Praziquantel for the treatment of schistosomiasis during human pregnancy
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Abstract In 2014, an estimated 40 million women of reproductive age were infected with Schistosoma haematobium, S. japonicum and/or S. mansoni. In both 2003 and 2006, the World Health Organization (WHO) recommended that all schistosome-infected pregnant and breastfeeding women be offered treatment; with praziquantel, either individually or during treatment campaigns. In 2006, WHO also stated the need for randomized controlled trials to assess the safety and efficacy of such treatment. Some countries have yet to follow the recommendation on treatment and many programme managers and pregnant women in other countries remain reluctant to follow the recommended approach. Since 2006, two randomized controlled trials on the use of praziquantel during pregnancy have been conducted: one against S. mansoni in Uganda and the other against S. japonicum in the Philippines. In these trials, praziquantel treatment of pregnant women had no significant effect on birth weight, appeared safe and caused minimal side-effects that were similar to those seen in treated non-pregnant subjects. Having summarized the encouraging data, on efficacy, pharmacokinetics and safety, from these two trials and reviewed the safety data from non-interventional human studies, we recommend that all countries include pregnant women in praziquantel treatment campaigns. We identify the barriers to the treatment of pregnant women, in the countries that already include such women in individual treatments and mass drug administration campaigns, and discuss ways to address these barriers.

Introduction
In 2014, over 230 million individuals, including 40 million women of reproductive age, were estimated to be infected with Schistosoma haematobium, S. japonicum and/or S. mansoni. Despite the widespread availability of effective, praziquantel-based treatment, schistosomiasis remains the cause of substantial morbidity and mortality in many low- and middle-income countries. In a meta-analysis of the disability-related outcomes of endemic schistosomiasis, the disability weight assigned to schistosomiasis – which was based on the disease’s impact on a range of functional domains, ranged between 2% and 15%. The most recent Global Burden of Disease estimates, from 1980–2016, indicate that approximately 10,000 schistosomiasis-related deaths occur each year. Among non-pregnant subjects, schistosomiasis has been implicated as a contributor to undernutrition, probably via the suppression of appetite and to inflammation-mediated cachexia. Schistosomiasis also contributes to the global burden of anaemia. Individuals with heavy infections may lose so much blood in their stools and/or urine that they develop iron-deficiency anaemia. Pregnant women may experience any of these morbidities and others, e.g. hepatic fibrosis and the associated increased risk of oesophageal varices, at approximately the same rates as seen among non-pregnant individuals.

Both S. haematobium and S. mansoni are known to contribute to the burden of anaemia in pregnancy, particularly at higher intensities of infection. The same may be true for S. japonicum. For example, in a recently completed randomized controlled trial in the Philippines, praziquantel given as a total dose of 60 mg per kg, to S. japonicum-infected pregnant women at 12–16 weeks’ gestation, led to improved maternal ferritin and a trend towards increased neonatal iron endowment.

In 2000, urogenital schistosomiasis, which is largely caused by S. haematobium, was considered endemic in 53 countries in Africa and the Middle East. In areas where S. haematobium is endemic, women of reproductive age may experience chronic female genital schistosomiasis and this may place the women at increased risk of the acquisition and transmission of human immunodeficiency virus (HIV).

Praziquantel was released in 1979, but the United States Food and Drug Administration (FDA) still places it in pregnancy class B, indicating that animal reproduction studies have failed to demonstrate a risk to the fetus but no adequate and well-controlled studies in pregnant women have been conducted. In 2002, the World Health Organization (WHO) sponsored an informal consultation on the use of praziquantel during pregnancy and lactation. The report from that consultation, published in 2003, recommended that all schistosome-infected pregnant and breastfeeding women be considered high-risk groups and be offered treatment with praziquantel either individually or during treatment campaigns.

