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Anti-Müllerian hormone and polycystic ovary syndrome: assessment of the clinical pregnancy rates in *in vitro* fertilization patients

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Abstract

Objective: The purpose of this study is to investigate the role of serum anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH) and antral follicle count (AFC) for the prediction of clinical pregnancy rates (CPR) in women with polycystic ovary syndrome (PCOS) undergoing IVF treatment.
Design: Prospective cohort study.
Setting: University hospital.
Patients: One hundred and fifty consecutive women with PCOS.
Interventions: All women underwent controlled ovarian stimulation with long agonist protocol followed by IVF procedure. Outcomes of pregnant and non-pregnant groups were compared.
Main outcome measure: CPR; AMH, FSH and AFC means and percentiles.
Results: Fifty-one (34%) clinical pregnancies were observed in 150 women. Mean AMH was 6.7 ± 2.8 and 7.1 ± 4.3 ng/mL in pregnant and non-pregnant women, respectively ($p = 0.594$). The CPR were 27.8%, 35.0% and 37.8% in <25%, 25%–75% and >75% AMH percentiles, respectively ($p = 0.656$). There were also no significant difference in mean FSH and AFC between pregnant and non-pregnant women ($p = 0.484$ and $p = 0.165$, respectively).
Conclusion: AMH, FSH and AFC are not predictive for CPR in women with PCOS undergoing IVF treatment. Mean AMH values were not significantly different between pregnant and non-pregnant women. Although CRP increased in parallel with the raise in AMH percentiles, this remained insignificant.

Keywords

Anti-Müllerian hormone, antral follicle count, clinical pregnancy rate, follicle stimulating hormone, polycystic ovary syndrome

History

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age, and the relation between PCOS and impaired reproductive capacity has been well established. PCOS is characterized by disordered folliculogenesis: notably increased progression from the primordial to the primary stage, causing cycle irregularities [1].

The inhibitory role of anti-Müllerian hormone (AMH) in antral follicle hold back follicle-stimulating hormone (FSH) responsiveness and steroidogenesis, and acquisition of luteinizing hormone (LH) receptors until the time of follicle selection [2].

AMH is functionally related to initial recruitment period leading to primary follicle development and possibly dominant follicle selection. It has been suggested that serum AMH concentrations might provide novel and useful information in patients with disturbed ovarian function such as anovulation [3].

The majority of women with PCOS constitute the largest group of women with WHO Class 2 ovulatory dysfunction. PCOS is the most frequent cause of oligo-anovulation [1,4] and characterized by a heterogeneous presentation of hyperandrogenism. AMH serum levels are decreased and tend to be associated with serum FSH levels. There is a negative correlation between FSH and AMH serum levels, concluding that the AMH level is highly predictive and an independent indicator of ovarian reserve [5,6].

As we have previously reported, AMH had a 2–3-fold increase in PCOS [7], and high AMH levels predicted ovarian hyperstimulation syndrome (OHSS) [8], hence women with PCOS should be considered as a different category in AMH. Moreover, PCOS has its unique properties such as increased antral follicle count (AFC) and change in LH/FSH ratio. Therefore, prediction of clinical pregnancy in PCOS is more challenging compared to women without PCOS.

AMH levels appear to be related to the severity of PCOS. Since pregnancy rates decrease as PCOS becomes more severe, it may be theorized that in women with PCOS, pregnancy rates may decrease as the AMH level increases [4,9,10].

There have been several studies about the relationship between AMH and oocyte or embryo quality [11,12]. In spite of this, few studies have been designed for evaluating the role of AMH in predicting the possible outcome in infertility treatment, exclusively in PCOS patients. The aim of this prospective study was to appraise the association between AMH levels, FSH and AFC, with the pregnancy rates in patients with PCOS, and efficacy of

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AMH as a marker of in-vitro fertilization (IVF) outcome in the patient population mentioned above.

We have also aimed to compare the predictive values of AMH, FSH and AFC for clinical pregnancy in a PCOS-only group since there is very limited data on this specific issue.

Materials and methods

A total of 150 consecutive women with PCOS who were admitted to Istanbul University Cerrahpasa School of Medicine, IVF Center of Reproductive Endocrinology and Infertility department from February 2010 to June 2012 were enrolled in this prospective cohort study.

