

USE OF MEFLOQUINE IN PREGNANCY

SUMMARY: Mefloquine is used for the prophylaxis of malaria. It is now rarely used for the treatment of malaria because of increased resistance and risk of adverse effects.

The limited data available on the use of mefloquine in human pregnancy are reassuring and do not indicate an increased teratogenic risk.

During pregnancy, travel to areas where malaria is endemic should be avoided wherever possible. If travel to such areas is unavoidable, chloroquine and proguanil are the antimalarials of choice during pregnancy and should not be withheld if the strain of malaria is sensitive to these drugs. Mefloquine may be considered as an option for prophylaxis in cases of chloroquine/proguanil resistance. If mefloquine is indicated it should not be withheld. Inadvertent exposure is not grounds for termination of pregnancy or invasive diagnostic tests.

Important: Please ensure that the selected antimalarial will provide appropriate prophylaxis for the area of travel. Current recommendations for the appropriate antimalarials for specific regions, based on malarial resistance, is available from a number of sources (e.g. BNF,¹ Fit For Travel,² NathNAC,³ TRAVAX⁴).

For general advice on malaria prevention in pregnancy please see the [Malaria prophylaxis in pregnancy](#) and [Insect Repellents in pregnancy](#) monographs.

Preclinical (animal) data

Animal studies have found mefloquine to be teratogenic in rats and mice; however the doses used in these studies were up to twenty times those used in humans. Abnormalities seen most often were soft tissue and skeletal anomalies in rats and cleft palate abnormalities in mice.⁵ Fetal resorption (equivalent to spontaneous abortion in human pregnancy) has occurred at doses of 160mg/kg/day which is significantly higher than the maximum human dose.⁶

Human data

Often, data from observational sources or case reports, including data collected by NTIS, may be confounded by maternal co-ingestion of a number of drugs, at varying doses, and for a range of indications. The severity of the underlying maternal condition, where relevant, is frequently unknown and information on other potential confounding variables may be incomplete. These factors should be considered when interpreting observational human pregnancy data.

The data available in human pregnancy is reassuring and does not indicate a teratogenic potential in humans,⁶⁻⁹ however one group of investigators found a possible association between the use of treatment doses of mefloquine during pregnancy and an increased risk of stillbirth.^{10, 11}

Antimalarial prophylaxis doses

The manufacturer of mefloquine published post-marketing data on 1627 women exposed to mefloquine prophylaxis during or prior to pregnancy. Of the 1627 exposures, 1526 were reported prospectively and of these, outcome data were available for 971. There were 646 deliveries, 79 spontaneous abortions and 246 elective terminations. Among the 1526 prospective exposures, there were 32 congenital malformations, 26 of which were in live born infants. This equates to an incidence of 4% for congenital malformations among live born infants which was not significantly higher than the background rate. The retrospectively reported cases included a further 24 malformations, though no specific pattern of congenital malformations was evident. Overall, the study found no evidence of a teratogenic effect of mefloquine.⁹

Four hundred and fifty five first trimester exposures to weekly mefloquine prophylaxis were summarised in a review which found no evidence of a teratogenic potential.⁶ The same review summarised two controlled studies of mefloquine prophylaxis in a total of 627 women in their second and third trimesters. Again, no evidence of an increased risk of spontaneous abortion, congenital malformation or growth retardation was found.

Seventy two exposures to mefloquine prophylaxis were reported in a study which included outcome data for 53 pregnancies. There were 23 healthy live births (no major malformations), 12 spontaneous abortions, 17 elective terminations of pregnancy and one molar pregnancy.¹²

An early dose-finding study in Thailand found no increase in adverse pregnancy outcomes among 20 women who took either 125mg or 250mg/week mefloquine prophylaxis during the third trimester of pregnancy.⁸

High dose (malaria treatment)

A comparative study of mefloquine and quinine followed 279 pregnant women with uncomplicated falciparum malaria who were treated with mefloquine at 25mg/kg in their last two trimesters of pregnancy. There was no noted increase in the incidence of adverse fetal effects compared with background levels among the women exposed to antimalarial medication.¹³

Pregnancy outcome was compared in one study after exposure to treatment doses of mefloquine (25mg/kg), quinine (10mg/kg), other antimalarials or no treatment,. Among the 208 pregnancies in the mefloquine group there were nine still births, a significant increase compared to quinine and other antimalarials. Mefloquine was not found to increase the risk of congenital malformation, spontaneous abortion or low birth weight.¹⁰ A similar

finding had been previously reported by the same authors in an early study involving 171 mefloquine exposures.¹¹ It appears that the same cases were reported again in the more recent study.

