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Case Report

Hydroxychloroquine Use to High-Risk Pregnant Woman with Cardiac Fetal Lupus in Asia: A Case Report

Toshihide Sakuragi, Emi Kondo*, Hidehiro Kawagoe and Naofumi Okura

Department of Obstetrics and Gynecology, Kokura Medical Center, Kokura Minami-ku, Kitakyushu, Fukuoka, Japan

***Corresponding Author:** Emi Kondo, Department of Obstetrics and Gynecology, Kokura Medical Center, Kokura Minami-ku, Kitakyushu, Fukuoka, Japan.

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Abstract

Neonatal lupus (NL) is an acquired autoimmune syndrome that causes cardiac lesions (congenital heart block; CHB) and extra-cardiac lesions (cutaneous lupus, cytopenia, and hepatic dysfunction). Cardiac lesions are irreversible. On the other hand, extra-cardiac lesions are transient.

Once CHB is diagnosed in the fetus, 30% result in intrauterine fetal death, and 70% require a neonate permanent pacemaker. Fetal CHB occurs in about 1% of anti-SSA/Ro antibody positive pregnant woman [1]. Recurrence rates in a subsequent pregnancy are approximately six to ten-fold the risk of cardiac-NL and the occurrence rate after a previous child with cutaneous-NL ranges from 13 to18% [2,3].

Maternal use of Hydroxychloroquine (HCQ) may decrease the occurrence of fetal CHB [1]. Thus, we report a case of using HCQ for a high-risk pregnancy with fetal CHB.

A 25-year-old woman, 1 gravid 1 para visited our department at 11 weeks, 3 days into gestation. Her previous child was diagnosed with cutaneous NL at birth. At the 13 weeks' gestation, we started HCQ treatment to prevent fetal CHB. At 37 weeks' gestation, she delivered by spontaneous vaginal birth. The baby had only cutaneous NL without CHB.

Keywords: *Congenital Heart Block; Neonatal Lupus; Anti-SSA/Ro Antibody; Hydroxychloroquine*

Introduction

Neonatal Lupus (NL) presents both cardiac manifestations such as cardiac NL and non-cardiac manifestations such as rashes, cytopenia, and hepatic abnormalities. Cardiac NL (congenital heart block: CHB; the most serious being third degree complete block) is a life-threatening heart condition with a mortality rate of 30% and a pacemaker implantation rate of 70% [2]. Pregnant women who are positive for anti-SS-A antibodies have different onset risks depending on the symptoms of the previous child. If the previous child has CHB, the subsequent child's risk of developing CHB increases 10-fold, and if the previous child has skin NL, it increases 6 - 10 times [3,4]. Unfortunately, even close monitoring by special techniques during pregnancy does not reverse complete heart blockage once it is observed. Thus, treatment aimed at prevention has been critical. Recently, it is suggested that the use of hydroxychloroquine (HCQ) in the high-risk pregnancy can prevent the occurrence of fetal CHB in subsequent pregnancies [2].

We report a case of using HCQ for a high-risk pregnant women with fetal CHB. HCQ was administered with the approval of the Kokura Medical Center Ethics Review Committee (Approval number: 205).

Case Report

A 25-year-old woman, 1 gravid 1 para, visited our department for prenatal management at 11 weeks 3 days gestation. Her previous child was diagnosed with a cutaneous NL at birth presenting systemic rashes and liver dysfunction. She had no symptom herself but the anti-SSA/Ro antibody and the anti-SSB/La antibody titers were very high. The maternal blood test at this pregnancy showed an anti-SS-A/Ro antibody titer (ELISA method) above 240 U/ml. Because the previous child was a cutaneous NL and the titer of anti-SSA/Ro antibody was very high, we thought this pregnant woman was a high-risk of fetal-NL, especially fetal CHB.