Given the evidence of praziquantel’s safety in animal models, encouraging post-market surveillance data and its successful use in the treatment of neurocysticercosis during pregnancy, a similar recommendation was made in 2006, as part of WHO’s Guidelines for Preventative Chemotherapy for Helminthiasis. These guidelines recommended that pregnant and breastfeeding women be included in mass administrations of praziquantel, but also noted the need for randomized controlled trials to assess praziquantel’s safety and efficacy when given to such women. Initially, the lack of sufficient safety data from controlled trials made many countries reluctant to

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follow this recommendation. Since 2006, however, there have been two relevant randomized controlled trials and the results of those trials have prompted some more countries, but not all, to follow the guidelines’ recommendations on praziquantel use. In Zanzibar, in the United Republic of Tanzania, where local guidelines do not recommend treatment of pregnant women, two of the most commonly cited reasons for not receiving praziquantel during community treatment campaigns were pregnancy and breastfeeding. China, Gabon, Kenya and Uganda have still to adopt policies to treat schistosome infections in pregnant women. Even in countries where the relevant national policy has been changed to include pregnant and breastfeeding women in mass administrations of praziquantel, some such women are still being excluded, because schistosomiasis programme managers and health-care providers remain unaware of the change. Millions of women of reproductive age may miss treatment for many years during repeated cycles of pregnancy and lactation.

Below, we review safety data from non-interventional human studies and summarize the data addressing safety, efficacy and pharmacokinetics from the relevant post-2006 randomized controlled trials. We identify current barriers to the treatment of pregnant women with praziquantel, in those countries where such treatment is already national policy and discuss ways in which these barriers may be overcome. Given the relevant data published since 2006, we recommend the inclusion of pregnant women in all praziquantel treatment campaigns.

**Praziquantel safety**

**Non-interventional studies**

Over more than 30 years of post-market experience with praziquantel, no reports of serious adverse events relevant to human pregnancy have been published, e.g. abortions, stillbirths or congenital anomalies. In a retrospective study in Sudan, 88 pregnancies in which there had been inadvertent praziquantel exposure, including 37 with exposure in the first trimester, were compared with 549 other pregnancies in which there had been no praziquantel exposure. None of the 88 exposed pregnancies ended in abortion or stillbirth and no congenital anomalies were noted by clinical examination of the babies born to the exposed women, or to the unexposed. In a small case series of travel-related acquisition of schistosomiasis, four pregnant women were treated with 60 mg praziquantel per kg, including two treated during the first trimester. Treatment did not culminate in any serious adverse events for the mothers or neonates. In a prospective study conducted in Sudan, 25 pregnant Sudanese women with *S. mansoni* infections were treated with a single dose of praziquantel, at 40 mg per kg, during different trimesters. Although one of these women experienced a spontaneous abortion at 10 weeks’ gestation and three weeks post-treatment, the frequency of abortion among the treated women was similar to the background rate in the study community. In the treatment of neurocysticercosis, pregnant women have been given daily doses of praziquantel for up to 21 days with no apparent adverse events.

**Post-2006 trials**

Two randomized, double-blind, placebo-controlled trials have been completed since WHO’s publication of its last, i.e. 2006, guidelines addressing the treatment of pregnant women with praziquantel. In Uganda, where *S. mansoni* is endemic, women attending a hospital-based antenatal clinic were assigned into one of four treatment groups: placebo plus placebo, albendazole plus placebo, praziquantel plus placebo or albendazole plus praziquantel. As women who did not have schistosomiasis were included in the randomized sample, the study mimicked a typical mass drug administration in which infection status is not known at the time of treatment. Each single treatment was given during the second or third trimester, at a mean gestational age of 26.6 weeks. This large trial, which included 2507 women in its baseline analysis, found that praziquantel had no significant effect on maternal anaemia or birth weight, even among the women who were each confirmed to be infected with *S. mansoni* by the examination of a single stool sample. Perinatal mortality and congenital anomalies were as common in the placebo plus placebo group as in any of the other groups. Although, the infants born to mothers who had been given albendazole or praziquantel when pregnant, and infected with *S. mansoni*, showed a relatively high risk of infantile eczema, this did not translate into an increased risk of asthma in adolescence.

**Philippines**

In Leyte in the Philippines, women who were infected with *S. japonicum* were recruited for another randomized controlled trial. Overall, 360 women were treated, at 12–16 weeks’ gestation, either with praziquantel, given as two doses, each of 30 mg per kg, with a four-hour interval, or with a placebo. Praziquantel treatment was found to have no significant impact on birth weight, i.e. the primary outcome, or on secondary outcomes such as the prevalences of low birth weight, intrauterine growth restriction and prematurity. Analysis of cytokine profiles indicated that such treatment also had no detectable effect on maternal inflammation, even by 32 weeks’ gestation. The treatment of schistosomiasis has complex effects on the immune system, including release of adult-worm antigens, enhanced responses to these antigens and a decline in immunoregulatory activity. At 32 weeks’ gestation, pregnant women have been found to have significantly higher blood concentrations of tumour necrosis factor-α when infected with *S. japonicum* than when uninfected, with mean values of 2.11 and 0.34 pg per mL, respectively. In the trial in Leyte, the corresponding concentrations, again at 32 weeks’ gestation, were 1.6 pg per mL for the placebo group and 1.3 pg per mL for the praziquantel group. These results indicate that, in the trial, praziquantel treatment did not resolve inflammation in the ensuing five or six months. The lack of a significant impact of praziquantel on birth weight may also be a reflection of the generally light infections; only 9.7% of the women enrolled in the trial had moderate or intense *S. japonicum* infections.

