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Correlation Between Serum Inhibin and FSH Levels in Women with Different Reproductive Disorders

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ABSTRACT

Inhibin was first identified as a gonadal factor that inhibits FSH (inhibin- B) and LH (inhibin- A) synthesis at the pituitary which proved by tissue culture. During the later years, the role of FSH was defined and the role of inhibin to control FSH biosynthesis and secretion was cleard. Inhibin is a member of the transforming growth factor beta (TGFβ) superfamily which includes molecules like activin . Inhibin is similar to activin in structure with both having β- subunits . Inhibin -B blocks the ability of activin to induce FSH secretion by blocking the activin-receptor interaction. In the female the ovary is the major source of inhibin synthesis , the granulosa cells in developing follicles , or lutein cells in the corpus luteum are the major source of inhibin. The study aimed to measure the level of inhibin hormone in normal and abnormal adult women, study the changes in inhibin hormone level and to explain the relationship between these changes and different pathological conditions. The experimental groups used consists of 80 women aged between 20-52 years old, which divided into: women with normal menstrual cycle, women with irregular menses, women with polycystic ovary and women with amenorrhea. The study demonstrated that inhibin- B concentrations negatively correlated with FSH concentrations in normal and abnormal patients .However in infertile patients, inhibin– B was significantly decreased and FSH was significantly increased . While in normal patients the result was found to be opposite of abnormal patients . These results suggest that the physiologically important hormone that exerts tonic negative feedback upon FSH secretion is inhibin- B.

Keywords- Inhibin-B, amenorrhea, polycystic ovary.

I. INTRODUCTION

Hormones and factors produced by the hypothalamus and pituitary maintain the normal reproductive cycle , regulate genital, gonadal, and sexual development in males and females (De Kretser *et al.* , 2000 ; Pezzani *et al.* , 2001). Follicle stimulating hormone (FSH) and luteinizing hormone(LH) are involved in the activation and regulation of the reproductive axis. Hormones produced by the gonads regulate FSH and LH secretion in a feedback loop mechanism (Burger *et al*., 1988).

Inhibin was first identified as a gonadal factor that inhibits FSH (inhibin- B) and LH (inhibin- A) synthesis at the pituitary which proved by tissue culture (Hayes *et al.*,1998). The concept of a gonadal factor relate to an endocrine action at the pituitary is often traced to Mottram and Cramer (1923). This activity was later named feedback mechanism (Mc Cullagh ,1932). During the later years, the role of FSH was defined and the role of inhibin to control FSH biosynthesis and secretion was cleard (de Jong ,1988 ; Groome *et al*.,1994). Inhibin is a member of the transforming growth factor beta (TGFβ) superfamily which includes molecules like activin . Inhibin is similar to activin in structure with both having β- subunits . Inhibin -B blocks the ability of activin to induce FSH secretion by blocking the activin-receptor interaction(deWinter *et al*., 1996). Inhibin is disulfide-linked heterodimeric glycoprotein consisting of an alpha (α) subunit and two β subunits (βA or βB) (Halder *et al*.,2007).

Only the dimeric forms of inhibin (α-βA , α-βB molecules)are biologically active (Ying , 1988). In the female the ovary is the major source of inhibin synthesis , the granulosa cells in developing follicles , or lutein cells in the corpus luteum are the major source of inhibin (Welt *et al*. ,2003 ; Inge *et al.*, 2009). In the male ,inhibin- B is produced in the testis by Sertoli cells. Inhibin-B secretion is positively correlated with Sertoli cell function to activate sperm number(Eldar-Geva *et al*.,2002; Suehrio *et al*.,2008).The spermatogenic status are negatively correlated with FSH serum level (Stefano *et al*., 2005 ;Torgac *et al*., 2005).

Aims of the study:

This study was designed :

1. To measure the level of inhibin hormone in normal and abnormal adult women.
2. To study the changes in inhibin hormone level and to explain the relationship between these changes and different pathological conditions.
3. To explain the role of inhibin-B level as a diagnostic test in some infertility cases.

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II. MATERIALS AND METHODS

The experimental groups used consists of 80 women aged between 20-52 years old.

Women group was divided in to:

1- Women with normal menstrual cycle (20).
2- Women with irregular menses (20).
3- Women with polycystic ovary (20).
4- Women with Amenorrhea (20).

