Assessment of Sex Hormones in Adolescent Females Suffering From ß-Thalassemia Major

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Abstract

Objectives: The present study was carried out to evaluate the effects of frequent blood transfusion on some female sex hormones beside the effects and relations with other parameters and puberty in a group of Iraqi female patients affected with ß-thalassemia major at adolescent age (age 13-17), whom was attending the Thalassemia Centre in Ibn-Al Atheer Pediatrics Hospital in Mosul city in Iraq. The study was conducted during the period from the 10th of November (2011) to the 28th of May (2012) .

Patients and Methods

Sixty patients employed in this study, while thirty healthy individuals were chosen as a control group from the attendants of the nursing school in Mosul city for comparison. In this work, the concentrations of Follicular Stimulating Hormones (FSH), Luteinizing Hormone (LH) and Estradiol (E2) were evaluated in the sera of female patients and controls , Also serum ferritin was assayed in the sera as well using .TOSOH AIA System Analyzers Device, AIA 360, Japan (which is an immunoenzymometric assay). Hb, PCV beside other non-laboratory measures were taken also such as weight, height and BMI.

Results

The mean concentration of serum FSH, LH and Estradiol had shown a highly significant decrease in female patients with ß-thalassemia major in comparison with control group ($p=< 0.001$) ,the same thing was also shown concerning Hb, PCV , Weight , height and BMI ; while the study had shown a highly significant increase in serum ferritin in the diseased females as compared with healthy control group. The study showed high significant inverse correlation between serum ferritin and Estradiol in thalassemic females; and the same relationship was found also regarding FSH and LH as well . The distribution of thalassemic patients according to weight-age and sex had shown a highest percentage of them (75%) less than <5th percentile in contrast to the control group (6.67%) in the presence of high significant difference, also the study showed that more than (76.0%) of thalassemic females has less than< 5th percentile height-age and the percentage decreased in control females to about (23.0%) . The results of this study reveal that (58.33%) of ß-thalassemia patients were suffering from hypogonadotropic hypogonadism with (16.67%) of patients suffering from primary hypogonadism .

Conclusions

In conclusion, delayed puberty and growth retardation are extremely frequent in patients with β-thalassemia major, but regular blood transfusion and appropriate iron chelation therapy can prevent or limit these complications. These data support the need for vigilant follow-up of patients with thalassemia in order to diagnose and treat endocrine dysfunction at an appropriate age .

Introduction

Beta thalassemia (ß-thalassemia) syndromes are group of hereditary blood disorders characterized by reduced or absent beta globin chain synthesis resulting in reduced hemoglobin (Hb) in red blood cells (RBC), decreased RBC production and anemia . Most thalassemias are inherited as recessive traits [5]. The World Health Organization (WHO) has estimated that at least 5% of the population are carriers for one or other of the most serious forms , the α, the ß-thalassemia and the structural variant hemoglobins S,C and E which are found at polymorphic frequencies in many countries [3] . The genes for ß-thalassemia are prevalent in several ethnic groups distributed in broad geographic belt from the Mediterranean basin through the Middle East and the Indian Subcontinent and into Southeast Asia [15]. In the past, children with ß-thalassemia rarely survived beyond adolescence [17] .

The improved expectancy and quality of life in ß-thalassemia patients in the late 1970s was due to the introduction of regular optimum RBC transfusions and almost daily subcutaneous iron chelation therapy made the necessity for normal reproductive and sexual life more pressing [20]. Repeated blood transfusions and increased gastrointestinal iron absorption lead to iron overload in the body [19] . Human are unable to eliminate the iron and the excess iron is deposited as hemosiderin and ferritin in the liver, spleen, endocrine organs and myocardium [25] . Poor growth and multiple endocrinopathies, including hypogonadotrpoic hypogonadism (HH), growth hormone (GH) deficiency are known complications in ß-thalassemia major and are considered the result of iron overload [21].

Failure of pubertal growth, delay or absence of sexual development, amenorrhea, sexual dysfunction and infertility due to hypogonadism are well-recognized disturbances of the hypothalamic pituitary-gonadal axis in ß-thalassemic patients [26] . Liver disease secondary to iron burden and HCV infection still a problem in adult thalassemic patients; besides the development of fibrosis and cirrhosis [16] .

