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# Controlling Maternal Anemia and Malaria

## Ensuring Pregnant Women Receive Effective Interventions to Prevent Malaria and Anemia: What Program Managers and Policymakers Should Know

### Background

The relationship between maternal anemia and both malaria in pregnancy (MIP) and nutritional deficiencies has been well documented. Pregnant women are particularly vulnerable to malaria infection and iron deficiency, which increase the risk of poor maternal and newborn outcomes including maternal anemia, maternal death, spontaneous abortion, stillbirth, prematurity, low birth weight, and newborn and infant death.<sup>1,2</sup>

This brief describes WHO recommendations for IPTp to prevent MIP and iron-folic acid (IFA) supplementation to prevent iron deficiency anemia in sub-Saharan Africa (SSA) countries, with an emphasis on giving the correct dose of folic acid to maximize the effectiveness of interventions to prevent malaria. The brief is for program managers of health programs and policymakers to guide them in designing programs and developing policies.

### Prevention of Malaria and Anemia

Routine IPTp using SP<sup>3</sup> is recommended by WHO in areas of moderate to high malaria transmission. IFA supplementation during pregnancy also is recommended by WHO and is recommended by the ministries of health in SSA countries. Table 1 shows the WHO regimen for IPTp-SP.<sup>4</sup>

### Key Messages

- Iron deficiency and malaria cause anemia in pregnancy, which increases the risk of poor delivery and birth outcomes.
- An integrated package of interventions is needed to prevent malaria, iron deficiency, and anemia in pregnancy.
- Countries should update their policies and guidelines to reflect World Health Organization (WHO) recommendations for preventing malaria and anemia in pregnancy and ensure that health providers are trained in their use.
- To ensure the effectiveness of sulfadoxine-pyrimethamine (SP) as an antimalarial when administered as intermittent preventive treatment for malaria in pregnancy (IPTp), the dose of folic acid should be limited to less than 5 mg—ideally, a combined supplement with 60 mg of iron and 0.4 mg of folic acid should be used.
- Both supply- and demand-side barriers need to be addressed to make the package of interventions effective.

Source: WHO 2013;<sup>1</sup> WHO 2012.<sup>2</sup>

<sup>1</sup> WHO. 2013. "Policy Brief for the Implementation of Intermittent Preventive Treatment of Malaria in Pregnancy Using Sulfadoxine-Pyrimethamine (IPTp-SP)."

<sup>2</sup> WHO. 2012. "Guideline: Daily Iron and Folic Acid Supplementation in Pregnant Women." Geneva: WHO.

<sup>3</sup> WHO refers to IPTp as IPTp-SP; therefore, this notation has been used throughout this document.

<sup>4</sup> WHO. 2013. "Policy Brief for the Implementation of Intermittent Preventive Treatment of Malaria in Pregnancy Using Sulfadoxine-Pyrimethamine (IPTp-SP)."

**Table 1: WHO Recommendation for IPTp-SP at Each Scheduled Antenatal Care (ANC) Visit**

|   |  |
|---|--|
| <b>Where malaria transmission is moderate to high</b>   | Give three SP tablets each containing 500 mg of sulfadoxine and 25 mg of pyrimethamine.  |
| <b>Where malaria transmission has been reduced but where there are no data to determine whether to stop IPTp-SP</b> | Use same regimen as above.   |
| <b>Mode of administration</b>   | IPTp-SP should be given as directly observed therapy (DOT) at each ANC visit, starting as early as possible in the second trimester <sup>5</sup> until the time of delivery, with each dose given at least 1 month apart.<br><br>IPTp-SP should not be given to women on cotrimoxazole because of a higher risk of adverse events. |

Table 2 shows the WHO regimen for IFA supplementation in pregnancy.<sup>6</sup>

**Table 2: WHO Recommendation for IFA Supplementation to Prevent Anemia in Pregnancy**

|  |  |
|--|--|
| <b>Where anemia prevalence in pregnancy is less than 40%</b> | Give 30-60 mg of elemental iron and 0.4 mg of folic acid.                                  |
| <b>Where anemia prevalence in pregnancy is 40% or more</b>   | Give 60 mg of elemental iron and 0.4 mg of folic acid.                                     |
| <b>Mode of delivery</b>                                      | Give daily starting as early as possible in pregnancy and continuing throughout pregnancy. |

Women should start taking IFA in their first trimester and continue taking it until they deliver. For women who attend ANC late in pregnancy, IFA supplementation should continue during the postpartum period.<sup>7</sup> To ensure folic acid does not interfere with SP as an antimalarial, WHO recommends a dose of 0.4 mg of folic acid daily. A daily dose of 5 mg folic acid or more should not be given concurrently with IPTp-SP as this counteracts the efficacy of IPTp-SP as an antimalarial.<sup>8</sup>



A health professional holds her hand next to that of a woman who is severely anemic in Lindi Hospital, Lindi, Tanzania

Table 3 reviews complementary actions when giving IPTp-SP, which is administered by a health professional, and IFA supplements, which are self-administered.

