

SYSTEMATIC REVIEW

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Pharmacologic safety of oral ivermectin in pregnant women Seguridad farmacológica de la ivermectina vía oral en gestantes

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ABSTRACT

This study was intended to determine the pharmacological safety of oral ivermectin in pregnant women. A systematic review of information published in the PubMed, MEDLINE, Scopus, Toxline, World Health Organization Clinical Trials Registry, US FDA List, ClinicalTrials, and Cochrane Central Registry databases was conducted from 1990 through 2020. From a total of 73 research articles reviewed, two animal experiments, one clinical and five analytical experiments were studied. Animal studies were found to show that ivermectin was associated with the risk of miscarriage, congenital malformations, stillbirth and maternal death. In humans, the effects presented in the animal study could not be determined. It is concluded that clinical studies are necessary to establish the presence of adverse effects in pregnant women from the consumption of ivermectin.

Key words: Ivermectin, Patient safety, Pregnancy.

RESUMEN

El presente estudio tuvo el propósito de conocer la seguridad farmacológica de la ivermectina por vía oral en gestantes. Se realizó una revisión sistemática de la información publicada en las bases de datos PubMed, MEDLINE, Scopus, Toxline, Registro de ensayos clínicos de la Organización Mundial de la Salud, lista de FDA de Estados Unidos, ClinicalTrials y el Registro Central de Cochrane. Se revisó un total de 73 artículos de investigación publicados entre 1990 y 2020. Se eligió dos experimentos en animales, un estudio clínico y cinco analíticos. Se encontró que los estudios realizados en animales mostraron que la ivermectina se asoció a riesgo de aborto, malformaciones congénitas, muerte fetal y materna. En humanos, no se pudo determinar los efectos presentados en el estudio en animales. Se concluye que es necesario realizar estudios clínicos para establecer la presencia de efectos adversos en gestantes por el consumo de ivermectina.

Palabras clave. Ivermectina, Seguridad del paciente, Gestación.

INTRODUCTION

The global pandemic of SARS-CoV-2 or Covid-19 has been wreaking havoc on people, especially in the vulnerable population including the elderly, people with chronic comorbidities and pregnant women, who are given medicines such as antibiotics, antiparasitic and antiviral drugs to combat Covid-19 viremia^(1,2). There is no evidence-based medicine related to this medication, running the risk of causing adverse effects⁽³⁾.

ivermectin is an antiparasitic used in animals and humans⁽⁴⁾. It is noted that, in in vitro cell culture, it inhibits the replication of SARS-CoV-2, suggesting further research on its possible benefit in humans⁽⁵⁾. For the U.S. Federal Drug Administration (FDA), its use in people is only approved for the treatment of intestinal strongyloidiasis and onchocerciasis, including topical use on prescription for the treatment of external parasites, such as lice, and skin conditions such as rosacea⁽⁶⁾. This medicine has aroused interest in medical and veterinary websites, which incorrectly describe the drug as treatment or cure for Covid-19. These inappropriate statements led to a warning from the FDA that ivermectin in veterinary products should not be used for human therapy^(7,8).

The FDA has previously classified ivermectin as category C for pregnancy, due to animal reproduction studies that showed adverse effects on the fetus, and there are no adequate and controlled human studies. However, the potential benefits could justify its use in pregnant women despite the potential risks. These studies have shown adverse pregnan-



cy outcomes at cumulative doses high enough to produce signs of maternal toxicity in animals⁽⁹⁾. However, subsequent evidence showed that the mouse strain (CF-1) used in initial studies of acute ivermectin toxicity was inappropriate, as CF-1 mice have poor expression of glycoprotein P, key to the flow pump to prevent ivermectin toxicity⁽¹⁰⁾.

The use of oral ivermectin in pregnant people is questioned, given the massification of its use in Peru in the Covid-19 pandemic. Despite the low level of scientific evidence and after a risk-benefit analysis, the National Institute of Health and EsSalud gave a favorable opinion regarding ivermectin treatment in mild cases with Covid-19 risk factors. However, this proposal indicates its contraindication during pregnancy and breastfeeding^(11,12).

