INTER-AGENCY TECHNICAL BRIEF

Treatment of uncomplicated *P. falciparum* malaria in the first trimester of pregnancy: Implementation of the revised WHO treatment guidelines (25 November 2022)

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Abbreviations

AAP	artesunate+atovaquone-proguanil
ABTs	artemisinin-based treatments
ACT	artemisinin-based combination therapy
aHR	adjusted Hazard Ratio
AL	artemether-lumefantrine
ASAQ	artesunate-amodiaquine
ASMQ	artesunate-mefloquine
DHA-PQP	dihydroartemisinin-piperaquine
G6PD	glucose-6-phosphate dehydrogenase
IPD	individual-patient data
IPTp	intermittent preventive treatment in pregnancy
ITNs	insecticide-treated nets
non-ABTs	non-artemisinin-based treatments
PYR-AS	pyronaridine-artesunate
SP	sulfadoxine-pyrimethamine
WHO	World Health Organization

Summary

On 25th November 2022, the World Health Organization (WHO) updated the guidelines for the treatment of uncomplicated malaria in the first trimester to include artemether-lumefantrine as the preferred treatment option[1]. The recommendation was based on a review of the evidence on the safety of artemisinin-based treatments used in early pregnancy. An updated meta-analysis of prospective observational studies of pregnancies exposed to artemisinin and non-artemisinin antimalarials in the first trimester showed no evidence of teratogenicity or embryotoxicity based on the risk of miscarriage, stillbirth, or major congenital anomalies associated with artemisinin treatments. Pregnancies treated in the first trimester with artemether-lumefantrine, the artemisinin-based combination therapy (ACT) with most safety data available for the first trimester, had a 42% lower risk of adverse pregnancy outcomes than those treated with oral quinine. The safety data from this meta-analysis, together with the superior tolerability and better adherence, higher efficacy, longer duration of post-treatment prophylaxis, and wide availability of ACTs, is the basis for the WHO recommendation that artemether-lumefantrine is the preferred treatment for uncomplicated *P. falciparum* malaria in the first trimester of pregnancy. For countries where AL is not recommended or not available, other ACTs such as artesunate-amodiaquine (ASAQ), dihydroartemisinin-piperaquine (DHA-PPQ) or artesunate-mefloquine (ASMQ) can be used. All malaria-endemic countries are to consider updating their national treatment guidelines to implement the new recommendation to ensure all pregnant women are treated with the best possible treatment in the first trimester.

Background

Malaria infection during pregnancy is a major public health problem, with the potential to cause severe maternal and fetal morbidity and mortality. Recent studies have shown that malaria in the first trimester induces maternal anaemia, fetal death, and fetal growth impairment, even when infections are subclinical.[1] The World Health Organization (WHO) recommends a three-pronged approach to prevent the consequences of malaria in pregnancy including the provision of intermittent preventive treatment in pregnancy (IPTp) using sulfadoxine-pyrimethamine (SP), the use of insecticide-treated nets (ITNs), and appropriate case management through prompt and effective treatment of malaria in pregnant women.[2] IPTp with SP is not recommended in the first trimester, i.e., before 13 weeks of gestation as the use of folate antagonists in the first trimester is associated with neural tube defects.[3],[4] Prompt and effective diagnosis and treatment of malaria infections in the first trimester of pregnancy is therefore particularly important, as is the use of ITNs to prevent infections. The WHO has

[1] https://www.who.int/publications/i/item/guidelines-for-malaria

recommended artemisinin-based combination therapies (ACTs) as first-line treatment for uncomplicated *falciparum* malaria in the general population since 2001, and in the second and third trimesters of pregnancy since 2006. Previously, quinine with or without clindamycin was recommended for the treatment of malaria in the first trimester, and ACTs were not recommended because of the embryotoxicity of artemisinin and its derivatives identified in animal studies unless no alternative treatment was available.[5,6] Also, until now, there was limited information on safety following inadvertent exposures of pregnant women in the first trimester to ACTs, although ACTs are widely available in both public and private antimalarial retail markets.[7,8] Observational studies have revealed that in practice, women in their first trimester were more likely to be treated with an ACT than with quinine in sub-Saharan Africa.[9-12] This is because women may not know or declare they are pregnant at the time of seeking care, and healthcare providers do not always assess pregnancy status in women of reproductive age. Also, there is a lack of compliance to quinine + clindamycin treatment regimens by both health workers and pregnant women due to poor tolerability and the complex 7-day treatment regimen, and clindamycin is often unavailable.

