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Effects of Deworming during Pregnancy on Maternal and Perinatal Outcomes: A Randomized Controlled Trial.

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ABSTRACT

Helminth infections during pregnancy may be associated with adverse outcomes, including maternal anemia, low birth weight, and perinatal mortality. Deworming during pregnancy has therefore been strongly advocated, but its benefits have not been rigorously evaluated. In SBMCH, Chennai, 500 pregnant women were recruited to a randomized, double-blind, placebo-controlled trial investigating albendazole and mebendazole in a 2×2 factorial design. Hematinics and sulphadoxine-pyrimethamine for presumptive treatment of malaria were provided routinely. Maternal and perinatal outcomes were recorded. Analyses were by intention to treat. At enrollment, 68% of women had helminths, 45% had hookworm, 18% had *Trichuris trichiura* infection; 40% were anemic (hemoglobin level, <11 g/dL). At delivery, 35% were anaemic; there was no overall effect of albendazole (odds ratio [OR], 0.95; 95% confidence interval [CI], 0.79–1.15) or Mebendazole (OR, 1.00; 95% CI, 0.83–1.21) on maternal anemia, but there was a suggestion of benefit of albendazole among women with moderate to heavy hookworm (OR, 0.45; 95% CI, 0.21–0.98; P=.15 for interaction). There was no effect of either anthelminthic treatment on mean birth weight (difference in mean associated with albendazole: −0.00 kg; 95% CI, −0.05 to 0.04 kg; difference in mean associated with praziquantel: −0.01 kg; 95% CI, −0.05 to 0.04 kg) or on proportion of low birth weight. Anthelminthic use during pregnancy showed no effect on perinatal mortality or congenital anomalies. In our study area, where helminth prevalence was high but infection intensity was low, there was no overall effect of anthelminthic use during pregnancy on maternal anemia, birth weight, perinatal mortality, or congenital anomalies. The possible benefit of albendazole against anemia in pregnant women with heavy hookworm infection warrants further investigation.

Keywords: helminth, pregnancy, deworming, albendazole, mebendazole

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INTRODUCTION

Two billion people are estimated to be infected with geohelminths, and mass deworming programs are widely advocated [1]. Previously, deworming has been avoided during pregnancy and lactation because of safety concerns; however, in areas where women are pregnant or lactating for over half of their reproductive lives, this may result in treatment delays and morbidity [2]. Moreover, detrimental effects of helminths on maternal anemia, fetal growth, and infant mortality have been suggested [2–4]. Therefore, in 1994, the World Health Organization recommended the treatment of hookworm during pregnancy in [2] areas where hookworm is endemic, in addition to evaluation of birth outcomes [5].

A benefit of albendazole for maternal anemia in a small study in Sierra Leone where albendazole and iron-folate supplementation were examined in a factorial design [7] was not confirmed by a larger trial of mebendazole in Peru, in which all women received iron supplements [8]. Observational studies of mebendazole during pregnancy in Sri Lanka [9] and albendazole in Nepal [3] suggested a benefit for birth weight and for infant survival, but the Peru trial showed no effect of mebendazole on these outcomes, except for the rare outcome of very low birth weight [8].

Therefore, in a large placebo-controlled trial of albendazole and mebendazole during pregnancy in Chennai; designed to address effects on immune responses and disease susceptibility in offspring [11]), we examined important additional outcomes: maternal anemia, birth weight, perinatal death, and congenital anomalies.

METHODS

Study area and participants

Tambaram and Chrompet areas, Chennai, is occupied by semi-urban, rural, and daily labourers' communities. Pregnant women were recruited from August 2011 through February 2012 at SBMCH Hospital.

Inclusion Criteria

Women were eligible if they were healthy on recruitment day, a resident in the study area, planning to deliver at the hospital, willing to know their HIV status, prepared to participate in the study, and in their second or third trimester (based on last menstrual period and midwife's assessment).

Exclusion criteria

Hemoglobin level <8 g/dL, clinically apparent severe liver disease, history of diarrhea with blood in stool, abnormal pregnancy, previous adverse reaction to anthelminthics, or enrollment during a previous pregnancy.
The Ethics Committee of Sree Balaji Medical College and Hospital, Chennai gave ethical approval.

Design

This was a randomized, double-blind, placebo-controlled trial of albendazole versus matching placebo and praziquantel versus matching placebo, with a 2×2 factorial design [11, 12]. At screening, written informed consent was obtained and a clinical examination was completed. Blood samples were obtained for hemoglobin level estimation and examination for microfilaria, malaria, syphilis, and HIV infection; stool samples were obtained for diagnosis of gastrointestinal helminths.

