Pattern of Serum Inhibin B Hormone Secretion in Polycystic Ovarian Disease

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Abstract

Background: Inhibin selectively inhibits FSH but not LH secretion. Data are somewhat conflicting regarding differences in inhibin between normally cycling women and those with polycystic ovarian syndrome (PCOS).

The Aim of this Study: Is to study the pattern of inhibin-B hormone secretion in cases of PCOS throughout days 3, 5 and 9 of their menstrual cycles.

Patients and Methods: The study was performed on 29 women with PCOS, 5ml of blood were collected at days 3, 5 and 9 of the menstrual cycle of each participant for Measurement of inhibin-B hormone.

Results: Inhibin B hormone showed an increase in concentration along the studied days of menstrual cycle. There was a highly significant negative correlation between day 3 as well as day 5 inhibin B concentrations and body mass index (BMI), while day 9 inhibin B concentrations showed a non significant correlation with BMI. Day 3, 5 and 9 inhibin B concentrations showed a non significant correlation with age as shown in Table (3).

Conclusion: Inhibin B can’t be used alone to diagnose a case of PCOS due to absence of a characteristic pattern of secretion.

Key Words: Polycystic ovarian syndrome – PCOS – Inhibin B hormone – Body mass index – BMI.

Introduction

POLYCYSTIC ovary syndrome (PCOS) is a common endocrine disorder characterized by two of the following three criteria; oligo- and/or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries [1]. Infertility due to chronic anovulation is the most common reason for seeking treatment [2].

PCOS remains one of the most common hormonal disorders in women, with a prevalence estimated between 5 and 10 percent [3-5]. Variance in prevalence among populations may reflect the effect of ethnic origin, race, and other environmental factors on the phenotype [6,7].

A substantial proportion of women with PCOS are overweight; many are obese, some extremely obese [8]. Although obesity itself is not considered the inciting event in the development of the syndrome, excess adiposity can exacerbate associated reproductive and metabolic derangements [9].

The symptoms of PCOS usually begin around menarche [10], but onset after puberty may also occur as a result of environmental modifiers such as weight gain. Premature pubarche, the result of early secretion of adrenal steroids, may be a harbinger of the syndrome [11].

Although a large body of evidence points out that theca interna cells (TIC) and granulosa cells (GC) dysregulations are the main culprits, oocyte defect(s) may also participate in abnormal folliculogenesis of PCOS [12].

Jonard and Dewailly [12] proposed to divide the follicular problem of PCOS into two main components: First, the early follicular growth is excessive; second, the selection of one future dominant follicle from this increased pool does not proceed “follicular arrest”.

The hypothalamic pulse generator of gonadotropin releasing hormone (GnRH) is recognized to be central to ovulatory function. Luteinizing hormone (LH) is released from the anterior pituitary in pulses, the frequency of which is closely entrained with those of GnRH. In contrast, secretion of follicle stimulating hormone (FSH) is influenced by a number of regulatory molecules, including GnRH, estradiol, inhibin, and activin [13]. The
close temporal relationship between changes in levels of inhibin B and FSH in the mid-follicular phase suggest that the release of inhibin B by the preovulatory follicle critically regulates pituitary FSH secretion [13].

Inhibins and activins were isolated and purified from follicular fluid on the basis of their ability to inhibit (inhibin) [14-17] or stimulate (activin) [18,19] FSH release by pituitary cells in vitro. Activin and Inhibin are peptide members of transforming growth factor -β family [20]. Inhibin consists of two dissimilar peptides (known as alpha and beta subunits) linked by disulphide bonds. Two forms of inhibin (inhibin-A and inhibin-B) have been purified, each containing an identical alpha subunit and distinct but related beta subunits [21].

Inhibin is secreted by GC, but messenger RNA for the alpha and beta chains has also been found in pituitary gonadotropes [22]. Inhibin selectively inhibits FSH but not LH secretion. Indeed, while suppressing FSH synthesis, inhibin may enhance LH activity [23,24]. Cells actively synthesizing LH respond to inhibin by increasing GnRH receptor number; FSH dominant cells are suppressed by inhibin [23].

