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The Pathogenetic Meaning (Pathogenetic Significance) of Inhibin in the Development of Premature Ovarian Failure

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Abstract

The end of a woman's reproductive life is marked by the beginning of menopause, which is defined as the last menstruation in a woman caused by the depletion of the ovarian reserve. Premature ovarian failure (POF) is an ovarian defect characterized by premature stop of folliculogenesis before the age of 40. Gonadal inhibin is the main peptide hormone that regulates the synthesis and secretion of FSH during folliculogenesis and spermatogenesis, and the main role of the inhibin is to selectively suppress the production of FSH by the pituitary gland. The aim of this study was to study the effect of the level of inhibin B as a marker of ovarian reserve in women with premature ovarian depletion. In our study, low levels of inhibin B were found among group A and there was a negative correlation between FSH and the level of inhibin B. The hormonal characteristics of patients with POF also suggest that inhibin is the cause of the disease mechanism. Impaired inhibin B secretion has been reported in women with POF.

Thus, the level of inhibin B is not affected by the intake of exogenous estrogen compared to FSH, and it can be used as a non-invasive method for determining ovarian reserve in women with premature ovarian depletion, in order to predict the restoration of fertility.

Keywords: premature ovarian failure, menopause, inhibin, ovarian reserve

INTRODUCTION

Premature ovarian failure (POF) is an ovarian defect characterized by premature depletion of follicles (folliculogenesis arrest) before the age of 40 [1,3]. The end of a woman's reproductive life is marked by the onset of menopause, which is defined as the last menstrual period in a woman caused by depletion of the ovarian reserve [4,5]. Natural menopause is observed among women of all ethnic groups aged 50-52 years [6,7].

POF is considered a common disease, as it affects 1-4% of all women under the age of 40 and 0.1% of women under the age of 30 [8]. According to Khaidarova F.A. and Fakhrutdinova S.S. et al. the prevalence of PID in Uzbekistan is 2.5%. [2]. Causes (POF) include idiopathic, genetic, autoimmune, iatrogenic factors, as well as toxins, occupational chemicals, and infections [9-12].

Most women with (POF) have menstrual irregularities, 10% of them have amenorrhea. In addition, women with POF have very low blood levels of estradiol. The observed clinical

symptoms are similar to those seen at the onset of menopause, such as hot flashes, vaginal dryness, dysparenuria, insomnia, vaginitis, and mood swings [13-15].

Inhibin is a protein secreted by granulosa cells (in women) and Sertoli (in men) in response to FSH [16-18]. It is found in blood and in large quantities in semen and follicular fluid. Gonad inhibin is the main peptide hormone that regulates the synthesis and secretion of FSH during folliculogenesis and spermatogenesis, and the main role of inhibin is to selectively suppress the production of FSH by the pituitary gland.

Inhibin enhances LH stimulation of androgen synthesis to serve as a substrate for estrogen aromatization in granulosa cells, while activin inhibits androgen synthesis. This is an important paracrine regulation of androgen as a substrate for estrogen aromatization in granulosa cells, but the production of activin in theca cells by inhibin and activin is mainly due to the modification of the expression of steroidogenic enzymes [14,16]. FSH and LH are secreted from specialized cells of the anterior pituitary gland called gonadotropes, while gonadoliberin from the hypothalamus, testosterone from the testes in men and estradiol, progesterone from the ovaries in women, as well as gonadal inhibin, activin and follistatin all together regulate the synthesis and secretion of gonadotropins [17.22]. FSH stimulates Sertoli cells in the testes and granulosa cells in the ovaries and then promotes the production of inhibin by these cells.

In women, ovarian granulosa cells produce inhibin, and inhibin production by each follicle increases as the granulosa cell population increases during normal follicle growth and maturation [18-21]. Inhibin B levels persist for up to 18-24 months due to postnatal activation of gonadotropin secretion. Serum inhibin B is positively associated with age several years before puberty due to increased follicular activity during pre-puberty, after which inhibin B levels progressively increase with stages of puberty indicating high follicular activity before the onset of ovulatory menstrual cycle [26].

During the follicular phase of the menstrual cycle, the main form of inhibin secreted by the ovaries is inhibin B, in which it rises sharply in the early follicular phase, reaching its peak after an increase in FSH levels, and then gradually falling during the rest of the follicular phase, another peak is observed at 2 day in the middle of the cycle of the peak of LH, then there is a rapid decline and a constant low level during the luteal phase [22-25].

The aim of this study was to investigate the effect of inhibin B levels as a marker of ovarian reserve in women with premature ovarian failure.

MATERIALS AND METHODS

This study was carried out in the advisory clinic of the RSNPMTSE them. Academician Y.Kh.Turakulov from September 2018 to September 2020. Written consent was obtained from all participating women in this study. The participants in this study were divided into 3 groups.

