Effects of malaria and its treatment in early pregnancy

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Malaria can have devastating consequences for pregnant women and their developing fetuses. The lack of information on the effect of malaria in the first trimester has been previously identified as an important knowledge gap in estimating the burden of malaria in pregnancy.[1] Similarly, few data are available on the safety in early pregnancy of the artemisinin class of compounds, alone or as combination therapies,[2] the most effective antimalarials to date. Although extrapolation of animal reprotoxicology data to human beings is ambiguous, it suggests that artemisinin derivatives could cause birth defects or pregnancy loss when used in the early first trimester of pregnancy.[3] Policy makers and health practitioners need reliable data to determine the best treatment for malaria in the first trimester of pregnancy.[4]

In *The Lancet Infectious Diseases*, R McGready and colleagues[5] report results of the largest retrospective analysis to date of the effect of malaria infection and treatment in early pregnancy. The investigators analysed 25 years of data from the Shoklo Malaria Research Unit (SMRU) clinics on the Thai–Burmese border, including over 48 000 pregnancies.[5] Their findings showed that the main risk factors for miscarriage were malaria infection (symptomatic and asymptomatic), smoking, and increasing maternal age. McGready and colleagues concluded that there was no evidence of increased miscarriage with first-trimester exposure to artemisinin derivatives when controlling for malaria infection and parasitaemia based on 64 exposures compared with women treated with chloroquine (354), or quinine (355), and women who had no malaria during pregnancy (16 668).

This study is the first time the potential risk of miscarriage associated with the use of the artemisinin antimalarials has been assessed in early pregnancy. Miscarriage is a difficult endpoint to assess because most pregnancy losses occur very early (before 8–9 weeks of gestation), and in many settings, most women only present for their first antenatal care visit in their second or third trimester of pregnancy. The unique set-up of the SMRU allows it to serve a stable refugee population where many pregnant women receive weekly antenatal care, pregnancies can be identified early, the gestational age assessed at every contact, health-care provided, and drug exposure and birth outcome recorded centrally. These factors help overcome some of the methodological challenges in assessing the effect of malaria and safety of artemisinin combination treatments in early pregnancy and cannot be easily replicated elsewhere. Only women presenting in their first trimester were included in the analyses, which enabled the investigators to assess miscarriage as an endpoint while minimising potential survivor bias. However, some misclassification of drug exposure cannot be ruled out due to uncertainty in the assessment of gestational age.

The evidence presented by McGready and colleagues highlights the importance of malaria prevention early in pregnancy, possibly as early as before conception.

	Exposed to unexposed ratio of 1:1			Exposed to unexposed ratio of 1:4		
	Number exposed	Number unexposed	Total	Number exposed	Number unexposed	Total
Miscarriage (p=0·20)						
1·2	1329	1329	2658	819	3277	4096
1·5	231	231	463	140	561	701
2	64	64	128	38	152	190
5	3	3	6	2	7	9
10	NA	NA	NA	NA	NA	NA
Stillbirths (p=0·03)						
1·2	10 991	10 991	21 981	6747	13 493	20 712
1·5	1988	1988	3976	1192	4767	5959
2	591	591	1182	343	1372	1715
5	69	69	139	37	146	183
10	22	22	45	11	45	56
Major malformations (p=0·02)						
1·2	16 674	16 674	33 348	10 233	40 934	51 884
1·5	3022	3022	6043	1810	7241	9052
2	901	901	1802	522	2090	2612
5	108	108	216	57	227	284
10	36	36	73	18	72	90
Specific birth defect (p=0·001)						
1·2	340 629	340 629	681 259	208 978	835 913	1 059 540
1·5	61 922	61 922	123 845	37 067	148 270	185 337
2	18 571	18 571	37 143	10 748	42 992	53 740
5	2317	2317	4634	1206	4824	6030
10	836	836	1673	409	1638	2047

Modified from Dellicour and colleagues.[6] Ratio of exposed to unexposed of 1:4, power 80%, and one-sided α=0·05. These sample-size calculations are based on a one-sided approach because registries of pregnancy exposure are designed to detect safety signals rather than to examine potential protective effects. The formula for cohort design described in Strom's *Pharmacoepidemiology*[7] is $N = 1/[p(1-R)]^2 \times [Z_{1-\alpha}\sqrt{[(1+1/k)U(1-U)]} + Z_{1-\beta}\sqrt{[pR(1-Rp) + (P[1-P])/k)]}]^2$ where p is the incidence of disease in unexposed; R is the minimum relative risk to detect; k is the ratio of unexposed controls to exposed and U is $(Kp + pR)/(k + 1)$. These estimates do not include loss to follow-up and do not account for the expected 16–18% of pregnancies that might not result in a livebirth. The latter needs to be considered for outcomes such as major malformation and specific birth defects.

Table: **Number of pregnancies needed in each group to detect various relative risks for pregnancy outcomes with different prevalence**

Although the number of well documented early exposures to artemisinins was relatively small (64), the study was adequately powered to rule out a doubling of the risk of late miscarriage associated with artemisinin exposure during the embryo-sensitive period, with a 19% (3198) detectable background rate of clinically recognised miscarriages (table). We congratulate McGready and colleagues for contributing valuable information about the risk of malaria and safety of artemisinin combination treatment in early pregnancy; lessons from this study will be relevant to many other settings. The investigators have highlighted one of the main challenges with drug safety studies—the requirement of very large sample sizes to acquire fewer than 100 well-documented early exposures to artemisinins. So, do we now have sufficient evidence to say that the risk of having malaria in early pregnancy outweighs any theoretical harm due to the artemisinin class of antimalarials? This study provides a level of reassurance regarding the potential risk associated with artemisinin exposure in early pregnancy, compared with the established risk of malaria. This study, combined with data from ongoing studies done in sub-Saharan Africa, will for the first time allow an informed risk–benefit assessment of disease versus treatment with artemisinin combination treatments in pregnancy.

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We declare that we have no conflicts of interest.

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