Management of Anaemia and Nutritional Deficiencies in Pregnancy and in the Postpartum Period: NATA Consensus Statement

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Conflicts of interest

I have received honoraria for consultancies/lectures and/or travel support from:

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Proposed tasks

1. Determine the scope of the problem.
2. **Identify the optimal methods to detect the problem and establish a differential diagnosis**.
3. Recommend methods to minimise peripartum blood losses.*
4. Define the role of red blood cell transfusions in pregnancy and in the postpartum period.*
5. **Issue recommendations on the use of oral iron, intravenous iron and erythropoiesis-stimulating agents to prevent and treat anaemia during pregnancy and in the postpartum period**

*These will presented in detail in the NATA Postpartum Haemorrhage Guidelines

Working methodology

Grading system

Strength of recommendation: is risk/benefit clear?

- Yes ⇨ strong recommendation=Grade 1: 'we recommend'
- No ⇨ weak recommendation=Grade 2: 'we suggest'

Quality of evidence

- High-quality evidence=A (meta-analyses, randomized controlled trials)
- Moderate-quality evidence=B (randomized controlled trials with limitations, observational studies with large effects)
- Low- or very low-quality evidence=C (obervational studies, randomized controlled tried with major limitations)

Grade of recommendation

- Grade 1A
- Grade 1B
- Grade 1C
- Grade 2A
- Grade 2B
- Grade 2C

Guyatt et al. Chest 2006; 129: 174-181

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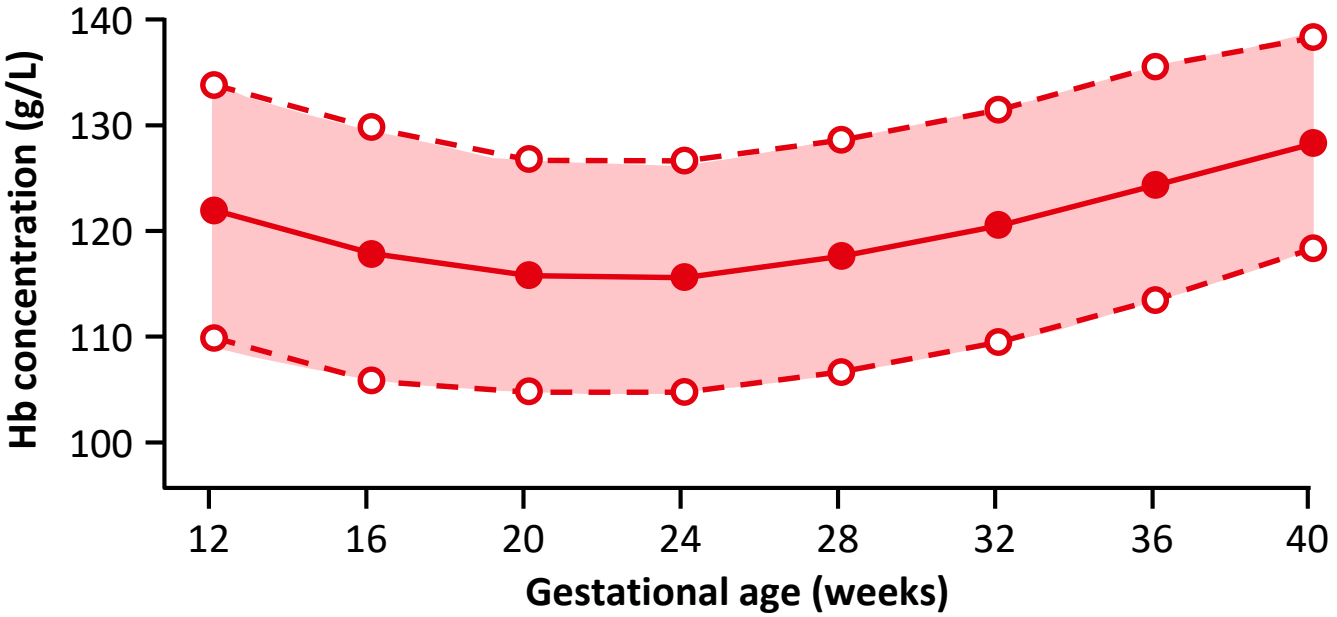
Anaemia of Pregnancy

Scope of the problem

- Anaemia in pregnancy is defined by haemoglobin levels less than 110 g/L in the first or third trimester, or less than 105 g/L the second trimester.



