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Comparison of Follicle-Stimulating-Hormone-Stimulated Dimeric Inhibin and Estradiol Responses as Indicators of Granulosa Cell Function in Polycystic Ovary Syndrome and Normal Women

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Context: Follicular phase secretion of inhibin B, like that of estradiol (E_2), correlates with the quantity and quality of developing follicles. However, it has not been established whether inhibin B responses to gonadotropin stimulation parallel those of E_2 as a reflection of granulosa cell functional capacity.

Objective: Our objective was to determine whether inhibin B responses to FSH stimulation are similar to those of E_2 in women with polycystic ovary syndrome (PCOS) and normal women.

Design and Setting: We conducted a prospective study to compare ovarian responses in two groups of women at a general clinical research center in a tertiary academic medical center.

Patients: Women with PCOS, 18–35 yr (n = 19), and normal ovulatory controls, 18–35 yr (n = 7), were recruited for study.

Interventions: Serum samples were measured over a 24-h period after an iv injection of recombinant human FSH, 150 IU.

Main Outcome Measures: Serum E_2, inhibin A, and inhibin B responses after FSH administration were assessed.

Results: In PCOS women, the 24-h production of inhibin B and E_2 after FSH was significantly greater than that of normal controls. Within the PCOS group, the fold change in inhibin B was significantly greater than that of E_2. Inhibin A responses between groups were similar and of markedly lower magnitude.

Conclusions: FSH-stimulated inhibin B responses may be employed to assess the functional capacity of granulosa cells in PCOS and normal women. **(*J Clin Endocrinol Metab* 91: 2920–2925, 2006)**

IN NORMAL WOMEN, basal and stimulated serum estradiol (E_2) levels have been used effectively as a clinical measure of granulosa cell health and viability. During the follicular phase of the normal menstrual cycle, progressive growth of the dominant follicle correlates extremely well with rising serum E_2 levels (1). In addition, during ovulation induction, E_2 levels have been correlated with multiple follicle development and risk for hyperstimulation syndrome (2, 3). In women with polycystic ovary syndrome (PCOS), the utility of serum E_2 to reflect the functional status of the follicle population is less clear. For instance, the modest level of circulating E_2 does not correlate with the rather high number of antral follicles present in the polycystic ovary. *In vitro* studies of cultured PCOS granulosa cells have demonstrated a markedly greater E_2 response to FSH compared with that of normal cells (4). In addition, recent *in vivo* studies have confirmed that women with PCOS exhibit significantly greater FSH-stimulated E_2 production than that observed in normal women (5). The increased magnitude of stimulated E_2 observed in PCOS women has been attributed to the greater number of antral follicles observed in these women or increased granulosa cell sensitivity to FSH or both. This concept is supported by studies that show serum inhibin B (Inh B) and anti-Mullerian hormone levels, both derived from preantral and small antral follicles, are greater in PCOS women than those of normal women (6–8). In addition, the secretion patterns of inhibins throughout the menstrual cycle have suggested that early follicular phase Inh B may signify the quantity and quality of developing follicles, whereas Inh A reflects follicle maturity (9–12). However, in PCOS women, increased circulating levels of Inh B have not been a consistent finding in all studies. Several reports have shown that in PCOS women, circulating Inh B levels are equal to or less than those observed in normal women (13–17). These results are perplexing because given the greater number of preantral and small antral follicles in PCOS, it would be expected that circulating Inh B levels would exceed those of normal women. To further explore the relationship of Inh B and E_2 as a reflection of the follicle population and granulosa cell function in PCOS, basal levels and acute 24-h patterns of dimeric inhibin and E_2 after provocative FSH stimulation were examined in women with PCOS and normal women.

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Abbreviations: A, Androstenedione; BMI, body mass index; COH, controlled ovarian hyperstimulation; CV, coefficients of variation; DHEAS, dehydroepiandrosterone sulfate; E_1, estrone; E_2, estradiol; Inh B, inhibin B; IVF, *in vitro* fertilization; 17-OHP, 17-hydroxyprogesterone; P_4, progesterone; PCOS, polycystic ovary syndrome; r-hFSH, recombinant human FSH; T, testosterone.

