HAL
open science

Antiparasitic treatments in pregnant women: Update and recommendations

E Boitel, Guillaume Desoubeaux

To cite this version:

E Boitel, Guillaume Desoubeaux. Antiparasitic treatments in pregnant women: Update and recommendations. Médecine et Maladies Infectieuses, In press, 10.1016/j.medmal.2018.09.008 . hal-02439523

HAL Id: hal-02439523

https://hal.science/hal-02439523v1

Submitted on 17 Jan 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Médicaments antiparasitaires chez la femme enceinte : actualités et recommandations

Antiparasitic treatments in pregnant women: update and recommendations

E Boitel[1], G Desoubeaux[1,*]

[1]CHU de Tours, Parasitologie – Mycologie – Médecine tropicale, 37044 Tours - France

***Corresponding author**: guillaume.desoubeaux@univ-tours.fr

Service de Parasitologie – Mycologie –Médecine tropicale

Hôpital Bretonneau, Bâtiment B2A 1er étage

2 boulevard Tonnellé

37044 CHU de Tours Cedex 9 - FRANCE

Téléphone : +33(0)2 47 47 39 27

Fax : +33(0)2 47 47 80 82

Mots clés : hypotrophie ; morts fœtales *in utero* ; mutagénicité ; tératogénicité ; paludisme

Keywords: fetal death; low birth weight; mutagenicity; teratogenicity; malaria

RESUME

Les parasitoses constituent une importante cause de morbi-mortalité dans le monde, et plus particulièrement dans les pays à faibles ressources où la prévalence de telles infections est très élevée. Leurs conséquences chez la femme enceinte constituent un problème de santé publique. Savoir maîtriser les infections, souvent associées entre elles, sans risquer de nuire à la grossesse et à l'intégrité du fœtus, représente donc un réel défi pour le thérapeute. Pourtant, en régions tempérées comme tropicales, les vraies révolutions antiparasitaires sont rares et l'arsenal thérapeutique demeure limité. Les informations scientifiques sont lacunaires car les études cliniques incluant des femmes enceintes sont peu nombreuses. Le prescripteur doit donc savoir jongler astucieusement avec les molécules actives à disposition, et connaître les effets embryo- et fœtotoxiques de chacune d'elles. Les pratiques médicales doivent être adaptées au terme de la grossesse et à l'urgence à traiter la mère.

Abstract

Parasitoses are a major cause of morbidity and mortality worldwide, especially in resource-poor countries where the prevalence of such infections is very high. Their consequences for pregnant women are a public health issue. It is very challenging to successfully control parasitic infections with the dedicated drugs, while protecting the fetus from the harmful effects of these medications. However, in both temperate and tropical regions, true antiparasitic innovations are rare, and the therapeutic armamentarium remains limited. Scientific data is incomplete as only a few clinical studies have included pregnant women so far. Therefore, physicians have to learn how to thoroughly handle the antiparasitic molecules available. They also need to know the embryo- and fetotoxic effects of each of them. Medical practices must be adapted to the trimester of pregnancy.

INTRODUCTION

A large part of the world's population is exposed to parasitic infections and several of them may even occur simultaneously. Consequences may be severe for pregnant women but also for the embryo or fetus (1,2). However, dedicated agents are scarce compared with the antibiotics available for pregnant women, and no specific vaccine is available (3). Research and development are limited in this field compared with antiviral drugs. Choosing the right antiparasitic chemotherapy is therefore extremely difficult because, besides cost and availability issues, the chosen chemotherapy must offer the perfect balance between control of the infection and of the drug-related embryotoxic or fetotoxic effects (4). Yet, literature data on the use of antiparasitic drugs in pregnant women is very limited. It is often ethically difficult for investigators and pharmaceutical companies to conduct large-scale clinical trials in this population.

Each parasitic infection used to be treated with specific drugs − most often toxic −, but the few recent agents tend to have a wider spectrum of activity and are overall better tolerated. We aimed to update knowledge on the use of antiparasitic drugs in pregnant women (Table 1).

1. ANTIMALARIAL DRUGS

Malaria is a parasitic infection which mainly occurs in intertropical regions. It is caused by erythrocytic protozoa of the *Plasmodium* genus, and the virus is transmitted by *Anopheles* mosquito bites. *P. falciparum* and to a lesser extent *P. vivax* are the only species with a real impact on pregnancy outcome (5). Malaria contracted during pregnancy is associated with a two- or three-fold increased risk of maternal anemia and severe presentations such as cerebral malaria (6). Consequences for the embryo and fetus are due to placental parasitism. The placenta loses its integrity and no longer ensures normal transplacental exchange (nutrients and oxygen). This results in a low birth weight, especially in newborns with primigravida or secundigravida mother (7). Malaria is therefore responsible for 14% of low birth weight cases worldwide. The outcome is often unfavorable as an estimated 200,000 infants die every year due to the consequences of maternal malaria contracted during pregnancy (5).

a. Aminoquinolines

i. 4-aminoquinolines

This class includes chloroquine (Nivaquine®); an old and well-absorbed product after oral administration. Its schizonticidal action relies on its alkaline properties which favor its

accumulation in the endocytic vacuole of the intraerythrocytic parasite. Inside the vacuole, chloroquine blocks the elimination of toxic heme residuals, especially ferriprotoporphyrin IX. The latter can thus no longer be metabolized into hemozoin, i.e. the soluble pigment (8).

Blood levels of chloroquine in the umbilical cord are equivalent to those of the mother. High doses of chloroquine are responsible for teratogenic effects in animal models. However, its use in humans does not induce spontaneous abortion nor does it induce the *in utero* death of the fetus or malformations (9). The structure of amodiaquine (Flavoquine®) is close to that of chloroquine. It does not induce severe toxicity for the embryo or fetus, but it is still poorly used because of its hepatic toxicity and myelotoxicity (10). Pyronaridine is quite similar to amodiaquine. It is used in combination with an artemisinin derivative (Pyramax®), but it has been shown toxic for the embryo in rats (11).

Chloroquine may be administered to pregnant women, irrespective of the pregnancy trimester. As a curative treatment, it can be administered without any restriction at a dose of 10 mg/kg on the first day, 10 mg/kg on the second day, and 5 mg/kg on the third day to treat uncomplicated malaria episodes caused by non-*P. falciparum Plasmodium* species.

ii. 8-aminoquinolines

Primaquine is an 8-aminoquinoline prescribed for the prevention of *P. vivax* and *P. ovale* malaria relapses. Primaquine is able to eradicate quiescent parasitic forms in the liver. It is readily absorbed from the gastrointestinal tract. It is contraindicated in pregnant women as it is responsible for severe hemolytic anemia.

b. Alkanolamines

i. Natural alkanolamines

Quinine (Quinimax®, Surquina®, Quinine Lafran®) is an alkaloid extracted from the bark of cinchona trees, with moderately rapid schizonticidal properties. Quinine is rapidly absorbed from the oral route, although with low transplacental passage. Ocular and hearing impairments have been reported in children whose mother had received high doses of quinine. Supratherapeutic doses of quinine are misused because of its oxytocic properties, which lead to using the drug as an abortion drug especially in women presenting with contractions.