In April 2022, WHO convened a Guideline Development Group meeting on malaria chemotherapy to develop new recommendations based on a review of new evidence on the safety of ACTs for treatment in the first trimester of pregnancy. This new evidence was based on an updated meta-analysis of safety data from documented human exposures in the first trimester from Asia and Africa (737 **artemisinin-based treatments** (ABTs) and 1,076 **non-artemisinin-based treatments** (non-ABTs). Results indicated that ABT exposure in the first trimester of pregnancy does not increase the risk of miscarriage, stillbirths or major congenital anomalies compared to non-ABTs including quinine.[13] Furthermore, first-trimester treatment with artemether-lumefantrine (AL) was associated with significantly fewer (42% lower) adverse pregnancy outcomes than first-trimester oral quinine treatment. These data together with evidence of better efficacy, post-treatment prophylaxis, tolerability, and adherence in the second and third trimester of pregnancy[14-16,17,18] indicate that **the 3-days, twice daily artemether-lumefantrine regimen, the ACT with the most safety evidence available, should replace the 7-day, 8-hourly quinine regimen as the preferred treatment for uncomplicated *P. falciparum* malaria in the first trimester of pregnancy.**

Based on the updated review, **WHO has generated a strong recommendation on the treatment of uncomplicated malaria in the first trimester of pregnancy**[19] and recommends national health authorities to implement the recommendation as part of their national treatment policies.

New WHO recommendation on malaria case management in the first trimester of pregnancy (STRONG RECOMMENDATION, LOW CERTAINTY OF EVIDENCE)[19]

Treat pregnant women with uncomplicated *P. falciparum* malaria with artemether-lumefantrine during the first trimester.

- Limited exposures to other ACTs (artesunate-amodiaquine, artesunate-mefloquine and dihydroartemisinin-piperaquine) suggest that the current evidence is insufficient to make a recommendation for routine use of these other ACTs in the first trimester of pregnancy. However, consistent with the previous WHO recommendation that provided for limited use of ACTs if the first-line recommended medicine was not available, these other ACTs may be considered for use where artemether-lumefantrine is not a recommended ACT for uncomplicated malaria or is not available, given the demonstrated poorer outcomes of quinine treatment, along with the challenges of adherence to a seven-day course of treatment.
- Antifolates are contraindicated in the first trimester of pregnancy. Therefore, ACTs containing sulfadoxine-pyrimethamine are contraindicated during the first trimester of pregnancy.
- There is currently no documented record of the use of artesunate-pyronaridine during the first trimester of pregnancy.
- Continued pharmacovigilance and clinical research, including prospective controlled trials on the efficacy and safety of antimalarial medicines for the treatment of malaria in pregnancy, should be supported

Expected benefits

- The adoption of the new WHO recommendation helps to simplify national treatment guidelines for uncomplicated *P. falciparum* malaria **as all adults, regardless of pregnancy status, can now be treated with AL**. Pregnancy will no longer need separate malaria treatment guidelines in settings where AL is the first line treatment. This will reduce confusion among health care workers about treatment of pregnant women.
- ACTs are faster acting and more effective with longer post-treatment prophylactic effects than quinine. It is expected that adherence, and therefore effectiveness, will be higher with AL than with quinine because the course is shorter, the regimen simpler to administer and better tolerated than quinine.

Considerations for implementation of the new recommendation

Indication

- The use of AL in the first trimester is recommended only for uncomplicated case management of malaria. AL is not currently recommended for malaria *prevention* strategies (i.e., intermittent preventive treatment, or mass drug administration, etc.) as the benefit-risk balance is different for uninfected patients which may not directly benefit from treatment and due to the remaining uncertainty of potential rare drug induced adverse pregnancy outcomes.
- Lumefantrine blood concentration on day-7 was reported to be significantly lower in pregnant than non-pregnant woman[20]; however, current AL dosing guidelines should be followed until dose optimization for pregnant women is determined. Absorption of AL is significantly increased by taking the medicines with fat.[20,21]