Group A: were 45 women with premature ovarian depletion (POF), with an age limit of less than 40 years, amenorrhea for more than 6 months, no history of medical diseases such as diabetes mellitus, hypertension, thyroid dysfunction, lack of exogenous estrogen intake during previous 3 months, no history of chemotherapy, serum FSH> 20 IU / ml.

Group B: were 35 menopausal women over the age of 45 with amenorrhea lasting more than one year, no history of disease such as diabetes mellitus or thyroid dysfunction, who had no previous hormone replacement therapy and serum FSH levels reached an interval of more than 40 IU / ml.

Group C: were 30 women with normal menstrual function and fertility who also did not receive hormonal contraception in the past year.

All participating women were interviewed in detail for their medical, surgical and therapeutic history (especially cytotoxic chemotherapy and exogenous estrogen production), and a thorough physical examination was performed to rule out any serious underlying medical conditions. None of the participants had a history of autoimmune disease, radiation or chemotherapy, or surgical removal of the gonads.

Blood samples from group C (normally fertile women) were taken on the 3-5th day of the menstrual cycle, blood samples from group A (women with POF) and group B (women during menopause) were taken at random.

Participants in Group A (women with POF) began receiving oral hormone replacement therapy. They were given estrogens and a progestogen in the form of Femoston 2/10 tablets (estradiol valerate 2 mg, dydrogesterone 10 mg) once daily for at least 12 weeks, then blood samples were collected and serum FSH and inhibin B levels measured.

The FSH concentration was measured on a Cobas e 411 immunochemiluminescence analyzer (Roche Diagnostics GmbH) with an Elecsys FSH reagent kit. The concentration of Inhibin B was investigated with a set of reagents "Beckman Coulter Inhibin B" by the enzyme immunoassay in duplicate. The measurements were made on a Mindrey MR-96A reader.

The data were analyzed using statistical software. Descriptive statistics are presented as mean and standard deviation, and an independent sample t test was used to determine the difference in mean significance between groups.

RESULTS

The average age of group A (women with POF) was 30.16 ± 5.05 years with a range of 19-39 years, in group B (women in menopause) the average age was 48.04 ± 1.6 years with a range of 45-50 years and in group C (normal menstruating women) - 29.33 ± 4.9 years with a range (21-40 years). Age differences were not significant between groups A and C (Table 1).

There was no statistical significance regarding the age of menarche between the three groups ($P > 0.05$), however, in group A, menarche occurred at an older age on average by almost 1 year (14.2 ± 0.15 versus 13.1 ± 0.13 and 13.4 ± 0.12, respectively). There was a significant increase in BMI in groups A and B in relation to group C ($P < 0.05$). Regarding the duration of amenorrhea, the following patterns were established, so in group A in 93.3% of women the last menstruation was more than 120 days (132.5 ± 4.5 days), however, in 6.7% of women the duration of amenoria averaged 54.8 ± 1.2 days. In group B, all women had amenoria duration over 120 days (148.1 ± 5.9 days). In group C, 93.3% of women noted the duration of amenorrhea less than 35 days (28.6 ± 2.3 days), but 6.7% indicated a duration of more than 35 days.

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Table 1
Characteristics of women in the study groups

Basic characteristics	Group A (n=45)		Group B(n=35)		Group C (n=30)		Value P (A/B)	Value P (B/C)	Value P (A/C)
Age	30,16±50,05 (19-39)		48,04±1,6 (45-50)		29,33±4,9 (21-40)		<0,0001	<0,0001	0,017
mean (years) ± SD,	26,1±2,3 (24-30)		27,4 ±2,4 (23-30)		23,6±1,5 (22-26)		0,73	<0,0001	<0,0001
BMI mean (kg / m2) ± SD, range	14,2±0,15 (12-15)		13,1±0,13(12-15)		13,4±0,12 (12-15)		0,024	0,042	0,029
Duration of amenorrhea									
	n	%	n	%	n	%			
Last menstruation <35 days	0	0	0	0	28	93,3			
Last menstruation 35-120 days	3	6,7	0	0	2	6,7			
Last menstrual period> 120 days	42	93,3	35	100	0				

Table 2 gives the average value of FSH and inhibin B levels in blood plasma in all three groups, the average FSH level in group A was (71.4 ± 28.4 IU / ml) and varied (25-120 IU / ml.), in group B, the mean FSH level was (87.7 ± 25.5 IU / ml) with a range (55-150 IU / ml), and in the last group C, the mean FSH level was (5.87 ± 2.3 IU / ml) with a range (3.2-12 IU / ml). a significant increase in the level of FSH in blood plasma was found in groups A, B in relation to group C (P <0.01).

