

# Serum anti-Müllerian hormone and inhibin B concentrations are not useful predictors of ovarian response during ovulation induction treatment with recombinant follicle-stimulating hormone in women with polycystic ovary syndrome

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**Objective:** To describe changes of anti-Müllerian hormone (AMH) and inhibin B during low-dose gonadotropin ovulation induction (OI) treatment in women with polycystic ovary syndrome (PCOS), and thus disturbed selection of the dominant follicle.

**Design:** Observational study.

**Setting:** A referral fertility clinic.

**Patient(s):** Women with PCOS (n = 48) and normo-ovulatory women (n = 23).

**Intervention(s) and Main Outcome Measure(s):** Serum AMH, inhibin B, FSH, and E<sub>2</sub> concentrations were measured at start of stimulation, on the day of follicle selection, and at administration of hCG during OI cycles and were compared with concentration measured during the normal menstrual cycle.

**Result(s):** Development of a single dominant follicle was observed in 92% of all OI cycles, reflected by similar E<sub>2</sub> concentrations compared with those in spontaneous cycles. AMH concentrations were constant during low-dose ovarian stimulation. Inhibin B concentrations remained elevated in patients with PCOS, suggesting prolonged survival of small antral follicles, whereas in controls inhibin B concentrations declined during the late follicular phase.

**Conclusion(s):** The lack of change in AMH and inhibin B concentrations suggest that follicle dynamics during low-dose stimulation seem different from those during controlled ovarian hyperstimulation. In addition, constant AMH and inhibin B levels suggest that neither AMH nor inhibin B is an accurate marker of ovarian response after low-dose gonadotropin OI in patients with PCOS. (Fertil Steril® 2011;96:459–63. ©2011 by American Society for Reproductive Medicine.)

**Key Words:** Anti-Müllerian hormone, inhibin B, ovulation induction, polycystic ovary syndrome (PCOS)

Chronic anovulation is a major cause of subfertility (1). The great majority of chronic anovulatory patients (80%) present with serum FSH and E<sub>2</sub> concentrations within the normal range and are classified as World Health Organization class II for anovulatory infertility (WHO II) (2). Typically, a large proportion of these women also have polycystic ovary syndrome (PCOS) (3). This syndrome is defined by the presence of at least two of three Rotterdam consensus criteria: anovulation, hyperandrogenism, and/or polycystic ovaries (PCOs) (4). Although the etiology of PCOS still remains unclear, this syndrome is characterized by

failure in dominant follicle selection (5). The selection of antral follicles is disturbed and follicles accumulate, resulting in anovulation and PCO (5, 6).

Fertility treatment in women with WHO II anovulation aims at restoring ovulation by inducing maturation and ovulation of a single dominant follicle (6). If first-line treatment with clomiphene citrate does not result in ovulation or pregnancy, second-line treatment consisting of exogenous gonadotropins is adopted (7). Further, in women with PCOS, the increased follicle number may facilitate multifollicular growth during low-dose stimulation, and so these women may be at risk of multiple pregnancies (8). In addition, inhibin B and AMH are considered as accurate predictors of ovarian response during ovarian stimulation cycles for IVF (9, 10). However, results are inconclusive regarding the prediction of ovarian response on stimulation with low-dose recombinant FSH (recFSH) (11, 12).

The aim of this study was to compare changes in serum AMH, inhibin B, FSH, and E<sub>2</sub> concentrations in women with PCOS during low-dose ovarian stimulation with those during normal menstrual cycles in healthy women with regular menstrual cycles, in order to gain insight into follicle dynamics in women with PCOS during low-dose gonadotropin ovarian stimulation.

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## MATERIALS AND METHODS

### Subjects

This study was approved by the local medical ethics review board. Written informed consent was obtained from each participant.

General patients' characteristics and phenotypical characteristics for a diagnosis of PCOS were obtained at initial clinical workup, as described earlier (13). Briefly, clinical, biochemical, and sonographic screening was performed, including history taking, anthropometric measurements, pelvic sonography, and endocrine measurements. The median age of the women with PCOS was 28.7 years (range 23.8–39.9 years). The median body mass index was at the upper limit of normal (median 25.1, range 16.6–38.9). Most women had primary infertility (63%,  $n = 30$  of 48), and at the start of OI treatment, the median duration of infertility was 2.8 years (range 0.5–17.5 years) (Table 1).

