Controlling disease due to helminth infections

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Control of intestinal helminthiasis in pregnancy—the Sri Lankan experience

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Introduction

Sri Lanka is one of the few countries that routinely administers anthelminthics during pregnancy, and it has been doing so for almost 20 years. Very few studies have been done in Sri Lanka to determine the prevalence rates of soil-transmitted nematode infections among adolescent girls and women of child-bearing age (see Table 1). The adverse effects of these infections on growth and nutrition are well known; recently it has been shown that trichuriasis is associated with significantly lower serum vitamin A levels (Atukorala & Lanerolle, 1999), and that even mild infection with *Trichuris* has adverse effects on serum vitamin A concentrations. Studies on iron metabolism suggest that vitamin A deficiency may impair mobilization of iron stores (Bloem et al., 1989). Hookworm infection is known to cause blood loss, sometimes leading to iron-deficiency anaemia. Intervention studies have shown that combined supplements—containing both vitamin A and iron—are more effective than iron alone in eliminating anaemia in women (Suharno & Muhilal, 1996).

Before 1980, treatment of helminthiasis in pregnancy in Sri Lanka was carried out only when stool samples submitted at antenatal clinics were found to be positive for intestinal nematode infections; treatment was not given routinely and coverage was poor. It was only when studies carried out around that time revealed that pregnant women in Sri Lanka had unacceptably high levels (56–78%) of

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Table 1. Prevalence of soil-transmitted nematode infections among adolescent girls and adult women in Sri Lanka

Study	Location	Age group (years)	No. of cases	Prevalence rate (%)		
				Ascaris	Hookworm	*Trichuris*
Sorensen et al. (1996b)	Plantations	18–44	246	69.5	41.4	56.7
Ismail & Naotunne (1997)	Plantations	13–18	161	45.6	29.1	49.2
Atukorala & Lanerolle (1999)	Urban	14–18	383	16.7	5.7	46.2
	Rural	14–18	231	2.2	4.8	4.3

anaemia (Ministry of Health, 1994) that serious attention was paid to the need to control anaemia in pregnancy.

Anthelminthics, anaemia, and pregnancy

In a study in the Colombo area, Atukorala & de Silva (1990) showed that 59% of adolescent females (14–18 years of age) had depleted iron stores and were therefore at risk of developing anaemia during times of higher iron demand such as in pregnancy.

Anaemia predisposes to severe morbidity in pregnant women and reduces tolerance to the normal blood loss during childbirth, which could pose a severe threat to life. Stillbirths and low birth weights are also associated with moderate and severe anaemia during pregnancy. Among the major causes of anaemia, nutritional deficiencies of iron and folate are by far the most common. However, hookworm disease is an important contributory factor in areas where this infection is endemic, especially among women of reproductive age (Pawlowski, Schad & Stott, 1991). In Sri Lanka, iron–folate supplementation had been in place for many years; mebendazole (100 mg twice daily for 3 days) was routinely supplied after the first trimester on an island-wide basis, but compliance was poor. All issues relating to the control of anaemia in pregnancy were re-examined by a Consultative Committee set up by the Ministry of Health and Women's Affairs. Its recommendations (Ministry of Health, 1994) include the use of a single 500-mg dose of mebendazole after the first trimester to control helminthiases in pregnancy. A single dose is much simpler to administer than the 3-day course of mebendazole used previously, and encourages better compliance.

Mebendazole is one of the most widely used anthelminthics in Sri Lanka because of its efficacy, safety, and low cost. The benefits of mebendazole therapy were shown by Atukorala et al. (1994) in a study of pregnant women in a hookworm-endemic area. There was a significant improvement in haemoglobin concentration and iron status when mebendazole was combined with iron–folate supplements compared with iron–folate alone. Mebendazole tablets—in both

Table 2. Cure rates (CR) and egg-reduction rates (ERR) for single-dose anthelminthic drugs

Anthelminthic drug	Sample size	*Ascaris*		Hookworm		*Trichuris*	
		CR (%)	ERR (%)	CR (%)	ERR (%)	CR (%)	ERR (%)
Mebendazole (locally produced)	145	95.8	98.0	28.7	72.0	29.1	31.6
Mebendazole (proprietary)	136	97.6	99.7	35.8	74.5	26.1	61.6
Albendazole (proprietary)	118	97.2	99.6	77.9	95.4	26.2	50.3

100-mg and 500-mg formulations—are now manufactured by the State Pharmaceutical Manufacturing Corporation in Sri Lanka at one-twentieth of the cost of the proprietary drug, which makes it affordable for community treatment programmes. Sorensen et al. (1996a) have shown that the anthelminthic efficacy of locally produced mebendazole is comparable to that of the proprietary preparation (see Table 2).

