Iron and folate supplementation

INTEGRATED MANAGEMENT OF PREGNANCY AND CHILDBIRTH **(IMPAC)**

The standard

All pregnant women in areas of high prevalence of malnutrition should routinely receive iron and folate supplements, together with appropriate dietary advice, to prevent anaemia. Where the prevalence of anaemia in pregnant women is high (40% or more), supplementation should continue for three months in the postpartum period.

Aim

To prevent and treat iron deficiency anaemia in women during pregnancy and in the postpartum period in order to improve maternal and perinatal health.

Requirements

- ☐ A national policy and locally adapted guidelines on iron and folate supplementation are in place and are correctly implemented.
- ☐ Health care providers of maternal and neonatal care are competent in: the importance of iron supplementation during pregnancy and the postpartum period; the correct dosage and duration of supplementation for the prevention and treatment of anaemia; anaemia detection in pregnant women; and when to refer women for further diagnosis and treatment.
- ☐ Iron and folate supplements are available at all levels of care.
- ☐ There is a functioning referral system that ensures timely referral of pregnant women for monitoring and treatment, especially in the case of severe anaemia.
- ☐ A mechanism is in place for recording cases and care of anaemia.
- ☐ Health education activities are carried out to increase awareness among women and in the community of the importance of iron and folate supplementation in pregnancy.

Applying the standard

Health providers, in particular skilled attendants, attending women during antenatal and postpartum visits must:

- Give all pregnant women a standard dose of 60 mg iron + 400 µg folic acid daily for 6 months or, if 6 months of treatment cannot be achieved during the pregnancy, either continue supplementation during the postpartum period or increase the dosage to 120 mg iron during pregnancy.
- Where the prevalence of anaemia in pregnancy is over 40%, advise the woman to continue the prophylaxis for three months in the postpartum period.
- Give iron supplementation even if folic acid is not available.
- Examine or screen all women for anaemia during antenatal and postpartum visits.

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- Treat anaemia with doses of 120 mg iron daily for three months.
- Follow up in two weeks to check clinical progress, test results and compliance and again four weeks later all women with severe anaemia that have been treated with iron and folate.
- Refer women with severe anaemia to a higher level of care if they are in the last month of pregnancy, have signs of respiratory distress or cardiac abnormalities such as oedema, or when the conditions do not improve or worsen after one week of iron/folate therapy.
- Provide advice on the consumption of iron-rich foods and vitamin C.
- Record test results and the treatment provided in the woman's card.

Audit

Input indicators

- National standards and locally adapted guidelines for the control of iron deficiency anaemia are available in health facilities.
- Iron/folate supplements are available and are properly managed.
- Staff are available in antenatal care (ANC) and postpartum care (PPC) to prescribe, provide and administer iron/folate supplements.

Process and output indicators

- The proportion of women routinely receiving iron/folate supplements during ANC or PPC.
- The proportion of women receiving dietary advice during ANC and PPC.
- The proportion of women with severe anaemia referred.

Outcome indicators

- Maternal mortality associated with severe anaemia.
- Maternal complications associated with severe anaemia.
- Perinatal mortality associated with severe anaemia in pregnancy.
- Incidence of low birth weight associated with anaemia in pregnancy.

Rationale

Burden of suffering

Iron-deficiency anaemia is the most common micronutrient deficiency in the world, affecting more than two billion people globally *(1)*. It contributes to low birth weight, lowered resistance to infection, poor cognitive development and reduced work capacity *(1)*. Pregnant and postpartum women and children aged 6–24 months are usually the most affected groups *(1,2)*. It is highly prevalent in less developed countries, where, in addition to poor nutrition, parasitic and bacterial infections can contribute to depletion of iron reserves *(1–4)*.

Anaemia in pregnancy is defined as haemoglobin <11g/dl or haematocrit <33% *(1)*. It aggravates the effects of maternal blood loss and infections at childbirth, and is associated with increased maternal and perinatal mortality and morbidity *(3,4)*. Where anaemia is prevalent, iron deficiency is usually the most common cause *(1)*.

A substantial reduction in iron deficiency anaemia by the year 2000 was among the most important nutritional goals adopted by the first World Summit for Children (1990), reiterated by the International Conference on Nutrition (1992) *(1)*.

Efficacy and effectiveness

Anaemia prophylaxis

Where the prevalence of anaemia in pregnant women is <40%, a dose of 60 mg iron and 400 µg folic acid daily for 6 months is considered to meet the physiological requirements for iron in pregnancy. If the duration of supplementation is shorter, a higher dose (120 mg) is recommended. However, the majority of the systematic reviews on this

topic refer to a dose of around 100 mg iron and 350–500 μg folic acid daily for 16 weeks or more during pregnancy *(5–7)*. In areas with a higher prevalence of anaemia, it is recommended that supplementation continue for three months postpartum.

