

The effect of inhibin B on ovarian response in subjects with polycystic ovary

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Summary:

Background: Inhibin B hormone is one of the indicative parameters in measuring ovarian reserve, which is important to be evaluated, since it is one of the markers of the female reproductive potential especially in polycystic ovary patients (PCOS) which is a common cause of anovulatory infertility.

Patients and methods: Ninety four infertile polycystic ovaries women, attending the infertility clinic at Baghdad teaching hospital, during the period of October 2005 to December 2006, were compared to 62 control group women who have unexplained infertility. After exact history and examination, inhibin level measurement was done in cycle day 3, the patients are divided according to age into 2 groups (more than 35 years and less than 35 years). Ovarian stimulation by one of 3 protocols (clomiphene citrate (CC), CC + gonadotropins, gonadotropins alone) was applied. Then the ovarian response is measured after that.

Results: It was found that inhibin is significantly higher in PCOS patients as compared to control [201.1 ± 122.40 vs 71.81 ± 40.63 pg/ml] ($P=0.0003$). After treatment with ovulation induction drugs, those who are less than 35 years with inhibin level less than 75 pg/ml, have no significant difference in response between the 3 protocols, while in those with inhibin more than 75 pg/ml the response was significantly high to protocol 1(CC only). In more than 35 years patients with inhibin level less than 75 pg/ml, there was no significant difference in response between protocols while in those with inhibin more than 75 pg/ml the response was significantly higher to protocol 2 (CC+ Gonadotropins).

Conclusion: Polycystic ovary patients have significantly higher concentration of inhibin B. Young patients less than 35 years with inhibin level less than 75 pg/ml showed no difference in response between the 3 protocols (CC, CC+ Gonadotropins, and Gonadotropins), while those with higher inhibin level, the response was significantly higher to protocol 1. In older patients with inhibin more than 75 pg/ml there is no significant difference in response among the 3 protocols.

Keywords: inhibin B, PCOS, ovarian stimulation.

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Introduction:

In recent years, it has become apparent that the polycystic ovary syndrome (PCOS) not only is the most frequent cause of anovulation and hirsutism, but is also associated with a characteristic metabolic disturbance, that may have important implications for long-term health (1). In fact any anovulatory state exists for a period of time, the "polycystic ovaries" emerges (2). Patients who desired to conceive are usually offered ovulation induction treatment, which is particularly challenging in patients with PCOS (3). The response of polycystic ovary to ovulation induction varies and differs significantly from that of normal ovaries. It tends to be slow with a significant risk of ovarian hyperstimulation and/ or cyst formation (4). PCOS patients are treated most successfully with low dose clomiphene citrate (CC) beginning on day 4-5 of the cycle. The dose is usually range from 50- 150 mg / day (5). If no response to 150 mg/day CC, the addition of gonadotropins is needed (6). Many gynecologists

Recommended clomiphene citrate, but women may receive a different treatments depending on the type of specialist consulted (7). The ability to achieve pregnancy either spontaneously or with assisted conception is governed largely by the response potential of the ovary, the so- called ovarian reserve. So the evaluation of ovarian reserve prior to initiation of ovarian stimulation is an important aspect of infertility workup (8). In the recent years inhibin level measurement emerged as a test for ovarian reserve, it is dimeric glycoprotein, principally produced in the ovary by granulosa cells and selectively inhibit follicular stimulating hormone secretion by the pituitary gland (9). It is an important intraovarian paracrine messenger which has a role in the maintenance of dominance of ovarian follicle (10). The bioactive inhibins are heterodimeric glycoproteins consisting of alpha- beta A or α - β A (inhibin A) and alpha-beta B or α - β B (inhibin B) subunits (11), linked by disulphide bridges. Whilst the alpha subunit remains constant, the different inhibins are defined by the beta subunit-currently A and B, although other beta subunits have been proposed (12).

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Inhibin B, which is the predominant form in small pre-ovulatory follicles, increases in concentration from early in the follicular phase to reach a peak coincident with the onset of the decrease in FSH which forms the basis of the pattern of mono-ovulation seen in normo-ovulatory women (11). The aim of the study is to evaluate the role of measuring inhibin B level in the beginning of the cycle on choosing the type of protocol used for ovulation induction in polycystic ovary patients according to the age of the patient.

