Effect of mebendazole therapy during pregnancy on birth outcome

N R de Silva, J L G J Sirisena, D P S Gunasekera, M M Ismail, H J de Silva

Summary

Background In areas endemic for hookworm, routine antenatal mebendazole therapy could greatly reduce the prevalence of anaemia in pregnancy. At present, however, this is not a widely accepted control strategy because of a lack of data on the safety of the drug. We assessed the effect of mebendazole therapy during pregnancy on birth outcome.

Methods A cross-sectional study was done in Sri Lanka, where prescription of mebendazole to women in the second trimester of pregnancy is recommended. Two hospitals were chosen for the study, and women who gave birth there between May, 1996, and March, 1997, were recruited. We compared the rates of major congenital defects, stillbirth, perinatal death, and low birthweight (<1500 g) among babies of mothers who had taken mebendazole during pregnancy with those whose mothers had not taken an anthelmintic (controls).

Findings The rate of major congenital defects was not significantly higher in the mebendazole group than in the control group (97 [1.8%] of 5275 vs 26 [1.5%] of 1737; odds ratio 1.24 [95% CI 0.8-1.91], p=0.39). Among 407 women who had taken mebendazole in the first trimester (contrary to medical advice), 10 (2.5%) had major congenital defects (odds ratio vs controls 1.66 [0.81-3.57], p=0.23). The proportions of stillbirths and perinatal deaths were significantly lower in the mebendazole group (1.9 vs 3.3% [95% CI 0.4-0.77]), as was the proportion of low-birthweight babies (1.1 vs 2.3%, 0.47 [95% CI 0.32-0.71]).

Interpretation Mebendazole therapy during pregnancy is not associated with a significant increase in major congenital defects, but our results indicate that it should be avoided during the first trimester. This therapy could offer beneficial effects to pregnant women in developing countries, where intestinal helmintiases are endemic.

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Introduction

WHO estimates that, at any given time, as many as 44 million pregnant women throughout the world are infected with hookworms (Necator americanus and Ancylostoma duodenale). Estimations indicate that over 50% of the pregnant women in developing countries have iron-deficiency anaemia. Although iron-deficiency anaemia has many contributing causes, hookworm infection is an important contributory factor in endemic areas, especially among women of the reproductive age-group.

The anthelmintic drugs levamisole, mebendazole, and albendazole are all highly effective against both species of hookworm. Mebendazole is probably the most widely used of these anthelmintics, especially in control strategies, because of its efficacy, lack of side-effects, and low cost. The manufacturers of the drug claim that where there has been evidence of mebendazole use in pregnant women, including that in the first trimester, the rates of babies born with malformations and spontaneous abortions are no greater than those observed in the general population. However, apart from a limited number of isolated case reports, the only other data available about the safety of mebendazole therapy during pregnancy are retrospective analyses. In a series of 112 pregnancies, one birth malformation was reported, and in another series of 306 pregnancies, there were 17 babies with various congenital defects, and 26 spontaneous abortions. No adequately controlled or large-scale studies on the safety of mebendazole therapy during human pregnancy have yet been carried out. The drug is known to be teratogenic in rats and mice however, so there has been an understandable reluctance to use it in pregnancy. Many standard pharmacology textbooks caution against its prescription to pregnant women. As a result, routine anthelmintic treatment is not a widely accepted strategy for the control of anaemia in pregnant women, despite the potential benefits to women living in hookworm-endemic areas.

