Efficacy of Ivermectin and Albendazole Alone and in Combination for Treatment of Soil-Transmitted Helminths in Pregnancy and Adverse Events: A Randomized Open Label Controlled Intervention Trial in Masindi District, Western Uganda

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Abstract. A randomized open-label trial, including 834 pregnant women, examined efficacy and recorded adverse events of ivermectin (ivc) and albendazole (alb) alone and combined (comb) on soil-transmitted helminth infections (STHs) in the second trimester of pregnancy. One abortion occurred in the alb group and 10 stillbirths (1, 5, 3, and 1) in the ivc, alb, comb, and the reference group (ref) with no STHs, respectively. Two babies were born with congenital abnormalities (1 [ivc] and 1 [ref]). The prevalence of anemia at first antenatal care (ANC) visit was 20.6% (23.7% [ivc], 21.1% [alb], 22.2% [comb], and 16.1% [ref]). Anemia was reduced to 8.5% at 36 weeks of gestation with 10.9% (ivc), 11.5% (alb), 7.7% (comb), and 6.9% (ref). Hookworm cure rates were 29.4% (ivc), 95.5% (alb), and 92.6% (comb). No severe adverse events were reported by the women after the administration of ivc, alb, or comb during the second trimester of pregnancy, but long-term pharmacovigilance is needed to assess safety of ivc, alb, or comb in pregnancy.

INTRODUCTION

In Africa, lymphatic filariasis (LF) and onchocerciasis are co-endemic in many areas.1,2 The current strategies for the control of onchocerciasis and LF are repeated annual mass treatment with ivermectin (ivm) and co-administration of ivermectin and albendazole, respectively.3,4 The expectation is to interrupt transmission if high treatment coverage is achieved. However, interruption of transmission may not be achieved if sections of the population (children < 5 years of age and pregnant women), who are microfilaria carriers, are excluded from mass drug administration (MDA) programs. Many African countries implementing community-based ivermectin treatment programs for the control of onchocerciasis reports that a number of people expel Ascaris lumbricoides worms after ivermectin treatment and for this reason, some pregnant women refuse to reveal that they are pregnant to get the drug for de-worming purposes. The Mectizan Expert Committee and the Mectizan Donation Program have recommended that pregnant and breastfeeding women and children < 5 years of age or with a weight < 15 kg or with height less than 90 cm should be excluded from ivermectin treatment5 because of uncertainty of the safety of the drug in these groups. Thus, many pregnant and breastfeeding women miss ivermectin treatment opportunities during community-based ivermectin distribution programs.6 However, there are no data indicating that ivermectin poses any danger to a fetus or neonate after inadvertent treatment during community-based distribution.7

In 1997, the World Health Assembly made a resolution call for the elimination of LF in Africa, and the strategy is based principally on a combination of albendazole and ivermectin MDA. Information on the safety and efficacy of this combination used in pregnancy on soil-transmitted helminths (STHs) as an additional health benefit is not available. Such information would be helpful in advocating for the program. Although there is information on the safety of ivermectin and albendazole administered separately during pregnancy,7,8 no studies have systematically examined the safety of ivermectin treatment and co-administration of ivermectin and albendazole to pregnant women. A randomized, open label, controlled trial was conducted to examine the efficacy of ivermectin and albendazole alone and in combination given in the second trimester of pregnancy and record adverse events after treatment.

MATERIALS AND METHODS

Study area. The study was conducted in Masindi district in western Uganda. The district lies at an altitude of 621–1,158 m above sea level. The average air temperature is 25°C and rainfall ranges from 100 to 1,000 mm/annum. According to the 2002 census, the district has a population density of 56 persons/km². Administratively, the district has 4 counties with 14 sub-counties with Masindi town as the administrative headquarter. Subsistence farming is the main economic activity. The prevalence of A. lumbricoides in school children in the region ranges from 0% to 55% with an average of 22%, Trichuris trichiura ranges from 0% to 37% with an average of 15%, whereas hookworm infection ranges from 34% to 74% with an average of 61%.9 However, there was no information on the prevalence of STHs among pregnant women in the area. The district is hyper-endemic for malaria and transmission takes place throughout the year peaking shortly after rainfall in April–June and September–November. Malaria is the leading cause of outpatient morbidity in the district (Health Information System Annual Report 2001, Masindi District).