WHO. Geneva 2011**; BCSH UK.** BJH 2012; 156:588-600;
CDC US 2015; **ACOG**. Obstet Gynecol 2008; 112:201-7

Haemoglobin levels to diagnose anaemia

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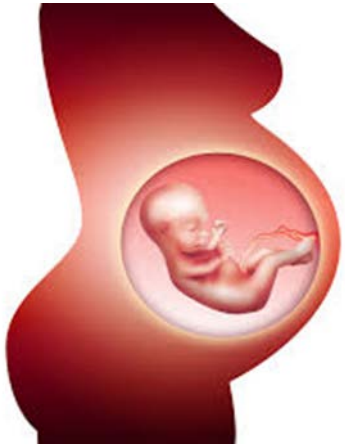
World Health Organization

Population age	Non-Anaemia	Anaemia (Haemoglobin concentration, g/L)		
		Mild*	Moderate	Severe
Children 6–59 months	≥110	100–109	70–99	<70
Children 5–11 years	≥115	110–114	80–109	<80
Children 12–14 years	≥120	110–119	80–109	<80
Non-pregnant women (≥15 years)	≥120	110–119	80–109	<80
Pregnant women	**≥110**	**100–109**	**70–99**	**<70**
Men (≥15 years)	≥130	110–129	80–109	<80

* "Mild" is a misnomer: iron deficiency is already advanced by the time anaemia is detected. The deficiency has consequences even when no anaemia is clinically apparent. (WHO/NMH/NHD/MNM/11.1; http://www.who.int/vmnis/indicators/haemoglobin.pdf)

Scope of the problem



- **Iron deficiency (ID) and IDA** affect around 20% of pregnant women in the western world, increasing to 56% in developing countries.
- **Iron deficiency anaemia (IDA)** may affect growth and development both in utero and in the long term (childhood, adolescence).

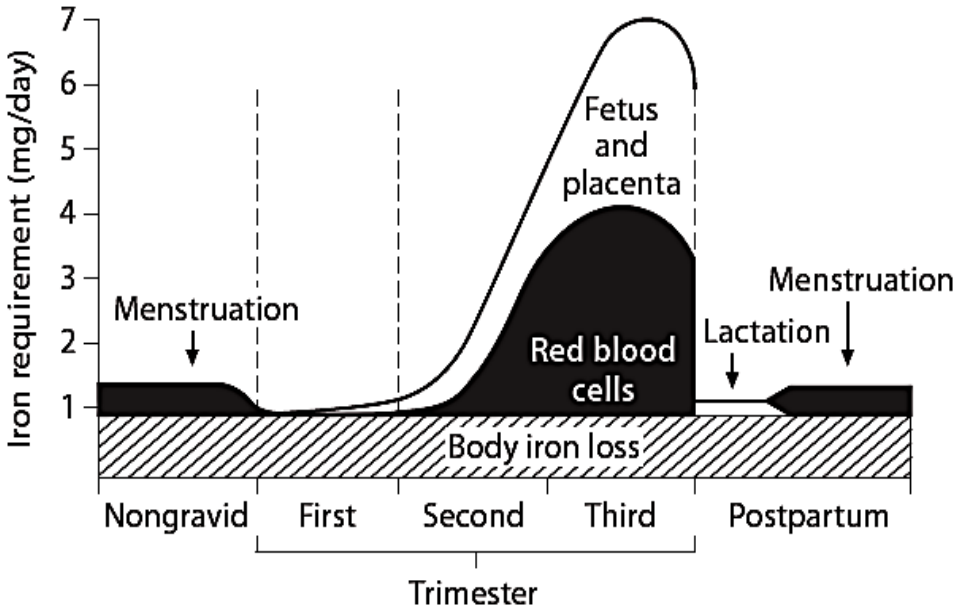
- **Moderate or severe anaemia during pregnancy** have been associated with an increased risk of premature delivery, maternal and child mortality, and infectious diseases.

WHO. Geneva 2011**; BCSH UK.** BJH 2012; 156:588-600;
CDC US 2015; **ACOG**. Obstet Gynecol 2008; 112:201-7

Causes of anaemia

❖ **Iron deficiency (ID) accounts for most cases of anaemia in pregnant women:**

- A total of ≈ 1000 mg of extra iron is required during a normal pregnancy.
- Without supplementation, 80% of women at term will have no detectable iron stores.
- Lactation will requires an extra supply of 1 mg/day.



Bothwell TH. *Am J Clin Nutr. 2000 ;72(1 Suppl):257S-264S.*

Stevens et al. *Lancet Glob Health. 2013;1:e16-25.*

Causes of anaemia

- **Iron deficiency (ID) accounts for most cases of anaemia in pregnant women.**

- **Additional, and often neglected, causes of anaemia include:**
  - Nutritional deficiencies of folate and vit B_{12}
  - Infectious diseases
  - Parasitic infections
  - Haemoglobinopathies

Stevens et al. *Lancet Glob Health*. 2013;1:e16-25. **WHO/UNICEF/UNU.** *Geneva 2001*.

