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Original Article

Obstetrics and Gynaecology Section

Pubertal Development in Girls with Beta Thalassaemia and Assessment of the Adequacy of Chelation Therapy: A Quasi-experimental Study

RUPALI MODAK[1], AMITAVA PAL[2], SHUVENDU DAS[3], DILIP KUMAR BISWAS[4]

ABSTRACT

Introduction: Beta thalassaemia is the most prevalent hereditary autosomal disorder, significantly impacting endocrine function during pubertal development. The pathology is rooted in the excessive deposition of iron in vital organs. If left untreated, this condition leads to serious morbidity and mortality. Hypogonadism stands as the most common endocrine complication.

Aim: To observe pubertal development in girls with thalassaemia and evaluate the adequacy of chelation therapy in such patients by measuring levels of Follicle Stimulating Hormone (FSH), Luteinising Hormone (LH), oestrogen, and serum ferritin.

Materials and Methods: A quasi-experimental study was conducted at the Thalassaemia Clinic at the Department of Obstetrics and Gynaecology, Burdwan Medical College, Purba Bardhaman, West Bengal, India involving 300 diagnosed Beta Thalassaemia Major (BTM) (case) patients aged 13 to 17 years over a period of one and a half years (January 2020 to June 2021). The girls in the study groups were sequentially enrolled from the Outpatient Department of the Thalassaemia Clinic after meeting inclusion and exclusion criteria. Demographic data, anthropometric measurements, and Sexual Maturity Rating (SMR) were recorded. Hormonal assays of serum FSH, LH, oestrogen, and serum ferritin levels were conducted. Thalassaemic girls with serum ferritin levels exceeding 500 ng/mL received chelation therapy. Serum ferritin levels were measured at two-month intervals for up to six months, with reassessment of serum FSH, LH, oestrogen, and ferritin levels at the end of the six-month period. Statistical analysis was conducted using Statistical Package for Social Sciences (SPSS) version 27.0, Microsoft excel spreadsheet, and Epi Info 7.

Results: A total of 190 (63.3%) of the thalassaemic girls were aged 13 to 15 years, with a mean Body Mass Index (BMI) of 22.5000±2.6100 kg/m^2, and 74 of them (38.94%) experienced menarche in this age group. Out of 300 cases, 269 thalassaemic girls (89.6%) received chelation therapy, and 89 cases (33.09%) reached menarche after chelation therapy. A significant ($p<0.0001$) increase in mean LH and FSH levels was observed after chelation therapy. The mean ferritin level decreased from 3168.85 ng/mL to 2227.24 ng/mL following chelation therapy.

Conclusion: Pubertal development failure is common in beta thalassaemic girls. Intervention in the form of adequate chelation therapy in girls with high serum ferritin levels yielded favourable outcomes, as evident from serum gonadotropin and oestrogen levels.

Keywords: Beta thalassaemic patients, Gonadotropin, Hormonal levels, Hypogonadism, Puberty, Sexual maturity rating

INTRODUCTION

Puberty is the transitional period between childhood and adulthood, characterised by the appearance of secondary sexual characteristics, maturation of gonads, and the ability to reproduce. Puberty and reproduction are controlled by the Hypothalamo-pituitary-ovarian axis [1].

Thalassaemia is the most common heterogeneous group of genetic haematological disorders in which the production of normal haemoglobin is partly or completely suppressed due to defective synthesis of one or more globin chains. Beta thalassaemia is characterised by reduced or absent beta globin chain synthesis. Thalassaemia major refers to the most severe form, frequently associated with lifelong transfusion-dependent anaemia. A 10% of the total world thalassaemic cases are born in India every year [2]. In India, Gujarat, Rajasthan, Punjab, and West Bengal are the most commonly affected states, with the incidence of beta thalassaemia varying from 1 to 17% [3].

The definitive treatment for thalassaemia is bone marrow transplantation, which is out of reach for most patients due to its limited availability and cost. Homozygous beta thalassaemic individuals require regular blood transfusions. Repeated blood transfusions may lead to iron overload and the deposition of excess iron in vital organs. If left untreated, this condition leads to significant morbidity and mortality. The combination of transfusion and treatment with chelating agents to reduce iron overload dramatically improves life expectancy into the fourth and fifth decades [4].