In Sri Lanka however, routine administration of mebendazole to pregnant women after completion of the first trimester became common practice in the 1980s, because N americanus infection was endemic in many parts of the country, and the proportion of pregnant women with anaemia was estimated to be as high as 60%. Furthermore, a study among pregnant women in a hookworm-endemic area showed a significant improvement in haemoglobin concentration and iron-status when mebendazole was combined with iron-folate supplements, compared with iron-folate supplements alone. Detailed data on current hookworm prevalence rates are not available, but a
whenever possible to confirm prescription of mebendazole and anthelmintic the women were asked when it was taken) how anthelmintic during that pregnancy. If they had used an and medical history) as well as details of tobacco and alcohol participants on the second (vaginal deliveries) or third day been obtain d by one of four trained research assistants) to al1 A questionn ire was administered after informed consent had be obtained (me only anmelmintics widely used in Sri Lanka) were remember the name of the anthelmintic, and the anthental Table 1: Comparison of factors known to be associated with birth study of women living in 14 government-owned plantations in the central hills and the low country in the southwest of Sri Lanka in 1994–95 found that 41-4% had hookworm infestation. In 1994, the Sri Lankan Ministry of Health formulated the document A National Strategy and Broad Plan of Action for the Prevention and Control of Anaemia in Pregnancy, which formally recommends that mebendazole is given to all pregnant women after their first trimester; without routine stool examination through government antenatal clinics. Mebendazole is also available over the counter from pharmacies, without prescription, and at low cost. There are however, a significant proportion of pregnant women who do not receive mebendazole therapy, because of a short supply of drugs in the government clinics, non-attendance at antenatal clinics, or because women do not take the drug during pregnancy as prescribed.

Partly on the basis of the Sri Lankan experience, in December, 1994, the report of the WHO Informal Consultation on Hookworm Infection and Anaemia in Girls and Mebendazole therapy during pregnancy as a priority.14

Methods
Study population
This cross-sectional study was carried out in two state-run hospitals in Sri Lanka. All women giving birth at obstetric units in the Colombo North Teaching Hospital at Ragama in the Western Province, and the Teaching Hospital in the Central Province, from August, 1996 respectively, were recruited to the study. About 85% of all births in Sri Lanka take place in government hospitals. Recruitment continued until the sample size was reached. The two hospitals are situated about 100 km apart. The served by the Colombo North Teaching Hospital is whereas the Peradeniya Teaching Hospital serves population. Although district-specific statistics are the two hospitals were chosen because they serve that are typical of Sri Lanka. Thus, the data we can be considered representative of the national status.

Design
A questionnaire was administered after informed consent had been obtained by one of four trained research assistants, to all on the second (vaginal deliveries) or third day sections) post partum. The questionnaire covered demographic details, current and past obstetric history, as well as details of tobacco and alcohol use. All women were questioned directly about their use during that pregnancy. If they had used an anthelmintic many times, the women were asked when it was taken, how was taken, the name of the anthelmintic, and the tablets taken. Antenatal notes were consulted to confirm prescription of mebendazole and prescription. Drugs prescribed in the antenatal outcome of a state-run hospital are mostly dispensed from the pharmacy of the outpatient department and, thus, cannot be administered under supervision. If the women could not remember the name of the anthelmintic, and the anthental hospital was not available, she was shown a card on which the commonly used preparations of mebendazole, albendazole, and pyrantel (the only anthelmintics widely used in Sri Lanka) were mounted, and asked to identify the drug she had taken. Details about the birth and the baby were also recorded. All babies were examined by a paediatric house-officer for congenital defects before discharge from hospital. All babies in whom the house-officer suspected an anomaly were then examined by a consultant paediatrician who confirmed or excluded the diagnosis. Major congenital abnormalities were defined as structural or functional defects that require surgical or medical intervention: anomalies of the nervous system (anecephaly, Dandy-Walker cyst, encephalocele, hydrocephalus, meningomyelocele, microcephaly), the cardiovascular system (atrial-septal defect, Fallot's tetralogy, patent ductus arteriosus, ventricular-septal defect), the gastro-intestinal tract (cleft lip, cleft palate, imperforate anus), the genito-urinary tract (chordea of the penis, cleft urethra, cyst of hydrocele, hydrocele, imperforate anus), the musculoskeletal system and skin (akathryda, dysmorphic features (malignant features, or a combination of two or more of—ear tags, low hairline, low-set ears, palmar triadius), and multisystem abnormalities (abnormalities involving two or more of the listed systems, prune-belly syndrome, Turner's syndrome). Women with a gestation period of less than 28 weeks were excluded from the study, because routinely, women with pregnancies of less than 28 weeks are admitted to the gynaecology wards rather than the obstetric wards.