After a stool sample was obtained, participants were assigned to receive albendazole (400 mg) and placebo, Mebendazole (100mg BD for 3 days) and placebo, albendazole and Mebendazole or placebo and placebo. The randomization sequence was prepared with blocks of 100 by the trial statistician with use of Stata, version 7 (Stata). Researchers in SBMCH who were not otherwise involved in the study prepared opaque, sealed envelopes numbered with the randomization code that contained albendazole tablets (GlaxoSmithKline) or matching placebo and 12 capsules of Mebendazole 100mg or matching placebo.

Treatment was given by interviewer counsellors in the order of the randomization sequence as a single, supervised, oral dose [11]. Staff and participants were blinded to the treatment allocation.

Women received a month's supply of daily ferrous sulphate (200 mg; 60 mg elemental iron) and folic acid (0.25 mg) at each antenatal visit. Repeat stool samples were obtained within 14 weeks after delivery, and blood samples were obtained within 6 weeks; thereafter, all women received a single dose of albendazole and course of Mebendazole. Infants were seen for vaccination and for interim illnesses at the research clinic.

Maternal anemia was defined as a hemoglobin level <11 g/d. Birth weight was measured within 72 h after delivery to a precision of 100 g. For babies not delivered in SBMCH, health card birth weight records were used. Low birth weight was defined as <2.5 kg, and very low birth weight was defined as <1.5 kg.

Statistical analysis

Maternal and perinatal outcomes were secondary for the trial; sample size calculations were not based on these outcomes. Observed standard deviations (SDs) were 2 g/dL for maternal anemia and 520 g for birth weight. Thus, the study had 80% power with 2-sided significance level of .05 to detect a 0.3 g/dL difference in maternal hemoglobin level and a 70 g difference in birth weight for either intervention.

Comparison of outcomes between treatment groups was based on intention-to-treat analysis. For each outcome, effects of albendazole versus its placebo and effects of mebendazole versus its placebo, adjusted for one another, were estimated using logistic regression or linear regression. For maternal anemia and birth weight, prespecified subgroup analyses were performed to examine the effects of albendazole in women infected with hookworm at enrollment and the effects of mebendazole among women with trichuris at enrollment. Exploratory analyses further assessed whether effects varied by intensity of hookworm or trichura, by maternal anemia at enrollment or by trimester during which treatment was given.

RESULTS

A total of 500 women were enrolled and treated; Randomization resulted in a similar distribution of baseline variables between treatment groups.

Most women were hindus (49%), were married (84%), were housewives (64%), and had no formal or only primary education (54%) and were poor (personal income < Rs.300 per month; 85%) [12]. Only 11 women (0.4%) reported smoking, and 761 (30%) reported drinking any alcohol. At enrollment, 68% had at least 1 helminth infection; 45% had hookworm, 21% had *Trichuris trichura* infection, 44% other helminths.

Of the hookworm-infected women, 85% had light infection, 11% had moderate infection, and 4% had heavy infection

Of the *Trichuris trichura* infected women, 65% had light infection, 19% had moderate infection, and 17% had heavy infection.

Forty-five percent of infected women had >1 helminth type. Helminth-infected women were younger, less educated, and poorer than were uninfected women (data not shown).

The mean hemoglobin level (±SD) before enrollment was 11.5±1.5 g/dL; 40% of the women were anemic. The mean gestational age (±SD) at intervention was 26.6±5.9 weeks.

Excluding 2 miscarriages, data were available for 498 deliveries.

Maternal helminths. Stool samples were obtained from 458 women (92%) after delivery. Women who received albendazole had substantially lower prevalence of hookworm and *Ascaris* infection after delivery than did those who received placebo; mebendazole was associated with lower prevalence of *Trichuris trichura* infection.

Maternal anemia. After delivery, blood samples were obtained from 458 women (92%); the median time from obtainment of samples was 1 day after delivery (interquartile range, 1–3 days). Of these women, 174 (35%) were anemic (hemoglobin level, <11.2 g/dL). There was no overall effect of albendazole or mebendazole on maternal hemoglobin level or anemia after delivery; for anemia, no effect of albendazole among women with hookworm (OR, 0.92; 95% CI, 0.69–1.23) or of mebendazole with Trichuris (OR, 1.27; 95% CI, 0.82–1.96) was observed. Although a reduction in anemia with albendazole treatment was observed in women with moderate to heavy hookworm infection, the evidence for effect modification by intensity of hookworm infection was weak (P=.15 for interaction). The effect of treatment did not differ between mothers with and without anemia at baseline for either drug (data not shown).

Birth weight. Birth weight was available for 408 (82%) births, 400 measured within 24 h; 367 (90%) of these were recorded in SBMCH. The mean birth weight (±SD) was 3.15±0.52 kg; 29 newborns (8%) had low birth weight, and 2 (0.6%) had very low birth weight. There was no overall effect of either anthelminthic treatment on mean birth weight or proportion of newborns with low birth weight, and no effect of albendazole among women with hookworm (difference in mean, 0.01 kg; 95% CI, −0.06 to 0.07 kg) or of mebendazole among women with trichuris (difference in mean, 0.06 kg; 95% CI, −0.04 to 0.17 kg). There was no difference in effect of albendazole by hookworm or trichuris infection intensity, respectively.