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Subjects and Methods

Subjects

Nineteen women with PCOS and seven normal women with regular menstrual cycles were recruited for study. All PCOS subjects exhibited

clinical and biochemical evidence of hyperandrogenism and were either oligomenorrheic or amenorrheic. In PCOS and normal control groups, the mean ages (± SE) were 26.6 ± 1.1 and 28.0 ± 1.6 yr, respectively, and not significantly different. The mean body mass index (BMI) was significantly greater in the PCOS subjects compared with that of the normal controls (34.1 ± 1.8 *vs.* 27.3 ± 1.8 kg/m^2, respectively; $P < 0.05$). Each PCOS subject exhibited ultrasound evidence of bilaterally enlarged polycystic ovaries. Late-onset congenital adrenal hyperplasia was excluded by a serum 17-hydroxyprogesterone (17-OHP) level of less than 3 ng/ml. Circulating TSH and prolactin levels were normal and not significantly different between groups. The normal subjects were monitored by menstrual calendar for 6 months and by urinary LH testing for 1 month before study to establish the regularity of their cycles. None of the subjects in either group had received any hormone medication for at least 3 months before study. The study had been approved by the Institutional Review Board at the University of California, San Diego, and written informed consent was obtained from each participant before study.

Procedures

Each subject was admitted to the General Clinical Research Center at the University of California, San Diego, on the day of testing. In normal subjects, testing was performed during the midfollicular phase defined as d 5–8. After baseline sampling, recombinant human FSH (r-hFSH) was administered as an iv bolus at a dose of 150 IU. The r-hFSH (Gonal-F) was kindly provided by Serono Laboratories, Inc. None of the PCOS subjects had experienced recent ovulation, as evidenced by serum progesterone (P_4) levels of less than 1 ng/ml at the baseline sample. Blood samples were drawn through an indwelling iv catheter at half-hour intervals for 2 h before and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 h after r-hFSH administration. Samples were allowed to clot, and sera were separated by centrifugation and stored at −20 C until assayed. Individual serum samples were analyzed in the same assay in duplicate. The E_2 responses to r-hFSH in a subset of 16 of the PCOS subjects and the seven normal women have been previously reported (5).

Assays

Serum concentrations of LH and FSH were measured by RIA with intra- and interassay coefficients of variation (CV) of 5.4 and 8.0%, respectively, for LH and 3.0 and 4.6%, respectively, for FSH (Diagnostic Products Corp., Los Angeles, CA). Serum concentrations of estrone (E_1), E_2, androstenedione (A), and testosterone (T) were measured by well-established RIA with intraassay CV less than 7%. P_4, 17-OHP, and dehydroepiandrosterone sulfate (DHEAS) were measured by RIA with intraassay CV less than 7% (Diagnostic Systems Laboratories, Inc., Webster, TX). Serum concentrations of Inh A and Inh B were measured by ELISA with inter- and intraassay CV of 7.1 and 3.3%, respectively, for Inh A and 6.7 and 4.6%, respectively, for Inh B (Diagnostic Systems Laboratories). The highly specific two-site ELISA kit allows for quantitative measurement of dimeric Inh A and dimeric Inh B in human serum. Assay sensitivity for Inh A was 1.0 pg/ml and for Inh B was 7.0 pg/ml. SHBG was determined by the DSL 6300 kit with intra- and interassay CV of 2.5 and 3.73%, respectively.

Statistical analysis

Baseline hormone values between PCOS and normal women were compared by group *t* tests using SPSS software (SPSS, Inc., Chicago, IL). E_2, Inh A, and Inh B responses were analyzed separately as maximal concentration, absolute maximal change from baseline, fold change, and area under the curve. Where applicable, significance testing was two-sided at a 5% significance level. To control for the effect of the confounding variables of A, T, BMI, insulin, LH, and SHBG on the difference in stimulated Inh B levels between PCOS and controls, analysis of covariance was performed.