Patients and methods:

Ninety four polycystic ovary patients were compared to 62 unexplained infertile patients, attending the infertility clinic at Baghdad teaching hospital, during the period of October 2005 to December 2006. The age range for control group was between 22 and 46 year (mean 33.45 ± 7.91 year), and for the patients group was between 20 and 45 year (mean 31.48 ± 7.48 year). The hormonal measurements were done in the hormonal laboratory in Al-Kindy teaching hospital by the use of ELIZA device. Exact and careful history was obtained from all patients involving the age. Also full obstetrical history was taken from the patients. They were asked also about contraceptives which were used, their types, and the time of their usage and the duration of using them. Drug history in general especially drugs used for ovulation induction. Semen analysis for the husband to exclude male factor of infertility is also done, especially to determine unexplained infertility. Patients were diagnosed as having polycystic ovaries according to the European society of human reproduction and embryology and American society for reproductive medicine criteria (13). Thyroid function test was estimated including T3, T4, and TSH, in addition to serum prolactin level, in order to exclude thyroid dysfunction and severe hyperprolactinemia. After diagnosing PCOS as the patients group and confirming the control group as unexplained infertility and excluding other possible causes of infertility, the study started from the next cycle. Blood samples were taken from all patients included in this study as follows:

5 ml of blood at cycle's day 3 to estimate Inhibin B concentrations. The protocol of ovulation induction then started. Three main ovulation-induction protocols are used. The first protocol includes using cloimphone citrate. 100 mg/ day (CC; 50 mg/ tablet, clomid, Yamanouchi pharma, the Neitherland), from cycle's day 2 to 6 alone after that an ultrasound made at cycle day 13 and if one or more follicles measure 16 mm or more, an intramuscular injection of human chorionic gonadotropin (HCG; Pregnyl, 1500 IU N.V., Organon, O.S.S, Holland, (3 vials given in a single dose). Or Profassi 5000 IU, Serono Company, Italy). After 24-36 hours, intercourse or intrauterine insemination is advised. The second protocol is using CC together with Gonal F (Follitropin alfa (r-hFSH), 75 IU/ ampoule, Serono company, Bari, Italy), in which CC

is used from day 2 - 6 of the cycle and after 2 days of using CC Gonal F is given as 1 ampoule/ day for 2 days then an ultrasound was done and according to it the dose was adjusted until reaching the optimal size then followed by hCG injection. The last regimen is using Gonal F alone from cycle day 2 -5 and serial ultrasound used until reaching the favorite follicular size. This protocol was used in 2 ways either in step up or step down i.e. either starting by one injection for several days then increasing the dose according to the follicular development or by starting with 2 injections then decreasing the dose. The patients were divided according to the age into 2 groups (less than 35 years group and above 35 years group, because as proposed, after the age of 35 the fertility of the female decreases). Each group was given three different protocols of ovulation induction that mentioned previously. Then they were divided according to inhibin B concentration to those having less than 75 pg/ml and those having more than 75 pg/ml (as it is mentioned in most studies to consider women with inhibin less than 45 pg/ml to having low ovarian reserve, others consider it 75 pg/ml or 76 pg/ml (14), so in this study 75 pg/ml was considered as a figure for dividing the patients because the number of patients having inhibin less than 45 pg/ml were very few). The response to treatment (ovulation-induction) after dividing the patients and control according to age and the level of inhibin B was considered as those having dominant follicle diameter ≥ 16 mm and with midluteal progesterone concentration of 6 ng/ml or more accompanying an evidence of ruptured follicle as it was seen in ultrasound. The ultrasonic device used in this study (transvaginal ultrasound), is (Sonolayer L, SAL-778 with a transvaginal 5mHz probe, Toshiba, Japan). All patients were asked to empty their bladders for good visualization. Ultrasound was done after that at day 13 of the cycle, to evaluate the number and size of the dominant mature follicles (≥ 16 mm in diameter). The diameter of the follicles were measured from the mean of 2 diameters (longitudinal and anteroposterior diameter), and the ovary was scanned from the inner to the outer margin. All data were coded and entered to the computer using statistical package for social sciences (SPSS 10). Differences between different variables measured by using student t- test. The P value given are 2-sided and 0.05 was considered the limit of statistical significance. Chi square test cross tab were used for categorical data for the tables more than 4 cells. A P value <0.05 was considered significant