In the trial in Leyte, all of the pregnant women given praziquantel showed parasitological cure at 22 weeks’ gestation. Praziquantel treatment culminated in increased maternal serum ferritin levels at 32 weeks’ gestation as well as a trend towards improved neonatal iron endowment. Such treatment was not found to have any significant impact on maternal haemoglobin or anaemia risk during the trial. However, significant improvements in haemoglobin may take more than three months to show.
after praziquantel treatment and the low prevalence of maternal anaemia and the generally low intensity of the *S. japonicum* infections in the trial may have masked any potentially beneficial effects of praziquantel on maternal anaemia. Praziquantel treatment was well tolerated in the trial and the reactogenicity rates in the treated pregnant women were similar to those observed in treated non-pregnant participants. Importantly, such treatment had no significant effect on key safety outcomes such as abortion, congenital anomalies and intrauterine fetal death.48

**Pharmacokinetics**

Praziquantel pharmacokinetics in non-pregnant adults are characterized by peak concentrations one to three hours after a dose and a terminal half-life that ranges between 0.8 and 1.5 hours. During pregnancy, however, important physiological changes could affect drug pharmacokinetics. For example, there is a decrease in gastric emptying, decreased bioavailability, decreased drug binding, altered liver metabolism and increased elimination.49 The pregnancy-related changes that occur in pharmacokinetic distribution and exposure parameters include decreased peak plasma concentrations, longer elimination half-lives and a reduction in the so-called area under the curve, which leads to lower levels of drug exposure.50 The appropriate drug dose and regimen to be given during gestation must therefore be carefully determined.

The first detailed study of the pharmacokinetics of praziquantel in pregnant women was conducted as part of the randomized controlled trial in Leyte. The results of this study, which included assays quantifying the concentrations of praziquantel in the milk of treated women have yet to be published. A preliminary analysis indicated that the pharmacokinetics of praziquantel in women in early pregnancy, women in late pregnancy and postpartum subjects were similar (M Mirochnick, Department of Pediatrics, Boston University School of Medicine, unpublished data, 2017). For example, the corresponding mean areas under the curve were found to be 8.9 mg-hour per L for women in early pregnancy, 15.0 for women in late pregnancy and 13.1 for postpartum subjects. Drawing conclusions from such data are difficult as there has only been one previous study of the pharmacokinetics of praziquantel in a study area with endemic *S. japonicum*, and that was confined to just two non-pregnant women.51 The results of the ongoing pharmacodynamic analysis from the Leyte trial, will hopefully help clarify the optimal dosing of praziquantel during pregnancy.

**Policy implications**

Since 2006, when WHO last published a recommendation on the use of praziquantel in pregnant and breastfeeding women, considerable relevant information has been published or, at least, analysed. This information, from two randomized controlled trials and additional observational and pharmacokinetic studies, provides support for WHO’s recommendation. In the trials, no increased risk of adverse pregnancy or neonatal outcomes was observed when praziquantel was given either at 40 mg per kg during the second or third trimester or at a total dose of 60 mg per kg at 12–16 weeks’ gestation. Given this improved evidence of the drug’s safety, we recommend that pregnant and breastfeeding women now be included in all praziquantel-based mass drug administrations.

Policies for the treatment of pregnant women with praziquantel must consider the timing of such treatment. The safety of giving praziquantel to pregnant women during the first trimester has not been well assessed. However, the apparent lack of teratogenic effects in mice, rats or rabbits given praziquantel while pregnant indicates that the drug may be safe to use during the classic teratogenic period of the human first trimester.52,53 The observations made, retrospectively, on women inadvertently exposed to praziquantel during the first trimester,54 case reports of treatment during the first trimester with no untoward effects55 and the encouraging results of over 30 years of post-market surveillance involving many millions of doses provide additional reassurance. Given the lack of data suggesting that praziquantel poses a risk to mothers or fetuses and the costs and logistical barriers of pregnancy testing, we do not advocate that routine pregnancy testing of women of reproductive age forms a part of any campaign of praziquantel-based mass drug administrations.

