

Effects of *Schistosoma mansoni* infection and Mirazid treatment on pregnant mice and their fetuses

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ABSTRACT

A total of 48 female albino mice, with average weight 23 g, have been used in this study, divided into 4 groups (12 mice for each group). Groups I & II served as uninfected groups. Group II was subjected to pregnancy and received an oral dose of Mirazid (300 mg/Kg) (Pharco Pharmaceuticals, Alexandria, Egypt) for three consecutive days. Groups III and IV were infected subcutaneously with 60 ± 10 *Schistosoma mansoni* cercariae (Egyptian strain) and were subjected to pregnancy. Group IV received an oral dose of Mirazid (300 mg/Kg). The results showed that the distribution of implantation sites of fetuses in the uterine horns was found unequal in infected groups which completed the pregnancy. The mean number of fetuses was smaller in infected, treated or both groups when compared with control groups. Also, there were many abortion cases, especially when infection progressed. In the present study, infection was found to induce some growth retardation among fetuses as compared with the control ones. Growth retardation was indicated by highly significant decrease in their body weight and length, abnormal skin and limbs, kinky tail, kyphotic body and hematoma formation. Treatment with Mirazid did not improve these malformation as well as control ones. In conclusion, more studies are needed regarding the relationship between the pregnancy and schistosomiasis as the present work reflects the deleterious effect of schistosomiasis on the pregnant mice and on the fetal outcomes. In addition, the results reflected, for the first time, the unsafely using of Mirazid during pregnancy where announcement should be clear to avoid Mirazid in treatment of schistosome-infected pregnant women.

Key words: Schistosomiasis, pregnancy, Mirazid, mice

INTRODUCTION

Schistosomiasis currently affects ~207 million people in tropical countries and ~40 million women of child-bearing age. Little is known about schistosome-associated morbidity in pregnant women and their offspring (Friedman *et al.*, 2007). It is estimated that 85% of people with schistosomiasis live in sub-Saharan Africa and the disease is also endemic in Western Pacific region (WHO, 2002). There are inadequate data that address schistosomiasis during pregnancy; hence, the number of pregnant and lactating women who are infected with schistosomiasis remains unknown (Friedman *et al.*, 2007). Data indicate that 10 million women in Africa per year have schistosomiasis during pregnancy (WHO, 2004).

Healthy successful pregnancies are characterized by a placental microenvironment (Hanna *et al.*, 2000; Kurtis *et al.*, 2011). Parasitic diseases, including malaria and leishmaniasis, caused a proinflammatory microenvironment and are associated with poor pregnancy outcomes (Stekete *et al.*, 1996; Okoko *et al.*, 2002). Human infection with schistosomes results in the elaboration of

proinflammatory cytokines that are detected in the systemic circulation. Each of these cytokines has been implicated in fetal growth restriction in human studies (Crocker *et al.*, 2003). Only two observational studies have reported decreased birth weights in schistosome-infected women (Kurtis *et al.*, 2011). The health status of a woman before pregnancy is crucial determinant of gestational morbidity and pregnancy outcomes. Because schistosomiasis causes both anemia and under nutrition, maternal schistosomiasis could have deleterious consequences during pregnancy (Kurtis *et al.*, 2011).

Rodent models provide strong evidence that maternal schistosomiasis leads to deleterious pregnancy outcomes (Amano *et al.*, 1990; El-Nahal *et al.*, 1998; Kurtis *et al.*, 2011). For example, *S. mansoni*-infected CBA/J mice have significantly poorer birth outcomes than uninfected age-matched controls (20% versus 1% abortions, 5% versus 0% maternal deaths, and 34% versus 77% surviving infants, respectively). In addition, pups born to *S. mansoni*-infected C57BL/6 mice had 17% lower birth weight than pups born to uninfected mothers (El-Nahal *et al.*, 1998; Kurtis *et al.*, 2011). In another study, infected females mice and an uninfected control group were bred. The pregnancy outcomes were 13% versus 2% abortion, 10.9% versus 0% maternal death and 41.7% versus 21% infant death in the experimental group versus the controls, respectively (Bittencourt *et al.*, 1980).

