Ocular Toxicity in Children Exposed *in Utero* to Antimalarial Drugs: Review of the Literature

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ABSTRACT. ***Objective.*** The antimalarial drugs chloroquine (CQ) and hydroxychloroquine (HCQ) have been used for decades to treat rheumatic diseases. CQ is still beneficial for the management of malaria during pregnancy. A growing body of research suggests that antimalarials are safe during pregnancy. There have been concerns about adverse longterm effects, mainly retinal toxicity, in offspring of women exposed to antimalarials during pregnancy. Our objective was to review the published evidence on safety of antimalarials during pregnancy, focusing on ocular toxicity in the offspring.

Methods. Ovid Medline, Embase, and Cochrane Library databases were searched for the period from their inception to May 2010 inclusive with no restrictions on language or year of publication. Randomized controlled trials (RCT) and observational studies examining the safety of CQ or HCQ during pregnancy and reporting on visual function or ocular toxicity in the offspring of exposed women at any point of the followup were eligible for inclusion. The quality of evidence was assessed according to established criteria (the GRADE approach).

Results. Twelve studies with a total of 588 offspring born to mothers treated with CQ or HCQ during pregnancy met the inclusion criteria. Five studies with a total of 251 exposed children reported no clinical visual abnormalities in any case. In an RCT on malaria prophylaxis, visual acuity in 251 infants exposed to CQ *in utero* did not differ from the placebo group. Detailed ophthalmological examination was performed in 4 studies and normal results were reported in all children (n = 59). Electrophysiological testing using electroretinogram was performed in 3 small cohorts and results were normal in all but 6 infants aged 3–7 months. All 6 children had normal fundoscopy before 4 years of age. Heterogeneity in comparison groups and in outcome measures precluded formal metaanalysis.

Conclusion. Current evidence suggests no fetal ocular toxicity of antimalarial medications during pregnancy. The clinical significance of early electroretinogram anomalies reported in a small subset of infants remains to be established. Larger followup studies are warranted to confirm low risk of ocular toxicity in children following antenatal exposure to antimalarial medications. (J Rheumatol First Release Oct 15 2011; doi:10.3899/jrheum.110686)

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Despite recent advances in the management of rheumatic diseases, antimalarial drugs still have an established beneficial role in the treatment of rheumatic conditions such as cutaneous and systemic lupus erythematosus (SLE) and rheumatoid arthritis. Hydroxychloroquine (HCQ) and chloroquine (CQ) have been demonstrated to reduce the risk of lupus flares and improve longterm survival of patients with SLE[1]. Additionally, CQ has been used extensively for the prophylaxis and treatment of malaria, but currently is replaced by other drugs because of parasite resistance. Still, CQ is recommended for the management of non-falciparum malaria during pregnancy in certain endemic areas[2,3]. Rheumatic conditions tend to have a chronic course and occur more often among women of childbearing age, therefore it is not uncommon for a woman taking antimalarial medications to have a successful pregnancy. Further, pregnant women are thought to be particularly susceptible to malaria infection, with an estimated 50 million pregnancies exposed annually to malaria worldwide[3].

For years, there have been concerns regarding potential harmful effects of antimalarial agents on the developing fetus. A growing body of research suggests no increased risk of teratogenicity following exposure to antimalarials during pregnancy. Recent systematic reviews including data on > 300 exposed offspring have shown concordant results: HCQ/CQ use in pregnancy is not associated with increased risk for birth defects, spontaneous abortions, fetal death, or prematurity in patients with autoimmune conditions[1,4,5]. Based on the experience with CQ for malaria prophylaxis, this drug is regarded as safe in pregnancy, although much lower doses are usually prescribed in comparison to those used for rheumatic conditions[2,3].

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Although the issue of possible teratogenicity of antimalarials appears to be addressed in the published literature, there is still a concern regarding potential toxic effects, mainly retinal toxicity, in the offspring of women exposed to antimalarials during pregnancy. Adverse ocular effects of antimalarials in adults are numerous and include keratopathy, ciliary body dysfunction, lens opacities, and retinopathy. Keratopathy with corneal deposits is a common, usually benign, ophthalmological finding, which is completely reversible upon drug discontinuation with no permanent corneal damage[6].

