Antimalarial drugs and pregnancy: safety, pharmacokinetics, and pharmacovigilance

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Before a recommendation for antimalarial drug use in pregnancy is made, it is essential that we understand the potential risks involved and have mechanisms in place to monitor risk during treatment. This requires data on drug disposition during pregnancy and potential toxicological liabilities to the developing fetus and mother. In most cases this information is not available. We review the reproductive toxicology of the main antimalarial drug classes in use or under development. Preclinical data are presented if appropriate, but as human experience overrides such data, in instances in which preclinical studies do not correlate with the human experience the data are reviewed only briefly. Additionally, we highlight the lack of appropriate drug disposition data in pregnancy and suggest mechanisms that can be used to capture data on risk after drug treatment in pregnancy.

Introduction

Despite the clear need for safe and effective antimalarial drugs for use in pregnancy, the pharmaceutical industry is reluctant to develop drugs specifically for this indication, and in almost all cases in which a new drug is being developed, use in pregnancy is contraindicated. This situation indicates the difficulties, risks, and costs associated with proving human safety throughout pregnancy by the use of traditionally designed clinical trials. In the case of malaria in pregnancy, the assessment of risk caused by drug administration is further compounded by the lack of quality baseline data on birth outcomes within the target populations. In practice, clinicians make decisions to use drugs in pregnancy on the basis of their pragmatic assessment of the risk–benefit ratio to the mother and the unborn child. In this way, experience of drug use in a specific clinical setting, gathered sporadically over many decades, accumulates to the point at which the drug is thought to be safe for use. A good example of such a process has been the acceptance of chloroquine as a drug suitable for use in all three trimesters of pregnancy, before its fall from favour because of parasite resistance. This unstructured approach to securing safety data in pregnancy is no longer acceptable because we anticipate the development and use of new antimalarials and antimalarial combinations at a time when treatment options for pregnant women are so limited (table).

Preclinical and clinical drug safety

Preclinical toxicology and, more importantly, preclinical reproductive toxicology (including embryotoxicology and teratogenicity), a pre-requisite to modern-day drug registration, provides some measure of potential human risk. However, these models are not always predictive and can never replace clinical experience.

4-Aminoquinolines

Chloroquine, extensively used in pregnancy, is generally thought to be safe for mother and fetus at the therapeutically recommended dose.[2] Treatment of *Plasmodium falciparum* malaria in pregnancy in Kenya[3] and Tanzania[4] have indicated the drug to be safe, although with the problem of treatment failure because of parasite resistance. A previous review provided details of all studies in which chloroquine has been used in pregnancy, including 755 first trimester exposures.[5] These studies, although generally indicating safety, did include cases of ototoxicity and retinal toxicity from the older literature.[6,7] These risks are not substantiated by recent data. Data secured from the use of hydroxychloroquine for non-malaria indications indicate that this 4-aminoquinoline analogue is safe in pregnancy.[8,9] The other clinically available drug in this class, amodiaquine, is generally thought to be safe for use in pregnancy, although there are almost no data to support this view.[5]

As an example of the potential shortcomings of relying on preclinical data to assess human risk, studies with chloroquine indicate that it has toxicological liabilities in the developing rat fetus,[10] whereas amodiaquine is weakly mutagenic and genotoxic in preclinical tests.[11] However, for both of these compounds there is a lack of any clinical evidence to suggest that this risk is carried forward to women who take the drug during pregnancy. Support for the safety of amodiaquine when used in the second and third trimester has been recently reported in a controlled clinical trial.[1]

The use of chloroquine and amodiaquine in pregnancy may be acceptable, but widespread resistance in *P falciparum* severely limits their use in most areas of the world. Use against other malaria species is possible, although recent reports of chloroquine-resistant *Plasmodium vivax* in southeast Asia needs careful monitoring.

Quinoline methanols and related drugs

The preclinical toxicity of quinine, including reproductive toxicity, has been studied in various species with some evidence of genotoxicity reported in the mouse.[12] Studies in rats, dogs, and primates have generally concluded that quinine does not have selective toxic effects on the fetus and does not induce malformations,[13–15] with the exception of one study reporting congenital malformations in the pups of female rats treated with quinine.[16] Although