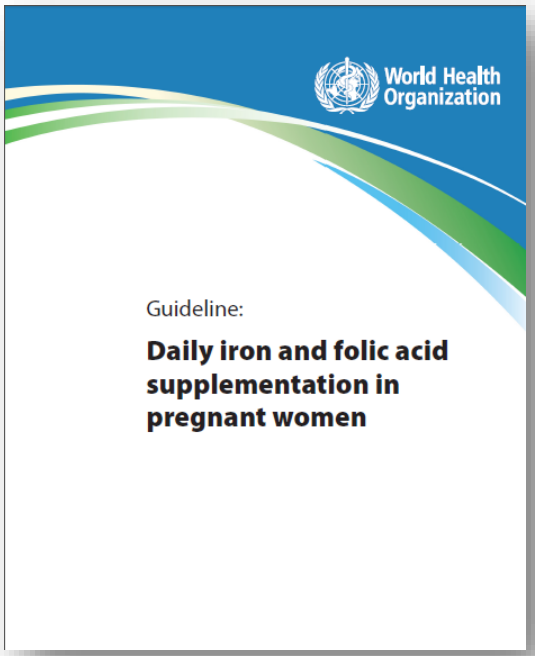
Perinatal anaemia management

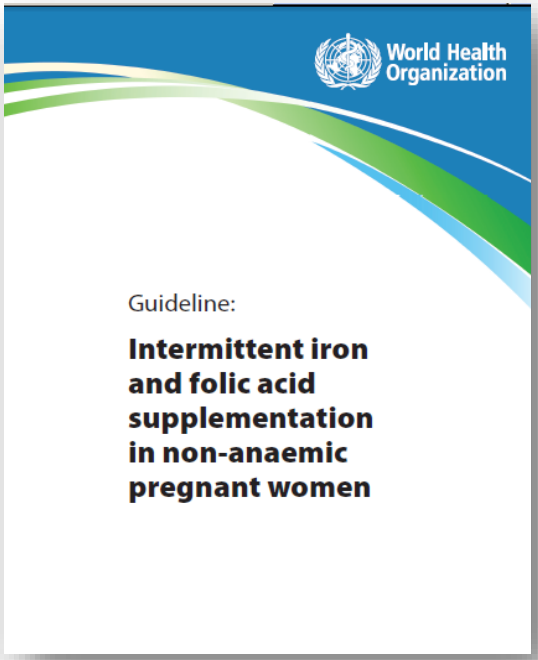
Prevention

(6) We recommend **daily oral iron (30-60 mg) and folic acid (400 µg) supplementation** as part of routine antenatal care to reduce the risk of low birth weight, maternal anaemia and iron deficiency (1B).

Peña-Rosas JP, et al.
Cochrane Database Syst Rev 2015;7: CD004736.

Peña-Rosas JP, et al
Cochrane Database Syst Rev. 2015;10:CD009997





Perinatal anaemia management

Prevention

THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE

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Taylor & Francis
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ORIGINAL ARTICLE

Effects of different regimens of iron prophylaxis on maternal iron status and pregnancy outcome: a randomized control trial

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Control vs. 30 mg Ferrous Iron vs. 14 mg Liposomal Iron vs. 28 mg Liposomal Iron

Perinatal anaemia management

Prevention

Gestational weeks	11–13	20	28–32	6 post-partum
Hb (g/dl)				
C	12.0 ± 0.6	11.0 ± 0.7	10.8 ± 0.3	11.6 ± 1.1
FI	11.9 ± 0.7	11.4 ± 0.4	11.0 ± 0.6	11.8 ± 0.8
LI14	12.0 ± 0.5	11.4 ± 0.6	11.3 ± 0.3	12.0 ± 0.9
LI28	11.9 ± 0.6	11.5 ± 0.6	11.4 ± 0.3	12.6 ± 0.7
RBC (cells × 10^6)				
C	4.1 ± 0.3	3.8 ± 0.3	3.7 ± 0.4	4.2 ± 0.5
FI	4.1 ± 0.2	3.9 ± 0.2	3.7 ± 0.3	4.2 ± 0.2
LI14	3.9 ± 0.3	3.7 ± 0.3	3.6 ± 0.4	4.2 ± 0.2
LI28	4.0 ± 0.3	3.8 ± 0.4	3.7 ± 0.3	4.1 ± 0.3
MCV (fl)				
C	86.5 ± 3.2	85.8 ± 3.3	86.7 ± 3.8	84.0 ± 1.8
FI	85.4 ± 3.2	84.6 ± 3.2	85.9 ± 4.2	85.9 ± 4.7
LI14	88.2 ± 3.0	87.8 ± 3.2[a]	89.1 ± 3.7	85.9 ± 3.0
LI28	87.2 ± 3.2	86.7 ± 3.3	88.3 ± 3.8	86.9 ± 3.3
Iron (µg/dl)				
C	115.9 ± 34.9	106.9 ± 38.4	71.7 ± 28.6	86.7 ± 22.4
FI	105.7 ± 30.5	98.2 ± 25.2	91.8 ± 26.6	89.8 ± 18.2
LI14	109.1 ± 44.9	101.9 ± 39.3	79.1 ± 37.3	88.3 ± 22.9
LI28	99.3 ± 20.9	88.5 ± 27.0	85.2 ± 15.6[a]	98.2 ± 16.4
Ferritin (µg/l)				
C	46.6 ± 47.4	27.9 ± 21.9	26.1 ± 16.5	31.3 ± 15.4
FI	43.7 ± 37.3	35.8 ± 16.3	31.9 ± 34.2	43.1 ± 20.6
LI14	52.4 ± 43.9	33.4 ± 17.2	30.8 ± 10.4	40.8 ± 32.5
LI28	52.6 ± 52.1	47.8 ± 32.9	38.7 ± 13.0	49.8 ± 12.6

Perinatal anaemia management

Detection and classification

(1) We recommend that a full blood count should be obtained to **screen for anaemia at booking and at 28 weeks**, as well as at any time during pregnancy if symptoms of anaemia are present (1A).