The prophylactic administration of HCQ decreases the occurrence rate of fetal CHB for high-risk pregnant woman [2]. In Japan, HCQ has been insured for cutaneous lupus erythematosus and systemic lupus erythematosus (SLE) from 2015. An application to the ethics committee to administer HCQ for this high-risk pregnant woman was accepted.

After informed consent from the parents, we started oral administration of HCQ from 13 weeks 1 day gestation. The applied dosage was 400 mg/day and 200 mg/day alternately. Ophthalmic examinations (for example, visual acuity test, visual field test, SD-OCT, fundus examination, slit lamp microscopy, color vision test and intraocular pressure test) were conducted before starting oral administration of HCQ. Prenatal check-ups and blood tests were performed every 2 weeks. From 16 weeks to 30 weeks gestation we evaluated fetal cardiac function every week by the Doppler method and the M-mode method (Figure 1).

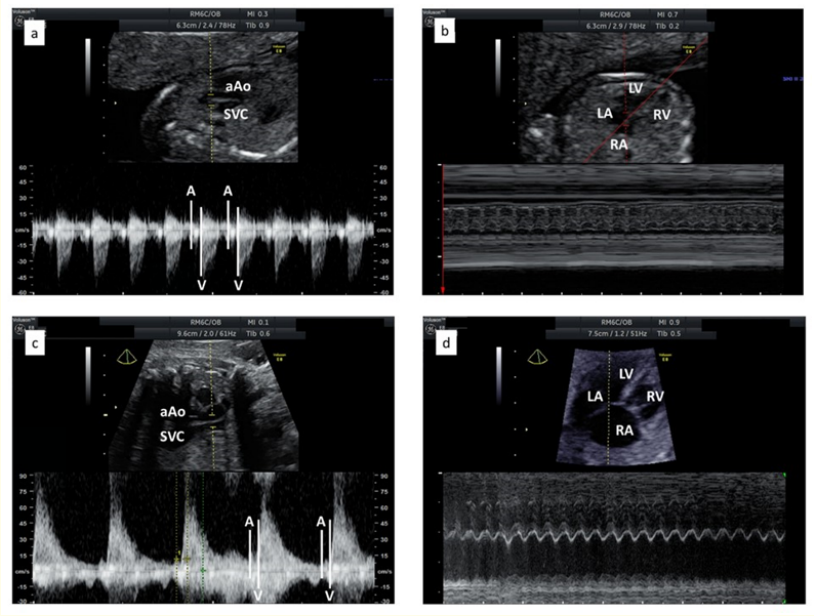


Figure 1: *In all images, the phases of the atrium and the ventricle are consistent. (a) Doppler method at 16 weeks gestation. A indicates start of atrial contraction and line B indicates ventricular contraction. (b) M-mode method at 16 weeks gestation. (c) Doppler method at 34 weeks gestation. (d) M-mode method at 34 weeks gestation.*

The course of pregnancy was favorable. At 37 weeks 3 days of gestation, a 3154g male was delivered by spontaneous vaginal delivery, with Apgar score of 9 points at one minute and 9 points at five minutes. At birth, electrocardiography and blood tests did not detect any

problems, and no systemic rashes were observed. At two weeks, systematic rashes were observed without cytopenia and hepatic dysfunction, and the baby was diagnosed with cutaneous-NL. The second child is 2 years old and has passed without problems in growth and development.

Discussion

NL represents a pathologic readout of passively acquired autoimmunity associated with anti-SSA/Ro-SSB/La antibodies. The manifestations are cardiac lesions (especially CHB) and extra-cardiac lesions (cutaneous lupus, cytopenia, and hepatic dysfunction). In anti-SS-A antibody positive pregnant women, approximately 10% will develop NL, of which CHB is present in approximately 1% [1]. Extra-cardiac lesions (erythema, hepatic function disorder, and cytopenia) may revers spontaneously by 1 year after birth because of the clearance of autoantibodies from the mother. Cardiac-NL is associated with significant mortality (17.5%, primarily fetal/neonatal; once the fetus develops CHB, 30% of them lead on intrauterine fetal death) and morbidity (70% require permanent pacing) [2,3].

