MAJOR ARTICLE

Effects of Deworming during Pregnancy on Maternal and Perinatal Outcomes in Entebbe, Uganda: A Randomized Controlled Trial

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Background. **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.**

Methods. **In Entebbe, Uganda, 2507 pregnant women were recruited to a randomized, double-blind, placebo-controlled trial investigating albendazole and praziquantel in a 2×2 factorial design [ISRCTN32849447]. Hematinics and sulphadoxine-pyrimethamine for presumptive treatment of malaria were provided routinely. Maternal and perinatal outcomes were recorded. Analyses were by intention to treat.**

Results. **At enrollment, 68% of women had helminths, 45% had hookworm, 18% had *Schistosoma mansoni* infection; 40% were anemic (hemoglobin level, <11.2 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 praziquantel (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.**

Conclusions. **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.**

Two billion people are estimated to be infected with schistosomes and 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, and in 2002, it recommended the use of praziquantel during pregnancy in areas where schistosomiasis is endemic, in addition to evaluation of birth outcomes [5].

Recommendations of benzimidazoles during pregnancy are supported by a small number of studies [6],

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and the results reported are inconclusive. 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]. There is even less data for praziquantel and, in 2005, a World Health Organization working group called for placebo-controlled trials of praziquantel during pregnancy [10].

Therefore, in a large placebo-controlled trial of albendazole and praziquantel during pregnancy in Uganda (ISRCTN32849447; 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. Entebbe peninsula, Uganda, is occupied by peri-urban, rural, and fishing communities. Pregnant women were recruited from April 2003 through November 2005 at Entebbe Hospital. 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 were 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 Science and Ethics Committee of the Uganda Virus Research Institute, Uganda National Council for Science and Technology, and London School of Hygiene and Tropical Medicine 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 and schistosomiasis.

After a stool sample was obtained, participants were assigned to receive albendazole (400 mg) and placebo, praziquantel (40 mg/kg) and placebo, albendazole and praziquantel, 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 Entebbe 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 praziquantel (300 mg; Medochemie) 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 and intermittent presumptive sulfadoxine-pyrimethamine treatment for malaria twice after the first trimester. They were treated for syphilis if indicated. HIV-infected women received single-dose nevirapine for prevention of mother-to-child HIV transmission. 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 praziquantel. Infants were seen for vaccination and for interim illnesses at the research clinic.

A single stool sample was examined using the Kato-Katz method for ova and with use of charcoal culture for *Strongyloides* species [13]. Two Kato-Katz slides were examined for each sample within 30 min for hookworm and the following day for other ova. Infection intensity was categorized for hookworm (light, <1000 eggs/g of stool; moderate, 1000–3999 eggs/g of stool; heavy, ⩾4000 eggs/g of stool [2]) and *Schistosoma mansoni* (light, <100 eggs/g of stool; moderate, 100–399 eggs/g of stool; heavy, ⩾400 eggs/g of stool [14]). Blood was examined for *Mansonella perstans* with use of a modified Knott's method [15] and for malaria by thick film. Hemoglobin level was estimated using Coulter analyzer (Beckman Coulter ACT 5 diff CP). HIV serological testing was performed using rapid test algorithm with same day results [11]. Quality assurance was provided by the Vector Control Division, Ministry of Health, Uganda, for Kato-Katz assessments; by the United Kingdom National External Quality Assessment Scheme, for hemoglobin level estimation; and by the Medical Research Council Laboratories at Uganda Virus Research Institute, for HIV serological testing, with consistently good results.

Maternal anemia was defined as a hemoglobin level <11.2 g/dL, allowing 0.2 g/dL above the standard cutoff of 11.0 g/dL for the altitude in Entebbe (1132 m above sea level) [16]. Birth weight was measured within 72 h after delivery to a precision of 100 g. For babies not delivered in Entebbe Hospital, 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. The perinatal period was defined as commencing at 28 weeks of gestation (age of fetal viability in Uganda) and ending at 7 completed days after birth. Perinatal deaths (stillbirths and neonatal deaths within 7 completed days after de-

