ISSN 1109-4486

ΤΡΙΜΗΝΙΑΙΑ ΕΚΔΟΣΗ ΤΜΗΜΑΤΟΣ ΝΟΣΗΛΕΥΤΙΚΗΣ Α΄ ΤΕΙ ΑΘΗΝΑΣ

ΑΠΡΙΛΙΟΣ-ΙΟΥΝΙΟΣ 2002 ΤΟΜΟΣ 1 ΤΕΥΧΟΣ 2

ΤΟ ΒΗΜΑ ΤΟΥ ΑΣΚΛΗΠΙΟΥ

VEMA OF ASKLIPIOS

APRIL-JUNE 2002 VOLUME 1 No 2

QUARTERLY EDITION BY THE 1st NURSING DEPARTMENT
OF ATHENS TECHNOLOGICAL EDUCATIONAL INSTITUTION

ΤΟ ΒΗΜΑ ΤΟΥ ΑΣΚΛΗΠΙΟΥ

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Would we expect a better menstrual cycle if ferritin levels can be maintained at a lower level?

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Abstract **This paper contains the findings of a scientific research project pertaining to a population of women with ß-thalassaemia and examining the frequency of their menstrual cycle. The evaluation of the menstrual cycle of the subjects (ß-thalassaemia women) was based on the ferritin levels in hemoglobin before transfusion, the level of deironization and the response of the FSH-LH (Folic Stimulating Hormone-Luteinizing Hormone) after stimulation with GnRH. This study is retrospective and covers the period from 1981 to 1999. A sample of 122 ß-thalassaemia women taken from the ß-thalassaemia patients referred to the "Nicosia Center for Thalassaemia" in Cyprus participated in the study. Subjects were divided into four groups according to their menstrual cycle. Women with a normal menstrual cycle were assigned to the first group, women with areomenorrhea to the second group, women with secondary amenorrhea to the third group and women with primary amenorrhea were put in the fourth group. The results obtained show that the age of the sample ranges from 15 to 48 years. The majority of the subjects (85%) were 20–40 years old. The largest group (34.1%) consisted of women with normal menstrual cycle. The results did not reveal any statistically important difference with reference to the frequency of deironization among the groups studied, while the hemoglobin levels ranged from 8.5–11 g/dL in all groups. An upward tendency in ferritin levels was found for every year (period studied=a total of 18 years) for the group with normal menstrual cycle in comparison to the group with primary amenorrhea. Statistically important differences were found for the minimum ferritin value between groups one and four (P<0.048). Finally, the average values of FSH and LH after stimulation with GnRH showed the minimum response in the secondary and primary amenorrhea groups. Statistically important differences (P<0.010) were reported for LH and (P<0.50) for FSH.**

Key words: *ß-thalassaemia, menstrual cycle, ferritin, hemoglobin, deironization, FSH (Follicle Stimulating Hormone), LH (Luteinizing Hormone)*