Recurrence rates in a subsequent pregnancy are approximately six to ten-fold the risk of cardiac-NL and the occurrence rate after a previous child with cutaneous-NL ranges from 13 - 18% [3,4]. High titer anti-SSA/Ro antibody is also correlated with fetal CHB and is an important marker of fetal CHB risk [5], for example 120 U/ml or more by the ELISA method is considered as a high-risk case [5].

In these high-risk cases, it is generally considered that prophylactic steroid administration can prevent a fetal CHB [6,7], but efficacy has not been established. Recently, several retrospective studies have suggested that HCQ may decrease the overall risk of cardiac-NL [2,8]. One retrospective study based on data from American, British, and French NL registries suggests that the prophylactic HCQ use in high-risk cases can decrease the risk of cardiac-NL [2]. According to the retrospective study, of 257 high-risk pregnant women (40 exposed and 217 unexposed to HCQ), the occurrence rate of cardiac-NL in fetuses exposed to HCQ was 7.5% (3/40) compared to 21.2% (46/217) in the unexposed group ($p = 0.050$) [2]. While there were no deaths in the exposed group, the overall cases fatality rate of the cardiac-NL fetuses in the unexposed group was 22% [2]. In HCQ case, the baby was only cutaneous NL, did not have CHB. Compared with the first baby, the second baby did not have cytopenia or liver dysfunction (Figure 2). The second baby skin eruption was delayed onset at two weeks as compared to the first baby. Perhaps HCQ suppressed the onset of eruption.

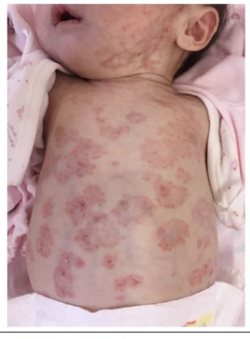
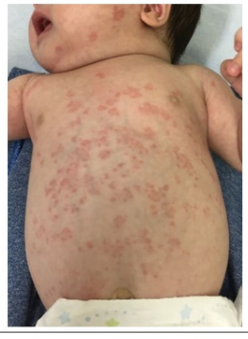
	The first baby	The second baby
cutaneous lupus		
cytopenia	+	-
hepatic dysfunction	+	-
time of onset	at birth	2 weeks after birth
complete heart block	-	-

Figure 2: *The difference of the lupus symptoms in the first and the second (birth presented here) baby.*

HCQ is an antimalarial drug that inhibits ligation of endosomal Toll-like receptors (TLRs) and inhibits macrophages releasing cytokines by anti-SSA/Ro antibody adhering to fetal cardiomyocytes [8]. Well-established side effects of HCQ to the mother include gastro-intestinal symptoms at the beginning of oral administration and retinopathy to use more than 2 years [9,10]. In this case, there was no maternal side effect. HCQ has no teratogenic and toxicity to the fetus. HCQ has placental permeability. It is reported that the exposure level of the fetus is about the same as that of the mother [11]. In Japan, HCQ has been insured against only cutaneous lupus erythematosus and systemic lupus erythematosus from 2015. Despite being available in Japan, there are no reports of the use in pregnant women as far as we could search out. We safely administered HCQ prophylaxis to high-risk pregnant woman to prevent fetal CHB. Finally, this baby did not develop CHB.

As a clinical trial of HCQ in Japan, Preventive Approach to Congenital Heart Block with Hydroxychloroquine in Japan (J-PATCH), started in September 2017 [12]. We hope that the accumulation of more cases will confirm this positive result with HCQ oral administration in high-risk cases in Japan.

Conclusion

We used HCQ safely for high-risk cases of fetal CHB. The second baby did not have CHB. There is no report on HCQ administration for fetal CHB prevention in Asia, and future case accumulation is expected.

Disclosure

Authors have nothing to disclose.

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