Table 2
FSH and inhibin B levels in examined women
(M ± standard deviation)

Parameter	**Group A**	**Group B**	**Group C**
FSH (IU / ml)	71,4±28,4* (25-120)	87,7±25,5* (55-150)	4,87±2,3 (4,2-12)
Inhibin B (pg / ml)	1,8±2,8* (0-11)	1±0,9*^ (0-4)	53,1±17,1 (30-80)

Note: * - reliability of data in relation to indicators of group C (P <0.001); ^ - reliability of data between groups A and B (P <0.05)

The mean inhibin B level in group A was (1.8 ± 2.8 pg / ml) with a range (0-11 pg / ml), the level of inhibin B in group B was (1 ± 0.9 pg / ml) with a range (0-4 pg / ml), while in group C the mean inhibin B value was (53 ± 17.1 pg / ml) in the range (30-80 pg / ml). The data obtained indicate that the level of inhibin in PJA and menopause is significantly reduced by almost 50 times in relation to the indicators of healthy women (P <0.001).

We carried out a quantitative assessment of the content of inhibin B depending on the level of FSH among the examined women of group A, the data obtained are presented in table 3.

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Table 3
Relationship between inhibin B levels and different FSH levels in group A before treatment (n = 45)

Inhibin level	FSH> 40 IU / ml	FSH 13-39 IU / ml	FSH <12 IU / ml	General
Inhibin <15 pg / ml	27 (60,0%)	18 (40,0%)	0	45 (100%)
Inhibin 16-25 pg / ml	0	0	0	0
Inhibin> 25 pg / ml	0	0	0	0
General	27	18	0	45

Table 3 shows the relationship between inhibin B levels and different serum FSH levels in group A (women with POF), the higher inhibin B level was ≤ 15 pg / ml in 27 cases with FSH> 40 IU / ml, and in two cases FSH levels ranged from 13 to 39 IU / ml. An inverse correlation was found between the level of inhibin B and the level of FSH (r = -0.789; P <0.05), i.e. the higher the FSH values, the lower the inhibin B level in women with POF.

Table 4 shows the content of inhibin B depending on the level of FSH in women with PJA after 4-6 months of hormone replacement therapy, in 21 cases there was a decrease in the level of FSH from> 40 IU / ml to <12 IU / ml, in contrast to an increase in the level inhibin B in only one case from <15 pg / ml to medium (16-25 pg / ml).

Table 4
Relationship between FSH and inhibin B after 4-6 months of hormone replacement therapy (n = 45).

Inhibin level	FSH> 40 IU / ml		FSH 13-39 IU / ml		FSH <12 IU / ml		General	
Inhibin <15 pg / ml	13	29,5	10	22,7	21	47,7	44	97,8
Inhibin 16-25 pg / ml	0	0,0	1	2,3	0	0,0	1	2,2
Inhibin> 25 pg / ml	0	0,0	0	0	0	0,0	0	0,0
General	13	28,9	11	24,4	21	46,7	45	100,0

Table 5 shows FSH and inhibin B levels after hormone replacement therapy in group A, in which the average FSH level was (17.16 ± 13.4 IU / ml) with a range (15-69 IU / ml), the average level of inhibin B was (1.8 ± 2.9 pg / ml) and the range (0-16 pg / ml). There was a significant decrease in FSH levels (P≤0.01) in the absence of significant changes in the level of inhibin B.

Table 5
FSH and inhibin B levels after HRT in group A

Group	Mean inhibin B ± standard deviation (pg / ml)	FSH mean ± standard deviation (IU / ml)
POF before treatment	1,8±2,8 (0-15)	71,4±28,4 (25-120)
POF after treatment	1,8±2,9 (0-16)	17,16±13,4 (16-69)*

Note: * - reliability of data before and after treatment (P <0.01)

DISCUSSION

The term ovarian reserve is based on the concept of a conserved follicular pool that remains in the ovary as they age, with anti-Müllerian hormone (AMH) being the first marker of a decrease in its function, followed by a decrease in inhibin B levels and an increase in FSH levels, all observed with a decrease in the number of antral follicles. Therefore, ovarian reserve can be monitored by various tests such as FSH, estradiol, ovarian volume, clomiphene stress test or antral follicle counts [23-29]. The Clomiphene Citrate Challenge Test (CCCT) is a common test for assessing ovarian reserve, but it requires days and several blood samples to be collected. The gonadotropin analog stimulation test is based on the determination of FSH, E2, LH before and after the administration of gonadotropin. This test is expensive, requires multiple injections, multiple blood samples, and has limited value. Other tests for determining ovarian reserve are ultrasound and antral follicle counts and ovarian biopsy [18,28,33]. Consequently, there is a need for a direct detection and accurate marker that will aid in the study of the measurement of ovarian reserve, which can help to distinguish between the complete absence of germ cells in the ovaries and small abnormalities in egg formation. Inhibin B is produced by ovarian granulosis cells, so it may be more accurate in this respect. Inhibin B can be used as a marker of ovarian aging as it decreases with age due to a decrease in the number of follicles. [30.35].