Methods. Pregnant women of any parity attending antenatal care (ANC) in their second trimester (≥ 16 weeks of gestation at first ANC booking) at a public health center (type 4) who gave informed consent were recruited. At enrollment, age, weight, height, and parity were recorded and a clinical examination undertaken. Thick smears of finger-prick blood were prepared and stained with Giemsa for the detection of malaria parasites. Parasites were counted against 200 leukocytes and expressed as parasites/μL assuming a standard leukocyte count of 8,000/μL. Women with severe anemia (< 7 g/L), a history of habitual abortion, delivering twins, and babies with congenital abnormalities were excluded at enroll-
ment. Women with severe anemia were treated with a single dose of sulfadoxine-pyrimethamine (SP), and ferrous sulphate 200 mg was given three times a day for at least three weeks. Gestational age was assessed by palpation of fundus height combined with information on last menstrual period. Hemoglobin (Hb) was measured using a portable Hemocue photometer. One stool sample was collected and duplicate 50-mg Kato-Katz cellophane thick smears were prepared for the detection of STHs. The stool smears were examined immediately after preparation for hookworm eggs and at a later stage for other intestinal helminths. Egg counts were given as eggs/gram feces (epg). Women infected with any intestinal helminth were randomly assigned to receive albendazole administered as a single dose of 400 mg or ivermectin or a combination of both. Ivermectin was administered according to height, as it is the current practice in ivermectin distribution programs (African Program for Onchocerciasis Control).10

Sample size estimation was based on the differences in cure rate for ivermectin and albendazole against hookworm. The estimated cure rate of the combination of ivermectin and albendazole was 75%, and the estimated cure rate of albendazole was 60%. Using a power of 90% and a significance level of 5% and a loss to follow-up of 30%, 216 women were needed in each group (total 864 pregnant women). The drugs were taken under direct supervision and women in addition received the routine ANC package (anti-tetanus toxoid, iron supplements, and intermittent preventive treatment with sulfadoxine-pyrimethamine [SP]). The study was an open label randomized controlled trial with four arms. Group A received ivermectin and Group B received albendazole. Group C received a combination of ivermectin and albendazole, whereas Group D was a reference group without STHs. The mothers were asked to return to the health unit whenever they had any problem or illness at any time and were examined for any possible adverse events. The mothers were followed up on day 21 after treatment and any maternal ill health was recorded. A stool sample was collected and examined as mentioned previously. Efficacy (cure rate of STHs) was defined as the proportion of pregnant women who were excreting eggs in their stool before treatment, but who had a negative test result at 21 days follow-up. Abortions and premature deliveries were recorded in time relation to the administration of the drug through weekly community surveillance. The Hb measurement was repeated at 36 weeks of gestation for women in all the four groups. At birth, the weight of the babies was measured to the nearest 10 gm and stillbirths were recorded. The babies were examined for any malformations at birth and for clinical jaundice and anemia. The Hb of newborns was measured using heel prick blood. The babies were followed up at one month and examined by a midwife for clinical jaundice, any other illness, and malformations.

### Data analysis
Data were entered and analyzed using EPIINFO version 6 (CDC, Atlanta, GA) supplemented by SPSS version 10.0 (Chicago, IL). Egg counts were normally distributed after log transformation and geometric mean parasite density was calculated. Student’s t-test was used for comparison of two means and analysis of variance (ANOVA) for comparison of three or more means. Proportions were compared using $\chi^2$ and $P$ values < 0.05 were considered significant in all tests.

