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.