Hypogonadism is the most common endocrinopathy followed by growth deficiency and diabetes [27]. Transfusion siderosis is responsible for increased iron deposition in all cell types of the pituitary gland, but mainly in the gonadotrophs [2] . The contribution of the underlying molecular defect the thalassemia major to the development of endocrinopathies and particularly hypogonadotropic hypogonadism is significant because the patients with more severe genetic defects have a greater rate of iron loading through higher red cell consumption [23] .

Although thousands of people worldwide have ß-thalassemia and therefore are at increased risk for reproductive health problems, the literature on these issues is scarce, particularly the relation between iron overload and hypogonadism .

Aims of the study

1- The present study is designed to assess some of female sex hormones (FSH, LH and E2) in adolescent females suffering from ß-thalassemia major at the age of (13-17) years in Nineveh Governorate and the effect of different factors on these hormones and to investigate growth and puberty of these patients . 2- To evaluate the levels of other laboratory parameters (hemoglobins, PCV and blood groups) and other non-laboratory parameters (weight, height and BMI) of those patients in comparison with age and sex matching healthy control group and the effect of iron overload estimated by serum ferritin on these hormones and other parameters of the patients .

3-To evaluate puberty and growth of the thalassemic patients in comparison with healthy individuals .

Subjects, Materials and Methods

Sixty female patients with ß-thalassemia major age 13-17 years (mean 14.96 ± 1.36) while thirty healthy individuals were chosen as a control group (mean 15.33 ± 1.37) from the attendants of the nursing school in Mosul city for comparison Fig (1) .

Sera samples were collected from the patient at Thalassemia Center at Ibn-Al Atheer Hospital for Pediatrics in Mosul city, Iraq .

The diagnosis of ß-thalassemia major was made by the consultant doctors considering the results of hemoglobin electrophoresis, laboratory investigations and clinical features of the patients .

The data were collected about name, age, residence, parent consanguinity, blood group and Rh, ethnicity, age of diagnosis, number of transfusions per year, age of stating chelation drugs, number of DFO doses per week, history of heart failure, DM, hepatitis, other blood diseases, history of menarche, hormonal therapy, splenctomy, medications history .

Thirty healthy adolescent females were taken to constitute the control group for comparison. Blood transfusions were conducted regularly for all patients with 10-15ml/kg packed cells and all the patients were under iron chelation therapy .

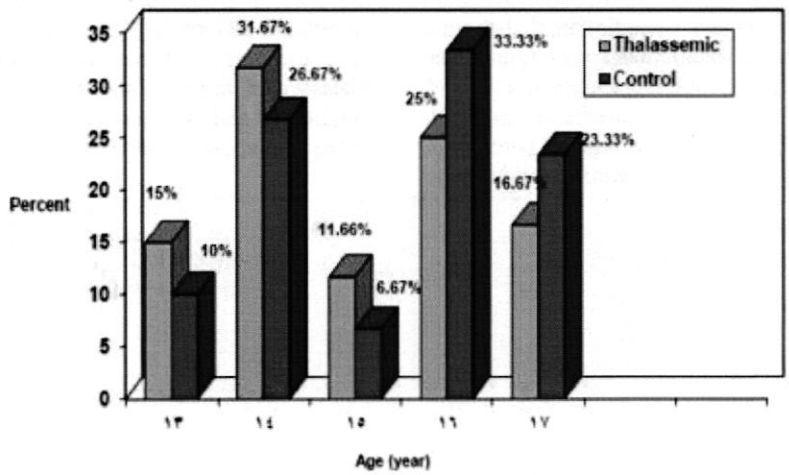

Fig. (1): Distribution of study samples according to age.

Exclusion Criteria

All the female patients who are below 13 years old or above 17 years old were excluded; all the patients having any type of hepatitis infection were excluded. Any patient having other blood diseases rather than ß-thalassemia major was also excluded .