The aim of our study was to evaluate the content of inhibin B in the determination of ovarian function in women with premature ovarian failure compared to the determination of the level of FSH.

The increase in FSH levels in older women is now well studied and used to measure ovarian reserve. FSH values above 25 IU / ml in two cases with an interval of 4-6 months indicate a lack of ovarian function. In this study, all women in groups A and B (with POF and menopause) had high FSH values in excess of 25 IU / ml. In group A, there was no case of reaching the normal threshold of inhibin B of 25 pg / ml, which corresponds to the description of Corson et al. [10,36], but does not correspond to the reports of Seifer et al. [34]. A likely explanation for this discoordination with Seifer et al. [34] is related to the methodology of the analysis, since there are still no international standards for the analysis of inhibin B [40]. We observed low levels of inhibin B <15 pg / ml in both group A (POF) and group B (during menopause), while among group C it was found that all women had inhibin B levels above 15 pg / ml. ml. It has been found that there is a cyclical change in inhibin B throughout the menstrual cycle; in addition, a low serum inhibin B concentration on the third day indicates a poor response to ovulation induction [40–41]. Hofman et al. Describe the correlation of inhibin B in 19 women with normal ovarian reserve and in 15 women with an abnormal clomiphene citrate challenge test. Inhibin B was low on day 3 in women with an abnormal clomiphene citrate challenge test and was higher in women with a normal reserve. In addition, a negative correlation was observed between FSH and inhibin B levels on day 3 after the clomiphene citrate challenge test. [18.38]

In our study, group A showed low levels of inhibin B and there was a negative correlation between FSH and inhibin B. The hormonal characteristics of patients with POF also suggest that inhibin is the cause of the disease mechanism. It has been reported that the secretion of inhibin B is impaired in women with POF [37-39], and inhibin concentrations were lower in

women with ovarian insufficiency during both ovulatory and anovulatory cycles compared with infertile women with a normal ovulatory cycle [33]. It was also noted that women with menopausal transition had lower concentrations of inhibin in the follicular and luteal phases [28]. In this study, the authors show that serum inhibin B concentrations were lower in women over 45 years than in younger women, which is consistent with the description of the study by Klein et al. [22], which found that women aged 40-45 years compared with younger women had a lower serum inhibin B concentration in the early follicular phase. Previous studies have shown that women with PJO and amenorrhea at 3 months were more likely to ovulate than women with a longer period of amenorrhea, and these ovulatory cycles are associated with lower FSH levels, although they remain elevated compared to FSH levels in women with a regular cycle [38].

In our study, after 4-6 months of hormone replacement therapy (HRT) among women with early PJA, an increase in inhibin B level was observed in only 6.7% of cases, in contrast to a decrease in serum FSH levels of 93.3%. Significant limitations of FSH analysis are related to the consumption of exogenous estrogen, as well as fluctuations in FSH levels, which are usually observed with the intake of exogenous estrogen, which is often observed with ovarian failure after chemotherapy or radiation therapy. Their levels can be reasonably stable [39] or they can also cause fluctuations in FSH levels, leading to resumption of ovulation.

In recent years, inhibin B has been a predictor of ovarian reserve; it is produced mainly in ovarian granulosis cells and is not found in women during menopause [17]. In approximately 40% of premenopausal women beginning 2 years before the last menstrual period, the level of inhibin B is not detected in the blood [22]. Halder A et al. [16] conducted a study that found that the level of inhibin B was not detected or was below the value of 18 pg / ml in all cases of POF, as well as in all women during menopause. Its level did not depend on the intake of exogenous estrogen 3 months before the test. Thus, inhibin B can be considered an extended test for recognizing women with POF [22]. In oophorectomy-induced surgical menopause, an increase in FSH levels is caused by a drop in blood levels of inhibin, estradiol, and progesterone after oophorectomy, in which inhibin B is cleared from the bloodstream within 12 hours after bilateral oophorectomy. This confirms the fact that the ovary is the predominant source of these circulatory proteins in women [26].

In the present study, we did not find a single case of POF with normal FSH and inhibin B levels, and both are good markers of oogenesis. However, it seems that the determination of inhibin B levels is more appropriate because it was not influenced by previous consumption of exogenous estrogen.

Thus, inhibin B levels are not influenced by exogenous estrogen intake compared to FSH, and can be used as a non-invasive method for determining ovarian reserve in women with premature ovarian depletion in order to predict fertility recovery.

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