World Health Organization

Special Programme for Research & Training in Tropical Diseases (TDR) sponsored by
UNICEF/UNDP/World Bank/WHO

Assessment of the safety of **artemisinin compounds in pregnancy**

REPORT OF TWO JOINT INFORMAL CONSULTATIONS CONVENED IN 2006 BY:

The Special Programme for Research and Training in Tropical Diseases (TDR) sponsored by UNICEF/UNDP/World Bank/WHO

and

The Global Malaria Programme of the World Health Organization

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GLOSSARY

Angioblast: alternative term for haemangioblasts.

Clonal production of primitive erythroblasts: early embryonic red blood cells are nucleated and derived from a limited number of haemangioblasts in the yolk sac, so show less heterogeneity than the later waves of blood cells from the liver.

Developmental toxicity: adverse effects on the development of the embryo, foetus or offspring which may lead to death, abnormal growth or abnormal structural, histological or functional development of the offspring up to puberty.

Embryotoxicity: any adverse effect on the developing embryo which may include death (embryolethality), malformations, growth or functional deficits.

Erythroblasts: nucleated erythrocytes.

Haemangioblasts: mesodermal cells in the yolk sac that are the precursors of the blood cells and the blood vessels. Small groups of haemangioblasts form blood islands in the yolk sac. These develop to form the primitive blood cells and the endothelium of the blood vessels. Later, haematopoiesis occurs in the liver, then the spleen and bone marrow.

Pluripotent stem cells: stem cells capable of developing into various types of definitive cells.

Primitive erythrocytes: earliest type of embryonic red blood cells that contain foetal haemoglobin and a nucleus.

Primordial blood islands: see haemangioblasts.

Sensitive period: critical periods in development of an embryo when exposure to a drug or chemical may induce particular types of malformation. The embryo may not be sensitive to the chemical at other times.

Teratogenicity: usually defined in the limited sense as the induction of structural malformations in the embryo. Developmental toxicity is used to include other types of adverse effect as defined above.

Yolk sac: early embryonic structure attached to, and outside, the developing embryo. Source of the earliest blood cells and haematopoietic stem cells that seed the liver. Structure of the yolk sac differs in primates and rodents. The yolk sac in rodents is inverted and completely surrounds the embryo proper. In rodents, the large size of the yolk sac and its close contact with the maternal blood vessels allows it to serve an important, transient nutritive function until the definitive chorioallantoic placenta forms around mid-gestation when embryo development is quite advanced.

Yolk sac haematopoiesis: earliest stage of blood cell formation in the embryo which is critical for establishing the early embryonic circulation. Only primitive erythrocytes are formed in the yolk sac. Other blood cell types are not formed until the liver and other embryonic sites are initiated by haematopoietic stem cells from the yolk sac.

BACKGROUND

Artemisinins have high therapeutic value in the current clinical situation so treatment of women in early pregnancy is inevitable. A clinician treating a febrile pregnant woman bears several possible outcomes in mind. Failure to treat adequately may result in death or severe damage to the mother, the baby or both. However, medicines themselves may cause toxicity and it is important that the best medicine be chosen whenever possible. Good knowledge about the actual risks of the medicine during human pregnancy is essential in order to balance the benefits against the risks.

Alone, or in combination with other antimalarials, artemisinin compounds represent a relatively new and highly efficacious treatment and it is important to determine their safety and efficacy in pregnancy. Where artemisinin compounds have been given during the second or third trimesters there has been no evidence of treatment-related, adverse pregnancy outcomes. Normal outcomes have also been observed in the limited number of pregnancies known to be exposed to artemisinin compounds in the first trimester.

The WHO recommendation in 2003 was that "artemisinin compounds cannot be recommended for treatment of malaria in the 1st trimester. However, they should not be withheld if treatment is considered lifesaving for the mother and other antimalarials are considered unsuitable. Because of the limited safety data, artemisinin compounds should only be used in the 2nd and 3rd trimesters when other treatments are considered unsuitable." This recommendation was based on the report of two informal consultations convened by WHO in 2002 (WHO, 2002).

In 2002, the mechanism of developmental toxicity in animals was not known. It was not clear whether the initial site of action was in the mother, the foetus or on the placenta. Detailed knowledge of the mechanism(s) involved in embryotoxicity in animals was recognized to be of value in extrapolating the risks for humans. An informal non-clinical consultation meeting was convened in January 2006 to review the findings of animal studies performed since 2002 and consider their impact on the clinical use of artemisinins. Experts in reproductive and developmental toxicity discussed new published and unpublished data on the toxicity of artemisinins in rodents and primates. In addition, other mechanistic studies using whole embryo culture as well as isolated cells were reviewed. This meeting was followed by an informal clinical consultation in October 2006 to discuss the safety in use of the artemisinins in early pregnancy and how to obtain more information on safety.

