

Serum insulin like growth factor-I and Inhibin B levels in patients with polycystic ovarian syndrome

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Abstract

Design: A cross section study the relationship between serum inhibin B level and Insulin Growth Factor I level, and the fertility outcome in Polycystic Ovarian Syndrome women.

Setting: The study conduct at Tikrit Teaching Hospital, Department of Obstetrics and Gynecology between May 2010- May 2011.

Patient: Ninety women participate with study they were included in one of the following groups:

Group A: includes fifteen normal fertile women.

Group B: includes fifty infertile Polycystic Ovarian Syndrome women

Group C: includes twenty five fertile Polycystic Ovarian Syndrome women.

Polycystic ovary syndrome is diagnosed according to the ESHRE/ ASRM Rotterdam criteria for Polycystic Ovarian Syndrome 2004.

Methods: Clinical, anthropometric measurements, ultrasound study and laboratory determinations of Leutanizing Hormone, Follicular Stimulating Hormone, Prolactin, inhibin B, Insulin like Growth Factor I.

Results: Serum inhibin B decreased in older infertile Polycystic Ovarian Syndrome women than fertile Polycystic Ovarian Syndrome women. Infertile Polycystic Ovarian Syndrome women have higher serum Insulin like Growth Factor I and Inhibin B than fertile PCOS and control group.

Conclusion: Infertile Polycystic Ovarian Syndrome women associated with elevated serum inhibin B and serum Insulin like Growth Factor I levels.

Key words: PolyCystic Ovary Syndrome (PCOS) ,Inhibin B,insulin like growth factor (IGF).

Introduction

The polycystic ovarian syndrome is a heterogeneous collection of sign and symptoms that together form a

spectrum of disorders with mild presentation in some while in other sever disturbances of reproductive, endocrine, and metabolic function, (1). The most recent definition was set out during a consensus meeting by European Society of

Human Reproduction and Embryology "ESHRE" in Rotterdam in may 2003, (1-3)

Based on modified criteria defined at this meeting, the diagnosis of polycystic ovary syndrome is made when two out of the following criteria are found:

1- Clinical or biochemical evidence of androgen excess after the exclusion of other related causes.

2- Oligomenorrhea and or anovulation.

3-Ultrasound appearance of ovaries: presence of >12 follicle in each ovary measuring 2-9 mm and or ovarian volume >10 ml by Rotterdam ESHRE/ ASRM- sponsored PCOS workshop group, 2004, (1,2,4). Polycystic ovary syndrome is diagnosed according to the Rotterdam criteria for Polycystic Ovarian Syndrome. Insulin like growth factors (IGF-I and IGF-II) act as paracrine regulators. Circulating levels do not change during the menstrual cycle, but follicular fluid levels increase toward ovulation, with highest level found in the dominant follicle. The action of IGF-I and IGF-II are modified by their binding proteins: insulin-like growth factor binding proteins (IGFBPs).

In follicular phase, IGF-I is produced by theca cells under the action of LH. IGF-I receptor are present on both theca and granulosa cells. Within the theca, IGF-I augments the

stimulatory effects of FSH on mitosis, aromatase activity and inhibin production. In pre- ovulatory follicles, IGF-I enhances LH induced progesterone production from granulosa cells. Following ovulation, IGF-II is produced from luteinized granulosa cells, and acts in an autocrine manner to augment LH induced proliferation of granulosa cells⁽⁵⁻⁷⁾. Inhibin is a protein secreted by granulosa cell

in female, and sertoli male cell in response to FSH and its major action is the negative feedback control of pituitary FSH secretion it's found in blood plasma although it's difficult to detect until recently. It found in great quantity in seminal plasma and follicular fluid, (7-9). Blood concentration of inhibin B appear to vary with the phase of menstrual cycle inhibin concentration increase during the early follicular phase and begin to fall 1 day after the FSH increase until the end of the follicular phase, (10-12). Inhibin B Concentration rise for brief period 2 days after the LH peak and decrease to low concentration during the luteal phase on the other hand ;the concentration of inhibin A is low during the follicular phase . Rise during ovulation and reaches its highest concentration in the middle of luteal phase .the changes in the concentration of inhibin A and inhibin B during menstrual cycle suggest that these forms process different physiological roles .the peak in inhibin A luteal phase and its fall with luteolysis are consistent with its being secretory product of corpus luteum, (13-15) .