Results

Baseline studies

Baseline hormone values are shown in Table 1. In PCOS women, mean (± SE) circulating levels of LH, A, T, E_1, and fasting insulin were significantly greater than those of normal controls, whereas mean SHBG levels were significantly lower than those of normal controls. Basal levels of serum FSH, DHEAS, 17-OHP, E_2, P_4, Inh A, and Inh B were similar in both groups.

TABLE 1. Mean endocrine-metabolic values (± SE) of PCOS and normal women

	PCOS (n = 19)	Normal women (n = 7)
LH (mIU/ml)	7.4 ± 1.2	3.4 ± 0.4[a]
FSH (mIU/ml)	4.5 ± 0.3	4.5 ± 0.3
T (ng/ml)	0.64 ± 0.05	0.34 ± 0.03[a]
A (ng/ml)	1.49 ± 0.11	0.97 ± 0.17[a]
17-OHP (ng/ml)	0.33 ± 0.04	0.23 ± 0.07
DHEAS (ng/ml)	1710 ± 135	1221 ± 394
E_1 (pg/ml)	95 ± 9	54 ± 3[a]
E_2 (pg/ml)	75 ± 6	75 ± 7
P_4 (ng/ml)	0.28 ± 0.03	0.21 ± 0.04
SHBG (μg/dl)	1229 ± 145	2081 ± 237[a]
Insulin (mU/ml)	46.1 ± 13.2	14.1 ± 2[a]
Inhibin A (pg/ml)	7.6 ± 2.4	8.6 ± 1.4
Inhibin B (pg/ml)	126.2 ± 11.6	136.2 ± 21.3

To convert to SI units, multiply by the following conversion factor: 3.47 for T, 3.49 for A, 3.03 for 17-OHP, 0.0027 for DHEAS, 3.69 for E_1, 3.67 for E_2, 3.18 for P_4, 40.2 for SHBG, 7.18 for insulin, 0.00003125 for Inh A, and 0.00003125 for Inh B.

[a] $P < 0.05$.

Inh B responses to r-hFSH administration

Serum Inh B responses to iv r-hFSH administration in PCOS and normal women are illustrated in Fig. 1. In women with PCOS after r-hFSH injection, serum Inh B levels began to increase by 4 h and progressively rose to achieve a 5-fold maximal concentration at 16 h, after which levels remained constant up to 24 h. A similar pattern of Inh B release after r-hFSH was observed in normal women, although the magnitude of response, 3.0-fold, was considerably less and the

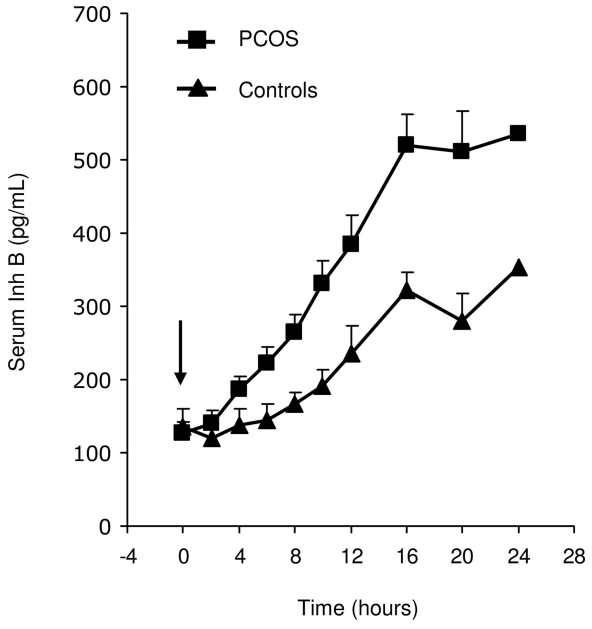

FIG. 1. Mean (± SE) serum Inh B levels after administration of r-hFSH, 150 IU, in PCOS and normal women.

initial increment was delayed. The rate of Inh B increase in PCOS women was considerably greater than that of normal women because equivalent responses in the PCOS group were achieved 6 h earlier compared with those observed in normal women. In PCOS women, maximally stimulated Inh B levels, absolute maximal change from baseline, fold change, and area under the curve were all significantly greater than those observed for the normal group (Table 2).

