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Micronutrients in pregnancy: Early investment, lifelong impact

Deficiencies of essential vitamins and minerals in pregnancy adversely affect health, development and survival of offspring. Early detection and prevention may have early and long-lasting benefits.

Vitamin and trace mineral deficiencies during pregnancy are a major public health concern in low-income countries, and appear to be particularly widespread in South Asia. Micronutrient requirements increase during pregnancy to meet physiologic changes of gestation and related fetal demands for growth and development. In poor societies these needs are superimposed on a diet chronically inadequate in essential nutrients due to lack of economic demand, stark seasonality in food insecurity, poor dietary bioavailability, pregnancy-related cultural food beliefs and practices, and a high burden of nutritionally demanding infections[1]. Micronutrients are essential for cell proliferation, differentiation, motility and maturation, and consequent tissue growth, development and function during gestation; yet, surprisingly few nutrients have received sufficient study to document the public health importance of their deficiencies during reproduction in poor societies. Those that have (e.g., vitamin A, iron, folic acid, zinc, iodine) reveal extensive inadequacy and consequence to mother and offspring.

For nearly two decades, the Johns Hopkins Center for Human Nutrition (JHU) has been, with support from the Gates Foundation, USAID and other funding agencies, investigating the extent and public health importance of maternal micronutrient deficiencies in Gangetic South Asia. Specifically, two large sites, in Nepal (Nepal Nutrition Intervention Project - Sarlahi, or NNIPS) and Bangladesh (JiVitA Project), have since the mid-nineties provided typical rural settings for the conduct of large epidemiological studies and intervention trials among 140,000 pregnant women and their nearly 100,000 live born infants. Two major studies, one in each site, have focused on understanding the potential health effects of multiple micronutrient supplementation during pregnancy on mothers and infants, in the short term and throughout later life stages.

The NNIPS Trial of Antenatal Micronutrient Supplementation: Short Term Effects

In 1999-2001, a double-blinded, placebo-controlled trial was conducted among 5000 mothers in the southern plains district of Sarlahi, Nepal (NNIPS-3), where multiple micronutrient deficiencies were evident early in pregnancy (***Figure 1***)[2]. The study evaluated the health and nutritional impact of four combinations of micronutrient supplements, all providing an approximate recommended dietary allowance (RDA), taken daily from early pregnancy through 3 months postpartum[3,4]. Test supplements contained folic acid alone, folic acid+iron, folic acid+iron+zinc, or a multiple (i.e., 14 vitamins and minerals) micronutrient formulation. All supplements, including the placebo, also contained vitamin A. The mean birth weight in the control group was 2.59 kg and the prevalence of low birth weight (below 2.5 kg) was high, 43%, and typical

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for rural births in the region (***Figure 2***). Folic acid provided alone did not increase birth weight but the combination of iron-folic acid did, by 32 g, and reduced risk of low birth weight by 16%, reflected by a relative risk (RR) of 0.84 (95% confidence interval [CI] of 0.72 to 0.99). The multiple micronutrient supplement increased mean birth weight the most, by 64 g, but reduced risk of low birth weight by a degree that was similar to iron-folic acid (14%). Infant mortality to three months of age did not significantly differ by supplement group overall; however, mortality was significantly lowered among preterm born infants by 40-60% with the folic acid, with or without iron ($p<0.001$). Thus, preterm infants born to folic acid supplemented mothers were not larger but more resilient post-natally, or less likely to been affected by potentially fatal gestational abnormalities. Surprisingly, however, this was not observed in the multiple micronutrient group (4), suggesting nutrient:nutrient interactions that are not currently understood.