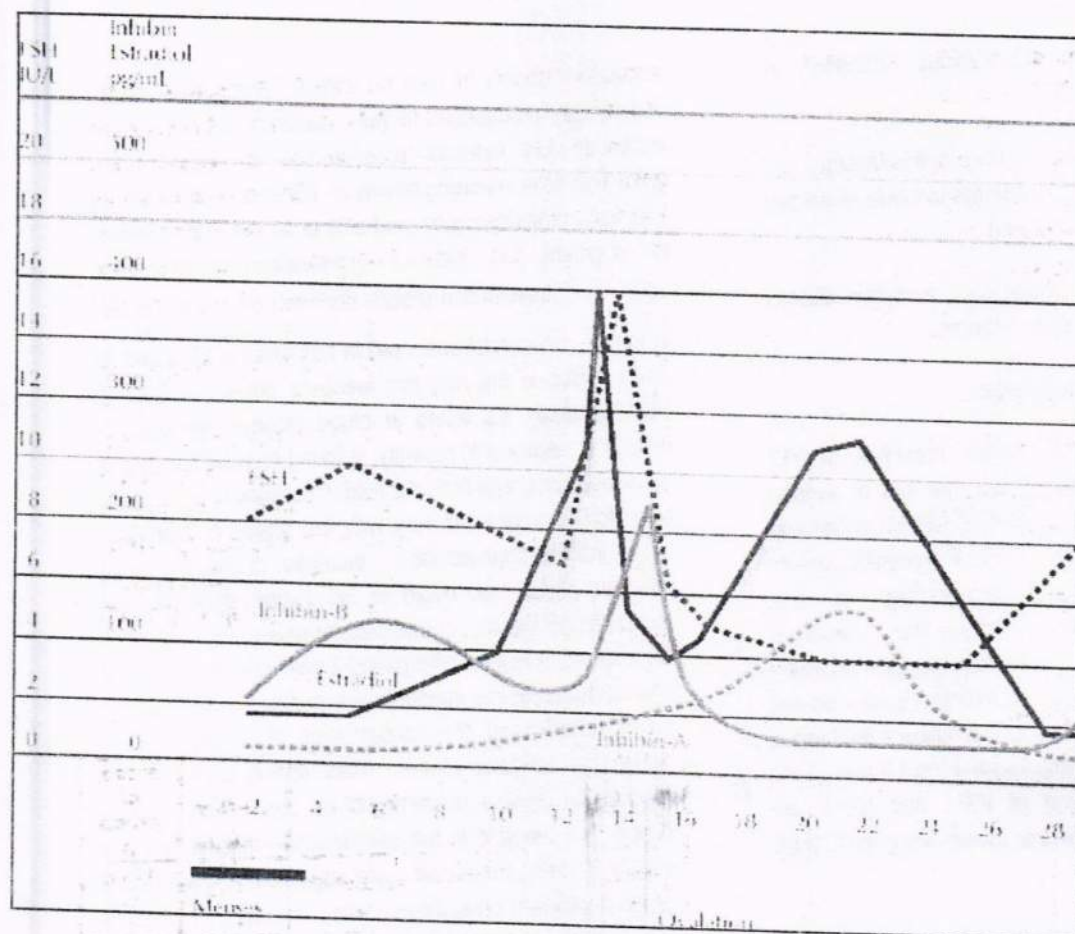


Figure 1-2:

Variability of inhibin level in different phases of menstrual cycle(1997,11).

Women with PCOS are at high risk for over responding to gonadotrophins stimulation. Inhibin B concentration are significantly elevated in patient with PCOS. The role played by inhibin in the pathogenesis of PCOS is still unclear. The increase number of antral follicles in polycystic ovaries increase in potential for inhibin secretion .high estrogen and inhibin concentrations may provoke the disparity between basal concentrations of LH

and FSH in patient with PCOS.

Inhibin B concentration with multiple follicular growth higher than that in those with single follicular development.

Patients and Methods

1-THE STUDY GROUPS

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The study groups consist of 50 infertile women (55.5%) diagnosed as PCOS second group 25 fertile women (27.77 %) also diagnosed as PCOS; and third group 15 normal fertile women (16.66 %). Aged between 16-46 year; women of sample groups not on contraceptive drugs, not lactating and pregnancy is excluded; samples were collected from gynecological consultant department in Tikrit Teaching Hospital and privet clinic of my supervisor; between May 2010-May 2011 .

1-1 Group A: normal fertile women not pregnant and they don't use any type of contraception and not lactating.

1-2 Group B: infertile women diagnosed as PCOS depending on the following criteria.

