

Effects of alternative maternal micronutrient supplements on low birth weight in rural Nepal: double blind randomised community trial

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Abstract

Objective To assess the impact on birth size and risk of low birth weight of alternative combinations of micronutrients given to pregnant women.

Design Double blind cluster randomised controlled trial.

Setting Rural community in south eastern Nepal.

Participants 4926 pregnant women and 4130 live born infants.

Interventions 426 communities were randomised to five regimens in which pregnant women received daily supplements of folic acid, folic acid-iron, folic acid-iron-zinc, or multiple micronutrients all given with vitamin A, or vitamin A alone (control).

Main outcome measures Birth weight, length, and head and chest circumference assessed within 72 hours of birth. Low birth weight was defined <2500 g.

Results Supplementation with maternal folic acid alone had no effect on birth size. Folic acid-iron increased mean birth weight by 37 g (95% confidence interval -16 g to 90 g) and reduced the percentage of low birthweight babies (<2500 g) from 43% to 34% (16%; relative risk=0.84, 0.72 to 0.99). Folic acid-iron-zinc had no effect on birth size compared with controls. Multiple micronutrient supplementation increased birth weight by 64 g (12 g to 115 g) and reduced the percentage of low birthweight babies by 14% (0.86, 0.74 to 0.99). None of the supplement combinations reduced the incidence of preterm births. Folic acid-iron and multiple micronutrients increased head and chest circumference of babies, but not length.

Conclusions Antenatal folic acid-iron supplements modestly reduce the risk of low birth weight. Multiple micronutrients confer no additional benefit over folic acid-iron in reducing this risk.

Introduction

Birth weight is closely associated with the health and survival of infants in the developing world, where 90% of the 250 million low birthweight babies (<2500 g) are born each year.¹ Studies of food supplementation have typically reported increases in birth weight of 25-84 g per 10 000 kcal of maternal energy intake

during pregnancy,² although mean increases of about 135 g may occur with higher energy intakes.^{3 4}

The effects of maternal micronutrient supplementation on birth weight and intrauterine growth have not been well studied, despite the potential benefits of such interventions on pregnancy outcomes. Unicef is currently promoting antenatal use of multiple micronutrient supplements among women in the developing world. Providing a full complement of micronutrients is expected to optimise functional and health benefits to the mother and infant. However, data are lacking on the efficacy of such a supplement in improving pregnancy outcomes.

We assessed the impact of daily antenatal supplementation with folic acid, folic acid-iron, folic acid-iron-zinc, or a multiple micronutrient supplement (containing 14 micronutrients including folic acid, iron, and zinc) on mean birth weight and percentage of low birthweight babies.

Methods

Study design and population

The study was a double blind cluster randomised controlled trial conducted in the south eastern plains district of Sarlahi, Nepal, from December 1998 to the end of April 2001. We defined as the study area 426 sectors, each of 75-150 households located in 30 "village development communities." We randomised sectors to the five different supplement arms by drawing numbered identical chips from a hat.

Eligibility and surveillance of pregnancy

All women of reproductive age were first screened by 426 local female workers ("sector distributors") to assess how likely it was that they would become pregnant over the next 12 months. Women who were currently pregnant, breast feeding a baby <9 months old, menopausal, sterilised, or widowed were excluded. Remaining women were registered and visited by sector distributors at home every five weeks for a year and were asked if they had menstruated in the previous month. If not, women underwent a urine test to ascertain pregnancies.

At baseline newly identified pregnant women were asked to recall morbidity, diet, alcohol and tobacco use,

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Table 1 Newborn anthropometry measured within 72 hours of birth by treatment group*