The Ministry of Health reported by the Digemid Alert No. 12 on adverse reactions caused by oral intake of ivermectin, common as dizziness, blurred vision and pain in the abdomen, and less common, diarrhea, headache, fever, hypotension, insomnia, conjunctivitis; included Mazzotti's reaction (rare, but severe) and alterations in the electrocardiogram, myalgias, lymphadenopathies, edema in limbs and face; also, dermal disorders, such as xerosis, burning sensation, erythema, itching, dryness and contact dermatitis⁽¹³⁾.

Taking into account the benefits and risks of conscious or inadvertent administration of ivermectin in pregnancy, it is important to inform all health service providers and decision-makers of public health policy about the therapeutic safety of the said drug. The overall objective of this study was to know the pharmacological safety of ivermectin orally in pregnant women. The specific objectives were the presence of abortion, fetal mortality, congenital malformations in pregnant fetuses that consumed ivermectin. Also, to identify side effects in pregnant women after use of ivermectin.

METHODS

The relevant databases and the registry platforms of randomized clinical trials and observational investigations that indicate adverse events after the consumption of ivermectin in pregnant women and their products of preg-

nancy were reviewed. This search was carried out in PubMed, MEDLINE, Scopus, Toxline, World Health Organization Clinical Trial Registry, US FDA List, ClinicalTrials, and the Cochrane Central Registry, including English, French, Spanish and German languages.

In addition, the CINAHL, EMBASE, LILACS and CUIDEN PLUS platforms were used in the Google Scholar academic search engine and references to the recovered articles were manually reviewed to detect literature not found in the preliminary search. The search period was between January 1990 and June 30, 2020.

As for the search terms, ivermectin or the trade names of stromectol and mectizan, associated with pregnancy, abortion, congenital malformation, stillbirth and adverse effects were applied.

The effects of ivermectin in the context of this review included: miscarriages (death of the embryo and fetus up to the 22nd week of gestation) preterm births (pregnancy before 37 weeks gestation), stillbirths, low birth weight (less than 2 500 grams), congenital abnormalities, and adverse effects on pregnant women following the use of ivermectin, such as weight loss, signs of intoxication, tremor, ataxia and stupor.

In order to establish the quality of the information, a special structure consisting of four distinct elements was proposed, which were referred to as "PICO". This mnemonic code makes it easy to remember the components of the structure: (P) patient or problem of interest: characteristics of the patient or group of patients; characteristics of the problem or condition; (I) intervention: main intervention to consider, therapeutic, preventive, diagnostic, risk exposure, others; (C) comparison intervention: alternative to comparing the main intervention; and, (O) outcomes or results to be assessed: effects of the intervention, in terms of improvement, side effects, others⁽¹⁴⁾.

RESULTS

Human studies on the effects of ivermectin on gestation are scarce. Some research has been published that serve as references and point out that, in experimental animals, ivermectin has harmful effects on pregnant females and their embryos or fetuses. In research on embryofetal development



in mice, rats and rabbits, at oral doses of 0.1 to 1.6 mg/kg/day of ivermectin administered during organogenesis in embryos of pregnant mice, maternal death, and presence of cleft palate, exencephaly was observed in their fetuses. When doses were greater than 6 mg/kg/day, there was presence of wavy ribs and abortion⁽¹⁵⁾.

Recently, the harmful effects of ivermectin on pig trophoblast (pTr) and uterine luminal epithelial cells (pLE) were published in 2019, inhibiting the proliferation of both cells by regulating genes associated with the cell cycle, and inducing pTr and pLE cell apoptosis. Its mitochondrial dysfunction effect was also verified, such as loss of mitochondrial membrane potential and mitochondrial Ca²⁺, overload and generation of reactive oxygen species (ROS) in pTr and pLE cells. Therefore, constant exposure and accumulation of ivermectin can cause abnormal fetal morphogenesis and placentation during the early stages of pregnancy, and it is necessary to establish a complete safety profile for ivermectin and its association with public health in humans and livestock⁽¹⁶⁾.