Inclusion criteria for the current study were as follows: a diagnosis of PCOS according to the Rotterdam consensus criteria, with the wish to conceive and ovulation induction (OI) treatment with recFSH (Gonal-F [follitropine  $\alpha$ ], Merck-Serono B.V.) between July 2006 and August 2009. Hyperandrogenism was defined as free androgen index (FAI)  $>4.5$  (calculated using the formula [serum testosterone concentrations in nmol/L  $\times$  100]/serum sex binding globulin hormone concentrations in nmol/L), testosterone concentrations  $>3.5$  nmol/L, and/or serum androstenedione concentrations  $>15.0$  nmol/L. PCOs were defined as 12 or more follicles of between 2 and 9 mm diameter (14).

Normo-ovulatory subjects had participated in an earlier study (15). They had regular menstrual cycles and did not use any hormonal treatment or oral contraceptive pills. In addition, they had not received treatment for infertility. At inclusion in the earlier study, the median age was 27.5 years (range 20.0–33.0 years) and the body mass index ranged between 19 and 25. Natural menstrual cycles were monitored with daily blood sampling and pelvic ultrasonography, starting 10 to 12 days after a positive urinary LH test during a first cycle until normal ovulation in the next cycle. The latter was confirmed sonographically and 7 days later by measuring serum P concentrations (15). For the current study, only data from the natural follicular phase were included.

### Treatment Protocol

Ovulation induction treatment was started on the 3rd to 5th day after spontaneous menstrual bleeding or after progestogen-induced bleeding. Treatment protocols and assessment of ovarian response have been described previously (8). In summary: the first treatment cycle was started with daily SC injections of 37.5 IU recFSH. If ovarian response was present on the starting dose during the first cycle, a second cycle was performed using the same fixed-dose

protocol. If not, the second treatment cycle was started at a dose 37.5 IU/d above the response dose during the first cycle, according to the step-down regimen. Then, the recFSH dose was decreased, with 37.5 IU/d during 3 days in case of response (16). Human chorionic gonadotropin (Pregnyl; Schering-Plough) was administered intramuscularly as a single dose of 5000 IU on the day when one or two follicles of 18 mm could be visualized. The presence of three or more follicles larger than 16 mm diameter was considered as hyperresponse and consequently, the cycle was cancelled. OI treatment was continued until pregnancy was achieved, with a maximum of six cycles.

### Endocrine Measurements

Serum was drawn at three sequential time points for assessment of AMH, inhibin B, FSH, and  $E_2$ . In study subjects, samples were drawn at the start of exogenous FSH administration (T1), at selection of the dominant follicle (T2) and on the day of hCG administration, at the end of ovarian stimulation (T3). The day of selection of the dominant follicle was defined as the day on which a follicle reached a diameter of 10 mm or larger and enlargement of this follicle during subsequent days until ovulation. In normo-ovulatory women, samples were drawn on cycle day 3, 4, or 5 on the day of follicle selection and on the day prior to the LH surge and used for comparison with samples from study subjects. Samples were stored at  $-20^\circ\text{C}$  until assessment of AMH. Inhibin B, FSH, and  $E_2$  were measured on the same day of withdrawal.

Serum AMH concentrations were measured with an in-house double-antibody ELISA (DSL-10-14400; Diagnostic Systems Laboratories Inc.) (17). Serum inhibin B concentrations were determined using an enzyme-linked immunoassay (Oxford Bio Innovation). Luminescence-based immunoassays were used to measure FSH concentrations (Immulate, Siemens DPC). A coated tube radioimmunoassay was used to assess  $E_2$  serum concentrations (Siemens DPC). Intra- and interassay coefficients of variance were  $<10\%$  and  $<5\%$  for AMH,  $<9\%$  and  $<15\%$  for inhibin B,  $<3\%$  and  $<8\%$  for FSH,  $<5\%$  and  $<7\%$  for  $E_2$ , respectively.

### Data Analysis

General characteristics of eligible patients and normo-ovulatory women were compared using nonparametric tests, because of skewed distribution of the data (not shown) and limited sample size. ANOVA for repeated measurements was used to compare the effect of time on endocrine parameters in women with PCOS and normo-ovulatory women and to compare changes in endocrine parameters between women with PCOS and normo-ovulatory women, followed by an independent samples  $t$  test in case of the presence of significant differences. Data are presented as medians with ranges.

**TABLE 1**

General patients' characteristics in women with PCOS and normo-ovulatory women.