1-3 Group C: fertile PCOS women

2-BLOOD SAMPLE COLLECTION

5ml of blood samples were aspirated from patient's brachial vein, in the 3 rd day of menstrual cycle.

2 ultrasound study

Transabdominal pelvic ultrasound examination was done, the diagnostic criteria of POLYCYSTIC OVARIES define by ESHRE/ ASRM consensus meeting was mentioned before but normal appearing ovaries may found.

Ovarian size measure in three dimensions, ovarian volume was estimated using the formula for prolate ellipsoid: $\text{volume} = 0.5233 D1 D2 D3$.

Where D1, D2 and D3 are the three maximal longitudinal anteroposterior and transverse diameter .the ovarian follicles were counted with their diameters. The uterus was measured in three dimentions (19,20,21)

Results

Changes in serum IGF I level in normal fertile women and PCOS women the mean of serum IGF I level were significantly lower ($p < 0.05$) in control group than in the infertile PCOS women, and fertile PCOS women, However;

serum IGF I level show no significant differences between group B and group C ($p > 0.05$) but slightly higher in group B. **There were significant differences of serum IGF I level in different age groups**, the lowest level of serum IGF I of group A women in the young, middle and older age group; however; its highest level in group B, group C show elevated level with significant differences ($p < 0.05$) but less than group B. This variability in the mean of IGF I level can be found in the **young age group (16-25 y)** with significant differences ($p < 0.001$). Group B serum IGF I its highest level, and the lowest level in the same age group in group A (, group C . **The middle age (26-35 y) higher serum IGF I level in group B** lowest serum IGF I in group A; group C found to show significant differences ($p < 0.001$). **The older age group (36-45 y) higher serum IGF I in group B** with no significant differences with group C ($P > 0.05$) lower serum IGF I in group A.

Study group s	16-25 y	26-35 y	36-45 y	mean of group s
Group A	127.7 \pm 27.6* b	87.3 \pm 30.8* C	130 \pm 50** C	113.6 C
Group B	392.5 \pm 114.6** a	432.2 \pm 97.3* A	500 \pm 11** A	441.6 A
Group C	328 \pm 116.1** a	302.4 \pm 124.7 B	392.12* \pm 89.88 B	340.8 B
mean of the age	282.7 B	273.9 B	340.7 A	299.1

* $p \leq 0.05$

** $p \leq 0.005$

a: higher mean for serum IGF I levels.

b: lower mean serum IGF I levels.

c: lowest level of serum IGF I.

Lower serum inhibin B level found in group A (control group normal fertile women) mean \pm SD (88.40 \pm 12.55 pg/ml) with significant statistical differences ($p < 0.05$). Group B women higher serum inhibin B level with non Significant statistical differences from group C mean serum inhibin B level. The statistical analysis of serum inhibin B level in

different age group were demonstrated in (table 3-2) there were significant differences of the serum inhibin B level in different ages within the same study group ($p < 0.05$); lower mean for serum inhibin B level in our study samples in group A in the all age groups.

Changes of serum inhibin B level in **young age group** (16 -25y) were significantly differ in the three study groups ($p < 0.05$). lower serum inhibin B level in group A, highest level in group B, Group C show significant differences ($p < 0.05$) with group B and group A. Lower serum inhibin B level in **the middle age group** (26-35) were found in group A, and the higher serum inhibin B level found in group B; group C show slightly lower serum inhibin B than group B with no significant differences ($p > 0.05$). **Older age group** (36-45 y) serum inhibin B level lower value found in group B, A higher serum inhibin B level in group C serum level of inhibin B in group A, from this data analysis we found that serum inhibin B level decrease with increasing age in infertile PCOS women (group B) while its unchanged in the other two study groups

TABLE (3-2) Changes of serum inhibin B level with age in normal fertile and infertile PCOS women

	16-25 y	26-35 y	36-45 y	Mean of group s
Group A	88.50* ±11.41 c	87.17±17.29** B	90.67 ±4.16* b	88.78 B
Group B	150.20 * ±35.65 a	125.87 ±36.55** A	45.10 ±59.26* c	107.10 A
Group C	113.41 * ±50.82 b	113.08±33.03 ** A	111.25±37.4 8* a	112.58 A
Mean of age	117.37 A	108.7 B	82.34 C	102.82 X

* $p \leq 0.05$

** $p \leq 0.005$

a: higher mean for serum Inhibin B levels.

b: lower mean serum Inhibin B levels.

c: lowest level of serum Inhibin B.