EXECUTIVE SUMMARY

It was considered important for WHO to monitor the outcomes of pregnancies with early exposures to artemisinin compounds so that any risks can be evaluated properly. The regulatory position on the minimum number of early pregnancies necessary to increase confidence about safety was that information showing no increase in overall congenital malformation rates in at least 300 first trimester pregnancies treated with artemisinins would demonstrate a less than tenfold increase in overall malformation risk. Information on the absence of increased malformations in 1000 pregnancies would demonstrate a less than twofold increase in malformation risk (EMEA, 2006). Therefore, further studies are necessary to try to achieve these numbers of first trimester pregnancy exposures. Current pregnancy warning labels were discussed. In the context of malaria-endemic countries, such warnings might be of limited value if medicines are commonly used without medical supervision. Antimalarial medicines may be used during the early stages of pregnancy without the woman being aware she is pregnant.

Studies in animals are very valuable in indicating possible risks from medicines. Preclinical studies in rodents have demonstrated that artemisinins can induce foetal death at high dose levels but that at lower doses congenital malformations may be produced. The malformations can be induced in rodents only within a narrow window in early embryogenesis. Evidence was presented that the mechanism by which embryotoxicity was produced was through a toxic action on the very earliest developing red blood cells causing severe anaemia in the embryo. If sufficiently severe the embryos died, but in surviving embryos malformations were induced.

Limited data in primates, presented for the first time at this meeting, suggest that artemisinins may have a similar mechanism of action in the monkey leading to anaemia and embryolethality. No malformations were observed in the primate studies but these were limited in scope.

In the rat the sensitive early red cells are produced synchronously over a very limited time period so that a single exposure to the drug can result in a high proportion of cell deaths. In contrast, primates required a longer period of treatment (12 days) to induce embryonic death. In humans only limited information is available about this stage of red cell development; however it is known to take place over a longer time period and it may well be that a limited period of treatment of two to three days for malaria would not produce such serious toxic effects.

Following the pre-clinical meeting in 2006 the clinical meeting reviewed new data from Thailand on 1530 first trimester exposures to a range of antimalarial medicines including 170 treated with artemisinins. Irrespective of the antimalarial medicine used, the higher the number of episodes of *P. falciparum* and the greater the number of times the women had to be treated in the first trimester, the greater the chance of abortion. In addition, fever, hyperparasitaemia and older maternal age were significant positive risk factors for an abortion in the first trimester, whereas antimalarial drug treatments were not significantly related. Preliminary data from other clinical work in progress in Zambia & Bangladesh (not yet published) were presented.

The meeting worked out the broad content of what might be achieved in the next two years. It focused on the potential for establishing antimalarial pregnancy registries but also discussed the nature of clinical research that might yield information on the risk-benefit of treatment. Elements of the successful collaborative Antiretroviral (ARV) Pregnancy Registry — a collaboration between the United States Food and Drug Administration (FDA), pharmaceutical industry and interested parties — were discussed. The meeting considered the registry model that could be applied to artemisinins in a similar collaborative effort. Pharmaceutical companies indicated that they would welcome being part of such a collaboration — especially if WHO were involved. The Global Fund to Fight Aids, Tuberculosis and Malaria (GFATM) indicated their support for such a registry, in principle.

It was concluded that there is insufficient evidence at present to warrant a change in current WHO policy recommendations on the use of artemisinin-based products for the treatment of malaria in pregnancy. Current WHO Guidelines (WHO Guidelines for Treatment of Malaria, 2006) recommend that in uncomplicated malaria, artemisinin-based combination treatment should be used in the second and third trimester, but should be used in the first trimester only if it is the only effective treatment available. In severe malaria, artemisinins are preferred over quinine in the second and third trimester because of the hypoglycaemia associated with quinine. However, in the first trimester until more evidence becomes available on the risk benefit ratio of artemisinins, both artesunate and quinine may be considered as options. In severe malaria treatment should be started without delay and whichever medicine is immediately available should be used.

REPRODUCTIVE (PRECLINICAL) RISK ASSESSMENT OF ANTIMALARIAL THERAPY WITH ARTEMISININ COMPOUNDS

Report of an informal consultation convened by WHO, Geneva, January 2006

RESULTS OF RECENT ANIMAL AND IN-VITRO STUDIES

There have been significant developments in our understanding of the developmental toxicity of artemisinins since the report of two informal consultations convened by WHO in 2002 (WHO, 2002).

Sensitive period

Developmental toxicity has been observed in rats following treatment on single days between days 10 and 14 postcoitum (pc) when artesunate was administered orally at 17 mg/kg (White et al., 2006). Day 11 pc was the most sensitive day for the induction of embryolethality; day 10 pc was the most sensitive day for the induction of malformations (cardiovascular defects and shortened and/or bent long bones). No developmental toxicity was seen following administration of the same dose administered on day 9 pc or following 30 mg/kg on day 16 or 17 pc.

