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Elsaid N*

Department of Obstetrics and Gynecology, Ain Shams University, Cairo, Egypt

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***Corresponding author:** Nashwa Elsaid, Assistant professor of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, Abbasyia, Cairo, Egypt.

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Research Article

Prediction of Ovarian Response by Antimullerian Hormone in Women with Polycystic Ovarian Syndrome: A Randomized Prospective Study

Abstract

Objective: To assess the effect of high level of circulating antimullerian hormone on the outcome of gonadotrophin ovulation induction in women with polycystic ovarian syndrome.

Patients and Methods: This was a prospective study performed at Ain Shams University Maternity Hospital, over a 3-year period, between Jan 2013 and Jan 2016, and included 300 women who were presented at the infertility clinic and scheduled for having gonadotrophin ovulation induction. Participant ages ranged from 18 to 35 years, the patients were divided into two equal groups; group I (N=150) included women with PCOS having antimullerian hormone < 7.7 mg/dl and group II (N=150) which included women with PCOS with antimullerian hormone ≥ 7.7 mg/dl. The two groups underwent gonadotrophin stimulation of the ovary, serum AMH concentrations were measured on cycle day 3 before the commencement of gonadotrophins ovarian induction. Ovarian response and the biochemical and clinical pregnancy rates were analyzed in both groups.

Results: The outcomes of 300 cycles were analyzed, the ovarian response and biochemical and clinical pregnancy rates were higher in group I women who ovulated after therapy compared with the group II. There was a statistically significant gradient rise of serum AMH levels with the increasing dose of gonadotrophins required to achieve ovulation ($P<0.05$). AMH was an independent predictor of ovulation induction by gonadotrophins in PCOS women. AMH was demonstrated to be a useful predictor of gonadotrophins ovulation induction in PCOS women, having 92 % specificity and 65 % sensitivity when the threshold AMH concentration was 7.7 ng/ml.

Conclusions: Serum AMH might be clinically helpful to predict which PCOS women are more likely to respond to gonadotrophin therapy and eventually to direct the selection of protocols of ovulation stimulation.

Abbreviations

AFC: Antral Follicles Count; AMH: Anti-Müllerian Hormone; BMI: Body Mass Index; FSH: Follicle Stimulating Hormone; hCG: Human Chorionic Gonadotrophin; IVF: *In-Vitro* Fertilisation; LH: Luteinizing Hormone; PCOS: Polycystic Ovarian Syndrome; T: Testosterone;

Introduction

Polycystic ovary syndrome (PCOS) is the most frequent endocrine abnormality in women of reproductive age, with a prevalence of nearly 5–10 %. PCOS is the main reason of an ovulatory infertility [1]. The recent reports demonstrate that ovarian dysfunction results from ovarian follicle disorders in PCOS women are 2-folds [2,3]. First, early follicular development is excessive, so women with PCOS are characterized by an increase number of developing small antral follicles (2- to 3-folds that of normal ovaries). Secondly, the selection of the dominant follicle from the excessive pool of selectable follicles does not occur. This second disorder in the process of folliculogenesis is named the follicular arrest (FA) and explains the ovulatory dysfunction of PCOS. Although the FA has not clearly explained, Anti-Müllerian hormone (AMH) is proved as an outstanding contributors to this disorder [4,5].

AMH is synthesized specifically by granulose cells of developing ovarian preantral and small antral follicles. Circulating AMH levels in women with PCOS are 2- to 3-fold more compared to ovulatory women with normal ovaries [6,7], which denotes to the 2- to 3-fold rise in the count of small follicles detected in PCOS. The excessive AMH has been hypothesized to decrease follicle sensitivity to FSH induction and oestradiol production, so hindering follicle selection, resulting in follicular maturation arrest at the small antral phase with the failure to reach maturity.

Gonadotropin induction is widely utilized for ovulation stimulation in clomiphene citrate resistant PCOS women [8]. Human menopausal gonadotropin (hMG) is prepared by extraction from postmenopausal women urine. Commercial preparations contain 75 units of FSH and 75 units LH (Pergonal, Serono and Humegon, Organon) [9]. The utilization of urofollitropin, a purified FSH free of LH activity, looks to be an advisable therapy, since there is a proof that pure FSH may significantly decrease persistently high LH levels, favorably change the intraovarian hormonal environment, and

excite the initial follicular growth with less risk of multiple follicular development or ovarian overstimulation [10]. Conventional dose protocol begins with a daily 150 IU of hMG for 14 day from 3rd-5th day of the menstrual cycle or at the start of progesterone withdrawal bleeding. If needed the dose is increased by 75 IU for more 7 days but the daily dose better not to exceed 225 IU [11,12]. Hence the medical and social effects of the increased incidence of twins have emerged, the need to re-estimate the dose of gonadotropin treatment for ovulation induction in PCOS women has become imperative, thus leading to the application of low-dose regimen [13].

