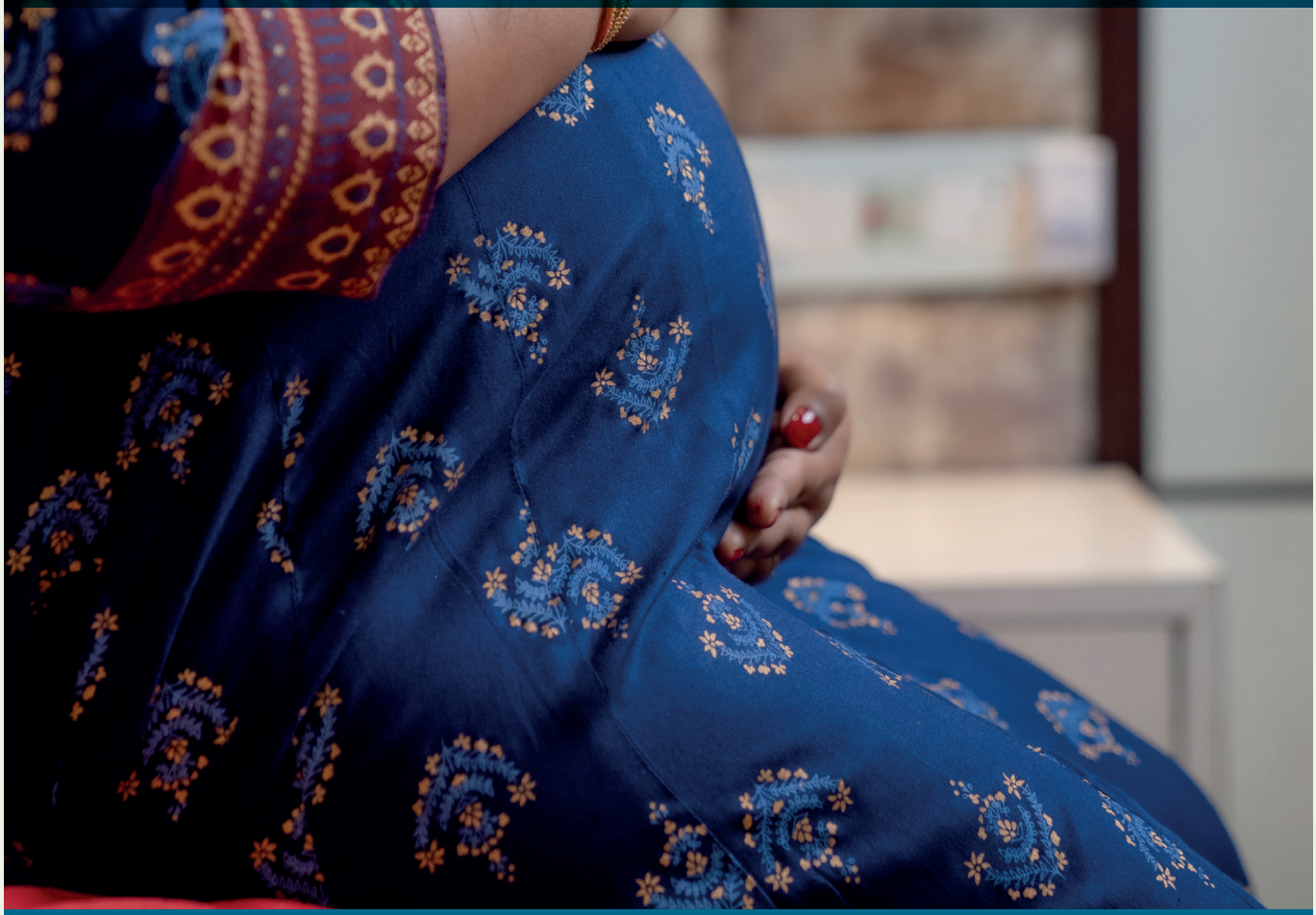
Multiple Micronutrient Supplementation in Pregnancy
TECHNICAL ADVISORY GROUP