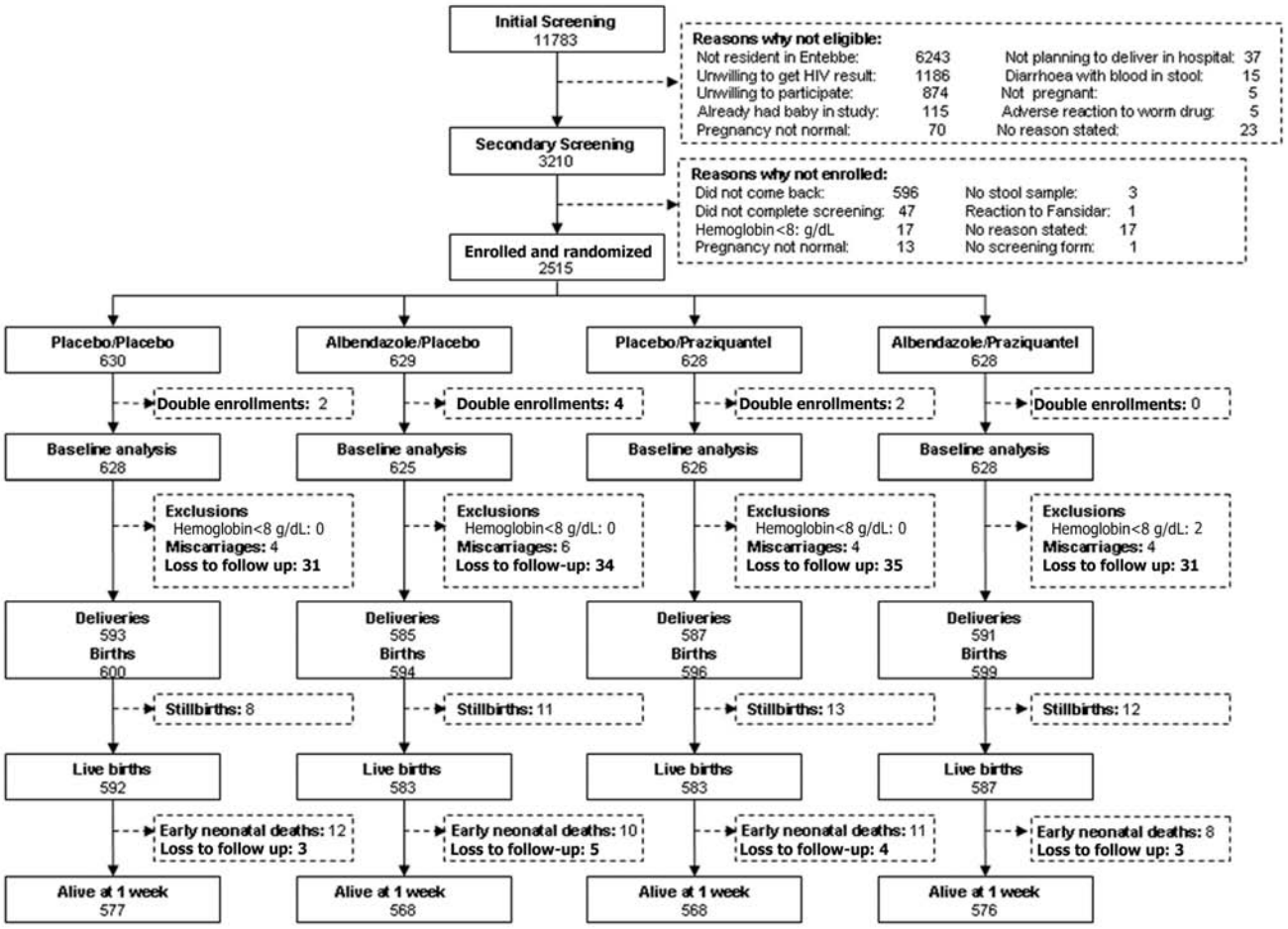

Figure 1. Study flow diagram.

livery) were documented by the midwife or by reports obtained from participants after follow-up in the community. Congenital anomalies (structural or functional defects present at birth) were identified at delivery by the midwife and accumulated to 1 year of age by physicians at follow-up, supported, when necessary, by referral to specialists.