Regarding the effect of ivermectin on the occurrence of abortions, research conducted by Chipaux et al., in Cameroon, was described in 1993. In a case-control study, they found that miscarriage occurred in 19% of women who inadvertently consumed ivermectin and 13% of women who did not receive ivermectin, obtaining an OR=1.5 with IC95% 0.8 to 2.7, with no significant statistical difference⁽¹⁷⁾. Doumbo et al., in Mali in 1992, in an analytical retrospective study found that miscarriage occurred in 3.7% of pregnant women who consumed ivermectin and 4.3% of those who did not consume it, establishing an OR=0.5 with IC95% 0.1 to 2.4, with no significant difference⁽¹⁸⁾. Pacque et al. reported that miscarriage occurred in 2.5% of pregnant women receiving ivermectin and 3.1% of women who did not consume it, with an OR=0.8 and IC95% 0.3 to 1.9, with no statistically significant difference. It follows that in none of the studies did the use of ivermectin pose a risk of abortion. However, there are methodological biases, as they are self-reported studies and abortions were not confirmed with any diagnostic method.

The subject of congenital malformations was described by Pacque et al., who in Liberia reported that these abnormalities occurred in 2.5% of

pregnant women receiving ivermectin orally and 1.2% of pregnant women who did not consume ivermectin, with an OR=2.1, IC95% 0.8 to 5.6 and $p=0.14$, which rules out the presence of risk⁽¹⁹⁾.

Doumbo et al. found that the frequency of women who received ivermectin during their pregnancy (inadvertently treated during the first trimester) was 17.7% during 1987 and 17.3% during 1988. No differences were found between women exposed and not exposed to inadvertent treatment with ivermectin, considering the frequencies of fetal mortality, newborn mortality and the presence of congenital malformations, not having significant statistical differences, not constituting any risk⁽¹⁸⁾. While Makene et al. found, following the consumption of ivermectin, abnormalities such as splenomegaly and associated changes, commonly expected in areas of high endemicity by malaria⁽²⁰⁾.

There are other studies that included combinations of ivermectin with other antiparasitic, such as albendazole. Such is the case of Gyapong J et al., who described that 14.6% of pregnant women had been inadvertently treated, finding that the relative risk of post-exposure congenital malformation was 1.05 ($p=1.0$), and that two of nine miscarriages found had been exposed to antiparasitic abortions ($p=0.62$)⁽²¹⁾. Ndyomugenyi R et al. observed the presence of congenital abnormalities in 11% of neonates whose mother ingested ivermectin/albendazole, compared with 7% of congenital malformations in mothers who did not consume this combination ($p>0.05$)⁽²²⁾.

It is important to know the effect of ivermectin in postpartum women. Low levels of ivermectin have been found in human breast milk after a single oral dose of 150 to 250 mcg/kg, with a peak at 1 hour after ingestion of 18.5 ng/mL; it even remained detectable in human milk at very low levels up to 14 days after a single dose. This prompted that nursing mothers in the first week after delivery were systematically excluded during deworming campaigns⁽²³⁾.

CONCLUSIONS

The Covid-19 pandemic has led to the widespread use of ivermectin as self-medication, a situation that would involve pregnant women in their first weeks of gestation. Abroad, the FDA, and in Peru, concern has been raised about the



use of ivermectin made for use in animals, assuming that its formula would replace preparations intended for humans. It is recommended that ivermectin be prescribed only by a licensed health professional, and that it has been obtained through legitimate sources⁽²⁶⁾.

Most of the studies reviewed record involuntary exposures to ivermectin, as a result of the annual mass treatment strategy against the transmission of lymphatic filariasis in areas where the disease exists. In Africa, they point out that the use of ivermectin does not harm the pregnant woman or the product of the pregnancy, despite the fact that studies with more scientific evidence present certain selection biases that lead to the search for new reliable scientific evidence⁽¹⁷⁻²¹⁾.