A total of 22 women with drug resistant falciparum malaria were exposed to artemether and mefloquine during the second and third trimesters. All pregnancies were reported to proceed uneventfully.¹⁴ A further study involving 85 pregnant women exposed to mefloquine in the treatment of multi-drug resistant falciparum malaria reportedly found no increased incidence of adverse pregnancy outcomes.⁷

UK malaria treatment guidelines (British Infection Society & Health Protection Agency)

The *Guidelines for malaria treatment in travellers from the United Kingdom*¹⁵ state that although mefloquine is effective in the treatment of uncomplicated falciparum malaria, the side effects and high rate of non-completion of courses mean that it is not recommended for this indication in the UK.

Paternal exposure

There were no reports found regarding paternal exposure to mefloquine.

Lactation

There were no reports found regarding neonatal toxicity following exposure to mefloquine during lactation.

NTIS data¹⁶

NTIS has followed up 42 prospective cases of therapeutic mefloquine exposure in pregnancy and seven retrospective outcomes.

Prospective Therapeutic Exposure Data

The frequency of congenital malformations in live born infants (1/33, 3.0%, 95% CI 0.02 to 17.5) was not significantly higher than the expected background rate.

<i>Trimester</i>	<i>Total pregnancies/ Total live borns</i>	<i>Normal infants</i>	<i>Neonatal problems</i>	<i>Congenital malformations</i>	<i>ETOP</i>	<i>SA</i>	<i>IUD</i>
1 st	41/32	28	3 ^{a, b, c}	1 ^d	7	2	-
1 st & 2 nd	1/1	1	-	-	-	-	-
Total	42/33	29	3	1	7	2	0

ETOP – elective termination of pregnancy, SA – spontaneous abortion, IUD – intrauterine death

^a Exposure to mefloquine from weeks six to eight of gestation and yellow fever vaccine at two weeks. Outcome was a live born infant with physiological jaundice.

^b Exposure to mefloquine for the first four weeks of gestation and pseudoephedrine and prochlorperazine for the first two weeks. Outcome was a live born infant with a transient heart murmur.

^c Exposure to mefloquine for the first seven weeks of gestation. Outcome was a live born infant with undescended testes.

^d Exposure to mefloquine from weeks two to eight of gestation and yellow fever vaccine at two weeks gestation. Paracetamol, a compound alginate preparation and an iron/folic acid product were also taken during pregnancy. Outcome was a live born infant with congenital hydronephrosis.

Retrospective Therapeutic Exposure Data

Seven cases of mefloquine exposure in early pregnancy, six of which were monotherapy, resulted in five live births, one spontaneous abortion and one elective termination of pregnancy. Among the live births there was one infant with bradycardia, another with craniosynostosis and a further case had mild eczema. The one case of polytherapy, where exposure to mefloquine and propranolol occurred, resulted in a live born with transverse finger abnormality of both hands. Causality cannot be established in any of these cases. The final live born infant was normal and healthy.

Conclusions

The available data on mefloquine exposure in pregnancy do not indicate an increased teratogenic risk. In areas where chloroquine/proguanil resistance is endemic and travel is unavoidable, mefloquine may be considered for prophylaxis of malaria during pregnancy due to the risks to mother and fetus from malaria infection. Mefloquine is rarely used in treatment of malaria in the general population due to concerns relating to resistance and adverse effects.

References

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Disclaimer: Every effort has been made to ensure that this monograph is accurate and up-to-date. However it cannot cover every eventuality and the information providers cannot be held responsible for any adverse outcomes of the measures recommended. There is a background incidence of congenital malformations (2-3%) and spontaneous abortions (10-20%) irrespective of any drug or chemical exposure. The final decision regarding which treatment is used for an individual patient remains the clinical responsibility of the prescriber.