Samples Collection

5ml of venous blood was obtained from all subjects included in this work after sterile cannula has been inserted in the antecubital vein between 9.00 am and 10.00 am. 1 ml of the blood sample was collected into Ethylene diamino tetracetic acid (E.D.T.A) tube, that was used for PCV measurement, with gentle shaking for proper mixing with anticoagulant. The remaining 4ml of blood was put into plain tube and left for at least one hour for clot formation, then centrifuged at 3000 RPM for 5 minutes. The resulted serum was collected into another plain tube to perform the following tests {serum ferritin, LH, FSH, and Estradiol for females}. In thalassemia patients sampling was done just before the blood transfusion (between 9-10 o'clock in the morning) .

In menstruating thalassemia major female patients and controls, blood samples were drawn during the 2nd and 3rd day of the cycle . The serum were freezed

at about -20°C until analysis (didn't exceed 10 weeks) [14] .

Serum Investigation

Basic serum biochemical parameters including Luteinizing hormone (LH), Follicular Stimulating hormone (FSH) and Estradiol (E2) were assayed for patients and control groups within eight weeks by (TOSOH AIA System analyzer Device which is immunoenzymometric assay. Also serum ferritin was measured by the same technique .

Examination

Height (in cm) standing height for all subjects with upright scale was taken to assay height. Weight (in kg), BMI, calibrated scale was used for all subjects with minimal clothing to assay weight and BMI later on .

Results

In this study, The mean concentration of serum FSH, LH and Estradiol had shown a highly significant decrease in female patients with ß-thalassemia major in comparison with control group ($p=< 0.001$) ,the same thing was also shown considering Hb, PCV, Weight , height and BMI; while the study had shown a highly significant increase in serum ferritin in the diseased females as compared with healthy control group as shown in (table 1) .

Table (1): Comparison of measured parameters between thalassemic females and controls

Parameters	Control (n=30)		Thalassemic (n=60)		p-value
	Mean	SD	Mean	SD	
Hb (g/dL)	12.84	0.74	8.64	1.59	<0.001
PCV (%)	42.47	240	27.00	4.00	<0.001
Ferritin (ng/ml)	16.79	10.87	3886.30	2364.25	<0.001
Estradiol (pg/ml)	76.42	43.67	44.07	41.97	<0.001
LH (mIU/ml)	7.53	5.38	1.58	1.74	<0.001
FSH (mIU/ml)	6.55	2.24	4.09	2.96	<0.001
Weight (kg)	53.56	10.02	36.53	7.53	<0.001
Height (cm)	157.10	6.40	142.40	11.15	<0.001
BMI (kg/m^2)	21.73	3.90	17.94	2.74	<0.001
Age (year)	15.33	1.37	14.96	1.36	0.280(NS)

NS = Not significant using unpaired t-test

The study showed high significant inverse correlation between serum ferritin and Estradiol in thalassemic females; and the same relationship was found also regarding FSH and LH as well (figure 2,3 and 4) .

The distribution of thalassemic patients according to weight-age and sex had shown a highest percentage of them (75%) less than <5th percentile in contrast to the control group (6.67%) in the presence of high significant difference (Table 2) .

Also the study showed that more than (76.0%) of thalassemic females has less than< 5th percentile height-age and the percentage decreased in control females to about (23.0%) (Table 3) .

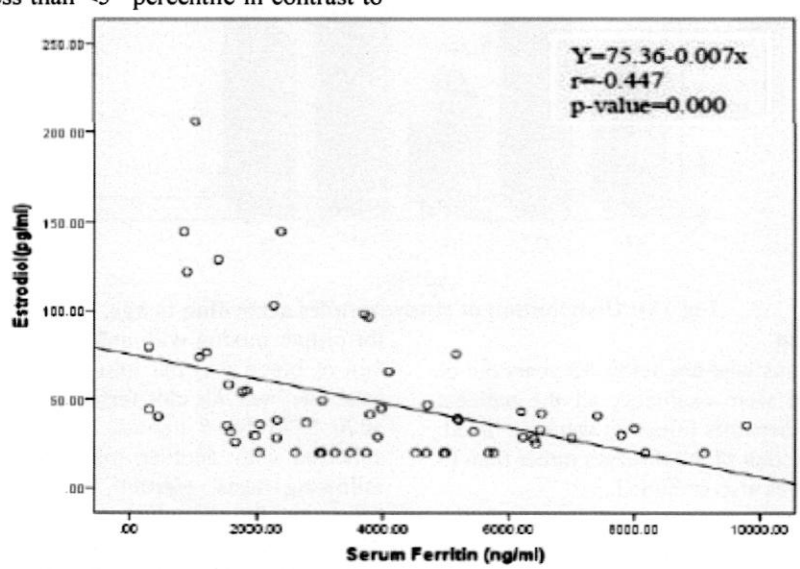

Fig. (2): Relationship between serum ferritin and Estradiol in female thalassemic patients