HEALTHY MOTHERS HEALTHY BABIES

Interim Guidance for Concurrent Antenatal Multiple Micronutrient Supplementation and Anemia Treatment in Pregnant Women

October 2023



Overview

This document provides guidance on the use of antenatal multiple micronutrient supplements (MMS) alongside the treatment of anemia in pregnant women. It is intended for national decision-makers, technical advisory groups, and program implementers who are considering or implementing programs to introduce MMS, especially the United Nations International Multiple Micronutrient Antenatal Preparation (UNIMMAP). This interim guidance is based on the expert opinion of the MMS Technical Advisory Group (TAG).

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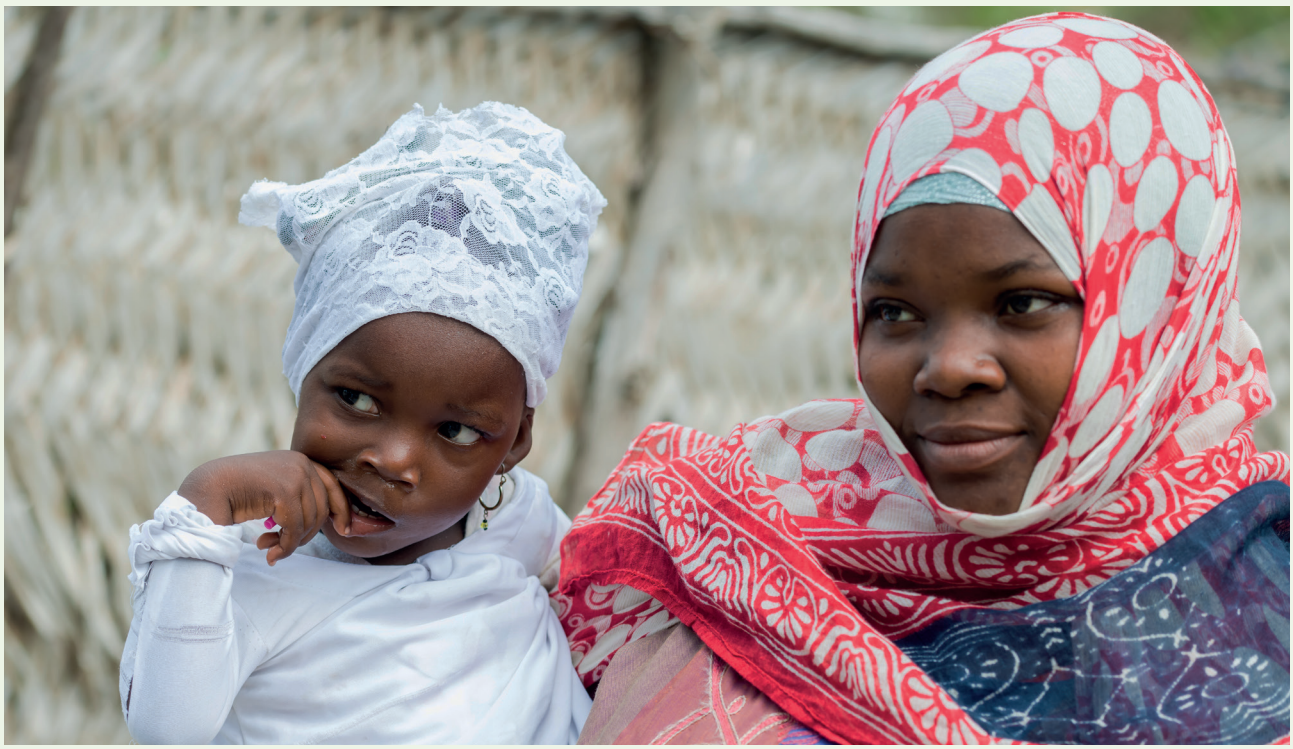