	Mean (SD)	Difference†	Difference‡ (95% CI)	P value§
Weight (g)				
Control	2587 (445)	—	—	
Folic acid	2587 (429)	-7	-20 (-71 to 32)	
Folic acid-iron	2652 (436)	60	37 (-16 to 90)	0.0014
Folic acid-iron-zinc	2598 (428)	1	-11 (-63 to 40)	
Multiple micronutrients	2659 (446)	64	64 (12 to 115)	
Length (cm)				
Control	47.2 (2.32)	—	—	
Folic acid	46.9 (2.42)	-0.29	-0.32 (-0.58 to -0.05)	
Folic acid-iron	47.4 (2.48)	0.16	0.05 (-0.25 to 0.34)	0.0061
Folic acid-iron-zinc	47.2 (2.38)	-0.04	-0.10 (-0.35 to 0.16)	
Multiple micronutrients	47.4 (2.31)	0.16	0.14 (-0.10 to 0.39)	
Chest circumference (cm)				
Control	30.4 (2.05)	—	—	
Folic acid	30.4 (2.13)	0.03	-0.04 (-0.29 to 0.21)	
Folic acid-iron	30.8 (2.19)	0.41	0.35 (0.09 to 0.61)	<0.0001
Folic acid-iron-zinc	30.4 (2.05)	0.05	0.001 (-0.26 to 0.26)	
Multiple micronutrients	30.8 (2.06)	0.36	0.36 (0.11 to 0.61)	
Head circumference (cm)				
Control	32.5 (1.46)	—	—	
Folic acid	32.5 (1.40)	0.03	-0.004 (-0.18 to 0.19)	
Folic acid-iron	32.7 (1.44)	0.20	0.16 (-0.03 to 0.34)	0.0123
Folic acid-iron-zinc	32.6 (1.46)	0.05	0.01 (-0.17 to 0.20)	
Multiple micronutrients	32.7 (1.40)	0.21	0.19 (0.02 to 0.37)	

*N=685, 628, 635, 672, and 705 for control, folic acid, folic acid-iron, folic acid-iron-zinc, and multiple micronutrients, respectively.

†Difference from control adjusted for design effect.

‡Difference from control adjusted for maternal weight at baseline and design effect.

§Using likelihood ratio test (χ^2 with 4 df) to determine whether five groups differ significantly from each other.

and household chores performed in the previous seven days; and weight, height and mid-upper arm circumference were recorded. During the third trimester, measurements were repeated.

Intervention

Sectors were randomly assigned for women to receive one of the following five micronutrient supplements: folic acid (400 µg); folic acid plus iron (60 mg ferrous fumarate); folic acid plus iron plus zinc (30 mg zinc sulphate); or multiple folic acid plus iron plus zinc plus vitamin D 10 µg, vitamin E 10 mg, vitamin B-1 1.6 mg, vitamin B-2 1.8 mg, niacin 20 mg, vitamin B-6 2.2 mg, vitamin B-12 2.6 µg, vitamin C 100 mg, vitamin K 65 µg, copper 2.0 mg, magnesium 100 mg); all with vitamin A, and vitamin A alone (1000 µg) as the control. The supplements were identical in appearance and participants, investigators, field staff, and statisticians did not know supplement codes until the study finished. At enrolment, each woman received 15 caplets in a bottle with instructions to take one caplet every night before bedtime. Sector distributors visited women twice each week to monitor supplement intake and replenish supplies.

Birth weight and other anthropometric measures

Most births occurred at home, assisted by traditional birth attendants, relatives, and neighbours.⁵ Once a birth was reported, the anthropometrist visited to record "day of birth" measurements.

Low birth weight was defined as weight <2500 g measured within 72 hours of birth. Small for gestational age babies were defined as those whose weight was below the 10th centile of the gestational age-sex specific US reference for fetal growth.⁶

Statistical analysis

Data were analysed on an intention to treat basis. The effects of the interventions in comparison with the control group were calculated with generalised estimating equations linear and binomial regression models (see bmj.com).

Results

Of 36 083 women of reproductive age, 14 185 were identified as likely to become pregnant. Over a year, 4998 pregnancies were confirmed by urine testing. Of these, six were false positive, three had unknown outcomes, and 63 ended as induced abortions and were excluded. Of the remaining, 4096 resulted in at least one live birth. The numbers of twin pregnancies (34 pairs of liveborn twins and eight pairs with one stillborn) were comparable across treatment groups. In all, 830 pregnancies (16.8%) ended in miscarriage, stillbirth, or maternal death. Of the 4130 liveborn infants, about 80% were measured within 72 hours and 70% within 24 hours of birth.

Baseline maternal characteristics were similar except for small differences in ethnic composition and land holding. Gestation and anthropometric variables were similar, except women in the control group weighed slightly less (see bmj.com).

Compliance with supplementation during pregnancy was high (median 88%) and did not vary by treatment. There were few self reported side effects, and the prevalence of nausea, vomiting, constipation, gastrointestinal distress, dizziness, and diarrhoea ranged from 0-4% and was comparable by treatment group.