There is active research assessing the safety and efficacy of praziquantel treatment for the pregnant women (Friedman *et al.*, 2007; Ndibazza, *et al.* 2010). The clinical decision to treat pregnant women is influenced in part by the potential adverse impact of maternal schistosome infection on pregnancy outcomes (Kurtis *et al.*, 2011). On the other hand, no information is available about Mirazid treatment for the pregnant women.

Consequently, this work aimed to study the possible effects of *S. mansoni* infection on the pregnant mice and their fetuses during different times of infection, in addition to the study of the effect of Mirazid treatment on the pregnancy.

MATERIAL AND METHODS

Experimental Animals

Forty eight female albino mice, weighing about 23 g, were purchased from Theodor Bilharz Research Institute and kept at room temperature ($25 \pm 2^\circ\text{C}$) in a light controlled room with an alternating 12 hour light/dark cycle. The animals were marked and housed in cages in the animal house of Department of Zoology, Faculty of Science, Suez Canal University. The mice weight at the beginning of experiment was (22 ± 2 g) Animals were allowed to become acclimatized to laboratory conditions before experimentation with free access to water and food *ad libitum*. They were fed on standard rodent pellets and some vegetables as a source of vitamins.

Experimental design

Mice were randomized into 4 groups (12 mice for each group). Groups I & II served as uninfected groups. Group II was subjected to pregnancy and received an oral dose of Mirazid (300 mg/Kg) dissolved in 1.5 ml distilled water (Pharco Pharmaceuticals, Alexandria, Egypt) for three consecutive days. Groups III and IV were infected subcutaneously with 60 ± 10 *Schistosoma mansoni* cercariae (Egyptian strain), and subjected to pregnancy. Group IV: received an oral dose of Mirazid (300 mg/Kg). The mice were sacrificed 18 days post pregnant.

Animal breeding

Daily examination of each virgin female was carried out to determine the estrus cycle. There are three different stages of estrus cycle (Allen, 1922), namely

Proestrus which lasts for about 25 hours and characterized by the presence of a large number of epithelial cells and a few number of cornified cells in the vaginal smears, Met estrus which lasts for 8 hours during which the smear contains cornified cells only or together with a few epithelial cells and leucocytes and Diestrus stage which lasts for 55 hours and the smear contains epithelial cells together with leucocytes.

Mating was introduced by housing females in the proestrus stage with males in separate cages at a ratio of three females with one male for overnight. In the next morning, the presence of vaginal bulges or the presence of sperms in the vaginal smear determined the zero date of gestation.

Pregnancy was confirmed by the presence of diestrus state for 5 days after mating and palpable fetal masses in the abdomen at the 5th day after mating in addition to a gradual increase in maternal body weight. A sudden decrease in the maternal body weight and/ or presence of blood drops were considered as signs of abortion. The gestation period in the mice was about 19 days. Maternal body weight of control and experimental groups were recorded every day throughout the gestation period.

Pregnant females of each group were sacrificed on day 18 of gestation by cervical dislocation. The uterine horns were inspected to determine the number of live, dead and resorbed fetuses. The average body weight and crown-rump lengths of fetuses were recorded for each group. Moreover, the fetuses were carefully examined for any morphological malformations. Photographs for the control and maternally treated fetuses were taken. Fetuses which were already chosen from different experimental groups were fixed in 10% neutral buffered formalin for 24 hours. The specimens were then kept in a mixture of 70% ethyl alcohol (95 %) and glycerin (5 %).

Statistical analysis

Results were expressed as mean \pm S.E. The results were analyzed for statistical significance using t-test or analysis of variance followed by Tukey test. Statistical evaluation was conducted with SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). Values of $p < 0.05$ were regarded as significant.

RESULTS

(A) Effect of infection, treatment and both on percentage of spontaneous abortion, resorption rate and number of fetus/dam

Results showed that percentage of spontaneous abortion was highly increased in group IV (subjected to pregnancy 23 day pi treated by Mirazid (300mg/k) at day 7 of pregnancy and sacrificed at 6 week pi (18 day post pregnancy) (83%) and (50%) in group III (subjected to pregnancy 23 day pi and sacrificed at 6 week pi (18 day post pregnancy) and (40%) in group II control mice treated by Mirazid (300mg/k) at day 7 of pregnancy and sacrificed at 6 week pi (18 day post pregnancy) (Table 1).

Table 1: Effect of infection, treatment and both on percentage of abortion and resorption rate.

