

Role of Hormones, Body Mass Index & Fasting Blood Glucose Levels in Amenorrhea Cases

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ABSTRACT

Introduction: Absence of menstruation is termed as amenorrhea prevalence of primary amenorrhea in India is higher when compared with worldwide prevalence with a potential social impact and due to higher prevalence of amenorrhea in Indian society; extensive evaluation is required to overcome the anxiety.

Aims: 1) To identify the average age of attainment of menarche in secondary amenorrhea. 2) To evaluate role of body mass index in the regulation of menstrual cycles. 3) To estimate serum hormonal levels in subjects of primary and secondary amenorrhea and their variation with that of control group. 4) To estimate fasting blood glucose levels and its correlation with amenorrhea in comparison with control group.

Materials and Methods: This study was performed on 200 women volunteers with detail history, parameters like body mass index (BMI), hormonal levels and fasting blood glucose (FBG) were estimated.

Results: Based on diagnosis the study group number of Primary amenorrhea (PA) (n=8), Secondary amenorrhea with unknown etiology (SA) (n=6), Polycystic ovarian disease (PCOD) (n=82) and Premature ovarian failure (POF) (n=4). The mean value of FSH among cases was 12.78 ± 20.6 mIU/ml and the mean value of FSH among controls was 5.31 ± 3.43 mIU/ml. The mean values of LH among cases and controls were 6.58 ± 4.40 mIU/ml and 4.67 ± 3.11 mIU/ml respectively. The value of ratio of FSH:LH was more than 2 in 29% of the cases and among 7% of the controls. The mean value of FBG levels in cases was 96.04 ± 18.56 , and in controls was 84.05 ± 7.03 .

Conclusion: In present study obesity has a direct effect on the menstrual cycle of the women leading to amenorrhea. The levels LH and FSH were above the normal limits in women with primary amenorrhea in our study and the ratio between the hormones was also high. FBG levels were found to be very high among amenorrhea patients when compared with controls this proves prevalence of high insulin resistance among females with menstrual irregularities

Key Words: Amenorrhea, Follicular Stimulating Hormone (FSH), Luteinizing hormone (LH), Thyroid stimulating hormone (TSH), Body mass index (BMI), Fasting blood glucose levels (FBG)

INTRODUCTION

In normal healthy women, menarche occurs between 10-16 years of age, mean age of menarche being around 12.5 years. [1]

Variations do occur in the normal menstrual cycle either as missed cycle, during

pregnancy, lactation, sports, duration and volume of bleed, extended cycle, with or without pain. Absence of menstruation is termed as amenorrhea. When there is no menstruation at all from the onset of reproductive period it is termed as primary

amenorrhea and when there is onset of menarche followed by cessation of menstruation is termed as secondary amenorrhea which can occur due to a number of anatomical, physiological and pathological factors.

The prevalence of primary amenorrhea in India is 11.1%, [2] which is higher when compared with worldwide prevalence that is 3% [3] with a potential social impact and higher prevalence of amenorrhea in Indian society, extensive evaluation is required to overcome the anxiety.

Hormones play a very important role in attaining puberty. The hypothalamic-pituitary development is the onset of positive feedback, leading to ovulation and menarche. According to the world health report life in the 21st Century, Obesity has been one of the most important contributors to ill health. [4] Type 1 diabetes mellitus in younger females increases the incidence of infertility which leads to reproductive disturbances effecting somatic growth, mental health. These women were at higher hazard of having menstrual disturbances, such as amenorrhea and oligomenorrhea and delay in attaining menarche. [5-8] Loss of weight occurs during diabetes which further reduces body fat proportion (low BMI). Abnormal decrease in lipids results in the impairment of transformation of androgens to estrogen. Estrogen hormonal level plays an important role in development of ovary and menarche. This condition leads to disruption of hypothalamo-pituitary-gonadal axis. [9-11] Normal level of blood glucose levels was considered as one of the important factor to attain menarche and for normal menstruation. [12,13]

As amenorrhea is one of the reasons for infertility and with a larger social impact of this in our part of the world, amenorrhea, primary or secondary has to be evaluated by all means to provide an idea for underlying pathology. In present study hormonal assay, body mass index and fasting blood glucose levels were analyzed and compared with the values of control samples and other

associated parameters of amenorrhea and to explore the multi factorial causes of amenorrhea, thereby providing an insight for the treatment.

