REVIEW ARTICLE

Treating Severe Malaria in Pregnancy: A Review of the Evidence

**Stephanie D. Kovacs · Marcus J. Rijken ·
Andy Stergachis**

Abstract Severe malaria in pregnancy is a large contributor to maternal morbidity and mortality. Intravenous quinine has traditionally been the treatment drug of choice for severe malaria in pregnancy. However, recent randomized clinical trials (RCTs) indicate that intravenous artesunate is more efficacious for treating severe malaria, resulting in changes to the World Health Organization (WHO) treatment guidelines. Artemisinins, including artesunate, are embryo-lethal in animal studies and there is limited experience with their use in the first trimester. This review summarizes the current literature supporting 2010 WHO treatment guidelines for severe malaria in pregnancy and the efficacy, pharmacokinetics, and adverse event data for currently used antimalarials available for severe malaria in pregnancy. We identified ten studies on the treatment of severe malaria in pregnancy that reported clinical outcomes. In two studies comparing intravenous quinine with intravenous artesunate, intravenous artesunate was more efficacious and safe for use in pregnant women. No studies detected an increased risk of miscarriage, stillbirth, or congenital anomalies associated with first trimester exposure to artesunate. Although the WHO recommends using either quinine or artesunate for the treatment of severe malaria in first trimester pregnancies, our findings suggest that artesunate should be the preferred treatment option for severe malaria in all trimesters.

S. D. Kovacs (✉) · A. Stergachis
Department of Epidemiology, University of Washington,
Seattle, WA, USA
e-mail: Kovacs2@uw.edu

A. Stergachis
e-mail: stergach@uw.edu

M. J. Rijken
Shoklo Malaria Research Unit, Mae Sot, Thailand

M. J. Rijken
University Medical Centre, Utrecht, The Netherlands

A. Stergachis
Department of Global Health, University of Washington,
Seattle, WA, USA

A. Stergachis
Global Medicines Program, University of Washington, Health
Sciences Building, F-342, Box 357236, Seattle, WA 98195, USA

Key Points
Intravenous artesunate is the most efficacious treatment for severe malaria, but data are limited on its use in pregnancy
No associations have been reported between artemisinin use in humans and increased risk of miscarriage, stillbirth, or congenital anomalies
The 2010 WHO guidelines recommend using either quinine or artesunate for the treatment of severe malaria in first trimester pregnancies
Current data suggest that WHO treatment guidelines should be changed to recommend artesunate as the preferred treatment option for severe malaria in pregnancy during all three trimesters

1 Introduction

An estimated 54.7 million pregnancies occurred in areas of stable *Plasmodium falciparum* malaria transmission, and

an additional 70.5 million pregnancies occurred in areas of low transmission or areas with only *Plasmodium vivax* malaria in 2007 [1, 2]. Malaria in pregnancy is associated with higher rates of parasitemia, severe anemia, hypoglycemia, and acute pulmonary edema than malaria in non-pregnant women [3]. Malaria in pregnancy is a major contributor to morbidity and mortality, resulting in an estimated 100,000 neonatal deaths and 10,000 maternal deaths annually [4, 5]. Severe malaria is defined as acute malaria with major signs of organ dysfunction and/or high levels of parasitemia [3]. Pregnant women living in areas of unstable transmission are at higher risk of severe malaria and corresponding mortality [6]. Pregnant women in such areas have a three-times higher risk of severe malaria than do non-pregnant women [7]. Despite the substantial morbidity and mortality associated with severe malaria in pregnancy, pregnant women are often excluded from randomized trials of treatment drugs due to ethical concerns about the safety of these drugs for pregnant women and their fetuses [8].

The management of severe malaria in pregnancy needs to weigh the risks and benefits of treating malaria and the potential for adverse events for the pregnancy and fetus. Early treatment is critical because fever and illness of the mother are major risk factors for adverse pregnancy outcomes beyond the effects of the malaria parasite itself. The World Health Organization (WHO) guidelines stress prioritizing the life of the mother when treating severe malaria [9]. In choosing an appropriate therapy, one must weigh the known risks to the life of the mother compared with the uncertain risks of the treatment on the fetus.

This review summarizes the current literature available on the treatment of severe malaria in pregnancy. We review the data used to support 2010 WHO treatment guidelines for severe malaria in pregnancy and assess whether the current data support these guidelines.

2 Literature Review Methodology

In order to identify all studies of the treatment of severe malaria in pregnancy, we conducted a review informed by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [10]. To identify all articles on severe malaria in pregnancy, we searched MEDLINE and Embase with the terms ('severe malaria' OR 'complicated malaria' OR 'falciparum malaria' OR 'cerebral malaria') AND 'pregnancy' AND ('treatment' OR 'artemisinin' OR 'artesunate' OR 'artemether' OR 'quinine') published before August 2014. We limited our search to English language articles. We also reviewed the references of key publications to ensure that all relevant literature was included in the review. We reviewed all of the literature that included the treatment of severe malaria in pregnancy. We included studies that reported the specific drug treatments pregnant women received and reported outcomes by drug regimen. Outcomes of interest included measures of efficacy in pregnancy, safety, and pharmacokinetics. The full results of our search are outlined in Fig. 1.