Quinine remains the first-line treatment of uncomplicated *P. falciparum* episodes during the first trimester of pregnancy (12). Its daily dosage is 25 mg/kg divided into three intakes, for seven days.

ii. Synthetic alkanolamines

Mefloquine (Lariam®) is readily absorbed from the oral route. Experimental studies performed in pregnant rats revealed that very high doses of mefloquine had a fetotoxic effect. In humans, mefloquine has long been suspected of increasing the risk of spontaneous abortions and *in utero* death of the fetus, even at low doses (13). However, a study monitoring the pregnancy of military women who were first unaware of their pregnancy and were inadvertently exposed to mefloquine, did not reveal any significant increase in fetal malformations (14). A larger scale retrospective study, based on the analysis of pregnancies from 1986 to 2010, did not report an increased incidence of malformations nor an increased rate of spontaneous abortions (15).

Mefloquine can therefore be used alone as a prophylactic treatment, irrespective of the number of weeks of amenorrhea (12). In such cases, the dosage is 250 mg every week (taken with food). Treatment must be continued for three weeks following return home. The curative treatment with mefloquine is prescribed to patients presenting with uncomplicated *P. falciparum* malaria only, when quinine is contraindicated (12). Its dosage is 25 mg/kg over one day only, divided into two intakes of 15 mg/kg followed by 10 mg/kg 12 hours later or into three intakes of 8 mg/kg every 6-8 hours.

Lumefantrine is an alkanolamine derivative associated with arthemeter, which is derived from artemisinin (Riamet®). Lumefantrine is indicated, during the second and third trimesters of pregnancy, in the curative treatment of uncomplicated malaria episodes. Its dosage is 80 mg twice daily for three consecutive days, combined with 480 mg of arthemeter twice daily. Halofantrine (Halfan®), another synthetic alkanolamine, is no longer commercialized in France since 2016. It was contraindicated in pregnant women because of its embryotoxicity.

c. Inhibitors of folic acid synthesis

Inhibitors of folic acid synthesis include antifolic drugs of the sulfonamide class such as sulfadoxine, and antifolates such as proguanil and pyrimethamine. Inhibitors of folic acid inhibit the dihydropteroate synthase while antifolates block the dihydrofolate reductase, which are both essential for the nucleic acid synthesis of the parasite.

Sulfonamides have a good transplacental diffusion. For instance, plasma levels of sulfadoxine in fetuses are comparable to those observed in mothers. A teratogenic effect has been observed in animals, although never confirmed in humans. However, sulfonamides have the

capacity to move bilirubin binding sites which can induce nuclear jaundice in fetuses, especially with products with a long half-life such as sulfadoxine. Administering sulfonamides at the end of pregnancy in case of congenital glucose-6-phosphate dehydrogenase deficiency is associated with a risk of neonatal hemolysis.

Pyrimethamine is associated with a very good transplacental passage as its serum concentration in fetuses is 50% to 100% that of the mother (16). Pyrimethamine administration during the first trimester of pregnancy has been associated with teratogenic effects in animals. Proguanil can be safely used, irrespective of the pregnancy term.

To prevent congenital malaria in endemic areas, it is recommended to initiate an intermittent preventive treatment (IPT) based on the combination of sulfadoxine and pyrimethamine (Fansidar®) administered three times one month apart, from Week 16 of amenorrhea (17). Folic acid administration during pregnancy at the dosage of 0.4 mg daily (18) or folinic acid administration at the dosage of 3-5 mg three times a week (19), remains beneficial to prevent congenital disorders as well as cytopenia in mothers.

d. Cyclins

The gastrointestinal absorption of cyclins is incomplete, but they do cross the feto-placental barrier. Whether for a prophylactic or a curative use, cyclins such as doxycycline (Vibramycine®) are not recommended in pregnant women beyond the first trimester. They may induce a coloration of the unborn child's deciduous teeth when administered for at least 15 days. When cyclins must imperatively be administered, the prophylactic dosage is 100 mg of doxycycline daily for the whole duration of the stay in a malaria-endemic area. Daily intakes must be continued for one month following return in the home country.

e. Artemisinin derivatives

Artemisinin derivatives are sesquiterpene lactones isolated from a plant called *Artemisia annua*. They are very fast-acting schizonticidal antimalarial drugs. They act at the parasite's food vacuole level by binding to the heme and inducing an oxidative stress which triggers the release of free radicals toxic for the parasite (20).

Artemisinin derivatives are embryotoxic for the heart and are responsible for skeletal malformations in various animal species. Studies of pregnant rats demonstrated harmful effects on the yolk bag which induced hematopoietic disorders in embryos. Exposure to higher doses of artemisinin derivatives decreased the angiogenesis which could lead to the *in utero* death of the fetus by hypoxia or to spontaneous abortion (21). A study performed with monkeys is currently ongoing to understand the mechanisms of this toxicity (22). However, the study of a very limited number of pregnant women accidentally exposed to artemisinin-based treatments during their first trimester did not show any major teratogenic effect (23). More exhaustive data is available for the second and third trimesters with bioclinical data from more than 4,000 pregnant women. These findings indicated that the use of artemisinin derivatives did not increase the rate of adverse events, both for the mother and fetus (23).

Artemisinin derivatives are indicated in the treatment of uncomplicated malaria when orally administered as part of a combination with piperaquine (Eurartesim®) or lumefantrine (Riamet®), but also in the treatment of complicated *P. falciparum* malaria (as injections) in pregnant women at the second and third trimesters of pregnancy. Artemisinin derivatives may also be urgently administered during the first trimester of pregnancy. The reference

treatment for severe malaria is parenteral artesunate in monotherapy (Malacef®, temporary marketing authorization in France) at the daily dosage of 2.4 mg/kg for seven days, except the first day as the dosage needs to be multiplied by three on that day (12).

f. Other antimalarial drugs

Atovaquone is an inhibitor of the pyrimidine biosynthesis. It is used as part of a two-drug combination with an antifolate: proguanil (Malarone®). Atovaquone targets the parasite's mitochondrion where it blocks the electron transfer chain at a key enzyme level (dihydroorotate reductase), as well as the cytochrome b1 complex replacing ubiquinone. This process results in the inhibition of the mitochondrial respiratory chain.

Atovaquone has sometimes been associated with embryotoxicity in animals, but the mechanism of action remains unknown and disputed. Clinical data in pregnant women is very reassuring. The atovaquone-proguanil combination may be suggested as a curative treatment at the daily dosage of 1,000 mg of atovaquone and 400 mg of proguanil for three consecutive days. Tablets must be taken with high-fat food. Its prophylactic use is also possible in pregnant women, when the travel cannot be delayed and when the visited area is highly endemic for malaria (12). The daily dosage is in that case one tablet containing 250 mg of atovaquone and 100 mg of proguanil. Treatment must be continued daily up to one week following return home.

