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Inhibin B as a Marker for Detection of Ovarian Activity in Premature Ovarian Failure

Maysoon Sharief*, Dhamya Salih Alharoon and Hutham Tariq Mohammed

Department of Gynecology and Obstetrics, College of Medicine, University of Basrah, Basrah Health Directorate, Basrah, Iraq

***Corresponding author:** Maysoon Sharief, Department of Gynecology and Obstetrics, College of Medicine, University of Basrah, Basrah Health Directorate, Basrah, Iraq, Tel: 964 40 219375, E-mail: maysoonsharief60@yahoo.com

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Abstract

Objective: To evaluate Inhibin B in women with premature ovarian failure POF and its role as a marker for ovarian reserve in comparison to FSH.

Methodology: This study was conducted in the infertility center in Basra Maternity and Child Hospital. About 75 women were divided into 3 groups, each of 25 women, group (A) with premature ovarian failure, Group (B) menopause women and group (C) normally fertile cycling women. Inhibin B and FSH were measured and comparison were made between the three groups, then Inhibin B and FSH level were studied in group (A) before and after (4-6 months) of hormonal replacement therapy.

Results: The mean FSH was (81.4 ± 28.4 IU/ml) in group A, (97.7 ± 25.5 IU/ml) in group B and (4.87 ± 2.3 IU/ml) in group C. Inhibin B was (1.8 ± 2.8 pg/ml) in group A, (1 ± 0.9 pg/ml) in group B and (53.1 ± 17.1 pg/ml) in group C. After hormonal replacement therapy in group A, mean FSH was (56.3 ± 13.4 IU/ml) and mean Inhibin B was (1.4 ± 12.4 pg/ml). There was significant decrease in FSH level but no significant changes in Inhibin B among group A women.

Conclusion: Inhibin B level in women with premature ovarian failure is so low when compared to normal cycling women and close to the levels in the menopause women, it was not affected by exogenous estrogen intake as seen with FSH. Because it's main source in the female body is the preantral follicles, all this indicates Inhibin B is a good marker for ovarian reserve in women with premature ovarian failure.

Keywords: Inhibin B; Premature ovarian failure; Menopause; Chemotherapy

Introduction

Premature ovarian failure (POF) is defined as ovarian defect characterized by premature depletion of ovarian follicles (arrested folliculogenesis) before the age of 40 years [1-3]. The end of a woman`s reproductive lifespan is marked by the beginning of menopause, which is defined as the last menstruation the woman had, which is caused by the depletion in the ovarian reserve [4,5]. In the general population and in many ethnicities in the recent human history the average age of natural menopause was not changed and remained at 50-52 years [6,7]. Premature ovarian failure considered a common condition as it affects 1% of all women under the age of 40 years, and 0.1% in women aged less than 30 years [8]. The causes of (POF) include idiopathic, genetic, autoimmune, latrogenic, toxins and occupational chemicals and infections [9-16]. Most of women with (POF) present with menstrual irregularity, 10% with amenorrhea. Additionally, affected women have very low levels of circulation estradiol. So clinical symptoms observed are similar to those observed with the onset of menopause, such as hot flushes, vaginal dryness, dyspareunia, insomnia, vaginitis and mood swings [17]. Inhibin is a protein secreted by granulosa (female) and Sertoli (male) cells in response to FSH [18]. It is found in blood, and in great quantities in seminal fluid and follicular fluid. Gonadal inhibin is the main peptide hormone that regulates FSH synthesis and secretion during folliculogenisis and spermatogenesis, the main role of inhibin is to selectively suppress the production of FSH by the pituitary.

Inhibin enhances LH stimulation of androgen synthesis in the theca cells to serve as substrate for aromatization to estrogen in the granulosa cells, whereas activin suppresses androgen synthesis. This important paracrine regulation of androgen as substrate for aromatization to estrogen in the granulosa cells, whereas activin production in thecal cells by inhibin and activin is exerted primarily through modification of the expression of steroidogenic enzymes [19]. The anterior pituitary gland secretes FSH and LH from a specialized cells call the gonadotrops, GnRH from the hypothalamus, testosterone from the testes in male and estradiol, progesterone from the ovaries in female as well as gonadal inhibin, activin and follistatin regulate the synthesis and secretion of gonadotropins from the pituitary gland [19]. FSH stimulates the sertoli cells in testes and the granulosa cells in ovary to produce inhibin. In females, the granulose cells of the ovary produce inhibin, and inhibin production by each follicle increases as the granulosa cell population expands during normal follicle growth and maturation [20,21]. Due to the postnatal activation of the gonadotropin secretion, Inhibin B level is sustained till 18-24 months. Then serum Inhibin B has a positive relationship with age. several years prior to the onset of puberty due to the increase in the follicular activity in the pre-puberty phase, after that Inhibin B levels increase progressively with the stages of puberty indicating high follicular activity prior to the development of ovulatory menstrual cycle [22].

