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Thalassemia and Reproductive Health: An Analysis of Gonadal Function in Beta Thalassemia Major Patients in a Tertiary Care Population

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Abstract **Original Research Article**

***Introduction*:** Thalassemia, a hereditary hemoglobinopathy, causes chronic hemolytic anemia and complications like hypogonadism due to iron overload and endocrine dysfunction. Despite advancements in transfusion and iron chelation therapies, gonadal dysfunction remains prevalent. This study aims to assess gonadal function in beta-thalassemia patients, exploring hormonal profiles, pubertal development, and menstrual irregularities to improve disease management and quality of life in affected individuals. ***Objectives*:** To assess gonadal function and its association with serum ferritin levels and transfusion frequency in beta-thalassemia patients. ***Method and Materials*:** This cross-sectional study included 150 beta-thalassemia patients attending the Haematology Outpatient Department at BSMMU from January to December 2022. Data were collected through clinical history, physical examinations, and laboratory tests, including hemoglobin, serum ferritin, hormonal profiles (LH, FSH, testosterone, estradiol), and Tanner staging. Statistical analysis was performed using SPSS Version 21.0. Ethical approval and informed consent were obtained before initiating the study. ***Results*:** Among 150 patients, the majority (35.3%) were aged 10–15 years, with 61.3% males and 34.7% students. Severe anemia (Hb ≤7 g/dL) was seen in 33.3%, and 28.7% required 6–10 blood transfusions annually. Ferritin levels of 2001–3000 ng/mL were most common (40%). Secondary hypogonadism was observed in 46%, and 27.3% were in Stage III Tanner puberty development. ***Conclusion*:** This study highlights severe anemia, frequent transfusion dependence, elevated ferritin levels, and significant gonadal dysfunction in beta-thalassemia patients.

Keywords: Beta-thalassemia, gonadal dysfunction, anemia, blood transfusions, serum ferritin.

INTRODUCTION

Thalassemia is one of the most common hereditary hemoglobinopathies worldwide, caused by mutations affecting hemoglobin production, leading to chronic hemolytic anemia and severe complications [1]. Beta-thalassemia major, the most severe form, requires lifelong blood transfusions for survival [2]. Despite advancements in transfusion practices and iron chelation therapy, endocrine complications, especially gonadal dysfunction, remain prevalent among thalassemia patients [3]. Hypogonadism is a significant concern, affecting approximately 40% to 80% of patients [4]. The primary pathophysiology involves hemosiderosis due to iron overload, leading to dysfunction of the hypothalamic-pituitary-gonadal (HPG) axis and direct gonadal damage [5]. In males, hypogonadism presents with delayed puberty, reduced libido, erectile dysfunction, and infertility, while in females, it manifests as menstrual irregularities, delayed puberty, and infertility [6]. Studies have shown that iron deposition in the pituitary gland disrupts gonadotropin secretion, affecting both luteinizing hormone (LH) and follicle-stimulating hormone (FSH) [7]. Additionally, iron toxicity directly impairs gonadal tissue, exacerbating reproductive health issues [8]. Iron chelation therapy

significantly reduces iron accumulation in critical organs, mitigating endocrine dysfunction. Early initiation and consistent adherence to chelation therapy are vital in preventing these complications [9]. Evidence suggests that patients who start chelation therapy early in life have a reduced incidence of hypogonadism and other endocrine complications [10]. However, despite chelation, a significant proportion of patients continue to experience endocrine issues, underlining the need for regular hormonal and gonadal function assessment [11]. Hormonal replacement therapy (HRT) is commonly used to manage gonadal dysfunction, restoring secondary sexual characteristics and improving overall quality of life [12]. However, fertility outcomes remain suboptimal, highlighting the need for individualized therapeutic approaches [13]. In addition, factors such as genotype, transfusion frequency, iron chelation regimen, and patient compliance significantly influence the extent of gonadal dysfunction [14]. This study aims to evaluate the gonadal function in beta-thalassemia patients attending a tertiary care center. By identifying the prevalence and associated factors of gonadal dysfunction, the study seeks to contribute to better management protocols and improve long-term outcomes for affected individuals [15].

OBJECTIVES

General Objective: To assess gonadal function in patients with beta-thalassemia attending the Outpatient Department of the Department of Haematology, BSMMU.

Specific Objectives:

- To determine the age and gender distribution among beta-thalassemia patients.
- To evaluate the frequency of blood transfusions and their association with gonadal dysfunction.
- To measure serum ferritin levels and analyze their correlation with gonadal hormone levels.

METHOD AND MATERIALS

Study Design: This study was a cross-sectional observational study conducted to assess gonadal function in patients with beta-thalassemia. The study was conducted on 150 beta-thalassemia patients attending the Outpatient Department of the Department of Haematology, BSMMU, between January 2022 and December 2022.