The possibility of treating pregnant women outside of mass drug administrations needs to be considered. Based on the demonstrated safety of praziquantel during the second and third trimesters, we recommend the treatment of pregnant women during routine visits for antenatal care if the women request such treatment or show the symptoms of schistosomiasis. We refrain from recommending that all pregnant women in areas with endemic schistosomiasis be treated with praziquantel as part of a routine package of antenatal care, at least until there has been a more detailed analysis of the potential costs and benefits. In the Ugandan randomized controlled trial, such an approach, in which all women were treated regardless of their infection status, did not reduce maternal anaemia status or increase birth weights significantly.56

Finally, provision of praziquantel for non-pregnant women of reproductive age, either as an individualized treatment or part of a mass drug administration, is important for women’s own health and well-being. If opportunities for such treatment are missed, women are placed at increased risk of chronic morbidity and the intense schistosome infections that are particularly associated with anaemia and undernutrition.1,3,4,6,13 If left untreated, women living in areas endemic for *S. haematobium* face developing female genital schistosomiasis which may, in turn, increase the risks of acquiring and transmitting HIV.15,53

**Barriers to policy adoption**

Although recent progress in many relevant areas should increase the access of pregnant women to praziquantel treatment, barriers to adopting policies for such treatment still remain. The relevant information collected since 2006 should provide reassurance to countries that have not yet adopted WHO’s recommendation on the treatment of pregnant and breastfeeding women with the drug. By creating this update, we hope to mitigate any remaining concerns of policy-makers.

Since the expiration of Bayer’s patent in 1994, the price of praziquantel, which was once a substantial barrier to the drug’s widespread use, has plummeted, to approximately 0.08 United States dollar (US$) per 600-mg tablet or approximately US$0.20–0.30 per treatment course in 2017.56 Furthermore, in recent years, the supply of praziquantel has increased dramatically. In 2016, to
meet the need for treatment, Merck Soreno pledged to donate 250 million tablets of praziquantel annually. Praziquantel is also now available from the United Kingdom of Great Britain and Northern Ireland’s Department for International Development, the United States Agency for International Development, the World Bank and World Vision, such that sufficient supply should be available to provide close to 130 million treatments annually.

Finally, even among countries that have adopted policies to include pregnant and breastfeeding women in praziquantel-based mass drug administrations, substantial gaps still exist in the implementation of those policies. One issue is the prioritization of school-based or community-based mass drug administrations in some areas. School-based programmes risk missing most women of reproductive age, as well as adolescent girls who cannot afford to attend school, especially if the schools involved are primary. Many programmes for the support of mass drug administrations are so poorly staffed and resourced that treatments cannot be delivered at the intervals indicated by the country prevalence of schistosome infection. Community health workers need to be resourced better and educated on the safety of praziquantel for pregnant and breastfeeding women.

In a collaboration with regulatory staff at the FDA and United States National Institutes of Health, we began work to change the Food and Drug Administration’s pregnancy designation for praziquantel, from class B to class A. In 2015, however, FDA moved away from the letter categories for pregnancy designations, to a more narrative approach.

Conclusion

Based on recent evidence of the safety of praziquantel in human pregnancy, we recommend that, in areas with endemic schistosomiasis, women of reproductive age, including pregnant and breastfeeding women, be treated with praziquantel either individually, in local antenatal clinics, or in mass drug administrations. As more women are treated, surveillance to identify any untoward effects of treatment should be continued. It is expected that treatment may improve both maternal and neonatal iron stores. Surprisingly, two randomized controlled trials did not reveal an impact of the praziquantel on subsequent birth weights. Between trials, any impact of praziquantel on birth weight was lost. None of the studies found any impact of praziquantel on birth outcomes during that pregnancy.

Conclusion

Several studies conducted during pregnancy in women of reproductive age, including pregnant and breastfeeding women, have shown that praziquantel is safe and effective in treating schistosomiasis.