	Main kinetic properties	Comments on the use in human pregnancy
4-Aminoquinolines		
Chloroquine	Limited pharmacokinetic data in pregnancy; very long half-life (>25 days).	Considered safe in all trimesters. Recent suggestions of preclinical embryotoxicity, but no signals raised with extensive experience over previous 60 years in human pregnancy (use for systemic diseases). Human data overrides animal models.
Amodiaquine	No data in pregnancy, medium half-life for metabolite (2–7 days).	Weakly mutagenic and induces bone-marrow toxic effects in mice. Recent publication suggestive of safety in second and third trimesters.[1]
Piperaqine	No pharmacokinetic data in pregnancy; very long half-life (>25 days).	No reliable preclinical data to date, but reproductive toxicology is being studied as part of the combination drug development (combined with dihydroartemisinin). No data on safety in pregnancy.
Quinoline methanols		
Mefloquine	Reduced concentrations in pregnancy; long half-life (7–25 days).	Skeletal and muscular malformations in animals. Over 1000 documented exposures in human pregnancy. One study reported an excess in stillbirths, although this was not found in other studies. Recommended by US CDC for prophylaxis in pregnant women.
Lumefantrine	Reduced concentrations in pregnancy; medium half-life (2–7 days).	No sign of toxicity in animal studies. Only available in combination with artemether, twice a day for 3 days with fat.
Antifolates		
Sulfadoxine-pyrimethamine	No pharmacokinetic data; half-life of sulfadoxine long (7–25 days).	Embryotoxic at high doses; use impaired by resistance.
Chlorproguanil-dapsone	No pharmacokinetic data; short half-life (8 h to 2 days) of combination proguanil (an analogue of chlorproguanil); biotransformation is reduced in pregnancy; medium half-life (2–7 days).	Dapsone not teratogenic but causes haemolytic anaemia. Cycloguanil toxic at ovum cleavage stage. Concerns over dapsone toxicity if dosage has to be increased because of the reduced biotransformation of cycloguanil.
Atovaquone proguanil	Reduced blood concentrations	No concerns raising from animal studies; very expensive.
Artemisinins	Reduced blood concentrations; very short half-life (<8 h).	Embryotoxic and teratogenic in rats and rabbits, and embryolethal in non-human primates at doses close to therapeutic range. The susceptible time window for these effects is in the first trimester, corresponding to 2–6 weeks pregnancy in human beings. Implications for use in human beings unclear. Safety data available in over 1000 carefully documented second and third trimester exposures. Limited first trimester data (about 100 late first trimester pregnancies).

Table: **General characteristics of antimalarial drugs with potential for use in pregnancy**

quinine has been used historically as an abortifacient, use of the drug in pregnancy is generally thought safe. A recent review of the clinical data on quinine use in pregnancy concluded that there was no evidence of poor birth outcomes in several hundred women treated with quinine during pregnancy, including almost 400 treated in the first trimester.[5]

Although somewhat limited, there are clinical data on mefloquine exposure in pregnancy in several thousand women when used for prophylaxis and treatment.[5] These data include over 1000 first-trimester exposures. The data support the view that the drug is safe, does not result in negative birth outcomes, and did not induce malformations. However, in one retrospective study in Thailand, mefloquine was associated with an increased incidence of stillbirth compared with women given quinine, other antimalarials, or women without malaria.[17] These data support the view that mefloquine use in pregnancy should be avoided unless there is clear benefit to the mother or fetus, if there are no alternatives, or until this question is resolved.

There are no data on the use of halofantrine in pregnant women, but preclinical data in rabbits indicate embryotoxic effects and identified skeletal abnormalities at doses of 60–120 mg/kg per day (gestational days 7–19). The related drug lumefantrine is in clinical use in combination with artemether, but there are no reported safety data on the use of the drug in pregnancy. Reassuringly, and by contrast with artemether, preclinical data with lumefantrine alone failed to show any embryotoxicity.

Atovaquone-proguanil

Preclinical data suggest that atovaquone-proguanil does not cause selective toxic effects on the developing fetus, although maternal toxicity-related fetal toxic effects were reported in rabbits.[5] Clinical experience of this drug in human pregnancy is limited.[18,19]

Antifolates

Sulfadoxine-pyrimethamine has been used extensively in pregnancy, including in intermittent preventive therapy strategies, but formal safety studies in pregnancy are limited. Preclinical studies indicate embryotoxic effects including cleft palate in rat pups exposed to suprapharmacological doses of pyrimethamine and other toxic effects associated with antifolate action.[20–22] A compilation of the available safety data on sulfadoxine-pyrimethamine use in pregnancy indicates that, from over 2000 pregnant women treated with the drug in the second and third trimesters, the drug did not increase the risk of malformations or other adverse events in the fetus.[5] The main concerns associated with use of the drug were clinical failures because of parasites resistant to antifolate combinations.