### Ethical considerations
The objectives of the study and its implications were explained to the pregnant women. Approval of the study was obtained from the National Council for Science and Technology in Uganda (ref.: MV 726). The Danish National Committee for Biomedical Research Ethics also reviewed the study and recommended it (ref.: 624-03-0004). Participation was voluntary after informed consent and a participant could withdraw from the study at any time without consequences for ongoing treatment or ANC services.

### RESULTS
Although 864 women were needed to be recruited for the study according to sample size calculations, it was found as the study progressed that the assumption of a loss to follow-up of 30% was too high. Actual loss to follow-up was about 15%. Therefore, recruitment was stopped before the originally planned 864 study participants were reached. As shown in Table 1, the baseline characteristics of the pregnant women were comparable except for Hb level, which was significantly higher in the reference group (difference in mean Hb between intervention and reference groups: A versus D, $P = 0.027$; B versus D, $P = 0.09$; and C versus D, $P = 0.0006$). Of the 832 pregnant women who were included, 5 women delivered twins (1 in Groups A, C, and D, and 2 in Group B) and were excluded from further birth weight analysis (Figure 1). There were 1 abortion and 10 stillbirths whose birth weights were not measured. Another 63 women had migrated to deliver at their mothers’ homes or had migrated to the Democratic Republic of Congo (DRC) because of tribal clashes between the Alurs from DRC and the indigenous Banyoro people. These were 8, 10, 13, and 32 in Groups A, B, C, and D, respectively. Data at delivery was thus included for 170, 160, 171, and 207 women in Groups A, B, C, and D, respectively.

A total of 834 pregnant women were examined for STHs at their first ANC clinic visit between January 2003 and May 2005 (Figure 1). Stool examination results were missing for two women (1 in Group A and 1 in Group B), and these were excluded from further analysis. Of the 832 pregnant women who had the stool examination results recorded, 591 (71%) were infected with one or more STHs (hookworm, *A. lumbricoides*).
or *T. trichiura*. A total of 198 (23.8%) were allocated to Group A (ivermectin), 194 (23.3%) to Group B (albendazole), and 199 (23.9%) to Group C (ivermectin plus albendazole). A total of 241 (29%) had no STH infections and were allocated to Group D (no intervention, reference group). The prevalence of hookworm infection was 66.6% (554), with 93.9% (186), 91.8% (178), and 95.5% (190) in Groups A, B, and C, respectively (Table 2). Only 4 persons were infected
with *A. lumbricoides* (2 in each of the Groups A and B). The prevalence of *T. trichiura* was 4.6% (38) with 4.5% (9) in Group A, 6.2% (12) in Group B, and 8.5% (17) in Group C, respectively. The prevalence of *Schistosoma mansoni* was very low (3.7% [31]), and those infected were treated with praziquantel 40 mg/kg as a single dose because the drug is now recommended for use in pregnancy.8,11 A total of 802 women had a blood smear prepared and 282 (35.2%) were positive for *Plasmodium falciparum* parasites with 35.1%, 35.8%, 35.5%, and 34% in Groups A, B, C, and D, respectively (P = 0.98). There was no significant difference in *P. falciparum* parasitaemia rate between any of the intervention groups and the reference group (A versus D, P = 0.79; B versus D, P = 0.66; and C versus D, P = 0.72).

### Efficacy of ivermectin, albendazole, and the combination on STH infections
Of the pregnant women seen at first ANC visit having STH infections, 180 (91.4%) in Group A, 178 (92.2%) in Group B, and 188 (94.5%) in Group C were available for follow-up at 21 days post treatment. Forty-five were lost to follow-up because of migration, and they were 18, 16, and 11 in Groups A, B, and C, respectively (Figure 1). Ivermectin, albendazole, and ivermectin/albendazole had reduced the prevalence of hookworm infection from 93.9% to 70.6%, 91.8% to 4.5%, and 95.5% to 7.4%, respectively (Table 2). A total of 53, 170, and 174 were negative for hookworm infection at 21 days follow-up in Groups A, B, and C giving a cure rate of 92.2% in Group B. No women reported any severe adverse event.