Data are scarce on treatment of severe malaria in pregnancy, so this review presents data on the drugs currently recommended for the treatment of severe malaria in

Fig. 1 Results of the systematic review of studies of the treatment of severe malaria in pregnancy
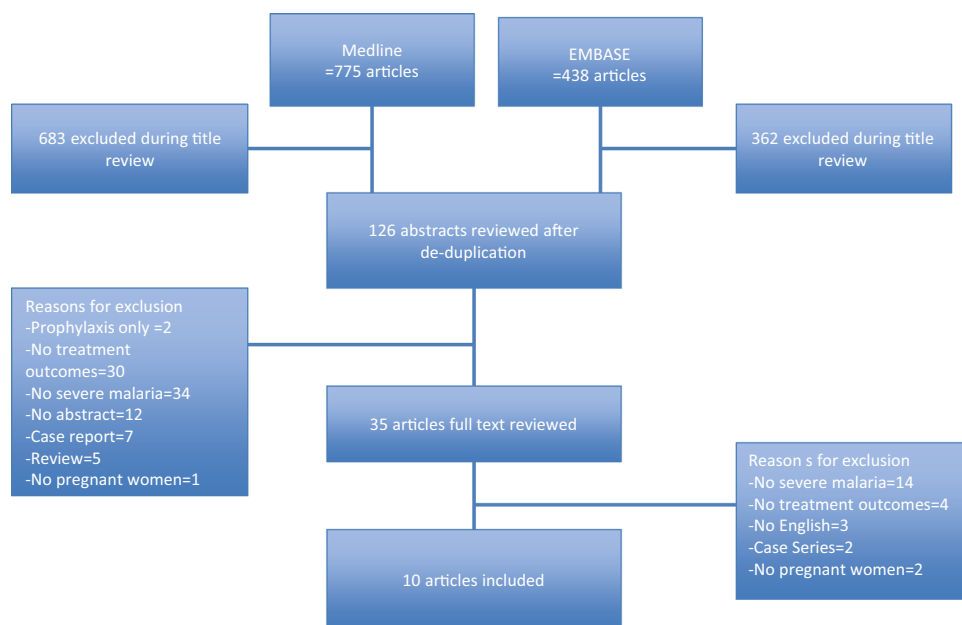
pregnancy from studies of the treatment of uncomplicated malaria in pregnancy and the treatment of severe malaria in adults. This information was included in order to fully describe the safety and efficacy of the currently used therapies for the treatment of severe malaria in pregnancy. We used data from both the systematic review of the treatment of severe malaria in pregnancy and the key studies of uncomplicated malaria in pregnancy and severe malaria in adults to inform our recommendations.

3 Severe Malaria

3.1 Definition

The WHO defines severe *P. falciparum* malaria as a patient with *P. falciparum* asexual parasitemia with evidence of organ dysfunction (Fig. 2). The WHO definition of severe malaria applies for all patients, including pregnant women. A case of uncomplicated malaria can rapidly progress to severe malaria due to either delayed treatment or treatment failure.

3.2 Epidemiology of Severe *P. falciparum* Malaria in Pregnancy

Pregnant women have a three-times higher risk of severe malaria than non-pregnant women [7, 11]. Before the introduction of malaria control programs in Western Thailand, 1 % (5/500) of pregnant women died of malaria in a year [12]. The clinical presentation of severe malaria varies by age and pregnancy status, with adults presenting with hyperparasitemia, jaundice, and renal insufficiency more often than children [13]. In a malaria epidemic in India, severe anemia and cerebral malaria were more common in pregnant women with severe malaria than in

non-pregnant women with severe malaria [20 % (5/45) versus 4 % (10/243), and 76 % (34/45) versus 33 % (80/243); *p* value <0.05], respectively [14]. Pregnant women with malaria are also at increased risk of hypoglycemia, acute respiratory distress syndrome (ARDS) [15], and hyperparasitemia [3] than non-pregnant women. In a review of severe malaria in pregnancy in the Asia Pacific region (227 women in eight studies) [14, 16–22], the median mortality rate was 39 % but ranged from 8 to 100 % [6]. This wide range is related to the broad WHO definition of severe malaria: the lowest mortality was reported in pregnant women whose only sign of severity was hypoglycemia. By contrast, all women with renal failure died [6]. There are limited mortality data from sub-Saharan Africa, but the percentage of maternal deaths attributed to malaria may be very similar between low- and high-transmission areas [4, 23, 24]. Two studies conducted in Sudan noted no maternal deaths among the pregnant women with severe malaria [25, 26]. In a retrospective case review of all maternal deaths 1985–1999, severe malaria was responsible for up to one-third of all maternal deaths in Sudan, a low-transmission setting [27]. Severe malaria accounted for 10 % of all deaths in an autopsy study of maternal mortality in Mozambique [24], and, similarly, was attributed to 9 % of maternal deaths in Western Kenya (a high-transmission setting) [28]. In addition to risk of death for the mother, infants born to women with clinical malaria infections late in pregnancy are at higher risk of early neonatal death during infancy [29, 30]. Young maternal age is an independent risk factor for severe malaria, with older age providing some protection [4]. Obstetric help should be sought, as severe malaria usually precipitates premature labor [31]. Even when the mother survives, there remains an increased risk of miscarriage and stillbirth, prematurity, and low birth weight for the fetus [6, 7, 9, 29, 32–34].

Fig. 2 World Health Organization (WHO) definition of severe malaria. *Hb* hemoglobin

WHO Definition of Severe Malaria
The WHO defines severe *P. falciparum* malaria as a patient with *P. falciparum* asexual parasitemia and one of the following clinical features:
• Impaired consciousness or coma, prostration, failure to feed, multiple convulsions, acidotic breathing, circulatory collapse, clinical jaundice with evidence of other vital organ dysfunction, hemoglobinuria, abnormal spontaneous bleeding, and/or pulmonary edema.
Laboratory findings can include:
• Hypoglycemia (blood glucose <2.2 mmol/l or <40 mg/dl), metabolic acidosis (plasma bicarbonate <15 mmol/l), severe normocytic anemia (Hb <5 g/dl), hemoglobinuria, hyperparasitemia (>2%/100,000 per μl in low intensity transmission areas or >5%/ 250,000 per μl in areas of high stable malaria transmission), and renal impairment (serum creatinine >265 μmol/l) [57].