Περίληψη **Β-θαλασσαιμία και φυσιολογικός καταμήνιος κύκλος. Μπορούμε να αναμένουμε ένα καλύτερο κύκλο αν τα επίπεδα φερριτίνης διατηρούνται σε ένα χαμηλότερο επίπεδο τιμών;** Μ. Γουρνή,[1] Δ. Σαπουντζή-Κρέπια,[2] Ζ. Ρούπα-Δαριβάκη,[3] Μ. Σκάντζος,[4] Ν. Σκορδής,[5] Χ. Μπαρτσόκας,[5] Ε. Θεοδοσοπούλου.[5] *[1]Τμήμα Νοσηλευτικής Α΄ ΤΕΙ Αθήνας, [2]Τμήμα Νοσηλευτικής Β΄ ΤΕΙ Αθήνας, [3]Τμήμα Επισκεπτών Υγείας ΤΕΙ Αθήνας, [3]Ιατρική Σχολή Πανεπιστημίου Θεσσαλίας, [5]Παιδιατρικό Τμήμα Νοσοκομείου Μακάριος Γ της Κύπρου, [6]Τμήμα Νοσηλευτικής Πανεπιστημίου Αθηνών, Αθήνα. Το Βήμα του Ασκληπιού 2002, 1(2):77–82.* **Η συχνότητα εμφάνισης και διατήρησης του καταμήνιου κύκλου σε ασθενείς με ομόζυγη ß-θαλασσαιμία μελετάται στο παρόν άρθρο. Η αξιολόγηση του καταμήνιου κύκλου πραγματοποιήθηκε με το συσχετισμό των επιπέδων φερριτίνης, της αιμοσφαιρίνης πριν από τη μετάγγιση αίματος, του βαθμού αποσιδήρωσης και της ανταπόκρισης των FSH και LH μετά από διέγερση με GnRH. Στη μελέτη αυτή λαμβάνουν μέρος 122 γυναίκες με ομόζυγη ß-θαλασσαιμία που παρακολουθούνται από το Κέντρο Μεσογειακής Αναιμίας και άλλων «Αιμολυτικών Αναιμιών» Λευκωσίας Κύπρου. Η μελέτη είναι αναδρομική και περιλαμβάνει το χρονικό διάστημα 1981–1999. Οι γυναίκες χωρίσθηκαν με βάση τον καταμήνιο κύκλο σε 4 ομάδες, στις γυναίκες με φυσιολογικούς κύκλους, με αραιομηνόρροια, με δευτεροπαθή αμηνόρροια και με πρωτοπαθή αμηνόρροια. Τα αποτελέσματα έδειξαν ότι το σύνολο του δείγματος της έρευνας παρουσιάζει μεγάλο εύρος ηλικίας 15–48 έτη, με μέση ηλικία 27,52 το 85% των γυναικών βρίσκεται μεταξύ 20–40 ετών και η ομάδα με φυσιολογικό κύκλο συγκεντρώνει το μεγαλύτερο ποσοστό 34,1%. Η συχνότητα αποσιδήρωσης δεν εμφάνισε στατιστικά σημαντική διαφορά**

Λέξεις κλειδιά: *Β-θαλασσαιμία, καταμήνιος κύκλος, φερριτίνη, αιμοσφαιρίνη, αποσιδήρωση, FSH, LH*

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για καμία ομάδα, ενώ τα επίπεδα αιμοσφαιρίνης κυμάνθηκαν από 8,5–11,5 g/dL. Η φερριτίνη παρουσίασε αυξητική τάση στο σύνολο των ετών (18 έτη) από την ομάδα των γυναικών με φυσιολογικούς κύκλους, προς την ομάδα με πρωτοπαθή αμηνόρροια και με στατιστικά σημαντική διαφορά όσον αφορά την ελάχιστη τιμή μεταξύ των ομάδων 1 και 4 (P<0,048). Τέλος, οι μέσες τιμές των FSH και LH μετά από διέγερση με GnRH εμφάνισαν την χαμηλότερη ανταπόκριση στην ομάδα της δευτεροπαθούς και πρωτοπαθούς αμηνόρροιας και με στατιστικά σημαντική διαφορά (P<0,010) για την LH και P<0,050 για την FSH.

Adolescence is a normal stage of human development, a period of transition between childhood and adulthood and it is considered to be a time of rapid physical, cognitive and emotional change. Several terms are commonly used to describe this particular stage of life. Puberty refers primarily to the process of maturing, hormone production and growth during which the reproductive organs begin to function and produce gonads. For girls, menarche occurs in this period of life.[1–5]

Amenorrhea is a symptom of menstrual disturbance and is usually due to an abnormality in the ovarian function during puberty or even later. The appearance of amenorrhea or absence of menstruation causes women to experience fear and anxiety, since they feel that they may never reach sexual maturity and have difficulty enjoying the normal physical and psychological pleasures of adolescence, or even of adult life later on.[3,5–7] The insufficient development of secondary sex characteristics in adolescents and the disruption of the normal menstrual cycle are among the most frequent endocrine malfunctions in women with β-thalassaemia.[3,8–13]