Key messages

1. MMS has benefits on maternal health and birth outcomes above and beyond iron and folic acid (IFA) supplementation, particularly for women with anemia.[1,2] It is being introduced as a preventive intervention for pregnant women in low- and middle-income countries, in the context of antenatal care informed by implementation research.
2. Globally, anemia affects about 32 million pregnant women.[3] If a pregnant woman is diagnosed with anemia, the World Health Organization (WHO) recommends treatment by increasing the total supplemental elemental iron dose to 120 mg per day,[4] although a lower dose may suffice. This treatment recommendation replaces the preventative recommendation of 30-60 mg of daily iron from IFA supplements until a woman's hemoglobin (Hb) concentration returns to normal (Hb ≥ 110 g/L).
3. Anemia is a complex condition with other nutritional (beyond iron) and non-nutritional causes. The WHO recommends context-specific preventative measures, including antenatal deworming and intermittent preventive treatment of malaria in pregnancy along with insecticide-treated bed nets.[4]
4. For anemia treatment, additional iron should be provided while daily MMS are continued as a preventive measure throughout pregnancy, as would be done with IFA supplementation. Once hemoglobin concentration rises to normal (Hb ≥ 110 g/L), MMS alone can be resumed.
5. MMS not only serves as a source of iron, but also provides other nutrients that can prevent other nutritional anemias caused by deficiencies of vitamins A, B2, B6, B9, B12, C, D and E, and the mineral copper,[5] and improve iron absorption/utilization. The benefits of MMS are particularly evident for anemic women.
6. If iron treatment does not demonstrate a rise in hemoglobin after a certain period, further assessments are necessary to identify other causes of anemia and determine the appropriate treatment according to the country's treatment protocols.

Background

Anemia is a condition in which the number of red blood cells or the hemoglobin concentration within them is lower than normal.[6] It is characterized by a decreased capacity of the blood to carry oxygen to the body tissues, causing fatigue, decreased productivity, poor cognitive and motor development in children, poor pregnancy outcomes, and increased morbidity and mortality.[6-9] According to a 2019 global estimate, 36% of pregnant women (32 million) suffer from anemia, with the most affected areas being the WHO African Region and the WHO South-East Asia Region.[3,10]

Anemia is a complex condition with multiple causes and risk factors, including nutritional deficiencies (iron and other micronutrients), infections, inflammation, gynecological and obstetric conditions, blood loss, and inherited red blood cell disorders. Iron deficiency anemia accounts for 10 to 60% of anemia cases, depending on the population and context.[10] Iron deficiency anemia occurs when the body does not have enough iron to produce sufficient hemoglobin. Pregnant women are particularly susceptible to this condition because of the significantly increased iron requirements imposed by pregnancy.[11] The Recommended Dietary Allowance (RDA) for non-pregnant and non-lactating women is 18 mg of daily iron, while the RDA for pregnant women is 27 mg per day.[12] In addition to taking routine iron-containing supplements (30-60 mg of daily iron) during pregnancy, the WHO also has context-specific recommendations that should be simultaneously considered for the prevention of maternal anemia.[4,10] These include providing deworming as a component of antenatal care, intermittent preventive treatment of malaria in pregnancy, and the use of insecticide-treated bed nets.

Deficiencies of micronutrients (vitamins and minerals, such as iron, zinc, vitamins A and D) are common among women of reproductive age, particularly in low- and middle-income countries as a result of inadequate dietary intake.[14,15] These deficiencies are magnified during pregnancy as the mother's requirements are increased to support fetal development.[16,17] MMS is an effective way to meet many of the micronutrient requirements for pregnancy in the context of inadequate diets. A solid body of evidence demonstrates that, when compared to IFA supplements, MMS is a safe and cost-effective intervention to reduce multiple maternal micronutrient deficiencies, promote adequate gestational weight gain, and reduce the risks of stillbirths, low birthweight, preterm birth, and small-for-gestational-age births.[1,2,18]

The most widely used MMS formulation is the United Nations International Multiple Micronutrient Antenatal Preparation (UNIMMAP), which was developed by the United Nations Children's Fund (UNICEF), along with the WHO and the United Nations University.[13] It contains 15 vitamins and minerals, including IFA (Table 1).