3.3 Epidemiology of Severe *P. vivax* Malaria

P. vivax malaria is not as benign as previously thought; recent data suggest that there is an increasing burden of morbidity and mortality due to *P. vivax* malaria in pregnant women [11, 35–38]. In high-prevalence areas such as regions in India, Myanmar, Asia Pacific, and South America, there have been cases where the *P. vivax* infections behaved more like *P. falciparum* [39–41]. *P. vivax* infections may trigger immune responses that could lead to potentially lethal clinical episodes independently or synergistically with other conditions or co-infections [42]. This inflammatory potential, in combination with *P. vivax*-induced hemolysis, increased red cell fragility, dyserythropoiesis, and retention of erythrocytes within the spleen contributes to severe anemia [43–45]. Localized exacerbations in the lung microvasculature have been proposed to cause ARDS [46]. Jaundice, renal failure, severe thrombocytopenia, acidosis, and, rarely, coma have also been reported in association with *P. vivax* [39]. In pregnancy, *P. vivax* malaria was reported to be associated with moderate anemia, but severe anemia could develop in pregnancy due to *P. vivax* malaria [47–50]. However, severe anemia in pregnancy may develop gradually via recurrent *P. vivax* episodes, and may not be reported as severe malaria in many settings. The burden of *P. vivax* malaria, and its severe manifestations, has been complicated by the emergence of resistance to chloroquine [39, 43].

The epidemiology of severe *P. vivax* malaria in pregnancy is difficult to determine. In the search for this manuscript, only four *P. vivax*-related maternal deaths were reported in the published literature. A cohort of 4,300 women with *P. vivax* malaria on the Thai-Myanmar border included one *P. vivax*-related maternal death: a third gravid, moderate anemic (known B-thalassemia trait) woman who was 36 weeks pregnant died from ARDS 7 days after commencement of treatment for *P. vivax* malaria (*P. vivax*-related malaria mortality 23/100,000 live births) [51]. In a cohort from Indonesia, 456 women were diagnosed with *P. vivax* malaria, ten of whom had severe *P. vivax* disease. Two of these women died; *P. vivax*-related maternal mortality 439/100,000 (2/456) [52]. In a description of malaria-infected placentas from Mandla district in India, the authors describe a woman with a fairly high *P. vivax* parasitemia, jaundice, and severe anemia who died before labor started [53].

4 Current Treatment Guidelines

4.1 World health organization treatment guidelines

In order to combat the burden of malaria in pregnancy, the WHO Malaria Policy Advisory Committee (MPAC) recommends a three-pronged approach, including the use of long-lasting insecticide-treated nets, intermittent preventative therapy (IPT) by which pregnant women receive a dose of sulphadoxine-pyrimethamine (SP) at each antenatal care visit after the first trimester, and effective case management [54]. For pregnant women who are infected with *P. falciparum*, the WHO recommends treatment with artemisinin-based combination therapies (ACTs) during the second and third trimesters [55]. Artemisinins are given in combination with other antimalarial drugs to prevent the development of drug resistance. The WHO does not recommend the use of ACTs in the first trimester unless there is no alternative and the life of the woman is in danger [5].

Table 1 summarizes the current WHO 2010 treatment guidelines for severe *P. falciparum* malaria in pregnancy. In the treatment of severe malaria in pregnancy, saving the life of the mother is the primary objective. Intravenous artesunate has been shown to significantly reduce the risk of death from severe malaria compared with intravenous quinine in adults and children with severe malaria [20, 56]. In a study of 1,461 adults, artesunate was associated with a 34.7 % [95 % confidence interval (CI) 18.5–47.6] reduction in mortality compared with quinine for the treatment of severe malaria [20]. A similar study in 5,424 children found a 22.5 % (95 % CI 8.1–36.9) reduction in mortality associated with treatment with artesunate compared with quinine. Therefore, the WHO guidelines recommend intravenous artesunate in preference over quinine in the second and third trimester for severe malaria. Quinine is associated with recurrent hypoglycemia. However, in the first trimester, the risk of hypoglycemia is lower and the uncertainties over the safety of artemisinin derivatives is greater. The WHO recommends using either quinine or artesunate for the treatment of severe malaria in first-trimester pregnancies, until more evidence becomes available [57].

Although the WHO recommends artesunate as the preferred treatment for severe malaria in pregnancy, the USA, through the Centers for Disease Control and Prevention (CDC), recommends the use of quinidine (Figs. 2, 3). Quinidine is associated with arrhythmias, and a recent case series of patients hospitalized in the USA with malaria noted that four of six patients receiving quinidine experienced QT prolongation and two of six patients experienced Torsades de Pointes, a life-threatening arrhythmia associated with QT prolongation [58].

The evidence used to support the WHO treatment guidelines was based, in part, on a Cochrane review conducted in 2007 [59], which was updated in 2012 [60]. Treatment with artesunate significantly reduced the risk of death both in adults [relative risk (RR) 0.61, 95 % CI 0.50–0.75; 1,664 participants, five trials] and children (RR 0.76, 95 % CI 0.65–0.90; 5,765 participants, four trials) [60]. Only one study in the systematic review, the South

Table 1 World Health Organization recommendations for the treatment of severe malaria in pregnancy

	First trimester	Second to third trimester
P. falciparum	Either IV artesunate or quinine can be used	IV artesunate should be used in preference to quinine
P. vivax	Either IV artesunate or quinine	IV artesunate should be used in preference to quinine
	Suppressive prophylaxis with chloroquine until delivery	Suppressive prophylaxis with chloroquine until delivery
	Post-delivery, women should receive radical treatment with primaquine	Post-delivery women should receive radical treatment with primaquine
All severe malaria	Treatment must not be delayed. If only one of the drugs artesunate, artemether, or quinine is available, it should be administered immediately	

IV intravenous

Fig. 3 Additional treatment guidelines for the treatment for severe malaria in pregnancy. *CDC* Centers for Disease Control and Prevention

Additional Recommendations
United States:
• Quinidine gluconate is the only parenterally administered antimalarial approved for the treatment of severe malaria in the United States.
• If quinidine is unavailable or for patients who cannot tolerate quinidine, or with parasitemia >10% of baseline 48 hours after initiating quinidine treatment, intravenous artesunate is available as an investigational drug through the CDC [150].
• Quinidine is associated with syncope [151] and requires electrocardiographic monitoring, and in a study of patients with malaria, quinidine was associated with QT interval prolongation [152].
United Kingdom
• The Royal College of Obstetricians recommends intravenous artesunate for the treatment of severe *P. falciparum* malaria in pregnancy. If intravenous artesunate is unavailable, intravenous quinine may be used [153].