Misleading ferritin levels also occur with chronic inflammatory liver diseases [22], hence serum ferritin is not the ideal parameter to assess iron overload .

The goal standard for body iron status is liver iron content [8]. There is a high significant decrease in weight and height percentile at p-value (p=<0.001) in thalassemic patient when compared with healthy control (table 1).

Hashemi et al. [9], observed in a cross-sectional study on seventy patients (36 boys and 34 girls) with transfusion dependent thalassemia major at age range 2-28 years that twenty three patients (45.71%) had weight less than five percentile (< 5^{th} percentile), these results are also in agreement with a study carried out by Hamidah et al . [8], who showed that high number of transfusion dependent thalassemia patients with standing height less than the third percentile (< 3^{rd}) (figure 5) .Although a delay in onset of puberty is a common cause of growth failure in adolescent thalassemic patients, growth retardation and abnormal body proportion with truncal shortening which are commonly seen could also be due to iron overload, the development of other endocrinopathies such as growth hormone insufficiency or primary hypothyroidism [13] .

Conclusion

Despite therapy with iron chelating agents to treat iron overload, the risk of delayed puberty and affected growth still high specially secondary hypogonadism which remain high in ß-thalassemia major patients at age range group (13-17) years than other age group both in females and males; therefore they need to be diagnosed at early age possibly to ensure normal puberty stage and avoid irreversible complications.

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References

1. Allegra, A., Capra, M., Cuccia, L., Pulejo, M. L., Raineri, L., Traina, M. C., Corselli, F., Giannola , C. and LA Grutta, A. (1990). Hypogonadism in beta-thalassemic adolescents: a characteristic pituitary-gonadal impairment . The ineffectiveness of long-term iron chelation therapy. Gynecol. Endocrinol., 4(3):181-191.

2. Bergeron, C. and Kovacs, K. (1978) . Pituitary siderosis:A histologic, immunocytologic , and ultrastructural study. Am. J. Pathol ., 93(2):295-309.

3. Clegg, J. B. and Weatherall, D. J. (1999). Thalassemia and malaria: new insights into an old problem . Proc. Assoc. Am- Physicians, 111(4) :278-282 .

4. De Sanctis. and Italian working group. (1995) Multicentre study on endocrine complications in thalassemia major. Italian working group on endocrine complications in non-endocrine diseases. Clin. Endocrinol. (Oxf)., 42(6):581-586.

5. Galanello, R. and Origa, R. (2010). Beta-thalassemia. Orphanet. Journal of Rare Disease , 5 (11): 330-345.

6. Griffin, J. E. and Wilson, J. D. (2004). Disorders of the tests. Harrison's principles of internal medicine. In: Endocrinology & Metabolism. New York NY. McGraw Hill. 15^{th} Ed., 335:2143-2154.

7. Gulati, R., Bhatia, V. and Agrawals, S. S. (2000). Early onset of endocrine abnormalities in β- thalassemia major in a developing country. J. Pediatr. Endocrinol. Metab., 13: 651-656 .

8. Hamidah, A., Rahmah, R., Azmi, T., Aziz, J. and Jamal, R. (2001). Short stature and truncal shortening in transfusion dependent thalassemia patients: results from a thalassemia center in Malaysia. Southeast Asian. J. Trop. Med. Public Health, 32(3):625-630.

9. Hashemi, A., Ghilian, R., Golestan, M., Akhavan, M., Zare, Z. and Dehghani, M. A. (2011). The Study of Growth in Thalassemic Patients and its Correlation with Serum Ferritin Level. Journal of Pediatric Hematology. Oncology,1(4): 147-151.