In this study, unfavourable birth outcome was defined as major congenital anomaly, stillbirth, death immediately after birth, or birthweight of 1500 g or less. Although the textbook definition of low birthweight (with its concomitant problems and complications) is less than, or equal to 2500 g, about 18% of all neonates in Sri Lanka have birthweights below this cut-off point. Therefore, we decided that a lower threshold of 1500 g (very low birthweight) would be more appropriate in this study. The primary outcome measure was the frequency of major birth defects; the frequencies of stillbirth, perinatal death, and low birthweight were secondary outcome measures.

Ethical clearance for this was obtained from the Higher Degrees, Research, and Ethics Committee of the Faculty of Medicine, University of Kelaniya, Sri Lanka.

Statistical analyses
Based on the results of a pilot study that indicated an anthelmintic usage rate of about 75% among women giving birth in the Ragama Hospital, and an estimated 2% incidence of birth defects, we calculated (using Epi-Info 6.03) that a sample size of about 6500 would be necessary to detect an odds ratio of 2.0 with 80% power and 95% confidence. The odds ratios for the risk of major congenital defects, very low birthweight, stillbirth, and perinatal death, in babies born to mothers who had taken mebendazole during the current pregnancy compared with that in babies born to mothers who had not taken any anthelmintic were also calculated with
Table 3: Congenital defects in mebendazole and control groups

<table>
<thead>
<tr>
<th>Congenital defect</th>
<th>Mebendazole group</th>
<th>Control group</th>
<th>Odds ratio* (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system</td>
<td>1.9</td>
<td>1.8</td>
<td>0.56 (0.33-0.94)</td>
<td>0.04</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td>1.1</td>
<td>1.0</td>
<td>0.62 (0.36-1.08)</td>
<td>0.12</td>
</tr>
<tr>
<td>Musculoskeletal system</td>
<td>3.5</td>
<td>3.8</td>
<td>1.13 (0.67-1.88)</td>
<td>0.63</td>
</tr>
<tr>
<td>Multisystem anomalies</td>
<td>1.8</td>
<td>1.6</td>
<td>1.17 (0.93-1.48)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*Fisher exact two-tailed test, with Yates' correction.

Table 4: Incidence of birth defects according to timing of mebendazole use

<table>
<thead>
<tr>
<th>Incidence of major congenital defects</th>
<th>Overall</th>
<th>Ragama Hospital</th>
<th>Peradeniya Hospital</th>
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<tr>
<td>First trimester</td>
<td>0.07</td>
<td>0.12</td>
<td>0.03</td>
</tr>
<tr>
<td>Second trimester</td>
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Table 2: Comparison of birth outcomes in mebendazole and control groups

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<td>Low birthweight (&lt;1500 g)</td>
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<td>Stillbirths and perinatal deaths</td>
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Epi-Info 6.03. The p-values were calculated from the Mantel-Haenszel χ² test using one degree of freedom, or by the Fisher exact probability calculation if an expected cell value was less than five. Because the three outcomes measured in this study are rare, odds ratios give a close approximation of the relative risks. Differences between the two subpopulations (Ragama and Peradeniya), as well as between cases and controls were analysed by means of χ² test for dichotomous variables, Student's t test for normally distributed continuous variables, and the Kruskal-Wallis H test for non-parametric variables. In multiple births, a major congenital defect, stillbirth, perinatal death, or low birthweight affecting one or both babies was counted as one case in our analyses.

