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ORIGINAL ARTICLE

Birth outcomes after exposure to mebendazole and pyrvinium during pregnancy – A Danish nationwide cohort study

Arendse Torp-Pedersen[a,b], Espen Jimenez-Solem[a,b], Vanja Cejvanovic[a,b], Henrik Enghusen Poulsen[a,b,c] and Jon T. Andersen[a,b]

[a]Department of Clinical Pharmacology, Copenhagen University Hospital, Bispebjerg, Copenhagen, Denmark; [b]Laboratory of Clinical Pharmacology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; [c]University of Copenhagen, Copenhagen, Denmark

ABSTRACT

Mebendazole and pyrvinium are anthelmintics used to treat infections with pinworms, a common infection in children. Other indications for treatment with mebendazole are infections with soil-transmitted helminths. These infections are rare in Denmark, but affect more than 1.5 billion people worldwide. Limited safety data of anthelmintics during pregnancy exists and the purpose of this study was to investigate the association between exposure to mebendazole or pyrvinium during pregnancy and the adverse pregnancy outcomes: congenital malformations, stillbirths, neonatal mortality and small for gestational age. The Danish Fertility Database was used to identify all births in Denmark from 1997 to 2007. Maternal exposure to anthelmintics was identified through The Danish Prescription Registry. Of 713667 births, 2567 mothers redeemed a prescription for mebendazole; 1588 for pyrvinium. Logistic regression analysis adjusted for potential confounders. We found no association between exposure to mebendazole and major congenital malformations (OR = 0.7 (CI 95% 0.5–1.1)) or other negative birth outcomes and we found no association between exposure to pyrvinium and major congenital malformations (OR = 0.8 (CI 95% 0.4–1.5)) or other negative birth outcomes. No increased risk was found of having negative birth outcomes after exposure at any trimester during pregnancy.

KEYWORDS

Congenital malformations; anthelmintics; pregnancy; pharmacoepidemiology; birth outcomes

Introduction

Mebendazole and pyrvinium are anthelmintics used for treating infections with enterobius vermicularis (also called pinworm, seatworm or threadworm), the most common roundworm infection in developed countries. Pinworm infection is particularly common among children and is easily transmitted to close family members. To prevent re-infection, treatment of the entire household is recommended if a family member has been infected (Petersen 2014). Outside pregnancy, mebendazole is the drug of choice, but during pregnancy the recommended treatment is pyrvinium due to the lower absorption level of the drug (Petersen 2014). In Denmark, 4715 (0.65%) pregnant women were exposed to mebendazole or pyrvinium between 1997 and 2007 (Torp-Pedersen et al. 2012). Mebendazole has been shown to be teratogenic and embryotoxic in rats (The European Agency for the Evaluation of Medicinal Products 1999), but in four previously conducted studies no association to negative pregnancy outcomes have been found (de Silva et al. 1999; Diav-Citrin et al. 2003; Acs et al. 2005; Larocque et al. 2006). We found no previously conducted studies concerning pyrvinium. Mebendazole is furthermore used for eradication of infections with soil-transmitted helminths (STH): hookworm (ancylostoma duodenalis and necator americanus), roundworm (ascaris lumbricoides) and whipworm (trichuris trichuria). These infections are rare in Denmark, but are estimated by the WHO to affect more than 1.5 billion people worldwide. The infections can cause iron deficiency anaemia in the mother, which is associated with low birth weight (Haider et al. 2013). In areas endemic for soil-transmitted helminths (STH), routine treatment of pregnant women with mebendazole has been recommended by the WHO after the first trimester (WHO 2006) and treatment with mebendazole has shown to reduce very low birth weight in a study conducted in a hookworm endemic area (Brooker et al. 2008).

We have previously shown that exposure to mebendazole among pregnant women in Denmark decreased significantly during pregnancy, when compared to before and after pregnancy (Torp-Pedersen et al. 2012). This could indicate uncertainty and possible fear of treatment among physicians and pregnant women. Furthermore, an Israeli study showed a significantly higher rate of elective terminations of pregnancy in a mebendazole exposed group when compared to a control group (Diav-Citrin et al. 2003). The authors suggested that it may be related to the fear, anxiety and concern by the women after exposure to the drug. The mentioned findings indicate that further data are needed to ensure that treatment with anthelmintics is safe during pregnancy.