<sup>5</sup> IPTp-SP should not be started in the first trimester.

<sup>6</sup> WHO. 2012. "Guideline: Daily iron and folic acid supplementation in pregnant women."

<sup>7</sup> Stoltzfus RJ, Dreyfuss ML. 1998. "Guidelines for the Use of Iron Supplements to Prevent and Treat Iron Deficiency Anemia." International Nutritional Anemia Consultative Group, World Health Organization, and United Nations Children's Fund (UNICEF). Washington, D.C.: International Life Sciences Institute.

<sup>8</sup> For more information, see: [http://www.who.int/malaria/publications/atoz/policy\\_brief\\_iptp\\_sp\\_policy\\_recommendation/en/](http://www.who.int/malaria/publications/atoz/policy_brief_iptp_sp_policy_recommendation/en/).

**Table 3: Complementary Actions for Health Workers When Giving IPTp-SP and IFA Supplements**

|                | Counseling  | Supervision   | Follow-up  |
|----------------|---|---|--|
| <b>IPTp-SP</b> | Provide messages on why IPTp-SP is important; what side effects might occur; when to return for follow-up.<br>Provide messages to sleep under long-lasting insecticide-treated bed nets (LLINs), which should be provided at the first ANC visit. | Health workers should administer IPTp-SP during routine ANC visits under directly observed therapy with the first dose starting early in the second trimester.  | IPTp-SP should be given at each scheduled ANC visit as long as each dose is 1 month apart. |
| <b>IFA</b>     | Provide messages on why, when, how many, and how long to take IFA; how to manage side effects, if they occur; when to return for follow-up.   | IFA supplements are taken at home; compliance can be improved when a family member observes pill-taking; a behavior change communication tool (e.g., a brochure, text message) can be used to motivate to take IFA and help women record their daily intake; the tool also can be used by health workers to monitor IFA intake. | Women should return to ANC, as needed, to receive a resupply of IFA supplements.           |

Because the causes of anemia vary by country or region, the mix of interventions to prevent and control anemia varies. In SSA, the intervention package for pregnant women should include IFA, IPTp, LLINs, and anthelmintics to control soil-transmitted helminths. Prompt treatment of malaria<sup>9</sup> and anemia with IFA supplements also should be part of the package (see below). Other important health- and nutrition-related interventions include optimal care at delivery and in the postnatal period, provision of family planning, and promotion of optimal nutrition, hygiene, and sanitation behaviors. Improving the supply of iron-rich foods and other micronutrient-rich foods through fortification and agriculture programs has the potential of reducing the nutritional causes of anemia and benefiting the nutritional status of all women of reproductive age as well as other family members.

### Treatment of Anemia

Pregnant women who have hemoglobin levels of less than 11.0 g/dL or who show clinical signs of pallor should be treated for anemia with a double dose of iron. Table 4 shows the WHO recommended<sup>10</sup> regimen for treating anemia and the dose of IFA depending on whether a combined IFA supplement is given or separate iron and folic acid supplements are given.



An anemic mother in Tanzania watches over her premature baby

<sup>9</sup> WHO. 2015. "Guidelines for the Treatment of Malaria." Geneva. WHO. Edition Three.

<sup>10</sup> WHO. 2012. "Guideline: Daily Iron and Folic Acid Supplementation in Pregnant Women."

**Table 4: WHO Recommendation for IFA Supplementation to Treat Anemia in Pregnancy**

| Regimen  | Type of supplement  | Total dose   | Length of time  |
|--|---|--|---|
| <b>120 mg elemental iron and 0.4 mg folic acid daily</b> | Combined IFA supplement with 60 mg of elemental iron and 0.4 mg of folic acid.                    | Two supplements of IFA per day providing: 120 mg elemental iron and 0.8 mg of folic acid.  | Until hemoglobin reaches normal (11.0 g/dL or above). |
|  | A separate supplement of elemental iron (60 mg) and a separate supplement of folic acid (0.4 mg). | Two supplements of iron per day providing: 120 mg of elemental iron<br>1 supplement of folic acid providing: 0.4 mg of folic acid. | Until hemoglobin reaches normal (11.0 g/dL or above). |