10. Karamifar, H., Shahriar, M. and Amirhakimi, G. H. (2005). Failure of puberty and linear growth in β-thalassemia major. Turk. J. Haematol., 22(2) : 65-69.

11. Kodaman, P. H. and Arici, A. (2007). Intra-uterine adhesions and fertility outcome: how to optimize success?. Curr. Opin. Obstet. Gynecol., 19(3):207-214.

12. Kwan, E. Y., Lee, A. C., Li, A. M., Tam, S. C., Chan, C. F., Low, L. C. and Lau, Y. L. (1995). A cross-sectional study of growth, puberty and endocrine function in patients with thalassaemia major in Hong Kong. J. Paediatr. Child Health , 31(2):83-87.

13. Low, L. C. (1997). Growth, puberty and endocrine function in beta-thalassemia major. J. Pediatr. Endocrinol. Metab., 10(2):175-184.

14. Marshall, W. J. and Bangert, S. K. (2004). Thyroid dysfunction, clinical biochemistry, Elsevier Health Sciences, Metabolic and clinical aspects 5^{th} ed, chapter, 19: 397.

15. Pearson, H. A., Cohen, A. R., Giardina , P. J. and Kazazian, H. H. (1996) .The changing profile of homozygous beta-thalassemia: demography, ethnicity, and age distribution of current North American patients and changes in two decades. Pediatrics , 97(3):352-356.

16. Poggi, M., Sorrentino, F., Pascucci, C., Monti, S., Lauri, C., Toscano, V., Cianciulli, p. and Bisogni, V. (2011). Malignancies in β-thalassemia patients: first description of two cases of thyroid cancer and review of the literature. Hemoglobin , 35(4): 439-446.

17. Politis, C., Di Palma, A., Fisfis, M., Giasanti, A., Richardson, S. C., Vullo, C. and Masera, G. (1990). Social integration of the older thalassemic patients. Arch. Dis. Child., 65(9):984-986.

18. Prakash, A. and Aggarwal, R. (2012). Thalassemia Major in Adults: Short Stature, Hyperpigmentation, Inadequate Chelation, and

Transfusion-Transmitted Infections are Key Features . N. Am. J. Med. Sci ., 4(3):141-144.

19. Radmilovic, M., Zukic, B., Stankovic, B., Karan-Djurasevic, T., Janic, D., Pavlovic, S., Stojiljkovic, M., Spasovski, V., Tosic, N. and Dokmanovic, L. (2010). Thalassemia syndromes in Serbia: an update. Hemoglobins, 34(5):477-485.

20. Rodgers, GP. (1998). Pharmacological therapy. Baillieres. Clin. Haematol .,11(1):239-255.

21. Rund, D. and Rachmilewitz, E. (2005). Beta-thalassemia. N. Engl. J. Med., 353(11):1135-1146.

22. Sabato, A. R., De Sanctis, V., Atti, G., Capra, L., Baqni, B. and Vullo, C. (1983). Primary hypothyroidism and the low T3 syndrome in thalassemia major. Arch. Dis. Child ., 58(2):120-127.

23. Skordis, N., Michaelidou, M., Savva, S. C., Skordos, G., Kleanthous, M., Loannou, Y., Rousounides, A. and Christou, S. (2006). The impact of genotype on endocrine complications in thalassaemia major. Eur. J. Haematol.,77(2) : 150-156.

24. Soliman, A. T., El Zalabany, M., Amer, M. and Ansari, B. M. (1999). Growth and pubertal development in transfusion-dependent children and adolescents with thalassemia major and sickle cell disease: a comparative study. Journal. Trop. Pediatr., 45(1):23-30.

25. Taher, A., Isma'eel, H. and Cappellini, M. D. (2006).Thalassemia intermedia: revisited. Blood Cells Mol Dis., 37(1):12-20.