2. ANTI-*TOXOPLASMA* DRUGS

Toxoplasmosis is a worldwide parasitic infection caused by the protozoa *Toxoplasma gondii*. It is orally transmitted from soiled water or plants or from undercooked meat. Clinical presentations in pregnant women are similar to those observed in any other adult (24). The mother-to-fetus transmission risk is directly related to the placental characteristics: the more permeable the placenta during pregnancy, the more likely the transmission of parasitic vegetative forms. Conversely, the congenital infection severity is higher when occurring at the early stage of pregnancy (25). The prognosis is often very poor, with spontaneous abortion, *in utero* fetal death, or severe malformations characterized by hydrocephalus, intracranial calcifications, retinochoroiditis, and various organogenesis disorders (24).

a. Macrolides

Spiramycin (Rovamycine®) is a macrolide with a parasitostatic action against vegetative forms of *Toxoplasma*, probably due to its metabolites produced in vivo. Spiramycin does not cross the feto-placental barrier and its safety has already been proven.

Although its efficacy is disputed (26), spiramycin is indicated in the antenatal prevention of congenital toxoplasmosis in women contaminated during pregnancy. The recommended dosing regimen is 3 million of units three times a day until delivery or until the congenital infection is confirmed.

b. Inhibitors of folic acid synthesis

Antifolic agents and antifolates are prescribed to pregnant women with confirmed congenital transmission (27). Even in the absence of well-conducted head-to-head clinical

trial (28,29), the pyrimethamine-sulfadiazine combination is still the most widely used to treat *in utero* congenital toxoplasmosis (30). The daily dosing regimen until delivery is 1 mg/kg for pyrimethamine and 100-150 mg/kg for sulfadiazine (31).

3. ANTILEISHMANIAL DRUGS

Visceral leishmaniasis is a severe parasitic infection observed in warm areas and associated with poor prognosis. The causative agent − *Leishmania* spp. − is transmitted to humans through the bites of sandflies. Clinical presentations in pregnant women are similar to those of any other infected individual (32). The risk of congenital transmission is low. Newborns usually develop signs of infection within the first 18 months of life (33).

a. Antimonial drugs

The class of pentavalent antimonials includes two drugs with similar efficacy: meglumine antimoniate (Glucantime®) and sodium stibogluconate (Pentostam®). Antimonial drugs acquire their in vivo activity following reduction with acid pH and high temperature. They are thus more active against intracellular presentations of leishmaniasis (32) as they can induce the reduced synthesis of ATP.

Antimonial drugs are able to cross the feto-placental barrier. A study conducted in pregnant rats did not report any adverse event in female rats but did report a higher lethality among embryos. A lower lethality was observed with a single administration of a high dose rather than repeated administrations − even at low doses. With the single administration, the antimony is preserved in only one compartment with a rapid elimination phase while

repeated administrations are associated with antimony conservation in two compartments including one with a slow elimination phase which is responsible for toxic accumulation (34). The authors of an animal study using dosages only 15 to 30 times higher than those used in humans, reported an increased rate of bone malformations and a lower fetal weight. Antimony derivatives also penetrate into the neural tissues of fetuses and may induce severe learning disability (35). The use of antimonial drugs at the early stage of pregnancy may highly impair the embryo development especially as treatment for visceral leishmaniasis usually requires daily administrations of high doses (70 mg/kg) for a month. Meglumine antimoniate and sodium stibogluconate may be prescribed from the end of the third month of pregnancy, but less toxic alternatives must be considered to treat visceral leishmaniasis.

b. Pentamidine

Pentamidine isethionate (Pentacarinat®) is a stable diamidine with a mechanism of action still not entirely understood. It is believed to inhibit the parasitic DNA synthesis by blocking the thymidine-synthetase following binding to the transfer RNA (36).

Pentamidine is able to cross the feto-placental barrier of female rats. At the end of gestation, it reaches cerebral concentrations in fetuses close to those observed in maternal serum. It is also observed at significant levels in the liver and renal tissues of baby rats. The placental transfer of pentamidine has never been studied in pregnant women (37). First-trimester miscarriages have been reported with pentamidine aerosol administration in other indications.

Usually prescribed as a short-term treatment at the dosage of 3-4 mg/kg every two or three days for two weeks, pentamidine is not recommended as the first-line treatment of

leishmaniasis in pregnant women, unless its use is essential. Such scenario is not very likely as alternatives are available with amphotericin B.

a. Amphotericin B

Amphotericin B is a lipophilic polyunsaturated organic compound of the polyenes family. It binds to the precursors of ergosterol of the *Leishmania* cell membrane, leading to an increased permeability through which ions leak out of the cell, and to the membrane lysis (38).

The molecule is able to cross the feto-placental barrier, but the fetal blood level does not exceed a third of the maternal blood level (32). Standard amphotericin B deoxycholate (Fungizone®) has been administered to animals at experimental doses up to 10 times higher than those used in humans. No teratogenicity has been observed, including during the first trimester of gestation. No lethality for the embryo or toxicity for the fetus has so far been observed in clinical studies of pregnant women (32). A few cases of moderate and transitory renal failure leading to a decreased amount of amniotic fluid have been reported with the administration of amphotericin B deoxycholate at the end of pregnancy. The authors of a head-to-head study did not report any significant increase in spontaneous abortions or malformations with the administration of lipid formulations of amphotericin B (39).

Liposomal amphotericin B (AmBisome®) is currently the first-line treatment of visceral leishmaniasis in pregnant women. It can be used at the dosage of 3 mg/kg per day for five consecutive days, followed by a sixth injection on day 10.

4. ANTI-HUMAN AFRICAN TRYPANOSOMIASIS (HAT) DRUGS

Trypanosomiasis is a severe parasitic infection due to flagellate protozoa of the *Trypanosoma* genus. They are transmitted by arthropods. Human African trypanosomiasis (HAT), also known as sleeping sickness, is caused by *Tr. brucei gambiense* or *Tr. brucei rhodesiense.* It is responsible for subacute neurological and psychiatric signs and may also lead to mother-to-fetus transmission (40) (41). The impact on pregnancy is an increase in spontaneous abortions, neonatal mortality, or premature births (42), but also an increased incidence of hydramnios or pre-eclampsia cases. Congenital presentations are responsible for severe and irreversible neurological disorders in newborns as well as for hydrocephalus (43). The American presentation of trypanosomiasis, known as Chagas disease, is caused by the *Tr. cruzi* species (44). Mothers present with the same symptoms − although more severe − as the ones observed in any other adult: cardiac diseases, megacolon, or achalasia. Congenital infections in newborns may present as a clinical manifestation with fever, jaundice, edema, hemorrhages, hepatomegaly, and possible cardiac and neurological disorders.

a. Suramin

Suramin sodium (Moranyl®) is believed to have a trypanocidal action against African *Trypanosoma* via the morphological impairment of the intracellular components of the membrane. It impacts the absorption and intralysosomal digestion of proteins.