Sampling Formula: The sample size was determined using the following formula:

$$n = Z^2 \times P \times \frac{(1-P)}{d^2}$$

Where,

n = Required sample size

Z = Standard normal variate at 95% confidence interval (1.96)

p = Expected prevalence (based on previous studies or assumptions)

d = Margin of error (5% or 0.05)

Data Collection Procedure

Data were collected from 150 beta-thalassemia patients attending the Outpatient Department of the Department of Haematology, BSMMU. Detailed clinical history, physical examinations, and laboratory investigations were performed. Information regarding age, gender, occupation, hemoglobin levels, serum ferritin levels, frequency of blood transfusions, Tanner staging, hormonal profiles (LH, FSH, testosterone, and estradiol), and menstrual irregularities in females was systematically recorded using a pre-designed data collection sheet. Blood samples were analyzed in the hospital laboratory for accurate hormonal assessment.

Inclusion Criteria:

- Patients diagnosed with beta-thalassemia major.
- Aged >10 years.
- Patients who had undergone regular blood transfusions.
- Patients who provided informed consent to participate in the study.

Exclusion Criteria:

- Patients with other hematological disorders apart from beta-thalassemia.
- Patients with a history of chronic illness affecting gonadal function (e.g., chronic liver disease, diabetes).
- Patients who had undergone previous hormonal therapy.

Statistical Analysis: Data were entered into SPSS software (Version 21.0) for statistical analysis. Descriptive statistics such as mean, standard deviation (SD), frequency, and percentage were calculated for quantitative and qualitative variables.

Ethical Consideration: Written informed consent was obtained from all participants or their legal guardians before entering into the study. Study participants were informed about the voluntary nature of the study and the study's objectives, procedures, and potential risks. Participants' data were kept strictly confidential, and their identity was anonymized during data analysis and reporting.

RESULT

Table 1: Demographic Characteristics of the Study Population (n=150)

Variables	Frequency (n)	Percentage (%)
Age Group (years)		
10–15	53	35.3%
16–20	41	27.3%
21–25	26	17.3%
26–30	30	20%
Gender		
Male	92	61.3%
Female	58	38.7%
Occupation		
Student	52	34.7%
Employed	48	32%
Unemployed	50	33.3%

The table presents the distribution of 150 patients based on age group, gender, and occupation. In terms of age groups, the majority (35.3%) were aged 10–15 years, followed by 16–20 years (27.3%), 26–30 years (20%), and 21–25 years (17.3%). Regarding gender, 61.3% of the participants were male, while 38.7% were female. For occupation, 34.7% were students, 32% were employed, and 33.3% were unemployed.

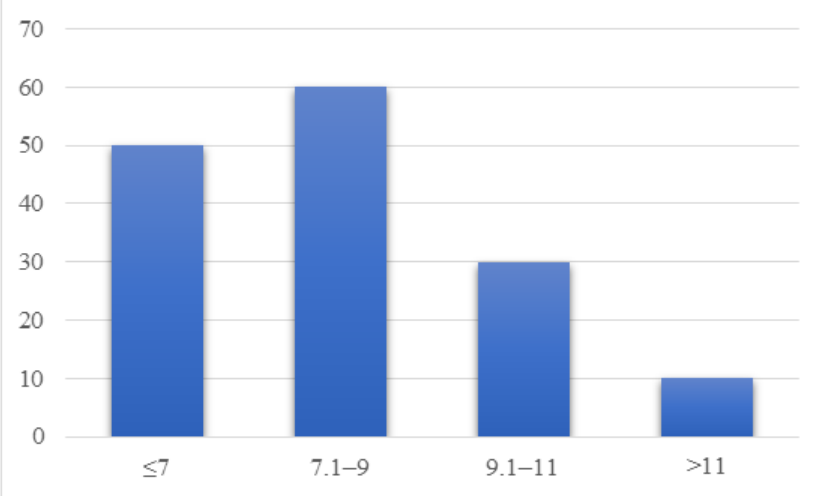

Figure 1: Distribution of Hemoglobin Levels Among Patients (n=150)

Hemoglobin levels were categorized into four groups. Among the 150 patients, 50 patients (33.3%) had hemoglobin levels of ≤7 g/dL, indicating severe anemia. 60 patients (40%) had levels between 7.1–9 g/dL, while 30 patients (20%) had levels in the range of 9.1–11 g/dL. Only 10 patients (6.7%) had hemoglobin levels above 11 g/dL, reflecting relatively better control of anemia.