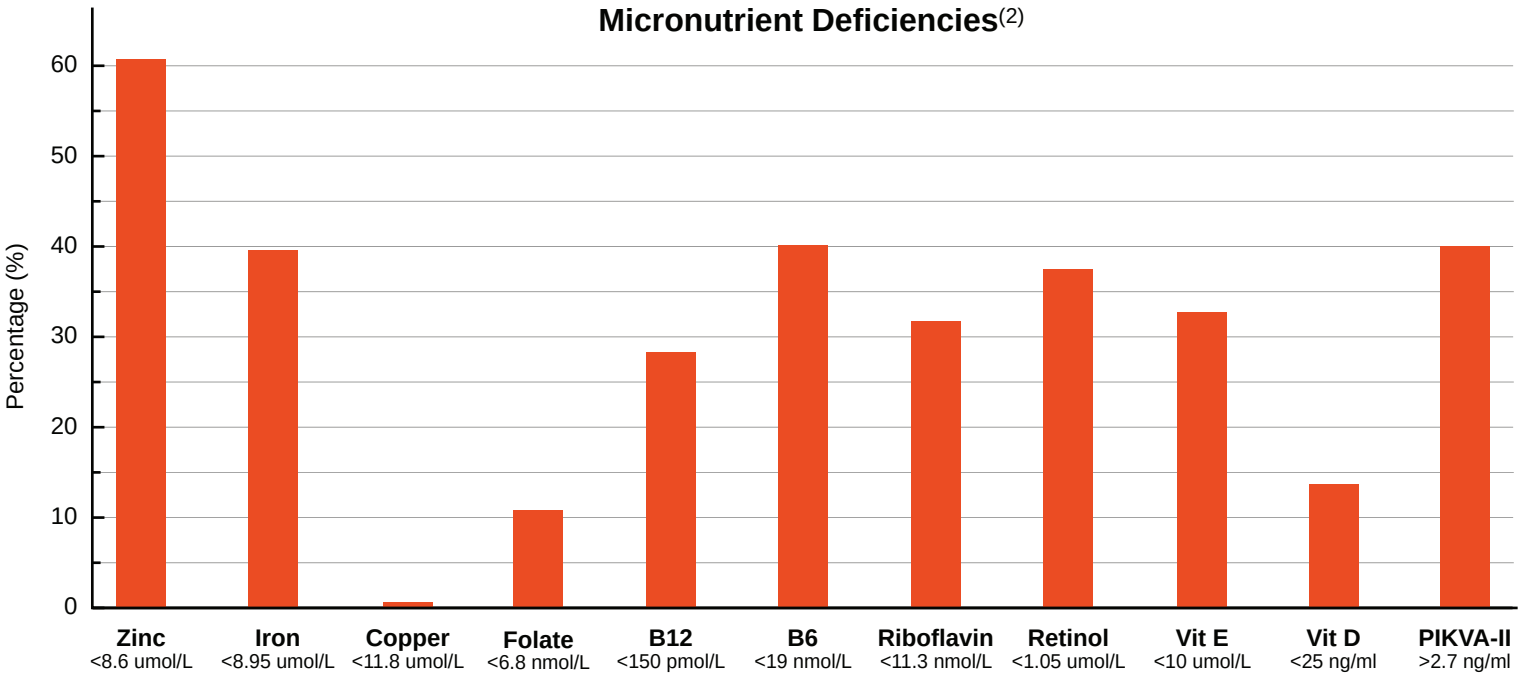

Figure 1. Micronutrient dificiencies are common in early pregnancy in Sarlahi, Nepal.

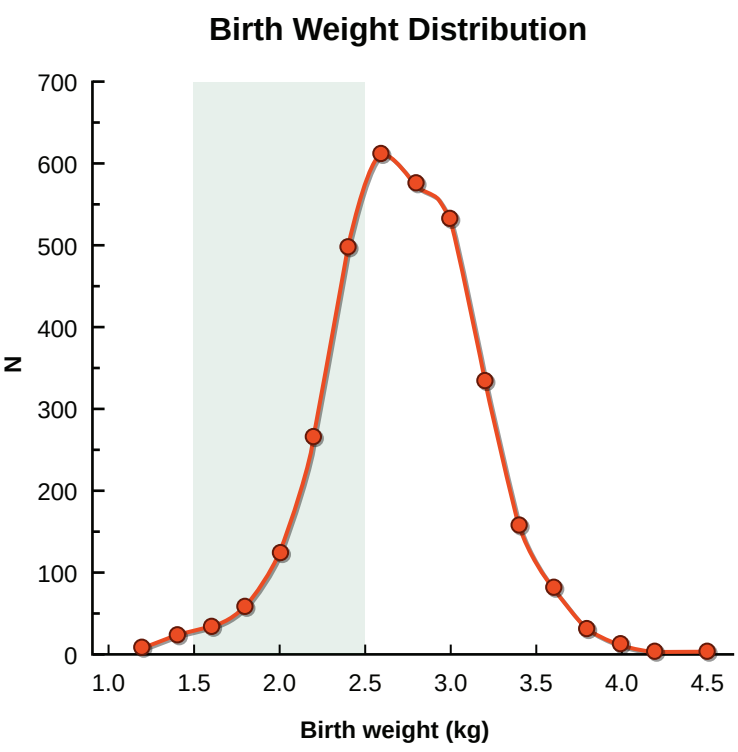

Figure 2. Birth weight distribution in rural Nepal showing high prevalence of babies born <2.5kg.

