

## CASE REPORT

# Primary Amenorrhea in a Thalassemia Major

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## ABSTRACT

**Background:** Thalassemia major is a severe type of hemolytic anemia. Hypertransfusion therapy in these patients can lead to iron overload and iron tissue toxicity leading to structural, metabolic and endocrine abnormalities.

**Case report:** We hereby present a case of 16-year-old unmarried girl with thalassemia major presenting with primary amenorrhea and poorly developed secondary sexual characteristics. A thorough history, clinical examination, laboratory and radiological investigations were conducted. These tests confirmed the diagnosis of hypogonadotropic hypogonadism. Patient was started on hormone replacement therapy. She is on regular follow-up and compliant with her treatment.

**Conclusion:** Timely recognition and management of hypertransfusion therapy in thalassemia major patients will have a favorable psychological outcome and improves the quality of life.

**Keywords:** Thalassemia major, Hypertransfusion therapy, Iron overload, Hypogonadotropic hypogonadism, Primary amenorrhea, Hormonal replacement therapy.

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## INTRODUCTION

Primary amenorrhea resulting from hypogonadotropic hypogonadism occurs when the hypothalamus fails to secrete adequate amounts of gonadotropin releasing hormone (GnRH) or when a pituitary disorder is associated with inadequate production or release of pituitary gonadotropins.<sup>1</sup> Thalassemia major, a severe hemolytic anemia due to a

genetic defect in the synthesis of hemoglobin chain, can produce hypopituitarism. This hypopituitarism leads to hypogonadotropic hypogonadism, an endocrinopathy occurring secondary to iron overload.<sup>2</sup> The iron overload is a consequence of frequent blood transfusion, which is the most important treatment modality for thalassemia major. Other possible causes of hypogonadism in beta thalassemia major include liver disorders, chronic hypoxia, diabetes mellitus and zinc deficiency.<sup>3</sup> The anterior pituitary is especially sensitive to increased iron concentration which disrupts the hormonal secretion leading to hypogonadism, short stature and acquired hypothyroidism.<sup>4</sup>

We present a case of primary amenorrhea in a thalassemic patient to highlight that hypertransfusion and regular chelation therapy may have allowed improved survival in patients with thalassemia major but despite medical advances, growth failure and hypogonadism remains a significant clinical problem in these patients in adolescence.

## CASE REPORT

A 16-year-old unmarried girl, a known case of thalassemia major reported to the gynecological outpatient department OPD with primary amenorrhea and poor development of secondary sexual characters. She gave history of receiving monthly blood transfusions since she was 6 months of age and daily table to defepirone as a chelating agent. She gave no history of weight loss, night sweats, headache, or visual disturbances. On examination, she was a thinly built, short statured girl with a height of 132 cm (52 inch). She had a hypoplastic nose with a thalassemic facies. The girl had mild pallor, but no thyromegaly, acanthosis nigricans, or galactorrhea. Her breast development was prepubertal (Tanner Stage I) and absent pubic and axillary hairs. The abdominal examination was within normal limits and undergone splenectomy 8 years back. Gynecological examination revealed the external genitalia to be prepubertal. Per speculum and vaginal examination was not carried out due to her unmarried status. However, uterus could be felt on per rectal examination.

**Table 1:** Hormonal assay of the patient

Hormones assayed	Patient values	Reference values
FSH	1.66 mIU/ml	3-8 mIU/ml
LH	1.01 mIU/ml	2-11 mIU/ml
Estradiol	10.0 pg/ml	20.4 pg/ml
TSH	5.97 mIU/ml	5.5-6.5 mIU/ml

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Laboratory investigations including whole hematological and biochemical parameters were carried out which were essentially normal except hemoglobin of 7.5 gm/dl and serum ferritin of 5237 ng/ml (N: 50-150 ng/ml). A detailed endocrinological profile was also conducted which was suggestive of hypogonadotropic hypogonadism (Table 1). Ultrasonography of the pelvis revealed a small uterus with small sized both ovary. Magnetic resonance imaging (MRI) of the pelvis showed small uterus (37 × 21 × 6 mm) and hypoplastic ovaries. MRI of the brain was suggestive of pituitary iron overload with a small sella and a reduced size of the pituitary gland. The clinical and endocrinological profile confirmed hypogonadotropic hypogonadism. Based on this diagnosis the patient was started on hormone replacement therapy to mature and maintain her secondary sexual characteristics.

She was put on conjugated estrogens and cyclical progestins to prevent unopposed estrogen stimulation of the endometrium. Patient is on regular follow-up and compliant with her treatment.

## DISCUSSION

The thalassemias are a heterogeneous group of genetic disorders in which the production of one or more globin chains of hemoglobin is suppressed. Depending on the defective chain, several types of thalassemias have been described like  $\alpha$  and  $\beta$  thalassemia. Frequent transfusion and chelation therapy is the most important treatment modality which has considerably prolonged.

The survival of thalassemic patients.<sup>5</sup> However, as a result of hypertransfusion therapy and prolonged longevity, iron tissue toxicity has become more common and contributes significantly to many structural, metabolic and endocrine consequences in these patients like hypothyroidism, hypogonadism and diabetes mellitus.<sup>6</sup> Hypogonadism resulting from iron induced pituitary.

Dysfunction is the most frequently reported endocrine abnormality in patients with  $\beta$  thalassemia major.<sup>7</sup> Hypogonadism is clinically diagnosed in a female by the presence of primary or secondary amenorrhoea with absent or poor development of secondary sexual characteristics. The history and clinical findings are substantiated by the laboratory investigations which was present in this patient. The circulating gonadotropins are inappropriately low and the levels of estradiol are extremely below the normal values. The anterior pituitary which is sensitive in a dose dependant manner to the effects of iron overload can be imaged by MRI. It may

show empty sella, decreased pituitary size or thinning of the stalk as was demonstrated in this girl.<sup>8</sup>

Serum ferritin levels indicates the efficacy of chelation therapy and was disproportionately higher (5237 ng/ml) in the present case. Multiple endocrinopathies, including hypogonadism, hypothyroidism and diabetes mellitus has been observed in patients who tend to have high serum ferritin levels.<sup>9</sup> Hypothyroidism and diabetes mellitus was however not present in our patient. The mainstay of treatment of hypogonadism consists of hormone replacement therapy with sex steroids. Sex steroids are important for the maintenance of normal body composition, skeletal health and induction and maturation of secondary sexual characteristics. It is the most important form of replacement therapy in patients not desirous of fertility.<sup>10</sup> Our patient being a young unmarried girl has been started on estrogens and cyclical progestin therapy. Timely recognition and prevention of the endocrine complications, by early and regular chelation therapy is mandatory for the improvement of the quality of life and favorable psychological outcome of thalassemic patients.

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