A new antimalarial combination of dapsone and chlorproguanil with the same mechanism of action as sulfadoxine-pyrimethamine retains activity against resistant parasites carrying a triple mutation in the dihydrofolate reductase gene *DHFR*. There are no clinical data on the use of this drug in pregnancy. Dapsone in pregnancy when used in the treatment of leprosy is

thought to be safe, although there are only 19 reported cases of dapsone exposure in the first trimester.[5] One study in Kenya reported the use of dapsone and chlorproguanil in pregnant women and no adverse events were reported, although birth outcomes were not documented.[23]

Artemisinins

The artemisinin-based peroxidic antimalarials are currently our most important class of antimalarial drugs, because they are effective against drug-resistant parasites. The malaria community has argued that the use of artemisinin-based combination chemotherapy is the only practical solution to controlling malaria and limiting the evolution and spread of resistance. As a consequence of these recommendations, WHO's Roll Back Malaria programme predicted a requirement of up to 210 million artemisinin-based treatment doses in 2005–2006 alone. Implicit in this strategy is the assumption that these drugs are safe for use in all clinical settings, including women of childbearing age. Although clinical experience to date indicates artemisinins to be safe, the area of reproductive toxicology demands special consideration. Data from the early Chinese literature indicated that the artemisinins were embryotoxic and potentially teratogenic in several animal species.[24–26] Importantly, these effects were seen in the absence of maternal toxic effects or impaired fertility. An investigation into the developmental toxicity of artesunate in the rat and rabbit according to regulatory International Conference on Harmonization standards has been done and confirmed the Chinese data.[27] The hallmark effect of artesunate exposure seen was a dramatic induction of embryo loss, apparent as abortions and resorptions. Additionally, low incidences of cardiovascular malformations and a syndrome of skeletal defects were induced at or close to embryolethal doses in both species. These effects were seen mainly in the absence of any apparent maternal toxic effects, at doses approximating those used in human exposure and at blood concentrations equivalent or less than those seen in human beings.[27] Further preclinical studies in the rat have shown that the heart and bone defects can be induced by a single oral administration of 10 mg/kg artesunate or other related artemisinins (including artemisinin, artemether, and dihydroartemisinin).[28] These observations prompted a response from WHO Tropical Diseases Research Programme, who have also concluded that the developmental toxicity of the artemisinins is a priority area for further research.[29]

One important aspect of the recent studies is that the critical window for drug exposure is approximately 10–14 days in the rat. At this developmental stage, rats and rabbits differ from human beings in their reliance on the visceral yolk sac rather than the placenta as the main maternofetal exchange system.[30,31] Recently, it has been shown that dihydroartemisinin causes a dose-dependent reduction in the number of fetal red cells circulating in the visceral yolk sac with a concomitant reduction in angiogenesis.[32] These primitive red cells appear at gestational day 10 in rats, which agrees with the critical window studies by Clark and co-workers.[27] The reliance on the inverted yolk sac in rats and rabbits might mean that these toxic effects would not be seen in primates. To address this hypothesis, a primate reproductive toxicity study (in *Macaca cynomologus*) has been done, although the results are yet to be reported.[33]

The teratogenic potential of the artemisinins in human beings is unknown. In total, less than 1000 cases