Sourcing of medicine and supply chain management

- Only AL of proven quality should be used. Sources of WHO-prequalified medicines can be found via the following link: https://extranet.who.int/prequal/content/prequalified-lists/medicines. WHO has prequalified several finished pharmaceutical products of artemether-lumefantrine with tablet strengths of 80mg/480mg which allow a reduction in the number of tablets per dose for adult patients. The Global Fund List of Pharmaceutical Products compliant with the quality assurance policy is accessible via: https://www.theglobalfund.org/media/4756/psm_productsmalaria_list_en.pdf. Both lists are regularly updated.
- As AL is already widely procured in settings where it is first line therapy, the additional procurement of AL to treat malaria in the first trimester should have minimal impact on supply chain management of antimalarials.[9-12]
- For countries where AL is not the recommended first-line treatment or is not available, then artesunate-amodiaquine (ASAQ), artesunate-mefloquine (ASMQ) and dihydroartemisinin-piperaquine (DHA-PPQ) may be used for treatment of uncomplicated malaria in the first trimester of pregnancy.
- The price of ACTs including AL is generally higher than quinine in the private sector. In many countries, malaria treatment in the public sector is provided free of charge to children under five and pregnant women.
- It will be important to ensure stock of oral quinine and clindamycin in case of known allergy to AL or other ACTs.[22]

Safety monitoring

- Monitoring the safety of antimalarial treatment in pregnancy is important and should continue to provide further reassurance, in particular to gather more data on ACTs other than AL as well as for specific congenital anomalies.[15] Malaria endemic countries are urged **to set up active pharmacovigilance surveillance for antimalarial drugs used in the first trimester of pregnancy**. There are several publications on the methods and protocols to assess drug safety in pregnancy in low-middle income countries.[23-25] Such active pharmacovigilance surveillance of pregnant women should be widely promoted, and healthcare providers should be encouraged to enroll women treated with antimalarials in pregnancy to enhance participation and recruitment. Research projects and surveillance programmes should be integrated at the country level and countries are encouraged to routinely contribute safety data to this WHO international registry.
- Key considerations for countries collecting safety data on antimalarial use in pregnancy are:
    - More data are needed on different ACTs as over 70% of the safety data gathered to date is for AL.
    - More data are needed on congenital anomalies, particularly on internal anomalies such as cardiovascular defects. This will require systematic assessment of in-utero exposed newborns by trained healthcare professionals.
    - Accurate pregnancy dating and pre-treatment fetal viability will also be needed to expand the cohort of women exposed in the putative embryo-sensitive window period.
    - The methodology for reporting pregnancy outcomes including miscarriage and stillbirth needs wider promotion and uptake.[26]
    - Given the relatively common co-occurrence of malaria and HIV, it is important to consider potential drug-drug interactions between antimalarials and antiretroviral treatment regimens.
    - Messages about the safety of drugs in pregnancy and the importance of assessment of pregnancy status at the point of care should be promoted to encourage rational drug use in this vulnerable group. This will require some behaviour change communication and addressing social norms around pregnancy.

Strengthening health systems

- National malaria control programmes should ensure inclusion of AL in national malaria control strategies and wide dissemination of clear malaria treatment guidelines based on the WHO recommendation, and ensure this is reflected in relevant guidelines for antenatal care and community healthcare workers in settings where they provide treatment for malaria.
- This change in policy is an opportunity to strengthen national technical working groups focusing on, or including, malaria in pregnancy to improve the quality and coverage of malaria in pregnancy interventions.
- Capacity development to improve healthcare workers' knowledge is important. Several studies have shown poor health care provider knowledge and poor patient adherence to malaria treatment in pregnancy as recommended in national treatment guidelines[12,27]; determinants of provider adherence need to be assessed in both the public and private sectors.[28]
- It will also be important to identify potential barriers to the use of ACTs in the first trimester at the patient/user level and in communities, as well as implementation barriers among health care providers and other stakeholders (including community leaders, programme managers, donors, policy makers and opinion leaders).[28]