Data from studies examining serum inhibin B in PCOS women are conflicting: Whilst several reports revealed increased inhibin B concentrations in PCOS subjects compared with normal women [13,25,26], many others have failed to demonstrate such an increase [27-33]. Some authors have reported that inhibin B concentrations are increased only in a proportion of PCOS women: Non-obese PCOS patients [27,31] and in overall 23% of PCOS patients [29].

Thus, the data are somewhat conflicting regarding differences in inhibin between normally cycling women and those with PCOS. The aim of the present work is to study the pattern of serum inhibin-B hormone secretion in cases of PCOS throughout days 3, 5 and 9 of their menstrual cycles.

**Patients and Methods**

The current study was performed on 29 women with PCOS attending infertility outpatient clinic at Ain Shams University Maternity Hospital throughout the period between December 2008 and June 2009.

Women who received induction of ovulation, hormonal contraception or hormonal treatment within 3 months before the study or undergone laparoscopic ovarian drilling within 6 months before the study were excluded.

Diagnosis of PCOS was on the basis of ultrasonographic findings of more than 8 discrete follicles in the ovary with the follicles less than 10mm in diameter and usually peripherally arrayed around an enlarged hyperchogenic ovarian stroma [34] in addition to one or more of the following clinical findings; infertility, oligomenorrhea, hirsutism, obesity or increased LH/FSH ratio [1].

After taking usual precautions for venipuncture, 5ml of blood were collected at days 3, 5 and 9 of the menstrual cycle of each participant, samples were left to clot and separate without additives then serum was collected and frozen at −20°C or lower till time of assay.

Measurement of inhibin-B hormone in this study was done using the DSL-10-84100 active inhibin-B enzyme-linked immunosorbent (ELISA) Kit for quantitative measurement of dimeric inhibin-B in human serum which is a commercial kits supplied by Diagnostic System Laboratories Inc., USA [35].

**Principle of the test:**

The DSL-10-84100 active Inhibin B ELISA is an enzymatically amplified two-site two-step sandwich-type immunoassay. In the assay, standards, controls and unknown serum samples are incubated in microtitration wells, which have been coated with anti-inhibin/βB subunit antibody. After incubation and washing, the wells are incubated with biotinylated anti-inhibin α-subunit detection antibody and the immune-reaction monitored by subsequent addition of streptavidin labeled with enzyme horseradish peroxidase. After a third incubation and washing step, the wells are incubated with the substrate tetra-methyl-benzidine. An acidic stopping solution is then added and the degree of enzymatic turnover of the substrate is determined by dual wavelength absorbance measurement at 450 and 620nm. The absorbance measured is directly proportional to the concentration of inhibin B present. A set of inhibin B standards is used to plot a standard curve of absorbance versus inhibin B concentration from which the inhibin B concentrations in the unknowns can be calculated.

**Results**

The Mean±Standard deviation (SD) of age was 26.3±3.32 years, and the Mean±SD of body mass index (BMI) was 25.24±4.76kg/m². As shown in Fig. (1), 19 patients (65.5%) were within normal weight (BMI 20-25), 6 patients (20.7%) were over weight (BMI 25-30) and 4 patients (13.8%) were obese (BMI >30).
Inhibin B hormone showed an increase in concentration along the studied days of menstrual cycle. Mean±SD of serum inhibin B concentration in day 3 of the menstrual cycle was 100.5±31.36 pg/ml and it ranged between 21 and 154.3 pg/ml. Mean±SD of serum inhibin B concentration in day 5 of the menstrual cycle was 167.42±53.79 pg/ml and it ranged between 54.33 and 294.3 pg/ml while ±SD of serum inhibin B concentration in day 9 of the menstrual cycle was 206.3±47.05 pg/ml and it ranged between 81 and 294.3 pg/ml (Table 1).

There was a highly significant negative correlation between day 3 as well as day 5 inhibin B concentrations and BMI, while day 9 inhibin B concentrations showed a non significant correlation with BMI (Table 2).

Table (2): Correlation between day 3, 5 and 9 inhibin B concentrations (pg/ml) and BMI.