In anemic pregnant women, MMS provide even greater benefits when compared to IFA supplements alone.[1] In this context, MMS reduces the risk of low birthweight by 19%, small-for-gestational-age births by 8%, stillbirth by 21%, and infant death at 6 months by 29% (Table 2).[1,2] In addition, recent analyses suggest that MMS containing 30 mg of iron have similar effects in preventing maternal anemia when compared with IFA supplements containing 30 or 60 mg of iron.[19]

Table 1. UNIMMAP Composition[13]

Vitamin A	800 µg	**Folic acid**	400 µg
Vitamin D	200 IU	**Vitamin B12**	2.6 µg
Vitamin E	10 mg	**Copper**	2 mg
Vitamin C	70 mg	**Iodine**	150 µg
Thiamine	1.4 mg	**Iron**	30 mg
Riboflavin	1.4 mg	**Selenium**	65 µg
Niacin	18 mg	**Zinc**	15 mg
Vitamin B6	1.9 mg		

Table 2. Risk reduction of MMS (versus IFA supplements) for adverse birth outcomes in the overall group of pregnant women and the subgroup of anemic women[1]

Outcome	Risk reduction* in overall pregnant women	Risk reduction* in anemic pregnant women
Low birthweight	-12%	-19%
Small-for-gestational age birth	-3%	-8%
Preterm birth	-8%	–
Stillbirth	-8%	-21%
6-month mortality	–	-29%

*Risk reduction of MMS compared to IFA supplementation.

Diagnosis and management of anemia

Routine hemoglobin measurements are recommended throughout pregnancy to detect anemia. Anemia in pregnancy is defined as a hemoglobin value less than 110 g/L in the first or third trimester, or less than 105 g/L in the second trimester.[4,20]

There are many different causes of anemia, including nutritional deficiencies (e.g., iron, copper and vitamins A, B2, B6, B9, B12, C, D and E),[5] infections (e.g. soil transmitted helminthic infections, HIV), inflammation, genetic hemoglobin disorders, gynecological and obstetric conditions. Iron deficiency anemia in pregnancy can be defined as the hemoglobin cut-off for pregnancy, as defined earlier, in addition to a serum ferritin concentration < 30 µg/L.[21] In the absence of inflammation, serum ferritin provides information about the total body iron stores.[22]

While additional clinical assessment (e.g., assessment of ferritin levels, inflammation biomarkers) of anemic pregnant women should ideally be conducted to identify the cause of anemia and determine the specific course of treatment, in practice the most common approach is to **initiate oral iron when pregnant women are diagnosed with anemia, based on hemoglobin levels**. Thus, presumptive oral iron treatment is often recommended, and the WHO advises that *"If a woman is diagnosed with anemia during pregnancy, her daily elemental iron should be increased to 120 mg until her hemoglobin concentration rises to normal (Hb ≥ 110 g/L)"*.[4]

This practice is not only common in low and limited resource settings,[23] but is also a practical approach reported in high income countries.[24,25] For example, UK guidelines state that if anemia without an obvious other cause is detected, a diagnostic trial of oral iron should be given without delay and unselected routine screening of serum ferritin is not recommended, except in women with a known hemoglobinopathy to identify concomitant iron deficiency and exclude iron loading states.[24]