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studies on humans, however, it remains possible that, although schistosomiasis adversely affects pregnancy outcomes, treatment during gestation is too late to impact birth outcomes during that pregnancy. Individualized treatment during antenatal care and treatment in mass drug administrations may, however, increase the likelihood that women enter subsequent pregnancies free of infection. Regular treatment is likely to impact both the overall prevalence of infection and the prevalence of the intense infections that are most closely associated with maternal morbidity.
Praziquantel and human pregnancy

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Definitive schistosomes, Schistosoma haematobium, S. japonicum, and S. mansoni, are endemic in many countries in Africa, Asia and Latin America. Schistosomiasis represents the most widespread parasitic disease in the world and is associated with significant morbidity and low levels of development. It affects millions of people and is also a major risk factor for several cancer. Praziquantel is the only drug approved for schistosomiasis treatment. Its efficacy and safety have been demonstrated in many clinical trials as well as in epidemiologic studies. However, despite the high efficacy and safety profile of the drug, only a few countries have implemented national control programs. This review describes the current status of schistosomiasis control and it highlights the challenges and potential solutions for its implementation.

Resumen

Praziquantel para el tratamiento de la esquistosomiasis durante el embarazo humano

En 2014, se estima que 40 millones de mujeres en edad reproductiva estaban infectadas con Schistosoma haematobium, S. japonicum y/o S. mansoni. Tanto en 2003 como en 2006, la Organización Mundial de la Salud (OMS) recomendó que todas las mujeres embarazadas y lactantes infectadas con esquistosoma recibieran tratamiento, con praziquantel, ya fuera individualmente o durante las campañas de tratamiento. En 2006, la OMS también informó de la necesidad de ensayos aleatorizados controlados para evaluar la seguridad y la eficacia del tratamiento. Nuevamente en 2014, la OMS recomendó que todos los países incluyan a las mujeres embarazadas en los programas de control de la esquistosomiasis. Así se ha producido una serie de ensayos clínicos sobre el uso de praziquantel durante el embarazo, siendo el principal de ellos Praziquantel and human pregnancy. Sin embargo, no todas las mujeres embarazadas son tratadas con praziquantel, aún en los países donde este medicamento está disponible y se recomienda su uso. Esto se debe a la falta de una correcta implementación de la recomendación de la OMS.

Résultats

En 2014, on estima que 40 millions de femmes en âge de procréer étaient infectées par Schistosoma haematobium, S. japonicum et/ou S. mansoni. En 2003 et 2006, l’Organisation mondiale de la Santé (OMS) a recommandé qu’un traitement au praziquantel soit offert, individuellement ou dans le cadre de campagnes de traitement, à toutes les femmes enceintes et allaitantes infectées par le schistosomiasis. En 2006, l’OMS a également confirmé la nécessité d’essais contrôlés randomisés pour évaluer l’innocuité et l’efficacité de ce traitement. Malgré ces recommandations, de nombreux pays, y compris des pays qui ont reçu l’approche recommandée, n’ont pas intégré l’utilisation du praziquantel pendant la grossesse dans leurs programmes de lutte contre le schistosomiasis. Les femmes enceintes et lactantes infectées par le schistosomiasis doivent recevoir un traitement au praziquantel, y compris lors des campagnes de traitement, selon l’OMS. Cependant, le traitement au praziquantel pendant la grossesse n’est pas toujours recommandé par les autorités sanitaires, et de nombreux pays n’ont pas encore adopté l’utilisation du praziquantel pendant la grossesse dans leurs programmes de lutte contre le schistosomiasis.
eficacia de dicho tratamiento. Algunos países todavía tienen que seguir la recomendación sobre el tratamiento y muchos gestores de programas y mujeres embarazadas en otros países siguen siendo reacios a seguir el enfoque recomendado. Desde 2006, se han llevado a cabo dos ensayos aleatorizados controlados sobre el uso de praziquantel durante el embarazo: uno contra el *S. mansoni* en Uganda y el otro contra el *S. japonicum* en Filipinas. En estos ensayos, el tratamiento con praziquantel en mujeres embarazadas no tuvo un efecto significativo sobre el peso en el momento del nacimiento, pareció seguro y causó efectos secundarios mínimos, similares a los observados en sujetos no embarazadas tratadas. Después de revisar los alentadores datos sobre la eficacia, la farmacocinética y la seguridad de estos dos ensayos y revisar los datos de seguridad de los estudios observacionales en humanos, recomendamos que todos los países incluyan a mujeres embarazadas en las campañas de tratamiento con praziquantel. Identificamos las barreras para el tratamiento de mujeres embarazadas, en países que ya incluyen a mujeres en los tratamientos individuales y en las campañas masivas de administración de medicamentos, y analizamos las formas de abordar estas barreras.

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**Policy & practice**

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