Endocrine complications due to iron overload become more common in individuals with thalassaemia. Apart from the failure of normal pubertal development, which affects 50% of patients, other endocrine complications include secondary amenorrhoea, primary hypothyroidism, diabetes mellitus, and hypoparathyroidism [5]. In transfusion-dependent patients, pituitary dysfunction leads to hypogonadotropic hypogonadism, which is usually the cause of abnormal sexual maturation, although primary gonadal failure has also been reported occasionally [6]. Studies on the evaluation of the effect of chelation therapy are limited and associated with contradictory results [7,8]. Some of this discrepancy could be due to the cross-sectional nature of the study designs in most reports, relying on information from a single time point. Endocrine disorders demand long-term exposure to excess iron, and the estimation of a single measurement would be biased [9]. According to some researchers, early initiation of Deferoxamine (DFO) before the age of 10 years with long-term chelation ensures normal puberty in most patients [10]. However, the initiation of DFO in younger age groups

is associated with bone toxicity, ultimately leading to decreased growth in the individual [11]. Therefore, starting chelation therapy at the earliest with adequate dosage and proper follow-up can reduce the consequences of iron overload.

The present study aimed to observe pubertal development and evaluate the adequacy of chelation therapy in beta thalassaemic girls, as measured by serum gonadotropin and oestrogen levels.

MATERIALS AND METHODS

A quasi-experimental study was conducted among girls aged 13 to 17 years suffering from BTM, attending the outpatient department of the Thalassaemia Clinic at the Department of Obstetrics and Gynaecology, Burdwan Medical College, Purba Bardhaman, West Bengal, India, the referral center for thalassaemic patients from the entire district, over a period of one and a half years (January 2020 to June 2021). After obtaining approval from the Institutional Ethics Committee (Memo no: BMC/Ethics/021 dated 28th January 2020), informed written consent was obtained in the local language from the legal guardians. Before enrollment, a clear explanation of the study's purpose and potential outcomes was provided. The participants were given the option to leave or withdraw their names at any point during the study period.

Inclusion criteria: All girls with beta thalassaemia between 13 and 17 years of age were included in the study.

Exclusion criteria: Girls with puberty disorders such as constitutional delay, chronic illness, malnutrition, hypothyroidism, intracranial tumours like craniopharyngioma, pituitary adenoma, anatomical causes like imperforate hymen, Müllerian agenesis, transverse vaginal septum, Polycystic Ovarian Syndrome (PCOS), precocious puberty, sickle cell disease, autoimmune haemolytic anaemia, and individuals receiving hormonal replacement therapy or having any accompanying disease that could cause delayed puberty were excluded from the study.

Sample size: Beta thalassaemic girls aged 13 to 17 years who attended the thalassaemia clinic during the study period were included in the study using a serial sampling method. A total of 322 cases were enrolled during that period. Twenty-two cases were lost during follow-up. Finally, 300 cases were used for statistical analysis.

Study Procedure

Detailed information for all patients in the study was recorded on a predesigned and presheduled proforma, which included demographic and anthropometric data and Sexual Maturity Rating (SMR). SMR was measured using Tanner's scale criteria, commonly used during puberty to assess the physical development of adolescent girls in five stages from preadolescent (Stage-I) to adult (Stage-V) [12].

Serum ferritin, FSH, LH, and oestrogen levels were estimated in all patients at the time of enrollment. For the assessment of serum levels of FSH, LH, oestrogen, and ferritin, blood samples were collected in the morning (8:00-9:00 am). Five millilitres of venous blood were taken, and the samples were sent to the Biochemistry Department of Burdwan Medical College and Hospital, where the tests were performed using Enzyme-linked Immunosorbent Assay (ELISA). The necessary tools for the tests included ELISA kits, an ELISA reader and washer, micropipettes and microtips, syringes, and cotton. Serum Ferritin was measured using the solid-phase sandwich assay method (CalBiotech Inc.). Measurement of Luteinising hormone and FSH was done by solid-phase sandwich ELISA (Accu-Diag). The oestrogen assay was performed by solid-phase competitive ELISA (DiaMetra- Italy).

Thalassemic girls with serum ferritin levels greater than 500 ng/mL were treated with the oral iron-chelating agent deferasirox at a dosage of 20-40 mg/kg/day. Serum ferritin levels were reassessed at two-month intervals for up to six months. Chelation therapy was stopped when the serum ferritin level was less than 500 ng/mL [13]. Chelation therapy was restarted if the serum ferritin level rose above 500 ng/mL during the study period. Thalassaemic girls who took the prescribed dosage and did not miss more than five doses per month were considered to be on regular chelation therapy [14]. Serum ferritin, FSH, LH, and oestrogen were reassessed at the end of the six-month study period.

