iron

- It takes 2 years of normal dietary iron to replace the iron lost with each pregnancy
- Only 50% of women have enough iron stored to fulfil the pregnancy requirements.
Hepcidin

- Central regulatory molecule in iron metabolism in mammals
- Regulates **ferroportin** → enterocytes, macrophages, hepatocytes and trophoblasts
- Low hepcidin = high ferroportin = iron absorption is promoted
- Hepcidin is lower in pregnancy compared to non-pregnant women
- Lowest levels in 3rd trimester
- Inflammation and infection increases hepcidin (including obesity and PET)

- Oral doses of supplemental iron acutely increase serum hepcidin
- Providing oral iron supplementation on alternate days and in single doses optimises iron absorption

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

A level of > 110g/L appears adequate in the first trimester and > 105g/L in the second and third trimesters.

Postpartum anaemia is defined as a haemoglobin of < 100g/L.
Consequences of IDA

• Impact of IDA on pregnant women

• Impact of IDA on the foetus

• Implications of prepartum iron deficiency in infancy

• Impact of postpartum IDA on the mother

• Health economic aspects
Consequences of IDA in pregnant women

- Preconception IDA can lead to chronic placental insufficiency
- Impaired physical performance
- Increased cardiac failure and maternal death from heart failure in severe anaemia
- Poor maternal thyroid status and wound healing

Consequences of maternal IDA for the fetus

Hb levels <90 g/L increase risk of: 1–5
- Spontaneous miscarriage
- Low birth weight/small for gestational age
- Pre-term delivery if anaemia present in early pregnancy

Hb levels <60 g/L associated with: 6
- Chronic placental insufficiency

Low Hct (<29%) associated with: 7
- Medical abnormalities
- Growth restriction
- Foetal death

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Prepartum Hb can affect newborn mortality

Defining the optimum Hb level in pregnancy: very high and low Hb levels are associated with perinatal mortality

L Hb<10.4 g/dL
M Hb 10.4–13.2 g/dL
H Hb>13.2 g/dL

* Significant difference in perinatal mortality between those with high and median Hb at 13-19 weeks' gestation (p<0.01)

Reprinted from The Lancet, Murphy JF et al. Relation of haemoglobin levels in first and second trimesters to outcome of pregnancy. Lancet 1986;327(8488):992–995, Copyright (1986), with permission from Elsevier
Prepartum ID affects neurological development of the foetus

Iron-deficient diet during pregnancy associated with iron depletion in embryonic CNS tissue (nonclinical study in rats)

Morath DJ & Mayer-Proschel M. Dev Neurosci 2002;24:197–207

*M = p<0.0001

Normal
Iron deficient

μg Fe/g tissue
(Spinal cord)

12
10
8
6
4
2
0

13.5 17 21
Day of gestation

μg Fe/g tissue
(Cortex)

12
10
8
6
4
2
0

17 21
Day of gestation

*SD=p<0.0001

Morath DJ & Mayer-Proschel M. Dev Neurosci 2002;24:197–207. With permission from S. Karger AG
Implications of iron deficiency anaemia in infancy

- Significant changes in brain biochemistry including dopamine metabolism and myelin fatty acid composition

- Poor locomotive development
  2. Lozoff B et al. *Nutr Rev* 2006;64:S34–S43

- Poor performance on behavioural tests

- Poor cognitive performance

- Impaired socio-emotional behaviour
A high proportion of infants born to anaemic mothers display iron deficiency themselves

- Iron deficient infants with iron replete mothers: 6.5%
- Iron deficient infants with iron deficient mothers: 42.4% *

* OR 6.57 (95%CI 1.8-26.0)

Long-term consequences of prepartum IDA: implications for child development

IDA associated with lowered scores on tests of mental and motor development in infancy

Adjusted Woodcock-Johnson preschool cluster score

<table>
<thead>
<tr>
<th></th>
<th>No IDA in infancy</th>
<th>IDA in infancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-value</td>
<td>&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>

Consequences of postpartum IDA

**Cardiac function**
- Increased risk of cardiac failure in severe anaemia

**Immune function**
- Lowered resistance to infection
- Impaired wound healing

**Cognitive function**
- Lower cognitive performance

**Blood transfusions**
- Increased risk

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

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

Postpartum Hb predicts postpartum depression, with a higher rate of self-reported depressive symptoms.