## Frequently Asked Questions about Folic Acid Use in Moderate to High Malaria Transmission Areas

### Why Is Folic Acid Given during Pregnancy?

Pregnant women are given 0.4 mg of folic acid primarily to meet the increased needs of the growing fetus and placenta because of rapidly dividing cells in the fetus and increased urinary losses during pregnancy.<sup>11</sup> Folic acid deficiency can cause anemia, but folic acid deficiency is a less common cause of anemia than iron deficiency and, where folic acid deficiency exists, 0.4 mg of folic acid is more than enough to prevent anemia.<sup>12,13</sup>

Humans obtain folate, the form of folic acid occurring in nature, exclusively from the diet. Folic acid may be given as a supplement or added to foods through fortification when dietary sources of folic acid are limited or insufficient to meet nutritional requirements. The active form of folic acid is tetrahydrofolate (THF), which is involved in deoxyribonucleic acid (DNA) synthesis; folic acid deficiency affects rapidly replicating cells, resulting in a number of cell changes that occur first in the blood and skin.<sup>14</sup> Folic acid also acts as a co-factor in enzymatic reactions in the body—for example, folic acid is a cofactor in the conversion of homocysteine to the amino acid methionine, which is needed for protein synthesis.<sup>15</sup>

### Why Should Folic Acid Be Limited When Giving IPTp-SP?

THF also is an essential vitamin for the malaria parasite, but, unlike humans, the malaria parasite can synthesize THF itself (*de novo* synthesis). SP prevents malaria from multiplying by acting as a folate antagonist, which means it blocks the synthesis of THF by the malaria parasite. However, the malaria parasite also can “salvage” the folic acid it needs to survive when folate is consumed or folic acid is taken as a supplement by the host.

### What Is the Evidence for Limiting the Dose of Folic Acid to Less than 5 mg?

In the mid-1980s, *in vitro* studies found folic acid reduced the effectiveness of SP as a treatment for *Plasmodium falciparum* malaria.<sup>16</sup> A study examining the efficacy for treatment of malaria in children 6 months to 9 years old found that co-administration of folic acid at a dose of 5 mg or more significantly

<sup>11</sup> WHO. 1968. “Nutritional Anaemias: Report of a WHO Scientific Group.” WHO Technical Report #405. Geneva: WHO.

<sup>12</sup> WHO. 2012. Guideline: Daily Iron and Folic Acid Supplementation in Pregnant Women. Geneva: WHO.

<sup>13</sup> Folic acid also causes neural tube defects (NTDs) in newborns, but because NTDs occur within 28 days after conception, taking IFA supplements during pregnancy will not prevent NTDs unless women take them before they become pregnant or intend to get pregnant.

<sup>14</sup> Gibson RS. 1990. *Principles of Nutritional Assessment*. New York and Oxford: Oxford University Press.

<sup>15</sup> Nzila A, et al. 2005. “Comparative Folate Metabolism in Humans and Malaria Parasites (Part I): Pointers for Malaria Treatment from Cancer Chemotherapy.” *Trends in Parasitology* 21: 292-8.

<sup>16</sup> Watkins WM, et al. 1985. Antagonism of Sulfadoxine and Pyrimethamine Antimalarial Activity *in vitro* by p-aminobenzoic acid, p-aminobenzoic Acid, p-amino-benzoylglutamic Acid and Folic Acid. *Molecular and Biochemical Parasitology* 14: 55-61.

increased the rate of treatment failure.<sup>17</sup> This finding was confirmed in a subsequent study in non-pregnant patients of all ages given SP with and without folic acid (2.5 mg daily for children younger than 2 years old and 5 mg daily for everyone 2 years and older) for treatment of acute, uncomplicated malaria.<sup>18</sup>

A study in pregnant women<sup>19</sup> investigated the effect of 0.4 mg and 5 mg doses of folic acid on treatment for malaria using SP. When pregnant women received the 0.4 mg dose of folic acid, treatment failure of SP was 14.5% after 14 days, which was similar to the treatment failure in women receiving a placebo (13.9%). In women who received the 5 mg dose of folic acid, treatment failure of SP was nearly twice as high at 27%. A second study in pregnant women showed that folic acid doses of 0.5-1.5 mg daily did not interfere with the efficacy of SP given as IPTp.<sup>20</sup>

## Are There Any Clinical Indications That Require a 5 mg Dose of Folic Acid?

There are no conditions during pregnancy that require more than 0.4 mg of folic acid.<sup>21</sup> Although folic acid deficiency is associated with an increased risk of neural tube defects (NTDs)—a debilitating birth defect in which the brain and spinal cord do not develop normally—folic acid must be administered immediately after conception to prevent NTDs as the neural tube closes within 28 days. Routine IFA supplementation begins when women attend their first ANC visit, usually several months after conception in most developing countries, making it too late to prevent NTDs. Folate-rich foods, folic acid supplements of 0.4 mg, or foods fortified with folic acid should be consumed before pregnancy to prevent NTDs.