To determine whether the difference in Inh B responses between the PCOS and normal women was influenced by potentially confounding variables such as A, T, BMI, insulin, LH, and SHBG, an analysis of covariance was performed. The analysis revealed that maximally stimulated Inh B levels and fold change remained significantly greater in the PCOS women than those observed for the normal group ($P = 0.01$) and were not influenced by these factors.

Inh A responses to r-hFSH administration

Serum Inh A responses to iv r-hFSH administration in PCOS and normal women are illustrated in Fig. 2. After injection, women with PCOS exhibited a steady and nearly 4-fold increment in Inh A and attained maximal concentrations at 24 h. A similar response of Inh A after r-hFSH was observed in normal women, although the 2.9-fold increment was somewhat less than that of the PCOS group. In contrast to Inh B, the rates of increase in Inh A in PCOS and normal women were relatively similar over the 24-h sampling period.

E_2 responses to r-hFSH administration

As expected, iv administration of r-hFSH to women with PCOS resulted in a rise of serum E_2 after 2 h that appeared to reach maximal levels at 6 h after injection. These elevated concentrations were sustained for about 10 h before declining to approximately 35% of peak values by 24 h. In the normal group, maximal E_2 concentrations after r-hFSH occurred at 6 h, and these peak levels were maintained for the duration of sampling. The E_2 responses to r-hFSH, 150 IU, in normal women have been previously reported (5). In PCOS women, r-hFSH-stimulated E_2 responses expressed as maximal concentration, maximal change from baseline, fold change, and area under the curve were significantly greater than those of normal controls (Table 2).

TABLE 2. Mean maximal (± SE) serum Inh B and E_2 responses to r-hFSH, 150 IU, in PCOS and normal women

	Normal women (n = 7)	PCOS (n = 19)
Inh B (pg/ml)		
Maximal concentration	369 ± 33	602 ± 55[d]
Absolute increment	233 ± 25	476 ± 49[d]
Fold change	3.0 ± 0.4	5.1 ± 0.4[c]
AUC	5425 ± 542	8626 ± 638[b]
E_2 (pg/ml)		
Maximal concentration	162 ± 13	226 ± 18[b]
Absolute increment	108 ± 10	168 ± 17[c]
Fold change	3.1 ± 0.3	4.0 ± 0.3[a]
AUC	3033 ± 222	4000 ± 303[a]

AUC, Area under the curve (pg/ml over 24 h).
Between-group comparisons: [a] $P < 0.05$; [b] $P < 0.01$; [c] $P < 0.005$; [d] $P < 0.001$.

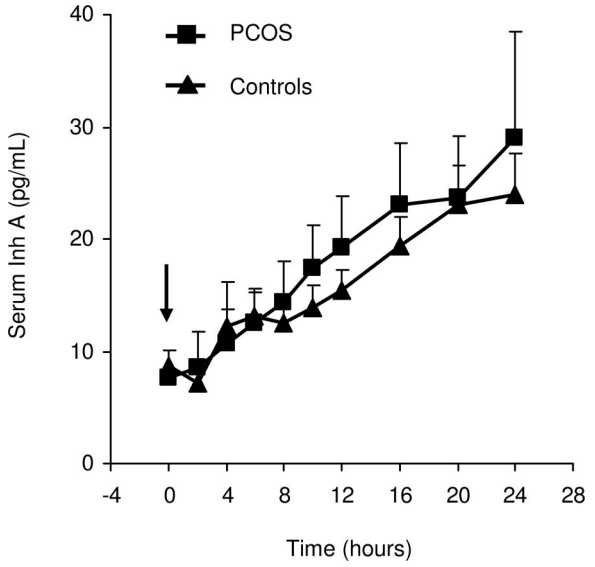

FIG. 2. Mean (± SE) serum Inh A levels after administration of r-hFSH, 150 IU, in PCOS and normal women.

Within-group comparisons of Inh B and E_2 responses to FSH administration

Within the group of PCOS women, the incremental fold change in Inh B was significantly ($P < 0.03$) greater than that observed for E_2 (Table 2). By comparison, in normal women, the increments of change for Inh B and E_2 were equivalent. Within both groups, fold changes in Inh A were similar to those for E_2.