Rationale for this update

Restriction of the use of ACTs during the first trimester of pregnancy was based on embryo toxicity identified in animal studies[6,29] and limited information on human exposures. The previous WHO reviews on the safety of artemisinin antimalarials in the first trimester of pregnancy took place in 2002 and 2006.[30,31] At the time of the second consultation, the evidence reviewed was limited to 170 first trimester human exposures from Thailand which was insufficient to assess whether the embryotoxicity observed in animal studies could also occur in humans. Since this initial consultation, several studies have provided additional information on the safety of artemisinin antimalarials in early pregnancy with data on over 1000 pregnancies treated in the first trimester with an artemisinin derivative (see Annex 2). **None of these studies found any evidence of artemisinin teratogenicity or increased risk of pregnancy loss compared to pregnant women exposed to quinine treatment.** In 2015, WHO convened an Evidence Review Group meeting on malaria in pregnancy[32] including a review of new evidence from a meta-analysis of safety data from documented human exposures in the first trimester from Asia and Africa (717 artemisinin and 947 quinine) which indicated that ACT exposure in the first trimester of pregnancy does not increase the risk of miscarriage, stillbirths or major congenital anomalies compared to quinine.[33] Although the Evidence Review Group and the Malaria Advisory Committee at the time recommended an update to the treatment guidelines to "consider the timely inclusion of ACTs as a first-line therapeutic option for uncomplicated *P. falciparum* malaria"[34], this did not materialise. In 2021, WHO requested an update to the original meta-analysis with any new safety data that has become available since 2015, with the goal to re-review the evidence on the safety of artemisinin used for the treatment of malaria in the first trimester of pregnancy.

In addition to the evidence summarised in the WHO Malaria Guidelines[19], WHO is preparing an update of a technical report on the safety of artemisinin and non-artemisinin antimalarials in the first trimester of pregnancy providing a thorough review of the evidence.[71]

Comparative data on the treatment of uncomplicated malaria with artemisinin antimalarials and quinine

There are currently no randomized controlled trials comparing the safety and/or efficacy of ACTs and quinine in the first trimester. A comparison of key characteristics of ACTs and quinine is shown in Table 1.

Evidence from clinical trials in non-pregnant adults and second/third trimester pregnancies show that ACTs are more effective than quinine-based therapies for the treatment of uncomplicated malaria.[14-16,35] A meta-analysis of four randomised controlled trials from sub-Saharan Africa and Thailand for uncomplicated *P. falciparum* malaria in the second and third trimesters showed that ACTs were more effective than oral quinine-based therapies with faster parasite clearance, lower PCR-corrected treatment failure rates, lower gametocyte carriage, and higher mean birth weights.[14] A recent meta-analysis of 48 efficacy studies confirmed that ACTs had significantly lower risk of treatment failure compared to quinine-based treatments in pregnancy.[15] This was confirmed by a recent meta-analysis reporting 2nd and 3rd trimester pregnancies treated with quinine were at 6-fold higher risk of treatment failure compared to those treated with AL.[16] ACTs were found to be much better tolerated than quinine, which is associated with cinchonism presenting as tinnitus, nausea, headache and blurred vision. In addition, adherence to ACTs, taken 1 or 2 times daily over 3 days, is expected to be higher than for quinine which has to be taken 3 times daily for 7 days.[36]

Table 1 Summary comparison of ACTs and Quinine

	Artemisinin-based combination therapies	Quinine

Safety and tolerability	• Common side effects include nausea, vomiting, and diarrhoea, which are also symptoms of malaria itself.[37,38] Side effects are generally mild; severe adverse events are rare.
	• There have been concerns for teratogenicity in early pregnancy due to animal embryo-toxicity (in rats, rabbits and monkeys) of artemisinin as a class at low dose.[29]
	• ACT partner drugs:
	  • SP, an antifolate, is contraindicated in the first trimester,
	  • lumefantrine, amodiaquine,[39] and piperaquine are considered likely to be safe,
	  • mefloquine is approved for use in the first trimester (US and UK)[40]
	  • data of pyronaridine use in any trimester of pregnancy are limited, although no safety signals were reported with pyronaridine in pre-clinical studies.[40]
	• Pregnancy registries found no increase in the risk of pregnancy loss (miscarriage or stillbirth), or major congenital anomalies associated with artemisinin exposures early in pregnancy compared to quinine.[33,41]
		• Poor tolerability; nausea, vomiting, and cinchonism are common but mild and resolve relatively rapidly upon stopping drug.35,36 Hypoglycaemia is a common side effect, particularly in pregnant women, and can be mild or severe. Serious adverse events are rare and include skin eruptions, asthma, thrombocytopaenia, hepatic injury, psychosis, cytopenia, and haemolytic-uremic syndrome.42
		• Recommended in pregnancy although evidence is mostly historical (no trial data in 1st trimester).
		• Animal studies reported that quinine affected the development of the brain and inner ear in the rabbit, chinchilla, and guinea pig at dose close to or below the therapeutic dose for malaria. Quinine caused embryonic deaths in the rabbit, mouse, chinchilla, and dog at relatively low dose.40