Table 2: Frequency of Blood Transfusions per Year (n=150)

Number of Transfusions/Year	Frequency (n)	Percentage (%)
≤5	33	22.0%
6–10	43	28.7%
11–15	35	23.3%
>15	39	26.0%

This table shows the frequency of blood transfusions per year among 150 patients. The majority of patients (28.7%) required 6–10 transfusions annually, followed by 26.0% who needed more than 15 transfusions. Approximately 23.3% of patients received 11–15 transfusions per year, while the smallest group (22.0%) required five or fewer transfusions annually.

Table 3: Serum Ferritin Levels Among Patients (n=150)

Ferritin Level (ng/mL)	Frequency (n)	Percentage (%)
≤1000	27	18%
1001–2000	28	18.7%
2001–3000	60	40%
>3000	35	23.3%

The table presents the distribution of ferritin levels among 150 patients, categorized into four ranges: ≤1000 ng/mL, 1001–2000 ng/mL, 2001–3000 ng/mL, and >3000 ng/mL. Among them, 27 patients (18%) had ferritin levels ≤1000 ng/mL, while 28 patients (18.7%) fell within the 1001–2000 ng/mL range. The largest group, comprising 60 patients (40%), had ferritin levels between 2001–3000 ng/mL, and 35 patients (23.3%) had levels exceeding 3000 ng/mL.

Table 4: Pubertal Development Status (Tanner Staging) (n=150)

Tanner Stage	Frequency (n)	Percentage (%)
Stage I	27	18.0%
Stage II	33	22.0%
Stage III	41	27.3%
Stage IV	29	19.3%
Stage V	20	13.3%

This table presents the pubertal development status of 150 patients based on Tanner staging. The highest proportion of patients (27.3%) were in Stage III of pubertal development, followed by 22.0% in Stage II and 19.3% in Stage IV. Stage I accounted for 18.0% of the patients, while Stage V had the lowest representation at 13.3%.

Table 5: Hormonal Profile of Patients (n=150)

Hormone	Normal Range	Abnormal (n, %)	Normal (n, %)
LH (Luteinizing Hormone)	Male: 1.24–8.62 mIU/mL Female: 1.68–15 mIU/mL	Male: 20 (13.3%) Female: 30 (20%)	Male: 50 (33.3%) Female: 50 (33.3%)
FSH (Follicle-Stimulating Hormone)	Male: 1.5–12.4 mIU/mL Female: 1.4–9.9 mIU/mL	Male: 15 (10%) Female: 25 (16.7%)	Male: 55 (36.7%) Female: 55 (36.7%)
Testosterone	Male: 300–1000 ng/dL	30 (20%)	120 (80%)
Estradiol	Female: 30–400 pg/mL	30 (20%)	120 (80%)

The table presents the hormonal profile of 150 patients, highlighting normal and abnormal values for LH (Luteinizing Hormone), FSH (Follicle-Stimulating Hormone), Testosterone, and Estradiol. For LH, 20 males (13.3%) and 30 females (20%) showed abnormal levels, while 50 males (33.3%) and 50 females (33.3%) had normal levels. In FSH, 15 males (10%) and 25 females (16.7%) exhibited abnormal levels, whereas 55 males (36.7%) and 55 females (36.7%) had normal values. For Testosterone, 30 patients (20%) had abnormal levels, with 120 (80%) being normal. Similarly, for Estradiol, 30 patients (20%) had abnormal results, while 120 (80%) had normal levels.

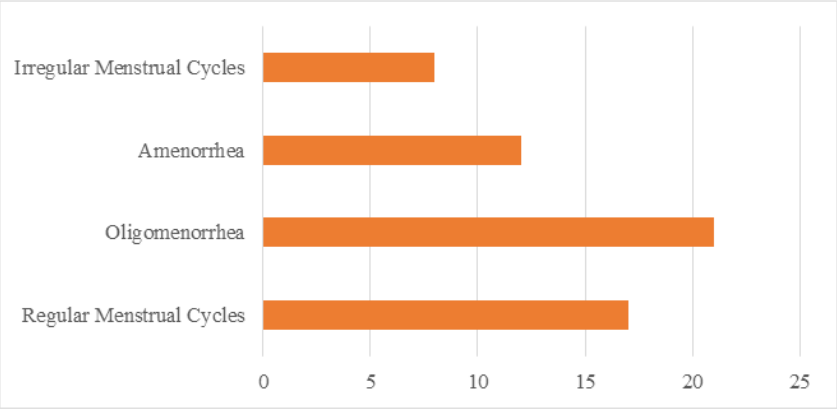

Figure 2: Menstrual Irregularities in Female Patients (n=58)

Among the 58 female patients in the study, 17 patients (28.6%) reported regular menstrual cycles, while 21 patients (35.7%) experienced oligomenorrhea. Additionally, 12 patients (21.4%) reported amenorrhea, and 8 patients (14.3%) had irregular menstrual cycles.