Based on the possible association between maternal anaemia and negative perinatal outcome *(8)*, it is assumed that effective iron-supplementing programmes where anaemia is prevalent may reduce the incidence of low birth weight and perinatal mortality, as well as maternal mortality and obstetrical complications associated to severe anaemia. According to currently available reviews, however, while there is clear evidence of a positive effect of routine iron supplementation during pregnancy in preventing low haemoglobin at delivery or at six weeks postpartum *(5,6)*, there is no evidence of any effect, beneficial or harmful, on clinical outcomes for the mother and the baby *(5,6)*. The lack of a positive effect might be due to the small sample size in the studies that tried to assess those clinical aspects. The results of the largest trial included in one review suggest that routine iron supplementation may reduce the need for postpartum blood transfusions *(5)*. This result must be interpreted with caution since, as noted by the authors of the review, the trial was not blind in respect of treatment allocation and therapeutic decisions could thus have been biased. Nevertheless, if confirmed, this result could have implications in HIV-prevalent areas.

Anaemia treatment

There is consensus on the need for higher dosages in treating women with anaemia *(9)*. There is evidence that a combined treatment with iron and vitamin A could have a greater impact in anaemia treatment during the second trimester of pregnancy *(9)*. Severe anaemia is not frequent, but may cause a large proportion of severe morbidity and mortality related to iron deficiency. Prompt detection and timely treatment or referral of women with severe anaemia are therefore important at the primary care level. With proper training, and using a multiple-site assessment (inferior conjunctiva, palm and nail bed) *(10)*, health workers can assess extreme pallor or very low haemoglobin levels with reasonable sensitivity and high specificity *(10–12)*. Further improvement of the sensitivity and specificity of the clinical assessment could be achieved by adding a few anamnestic symptoms to the pallor assessment and using a simple colorimetric scale *(12)*.

Since the effectiveness of oral iron supplementation is hindered by many factors, including supply problems and poor adherence to regimens owing to the frequency of side-effects *(5,13,14)*, a variety of other interventions have been proposed to prevent and correct iron-deficiency anaemia, including food fortification, healthy dietary education and antiparasitic treatment. The effectiveness of these interventions is still unclear. Dietary improvements *(15)* and fortification of water *(16)* and foods *(17)* are not supported by strong evidence of effectiveness, while control of parasitic (helminth and plasmodium) infections seems to enhance iron prophylaxis and the efficacy of therapy *(14,18)*. More research is needed in communities where iron-deficiency anaemia is prevalent to establish the most appropriate strategies.

There is promising evidence from studies whereby iron cooking pots are introduced at community level. Cooking in iron pots has led to a significant increase in haemoglobin concentrations, especially among adults *(19)*, but there are problems of acceptability (pots are heavy and when not properly dried will become rusty) *(20)*.

The table below summarizes the evidence from the most relevant studies. The level of evidence is presented using the NICE methodology which applies a coding from 1 (high level) to 4 (low level). For details, see also the *Introduction to the Standards for Maternal and Neonatal Care* and the *Process to develop the Standards for Maternal and Neonatal Care* on http://www.who.int/making_pregnancy_safer/publications/en. For an overview of a comprehensive list of evidence, please refer to the reference section of the standard.