(2) In anaemic women from the Mediterranean, Middle and Far East and Africa, we recommend confirming the **presence or absence of a haemoglobinopathy** (1C).

BCSH UK. BJH 2012; 156:588-600;
ACOG. Obstet Gynecol 2008; 112:201-7

Perinatal anaemia management

Detection and classification

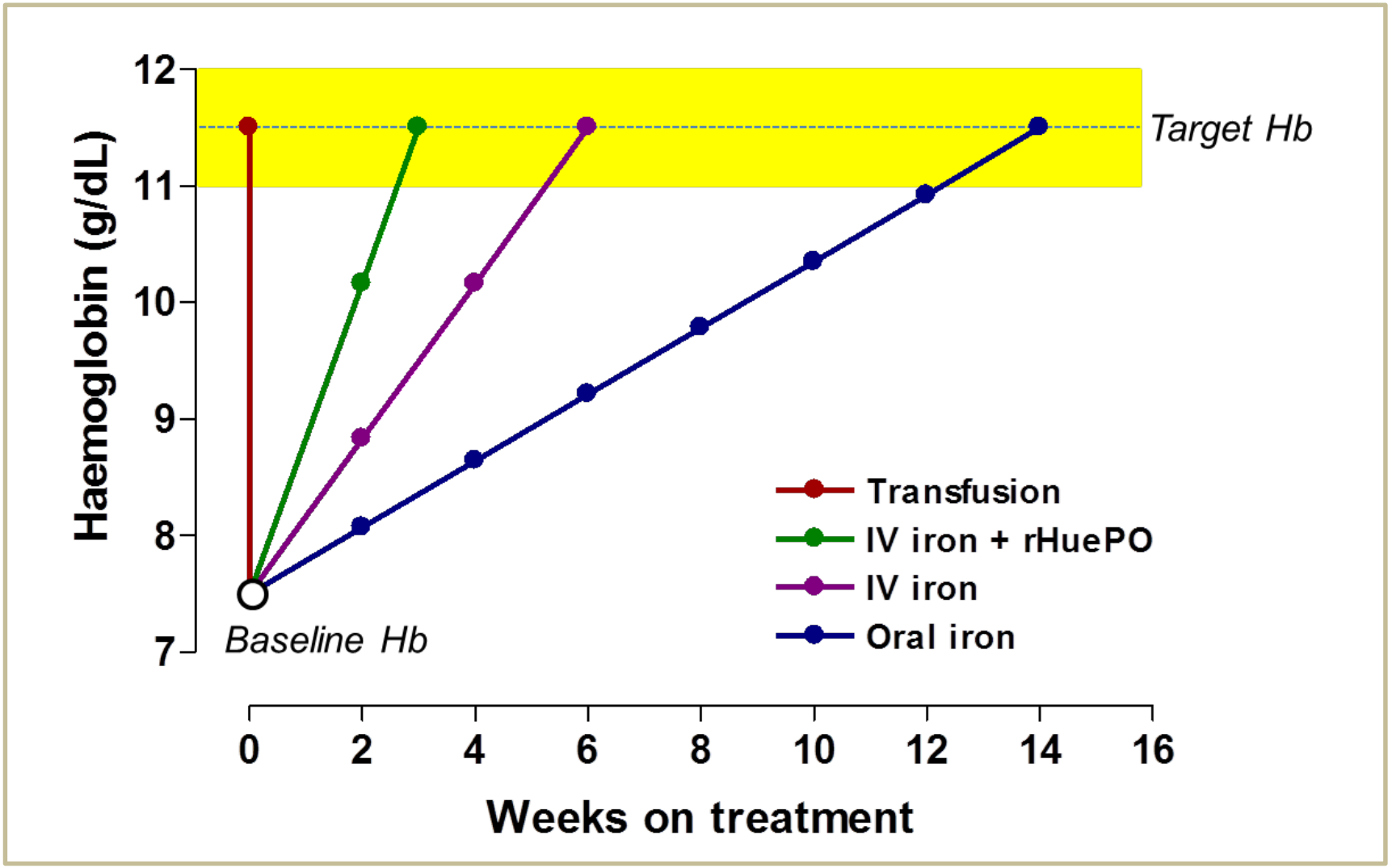
Good practice points:

- ✓ The **serum ferritin level** is the most useful and easily available parameter for assessing ID during pregnancy.
- ✓ Ferritin levels <12 ng/mL indicate established ID.
- ✓ A serum ferritin level <30 ng/mL, with or without anaemia, indicates insufficient iron stores and should prompt treatment.
- ✓ If iron status is normal, **Vitamin B_{12} and folate** should be checked (1C).