Class effect

In vivo studies (White et al., 2006) showed that four artemisinins: artesunate, dihydroartemisinin (DHA), artemether and arteether, administered orally to pregnant rats on day 10 pc caused nearly equivalent effects in terms of embryolethality and teratogenicity (cardiovascular defects and shortened and/or bent long bones). This suggests that embryotoxicity (lethality and teratogenicity) is an artemisinin class effect.

Comparison of species — embryotoxicity in monkeys

Previously, artemisinins had been demonstrated to be embryolethal and teratogenic in rats and rabbits. A recent study in cynomolgus monkeys (Clark et al., 2006) found that 12 mg/kg/day and 30 mg/kg/day artesunate treatment given on days 20 to 50 of gestation caused embryo death between days 30 and 40 of gestation. The no-adverse-effect level was 4 mg/kg/day. No malformations were observed in four surviving foetuses in the 12 mg/kg/day group but the sample size is not adequate to conclude that artesunate is not teratogenic at that dose in monkeys. All three live embryos in the 30 mg/kg/day artesunate group dosed from day 20 of gestation and removed by caesarean section on days 26, 32 and 36 of gestation respectively had marked reductions in erythroblasts. Since embryo death was observed only after more than 12 days of treatment, work is currently being undertaken to investigate the effects of short-term treatments to see whether these also cause developmental toxicity.

DISCUSSION OF THE EMBRYOTOXICITY OF ARTEMISININS IN PREGNANCY IN ANIMALS

During the two-day discussion, experts in reproductive and developmental toxicity reviewed the recently published and unpublished studies on the toxicity of artemisinins in rodents and primates outlined above. Related studies in-vitro using whole embryo culture as well as isolated cells were also reviewed to help elucidate the mechanism of toxic action of artemisinins in pregnancy. The following major conclusions were agreed by the group.

MECHANISM OF ACTION

Two laboratories working independently made the same observations regarding early steps in the developmental toxicity of artesunate. One laboratory (White et al., 2006) treated rats in vivo with artesunate and removed embryos for examination at various intervals after treatment. The other (Longo et al., 2006) treated embryos in whole embryo culture with DHA, the primary active metabolite of artesunate, in addition to performing in-vivo studies. The common results demonstrated that the primary mechanism of artemisinin-induced embryo toxicity in the rat is a sustained depletion of primitive erythrocytes (embryonic erythroblasts). There was a marked reduction in primitive erythrocytes within 24 hours following a single dose of 17 mg/kg on day 10 or 11 pc. Embryos were viable until day 13 pc, but the majority had died by day 14 pc (White et al., 2006). It is thought that hypoxia associated with this embryonic anaemia leads to cell death and dysmorphogenesis including cardiovascular defects.

It was reported that the coadministration of amodiaquine ameliorates the developmental toxicity of artesunate in rats and rabbits. It was suggested that this interaction could result from competition for binding to haem.

The results of in-vivo and in-vitro experiments presented at this meeting suggest that the primary mechanism of artemisinin embryo toxicity in the rat is the depletion of primitive erythrocytes leading to anaemia and hypoxia with consequent cell death. Depending upon the degree of hypoxia, the consequences for the embryo include embryolethality and/or congenital skeletal and cardiovascular malformations. In some cases the foetus may recover from the hypoxic event and have normal, albeit delayed, development. Congenital malformations occur as a result of cell damage in the most sensitive organs developing at the time the hypoxia occurs. The duration of hypoxia necessary to lead to these events is unknown, but there is a delay of three to four days before malformations or embryonic deaths are observed. In the rat, the primitive erythrocytes are formed in the blood islands of the yolk sac over a short period (~day 8.5-10) and begin circulating around gestational day (GD) 10. This leads to a critical time window of sensitivity to artemisinin exposure in rats around GD 10-14. Dosing during these days may lead to embryonic damage or death which becomes obvious by GD 13-14. The fact that the sensitive period begins on day 10 pc suggests that the primitive erythrocytes need to be circulating in order to be sensitive to artemisinins in vivo. The end of the sensitive period may correspond to the time when the foetal blood cells are no longer metabolically active and cannot activate artesunate or DHA.

In the rat, primitive erythrocyte populations arise in a clonal manner over a short time around GD 8.5-10, being replaced by further populations of embryonic erythrocytes from GD 13. Thus, between GD 10 and GD 13 there is a homogenous population of cells in the rat that is equally sensitive to the toxic effects of the artemisinin compounds, leading to the profound anaemia observed. Definitive erythrocytes formed in the liver enter the circulation by ~day 13-14 pc and are not synchronized, but produced in waves. These definitive cells become enucleated and less metabolically active than the primitive erythrocytes. Taken together this information suggests that if the synchronized primitive erythrocytes are killed by artemisinins, they will not be replaced until sufficient numbers of definitive erythrocytes enter the circulation. This would explain the sustained anaemia observed after in-vivo dosing on day 10 or 11 pc. The heterogeneity provided by maturing definitive erythrocytes could contribute to the diminution of artesunate effects after day 13 pc, as only a subset of cells might be sensitive to artemisinin toxicity and, presumably, dead cells would be replaced by new waves of definitive erythrocytes more rapidly than occurs during the primitive erythrocyte stage. This is also the period when angioblasts are developing but these appear to be less sensitive to the artemisinins since the blood vessels appear normal following low-dose exposure, though effects may be observed at higher dose levels.