In contrast, retinal toxicity, although rare, is a major concern following treatment with antimalarial medications as it may lead to visual field defects, decreased visual acuity, and permanent visual loss. It is believed that CQ and HCQ bind to melanin in the retinal pigment epithelium and this may contribute to the drug-induced toxicity[7,8]. CQ binds more tightly and is thought to be more toxic than HCQ[9]. It has been suggested that daily and cumulative doses of antimalarials are important risk factors for retinopathy associated with longterm use of these medications. The majority of reports described retinal toxicity on daily doses exceeding 6.5 mg/kg/day HCQ (or 3 mg/kg/day CQ) or after prolonged treatment (> 7 years)[6,10,11], providing a basis for the guidelines for risk assessment of retinopathy in CQ- and HCQ-treated patients. The most recent update on screening recommendations advises not to exceed daily doses of 400 mg HCQ or 250 mg CQ. Even lower doses are suggested for patients with short stature, who are at risk of overdose. For such individuals, the "ideal" body weight must be taken into consideration while calculating the daily doses. Similarly, obese patients should be medicated on the basis of their "ideal" body weight[12].

Given a risk of retinal toxicity following longterm treatment with antimalarials, it is plausible to consider similar toxicity in the offspring of women taking these medications during pregnancy. There have been studies demonstrating that CQ and HCQ cross the placenta and accumulate in fetal eye tissues[8,13,14,15]. Isolated case reports of retinal degeneration in infants prenatally exposed to CQ have led to further concerns[16]. Studies examining visual function of babies exposed *in utero* to antimalarials reported no cases of retinal toxicity[17,18]. Nevertheless, the issue has not been addressed sufficiently in literature reports and recent systematic reviews have not focused on retinal toxicity in the offspring of exposed women.

The objective of our study was to perform a systematic review of the current literature on safety of antimalarial agents during pregnancy with a focus on ocular toxicity in the offspring.

MATERIALS AND METHODS

Search strategy and study selection. Two authors searched Ovid Medline, Embase, and Cochrane Library electronic databases for the period from their inception to May 2010 inclusive, with no restrictions on language or year of publication. Our search strategy included the following US National Library of Medicine Medical Subject Headings terms: "chloroquine" OR "hydroxychloroquine" combined with "pregnancy" OR "congenital, hereditary, and neonatal diseases and abnormalities" OR "prenatal exposure delayed effects" OR "embryo and fetal development" OR "embryonic structures" OR "teratogens." The search was further limited to human data and we excluded editorials and case reports. Review articles were not included but were searched further to identify potentially relevant publications. Reference lists of all retrieved studies and review articles were hand-searched to identify additional studies.

Eligible studies included randomized controlled trials (RCT) and observational studies examining ocular effects of CQ or HCQ exposure during pregnancy and reporting clinical outcomes in the offspring of exposed women. The titles and abstracts were screened for relevance by assessing the population of interest (pregnant women), exposure to antimalarials, and outcome of interest (visual function or ocular toxicity). Potentially relevant articles were thereafter retrieved as a full text and examined further. Two authors reviewed all full-text articles independently to determine eligibility for inclusion. Differences in judgment between the reviewers were resolved by consensus. The following information was extracted from studies deemed eligible: study design, drug of exposure, length of followup, number of subjects exposed, comparison group, outcome of interest, outcome measurement instruments, and reported findings.

Quality assessment. The selected studies were critically appraised utilizing the GRADE approach (grading of recommendations, assessment, development and evaluation)[19]. The GRADE system was developed by a group of experts and adopted by the Cochrane Collaboration to assess the quality of evidence for each individual outcome reported in systematic reviews. The GRADE evaluates the risk of bias across 6 domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. Each of the domains is judged as having high, low, or uncertain risk of bias. The overall quality of evidence is rated as high, moderate, low, and very low. Randomized trials are generally graded as high quality, whereas observational studies are graded as low quality evidence. However, the reviewers may downgrade or upgrade the quality of evidence based on the specific criteria.