Congenital malformations have been observed in pregnant rats (45). Suramin sodium is currently indicated in the treatment of HAT caused by *Tr. b. rhodiense* during the first stage of the infection, known as the hemolymphatic phase. Although theoretically contraindicated

in pregnant women, it may be administered at the dosage of 20 mg/kg via slow intravenous injections every five to seven days when mothers incur high risks at the neurological phase of the infection.

b. Pentamidine

Pentamidine isethionate may be used to treat the mother and to reduce the vertical transmission risk during *Tr. b. gambiense* infection at the hemolymphatic phase. However, its use is only recommended after the first trimester because of the abortive action of the drug (43). Pregnant women presenting with neurological presentations of *Tr. b. gambiense* infection may, however, receive pentamidine without any restriction and irrespective of the pregnancy stage. The expected benefit overcomes the risk incurred by the fetus. The recommended dosing regimen is 7 to 10 intramuscular injections of 4 mg/kg every day or every other day (46).

c. Eflornithine

Alpha-difluoromethylornithine, or eflornithine (Ornidyl®), has a trypanostatic action (47). Alpha-difluoromethylornithine has a slow mechanism of action based on its structural analogy with ornithine, leading to the inhibition of ornithine decarboxylase and of the cell division cycle. Eflornithine is more active against *Tr. b. gambiense* than *Tr. b. rhodesiense,* probably because the cycle of ornithine in *Tr. b. rhodesiense* is too rapid (48).

Eflornithine was found toxic for the embryo and the fetus in pregnant animal models. It was associated with growth retardation and central nervous system impairment in fetuses. The

topical use of eflornithine in pregnant women presenting with facial hirsutism was associated with spontaneous abortions, but the study lacked power to conclude on a real effect (49).

The use of eflornithine alone is possible in pregnant women, especially when the mother's general status is moderately or highly impaired (50). The recommended dosing regimen is one intravenous injection of 100 mg/kg every six hours for 14 days. At the end of the treatment cycle, the cure rate is approximately 97% (51).

d. Melarsoprol

Melarsoprol (Arsobal®) is a highly toxic organic arsenic compound. It is currently only indicated at the neurological phase of *Tr. b. rhodesiense* HAT and at the advanced stages of *Tr. b. gambiense* presentations in case of relapse following an initial treatment with eflornithine. Melarsoprol cannot be used in pregnant women. Treatment must be delayed until the mother has given birth, or it must be based on another HAT drug such as pentamidine.

e. Other American trypanosomiasis drugs

Benznidazole (Radanil®), a nitroimidazole derivative, and nifurtimox (Lampit®), a nitrofuran derivative, are two trypanocidal drugs with a temporary marketing authorization in the treatment of Chagas disease.

They are readily absorbed from the digestive route. They are not officially contraindicated in pregnant women, except at the first trimester. After the first trimester, they can only be

used when absolutely essential because of the medullary and neurological toxicity of benznidazole and because of severe digestive, neuropsychiatric, and neurological disorders associated with nifurtimox.

5. ANTHELMINTICS

Helminthiases are parasitic infections caused by various species of worms. Carriage may have a major indirect impact on pregnancy. For instance, hookworms are duodenal roundworms feeding from the abrasion of the digestive mucous membrane. They are associated with blood loss resulting in iron deficiency anemia. Besides anemia, trichuriasis is responsible for dysenteric symptoms. Helminthiases are associated with deficiencies, which in turn increase the risk of premature birth or low birth weight (52).

a. Benzimidazole derivatives

i. Nematicides

The benzimidazole family includes albendazole (Zentel®), mebendazole (Vermox®) and its fluorinated derivative, i.e. flubendazole (Fluvermal®). Benzimidazoles act on the cytoskeleton of helminths by inhibiting the polymerization of tubulins and their incorporation into the microtubules (53). This phenomenon induces a decreased release of neuromuscular mediators and interferes with the absorption of glucose. The parasite is thus paralyzed. It can then be passively eliminated in stools. Benzimidazoles are mainly nematicide − especially against hookworms, roundworms, whipworms, and oxyuris − and to a lesser extent trematocidal and cestocidal.

Benzimidazoles have low bioavailability or even non-existent bioavailability for flubendazole. Preclinical studies of animal models showed that these derivatives may have a teratogenic effect. For instance, when administered at the pre-implantation phase, albendazole was associated with a decreased bovine embryonic cell division capacity (54). At the organogenesis phase, its prolonged use in pregnant rats was associated with skeleton impairment at concentrations close to those used in humans. Mebendazole and flubendazole were always associated with teratogenic effects and embryonic lethality at high doses, respectively (55,56). At intermediate doses, flubendazole was responsible for malformations mainly impairing the eyes and neurological development. Published data on pregnant women exposed to albendazole during the first trimester is scarce. However, no safety signal has been reported so far. Data on the use of albendazole during the second and third trimesters of pregnancy is reassuring. At therapeutic doses, a randomized controlled study did not report any teratogenic effect of mebendazole in pregnant women at 10 weeks of amenorrhea (57). Flubendazole has been extensively used and no safety signal has so far been reported.

Flubendazole may be used in pregnant women, irrespective of the stage and even at the first trimester. Albendazole and mebendazole may be prescribed without any restriction during the last two trimesters of pregnancy, but they are usually administered as a second-line treatment during the first trimester. The recommended dosing regimen for flubendazole is 200 mg daily for three days. For the particular cases of oxyuriasis, the recommended regimen is a single dose of 100 mg to be repeated two or three weeks later. The recommended regimen for albendazole is a single dose of 400 mg, except for trichocephalosis which requires two administrations of the initial dose and for some larval cestodiases such as echinococcosis or cysticercosis requiring 15 mg/kg per day for 15-30

days. Mebendazole has a temporary marketing authorization. It must preferably be taken without food as a single dose of 500 mg for ascaridiosis, and 100 mg twice daily for three days for ankylostomosis and trichocephalosis. Oxyuriasis may be treated with 100 mg of mebendazole, but the administration must be repeated two or three weeks later. For the particular cases of larval cestodiasis, the dosing regimen of mebendazole is 4.5 g per day divided into three daily intakes for six months.

ii. Trematocides

Triclabendazole (Egaten®) is indicated in trematode infections such as *Fasciola hepatica* or *F. gigantica* fascioliasis at the single dose of 10 mg/kg following food ingestion. No teratogenic effect has been observed in preclinical studies of pregnant rats and rabbits. As a precaution, triclabendazole must only be used in pregnant women when absolutely necessary and preferably after the first trimester.

b. Pyrantel

Pyrantel pamoate (Combantrin®) is mainly active against nematodes. Just like an acetylcholine agonist, although 100 times more efficient, pyrantel is able to activate the parasite's nicotinic receptors in the long-term. This leads to a neuromuscular inhibition and induces spastic paralysis. Worms are then eliminated through intestinal peristalsis (58).