East Asian Quinine Artesunate Malarial Trial (SEAQUA-MAT), enrolled pregnant women and presented results stratified by pregnancy status [20]. In this large trial of 1,461 participants, 23 women in the artesunate arm and 26 in the quinine arm were pregnant at enrollment, but trimester of pregnancy was not reported. Mortality among pregnant women with severe malaria was 9 and 12 % [odds ratio (OR) 0.75; 95 % CI 0.09–6.41] for artesunate and quinine arms, respectively [20]. The WHO justified their recommendation for the use of artesunate instead of quinine despite limited data in pregnancy due to the large reduction in mortality associated with artesunate and the increased risk of hypoglycemia associated with the use of quinine [57]. Treatment must not be delayed; if only one of the drugs artesunate, artemether, or quinine is available, then it should be started immediately. We conducted an updated review of the literature using the same search terms as Dondorp et al. [56] ('malaria', 'cerebral malaria', 'severe malaria', 'complicated malaria', 'malaria falciparum', 'quinine', and 'cinchona alkaloids' and 'artemisinin' and 'artesunate'), but no new clinical trials including pregnant women were identified.

4.1.1 World Health Organization Treatment Guidelines for Severe P. vivax Malaria

Severe malaria has been assumed to be associated with *P. falciparum* infection, but a recent review highlighted the substantial burden of severe malaria due to *P. vivax* infections [38]. While pregnant women were excluded, the results of meta-analysis showed a similar incidence of adult severe malaria due to *P. vivax* infections *or P. falciparum* mono-infection in adults [38]. In all trimesters of pregnancy, the WHO recommended treatment for uncomplicated *P. vivax* malaria is chloroquine, a total dose of 25 mg base/kg body weight in 3 days [57]. In an area with chloroquine-sensitive parasites, chemoprophylaxis with weekly chloroquine (500 mg phosphate or 300 mg base) prevented any recurrent *P. vivax* episodes in pregnant women [61]. However, reports of chloroquine-resistant parasites in pregnant women suggest that alternative treatment guidelines are needed to prevent repeated dosing of an ineffective drug [62]. Many countries in the Asia-Pacific region have changed the first-line treatment of *P. vivax* malaria to ACTs. Quinine and clindamycin

remain the treatment of choice for *P. vivax* malaria in the first trimester [52].

For pregnant patients with severe *P. vivax* malaria, the WHO recommends the same treatments as for severe *P. falciparum* infections (Table 1) [57]. *P. vivax* has liver stages (hypnozoites) that cause recurrent blood-stage infections (relapses). Primaquine—the only drug effective against liver stages—is contraindicated in pregnant women because fetal red blood cells are susceptible to hemolysis [63]. Pregnant women should receive suppressive prophylaxis with chloroquine until delivery, at which point they can receive radical treatment with primaquine [61].

5 Summary of Drugs for Treatment of Severe Malaria

5.1 Artemisinins

The most efficacious drugs for treating severe malaria are artemisinin-based compounds. Artemisinins, derived from the plant *Artemisia annua,* have been used for centuries in China to treat fever. Currently, three artemisinin compounds are used to treat malaria: artesunate, artemether, and dihydroartemisinin.

5.1.1 Safety of Artemisinins in Pregnancy

Despite their proven efficacy, artemisinins are embryotoxic and teratogenic in animal studies [64]. Artesunate is toxic to rat and rabbit embryos, with fetal reabsorption in rats reported at low doses (28–223 mg/kg/day) given orally on days 9–14 of gestation [55]. High rates of congenital malformations, including bent and/or shortened long bones and treatment-related heart defects, were observed in rat litters [55]. Primate studies demonstrated similar embryo toxicity, with 55 and 100 % embryo lethality for 12 and 30 mg/kg/d oral doses, respectively, after 12 days of treatment [65]. In addition, observations of three live primate embryos from the 30 mg group noted reductions in blood cells in the vasculature, and the cardiac chambers were distended with thin walls [65]. The primary embryonic targets for artemisinins are the primitive erythroblasts proliferating during gestational periods of 10–14 days in the rat and 18–40 days in the monkey. In humans, this corresponds to a sensitive period from post-conception week 3 to approximately post-conception week 9 [65].

The findings from animal reproductive toxicology studies and the dearth of human studies led the WHO to not recommend the use of artemisinins in the first trimester of pregnancy for uncomplicated malaria. The WHO recommends that artesunate may be used to treat severe malaria in the first trimester because of the high rates of mortality, stillbirth, and miscarriage associated with severe malaria

[57]. Observational data on the safety and efficacy of artemisinins in the first trimester of pregnancy are very limited. A recent systematic review identified eight studies of antimalarials from 1997 to 2013 that included first-trimester pregnancies and a total of 35 studies including pregnant women of any gestational age, but the vast majority of patients had uncomplicated malaria [66]. The systematic review identified 555 first-trimester exposures to artemisinins in clinical trials [66], and an additional 945 women with a single malaria episode in the first trimester were described along the Thai-Burma border, 92 of whom were exposed to an artemisinin [9]. Neither the clinical trials nor the large cohort study observed an increased risk of adverse pregnancy outcomes associated with exposures to artemisinins. Birth outcomes did not differ significantly for women exposed to artesunate compared with quinine and chloroquine during the first trimester, and artemisinins were not associated with miscarriage after controlling for maternal and malaria characteristics [9].

Studies in animals suggest that artesunate is a teratogen when given alone or in combination with mefloquine [67, 68]. The limited safety data in humans have not shown any increased risk of miscarriage, stillbirth, or congenital anomalies associated with exposure during the first trimester or later in pregnancy [9, 69–72]. Animal studies suggest that, similar to artesunate, artemether is embryotoxic in rat models [73, 74]. The limited safety data in humans have failed to find an association with artemether exposure and increased risk of stillbirth, miscarriage, or congenital anomalies [69, 75–77].