Group	Abortion %	Mean resorption
I Uninfected pregnant	0	0
II Uninfected pregnant / treated with Mirazid (300mg/k)	40%	3.66 \pm 0.88
III Infected pregnant / Sacrificed at 6 week pi	50%	2.83 \pm 0.40
IV Infected pregnant / treated with Mirazid (300mg/k) Sacrificed at 6 week pi	83%	3 \pm 0

As shown in results, there was not resorption rate in control group I but found in treated, infected and infected treated groups II, III and IV (3.66 ± 0.88 , 2.83 ± 0.40 , 3 ± 0) respectively (Table 1).

(B) Effect of infection, treatment and both on number, weight, length of mice fetuses and weight of placenta in day 18th of gestation

Results showed that number of fetuses which their mother subjected to treatment, infection, or both (subjected to pregnancy 23 pi) were significantly decreased in groups II, III, IV (7.66 ± 1.85 , 7.66 ± 1.85 , 7 ± 0) respectively as compared to control fetuses group I (11.42 ± 0.52) (Table 2).

Length of fetuses which their mother subjected to treatment, infection, or both (subjected to pregnancy 23 pi) were significantly decreased in groups II, III (3.67 ± 0.13 , 3.43 ± 0.35) respectively but increased in group IV (3.91 ± 0.05) as compared to control fetuses group I (3.9 ± 0.02) (Table 2).

Weight of fetuses which their mother subjected to treatment, infection, or both (subjected to pregnancy 23 pi) were significantly decreased in groups II, III (1.06 ± 0.03 , 0.6 ± 0.03) respectively but increased in group IV (1.61 ± 0.02) as compared to control fetuses group I, (1.3 ± 0.02) (Table 2).

Results showed that weight of placenta in mother subjected to treatment, infection, or both (subjected to pregnancy 23 pi) were significantly increased in groups III, IV (0.14 ± 0.02 , 0.15 ± 0.01) respectively but decreased in group II (0.09 ± 0.00) as compared to control fetuses group I (0.11 ± 0.00) (Table 2).

Table 2: Effect of infection, treatment and both number, weight, length of mice fetuses and on weight of placenta in day 18th of gestation.

Group	No fetus	Length of fetus	Wt of fetus	Weight of placenta
I Uninfected pregnant	11.42 ± 0.52	3.9 ± 0.02	1.3 ± 0.02	0.11 ± 0.00
II Uninfected pregnant / treated with Mirazid (300mg/k)	$7.66\pm 1.85^{**a}$	3.67 ± 0.13	1.06 ± 0.03	0.09 ± 0.00
III Infected pregnant / Sacrificed at 6 week pi	$9.5\pm 0.98^{**a}$	3.43 ± 0.35	$0.6\pm 0.03^{**a}$	0.14 ± 0.02
IV Infected pregnant / treated with Mirazid (300mg/k) Sacrificed at 6 week pi	7 ± 0	3.91 ± 0.05	1.61 ± 0.02	0.15 ± 0.01

(C) Morphological malformation of 18th day mice fetuses in infected, treated and both groups

The morphological examination of fetuses maternally treated, infected and infected treated showed that some fetuses exhibit soft, membranous skin as well as kinky tail. In addition, other fetuses exhibit hematomas formation as one or two hematoma localized in the skull, limbs or tail and abnormal limbs (Table 3). Besides, the weight and length of maternally infected fetuses were significantly decreased as compared to control group (Figs. 1, 2 & 3).

Table 3: Incidence of morphological abnormalities of 18-day old fetuses maternally infected, treated and both.

Group	Membranous skin	Kyphotic body	Hind limb	Fore limb	Kinky tail	Hematoma
I Uninfected pregnant	0	0	0	0	0	0
II Uninfected pregnant / treated with Mirazid (300mg/k)	30%	0	15%	35%	17%	3%
III Infected pregnant / Sacrificed at 6 week pi	1%	9%	18%	21%	27%	9%
IV Infected pregnant / treated with Mirazid (300mg/k) Sacrificed at 6 week pi	18%	11%	18%	29%	24%	0