### Adverse reactions to ivermectin, albendazole, and the combination among pregnant women
Overall, 47 pregnant women reported having experienced mild and short lived adverse reactions; 23 (48.9%) in Group A, 16 (34%) in Group B, and 8 (17%) in Group C, and the difference among the groups was significant (P = 0.005). Significant difference was noted in reported mild adverse reactions between Groups A and C (P = 0.67) but not between Groups A and B (P = 0.14) and Groups B and C (P = 0.61). The most common reactions were: abdominal pain (7 [30.4%], 8 [50%], and 4 [50%] in Groups A, B, and C, respectively [P = 0.39]). There was no significant difference in reported abdominal pain between Groups A and B (P = 0.22), Groups A and C (P = 0.57), and Groups B and C (P = 0.67). Another reported reaction was fever (4 [17.4%], 2 [12.5%], and 4 [50%] in Groups A, B, and C, respectively [P = 0.087]), and there was no significant difference between Groups A and B (P = 0.97), between Groups A and C (P = 0.18), and between Groups B and C (P = 0.13). Body rash/itchiness was the least reported mild adverse reaction with (4 [17.4%], 2 [12.5%], and 2 [25%] in Groups A, B, and C, respectively [P = 0.74]), and there was no significant difference between Groups A and B (P = 0.97), Groups A and C (P = 0.96), and Groups B and C (P = 0.13). Six women reported headache (4 [17.4%] in Group A and 2 [12.5%] in Group B). Three women reported anorexia/vomiting (2 [8.7%] in Group A and 1 [6.3%] in Group B). No women reported any severe adverse event.

### Effect of the interventions on mean birth weight and low birth weight (LBW)
As shown in Table 5, there was no significant difference in mean birth weight among the groups (P = 0.52) and between Groups A and D (P = 0.41), Groups B and D (P = 0.83), and Groups C and D (P = 0.29). Similarly, there was no significant difference in the frequency of LBW (birth weight < 2.5 kg) among the groups (P = 0.47). A comparison was also made between each of the intervention groups and reference group on the frequency of LBW. There was no significant difference between Groups A and D (P = 0.56), Groups B and D (P = 0.25), and Groups C and D (P = 0.14).

### Effect of interventions on abortions, premature deliveries, stillbirths, and congenital abnormalities
Only one abortion was recorded (Group B). According to the midwife’s assessment, there were 13 premature deliveries with 3 (1.8%), 2 (1.3%), 3 (1.8%), and 5 (2.4%) in Groups A, B, C, and D, respectively (P = 0.87). A comparison was made between each of the intervention groups and reference group on premature deliveries, and there was no significant difference between any of the intervention groups and the reference group (A versus D, P = 0.94; B versus C, P = 0.67; C versus D, P = 0.94). Babies were also categorized as premature and full

### Table 2
Prevalence of soil transmitted helminth (STH) infections by interventions at first antenatal care (ANC) visit and at 21 days post treatment in Masindi district, western Uganda

<table>
<thead>
<tr>
<th>Intervention group</th>
<th>Hookworm</th>
<th>Ascaris lumbricoides</th>
<th>Trichuris trichiura</th>
<th>Hookworm</th>
<th>Ascaris lumbricoides</th>
<th>Trichuris trichiura</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (ivermectin)</td>
<td>93.9 (198)</td>
<td>1.0 (198)</td>
<td>4.5 (198)</td>
<td>70.6 (180)</td>
<td>0 (180)</td>
<td>2.2 (180)</td>
</tr>
<tr>
<td>B (albendazole)</td>
<td>91.8 (194)</td>
<td>1.0 (194)</td>
<td>6.2 (194)</td>
<td>4.5 (178)</td>
<td>0 (178)</td>
<td>4.5 (178)</td>
</tr>
<tr>
<td>C (ivermectin + albendazole)</td>
<td>95.5 (199)</td>
<td>0 (199)</td>
<td>8.5 (199)</td>
<td>7.4 (188)</td>
<td>0 (188)</td>
<td>2.7 (188)</td>
</tr>
</tbody>
</table>

