Reproductive Toxicology 65 (2016) 194–203

Contents lists available at ScienceDirect

Reproductive Toxicology

journal homepage: www.elsevier.com/locate/reprotox

Review

# Clinical and non-clinical safety of artemisinin derivatives in pregnancy

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ARTICLE INFO

*Article history:*
Received 5 April 2016
Received in revised form 3 August 2016
Accepted 5 August 2016
Available online 6 August 2016

*Keywords:*
Artemisinin derivative
Embryotoxicity
Clinical study
Non-clinical study
Pregnancy

ABSTRACT

Malaria in pregnancy is a clinically wasting infectious disease, where drug therapy has to be promptly initiated. Currently, the treatment of this infection depends on the use of artemisinin derivatives. The World Health Organization does not recommend the use of these drugs in the first trimester of pregnancy due to non-clinical findings that have shown embryolethality and teratogenic effects. Nevertheless, until now, this toxicity has not been proved in humans. Artemisinin derivatives mechanisms of embryotoxicity are related to depletion of circulating embryonic primitive erythroblasts. Species differences in this sensitive period for toxicity and the presence of malaria infection, which could reduce drug distribution to the fetus, are significant to the risk assessment of artemisinin derivatives treatment to pregnant women. In this review we aimed to assess the results of non-clinical and clinical studies with artemisinin derivatives, their mechanisms of embryotoxicity and discuss the safety of their use during pregnancy.


**Contents**



## 1. Introduction

Malaria is a severe infectious disease that remains a major public health challenge in endemic regions, including countries from South and Central America, Africa and Asia. This disease is caused by parasites of the *Plasmodium* genus and transmitted by *Anopheles* mosquitoes. The most severe form of malaria is triggered by *P. falciparum*. It is estimated that annually more than 3 billion people are at risk of contracting malaria and 400,000 deaths are recorded as a result of this disease [1].

During pregnancy, malaria can be a clinically wasting condition. Its complications are remarkable in pregnant women, such as severe anemia and cerebral malaria, and their offspring face possibility of stillbirths, miscarriages or low birth weight [2]. Antimalarial drug therapy during pregnancy has to be promptly initiated, making the safety of currently available drugs and their combination for mothers and their babies a research topic of paramount relevance. Moreover, due to the risk of malaria to the mother and the fetus, the World Health Organization (WHO) recommends chemoprophylaxis for pregnant women living in high-intensity transmission areas [3]. Nevertheless, based on non-clinical data, there are restrictions about malaria treatment for pregnant women, especially in the first trimester [4].

Currently, there are few drugs available for the treatment of malaria. Parasites, particularly *P. falciparum*, have become resistant

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http://dx.doi.org/10.1016/j.reprotox.2016.08.003
0890-6238/

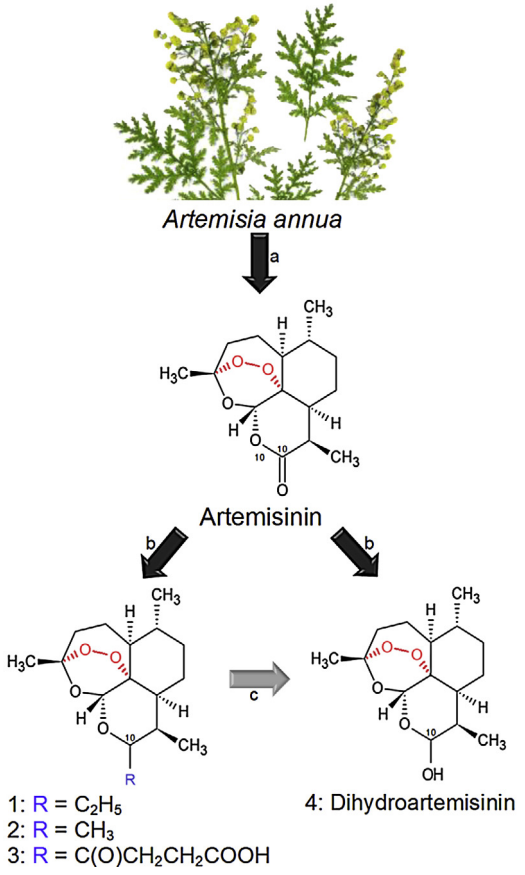


**Fig. 1.** Chemical structures of artemisinin (ART) and some of its derivatives. ART is extracted from *Artemisia annua* (a) [6]. Different compounds can be synthetically (b) obtained from ART by chemical modifications at C10 position (R = radical), such as arteether (1), artemether (2), artesunate (3) and dihydroartemisinin (DHA) (4) [17]. The ART derivatives 1–3 are converted *in vivo* (c) into DHA (4), which has higher antimalarial activity than ART and contributes significantly to the antimalarial activity of these drugs [15,16]. Artemisinin and its derivatives have an endoperoxide bridge (—O—O—), which is the pharmacophore for their activity. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

to conventional drugs [5]. In the 70's, the antimalarial substance artemisinin was isolated from *Artemisia annua* L. (Fig. 1a). Subsequently, higher power semi-synthetic derivatives of artemisinin were developed. Due to the high efficacy and rapid action of artemisinin derivatives in combination with other antimalarial agents, they have become one of the first line treatments for malaria. These drugs have had great importance in reducing the incidence of malaria [1,6]. This discovery has saved thousands of lives and rewarded the Chinese pharmacologist Youyou Tu the Nobel Prize for Physiology and Medicine in the last year [6].