5.1.2 Artesunate

Artesunate is a water-soluble artemisinin derivative. The drug is available orally in combination with other antimalarials, or in rectal and parenteral formulations used for the treatment of severe malaria. Artesunate is associated with faster parasite clearance than quinine because the drug targets young circulating ring-stage parasites [78, 79]. Artesunate does not require a loading dose. For the treatment of severe malaria, the WHO recommends 2.4 mg/kg to be given immediately intravenously or by intramuscular injection, with repeat doses at 12 and 24 h. Continued injections can be given once daily as necessary.

A review of the literature identified three pharmacokinetic studies of artesunate in pregnant women. Pharmacology data suggest that pregnant women receiving oral artesunate may have accelerated clearance rates of the metabolite dihydroartemisinin compared with non-pregnant women [80, 81]. A single study of intravenous and oral artesunate noted no significant differences in the pharmacokinetics between pregnant women with malaria compared with the same women in a healthy state after

administration of intravenous artesunate. The same study noted that pregnant women with malaria had significantly higher drug exposure after receiving oral artesunate than the same women when healthy and not pregnant [82].

Clinical data on the efficacy of artesunate in the treatment of severe malaria in pregnancy are limited [9, 20, 52]. Only the SEAQUAMAT trial reported data on pregnant women with severe malaria comparing artesunate with quinine in a clinical trial setting. A systematic review by Visser et al. [66] identified ten studies reporting outcomes of pregnant women treated with artesunate. Artesunate is associated with higher cure rates, lower gametocyte carriage, and lower treatment failure than quinine-based therapies for the treatment of uncomplicated malaria in pregnancy [69, 70, 72, 83, 84]. Our systematic review of the literature identified two additional studies presenting data on artesunate to treat severe malaria in pregnancy [9, 52]. Poespoprodjo et al. [52] found no statistically significant increased risk of poor maternal or fetal outcomes associated with artesunate compared with quinine, and noted than none of the ten women exposed to intravenous artesunate in the first trimester had a miscarriage. McGready et al. [9] noted that, although miscarriage rates were very high for women with severe malaria in the first trimester (58 %), there was no difference in the rates between pregnant women treated with artesunate or quinine.

Artesunate is generally associated with better tolerability than quinine [20, 83, 85]. The most important reported side effect of artesunate is anaphylaxis, with an estimated risk of approximately 1 in 3,000 patients. Additional common minor side effects associated with intravenous administration include dizziness, light-headedness, rash, and taste alterations. Nausea, vomiting, and diarrhea have been reported, but it is unclear whether these are associated with artesunate or are symptoms of severe malaria [86]. Cardiotoxicity has been observed after administration of high doses of artesunate [87]. Multiple studies in adults and children suggest that up to 25 % of patients treated with intravenous artesunate for severe malaria developed delayed hemolytic anemia 7–31 days after treatment, but the etiology is unknown [88–92].

5.1.3 Artemether

Artemether is a commonly used artemisinin for the treatment of uncomplicated malaria when combined with lumefantrine (marketed as Coartem®). According to the WHO, artemether can be used to treat severe malaria in pregnancy when artesunate is unavailable [57]. Artemether should be given at 3.2 mg/kg body weight intramuscularly at admission and then 1.6 mg/kg body weight per day as needed. The parenteral formulation is oil based; data suggest that it is poorly or erratically absorbed in this formulation [93].

A review of the literature identified four pharmacokinetic studies of artemether in pregnant women. All four studies demonstrated that pregnant women have lower concentrations of artemether and its metabolite dihydroartemisinin than non-pregnant controls [94–97]. These results suggest that further research is needed to identify the correct oral dose of artemether for pregnant women to decrease the likelihood of treatment failure and to prevent resistance. No studies were identified that examined the pharmacokinetics of artemether as an injection in pregnant women, but, because it is oil based it is hypothesized that absorption is erratic [93].

A systematic review of artemether for the treatment of severe malaria, conducted in 2001 using data from seven trials, noted that 14 % of those treated with artemether and 17 % of those treated with quinine died (OR 0.08, 95 % CI 0.62–1.02; $p = 0.08$), but none of the trials included pregnant women [98–102]. The authors concluded that artemether was equivalent to quinine for the treatment of severe malaria [103]. The systematic review noted that treatment with artemether was not associated with an increased number of adverse events compared with quinine, but artemether was associated with significantly faster parasite clearance, hazard ratio (HR) 0.62 (95 % CI 0.56–0.69). An updated systematic review of the literature by the authors failed to identify any studies published since 2001 that included results for pregnant women.

A systematic review of the treatment of malaria in pregnancy by Visser et al. identified 16 studies reporting pregnancy outcomes in women exposed to artemether–lumefantrine (AL) or artemether for treatment of uncomplicated malaria [66, 69, 72, 75, 76, 94, 104–109]. An additional systematic review of the use of artemether and AL to treat uncomplicated malaria in pregnancy identified 1,103 reports of AL use in pregnancy [110]. Broadly, the efficacy of artemether was non-inferior or superior to that of quinine. Specifically, one study comparing quinine with artemether combined with atovaquone–proguanil (A + AP) saw much higher day 63 cure rates in the A + AP group than in the quinine group [94.9 % (95 % CI 81.4–99.1) vs. 63.4 % (95 % CI 46.9–77.4) respectively] [109].

Intramuscular artemether is generally well tolerated, with very few side effects reported [93, 111–113]. Pain and swelling at the injection site is a common, mild side effect [113]. Cardiotoxicity has been observed rarely, resulting in arrhythmias such as ventricle tachycardia [87].

We identified two trials, both conducted in Vietnam, that directly compared artemether with artesunate for treating severe malaria in adults [114, 115]. Both trials excluded women pregnant in their first trimester and did not report results stratified by pregnancy status. One trial compared four different regimens with no statistically significant difference in mortality across the treatments. The mortality

rates were 11.1 % (5/45) for intramuscular artemether, 17.6 % (9/51) for artemisinin suppositories, 10.2 % (6/49) for intramuscular artesunate, and 17.6 % (5/30) for intravenous artesunate [114]. A second double-blind trial conducted between 1996 and 2003 compared intramuscular artesunate with intramuscular artemether for the treatment of severe malaria. The trial reported 7 % (13/186) mortality in the artesunate group and 13 % (24/184) mortality in the artemether group; however, the results were not statistically significant ($p = 0.052$). The authors concluded that intramuscular artemether may not be the best artemisinin therapy for treating severe malaria because the drug releases slowly and erratically compared with water-soluble artesunate [115].