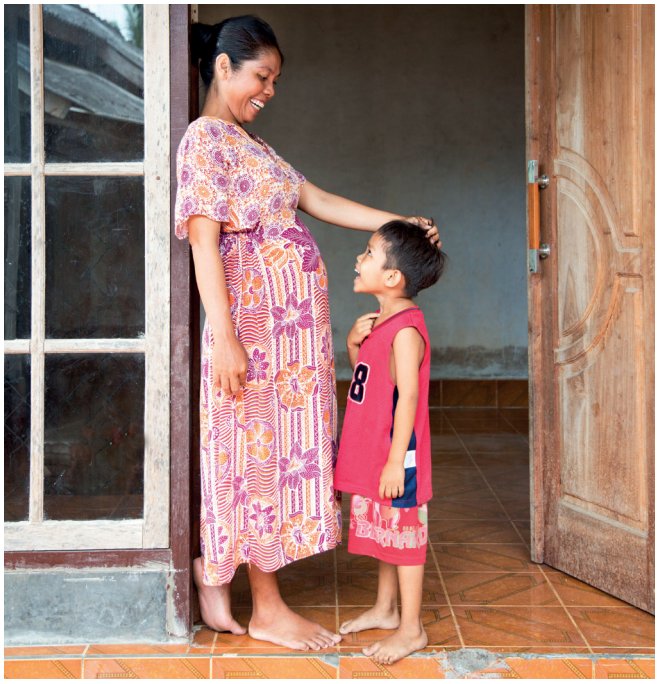
It should be noted that the WHO-recommended iron dose for treatment of anemia of 120 mg per day is based on scant evidence. Given that other guidelines[24] suggest treatment with 40-80 mg of iron, it is possible that a lower dose might be sufficient.

Furthermore, the required iron dose to reduce or eliminate the deficit in iron stores varies according to the duration of treatment, with longer treatment requiring a lower daily iron dose. For example, if the treatment to replenish iron stores in mild to moderate anemia requires a total dose of 5000 mg of iron, assuming 10% fractional absorption of iron – which is likely an underestimate, as iron absorption is generally increased during pregnancy – this could be achieved with 120 mg/day over 42 days or 90 mg of iron over 56 days.

Treatment instructions should be accompanied by appropriate counseling of the woman regarding the rationale for therapy, as well as presumptive guidance and self-care strategies to manage common side effects. Other context-specific antenatal care recommendations from the WHO, such as preventive anthelminthic treatment and interventions to prevent and control malaria in malaria endemic areas, should also be considered in the management of maternal anemia.[4]

Once iron treatment is initiated, a follow-up appointment – e.g., 2-4 weeks after treatment begins or at the next ANC visit, whichever comes first – should include assessment of adherence and response to the recommended supplementation regimen.

If there is an increase in hemoglobin demonstrating response to iron supplementation, another assessment later in pregnancy is required to determine if anemia has been fully corrected. If a rise in hemoglobin is not demonstrated after a certain period of iron treatment, an **additional assessment will need to be conducted to determine further treatment options, following the country's treatment protocols**, which are context-specific.



There are several reasons why a patient may not respond to iron treatment, including concurrent disease, malabsorption of iron, adherence challenges, and/or blood loss. Ultimately it is up to the clinician to decide which additional assessments are needed. Depending on the personal and family medical history, severity of anemia (which may determine the need for specialized/hospital-based care) and available resources, the additional investigations may include tests to diagnose malaria, HIV, parasites, and hemoglobinopathies, and determine full blood count. From the latter, the mean corpuscular volume (MCV) suggests the need for additional steps, e.g.,:

- A low MCV suggests iron deficiency anemia and requires iron studies (ferritin, total iron-binding capacity (TIBC) test, and % saturation)
- A normal MCV may require a peripheral smear and consultation with a hematologist
- A high MCV suggests folate and/or vitamin B12 deficiency and requires assessment of the status of these micronutrients.[23,26]

Oral iron supplements are mostly recommended to treat mild to moderate anemia. Most guidelines recommend intravenous iron for women who cannot tolerate or do not respond to oral iron, as well as for those with moderately severe to severe anemia (Hb ≤ 90 g/L).[20] The recommended treatment of severe anemia should follow the local standard of care, which may include intravenous iron or packed cell transfusion.

Two examples of protocols for anemia management during pregnancy in low- and middle- income countries, namely the guidelines for maternity care in South Africa[23] and the Malawi Obstetrics & Gynecology Protocols[26] are provided in appendices 1 and 2, respectively. These protocols demonstrate that the approach is complex, context-specific, and dependent on the personal history and severity of anemia.