Discussion

The results of this study have demonstrated that in women with PCOS, the 24-h production of Inh B and E_2 in response to iv administration of FSH was significantly greater than that of normal controls. In addition, maximal Inh B and E_2 responses exhibited a strong positive correlation. Within PCOS women, the relative increase of Inh B from baseline was significantly greater than the increment observed for E_2. Inh A responses between groups were similar and of markedly lower magnitude. In PCOS women, the time-course patterns of response revealed that initial FSH-stimulated increases of Inh B, Inh A, and E_2 occurred about 2–4 h after injection, which were equivalent to those noted in normal women, with the exception of a delayed response in Inh B. Maximal concentrations of E_2 were achieved by 6 h in PCOS and normal women, whereas peak values of Inh B occurred approximately 10 h later. Inh A levels rose gradually to achieve maximal levels 24 h after FSH administration.

The substantial increased production of Inh B and E_2 in response to FSH in women with PCOS compared with that of normal women is consistent with results of previous studies that have examined Inh B responses after gonadotropin administration during controlled ovarian hyperstimulation (COH). Anderson *et al.* (6) showed that in PCOS women undergoing ovulation induction, administration of highly purified FSH induced progressive increases in circulating Inh B that were significantly greater than those observed in normal women receiving similar therapy. The disparate

Inh B responses between groups reflected the likely increased number of preantral and small antral follicles in PCOS women, because induced cycles in both groups were monoovulatory. In addition, the similarity of E_2 responses between groups suggested that Inh B may more accurately reflect the functional capacity of granulosa cells compared with FSH-stimulated E_2 production. Consistent with this notion, it was demonstrated that before COH and *in vitro* fertilization (IVF), the mean Inh B response in PCOS women 24 h after a sc injection of r-hFSH, 300 IU, was higher than that observed in normal women (18). Interestingly, a difference in serum E_2 responses was not detected, although PCOS women exhibited greater ovarian volume, implying an increased number of antral follicles. During COH, incremental changes in Inh B and E_2 during stimulation were significantly higher than those of normal women using the same treatment protocol. Notably, Inh B responses to FSH correlated with follicle cohort size and appeared to predict follicle growth in both PCOS and normal women. These results are in agreement with other studies performed in women undergoing COH for IVF, which revealed that gonadotropin-stimulated Inh B responses, as well as those of Inh A, correlated with the number of oocytes retrieved and were associated with an increased likelihood of successful IVF outcome (13, 19–22). In the women who achieved successful pregnancy after IVF or gamete intrafallopian tube transfer, Inh B and Inh A responses on the day of human chorionic gonadotropin administration were greater than those of women who did not become pregnant (19). Of those women that sustained pregnancy, the follicular fluid concentration of Inh B in the lead follicle was 1.5-fold higher compared with the value observed in the nonpregnant group. These findings together with similar supportive evidence in the rodent model have led to the suggestion that Inh B represents granulosa cell secretory capacity and follicle quality, whereas Inh A reflects follicle maturation and oocyte quality (19, 21, 23). The results of the current study are compatible with the concept that Inh B responses to FSH may serve as an equivalent if not better functional measure of granulosa cell secretory capacity than E_2 because among PCOS women, the incremental change of Inh B, 5.1-fold, was significantly greater than that observed for E_2, 4.0-fold, whereas among normal women, the relative increases of Inh B and E_2 were similar, 3.0-fold and 3.1-fold, respectively. This role of Inh B as a predictor of the functional capacity of granulosa cells is further supported in the current study by the strong positive correlation between maximal stimulated Inh B and E_2 levels in PCOS women (Fig. 3). The greater release of Inh B in women with PCOS compared with that of E_2 is consistent with the known increased numbers of preantral and small antral follicles in this disorder and the commensurate higher risk of excessive ovarian responsiveness and ovarian hyperstimulation syndrome during ovulation induction (24, 25).