Efficacy	• No randomized controlled trials have been performed using either ACTs or quinine for treatment of malaria in the first trimester of pregnancy. • ACTs have better efficacy than quinine in 2nd/3rd trimester of pregnancy and non-pregnant populations for uncomplicated malaria.[14,15] • Longer duration of post-treatment prophylaxis conferred by ACTs is another important benefit in pregnancy as they prevent new infections for several weeks, whereas quinine has no post-treatment prophylactic effect due to its short half-life.[17,18] • Parenteral artesunate treatment is superior to quinine in the treatment of severe malaria.[2,43, 44]	
Drug resistance	• Emergence of partial-resistance to artemisinins in southeast Asia[45,46] and parts of sub-Saharan Africa (Uganda, Rwanda and Eritrea).[47] • Treatment failure <10% for AL and AS-AQ in some areas of Africa.[15,46]	• Quinine resistance documented in southeast Asia.[48] • Limited evidence of quinine resistance in Africa.[35,49]
Administration /patient adherence	• 2 times daily for 3 days • AL best taken with fat (meal) to ensure adequate lumefantrine absorption[20] • Adherence varies by setting and population[50,51]	• 3 times daily for 7 days • Adherence is low due to poor tolerability and long treatment regimen[36] • Poor adherence to recommended use with clindamycin
Cost	• Prices of ACTs have decreased substantially in recent years and are comparable to those for quinine.[7,8]	• Quinine is inexpensive, but the price of the combination of quinine and clindamycin is high.
Availability	• Fixed-dose ACTs are widely available and recommended as first line therapy for treatment of uncomplicated malaria in most malaria endemic countries. Coverage in both public and private sector has increased.	• Quinine has been widely available, although use of combination therapy with clindamycin is rare, particularly in Africa. • In the private sector, multiple quinine brands, with different salts and tablet strengths, makes the administration of correct treatment doses difficult. • There have been reports of limited availability and supply of quinine in the public sector in parts of Africa as it is solely used for 1st trimester patients.

A recent updated systematic review and individual-patient data (IPD) meta-analysis of seven prospective studies (including 12 cohorts) found no increase in the risk of adverse pregnancy outcomes (composite including miscarriage, stillbirth or major congenital anomalies) associated with artemisinin exposures in the first trimester of pregnancy (n=736) compared to non-artemisinin based exposures (n=1074 [85% were quinine], adjusted Hazard Ratio (aHR: 0·71, 95% confidence interval 0·49-1·03) (Table 2).[13] Fourteen studies were identified reporting artemisinin exposure in the first trimester, of which seven were eligible and all included in the IPD analysis; five from sub-Saharan Africa and one from the Shoklo Malaria Research Unit (SMRU) on the Thailand-Myanmar border.

AL was the only ACT with sufficient data for a sub-group analysis. The risk of adverse pregnancy outcomes was lower with AL than with oral quinine in the first trimester (25/524 [4·8%] vs 84/915 [9·2%], aHR=0·58, 0·36-0·92). Similar results were seen for the individual components: miscarriage (AL=15/465] vs Quinine=68/915, aHR=0·67, 0·37-1·23), stillbirth (AL=10/488 vs quinine=12/592, aHR=0·53, 0·22-1·24). There were no major congenital anomalies in the AL exposed group and the estimated upper limit of prevalence of major congenital anomalies was similar to that observed in the quinine or unexposed group. The corresponding risk of adverse pregnancy outcome in analysis restricted to exposure to artemisinins during the putative embryo-sensitive period (6–12 weeks of gestation) was aHR = 0·95 (0·63–1·45).

Table 2. Summary of effect estimates from the meta-analysis data reviewed by WHO: Adverse pregnancy outcomes in women treated with antimalarials in the first trimester.