Compared with the control group, folic acid supplementation had no effect on birth size except for a small decrement in birth length (table 1). Birth weight in the folic acid-iron group was slightly higher than in the control group. Chest circumference and head circumference were also higher. There was no difference in length. Folic acid-iron-zinc supplementation had no apparent effect on any aspect of birth size compared with the control group. Birth weight in the multiple micronutrients group was higher, as were chest and head circumference but not length.

Birth weight was higher by 53 g (95% confidence interval 0 g to 108 g) in the folic acid-iron group compared with the folic acid-iron-zinc group. The effects of supplementation with folic acid-iron and multiple micronutrients may have differed in the distribution of the added weight at birth, with multiple micronutrients increasing weight disproportionately at the upper end. There were 50% more infants in the multiple micronutrient group who weighed \geq 3300 g compared with the control group. Proportions were similar in the folic acid-iron group and the control group.

As we expected, the increases in birth weight among the folic acid-iron and multiple micronutrient groups translated into modest reductions in the proportions of low birthweight babies (<2500 g) (table 2). There was also a lower incidence of babies who were small for gestational age in the folic acid-iron group than in the control group. There was no discernable effect on preterm births, all relative risks being about 1.0.

Discussion

In rural Nepal, over two fifths (43%) of babies weigh less than 2500 g at birth. In our large community trial the incidence of low birth weight was 34% in the folic acid-iron group and 35% in the multiple micronutrient group after supplementation, relative to 43% in the control group, corresponding to modest declines of 16% and 14%, respectively. From our results we calculate that 11 women would need to take folic acid-iron supplements (or 12 to take multiple micronutrient supplements) to avert one low birthweight baby. Neither combination of supplements seemed to affect linear growth, although measures of head and chest circumference were higher in these groups than in the control group.

Study strengths

This was a double blind randomised controlled trial that was adequately powered to examine modest reductions in the incidence of low birth weight. Our results are more generalisable than hospital based studies. We achieved high accuracy and precision in the birth measurements in a setting where 90% of births occur in remote village homes. The high quality of field performance was reflected by a median 88% maternal compliance with supplementation. Randomisation generated comparable groups with respect to most assessed factors, except for the lower baseline maternal weight (up to 1 kg) among women in the control group. This probably occurred by chance, and we adjusted for it in the analysis. Loss to follow up due to neonatal death and delay in measurement resulting from women leaving to deliver at their parental homes resulted in 20% of the newborns not being weighed or being weighed later than the 72 hour criteria for measuring birth weight.

In Nepal mean maternal weight is low (about 43.5 kg), probably because of energy and protein malnutrition. Micronutrient supplementation alone ameliorated the burden of low birth weight by 14-16%. What are the possible health or survival benefits of such an effect? Across different populations, low birthweight infants experience 4-10 times the risk of neonatal death.⁷ However, direct assessment of survival is needed as increases in birth weight may not always result in improved health or survival.⁸ In the present study we followed infants through the first six months

Table 2 Percent of low birthweight, small for gestational age,* and preterm babies* by treatment group

	No (%)	Relative risk (95% CI)†	P value‡
Low birth weight (<2500 g)			
Control	685 (43.4)	1.0	
Folic acid	628 (41.7)	1.00 (0.88 to 1.15)	0.0103
Folic acid-iron	635 (34.3)	0.84 (0.72 to 0.99)	
Folic acid-iron-zinc	672 (39.4)	0.96 (0.83 to 1.11)	
Multiple micronutrients	705 (35.3)	0.86 (0.74 to 0.99)	
Small for gestational age§			
Control	685 (58.7)	1.0	
Folic acid	628 (57.8)	1.02 (0.93 to 1.11)	0.1712
Folic acid-iron	633 (51.7)	0.91 (0.83 to 1.00)	
Folic acid-iron-zinc	670 (56.4)	0.98 (0.89 to 1.08)	
Multiple micronutrients	704 (53.8)	0.95 (0.87 to 1.04)	
Preterm (gestational age at birth <37 wk)			
Control	685 (20.4)	1.0	
Folic acid	628 (22.1)	1.08 (0.86 to 1.40)	0.7725
Folic acid-iron	633 (23.1)	1.13 (0.90 to 1.40)	
Folic acid-iron-zinc	670 (20.2)	0.99 (0.80 to 1.29)	
Multiple micronutrients	704 (20.6)	1.01 (0.82 to 1.26)	

*Data on gestational age missing for five babies.

†Adjusted for maternal weight and design effect.

‡Using likelihood ratio test (χ^2 with 4 df) to determine whether three groups differ significantly from each other.