Our results demonstrated that maximally stimulated E_2 levels preceded the peak production of Inh B and Inh A in response to FSH by 10 h. In contrast, there are several lines of evidence that indicate FSH stimulation of granulosa cells is associated with an initial rise of Inh B followed by increases in serum E_2. First, in normal women studied during the follicular phase of the menstrual cycle, gonadotropin recovery from GnRH antagonist suppression was associated with an earlier increase in Inh B compared with that of E_2 by 3 d (26). The rise in Inh B was likely caused by restoration of FSH secretion as recovery of gonadotropin secretion after pituitary desensitization is marked by an initial rise in serum FSH followed by a later increase of LH (27). Accordingly, the delayed increase in E_2 was attributed to a subsequent cohort of follicles generated by the incipient rise in FSH (26). Second, in GnRH-deficient women treated with pulsatile GnRH administered at physiological frequency, every 90 min, or slow frequency, every 4 h, increments in Inh B production were directly related to the rate of GnRH delivery (10). Notably, the increase in circulating Inh B resulting from slow-frequency GnRH administration was not accompanied by changes in serum E_2 until the GnRH pulse frequency was increased to the physiological rate. A similar lack of incremental serum E_2 was evident during initial Inh B increments in response to daily low-dose FSH in PCOS women undergoing ovulation induction (6). These discordant patterns suggest that relative Inh B and E_2 responsiveness to FSH may be dose related with the possibility that Inh B may be a more sensitive measure of granulosa cell functional capacity than E_2. Collectively, the results of the above studies have demonstrated a direct effect of FSH on Inh B production in granulosa cells from immature follicles that have not yet acquired the capacity to express the aromatase gene. In the current study, a pharmacological dose of FSH, 150 IU, was used in women not subjected to ovarian suppression and capable of spontaneous steroid production, which probably accounted for the temporal pattern of maximal E_2 and Inh B production. Without inhibition of pituitary gonadotropin secretion, continuous androgen substrate production was maintained and available for conversion to E_2 after activation of aromatase, a process that *in vivo* appeared to occur within a relatively short interval of time, 2–4 h. By comparison, the peak production of Inh B in both groups of women at 16 h was

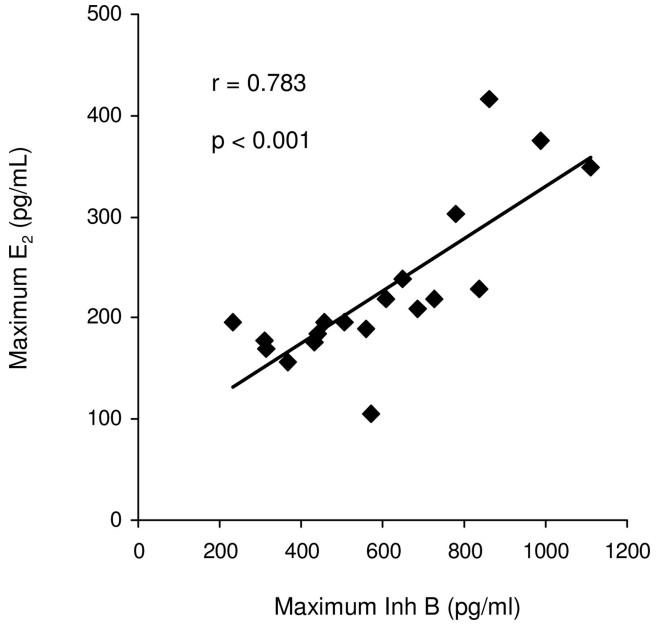

FIG. 3. Correlation of maximal Inh B and E_2 responses to r-hFSH, 150 IU, in PCOS women.

consistent with the established pattern of dimeric inhibin release after FSH stimulation as previously reported (28). Thus, in women, it appears that the temporal pattern of maximal Inh B and E_2 responsiveness is dependent on the dose of FSH administered as well as the maturational development of the existing ovarian follicle population.