Limited data in primates (*Macaca cynomolgus*) presented for the first time at this meeting suggest that the artemisinins may have a similar mechanism of action in the monkey. Artesunate dosing during organogenesis led to anaemia and embryolethality (Clark et al., 2006) and embryonic erythroblasts were depleted in three live embryos in the 30 mg/kg/day group by GD 26. No malformations were observed but the limited sample size of the primate groups studied did not allow any conclusion to be drawn as to congenital abnormalities. In

the reported studies, a 12-day treatment period was required before embryolethal effects were seen. Work is currently underway to investigate the effects of short-term treatments over a few days, to see whether these would also cause damage, and to define better the window of sensitivity in primates. The studies mentioned above have identified a target-cell population, the primitive erythrocytes and a chain of pathogenesis that may be sufficient to account for the embryotoxicity and embryolethality observed in previous animal studies.

Comparison of period of sensitivity in animals and humans

The time window of sensitivity observed in the animal studies would correspond in the human to part of the first trimester during organogenesis. Currently available information is inadequate to define precisely the likely period of maximum sensitivity in humans. Yolk sac haematopoiesis extends from day 14 to week 6 in humans, but it is not known whether the clonal production of primitive erythroblasts occurs similarly to that observed in rats.

In man, the mesoderm of the yolk sac has been shown to exhibit localized thickenings, probably representing the primordial blood islands, at around 16 days of development. The blood islands are composed of haemangioblasts — precursors of primitive erythroblast and endothelial lineages. The earliest primitive erythrocytes are formed in the yolk sac from GD 18.5 (Lensch & Daley, 2004). The onset of blood circulation coincides with the onset of embryonic heartbeat, which probably occurs between GD 19 and GD 21 in humans, evidenced by the appearance of primitive erythrocytes in the cardiac cavity. The liver is the first organ to be colonized by yolk sac and aorta-gonad-mesonephros (AGM)-derived haematopoietic stem cells around week 5 of gestation. Thereafter, the liver is the main site of definitive erythropoiesis through 24 weeks of gestation (Segel & Palis, 2001). Primitive erythrocytes are the predominant circulating form in the first 8 to 10 weeks of gestation. Liver-derived definitive erythrocytes begin to enter the circulation by 8 weeks of gestation, but do not predominate until 11 to 12 weeks (Kelemen et al., 1979). All available studies agree that yolk sac haematopoiesis disappears completely after the 60th day of development. Hence, the relative duration of yolk sac haematopoiesis during human gestation is shorter than in rodents (Tavian & Peault, 2005).

The nomenclature of erythrocyte development distinguishes *primitive* erythrocytes (nucleated, megaloblasts), produced as the first wave of erythropoiesis in the yolk sac, from *definitive* erythrocytes (enucleated, macrocytes) that develop later in the liver. This is reflected by the change from embryonic to foetal type globin production.

It is not known whether the clonal production of primitive erythrocytes in primates, including humans, occurs in a similar way to that observed in rats. If primitive erythrocytes are formed over a longer period and less synchronously than in rodents, then (unlike rats) multiple daily doses may be required to produce a severe effect on the early blood cell population in primates. In addition, the relative duration of exposure to three-day artemisinin treatment for malaria, with respect to the duration of organogenesis, is very different in the human from that in the rat. Further work is necessary to elucidate this aspect of embryogenesis in humans and other primates.

In-vitro studies

The mechanisms above, elucidated in vivo, are supported by in-vitro studies of DHA and artesunate also reported at this meeting. DHA was a direct-acting embryotoxicant in studies using rat whole embryo cultures (WEC). Artesunate was more toxic to isolated primitive erythrocytes than to foetal or adult erythrocytes in vitro. Other artemisinins and artemisinin metabolites have not been investigated for direct embryotoxicity. However, structural and mechanistic data suggest that they would be embryotoxic too. The concentrations of DHA required to cause severe embryotoxicity in vitro are higher than the plasma levels of DHA reported in rats, so it is still not known if more highly toxic metabolites are produced in rodents.

Relationship to antimalarial activity

The mechanism by which artemisinins kill malaria parasites has been studied intensely (albeit not resolved completely). Artemisinins owe their activity to their endoperoxide bridge (two oxygens embedded in the three-oxygen atom trioxane pharmacophore). The prevailing hypothesis is that in order for the molecule to act as an antimalarial, it must be "activated" through the cleavage of the peroxide bridge. The final target has yet to be identified — the activated artemisinin could either alkylate vital molecules or cause oxidative damage. The activation is a one-electron transfer which requires an electron donor; this may be ferrous iron (Fe^{2+}), which is abundant in the parasite as haem iron (although free iron or other electron donors also may be involved). It may be that the same processes mediate the embryotoxic effects on primitive erythrocytes. Like the malaria parasite, primitive erythrocytes have high amounts of iron and free haem as they actively synthesize the haem to be included in haemoglobin.