In animals pyrantel is poorly absorbed and is not teratogenic. Very few clinical studies have been performed in humans to assess its potential toxic effects during pregnancy. It has, however, been used for many years in the mass treatment of hundreds of millions of people,

including pregnant women. One may thus assume that there is no major risk associated with its use.

Pyrantel is indicated in the treatment of oxyuriasis, ascariasis, and hookworm infections. The usual dosing regimen is 10-12 mg/kg, that should be repeated two or three weeks later in case of oxyuriasis. Hookworm infections must be treated with the daily dosage of 20 mg/kg for two or three days.

c. Avermectins

Avermectin derivatives are generated as fermentation products by *Streptomyces avermitilis*. They have potent anthelmintic and acaricidal-insecticidal properties mainly against nematodes. They bind to glutamate-gated chloride channels in invertebrate nerve and muscle cells. Membrane permeability to chloride ions is thus increased, leading to the definitive hyperpolarization of the cell. The worm is thus paralyzed and dies.

The repeated use of avermectins at high doses in pregnant animals was associated with fetal toxicity on the central nervous system and with cleft palate occurrences. However, in humans, the accidental exposure to avermectins of more than 200 pregnant women during the first trimester of pregnancy was not associated with increased embryotoxic effects or malformations (59).

Ivermectin (Stromectol®) is the most frequently used drug among the avermectin family. It is indicated in the treatment of nematosis, but its action is quite varied, and its use is particularly interesting in endemic areas. The massive prescriptions of ivermectin during mass campaigns to women with unknown pregnancy were not associated with any specific adverse event. However, the WHO does not recommend its use in pregnant women as a

systematic chemoprevention of helminthiases as clinical studies evaluating its safety are not robust enough (60). However, ivermectin may be used as a curative treatment if its prescription is absolutely required, irrespective of the pregnancy term. The recommended dosing regimen is 200 µg/kg as a single dose to be taken without food.

d. Praziquantel

Praziquantel (Biltricide®) is a compound of the pyrazinoisoquinolines family active against various genuses of trematodes, and mainly against all species of *Schistosoma* (61). The drug induces the contraction of the parasites, resulting in paralysis in the contracted state. Praziquantel increases the permeability of the membranes of schistosome cells towards calcium ions, leading to hyperpolarization and paralyzing contraction of the helminth which is then dislodged from the host's tissues. The increased permeability towards calcium induced by praziquantel also leads to the vacuolation of the worm's membrane. It kills both adult and larval stage worms.

Praziquantel is readily absorbed from the oral route. No mutagenic, toxic, or teratogenic effect has been observed in animal models. A randomized double blind clinical trial of pregnant women between 12 and 16 weeks of amenorrhea did not report any increased risk of *in utero* fetal death or spontaneous abortion, nor any congenital malformation or low birth weight (62). A study performed in Uganda demonstrated the safety of praziquantel during the second trimester and at the beginning of the third trimester of pregnancy (63).

Besides for treating schistosomiasis, praziquantel is indicated in the management of tropical fascioliasis with three doses of 25 mg/kg over 24 hours. Praziquantel is also used as the first-line one-dose treatment of intestinal teniasis. This use is, however, off-label and must be

avoided during the first trimester of pregnancy: the recommended dosing regimen is 10 mg/kg. It must be taken with fluid and food or just after food ingestion. The recommended dosing regimen is 20 mg/kg in case of bothriocephalosis or teniasis caused by *Hymenolepis nana*. Cysticercosis usually requires a long-term treatment with high doses of praziquantel: 45 to 60 mg/kg per day divided into three fractionated intakes for 14 days. This dosing regimen is *a priori* contraindicated in pregnant women except for severe clinical presentations.

e. Niclosamide

Niclosamide (Trédémine®) is only active against adult tenia and is inactive against larval stage worms. It blocks the citric acid cycle of the parasite, thus impairing the worm metabolism and making it more vulnerable to proteolytic enzymes of the host. Tenia then dies inside the host's intestine (58).

Niclosamide is poorly absorbed from the oral route. Preclinical studies demonstrated that niclosamide was not associated with mutagenic, teratogenic, or embryotoxic effects. Such effects have also not been observed with therapeutic doses in humans.

Niclosamide is currently used as the second-line treatment of teniasis, following praziquantel (64). The treatment is administered over one day: fasting pregnant women must chew very slowly 1 gram of niclosamide and must renew the intake one hour later. Patients cannot drink nor eat in the following three hours of the last intake. In particular cases of *H. nana* infection, the daily dose is four tablets on the first day to be taken with food and with acid fruit juice, followed by two tablets at the end of meals for a week.

6. ANTIAMOEBIC DRUGS AND OTHER DIGESTIVE ANTIPARASITIC DRUGS

Consequences of a parasitic infection caused by a digestive protozoan in mothers are overall less severe than those of helminthiasis.

a. Imidazoles

Metronidazole (Flagyl®) is the most frequently used drug among the 5-nitroimidazole derivatives. Metronidazole reduction, in anaerobic condition, results in the formation of an intermediate body that binds to the DNA and proteins of the protozoan. This phenomenon inhibits the nucleic acid synthesis.

Niclosamide is almost entirely absorbed from the oral route. Metronidazole has a well-known mutagenic action against various animal species but disputed in humans based on extensive reassuring data available in pregnant women exposed to metronidazole. Metronidazole can therefore be used in pregnant women irrespective of the pregnancy term, although with caution during the first trimester. It is indicated in the treatment of amoebiasis at the dosage of 20-30 mg/kg per day divided into three daily intakes with food, for 7 to 10 days. Shorter treatment durations are possible to treat giardiasis or trichomoniasis. Alternatives with second-generation products, prescribed at the oral dose of 2 grams as a one-dose treatment, such as tinidazole (Fasigyne®) or secnidazole (Secnol®), or injectable drugs such as ornidazole (Tiberal®) may be considered after the first trimester. Although no teratogenic effect has been reported in animal models, data is currently scarce to recommend this treatment in a first-line setting.

b. Benzimidazoles

Albendazole may be prescribed to treat giardiasis patients who do not respond to a 5-nitroimidazole-based treatment (65).

c. Aminoglycosides

Paromomycin (Humagel®) is a topical aminoglycoside with partial efficacy against cryptosporidiosis. It only has a temporary marketing authorization and is contraindicated in pregnant women.

d. Inhibitors of folic acid synthesis

The combination of sulfamethoxazole-trimethoprim (Bactrim®), at the dosage of 800 mg - 160 mg four times a day for 10 days, is effective against some coccidia such as *Cyclospora cayetanensis* and *Cystoisospora belli.*

e. Nitrothiazoles

Nitazoxanide (Alinia®) has a temporary marketing authorization and has been proved effective in controlling the parasitic load during intestinal cryptosporidiosis at the daily dose of 1 to 2 gram(s) (65). This drug must be used with caution in pregnant women because of the lack of hindsight and studies performed in this population (66).