The initial inclusion criteria were: (1) <40 years of age, (2) FSH < 15 mIU/mL, (3) normal prolactin (PRL) and thyroid stimulation hormone (TSH) levels, (4) both ovaries present on transvaginal ultrasound scan, (5) no previous history of ovarian surgery. The exclusion criteria were current or past any systemic diseases, which may affect ovaries, or gonadotropin or sex steroid secretion, clearance, or excretion; exposure to cytotoxic drugs or pelvic radiation therapy or any hormonal therapy in the past 6 months before the therapy. To preclude the introduction of a potential bias on patient selection, only first fresh treatment cycles were included.

Baseline serum AMH, FSH, LH, E2, PRL, 17-hydroxyprogesterone (17-OHP) and TSH, total testosterone and dehydroepiandrosterone sulfate (DHEAS) were measured at cycle day 2–4 prior to the IVF cycle.

The assay for serum AMH involved an enzymatically amplified two-site immunoassay, DSL-10–14400 active MIS/AMH enzyme-linked immunosorbent assay (ELISA) kit. According to the manufacturer's manual, the theoretical sensitivity of the method is 0.006 ng/mL, the intra-assay coefficient of variation for high values is 3.3% and the interassay coefficient of variation for high values is 6.7%.

PCOS was diagnosed using the Rotterdam-2003 criteria [13]. Transvaginal ultrasound scans of the ovaries were performed by experienced sonographers who participated in the study. Polycystic ovary morphology was described by the appearance of 12 or more follicles in each ovary measuring 2–9 mm in diameter and/or increased ovarian volume (>10 cm^3).

All women underwent gonadotropin-releasing hormone (GnRHa) agonist, leuprolide acetate 1 mg/d s.c. (Lucrin®, Cedex, France) beginning on the 21st day of the previous cycle. Leuprolide acetate was reduced to 0.5 mg/d, and gonadotropin (Gonal F®, Serono, Swiss or Puregon®, Schering Plough, Istanbul) 150 IU was started daily. When more than two follicles were seen that were >17 mm, hCG (Pregnyl®, 10 000 IU, Schering Plough, Istanbul or Ovitrelle® 250 mcg, Serono, Swiss) was injected to induce final oocyte maturation, and 36 h later, ovum pick-up was performed. The embryos were transferred after 3 d if fertilization had occurred. The luteal phase was supported with progesterone.

Clinical pregnancy was established as the ultrasound observation of fetal heart movements at 7–8 weeks of gestation. The study was approved by the ethical committee of Istanbul University Cerrahpasa School of Medicine. Informed consent was obtained from all the patients. The STROBE guidelines were followed.

Statistics

Group characteristics were calculated and compared using the arithmetical means and the standard deviations were for each group as well. Independent sample *t*-test was used for comparison of parametric variables and Chi-square test was used where appropriate. A p value <0.05 was considered statistically significant. The AMH concentrations were classified as below the 25th percentile, between the 25th and the 75th percentiles, or above the 75th percentile. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS®, IBM, NY, USA) software version 15.0.

Table 1. Comparison of demographical and clinical parameters in pregnant and non-pregnant women.

	Pregnancy (+) ($n = 51$)	Pregnancy (−) ($n = 99$)	p Value
Age (years)	28.6 ± 3.86	29.6 ± 4.33	0.189
Duration of infertility (years)	5.75 ± 3.23	5.94 ± 3.34	0.744
BMI (kg/m^2)	25.8 ± 3.77	25.6 ± 4.26	0.783
AMH (ng/mL)	6.79 ± 2.9	7.16 ± 4.29	0.594
LH (mIU/mL)	3.8 ± 1.9	4.2 ± 2.4	0.257
FSH (mIU/mL)	5.44 ± 3.83	4.78 ± 2.81	0.484
E2 (pg/mL)	41.88 ± 18.21	62.68 ± 25.1	0.496
TSH (mIU/L)	1.48 ± 0.79	1.66 ± 0.86	0.264
AFC (n)	13.61 ± 5.32	12.25 ± 5.33	0.165
Total oocyte	11.1 ± 4.5	11.5 ± 5.5	0.620

AFC: antral follicle count; AMH: anti-Müllerian hormone; BMI: body-mass index; E2: estradiol; FSH: follicle-stimulating hormone; LH: luteinizing hormone; TSH: thyroid-stimulating hormone.
$p > 0.05$ is significant.

Results

Table 1 summarizes the clinical and demographic characteristics of the study population. There was no significant difference in terms of mean age, duration of infertility, BMI, AMH, LH, FSH, E2, TSH, AFC and the total number of oocytes between pregnant and non-pregnant women.