### Table 3
Cure rates of ivermectin, albendazole, and a combination of both on soil-transmitted helminth (STH) infections

<table>
<thead>
<tr>
<th>Intervention group</th>
<th>No. of women with STH infection at ANC visit (%)</th>
<th>No. of women negative for STH 21 days post treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hookworm</td>
<td>Ascaris lumbricoides</td>
</tr>
<tr>
<td>A (ivermectin)</td>
<td>186 (93.9)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>B (albendazole)</td>
<td>178 (91.8)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>C (ivermectin + albendazole)</td>
<td>190 (95.5)</td>
<td>0</td>
</tr>
</tbody>
</table>

ANC = antenatal care.
term using Ballard score where a score < 46 (gestational age 36.7 weeks) was considered as premature. According to Ballard score, 36 babies were premature of which 9 (5.3%) were in Group A, 9 (5.6%) in Group B, 8 (4.7%) in Group C, and 10 (4.8%) in Group D ($P = 0.98$), and there was no significant difference between any of the intervention groups and the reference group (A versus D, $P = 0.65$; B versus D, $P = 0.74$; C versus D, $P = 0.95$). There were 10 stillbirths with 1 (0.6%), 5 (3.1%), 3 (1.8%), and 1 (0.5%) in Groups A, B, C, and D, respectively ($P = 0.13$). A comparison was made between each of the intervention groups and reference group on stillbirths, and there was no significant difference between any of the intervention groups and the reference group (A versus D, $P = 0.99$; B versus D, $P = 0.12$; C versus D, $P = 0.49$). Only 2 babies (one in Group A and one in Group D) were born with congenital abnormalities. The one in Group A had talipes equinovarus of the right foot, whereas the one in Group D had talipes equinovarus of the left foot, cleft palate, and multiple fingers, and the baby died shortly after birth.

**Effect of the interventions on maternal and neonatal Hb concentration.** The mean maternal and infant Hb levels and anemia status are summarized in Table 6. A total of 832 pregnant women had their Hb measured at first ANC visit and the mean Hb was 110.6 g/L, 111.2 g/L, 108.8 g/L, and 113.7 g/L in Groups A, B, C, and D, respectively ($P = 0.001$). Significant differences were noted in mean Hb levels at first ANC visit between Groups A and D ($P = 0.027$) and between Groups C and D ($P = 0.0006$) but not between Groups B and D ($P = 0.09$). Overall, 171 (20.6%) pregnant women were anemic at first ANC visit with 23.7%, 21.1%, 22.2%, and 16.1% in Groups A, B, C, and D, respectively ($P = 0.22$). The difference in the prevalence of anemia at first ANC visit was significant between Groups A and D ($P = 0.047$) but not between Groups B and D ($P = 0.19$) and Groups C and D ($P = 0.11$). At 36 weeks of gestation, 579 women had their Hb measured, and the mean Hb level was 113.8 g/L, 117.9 g/L, 115.6 g/L, and 117.8 g/L in Groups A, B, C, and D, respectively ($P = 0.062$). The difference in mean Hb levels at 36 weeks of gestation was significant between Groups A and D ($P = 0.015$), but not between Groups B and D ($P = 0.96$) and between Groups C and D ($P = 0.13$). The difference in mean Hb levels between first ANC visit and at 36 weeks of gestation was significant in all the groups except in Group A (Table 6). At 36 weeks of gestation, 8.5% pregnant women were anemic (Group A 10.9%, Group B 11.5%, Group C 7.7%, and Group D 6.9% [$P = 0.40$]). The difference in maternal anemia at 36 weeks of gestation was insignificant between any of the intervention groups and the reference group (Groups A and D [$P = 0.21$], Groups B and D [$P = 0.16$], and Groups C and D [$P = 0.85$]). A total of 693 infants had their Hb measured at birth (Group A 170, Group B 157, Group C 170, and Group D 196). Overall, 4.5% (31) infants were anemic at birth (infant anemia defined as Hb concentration < 140 g/L$^{11}$). Of those who were anemic at birth, 10 (5.8%), 6 (3.8%), 6 (3.5%), and 9 (4.6%) were in Groups A, B, C, and D, respectively ($P = 0.73$). There was no significant difference in infant anemia between Groups A and D ($P = 0.58$), Groups B and D ($P = 0.72$) and between Groups C and D ($P = 0.61$). As shown in Table 6, the mean infant Hb at birth was not significantly different among the groups ($P = 0.12$), but significant difference was noted between Groups C and D ($P = 0.044$) but not between Groups A and D ($P = 0.71$) and Groups B and D ($P = 0.074$).