CES-D scores

- **Hb ≤ 12.0 g/dL** (n=8)
- **Hb > 12.0 g/dL** (n=29)

p < 0.001

Corwin EJ et al. *J Nutr* 2003;133:4139–4142

CES-D, Center for Epidemiological Studies-Depressive Symptomatology Scale
Iron deficiency in pregnant women can result in economic burden on society

Complications during pregnancy and postpartum, including blood loss and need for transfusion, have cost implications on healthcare systems.\(^1\)

Iron deficient pregnant women have impaired cell-mediated immunity,\(^2\) making them more susceptible to infection\(^1\) (cost to society).

Reduction in capacity to work caused by anaemia well established; may be extrapolated to pregnancy.\(^2\)

Iron deficiency during pregnancy: economic burden

Ongoing impact on child can result in economic burden on society

Negative effects on infant as a result of foetal abnormalities\(^1\) and preterm delivery\(^2\) requiring additional neonatal care

Impact of IDA on future mental development of child\(^3\) requiring increased care and education, and potentially affecting future work capacity\(^4\)

Possible effect on coronary function of child in later life\(^5\) could have far-reaching impact on future societal burden

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Management of anaemia
• Accuracy of Hb measurement in pregnant women still debated:¹
  – Physiological alterations in blood volume and red blood cell mass during pregnancy reduce the reliability of Hb or Hct assays

• Hb value and erythrocyte indices, such as MCV and MCH, have low specificity and sensitivity for detection of iron deficiency²,³
  – Significant changes manifest only in late phases of iron deficiency²

MCV, mean corpuscular volume
MCH, mean corpuscular Hb

Serum ferritin

• Serum ferritin is commonly used to determine adequate iron stores\(^1\)–\(^3\)

- Ferritin levels <30 µg/L suggest low iron status\(^4\),\(^5\)
- Ferritin levels <15 µg/L indicate iron deficiency\(^1\),\(^4\)–\(^7\)
- Ferritin levels <12 µg/L are often associated with anaemia\(^4\),\(^6\),\(^8\)

• Serum ferritin may be elevated in women with infections or inflammatory disorders\(^1\),\(^3\),\(^4\)
  - If suspected, plasma C-reactive protein should be measured to assess inflammation\(^4\)

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Hb and ferritin checked in all patients at booking (ANC)

Hb rechecked in all patients at 28 weeks (ANC). Check ferritin if booking Hb was normal.

Is Hb < 110g/L in 1st trimester < 105g/L in 2nd / 3rd trimester?

No

Is Ferritin < 30?

No

Offer dietary advise and reassure Recheck Hb and ferritin at 28 weeks as standard (ANC)

Yes

Commence oral iron 200mg OD (ANC)

Commence oral iron 200mg BD (ANC)

Recheck FBC and ferritin with CRP. If CRP is raised (ferritin raised in inflammation)

Yes

Recheck Hb levels in 4 weeks Is there an acceptable Hb rise / normal Hb? (ANC/Primary care)

No

Continue oral iron Recheck Hb in In 4 weeks or At 38 weeks Whichever is sooner (ANC/ Primary care)

Check result of haemoglobinopathy screen from booking.

If report states α or β thalassaemia trait of Hb E, no further action required unless anaemia is new at booking and significant in which case haematology should be consulted

Yes

Consider IV iron if:
- Patient non compliant with oral iron secondary to side effects
- Not responding despite oral iron therapy and other causes excluded (such as haemoglobinopathy trait)
(ANC/Primary Care)
Anaemia in Pregnancy

An e-learning package

Click here to start...
1. Why anaemia in pregnancy is important?

2. How can I detect it?

3. What I can do to prevent it?

4. Extra resources & mini test

Click on the boxes above to go to the different sections
How can I detect it?

Consider these ‘at risk groups’

• younger mothers
• short pregnancy intervals
• diets low in iron
What can I do to prevent it?

In general follow this sequence...

Diet  Oral Iron  IV Iron
What can I do to prevent it?