Characteristic	Women with PCOS	Normo-ovulatory women
n	48	23
Age (y), median (range)	28.7 (23.8–39.9) <sup>a</sup>	27.5 (20.0–30.0)
Menstrual cycle, n		
Regular	0	23
Oligomenorrhea	27	0
Amenorrhoea	21	0
Fertility, n		
Spontaneous pregnancy	0	14/23
Primary subfertility	30	0
Secondary subfertility	18	0
Total follicle count in both ovaries, mean (range)	22 (4.5–51)	11 (4–21)
Hyperandrogenism, n	27	0

<sup>a</sup> Nonparametric test between women with PCOS and normo-ovulatory women;  $P = .09$ .

Lie Fong. Serum AMH during ovulation induction. *Fertil Steril* 2011.

AMH and E<sub>2</sub> concentrations were transformed logarithmically to achieve normal distribution. Serum AMH concentrations are presented in micrograms per liter (1 μg/L = 7.14 pmol/L). Statistical analysis was performed using SPSS, version 15.0 (SPSS Inc.). A *P* value < .05 indicates statistical significance.

## RESULTS

### Subjects' Characteristics

In accordance with the inclusion criteria, 48 women with PCOS were eligible for analysis. All 48 women had irregular cycles. All but 2 women had PCO, and 27 women (56%) were hyperandrogenic (Table 1). The median age of the women with PCOS was not significantly different from that of 23 normo-ovulatory women (median 27.5 years, range 20.0–33.0 years) (*P* = .09). Fourteen of the 23 normo-ovulatory women had been pregnant previously (15).

### Characteristics of Ovarian Stimulation

One treatment cycle per woman was included. In 18 patients, the 1st day on which the dominant follicle was observed coincided with the day on which hCG was administered. Consequently, in these patients serum was drawn on only two occasions. In the remaining 30 patients, serum sampling was performed on 3 independent days. In 5 patients, OI cycles were cancelled: in 3 patients, at least two follicles larger than 16 mm were observed at hCG administration, which indicated hyperresponse and the risk of multiple pregnancy; in another patient, surplus follicles were punctured before hCG administration and, finally, in one patient a postovulatory follicle was observed during monitoring of ovarian response, indicative of premature LH surge. In 42 of the 43 ongoing OI cycles, monofollicular growth was observed, whereas one ongoing cycle had resulted in two follicles of 16 mm. The median duration of stimulation was 15 days (range 5–38 days). Eventually, analysis was performed in 43 women with ongoing OI cycles.

### Endocrine Parameters

Serum AMH concentrations remained constant during FSH-stimulated cycles and normal cycles (*P* = .136), although AMH concentrations in women with PCOS were significantly higher than in normo-ovulatory women (*P* = .007) (Fig. 1). Indeed, post hoc analysis showed that at all time points women with PCOS had higher serum AMH concentrations than normo-ovulatory women (*P* = .004 at start, *P* = .003 at selection, *P* = .02 at end of stimulation) (Table 2).

Inhibin B concentrations within OI or natural cycles did not change significantly over time (*P* = .343). However, the repeated measures analysis revealed that there was a significant interaction between time and group (*P* = .039), suggesting that there is a change in inhibin B concentrations during OI and natural cycles and that this change differs between both groups. In OI cycles, inhibin B concentrations remained relatively constant, whereas in natural cycles inhibin B concentrations increased from T1 to T2 and declined from T2 to T3. As a consequence, inhibin B concentrations were nearly twice as high in women with PCOS at the end of an OI cycle than in normo-ovulatory women on the day before the LH surge (*P* < .0001) (Table 2) (Fig. 1).

FSH concentrations were significantly different between PCOS and normo-ovulatory women (*P* < .0001). At all time points, FSH concentrations were higher in women with PCOS compared with normo-ovulatory women (*P* < .0001 at T1 and T2; *P* = .01 at T3) (Table 2) (Fig. 1). However, concentrations remained constant during both OI and natural cycles (*P* = .557) (Fig. 1).

Estradiol concentrations changed significantly within OI cycles and natural cycles (*P* = .032); however, the change over time was similar in both groups (*P* = .396). Both cycles showed an increase in E<sub>2</sub> concentrations at T3 (Fig. 1). Overall, E<sub>2</sub> concentrations in OI cycles were not significantly different from concentrations in natural cycles (*P* = .883).

## DISCUSSION

To our knowledge, our study is the first to describe the dynamics of AMH, inhibin B, FSH, and E<sub>2</sub> concentrations during low-dose FSH ovarian stimulation in normogonadotropic anovulatory women. This treatment regimen has been shown to be successful and cost-effective in several studies (6, 18, 19). In the present study, mono-ovulation was achieved in the majority of women with PCOS, as confirmed by the development of a single dominant follicle and a similar pattern and degree of increasing E<sub>2</sub> concentrations in both OI cycles and spontaneous cycles.