Lately, AMH has been demonstrated as an outstanding novel clinical biomarker of ovarian reserve and eventually predicting ovarian response to induction by gonadotrophins during *in vitro* fertilization (IVF) regimens in women without PCOS [9-11]. In PCOS women, we recently demonstrated that AMH concentrations on day 3 of the IVF stimulation regimens still positively expect ovarian response to induction by gonadotrophins [12]. However, in disagreement with our study, the predictive value of AMH was proved to be different between women with and without PCOS, for the researchers found circulating AMH concentrations were negatively related to ovarian response to gonadotrophin stimulation during ovarian stimulation in PCOS women [13]. So, the outcomes of hitherto published articles appeared not to be totally in consensus. Hence we made a study to assess whether serum AMH levels has a value in predicting ovarian response to gonadotrophin therapy in a large cohort of infertile women with PCOS.

Patients and Methods

This was a prospective study performed at Ain Shams University Maternity Hospital, over a 3-year period, between Jan 2013 and Jan 2016, and included 300 women who were presented at the infertility clinic and scheduled for having ovulation induction by gonadotrophins. The patients were divided into two groups; group I (N=150) included women with PCOS having antimullerian hormone < 7.7 mg/dl and group II (N=150) which included women with PCOS with antimullerian hormone ≥ 7.7 mg/dl. Both groups underwent gonadotrophin ovarian stimulation, serum AMH concentrations were measured on cycle day 3 before the commencement of gonadotrophins ovarian induction. Ovarian response and the biochemical and clinical pregnancy rates were analyzed in both groups.

Inclusion criteria

1. Primary or secondary infertility ≥ one year
2. Participant age: 18 - 35
3. Diagnosis of polycystic ovarian syndrome according to the Rotterdam criteria 2003 [14].
4. Anti-Müllerian hormone ≥ 0.4 ng/mL and/or follicle stimulating hormone ≤13 IU/L in early follicular phase
5. Normal semen analysis according to WHO 2010 criteria [15].
6. No uterine cavity abnormalities
7. Normal Fallopian tubes
8. Negative genitourinary test for chlamydia and gonorrhea ≤ one year

Exclusion criteria

1. Body mass index (BMI) ≥35 kg/m2.
2. Previous ovarian drilling or ovarian surgery.
3. Other causes of infertility e.g. endometriosis.

All included women were subjected to revising history and examination sheets with particular emphasis on personal history: age, residence, education level and socioeconomic status, Complaint regarding infertility, obstetric history including parity and gravidity and ultrasound for any uterine or tubal abnormality, the number of ovarian follicles and the diameter of the dominant follicle. The endometrium was measured at the greatest anterioposterior dimension under a longitudinal section.

Ovulation induction

Ovarian stimulation was then accomplished administering HMG (Merional® 75 IU) at a daily dose that was individually established according to age, body mass index (BMI), basal FSH, and AFC (starting from 3rd day of the cycle). Ovarian response to stimulation was monitored by transvaginal US examination plus serum estradiol measurement. From day 6, the HMG dose was adjusted according to ovarian response. When at least two leading follicles reached 18 mm diameter, intramuscular injection of up to 10.000 IU human chorionic gonadotropin (HCG) (chriomon® or ovitrelle®) was administered, and timed intercourse or IUI or ovum pick up was scheduled 36 hours later.

Hormone assays

Blood samples were collected on cycle day 3 before the commencement of gonadotrophins in the first cycle of treatment to measure baseline serum concentrations of AMH. AMH was measured by using a second-generation enzyme-linked immunosorbent assay (ELISA) (Immunotech Beckman Coulter Laboratories, Villepinte, France). Serum other hormonal concentrations including luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone (T) were measured using electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany).

Transvaginal scan

In the same morning of the blood tests, a transvaginal ultrasound scan was performed to assess the ovarian volume (milliliters), and antral follicles count (AFC). The volume of each ovary was calculated by measuring the ovarian diameters (D) in three perpendicular directions and applying the formula for an ellipsoid: $D1 \times D2 \times D3 \times 0.5236$. For the determination of the AFC, we calculated small follicles with a diameter between 2 and 9 mm, following the recommendations as described previously [16].

The hospital ethics committee approved the study. All patients gave their informative consent before entering into the study.

Statistical analysis

Retrieved data were recorded on an investigative report form. The data were analyzed with SPSS® for Windows®, version 15.0 (SPSS, Inc, USA). Description of quantitative (numerical) variables

Table 1: The clinic-demographic differences between the two groups.