Taken together, these results indicate that the toxicity seen is likely to be a class effect (common to any substance with an endoperoxide bridge) and species-independent. Differences in yolk sac structure and arrangement in different species are not likely to be relevant in risk assessment.

We do not know whether, and to what extent, antimalarial activity and embryotoxicity can be divorced. For species other than rodents, we do not know the precise time of maximum sensitivity and duration of treatment required to induce the irreversible effects. Although the data on first trimester exposure in humans are very limited, it could well be that the reason why adverse effects have not been reported in humans is the short episodic exposure to artemisinins.

KINETICS AND METABOLISM

The metabolic profile of artemisinins in all species except humans is not fully characterized. Available data indicate much greater systemic exposure (higher plasma levels of artesunate and DHA) in humans compared to rodents and primates. However, the in vivo dose that is effective against malarial infections is similar among rodents, non-human primates and humans (Clark et al., 2006). Current evidence suggests that there may be substantial differences in metabolism and volume of distribution among species. In humans, artesunate is metabolized to DHA, DHA-glucuronide and a THF acetate rearrangement product. In contrast, rats have a complex metabolic profile including a number of deoxy and monohydroxylated metabolites which are eventually eliminated as glucuronides. Moreover, in-vitro microsome work suggests that rats may produce additional metabolites compared with humans. Taken together, this information suggests that drug plasma concentrations of parent drug plus DHA alone may not be appropriate for risk assessment. Additional work is needed to reconcile apparent differences in plasma concentrations and distribution profiles among experimental species and humans.

COMBINATION THERAPY

Since all artemisinins will be used in combination with other antimalarials in the treatment of uncomplicated malaria, the possibilities of interactions must be considered. This is especially the case where the partner medicine has haem as the target, which may interfere with artemisinin "activation". This could result in interference with therapeutic effects as well as toxic effects so both types of interactions should be considered.

FUTURE STUDIES

Experimental/animal investigations

1. There is a need to understand more fully the critical period of exposure, and the duration of exposure necessary to induce embryotoxicity in primates.

2. There is a need to perform embryotoxicity studies on newer artemisinins (synthetic trioxanes and modified artemisinins) and other peroxidic molecules in order to evaluate their potential for developmental toxicity.

3. There is a need for metabolic profile studies in rodents and primates to compare their profiles of metabolism with that in humans.

4. Whole embryo culture studies in vitro should be extended to investigate the role of metabolites, oxygen and reactive species. Studies on the toxic activity of rat and human blood following artemisinin administration would give an indication of the presence of active metabolites.

Human investigations

5. It is not known whether, in the human, clonal expansion of primitive erythroblasts occurs similarly to that observed in rodents, leading to a period of heightened sensitivity to artemisinins. Further work is necessary to elucidate this aspect of embryogenesis in humans.

6. There is need for a review of the safety of all antimalarial medicines in pregnancy, especially when used during the first trimester. In particular an up-to-date review of pregnancy outcomes following exposure to artemisinins during the first trimester is required urgently.

7. Since 2002, population studies have been carried out by WHO and others in Bangladesh, Kenya, South Africa, the United Republic of Tanzania and Zambia. Some of these studies have included exposures of pregnant women to artemisinins. These data should be made available for review by experts in reproductive epidemiology with a view to assessing the strength of the information involving first-trimester exposures.

8. There is a need to establish how we can move ahead to obtain the required information about safety in pregnancy.

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THE SAFETY AND EFFICACY OF ANTIMALARIAL THERAPY WITH ARTEMISININ COMPOUNDS IN PREGNANCY

Report of an informal consultation of clinical investigators convened by WHO, Geneva, October 2006

INTRODUCTION

The conclusions from preclinical studies presented in detail in the first part of this document showed essentially that the actions of the artemisinins are a class effect. Teratogenic effects are observed in the absence of maternal toxicity and are limited to a narrow dose range at an early stage of embryogenesis. The primary effect in rodents was an interference with yolk sac haematopoiesis on GD 9-14 (equivalent to weeks 2-6 in humans) that could lead to malformations or embryolethality. Studies in primates also demonstrated a time window of sensitivity but resulted in embryolethality with no malformations being seen. It is uncertain whether the results in animals are directly applicable to humans and whether a similar sensitive period might exist.