Benefits of treatment with mebendazole during pregnancy may be easier to recognize in cases where anaemia is a common negative effect of the infection with hookworms and other STH. Pinworm infection, on the other hand, is known to

CONTACT Arendse Torp-Pedersen Arendse.laerke.torp-pedersen@regionh.dk Laboratory of Clinical Pharmacology, Copenhagen University Hospital, Rigshospitalet, Tagensvej 20, 2200 Copenhagen, Denmark

be a harmless but bothersome infection. Rare adverse outcomes of pinworm infections include the migration of worms from the intestine to the female genital tract causing symptoms such as vaginitis, cervicitis, endometritis, myometritis and salpingitis. The benefits of treatment of pinworm infection are primarily avoiding re-infection of the family and the bothering symptoms pinworms can cause, such as nausea and itching. The purpose of this study was to investigate the association between exposure to mebendazole or pyrvinium during pregnancy and adverse pregnancy outcomes: congenital malformations, stillbirth, neonatal mortality and small for gestational age (SGA).

Materials and methods

Study population

Our study cohort includes all births in Denmark between 1997 and 2007. All subjects and information about them were gathered from five Danish national registers: The Danish Fertility Database (Knudsen 1998), The Danish National Hospital Register (Lynge et al. 2011), The Danish National Prescription Register (Kildemoes et al. 2011), The Income Statistics Register (Jensen and Rasmussen 2011) and The Populations Education Register (Baadsgaard and Quitzau 2011). Information from the five registers were linked using the mother's unique personal identification number given to all Danish residents at birth or upon immigration, and included in all national registers (Pedersen 2011). The Danish Fertility Database (FTDB) consists of all women aged 13–49, all men aged 13–65 and their children. FTDB includes people with permanent residence in Denmark and is updated on 1st January every year. A wide range of data on both the adult population and the children exist in the FTDB. In this study, we used FTDB to identify all births in Denmark between 1 January 1997 and 31 December 2007 and the personal id-numbers of the respective mothers and children. Furthermore, we gathered information on maternal parity (the number of viable previous pregnancies), date of conception, date of delivery, birth weight and if relevant, child's time of death. Date of conception is based on ultrasound estimates and information on date of last menstrual period. The Danish National Hospital Register has since 1977 included individual level data on all discharges from Danish hospitals, and since 1994 also included individual level data on all outpatient visits (Lynge et al. 2011). From this register, we acquired information on congenital malformations within one year after birth and the pregnant women's smoking habits according to the International Classification of Diseases (ICD-10, Danish revision), codes Q0.0–Q99.9 and DUT0.0–99.9, respectively. The Danish National Prescription Register includes individual level information on all prescriptions from Danish pharmacies since 1995 (Kildemoes et al. 2011). It contains data related to 'the redeemer', 'the prescriber', the drug and the pharmacy at which the drug was redeemed. We used this register to identify redeemed drugs using the Anatomical Therapeutic Chemical (ATC) classification; P02CX01 for pyrvinium and P02CA01 for mebendazole. The Income Statistics Register includes anyone who has submitted a tax return to the tax administration in Denmark and thereby anyone in Denmark who is economically active (Jensen and Rasmussen 2011). From this register, we identified the annual household income of the year of giving birth. Finally, The Population's Education Register (Baadsgaard and Quitzau 2011) was used to identify the mothers' highest level of completed education of the year of giving birth.

Definition of exposure

The date of redemption of a prescription for mebendazole or pyrvinium was used to identify the maternal exposure, which was classified according to first, second and third trimester. First trimester was defined as the period between day of conception and day 84 of pregnancy, second trimester between day 85 and 196 of pregnancy and third trimester between day 197 of pregnancy and birth. We used the ATC-classification to identify the exposure; P02CX01 for pyrvinium and P02CA01 for mebendazole (WHO 2011).

Pregnancy outcomes

We analysed the following pregnancy outcomes: congenital malformations, stillbirth, neonatal mortality and SGA. When analysing the risk of congenital malformations, the exposure time window comprised the first trimester. For all other outcomes, we analysed risks associated with exposure throughout pregnancy. Congenital malformations recognized within a year after birth were included in the study. Births with a follow-up period of less than a year were excluded from the analysis for congenital malformations. Malformations were classified as major/minor according to the categorization by the European Surveillance of Congenital Abnormalities (EUROCAT 2005). Stillbirth was defined as a child showing no signs of life at birth. Fetal deaths occurring before April 2004 were considered stillbirths if death occurred after 28 completed weeks of gestation. From April 2004, all fetal deaths were recorded as stillbirths after 22 completed weeks of gestation. Neonatal mortality was defined as death within 28 full days of life. Finally, SGA was defined as birth weight below the 10th percentile, which was calculated according to the week of gestation.