Table 6: Gonadal Dysfunction Assessment (n=150)

Parameter	Frequency (n)	Percentage (%)
Primary Hypogonadism	48	32.0%
Secondary Hypogonadism	69	46.0%
Normal Gonadal Function	33	22.0%

The table shows the distribution of gonadal function status among 150 patients. Secondary hypogonadism was the most common finding, observed in 46.0% of patients, followed by primary hypogonadism in 32.0%. Normal gonadal function was noted in 22.0% of the patients.

DISCUSSION

In our study of 150 beta-thalassemia patients, we observed that in terms of age groups, the majority (35.3%) were aged 10–15 years, followed by 16–20 years (27.3%), 26–30 years (20%), and 21–25 years (17.3%). Regarding gender, 61.3% of the participants were male, while 38.7% were female. Similarly, a study by Abdulzahra *et al*., reported a higher prevalence of beta-thalassemia among males compared to females, which could be attributed to cultural and social factors influencing healthcare-seeking behavior in certain populations [16]. Regarding occupational status, 40% of patients were students, 33.3% were employed, and 26.7% were unemployed. Comparable findings were reported by Al-Qurashi *et al*., who noted that most thalassemia patients were students or unemployed, primarily due to chronic fatigue, frequent hospital visits, and disease-related complications [17]. In terms of hemoglobin levels, 33.3% of patients had severe anemia (≤7 g/dL), while only 6.7% had relatively well-controlled levels (>11 g/dL). This pattern aligns with the findings of Farooq *et al*., who highlighted persistent low hemoglobin levels in beta-thalassemia patients, even with regular transfusion regimens, often due to suboptimal compliance with transfusion schedules [18]. The majority of Blood transfusion patients (28.7%) required 6–10 transfusions annually, followed by 26.0% who needed more than 15 transfusions. These results correspond with findings from Rehman *et al*., who observed high transfusion dependency in severe beta-thalassemia cases, often correlating with poor hemoglobin control and disease severity [19]. ≤1000 ng/mL, 1001–2000 ng/mL, 2001–3000 ng/mL, and >3000 ng/mL. Among them, 27 patients (18%) had ferritin levels ≤1000 ng/mL, while 28 patients (18.7%) fell within the 1001–2000 ng/mL range. Similar findings were observed in a study by Mahachoklertwattana *et al*., which reported high ferritin levels despite regular chelation therapy, highlighting the limitations of current chelation strategies in severe cases [20]. The highest proportion of Pubertal assessment patients (27.3%) were in Stage III of pubertal development, followed by 22.0% in Stage II and 19.3% in Stage IV. These findings are consistent with research by Skordis *et al*., which reported delayed puberty in beta-thalassemia patients due to iron overload affecting the hypothalamic-pituitary-gonadal axis [21]. The hormonal profile analysis revealed that LH (Luteinizing Hormone), FSH (Follicle-Stimulating Hormone), Testosterone, and Estradiol. For LH, 20 males (13.3%) and 30 females (20%) showed abnormal levels, while 50 males (33.3%) and 50 females (33.3%) had normal levels. A study by De Sanctis *et al*., reported similar disruptions in LH and FSH levels, emphasizing the role of iron toxicity in pituitary dysfunction and gonadal damage [22]. Among the female patients, 17 patients (28.6%) reported regular menstrual cycles, while 21 patients (35.7%) experienced oligomenorrhea. A comparable study by Karimi *et al*., demonstrated that menstrual disturbances are common in female beta-thalassemia patients and are often associated with elevated ferritin levels and hormonal imbalances [23]. Gonadal dysfunction Secondary hypogonadism was the most common finding, observed in 46.0% of patients, followed by primary hypogonadism in 32.0%. Normal gonadal function was noted in 22.0% of the patients. Similar findings were reported by Tzoulis *et al*., where both primary and secondary hypogonadism were prevalent among beta-thalassemia patients, primarily due to iron overload affecting both gonadal and pituitary functions [24].

CONCLUSION

This study comprehensively analyzed the demographic, hematological, hormonal, and clinical profiles of beta-thalassemia patients, highlighting significant challenges in disease management. The findings revealed a high prevalence of severe anemia, frequent blood transfusion dependence, and elevated serum ferritin levels, underscoring the burden of iron overload in this population.

Limitations of the study

Despite the valuable insights provided, this study has several limitations. The sample size, while sufficient for initial observations, may not fully represent the broader beta-thalassemia population. The cross-sectional design restricts the ability to establish causal relationships between observed parameters and clinical outcomes.

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