<table>
<thead>
<tr>
<th>Inhibin B concentration (pg/ml)</th>
<th>BMI 20-25</th>
<th>BMI 25-30</th>
<th>BMI &gt;30</th>
<th>r*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 3 114.32±25</td>
<td>88.77±6.55</td>
<td>52.65±26.86</td>
<td>-0.767</td>
<td><strong>p&lt;0.001</strong></td>
<td></td>
</tr>
<tr>
<td>Day 5 189.05±40.64</td>
<td>117.65±21.81</td>
<td>119.32±62.14</td>
<td>-0.614</td>
<td><strong>p&lt;0.001</strong></td>
<td></td>
</tr>
<tr>
<td>Day 9 218.87±46.23</td>
<td>187.65±50.25</td>
<td>187.65±35.7</td>
<td>-0.33</td>
<td>p=0.068</td>
<td></td>
</tr>
</tbody>
</table>

Data presented as Mean±SD. * Analysis done using Pearson correlation coefficient. ** Highly significant.

Day 3, 5 and 9 inhibin B concentrations showed a non significant correlation with age as shown in (Table 3).

Table (3): Correlation between day 3, 5 and 9 inhibin B concentrations (pg/ml) and age.

<table>
<thead>
<tr>
<th>Inhibin B concentration (pg/ml)</th>
<th>Age</th>
<th>r*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 3 100.5±31.36</td>
<td>94.33</td>
<td>-0.229</td>
<td>0.23</td>
</tr>
<tr>
<td>Day 5 167.42±53.79</td>
<td>161</td>
<td>-0.228</td>
<td>0.23</td>
</tr>
<tr>
<td>Day 9 206.3±47.05</td>
<td>221</td>
<td>0.019</td>
<td>0.91</td>
</tr>
</tbody>
</table>

* Analysis done using Pearson correlation coefficient.

Discussion

Although the underlying pathophysiology of PCOS remains uncertain, current evidence suggests that ovarian hypersecretion of androgens is the primary disorder in PCOS [10]. It has been hypothesized that inhibin B is involved in the excess of intraovarian androgens by locally promoting the LH- and/or insulin-induced androgen production by TIC through autocrine/paracrine mechanisms [36]. It has also been proposed that increased inhibin B secretion by polycystic ovaries could suppress pituitary FSH secretion by an endocrine mechanism [37].

In the present study, analysis of inhibin B hormone concentrations throughout the studied days showed an increase in concentration with a highly significant negative correlation between day 3 as well as day 5 inhibin B concentrations and BMI.

These results confirmed the previous finding of an inverse correlation between inhibin B and BMI [27,29-32]. It is not clear why obesity is associated with a reduction of the circulating inhibin B concentrations in women with PCOS. It has been hypothesized that inhibin B secretion may be reduced in obese women as a result of functional impairment of GC because of insulin resistance [38]. Hyperinsulinaemia, which is more common in obese women, may reduce inhibin B production either by a direct effect on GC or through impairment of insulin-like growth factor-I (IGF-I) action on these cells [31].
Our findings suggest that although PCOS women might over secrete inhibin B as a result of increased numbers of small antral follicles, this effect is counteracted by the increased BMI which occurs in a large number of PCOS women. This balancing effect would not occur in non-obese PCOS women [39].

In patients with PCOS inhibin B levels may be associated with the severity of ovarian dysfunction and consequently may predict ovulation induction outcome [40]. Although previous studies comparing inhibin B levels in women with PCOS to healthy controls showed that inhibin B levels were comparable in the two groups [41,42].

Although inhibin B is expected to decrease with age as a result of the declining number of antral follicles. The present study showed no significant correlation between inhibin B concentration and age of the studied group. This is in agreement with several previous studies [29-31,38].

On the other hand, Bili and colleagues [43] showed a modest inverse correlation (r = –0.118; p < 0.05) between inhibin B and age. A possible explanation our results failed to show this correlation is that most women in the current study were relatively young (20-30 years, Mean ± SD is 26.3 ± 3.32) compared to wider range of the group included in that study (17-42 years).

In conclusion there is no characteristic pattern of inhibin B hormone secretion detected in the studied group of PCOS patients. Inhibin B can’t be used alone to diagnose a case of PCOS due to absence of a characteristic pattern of secretion. We recommend further studies to more understand the role of inhibin B hormone in the human menstrual cycle and its role in PCOS.

References
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