The continuously increasing percentage of amenorrhea among β-thalassaemia women has recently attracted the interest of various researchers.[14,15]

Blood iron levels in women with homozygous β-thalassaemia are considerably higher than in normal people. This is also true for female β-thalassaemia patients with amenorrhea or even normal menstrual cycle.[10]

Recent research has focused on developing a better understanding of the pathophysiology of patients with homozygous β-thalassaemia, who, in an attempt to maintain hemoglobin at normal levels, accept transfusions more frequently than patients with other conditions. However, this practice results in the accumulation of high iron levels in patients' blood and tissues.[14]

Cyprus is an island in the Mediterranean sea with a population of 744,000. Historically, thalassaemia major has been seen as a problem for Mediterranean populations and because of the gravity of the problem of β-thalassaemia in Cyprus, it has been officially recognized since 1972 thanks to a special introduction to this condition submitted to the World Health Organization[16] by Professor K.G. Stamatoyanopoulos in May 1972. Professor K.G. Stamatoyanopoulos went on to be one of the founders of the "Nicosia Center for Thalassaemia" in Cyprus in 1973.[9,16–19]

The measures taken by the "Nicosia Center for Thalassaemia" in Cyprus have contributed to the containment of the disease, as well as to the improvement of services provided to patients. In Cyprus today there are almost no new affected births.[10,20,21]

The purpose of this study is to examine frequency of menstruation in β-thalassaemia women referred to the "Nicosia Center for Thalassaemia" in Cyprus. As the "Nicosia Center for Thalassaemia" is the only specialized center on the island, the population studied includes almost the whole female β-thalassaemia population of the Republic of Cyprus.

The formulated hypothesis was the following: the menstrual cycle of β-thalassaemia women is related to the levels of ferritin and hemoglobin before transfusion, the level of deironization and the response of FSH/LH after stimulation with GnRH.

Material and method

Our subjects were 122 female β-thalassaemia cases from 15–48 years of age who had been referred to the "Nicosia Center for Thalassaemia" in Cyprus. The study is a retrospective one and covers the period from 1981 to 1999. The β-thalassaemia diagnosis for the women involved was based on clinical and laboratory examinations. We chose to evaluate the following data: sex, age, whether or not menstruation occurred and if so, how regularly. The evaluation of our subjects' menstrual cycle was carried out by using data selected from medical records and by interviewing the patients. Furthermore, we collected objective measurements pertaining to the calculation of ferritin, hemoglobin before blood transfusion, Folic Stimulating Hormone (FSH) and Luteinizing Hormone (LH) after stimulation with GnRH made during the period bet-

ween 1981 and June of 1999. The definitions of the terms menstruation, ferritin-hemoglobin, FSH-LSH and deironization are set out in the following:

Menstruation. The absence of menstruation as well as the frequency of menstruation were recorded and subjects were classified in the following categories: women with normal menstruation, women with areomenorrhea, women with secondary amenorrhea and finally women with primary amenorrhea.

Ferritin-Hemoglobin. All the tests measuring the Ferritin-Hemoglobin levels were carried out using the same method and the same type of analyzer for all women involved in this study and for the full period of time under examination.

FSH-LH. In order to measure FSH and LH, a dose of 100 μg iv GnRH was given to the patients and blood samples were taken every 30 min for two hours from the moment of injection with GnRH.

Deironization. Deironization was carried out by way of intramuscular and subcutaneous injection of desferal.

For the purpose of examining the modifications of the ferritin, hemoglobin and desferrioxamine levels that are the subject of the present research, the highest, the lowest and the average values of all measurements were selected for the period from 1981 to 1999.

The basic secretion of FSH and LH was calculated by selecting the highest value recorded in the 2 hours subsequent to effusion of GnRH.