5.2 Quinine

Quinine was first discovered as a treatment for malaria in the 17th century [85]. Quinine is available as oral or intravenous preparations and reaches peak concentrations 1–3 h after administration [116]. Quinine attacks intra-erythrocytic malaria parasites, and it has gametocytocidal properties against *P. vivax* and *Plasmodium malariae* but not *P. falciparum* [85]. The pharmacokinetic properties of quinine vary by age of the patient and malaria status.

Unlike artemisinin-based therapies, quinine is not considered embryotoxic or teratogenic in studies of rats [117], rabbits [55], dogs [55], or macaque monkeys [118]. The primary safety concern for quinine in pregnancy is the potential for auditory nerve damage [55]. Quinine exposures during the first trimester were not associated with an increased risk of congenital malformation in refugees along the Thai-Burma border [9, 70]. One study reported an increased risk of miscarriage and stillbirth associated with first-trimester exposure to quinine compared with AL [119]. Despite previous concerns, quinine at treatment doses does not induce abortion or labor [18].

A literature review identified six studies of the pharmacokinetics of quinine for treating uncomplicated malaria in pregnancy [95, 120–123]. The results of these studies varied in their findings, with some studies suggesting that that was no difference in the metabolism of quinine between pregnant and non-pregnant women [122], and other studies suggesting that pregnant women metabolize quinine faster than non-pregnant women, requiring further research into the proper dosing for pregnancy.

Despite quinine being used for hundreds of years for the treatment of severe malaria in pregnancy, the systematic review identified only ten relevant studies [9, 14, 16, 19, 20, 25, 26, 52, 124, 125] (Tables 2, 3). Of concern, quinine has been associated with a higher risk of hypoglycemia, which can be fatal, than treatment with artemisinins [126]. A recent systematic review identified ten studies conducted between 1997 and 2013 on the efficacy of quinine compared with artemisinin-based therapies for the treatment of uncomplicated malaria in pregnancy [66]. McGready et al. [70] reported statistically significantly lower 63-day cure rates for quinine when compared with mefloquine + artesunate (67 vs. 98.2 %; $p = 0.0001$) for the treatment of uncomplicated malaria [70]. Quinine + clindamycin had similar cure rates to those of artesunate, but significantly higher rates of side effects [83]. Additional studies noted very high mortality rates among pregnant women with severe malaria: from 0 to 80 % for those treated with intravenous quinine [16, 25].

Intravenous quinine is less well tolerated than intravenous artesunate [83]. Mild to moderate cinchonism, including tinnitus, headache, blurred vision, altered auditory acuity, nausea, and diarrhea often arise after 3 days of treatment [87]. Poor tolerability of oral quinine has been linked to lower adherence and subsequent treatment failures in patients [127–129]. A study of the compliance with artesunate compared with quinine + tetracycline found that non-pregnant patients who were taking artemisinins were more likely to be compliant with treatment [adjusted RR (aRR) 1.39, 95 % CI 1.15–1.68], and the reasons cited for non-compliance were adverse drug reactions and forgetting to take drugs [127]. Tinnitus is the most commonly reported side effect in pregnant women [85]. Pregnant women are also at risk for a rare triad of complications: massive hemolysis, hemoglobinemia, and hemoglobinuria [130]. Additional side effects include muscle necrosis and sterile abscesses due to intramuscular injections. Dose-related adverse events include cardiovascular symptoms such as transient ventricular tachycardia, and gastrointestinal and central nervous system disorders resulting from excessive infusions [87].

5.3 Partner Drugs

After initial treatment for severe malaria with intravenous quinine or artesunate, patients should receive oral regimens. The WHO recommends either quinine + clindamycin for 7 days or an oral ACT for the treatment of pregnant women [57], but the safety of these partner drugs should also be considered [131]. Quinine + clindamycin is recommended by the WHO for the treatment of malaria in the first trimester. Clindamycin, a common partner drug, has been associated with abdominal side effects, including nausea, vomiting, and diarrhea [132, 133]. However, a more recent RCT comparing quinine + clindamycin and artesunate for the treatment of uncomplicated malaria in pregnancy did not report abdominal side effects, but women in the trial taking quinine + clindamycin did experience significantly higher rates of tinnitus than did the artesunate group [83]. Because of relatively high rates of