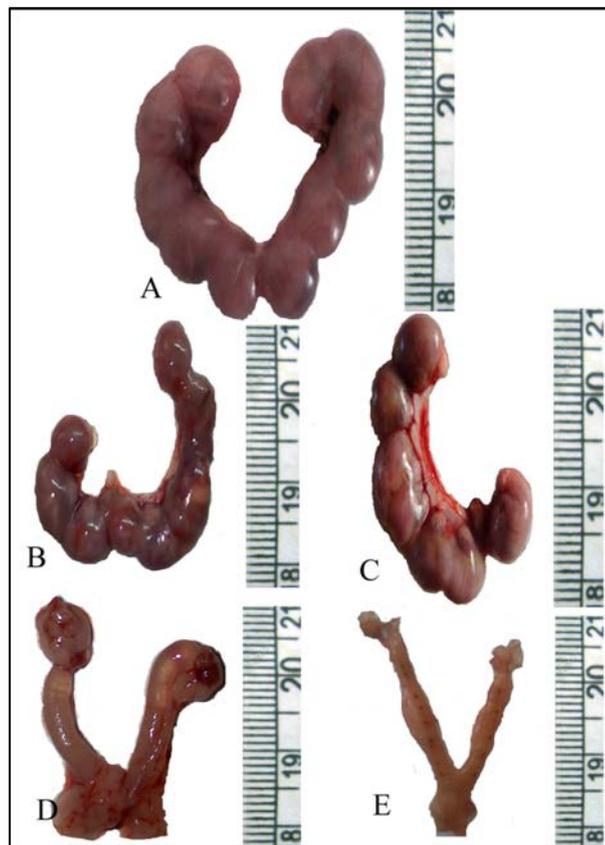


Fig. 1: Photomicrographs of the uteri of pregnant mice at 18th day of gestation:
 A: Uterus of a control mouse with equal distribution of implantation sites on the uterine horns.
 B, C: Unequal distribution of implantation sites on uterine horns. D, E: Uteri of aborted mice.

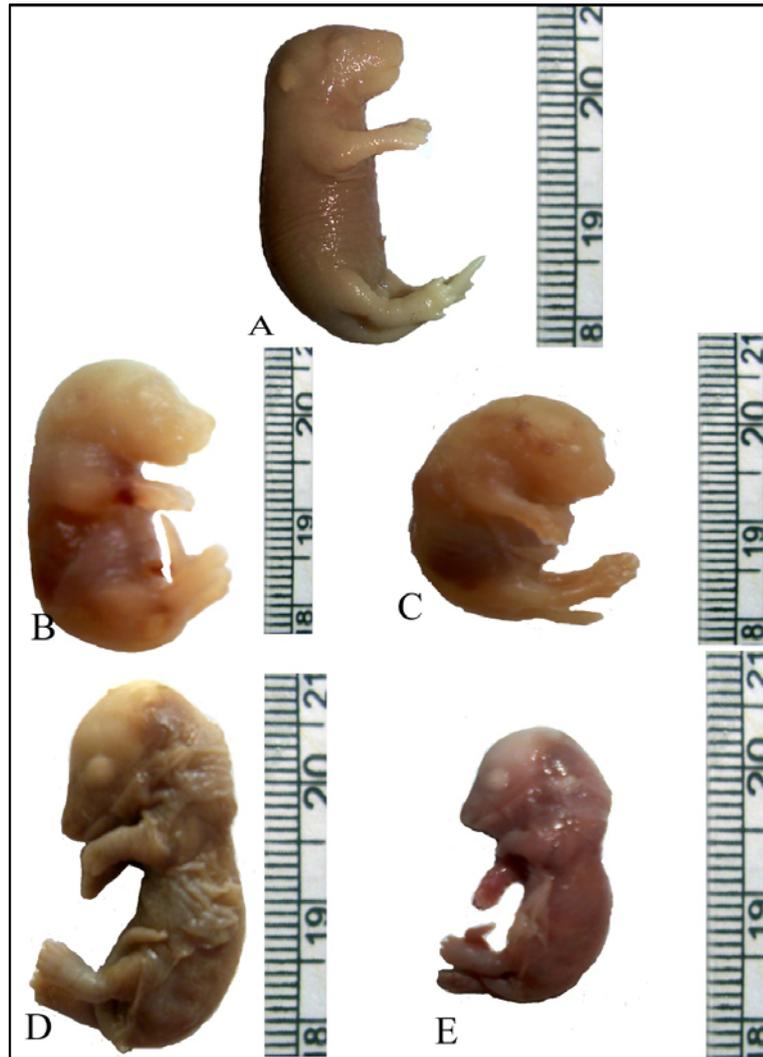


Fig. 2: Photomicrographs showing the normal external morphology of control 18 days mouse fetus maternally infected by *S. mansoni* cercaria, subjected to pregnancy 23 day pi and scarified at 6 week pi showing:

- A: Normal external morphology of control 18 days mouse fetus.
- B: Fetus with hematomas and retarded length.
- C: Fetus with soft membranous skin and kinky tail.
- D: Fetus with abnormal fore, hind limbs and kinky tail.
- E: Fetus with kyphotic body

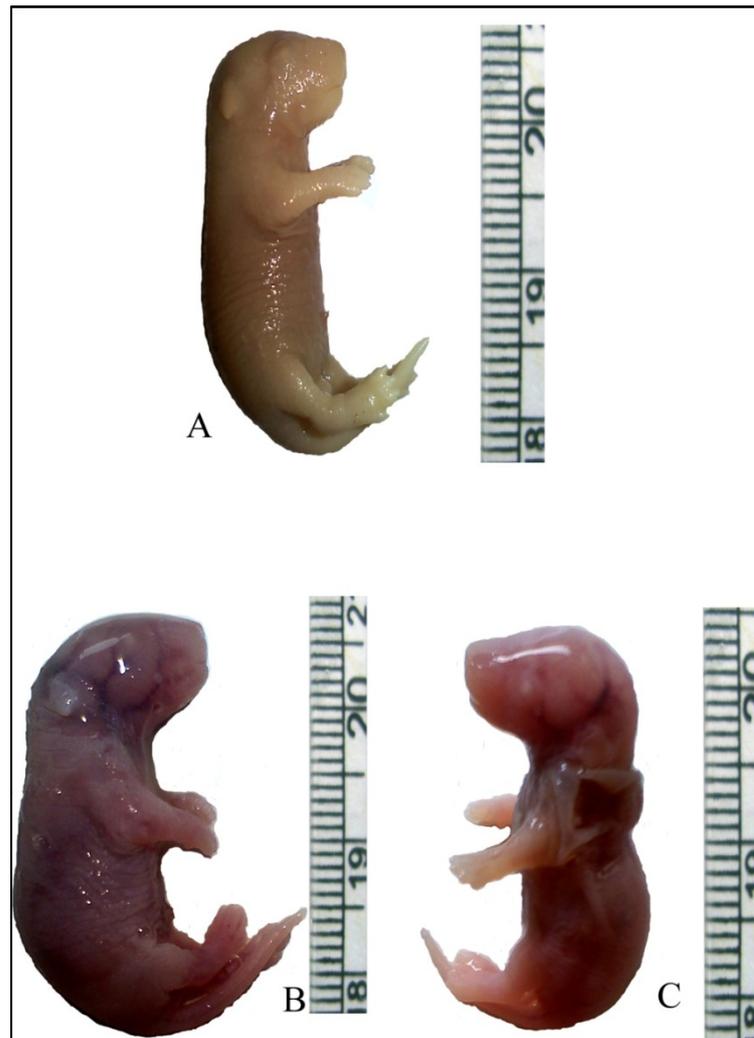


Fig. 3: Photomicrographs showing the normal external morphology of control 18 days mouse fetus maternally infected by *S. mansoni* cercaria, subjected to pregnancy 23 day pi treated by Mirazid (300mg/kg) and scarified at 6 week pi showing:
A: Normal external morphology of control 18 days mouse fetus.
B: Fetus with size reduction.
C: Fetus with soft membranous skin and kyphotic body.

DISCUSSION

In this study, the possible effects of different stages of *S. mansoni* infection on the pregnancy and the fetuses using physiological, parasitological and embryological approaches were studied. The effect of Mirazid treatment on the pregnant mice and their fetuses were considered as well.

Effects of Mirazid treatment during pregnancy on responses among offspring are unknown. There is active research assessing the safety and efficacy of praziquantel treatment for childbearing age women (Friedman *et al.*, 2007 and Ndibazza *et al.*, 2010). The clinical decision to treat pregnant women is influenced in part by the potential adverse impact of maternal schistosome infection on pregnancy outcomes. A randomized controlled trial of praziquantel treatment during the second or third trimester of pregnancy did not detect a birth weight difference in 458 *S. mansoni* infected Ugandan women, although the infection intensity was low in this population

and treatment occurred late in gestation (Ndibazza *et al.*, 2010). Together, these human and animal studies suggest that maternal schistosomiasis may lead to poor birth outcomes. However, none of these studies have examined the potential mechanisms of this relationship.