Outcomes	Number of participants		Adjusted Hazard ratio (95% CI)	Risk difference (95% CI)
	non-ABT#	ABT*		
Composite	96/1074	42/736	0.71 (0.49,1.03)	-25 (-45, 3)
Miscarriage	76/1070	27/669	0.74 (0.47,1.17)	-18 (-37, 12)
Stillbirth	12/743	13/646	0.71 (0.32, 1.57)	-5 (-11, 9)
Fetal loss	88/1074	40/736	0.70 (0.47, 1.02)	-24 (-43, 2)
Major congenital anomalies	8/1074	2/736	0.60 (0.13, 2.87)	-3 (-6, 14)
	Quinine	AL		
Composite	84/915	25/524	0.58 (0.36-0.92)	-37 (-58, -7)
Miscarriage	68/913	15/464	0.67 (0.37-1.23)	-24 (-46, 16)
Stillbirth	12/590	10/488	0.53 (0.22-1.24)	-10 (-16, 5)
Fetal loss	80/915	25/524	0.56 (0.35-0.90)	-37 (-56, -8)
Major congenital anomalies	4/915	0/524	NA	NA

Acronyms: ABT, artemisinin-based treatment; non-ABT, non-artemisinin-based treatment; AL, artemether-lumefantrine.

*ABT included in the analysis: 637 ACT (525 AL, 32 ASAQ, 58 ASMQ, 19 DHA-PPQ, 3 artesunate+atovaquone-proguanil), 95 AS (with and without clindamycin), 5 parenteral artesunate.

#Non-ABT included in the analysis: 917 oral quinine (715 quinine monotherapy, 202 quinine+clindamycin), 9 parenteral quinine, 147 chloroquine, 1 mefloquine, 1 atovaquone-proguanil, 1 quinine+mefloquine

Annex 1. Frequently Asked Questions (FAQs)

Which antimalarials are considered safe in the first trimester of pregnancy?

Antimalarials considered safe in first trimester	Antimalarials with limited data on use in first trimester of pregnancy	Antimalarials contraindicated in first trimester
• Chloroquine • Amodiaquine • Quinine • Clindamycin • Mefloquine • Artemether-lumefantrine	• Dihydroartemisinin-piperaquine* • Mefloquine-artesunate* • Amodiaquine-artesunate* • Pyronaridine-artesunate¥	• Sulfadoxine-pyrimethamine# • Trimethoprim-sulfamethoxazole# • Primaquine • Tafenoquine • Doxycycline • Tetracycline

- *Can be prescribed in 1st trimester if artemether-lumefantrine is not available.
- ¥ Not currently recommended in the 1st trimester due to very limited data on human exposures in the 1st trimester (see annex 2).
- # Contra-indicated in first trimester but approved for use in 2nd and 3rd trimesters.

For more details on pre-clinical and clinical data on these antimalarial in the first trimester see WHO report "Safety of artemisinins and non-artemisinin antimalarials in the first trimester of pregnancy: review of the evidence".[71]

Can AL be used for the treatment of malaria infections with other Plasmodium species including P. vivax?

The current WHO guidelines for malaria treatment recommend treating adults and children with uncomplicated P. vivax, P. ovale, P. malariae *or* P. knowlesi malaria with either an ACT or chloroquine (in areas with chloroquine-susceptible infections, see section 5.2.1.5[19]). The same recommendations apply for treatment with ACTs in the first trimester of pregnancy, namely to treat pregnant women with uncomplicated malaria with AL during the first trimester. If AL is not a recommended ACT for uncomplicated malaria or is not available, other ACTs may be used except artesunate + sulfadoxine-pyrimethamine or pyronaridine-artesunate.

Why are there no randomized clinical trials of antimalarials in the first trimester?

Clinical trials that assess the safety and efficacy of new drugs, including antimalarials, typically exclude pregnant women due to fear of harm to the mother and her fetus. The period of particular concern is the first trimester (gestational age <13 weeks) when organogenesis occurs, and the fetus is most vulnerable to potential developmental toxicity. Recruiting women this early in pregnancy is ethically and practically challenging. Therefore, evidence for treating pregnant women in early pregnancy is scarce and to date has been based on observational studies from inadvertent exposure rather than interventional clinical trials. However, it has taken over 20 years to generate robust evidence for AL from observational studies. There is increasing recognition that data gaps on the safe use of medicines in pregnant women generally need to be addressed ethically and rapidly. In addition, there is growing international support for trial designs that are more inclusive of pregnant participants. It is important to assess the options for conducting clinical trials of antimalarial treatments in the first trimester to enable these pregnant women to promptly access the best treatments.