**Effect of the interventions on maternal and neonatal mortality.** Of the 708 women who delivered live singleton babies, 636 (89.8%) were seen at one month post delivery with 148, 140, 146, and 202 in Groups A, B, C, and D, respectively (Figure 1). After delivery, 70 mothers had migrated to DRC because of tribal clashes or to their homes (22, 19, 24, and 5 in Groups A, B, C, and D, respectively). Fourteen babies had died at one-month post partum (6 [4.1%], 1 [0.7%], 2 [1.4%], and 5 [2.5%] in Groups A, B, C, and D, respectively [$P = 0.23$]). A comparison was made between each of the intervention groups and reference group on neonatal mortality, and there was no significant difference between any of the intervention groups and the reference group (A versus D, $P = 0.60$; B versus D, $P = 0.42$; C versus D, $P = 0.74$). The cause of death was respiratory tract infection (57.1%), prematurity related death (21.4%), and gastroenteritis/vomiting (14.3%). Of those mothers who had live babies at one-month post delivery, 204 reported that their children had problems, most of which were flu/cough (32.4%), skin rashes (16.7%), eye infection (5.9%), fever (4.9%), and anemia (4.4%). There were no differences among the groups (data not shown). Two women died of which 1 was in Group C who died shortly after an injection of procaine penicillin, and the cause of death was thought to be anaphylactic shock. Another woman (in Group B) died shortly after a caesarean section.

**DISCUSSION**

Anthelminthics are not widely used during pregnancy because of a lack of adequate information regarding their safety in pregnancy. However, in a review of 49 cases of inadvertent treatment with albendazole in the first trimester, no abnormal birth outcomes were recorded. In another report on the safety of albendazole use in pregnancy, there were no cases of malformation after inadvertent exposure of 15 patients with albendazole, but the sample size was small in all these stud-

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**Table 4**

Mean parasite density among hookworm positives by intervention group at enrollment and at 21 days post treatment in Masindi district, western Uganda.

<table>
<thead>
<tr>
<th>Intervention group</th>
<th>Mean parasite density (eggs/g) ±SD at first ANC visit</th>
<th>Mean parasite density (eggs/g) ±SD at 21 days post treatment</th>
<th>$P$ value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (ivermectin)</td>
<td>503.5 ± 4.7 (180)†</td>
<td>493.2 ± 4.3 (127)‡</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>B (albendazole)</td>
<td>653.5 ± 4.4 (178)†</td>
<td>237.1 ± 33.3 (8)‡</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>C (ivermectin + albendazole)</td>
<td>629.5 ± 4.3 (190)‡</td>
<td>227.5 ± 2.8 (14)‡</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>$P$ value‡</td>
<td>0.24</td>
<td>0.074</td>
<td></td>
</tr>
</tbody>
</table>