BCSH UK. BJH 2012; 156:588-600;
ACOG. Obstet Gynecol 2008; 112:201-7

Perinatal anaemia management

Treatment: severity & response time



Perinatal anaemia management

Treatment: oral iron

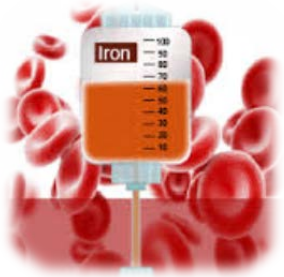
(7) We recommend treatment of **mild-to-moderate IDA (Hb >90 g/L) in 1st and 2nd trimesters** should be started with oral iron (80 mg/day elemental ferrous iron) and folic acid (400 µg/day) (1A).

(8) Once the Hb is in the normal range, we recommend that iron supplementation **should be continued for at least 3 months** to replenish iron stores (1A).

WHO. Geneva 2012
BCSH UK. BJH 2012; 156:588-600
ACOG. Obstet Gynecol 2008; 112:201-7

Perinatal anaemia management

Treatment: IV iron



(9) We recommend that the administration of IV iron should be considered in women with more **severe IDA** (Hb <80 g/L) **or newly diagnosed of IDA in the third trimester of pregnancy** (1B).

(10) We recommend that the administration of IV iron should be considered in **women with confirmed IDA who fail to respond** (Hb concentration increase <10 g/L in 2 weeks) **or are intolerant to oral iron** treatment, if the gestational age is >14 weeks (1B).

Perinatal anaemia management

IV iron *vs.* oral iron: Summary of evidence

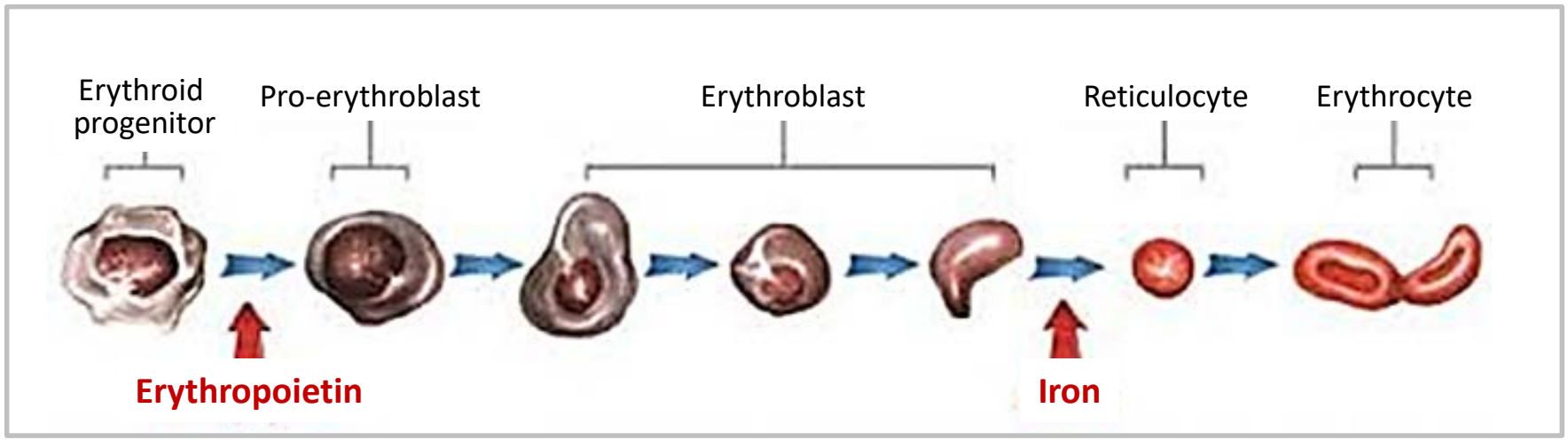
- **11 RCT and one OBS (n=1809)**
- **Compared to oral iron, IV iron resulted in:**
  - Faster Hb increment during treatment (11/11)*
  - Higher final Hb increment (10/11)
  - Higher rates of anaemia correction (5/7)
  - Better replenishment of iron stores (8/9)
  - Lower rates of ADEs (9/10)
  - Better compliance (6/9).
- **No study showed superiority of oral iron over IV iron**
- **Moderate quality studies**

*(positive studies/total studies)

Prenatal anaemia management

Treatment: IV iron ± ESAs

(11) We suggest that administration of an ESA be considered in women with **moderate-to-severe anaemia not responding to IV iron** due to inappropriate synthesis of and/or response to endogenous EPO (2C).