Although the routine use of mebendazole during pregnancy is now in place, there is still room for improvement. Some pregnant women do not attend antenatal clinics and sometimes the clinics run out of drug supplies. Nevertheless, it is estimated that about 75% of pregnant women receive anthelminthic treatment in Sri Lanka (de Silva et al., 1999).

Safety of anthelminthic therapy

Concerns about the safety of anthelminthic therapy in pregnancy have been expressed from time to time. In 1994, WHO convened an Informal Consultation on Hookworm Infection and Anaemia in Girls and Women to consider this issue. The Consultation promoted the use of anthelminthics in pregnancy after the first trimester, but it also recommended evaluation of the long-term safety—particularly in terms of birth outcomes—of anthelminthic therapy in pregnancy.

In a major cross-sectional retrospective study carried out in Sri Lanka, de Silva et al. (1999) assessed the effect on birth outcomes of mebendazole therapy during pregnancy. The rates of major congenital defects, stillbirth, perinatal death, and very low birth weight (<1500 g) were compared in babies of mothers who had taken mebendazole during pregnancy and babies whose mothers had taken no anthelminthic (controls). The study was carried out in two state-run tertiary care hospitals: all women giving birth at the university obstetric units in the Colombo North Teaching Hospital at Ragama (serving a largely urban community) and the Peradeniya Teaching Hospital (serving a more rural population) were recruited to the study. The primary outcome measure was the frequency of major birth defects, defined as structural or functional defects requiring surgical or medical

intervention. Frequencies of stillbirth, perinatal death, and very low birth weight were secondary outcome measures.

Of the 7087 women recruited to the study, 5275 (74.4%) said they had taken a course of mebendazole at least once during the current pregnancy (mebendazole group) while 1737 (24.5%) had taken no anthelminthics (control group). Those who had taken an anthelminthic other than mebendazole and those who could not recall what drug they had taken were excluded from the study. In the mebendazole group, 4890 women (92.7%) had taken a total dose of 600 mg (100 mg twice daily for 3 days). The prescription of mebendazole was verified from antenatal notes in 67% of the mebendazole group (documented exposures). Analyses of certain factors in the two study populations showed that the extent of mebendazole use was similar in Ragama and Peradeniya (74.7% vs 75.8%) as was the baseline (background) frequency of major congenital defects (1.9% vs 1.6%) and of stillbirth and perinatal deaths (2.2% vs 2.3%).

The two study populations showed differences in several factors that are known or suspected to be associated with an increased risk of congenital defects, and data analyses were therefore stratified according to hospital wherever possible. There were 97 (1.8%) babies with major congenital defects in the mebendazole group and 26 (1.5%) in the control group; these frequencies were not statistically different (see Table 3). No significant differences were observed in the Ragama and Peradeniya sub-analyses or when the analysis was limited to documented exposures. The incidence of major congenital defects was slightly higher in women who had taken mebendazole in the first trimester (against current recommendations) than in the control group, but the differences were not significant; this was true overall as well as in Ragama and Peradeniya separately. The overall incidence of major congenital defects in this study (1.75%) is comparable to that reported in other studies (Nevin, 1982; Sirisena, Nanayakkara & Jayasena, 1993).

Rates of stillbirth, perinatal death, and very low birth weight were significantly lower in the mebendazole group than in the controls (Table 4). A high proportion of the stillbirths and perinatal deaths were among babies of very low birth weight, which is to be expected. If antenatal treatment with mebendazole does have a beneficial effect on birth outcome, one possible explanation would be

Table 3. Incidence of major birth defects in mebendazole group and controls

	Mebendazole group	Control group	Odds ratio (95% CI)[a]	*P*
All potential exposures	97/5275 (1.8%)	26/1737 (1.5%)	1.24 (0.8–1.91)	0.39
Documented exposures only	67/3540 (1.9%)	25/1670 (1.5%)	1.31 (0.82–2.09)	0.31

[a] Mantel–Haenszel weighted odds ratio (95% confidence limits).