From 30 October to 1 November 2006 a clinical consultation was held to address these issues by reviewing current clinical knowledge of first trimester risks of exposure to artemisinins in pregnancy. The meeting was divided into three parts. Firstly, the current information on the outcome of pregnancies treated with standard antimalarial medicines was reviewed. Secondly, these results were compared with the outcomes of pregnancy following artemisinin use, with emphasis on first trimester exposure. Thirdly, the use of pregnancy registries to detect adverse effects following first trimester exposures, and how the information obtained might be used to influence drug-treatment policy was discussed. The meeting also suggested future research to shed further light on the safety of artemisinins in early pregnancy.

Malaria in pregnancy is associated with low birth weight, increased anaemia and, in low-transmission areas, an increased risk of severe malaria. In high-transmission settings, despite the adverse effects on foetal growth, malaria is usually asymptomatic in pregnancy (Desai, 2007). There is limited information on the safety and efficacy of most antimalarial medicines in pregnancy, particularly for exposure in the first trimester, and so treatment recommendations differ from those for non-pregnant adults. Organogenesis occurs mainly in the first trimester, therefore the time of greatest concern for potential teratogenicity, although nervous system development continues throughout pregnancy and postnatally. Antimalarials considered safe in the first trimester of pregnancy are quinine, chloroquine, proguanil, pyrimethamine and sulfadoxine–pyrimethamine. Of these, quinine remains the most effective and can be used in all trimesters of pregnancy, including the first. In reality women often do not declare their pregnancies in the first trimester and so early pregnancies are often exposed inadvertently to the available first-line treatment. Inadvertent exposure to antimalarials is not an indication for termination of pregnancy.

WHO RECOMMENDATIONS

There is increasing experience with artemisinin derivatives in the second and third trimesters of pregnancy (over 1000 documented cases) and no adverse effects on the mother or foetus have been reported. The current assessment of benefits and potential risks suggests that the artemisinin derivatives should be used to treat uncomplicated falciparum malaria in the second and third trimesters of pregnancy. They should not be used as first-line treatment in the first trimester until more information becomes available. Despite these many uncertainties, effective treatment must not be delayed in seriously ill pregnant women. In practice, if first-line treatment with an artemisinin combination is all that is immediately available to treat pregnant women who have symptomatic malaria in the first trimester of pregnancy, it should be given. Pharmacovigilance programmes to document the outcome of pregnancies exposed to artemisinin combination therapy (ACTs), and (if possible) the development of the infant, are encouraged so that future recommendations can stand on a firmer footing.

Particularly in the second and third trimesters of pregnancy, women are more likely to develop severe malaria. Often this is complicated by pulmonary oedema and hypoglycaemia; maternal mortality may be up to approximately 50%, higher than in non-pregnant adults. Foetal death and premature labour are common.

Treatment of malaria in pregnancy has to be considered in two parts: uncomplicated malaria where the life of the mother is not necessarily at risk, and severe malaria where the life of the mother is at risk and needs to be considered as well as the life of the child. For uncomplicated malaria, current WHO Guidelines (WHO Guidelines for Treatment of Malaria, 2006) recommend that artemisinin-based combination treatment should be used in the second and third trimester, but should only be used in the first trimester if it is the only effective treatment available. In severe malaria, the artemisinins are preferred over quinine in the second and third trimester because of the hypoglycaemia associated with quinine. However, in the first trimester both artesunate and quinine may be considered as options until more evidence becomes available on the risk-benefit ratio of artemisinins. Treatment should be started without delay and whichever medicine is immediately available should be used.

RISK OF MALARIA INFECTION IN PREGNANCY

In addition to the well-known high incidence of parasites in peripheral blood in malaria in pregnancy, there is extensive evidence of infection of the placenta, in both low- and high-transmission settings. In high-transmission areas, primigravidae are indisputably at greater risk of infection. The gravidity effect is less marked in low-transmission areas and absent in areas with epidemic malaria. The burden of malaria in pregnancy is exacerbated by co-infection with HIV. Sub-Saharan Africa bears the brunt of this co-morbidity. HIV infection seems to compromise immunity to malaria and increase the risk of malaria for mutigravidae to equal that for primagravidae. In some areas, malaria-related mortality may occur in 1% of pregnant women, but there is little information on malarial morbidity and mortality globally (Desai et al, 2007).

CURRENT STUDIES ON TREATMENT OF MALARIA WITH ARTEMISININS IN PREGNANCY

During this meeting, evidence was presented on artemisinin exposure in pregnancy from ongoing studies in Thailand, Zambia and Bangladesh. Data will be published fully in due course. These studies involved investigations on antimalarial treatments in pregnancy including first trimester exposures. Important results were presented from Thailand on the risk of abortion related to severity of malaria infection compared with risks from the use of antimalarial medicines (mainly quinine, chloroquine, mefloquine and artemisinin based combinations). There was clear evidence that the risk of abortion could more than double (from around 15% to 40% or greater). The major risk factors for abortion are the number of malaria episodes with fever, hyperparasitaemia, older maternal age and early first trimester infection. Antimalarial treatment per se was not associated with increased risk of abortion. Data on congenital abnormalities were insufficient to draw any conclusions but the overall conclusion was that the risks of abortion due to malaria infection far outweighed any risks of abortion due to the use of antimalarial medicines.

