Mwangi MN, Roth JM, Smit MR, Trijsburg L, Mwangi AM, Demir AY, Wielders JP, Mens PF, Verweij JJ, Cox SE, Prentice AM, Brouwer ID, Savelkoul HF, Andang'o PE, Verhoef H. **Effect of Daily Antenatal Iron Supplementation on Plasmodium Infection in Kenyan Women: A Randomized Clinical Trial.** Journal of the American Medical Association, 2015, 314 (10):1009-1020.

Introduction

The anemia prevalence is alarmingly high in Africa, with almost 57% of the pregnant women affected (1). Iron deficiency is one of the major risk factors contributing to anemia; at least 20% of anemia among women in sub-Saharan Africa is due to iron deficiency (2). The World Health Organization recommends a daily supplement of oral iron and folic acid (IFA) (60 mg iron with 400 mcg folic acid) during pregnancy to reduce the risk of low birth weight, maternal anemia and iron deficiency (3). However, concerns have been raised that IFA supplementation may increase maternal malaria risk in areas of high malaria transmission (4). Although, a very recent Cochrane review concluded that iron supplementation does not increase the risk of clinical malaria in children when regular malaria prevention or management services are provided (5), this needs to be investigated in pregnant women in the context of malaria endemic settings.

The current issue of NNA presents the results of a randomized controlled trial published in the Journal of the American Medical Association (6). The objective of the trial was to examine the effect of antenatal iron supplementation on maternal plasmodium infection risk, maternal iron status and neonatal outcomes in rural Kenyan women.

Methods

The study was a double-blind, randomized placebo-controlled trial conducted from October 2011 to April 2013 in Nyanza Province, Kenya which is a malaria endemic rural area. Women 15-45 years of age were invited for "pregnancy screening" through a community-based surveillance program. Pregnancy and gestational age were ascertained by medical examination, urine pregnancy test and obstetric ultrasonography. Women who were pregnant between 13 and 23 weeks, planned to deliver in the pre-designated health facility and were likely to be available until 1 month postpartum were enrolled in the study after written, informed consent was obtained. A baseline venous blood sample was collected during a follow-up visit 14 to 21 days after the initial visit, and women were randomized to receive 60 mg elemental iron as ferrous fumarate or placebo supplements. Research assistants supervised supplementation intake daily to ensure high adherence to supplementation. Study participants and field staff were blinded to the intervention. All women received preventive anti-helminth chemotherapy before randomization, and during the intervention they received 5.7 mg

iron/day through flour fortification. They were referred to the health center for regular health services, including intermittent preventive treatment (IPT) for malaria, and were instructed not to take micronutrient supplements other than those supplied by the project field staff. Maternal venous blood, maternal placental blood, cord blood and placental biopsies were collected within 1 hour postpartum for facility deliveries and within 2 hours postpartum for home deliveries. Iron or placebo supplementation continued for 1 month postpartum, when maternal venous blood and neonatal capillary blood were collected.

The primary study outcome was maternal plasmodium infection at birth. Secondary outcomes were birth weight and gestational age at delivery, and maternal and infant iron status at 1 month after birth. Among 2015 women invited for pregnancy screening, 470 (23%) were randomized (237 to receive iron and 233 to receive placebo) and included in the intention-to-treat analysis. Plasmodium falciparum infection was assessed by rapid diagnostic test based on histidine-rich protein-2 (HRP2) and lactate dehydrogenase (pLDH) specific to either Plasmodium falciparum or to nonfalciparum human Plasmodium species. Placental biopsies were examined histologically to detect Plasmodium infection and real-time polymerase chain reaction (PCR) was used to detect Plasmodium falciparum-specific DNA in erythrocytes. Plasmodium infection at parturition was defined as positive if any one of these assessments was positive, independent of species. Iron status was assessed based on zinc protorphyrin, and plasma ferritin, soluble transferrin receptor and transferrin concentrations and inflammation based on C-reactive protein and alpha-1-acid glycoprotein concentrations. Multiple linear regression and multiple logistic regression was were used to compare effect estimates with or without adjustment for baseline factors. Subgroup analyses were performed to assess effect modification by baseline iron status and baseline proxy markers of immunity against malaria (gravidity, maternal age, HIV infection).

Results and conclusions

At baseline, 59.7% of women without inflammation were iron deficient (plasma ferritin <15 µg/L). Adherence in the iron and placebo groups was 100% and 99.1% respectively. Both groups were similar at baseline except for small disparities in marital status and gravidity. All women except 1 were in their early second trimester of pregnancy [median (IQR), wk: 17.6 (15.7-19.6) and 17.4 (15.6-19.8) for iron vs. placebo respectively].