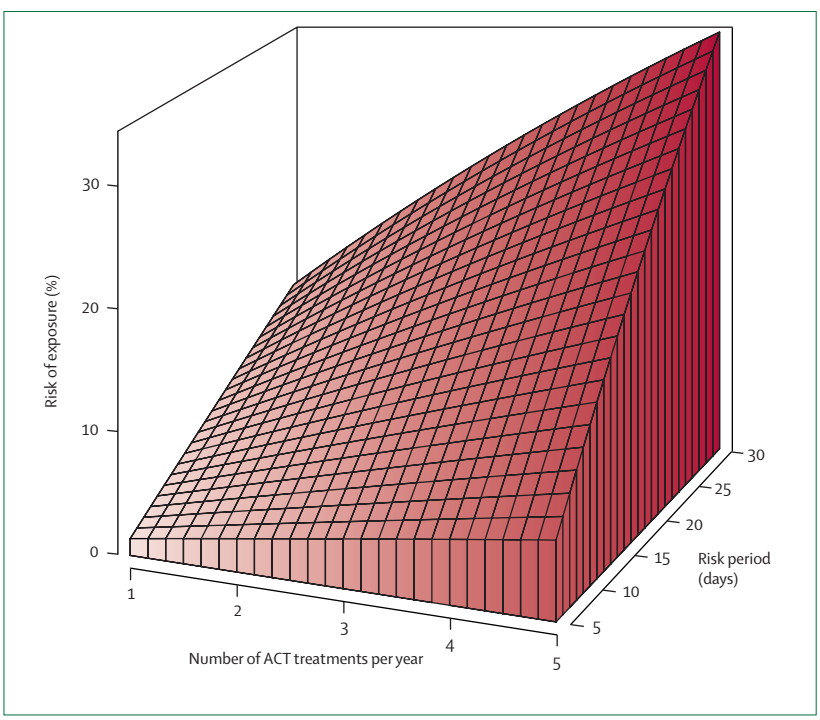

Figure: **Calculated risk of artemisinin exposure during the critical pregnancy period**
The probability that an embryo will encounter artemisinins during the critical phase of its development can be calculated. If the critical period is *t* days (eg, from days 20 to 40 of gestation then *t*=21) and the period of persistence of artemisinin is *p* days (usually 3 days because artemisinin-based combination treatments [ACTs] are normally deployed as a 3-day regimen and have a very rapid elimination), then the embryo is at risk if a mother starts an ACT during the period of *t*+*p* days. If the mother takes *x* courses of ACTs per year, which may be on confirmed malaria or taken presumptively, then the calculation is simple: *x*/365 is the probability that a mother does start ACT on any given day; 1–*x*/365 is the chance she does not start ACT on any given day; $(1–x/365)^{(t+p)}$ is that chance of not taking ACT during the at-risk period; and $1–(1–x/365)^{(t+p)}$ is the chance that the mother does take ACT during the embryo's at-risk period. For example (assuming *p*=3), if the embryo is at risk for a critical 5-day period of its development and the mother takes one ACT course per year, then the chance of an embryo being treated during the at-risk period is 2%. More pessimistically (and realistically), if the critical period is 20 days and the mother take on average three ACT courses per year, then an embryo has a 17% chance of being treated during the at-risk period (ie, 17% of all embryos will have encountered artemisinins during their critical development period). A more direct, but approximate, calculation can be used. If the at-risk period is 23 days and the mother takes three ACTs per year, then the expected number of ACTs falling in the critical period is (23/365)×3=0·19 per embryo, assuming a maximum of one treatment per embryo gives the proportion treated as 19%. The true chance of treatment is slightly lower (17%, see above), because this approximate calculation includes double and triple treatments per embryo; using the Poisson distribution, the chance of being treated is $1–e^{-0.19}$=17%, regaining the result above. Note that the percentage of ACTs that actually encounter an at-risk embryo will be much smaller. For example, if 20% of treatments are given to women of reproductive age, who have a pregnancy on average every 3 years, and the window of risk is 24 days, then the probability of any single ACT treatment hitting an at-risk embryo is 0·2×24/(3×365)=0·004 or 0·4%. A disparity between risks occurs because the risk per treatment course is low, but there are so many treatments being deployed that the risk per embryo may be substantial.

of monitored artemisinin exposure during pregnancy have been reported (250 exposures to artemether-lumefantrine); reassuringly, these data show no differences in birth outcomes compared with community controls, and no evidence of teratogenic or other embryotoxic events.[5] However, the number of pregnant women exposed to artemisinins during the first trimester of pregnancy, the sensitive period by extrapolation from our critical window studies (figure), is less than 100, which is far too small a dataset on which to base a claim for safety. Extrapolation from rat data would indicate a sensitive period in human beings of weeks 2–6 of pregnancy. Malaria during pregnancy is itself associated with substantial mortality and morbidity to the mother and the unborn child,[34] and so we need to balance the risk–benef it ratio of artemisinin use. However, it is essential that all efforts are made to measure the true risk, because most women receive their antimalarials in an unsupervised way, most will not be aware of their pregnancy (if the extrapolated critical window from the rodent is correct), and most antimalarial treatments in adults are not given to true malaria cases. However, the detection of fetal toxic effects so early in pregnancy will be very difficult to achieve.

Pharmacokinetics

The need for accurate pharmacokinetic data on antimalarials in pregnancy is one of the highest priority areas for research on malaria and pregnancy. Host defences against malaria are impaired in pregnancy, and pregnancy itself creates huge physiological changes—increased volume of distribution, reduced gut motility, increased renal blood flow, hormonal changes, and increased protein binding—all of which can alter drug disposition and metabolism. Unfortunately, when pharmacokinetic studies are done, they usually only include adult men. The number of pregnant women treated with antimalarials who have been included in drug pharmacokinetics studies worldwide is less than 100 (table).[5]

Incorrect dosing could result in maternal and fetal toxic effects, therapeutic drug failures resulting in poor pregnancy outcomes or maternal death, and could increase the risk of drug resistance with large-scale deployment of intermittent preventive treatment. There are few pharmacokinetic and toxicity studies of antimalarials in pregnancy, which makes this review diminutive. The problem for pharmacokinetic studies is that, to understand the pregnancy effects on antimalarials, comparable controls are needed. Future studies need to make a serious effort to address this by finding concurrent controls matched by sex, malaria, and age, or alternatively, by having the same woman return for sampling in the 2–3-month post-partum period. The methods of drug analysis (eg, HPLC, drug bioassay) and drug dosages also need to be consistent.