Prenatal anaemia management

Treatment: IV iron ± ESAs

Summary of evidence

- **1 RCT, 1 OBS and 1 case series** (n=135)
  - In the RCT, the addition of rHuEPO resulted in higher Hb increments and higher rate of anaemia correction, compared to intravenous iron alone.
- **Moderate-to-low quality studies**

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Postpartum anaemia

Scope of the problem

- Postpartum anaemia (PPA) is defined by a Hb <100 g/L within 24-48h after delivery, Hb <110 g/L at 1 week postpartum or Hb <120 g/L at 8 weeks postpartum.

- The prevalence of PPA 48 h after delivery is approximately 50% in Europe and 50-80% in developing countries.

Milman N. Ann Hematol 2011; 90: 1247-53; **Milman N.** Ann Hematol 2012; 91; 143-54.

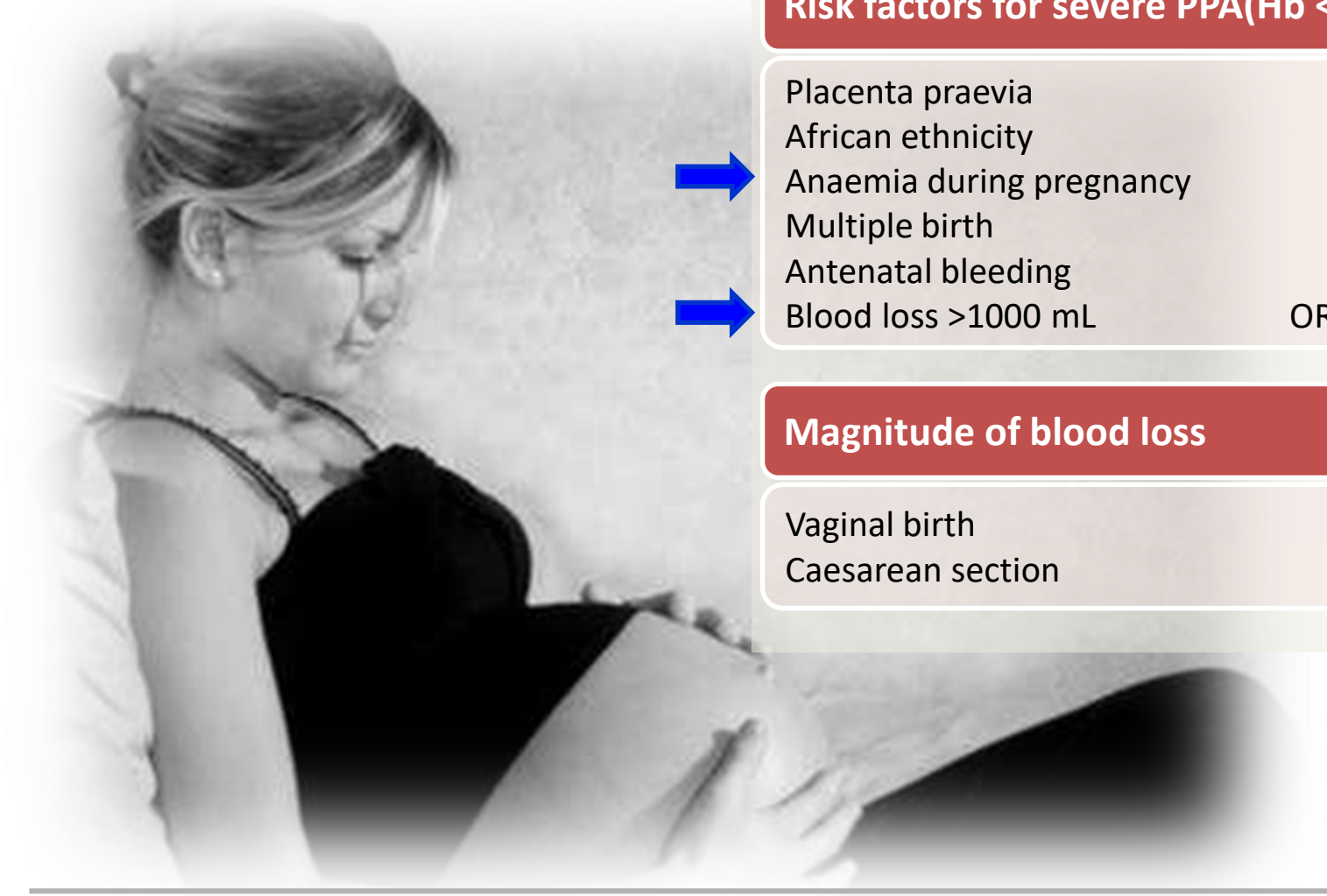
Scope of the problem

- PPA constitutes a significant health problem in women of reproductive age, as it associated with:
  - Prolonged hospital stay
  - Impaired quality of life.
  - Reduced cognitive abilities
  - Emotional instability and depression.