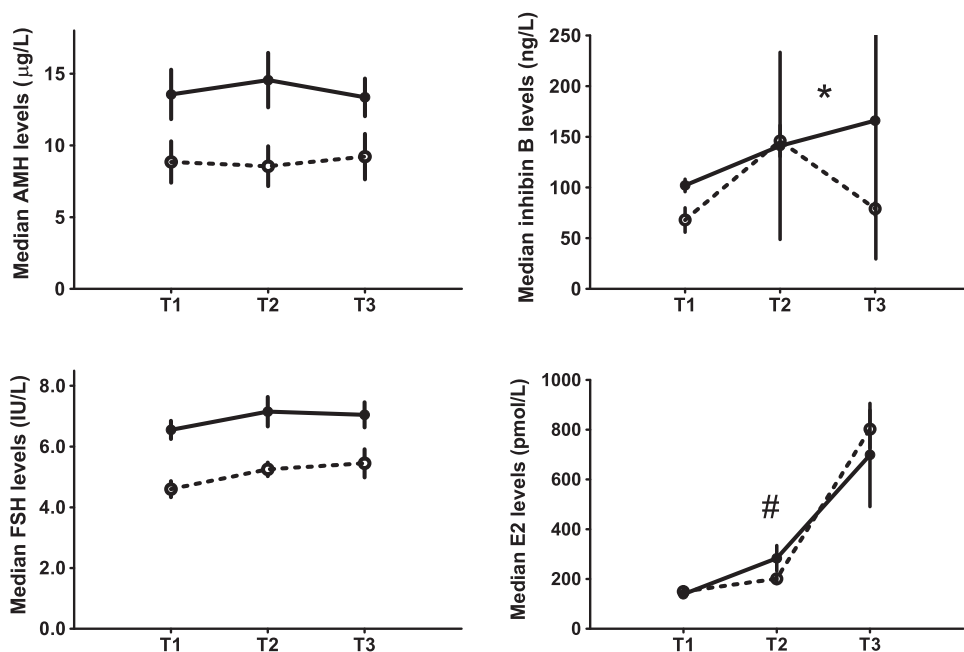
Serum AMH concentrations were constant in both women with PCOS and normo-ovulatory women, in accordance with previous studies (20, 21). This is in contrast with the decline in serum AMH concentrations observed during controlled ovarian hyperstimulation for IVF (22, 23). It has been suggested that the decline in AMH concentrations reflects the shift of AMH-producing, small antral follicles to the subsequent stage on supraphysiological doses of recFSH, because AMH expression gradually decreases in antral follicles sized 6 mm and larger (24). The constant AMH concentrations in women with PCOS suggest, however, that on low-dose recFSH stimulation, the cohort of small antral follicles was not significantly reduced, despite the presence of an increased number of follicles, reflected by high serum AMH concentrations at start of stimulation. Thus, ovarian stimulation with low-dose recFSH mimics a physiological cycle, as reflected by mono-ovulation in most women with PCOS.

In contrast with AMH concentrations, inhibin B concentrations did show different dynamics between PCOS and control women. At the end of low-dose ovarian stimulation, inhibin B concentrations remained elevated, whereas in natural cycles, inhibin B declined. This prolonged elevation of inhibin B concentrations has been described previously (25) and would be suggestive of sustained multiple follicular development during the late follicular phase. In spontaneous cycles, multiple antral follicles are recruited by FSH. Because of decreasing FSH concentrations, most of them will become atretic, resulting in the development of a single dominant follicle. Apparently, on continuous low-dose FSH administration, the physiological decrease in FSH was overruled and the FSH-recruited follicles survived longer during OI cycles, explaining the significantly elevated inhibin B concentrations at the end of stimulation in our treated subjects.