26. Thein, SL. (1998). Beta-thalassemia. Baillieres. Clin. Haematol.,11(1):91-126 .

27. Tiosano, D. and Hochberg, Z. (2001). Endocrine complications of thalassemia. J. Endocrinol. Invest., 24(9):716-723.

تقييم الهرمونات الجنسية في الاناث اليافعات والمصابات بالثلاسيميا نوع بيتا العظمى

(تاريخ الاستلام: 1 / 4 / 2013 ---- تاريخ القبول: 9 / 6 / 2013)

الملخص

فهدا: تضمنت الدراسة الحالية تقييم تأثير عمليات نقل الدم الدائمة على بعض الهرمونات الجنسية الانثوية بجانب التأثيرات والعلاقات مع مؤشرات اخرى والبلوغ في مجموعة من الاناث العراقيات المريضات والمصابات بمرض فقر الدم البحر الابيض المتوسط نوع بيتا (العظمى) اليافعات في سن (13-17) سنة والذين يراجعون مركز الثلاسيميا في م. ابن الاثير للأطفال في مدينة الموصل ، العراق وقد اجريت الدراسة واخذ العينات من المرضى خلال الفترة الممتدة من الاول من شهر تشرين الثاني 2011 لغاية الثامن والعشرين من شهر أيار 2012 .

المرضى والطرائق: تم ادخال ستون مريضة في الدراسة بينما تم اختيار ثلاثون من الاناث الاصحاء ظاهريا كمجموعة سيطرة من المنتسبين للدراسة في اعدادية الموصل للتمريض في مدينة الموصل للمقارنة . تم في هذا العمل تقدير تركيز كل من هرمون منبه الجريبات والهرمون اللوتيني اضافة لهرمون الانوثة (الاستراديول) في مصول كل من الاناث المريضات والأصحاء كذلك تم قياس مستوى حديدين المصل وذلك باستخدام جهاز (توسو) الياباني الحديث المنشأ والذي يعتمد قياس الفحص المناعي الانزيمي. تم خلال الدراسة ايضا قياس تركيز الهيموجلوبين ، مكداس الدم اضافة لقياس مؤشرات اخرى غير مختبريه مثل الوزن الطول ومعامل كتلة الجسم الخ.....

النتائج: اظهرت الدراسة بان هناك انخفاضا معنوي عالي المعنوية في معدل (الهيموجلوبين)، مكداس الدم ، الوزن ، الطول ، معامل كتلة الجسم ، وكذلك بالنسبة لتركيز هرمون منبه الجريبات والهرمون اللوتيني وهرمون الانوثة في الاناث المصابات بفقر الدم البحر الابيض المتوسط نوع بيتا العظمى بالمقارنة مع تركيزها في مصل الاناث الاصحاء (**p=<0.001**) مع وجود ارتفاع معنوي عالي المعنوية بالنسبة لتركيز حديدين المصل عند الاناث المصابات عند مقارنته مع مجموعة السيطرة . الدراسة اظهرت ايضا وجود علاقة عكسية عالية المعنوية بين حديدين المصل وبين كل من الهرمون اللوتيني، الهرمون المنبه الجريبات، وهرمون الانوثة لدى الاناث المصابات. اظهرت النتائج ان نسبة مرضى فقر الدم البحر الابيض المتوسط الذين هم اصغر وزنا من 5 من بين 100 شخص مشابه بالعمر والجنس كانت 75% في الاناث (**<5rd percentile**) . مشابها لذلك 76.67% من المريضات لديهم طول قامة اقل من 5 من بين 100 شخص مشابه بالعمر والجنس (**<5rd percentile**) بوجود فرق معنوي كبير بالمقارنة مع الاشخاص الاصحاء (**p=<0.001**) . اظهرت نتائج الدراسة اضافة لما تقدم بان (58.33%) من المريضات المصابات بفقر الدم البحر الابيض المتوسط لديهم ايضا نقص افراز الغدد التناسلية الناتج عن نقص المنبه المنسلي (قصور القند الناجم عن نقص موجهة القند) ، وبان (16.67%) من المرضى لديهم نقص افراز الغدد التناسلية الناتج عن زيادة المنبه المنسلي (قصور القند الاولي) . نستنتج من كل هذه النتائج ان تأخر البلوغ و تأخر النمو من المضاعفات الشائعة لدى مرضى الثلاسيميا ولكن المنهاج الصحيح في نقل الدم و الاستخدام المنتظم والصحيح لعقار الدسفيرال يمكن ان يمنع او يقلل هذه المضاعفات بالإضافة الى ذلك ،بيّنت هذه الدراسة الحاجة الماسّة لمتابعة مرضى الثلاسيميا لغرض علاج هذه المضاعفات في الوقت المبكر.