The Bangladesh study treated about 3800 women, 10% of whom were pregnant, but an analysis of results was not yet available. Very preliminary results were presented from a combined WHO-Novartis study on Coartem being performed in Zambia. Around 500 pregnancies had been enrolled in the study of an intended 1000 pregnancies; many of the women had not yet delivered and therefore no analysis of the outcome of pregnancy results could be made.

The evidence presented at the meeting regarding first trimester exposures to artemisinins was reassuring but still inadequate to warrant a change in the current WHO recommendations for treatment of malaria in first trimester pregnancy. Consequently, these are still valid. The medicine of choice for initial treatment in the first trimester of pregnancy varies because of differences in drug sensitivities in different regions. However, because of the dangers of repeated malaria infections in pregnancy, the immediate use of artemisinins is justified in situations where the first treatment fails.

DISCUSSION OF PREGNANCY REGISTRIES

Core elements of a pregnancy registry

Generally, it is considered unethical to conduct clinical trials in women during the first trimester of pregnancy because of the risks of irreversible changes to the embryo. The use of pregnancy registries has increased in recent years as an active method of detecting outcomes of pregnancies exposed to drugs inadvertently or deliberately. This has been encouraged by the drug regulatory authorities as part of the post-authorization monitoring of medicines.[1]

The setting up of such registries to detect adverse effects of malaria and drug exposure during pregnancy in disease-endemic countries was discussed since inadvertent exposures to antimalarials during the first trimester of pregnancy will occur. Ideally, a registry should be a prospective, observational study that actively collects information on drug exposures during pregnancy and associated pregnancy outcomes. Women with and without exposure to the treatment of interest should be enrolled in these studies as early as possible, and before the outcome of pregnancy is known. This avoids any bias introduced by the tendency to preferentially report adverse outcomes.

Setting up a pregnancy registry requires pregnant women to be enrolled and data recorded on demographics, maternal medical history, obstetrical history and details of the current pregnancy (concomitant infections, medications [drugs, dose, route, timing of exposure] complications, severity and timing of malaria). Data should be confidential. Women need to be followed up to term and birth outcomes should be recorded: abortion, stillbirths, live births, neonatal deaths, presence/absence of major/minor malformations and postnatal developmental assessment. It was recognized that a study of malaria would present a number of problems relating to the availability of medical care; multiple short-term infections; presence of HIV; prophylactic use of antimalarials; and difficulties confirming malaria and measuring the severity of infection. A major difficulty in many countries is the lack of background data on pregnancy outcomes in a normal or unexposed population. Data from different populations with different background diseases and exposures strengthen understanding of drug effects.

Antiretroviral pregnancy registries

Antiretroviral medicines (ARVs) are a drug class that has been studied extensively via this method. Results from the ARV Registry were reported at the meeting — a collaborative venture between pharmaceutical companies, regulatory authorities and interested parties. The management of this registry was passed from the individual initiating companies to a contract research organization because of the magnitude and complexity of the work.

Methodological factors

It is essential that the design of a prospective pregnancy register outlines what will be assessed and what will be excluded from assessment. At its simplest the assessment of the pregnancy outcome may be limited to recording of the vitality of the baby, its sex, birth weight and general appearance. Detection of the presence or absence of malformations depends upon the skill and experience of the assessor (e.g. paediatrician, nurse/midwife) and the availability of advanced diagnostic equipment. It also depends upon the age of the child at assessment, for example cardiac malformations may not become obvious until the child is several years old. These issues should be incorporated within the design of the study. Another problem is the definition of comparator groups such as country- or region-specific data on pregnancy outcomes or groups treated with other antimalarial medicines.

1 Guidance for industry: establishing pregnancy exposure registries. Available at: http://www.fda.gov/cder/guidance/3626fnl.htm, accessed 23 September 2007.
European Medicines Agency. Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data (EMEA/CHMP/313666/2005). Available at: www.emea.europa.eu/pdfs/human/phvwp/31366605en.pdf, accessed 23 September 2007.

The sample size necessary to detect a significant increase in congenital malformations depends very much upon the frequency of the malformations and can vary from less than 100 to more than 1000 exposures.

Design of Zambian Electronic Perinatal Record System (ZEPRS) Register

An example of the setting up of a successful registry in disease-endemic countries was presented. The ZEPRS Register is a population-based pregnancy registry recording 45 000 deliveries per annum at the University Teaching Hospital, Lusaka. Information is recorded by midwives as part of antenatal care. This system aims to provide basic data on birth weights, birth measurements and general aspects of pregnancy outcomes via electronic records. Ultimately, it is hoped to include the majority of the pregnant population in Zambia so that this registry can provide background data against which effects on pregnancy outcome from diseases and infections (including antimalarial medicines) could be compared.