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. There were no stopping rules; however, serious adverse events were reported as they occurred, and for these, unblinded analyses were conducted by the data monitoring committee twice during recruitment so that the study could be stopped if an excess occurred in any group.

Analyses were performed using Stata, version 9 (Stata). 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 praziquantel 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 praziquantel among women with schistosomiasis at enrollment. Exploratory analyses further assessed whether effects varied by intensity of hookworm or schistosomiasis, by maternal anemia at enrollment or by trimester during which treatment was given.

RESULTS

The trial profile is shown in Figure 1. A total of 2515 women were enrolled and treated; 8 were subsequently excluded because they had enrolled during a previous pregnancy. Therefore, 2507 women were available for baseline analysis. Two were excluded from subsequent analyses because they had a hemoglobin level below the enrollment cutoff, and their treat-

Table 1. Comparison of Maternal Baseline Characteristics among 2507 Women by Treatment Group

Characteristic	Treatment group			
	Placebo and placebo (n = 628)	Albendazole and placebo (n = 625)	Praziquantel and placebo (n = 626)	Albendazole and praziquantel (n = 628)
Maternal age, mean years ± SD	23.34 ± 5.2	23.49 ± 5.3	23.52 ± 5.4	23.97 ± 5.5
Tribe[a]				
Baganda	301 (48.0)	313 (50.1)	314 (50.2)	303 (48.3)
Banyankole	67 (10.7)	56 (9.0)	47 (7.5)	64 (10.2)
Batoro	32 (5.1)	24 (3.8)	27 (4.3)	19 (3.0)
Basoga	20 (3.2)	27 (4.3)	23 (3.7)	36 (5.7)
Luo	37 (6.0)	30 (4.8)	41 (6.7)	32 (5.1)
Banyarwanda	37 (6.0)	31 (5.0)	36 (5.8)	38 (6.1)
Other	133 (21.2)	144 (23.0)	138 (22.0)	136 (21.7)
Maternal education[b]				
None	32 (5.1)	17 (2.7)	23 (3.7)	25 (4.0)
Any primary	316 (50.4)	318 (51.0)	318 (51.0)	311 (49.6)
Any secondary	226 (36.0)	244 (39.1)	229 (36.6)	235 (37.5)
Any tertiary	53 (8.5)	45 (7.2)	55 (8.8)	56 (8.9)
Household socioeconomic status index[c]				
1	39 (6.3)	35 (5.7)	40 (6.6)	33 (5.3)
2	52 (8.5)	54 (8.8)	57 (9.3)	54 (8.7)
3	194 (31.5)	182 (29.6)	199 (32.6)	190 (30.7)
4	183 (29.8)	179 (29.2)	174 (28.5)	174 (28.2)
5	115 (18.7)	131 (21.3)	109 (17.8)	130 (21.0)
6	32 (5.2)	33 (5.4)	32 (5.2)	37 (6.0)
Trimester at treatment[d]				
2	325 (52.0)	321 (51.4)	325 (52.0)	338 (53.8)
3	301 (48.1)	304 (48.6)	300 (48.0)	290 (46.2)
Parity[e]				
1	164 (26.1)	181 (29.0)	172 (27.5)	177 (28.3)
2–4	369 (58.8)	350 (56.0)	354 (56.6)	338 (54.0)
⩾5	95 (15.1)	94 (15.0)	100 (16.0)	111 (17.7)
Place of delivery[f]				
Hospital	418 (70.6)	426 (72.7)	405 (69.2)	442 (75.0)
Home	69 (11.7)	68 (11.6)	68 (11.6)	61 (10.4)
Other	105 (17.7)	92 (15.7)	112 (19.2)	86 (14.6)
HIV status				
Negative	540 (86.0)	554 (88.6)	565 (90.3)	549 (87.4)
Positive	88 (14.0)	71 (11.4)	61 (9.7)	79 (12.6)
Malaria parasites[g]				
No	532 (86.2)	552 (89.8)	552 (90.3)	555 (90.1)
Yes	85 (13.8)	63 (10.2)	59 (9.7)	61 (9.9)
Active syphilis[h]				
No	600 (95.7)	599 (96.0)	601 (96.5)	596 (95.1)
Yes	27 (4.3)	25 (4.0)	22 (3.5)	31 (5.0)
Helminth prevalence[i]				
Hookworm	277 (44.2)	262 (42.1)	301 (48.3)	270 (43.3)
Mansonella perstans	143 (22.8)	117 (18.8)	136 (21.8)	135 (21.7)
Schistosoma mansoni	114 (18.2)	123 (19.8)	104 (16.7)	117 (18.8)
Strongyloides stercoralis	78 (12.5)	68 (11.0)	78 (12.6)	82 (13.2)
Trichuris trichiura	54 (8.6)	59 (9.5)	57 (9.2)	56 (9.0)
Ascaris lumbricoides	17 (2.7)	14 (2.2)	16 (2.6)	11 (1.8)