2.1: Blood samples collection :

Five millileter (ml) of blood samples were aspirated from patients cubitus vein. Blood samples were centrifuged at 3000 round per minute (r.p.m) for ten minutes.

2.2: Methods:

Serum was collected by using micropipette. Serum follicle stimulating hormone (FSH) levels were measured and the remainder of the serun was stored at -10 degree centigrade (c^o) until it was assayed for inhibin -B.

2.3: Measuring of FSH concentration in the serum:

FSH concentration was measured in the serum of sample by using Immuno Radiometric Assay (IRMA) test and following the steps in the kit of FSH.

2.5: Measuring of Inhibin –B concentration in the serum:

Measuring of Inhibin- B concentration in the serum by using Enzyme-Linked Immunosorbent Assay (ELISA) test:

Inhibin- B concentration was measured in the serum of sample by following the steps in the kit of inhibin- B hormone.

2.5: Statistical analysis:

Data were analyzed using statistical analysis system –SAS (2001) to study the effect of case on hormones (FSH and Inhibin). Least significant difference (LSD) was used to compare the significant difference between means in this study.

III. RESULTS

Changes in FSH and Inhibin hormone in women

The statistical analysis of normal , pathological cases of Inhibin and FSH hormones in women were demonstrated in table 3.1 . Mean ±SD of inhibin -B level were significantly lower ($P < 0.05$) in women with amenorrhea (36.40 ± 5.19 pg/ml) than in the nomal (375.00 ± 48.63) . However, FSH levels were significantly higher ($P < 0.05$) in women with amenorrhea (31.50 ± 1.88 U/L) than in normal (5.86 ± 0.62) (table 3.1).

The mean ±SD of inhibin -B was significantly lower ($P< 0.05$) in women with irregular menses (65.80 ± 3.07 pg/ml) than in normal (375.00 ± 48.63) .While FSH levels were significantly higher ($P< 0.05$) in women with irregular menses (16.30 ± 1.59) than in normal (5.86 ± 0.62) as shown in table (3.1).

The levels of inhibin -B were significantly lower ($P < 0.05$) in women with PCOS (41.93 ± 1.44 pg/ml) than in nomal (375.00 ± 48.63) .While FSH levels were significantly higher ($P < 0.05$) in women with PCOS (29.28 ±2.72) than normal (5.86 ± 0.62) (Table 3.1).

Table 3.1 : The serum levels of FSH and Inhibin in different cases of women .

Case	No.	FSH (U/L)		Inhibin (pg/ml)	
		Level U/L	Range	Level pg/ml	Range
Normal women (20-47 years)	10	5.86 ± 0.62 c	4.62 – 7.10	375.00 ±48.63 a	277.74 – 472.26
Women with amenorrhea (43-52 years)	10	31.50 ± 1.88 a	27.74 – 35.26	36.40 ± 5.19 b	26.02 – 46.78
Women with irregular menses (20-45 years)	15	16.30 ± 1.59 b	13.12 – 19.48	65.80 ± 3.07 b	59.66 – 71.94
Women with PCOS (20-45 years)	15	29.28 ± 2.72 a	23.84 – 34.72	41.93 ± 1.44 b	39.05 – 44.81

The different letters (a,b,c) within the same column refere to significant differences (P<0.05) between groups

There were no significant differences in inhibin-B hormone levels between the pathological cases in women.

A significant differences was found in FSH levels between the women with amenorrhea and women with irregular menses.

A significant ($P<0.05$) difference in FSH levels of women with irregular menses and women with PCOS .While no significant differences were observed in the level of this hormone in the women with amenorrhea and women with PCOS ($P>0.05$) (Table 3 .1).

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It was found that the highest level of FSH observed was in women with amenorrhea while the lowest level of this hormone was in normal (Figure 3.1). However , it was found that the highest level of inhibin observed was in normal women and the lowest level of this hormone was in the women with amenorrhea (Figure 3.2).