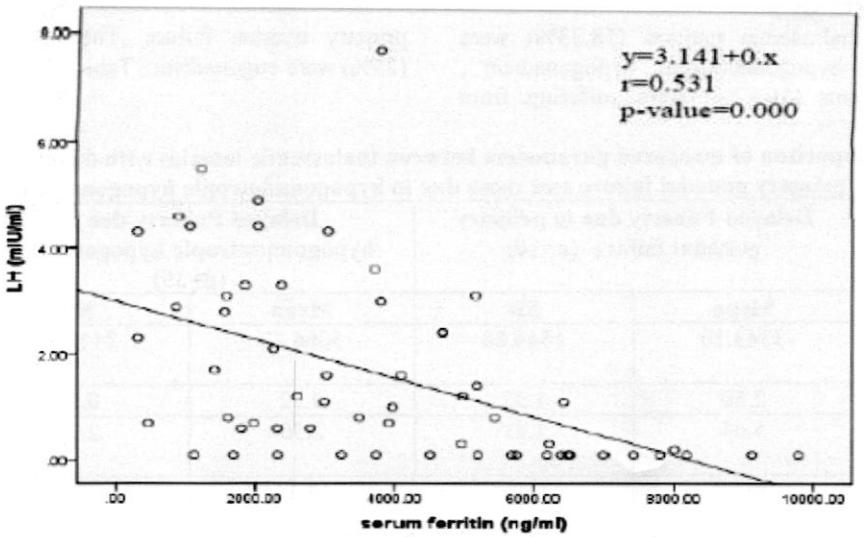

Fig. (3): Relationship between serum ferritin and LH in female thalassemic patients

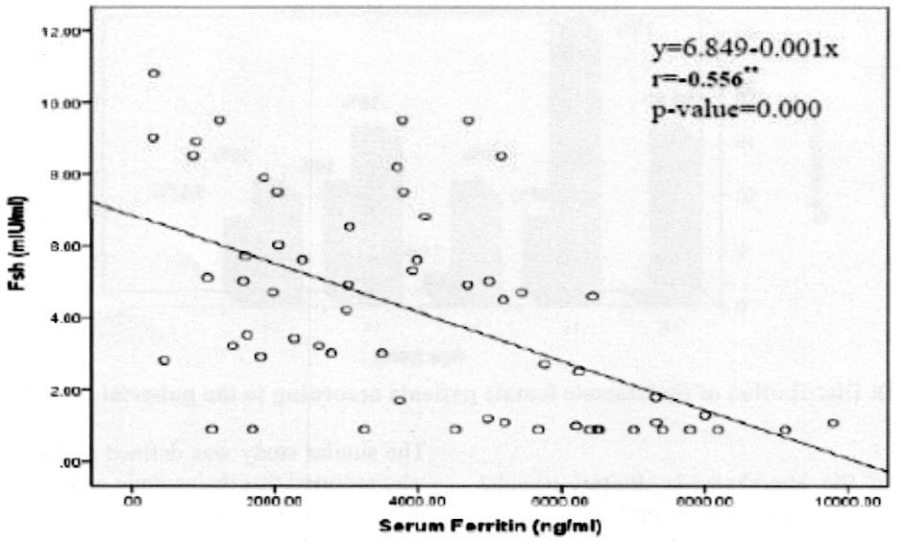

Fig. (4): Relationship between serum ferritin and FSH in female thalassemic patients

Table (2): Weight - age percentiles in thalassemic females and control

Wt-Age	Thalassemic female n=60		Control Female n=30	
	No.	%	No.	%
$<5^{th}$	45	75.00	2	6.67
$>5^{th}$-25^{th}	8	13.33	6	20.00
$>25^{th}$-50^{th}	7	11.67	9	30.00
$>50^{th}$	-	0.00	13	43.33

Table (3): Height - age percentiles in thalassemic females and control

Ht-Age	Thalassemic female n=60		Control Female n=30	
	No.	%	No.	%
$<5^{th}$	46	76.67	7	23.33
$>5^{th}$-25^{th}	8	13.33	8	26.67
$>25^{th}$-50^{th}	4	6.67	5	16.67
$>50^{th}$	2	3.33	10	33.33

Thirty five ß-thalassemia patients (58.33%) were suffering from hypogonadotropic hypogonadism , while ten patients (16.67%) were suffering from primary ovarian failure ,The last fifteen patients (25%) were eugonadism . Table (4) Fig.(5) .