* Student’s $t$ test for significance of difference in the groups between first antenatal care (ANC) visit and at 21 days post treatment.
† Analysis of variance (ANOVA) test for significance of difference among the groups at first ANC visit and 21 days post treatment.
‡ Number in parenthesis indicates number of pregnant hookworm positives women.
Infant anemia status (Hb < 140 g/L) at mean (SD) infant Hb at birth (g/L) and lower than what has been recorded in earlier reports.7,14 This stillbirths) we still found that the abortion rate in our study is adverse pregnancy outcomes (e.g., abortions, malformations, sample size is too small to measure significant differences in treatment when given in the second trimester. Although the women does not lead to severe adverse events in relation to mectin and albendazole alone and in combination to pregnant treatments. Our results confirm earlier reports7,12,14 that ivermectin and albendazole during MDA for lymphatic filariasis, although the sample size was small.14 The present study is the first randomized open label controlled trial to examine the efficacy of ivermectin, albendazole, and the co-administration of both drugs during the second trimester of pregnancy for treatment of helminth infections and to provide data on adverse events related to these treatments. Our results confirm earlier reports7,12,14 that ivermectin and albendazole alone and in combination to pregnant women does not lead to severe adverse events in relation to treatment when given in the second trimester. Although the sample size is too small to measure significant differences in adverse pregnancy outcomes (e.g., abortions, malformations, stillbirths) we still found that the abortion rate in our study is lower than what has been recorded in earlier reports.7,14 This might be because of exclusion of women with a history of habitual abortion and enrollment of women in their second trimester, because most abortions are a result of congenital malformations after drug exposure, which normally occurs in the first trimester of pregnancy. The mean birth weight and the proportion of babies with low birth weight were not significantly different among the interventions and the reference group. The rate of stillbirths, birth weights and maternal anemia at 36 weeks of gestational age were comparable with what was observed from other populations of Uganda.15 The rate of stillbirths was higher in the albendazole groups than the ivermectin group but, as mentioned previously, the study was not powered to detect a difference given the low frequency of this event. The prevalence of infant anemia observed in our study is less than the infant anemia of 30% observed in previous studies.16 This might be explained by the fact that all women were given IPT with SP and thus had lower levels of malaria parasitaemia and higher Hb levels. Two children were born with congenital malformations and only one was exposed to ivermectin in utero. The second one was born to a mother from the reference group with no exposure to ivermectin or albendazole. This is comparable to findings by Gyapong and others,14 where there was only one child with congenital malformation after inadvertent exposure of ivermectin and albendazole in utero during mass drug administration for lymphatic filariasis control/elimination.

The effectiveness of ivermectin against hookworm in our study was comparable to the effectiveness of 0–20% observed by Richard and others.17 Likewise, the effect against T. trichiura was comparable to what is reported elsewhere (11–100%).18-19 The effectiveness of albendazole was also comparable to earlier reports of a 57–95% cure rate against hookworm, 92–100% for A. lumbricoides, and 10–77% for T. trichiura.20-22 There was no advantage of adding ivermectin to albendazole against hookworm or T. trichiura infections. The absence of helminth infection in Group D could explain the higher Hb in this group at recruitment, whereas malaria parasitaemia could not be the explanation, as the difference in the prevalence of malaria parasitaemia was insignificant among the groups. Furthermore, all women received IPT with SP, and the exclusion of women with severe anemia at enrollment could have resulted in the lack of difference in ane-

### Table 5
Mean birth weight of live singleton babies and frequency of low birth weight (LBW) by intervention groups in Masindi district, western Uganda

<table>
<thead>
<tr>
<th>Intervention group</th>
<th>Mean birth weight in kg ± SD (no. of pregnant women)</th>
<th>No. of babies with LBW (%) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (ivermectin group)</td>
<td>2.98 ± 0.43 (170)</td>
<td>16 (9.4%) [5.6–15.1]</td>
</tr>
<tr>
<td>B (albendazole group)</td>
<td>3.03 ± 0.46 (160)</td>
<td>18 (11.3%) [6.8–17.2]</td>
</tr>
<tr>
<td>C (ivermectin + albendazole)</td>
<td>2.97 ± 0.46 (171)</td>
<td>21 (12.3%) [7.8–18.2]</td>
</tr>
<tr>
<td>D (reference group)</td>
<td>3.02 ± 0.46 (207)</td>
<td>16 (7.7%) [4.5–12.0]</td>
</tr>
</tbody>
</table>

* P value*

| P value* | 0.52 | 0.47 |

* Analysis of variance (ANOVA) test for significance of difference in mean birth weight and χ² test for LBW among the groups.

