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Is ivermectin safe in pregnancy?

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onchocerciasis = river blindness

Ivermectin is one of the most important antibiotics discovered. It is recognised as a landmark drug by the American Chemical Society and its discoverers received the Nobel Prize in 2015. Additionally, ivermectin is one of the most widely used anti-parasitic drugs for animals and humans. Since 1987, about 3·7 billion treatments have been given worldwide primarily for mass drug administration (MDA) campaigns for onchocerciasis and lymphatic filariasis in sub-Saharan Africa. Ivermectin is also highly effective against strongyloides, scabies, and ticks, and it has recently been shown to be an effective endectocide that kills feeding mosquitoes with the potential to reduce malaria transmission.[1] The use of ivermectin will expand. For example, findings showed that ivermectin combined with diethylcarbamazine and albendazole is more effective than diethylcarbamazine plus albendazole as part of an MDA campaign for the treatment of lymphatic filariasis, resulting in greatly expanded use of ivermectin in MDA programmes worldwide.[2,3]

MDA = Mass Drug Administration

Currently women are told not to take ivermectin if pregnant based on their last menstrual period; however, many women might not know if they are pregnant and about 15% of pregnant women in MDA programmes inadvertently take ivermectin, primarily in their first trimester.[4] In *The Lancet Global Health*, Patricia Nicolas and colleagues have done the first systematic review and meta-analysis[5] that focuses on six published studies designed to address whether inadvertent ingestion of ivermectin during pregnancy results in abnormal birth outcomes. Five of six studies were retrospective case-control studies of women who delivered within 40 weeks of an MDA programme that compared abnormal birth outcomes (stillbirths, spontaneous abortions, and congenital abnormalities) between women who subsequently were found to have taken ivermectin and those who had not. One of six studies was a randomised controlled trial of pregnant women who received ivermectin in the second trimester.[6] Overall, Nicolas and colleagues' systematic review and meta-analysis identified no studies showing evidence for excess abnormal birth outcomes in woman who received ivermectin during pregnancy. They then applied the rigorous Cochrane Risk of Bias Tool for randomised trials and classified all studies to have very low certainty of evidence. Consequently, they concluded that current evidence does not support whether ivermectin is safe during pregnancy and recommended to continue to exclude pregnant women from treatment during MDA programmes. This conclusion is a safe assessment considering the cumulative number of women exposed in these studies, which is small (overall 899 exposed *vs* 3104 not exposed), but downgrades some well performed studies under challenging circumstances. In these studies, poor birth outcomes were not rare; a total of 47 congenital anomalies and 177 stillbirths or spontaneous abortions were identified, so it is difficult to say the studies were underpowered. Yet more studies are needed because safe use of ivermectin in pregnancy would be an important advance for MDA programmes.

Determining whether the use of ivermectin is safe in pregnancy is of utmost importance because women of reproductive age are often pregnant and frequently infected with larval stages of parasites in endemic areas in which they can be reservoirs of infections. Most MDA programmes for onchocerciasis and lymphatic filariasis require repeated rounds of treatment, usually annually for at least 5 years such that women who missed MDA in one round because of pregnancy will be treated in subsequent rounds. However, with more efficacious treatments, the number of MDA rounds will decline, thus increasing the likelihood that pregnant women remain untreated. A case in point is the recent introduction and rapid scale-up of the new triple drug regimen in which a single co-administered dose of ivermectin with diethylcarbamazine and albendazole might permanently sterilise adult *Wuchereria bancrofti* worms, thus requiring only one or two rounds of MDA.

The question therefore remains, what can be done to provide more robust data evaluating ivermectin in pregnancy? One suggestion provided by the authors is to set up a registry of inadvertent drug exposures to ivermectin and see if the prevalence of adverse birth outcomes exceed those in similar populations without recent MDA with ivermectin. However, to sustain and adequately support such registries with high-quality data, extra burden will be placed on programme managers who are already challenged. The registries often fail to report any adverse events following MDA with ivermectin, including inadvertent exposure during

pregnancy. Another interpretation of the review is that risk of adverse events associated with ivermectin exposure in pregnancy is sufficiently low to justify a multicentre, randomised trial to administer ivermectin to infected pregnant women. This justification is not unprecedented. Such a clinical trial was done in Kenya in the past without adverse outcomes.[6]

Determining the safety of ivermectin in pregnancy is a priority. Such information might also have relevance to a recently licensed and closely related drug, moxidectin, which has a much longer half-life than ivermectin; and if moxidectin is ever used in MDA programmes, it has a higher risk of exposure to women that could become pregnant after treatment. The review might sensitise the global community on the need to design and support implementation of an effective system to monitor and report ivermectin safety during pregnancy as part of the national pharmacovigilance systems where ivermectin mass distribution is ongoing.

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I declare no competing interests.

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1 Kobylinski KC, Sylla M, Chapman PL, Sarr MD, Foy BD. Ivermectin mass drug administration to humans disrupts malaria parasite transmission in Senegalese villages. *Am J Trop Med Hyg* 2011; **85:** 3–5.
2 King CL, Suamani J, Sanuku N, et al. A trial of a triple-drug treatment for lymphatic filariasis. *N Engl J Med* 2018; **379:** 1801–10.
3 WHO. Guideline: alternative mass drug administration regimens to eliminate lymphatic filariasis. 2017. Geneva: World Health Organization. https://www.who.int/lymphatic_filariasis/resources/9789241550161/en/ (accessed Oct 22, 2019).
4 Gyapong JO, Chinbuah MA, Gyapong M. Inadvertent exposure of pregnant women to ivermectin and albendazole during mass drug administration for lymphatic filariasis. *Trop Med Int Health* 2003; **8:** 1093–101.
5 Nicolas P, Maia MF, Bassat Q, et al. Safety of oral ivermectin during pregnancy: a systematic review and meta-analysis. *Lancet Glob Health* 2020; **8:** e92–100.
6 Ndyomugyenyi R, Kabatereine N, Olsen A, Magnussen P. Efficacy of ivermectin and albendazole alone and in combination for treatment of soil-transmitted helminths in pregnancy and adverse events: a randomized open label controlled intervention trial in Masindi district, western Uganda. *Am J Trop Med* 2008; **79:** 856–63.