Table 1. ***(Continued.)***

Characteristic	Treatment group			
	Placebo and placebo (n = 628)	Albendazole and placebo (n = 625)	Praziquantel and placebo (n = 626)	Albendazole and praziquantel (n = 628)
Trichostrongylus species	10 (1.6)	6 (1.0)	5 (0.8)	5 (0.8)
Baseline hemoglobin level, mean g/dL ± SD	11.45 ± 1.50	11.45 ± 1.47	11.55 ± 1.50	11.53 ± 1.47
Anemia (hemoglobin level <11.2 g/dL)[j]				
No	362 (57.9)	374 (60.0)	381 (61.1)	382 (61.5)
Yes	263 (42.1)	249 (40.0)	243 (38.9)	239 (38.5)

NOTE. Data are no. (%) of women, unless otherwise indicated. SD, standard deviation.

[a] Tribe had 1 missing value.
[b] Maternal education had 4 missing values.
[c] Household socioeconomic status is a score based on building materials, number of rooms, and items owned. High scores indicated high status. There were 49 missing values.
[d] Trimester at treatment had 3 missing values.
[e] Parity had 1 missing value.
[f] Place of delivery had 2 missing values.
[g] Malaria parasites had 48 missing values.
[h] Active syphilis had 6 missing values.
[i] Eleven missing values for hookworm, *S. mansoni, T. trichuris, A. lumbricoides,* and *Trichostrongylus* species; 8 missing values for *M. perstans;* and 24 missing values for *S. stercoralis.*
[j] Anemia had 12 missing values.

ment was unblinded for clinical care. Randomization resulted in a similar distribution of baseline variables between treatment groups (Table 1).

Most women were Baganda (49%; the main tribe in central Uganda), were married (84%), were housewives (64%), and had no formal or only primary education (54%) and were poor (personal income <£10 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 *M. perstans* infection, 18% had *S. mansoni* infection, 12% had *Strongyloides stercoralis* infection, 9% had *Trichuris trichuria* infection, and 2% had *Ascaris lumbricoides* infection. Of the hookworm-infected women, 85% had light infection, 11% had moderate infection, and 4% had heavy infection; of the *S. mansoni*–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 prevalence of asymptomatic *Plasmodium falciparum* parasitemia was 11% and of HIV infection was 12%. 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 18 miscarriages, data were available for 2356 deliveries resulting in 2389 births, including 31 sets of twins and 1 set of triplets. Multiple births were equally distributed between treatment groups. Women lost to follow-up at delivery (n = 131) were younger, more frequently primi-gravidae, enrolled earlier in pregnancy, and more likely to have hookworm and a lower hemoglobin level at enrollment (data not shown).

Maternal helminths. Stool samples were obtained from 2051 women (82%) after delivery. Women who received albendazole had substantially lower prevalence of hookworm and *Ascaris* infection after delivery than did those who received placebo; praziquantel was associated with lower prevalence of *S. mansoni* infection (Tables 2 and 3). Albendazole showed no effect on schistosomiasis; praziquantel showed no effect on helminths other than *S. mansoni.*