The sample of patients was divided into groups in order to examine the hypothesis of the study. The type of menstrual disturbances determined the division of the sample into four groups of women with normal menstruation, areomenorrhea and secondary and primary amenorrhea respectively.

Statistical analysis

The statistical analysis of the data covered two phases. During the first stage, mean rates, minor and major rates, standard deviation, other percentage rates and simple frequencies were calculated. In the second stage intergroup comparisons were made using the chi-square test and the non-parametric Mann-Whitney U test. Data analyses were conducted using SPSS/PC+software ($P<0.005$ was considered to be the accepted level of significance).

Results

The sample population consisted of 122 women with β-thalassaemia aged 15–48, the mean age being 27.52 and the SD:6.74 (tabl. 1).

The majority of the women were between 20 and 40 years of age. The question as to whether or not menstruation occured showed that 42 women (34.1%) in the study had normal periods, 13 (11.4%) areomenorrhea, 38 (30.7%) secondary amenorrhea and 29 (23.6%) primary amenorrhea (tabl. 2).

Table 1. The distribution of the sample according to age.

Age	Number of patients	%
17	1	0.8
19	3	2.5
20	8	6.6
21	3	2.5
22	8	6.6
23	12	9.8
24	13	10.7
25	9	7.4
26	5	4.1
27	9	7.4
28	7	5.7
29	6	4.9
30	5	4.1
31	1	0.8
32	3	2.5
33	6	4.9
34	1	0.8
35	7	5.7
37	3	2.5
38	1	0.8
39	1	0.8
40	1	0.8
42	2	1.6
44	1	0.8
45	1	0.8
47	2	1.6
48	1	0.8
Total	122	100.0

The mean age at the time of the subjects' first period was 13.4 years (SD:1.08) for the women with a normal menstrual cycle and 14.34 years (SD:1.46) for women with secondary amenorrhea.

The mean duration of the time span, from their first period until menopause for women with a normal cycle, was 14.62 years and for women with secondary amenorrhea 6.94 years.

The average age at the commencement of amenorrhea for the group with secondary amenorrhea was 21.2 years (SD:7.12). The mean value of frequency of deironization for women with a normal cycle was 160, 169 for those with areomenorrhea, 150 for those with

Table 2. The distribution of the subjects according to the menstruation disturbances.

Menstruation disturbances	n	%
Normal period	42	34.1
Areomenorrhea	13	11.4
Secondary amenorrhea	38	30.9
Primary amenorrhea	29	23.6
Total	122	100.0

secondary amenorrhea and 157 for those with primary amenorrhea.

The mean values of lower, middle and higher ferritin levels appeared to be higher (tabl. 3) in women with normal cycle by comparison to women with secondary and primary amenorrhea, but no statistically significant difference for most of the values was found.

However, a statistically significant difference was found ($P<0.048$) with reference to the mean value of the minor mean values of ferritin levels between the group of women with normal cycle and the primary amenorrhea group (fig. 1).

Mean hemoglobin values for all groups varied from 8.5 g/dL to 11.5 g/dL with no statistically significant difference.

Mean FSH and LH values after stimulation with GnRH were found to be clearly lower for women with secondary and primary amenorrhea and displayed a statistically significant difference ($P<0.1$ for LH and $P<0.05$ for FSH).

Table 3. Means, minimum, maximum level, standard deviation and range of the ferritin levels among the patients groups.

