Antenatal anthelmintic treatment, birthweight, and infant survival in rural Nepal

Parul Christian, Subarna K Khatry, Keith P West Jr

Anthelmintic treatment, which is recommended during pregnancy in areas where there is a high rate of anaemia, needs further investigation. We examined prospectively the association between anthelmintic treatment and maternal anaemia, birthweight, and infant mortality in a study of prenatal supplements, in which women received albendazole twice during pregnancy. Women given albendazole in the second trimester of pregnancy had a lower rate of severe anaemia during the third trimester. Birthweight of infants of women who had received two doses of albendazole rose by 59 g (95% CI 19–98), and infant mortality at 6 months fell by 41% (RR 0.59; 95% CI 0.43–0.82). Antenatal anthelmintics could be effective in reducing maternal anaemia and improving birthweight and infant survival in hookworm-endemic regions.

Antenatal anthelmintic treatment in hookworm endemic areas is recommended for control of anaemia. However, despite the substantial role of this treatment, particularly for severe anaemia, it is uncommon in many developing countries. The recommendation for anthelmintic treatment during pregnancy came from Sri Lanka, where antenatal mebendazole lowered the frequency of anaemia and safely reduced the proportion of infants of very low birthweight (<1500 g). However, confounding factors could not be ruled out in these investigations.

In previous studies, we have shown that 74% of pregnant women in the district of Sarlahi, Nepal, were infected with hookworm (Ancylostoma duodenale); 59% of whom had Ascaris lumbricoides and only 5–3% had Trichuris trichiura. Of the 74% with hookworm, 61–6% had mild infection (one to 1999 eggs per g of faeces) and 6–3% had moderate (2000–3999 eggs per g of faeces) or heavy (>4000 eggs per g of faeces) infection. 54% of women had moderate to severe anaemia (haemoglobin <90 g/L) attributable to hookworm infection. We undertook a subsequent trial, in the same area, of antenatal micronutrient supplementation for pregnant women to assess effect on birthweight and infant mortality. Pregnant women were also given a single dose of albendazole (400 mg) in their second and third trimesters. Here, we investigated the association between albendazole receipt and severity of anaemia in late pregnancy, birthweight, and infant mortality at 6 months.

We undertook this community-based study in 30 village development communities (large units representing a population of five to seven villages) in Sarlahi district, where the population is about 280 000. At the outset, married women of reproductive age in the study area were identified and those who were pregnant, breastfeeding an infant older than 9 months, sterilised, menopausal, or widowed were excluded. We did a surveillance of the remaining women every 5 weeks to identify incident pregnancies by testing the urine of those who had not menstruated in the past 30 days. Women ascertained to be pregnant received one of the five groups of micronutrient supplements daily (ie, folic acid [400 µg]; folic acid and iron [60 mg]; folic acid, iron, and zinc [30 mg]; folic acid, iron, zinc, vitamin D [10 µg], vitamin E [10 mg], thiamine [1.6 mg], riboflavin [1.8 mg], niacin [20 mg], vitamin B6 [2.2 mg], vitamin B12 [2.6 µg], vitamin C [100 mg], vitamin K [65 µg], copper [0.2 mg], and magnesium [100 mg] all with vitamin A [1000 µg]; versus vitamin A alone as the control), throughout pregnancy, until 3 months postpartum.

Over a year, 4998 pregnant women were enrolled in the study, giving birth to 4130 liveborn babies. Weight was measured within 72 h of birth in 80% (n=3325) of these babies. Vital status was ascertained at 6 months of age, marking the end of follow-up. In nine of the 30 village development communities, which were selected for accessibility to main roads and made up a rough 25% subsample (n=1206), maternal venous blood was collected before supplementation (baseline) and in the third trimester (32 weeks of gestation) for haemoglobin estimation and other nutrient analyses. At mid and late gestation women were offered one 400 mg dose of albendazole, for treatment of possible geohelminth infection, under direct supervision of project staff. The first dose was not offered until 12 weeks from the time of urine-based detection of pregnancy thus avoiding drug administration in the first trimester. The second dose, given in the third trimester, coincided with the week of the second venous blood draw. We compared the difference in third-trimester distribution of haemoglobin concentrations in women who had received albendazole at mid-gestation and those who had not, using the χ2 test. Since hookworm infection is associated with severe anaemia, we compared the frequency of this disorder (haemoglobin <70 g/L) in the third trimester in women who received albendazole and those who did not by logistic regression after adjustment for potential confounding factors. Finally, birthweight and 6-month infant mortality was examined by albendazole receipt adjusted for confounding factors by multiple logistic regression. Confounding factors included variables that were associated with albendazole receipt in women, and...
Figure: Distribution of haemoglobin concentrations in women in third trimester of pregnancy after receipt of albendazole in second trimester compared with non-receipt (p=0.021 with χ² test)

with either or both of the outcomes. All analyses were done with SAS version 8.0 (Cary, NC, USA). Oral informed consent was obtained from all participants and the study received ethics approval from review boards in Nepal and the USA.