## Are There Countries That Still Give the 5 mg Dose of Folic Acid?

Many countries have transitioned from giving pregnant women separate iron and folic acid supplements to the combined IFA supplement that has 0.4 mg of folic acid. This ensures the effectiveness of SP as an antimalarial for the prevention of malaria in pregnancy and also improves compliance because fewer pills have to be taken. This form of IFA is on the WHO Model List of Essential Medicines<sup>22</sup> and is available from UNICEF.<sup>23</sup> However, in some countries, the 5 mg dose may still be given, either routinely with a separate dose of iron or for treatment of anemia. Anecdotal reports suggest that even in countries that have made a policy change to provide the combined IFA supplement, excess supplies of the 5 mg dose of folic acid have yet to be removed from stores.

Discussions with nutritionists from African countries and other sources of information confirm that although about half of SSA countries are ordering the combined IFA supplement with the lower dose of folic acid, an equal number of countries are still ordering the higher dose of folic acid, which is not needed and interferes with SP as an antimalarial.

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<sup>17</sup> Van Hensbroek MB, et al. 1995. Iron, but Not Folic Acid, Combined with Effective Antimalarial Therapy Promotes Haematological Recovery in African Children after Acute Falciparum Malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 89:672-6.

<sup>18</sup> Carter JY, et al. 2005. Reduction of the Efficacy of Antifolate Antimalarial Therapy by Folic Acid Supplementation. *American Journal of Tropical Medicine and Hygiene* 73:166-70.

<sup>19</sup> Ouma P, et al. 2006. Randomized Controlled Trial of Folate Supplementation When Treating Malaria in Pregnancy with Sulfadoxine-Pyrimethamine. *PLoS Clinical Trials* 1:e28.

<sup>20</sup> Mbaye A, et al. 2006. "Lack of Inhibition of the Anti-malarial Action of Sulfadoxine-Pyrimethamine by Folic Acid Supplementation When Used for Intermittent Preventive Treatment in Gambian Primigravidae." *American Journal of Tropical Medicine and Hygiene* 74:960-4.

<sup>21</sup> There may be some health conditions that require a higher dose of folic acid; however, these conditions are rare. Giving a higher dose of folic acid to any individual should be made in consultation with Ministry of Health protocols.

<sup>22</sup> WHO. 2013. "Model List of Essential Medicines." Geneva: WHO.

<sup>23</sup> UNICEF Supply Catalogue. [https://supply.unicef.org/unicef\\_b2c/app/displayApp/\(layout=7.0-12\\_1\\_66\\_67\\_115&carearea=%24ROOT\)/do?rf=y](https://supply.unicef.org/unicef_b2c/app/displayApp/(layout=7.0-12_1_66_67_115&carearea=%24ROOT)/do?rf=y).

## Conclusions

Providing an effective and comprehensive package of services to pregnant women, including anemia and malaria prevention, improves outcomes for both the mother and her newborn. The Roll Back Malaria/MIP working group, recognizing the link between malaria and anemia, recently developed a consensus statement asking countries to ensure the use of the correct dose of folic acid (0.4 mg). Demographic and Health Surveys from SSA report that coverage of the full regimen for IFA and IPTp-SP is still low in most countries. To have an effective package, supplies of IFA supplements and IPTp-SP should be based on the estimated number of pregnant women in countries rather than past use of IFA or SP. For programs to be effective, both supply- and demand-side barriers need to be identified and addressed. To ensure the effectiveness of SP as an antimalarial when administered as IPTp, the dose of folic acid should be limited to less than 5 mg, ideally through the use of the combined IFA supplement, which provides 60 mg of elemental iron and 0.4 mg of folic acid. Current supplies of the 5 mg dose of folic acid should be reduced in stores and facilities at all levels. In addition, countries should update their policies and guidelines to reflect WHO recommendations for preventing malaria and anemia in pregnancy and ensure that health providers are trained in their use.

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