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Original Article

Follow-Up of Infants Exposed to Hydroxychloroquine Given to Mothers during Pregnancy and Lactation

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OBJECTIVE:

To determine the effect of hydroxychloroquine treatment during pregnancy and lactation on babies of mothers affected by rheumatic diseases.

STUDY DESIGN AND METHODS:

A total of 40 infants born from mothers affected by rheumatic diseases and treated with hydroxychloroquine during pregnancy were enrolled in a prospective observational study. Main outcome measures at birth were incidence of prematurity, congenital malformations and neonatal infections. Of these babies, including 13 who were breast-fed, 24 were followed up during early infancy for visual function and neurodevelopmental outcome.

RESULTS:

Preterm delivery was the main complication (20.5%). No significant congenital malformations or neonatal infections were detected. All infants, including those who were breast-fed, had normal visual function and neurodevelopmental outcome.

CONCLUSIONS:

Hydroxychloroquine treatment during gestation and lactation appeared to be safe. The relatively high incidence of preterm deliveries may reflect the maternal disease state.

Journal of Perinatology (2005) **25,** 86–89. doi:10.1038/sj.jp.7211208
Published online 14 October 2004

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INTRODUCTION

Chloroquine (CQ) and hydroxychloroquine (HCQ) are widely used for the treatment of rheumatic diseases due to their immune-modulating activity. These antimalarial agents have an inhibitory effect on antigen processing cells causing downregulation of immune response against autoantigenic peptides and reduction of inflammatory cytokines production and release.[1]

Retinal toxicity is the most serious and feared complication. Fetal retinopathy following antimalarial treatment during pregnancy is well documented in animal models.[2,3] Furthermore, Hart and Naughton[4] 40 years ago reported congenital abnormalities in infants exposed to high doses of CQ.

Discontinuing treatment at the beginning of pregnancy does not reduce the risk of deposition in pigmented fetal tissues due to the long half-life (6 to 8 weeks) of HCQ and its metabolites.

Moreover, interruption of therapy can induce a flare of maternal disease and increase the risk of unfavorable pregnancy outcome.[5–7] Thus, it has been our policy not to suspend HCQ treatment during pregnancy.

Women are disproportionately affected by autoimmune diseases, particularly those with age of onset in childbearing years. The aim of this study was to assess the safety of HCQ on infants of mothers treated with HCQ owing to rheumatic diseases.

PATIENTS AND METHODS

From June 1996 to September 2002, 40 patients affected by rheumatic diseases were treated with HCQ during pregnancy, in our hospital. One of 40 pregnancies aborted spontaneously at 6 weeks of gestation. The remaining 39 pregnancies ended in 40 live infants (one twin pregnancy). All these infants, with parental informed consent, were enrolled at birth in the study (Table 1).

All mothers had been treated with 200 mg/day HCQ (Plaquenil, Sanophi-Winthrop, Gentilly, France) for 1 year or more before pregnancy, during gestation and after delivery.

Treatment included steroids and low-dose acetylsalicylic acid as antiplatelet agent (100 mg/day); one mother received azathioprine and another one cyclosporin-A. Aspirin was substituted with heparin during the last month of pregnancy and the first month after birth.

Congenital malformations, neonatal infections (diagnosed on the basis of clinical manifestations, elevated C-reactive protein test and positive cultures), hematological investigation,

Table 1 Number of Infants in Relation to Maternal Diagnosis and Treatment

Number of infants	*Maternal diagnosis*	*Maternal treatment*
16	Systemic lupus erythematosus	HCQ, steroid, aspirin, (in one case also azathioprine)
4	Mixed connective tissue disease	HCQ, steroid, aspirin
3	Subacute cutaneous lupus erythematosus	HCQ, steroid, aspirin
6	Undifferentiated connective tissue disease	HCQ, steroid, aspirin
3	Primary antiphospholipid syndrome	HCQ, aspirin
2	Rheumatoid arthritis	HCQ, steroid, aspirin
1	Sjögren's syndrome	HCQ, steroid, aspirin
4	Antiphospholipid syndrome within systemic lupus erythematosus	HCQ, steroid, aspirin
1	Systemic lupus erythematosus — polimyositis overlap syndrome	HCQ, steroid, aspirin, cyclosporin-A

and liver and kidney function test were recorded in 40 infants at birth.

According to American Academy of Pediatrics guidelines and to previous studies, breast feeding during HCQ daily therapy is compatible if undertaken cautiously. Therefore, parents were informed about both the low risks of accumulating a toxic amount of HCQ and the well-known benefits of breast feeding.[8–10] The final decision was left to the mothers. In all, 13 babies were breast-fed at discharge.

A total of 24 infants were followed up to evaluate growth, visual function and neurodevelopmental outcome.

A thorough physical examination, including weight, length and cranial circumference assessment, was performed at 1, 3, 6 and 12 months of life. In addition, a screening neurodevelopmental test that provides a motor quotient (MQ), as described by Capute and Shapiro, was performed in each infant.[11]

Motor quotient was calculated by dividing the child best motor achievement age (motor age) by his/her chronological age (MQ = motor age/chronological age × 100). Motor age was the normal age of attainment of best reported gross and fine motor performance; it was derived using a list of average ages of attainment. Quotients greater than 85 were reported as normal, while quotients lower than 50 were considered predictive of motor delay.

An ophthalmological evaluation was performed at birth and repeated during the first year of age in 24 infants. The 13 breast-fed babies underwent an additional examination at 3 months of age. Eye examination was performed by different steps: first with inspection of anterior segment, evaluation of ocular motility, pupillary size and reaction to light. Then, after obtaining midriasis with 1% tropicamide and 1% phenylephrine, refraction and optic nerve head, retina and retinal vessels were evaluated by Schepens indirect ophthalmoscopic method.