PRIORITIES FOR RESEARCH

Clinical studies

In order to hasten the acquisition of knowledge about the safety of artemisinins in early pregnancy, two possible lines of investigation were discussed: (i) possible use of randomized controlled trials and (ii) use of observational studies.

Randomized controlled trials (RCTs)

Generally there are major ethical barriers to the deliberate conduct of controlled drug trials in the first trimester of pregnancy. However, there are exceptions where the benefits to the mother and foetus might outweigh the potential disadvantages for foetal development. Two possible scenarios are detailed below.

1. It would be ethical to conduct first trimester exposure studies in severe *P. falciparum* malaria where investigation of the efficacy and safety of new drug classes would be justified in the context of high maternal mortality. Maternal mortality would be the primary endpoint; pregnancy outcome the secondary endpoint. For example, the safety and efficacy of intravenous artesunate could be compared against intravenous or intramuscular quinine. Such a trial could be justified by the risk-benefit ratio. Studies should be undertaken in both south-east Asia and Africa since the outcomes might be different.

2. Where current treatments have been demonstrated to be ineffective it would be considered ethical to conduct an open label study to compare artemisinin-based and standard treatment for women recrudescing from treatment for uncomplicated malaria. If first trimester exposure was monitored, this could provide valuable information on abortions and malformations; second- and third-trimester exposure would provide valuable information on the incidence of low birth weight and stillbirths.

Although studies in pregnancy are difficult to perform because large sample sizes and longitudinal monitoring would be needed for safety evaluations, nevertheless even with limited numbers of patients, valuable additional information on kinetics and the optimum doses of the medicines can be obtained. In addition to the primary endpoints of cure rates, other endpoints such as neonatal mortality, maternal anaemia, placental parasitaemia and developmental delays in the offspring could be studied.

Observational studies

The two major pregnancy-related effects of artemisinins observed in the animal studies are early pregnancy loss and, occasionally, congenital malformations. Clinical detection of these effects is particularly difficult

as, normally, most women will not know that they are pregnant in the equivalent window of sensitivity. The primary value of prospective observational studies would be to capture information on early pregnancy loss. Studies could be undertaken only in communities where it is acceptable to perform early pregnancy tests. Serum βhCG could be used to identify pregnancy and foetal age in women with severe malaria and followed, for example, by hCG at 10 weeks to see if the women are still pregnant or foetal death has occurred. Indirect methods to detect early foetal loss could also be used, such as intervals between pregnancies or number of pregnancies per year.

For the detection of birth defects it is important to know the gestational age at the time of exposure to artemisinins in pregnancy; the difficulties about detecting the time of conception (discussed above) are therefore relevant. Important design factors include the need for a control group which includes women with exposures to other antimalarial medicines and women with none. Detection of malformations may be difficult and dependant upon the training of assessors and the equipment available; one possibility is to include only easily visible defects. A different approach would be the use of a retrospective case-control study design to look at, for example, babies with cardiac defects whose mothers had malarial infections during early pregnancy. This would enable comparisons between those treated with artemisinins, those treated with other antimalarials and those without malarial infection.

The difficulties in the conduct of these studies are not only the numbers of patients involved but also the necessity of obtaining reliable and valid data. For example, the design and conduct of the study must be able to detect changes in the incidence of cardiac malformations in order to remove concerns about possible cardiac malformations. This may require a special study, employing the services of both a cardiologist and a paediatrician with the necessary equipment, to investigate children born to women exposed to artemisinins in early pregnancy and compare outcomes with a control unexposed population. Only by using methods such as these will we be able to alter with confidence the contraindications for early pregnancy exposure to artemisinins.

Collaborative studies and registries in settings where artemisinins are now being deployed as first-line treatment are important for extending the database of pregnancies exposed to antimalarials and confidence on risks and benefits of treatment. Consequently it should be of general interest that procedures are in place to provide adequate training and monitoring to assure and maintain the quality of data. There may be advantages in conducting smaller pilot studies to assess the feasibility of the planned work.

INVOLVEMENT OF THE PHARMACEUTICAL INDUSTRY

The manufacturers of artemisinin-based medicines and drug combinations have a responsibility for post-marketing surveillance of their products. Representatives of these companies who were present at the meeting expressed an interest in being involved in the investigations described above, in collaboration with WHO.

SUMMARY

The current WHO guidelines recommending the use of artemisinin combinations in the second and third trimesters of pregnancy are supported by the increasing evidence of their safety in use. In uncomplicated malaria, only where no other medicines are effective should the artemisinins be used in the first trimester. However, in severe malaria (where the mother's life is at risk) and in cases where inadequate therapy has led to recurrent attacks, the dangers associated with the malarial disease justify the use of artemisinins in the first trimester. The setting up and use of pregnancy registries, clinical trials and other epidemiological methods should be encouraged in order to increase information on the safety of artemisinins in the first trimester.

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