South African National Essential Medicine List
Primary Healthcare Medication Review Process
Component: Obstetrics

1. Executive Summary

Date: 6 November 2017
Medicine (INN): Iron preparations, oral - intermittent dosing
Medicine (ATC): B03A
Indication (ICD10 code): Iron supplementation in pregnancy (O26.9)
Patient population: Pregnant women
Prevalence of condition: n/a
Level of Care: Primary level of Care
Prescriber Level: Nurse Practitioner
Current standard of Care: Iron preparations, oral - daily dosing
Efficacy estimates: (preferably NNT):
Motivator/reviewer name(s): Dr Sandy Picken
PTC affiliation: n/a

2. Name of author(s)/motivator(s)

Author: Dr Sandy Picken

3. Author affiliation and conflict of interest details

Affiliation: PHC Expert Review Committee; Knowledge Translation Unit, University of Cape Town.
Conflict of interest: None

4. Objective: Response to Cochrane Review: Intermittent oral iron supplementation during pregnancy, Peña-Rosas JP, 2015.

5. Background

Iron requirements increase during pregnancy, to accommodate foetal and placental needs, expansion of the maternal RBC mass, and blood loss during delivery.Iron and folic acid supplementation has been the preferred intervention to improve iron stores and prevent anaemia among pregnant women. Anaemia in pregnancy is defined as a haemoglobin (Hb)< 11 g/dL, most commonly due to iron deficiency. Treatment of anaemia is generally recommended when the Hb falls below 10g/dL.

Anaemia is a major global health problem affecting an estimated 38% of pregnant women worldwide(1).It is also a common problem in South Africa – a study by Tunkyi, showed the prevalence of anaemia in pregnancy in a regional health facility in South Africato be 42.7% (2). Furthermore, the Saving Mothers Report (2014) found that 39.4% of maternal deaths in South Africa (SA) were associated with anaemia, despite the fact that micronutrients (prophylactic iron, folic acid and multivitamins) are provided routinely throughout pregnancy(3).

6. Summary of evidence

The Cochrane review of intermittent regimens of iron supplementation during pregnancy (4)included

27 trials from 15 countries; however, only 21 trials (involving 5490 women) contributed data to the review's meta-analyses. It concluded that findings suggest that intermittent regimens produced similar maternal and infant outcomes as daily supplementation but was associated with fewer side effects and reduced the risk of high levels of Hb in mid and late pregnancy, although the risk of mild anaemia near term was increased. The conclusion continues to state that while the quality of the evidence was assessed as low (infant outcomes) or very low (maternal outcomes), intermittent may be a feasible alternative to daily iron supplementation among those pregnant women who are not anaemic and have adequate antenatal care.

A recent WHO guideline outlining recommendations on antenatal care for a positive pregnancy experience (5) summarises the evidence presented in this Cochrane review as follows:

"Low-certainty evidence suggests there may be little or no difference between intermittent and daily iron supplementation in the effect on anaemia at term (4 trials, 676 women; RR: 1.22,95% CI: 0.84–1.80). Moderate-certainty evidence shows that anaemia at or near term (defined as a Hb of < 110 g/L at 34 weeks of gestation or later) probably occurs more frequently with intermittent than daily iron supplementation (8 trials, 1385women; RR: 1.66, 95% CI: 1.09–2.53), and that intermittent iron supplementation is probably less likely to be associated with a Hb concentration of more than 130 g/L than daily iron (15 trials, 2616women; RR: 0.53, 95% CI: 0.38–0.74). No events of severe anaemia occurred in either group in six trials reporting this outcome (1240 women). The evidence on mean Hb concentrations at or near term and severe postpartum anaemia is of very low certainty.