MATERIALS AND METHODS

This study was performed on 200 women volunteers after taking an informed consent. The volunteers were outpatients attending the OPD of Vinayaka Missions Medical College Hospital, Salem. Tamilnadu, India. Ethical clearance and approval for the study was obtained from Institutional Ethics Committee and Institutional Review Board of Vinayaka Missions Medical College.

In the study group women aged between- 17 to 40 years with primary amenorrhea due to non-attainment of menarche, with secondary amenorrhea due to endocrinopathies, anatomic defects of the genital tract, Polycystic ovarian syndrome, hypothalamic/pituitary causes, Premature ovarian failure and Chronic oligomenorrhea or anovulation were included. In control group women aged between 17 to 40 years, with history of regular menstrual cycles, with normal serum hormonal levels were included.

Females aged below 17 and above 40, pregnant and lactating, undergoing any treatment with medication or drugs effecting menstrual cycle were excluded from the study. Age of attainment of menarche was also noted from study and control groups.

Estimation of Body Mass Index: The body mass index (BMI) is a measure of relative weight based on an individual's mass and height. It is a simple index to classify obesity of an individual. The Body mass index was calculated using the formula: weight in Kilograms/square of height in meters. Based on Asia-Pacific criteria of Body mass index for obesity subjects were divided into four groups. [14] Group 1 (under weight): < of 18.0 kg/m²; Group 2 (normal weight): Between 18.1 and 22.9 kg/m²; Group 3 (over weight): Between 23.0 and 24.9 kg/m²; Group 4 (obesity): >25 kg/m²

Estimation of serum hormonal levels:

Sample collection: Around 3ml of peripheral blood was collected in a sterile clot activating vacutainers with aseptic precautions. The serum was alienated from the blood using clot activating tube. AIA-360 Automated Immunoassay Analyzer manufactured from Tosoh-X (Fig-15) was used to analyze serum FSH, serum LH, serum Prolactin and serum Thyroid stimulating hormones with fully automated analyzer and kit methods.

Estimation of Fasting blood glucose levels: Fasting blood glucose levels were analyzed using 1ml of blood with Bio system serum-glucose analyzer.

Diagnosing primary and secondary amenorrhea was carried out with the help of detailed history, physical examination and laboratory testing. Cytogenetic analysis was also performed to know chromosomal aberrations.

RESULTS

In present study out of 200 participants, 100 subjects were grouped as study group and 100 were included under control group. Based on diagnosis the study group was subdivided in to following groups.

- 1) Primary amenorrhea (PA) (n=8), 2) Secondary amenorrhea with unknown etiology (SA) (n=6), 3) Polycystic ovarian disease (PCOD) (n=82) 4) Premature ovarian failure (POF) (n=4)

Age of attaining menarche: In this study out of 100 study subjects, eight cases with primary amenorrhea were not included due

to non-attainment of menarche. Around 56.5% of the cases the age of menarche were between 12 – 13 years and the mean age of attaining menarche among these cases was 12.57 years. Around 69% of the controls had attained menarche between the age of 11-12 years and mean age of attaining menarche among control group was 12.15 years.