Table 4. Incidence of stillbirths and perinatal deaths, and low birth weight in mebendazole and control groups

	Mebendazole group	Control group	Odds ratio (95% CI)[a]	*P*
All potential exposures				
Stillbirths and perinatal deaths	99/5275 (1.9%)	58/1737 (3.3%)	0.55 (0.40–0.77)	0.0004
Birth weight <1500 g	59/5271 (1.1%)	40/1735 (2.3%)	0.47 (0.32–0.71)	0.0003
Documented exposures only				
Stillbirths and perinatal deaths	62/3540 (1.8%)	56/1670 (3.4%)	0.52 (0.36–0.75)	0.0005
Birth weight <1500 g	40/3540 (1.1%)	40/1670 (2.4%)	0.43 (0.27–0.67)	0.0002

[a] Mantel–Haenszel weighted odds ratio (95% confidence limits).

through an increase in birth weight. However, increased mebendazole use and the lower proportion of very low birth weight could be linked simply by the fact that both are reflections of better health-seeking behaviour and antenatal care, rather than being causally linked. Data derived from this study are consistent with the long-standing views of medical practitioners in Sri Lanka that mebendazole therapy is safe during pregnancy.

Anthelminthic treatment during adolescence

Although Sri Lanka now has a strategy for combating intestinal helminthiasis during pregnancy by routinely administering mebendazole to all pregnant women after the first trimester, there is room for improvement. The present estimated coverage of about 75% could be increased by ensuring uninterrupted drug supplies and by encouraging greater attendance at antenatal clinics through awareness programmes. Such programmes should be extended to include adolescents, particularly with a view to reducing the prevalence and intensity of intestinal helminthiases among adolescent girls—the future mothers. The plantation sector of Sri Lanka already has a programme of this nature in place.

Nearly one million people live in the plantations in Sri Lanka. Until about a decade ago, their health was poorer than that of the rest of the island's population. Although there has been substantial investment in improving health facilities, housing, water supplies, and sanitation since the mid-1980s, a large proportion of these people still have poor housing and no access to safe water and sanitation. In 1992–1993, a cross-sectional study of 1614 children aged 3–12 years and 246 women aged 18–44 years, randomly selected from 14 state-owned plantations, revealed a wide prevalence of intestinal nematode infections (Sorensen

et al., 1996b) (see Table 1). At that time, only pregnant women after the first trimester were given mebendazole routinely.

A major deworming programme began in 1994 in all the plantations (about 400 estates), providing more than 200 000 children up to the age of 12 years with a single 500-mg dose of mebendazole twice a year. The programme, now in its sixth year, has achieved a considerable decline in the intensity and prevalence of intestinal worm infections. To make the programme more effective, biannual deworming was extended in 1997 to include 13–18-year-olds after examination of a small number of stool samples (161 from 10 estates) revealed the following prevalence rates of infection: *Ascaris* 45.6%, hookworm 29.1%, and *Trichuris* 49.2% (Ismail & Naotunne, 1997). This programme should be effective in controlling intestinal helminthiases in adolescent girls in the plantations and in reducing the prevalence of hookworm anaemia. Indeed, although no causal relationship has been established, subsequent studies have shown that the prevalence of anaemia in the plantations, which was 58.2% during pregnancy and 51.9% postpartum (de Silva & Atukorala, 1996), has declined to 25.1% and 35.0% respectively (Atukorala, 1999, unpublished data). Prevalence of anaemia among non-pregnant women was 27.8% (see Table 5). Targeting adolescent girls for routine anthelminthic therapy, especially in areas where soil-transmitted helminthiases are widely prevalent, seems likely to prove to be a beneficial strategy.

Conclusions

The routine administration of mebendazole in pregnancy, after the first trimester, is now well established in Sri Lanka, with an estimated coverage of 75%. With more vigorous efforts to raise health awareness and greater attendance at antenatal clinics, this proportion should increase. The low cost of mebendazole makes the treatment programme sustainable. Studies in Sri Lanka have proved that mebendazole is safe in pregnancy and does not affect birth outcomes in terms of birth defects, stillbirths, perinatal deaths, and very low birth weights. To target women before the onset of pregnancy, it is recommended that adolescent girls be included in community deworming programmes. Such a scheme now exists in the

Table 5. Prevalence of anaemia in the plantations during pregnancy and postpartum

Prevalence of anaemia	1989–1991[a]		1999[b]	
	n	%	*n*	%
Pregnancy (Hb < 110 g/litre)	309	58.2	181	25.1
Postpartum (Hb < 120 g/litre)	108	51.9	100	35.0
Non-pregnant women (Hb < 120 g/litre)	—	—	97	27.8

[a] de Silva & Aturokala, 1996.
[b] Aturokala, 1999 (unpublished data).

plantation sector in Sri Lanka and the feasibility of extending it to the wider community should be explored.

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