Research in experimental animals establishes the risk of harm in mice, rabbits and pigs, including the hepatotoxic effect of ivermectin in rats⁽²⁴⁾. However, research in humans is controversial. A recent study on the use of ivermectin against malaria indicates probable harmlessness in humans⁽²⁵⁾. However, the study by Foy B et al. warns that care should be taken of the use of ivermectin in the treatment of malaria due to its adverse effects, especially in pregnant women and children⁽²⁶⁾.

Given what has been reviewed in these studies, exclusion criteria for the administration of ivermectin should be taken into account, such as pregnant women, children under 15 kg and women who breastfeed babies under one week of age. This given that there is preclinical evidence of maternal and/or fetal toxicity at very high doses of ivermectin in pregnant mammals. Although some clinical studies, when evaluating the effects of inadvertent treatment of ivermectin during pregnancy, have not observed negative effects on the mother or the newborn^(28,29), exposure to ivermectin could adversely affect pregnancy, especially during the first trimester⁽³⁰⁾. At this stage, women are less likely to reveal their gestation status due to social risk, privacy and doubts, and are therefore potentially more exposed to inadvertent treatment.

For this reason, it is concluded that ivermectin should not be administered to pregnant women or to those women who suspect they are preg-

nant, until new clinical trials are published indicating its safety, given the possibility of abortion, congenital malformations, stillbirth, adverse reactions in the pregnant woman.

REFERENCES

1. Instituto de evaluación de tecnologías en salud e investigación. Reporte breve n° 17 versión 2: Uso de ivermectina para el tratamiento de pacientes con covid-19. Lima. Es-salud: 2020.
2. Ticona E, Saavedra C, Ticona C, Hidalgo A. COVID-19: En este momento podría ser útil el tratamiento antiviral en casos leves. *An Fac med.* 2020;81(1):87-91. DOI: <https://doi.org/10.15381/anales.v81i1.17685>
3. Molina JM, Delaugerre C, Goff JL, Mela-Lima B, Ponscarme D, Goldwirt L, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. *Med Mal Infect.* 2020; pii: S0399-077X(20)30085-8. DOI: 10.1016/j.medmal.2020.03.006
4. Laurence L, Brunton, Bruce A, Chabner, Björn C, Knollmann. Goodman & Gilman: Las Bases Farmacológicas de la Terapéutica. 13ª edición. México: Mc Graw Hill Interamericana. 2019.
5. Caly L, Druce JD, Catton MG, Jans DA. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res.* June 2020;178:104787. <https://doi.org/10.1016/j.antiviral.2020.104787>
6. Bray M, Rayner C, Noël F, Jans D, Wagstaff K. Ivermectin and COVID-19: A report in antiviral research, widespread interest, an FDA warning, two letters to the editor and the authors' responses. *Antiviral Res.* 2020;178:104805. doi:10.1016/j.antiviral.2020.104805
7. Merck Product information Stromectol tablets (ivermectin 3 mg). 2014. <https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2011-PI-02659-3&d=2016071016114622483>
8. Brucker MC, King TL. The 2015 US Food and Drug Administration pregnancy and lactation labeling rule. *J Midwifery Womens Health.* 2017;62:308-16.
9. US Food & Drug Administration. Center for drug evaluation and research: approval package for Mectizan. https://www.accessdata.fda.gov/drugsatfda_docs/nda/96/050742ap.pdf
10. Lankas GR, Wise LD, Cartwright ME, Pippert T, Umbenhauer DR. Placental P-glycoprotein deficiency enhances susceptibility to chemically induced birth defects in mice. *Reprod Toxicol.* 1998;12:457-63.
11. Ministerio de Salud. Documento técnico: prevención, diagnóstico y tratamiento de personas afectadas por COVID 19 en el Perú. RM 193-2020. MINSA. Lima. MINSA. 2020.
12. Ministerio de Salud. Documento Técnico: Manejo ambulatorio de personas afectadas por COVID-19 en el Perú, Lima. MINSA. 2020.
13. Dirección General de Medicamentos, Insumos y Drogas. Alerta Digemid N° 12-2020. Ivermectina: recomendaciones de uso asociadas a infección por COVID-19. MINSA. 2020.