However, albendazole was associated with lower birth weight, compared with placebo, when given during the second trimester (difference in mean, −0.08 kg; 95% CI, −0.14 to −0.01 kg) but higher birth weight when given during the third trimester (difference in mean, 0.07 kg; 95% CI, 0.01–0.14 kg; P=.001 for interaction). This finding was similar for infants of women with or without hookworm.

DISCUSSION

In the present study, deworming with albendazole or mebendazole during the second or third trimester of pregnancy effectively treated susceptible infections but had no overall effect on maternal anemia, birth weight, perinatal mortality, or congenital anomalies. The effect of treatment on the prevalence of helminths was assessed after delivery and, although not a formal assessment of cure, showed a marked decrease in the number of both major treatable species, hookworm and *Trichuris trichura*. The study had adequate power to estimate small effects in the whole group but limited power to detect small effects for rare outcomes (particularly perinatal mortality) in subgroup analyses. Helminth infections were mostly light to moderate in intensity, which is the common pattern globally [17]; results might differ in regions of high transmission.

Exclusion of women with hemoglobin levels <8 g/dL or diarrhea with blood in stool may have excluded those particularly likely to benefit from the interventions, but these constituted only 31 of the 1000 women screened. Contamination of the placebo group with anthelminthics is unlikely to have occurred, because the prevalence of helminths was not reduced in this group. Our results may therefore be generalized to other pregnant populations with a similar prevalence and intensity of helminth infection, similar prevalence of anemia, and good basic antenatal care.

Our findings showing no overall benefit of albendazole for maternal anemia are in accordance with the trial in Peru, in which mebendazole was used and initial hemoglobin level, prevalence and intensity of hookworm, and daily iron received (60 mg elemental iron) were similar to those in Chromepet. [8]. They contrast with the trial in Sierra Leone, in which albendazole showed a benefit that was small but additive to the benefit of a lower dose of iron (36 mg) plus folic acid [7]. In Sierra Leone, the initial hemoglobin level was lower (10.8 g/dL, compared with 11.5 g/dL), and the prevalence of hookworm was higher (66%), although the intensity of infection was similar. We found a possible benefit of albendazole for women with moderate to heavy hookworm infection, which is in accordance with the conclusions of a recent review [19] and with our own findings at baseline [12] that suggest that increasing hookworm intensity is associated with lower hemoglobin levels during pregnancy. However, evidence for effect modification by hookworm intensity was weak in our study. The prevalence of anemia during pregnancy in our study was less than the national figure of 64% in 2006 [20], and even in india, the prevalence of hookworm is highly variable [21]. Deworming directed against hookworm-induced maternal anemia may be most effective in areas where the prevalence of anemia and the intensity of hookworm are high and the provision of hematinics is inconsistent; studies in different settings are warranted. Mebendazole showed no benefit for maternal anemia overall or among women with

schistosomiasis at any intensity. Thus, although schistosomiasis may be associated with anemia during pregnancy in some settings [22], this was not the case at enrollment in our study [12], and we have not found that treatment of schistosomiasis during pregnancy confers any benefit.

Our findings further accord with observations from the mebendazole trial in Peru in relation to birth weight and perinatal mortality [8]; no overall benefit was found for birth weight, low birth weight, or perinatal mortality. Because only 2 infants in our study had very low birth weight, we could not analyze this outcome.

Our results contrast with 2 previous observational studies, in which women who received mebendazole [9] or albendazole [3] were compared with those who did not. One possible mechanism for a beneficial effect on birth weight would be through increased maternal hemoglobin level, and an effect of anthelminthics on perinatal mortality might be mediated by improved birth weight. This would fit with results for albendazole in Nepal [3]: mothers who received albendazole had a higher third trimester hemoglobin level, higher birth weight, and lower infant mortality. However, the Nepal study was conducted in the context of a trial of micronutrients; women who missed one or both doses of albendazole may also have missed their dose(s) of hematinics or have differed in other, important ways from those who received albendazole. Similarly, the findings of the cross-sectional study in Sri Lanka [9], in which a lower rate for perinatal deaths occurred among women who had taken mebendazole, may have been affected by selection bias and unmeasured confounders. Our unexpected finding of a reduction in birth weight associated with the use of albendazole during the second trimester may have occurred by chance.

In view of the absence of a significant benefit of deworming during pregnancy on perinatal outcomes, deworming during pregnancy may not be a priority in regions with consistent antenatal hematinic supplementation and low-intensity helminth infections. However, deworming is important to prevent the direct pathological effects of worms. Moreover, our hypothesis remains that maternal helminth infection may have long-term effects on the development of the fetal immune system and both risks and benefits for disease susceptibility in later life [11]. These aspects of deworming during pregnancy are being explored in the on-going trial.

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