What is the level of risk associated with artemisinin that can be excluded with the current evidence?

Level of risk detectable for miscarriage and stillbirth

A recent meta-analysis of seven prospective cohort studies found no increase in the risk of adverse pregnancy outcomes (including miscarriage, stillbirth or major congenital anomalies) associated with artemisinin exposures early in pregnancy (Table 2).[13] This study could exclude an increase in miscarriage (spontaneous fetal loss before 28 weeks gestation) risk greater than 1.45-fold (as suggested by the upper limit of the confidence interval for the most conservative estimate looking at the postulated embryo-sensitive period for artemisinin and a 3.18-fold or greater increase in the risk for stillbirth (fetal loss at or after 28 weeks gestation).

Level of risk detectable for major congenital anomalies

The meta-analysis of observational studies showed no difference in the prevalence of major congenital anomalies (defined as any structural anomaly deemed to be of surgical, medical, or cosmetic importance at birth, detected by surface examination of livebirths by trained birth attendants) between first trimester exposures to artemisinin-based treatments (ABTs) compared to non-ABTs (aHR 0·60, 95%CI 0·13–2·87) or those unexposed to antimalarials in the first trimester (aHR 0·99, 95%CI 0·24–4·03). No major congenital anomalies were observed in the AL-exposed group (0/482), and the 95% CI estimates suggest that the prevalence of major congenital anomalies would lie between 0% and 0·79%. This upper confidence limit is similar to the 0·69% background rate of major congenital anomalies detected at birth by surface examination in the group unexposed to antimalarials (182/26270, 95% CI 0·60–0·80) and the in the quinine-exposed group (4/545, 0·74%, 95%CI 0·29–1·88). Neither limb deformities nor congenital heart defects, which were reported in animals, were observed in ABT-exposed pregnancies, although cardiac auscultation of newborns was systematically assessed only in one study and other studies did not systematically screen for heart defects. Major congenital anomalies observed in ABT-exposed pregnancies included a cleft lip and palate, a case of bilateral syndactyly and one case of imperforated anus. This study could exclude an increased risk of major congenital anomalies greater than 3.49-fold (as suggested by the upper limit of the confidence interval for the most conservative estimate looking at the postulated embryo-sensitive period for artemisinin.

Annex 2. Number of confirmed exposed pregnancies for each artemisinin treatment type

Author	Country	Publication Year	Number of confirmed first trimester exposures	AL	DHA - PPQ	AS - AQ	AS - MQ	AAP	AS - SP	PYR - AS	AS	AS (IV/IM)
McGready[59,60]	Thai-Myanmar Border	Published and Unpublished between 2000-2020	351	28	28	0	65	3			228	10
Deen[61]	The Gambia	2001	77						77			
Adam[62]	Sudan	2001	1									1
Adam[63]	Sudan	2009	62	3					11			48
Dellicour[64]	Senegal	2013	7			7						
Manyando[65]	Zambia	2010	156	156								
Rulisa[66]	Rwanda	2012	96	96								
Mosha[10]	Tanzania	2014	168	168								
Poespoprodjo[67]	Indonesia	2014	18		13							10
Dellicour[9,25]	Kenya	2017	85	85								
Sevene[25]	Mozambique	2017	21	21								
Tinto[25]	Burkina Faso	2017	41	1		40						
Ahmed[68]	Indonesia	Unpublished	204		204							
Gomes[24]	Kenya, Ghana, Tanzania, Uganda	2022	15	10	2	2						1
Rouamba[69]	Burkina Faso	2022	19	7	5	5					2	
Rouamba[70]	Burkina Faso	2020	13			13						
Lutete [58]	DRC	2021	6							6		
Total	**13**	**2000-22**	**1340**	**575**	**252**	**67**	**65**	**3**	**88**	**6**	**230**	**70**

Acronyms: AAP, artesunate+atovaquone-proguanil; AL, artemether-lumefantrine; AS-AQ, artesunate-amodiaquine; AS, artesunate; AS-SP, artesunate + sulfadoxine-pyrimethamine; DHA-PPQ, dihydroartemisinin-piperaquine; DRC, Democratic Republic of the Congo IM, intramuscular; IV, intravenous; AS-MQ: artesunate-mefloquine, PYR-AS: pyronaridine-artesunate.

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