CONCLUSION

The management of parasitic infections in pregnant women is difficult because of data scarcity and lack of power of current guidelines. The analysis of literature data published over the past decades highlights the numerous remaining uncertainties. Numerous pieces of data cannot be used because of the poor methods used in the initial clinical studies and because of the small number of pregnant women included in the studies. The example of mefloquine, which safety in pregnant women was discovered inadvertently, highlights that the choice of antiparasitic drugs is rather based on acquired experience than robust experimental data. The benefit-risk ratio associated with the prescription of an antiparasitic drug in case of a fatal infection is evaluated based on the severity and on the life-threatening risk incurred by the mother, and sometimes despite the associated consequences for the unborn child.

CONTRIBUTION OF AUTHORS

EB collected the data and performed the literature review. GD wrote the article and supervised the work.

DECLARATION OF INTERESTS

The authors declare no competing interests. This article was written based on the thesis of Emmanuelle Boitel.

FUNDING

The authors did not receive any funding.

REFERENCES

1. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller A-B, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014 Jun;2(6):e323-333.

2. Alkema L, Chou D, Hogan D, Zhang S, Moller A-B, Gemmill A, et al. Global, regional, and national levels and trends in maternal mortality between 1990 and 2015, with scenario-based projections to 2030: a systematic analysis by the UN Maternal Mortality Estimation Inter-Agency Group. Lancet. 2016 Jan 30;387(10017):462–74.

3. Liu LX, Weller PF. Antiparasitic drugs. N Engl J Med. 1996 May 2;334(18):1178–84.

4. Médicaments et grossesse - ANSM : Agence nationale de sécurité du médicament et des produits de santé [Internet]. [cited 2017 Jul 5]. Available from: http://ansm.sante.fr/Dossiers/Medicaments-et-grossesse/Medicaments-et-grossesse/(offset)/0

5. Martínez-Espinosa FE, Daniel-Ribeiro CT, Alecrim WD. Malaria during pregnancy in a reference centre from the Brazilian Amazon: unexpected increase in the frequency of Plasmodium falciparum infections. Mem Inst Oswaldo Cruz. 2004 Feb;99(1):19–21.

6. Starr M. Malaria affects children and pregnant women most. BMJ. 2000 Nov 18;321(7271):1288.

7. Nosten F, ter Kuile F, Maelankirri L, Decludt B, White NJ. Malaria during pregnancy in an area of unstable endemicity. Trans R Soc Trop Med Hyg. 1991 Aug;85(4):424–9.

8. Moreau S, Prensier G, Maalla J, Fortier B. Identification of distinct accumulation sites of 4-aminoquinoline in chloroquine sensitive and resistant *Plasmodium berghei* strains. Eur J Cell Biol. 1986 Dec;42(2):207–10.

9. Phillips-Howard PA, Wood D. The safety of antimalarial drugs in pregnancy. Drug Saf. 1996 Mar;14(3):131–45.

10. Brasseur P, Guiguemde R, Diallo S, Guiyedi V, Kombila M, Ringwald P, et al. Amodiaquine remains effective for treating uncomplicated malaria in West and Central Africa. Trans R Soc Trop Med Hyg. 1999 Nov 1;93(6):645–50.

11. Croft SL, Duparc S, Arbe-Barnes SJ, Craft JC, Shin C-S, Fleckenstein L, et al. Review of pyronaridine anti-malarial properties and product characteristics. Malar J. 2012 Aug 9;11:270.

12. Guidelines for the treatment of malaria [Internet]. 3rd ed. Geneva: World Health Organization; 2015 [cited 2017 Jul 5]. (WHO Guidelines Approved by the Guidelines Review Committee). Available from: http://www.ncbi.nlm.nih.gov/books/NBK294440/

13. Nosten F, Vincenti M, Simpson J, Yei P, Thwai KL, de Vries A, et al. The effects of mefloquine treatment in pregnancy. Clin Infect Dis Off Publ Infect Dis Soc Am. 1999 Apr;28(4):808–15.

14. Smoak BL, Writer JV, Keep LW, Cowan J, Chantelois JL. The effects of inadvertent exposure of mefloquine chemoprophylaxis on pregnancy outcomes and infants of US Army servicewomen. J Infect Dis. 1997 Sep;176(3):831–3.

15. Schlagenhauf P, Blumentals WA, Suter P, Regep L, Vital-Durand G, Schaerer MT, et al. Pregnancy and fetal outcomes after exposure to mefloquine in the pre- and periconception period and during pregnancy. Clin Infect Dis Off Publ Infect Dis Soc Am. 2012 Jun;54(11):e124-131.

16. McLeod R, Mack D, Foss R, Boyer K, Withers S, Levin S, et al. Levels of pyrimethamine in sera and cerebrospinal and ventricular fluids from infants treated for congenital toxoplasmosis. Toxoplasmosis Study Group. Antimicrob Agents Chemother. 1992 May;36(5):1040–8.

17. Kayentao K, Garner P, van Eijk AM, Naidoo I, Roper C, Mulokozi A, et al. Intermittent preventive therapy for malaria during pregnancy using 2 vs 3 or more doses of sulfadoxine-pyrimethamine and risk of low birth weight in Africa: systematic review and meta-analysis. JAMA. 2013 Feb 13;309(6):594–604.

18. Hernández-Díaz S, Werler MM, Walker AM, Mitchell AA. Folic acid antagonists during pregnancy and the risk of birth defects. N Engl J Med. 2000 Nov 30;343(22):1608–14.

19. van der Ven AJ, Schoondermark-van de Ven EM, Camps W, Melchers WJ, Koopmans PP, van der Meer JW, et al. Anti-toxoplasma effect of pyrimethamine, trimethoprim and sulphonamides alone and in combination: implications for therapy. J Antimicrob Chemother. 1996 Jul;38(1):75–80.

20. Park BK, O'Neill PM, Maggs JL, Pirmohamed M. Safety assessment of peroxide antimalarials: clinical and chemical perspectives. Br J Clin Pharmacol. 1998 Dec;46(6):521–9.

21. Clark RL, White TEK, A Clode S, Gaunt I, Winstanley P, Ward SA. Developmental toxicity of artesunate and an artesunate combination in the rat and rabbit. Dev Reprod Toxicol. 2004 Dec;71(6):380–94.

22. Ward SA, Sevene EJP, Hastings IM, Nosten F, McGready R. Antimalarial drugs and pregnancy: safety, pharmacokinetics, and pharmacovigilance. Lancet Infect Dis. 2007 Feb;7(2):136–44.

23. Dellicour S, Hall S, Chandramohan D, Greenwood B. The safety of artemisinins during pregnancy: a pressing question. Malar J. 2007 Feb 14;6:15.

24. Davenel S, Galaine J, Guelet B, Marteil S, Robert-Gangneux F. La toxoplasmose congénitale en France en 2009. J Pharm Clin. 2010 Jan 1;29(1):5–30.