Maternal anemia. After delivery, blood samples were obtained from 1918 women (81%); the median time from obtainment of samples was 1 day after delivery (interquartile range, 1–3 days). Of these women, 669 (35%) were anemic (hemoglobin level, <11.2 g/dL). There was no overall effect of albendazole or praziquantel on maternal hemoglobin level or anemia after delivery (Tables 2 and 3); for anemia, no effect of albendazole among women with hookworm (OR, 0.92; 95% CI, 0.69–1.23) or of praziquantel among women with schistosomiasis (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). Praziquantel showed no effect on anemia at any intensity of schistosomiasis (Table 4). 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 1964 (82%)

Table 2. Comparison of Outcomes at Delivery among Albendazole, Praziquantel, and Placebo Groups

Outcome	Placebo and placebo	Albendazole and placebo	Praziquantel and placebo	Albendazole and praziquantel
Helminth prevalence				
Hookworm	220/505 (43.6)	28/516 (5.4)	228/498 (45.8)	28/532 (5.3)
Mansonella perstans[a]	117/470 (24.9)	92/486 (18.9)	94/458 (20.5)	105/498 (21.1)
Schistosoma mansoni	98/505 (19.4)	119/516 (23.1)	24/498 (4.8)	25/532 (4.7)
Strongyloides stercoralis[b]	48/500 (9.6)	27/510 (5.3)	43/490 (8.8)	42/524 (8.0)
Trichuris trichiura	43/505 (8.5)	39/516 (7.6)	52/498 (10.4)	37/532 (7.0)
Ascaris lumbricoides	19/505 (3.8)	3/516 (0.6)	13/498 (2.6)	3/532 (0.6)
Trichostrongylus species	3/505 (0.6)	4/516 (0.8)	4/498 (0.8)	5/532 (0.9)
Maternal anemia	166/472 (35.2)	169/488 (34.6)	164/458 (35.8)	170/500 (34.0)
Maternal hemoglobin level				
No. tested	472	488	458	500
Mean g/dL ± SD	11.69 ± 1.98	11.73 ± 1.93	11.89 ± 1.87	11.84 ± 1.96
Cord blood hemoglobin level				
No. tested	322	332	312	367
Mean g/dL ± SD	14.53 ± 1.75	14.55 ± 1.83	14.67 ± 1.74	14.60 ± 1.93
Birth weight				
No. measured	486	506	475	497
Mean kg ± SD	3.16 ± 0.52	3.15 ± 0.52	3.15 ± 0.53	3.15 ± 0.50
Low birth weight	42/486 (8.6)	43/506 (8.5)	45/475 (9.5)	35/497 (7.0)
Very low birth weight	4/482 (0.8)	2/504 (0.4)	1/474 (0.2)	4/493 (0.8)
Stillbirths[c]	8/600 (1.3)	11/594 (1.9)	13/596 (2.2)	12/599 (2.0)
Early neonatal deaths[d]	12/592 (2.0)	10/583 (1.7)	11/583 (1.9)	8/587 (1.4)
Perinatal deaths[c]	20/600 (3.3)	21/594 (3.5)	24/596 (4.0)	20/599 (3.3)
Congenital anomalies	42/596 (7.1)	45/586 (7.7)	43/588 (7.5)	50/595 (8.4)

NOTE. Data are proportion (%) of women, unless otherwise indicated. SD, standard deviation.

[a] Results were available for 1912 of the 1918 women who had blood samples obtained within 6 weeks after delivery.
[b] Results were available for 2024 of the 2051 women who provided a stool sample within 14 weeks after delivery.
[c] The denominator for stillbirths and perinatal deaths was all births.
[d] The denominator for early neonatal deaths was all live births.

births, 1941 measured within 24 h; 1764 (90%) of these were recorded in Entebbe Hospital. The mean birth weight (±SD) was 3.15 ± 0.52 kg; 165 newborns (8%) had low birth weight, and 11 (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 (Tables 2 and 3), 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 praziquantel among women with schistosomiasis (difference in mean, 0.06 kg; 95% CI, −0.04 to 0.17 kg). There was no difference in effect of albendazole or praziquantel by hookworm or schistosomiasis infection intensity, respectively (Table 5). 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.

Perinatal mortality. There were 44 stillbirths and 41 early neonatal deaths (perinatal mortality, 36 deaths per 1000 births). The most common cause of perinatal death was birth asphyxia. Neither drug showed any effect on perinatal mortality (Tables 2 and 3).

