**Micronutrient supplementation during pregnancy, birth weight and neonatal mortality in Uganda: a causal mediation analysis**

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**Background**

Low birth weight is a significant risk factor for neonatal death (death in days 0-28 of life). A prominent cause of low birthweight is maternal iron-deficiency anemia during pregnancy. Published literature on the association of antenatal iron/folic acid (IFA) supplementation and the risk of LBW and neonatal mortality is inconsistent. We aimed to explore whether antenatal IFA reduces neonatal mortality in Uganda and to examine if the protective effect of IFA supplementation on the risk of neonatal death is mediated through the improved birth weight.

## **Methods**We used a retrospective birth cohort from the 2016 population-based Ugandan demographic and health survey. We examined information on neonatal survival (time to death in days), sociodemographic, intake of IFA supplementation, antenatal care, antimalarial prophylaxis with sulfadoxine-pyrimethamine intermittent preventive treatment (SP-IPTp) during pregnancy, mode of delivery, place of delivery, tetanus toxoid (TT) injection during pregnancy and breastfeeding of 9,203 women and 17,202 live-born infants ≤ 5 y before the survey. Neonatal death was defined as the death of a live-born infant during the first 30 d of life. Multivariable Cox proportional hazards models were used to identify factors linked to neonatal death. We controlled for potential confounding factors associated with both the exposure to anemia prevention in pregnancy and birth outcomes, including maternal age and education and household wealth. We defined IFA intake as any intake of IFA by the mother during pregnancy. Birth weight was categorized as very low (VLBW), low (LBW), and normal (NBW). VLBW was defined as a birth weight of <2500 g or baby smaller than average as perceived by the mother, VLBW as <1500 g or very small baby as perceived by the mother and NBW as ≥ 2500 g or an average and larger baby as perceived by the mother). Causal mediation analysis treating the birth weight as a mediator was conducted to measure the direct and indirect effects of IFA on neonatal mortality.

## **Findings**The prevalence of pregnant women on IFA supplementation was 89%. The prevalence of LBW and VLBW of the live-births was 21% and 7% respectively. 474 (3%) babies died within the 30 d after birth, 320 (66%) died within the first 24 hours and 469 (99%) died within the first week of life (early neonatal mortality). IFA supplements during pregnancy was associated with a 56% reduction in neonatal mortality [(hazard ratio (HR): 0.44; 95% CI 0.31, 0.61); p <0.0001] and 26 % reduction in VLBW (HR; 0.74; 95% CI 0.60, 0.92, p=0.007), after controlling for potential confounding factors. IFA was not associated with LBW. There was a linear dose-response relationship between the category of birth weight and increased neonatal mortality (LBW versus NBW: Relative risk (RR): 1.39 95% ci: 1.05-1.81, p=0.02, VLBW versus NBW: RR; 3.6: 95% CI: 2.83-4.53, p=<0.0001). Causal mediation analysis showed that 6% of the effect of IFA supplement on reducing neonatal mortality was meditated through reducing the risk of VLBW (β= 0.001341, p<0.0001) but not through LBW (β=0.0005, p=0.18) and 94% of the causal effect were direct β=0.02, p<0.0001). Among the sociodemographic and birth characteristics, factors that significantly increased the risk of neonatal death included lack of antenatal TT injection, maternal education of less than secondary, lack of prenatal antimalarial prophylaxis with SP-IPTp, first-born infants, a birth interval of <24 months, maternal age at delivery of ≥30 y, birth in a private health center, and male neonates.

**Interpretation**

The use of antenatal iron/folic acid supplements during pregnancy is an important intervention to reduce neonatal mortality but its causal effect is weakly mediated through improved birth weight. The causal effect of iron/folic acid supplementation is likely to be direct. Nevertheless, other biological mechanisms that may explain the significant protective efficacy of iron/folic acid supplementation in reducing neonatal mortality need to be explored. A major limitation of this study is the lack of information on stillbirths and preterm delivery. So the effect of LBW on neonatal mortality could be underestimated.