25. Bessières MH, Berrebi A, Cassaing S, Fillaux J, Cambus JP, Berry A, et al. Diagnosis of congenital toxoplasmosis: prenatal and neonatal evaluation of methods used in Toulouse University Hospital and incidence of congenital toxoplasmosis. Mem Inst Oswaldo Cruz. 2009 Mar;104(2):389–92.

26. SYROCOT (Systematic Review on Congenital Toxoplasmosis) study group, Thiébaut R, Leproust S, Chêne G, Gilbert R. Effectiveness of prenatal treatment for congenital toxoplasmosis: a meta-analysis of individual patients' data. Lancet Lond Engl. 2007 Jan 13;369(9556):115–22.

27. Binquet C, Wallon M, Metral P, Gadreau M, Quantin C, Peyron F. [Toxoplasmosis seroconversion in pregnant women. The differing attitudes in France]. Presse Medicale Paris Fr 1983. 2004 Jul 10;33(12 Pt 1):775–9.

28. Olariu TR, Remington JS, McLeod R, Alam A, Montoya JG. Severe congenital toxoplasmosis in the United States: clinical and serologic findings in untreated infants. Pediatr Infect Dis J. 2011 Dec;30(12):1056–61.

29. McLeod R, Boyer K, Karrison T, Kasza K, Swisher C, Roizen N, et al. Outcome of treatment for congenital toxoplasmosis, 1981-2004: the National Collaborative Chicago-Based, Congenital Toxoplasmosis Study. Clin Infect Dis Off Publ Infect Dis Soc Am. 2006 May 15;42(10):1383–94.

30. Guerina NG, Hsu HW, Meissner HC, Maguire JH, Lynfield R, Stechenberg B, et al. Neonatal serologic screening and early treatment for congenital *Toxoplasma gondii* infection. The New England Regional Toxoplasma Working Group. N Engl J Med. 1994 Jun 30;330(26):1858–63.

31. Ambroise-Thomas P, Schweitzer M, Pinon JM, Thiebaugeorges O. [Prevention of congenital toxoplasmosis in France. Risk assessment. Results and perspectives of prenatal screening and newborn follow up]. Bull Acad Natl Med. 2001;185(4):665-683; discussion 684-688.

32. Figueiró-Filho EA, Duarte G, El-Beitune P, Quintana SM, Maia TL. Visceral leishmaniasis (kala-azar) and pregnancy. Infect Dis Obstet Gynecol. 2004;12(1):31–40.

33. Boehme CC, Hain U, Novosel A, Eichenlaub S, Fleischmann E, Löscher T. Congenital visceral leishmaniasis. Emerg Infect Dis. 2006 Feb;12(2):359–60.

34. Chulay JD, Fleckenstein L, Smith DH. Pharmacokinetics of antimony during treatment of visceral leishmaniasis with sodium stibogluconate or meglumine antimoniate. Trans R Soc Trop Med Hyg. 1988;82(1):69–72.

35. Paumgartten FJ, Chahoud I. Embryotoxicity of meglumine antimoniate in the rat. Reprod Toxicol Elmsford N. 2001 Jun;15(3):327–31.

36. Carré N, Collot M, Guillard P, Horellou M, Gangneux J-P. La leishmaniose viscérale. J Pharm Clin. 2010 Jul 1;29(3):121–48.

37. Little BB, Harstad TH, Bawdon RE, Sobhi S, Roe DA, Knoll KA, et al. Pharmacokinetics of pentamidine in Sprague-Dawley rats in late pregnancy. Am J Obstet Gynecol. 1991 Mar;164(3):927–30.

38. Scholar EM, Pratt WB, editors. The antimicrobial drugs. 2 edition. Oxford: Oxford University Press; 2000. 607 p.

39. Pilmis B, Jullien V, Sobel J, Lecuit M, Lortholary O, Charlier C. Antifungal drugs during pregnancy: an updated review. J Antimicrob Chemother. 2015 Jan;70(1):14–22.

40. Pepin J, Guern C, Milord F, Ethier L, Bokelo M, Schechter PJ. [The use of difluoromethylornithine in congenital trypanosomiasis due to Trypanosoma brucei-gambiense]. Med Trop Rev Corps Sante Colon. 1989 Mar;49(1):83–5.

41. Lindner AK, Priotto G. The Unknown Risk of Vertical Transmission in Sleeping Sickness—A Literature Review. PLoS Negl Trop Dis. 2010 décembre;4(12):e783.

42. Buyst H. Pregnancy complications in Rhodesian sleeping sickness. East Afr Med J. 1973 Jan;50(1):19–21.

43. De Kyvon M-AL-C, Maakaroun-Vermesse Z, Lanotte P, Priotto G, Perez-Simarro P, Guennoc A-M, et al. Congenital Trypanosomiasis in Child Born in France to African Mother. Emerg Infect Dis. 2016 May;22(5):935–7.

44. Carlier Y, Truyens C, Deloron P, Peyron F. Congenital parasitic infections: a review. Acta Trop. 2012 Feb;121(2):55–70.

45. Freeman SJ, Lloyd JB. Evidence that suramin and aurothiomalate are teratogenic in rat by disturbing yolk sac-mediated embryonic protein nutrition. Chem Biol Interact. 1986 May;58(2):149–60.

46. Bronner U, Gustafsson LL, Doua F, Ericsson O, Miézan T, Rais M, et al. Pharmacokinetics and adverse reactions after a single dose of pentamidine in patients with Trypanosoma gambiense sleeping sickness. Br J Clin Pharmacol. 1995 Mar;39(3):289–95.

47. Burri C, Brun R. Eflornithine for the treatment of human African trypanosomiasis. Parasitol Res. 2003 Jun;90 Supp 1:S49-52.

48. Louis FJ, Keiser J, Simarro PP, Schmid C, Jannin J. [Eflornithine in the treatment of African trypanosomiasis]. Med Trop Rev Corps Sante Colon. 2003;63(6):559–63.

49. Schmid C, Kuemmerle A, Blum J, Ghabri S, Kande V, Mutombo W, et al. In-hospital safety in field conditions of nifurtimox eflornithine combination therapy (NECT) for T. b. gambiense sleeping sickness. PLoS Negl Trop Dis. 2012;6(11):e1920.

50. World Health Organization. Control and surveillance of human African trypanosomiasis. World Health Organ Tech Rep Ser. 2013;(984):1–237.

51. Pépin J, Khonde N, Maiso F, Doua F, Jaffar S, Ngampo S, et al. Short-course eflornithine in Gambian trypanosomiasis: a multicentre randomized controlled trial. Bull World Health Organ. 2000;78(11):1284–95.

52. Haider BA, Humayun Q, Bhutta ZA. Effect of administration of antihelminthics for soil transmitted helminths during pregnancy. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD005547.

53. McKellar QA, Scott EW. The benzimidazole anthelmintic agents: a review. J Vet Pharmacol Ther. 1990 Sep;13(3):223–47.

54. Piscopo SE, Smoak IW. Comparison of effects of albendazole sulfoxide on in vitro produced bovine embryos and rat embryos. Am J Vet Res. 1997 Sep;58(9):1038–42.