	Group I (150)	Group II (150)	P- value
Age	29.3 ± 2.1	30.1 ± 2.2	> 0.05
Menarche age	10.4 ± 3.1	11.1 ± 2.7	> 0.05
Body mass index (kg/m2)	27.1 ± 2.6	27.3 ± 1.8	> 0.05
Type of infertility 1ry 2ry	 88 62	 91 59	> 0.05
Duration of infertility	8.2 ± 2.1	8.5 ± 2.4	> 0.05
Number of developing follicles at insemination	3.4±1.8	3.6±1.5	> 0.05
Mean diameter of dominant follicles at insemination	21.1 ± 1.5	20.3± 1.6	> 0.05
Mean endometrial thickness	8.4 ± 1.3	8.7 ± 1.2	> 0.05
Mean ovarian volume	10.1 ± 1.1	10.6 ± 1.2	> 0.05
LH (U/L)	7.4 ± 1.8	7.8 ± 2.1	> 0.05
FSH (U/L)	5.2 ± 2.2	5.3 ± 1.8	> 0.05
LH/FSH	1.5 ± 0.8	1.6 ± 0.5	> 0.05
T (ng/ml)	0.61 ± 0.1	0.59 ± 0.2	> 0.05
AMH	5.1 ± 1.6	9.2 ± 1.2	< 0.05 (S)

* Analysis using independent student's t-test. NS = non-significant, S = significant.

Table 2: shows a comparison between the two studied groups as regards the biochemical and clinical pregnancy rates as well as the total dose of HMG used per cycle.

Pregnancy rates	Group I No (%)	Group II No (%)	P
Biochemical pregnancy	46 30.6	34 22.6	< 0.05(sig)
Clinical pregnancy	31 20.6	22 14.6	< 0.05(sig)
Dose of HMG (IU/cycle)	687.8 ± 41.5	862.7 ± 67.2	< 0.05(sig)

Table 3: Shows the sensitivity, specificity, PPV, NPV, accuracy and diagnostic odd ratio of AMH when the threshold concentration was 7.7 ng/ml.

	Sensitivity 95% CI	Specificity 95% CI	PPV 95% CI	NPV 95% CI	ACCURACY 95% CI	Diagnostic OR
AMH	65	92	67	84	72.1	18.54
(7.7 ng/ml)	(45 - 80)	(87 - 95)	(41 - 89)	(77 - 90)	(70 - 91)	

was performed in form of mean, standard deviation (SD) and range. Description of qualitative (categorical) data was performed in the form of numbers and percent. Analysis of numerical variables was performed by using student's unpaired t-test (for two groups) or ANOVA (for more than two groups). Analysis of categorical data was performed by using Fischer's exact test and Chi-squared test. Logistic regression analysis was performed to calculate association between variables and their odds ratios. Association between variables was estimated using Pearson's correlation coefficient (for parametric variables) and Spearman's correlation coefficient (for non-parametric variables). Significance level was set at 0.05.

Results

The current study was conducted on 300 women presented at infertility clinic of Ain Shams Maternity Hospital, during the period between Jan 2013 and Jan 2016 and included 300 women who were presented at the infertility clinic and scheduled for having ovulation induction by gonadotrophins.. The study included 2 groups of women: group I [n=150]; women with PCOS having antimullerian hormone < 7.7 mg/dl and group II [n=150]; women with PCOS with antimullerian hormone ≥ 7.7 mg/dl. There was no statistically significant difference between the two groups concerning the clinic-demographic parameters including mean age, menarche age, BMI, mean gravidity, duration and type of infertility, educational level, occupation, number of developing follicles at time of insemination, mean diameter of dominant ovarian follicle and mean endometrial thickness (Table 1).

Table 2 shows a comparison between the two studied groups as regards the biochemical and clinical pregnancy rates as well as the total dose of HMG used per cycle. In group I; the biochemical pregnancy rate was 30.6% and clinical pregnancy rate was 20.6% while in group II; the biochemical pregnancy rate was 22.6% and clinical pregnancy rate was 14.6% with statistically significant difference between both groups (P <0.05). Also the total dose of HMG was significantly different between the two groups (in group I was 687.8 ± 41.5 while in group II was 862.7 ± 67.2).

Table 3 shows the sensitivity, specificity, PPV, NPV, accuracy and diagnostic odd ratio of AMH when the threshold concentration was 7.7 ng/ml.

Discussion

Since the excessive AMH would hinder the effect of FSH and participate in the pathogenesis of PCOS, this proof has led to hypothesise that there is a subgroup of women suffering from PCOS who have the excessive levels of AMH and who are the more resistant to gonadotrophins therapy [17]. In this study, we proved that women with excessive AMH level are more likely to be resistant to gonadotrophin therapy. Moreover, it was identified a cut-off level of AMH (7.7 ng/ml), above this level the chances of conception seem to be significantly decreased. These observations suggest that high circulating values of AMH reflect less likely progression in folliculogenesis and granulosa cell function.