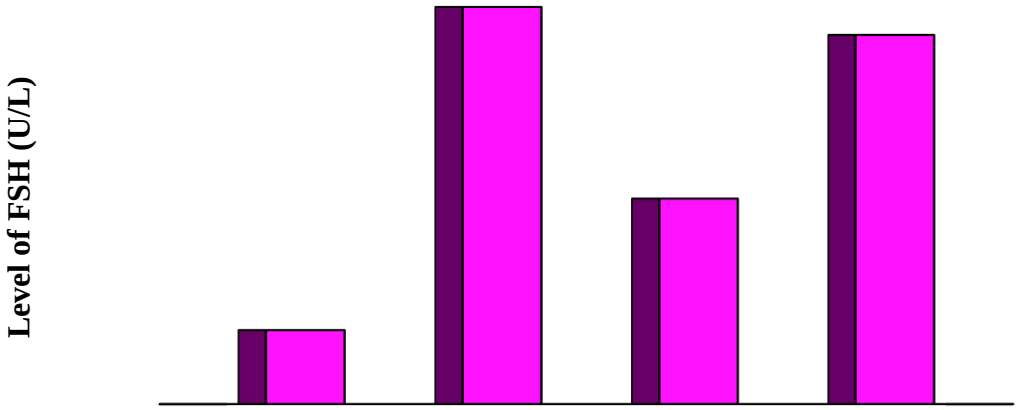

Figure 3.1: The level of FSH in different cases of women

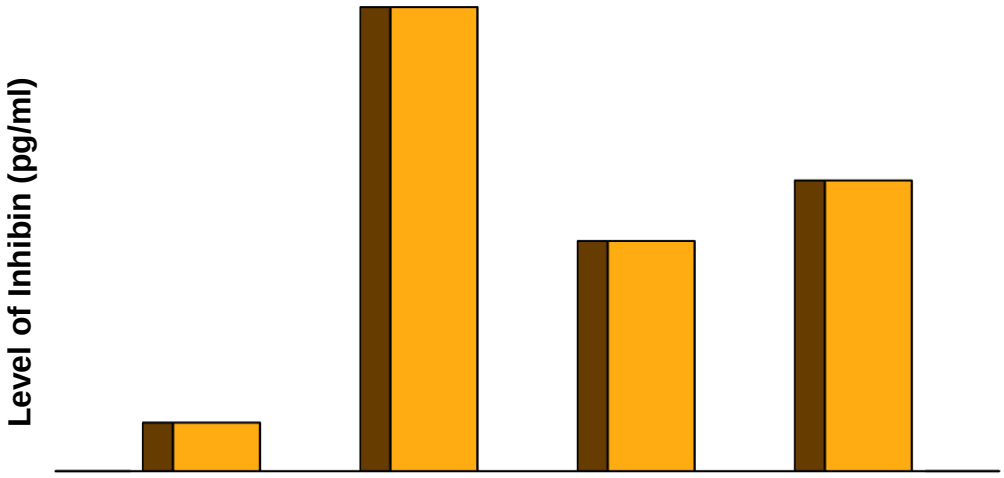

Figure 2.2: The level of inhibin in different cases of women

When the correlation coefficient between the two hormones were studied (Table 3.2). It was found that serum FSH levels in normal women showed a significant ($P<0.05$) correlation coefficient of (-0.37) with serum inhibin levels. Serum FSH levels in women with amenorrhea showed a non significant ($P>0.05$) correlation coefficient of (-0.18) with serum inhibin levels , but serum FSH levels in women with irregular

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menses showed a non significant (P>0.05) correlation coefficient of (-0.20) with serum inhibin levels . Serum FSH levels in women with PCOS showed a significant (P<0.05) correlation coefficient of (-0.39) with serum inhibin levels .

Table 3.2 : The correlation coefficient (r) between FSH and Inhibin in women

Case of women	Correlation coefficient (r) between FSH and Inhibin	Level of significancy
Normal women	**- 0.37**	**P<0.05**
women with Amenorrhea	**- 0.18**	**Ns**
Women with irregular menses	**- 0.20**	**Ns**
Women with PCOS (20-45)	**- 0.39**	**P<0.05**

Ns: non-significant

IV. DISCUSSION

The study demonstrated that inhibin- B concentrations negatively correlated with FSH concentrations in normal and abnormal patients .However in infertile patients, inhibin– B was significantly decreased and FSH was significantly increased . While in normal patients the result was found to be opposite of abnormal patients . This results suggest that the physiologically important hormone that exerts tonic negative feedback upon FSH secretion is inhibin-B . These result were found to be similar to that of Illingworth *et al.* (1996 a) ; which imphysis that the FSH concentration is inversely correlated with inhibin–B in normal and abnormal cases.