Artemisinins

Pregnant women who are infected with *P falciparum* are at particular risk and need to be treated with effective antimalarials. The artemisinin derivatives are now recommended for the treatment of *P falciparum* malaria in the second and third trimesters of pregnancy. In severe malaria at any time in gestation, intravenous artesunate is the drug of choice.[35] The recommendations for dosing of artesunate used in monotherapy and artemisinin-based combination therapies (ACTs) have mainly been derived empirically.[36] Artesunate is rapidly hydrolysed in vivo to dihydroartemisinin, which has equivalent antimalarial activity. Thus, in terms of biological (ie, antimalarial) effect kinetics, plasma concentrations of both compounds are assessed.

There is one preliminary report of artesunate and dihydroartemisinin pharmacokinetics in 24 pregnant women with acute uncomplicated *P falciparum* malaria from the Thai-Burmese border.[37] As with other pharmacokinetic studies, artesunate was very rapidly eliminated. The maximum dihydroartemisinin drug concentration (C_{max}) and area under the concentration–time curve for time 0–24 h ($AUC_{0–24}$) values were 4·2 and 1·8 times lower in Karen pregnant women (dose 4 mg/kg) than in non-pregnant Thai adults given less than half that dose (1·79 mg/kg).[38] The dihydroartemisinin apparent volume of distribution and oral clearance in non-pregnant Asian patients were 2·3 and 2·7 times lower than Karen pregnant women. Pregnant women had C_{max} and $AUC_{0–24}$ values that were nine and four times lower than in non-pregnant adults, respectively, assuming dose linearity and correcting for dose. Although the lower plasma concentrations of dihydroartemisinin could be explained by reduced absorption, it is more likely that the physiological changes of pregnancy, resulting in a larger volume of distribution and more rapid clearance, are responsible.

The fixed combination of artemether and lumefantrine is the result of research undertaken by Chinese scientists. Artemether-lumefantrine is the only coformulated ACT currently manufactured to European Union Good Manufacturing Process standards and widely registered. The combination has proved safe and effective against multidrug-resistant infections on the Thai-Burmese border.[39,40] In 13 pregnant women in the second or third trimester with acute uncomplicated *P falciparum* malaria from the same area, artemether-lumefantrine was used for treatment.[41] Again, artemether was rapidly hydrolysed to dihydroartemisinin, which in turn was rapidly eliminated. Pharmacokinetic variables for artemether C_{max} and $AUC_{0–8}$ were approximately 50% lower, and for dihydroartemisinin C_{max} and $AUC_{0–8}$ were approximately 20% and 40% lower, respectively, than in non-pregnant women.[41]

The kinetics of dihydroartemisinin and artemether are modified by pregnancy. The plasma concentrations of the active antimalarial metabolite dihydroartemisinin are lower than reported previously in non-pregnant adults.[38]

These findings are also consistent with the lower cure rates observed with artesunate in pregnancy compared with non-pregnant patients. Dose-optimisation studies in pregnant women are needed.

4-aminoquinolines

Even chloroquine, which has been consumed worldwide by pregnant women in vast quantities, is poorly described by current pharmacokinetic data. Chloroquine readily crosses the placenta in human beings.[42] Two African studies, in which malaria status was not known, suggested that chloroquine clearance is increased in the third trimester, and that higher doses should be studied.[43,44] Pharmacokinetic variables after treatment with chloroquine (10 mg/kg on days 1 and 2, 5 mg/kg on day 3) in four Nigerian women with slide-confirmed uncomplicated *P falciparum* malaria did not show lower concentrations in plasma.[45] The pharmacokinetic data on the related 4-aminoquinoline, amodiaquine, in pregnancy are non-existent.