Results:

After measuring inhibin B concentration in cycle day 3 in PCOS patients and unexplained infertility control women, it was found that inhibin is significantly higher in PCOS patients as compared to control (table 1).

Table (1): Inhibin concentration in patients and control groups.

	Patients (n= 94)	Control (n= 62)	P value
Inhibin B pg/ ml	201.1 ±122.40	71.81± 40.63	0.0003

n= number.

Values are in Mean ± SEM.

When comparing the response to treatment in patients in the three different protocols, it was found that in those aging less than 35 years with inhibin B level less than 75 pg/ ml (table 2), the response to treatment in the three different protocols in general was not significantly different and the same thing applies to the other groups (tables 3, 4, 5), but the differences observed between individual protocols within the group as will be shown later. In those less than 35 years group with an inhibin level less than 75, the response to protocol 1 (CC only) is highly different but not significant from the response to protocol 2 or the response to protocol 3 with a recorded confidence of not less than 89% difference between them while the response to treatment between protocol 2 and 3 was not highly different (table 2). While in those more than 35 years with the same inhibin concentration, the response to treatment was not significantly different between protocols (table 3). In those aging less than 35 years and with inhibin B concentration more than 75pg/ml, the response was observed to be of a high significant difference between those treated with protocol 1 and those with protocol 2 and also significantly between those with protocol 1 and 3, and it was high but not significant between protocol 2 and 3 (table 3). Finally those with more than 35 years with inhibin less than 75 pg/ml and those with inhibin more than 75 pg/ml, have no significant difference in response among the 3 protocols (table 4 and 5).

Table (2): The response to ovulation induction in patients aging less than 35 years with inhibin level less than 75pg/ml in protocol 1, 2 and 3.

Groups	Respond	Not respond	Total	P
Protocol 1	77.7% 77 % 7	33.3% 2	%100 9	0.070
Protocol 2	37.5 % 3	62.5 % 5	%100 8	0.218
Protocol 3	60 % 3	40 % 2	%100 5	0.312
Total	59.1 % 13	40.9 % 9	%100 22	

P>0.05

Table (3): The response to ovulation induction in patients aging more 35 years with inhibin level less than 75 pg/ml in protocol 1, 2 and 3.

Groups	Respond	Not respond	Total	P
Protocol 1	25 % 1	%75 3	%100 4	0.250
Protocol 2	66.6 % 4	33.3 % 2	%100 6	0.234
Protocol 3	%50 2	50 % 2	%100 4	0.375
Total	50 % 7	50 % 7	100% 14	

P>0.05

Table (4): The response to ovulation induction in patients aging less than 35 years with inhibin level more than 75 pg/ml in protocol 1, 2 and 3.

Groups	Respond	Not respond	Total	P
Protocol 1	88.2 % 15	11.76 % * 2	%100 17	0.001
Protocol 2	45.45% 5	54.54% 6	%100 11	0.225
Protocol 3	77.77% 7	33.33% 2	%100 9	0.070
Total	72.97 % 27	27.02 % 10	%100 37	

P>0.05

* P <0.05 the respond group is significantly different.

Table (5): The response to ovulation induction in patients aging more than 35 years with inhibin level more than 75 pg/ml in protocol 1, 2 and 3.