In our study, a total of 51 (34%) clinical pregnancies were observed in 150 PCOS women. Mean AMH was 6.79 ± 2.9 and 7.16 ± 4.29 ng/mL in pregnant and non-pregnant groups, respectively ($p = 0.594$). Cut-off levels of AMH in the 25th and 75th percentiles were 4.23 and 8.66 ng/mL, respectively. Mean FSH was 5.44 ± 3.83 and 4.78 ± 2.81 mIU/mL in pregnant and non-pregnant women, respectively ($p = 0.484$). Cut-off levels of FSH in the 25th and 75th percentiles were 4.03 and 5.98 mIU/mL, respectively. Mean AFC was 13.61 ± 5.32 and 12.25 ± 5.33 in pregnant and non-pregnant women, respectively ($p = 0.165$). Cut-off levels of AFC in the 25th and 75th percentiles were 9 and 17 follicles, respectively. The distributions of AMH, FSH and AFC according to pregnancy status were presented in Figure 1(a–c), respectively.

Furthermore, no significant difference in the clinical pregnancy rates (CPR) between the quartiles of AMH, FSH and AFC was identified (Table 2). The CPR were 27.8%, 35.0% and 37.8% in <25%, 25%–75% and >75% AMH groups, respectively ($p = 0.656$). The CPR were 43.2%, 33.7% and 27% in <25%, 25%–75% and >75% FSH groups, respectively ($p = 0.324$). Those were 32.6%, 28.9% and 48.5% in <25%, 25%–75% and >75% AFC groups, respectively ($p = 0.130$). The CPR in different percentiles of AMH, FSH and AFC were shown in Table 2.

Discussion

PCOS affects spontaneous pregnancy rates, possibly due to anovulation, decreased embryo quality and endometrial receptivity. Thus, it may be reasonable to expect that conception becomes more difficult with the increasing AMH levels. However, in our study, AMH levels were not significantly different between pregnant and non-pregnant women. Although the difference was insignificant, CPR tends to increase as AMH levels increase. The value of AMH in the prediction of pregnancy has been investigated in various studies which showed conflicting results.

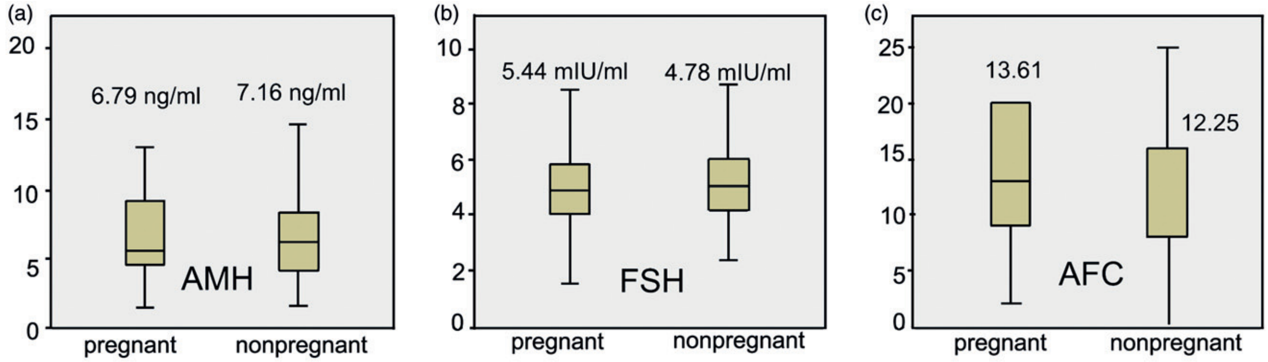

Figure 1. The distributions of (a) AMH, (b) FSH and (c) AFC according to pregnancy status. AMH: anti-Mullerian hormone; FSH: follicle stimulating hormone; AFC: antral follicle count.

Table 2. Pregnancy rates according to the quartiles of AMH, FSH and AFC.

	<25%			25%–75%			>75%			p
	Range	n	CPR%	Range	n	CPR%	Range	n	CPR%	
AMH (ng/mL)	<4.23	36	27.8	4.23–8.66	77	35.0	>8.66	37	37.8	0.656
FSH (mIU/mL)	<4.03	38	43.2	4.03–5.98	74	33.7	>5.98	38	27.0	0.324
AFC (number)	<9	45	32.6	9–17	69	28.9	>17	36	48.5	0.252

AFC: antral follicle count; AMH: anti-Müllerian hormone; CPR: clinical pregnancy rate; FSH: follicle-stimulating hormone; n: number of patients.