STATISTICAL ANALYSIS

Statistical analysis was conducted using SPSS (version 27.0; SPSS Inc., Chicago, IL, USA), Microsoft Excel spreadsheet, and Epi Info 7. The data were presented as means and Standard Deviation (SD) for numerical variables, and as counts and percentages for categorical variables. Categorical data between the two groups were compared using the Chi-square/Fisher-exact test, while quantitative data was compared using Student's t-test. A p-value of <0.05 was considered significant.

RESULTS

A total of 300 beta thalassaemic girls were enrolled in the study for analysis. The demographic profiles showed that 190 patients (63.3%) were in the age group of >13-15 years with a mean BMI of 22.5000±2.610 kg/m^2. A total of 156 (52.0%) patients had SMR Stage-II using Tanner's scale [Table/Fig-1].

Parameters	n (%), N=300	Mean±SD	Median	Minimum	Maximum	
Age (years)		14.8933±1.517	15.000	13.0000	17.0000	
≥13-15	190 (63.3)					
>15-17	110 (36.7)					
BMI (kg/m^2)						**p-value**
≥13-15 years	190 (63.3)	22.5000±2.6100	22.3000	16.2000	30.9000	0.3381
>15-17 years	110 (36.7)	22.2000±2.6100	21.7000	17.6000	30.3000	
Menarche (years)						
		Yes (%)	**No (%)**	Chi-square value; 13.9624		**p-value**
≥13-15	190	74 (38.94)	116 (61.05)			0.00019
>15-17	110	20 (18.18)	90 (81.82)			
Sexual maturity rating by using Tanner's stage		**n, N=300**	**Percentage**			
I		87	29.0			
II		156	52.0			
III		26	8.7			
IV		17	5.7			
V		14	4.7			

[Table/Fig-1]: Demographic profile of thalassaemic girls.

Height showed no significant association with SMR stages, but mean BMI values were significantly higher in Tanner's Scale IV and V compared to Tanner's Scale I, II, and III (p<0.001) [Table/Fig-2].

Serum LH, FSH, and oestrogen levels were significantly higher in Tanner's Scale III, IV, and V patients compared to Tanner's Scale I and II. Serum ferritin levels significantly decreased in Tanner's Scale III, IV, and V compared to I and II (p<0.001) [Table/Fig-3].

A total of 269/300 (90%) of thalassaemic patients received chelation therapy. Overall, 89 (33.09%) thalassaemic girls who received chelating agents had attained menarche. In Tanner's Scale III, menarche began in 5 (19.23%) cases who received chelation therapy. Conversely, in Tanner's Stage IV and V, 3 (17.64%) and 2 (14.29%) cases, respectively, started menstruation spontaneously without chelation therapy [Table/Fig-4].

Serum ferritin levels significantly decreased after chelation in Tanner's Scale III compared to Tanner's Scale I and II patients. After chelation therapy, serum LH and FSH levels significantly decreased in Tanner's Scale II patients compared to Tanner's Scale I and III patients (p<0.001) [Table/Fig-5]. Chelation therapy showed significant improvement in hormone levels and menarche (p<0.0001) [Table/Fig-6].

Parameters		Tanner's scale (N=300)					p-value
		I (n=87)	II (n=156)	III (n=26)	IV (n=17)	V (n=14)	
Age (years)	Mean±SD	14.862±1.212	14.943±1.085	14.923±1.294	14.529±1.068	14.923±1.385	0.724
Weight (kg)	Mean±SD	41.229±2.666	42.615±3.878	42.039±3.458	50.177±2.506	51.357±1.151	<0.001
Height (cm)	Mean±SD	138.057±4.559	138.006±4.12	138.615±5.24	137.94±3.83	137.643±4.94	0.965
BMI (kg/m^2)	Mean±SD	21.707±2.067	22.425±2.343	21.972±2.523	26.442±2.191	27.194±1.878	<0.001

[Table/Fig-2]: Distribution of different parameters of Sexual Maturity Rating (SMR) by Tanner's scale of I-V.

Parameters	Tanner's scale (N=300)					p-value
	I (n=87) Mean±SD	II (n=156) Mean±SD	III (n=26) Mean±SD	IV (n=17) Mean±SD	V (n=14) Mean±SD	
Oestrogen (pg/mL)	55.74±8.05	55.64±8.24	119.04±13.34	345.94±21.60	337.86±23.85	<0.001
LH (mIU/mL)	1.37±0.25	1.36±0.24	8.41±0.58	9.42±0.15	9.60±0.20	<0.001
FSH (mIU/mL)	1.37±0.24	1.37±0.24	8.40±0.57	9.39±0.17	9.60±0.20	<0.001
Serum ferritin (ng/mL)	3308.62±468.45	3090.89±363.68	758.50±127.58	303.47±59.12	194.43±47.60	<0.001

[Table/Fig-3]: Distribution of mean hormones and ferritin levels: Sexual Maturity Rating (SMR) by using Tanner's scale.