- **The importance of PPA seems to be overlooked by both obstetricians and patients.**

Milman N. Ann Hematol 2011; 90: 1247-53; **Milman N.** Ann Hematol 2012; 91; 143-54.

Scope of the problem



Risk factors for severe PPA(Hb <8 g/L)	
Placenta praevia	OR 4.8
African ethnicity	OR 2.9
Anaemia during pregnancy	OR 2.7
Multiple birth	OR 2.2
Antenatal bleeding	OR 2.1
Blood loss >1000 mL	OR 74.7

Magnitude of blood loss	
Vaginal birth	<500 mL
Caesarean section	<1000 mL

Bergmann RL *et al*. *Eur J Obstet Gynecol Reprod Biol* 2010;150:126–31

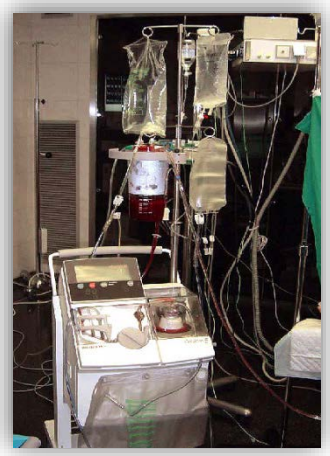
Management of postpartum anaemia

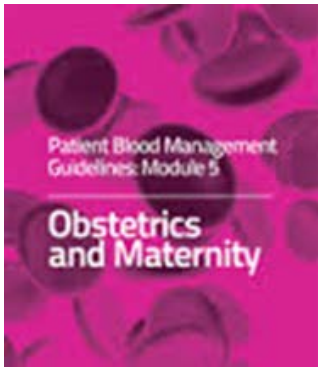
Prevention

(18) We recommend that **every effort be made to correct anaemia prior to delivery** (1A).

Management of postpartum anaemia

Prevention





(19) We recommend that women with anaemia or at high risk of haemorrhage be advised to **deliver in hospital** (1C).

(20) We recommend **active management of the third stage of labour** to minimise blood losses (1A).

(21) We recommend **cell salvage** for women undergoing Caesarean section in whom excessive blood losses are anticipated (1C).

(22) We recommend that a clear **multidisciplinary, multimodal protocol for management of major obstetric haemorrhage** be in place.
This protocol should be activated as soon as major obstetric haemorrhage is identified (1C).

***To be developed in the NATA Postpartum Haemorrhage Guidelines**

Management of postpartum anaemia

Early detection

(16) We recommend that every parturient should have an **Hb determination when labour starts,** especially in women with antenatal anaemia (1C).

(17) We recommend that the Hb concentration be determined **after significant peripartum bleeding** (1C).

Management of postpartum anaemia

Treatment: oral iron

(24) We recommend that **80 mg elemental ferrous iron daily** for 3 months be given to women with mild-to-moderate anaemia postpartum (Hb 90-110 g/L) who are haemodynamically stable, asymptomatic or mildly symptomatic (1B).

Management of postpartum anaemia

Treatment: oral iron

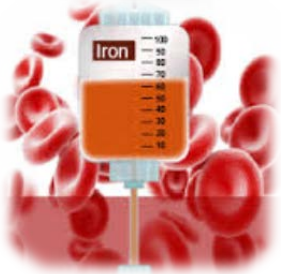
Good practice points:

- ✓ Whenever possible, **Hb concentration should be determined after 2-4 weeks** in order to validate the efficacy of treatment in women receiving ferrous oral iron for postpartum anaemia.

- ✓ **A complete CBC plus ferritin level at 8 week postpartum** are adequate to assess anaemia and iron status in the majority of women with antenatal anaemia or significant peripartum bleeding (General practitioner).

Management of postpartum anaemia

Treatment: intravenous iron



(25) We recommend that women with confirmed ID and **lack of response** (Hb increase <10 g/L in 2 weeks) **or intolerance to oral iron** be switched to IV iron (1B).

(26) We recommend the administration of IV iron to cover individually calculated total ID in women with **moderate-to-severe postpartum anaemia** (Hb 60-90 g/L) (1B).

Management of postpartum anaemia

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IV iron *vs.* oral iron: Summary of evidence