The present study showed that the numbers of maternally infected, or infected and mirazid-treated fetuses (subjected to pregnancy 23 pi) were significantly decreased as compared to corresponding control. Also, weight and length of maternally Mirazid-treated or infected fetuses (subjected to pregnancy 23 pi) were significantly decreased but increased in which their mother subjected to infection then treatment with Mirazid as compared to control fetuses. These results were in agreement with Amano *et al.* (1990) and El-Nahal *et al.* (1998) where *S. mansoni*-infected CBA/J mice have significantly poorer birth outcomes than uninfected age-matched controls (20% versus 1% abortions, 5% versus 0% maternal deaths, and 34% versus 77% surviving infants, respectively). In addition, pups born to *S. mansoni* infected C57BL/6 mice had 17% lower birth weight than pups born to uninfected mothers (El-Nahal *et al.*, 1998). Siegrist *et al.* (1992) recorded a case-control study of *Schistosoma haematobium* infection in Ghana and found differences in birth weight between infected and uninfected women, though this reached significance only in a stratum of premature deliveries (comprising eight *S. haematobium*-infected women). Schistosomiasis causes iron deficiency and anemia (Roche and Layrisse, 1966) and maternal iron deficiency anemia is associated with adverse pregnancy outcomes including still birth, prematurity, low birth weight and possibly maternal mortality (Allen, 2000).

The current study revealed that weight of placenta in mothers whom subjected to infection or treated with Mirazid after infection (subjected to pregnancy 23 pi) were increased but placental weight of Mirazid-treated dams showed significant decrease as compared to corresponding control. The present results are in agreement with Renaud *et al.* (1972) who stated that maternal schistosomiasis may lead to a placental proinflammatory response either by direct deposition of eggs in the placenta or by circulation of parasite antigens to the placenta. Trapping of parasite eggs in the placenta has been reported in up to 22% of 322 placentas obtained from an area of schistosome endemicity in the Ivory Coast using a digestion/sedimentation approach. However, Bittencourt *et al.* (1980) reported that the density of trapped eggs in the placenta appears to be too low for routine histologic detection. Kurtis *et al.* (2011) demonstrated that maternal schistosomiasis results in a proinflammatory signature that is detectable in maternal, placental, and fetal compartments. Also, they demonstrated that this inflammatory signature is associated with decreased birth weight.

Percentage of spontaneous abortion was highly increased in Mirazid- treated (300mg/k) group at day 7 of pregnancy and sacrificed at 6 week pi (18 day post pregnancy) more than the group which Mirazid-treated for 23 day and sacrificed at 6 week pi (18 day post pregnancy) and in the group which act as control mice treated by Mirazid (300mg/k) at day 7 of pregnancy and sacrificed at 6 week pi (18 day post pregnancy). Also, there was no resorbed fetuses recorded in control group but found in Mirazid-treated, infected and infected then Mirazid-treated groups.

Our results showed that maternally treated fetuses, infected and infected Mirazid-treated exhibited some developmental malformation such as soft, membranous skin as well as kinky tail. In addition, other fetuses exhibit hematomas formation as one or two hematoma localized in the skull, limbs or tail, kyphotic body and abnormal limbs. Besides, the weight and length of maternally treated and infected fetuses were significantly decreased as compared to control group. Also Kurtis *et al.*

(2011) recorded that schistosomes infect ~40 million women of childbearing age and result in the elaboration of proinflammatory cytokines that have been implicated in fetal growth restriction. In marine models and two observational studies in humans, *Schistosoma* infection during pregnancy was associated with reduced birth weight, although a recent treatment trial in *Schistosoma mansoni* did not detect this association.

Adam *et al.* (2004) reported that there were no significant differences between the group which received PZQ during pregnancy compared with which had not received the drug during pregnancy in the rate of abortion or preterm deliveries. No congenital abnormalities were noted by clinical examination in any of the babies born to either group. This retrospective study suggested that PZQ therapy is safe during pregnancy.