Quinoline methanols and related drugs

It is ironic that mefloquine, the best characterised drug in terms of pharmacokinetics in pregnancy, is one of the least used. In a dose-finding pharmacokinetic study, mefloquine clearance was increased in pregnancy with lower resultant blood mefloquine concentration for a given dose.[46] A subsequent study also found that the peak concentrations of mefloquine were lower, and the apparent volume of distribution larger, so that treatment doses lower than 25 mg/kg may lead to suboptimum circulating drug concentrations.[47]

The pharmacokinetics of quinine in uncomplicated malaria in pregnancy have not been examined. A study in third-trimester pregnant women with severe malaria, who were treated with a quinine loading dose of 20 mg/kg, showed a smaller volume of distribution and more rapid elimination of the drug than non-pregnant adults.[48] Characterisation of the pharmacokinetics of quinine is very important because there are so few drugs known to be safe in the first trimester of pregnancy, and because the physiological changes of pregnancy are proactive (ie, not proportional to the size of the fetus), so that by the end of the first trimester many body systems are actually functioning at levels close to term.

In the study on artemether-lumefantrine,[41] it was possible to compare pharmacokinetic data of lumefantrine collected in pregnant and non-pregnant Karen adults. Lumefantrine AUC values were substantially lower in pregnant than in non-pregnant women with uncomplicated *P falciparum* malaria, and this was because of more rapid elimination in pregnant women. Pregnant women who smoked had substantially reduced AUC values. Low concentrations of lumefantrine in combination with artemether are likely to lead to reduced cure rates because the residual lumefantrine in the third and subsequent post-treatment cycles must be sufficient to remove all residual parasites. Low lumefantrine concentrations in combination with artemether present a substantial problem for a fixed combination drug. There is no point increasing the dose to be given over 3 days because lumefantrine absorption is rate limited and can increase toxic effects to the mother and fetus; extending the dosing regimen to 5 days treatment can decrease compliance. Urgent work is necessary, since many countries now use artemether-lumefantrine as first-line therapy.

Antifolates

Sulfadoxine-pyrimethamine seems to have been widely deployed in Africa for intermittent preventive treatment on the basis of the assumption that the dose in non-pregnant adults is correct for pregnant women. There are also no pharmacokinetic data on the efficacy of sulfadoxine-pyrimethamine when used for case management in pregnancy. Chlorproguanil is thought to be the safest of all antimalarial drugs. Proguanil is metabolised to the triazine cycloguanil, mediated by the cytochrome P450 enzyme CYP2C19. As a result, some pharmacokinetic data has been derived from the use of proguanil in pregnancy and the plasma concentrations are lower than would be predicted from literature data in non-pregnant adults. Pregnancy reduces the conversion of proguanil to the active metabolite.[49] Chlorproguanil has been combined with dapsone, which has been found to be more active than sulfadoxine-pyrimethamine against resistant *P falciparum* in East Africa.[50] In a recent review, very limited safety data and no pharmacokinetic data were found on the use of dapsone for any indication in pregnant women.[51] The changes in the disposition of proguanil in pregnancy (lower plasma concentrations) are likely to be very similar for chlorproguanil. This has important implications for the use of dapsone-chlorproguanil in pregnancy. Increasing the dose of chlorproguanil in the fixed combination could result in toxicity problems from dapsone. The dose is likely to require optimisation, which is problematic for all fixed combinations.

Atovaquone-proguanil

The pharmacokinetics of atovaquone and proguanil were examined as part of a treatment study on atovaquone-proguanil-artesunate combination therapy for multidrug-resistant *P falciparum* malaria in pregnant women in the second and third trimesters.[52] A previous study found no interaction between atovaquone-proguanil and artesunate.[40] Plasma concentrations for atovaquone were less than half, and for proguanil approximately two-thirds of those in non-pregnant patients with malaria who were given the same dose. Cycloguanil concentrations were substantially lower than reported in non-pregnant patients with malaria, but this impaired conversion in pregnancy is unlikely to be of therapeutic relevance because the parent

compound, not cycloguanil, synergises with atovaquone. The triple combination was effective in this preliminary study; nevertheless, the dose for optimum cure rates in pregnancy probably needs to be increased. Similar findings were reported in a subsequent study in eight Thai and 18 Zambian women in their third trimester of pregnancy treated with malarone alone.[53] This study suggested that the C_{max} and AUC were approximately halved by pregnancy status.[53]

Dihydroartimisinin-piperaquine

There are currently no data on the use of dihydroartimisinin-piperaquine in pregnancy. The data in non-pregnant individuals are limited.