55. ELLIOTT AM, NDIBAZZA J, MPAIRWE H, MUHANGI L, WEBB EL, KIZITO D, et al. Treatment with anthelminthics during pregnancy: what gains and what risks for the mother and child? Parasitology. 2011 Oct;138(12):1499–507.

56. Longo M, Zanoncelli S, Colombo PA, Harhay MO, Scandale I, Mackenzie C, et al. Effects of the benzimidazole anthelmintic drug flubendazole on rat embryos in vitro. Reprod Toxicol Elmsford N. 2013 Apr;36:78–87.

57. Diav-Citrin O, Shechtman S, Arnon J, Lubart I, Ornoy A. Pregnancy outcome after gestational exposure to mebendazole: a prospective controlled cohort study. Am J Obstet Gynecol. 2003 Jan;188(1):282–5.

58. Bohand X, Edouard B, Maslin J. Médicaments antihelminthiques. EMC - Mal Infect. 2005;1–9.

59. Pacqué M, Muñoz B, Poetschke G, Foose J, Greene BM, Taylor HR. Pregnancy outcome after inadvertent ivermectin treatment during community-based distribution. Lancet Lond Engl. 1990 Dec 15;336(8729):1486–9.

60. 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 Hyg. 2008 Dec;79(6):856–63.

61. Nour NM. Schistosomiasis: health effects on women. Rev Obstet Gynecol. 2010;3(1):28–32.

62. Olveda RM, Acosta LP, Tallo V, Baltazar PI, Lesiguez JLS, Estanislao GG, et al. Efficacy and safety of praziquantel for the treatment of human schistosomiasis during pregnancy: a phase 2, randomised, double-blind, placebo-controlled trial. Lancet Infect Dis. 2016 Feb;16(2):199–208.

63. Ndibazza J, Muhangi L, Akishule D, Kiggundu M, Ameke C, Oweka J, et al. Effects of deworming during pregnancy on maternal and perinatal outcomes in Entebbe, Uganda:

a randomized controlled trial. Clin Infect Dis Off Publ Infect Dis Soc Am. 2010 Feb 15;50(4):531–40.

64. Brown M. Intestinal helminths. Medicine (Baltimore). 2005 Aug 1;33(8):54–7.

65. Doumbo O, Rossignol JF, Pichard E, Traore HA, Dembele TM, Diakite M, et al. Nitazoxanide in the treatment of cryptosporidial diarrhea and other intestinal parasitic infections associated with acquired immunodeficiency syndrome in tropical Africa. Am J Trop Med Hyg. 1997 Jun;56(6):637–9.

66. de Silva N, Guyatt H, Bundy D. Anthelmintics. A comparative review of their clinical pharmacology. Drugs. 1997 May;53(5):769–88.

Tableau I. Liste des principaux médicaments antiparasitaires possiblement utilisables chez la femme enceinte

Table I. Listing of the main antiparasitic drugs that can be used in pregnant women

International Nonproprietary Name (Drug)	**Administration route**	**Potential administration in pregnant women**		
		1st trimester	**2nd trimester**	**3rd trimester**
Chloroquine (NIVAQUINE®)	Oral and parenteral	✓	✓	✓
Chloroquine/proguanil (SAVARINE®)	Oral	✓	✓	✓
Primaquine	Oral	×	×	×
Quinine (QUINIMAX®, SURQUINA®, QUININE LAFRAN®)	Oral and parenteral	✓	✓	✓
Mefloquine (LARIAM®)	Oral	May be considered	✓	✓
Lumefantrine/artemether (RIAMET®)	Oral	May be considered	✓	✓

Pyrimethamine/sulfadoxine (FANSIDAR®)	Oral	×	✓	✓
Doxycycline (Vibramycine®)	Oral	✓	May be considered	May be considere
Artesunate (MALACEF®)	Parenteral	×*	✓	✓
Atovaquone/proguanil (MALARONE®)	Oral	May be considered	May be considered	May be considere
Spiramycin (ROVAMYCINE®)	Oral and parenteral	✓	✓	✓
Pyrimethamine (MALOCIDE®)	Oral	×	✓	✓
Sulfadiazine (ADIAZINE®)	Oral	×	✓	✓
Sulfamethoxazole/trimethoprim	Oral and	May be considered#	✓	✓

(BACTRIM®)	parenteral			
Meglumine antimoniate **(GLUCANTINE®)**	Intramuscular	✗	✓	✓
Sodium stibogluconate **(PENSTOTAM®)**	Parenteral	✗	✓	✓
Pentamidine **(PENTACARINAT®)**	Parenteral and intramuscular	✗ˆ	May be considered	May be considere
Amphotericin B deoxycholate **(FUNGIZONE®)**	Parenteral	✓	✓✧	✓✧
Liposomal amphotericin B **(AMBISOME®)**	Parenteral	✓	✓✧	✓✧
Suramin **(MORANYL®)**	Parenteral	✗ˆ	✗ˆ	✗ˆ
Eflornithine **(ORNIDYL®)**	Parenteral	May be considered ˆ	May be considered ˆ	May be considere

Melarsoprol (ARSOBAL®)	Parenteral	×	×	×
Benznidazole (RADANIL®)	Oral	×	May be considered	May be considere
Nifurtimox (LAMPIT®)	Oral	×	May be considered	May be considere
Albendazole (ZENTEL®)	Oral	May be considered	✓	✓
Flubendazole (FLUVERMAL®)	Oral	May be considered	✓	✓
Mebendazole (VERMOX®)	Oral	May be considered	✓	✓
Triclabendazole (Egaten®)	Oral	May be considered[^]	May be considered	May be considere
Pyrantel	Oral	✓	✓	✓

(COMBANTRIN®)				
Ivermectin (STROMECTOL®)	Oral	✓*	✓*	✓*
Praziquantel (BILTRICIDE®)	Oral	✓	✓	✓
Niclosamide (TREDEMINE®)	Oral	✓	✓	✓
Metronidazole (FLAGYL®)	Oral and parenteral	May be considered	✓	✓
Tinidazole (FASIGYNE®), secnidazole (SECNOL®), ornidazole (TIBERAL®)	Oral and parenteral	May be considered	May be considered	May be considere

Abréviation : # supplémentation en acide folique à la dose journalière de 5 mg par jour, et surveillance échographique ciblée ; ⅄ uniquement envisageable en cas de risque vital ; ✧ surveillance du volume de liquide amniotique ; un bilan de la fonction rénale du nouveau-né pourra être envisagé à la naissance, en particulier dans les cas exceptionnels de traitements prolongés ; * uniquement envisageable en cas d'usage prophylactique.

Abbreviation: # folic acid supplementation at the daily 5-mg dosage, and targeted ultrasound monitoring; ⅄ only possible in the event of a life-threatening condition; ✧ monitoring of amniotic fluid volume; a control of the newborn's renal function may be considered at birth, especially in exceptional cases of prolonged treatment; * only possible in case of a prophylactic use.