Some studies suggest that serum AMH level is associated with pregnancy rates [14–17]; whereas others concluded that serum AMH levels are not associated with pregnancy outcomes [18–21]. However, the value of serum AMH for pregnancy prediction in a PCOS-only group was evaluated in very few studies [22–27]. The conflicting results of those studies can be attributed to the lack of uniformity as well as the presence of various PCOS phenotypes.

In our study, we detected that early follicular phase serum AMH, FSH and AFC measurements in women with PCOS were not found to be associated with pregnancy rates.

There are very few studies exclusively evaluating women with PCOS. Kaya et al. [24] conducted a prospective clinical trial in 60 women with PCOS. When we analyze other studies, we have found that mean serum AMH level ranges between 5.8 and 9.8 ng/mL [23,25–27]. Mean serum AMH levels for the pregnant and non-pregnant women were not mentioned in the study of Kaya et al. [24] and the AMH cut-off values for the 25th and 75th percentiles were lower than referred AMH levels for PCOS patients. Our results were compatible with the mean AMH levels stated in the literature [23,25–27].

Nelson et al. [15] conducted a prospective study of 340 patients and reported that live birth rate increased with increasing AMH levels. However, this is valid only for patients with basal AMH levels <7.8 pmol/L. Above this value there was no discrimination for live birth. Moreover, after adding oocyte yield into a multivariable analysis, they found that oocyte yield was the only variable that predicted the live birth.

Broer et al. [28] published a meta-analysis and elucidated the performance of AMH for non-pregnancy prediction. They found that the accuracy for predicting non-pregnancy was poor for both AMH and AFC. Furthermore, there was no significant difference between the ROC curves among both tests.

Contrarily, Xi et al. [22] have suggested that pregnancy rates were lower in a high-level AMH group of women with PCOS. The AMH cut-off levels (25% and 75%) were similar to our study. In their study, CPR were 65%, 66.7% and 45.9%, respectively, in the <25%, 25%–75% and >75% percentiles of day-3 serum AMH groups. The indicated pregnancy rates are considerably high compared to the other studies in the literature.

In our previous studies [11], we evaluated the ongoing pregnancy rates and embryologic parameters according to AMH percentiles in the general population ($n = 209$) without sparing women with PCOS. We observed that the ongoing pregnancy rates decreased as AMH percentile increased above 50%, although this remained insignificant (39.3%, 30.9% and 19% in 50%–75%, 75%–90% and ≥90% AMH percentiles, respectively; $p > 0.05$) [11].

At the beginning of this study, preliminary results had suggested that CPR decreased as AMH levels increased. This tendency was quite significant at AMH levels higher than 12 ng/mL. However, as the study proceeded, the number of patients increased, and this tendency changed in the opposite direction. This alteration in tendency displays us the importance of population size in these studies. AMH is still experimental and there is no well-defined AMH level for both general and infertile population. Therefore, since a power analysis is not suitable for an unknown universe, we did not calculate the power of the study. However, compared to the number of women in other studies, our study is one of the largest sample-sized study among others. It is important to preclude the introduction of a potential bias on patient selection; and effects of demographic features and hormone levels on stimulation protocols. For this purpose, only first fresh treatment cycles were included and a fixed dose of 150 IU was used for all patients regardless of the AMH and FSH level, AFC or age.

In our previously published study, we demonstrated the pregnancy rates to be 21.3%, 24.5% and 29.2%, respectively, in the <25% (<1.81 ng/mL), 25%–75% (1.81–4.92 ng/mL), and >75% (>4.92 ng/mL) percentiles of serum AMH groups on day 3 in 189 consecutive women (PCOS and non-PCOS groups were all included) [18]. In the present study, the CPR were 27.8%, 35.0% and 37.8% in <25%, 25%–75% and >75% AMH percentile groups, respectively. These ratios show that pregnancy rates are higher in women with PCOS compared to the general population but broader studies are needed.

Heijnen et al. [29] performed a large systematic review and meta-analysis of nine observational studies comparing 458 PCOS women (793 cycles) with 694 matched controls (1116 cycles) and concluded that women with PCOS undergoing IVF treatment have similar pregnancy, miscarriage and live birth rates compared to those of non-PCOS patients. Our results from the present study also support this conclusion.

In conclusion, AMH, FSH and AFC are not predictive for clinical pregnancy in women with PCOS. Mean AMH values were not significantly different between pregnant and non-pregnant groups in PCOS patients undergoing IVF treatment. Although CPR tended to increase as AMH percentiles increased, this remained insignificant.

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Declaration of interest

All authors have nothing to disclose. There have not been any financial support.

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