The possibility that birth weight would be improved by routine treatment with benzimidazoles during pregnancy in areas of high hookworm prevalence was suggested by the cross-sectional study in Sri Lanka (de Silva *et al.*, 1999). Very low birth weight (below 1.5 kg) was less common among women who reported taking mebendazole during pregnancy than among those that did not. Similarly, a nonrandomized study of albendazole treatment in Nepal suggested a benefit for birth weight (Christian *et al.*, 2004). The principal limitation of these studies was the possibility that taking anthelmintics was associated with better overall care-seeking behavior and hence better outcomes mediated by a variety of factors. More recently, studies on animals suggested possible adverse effects of schistosomiasis on birth weight and other prenatal outcomes, but no adequate studies have been conducted to explore similar effects in humans (Friedman *et al.*, 2007). Larocque *et al.* (2006) did not find any benefit of anthelmintic treatment during pregnancy for mean birth weight or low birth weight (below 2.5 kg) (Ndibazza *et al.*, 2010). Larocque and colleagues found a possible benefit of mebendazole for very low birth weight (below 1.5 kg), but only seven infants fell into this category in their study. In our study, 11 infants were very low birth weight and there was no association between this outcome and the treatment the mother had received. Again, the provision of adequate haematinics could be a factor in preventing an adverse effect of hookworm mediated by iron deficiency, and a consequent benefit of albendazole, from becoming evident, but the role of iron and folic acid supplementation in determining pregnancy outcomes other than anemia remains uncertain (Pena-Rosas and Viteri, 2006).

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ARABIC SUMMARY

تأثيرات الإصابة بالبلهارسيا والعلاج بالميرازيد على الفئران الحوامل وأجنحتها

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تمت الدراسة على عدد 48 من إناث الفئران البيضاء متوسط أوزانها 23 جرام ولقد تم تقسيم الفئران إلى أربع مجموعات كالتالي: مجموعة 2 و 4 تم تخصيصها كمجموعات ضابطة لم تتعرض للعدوى بالبلهارسيا. وتم إحداث الحمل في المجموعة 2 وتم العلاج بالميرازيد (300 ملجم/كجم) لمدة ثلاثة أيام متتالية. تمت عدوى الفئران بعدد 60 سركاريا شيبستوسوما مانسوني للمجموعات 3 و 4. وتم إحداث الحمل في اليوم 23 من بداية الإصابة وتم العلاج بالميرازيد (300 ملجم/كجم) لمدة ثلاثة أيام متتالية للمجموعة 4 حيث تم إحداث الحمل في المجموعة 4 أيضا عند اليوم 23 من الإصابة. و تم ذبح الفئران عند اليوم 18 من بداية الحمل في كل المجموعات.

وفيما يتعلق بدراسة تأثير الإصابة والعلاج على الأجنة، فقد أظهرت النتائج ان توزيع مواقع الأجنة في تجويف الرحم كانت غير متساوية في المجموعات المصابة التي أكملت فترة الحمل كما ان متوسط عدد الأجنة كان اقل في المجموعات المصابة والتي تم علاجها او كليهما مقارنة بمجموعاتهم الضابطة. كما ان كثير من حالات الإجهاض سجلت عند تقدم الإصابة. ووضحت الدراسة الحالية ان الإصابة قد تسببت في تأخر نمو الأجنة مقارنة بمجموعاتهم الضابطة وكان ذلك في صورة انخفاض ملحوظ للغاية في وزن وأطوال الأجنة ، تشوه بالجلد والاطراف ، الذيل الملفوف ، الجسم الحدابي وتكوين نزيف تحت الجلد. كما ان العلاج بالميرازيد لم يحسن هذه التشوهات مقارنة بالمجموعات الضابطة.

ختاما ، فإننا نحتاج الى دراسات كثيرة تتعلق بالعلاقة بين فترة الحمل والإصابة بالبلهارسيا وتأثير كل منهما على الآخر، حيث ان العمل الحالي يعكس الاثر الضار للبلهارسيا على الحالة الفسيولوجية للفئران الحوامل وعلى و الاجنة. بالإضافة الى انه وللمرة الأولى تعكس النتائج الاستخدام الغير امن للميرازيد خلال فترة الحمل و هذا يؤدي الى ضرورة التوعية بخطورة تناول هذا العقار أثناء الحمل وتجنبه تماماً.