The therapeutic options for the treatment of malaria during pregnancy are even scarcer. In the second and third trimesters of pregnancy, or in severe cases, the use of antimalarial combinations containing artemisinin derivatives is advised [3]. The WHO recommends the use of quinine and clindamycin in the first trimester, because the safety of artemisinin derivatives has not been well established in this period. Concerns were raised in non-clinical studies that have shown embryonic lethality and teratogenicity in several species [7–9]. However, such toxicity has not been proved in humans [3].

This review intends to provide data on developmental toxicity of artemisinin derivatives and discuss their safety during pregnancy in clinical and non-clinical trials, as well as discuss their mechanisms of embryotoxicity.

## 2. Artemisinin and its derivatives

Artemisinin is extracted from the leaves of the *A. annua* L. (Fig. 1a), and has been used in China for 2000 years as an antipyretic, referred to as *qinghao* [10,11]. It was discovered, purified and identified in 1972 [12]. Artemisinin is a sesquiterpene lactone containing an endoperoxide bridge, which is believed to be necessary for antimalarial activity (Fig. 1) [13]. Artemisinin is an extremely active antimalarial to treat uncomplicated and severe malaria [6].

The artemisinin content in dried leaves is between 0.06–2% and it is poorly soluble in water or oil [14]. The artemisinin low bioavaibility and poor pharmacokinetics properties are the major drawback of its use. After its discovery, several semisynthetic derivatives were identified including the dihydroartemisinin (DHA) which is more potent and chemically stable than artemisinin (Fig. 1b) [15]. Water-soluble (artesunate and artelinate) and oil-soluble (artemether and arteether) artemisinin derivatives were synthetized and developed (Fig. 1b), and they are known as first generation endoperoxides [14]. After administration, these derivatives are metabolized in DHA (Fig. 1c). The antimalarial effect of the artemisinin derivatives results primarily from DHA, which disappears from plasma with a half-life of approximately one hour [16]. Artemisinin derivatives are currently the most important class of antimalarial drugs [3].

Efforts to find more metabolically stable artemisinin derivatives are ongoing and have highlighted the second generation of endoperoxides, including 10-(alkylamino)-artemisinins, as artemisone and artemiside [10]. They are called second generation because they are more stable and potent than the others derivatives [14]. As only endoperoxide bridge is required for antimalarial activity, significant efforts have been focused on identification of fully synthetic artemisinin-like peroxides with a simple and cheaper synthesis, as for example trioxanes and diterpenes peroxides with antimalarial activity. However, these newly developed semi-synthetic and synthetic derivatives are still undergoing development [10].

Artemisinin and derivatives are rapidly effective and well tolerated but, due to the fact they have short half-life, monotherapy is not recommended to avoid resistance [6,11,14]. Therefore, artemisinin derivatives are administered combined with others antimalarial to increase efficacy and adherence to the treatment [6,18]. The use of artemisinin-based combination therapies (ACTs) for uncomplicated malaria has enabled a reduction of treatment from 7 (artemisinin monotherapy) to 3 days, avoiding recrudescence [3,6].

The most common ACTs used for malaria treatment are artemether-lumefantrine, artesunate-amodiaquine, artesunate-mefloquine and artesunate-sufadoxine-pyrimethamine [10,19]. ACTs for treatment of *falciparum* malaria reduce load gametocytes, reducing retransmission, but this effect is incomplete without the inclusion of primaquine, which is a known gametocytocide [3].

The exact mechanism of the antimalarial activity of the artemisinin derivatives remains controversial. Within the malaria parasitized erythrocyte, hemoglobin is degraded by a series of protease enzymes of parasite to release peptides and amino acids required for its development and to create space within its digestive vacuole, increasing the amount of free iron and heme [20]. One possible mechanism of action suggests that artemisinin derivatives, into the parasitized erythrocyte, accumulate and release free radicals through loss of endoperoxide bridge by iron or heme, which kills the parasite [21]. Recently, Wang et al. [22] showed that heme, rather than free ferrous iron, is predominantly responsible for artemisinin activation.

The artemisinin activation generates carbon-centered radicals which are highly reactive and can covalently bind to several proteins and alkylate them impairing their function [20]. These radicals