Statistics

Statistical analyses and data management were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC). We conducted logistic regression analysis for dichotomous outcomes: major/minor congenital malformation (yes/no), stillbirth (yes/no), neonatal mortality (yes/no) and SGA (yes/no). We calculated both crude and adjusted odds ratios. We adjusted for the following potential confounders: maternal age at conception [(<20, 20–24, 25–29, 30–35 and >35 years), parity (0, 1, 2 and >2 previous birth(s))], income (divided into quartiles), level of education (low, medium and high) and smoking (yes/no). In the model analysing the risk of stillbirth and neonatal mortality, we furthermore adjusted for gestational age. Less than 1% missing data was present in all adjustment variables except for smoking data and educational level, which had 6.8

and 4.0%, respectively. Maternal characteristics (age, parity, smoking, income and education) are presented as frequencies with percentages. Differences between categorical variables for the exposed versus unexposed were assessed by chi squared (χ^2) tests. We considered two-sided $p < 0.05$ to be statistically significant. We excluded 534 records due to coding errors, 17 duplicate records and 45,472 records with missing data on gestational age or birth weight. Our final study population consisted of 713,667 births – 93.9% of all recorded births.

Ethics

This study has been approved by The Danish Data Protection Agency (No. 2008-41-2518). Ethical approval is not required for register-based studies in Denmark. All the personal information held in the registers was encrypted and thereby anonymised, and analysed on computers held by Statistics Denmark.

Results

We identified 713,667 births between 1997 and 2007 from the Danish fertility database. We identified 4155 mothers redeeming a prescription for pyrvinium or mebendazole during pregnancy; 1588 for pyrvinium and 2567 for mebendazole. Of these, 1467 (35%) were redeemed during the 1st trimester (445 for pyrvinium and 1022 for mebendazole).

Pregnancy outcomes

The results of multivariable logistic regressions are seen in Table 1.

Congenital malformations

The rate of major malformations was 3.2%, and minor malformations 1.9% among children with unexposed mothers. We found 24 (2.3%) major and 12 (1.2%) minor malformations among the 1022 women exposed to mebendazole during the 1st trimester and neither the crude nor adjusted analysis showed increased risk of major (crude OR: 0.7 95% CI: 0.5–1.1 adj. OR: 0.7; 95% CI: 0.4–1.1) or minor (crude OR: 0.6 95% CI: 0.3–1.1 adj.: OR: 0.8; 95% CI: 0.5–1.4) malformations. Of the 445 women exposed to pyrvinium during the 1st trimester, we identified 10 major (2.2%) and 10 minor (2.2%) malformations and neither the crude nor adjusted analysis showed increased risk of major (crude OR: 0.7; 95% CI: 0.4–1.3 adj.: OR: 0.8; 95% CI: 0.4–1.5) or minor (crude OR: 1.2; 95% CI: 0.6–2.2 adj. OR: 1.0; 95% CI: 0.5–2.2) malformations. In addition, the odds ratios of malformations according to EUROCAT subgroupings were not increased with the exposure to either mebendazole or pyrvinium (data not shown).

Stillbirth and neonatal mortality

Among the unexposed pregnancies 0.4% resulted in stillbirth. The equivalent percentage of mebendazole and pyrvinium exposed women was 0.3% (crude OR: 0.8; 95% CI: 0.4–1.6 adjusted OR: 0.9; 95% CI: 0.4–2.1) and 0.3% (crude OR: 0.9; 95% CI: 0.4–2.1 adjusted OR: 1.0; 95% CI: 0.4–2.8), respectively, indicating no increased risk of stillbirth after exposure to mebendazole or pyrvinium during pregnancy. Of the unexposed pregnancies, 0.3% resulted in neonatal death. The equivalent percentage of mebendazole and pyrvinium exposed women was 0.2% (crude OR: 0.7; 95% CI: 0.3–1.6 adjusted OR: 0.8; 95% CI: 0.3–2.2) and 0.3% (crude OR: 1.1; 95% CI: 0.5–2.6 adjusted OR: 1.1; 95% CI: 0.3–3.3), respectively, indicating no increased risk of neonatal mortality after exposure to either mebendazole or pyrvinium.