Limited evidence on maternal morbidity from one small trial (110 women) was assessed as very uncertain. Maternal infections and maternal satisfaction were not evaluated in the review.
Moderate-certainty evidence shows that intermittent iron supplementation is probably less commonly associated with nausea than daily iron supplementation (7 trials, 1034 women; RR: 0.60, 95% CI: 0.37–0.97). However, the evidence on other specific side-effects (constipation, diarrhoea, heartburn or vomiting) or any side-effect is of very low certainty.

Low-certainty evidence suggests that intermittent iron supplementation may have a similar effect to daily iron supplementation on low birth weight (< 2500 g) (8 trials, 1898 neonates; RR: 0.82, 95%CI: 0.50–1.22). However, the evidence on preterm birth and very preterm birth was assessed as very uncertain. Evidence on the relative effects of intermittent versus daily iron supplementation on neonatal mortality is also very uncertain. Neonatal infections and small for gestational age outcomes were not included in the review".

Based on this, this WHO guideline (2016) concludes that intermittent oral iron and folic acid supplementation with 120 mg of elemental iron and 2800 µg (2.8 mg) of folic acid once weekly is recommended for pregnant women to improve maternal and neonatal outcomes if daily iron is not acceptable due to side effects, and in populations with an anaemia prevalence among pregnant women of less than20%.The WHO global prevalence of anaemia in 2011, estimated the percentage of pregnant women with blood haemoglobin concentration <11g/dL in South Africa was 30% (95% CI 13-54) (6), whilst a local study done estimated the prevalence of anaemia in pregnancy in a regional health facility in South Africa to be 42.7%(2).

EB Table A.2.2: Intermittent iron and folic acid supplements versus daily regimen with no iron

Source: Peña-Rosas JP, De-Regil LM, Gomez Malave H, Flores-Urrutia MC, Dowswell T. Intermittent oral iron supplementation during pregnancy. Cochrane Database Syst Rev. 2015;(19):CD009997.

Quality assessment							No. of women		Effect		Certainty
No. of studies	Design	Design limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Any intermittent iron regimen (with or without other vitamins and minerals)	Daily regimen (with same vitamins and minerals but no iron)	Relative (95% CI)	Absolute	
Maternal anaemia at term (Hb < 110 g/L at 37 weeks of gestation or more)											
4	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	54/339 (15.9%)	57/337 (16.9%)	RR 1.22 (0.84 to 1.8)	37 more per 1000 (from 27 fewer to 135 more)	⊕⊕OO LOW
Maternal anaemia at or near term (Hb < 110 g/L at 34 weeks of gestation or more)											
8	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	167/751 (22.2%)	99/634 (15.6%)	RR 1.66 (1.09 to 2.53)	103 more per 1000 (from 14 more to 239 more)	⊕⊕⊕O MODERATE
Severe anaemia at or near term (Hb < 70 g/L at 34 weeks of gestation or more)											
6	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/546 (0%)	0/504 (0%)	not estimable	not estimable	⊕⊕⊕O MODERATE
Severe postpartum anaemia (Hb < 80 g/L)											
1	randomized trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[2,4]	none	1/91 (1.1%)	2/78 (2.6%)	RR 0.43 (0.04 to 4.64)	15 fewer per 1000 (from 25 fewer to 93 more)	⊕OOO VERY LOW
Maternal haemoglobin concentration at or near term (in g/L at 34 weeks of gestation or more) (MD; better indicated by lower values)											
8	randomized trials	serious[1]	serious[5]	no serious indirectness	serious[2]	none	717	589	MD 2.57 lower (5.18 lower to 0.04 higher)	-	⊕OOO VERY LOW
Maternal high haemoglobin concentrations during second or third trimester (Hb > 130 g/L)											
15	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	154/1351 (11.4%)	252/1265 (19.9%)	RR 0.53 (0.38 to 0.74)	94 fewer per 1000 (from 52 fewer to 124 fewer)	⊕⊕⊕O MODERATE
Antepartum haemorrhage											
1	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,4]	none	1/55 (1.8%)	1/55 (1.8%)	RR 1 (0.06 to 15.59)	0 fewer per 1000 (from 17 fewer to 265 more)	⊕OOO VERY LOW