Continued used of MMS during anemia treatment

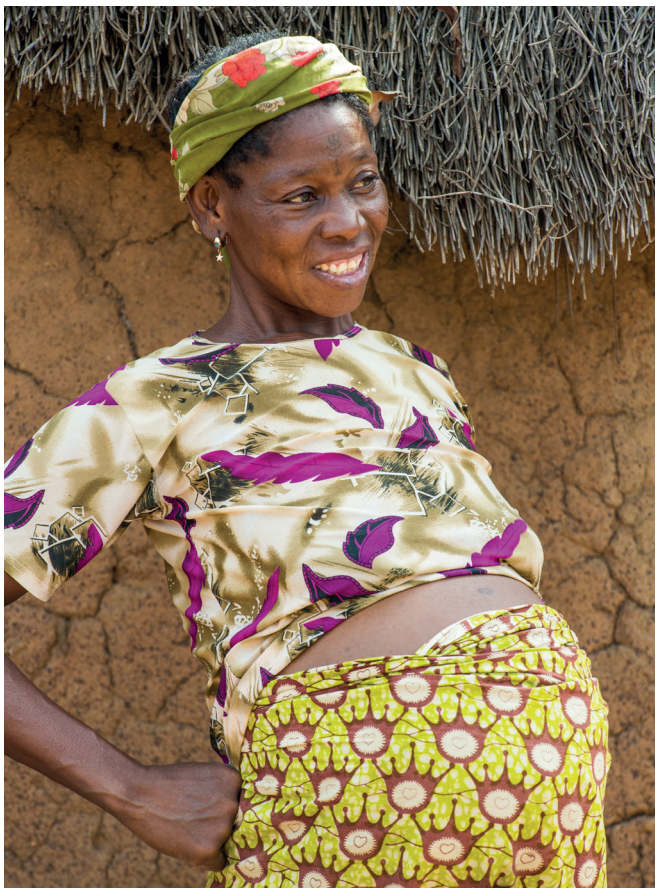
MMS is a preventive intervention that should be provided to pregnant women in low- and middle-income countries as part of antenatal care. The most commonly used formulation contains 30 mg of iron (in addition to several other vitamins and minerals), which is very close to the recommended intake of 27 mg/day of during pregnancy.[12]

If pregnant women develop anemia, additional iron supplements (or other interventions) for anemia treatment can be provided. However, the continued use of daily MMS should be encouraged.

If the target iron dose for anemia treatment is 120 mg/day as per the WHO guidelines,[4] depending on the type of iron supplements available, this can be achieved through the combination of, e.g.,:

- One MMS containing 30 mg of elemental iron + three iron supplements containing 30 mg of elemental iron each, or
- One MMS containing 30 mg of elemental iron + one iron supplement containing 30 mg + one iron supplement containing 60 mg of elemental iron (or, if not available, IFA containing 60 mg of iron).

Ideally, the additional elemental iron required for anemia treatment should not come from IFA supplements, since the combination of different sources of folic acid (from MMS, IFA, and diet) may exceed the tolerable upper intake level of 1000 ug/day and the potential risks of long-term excessive intake of folic acid in pregnant women are not known.[27-29] However, in some countries this may not be possible, and in these instances, IFA may be used for anemia treatment.



As mentioned above, the optimal dose of iron for treating anemia during pregnancy has not yet been determined and it is possible that a dose lower than 120 mg of iron might be sufficient (e.g., UK guidelines suggest a treatment dose of 40-80 mg[24]). Iron doses ≥60 mg have been shown to trigger a transient increase in circulating hepcidin that reduces iron absorption, but lower iron doses (< 40 mg) do not trigger this response in iron-deficient individuals, which is an argument in favor of using lower iron treatment doses.[30] Thus, the following combinations of supplements may be considered to provide a total treatment dose of 90 mg of elemental iron:

- One MMS containing 30 mg of elemental iron + one iron supplement containing 60 mg of elemental iron, or
- One MMS containing 30 mg of elemental iron + one IFA supplement containing 60 mg of elemental iron and 400 ug of folic acid, if iron supplements are not available. Despite the increased dose of folic acid, the total amount of this combination does not exceed the tolerable upper intake level of 1000 ug/day.