SGA

We expected to find 10% of both mebendazole and pyrvinium exposed pregnancies in the category of SGA in accordance with the definition. The percentage was 7.7% (crude OR: 0.8; 95% CI: 0.7–0.9 adjusted OR: 1.0; 95% CI: 0.8–1.1) for mebendazole exposed and 8.0% (crude OR: 0.8 95% CI: 0.7–1.0 adjusted OR: 0.9; 95% CI: 0.8–1.1) for pyrvinium exposed pregnancies, indicating no increased risk of SGA after exposure to either of the two drugs.

Maternal characteristics

Characteristics of exposed and unexposed women are shown in Table 2.

Discussion

In this Danish nationwide cohort study, we investigated adverse pregnancy outcomes for infants of mothers exposed to mebendazole or pyrvinium during pregnancy. We found no

Table 1. Odds ratios for negative pregnancy outcomes after redemption of a prescription for either mebendazole or pyrvinium.

	Unexposed	Mebendazole exposed	Adjusted OR (95% CI)[a]	Crude OR (95% CI)	Pyrvinium exposed	Adjusted OR (95% CI)[a]	Crude OR (95% CI)
Major congenital malformations	22,580/708,982 (3.2%)	24/1022 (2.3%)[b]	0.7 [0.4,1.1]	0.7 [0.5,1.1]	10/445 (2.2%)[b]	0.8 [0.4,1.5]	0.7 [0.4,1.3]
Minor congenital malformations	13,629/708,982 (1.9%)	12/1022 (1.2%)[b]	0.8 (0.5,1.4)	0.6 [0.3,1.1]	10/445 (2.2%)[b]	1.0 [0.5,2.2]	1.2 [0.6,2.2]
Stillbirth	2548/708,982 (0.4%)	7/2567 (0.3%)	0.9 (0.4,2.1)	0.8 [0.4,1.6]	5/1588 (0.3%)	1.0 [0.4,2.8]	0.9 [0.4,2.1]
Neonatal mortality	2055/708,982 (0.3%)	5/2567 (0.2%)	0.8 (0.3,2.2)	0.7 [0.3,1.6]	5/1588 (0.3%)	1.1 [0.3,3.3]	1.1 [0.5,2.6]
Small for gestational age	70,005/708,982 (9.9%)	198/2567 (7.7%)	1.0 (0.8,1.1)	0.8 [0.7,0.9]	127/1588 (8.0%)	0.9 [0.8,1.1]	0.8 [0.7,1.0]

[a]Adjusted for maternal age, parity, level of highest completed education, income and smoking.

[b]Analysed for women exposed only during the first trimester.

Table 2. Characteristics of exposed and unexposed women.

Drug exposure:	Pyrvinium*n* (%)	Mebendazole*n* (%)	Unexposed*n* (%)
Age			
<20	32 (2.0)	27 (1.1)	19438 (2.7)
20–24	174 (11.0)	210 (8.2)	110889 (15.6)
25–29	492 (31.0)	771 (30.0)	272260 (38.4)
30–34	633 (39.9)	1067 (41.6)	222806 (31.4)
>35	257 (16.2)	492 (19.2)	83,589 (11.8)
p[a]	<0.0001	<0.0001	
Income			
Quartile 1	394 (24.8)	652 (25.4)	177,255 (25.0)
Quartile 2	382 (24.1)	673 (26.2)	177,844 (25.0)
Quartile 3	420 (26.5)	615 (24.0)	177,781 (25.0)
Quartile 4	391 (24.6)	626 (24.4)	177,799 (25.0)
p[a]	0.57	0.36	
Parity			
0	301 (19.0)	227 (8.8)	308,303 (43.5)
1	569 (35.8)	861 (33.5)	265032 (37.4)
2	495 (31.2)	955 (37.2)	99796 (14.1)
>2	223 (14.0)	524 (20.4)	35840 (5.1)
p[a]	<0.0001	<0.0001	
Education class			
Low	525 (33.0)	830 (32.3)	225,703 (31.8)
Medium	492 (31.0)	747 (29.1)	226,256 (31.9)
High	526 (33.1)	899 (35.0)	231,232 (32.6)
Missing values	45 (2.8)	91 (3.5)	25,795 (3.6)
p[a]	0.55	0.004	
Smoking			
Yes	265 (18.0)	433 (18.2)	120,254 (18.2)
No	1206 (82.0)	1946 (81.8)	540,766 (81.8)
p[a]	0.86	0.99	

[a]The *p* values are results of χ^2-tests comparing each exposure group with the unexposed group.

association between maternal exposure to mebendazole or pyrvinium and major or minor congenital malformations, increased neonatal mortality, stillbirth or SGA.