Groups	Respond	Not respond	Total	P
Protocol 1	66.66 % 2	33.33 % 1	%100 3	0.500
Protocol 2	70 % 7	30 % 3	%100 10	0.117
Protocol 3	75 % 6	25% 2	%100 8	0.109
Total	71.42 % 15	28.57 % 6	%100 21	

Discussion:

Measuring inhibin concentration in patients with PCOS and control women demonstrated that inhibin level in PCOS patients was significantly higher than that in control group (201.1± 122.40 vs 71.81± 40.63 pg/ml). This goes with (Lockwood 2000), who found that inhibin B is high in females with PCOS (11). In fact, there is no clear cut increase in inhibin B in PCOS patients (15). Others found that there is no difference in the mean inhibin B between patients and control (16, 17). Also Anderson said that despite the large ovarian volume and increased follicle number typically detected in women with PCOS, previous studies demonstrate that inhibin B is not elevated as could be expected in PCOS patients (18). Regarding the response to treatment, it has been studied in relation to age and inhibin B level. Patients less than 35 years but with inhibin level more than 75 pg/ml, the response to protocol 1 was significantly high, but those with low inhibin level there was no significant

difference in response among the 3 protocols. In patients more than 35 years, there was no significant difference in response among the protocols neither in the high nor the low inhibin level. So, the results of this study demonstrated that PCOS patients with inhibin B less than 75 pg/ml whether they were less or more than 35 years have no significant difference in response between protocols, but in the younger group there was higher response to CC than the older group. This means that when inhibin level is low, the response to ovulation induction was low whether the patient was less or more than 35 years, but those who were younger have better response, which was noticed also in those with inhibin more than 75 pg/ml, in whom the response in younger group was higher than older group. One of the reasons is that there is a gradual loss of follicles from 35 years onwards which leads to poor response (19). So inhibin predicts the poor response to ovarian hyperstimulation in infertile patients (15). Also it was found that women with inhibin B less than 45 pg/ml have poor ovarian response during assisted reproductive technique (20, 21). This can be explained by the fact that as inhibin has the ability to enhance small follicle growth; decreased inhibin B secretion in individual PCOS follicles may be responsible for their arrested development (21). This goes also with the work of Lee et.al. (1988) and Yamoto et.al. (1997) (22,23), who found that when day 3 inhibin B <45 pg/ml, the response to fertility treatment is less, the cancellation rate is higher, the number of oocytes retrieved are less and the pregnancy rate is lower. Others found that patients with inhibin >100 pg/ml are advised to continue the treatment cycle with the same initial daily FSH dose without increasing it because the response is expected to be good (24). It was reported that serum inhibin B measured during early FSH treatment may be of predictive value in monitoring ovarian stimulation treatment and can indicate whether sufficient oocytes will be retrieved in both normal and low responders (24, 21). Hall et.al. (1999) recorded that inhibin levels higher than the median value (76.5 pg/ml) are associated with pregnancy (14). So inhibin is important for determination of the FSH threshold of the cohort of follicles (25). Regarding the response to CC, it was reported that CC was generally shown to be effective in females with high androgen level (i.e PCOS patients), and some 75% of PCOS patients treated with CC will ovulate (26). This high response to CC in polycystic ovary patients is found also by Adashi, 1996, and Portnisky, 1991 who reported that the percentage of ovulation in these patients was 80% (27, 28). Ovarian steroid secretion capacity starts to decline as early as around the age of 35 years, and the age related decline in androgen secretion in normal females, also occur in PCOS patients, and this explains the lower response to treatment in older group (29).

Lowckwood et al., 2000, found that low inhibin B levels were independently more prognostic of reduced ovarian reserve and imminence of perimenopausal transition than age, cycle characteristics or basal FSH level and it was concluded that a low inhibin B, in spite of normal FSH in some patients is a prognostic factor for a poor outcome of ART (30, 31). Seifer and coworkers (1999), have demonstrated that women with declining ovarian reserve show evidence of a decrease in day 3 inhibin B levels before a rise in FSH levels which support its significance as an earlier marker of ovarian reserve than other markers (32, 33).

Conclusion:

Inhibin B level is significantly higher in polycystic ovary patients than control unexplained infertility group, and after treatment with ovulation induction drugs, within patients group aging less than 35 years, the response was significantly higher to protocol 1 in those with inhibin level more than 75 pg/ml, and high but not significant in those having less than 75 pg/ml inhibin. In patients more than 35 years, the response to the 3 different protocols showed no significant differences in high and low inhibin levels.

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