Antibiotics

Antibacterial drugs can have substantial antimalarial activity, although they are not sufficient to use on their own to treat malaria. There are no pharmacokinetic studies in women with malaria. However, antibiotics can provide an important adjunct when treatment options are limited, such as in pregnancy (eg, clindamycin has been shown to enhance the efficacy of quinine in multidrug-resistant *P falciparum* infections in pregnancy).[54] Clindamycin given to full-term pregnant women before caesarean section showed concentrations in the normal range compared with decreased concentrations for gentamicin.[55] Azithromycin pharmacokinetic studies in full-term pregnant women showed a rapid serum half-life and high-sustained antibiotic concentrations within the myometrium, adipose, and placental tissue.[56] Azithromycin, an antimalarial with activity in vitro, has been disappointing in vivo when used in malaria as a monotherapy (Nosten F, unpublished data).

Drug interactions

Antimalarial drug interactions are important to define. For example, inducers of the cytochrome P450 enzyme CYP3A4, such as rifampicin and anticonvulsant drugs, accelerate the clearance of quinine and mefloquine with resultant lower drug concentrations and hence a greater chance of treatment failure. Studies of the synergy or antagonism between antiretrovirals and antimalarials are also essential to ensure effective and safe malaria case management, intermittent preventive treatment, and HIV treatment for pregnant women.

Pharmacovigilance

WHO defines pharmacovigilance as the science and activities relating to the detection, assessment, understanding, and prevention of adverse reactions or any other possible drug-related problems.[57] The major aims of pharmacovigilance studies are the early detection of unknown safety problems, the detection of increases in frequency of known adverse drug reactions, the identification and quantification of risk factors for adverse reactions, and the prevention of unnecessary risk to the patient by promoting the rational and safe use of medicines. Preclinical drug studies and formal phase I, II, and III clinical trials are generally accepted to have serious limitations in terms of establishing safety.

Antimalarial drugs

Spontaneous reporting is a relatively new phenomenon in the history of medicine. The first national reporting schemes for adverse drug reactions were set up in the 1960s in ten countries after the thalidomide disaster.[58] However, only a few African countries have implemented a reporting mechanism.[59]

Implementation of spontaneous reporting in low-income countries is particularly problematic because of other pressing health-care priorities and specific challenges such as geographical remoteness of many of the health facilities, poor telecommunication systems, and inadequate education of health professionals and patients. Additionally, problems with availability of drugs, caused by lack of funds and failures in systems and markets,[60] could also interfere with the reporting process. Since most of these countries have well established (although often overstretched) public-health programmes, which operate according to standard guidelines and are supported at both national and international level, there is an opportunity for these structures to interact with pharmacovigilance initiatives. WHO is promoting the introduction of pharmacovigilance into public-health programmes, and some countries have started to implement their monitoring systems in collaboration with malaria control programmes.[61,62]

Recently, a new policy in the treatment of malaria, with ACTs, was adopted by several countries. The therapeutic profile of these artemisinin-based drugs seems to be good under well-conducted clinical trials, but their efficacy and safety have not been adequately monitored in large-scale use in populations outside southeast Asia.[63,64] Safety monitoring is important in all countries, but especially in African populations in which the presence of comorbid conditions such as HIV/AIDS, malnutrition, and tuberculosis could be important issues. As mentioned previously, there are concerns related to the safety of ACTs during the first trimester of pregnancy.[32,65] Use of artemisinin combined with amodiaquine or sulfadoxine-pyrimethamine has raised different concerns over dermatological, haematological, and hepatic toxicity.[63]

To address the issue, five African countries (Burundi, Democratic Republic of Congo, Mozambique, Zambia, and Zanzibar), supported by WHO Roll Back Malaria, participated in a training course in which they designed action plans to introduce pharmacovigilance systems, together with the implementation of new antimalarial therapy.[61] In each of these countries, mechanisms are being established to collect information about adverse reactions, and some of them have become members of a WHO monitoring programme.[59] In addition, Ghana[66] and South Africa[67] are reinforcing established pharma-

covigilance systems to better monitor the safe use of antimalarial drugs. Nevertheless, none of these activities have focused on safety monitoring of drugs used during pregnancy. However, some have included safety monitoring of antimalarial drugs used during the implementation of intermittent preventive treatment during pregnancy. These studies were designed to monitor adverse events in the mother rather than the unborn child, and have not produced any signals of significant risk.[68]

Antimalarial drug use in pregnancy

During implementation of the pharmacovigilance systems, special attention should be given to specific risk groups, particularly pregnant women. The first trimester of pregnancy carries the highest risk of fetal adverse reactions, and some women are exposed to medicines during this period because they are unaware that they are pregnant or do not declare their pregnancy. Recently, studies have described drug exposure prevalence of 86–97%,[69,70] with an average of 2·9–4·2 drugs per woman. The most commonly prescribed medicines are antimicrobials, analgesics, anti-emetics, tranquilisers, vitamins, mineral salts, and vaccines. In areas of high malaria prevalence, this list also includes antimalarial drugs.