Comparison with existing studies

Information on pregnancy outcomes after exposure to mebendazole or pyrvinium is sparse. We found no published studies assessing birth outcomes after gestational exposure to pyrvinium. We found four studies assessing birth outcomes after gestational exposure to mebendazole (de Silva et al. 1999; Diav-Citrin et al. 2003; Acs et al. 2005; Larocque et al. 2006) conducted in Sri Lanka (de Silva et al. 1999), Peru (Larocque et al. 2006), Hungary (Acs et al. 2005) and Israel (Diav-Citrin et al. 2003). None of the four studies found any association between treatment with mebendazole during pregnancy and negative pregnancy outcomes. The Peruvian study found a numerical higher rate of major congenital defects, although not statistically significant. Two of the four studies were conducted in areas endemic for hookworm infections [Sri Lanka (de Silva et al. 1999) and Peru (Larocque et al. 2006)]. Infection with hookworms can cause anaemia, why treatment with mebendazole in endemic areas is recommended by the WHO after completion of the 1st trimester of pregnancy to improve birth outcomes (de Silva et al. 1999). The Sri Lankan study found no increased risk after mebendazole intake for development of major congenital defects, perinatal mortality and very low birth weight (<1500 g) (de Silva et al. 1999). The Peruvian study found a significant reduction in very low birth weight of the children born to women treated with mebendazole during pregnancy. This positive result may be due to treatment of the hookworm infection and anaemia.

The Israeli prospective controlled cohort study included 192 cases of women exposed during pregnancy to mebendazole, the majority (71.5%) being exposed during the 1st trimester (Diav-Citrin et al. 2003). The study found no significant difference in number of major malformations or stillbirths between mebendazole exposed cases and matched controls (1:1). These results are similar to the results in this study. Finally, a population-based case–control study in Hungary included 14 cases and 14 controls exposed to mebendazole during pregnancy. The study did not find an association between congenital malformations and treatment with mebendazole during pregnancy. A limitation to this study, however, is the small number of participants in the study.

Pyrvinium

We found no studies analysing pregnancy outcomes after pyrvinium exposure. A non-peer reviewed report with results from the Swedish birth registry includes 361 women treated with pyrvinium during early pregnancy (Källén 2011). They did not find a higher incidence of congenital malformations among these pregnancies compared to unexposed pregnancies. These results are similar to ours, but are difficult to compare, since the results from The Swedish Birth Registry are presented without description of statistic methods used, baseline characteristics of the women included and other detailed information of the results.

Strength and limitations

This study is based on large Danish national registers, which contain important information on health and social issues of all Danish residents. The extraordinary quality of the registers has been recognized and validated for public health and health-related welfare research (Thygesen and Ersboll 2011). All the information concerning each individual in the different nationwide registers can be linked across registers on an individual level by means of the unique identification number given to all Danish residents upon birth or immigration. This feasibility to link information across nationwide registers is very unique and only available in few countries worldwide. This Danish nationwide cohort study includes information on nearly all births and the mothers' redemption of prescriptions of pyrvinium and mebendazole from 1997 to 2007.

It is one of the largest studies to date evaluating pregnancy outcomes after exposure to mebendazole during pregnancy and the only study examining pregnancy outcomes after exposure to pyrvinium during pregnancy. Information from the Danish national registers used in this study was obtained prospectively and not based on questionnaires or interviews, why recall bias is avoided. In addition, since our data include nearly all births in Denmark in the study period, selection bias is also prevented. Danish pharmacies are obliged to register all redeemed prescriptions as part of the national health care reimbursement scheme, and as a result The Danish National Prescription Register includes ~97.5% of all redeemed prescriptions in Denmark