Prior to stimulation, FSH concentrations were higher in women with PCOS than in normo-ovulatory women. Because age was similar in women with PCOS and normo-ovulatory women, these high FSH concentrations may reflect impaired FSH sensitivity in our PCOS cohort. Indeed, it widely is considered that selection of the dominant follicle is impaired in women with PCOS, because of failure of FSH-dependent follicle recruitment (26). Apparently, by administration of a small amount of exogenous FSH, the “blocked” cyclic recruitment in women with PCOS can be overruled and multiple follicles surpass the FSH threshold (27). Despite this prolonged survival of follicles with continuous low-dose FSH administration after cyclic recruitment, development of a single dominant follicle was unaffected in the majority of treated PCOS subjects, as reflected by mono-ovulation. This implies that on

**FIGURE 1**

Changes in median (and ranges) anti-Müllerian hormone, inhibin B, FSH, and E<sub>2</sub> concentrations during ovulation induction cycles in patients with PCOS (filled dots and solid lines) and natural cycles (open squares and dashed lines) at three time points (T1 = at start of stimulation; T2 = at selection of the dominant follicle; T3 = on the day of hCG administration in patients with PCOS and 1 day before the LH surge in normo-ovulatory women). \*P < .05: significant change over time, which was different between women with PCOS and normo-ovulatory women. #P < .05: significant change over time, which was similar in both women with PCOS and normo-ovulatory women.



Lie Fong. Serum AMH during ovulation induction. Fertil Steril 2011.

stimulation with low-dose exogenous FSH, multiple antral follicles are present, but they seem to be less responsive to FSH and possibly less viable.

We hypothesized that in the studied population of women with PCOS, several treatment cycles would result in hyperresponse to

low-dose stimulation. Then, multifollicular growth would be expected and AMH concentrations would decrease during low-dose stimulation. It might be expected that this decrease is predictive for ovarian hyperresponse and thus cycle cancellation. Ovulation induction cycles were cancelled in five patients, of whom four had

**TABLE 2**

Median serum anti-Müllerian hormone (AMH), inhibin B levels, FSH, and E<sub>2</sub> (and ranges) in PCOS patients during ovulation induction cycles compared with levels in normo-ovulatory controls during normal menstrual cycles at the start of ovarian stimulation (T1), at selection of the dominant follicle (T2), and at the end of stimulation (T3).

	T1	P value	T2	P value	T3	P value
AMH (µg/L)		.004 <sup>a</sup>		.003 <sup>a</sup>		.02 <sup>a</sup>
PCOS	13.6 (3.4–56.4)		14.6 (2.1–37.7)		13.4 (2.8–42.9)	
Controls	8.8 (2.1–27.8)		8.5 (1.8–25.8)		9.2 (2.0–30.8)	
Inhibin B (ng/L)		.15		.98		< .001 <sup>a</sup>
PCOS	102 (9–212)		141 (67–2,554)		166 (39–4,757)	
Controls	68 (11–164)		146 (48–310)		79 (31–131)	
FSH (IU/L)		< .001 <sup>a</sup>		< .001 <sup>a</sup>		.01 <sup>a</sup>
PCOS	6.6 (0.1–11.9)		7.2 (4.3–19.1)		7.1 (3.7–15.1)	
Controls	4.6 (3.1–7.7)		5.3 (3.1–7.3)		5.2 (2.6–10.2)	
E <sub>2</sub> (pmol/L)		—		—		—
PCOS	139 (57–387)		283 (93–1,404)		699 (180–6,886)	
Controls	149 (98–404)		201 (123–432)		788 (387–1,600)	

Note: P values are results of the independent samples t test, performed following a significant difference in the repeated measurement analysis.  
<sup>a</sup> Significant P values.

Lie Fong. Serum AMH during ovulation induction. Fertil Steril 2011.

multiple follicular growth. This may indicate that the studied cohort of women with PCOS had rather favorable factors of successful OI treatment outcome (8). Consequently, in a more obese population with a higher follicle number or a higher percentage of more severe hyperandrogenism, multifollicular growth might occur more often than in the currently studied subjects. In addition, in our study, a starting dose of 37.5 IU recFSH was applied and seemed quite efficient and safe, with respect to hyperstimulation. Moreover, the low cancellation rate also may suggest that follicle growth was well monitored.

In conclusion, serum AMH concentrations were constant during low-dose ovulation induction. Although inhibin B concentrations at

the end of stimulation were indicative of prolonged survival of antral follicles, mono-ovulation was not affected. Unfortunately, in the current study, data on the number of growing antral follicles during stimulation was not available. However, the lack of change of serum AMH and inhibin B concentrations during low-dose stimulation and mono-follicular development in women with PCOS seem distinctly different from that during controlled ovarian hyperstimulation. This suggests that follicle dynamics during ovulation induction are different from that during controlled ovarian stimulation with pharmacologic doses of recFSH. In addition, neither AMH nor inhibin B seems useful as a marker of ovarian response after low-dose ovarian stimulation in women with PCOS.

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