Menstrual cycle	**Ferritin µg/L**	**Ferritin µg/L**	**Ferritin µg/L**
Normal period			
Mean	3839.2264	2371.6281	1107.3002
N	42	42	42
SD	1846.0462	1267.7175	752.7638
Min	343.60	249.09	60.38
Max	7047.52	5469.35	2930.62
Range	6703.92	5220.26	2869.62
Areomenorrhea			
Mean	3966.7311	2309.3892	1146.8807
N	14	14	14
SD	1947.1404	1104.2990	734.6242
Min	1069.00	615.48	61.50
Max	8552.40	4335.78	2137.20
Range	7483.40	3720.30	2075.70
Secondary amenorrhea			
Mean	4507.7975	2749.3348	1471.9831
N	38	38	38
SD	2735.3060	1588.4828	875.5672
Min	1786.60	608.50	65.40
Max	15508.90	8630.93	4375.60
Range	13722.30	8022.43	4310.20
Primary amenorrhea			
Mean	4677.3030	2820.3774	1524.4720
N	28	28	28
SD	1754.7200	1201.9181	1042.058
Min	1511.50	923.12	104.90
Max	9614.60	6490.43	4464.30
Range	8103.10	5567.31	4359.40
Total			
Mean	4254.4470	2585.1239	1321.1763
N	122	122	122
SD	2160.5424	1347.3677	873.3891
Min	343.60	249.09	60.38
Max	15508.90	8630.93	4464.30
Range	16165.30	8381.84	4403.92