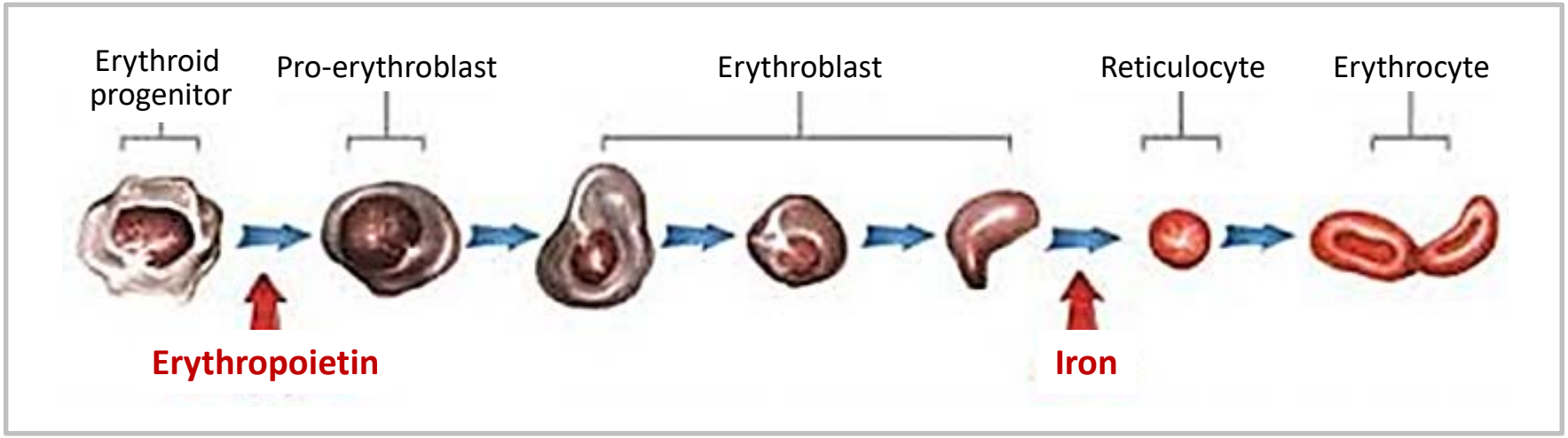
- **14 RCT Intravenous iron vs. Oral iron (n=2012)**
  - IVI formulations: 9 IS, 3 FCM, 1 LMWID, 1 MNF
  - IVI dose : 300 – 1600 mg (n=1050)
- **Compared to oral iron, IV iron resulted in:**
  - Faster Hb increment during treatment
  - Higher final Hb (6/12)
  - Higher rates of anemia correction (2/3) (FCM)
  - Higher final Ferritin (9/11)
  - Lower rates of ADEs (6/10)
  - No significant differences in transfusion rates
- **No trial showed superiority of oral iron**
- **Moderate-to-high quality studies**

*(positive studies/total studies)

Management of postpartum anaemia

Treatment: IV iron + ESAs

(27) We suggest the administration of an ESA, after consultation with the haematologist, in **severely anaemic patients with blunted erythropoiesis** and not responding adequately to IV iron treatment, as well as in severely anaemic **patients who refuse blood transfusion** (2B).



Management of postpartum anaemia

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IV iron *vs.* IV iron + ESA : Summary of evidence

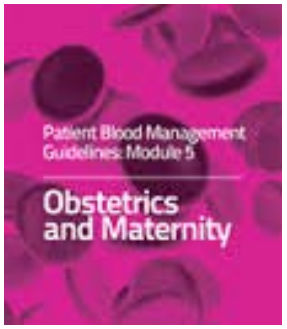
- **5 RCT Intravenous iron ± rHuEPO** (n=272)

- **Compared to IV iron alone, rHuEPO resulted in:**
  - Faster Hb increment during treatment (3/5)
  - Similar Hb increment at 6 weeks (1/5)
  - Similar Ferritin increment at 6 weeks (1/5)
  - Similar rates of ADEs (3/5)
  - No significant differences in transfusion rates (very low)

- **No trial showed superiority of IV iron alone**
- **Moderate quality studies**

Perinatal anemia management

Treatment: transfusion



(13) We recommend that obstetric units should have **guidelines for red cell transfusion** in women with antenatal and postnatal anaemia who are not actively bleeding (1C).

(12) We recommend **referral to a secondary care facility** be considered if there are **significant symptoms and/or severe anaemia** (Hb <70 g/L) or **late gestation** (>34 weeks) (1C).

Perinatal anemia management

Treatment: transfusion

(30) We recommend that transfusion be considered in **patients with an Hb <60 g/L and the absence of bleeding**, according clinical signs and symptoms (risk of bleeding, cardiac compromise or symptoms requiring immediate attention) into consideration (1A).

(31) Should transfusion be deemed necessary, we recommend a **single-unit transfusion** followed by clinical reassessment and/or repeated Hb to determine the need for further transfusion (1C).

Treatment: transfusion

Good practice points:

- ✓ Women receiving a red cell transfusion **should be given full information** regarding the indication for transfusion and alternatives available, according to national policy procedures.

- ✓ **Informed consent** should be given by the patient and documented in the clinical notes.

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Disclaimer

1. **Panel members alone are responsible for the views expressed in this CS.** They do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

2. **Panel members have given what they consider at the present to be "optimal" guidelines.** However, they also acknowledge that the evidences are not clear cut for all circumstances.

3. **Panel members consider these recommendations have to be adapted** to the specific situations, the resources and strategies of the individual countries and territories.

CENTRO NAZIONALE SANGUE

PATIENT BLOOD MANAGEMENT ITALY

Thank you very much for your kind attention!