Table (4) : Comparison of measured parameters between thalassemic females with delayed puberty due to primary gonadal failure and those due to hypogonadotropic hypogonadism

Parameters	Delayed Puberty due to primary gonadal failure (n=10)		Delayed Puberty due to hypogonadotropic hypogonadism (n=35)		p-value
	Mean	SD	Mean	SD	
Ferritin (ng/ml)	3343.10	1544.80	5066.42	2442.73	<0.05
LH (mIU/ml)	2.50	1.52	0.52	0.72	<0.001
FSH (mIU/ml)	5.64	1.81	2.50	2.28	<0.001
Estradiol (pg/ml)	20.57	6.14	18.14	15.16	0.214(NS)

NS = Not significant using unpaired t-test

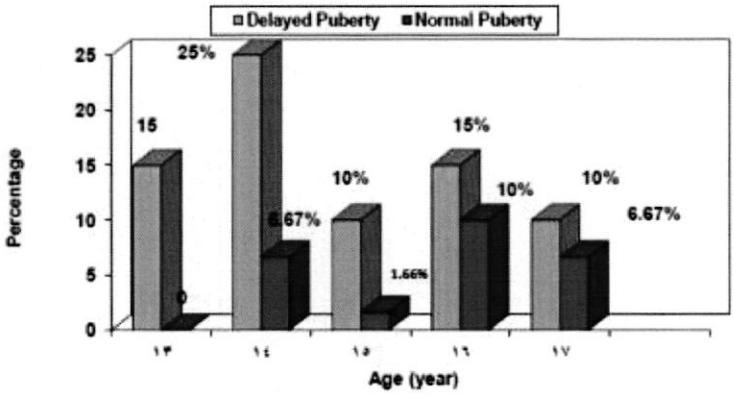

Fig.(5): Distribution of thalassemic female patients according to the pubertal development

Discussion

The damage of the hypothalamic-pituitary-gonadal axis is most likely localized at a central level .

The classic knowledge is that in transfusion-dependent ß-thalassemia patients, increased iron deposition in the pituitary gland has a cytotoxic effect, Our data suggest that the hypogonadotropic condition of the thalassemic adolescents is due to pituitary hyporesponsiveness to GnRH and that most of these patients also have an impairment of ovarian function. Both conditions are a consequence of iron deposits in glands. Moreover, there is evidence that pituitary-gonadal function cannot be preserved by long-term iron chelation therapy[1]. Primary hypogonadism is associated with low levels of Estradiol and high-normal to high levels of LH and FSH. Secondary hypogonadism (hypogonadotropic hypogonadism) (HH) is associated with low level of Estradiol and normal to low levels of LH and FSH [6, 11] .

In the present study, 55.33% of female patients with ß-thalassemia major developed hypogonadotropic hypogonadism (HH) as shown in table (4) .

The similar study was defined by Soliman et al [24], who reported that thalassemic patients had a complete lack of pubertal change in 73% of boys and 42% of girls with thalassemia between the age of 13 and 21 years . De Sanctis et al [4], reported that there is a considerable percent (30%) of patients with ß-thalassemia major having hypogonadotropic hypogonadism (HH). Kwan et al [12], have reported similar results; 62% of boys and 75% of girls over the age of 12 years had HH. Karamifar et al.(2005) study[10], reported delayed puberty in (75.6%) of boys all of whom were above the age of (14) years and in(68.4%) of girls all of whom were above the age of (12) years with β-thalassemia major . In a study by Gulati et al . (2000) [7], 10 out of 11 adolescent or young adult thalassemic patients had hypogonadism .

The absence of relationship between serum ferritin and endocrinopathy or liver function tests may be due to the fact that other causes rather than iron over load such as chronic viral hepatitis would be the main cause of elevated liver enzymes [18] .