Indiscriminate use of medicines in pregnancy is not recommended because of the risk of adverse reactions in the mother and fetus, and the possibility of irreversible effects. The decision to give drugs to pregnant woman must be made based on a balance between risk and benefits. In particular, the potential benefits must outweigh the potential risk to the fetus. The adverse consequences of malaria in pregnancy are well described: untreated malaria poses a far greater risk than treatment, although the mechanism for monitoring pregnant women exposed to these drugs is limited.

Causality assessment is difficult in pregnant woman because some adverse reactions can only be identified after delivery. Date of the last menstrual period, or some other reliable method of gestational age, is notoriously difficult to obtain in low-income countries, but is crucial in determining first trimester exposures. Different factors should be considered to estimate the strength of the association between the drug and the reaction, including specific and possibly unique pathognomonic defects, plausible temporal exposure, consistency of the observed evidence, dose-response relations, duration of exposure, and confounding factors (eg, drugs, environmental factors, chemicals, and traditional medicines).

Pregnancy registries are recognised as one method for detecting major risks associated with a drug or biological exposure during pregnancy. At the time of pregnancy registration, information is collected on drug exposure, maternal disease status, gestation, and other factors that may affect pregnancy outcome. An active follow-up of these pregnancies including outcome of the pregnancy and the infant are done using various approaches, including maternal interviews, medical record abstraction, or a combination of these methods to avoid recall bias. From this system, accurate data should be recorded to calculate the prevalence of adverse reactions, identify risk factors, better estimate the magnitude of exposure risk, and detect long-term reactions such as delayed development, neurological impairment, or any effects that might be detected in older children of at least 1 year who might have been exposed to antimalarial drugs in the uterus.

These surveillance mechanisms are susceptible to under-reporting, selection bias (some pregnancies will not be registered, and some defects will not be diagnosed at birth), and loss to follow-up, and there may be difficulties linking specific maternal exposures to fetal anomalies. Despite limitations of these methods, they have been used to supplement animal toxicology studies and clinical trials, and to generate signals of risk to help health-care providers assess the risk of antimalarial drug use in pregnant woman. Single methods should not be used alone to identify increases in the prevalence of adverse events, particularly in pregnant women. Combinations of different methods are needed for the early detection of any safety issue.

***Panel:* Research priorities**

Preclinical and clinical drug safety

- Unified design strategy for clinical trials to capture safety data in all phases of pregnancy.
- Validated baseline data on birth outcomes in target populations.
- Assessment of safety and tolerability of all drugs and drug combinations proposed for use in pregnancy for case management and intermittent preventive treatment.
- Investigation of the prescribing practices of antimalarials in Africa: are women of childbearing age routinely asked about possible pregnancy?
- Critical artemisinin exposure period in relevant species needs to be defined.
- Metabolic profiling of artemisinins in relevant species need to be determined to assess whether parent drug or metabolites are correlated with toxic effects.
- Embryotoxicity of non-semisynthetic peroxides needs to be addressed.

Pharmacokinetics

- Pharmacokinetics and metabolic fate of all antimalarials used in pregnancy need to be further studied (at different gestational periods, and when used for case management or intermittent preventive treatment during pregnancy).
- Population pharmacokinetic/pharmacodynamic models need to be developed for use in pregnancy.
- Pharmacokinetic interactions of antimalarials with highly active antiretroviral therapy in HIV/AIDS should be studied.

Pharmacovigilance

- Feasibility of spontaneous reporting systems and pregnancy registries in low-income countries.

Conclusions

P falciparum malaria remains a potentially lethal yet treatable disease. However, we remain ignorant of the best treatments. Use of antimalarial drugs in pregnant

Search strategy and selection criteria

Data for this Review were identified by searches of Medline, Current Contents, and references from relevant articles; numerous articles were identified through searches of the extensive files of the authors. Search terms were "malaria and pregnancy", "malaria chemotherapy", "antimalarial drug toxicity", "antimalarial drug safety", "antimalarial pharmacokinetics", "pharmacovigilance". English language papers were reviewed. The search was not restricted by date.

women continues to be a problem in which the risks to the woman and fetus are not completely known. More information on the correct doses to be given to pregnant women is desperately needed. Large-scale trials and post-market surveillance systems to monitor drug safety in pregnancy are required (panel).

Conflicts of interest

All authors contributed equally to the manuscript and have no conflicts of interest.

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