Table 2 Studies of the treatment of severe malaria in pregnancy

References	Country (study site)	Study design	Study population	Trimester	Antimalarials	Measure of outcome	Findings
Poespoprodjo et al. [52]	Indonesia	Prospective cohort	1,806 pregnant women with malaria (559 treated with IV therapies)	1, 2, 3	QUI IV before 2006; after 2006 ART IV followed by PO DHA in 2nd or 3rd trimester or PO QUI in 1st	Stillbirth, early neonatal death	Stillbirth 3.3 % (1/30) for QUI, 4.4 % (2/45) for ART + DHP and 0 % (0/13) for ART alone; early neonatal death 3.3 % (1/30) for QUI, 0 % (0/45) for ART + DHP and 7.7 % (1/13) for ART alone; no miscarriages among 10 women exposed to ART IV in the first trimester
Elbadawi et al. [26]	Sudan	Cross-sectional	150 pregnant women with P. falciparum malaria and 50 healthy controls	1, 2, 3	QUI IV	Plasma glucose levels	QUI was associated with rise in plasma insulin concentration and decrease plasma glucose. No pts experienced hyperglycemia
Adam et al. [25]	Sudan	Prospective cohort	35 pregnant women with severe P. falciparum malaria	2, 3	QUI IV then PO for 7 days	Treatment response, pregnancy outcomes	All pts had negative blood films on day 7; 3 (6.1 %) had reoccurrences by day 20; 3 (6.1 %) delivered prematurely; no maternal or neonatal deaths, miscarriages, or stillbirths reported
Krishnan and Karnad [124]	India	Prospective cohort	301 pts aged 12–90 admitted to ICU with P. falciparum malaria (23 pregnant women)	NR	QUI IV then PO for 7 days	Mortality	Mortality rate in pregnant women was 17.4 % but was not significantly higher than mortality in men or non-pregnant women
Looareesuwan et al. [125]	Thailand	Prospective cohort	12 pregnant pts with severe malaria; and 8 women given quinine during labor	3	QUI IV then PO for 7 days	PK and toxicity in pregnancy	Hypoglycemia developed in 7 pts, 1 pt died; no increased uterine activity after administration of QUI; no stillbirths
Singh et al. [16]	India	Prospective cohort	200 pregnant pts and 140 non-pregnant women; 22 pregnant pts with high parasite density infections due to P. falciparum and P. vivax malaria	NR	QUI/Chloroquine IV	Mortality	16/20 (80 %) pregnant women treated with IV QUI died; 4/7 (36.4 %) treated with IV chloroquine died
Dondorp et al. [20]	Bangladesh, India, Indonesia, Myanmar	RCT	1,461 pts with severe P. falciparum malaria (49 pregnant women)	NR	ART or QUI IV	Mortality	9 % mortality for ART and 12 % mortality for QUI in pregnant women
McGready et al. [9]	Thailand	Retrospective cohort	48,426 pregnant women who attended an antenatal clinic (24 severe malaria cases either P. vivax or P. falciparum) during the first trimester	1	ART or QUI IV	Miscarriage	14/24 (58 %) women with severe malaria had a miscarriage; no difference in rates between ART and QUI
Kochar et al. [19][a]	India	Prospective cohort	441 adult pts with cerebral malaria age 14–74 years; 56 pregnant women	NR	PO or IV QUI	Mortality	22 (39.3 %) pregnant and 53 (32.9 %) non-pregnant women died ($p > 0.05$)

Table 2 continued

References	Country (study site)	Study design	Study population	Trimester	Antimalarials	Measure of outcome	Findings
Kochar et al. [14][a]	India	Prospective cohort	45 pregnant and 243 non-pregnant women with *P. falciparum* or mixed *P. falciparum* and *P. vivax* infection	NR	PO or IV QUI	Mortality, birth outcomes	37.8 % of pregnant women and 14.8 % of non-pregnant women died ($p < 0.05$); normal pregnancy continued in only 16 (6.5 %) primiparous and 10 (34.5 %) multiparous pregnant women

ART artesunate, *DHA* dihydroartemisinin, *ICU* intensive care unit, *IV* intravenous, *NR* not reported, *PK* pharmacokinetics, *PO* oral administration, *pt(s)* patient(s), *QUI* quinine, *RCT* randomized clinical trial

[a] Studies represent the same ongoing cohort of women

side effects and the high cost per treatment (US$18.50) [83], quinine + clindamycin may result in poor adherence in resource-poor settings.

6 Special Considerations

6.1 HIV and Severe Malaria in Pregnancy

Pregnant women have the greatest burden of the morbidity and mortality associated with co-infection with HIV and malaria [134]. HIV infection is associated with a greater risk of severe malaria [135, 136]. Despite this large burden, very little information exists about interactions between ACTs and antiretroviral therapy (ART) and the optimal treatment options for severe malaria in pregnant women with HIV. One study of the pharmacokinetics of quinine in HIV-positive pregnant women noted that quinine concentrations may be lower in women receiving nevirapine-based ART [123]. The WHO recommends that HIV-infected patients receiving zidovudine or efavirenz should avoid amodiaquine-containing ACT regimens because of reports of hepatotoxicity [57]. A review of the concurrent management of HIV in pregnancy recommends that women receiving highly active antiretroviral therapy (HAART) regimens including protease inhibitors (PIs) and/or non-nucleotide reverse transcriptase inhibitors (NNRTIs) receive quinine when cardiac monitoring is available. Parenteral artesunate or artemether should be used when quinine and cardiac monitoring are not available because of an increased risk of cardiotoxicity associated with quinine [137, 138]. Women receiving no PIs or NNRTIs may be treated with either parenteral quinine or artesunate [139]. Current clinical data suggest that artemether when co-administered with PIs or NNRTIs may result in a reduction in the active metabolite of artemether, but the clinical importance is unclear [137].

6.2 Rectal Administration of Antimalarial Drugs for Severe Malaria in the Community

The WHO recommends rectal administration of artesunate as a pre-referral treatment for severe malaria [57]. There are currently no data comparing rectal administration with intravenous and intramuscular injections of artemisinin derivatives; therefore, the WHO guidance states that suppositories only be used for pre-referral treatment. Furthermore, there are no studies of rectal administration of artesunate to treat malaria in pregnancy. According to the WHO, if referral is impossible, patients may be treated with artesunate suppositories until able to receive oral medication. A systematic review of randomized clinical