More than 90% (n=3791) of pregnant women at mid-gestation and about 75% (n=3067) at late gestation received albendazole. Mean (SD) gestational age when albendazole was given was 21·5 (8·0) weeks for the first dose and 34·6 (6·0) weeks for the second. The main reason for non-receipt of albendazole was not meeting the woman during home visits. Since many women were likely to have returned to their parental home for delivery late in gestation, there was a high proportion of non-receipt for the second dose of albendazole offered in the third trimester. Younger, nulliparous women are more likely to go to their parents’ home for delivery. Thus, we found parity and place of delivery to be associated with non-receipt of albendazole. Women’s literacy, diet, substance use, ethnic group, height, and study allocation did not differ by albendazole receipt. However, women who did not receive any albendazole were less likely to be of lower weight (<45 kg) than those who did.

Albendazole receipt in the second trimester was associated with increased haemoglobin concentration (p=0.021) in the third trimester (figure). The difference was apparent as a distinct shift from severe (<70 g/L) toward mild (90–<110 g/L) anaemia. Severe anaemia in the third trimester was reduced with albendazole in the second trimester adjusted for supplement intake, baseline haemoglobin, and intake of meat, fish, dairy products, and dark green leafy vegetables in pregnancy (adjusted odds ratio=0·23, 95% CI 0·05–0·99).

Birthweight of infants of women who received two doses of albendazole during pregnancy was higher, and mortality at 6 months of age was 41% lower than in those born to non-recipients, after adjustment for confounding factors (table).

Our data show a reduction in severity of anaemia in late pregnancy that can be attributed to albendazole treatment earlier in pregnancy, an effect that could improve maternal survival and pregnancy outcome. Our findings suggest that two doses of antenatal anthelmintics can improve birthweight and infant survival in the first 6 months of life. In this setting, in which frequency of low birthweight was high (43%), albendazole treatment given twice during pregnancy was associated with an increase in birthweight of about the same magnitude as was achieved with daily micronutrient supplementation throughout pregnancy (60 g). Although one dose might be beneficial to these outcomes, it seems less effective than the two-dose regimen. We postulate that reinfection after treatment with one dose is a factor in a setting, such as ours, in which hookworm is highly endemic. The low proportion of women who received only one dose of albendazole probably created a low sample size in the albendazole category limiting our ability to assess its effect.

In this community-based study, a two-dose albendazole regimen during pregnancy was associated with improved birthweight and noticeable reduction in early infant mortality compared with non-receipt. We attempted to control for selection bias due to non-receipt, by simultaneous adjustments for factors that were associated with differences in maternal albendazole receipt, infant birthweight, or vital status outcome. This adjustment was an improvement on previous unadjusted studies that have claimed functional benefits of deworming. Our findings have implications for antenatal anthelmintic strategies in areas of the world where the rate of hookworm infection is high, to reduce maternal anaemia and improve birthweight and infant survival, and emphasise the need for randomised antenatal anthelmintic trials.

<table>
<thead>
<tr>
<th>Birthweight (g)</th>
<th>N (Mean (SD))</th>
<th>Difference in g* (mean, 95% CI)</th>
<th>6-month mortality (number of deaths/total, rate per 1000)</th>
<th>Relative risk* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No albendazole</td>
<td></td>
<td></td>
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<tr>
<td>No doses</td>
<td>58 (2473 (520))</td>
<td>-17 (95% CI -26 to -9)</td>
<td>25/261, 95.8</td>
<td>1.0</td>
</tr>
<tr>
<td>One dose</td>
<td>543 (2519 (490))</td>
<td>-31 (95% CI -49 to 157)</td>
<td>88/866, 101.6</td>
<td>0.86 (0.49–1.54)</td>
</tr>
<tr>
<td>Two doses</td>
<td>2726 (2639 (420))</td>
<td>-59 (95% CI -98 to -19)</td>
<td>116/2981, 38.9</td>
<td>0.59 (0.34–0.92)</td>
</tr>
</tbody>
</table>

*Multiple linear regression analysis of differences in birthweight, and logistic regression analysis for the relative odds of mortality, were adjusted for nutrient supplement group, maternal parity, tobacco smoking, early pregnancy weight, height, ethnic group, literacy, gestational duration of pregnancy, and social status.

Table: Effect of anthelmintics during pregnancy on birthweight and 6-month infant mortality
Contributors
P Christian was the principal investigator, designed the study, formulated the hypotheses, directed the study and the analyses, wrote the report, and is guarantor for the study. S K Khatry directed the field implementation of the study, helped develop study forms and procedures, and helped with the manuscript. K P West Jr helped in the conceptualisation of the study, development of forms and procedures, interpretation of the findings, and preparation of the manuscript.

Conflict of interest statement
We declare that we have no conflict of interest.

Acknowledgments
This study was done under cooperative agreement HRN-A-60–57–00015–00 between Office of Nutrition, US Agency for International Development (USAID), Washington, DC, and the Center for Human Nutrition (CHN), Department of International Health, and the Sight and Life Research Institute, Johns Hopkins University, Bloomberg School of Public Health, Baltimore, MD, USA. It was a joint collaboration between the CHN and the National Society for the Prevention of Blindness, Kathmandu, Nepal, under the auspices of the Social Welfare Council of His Majesty’s Government of Nepal. The study was funded by USAID and received additional support from the UNICEF Country Office, Kathmandu, Nepal, and Bill and Melinda Gates Foundation, Seattle, WA, USA. The supplements were provided by Roche, Brazil, and manufactured by NutriCorp International, C E Jamieson, Canada. The funding sources had no role in study design, data collection, data analysis, data interpretation, or writing of the report. We thank members of the Nepal study investigative team and the 350 project staff who helped in the successful implementation of the study.

References