RESULTS

The initial search strategy yielded 790 abstracts; 753 were excluded as not relevant. The remaining 37 abstracts were evaluated further as full text. Of these, 12 studies met the inclusion criteria and were included in this review[17,18,20,21,22,23,24,25,26,27,28,29]. They included 588 children born to mothers treated with CQ or HCQ during pregnancy. Eleven of 12 studies reported the use of antimalarial medications, predominantly HCQ, for the treatment of rheumatic diseases and included 337 exposed children[18,19,20,21,22,23,24,25,26,27,28]. There was one trial on CQ use for malaria prophylaxis, reporting on 251 exposed infants[29]. Of the 11 studies in rheumatic conditions, 1 was an RCT[28] and the remaining 10 were cohort studies[18,19,20,21,22,23,24,25,26,27]. Three cohort studies used control groups of women with similar diseases[19,20,21], 2 other cohort studies used comparisons to normal values in healthy subjects[16,26]. The remaining 5 cohorts lacked comparison groups[18,23,24,25,26]. The single eligible study on malaria prophylaxis was an RCT[29].

Methods of visual assessment varied greatly among studies. Five studies with a total of 251 exposed children performed clinical evaluation of visual function and found no visual abnormalities in any case as reported by mother, general practitioner, or pediatrician[20,21,22,23,24]. The time of clinical

assessment ranged widely from 10 months[24] to 19 years[23] and was not specified in 2 studies[20,22]. In an RCT on malaria prophylaxis[29], visual acuity was assessed in 251 infants exposed to CQ *in utero* at 1 year of age, and it did not differ from the placebo group. Detailed ophthalmological examination was performed in 4 studies[17,18,26,28] and normal results were reported in all children (n = 59). Ophthalmological examination was performed during the first year of life[18,26] or later[17,28].

Electrophysiological testing using electroretinogram (ERG) was performed in 3 small cohorts of infants exposed to HCQ prenatally (n = 31) and results were normal in all but 6 infants of 3–7 months of age[24,25,26]. These 6 children had normal fundoscopy results by 4 years of age.

Study quality. The majority (83%) of the reports were observational studies[17,18,20,21,22,23,24,25,26,27] rated as providing low-quality evidence. Two RCT[28,29] were ranked as having uncertain risk of bias. The study by Villegas, *et al*[29] demonstrated adequate sequence generation and allocation of concealment; however, it is unclear whether the outcome assessor was blinded to the exposure and no reasons were given for missing outcome data (> 25%). The study of Levy, *et al*[28] did not provide adequate description of the method of randomization and concealment. Outcome assessors were blinded and outcome data were complete. Overall, both studies were downgraded from high to moderate-quality evidence based on the limitations in study design and implementation described above.

DISCUSSION

To our knowledge, this is the first attempt to systematically assess the potential harmful effect of antimalarial medications on visual function in offspring exposed *in utero* to these medications. Collectively, the total number of exposed children (n = 588) and the nearly uniform absence of visual abnormalities across the studies suggest low to nonexistent risk of retinal toxicity in the infants following antenatal exposure to antimalarial medications. The majority of studies (92%) were conducted on offspring of women with rheumatic diseases, mainly SLE. Of 337 children born to mothers with rheumatic conditions, 319 (nearly 95%) were exposed to HCQ, which was continued throughout the entire pregnancy in most cases. The doses of HCQ used were reasonably similar and consistent with traditional doses for patients with SLE, between 200 and 600 mg/day, although a few studies did not report dosage information[22,28]. Hence, reasonable degree of similarity among the treatment groups and homogeneity in drug exposure across studies can be assumed.