Table 3 Summary of treatment drugs for severe malaria in pregnancy

	Quinine	Quinidine	Artesunate	Artemether
Dosage	20 mg salt/kg BW on admission (IV infusion or divided IM injection), then 10 mg/kg BW every 8 h[a]	6.25 mg base/kg infused IV over 1–2 h, then continuous infusion of 0.0125 mg base/kg/min[b]	2.4 mg/kg BW or IM at admission then at 12 h and 24 h, then once a day[a]	3.2 mg/kg BW IM at admission, then 1.6 mg/kg BW per day[a]
Efficacy	Lower cure rates vs. ART	No data available on efficacy in pregnancy	More efficacious in adults and children than QUI	No data on efficacy in pregnancy; equivalent to QUI in adult populations
Pharmacokinetics	Some studies suggest pregnant women metabolize QUI faster than do non-pregnant women	No data available on pharmacokinetics in pregnancy	Limited data suggest that pregnant women may have accelerated clearance of the metabolite DHA	Pregnant women have lower concentrations metabolite DHA than non-pregnant women; erratic drug release
Tolerability	Mild to moderate cinchonism including tinnitus, headache, blurred vision, altered auditory acuity, nausea, and diarrhea	No data on tolerability in pregnancy	Good tolerability vs. QUI. Some nausea and vomiting but may be due to malaria infection	Good tolerability. Some swelling and pain at injection site
Safety in pregnancy	Safe in pregnancy	Safe in pregnancy	Teratogen in animal studies; limited human studies found no association between exposure and miscarriage, stillbirth, or congenital anomalies	Teratogen in animal studies; limited human studies found no association between exposure and miscarriage, stillbirth, or congenital anomalies
Other serious adverse events	Increased risk of hypoglycemia	Increased risk of QT prolongation requiring electrocardiographic monitoring, hypoglycemia	Delayed hemolysis reported (day 7–31)	None reported; limited data
Interactions with HAART	Women on PIs and NNRTIs need cardiac monitoring due to cardiotoxicity	No data on interactions with HAART	Preferred choice for women on PIs and NNRTIs	When co-administered with PIs or NNRTIs may result in a reduction in the active metabolite of artemether
WHO Recommendation	Recommended to be used in first trimester or in 2nd and 3rd trimester if ART and artemether unavailable	Recommended to be used in the USA;[b] Not recommended by WHO	Recommended treatment for severe malaria in 2nd–3rd trimester, can be used in 1st trimester	Recommended to be used if ART is unavailable

ART artesunate, *BW* bodyweight, *CDC* Centers for Disease Control and Prevention, *DHA* dihydroartemisinin, *HAART* highly active anti-retroviral therapy, *IM* intramuscular, *IV* intravenous, *NNRTI* non-nucleotide reverse transcriptase inhibitors, *PI* protease inhibitor, *QUI* quinine, *WHO* World Health Organization

[a] Treatment guidelines according to WHO

[b] Treatment guidelines according to CDC

trials of pre-referral rectal administration of artesunate identified only one study. The study found a protective effect in young children who received rectal artesunate compared with placebo (RR 0.74, 95 % CI 0.59–0.93), but older children and adults were at greater risk of death than the placebo group (RR 2.21, 95 % CI 1.18–4.15) [140]. Despite these contradictory findings, it is critical to treat malaria early, especially in pregnancy.

6.3 Drug Quality

Poor-quality antimalarials have important health consequences, including the potential for treatment failure, development of antimicrobial resistance, and serious adverse drug reactions. Treatment with counterfeit oral artesunate has led to deaths due to severe malaria [141]. Reports from surveys conducted in sub-Saharan Africa (SSA) samples and south-east Asia indicate that orally administered antimalarial drugs are commonly of poor quality [142]. Nayyar et al. [143] reviewed published and unpublished studies and found that 35 % (497/1,437) of samples from south-east Asia failed chemical testing. Using the same criteria, this analysis also reported that 35 % (796/2,297) of samples from SSA failed chemical analysis. Substandard drugs fail to meet the specifications set forth by a regulatory agency and as specified in a standard pharmacopeia or the manufacturer's dossier. Most surveys of drug quality emphasize sampling from licensed pharmacies and dispensaries, not hospitals or even the informal, unregulated markets. WHO pre-qualification process that includes dossier reviews, site inspections, and recognition of approval by stringent regulatory agencies are the methods used by donors for assuring the quality of medicines, including antimalarials [144]. One manufacturer of injectable artesunate, Guilin Pharmaceuticals, achieved WHO pre-qualification status in 2010 [145]. A multitude of methods are used to assess the quality of medicines and can be implemented at the health facilities and ports of entry [146]. Ensuring the quality and safety of antimalarials is critical in the treatment of severe malaria.

7 Discussion and Conclusions

Severe malaria (*P. falciparum* as well as *P. vivax* malaria) in pregnancy presents an immediate danger to the life of the mother and fetus, and therefore effective treatment must be delivered immediately. Despite the importance of malaria in pregnancy, we identified only ten studies that presented treatment outcomes of pregnant women with severe malaria, demonstrating a paucity of data. Multiple studies have shown that artemisinin derivatives,

specifically artesunate, are more effective at treating severe malaria than quinine [9, 20, 52, 56]. Others have reported on the economic advantages of intravenous artesunate over intravenous quinine [147, 148]. Despite concerns about the signal from animal studies of the embryo-lethality and teratogenicity of artemisinins, no studies have shown an association between artemisinin exposures during pregnancy and increased risk of miscarriage, stillbirth, or congenital anomalies in humans [9, 75, 76]. Safety data suggest a need for strong pharmacovigilance, especially regarding the reported delayed hemolysis after treatment with intravenous artesunate. As the use of intravenous artesunate expands, the potential to detect rare but severe adverse events will increase with the proper surveillance. Additionally, pharmacovigilance systems are necessary to aid in combatting the threat of falsified and substandard antimalarials [149].

Given the high morbidity and mortality associated with severe malaria in pregnancy, additional research is needed on the pharmacokinetics of intravenous and intramuscular artemisinin derivatives in pregnancy. Multiple studies have suggested that pregnancy and malaria infection alter the metabolism of artemisinins, and therefore the ideal therapeutic dosages in pregnancy are unclear. Furthermore, additional research is needed on the efficacy of pre-referral use of rectal artesunate in pregnant women with severe malaria.

The current evidence suggests that intravenous artesunate should be used in preference to intravenous quinine for the treatment of severe malaria in first-trimester pregnancies. We recommend that WHO guidelines consider artesunate as the preferred treatment for severe malaria in pregnancy during all three trimesters in order to ensure that pregnant women receive the most efficacious treatment. We also recommend that the US Food and Drug Administration (FDA) approve artesunate for the treatment of severe malaria, therefore allowing the CDC to update its treatment guidelines to recommend the most efficacious treatment. Recommendations for the treatment of severe malaria in pregnancy must balance efficacy with prevention of serious adverse advents by incorporating new evidence as it becomes available.

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