RESULTS

Preterm premature rupture of the membranes (PPROM) was observed in four out of 39 pregnancies (10.2%). No cases of eclampsia, pre-eclampsia, or hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome were recorded.

Mean gestational age at delivery was 37.7 weeks (range 31 to 41 weeks). Eight pregnancies (20.5%) ended with a preterm delivery (<37 weeks), although only one infant was <32 weeks and <1500 g birth weight and required intensive care.

Mean birth weight was 2941 g (range 1420 to 3970 g), four babies (10%) were small for gestational age. Apgar scores were normal in all newborns, but in two preterm babies, who scored 3, 6 and 4, 6 at 1 and 5 minutes, respectively. No congenital malformations were observed. Hematological investigation and liver and kidney function test were normal at birth. One neonate had urinary tract infection. Two babies, born from vaginal delivery, had retinal hemorrhages at birth, which completely resolved at 1 month of age. In all, 13 babies were breast-fed for a mean period of 2.8 months (range 1 to 6 months). Ophthalmological examination, performed during the first year of life, was normal in all 24 infants, including the breast-fed ones. Similarly, growth rate in both term and preterm babies was normal. All children had an MQ within the normal range (higher than 85). No child underwent severe or recurrent infection.

DISCUSSION

Since HCQ can reach the fetus through the placenta, its use in mothers affected by rheumatic diseases during pregnancy remains controversial.[12,13] Likewise, treatment during lactation is not universally accepted because of the prolonged infant exposure to the drug, although excretion in human milk is very low (ranging between 0.0005 and 1% of the maternal daily dose).[9,10,12] As stated before, our policy is to not suspend HCQ treatment during pregnancy.

Our study, by providing a longitudinal follow-up of infants whose mothers were treated during gestation and lactation, seems to suggest that maternal HCQ treatment is safe to both the fetus and the breast-fed infant.

In agreement with data reported in the literature, the incidence of preterm delivery was higher in these patients than in normal

population. We believe that prematurity can be related more to the severity of the maternal autoimmune diseases than to HCQ exposure, as already observed in our and other experiences.[6,14,15–17] On the contrary, HCQ intake during pregnancy may reduce corticosteroids requirement, lowering the risk of steroid-induced PPROM.

According to our data, HCQ treatment during gestation does not appear to place the fetus at increased risk of congenital malformations. These findings are consistent with previous reports of Parke and Rothfield,[6] who studied 16 systemic lupus erythematosus (SLE) affected patients treated with HCQ throughout pregnancy, with the British experience of Khamashta et al.,[16] who documented 33 women with SLE who had taken HCQ during pregnancy, and with a recent large French study on safety of HCQ in pregnant patients, which reported data at birth on 117 babies from mothers with rheumatic disease.[17] In all of these reports, HCQ appears not to be teratogenic. In addition, we observed that this drug does not adversely affect fetal liver, kidney or visual function.

Possible side effects of aminoquinoline are benign corneal deposits and pigmentary retinopathy, which can lead to a decreased visual acuity, visual fields, color-vision defects, electroretinogram and electro-oculogram alterations. Two of our babies displayed retinal hemorrhages at delivery, that disappeared within 1 month. We believe that these complications were not related to the drug, because the effects of HCQ and its metabolites last longer.

A total of 24 neonates, including those who were breast-fed, were followed up for a 12-month period. None of these infants showed any evidence of retinal disease. These data are consistent with those of Klinger et al.,[3] who focused their attention on fetal potential risks of developing pigmentary retinopathy after chronic maternal use of CQ and HCQ during pregnancy. In their study, 21 children, born from women who were treated with antimalarial drugs during pregnancy, underwent ophthalmologic examination; as no ocular abnormalities were detected, the authors concluded that therapeutic use of these drugs may not pose the offspring at significant risk of ocular toxicity.

During follow-up, all our babies had normal growth and neuro-motor development. Only limited data have been reported on follow-up of babies exposed to HCQ. Levy et al.[18] found no teratogenic effect in 10 infants at 1.5 to 3 years of age. In the French study, infants data were only gathered from the mothers and not directly obtained from Costedoat-Chalumeau et al.[17] Moreover, first postnatal examination was performed at 4 months of age, thus records on early neonatal period, where transient side effects may be present, are unavailable. Our follow-up included repeated examinations (1 to 3 months after birth) to rule out the presence of early side effects of HCQ exposure. In addition, we studied 13 infants who were successfully breast-fed during the first 6 months of life.

In our study no infant had history of recurrent infections, probably because the HCQ immune-modulating effect is produced through inhibition of antigen processing and inflammatory cytokines synthesis and release. Furthermore, HCQ can reduce maternal requirement and fetal exposure to corticosteroids and other immunosuppressing drugs during gestation.

The evaluation of immune system development and function in one baby whose mother treatment included cyclosporin was found to be normal.[19]

CONCLUSIONS

This study provides a 12-month follow-up of infants from mothers with rheumatic diseases and treated with HCQ during pregnancy and lactation.

In agreement with previous reports, our study confirms that HCQ treatment during gestation does not seem to expose the fetus to an increased risk of congenital malformations or other neonatal adverse effects. The relatively high incidence of preterm delivery is probably related to the severity of maternal disease. The use of this drug allows for the reduction of other drugs dosage, potentially decreasing the risk of pregnancy and neonatal complications.

In addition, our experience suggests the feasibility of breast-feeding, under strict clinical observation, because the known benefits of human milk outweigh the theoretical risk of drug toxicity.

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