During the follicular phase of menstrual cycle the major form of Inhibin secreted from the ovary is Inhibin B in which it rises sharply in early follicular phase with the peak following the FSH rise and then progressively fall during the rest of the follicular phase, another peak is on day 2 mid cycle LH peak then a rapid decline and constant low levels during the luteal phase [22].

Material and Methods

This study was conducted in the infertility center at Basra Maternity and Child Hospital during a period from October 2015 till September 2016. Written consent was taken from all women who participated in this study. The participants in this study were divided in to 3 groups.

Group A: About 25 women with premature ovarian failure POF, with age less than 40 years, amenorrhea more than 6 months, no history of medical diseases like diabetes mellitus, hypertension, thyroid disorder, no exogenous estrogen intake in the preceding 3 months, no history of chemotherapy, with serum FSH more than 40 IU/ml.

Group B: About 25 menopausal women aged more than 45 years with amenorrhea more than one year, with no history of medical diseases like diabetes mellitus or thyroid disorder, no hormonal replacement therapy, and serum FSH levels 6 months apart more than 40 IU/ml.

Group C: About 25 normal women were proven fertile with regular menstrual cycle, with no history of hormonal contraception since one year.

All participating women were interviewed in detail for medical, surgical and treatment (especially cytotoxic chemotherapy and exogenous estrogen) history and thorough physical examination was done for exclusion of any gross underlying disease. No one of the participants had any history of auto immune disease or radiotherapy or chemotherapy treatment or history of surgical removal of gonads. Blood samples from group C (normally fertile women) were taken at day 3 of menstrual cycle, blood samples from group A (women with POF) and group B (menopause women) were taken randomly and FSH and Inhibin B levels were measured in all 3 groups.

Participant in group A (women with POF) started oral hormonal replacement therapy. They were given estrogens and Progestogen in the form of tablet Proglyuton (estradiol valerate 2 mg, Norgestrel 0.5 mg) once daily for at least 12 weeks then blood samples were collected and serum FSH and Inhibin B were measured. Serum was collected after centrifugation and stored at -80°C until assayed. Serum concentration of FSH was measured by using highly specific micro particle enzyme assay (MILA). Inhibin B was measured in duplicate using a solid phase sandwich ELISA (Oxford Bio-Innovation, Oxford, UK). Data were analyzed using SPSS statistical software. Descriptive statistics are given as the Mean and SD, independent sample t-test was used to see the mean significance difference between groups.

Results

In this study, 75 women were included who were divided into 3 groups as mentioned in the methodology. Table 1 shows the characteristic features of all 3 groups regarding age, BMI and menstrual cycle. The mean (± SD) age of group A (women with POF) was (30.16 ± 5.05 years) with a range of (19-39 years), while group B (menopaused women) with mean age of (48.04 ± 1.6 years) with a range of (45-50 years), and the last group C (normal menstruating women) its mean was (29.33 ± 4.9 years) with a range of (21-40 years). Age differences were not significant between group A and C. No statistical significance regarding the age of menarche between the three groups. But, there was significant difference between the three groups especially A, C and B, C regarding BMI. And a significance difference between the three groups especially A, C and A, B regarding the duration of amenorrhea.

Baseline Characteristics	Group A	Group B	Group C	P-value (A/B)	P-value (B/C)	P value (A/C)
Age Mean (years) ± SD	30.16 ± 50.05	48.04 ± 1.6	29.33 ± 4.9	<0.0001	<0.0001	0.017
(Range)	(19-39)	(45-50)	(21-40)	Significant	Significant	No Significance
BMI Mean (kg/m^2) ± SD	26.1 ± 2.3	27.4 ± 2.4	23.6 ± 1.5	0.73	<0.0001	<0.0001
(Range)	(24-30)	(23-30)	(22-26)	No Significance	Significant	Significant
Age of Menarche (Years)	14.2	13.1	13.4	0.024	0.042	0.029
(Range)	(12-15)	(12-15)	(12-15)	No Significance	No Significance	No Significance
Duration of Amenorrhea						
Last mense <35 days	0	0	23			
Last Mense 35-120 days	3	0	2			
Last mense >120 days	22	25	0			

Table 1: The base line characteristics of the entire studied group.

A Table 2 shows the mean (± SD) of the plasma levels of FSH and Inhibin B in all the three groups, the mean FSH level in group A was (81.4 ± 28.4 IU/ml) and ranged (37-150 IU/ml), in group B the mean level of FSH was (97.7 ± 25.5 IU/ml) with a range of (65-150 IU/ml), and the last group C the mean FSH level was (5.87 ± 2.3 IU/ml) with a range of (3.2-12 IU/ml). Plasma level of FSH was elevated in group A, B in contrast to group C, which was highly significant.