EB Table A.2.2: Intermittent iron and folic acid supplements versus daily regimen with no iron (continued)

Quality assessment							No. of women		Effect		Certainty
No. of studies	Design	Design limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Any intermittent iron regimen (with or without other vitamins and minerals)	Daily regimen (with same vitamins and minerals but no iron)	Relative (95% CI)	Absolute	
Placental abruption											
1	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,4]	none	0/55 (0%)	1/55 (1.8%)	RR 0.33 (0.01 to 8.01)	12 fewer per 1000 (from 18 fewer to 127 more)	⊕OOO VERY LOW
Any side-effects											
11	randomized trials	very serious[3]	serious[5]	no serious indirectness	no serious imprecision	none	198/916 (21.6%)	284/861 (33%)	RR 0.56 (0.37 to 0.84)	145 fewer per 1000 (from 53 fewer to 208 fewer)	⊕OOO VERY LOW
Diarrhoea											
5	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[6]	38/308 (12.3%)	35/305 (11.5%)	RR 0.8 (0.32 to 2)	23 fewer per 1000 (from 78 fewer to 115 more)	⊕OOO VERY LOW
Constipation											
6	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[6]	89/364 (24.5%)	87/369 (23.6%)	RR 0.85 (0.45 to 1.59)	35 fewer per 1000 (from 130 fewer to 139 more)	⊕OOO VERY LOW
Nausea											
7	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	33/520 (6.3%)	55/514 (10.7%)	RR 0.6 (0.37 to 0.97)	43 fewer per 1000 (from 3 fewer to 67 fewer)	⊕⊕⊕O MODERATE
Heartburn											
4	randomized trials	serious[1]	serious[5]	no serious indirectness	serious[2]	none	54/268 (20.1%)	59/265 (22.3%)	RR 0.75 (0.31 to 1.81)	56 fewer per 1000 (from 154 fewer to 180 more)	⊕OOO VERY LOW
Vomiting											
6	randomized trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	69/480 (14.4%)	50/474 (10.5%)	RR 1.3 (0.79 to 2.15)	32 more per 1000 (from 22 fewer to 121 more)	⊕OOO VERY LOW
Preterm rupture of membranes											
1	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,4]	none	0/40 (0%)	1/40 (2.5%)	RR 0.33 (0.01 to 7.95)	17 fewer per 1000 (from 25 fewer to 174 more)	⊕OOO VERY LOW

EB Table A.2.2: Intermittent iron and folic acid supplements versus daily regimen with no iron (continued)

Quality assessment							No. of women		Effect		Certainty
No. of studies	Design	Design limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Any intermittent iron regimen (with or without other vitamins and minerals)	Daily regimen (with same vitamins and minerals but no iron)	Relative (95% CI)	Absolute	
Low birth weight (< 2500 g)											
8	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	44/1026 (4.3%)	51/872 (5.8%)	RR 0.82 (0.55 to 1.22)	11 fewer per 1000 (from 26 fewer to 13 more)	⊕⊕OO LOW
Preterm birth (< 37 weeks of gestation)											
5	randomized trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	78/613 (12.7%)	72/564 (12.8%)	RR 1.03 (0.76 to 1.39)	4 more per 1000 (from 31 fewer to 50 more)	⊕OOO VERY LOW
Very preterm birth (< 34 weeks of gestation)											
2	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,4]	none	1/116 (0.9%)	1/111 (0.9%)	RR 0.98 (0.06 to 15.31)	0 fewer per 1000 (from 8 fewer to 129 more)	⊕OOO VERY LOW
Neonatal death (within 28 days after delivery)											
1	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,4]	none	1/400 (0.3%)	2/395 (0.5%)	RR 0.49 (0.04 to 5.42)	3 fewer per 1000 (from 5 fewer to 22 more)	⊕OOO VERY LOW

1. Most of the pooled effect provided by trials "B" or "C" without a substantial proportion (< 40%) from trials "C".
2. Wide CI crossing the line of no effect.
3. Most of the pooled effect provided by trials "B" or "C" with a substantial proportion (> 40%) from trials "C".
4. Small sample size and few events.
5. Severe unexplained heterogeneity.
6. Evident asymmetry in funnel plot with at least five trials.