Additional increases in FSH-stimulated Inh B levels between 16 and 24 h were not detected. Interestingly, in PCOS women, the maintenance of maximal Inh B concentrations over this time period coincided with the interval during which serum E_2 levels declined by 35% from stimulated peak values. The decrement in E_2 levels was not likely the result of inhibition of endogenous FSH by relatively high Inh B levels for the following reasons. First, a similar pattern of Inh B responsiveness in normal women was not associated with a late decline in E_2 production. Second, we have not observed a corresponding decrease of circulating FSH during the interval of E_2 decline in PCOS as previously reported (5). These findings suggest that increased Inh B was probably not responsible for the diminished E_2 response in PCOS women. The possibility also exists that PCOS granulosa cells may have limited functional capacity in the production of E_2 beyond 16 h after a single injection of FSH.

In the current study, baseline levels of Inh B were equivalent in women with PCOS and normal women. This finding is consistent with most studies, although some reports have documented increased Inh B levels in PCOS women (6, 7). The similarity between baseline levels may reflect the consequence of diminished FSH secretion in PCOS despite the presence of increased numbers of preantral and small antral follicles. Conversely, *in vitro* studies have shown that granulosa cells of small antral follicles isolated from polycystic ovaries failed to demonstrate an increase in Inh B after FSH stimulation, suggesting that any lack of Inh B production in PCOS was not a result of deficient FSH (29). However, when combined with IGF-I, FSH stimulated a significant amount of Inh B release from cultured granulosa cells. Because circulating free IGF-I is increased and intrafollicular concentrations of IGF-I and IGF-II are decreased in women with PCOS, the consideration remains that the degree of FSH stimulation may determine granulosa cell Inh B production in these women (30, 31). Alternatively, it has been suggested that increased LH secretion in PCOS may stimulate granulosa cell luteinization and terminal differentiation resulting in a reduced capacity for inhibin production (14). Circulating Inh B has been inversely correlated with BMI and serum insulin levels and positively associated with LH and SHBG (32). In our study, the PCOS women exhibited significantly greater BMI and circulating insulin concentrations, whereas SHBG levels were lower compared with the normal group. In an effort to determine whether baseline differences in A, T, BMI, insulin, LH, and SHBG may have contributed to the difference in Inh B responses between the PCOS and normal women, an analysis of covariance was performed. Interestingly, the FSH-stimulated Inh B responses in the PCOS women remained significantly increased over the normal women after controlling for these variables. Therefore, it may be the increased numbers of preantral and small antral follicles in women with PCOS, not differences of A, T, BMI, insulin, LH, and SHBG between groups, which is responsible for the exaggerated Inh B response to iv FSH stimulation.

Inh A responses to FSH stimulation were similar in PCOS and normal controls, which is in keeping with previous published studies (33, 34). In both groups, the magnitude of response was markedly lower than Inh B and E_2 responses. Because FSH stimulation was performed in the absence of a late dominant follicle or corpus luteum formation, the primary sources of ovarian Inh A, our findings were not unexpected.

Notable aspects of this study differ from previous efforts that have described granulosa cell responses to FSH primarily during treatment regimens for infertility. A standardized format of iv FSH administration was employed to assess dimeric inhibin and E_2 release, whereas all previous reports have involved varying doses of FSH injected either im or sc (6, 13, 18–22). Within this paradigm, we have carefully examined the 24-h response in 2- to 4-h intervals, whereas most other studies have involved sampling intervals on a daily basis or greater. Our results revealed a different temporal sequence of Inh B and E_2 release compared with previous reports (10, 26). The reversed sequence of Inh B and E_2 release was attributable to spontaneous stimulation without previous GnRH agonist suppression.

In summary, using a prescribed format of iv FSH administration, we have determined that in women with PCOS, acute 24-h Inh B release was significantly greater than that observed in normal women. Moreover, the fold change in Inh B response for PCOS women was greater than that observed for E_2, which is consistent with the higher number of preantral and small antral follicles in the polycystic ovary. Our findings also revealed that the temporal sequence of E_2 and Inh B release after FSH was reversed in the absence of ovarian suppression. We conclude that among PCOS women, Inh B responses to FSH stimulation provide at least an equivalent if not more accurate reflection of granulosa cell functional capacity compared with that afforded by E_2 responsiveness. Furthermore, FSH-stimulated Inh B release may be particularly useful in future clinical investigation of granulosa cell function in women with PCOS.

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