Mean Inhibin B level in group A was (1.8 ± 2.8 pg/ml) with a range of (0-15 pg/ml), Inhibin B level in group B was (1 ± 0.9 pg/ml) with a

range of (0-4 pg/ml), while in group C the mean Inhibin B was (53 ± 17.1 pg/ml) and a range of (30-80 pg/ml).

This table showed that serum Inhibin B level was high in group C in comparison to group A and B which is statistically significant.

Parameter	Group A	Group B	Group C	Significance P-value
FSH mean ± SD (IU/ml)	81.4 ± 28.4	97.7 ± 25.5	4.87 ± 2.3	(A/B) 0.065
Range	(37-150)	(65-150)	(4.2-12)	(A/C)<0.0001
				(B/C)<0.0001
Inhibin B Mean ± SD (pg/ml)	1.8 ± 2.8	1 ± 0.9	53.1 ± 17.1	(A/B) 0.19
Range	(0-15)	(0-4)	(30-80)	(A/C)<0.0001
				(B/C)<0.0001

Table 2: Relationship between FSH and Inhibin B in all three groups.

Table 3 shows the relationship between Inhibin B levels with different levels of serum FSH in group A (women with POF), the higher level of Inhibin B was ≤ 15 pg/ml in 23 cases with FSH level >40 IU/ml, and two cases with FSH level between 13 and 39 IU/ml. The table presents a reverse relationship between Inhibin B level and FSH level.

Inhibin Level	FSH >40 IU/ml	FSH 13-39 IU/ml	FSH <12 IU/ml	Total
Inhibin <15 pg/ml	23	2	0	25
Inhibin 16-25 pg/ml	0	0	0	0
Inhibin >25 pg/ml	0	0	0	0
Total	23	2#	0*	25

Table 3: The relationship between Inhibin B level with different levels of FSH in group A before treatment (n=25).

Table 4 shows the relationship between the level of Inhibin B and FSH level in women with POF after 4-6 months of hormone replacement therapy, there was a decline in FSH level in 17 cases from >40 IU/ml to <12 IU/ml, in contrast to an increase in the level of Inhibin B in one case only from <15 pg/ml to between (16-25 pg/ml).

Inhibin Level	FSH >40 IU/ml	FSH 13-39 IU/ml	FSH <12 IU/ml	Total
Inhibin <15 pg/ml	3	4	17	24
Inhibin 16-25 pg/ml	0	1	0	1
Inhibin >25 pg/ml	0	0	0	0
Total	3	5	17	25

Table 4: The relationship between FSH and Inhibin B after 4 to 6 months of treatment with hormonal replacement therapy (n=25).

Table 5 shows the levels of FSH and Inhibin B after hormonal replacement therapy in group A, in which the mean FSH was (17.16 ± 13.4 IU/ml) with a range of (15-69 IU/ml), mean Inhibin B was (1.8 ± 2.9 pg/ml) and a range of (0-16 pg/ml). There was a significant decrease in FSH (P ≤ 0.0001) while no significant change in Inhibin B.

Group	Inhibin B Mean ± SD Range (pg/ml)	FSH B Mean ± SD Range (IU/ml)
POF prior to treatment	1.8 ± 2.8 (0-15)	81.4 ± 28.4 (37-150)
POF after Treatment	1.8 ± 2.9 (0-16)	17.16 ± 13.4 (16-69)

Table 5: FSH and Inhibin B levels after HRT in group A.

Discussion

Premature ovarian failure is common condition and had led to increase the concern in general population because in the current society there is a trend towards delaying pregnancy to later life and this had led to increase the infertility issues related to old age. Also the use of hormonal contraception might conceal this condition until the woman decides to discontinue the hormonal contraception and get pregnant. Diagnosis usually delayed due to the wide variety of symptoms for patient with premature ovarian failure. Also, there are no predictive factors for idiopathic POF and for the largest portion of the causes. All these issues together with the health and emotional impact of being menopaused at young age urge the need for finding and researching markers for early detection and even prediction of the condition. The term ovarian reserve have been based on the remaining follicular pool that's left in the ovary, when the process of ovarian aging occur usually the first marker to decrease is the anti mullarian hormone (AMH) followed by a decline in Inhibin B levels and lastly increasing in the FSH all these with the decrease in the antral follicular count. Therefore, ovarian reserve can be screened by variety of tests as FSH, estradiol, ovarian volume, clomiphene challenge stress test or antral follicles count [23-26].