However, further research is needed to demonstrate the efficacy of lower doses of elemental iron in supplementation regimens that include MMS.

The continued use of MMS during anemia treatment with iron supplementation in pregnancy is important in low- and middle-income countries, where the evidence shows that MMS leads to lower risk of adverse birth outcomes, particularly among anemic women.[1,2] This practice of continued used of MMS during anemia treatment is also recommended in high income countries.[25] MMS will not only be a source of iron, but also provide vitamins A, B2, B6, B9, B12, C, D and E, and the mineral copper[5] (needed for synthesis of hemoglobin and/or erythrocyte production), which can prevent other types of nutritional anemias beyond iron deficiency and improve the absorption and/or utilization of iron. This may explain why the lower amount of iron in MMS (30 mg) has been shown to have effects comparable to the higher amounts of iron (60 mg) in IFA on third trimester maternal anemia and hemoglobin concentration.[19]

Procurement of MMS and IFA

While MMS should be provided to all pregnant women as a component of appropriate antenatal care, iron supplements will still be needed for women who are diagnosed with anemia. Therefore, procurement plans should include MMS for the full duration of pregnancy and iron supplements for treatment duration of pregnant women diagnosed with anemia.

Future research

This document provides interim guidance on the use of MMS alongside the treatment of anemia during pregnancy. It is not based on a formal guideline development process, but rather on the expert opinion of the MMS TAG, taking into consideration the current, albeit limited, evidence. Future implementation research and clinical research are needed to draw firm conclusions, such as determining the ideal dose of iron for anemia treatment, particularly in the context of continuing to provide MMS.

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Appendices

Appendix 1

Protocol to manage anemia during pregnancy according to the guidelines for maternity care in South Africa[23]

Referral criteria

Refer from a primary health clinic/ community health center as follows:

- Hb < 6.0 g/dL: Urgent transfer to hospital the same day.
- Hb 6.0-7.9 g/dL: Urgent transfer to a hospital if symptomatic (dizziness, tachycardia, shortness of breath at rest). If not symptomatic, refer to the next high-risk clinic within one week.
- Hb 8.0 to 9.9 g/dL: Transfer to a high-risk clinic if no improvement after one month of treatment.
- Hb < 10 g/dL at 36 weeks gestation or more: Transfer to hospital for further antenatal care and delivery.

Management of mild anemia (hemoglobin 8-9.9 g/dL)

- Increase ferrous sulphate 200 mg to orally 3 times daily and continue with folic acid 5 mg orally daily.
- Follow up all women < 36 weeks pregnant with mild anemia with a repeat Hb after four weeks.
- If there is no response to oral iron/ folate treatment or if ≥36 weeks, refer to the district hospital for further investigations.
- If no response to oral iron treatment or if ≥36 weeks, and if iron deficiency confirmed (minimum investigation: full blood count), consider intravenous iron therapy (in hospitals only). Intravenous iron will raise the Hb faster than oral iron.
- Avoid blood transfusion if there are no other complications.

Management of moderate to severe anaemia (Hb ≤7.9 g/dL)

Investigate the anemia at the hospital/high risk clinic and look for underlying causes:

- Take blood for a full blood count (FBC): the mean cell volume (MCV) indicates the probable cause of anemia:
  - a below-normal MCV suggests iron deficiency anemia (microcytic).
  - a normal MCV suggests anemia of chronic disease (normocytic).
  - an above-normal MCV suggests folate or vitamin B12 deficiency anemia (macrocytic).
  - if the FBC shows a microcytic picture, it is reasonable to initially treat as iron-deficiency anemia.
  - if the FBC shows a normocytic or macrocytic picture, do further tests: iron studies, red cell folate and vitamin B12 levels to identify the cause.
- send urine away for microscopy and culture, and a stool sample for occult blood and parasites.
- do a malaria smear.
- start treatment for anemia with ferrous sulphate 200 mg oral 3 times daily, and continue with folic acid 5 mg oral daily.
- if the Hb is < 6.0 g/dL or if the patient is symptomatic (dizziness, tachycardia, shortness of breath at rest), then
- she must be admitted to hospital.
- avoid overloading with intravenous fluids.
- transfuse only if symptomatic.
- give one unit at a time over four to six hours.
- review need for further transfusion after each unit transfused, based on symptoms, rather than Hb level. Give furosemide 20 mg intravenously after each unit transfused.

If there is a failure to respond to oral iron therapy, compliance with the supplements should be checked and the results of iron studies, red cell folate and vitamin B12 levels should be checked and treat accordingly. If there is no response to oral iron treatment or if ≥36 weeks, and if iron deficiency confirmed, consider administering parenteral iron therapy (in hospitals only).

Appendix 2

Protocol to manage anemia during pregnancy according to the Malawi Obstetrics & Gynecology Protocols[26]

Anemia in pregnancy is defined as Hb < 11 g/dL (severe anemia as Hb < 7 g/dL) at any gestational age.

Iron deficiency and acute blood loss are the most common causes of anemia in pregnancy, but other causes should be considered with severe anemia.

Diagnosis

History: easy fatigability, dizziness, headache, palpitations, PV bleeding.

Exam: pallor, tachycardia, +/- jaundice, +/- splenomegaly, +/- petechiae.

Investigations: point-of-care Hb to determine severity immediately; malaria RDT (or peripheral smear), stool for ova and parasites, FBC if Hb < 8 g/dL, HIV.

Management

- Check FBC and treat according to the result.
  - If Hb < 7 g/dL, especially if symptomatic, then blood transfusion.
    - Transfuse rapidly if anemia due to acute blood loss.
    - Transfuse slowly if chronic anemia (Consider use of diuretics as necessary to reduce risk of congestive cardiac failure due to sudden circulatory overload).
    - Treat with folate and FeFol 325 mg PO BD and recheck Hb in 2-4 weeks.
  - If MCV < 80, then send blood for iron studies (ferritin, TIBC and % saturation) if available.
  - If MCV 80-93, then send blood for peripheral smear and consult hematologist as needed.
  - If MCV ≥ 94, then treat for folate or vitamin B12 deficiency.
- Treat with Albendazole 400 mg once on empty stomach.
- Treat for malaria or schistosomiasis if indicated.
- Mixed anemia may occur and complicate laboratory findings.
- If Iron deficiency, then treat with elemental iron 200 mg PO OD. Titrate up to reduce side effects and encourage compliance. Take iron on empty stomach with vitamin C and without antacids.
- If folate deficiency, then treat with folate 1-4 mg PO OD.
- If vitamin B12 deficiency, then treat with vitamin B12 1000 mcg IM q week x 4 weeks, then 1000 mcg IM monthly or until deficiency is corrected.
- If hemolytic anemia, then send blood for direct and indirect Coombs tests.
  - Treat with corticosteroids.
  - Drug-induced (i.e. methyldopa, penicillin, cephalosporin) hemolytic anemia is typically milder and is treated by stopping the offending medication.

About HMHB and MMS TAG

The Healthy Mothers Healthy Babies (HMHB) Consortium is a collective working to raise awareness, drive policy change, and strengthen the implementation of women's nutrition interventions, especially MMS. Coordinated by HMHB, MMS TAG is an interdisciplinary, diverse group of members with expertise in nutrition, maternal health, and public health that serve to interpret the evidence on MMS and provide high-fidelity guidance for stakeholders and decision-makers, including national governments, considering introduction and use of MMS in antenatal care services.

HMHB is hosted by the Micronutrient Forum, a non-profit organization that serves as the central global platform for evidence, collaboration, and advocacy on micronutrient health.

For additional support or feedback, please contact **hmhb@micronutrientforum.org**