BMI variability in different study groups: Significant differences were found between normal fertile women and infertile PCOS women ($p < 0.05$). Higher were group B, lower MBI in group A no significant differences between group B & C.

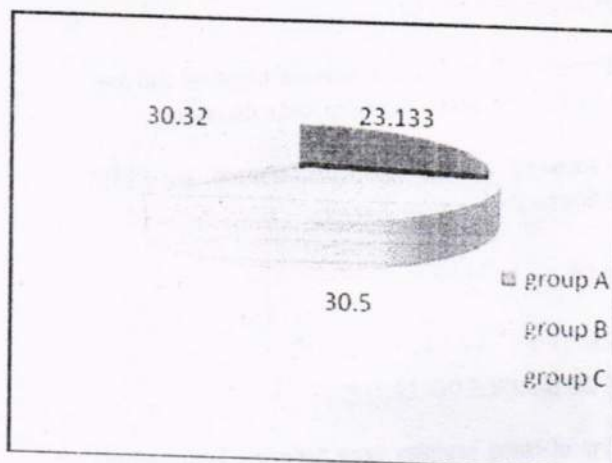


Figure 3-1:

Changes of BMI in different in fertile normal women and infertile PCOS women.

Discussion

This study show low serum level of IGF I in group A mean serum level of control group (112 ± 37.4 ng/ml) were significant differences in which ($p < 0.05$) while higher mean serum IGF I in group B (405.8 ± 100.1 ng/ml) and group C (353.6 ± 127.9 ng/ml) but with no significant differences).

Because PCOS associated with multiple metabolic disorders in this study found variable serum IGF I level in different age groups, This variability in the mean of IGF I level can be found in **the young age group** (16-25 y) with significant differences ($p < 0.001$). Group B (Infertile PCOS) serum IGF I its highest level (392.5 ± 114.6 ng/ml), and the lowest level in the same age group in group A (127.7 ± 27.6

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ng/ml), group C (fertile PCOS) mean \pm SD (328 \pm 116.1 ng/ml).

The middle age (26-35 y) higher serum IGF I level in group B (432.2 \pm 97.3 ng/ml) lowest serum IGF I in group A; group C found to show significant differences ($p<0.001$) (302.4 \pm 124.7 ng/ml).

The older age group (36-45 y) higher serum IGF I in group B with no significant differences with group C ($P>0.05$) lower serum IGF I in group A. Serum IGF I level elevated with increasing age that's why risk of hyperinsulinemia and insulin resistant increase with age in PCOS women and carry high risk to develop adult onset diabetes, (22-25).

Serum IGF I hormone level higher concentration in infertile PCOS women this agreement with San Millan, (26-29). Elevated serum IGF I increase oxidative stress, insulin resistance and hyperandrogenism, and agree with Liang F J et al, who found that elevated serum IGF I associated with infertility, (30-33).

High serum IGF I level mainly associated with hyperinsulinemia and insulin resistant cases of PCOS women elevated serum IGF I induce granulosa proliferation and protein synthesis but the influence of folliculogenesis not yet fully investigated, (34), that's why we thought that elevated serum IGF I implicated the pathogenesis of PCOS. This agrees with Kaser R. et al who found that high serum IGF I associated with increased incidence of infertility and obesity, (35-36)

serum inhibin B level high in PCOS women, The statistical analysis of normal fertile and infertile PCOS women serum inhibin B level was demonstrated (see figure 3-3). Lower serum inhibin B level found in group A (control group normal fertile women) mean \pm SD (88.40 \pm 12.55 pg/ml) with significant statistical differences ($p<0.05$). Group B women higher serum inhibin B level with non Significant statistical differences (117.56 \pm 35.91 pg/ml) from group C mean serum inhibin B level (116.66 \pm 46.55 pg/ml).

The concept BMI in PCOS play a role in inhibin regulation, although obesity not necessary feature of PCOS large number of PCOS women are obese and some found weight loss increase rate of spontaneous ovulation in

these women therefore as inhibin B serves marker of small antral follicle growth, The BMI mean \pm SD in different study groups associated with significant correlation with serum inhibin B level changes serum inhibin B level elevated associated with the elevation of the BMI. The suppression of inhibin B with increased BMI suggesting that granulosa cell or follicular production of inhibin B and possibility follicle health are decreased with obesity this may true even with normal cycling obese women because obesity itself associated with anovulation, increase body weight associated with elevated serum inhibin B level, (37-39).

Conclusion

Subfertility in PCOS women can be evaluated by measuring their serum level of inhibin B and IGF I during early follicular phase of menstrual cycle.

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