Body Mass Index (BMI): In the present study the distribution of BMI among study and control groups is illustrated in Table 1 and 2

Hormones: Hormones which were considered in the present study are Follicle stimulating hormone (FSH), Luteinizing hormone (LH), Prolactin (Prl), Thyroid stimulating hormone (TSH). In the present study the mean value of “FSH” among cases was 12.78 ± 20.6 mIU/ml and the mean value of “FSH” among controls was 5.31 ± 3.43 mIU/ml. The mean values of “LH” among cases and controls were 6.58 ± 4.40 mIU/ml and 4.67 ± 3.11 mIU/ml respectively. The value of ratio of “FSH:LH” was more than 2 in 29% of the cases and among 7% of the controls. The mean value of TSH level was found to be $3.89 \mu\text{g/L}$ among study cases and $4.72 \mu\text{g/L}$ among controls. The P value by applying ‘paired t test’ for FSH-0.0004, LH- 0.0004, Prl- 0.00001, TSH-0.0595, ratio of FSH&LH-0.0159. The ANOVA analysis of the hormonal levels among the study cases with different diagnosis is shown in Table 3 Fasting blood glucose levels (FBG): Distribution of FBG among study and control groups are shown in Table 4.

Table 1: Distribution of BMI in the study group

BMI (Kg/m ²)	Number	Percentage	Mean (kg/m ²)±SD	95% CI
<18.0	2	2	26.1 ± 3.47	25.42 – 26.78
18.1 – 22.9	11	11		
23 – 24.9	29	29		
≥25	58	58		
Total	100	100		

SD- Standard deviation, CI- Confidence interval

Table 2: Distribution of BMI among the controls

BMI (Kg/m ²)	Number	Percentage	Mean	SD	95% CI
<18.5	6	6	20.88	±1.18	20.65 – 21.11
18.1 – 22.9	94	94			
23 – 24.9	0	0			
≥25	0	0			
Total	100	100			

SD- Standard deviation, CI- Confidence interval

Table 3: ANOVA analyses of the hormonal levels among the study cases

Hormones	STUDY CASES				P value (by applying ANOVA)
	PA MEAN±SD	PCOD MEAN±SD	SA MEAN±SD	POF MEAN±SD	
LH(mIU/ml)	71.95±38.35	5.75±3.55	7.71±5.74	8.95±7.45	<.0001(HS)
FSH(mIU/ml)	13.1±4.46	7.21±3.32	12.3±5.84	9.25±4.26	0.0356(S)
Prl(ng/ml)	20.52±13.15	16.31±8.87	11.63±8.41	16.6±5.08	<.0001(HS)
TSH(µg/L)	5.14±3.55	3.92±3.27	2.64±1.81	2.62±1.64	<.0001(HS)
FSH/LH	2.83±3.03	1.54±1.05	1.96±1.33	1.50±1.35	0.0418(S)

PA- Primary amenorrhea, PCOD- Polycystic ovarian disease, SA-Secondary amenorrhea, POF-Premature ovarian failure, LH- Luteinizing hormone, FSH-Follicle stimulating

Table 4: Comparison of blood glucose levels among the cases and controls

FBG(mg/dl)	Cases		Controls		P value (by applying unpaired T test)
	Number	Mean±SD	Number	Mean±SD	
<80	15	96.04±18.56	40	84.05±7.03	<.0001(HS)
80 – 100	61		60		
101 – 120	19		0		
>120	5		0		
Total	100	100			

FBG- Fasting blood glucose levels, SD-Standard deviation, HS- Highly significant

Table 5: Comparison of BMI among the study cases and controls

BMI (Kg/m ²)	Number		P value (by applying unpaired T test)
	Cases	Controls	
<18.5	2	6	<.00001(HS)
18.1 – 22.9	11	94	
23 – 24.9	29	0	
≥25	58	0	
Total	100	100	

BMI- Body mass index, HS- Highly significant
Hormone, Prl- Prolactin, TSH- Thyroid stimulating hormone, HS- Highly significant, S-Significant

DISCUSSION

Age of attaining menarche: In normal healthy women, menarche occurs between the ages 10-16 years, mean age of menarche is around 12.5 years. [1] Distribution of age attaining menarche is shown a marginal variation in the distribution of age of attaining menarche between test and control groups. This study shows that there is no significant deviation of age attaining puberty from literature

Body Mass Index (BMI): In the present study in study group 58% of individuals were obese with BMI of more than 25 and the mean BMI of study group was 26.1. In control group 94% had the BMI between 18.1 – 22.9 kg/m² and the mean BMI of control group was 20.88kg/m². In the present study 58% of amenorrhea cases had a BMI equal to or more than 25 Kg/m² and none of the control group individuals were obese. This implies obesity has a major role in regulation of hormonal levels and there by menstrual cycle.