However, it seems paradoxical that serum AMH level are demonstrated to positively expect ovarian response to gonadotrophin induction during IVF programs. High AMH levels are proved to predict excessive response of ovarian follicles to gonadotropin stimulation. However, low AMH circulating concentrations indicative of a decreased ovarian reserve, is linked to poor ovarian response [18]. Amer SA et al. [19], demonstrated the contradiction may be attributed to the different spectrum of AMH levels in women with and without PCOS. Since AMH concentrations were significantly more in women with PCOS, they agreed that levels above the optimum AMH concentrations are linked to inadequate ovarian response to induction. It seems interesting to observe that, in disagreement to Amer's opinion, Kaya et al. [20], demonstrated a positive correlation between serum AMH concentrations and ovarian response to gonadotrophins stimulation during IVF programs in women with PCOS. In that study, it was noted that as serum AMH concentrations increased, the occurrence of biochemical and clinical conception rates were reduced, with significantly more total dose of the gonadotrophins.

It is proved that in anovulatory women with PCOS, the higher level of serum FSH level may decrease the AMH excess, so decreasing its inhibitory effect on the follicular development, and allowing the development of a dominant follicle [21]. In ovulation stimulation, it is aimed to reach the development of a single dominant follicle. Chronic low-dose gonadotrophins (with a starting dose 37.5 or 50U daily) have been used to stimulate ovulation in women who previously failed to ovulate with clomiphene citrate. However, both clomiphene citrate and low-dose gonadotrophins rinder the circulating FSH concentrations increased gently and may be not enough to decrease intra-ovarian AMH to a level enough for resumption of ovulation in women with high AMH concentration. So, as reported, women with more AMH were more inhibited and remained anovulatory after ovulation stimulation. The aim of gonadotrophin induction, however, is a normally designed multifollicular development and this will usually need higher levels of FSH (the starting dose should be at least 112.5U per day). If the 'threshold' FSH level for follicular development is quickly exceeded and growth arrest from AMH inhibition was stopped, leading to an early development of multiple dominant follicles.

Our findings are in agreement with previous article by Mahran A and co-workers [21], who have assessed the impact of serum AMH on the success rate of clomiphene citrate ovulation stimulation in 60 patients with anovulatory PCOS in 187 cycles of therapy, and found serum AMH concentrations to be negatively related to the chances of ovulation. Similarly, Amer SA et al. [19], have assessed the effect of serum AMH levels on the outcome of ovarian induction in 20 women with anovulatory PCOS receiving 34 cycles of gonadotrophin regimens. They reported circulating AMH concentrations to be negatively related to ovarian response to gonadotrophin. On the other hand, our findings meet with those of El-Halawaty et al. [22], in that AMH concentrations were significantly more in responders when compared to non-responder. However, their findings included a subgroup of overweight PCOS women taking a higher doses of clomiphene citrate (150 mg/d).

AMH was demonstrated to be an important one of the local inhibitors of FSH effects by reducing granulosa cell sensitivity to FSH [23,24], so the antral follicles from AMH knockout mice had higher sensitive to FSH compared to those from the wild type [25]. This impact of AMH was primarily due to inhibited aromatase enzyme activity in granulosa cell. In keeping with our study, an inhibitory impact of serum AMH on FSH- induced aromatase mRNA expression and estradiol synthesis has been demonstrated in human granulosa cells [26]. Similarly, the inverse correlation between AMH and estradiol has been found in PCOS patients [27]. The fact that AMH inhibits factors needed for follicle development and subsequently selection program of the dominant follicle [28], so it is not astonishing that AMH is a negatively predictive valuable factor for ovarian response to treatment in PCOS women.

In current study, the AMH concentrations were significantly more in non-pregnancy compared to pregnancy group. This might be explained by the fact that most resistant patients in this study had more AMH were excluded from the non-pregnancy group.

In the present study, it was found serum AMH concentrations with a threshold of 7.7 ng/ml had a sensitivity of 92 % and specificity of 65 % in expecting ovarian response to gonadotrophin therapy. This cut-off is higher two times than those of previously mentioned by Mahran et al. [21], who demonstrated that 3.4 ng/ml was an optimal cut-off among 60 women with PCOS. It is not impossible that different kits for detecting AMH may result in substantial difference in the serum concentration of AMH. Moreover, changes in PCOS symptoms and AMH levels among different racial/ethnic backgrounds might explain these differences. So, it should be observed that this cutoff AMH concentration applies only to the AMH kit utilized in this article.

Conclusions

In summary, this study proved that the circulating serum AMH can predict ovarian response to induction by gonadotrophins therapy. So, evaluation of serum AMH level for anovulatory women suffering from PCOS before therapy might be a helpful tool in outcome prediction. This could be of value when counselling PCOS women concerning the prediction of the success of gonadotrophin regimens and make the ovulation-induction regimens more patient-tailored with less cost.

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