At birth, there was no significant difference in maternal Plasmodium infection (past or present infection regardless of species) among women who received iron vs. placebo supplements (50.9% vs. 52.1%; crude difference: -1.2%; 95% CI: -11.8% to 9.5%; P=0.83). The effect of iron supplementation on maternal Plasmodium infection was not influenced by baseline characteristics or by IPT use. Iron supplementation resulted in a significant increase in birth weight (3202 g vs. 3053 g; crude difference: 150 g; 95% CI: 56 g to 244g; P=0.002), a reduced risk of low birth weight (4.3% vs. 10.3%; crude difference: -6.0% ; 95% CI: -11.1% to 0.8%; p=0.02) and an increase in gestational age at delivery (274.4 d vs. 271.0 d; crude difference: 3.4 d; 95% CI: 0.8 d to 5.9 d;

P=0.009). The effect on birth weight was greater among women who were iron deficient at baseline than those who were iron sufficient.

At 1 month postpartum, maternal hemoglobin concentration was significantly higher in the iron group compared with the placebo group (12.9 vs. 12.0 g/dL; crude difference: 0.9 g/dL; 95% CI: 0.6 to 1.2 g/dL; P=<0.001) and significantly fewer women were anemic (hemoglobin concentration <12.0 gm/dL; P=<0.001) and iron deficient (plasma ferritin concentration <15 µg/L; P=<.001). Neonatal mean plasma ferritin concentration was greater in the iron group vs. the placebo group (163.0 vs. 138.7 µg/L; crude difference: 17.5%; 95% CI: 2.4 to 34.8%; P=0.02) but there was no significant difference in hemoglobin concentration.

Policy implications

The study suggests that antenatal oral iron supplementation benefitted rural Kenyan women with singleton pregnancies by increasing birthweight of their newborn infants without a significant increase in risk of overall maternal Plasmodium infection when compared with placebo supplementation. The gain in birthweight was at least partly due to the increase in pregnancy duration. Gains in birth weight were independent of maternal gravidity, age, HIV infection, anemia and IPT use, which indicates that all defined subgroups may have benefitted. The results of this clinical trial may be applicable to pregnant women in other low and middle income countries, including other countries in the African region, and highlights the importance of increasing coverage of prenatal iron supplementation.

NNA Editor's Comments *

The trial by Mwangi and colleagues (6) demonstrated that 60 mg of oral iron supplementation during pregnancy in a malaria endemic setting of rural Kenya did not increase the prevalence of maternal Plasmodium infection at birth. The secondary outcomes of the trial were in line with a recent meta-analyses, which found that women taking iron supplements were less likely to give birth to a low-birthweight infant and have a lower risk of anemia and iron deficiency compared to women in the control group (7).

Because of the fairly small sample size, the study is not able to provide evidence of safety of iron supplementation during pregnancy. Unfortunately, the study only evaluated iron supplementation and did not include folic acid, which is the current recommendation by the World Health Organization (3). Folic acid may favor Plasmodium falciparum growth, inhibit parasite clearance of sulphadoxine-pyrimethamine (SP)-treated malaria and increase subsequent recrudescence (8). Further research is needed to evaluate the safety of combined iron folic acid use during pregnancy in malaria endemic areas using adequately powered study to detect small differences.

References

1. World Health Organization. Vitamin and Mineral Nutrition Information System (VMNIS): Worldwide prevalence on anaemia 1993-2005, accessed on June 15, 2016 through: http://www.who.int/vmnis/anaemia/prevalence/summary/anaemia_status_summary/en/
2. Black RE, Bhutta ZA, Alderman H, Ruel M, Gillespie S, Haddad L. Maternal and child nutrition - Authors' reply. Lancet 2013;382(9904):1551-2.
3. WHO. Guideline: Daily iron and folic acid supplementation in pregnant women: Geneva, World Health Organization; 2012.
4. Sazawal S, Black RE, Ramsan M, Chwaya HM, Stoltzfus RJ, Dutta A, et al. Effects of routine prophylactic supplementation with iron and folic acid on admission to hospital and mortality in preschool children in a high malaria transmission setting: community-based, randomised, placebo-controlled trial. Lancet 2006;367(9505):133-43.
5. Neuberger A, Okebe J, Yahav D, Paul M. Oral iron supplements for children in malaria-endemic areas. Cochrane Database Syst Rev 2016;2:CD006589.
6. Mwangi MN, Roth JM, Smit MR, Trijsburg L, Mwangi AM, Demir AY, et al. Effect of Daily Antenatal Iron Supplementation on Plasmodium Infection in Kenyan Women: A Randomized Clinical Trial. JAMA 2015;314(10):1009-20.
7. Pena-Rosas JP, De-Regil LM, Garcia-Casal MN, Dowswell T. Daily oral iron supplementation during pregnancy. Cochrane Database Syst Rev 2015;7:CD004736.
8. Kupka R. The role of folate in malaria - implications for home fortification programmes among children aged 6-59 months. Matern Child Nutr 2015;11 Suppl 4: 1-15.

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