Both inhibin- B and FSH have been demonstrated also to be a more sensitive and specific marker for spermatogenesis , oogenesis when given together than when each of the hormone was given alone (Pierik *et al*., 2001 ; Fried *et al*., 2003).

Changes in serum FSH and inhibin-B in women:

The present study found that circulating concentrations of inhibin-B were significantly (p<0.05) lower in women of 43-52 years with raised FSH. However , it has been shown by Welt *et al.* (1999) and in the present study that inhibin concentrations were significantly low in the raised FSH group of women. The data may suggest that the reduction in the number and quality of the follicles in menopausal women results in a decrease in circulating concentrations of inhibin-B, which cause the rise in FSH in the serum. This finding was concised with that of Agha-Hosseini *et al.* (2009); they found that a granulosa cell tumor secretes inhibin - B, which suppress follicle-stimulating hormone which leads to amenorrhea.

In women with irregular menses the seum level of inhibin-B was found to be significantly (p<0.05) decreased ,while serum FSH was significantly (p<0.05) increased. This result may be due to abnormal secretions of hypothalamus, pituitary or ovaries causing hormonal imbalance. As a result this probably leads to irregular menstrual cycle and folliculogenesis processes. However, inhibin-B was found to be positively correlated with folliculogenesis thus circulating level of inhibin-B was decreased. While FSH was increased in the serum due to the absence of the role of inhibin-B in a negative feedback loop mechanism . The present result is in agreement with Shideler *et al.* (2001) , they observed a significant decline in circulating inhibin- B in premenopausal females which is similar to that observed in older postmenopausal women . However Casper *et al.* (2000) , found a high inhibin- B baseline levels and a small increase of FSH in women with ovulatory disturbances.

Polycystic ovarian syndrome is caused by an imbalance in the hormones in the brain and ovaries (Abdel Gadir *et al.* , 1992).

Disorder in circulating level of GnRH affects the ovarian function , oogenesis process and ovulr maturity , thus ova did not liberate from the follicles which leads to the formation of cyst . In the present study serum inhibin-B level in women with PCOS was decreased despite the large ovarian volume and increased follicle number , while serum FSH level was increased our result disagrees with Tsigkou *etal.* (Tsigkou *et al.* , 2008) who found that women with PCOS had serum total inhibin levels twice as high as in the control group , inhibin- B concentration did not differ significantly between PCOS and control groups , also disagrees with (Anderson *et al*., 1998; Amer *et al*., 2007), they found that inhibin- B concentrations are significantly elevated in patients with PCOS.

Several studies have investigated the changes in the ovarian follicular reserve markers (Wada *et al.* , 1996). Serum FSH levels increase in old reproductive age women, a fact that has been well documented and recognized for many years by many investigators (Lee *et al.* , 1988). In women approaching 40 year of age, serum FSH levels usually begin to rise, which reflects a reduction in the number of early antral follicles present that can be recruited to ovulate (Chang *et al.* , 1998). Serum FSH levels increase over time because inhibin B and E_2 production are reduced by a diminished cohort of growing follicles (Klein *et al.* , 1996 ; McGee and Hsueh , 2000). Nevertheless, prior to age 40, FSH levels are not correlated with age, which confirms the lack of correlation between FSH and age in women aged 20-35

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(van Rooij *etal*., 2005 ; Schipper *etal.* , 1998). Therefore, a new marker of ovarian function in women is needed.

Inhibin- B is a direct product of small, developing follicles in the ovary and, as such, indicates a woman's ovarian reserve. The amount of inhibin- B measured in serum during the early follicular phase of the menstrual cycle (days 2-6) directly reflects the number of follicles in the ovary; in other words, the higher the inhibin- B, the more ovarian follicles are present and oogenesis process is normal , thus serum inhibin-B level in normal women was elevated while serum FSH was decreased . It is believed that the decline in FSH after its peak in the early follicular phase of the normal cycle results from a negative feedback action of inhibin- B at the pituitary level , this result is in agreement with Halder *et al*. (2007) ; found that inhibin-B level was significantly lower in group A (premature ovarian failure) & B(menopause) than group C (normally cycling fertile women) ($p<0.0001$) .

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