Results

7087 women were recruited to the study, 3624 (51.1%) from Ragama and the rest from Peradeniya, during the period May, 1996, to March, 1997. Of the 7087 women, 5275 (74.4%) said they had taken a course of mebendazole at least once during the current pregnancy (mebendazole group), 1737 (24.5%) had not taken any (control group), 20 (0.3%) had taken an anthelmintic other than mebendazole, and those who could not remember what drug they had taken were excluded from further analysis. Of the women who had taken mebendazole (4890 (92.7%) had taken a total dose of 600 mg (100 mg twice daily for 3 days). We were able to verify prescription of mebendazole from antenatal notes in 3540 (67%) of 5275 women (documented exposures).

Analyses of certain factors in the two study populations in Ragama and Peradeniya showed that the amount of mebendazole use was similar in Ragama and Peradeniya (74:7 vs 75.8%), as were the rates of major congenital defects (1.9% vs 1.6%), and stillbirths and perinatal deaths (2.2% vs 2.3%). However, there were significant differences in several factors that are known, or suspected to be associated with, an increased risk of congenital defects. These included mean maternal age (28.3 vs 29.0 years, p<0.01), parity (median [two to one] vs two [one to three], p<0.05), prevalence of consanguinity (4.9% vs 10.1%, p<0.01), and use of alcohol (17.8 vs 3.0%, p<0.01) and tobacco (3.1% vs 0.6%, p<0.01). The proportions of babies with birthweight of 2500 g or less (18.6% vs 27.4%, p<0.01) and of birthweight 1500 g or less (1.9% vs 1.6%, p<0.01), and stillbirths and perinatal deaths (1.8% vs 1.9%, p<0.01) also differed significantly. Because of these differences, data analyses were stratified according to hospital wherever possible.

There were small but significant differences in age and parity between the mebendazole and control groups (table 1). However, the frequencies of other factors known to be associated with an increased risk of birth defects, such as consanguinity, use of alcohol (including consumption in the first trimester), and smoking were similar. This pattern was also found when the Ragama and Peradeniya study populations were analysed separately, except for alcohol consumption in the Peradeniya population. We judged, however, that this difference was unlikely to affect the overall results because it involved only 11 mothers (two mebendazole group, nine control group).

There were 97 (1.8%) babies with major congenital defects in the mebendazole group, and 26 (1.5%) in the control group (odds ratio 1.24 [95% CI 0.80-1.91], p=0.39; table 2). The odds ratios were similar in the Ragama and Peradeniya subanalyses and also when the analysis was limited to documented exposures.

The odds ratio for the occurrence of any single type of defect was not significantly associated with the use of mebendazole.
mebendazole (table 3), although the frequencies of genitourinary-tract and musculoskeletal-system anomalies were higher in the mebendazole group than in controls. Major congenital defects of the genitourinary tract included hypospadias (seven babies), undescended testes (six), gross cliteromegaly (four), chordea of the penis (two), cyst of hydrocele (one), micropenis (one), and vaginal polyps (one). Apart from the two cases of chordea of the penis, the mothers of all these babies had taken mebendazole.

Of the 5275 women who had taken mebendazole, only 5218 could state exactly when the drug had been taken. In addition, 103 women had taken mebendazole on more than one occasion during the pregnancy. The incidence of major congenital defects was slightly higher in women who had taken mebendazole in the first trimester than in the control group, overall, as well as in Ragama and Peradeniya separately, but these differences were not significant (table 4).

The rate of stillbirths and perinatal deaths was significantly lower in the mebendazole group than in the control group, overall, as well as in both populations and when data analysis was limited to documented exposures.

The distribution of birthweights and the frequency of mebendazole use in each birthweight group is shown in table 5. The proportion of mothers who had babies with very low birthweight was significantly lower in the mebendazole group than in the control group, overall, in both hospital populations, and when analysis was limited to documented exposures (table 2).