Study (Type & Level of evidence)	Population & Setting	Objective & intervention	Outcomes linked to the Standard	Results	Comments
5. Mahomed 2004 Most recent substantive amendment, August 1997 **Systematic review** **1++**	20 trials; pregnant women prior to 28 weeks' gestation and with normal haemoglobin levels (>10 g/dl) (number of enrolled women not specified) Europe, North America, Australia, Gambia, India, Myanmar, Niger Baseline risk Low pre-delivery haemoglobin level – minimum 9% – maximum 56% Low post-delivery haemoglobin level – minimum 9.7%	To assess the effects of iron supplementation on haematological and biochemical parameters and on pregnancy outcomes Intervention: 100 mg elemental iron orally compared with placebo or no treatment In one study: iron given routinely vs iron given selectively to women with haemoglobin <10 g/dl	Low pre-delivery haemoglobin (<10 g/dl) Low haemoglobin 6 weeks postpartum Caesarean section Mother: blood transfusion needed Stillbirth/neonatal death Side-effects from treatment avoided	*Iron vs no iron* min. NNT [a] 13 (12–14) max. NNT 2 (2–3) 12 studies, 1802 women min. NNT 15 (13–19) max. NNT 7 (6–10) 2 studies, 1482 women *Selective vs routine iron* NNH [b] 42 (20–369) NNH 75 (31–1011) NNT 200 (150–13 459) NNT 11 (9–13) 1 study, 2694 women	Comment from the authors: increase in caesarean sections and blood transfusions in the selective iron supplementation group possibly due to fear of midwife and doctors (not blind to treatment)
6. Mahomed 2004 Most recent substantive amendment, August 1997 **Systematic review** **1++**	8 trials involving 5449 pregnant women prior to 28 weeks' gestation and with normal haemoglobin levels (>10g/dl) including adolescent women Myanmar, Nigeria, United Kingdom, Baseline risk Low pre-delivery haemoglobin level – minimum 14% – maximum 56% Low post-delivery haemoglobin level – minimum 10% – maximum 20% Caesarean section – minimum 9% – maximum 11%	To assess the effects of routine iron and folate supplementation on haematological and biochemical parameters and on pregnancy outcomes Intervention: 100 mg elemental iron plus 350 µg folic acid taken daily by mouth compared with placebo or no treatment	Low pre-delivery haemoglobin (<10 g/dl) Low haemoglobin 6 weeks postpartum Caesarean section Low birth weight Stillbirth/neonatal death	*Iron & folic acid vs placebo* min. NNT 9 (9–10) max. NNT 3 (2–3) 6 studies, 1099 women min. NNT 11 (11–12) max. NNT 5 (5–6) 2 studies, 2896 women min. NNT 14 (12–69) max. NNT 11 (9–55) 2 studies, 104 women NS [c] 1 study, 48 women NS 1 study, 48 women	Results of relevant clinical outcomes are based on a very small single study (low birth weight, stillbirth, preterm delivery)

[a] Number needed to treat. (95% confidence interval)
[b] Number needed to harm. (95% confidence interval)
[c] Non-significant

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2. *Mother–baby package: implementing safe motherhood in countries.* Geneva, World Health Organization, 1996 (document WHO/FHE/MSM/ 94.11) (http://www.who.int/reproductive-health/publications/MSM_94_11/MSM_94_11_table_of_contents.en.html, accessed 13 December 2004).

Study (Type & level of evidence)	Population & setting	Objective & intervention	Outcomes linked to the standard	Results	Comments
13. Sloan, Jordan & Winikoff 2002 **Systematic review** **1++**	23 randomized controlled trials, 15 of which conducted in developing countries; the majority set in antenatal clinics; only 2 set in rural areas; around 1000 pregnant women Average baseline haemoglobin level <11 g/dl	To review the efficacy of iron supplementation on haemoglobin level in pregnant women Here results refer only to developing country studies Supplementation dosages vary from <60 mg/day to >120 mg/day, the majority being >90 mg/day	Haemoglobin increase by daily dose of iron supplement Haemoglobin increase by additional effect of folate Haemoglobin increase by iron and antimalarials Haemoglobin increase by iron and vitamin A Adherence to supplementation	60 mg: + 0.41 (±0.027) g/dl 61–90 mg: + 0.86 (±0.018) g/dl 91–120 mg: + 1.87 (±0.027) g/dl >120 mg: + 1.78 (±0.042) g/dl No additional effect of folate compared to iron alone (6 studies) Only one small study: iron + antimalarial is not more effective than antimalarial alone In one study there is additive effect The majority of the studies reported it as a problem Only two studies quantify this aspect: 42% adherence that increases (61%) with slow-release gastric delivery system; low adherence is due to side-effects and these are dose-dependent	The authors question the opportunity of recommending large-scale, public health oral iron supplementation programmes as a means of reducing global maternal anaemia and call for further studies to determine the effectiveness of other approaches (prevention of hookworm infection, food fortification, prenatal prophylactic treatment of falciparum malaria)
10. Stoltzfus et al. 1999 Validation study	945 pregnant women and 720 women at 3 months postpartum from rural area Nepal	To study the association between clinical pallor as detected by health workers opportunely trained and haemoglobin concentration (sensitivity and specificity) Clinical pallor assessed in three sites: inferior conjunctiva, palm and nail bed Two days of training	Haemoglobin 10 g/dl – sensitivity – specificity Haemoglobin 9 g/dl – sensitivity – specificity Haemoglobin 8 g/dl – sensitivity – specificity Haemoglobin 7 g/dl – sensitivity – specificity	Pregnancy / 3 months postpartum 18.2% / 35.7% 94.1% / 94.3% 28% / 51.5% 93.4% / 92.2% 45.8% / 62.7% 92.3% / 89.8% 67.5% / 81.0% 91.5% / 88.1%	Multiple site assessment is highly recommended (increase in sensitivity with just slight decrease of specificity)

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