Congenital anomalies. Congenital anomalies were recorded at birth for 2365 infants (99%), and 40 were identified; an additional 131 were diagnosed at the 6-week postnatal visit and 9 at illness-related visits (overall prevalence, 76 anomalies per 1000 births). The most frequently recorded anomalies were those involving the musculoskeletal system (56%) and skin (21%). Anthelminthic treatment during pregnancy showed no association with congenital anomalies (Table 6).

DISCUSSION

In the present study, deworming with albendazole or praziquantel 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

Table 3. Effect of Deworming with Albendazole or Praziquantel during Pregnancy on Outcomes at Delivery

Outcome	Albendazole vs placebo	Praziquantel vs placebo
Helminth, OR (95% CI)		
Hookworm	0.07 (0.05–0.09)	1.07 (0.85–1.34)
Mansonella perstans	0.85 (0.68–1.06)	0.94 (0.76–1.17)
Schistosoma mansoni	1.18 (0.90–1.54)	0.18 (0.13–0.26)
Strongyloides stercoralis	0.71 (0.51–0.98)	1.15 (0.83–1.59)
Trichuris trichiura	0.75 (0.54–1.02)	1.09 (0.79–1.49)
Ascaris lumbricoides	0.18 (0.07–0.42)	0.73 (0.38–1.39)
Trichostrongylus species	1.23 (0.46–3.31)	1.27 (0.47–3.43)
Maternal hemoglobin level, difference in mean, g/dL (95% CI)	−0.01 (−0.18 to 0.17)	0.15 (−0.02 to 0.32)
Maternal anemia, OR (95% CI)	0.95 (0.79–1.15)	1.00 (0.83–1.21)
Cord blood hemoglobin level, difference in mean, g/dL (95% CI)	−0.03 (−0.22 to 0.17)	0.09 (−0.10 to 0.29)
Birth weight, difference in mean, kg (95% CI)	−0.00 (−0.05 to 0.04)	−0.01 (−0.05 to 0.04)
Low birth weight, OR (95% CI)	0.85 (0.62–1.17)	0.96 (0.70–1.32)
Stillbirth, OR (95% CI)	1.10 (0.61–2.00)	1.32 (0.72–2.42)
Early neonatal mortality, OR (95% CI)	0.78 (0.42–1.46)	0.87 (0.47–1.61)
Perinatal mortality, OR (95% CI)	0.93 (0.61–1.44)	1.08 (0.70–1.66)
Congenital anomaly, OR (95% CI)	1.13 (0.83–1.53)	1.07 (0.79–1.45)

NOTE. ORs for the effect of albendazole and praziquantel are adjusted for one another. CI, confidence interval; OR, odds ratio.

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 *S. mansoni*. 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. The research program aimed to provide basic antenatal care in accordance with Ugandan Ministry of Health guidelines; therefore, supplies of hematinics and of sulphadoxine-pyrimethamine for sulfadoxine-pyrimethamine were ensured [18]; results might differ in areas where antenatal care is poor. 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 11,766 women screened. Similarly, women lost to follow-up (younger women with a slightly higher prevalence of hookworm and lower hemoglobin level) may have been particularly likely to benefit, but loss to follow-up was low (7%) and did not differ between treatment groups. Perinatal mortality may have been under-

Table 4. Effect of Deworming during Pregnancy on Maternal Anemia after Delivery, According to Intensity of Hookworm and *Schistosoma mansoni* Infection

	Prevalence of anemia, proportion of women (%)		
Variable	Drug	Placebo	OR (95% CI)[a]
Albendazole			
Effect according to hookworm intensity at enrollment			
Uninfected	203/573 (35)	187/513 (36)	0.96 (0.75–1.23)
Light (<1000 eggs per g)	118/356 (33)	116/358 (32)	1.03 (0.76–1.41)
Moderate to heavy (⩾1000 eggs per g)	17/56 (30)	27/55 (49)	0.45 (0.21–0.98)
Praziquantel			
Effect according to *S. mansoni* intensity at enrollment			
Uninfected	264/779 (34)	274/776 (35)	0.94 (0.76–1.16)
Light (<100 eggs per g)	45/119 (38)	43/117 (37)	1.05 (0.62–1.78)
Moderate to heavy (⩾100 eggs per g)	24/56 (43)	18/64 (28)	1.92 (0.90–4.11)