Below are foods rich in iron – click on them to see how much iron they contain

- 2 Tbsp Pumpkin seeds = 2.5mg Iron
- 1 bowl of fortified cereal = 3.0mg Iron
- 6 prunes = 0.5mg Iron
- 5 figs = 2.0mg Iron
- 1 slice of Wholemeal Bread = 0.9mg Iron
- 30g spinach = 3.0mg Iron
- 175g cooked broccoli = 1.1mg Iron
- 1 medium sized steak = 4.3mg Iron
- Small can of Baked Beans = 3.25mg Iron

Nuts & Dried Fruits  Wholegrain & Cereals  Green vegetables  Protein
Iron in your diet

IMPORTANT PATIENT INFORMATION
Recommendation

- All women should be counselled regarding diet including
  - details of iron-rich sources
  - factors that may inhibit or promote iron absorption

- Written information for patients, which is appropriate for dietary type and language
What can I do to prevent it?

Oral Iron

• safe, effective, cheap
• 1\textsuperscript{st} – try tablets
• 2\textsuperscript{nd} try liquid
  (if tablets are not tolerated)
• re-check Hb after 4 weeks
### What can I do to prevent it?*

Oral iron – **tablet options:**

<table>
<thead>
<tr>
<th></th>
<th>Ferrous Sulphate</th>
<th>Ferrous Fumarate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage</strong></td>
<td>200mg - BD</td>
<td>210mg - BD</td>
</tr>
<tr>
<td><strong>Elemental iron</strong></td>
<td>65mg</td>
<td>68mg</td>
</tr>
<tr>
<td><strong>Cost per tablet</strong></td>
<td>Hospital – 1p, Community – 5p</td>
<td>Hospital – 2p, Community – 2p</td>
</tr>
</tbody>
</table>
Appendix 2


Ferric Carboxymaltose (Ferinject®) is a parenteral iron treatment which can give up to 1000mg over 20 minutes as an infusion and has a low side effect profile. Ferinject® enables women to be treated quickly, potentially with one infusion therefore increasing patient compliance and decreasing both time in the antenatal day unit and postnatal stay.

Ferinject® is not licensed for use within the first trimester; however it is licensed for use in the second and third trimester and the postpartum period. (1)

DIAGNOSIS AND INVESTIGATION

Prior to treatment with Ferinject®, a haemoglobin and ferritin levels should be taken and a target haemoglobin level decided. Vitamin B12 and folate deficiency should be treated.

Each woman who is going to receive Ferinject® needs to have their weight taken and documented on the drug chart so that the dosage of Ferinject® can be double checked by both the midwife and the pharmacist.

Indications for Parenteral Iron therapy

1. Second, third trimester of pregnancy, or the immediate postpartum period
2. Demonstrable intolerance to oral iron therapy
3. Clinical need to deliver iron quickly to iron stores
4. Non-compliance or resistance to oral iron therapy
5. Contraindication to oral iron therapy such as inflammatory bowel disease
6. Refusal of blood products on religious or principle basis

Contraindications to parenteral iron therapy (1)

1. First trimester
IV Iron Therapy during pregnancy

- 291 women <10d after delivery with Hb 100g/l or less: ferric carboxymaltose vs ferrous sulphate
- Christoph et al – journal of perinatal medicine 2012
- Retrospective analysis of 206 women treated with either ferric carboxymaltose or iron sucrose for iron-deficiency anaemia

<table>
<thead>
<tr>
<th></th>
<th>Ferric Carboxymaltose</th>
<th>Iron Sucrose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean rise in Haemoglobin (g/l)</td>
<td>15.4</td>
<td>11.7</td>
</tr>
<tr>
<td>Adverse effects (mild) - %</td>
<td>7.8</td>
<td>10.7</td>
</tr>
</tbody>
</table>
Use of Ferric Carboxymaltose in Leeds

- 30 women over 11 months (2014)
- 23 – antenatally
- 7 – postnatally
- Antenatal rise in Hb – 30g/L
- Postnatal Hb pre treatment – 65-97g/L
- No adverse effects
Not only IDA
27 year old
- Previous h/o (L) common femoral and iliac vein DVT extending to IVC – thrombolysed
- Conceived three months later
- On prophylactic LMWH
- Significant haemorrhoids
- Presented with Hb of 57g/l and platelets of 90 (dropped to 56)
- LDH >6,000
- High MCV and MCH
- Blood film in keeping with megaloblastic anaemia
- Folate 0.7
- B12 100
- Treated with FA and B12 supplements
- **Hb 117g/L; Platelets 264 pre-delivery**
Conclusion

- **Anaemia in Pregnancy**
  - prevalent
  - can lead to significant consequences to mum and baby
  - treatable
  - we are trying hard but still not enough
  - partnership between primary and hospital care can improve management