CI = confidence interval.

### Table 6
Maternal mean hemoglobin (Hb) levels and anemia status at first antenatal care (ANC) visit and at 36 weeks of gestation and infant mean Hb and anemia status at birth in Masindi district, western Uganda

<table>
<thead>
<tr>
<th>A (ivermectin)</th>
<th>B (albendazole)</th>
<th>C (ivermectin + albendazole)</th>
<th>D (reference)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) maternal Hb concentration in g/L [No. of subjects]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At first visit</td>
<td>110.6 (14.5) [198]</td>
<td>111.2 (15.3) [194]</td>
<td>108.8 (14.2) [198]</td>
<td>113.7 (16.5) [241]</td>
</tr>
<tr>
<td>At 36 weeks of gestation</td>
<td>113.8 (15.7) [138]</td>
<td>117.9 (18.0) [131]</td>
<td>115.6 (11.9) [135]</td>
<td>117.8 (13.2) [175]</td>
</tr>
<tr>
<td>Difference in mean Hb in g/L between first visit and 36 weeks of gestation</td>
<td>3.2</td>
<td>6.7</td>
<td>6.8</td>
<td>4.1</td>
</tr>
<tr>
<td>P value*</td>
<td>0.063</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.007</td>
</tr>
<tr>
<td>Maternal anemia status (Hb &lt; 100 g/L), number (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At first visit</td>
<td>47 (23.7)</td>
<td>41 (21.1)</td>
<td>44 (22.2)</td>
<td>39 (16.1)</td>
</tr>
<tr>
<td>At 36 weeks of gestation</td>
<td>15 (10.9)</td>
<td>12 (11.5)</td>
<td>11 (7.7)</td>
<td>12 (6.9)</td>
</tr>
<tr>
<td>P value</td>
<td>0.003</td>
<td>0.023</td>
<td>0.0003</td>
<td>0.004</td>
</tr>
<tr>
<td>Mean (SD) infant Hb at birth (g/L) and at birth, number (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb &lt; 140 g/L</td>
<td>180.8 (24.5) [170]</td>
<td>184.6 (24.6) [157]</td>
<td>184.9 (22.5) [170]</td>
<td>179.8 (25.3) [196]</td>
</tr>
</tbody>
</table>

* Significance of difference among the groups.

† Student’s t test for significance of difference in mean Hb in the groups at first visit and 36 weeks of gestation.

‡ χ² test for significance of difference in the prevalence of anemia in the groups at first visit and 36 weeks of gestation in each group.
nia status among the groups at 36 weeks of gestation. Mass ivermectin treatment and the co-administration of ivermectin and albendazole for the control of onchocerciasis and LF, respectively, will in the long term improve the quality of life by controlling STH infections. The commonly reported adverse events after administration of ivermectin or albendazole and a combination of both drugs were abdominal pain, fever, and body rashes, and they were all mild. No severe adverse events were reported. In this study, administration of ivermectin or albendazole or the drugs combined during the second trimester of pregnancy showed no severe adverse effects. To interrupt transmission of LF where it is co-endemic with onchocerciasis, co-administration of ivermectin and albendazole to pregnant women should be encouraged. However, there is a need to establish a pharmacovigilance system to monitor MDA programs for LF and STH infection to report side effects and safety of ivermectin and albendazole treatment in women who inadvertently have taken the drugs in the first trimester of pregnancy. Safety studies of the co-administration of ivermectin and albendazole in the first trimester of pregnancy are needed because it might be difficult to identify only pregnant women in the second or third trimester based on the last normal menstruation period, especially during large-scale MDA programs. Safety studies on administration of ivermectin or co-administration of ivermectin and albendazole in children < 5 years of age are also desirable, because some of these children are LF microfilaria carriers and remain a source of re-infection to the treated population.23 For treatment of STH infections during pregnancy, albendazole alone is recommended, as ivermectin has no added advantage in the treatment of STHs, particularly hookworm infection, the commonest intestinal parasite in pregnancy.24,25

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