The Cochrane review suggests that intermittent iron is a feasible alternative to daily iron supplementation among those pregnant women who are "not anaemic and have adequate antenatal care". Strategies should always be tailored to local conditions, and it may be important to keep in mind the large differences that exist in South Africa at provincial level that may impact on the success of intervention programmes in this regard(7). Basic antenatal care in South Africa prompts finger prick Hb screening at the booking visit and again between 28 and 32 weeks, and around 36 weeks. This method may not be accurate enough to monitor for anaemia if lower-dose antenatal iron regimens are used.

Furthermore, the effect of providing lower doses of antenatal elemental iron through intermittent regimes on longer-term health outcomes in childhood is unclear. The Cochrane review incorporates an initial RCT, conducted by Hanieh(8) comparing intermittent and daily supplementation on infant outcomes, where results showed no clinically important difference in birth weight and even showed improved infant cognitive outcomes at 6 months in favour of intermittent iron supplementation. However, Hanieh has gone onto conduct a prospective cohort study among children of 36 months of age, born to women previously enrolled in the same RCT(9). This study concluded that low-dose antenatal IFA supplementation (120 mg elemental iron per week) resulted in lower height-for-age Z-scores and motor composite scores in children compared with higher-dose antenatal IFA supplementation (420 mg elemental iron per week). This again highlights the importance of adequate iron stores during pregnancy and the need for careful monitoring when lower-dose antenatal iron regimens are used, which may not be guaranteed in a South African context.

	JUDGEMENT	**SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS**
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident [ ] Not confident [X] Uncertain [ ]	See above – overall assessment of quality of evidence in Cochrane review was low and very low.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [ ] Harms outweigh benefits [ ] Benefits = harms or Uncertain [X]	• Immediate side effects may be less with intermittent therapy. • Anaemia was present in 39.4% of women who died. Deaths due to obstetric haemorrhages most commonly occur at the primary level of care (38.2%)(3). • Longer term health outcomes still unknown.

<table>
<tr><td>THERAPEUTIC INTERCHANGE</td><td>Therapeutic alternatives available:
Yes [ ] No [X]

List the members of the group.

List specific exclusion from the group:</td><td>Rationale for therapeutic alternatives included:

References:

Rationale for exclusion from the group:

References:</td></tr>
<tr><td>VALUES & PREFERENCES / ACCEPTABILITY</td><td>Is there important uncertainty or variability about how much people value the options?
Minor [ ] Major [ ] Uncertain [X]

Is the option acceptable to key stakeholders?
Yes [ ] No [ ] Uncertain [X]</td><td>Qualitative evidence suggests that the availability of iron supplements may actively encourage women to engage with ANC providers (low confidence in the evidence)(5, 10). However, where there are additional costs associated with supplementation or where the supplements may be unavailable (because of resource constraints) women are less likely to engage with ANC services (high confidence in the evidence). Women may find intermittent iron supplementation more acceptable than daily iron supplementation, particularly if they experience side-effects with daily iron supplements(5).</td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?

More intensive [ ] Less intensive [X] Uncertain [ ]</td><td>Cost of medicines/ month:
<table><tr><th>Medicine</th><th>Cost (ZAR)*</th></tr><tr><td>Ferrous Sulfate Co 170mg, daily (28d)</td><td>R3.15</td></tr><tr><td>Ferrous Sulfate Co 170mg, weekly (28d)</td><td>R0.45</td></tr></table>*Contract circular HP09-2016SD (R11.25/100 tabs)
Additional resources: n/a</td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?