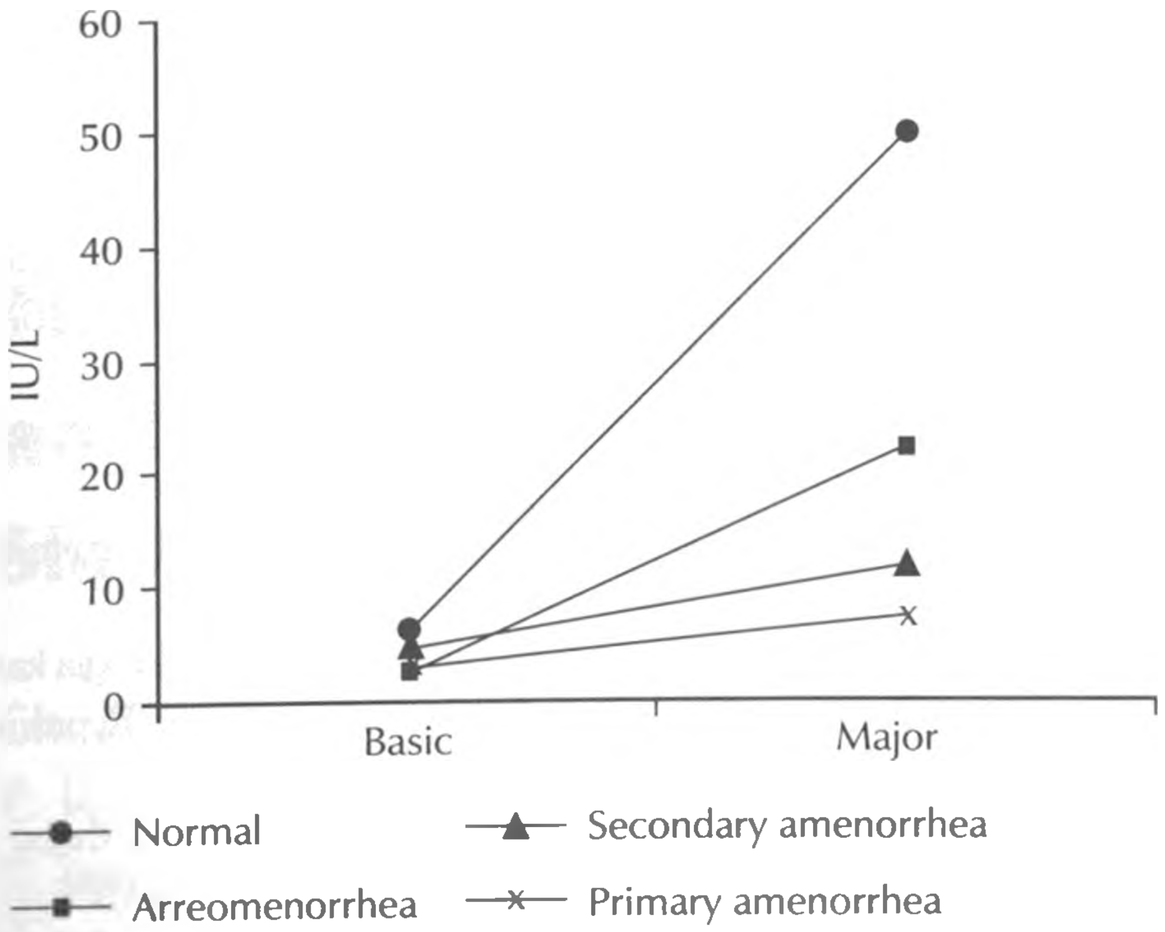

Figure 1. Basic secretion and major response of LH after stimulation with GnRH related to menstrual disturbances.

Discussion

Amenorrhea is one of the most frequent disruptions of the menstrual cycle in women with homozygous β-thalassaemia and the evaluation of amenorrhea as well as of the frequency of menstruation is a fundamental medical course of action that has a direct bearing on therapeutic treatment related to β-thalassaemia.

In the present study, the frequency of the menstrual cycle was evaluated in 122 female β-thalassaemia patients with normal menstrual cycle. The frequency of menstrual disturbances was correlated with several variables for the purpose of estimating the contribution of chronic iron deposition to the establishment of chronic amenorrhea. Special attention was paid to ferritin and hemoglobin levels before transfusion, the degree of deironization as well as to the reaction of FSH and LH after stimulation with GnRH.

Due to the low survival rates of β-thalassaemia women, no prevalence studies were published until 1980. However, in more recent studies (after 1980) it has been reported that 40% of β-thalassaemia patients showed disturbances of the hypothalamus-hypophysis-gonads axis and 42.9% of women with β-thalassaemia developed secondary amenorrhea 1 month to 15 years after menarche (mean=3.8 years).[10 11 14 15]

Our analysis of the findings of the present study shows that the "Nicosia Center for Thalassaemia" in Cyprus had treated a great deal of women (122) with homozygous β-thalassaemia, aged 15–48 (mean age: 27.52) and that 85% of these women are between 20 and 40 years of age. This increase in mean age is related to the systematic treatment of our subjects as a result of the foundation of the center in 1974 and its introduction of a compulsory weekly deironization program. The Ferrara group has published findings similar to those of our study.[10]

Table 2 shows that for 34.1% of women with normal menstruation and for secondary amenorrhoic women, the mean duration of menstruation appeared to be higher than in other studies.[22]

The mean values of deironization frequency do not point to a statistically significant difference between the individual groups. This finding can be linked to the increase of the duration of menstruation for the group with secondary amenorrhea, as has also been reported in earlier studies.[7,10,11,22–24]

The mean value of the highest, middle and lowest ferritin values among these two groups displays a stable domination of the highest ferritin values in women with secondary amenorrhea, with no statistically significant difference except for the lowest value among women with normal menstruation and women with primary amenorrhea. This finding is similar to the results reported in earlier research[7,23–26] and corroborates the finding that chronic deposition of iron causes irreversible damage. As to FSH and LH, the result was almost as we expected, i.e. women with amenorrhea showed the clearer response in comparison to women with normal menstruation. These results consolidate our view that chronically high iron levels provoke damage to the cells of the pituitary that produce FSH and LH, [10,11,23,25–27] since women with secondary and primary amenorrhea have the highest ferritin levels and have a lower frequency of deironization.

In conclusion, the results of the present study revealed an increase of mean age in women with β-thalassaemia. The majority of the women involved had a normal menstrual cycle and we observed an increase of the mean duration of menstruation in women with secondary amenorrhea.

It seems that the optimization of these parameters is related to the degree of deironization, which does not show any statistically significant difference between the groups, the hemoglobin levels being at the same levels as ferritin. They showed no statistically significant difference between groups, but there was a steady domination of high values for about two decades. In the groups with primary and secondary amenorrhea there is room for speculation. Would we have more favorable findings if ferritin levels had been maintained at a lower level?

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