**Discussion**

Our data indicate no significant association between the use of mebendazole in pregnancy and an increase in major congenital defects. However, the upper CI of the relative risk, as estimated by the odds ratio, is about two, and therefore a relative risk as high as two cannot be ruled out. There was some increase in the rate of congenital defects associated with mebendazole use in the first trimester (against current recommendations), but this was not significant. The numbers of anomalies of the genitourinary tract and the musculoskeletal system were higher in the mebendazole group than in the control group, but the odds ratios for groups of anomalies by organ system were not significantly increased. These findings are consistent with the views of medical practitioners in Sri Lanka that mebendazole therapy is safe during pregnancy. The overall incidence of major congenital defects in this study (1.75%) is comparable reported in other studies. 11,18

Previous research indicates that women who give birth to babies with major congenital defects are likely to recall bias (the likelihood that recall of drug use will be greater in women who have given birth to babies with malformations than in women with healthy babies) may be an explanation for our findings. Such bias, however, does not appear to have been introduced in this study because analysis of documented exposures alone gives odds ratios and CI similar to those of the overall analysis.

Rates of stillbirth, perinatal death, and very low birthweight were significantly lower in the mebendazole group than in the controls. A high proportion of the stillbirths and perinatal deaths were among babies of very low birthweight, which is to be expected. If antenatal treatment with mebendazole does have a beneficial effect on birth outcome, one possible explanation would be through an increase in birthweight. However, increased mebendazole use and the lower proportion of very low birthweight could simply be linked because they are two reflections of better health-seeking behaviour and antenatal care, rather than being causally linked variables.

Interpretation of the results of an unmatched case-control study such as this can be confounded by many variables associated with the presence or absence of the risk factor in question, which are also independently associated with the outcome. In this study, maternal age could be such a variable. Women who had taken mebendazole were significantly younger than the women who had not taken an anthelmintic, and high maternal age is well known to be associated with poor birth outcome, especially the occurrence of congenital abnormalities. However, although the differences in mean maternal ages were significant, they were not strongly so, and, therefore, unlikely to have masked the effect of mebendazole on birth outcome.

The two hospitals targeted for this study were both located in large towns. However, whereas Ragama Hospital is in the urbanised Western Province, Peradeniya Hospital is in the more rural Central Province. This difference probably accounts for many of the differences in the characteristics of the two populations, such as maternal age and parity, frequency of alcohol consumption and tobacco use, and the incidence of low birthweight. Consanguineous marriages are more common among the rural people of Sri Lanka, especially in the Central Province, than among the urban population. Despite these contrasting characteristics, however, proportions of women taking mebendazole were similar in the two populations as were the associations between mebendazole use and birth outcomes.

The safety of a drug is best tested in a prospective, randomised, double-blind placebo-controlled cohort study, but for obvious ethical reasons, this cannot be achieved in groups of pregnant women without very good evidence supporting a lack of teratogenicity. Within the limitations of our study design, these data
suggest mebendazole therapy during pregnancy is not associated with a significant increase in the risk of major congenital defects in the fetus, although the possibility of an increase in relative risk of up to two-fold cannot be ruled out. Given that mebendazole may even have beneficial effects in terms of a lower rate of stillbirth, perinatal death, and very low birthweight, the benefits of mebendazole therapy in pregnancy seem to outweigh any possible risk of congenital defects. Moreover, the only other anthelmintic of similar efficacy against hookworm is albendazole,\(^1\) for which there are very few data on teratogenicity. Since albendazole is absorbed at a greater rate than mebendazole, it could be more teratogenic.\(^1\) Thus, although we realise that the absolute safety of mebendazole therapy during pregnancy needs to be confirmed by further studies, we recommend its use after completion of the first trimester of pregnancy, as a strategy for the control of anaemia in pregnant women living in hookworm-endemic areas.

**Contributors**

The study was jointly designed by all the investigators. Its execution was supervised by N R de Silva, J L G J Sirisena, and H J de Silva. D P S Unanasekara was the consultant paediatrician responsible for the clinical part of the study. All the investigators were involved in analysis of data as well as drafting the paper.

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**References**