The JiVitA Trial of Multiple Micronutrient Supplementation: Policy and Program Potential

On the eastern flank of Gangetic South Asia, in Gaibandha, Bangladesh, Johns Hopkins is about to complete (in mid-2012) field work on a Foundation supported, 44,500 pregnancy, randomized controlled trial that will assess multiple health effects of daily multiple micronutrient versus iron-folic acid supplement use. Nearly 10 times the size of the above trial in Nepal, outcomes that will be evaluated include aspects of fetal health, gestational duration and loss, infant growth, health, cognition and survival to from 6-24 months of age, and multiple aspects of maternal health, body composition and nutritional status. When completed, the trial will be one of the largest, most comprehensively evaluated maternal nutrition trials in Southern Asia, expected to provide actionable, policy relevant guidance on the benefits of multiple micronutrient over iron-folic acid supplementation in rural Bangladesh.

The UNIMAPP Trials and Meta-Analysis: A Limited Global View

Eleven, smaller randomized trials of multiple micronutrient versus iron-folic acid supplementation have been undertaken in developing countries throughout Asia, Africa and Latin America. A supplement (called UNIMMAP, for United Nations International Multiple Micronutrient Preparation developed by UNICEF) containing 15 micronutrients at dosages that approximated the

RDA for pregnancy was tested in most trials. A meta-analysis of these 11 studies, plus our NNIPS-3 trial in Nepal, found that the multiple micronutrient supplement increased mean birth weight by 22 g (95% CI: 8 to 37; p=0.002), reduced risk of low birth weight by 11% (95% CI 3% to 19%; p=0.01) and small for gestational age at birth by 10% (95% CI 1% to 18%; p=0.03) while increasing the probability of giving birth to a large for gestational age infant by 13% (95% CI 0% to 28%; p=0.04)[5]. Yet, birth length, duration of gestation or the risk of being born preterm were unaffected, as were risks of stillbirth, or perinatal or neonatal mortality[6]. Such overview estimates can be useful to gain a global impression on effects, to the extent possible by included data, but require caution interpreting because of the small sample sizes of most individual studies, their uncertain applicability to a particular region, and their inability to offer insight into the composition, quality, functionality or tissue specificity of gains in body mass. For these reasons, larger, individual, more comprehensive short and longer-term intervention assessments can offer more actionable data on a regional, contextual basis.

Long-term Effects of Developmental Micronutrient Exposure: A New Frontier

Micronutrients, when adequately consumed, guide normal embryo-fetal tissue and organ development; thus, their deficiencies during critical windows of development may be expected to have long-term, and possibly, permanent consequences for postnatal development and lifelong health. However, causality has been rarely tested because of lack of opportunities to follow randomized trial cohorts into older childhood and adult ages in chronically undernourished settings. Discerning such effects could raise the visibility, importance and motivation to detect and correct antenatal micronutrient deficiencies in poor societies.

From 2006-2008, Johns Hopkins/NNIPS undertook a comprehensive follow-up assessment of the mothers and children who had participated in its early micronutrient trials in Sarlahi Distrct. Its purpose was to evaluate effects of maternal micronutrient supplementation during pregnancy on school entrant child survival, growth, body composition, function and biomarkers and tests of early chronic disease, including blood pressure, insulin resistance, dyslipidemia, adiposity and kidney function.

The following are highlights of the study findings to date among followed children 7 to 9 years of age by type of supplement received by Nepalese mothers during pregnancy:

Maternal antenatal supplementation with iron-folic acid:

- Reduced child mortality by 31%[7]
- Improved aspects of intellectual functioning including working memory, inhibitory control and fine motor functioning[8]

Maternal antenatal supplementation with folic acid:

- Reduced the risk of microalbuminuria by 44%[9]
- Reduced the risk of metabolic syndrome by 37%[9]

Maternal supplementation with zinc plus iron-folic acid:

- Increased height and reduced adiposity(perhaps reflecting greater energy utilization to support growth), evident by decreased triceps and subscapular skin folds and arm fat area[10]
- Reduced the risk of microalbuminuria by 47%[9]

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JiVitA is a project of the Center for Human Nutrition of Johns Hopkins University, spanning 19 unions of Gaibandha and Rangpur Districts in rural Northwestern Bangladesh. JiVitA has been conducting community trials, supported by epidemiologic, ethnographic, and laboratory research since 2000, to reveal the impact of public health interventions in order to guide nutrition and health programs and policies in Bangladesh & elsewhere in South Asia.

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