Higher body mass index is major risk factor causing long term complications

like cardio vascular diseases, diabetes due to insulin resistance. [15,16] In a study among Japanese women the frequency of obesity was 9–13% among women with a normal menstrual cycle, whereas it reached 45% among those with menstrual disorders. [17]

In women with co-morbid conditions like polycystic ovarian syndrome, many menstrual cycles are anovulatory due to increase in the BMI. Reduction of weight leads to reduced BMI. This reduction in weight can be done by increasing physical exercises and obesity treatment. The fertility rates improved in the affected persons who had undergone such therapy. [18]

Several studies reported that regulation of body mass index among infertile female patients showed better results in gaining regular menstrual cycles. The result of the comparison of body mass index among the cases and controls of the present study is shown in Table 5. The cases had higher body mass index when compared to the controls and this difference was found to be statistically significant (p<.00001).

In the present study the sample size of primary amenorrhea cases was eight. Out of these eight primary amenorrhea cases three were with Turner’s syndrome. Among these three cases two cases were having body mass index less than 18.0Kg/m² and in one case BMI was 18.5Kg/m².The mean value of body mass index among primary amenorrhea cases was 20.76.This explains that underweight was associated with

Turner's syndrome.

Hormones: The levels of FSH and LH were considered as markers in diagnosing the condition associated with amenorrhea. Increased levels of FSH and LH have been found to be associated with gonadal failure with a normal chromosomal complement. [19] Hypogonadotropic amenorrhea occurs due to decrease of serum FSH and LH levels, resulting in constitutional delay of growth and puberty. [20,21]

The serum FSH and LH levels remain normal in anatomical defects causing obstruction of vaginal tract and hyper androgenic chronic anovulation resulting normogonadotropic amenorrhea. Vaginal obstruction is the most common etiology in Asherman's syndrome which is characterized by secondary amenorrhea with intra uterine synechia and infection. [22]

In the present study the mean value of FSH among cases was 12.78 ± 20.6 mIU/ml which was high when compared with the mean value of FSH among controls which was 5.31 ± 3.43 mIU/ml. Levels of FSH exhibited a highly significant difference between cases and controls with a p value of 0.0004. The levels of LH were also significantly high. The mean values of LH among cases and controls were 6.58 ± 4.40 mIU/ml and 4.67 ± 3.11 mIU/ml respectively and result of paired t-test showed p value of 0.0004 which was highly significant.

Hyperprolactinemia is also an etiological factor of secondary amenorrhea. [23] In the present study the Prolactin levels in all samples which include both the test samples as well as control samples were within normal limits which mean the values were less than 20 ng/ml during follicular phase of menstrual cycle and less than 40 ng/ml during luteal phase of menstrual cycle. [24] This statement explains that in the present study none of the cases were with hyperprolactinemia. But, the mean values show marked difference between test and control groups.

Thyroid stimulating hormone (TSH) is produced by the pituitary gland. The level

of TSH is of help in diagnosis of thyroid dysfunction. The prevalence of thyroid dysfunction is more common in females than males. Amenorrhea can occur due to hypothyroidism and hyperthyroidism has reported the occurrence of amenorrhea in 20% to 70% of the cases due to hypothyroidism. [25,26]

The hypothyroidism and hyper prolactinemia were often associated with each other as TSH-releasing hormone stimulates the pituitary gland to secrete more TSH and Prolactin. Thus prolactin level increases along with TSH levels. Amenorrhea may also be associated with hyperthyroidism but the mechanism is unclear. [27] In the present study there was no significant difference in TSH levels between cases and controls. The association between TSH and Prolactin levels was also not statistically significant.