NOTE. Anemia was defined as a hemoglobin level <11.2 g/dL. Results are given for 1911 women (7 women who had hemoglobin results at delivery had missing values for helminth infection intensity at baseline). For albendazole, $P = .15$ for interaction. For praziquantel, $P = .20$ for interaction. CI, confidence interval; OR, odds ratio.

[a] ORs for the effect of albendazole and praziquantel are adjusted for one another.

Table 5. Effect of Deworming during Pregnancy on Birth Weight, According to Intensity of Hookworm and *Schistosoma mansoni* Infection

Variable	Mean birth weight (95% CI)		Difference in mean birth weight[a] (95% CI)
	Drug	Placebo	
Albendazole			
Effect according to hookworm intensity at enrollment			
Uninfected	3.17 (3.12–3.21)	3.17 (3.12–3.21)	−0.00 (−0.06 to 0.06)
Light (<1000 eggs per g)	3.13 (3.08–3.18)	3.15 (3.09–3.20)	−0.01 (−0.11 to 0.08)
Moderate to heavy (≥1000 eggs per g)	3.13 (3.03–3.24)	3.05 (2.92–3.18)	0.08 (−0.11 to 0.28)
Praziquantel			
Effect according to *S. mansoni* intensity at enrolment			
Uninfected	3.14 (3.10–3.18)	3.16 (3.13–3.20)	−0.02 (−0.07 to 0.03)
Light (<100 eggs per g)	3.20 (3.12–3.28)	3.11 (3.02–3.20)	−0.06 (−0.16 to 0.04)
Moderate to heavy (≥100 eggs per g)	3.17 (3.03–3.30)	3.16 (3.03–3.30)	−0.00 (−0.14 to 0.13)

NOTE. Results are given for 1958 women (6 women who had birth weight results had missing values for helminth infection intensity at baseline). For albendazole, $P = .65$ for interaction. For praziquantel, $P = .29$ for interaction. CI, confidence interval; OR, odds ratio.

[a] The effects of albendazole and praziquantel are adjusted for one another.

estimated, because deaths could have contributed to women lacking outcome information. 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 Entebbe [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 ane-

Table 6. Congenital Abnormalities in the Albendazole, Praziquantel, and Placebo Groups

Location of abnormality	Treatment group, no. of women				All
	Placebo and placebo (n = 596)	Albendazole and placebo (n = 586)	Praziquantel and placebo (n = 588)	Albendazole and praziquantel (n = 595)	
Cardiovascular system	1	2	0	1	4
Nervous system	0	2	0	1	3
Gastrointestinal system	0	0	1	0	1
Genitourinary system	1	1	1	3	6
Dysmorphic and/or chromosomal features	2	1	0	1	4
Musculoskeletal system[a]	24	27	24	26	101
Skin[b]	11	8	8	11	38
Head and neck	1	4	5	2	12
Multiple malformations	1	0	4	5	10
Unspecified anomaly of the cardio-respiratory system	1	0	0	0	1
Total, no. (%)	42 (7.1)	45 (7.7)	43 (7.5)	50 (8.4)	180

[a] Sixty-seven abdominal wall hernias, 26 polydactyly, and 8 other limb deformities.

[b] Thirty-seven birthmarks and 1 poliosis (localized patch of white hair).

mia during pregnancy in our study was less than the national figure of 64% in 2006 [20], and even in Uganda, 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. Praziquantel 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 11 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; however, benzimidazoles act on microtubules in the cytoskeleton, have some toxicity to mammalian cells, and have been associated with reduced fetal weight in studies in rats [23, 24]. This potential adverse effect of the use of benzimidazoles during pregnancy warrants further surveillance.

As in the trial from Peru, we observed no association between the use of benzimidazoles during pregnancy and congenital anomalies. We found no association between praziquantel and congenital anomalies, in keeping with earlier reports [5].

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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