The clomiphene citrate challenge test (CCCT) is a an accepted test for evaluating ovarian reserve but it requires days and multiple blood samples to be collected, the gonadotropins analogue stimulation test is based on FSH, E2, LH before and after GnRh administration. This test is expensive, need multiple injections, multiple blood samples and with limited value. Another tests for ovarian reserve is ultrasound and antral follicular count, and ovarian biopsy [27,28]. Hence, the need for a direct and precise marker for measuring ovarian reserve that can distinguish between complete absence of germ cells in ovary and lesser abnormality in ova production. Inhibin B is produced by granulosa cells so it might be more accurate in this regard. Inhibin B can be used as a marker for ovarian aging as it decreases with increasing age due to the decrease in number of follicles. This study was conducted to find the rule of Inhibin B in the assessment of ovarian function in women with premature ovarian failure in comparison with FSH.

The increase in FSH in old women is well documented, and it is commonly used to measure the ovarian reserve. FSH values are above 40 IU/ml at two occasions 4-6 months apart is indicative for ovarian failure. In this study, all women in group A and B (POF and menopaused) had high FSH results above 40 IU/ml. In group A there was no case reached the normal threshold of Inhibin B 25 pg/ml which goes with Corson et al. [25] but disagreed with what is reported by Seifer et al. [29]. The explanation probable for this disco-ordination with Seifer et al. [29] is due to the assay methodology, because till now there are no international assay standards for Inhibin B [30]. We found undetectable levels of Inhibin B <15 pg/ml in both group A (POF) and group B (menopaused), whereas among group C all women were found to have above the detectable levels of Inhibin B (15 pg/ml). It has been clarify that there is cyclical variation of Inhibin B throughout the menstrual cycle; beside low day 3 serum Inhibin B concentration was predictive of poor response to ovulation induction [29].

Hofman et al. [30] correlates Inhibin B in 19 women with normal ovarian reserve and 15 women with abnormal clomiphene citrate challenge test, Inhibin B was low at day 3 in women with abnormal CCCT and was higher in women with normal reserve In addition there was a negative correlation between day 3 FSH and Inhibin B. In our study among group A there were undetectable Inhibin B levels and a negative correlation between FSH and Inhibin B. The hormonal patterns of POF patients also implicate Inhibin as being causative in the disease mechanism. A defect in Inhibin secretion has been reported in women with POF [31] and Inhibin concentrations were lower in women with ovarian failure during both ovulatory and anovulatory cycles compared with infertile women with normal ovulatory cycle [32]. It has also noted that women with impending POF had lower follicular and luteal phase Inhibin concentration [33].

In this study women age above 45 years had lower serum Inhibin B concentration in comparison with younger women this is an agreement with Klein et al. study [34] who found that women aged 40-45 years compared with younger women had lower serum Inhibin B concentration in the early follicular phase. Previous studies demonstrated that women with POF and amenorrhea for less than 3 months are more likely to ovulate than women with longer period of amenorrhea and these ovulatory cycles are associated with lower FSH levels, although they remain elevated compared with FSH levels in regularly cycling women [35].

In this study after 4-6 months of hormonal replacement therapy (HRT), there was an increase in Inhibin B levels in one case only in contrast to decline in serum FSH levels in 17 cases. The significant limitations of the FSH assay derives from exogenous oestrogen intake, the fluctuation in FSH level as commonly seen with exogenous estrogen intake which is frequent in ovarian failure following chemotherapy or radiotherapy may be reasonable [36] and may cause fluctuation in FSH level as well as resumption of ovulation. Furthermore, FSH is an indirect marker, its rises takes long time and mildly elevated FSH may be seen in women with reduces ovarian reserve. Recent years have witnessed Inhibin B as a predictor of ovarian reserve, it is produced mainly in granulosa cells and it's undetectable in menopaused women [37]. Approximately, 40% of premenopausal women starting 2 years before final menstruation have undetectable Inhibin B level [38].

A study was done by Halder A et al. [39] who found that undetectable or less than 18 pg/ml Inhibin B levels in all POF cases as well in all menopausal women. Its level did not influenced by exogenous oestrogen intake 3 months prior to test. Thus, Inhibin B might offer an enhanced test for distinguishing women with POF [39]. In case of surgical menopause caused by oophorectomy, the rise in FSH is caused by the fall in inhibin, estradiol and progesterone after oophorectomy in which Inhibin B is cleared from circulation within 12 h of bilateral oophorectomy, confirming the ovary as the predominant source for these circulatory proteins in women [40].

In the present study we did not find any case of POF with normal FSH and Inhibin B and both are good markers for oogenesis. However, it appears that Inhibin B level is superior because it was not influenced by previous exogenous oestrogen intake. In conclusion, Inhibin B is not affected by exogenous oestrogen intake in comparison to FSH; it can be used as a non-invasive method in determining the ovarian reserve in women with premature ovarian failure seeking fertility.

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