Yes [ ] No [ ] Uncertain [X]</td><td>Intermittent iron and folic acid supplementation may have less impact on health inequalities than daily iron and folic acid supplementation, as anaemia is more common in disadvantaged populations(5). However, daily iron supplementation already forms part of the STG/EML.</td></tr>
<tr><td>FEASIBILITY</td><td>Is the implementation of this recommendation feasible?
Yes [ ] No [ ] Uncertain [X]</td><td>This is certainly feasible but may impact on messaging around importance of iron supplementation.</td></tr>
</table>

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	☐	☐	☒	☐	☐

Recommendation: Based on the evidence review above, the PHC Committee was of the opinion that intermittent iron is not appropiate as antenal supplemenattion for all pregnant women. Iron supplementation in pregnancy should be recommended as daily iron dosing. However, if iron is poorly tolerated, intermittent iron supplementation should be considered as an alternative.

Rationale: Current low quality evidence suggests that intermittent iron supplementation is as efficacious as daily dosing in pregnant women. "Moderate-certainty evidence shows that anaemia at or near term (defined as a Hb of < 110 g/L at 34 weeks of gestation or later) probably occurs more frequently with intermittent than daily iron supplementation (8 trials, 1385 women; RR: 1.66, 95% CI: 1.09–2.53)". Findings from Cochrane review suggests "that intermittent regimens produced similar maternal and infant outcomes as daily supplementation but were associated with fewer side effects and reduced the risk of high levels of Hb in mid and late pregnancy, although the risk of mild anaemia near term was increased"(4). Furthermore, local prevalence study estimates that 30-40% of pregnant women have anaemia (2).

Level of Evidence: I Systematic review, Prevalence study

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
X	X	

VEN status:

Vital	Essential	Necessary
	X	

Monitoring and evaluation considerations

Research priorities

References

1. Stevens GA, Finucane MM, De-Regil LM, Paciorek CJ, Flaxman SR, Branca F, et al. Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995-2011: a systematic analysis of population-representative data. The Lancet Global health. 2013;1(1):e16-25.
2. Tunkyi K, Moodley J. Prevalence of anaemia in pregnancy in a regional health facility in South Africa. S Afr Med J. 2015;106(1):101-4.
3. (NCCEMD) NCoCEiMD. SAving Mothers Annual report. 2014.
4. Pena-Rosas JP, De-Regil LM, Gomez Malave H, Flores-Urrutia MC, Dowswell T. Intermittent oral iron supplementation during pregnancy. The Cochrane database of systematic reviews. 2015(10):Cd009997.
5. WHO. WHO recommendations on antenatal care for a positive pregnancy experience. Geneva: World Health Organization.; 2016.
6. WHO. The global prevalence of anaemia in 2011. Geneva: 2015.
7. Visser J, Herselman M. Anaemia in South Africa: the past, the present and the future. S Afr J Clin Nutr. 2013;26(4).
8. Hanieh S, Ha TT, Simpson JA, Casey GJ, Khuong NC, Thoang DD, et al. The effect of intermittent antenatal iron supplementation on maternal and infant outcomes in rural Viet Nam: a cluster randomised trial. PLoS medicine. 2013;10(6):e1001470.
9. Hanieh S, Ha TT, Simpson JA, Braat S, Thuy TT, Tran TD, et al. Effect of low-dose versus higher-dose antenatal iron supplementation on child health outcomes at 36 months of age in Viet Nam: longitudinal follow-up of a cluster randomised controlled trial. BMJ global health. 2017;2(3):e000368.
10. Downe S, Finlayson K, Tunçalp Ö, Gülmezoglu AM. Factors that influence the uptake of routine antenatal services by pregnant women: a qualitative evidence synthesis. Cochrane Database of Systematic Reviews. 2016(10).