§Below 10th centile of US national reference for fetal growth.²³

of life and found differences in survival by treatment group that were not significant and were apparently unrelated to birth weight (Christian et al, unpublished).

As folic acid alone failed to affect birth weight, we attributed the observed effects on birth size to treatment of maternal iron deficiency. Iron supplementation may improve maternal appetite,⁹ thereby increasing energy consumption during pregnancy with resultant increased intrauterine growth.

We do not know why the observed effects of folic acid-iron on birth size were absent with added zinc, though it may be because of competition between bivalent iron and zinc for mucosal uptake.^{10 11} However, multiple micronutrients, which included iron, zinc, and presumably their interactions, did increase birth weight and other measures of growth, suggesting that mechanisms responsible for this effect may have involved pathways dependent more on other micronutrients than iron. For example, thiamine and vitamins B-6 and B-12 provided in the supplement have a role in numerous aspects of intermediary protein and energy metabolism, which could affect fetal growth.¹²

Our findings may be most relevant to rural South and, possibly, South East Asia, where prevalence of iron deficiency anaemia and low birth weight are high. In these settings iron supplementation may be effective in reducing, by a modest degree, the incidence of low birth weight. It is noteworthy that a fairly large array of micronutrients failed to reduce the risk of low birth weight beyond that achieved by folic acid-iron alone. Micronutrients beyond this combination should be added only if there is evidence of a health benefit.

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What is already known on this topic

Deficiencies in micronutrients are common in women in developing countries and have been associated with low birth weight and preterm delivery

What this study adds

In rural Nepal maternal supplementation with folic acid-iron reduced the incidence of low birth weight by 16%

A multiple micronutrient supplement of 14 micronutrients, including folic acid, iron, and zinc, reduced low birth weight by 14%, thus conferring no advantage over folic acid-iron

study design and procedures. Gwendolyn Clemens was responsible for computer programming and data management. Ravi Ram, Seema Rai, and Sunita Pant helped in data cleaning and supervision. Lee Wu helped with statistical analysis.

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Competing interests: None declared.

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Impact of DOTS compared with DOTS-plus on multidrug resistant tuberculosis and tuberculosis deaths: decision analysis

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Abstract

Objective This study sought to determine the impact of the World Health Organization's tuberculosis treatment strategy (DOTS) compared with that of DOTS-plus on tuberculosis deaths, mainly in the developing world.

Design Decision analysis with Monte Carlo simulation of a Markov decision tree.

Data sources People with smear positive pulmonary tuberculosis.

Data analysis Analyses modelled different levels of programme effectiveness of DOTS and DOTS-plus, and high (10%) and intermediate (3%) proportions of primary multidrug resistant tuberculosis, while accounting for exogenous reinfection.

Main outcome measure The cumulative number of tuberculosis deaths per 100 000 population over 10 years.

Results The model predicted that under DOTS, 276 people would die from tuberculosis (24 multidrug resistant and 252 not multidrug resistant) over 10 years under optimal implementation in an area with 3% primary multidrug resistant tuberculosis. Optimal implementation of DOTS-plus would result in four (1.5%) fewer deaths. If implementation of DOTS-plus were to result in a decrease of just 5% in the effectiveness of DOTS, 16% more people would die with tuberculosis than under DOTS alone. In an area

with 10% primary multidrug resistant tuberculosis, 10% fewer deaths would occur under optimal DOTS-plus than under optimal DOTS, but 16% more deaths would occur if implementation of DOTS-plus were to result in a 5% decrease in the effectiveness of DOTS

Conclusions Under optimal implementation, fewer tuberculosis deaths would occur under DOTS-plus than under DOTS. If, however, implementation of DOTS-plus were associated with even minimal decreases in the effectiveness of treatment, substantially more patients would die than under DOTS.

Introduction

The current recommendation for initial treatment of tuberculosis includes the standard first line regimen of isoniazid, rifampicin, pyrazinamide, and ethambutol. Since 1993 it has been recommended that treatment be given as part of a policy known as DOTS (directly observed treatment, short course; box).¹ However, outcomes are poor when patients who are infected with *Mycobacterium tuberculosis* resistant to isoniazid and rifampicin (multidrug resistant tuberculosis) are treated with the standard regimen.^{2,3} Reserve or second line antituberculosis drugs have therefore become components of an approach known as DOTS-plus (box).⁴ Although reported to attain high rates of