(Kildemoes et al. 2011). The quality of the diagnoses of congenital malformations has been validated and found to have a predictive value of 88.2% for having a congenital malformation, with a completeness of 89.9% (Larsen et al. 2003). Information from Danish nationwide registers allowed us to adjust for potential confounders as maternal age at conception, parity, income, level of completed education, gestational age and smoking. We found no difference between the crude and adjusted results except for the SGA analysis where the crude analyses showed a significantly lower risk of having a newborn categorized SGA, if exposed to mebendazole. This association disappeared when adjusting for parity, since higher parity is protective of SGA (Table 2). However, the risk of bias due to unaccounted confounders cannot be ruled out. The redeemed prescriptions for pyrvinium or mebendazole are used as proxy measures for exposure to the drugs. Lack of compliance would lead to misclassifying unexposed women to be exposed, which would overestimate the exposure. However, since the women have redeemed the drug, we believe the probability of exposure is high. In contrast, it is possible we have underestimated the exposure to pyrvinium, since this drug also is available over-the-counter in Danish pharmacies. Another limitation is that the exact date of exposure to the drugs is not available, since the date of redemption is used as exposure date. Some of the women could have been exposed later in the pregnancy or even after the pregnancy. In contrast, since the treatment is for an acute infection, we believe the exposure date is close to the date of redemption.

Relevance of these finding

Due to the lack of safety data on anthelmintics, there still remains an uncertainty about the ethics of exposing pregnant women.

Deworming pregnant women with soil-transmitted helminths (STH)

Risk-benefit analyses have shown that the benefits from deworming pregnant women far outweigh the risk to their health and the health of their babies, when infected with STH (Savioli et al. 2003). Studies have shown that treating pregnant women helped reducing maternal anaemia (Torlesse and Hodges 2000; Torlesse and Hodges 2001) as well as improving infant birth weight and survival (Christian et al. 2004). The WHO stated in a report from 2006: 'The proven benefits of antenatal deworming in the absence of any evidence indicative of drug teratogenicity or embryotoxicity in humans [. . .] provides compelling evidence to support the treatment with albendazole or mebendazole of women for STH after the first trimester of pregnancy' (WHO 2006). WHO therefore recommend treatment with anthelmintics in pregnant women in 2nd and 3rd trimesters in areas where the prevalence of STH infection exceeds 20%. Regardless of these suggestions, only Madagascar, Nepal and Sri Lanka had in 2008 added deworming to their antenatal care programmes, which was probably due to the fear of adverse pregnancy outcomes (Brooker et al. 2008). Our study, together with the already published studies support that treating women during pregnancy is safe in regards to the negative birth outcomes: congenital malformations, small for gestational age, stillbirth and neonatal mortality. The concerns for treatment during pregnancy are probably due to the teratogenicity or embryotoxicity shown in rats. The cautiousness is understandable, but it should be considered, that no human studies have shown any significant evidence of teratogenicity or embryotoxicity. That mebendazole and pyrvinium are safe during pregnancy is furthermore supported by the low absorption rate in the intestinal tract (Smith et al. 1976; Edwards and Breckenridge 1988). The majority of women in this study have in all probability been treated due to pinworm infection since soil-transmitted helminths are not endemic in Denmark. The treatment dosage for soil-transmitted helminths exceeds that of pinworm infection, why extrapolations from this study to safety for treatment of STH at all times during pregnancy may be difficult. Nonetheless, it is important that the safety of mebendazole during pregnancy has been validated for the doses used in pinworm infections.

Conclusion

In the present nationwide cohort study, we found no association between redeeming a prescription for mebendazole or pyrvinium during the 1st trimester and congenital malformations. We furthermore found no association with small for gestational age, stillbirth or neonatal mortality when redeeming a prescription for mebendazole or pyrvinium. We observed no fetal harm in receiving treatment with neither mebendazole nor pyrvinium at any time during pregnancy in doses used for pinworm infections. The absolute safety of using mebendazole in doses used for STH-infections is difficult to state based on only this study, but we do believe that our results together with already conducted studies show a good safety profile of mebendazole and pyrvinium during pregnancy. It should be taken into consideration, the increasing amount of data confirming the safety of using mebendazole during pregnancy, including treatment during the 1st trimester. We believe that the knowledge this study offers is beneficial during pregnancy for treatment of both pinworm infections and to a certain extent soil-transmitted helminth infections in third-world countries.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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