short report
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SUCCESSFUL PREGNANCY FOLLOWING GONADOTROPIN THERAPY IN A YOUNG FEMALE WITH JUVENILE IDIOPATHIC HEMOCHROMATOSIS AND SECONDARY HYPOGONADOTROPIC HYPOGONADISM

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ABSTRACT

Heart failure and hypogonadotropic hypogonadism are the most frequent clinical problems encountered in patients with juvenile idiopathic hemochromatosis (JIH). In this context, amenorrhea is one of the first symptoms in female patients, and hormone therapy must be added to phlebotomy to restore menstrual cycles. Here we report the case of a woman in childbearing age with hypogonadotropic hypogonadism due to JIH. Following therapy with gonadotropinic hormones the patient had a twin pregnancy with term delivery. The newborns presented a normal iron status. This confirms that early diagnosis and treatment of JIH are important to prevent irreversible organ damage and shows that the female reproductive function can be preserved in adequately treated patients.

Key words: hemochromatosis, hypogonadism

Heart failure and multiple endocrine dysfunctions are the main clinical features of juvenile idiopathic hemochromatosis (JIH).[1] Whereas heart failure is a poor prognostic factor and the most frequent cause of death,[2] endocrine disorders frequently compromise the sexual development and reproductive function of affected patients. In fact, hypopituitarism is a typical feature of iron overload and amenorrhea due to hypogonadotropic hypogonadism is its most frequent clinical sign.

Early institution of phlebotomy treatment to remove iron overload prevents heart failure,[3-7] whereas fertility can be restored by therapy with gonadotropins.

Here we present the case of a woman with hypogonadotropic hypogonadism due to JIH who became pregnant following gonadotropin therapy.

Case report

A 26-year-old Italian woman with a 5-year history of secondary amenorrhea and a diagnosis of JIH was admitted to our hospital for further investigation. Her parents were alive and apparently healthy. A 21-year-old brother had died four years earlier because of heart failure of undetermined origin, possibly related to iron overload in the course of JIH. The sexual development of our patient was normal with menarche reported at the age of 14. At 21 she experienced amenorrhea; blood tests showed the presence of iron overload and a liver biopsy showed iron loaded hepatocytes with mild fibrosis. A diagnosis of JIH was formulated. Phlebotomies were performed at irregular intervals and cyclic estro-progestinic therapy was instituted with normal bleeding upon hormone withdrawal between cycles.

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The patient came to our observation for a reassessment of her clinical situation and to evaluate the possibility of restoring her reproductive function. Physical examination was negative with the exception of isolated areas of skin hyperpigmentation.

Blood counts on admission were normal, while tests of body iron status showed iron overload (Table 1). A liver biopsy performed in the course of a laparoscopic examination showed liver fibrosis with accumulation of hemosiderinic pigment in both hepatocytes and Kupffer cells, thus confirming the presence of parenchymal iron overload. Endocrine pancreas function, as evaluated by the basal serum glucose and oral carbohydrate tolerance tests, was in the normal range. Serum levels of estradiol and progesterone were low and the gonadotropinic response to LHRH was inadequate. Electrocardiogram showed sinusal tachycardia. The ejection fraction as evaluated by echocardiography and right heart catheterization was normal. Endomyocardial biopsies from the right ventricle showed massive iron pigment deposition in the myocytes and cytolytic damage; the picture was suggestive of heart hemochromatosis (Figure 1). HLA typing showed a haplotype which is not commonly associated with idiopathic hemochromatosis. No relatives were HLA identical to the patient.

In June 1987 a therapeutic program with twice weekly phlebotomy (250 mL each time) was undertaken. Two months later the frequency of phlebotomy was reduced to one per week. Two years later serum ferritin and serum iron levels were markedly reduced, while the hemoglobin level was maintained at about 13 g/dL (Table 1). Starting in July 1990 phlebotomies were performed once every other month and, from 1992 on, once every four months.

Table 1. Hemoglobin level and iron status of the patient.

	1987	1989
Hemoglobin (g/dL)	13.7	13.0
Serum iron (mg/dL)	230	86
Transferrin saturation (%)	84	16
Serum ferritin (mg/L)	3500	17

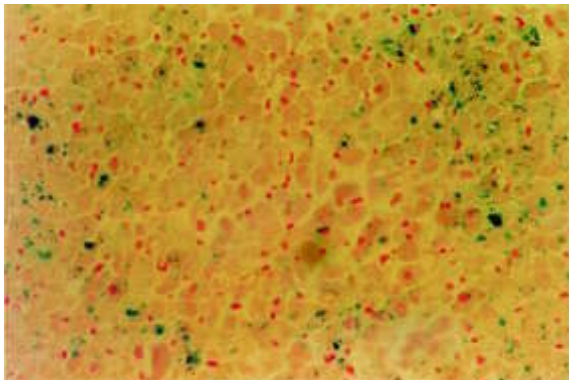

Figure 1. Endomyocardial biopsy showing massive iron pigment deposition in the myocytes and cytolytic damage (Perls' staining, 100×).

Estro-progestinic therapy was administered at the same time. Since the patient wanted to have children, a biopsy of the ovary was performed and no stainable iron found. Induction of ovulation was then attempted with FSH and LH 75 I.U./day from the 1st to the 11th day of the cycle, and human chorionic gonadotropin, 5000 I.U. on day 12.

In November 1991 the patient became pregnant. Ultrasound examination showed a twin, dichorial and biamniotic pregnancy. After an uneventful course pregnancy was ended at term, by cesarean section, on July 13, 1992. The newborns presented normal levels of serum iron, transferrin and ferritin. The *postpartum* clinical course of both mother and children was regular, and the patient continues to undergo phlebotomy and estro-progestinic therapy.

Discussion

The heart and pituitary gland are among the organs primarily involved by iron overload in JIH.[1] Arrhythmias are frequent and congestive heart failure, refractory to digitalis therapy, is the most common cause of death in inadequately treated patients. Endocrine dysfunction is evidenced by defects in the development of sexual characteristics, diminished libido and, in

women, secondary amenorrhea. We describe the case of a woman with JIH presenting with the onset of amenorrhea at the age of 21. This case shows that when iron status is normalized by phlebotomy ovulation can be induced through gonadotropic therapy, making pregnancy a viable option in women with JIH. Successful pregnancies can also be obtained in females with thalassemia and transfusional iron overload.[8]

In conclusion, we confirm the importance of early and adequate treatment with phlebotomy in JIH. When heart failure and liver damage are prevented, treated patients are able to lead a normal life and hormone therapy can also preserve the reproductive function of female JIH patients.

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