14. Martínez J, Ortega V, Muñoz F. El diseño de preguntas clínicas en la práctica basada en la evidencia: modelos de formulación. *Enferm glob*. 2016 Jul;15(43):431-8. DOI:<https://doi.org/10.6018/eglobal.15.3.239221>
15. DPT Laboratories. Sklice package insert. 2012. [accessed on 2016 Mar 05]. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202736s000lbl.pdf
16. Lee J, Li W, Ham J, Kim J, You S, Song G. Ivermectin induces apoptosis of porcine trophectoderm and uterine luminal epithelial cells through loss of mitochondrial membrane potential, mitochondrial calcium ion overload, and reactive oxygen species generation. *Pesticide Biochem Physiol*. 2019;159:144-53. ID: mdl-31400776
17. Chippaux J, Gardon-Wendel N, Gardon J, Ernoult J. Absence of any adverse effect of inadvertent ivermectin treatment during pregnancy. *Trans R Soc Trop Med Hyg*. 1993 Jun 1;87(3):318-33. [https://doi.org/10.1016/0035-9203\(93\)90146-H](https://doi.org/10.1016/0035-9203(93)90146-H)
18. Doumbo O, Soula G, Kodio B, Perrenoud M. Ivermectin and pregnancy in mass treatment in Mali. *Bull Soc Pathol Exot*. 1992;85:247-51.
19. Pacque M, Munoz B, Poetschke G, Foose J, Greene BM, Taylor HR. Pregnancy outcome after inadvertent ivermectin treatment during community-based distribution. *Lancet*. 1990;336:1486-9.
20. Makene C, Malecela M, Kabali C, Charles E, Swai E, Lekashingo L. Inadvertent treatment of pregnant women in the Tanzanian mass drug administration program for the elimination of lymphatic filariasis. 52nd. Annual Meeting and Centennial Celebration.
21. 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.
22. Ndyomugenyi 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 Hyg*. 2008;79:856-63.
23. Ogbuokiri JE, Ozumba BC, Okonkwo PO. Ivermectin levels in human breastmilk. *Eur J Clin Pharmacol*. 1993;45:389-90.
24. Dadarkar SS, Deore MD, Gatne MM. Comparative evaluation of acute toxicity of ivermectin by two methods after single subcutaneous administration in rats. *Regul Toxicol Pharmacol*. 2007;47(3):257-60. doi:10.1016/j.yrtph.2006.10.009
25. Chaccour C, Rabinovich NR. Ivermectin to reduce malaria transmission II. Considerations regarding clinical development pathway. *Malaria J*. 2017;16:166. <https://doi.org/10.1186/s12936-017-1802-3>
26. Foy B, Alout H, Seaman JA, Rao S, Magalhaes T, Wade M, et al. Efficacy and risk of harms of repeat ivermectin mass drug administrations for control of malaria (RIMDAMAL): a cluster-randomised trial. *Lancet*. 2019;393(10180):1517-26. doi:10.1016/S0140-6736(18)32321-3
27. U.S. Food & Drug Administration. Letter to Stakeholders: Do not use ivermectin intended for animals as treatment for COVID-19 in humans. April 10, 2020. <https://www.fda.gov/animal-veterinary/product-safety-information/fda-letter-stakeholders-do-not-use-ivermectin-intended-animals-treatment-covid-19-humans>
28. The Ivermectin Roadmappers. A roadmap for the development of ivermectin as a complementary malaria vector control tool. *Am J Trop Med Hyg*. 2020;102(2s):3-24. doi:10.4269/ajtmh.19-0620
29. Wilkins AL, Steer AC, Cranswick N, Gwee A. Question 1: is it safe to use ivermectin in children less than five years of age and weighing less than 15 kg? *Arch Dis Child*. 2018 May;103:514-9. doi: 10.1136/archdischild-2017-314505
30. González A, Fernández N, Sahagún A, García J, Tamame P, Sierra M. Seguridad de la ivermectina: toxicidad y reacciones adversas en diversas especies de mamíferos. *Rev MVZ Córdoba*. 2010;15(2):2127-35.