In contrast, variations in the methods used for visual function assessment represent a significant limitation of our review. Clinical assessment of visual function performed in 5 out of 12 studies was poorly described, making it impossible to assess validity and reliability[20,21,22,23,24]. Only a small number of exposed infants received a comprehensive ophthalmological evaluation that included various combinations of the following tests: inspection of anterior/posterior segment, visual acuity testing, color vision, visual fields assessment, and fundoscopic appearance[17,18,26,28]. Nevertheless, normal findings reported in all children assessed provide a reasonable degree of reassurance.

Given the difficulties in assessing visual function in young children who cannot cooperate or communicate, electrophysiological testing such as electroretinogram (ERG) and visual evoked potential recording may be particularly useful for this age group. It has also been suggested that multifocal ERG is more sensitive in detection of early subclinical retinal changes following longterm exposure to antimalarials in adults, and this is now recommended as one of the objective screening tests[12]. Importantly, standard protocols for the technical procedures and reporting of ERG have been proposed by the International Society for Clinical Electrophysiology of Vision (ISCEV) to allow comparability of test results[30]. However, it has been demonstrated that ERG responses mature at different rates in early infancy[31] and therefore must ideally be compared to the values of healthy subjects of the same age[32]. As noted, ERG testing was conducted on a small number of infants, which is not surprising because of the labor- and resource-intensive requirements of the testing. Two small series[25,26] did not provide sufficient details on the testing technique and expected normal values for comparison, making it difficult to interpret the reported normal ERG results. In contrast, the study by Renault, *et al*[27] stated explicitly the method and normative data used, although those seemed to deviate from the ISCEV standards. The study demonstrated neurophysiological visual abnormalities in more than 28% of assessed infants. As highlighted in response to that study, the clinical significance of the findings remains unclear and requires longterm continuing assessments[33]. Future studies with standard protocols are warranted to corroborate these results. In general, the ERG findings have probably not been significant in these studies, as significant ERG occurs only in very advanced retinopathy from antimalarials.

A limitation of our review is a generally low quality of included studies, the majority being observational. It is important to bear in mind the following considerations. The incidence of the true retinal toxicity in adults following longterm treatment with antimalarial medications is low: 2.5% for CQ and 0.1% for HCQ[1]. Hence, it is unlikely that RCT of sufficiently large sample size and adequate length of followup will ever be conducted in infants to answer the specific research question we attempted to address in this review. That only 2 small RCT were available for inclusion in this review confirms that observational studies remain the main source of evidence, especially for uncommon medical conditions such as SLE or rare adverse effects. Further, observational data gathered in a real clinical setting are more likely to address relevant clinical problems encountered in daily practice. This may also enhance the external validity and feasibility of future

research. Thus, it has been argued that observational studies are a valuable and critical source of data, especially on drug safety, and therefore should complement RCT to enable informed decision making by physicians and patients[32,33,34].

The evidence of observational studies included in this review was graded at low quality because of high risk of bias. For instance, criteria for selection of participants exposed to antimalarials were not specified[20] and were based on medication-use patterns[22] or personal preferences of physicians or patients[21]. No information on potential confounders and methods to control for them was reported. Thus, selection bias is of particular concern. Further, none of the observational studies used blinded assessment of the visual function. Although detection bias is unlikely to play a role, because virtually no case of retinopathy was detected, this might be a shortcoming in the study by Renault, *et al*[27]. Finally, the heterogeneity in study designs and outcome measures, dissimilarity in comparison groups or the lack of a comparison group in a great proportion of reports[18,23,24,25,26], and no reported events of interest in either treatment or control groups made it impossible to apply any statistical methods to estimate the effects in separate studies and then to undertake a formal metaanalysis. As indicated by the American Academy of Ophthalmology guidelines of 2011, future studies should aim at using other forms of object testing OCT and autofluorescence, as well as ERG.

The current evidence from small and relatively low-quality studies suggests negligible to no fetal ocular toxicity of antimalarial medications used during pregnancy. The clinical significance of early electroretinogram anomalies reported in a small subset of infants remains to be established. Larger followup studies are warranted to rule out low risk of ocular toxicity in children exposed *in utero* to antimalarial medications.

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