Parameters	Tanner's scale							
	I	II	III	IV	V	Total	Chi-square	p-value
Chelation therapy: n (%)								
No	0	0	0	17 (54.84)	14 (45.16)	31 (100)	300.000	<0.001
Yes	87 (32.34)	156 (57.99)	26 (9.67)	0	0	269 (100)		
Menarche								
After chelation: n (%)					**Without chelation n (%)**			
Tanner's scale	**I n=87**	**II n=156**	**III n=26**	**Total 269**	**Tanner's Scale**	**IV n=17**	**V n=14**	**Total 31**
No Row%	47 26.11	112 62.22	21 11.67	180 100	No Row%	14 53.85	12 46.15	26 100
Yes	40	44	5	89	Yes	3	2	5
Row% Column %	44.94 45.98	49.44 28.21	5.62 19.23	100 33.09	Row% Column%	60 17.64	40 14.29	100 16.13
Chi-square value: 10.4634; p-value=0.005344					Chi-square value: 0.0641241; p=0.8001			

[Table/Fig-4]: Association of chelation therapy and menarche after chelation in different sexual maturity groups.

Tanner's scale (no.)	After chelation			
	Oestrogen (pg/mL) Mean±SD	LH (mIU/mL) Mean±SD	FSH (mIU/mL) Mean±SD	Ferritin (ng/mL) Mean±SD
I (87)	184.89±140.24	4.94±3.83	4.80±3.78	2054.13±1626.34
II (156)	135.64±127.78	3.50±2.43	3.52±2.43	2323.78±1282.93
III (26)	148.73±78.91	7.88±1.39	8.17±0.45	836.96±398.29
p-value	0.017	<0.001	<0.001	<0.001

[Table/Fig-5]: Distribution of hormones and ferritin after chelation according to Tanner's scale.

Parameters	Pre-chelation	Post-chelation	p-value
Oestrogen (pg/mL)	55.67±7.05	153.27±75.92	<0.0001
LH (mIU/mL)	1.37±0.24	4.02±1.13	<0.0001
FSH (mIU/mL)	1.39±0.17	3.97±1.45	<0.0001
Serum ferritin (ng/mL)	3168.85±343.47	2227.24±275.49	<0.0001

Menarche			Chi-square value	p-value
Yes	0	89		
Row (%)	0	100	117.66	<0.0001
Column (%)	0	33.09		
No	300	180		
Row (%)	62.5	37.5		
Column (%)	100	66.91		

[Table/Fig-6]: Distribution of hormone levels and menarche before and after chelation therapy.

DISCUSSION

In the present study, a significant improvement in the levels of LH, FSH, and oestrogen was observed post-chelation therapy. A total of 74 (38.94%) patients in the age group of 13-15 years and 20 patients (18.18%) in the >15-17 years age group attained menarche. Sutay NR et al., in their cross-sectional case-control

study, found that 0% of thalassaemic cases and 26.3% of controls had attained menarche in the age group of 8-12 years, whereas 11.4% of cases and 93.3% of controls in the age group of >12 years had started menarche [14].

Out of 300 patients in the present study, 190 (63.3%) cases were in the age group of 13-15 years, and 110 (36.7%) patients were in the more than 15-17 years age group. The mean height of patients in the age groups of 13-15 years and >15-17 years was 138±0.042 cm and 138±0.035 cm, respectively. Karamifer H et al., evaluated the growth and sexual development of 146 patients with thalassaemia major in the age group of 10-12 years and found that 68.4% of girls aged 12-22 years experienced failure of puberty, and gonadotropin deficiency was noted in most patients lacking puberty. The height of patients with pubertal development was 153±9.1 cm [15].