The intra group comparison of the hormonal levels (Fig 1) was done through ANOVA among the cases and it was found that the LH, FSH and FSH/LH ratio were comparatively higher among the patients with primary amenorrhea than that of the patients with polycystic ovarian syndrome, secondary amenorrhea and premature ovarian failure and the difference was statistically significant ($p < .05$).

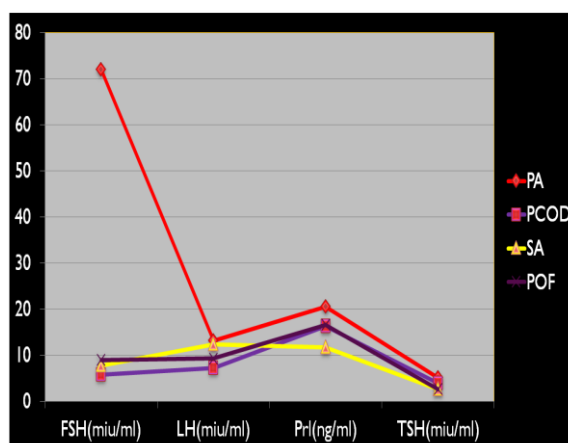


Figure 1: Hormonal levels among the cases

Fasting blood glucose levels (FBG): In the present study the FBG level of the cases were comparatively higher than that of the controls and the difference was found to be statistically significant ($p < .0001$). The FBG

levels were more than 100 mg/dl in 24% of the study cases which proves that these were already diabetic. Comparison of FBG levels among study and control groups was shown in Fig-2.

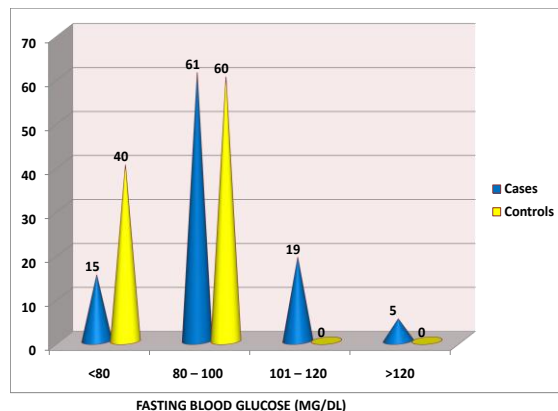


Figure 2: Fasting Blood glucose levels among the cases and controls

In a study around 45% of the subjects with PCOD showed insulin resistance. This implies majority of the women with menstrual disturbances exhibits high glucose levels which indicates insulin resistance, diabetes related condition. [28] In the present study the mean of FBG levels of the cases was 98.04 mg/dl which was very high than the mean value of the control group 84.05 mg/dl. Thus most of the women with PCOD should have a regular FBG test, glucose tolerance test, as high serum glucose indicates insulin resistance which may interfere with menstrual cycles leading to infertility.

CONCLUSION

Age of attainment of menarche was not statistically significant in the present study. But, there was a marginal difference between study and control groups. This study shows that there is no significant deviation of age attaining puberty from literature.

Body Mass Index: In our study the body mass index in women with polycystic ovarian syndrome was very high when compared with similar studies of the same nature. Obesity has a direct effect on the menstrual cycle of the women leading to amenorrhea. Effort should be made to

counsel the affected women regarding the effect of obesity on their reproductive ability.

Hormones: The levels of Luteinizing hormone and Follicle stimulating hormone were above the normal limits in women with primary amenorrhea in our study and the ratio between the hormones was also high. So estimation of the aforesaid hormones should be made mandatory while investigating cases of primary amenorrhea. Fasting blood glucose levels were found to be very high among amenorrhea patients when compared with controls this proves prevalence of high insulin resistance among females with menstrual irregularities. Regulation of normal blood glucose levels may regularize menstrual cycles.

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