From the present study, it was evident that menarche and prepubertal parameters (SMR), as assessed by Tanner's scale, were lower in thalassaemic patients. Endocrine dysfunction has been reported as the most common and earliest organ toxicity observed in individuals with iron overload due to thalassaemia [16]. Growth impairment in children with Beta Thalassaemia Major (BTM) has several possible aetiologies, including an excess of iron overload and endocrinological abnormalities [17]. Deposition of iron in the pituitary gland and/or gonads leads to hypogonadism. However, iron deposition in the pituitary gonadotropic cells is more common and causes hypogonadotropic hypogonadism. Ovaries are less commonly affected, as most amenorrhoeic women can ovulate with hormonal treatment [18]. The current study demonstrates statistically significant low FSH and LH levels in the early stages of SMR, as assessed by using Tanner's scale, in thalassaemic females, and there was significant iron overload as the mean ferritin level was significantly high ($p<0.0001$) when comparisons were made across Tanner's scale from I to V. The oestrogen level was also low in such cases. The results also indicate gonadotropin as well as gonadal steroid deficiency in thalassaemic females suffering from iron overload. Sinharay M et al., in their study, also noted that serum FSH, LH, and estradiol levels were significantly low in thalassaemic females [19]. Among the thalassaemic girls, it was found that the levels of gonadotropins were low, and during puberty, the cut-off values of mean ferritin levels for hypogonadism and short stature were 2500 ng/mL and 3000 ng/mL, respectively [20].

Iron-induced hypogonadism may be reversed by intensive iron chelation regimens [21]. During the study period, chelation therapy was started only when the serum ferritin level was more than 500 ng/mL. In the present study, chelation therapy was received by 89.66% of cases (269/300), including Tanner's Stage I, II, and III, where ferritin levels were >500 ng/mL. Chelation therapy was not started in Stage IV and V as these had no iron overload indicated by a low serum ferritin level of <500 ng/mL. Menarche resumed in 33.09% (89/269) of cases after chelation therapy. Mean serum LH and FSH levels after chelation were also significantly higher ($p<0.0001$) in this study. The chelating agent Deferasirox has a long half-life and is present in the plasma for 24 hours with once-daily dosing, and it is a convenient, effective, well-tolerated therapy in the management of iron overload [22]. Chelation therapy before the age of puberty has helped patients to attain normal sexual maturation in some studies but not in others [18]. Early chelation therapy could help children with BTM to attain normal sexual maturation, better growth, and menarche without toxicity, and the median serum ferritin levels decreased significantly from 2117 to 1124 ng/mL ($p<0.001$) [21,23].

Despite recent advances in iron chelation therapy, excess iron deposition in pituitary gonadotropic cells remains one of the major problems in thalassaemia patients. Early detection and subsequent treatment of hypogonadism are the most important steps for normal pubertal development and for the reduction of complications. Accurate assessment of risks and benefits of hormonal replacement therapy, especially regarding thromboembolic events, remains a challenging task for the caregiver of thalassaemic patients [18].

Limitation(s)

Despite very sincere effort, the present study was not without limitations. The main limitations are the assessment of factors and considering the nature of the disease. Point-measurement was not without bias, as endocrine disorders in these cases demand long-term exposure of three months to excess iron, and estimation of a single measurement would be biased. Therefore, multiple serum ferritin measurements would be more valuable. Hypogonadotropic hypogonadism in thalassaemia is not only related to iron toxicity on gonadotroph cells, but detection of bias may be due to unseen confounders like liver disorder, zinc deficiency, and chronic hypoxia, which were not explored.

CONCLUSION(S)

Delay or failure of pubertal development was common in girls with thalassaemia major. Adequate chelation therapy in patients with a high level of serum ferritin caused a significant increase in serum FSH and LH levels, as well as an increase in oestrogen levels. Treatment with chelating agents also contributed to sexual maturity, as 33.09% attained menarche postchelation. Therefore, timely and adequate chelation has a major impact on the pubertal development of beta thalassaemic girls. Additionally, a larger sample size and multicentre studies are important to validate the results.

Authors contribution: RM-Framing and drafting of the paper; SD-Data collection; AP-Statistical work; DKB-Selection of the topic, helped co-author in primary manuscript writing and subsequent corrections as and when required.

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PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Obstetrics and Gynaecology, RG Kar Medical College, Kolkata, West Bengal, India.
2. Professor, Department of Obstetrics and Gynaecology, MJN Medical College, Coochbehar, West Bengal, India.
3. Junior Resident, Department of Obstetrics and Gynaecology, Burdwan Medical College, Burdwan, West Bengal, India.
4. Associate Professor, Department of Obstetrics and Gynaecology, Burdwan Medical College, Burdwan, West Bengal, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Dilip Kumar Biswas,
Associate Professor, Department of Obstetrics and Gynaecology, Burdwan Medical College, Burdwan, Purba Bardhaman-713104, West Bengal, India.
E-mail: drdkb75@gmail.com

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