PREDICTION OF OVARIAN RESPONSE BY ANTI-MULLERIAN HORMONE IN WOMEN WITH PCOS

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ABSTRACT

BACKGROUND

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 gonadotropins therapy.

The aim of the study was to evaluate the serum AMH levels in predicting ovarian response in infertile women with PCOS.

MATERIALS AND METHODS

This study was a prospective study conducted in Laxmi Narasimha Hospital, Warangal Telangana, for a period of 2 years from January 2014 to February 2016. Totally, 200 women who were admitted in infertility clinic and having induction of ovulation by gonadotropins. The patients were divided into two groups- namely, Group A, which included 100 patients who were women with PCOS having anti-Mullerian hormone <7.77 mg/dL, Group B which included 100 patients who were women with PCOS having anti-Mullerian hormone >7.77 mg/dL.

RESULTS

Body mass index in kg/m^2 of 27.3 ± 3.2 in group A, 27.8 ± 1.5 in group B and the 'p' value was nonsignificant, duration of infertility in minutes of 8.0 ± 1.8 in group A, 8.4 ± 2.7 in group B and the 'p' value was nonsignificant, number of developing follicles at insemination of 3.2 ± 1.4 in group A, 3.7 ± 1.2 in group B and the 'p' value was nonsignificant, mean diameter of dominant follicles at insemination of 22.3 ± 1.1 in group A, 21.0 ± 1.8 in group B and the 'p' value was nonsignificant. Biochemical pregnancy rates were 4411.2 in group A, 3122.5 in group B, clinical pregnancy rates were 3022.8 in group A and 2478.1 in group B, dose of HMG (IU/cycle) was 658 ± 35.8 in group A and 820.9 ± 54.9 in group B. AMH sensitivity, specificity, PPV, NPV, accuracy and diagnostic odds ratio was 62, 90, 65, 80, 71.8, 18.25, respectively when threshold concentration was 7.77 ng/mL.

CONCLUSION

In outcome prediction, circulating serum AMH level evaluation for anovulatory women suffering from PCOS before undergoing therapy acts as a helpful tool. It can act in predicting ovarian response in inducing gonadotropins therapy.

KEYWORDS

Polycystic Ovary Syndrome, Anti-Mullerian Hormone, Estradiol.

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BACKGROUND

One of the most common endocrinopathies in females and female infertility is Polycystic Ovary Syndrome (PCOS). During the reproductive age, it affects 5-10% of women. In 1935, it was first explained by Stein and Leventhal who found women with polycystic ovaries and amenorrhea where few had obesity and hirsutism.[1,2] These patients had infertility as a major complaint, which showed anovulation as a major defect responsible for conception.[3]

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Anti-Mullerian Hormone (AMH) is a dimeric glycoprotein, a member of the transforming growth factor-beta superfamily, which acts on tissue growth and differentiation. AMH was originally identified because of its fundamental role in male sex differentiation. Indeed, expressed in the Sertoli cells of foetal testis, AMH induces the regression of the Mullerian ducts. In the absence of AMH, Mullerian ducts evolved into uterus, fallopian tubes and the upper part of the vagina. Serum AMH levels in women with PCOS are 2- to 3-fold higher than in ovulatory women with normal ovaries, which corresponds to the 2- to 3-fold increase in the number of small follicles seen in PCOS. The increased AMH has been hypothesised may reduce follicle sensitivity to FSH and estradiol production, thus preventing follicle selection resulting in follicle arrest at the small antral phase with the failure of dominance. At present, the treatment of oligo or anovulatory infertility is referred to as induction of ovulation. Clomiphene Citrate (CC) is the treatment of first choice for ovulation induction in

anovulatory women with PCOS. There are 20-25% of women, however, remain anovulatory after receiving CC medication and the exact cause of CC failure in some patients remain uncertain. Identifying factors that determine the response of women with PCOS to CC will help selecting patients who are likely to benefit from this treatment, thus avoiding fruitless treatment and improving success rates.

An important marker for women with PCOS is anti-Mullerian hormone, which is a member of Transforming Growth Factor-Beta (TGF-β) and which is 2-3 folds higher when compared to healthy women.[4,5] These increased levels of AMH are directly proportional to enhanced number of follicles in women with PCOS. This leads to decreased follicle sensitivity to FSH induction and estradiol production, thus follicle selection is hindered, which results in arrest of follicular maturation at the small antral phase with failure to reach maturity. This study was conducted to evaluate the serum AMH levels in predicting ovarian response in infertile women with PCOS.

MATERIALS AND METHODS

This study was a prospective study conducted in Laxmi Narasimha Hospital, Warangal, Telangana, during a 2-year period, between January 2014 to February 2016. This study included 200 women who were admitted in infertility clinic and having induction of ovulation by gonadotropins.

The patients were divided into two groups, namely Group A, which included 100 patients who were women with PCOS having anti-Mullerian hormone <7.77 mg/dL, Group B, which included 100 patients who were women with PCOS having anti-Mullerian hormone >7.77 mg/dL.

Gonadotropin ovarian stimulation was done in both groups and serum AMH concentrations were measured on day 2 before gonadotropin ovarian induction. Biochemical, clinical pregnancy rates and ovarian response were evaluated in both the groups.

Inclusion criteria was patients with primary or secondary infertility ≥1 year, age should be between 18-35 years, according to Rotterdam criteria, polycystic ovarian syndrome diagnosis, in early follicular phase, anti-Mullerian hormone of ≥0.4 ng/mL, FSH ≤13 IU/L, no uterine cavity abnormalities, normal fallopian tubes, negative genitourinary test for chlamydia and gonorrhoea ≤1 year.

Exclusion criteria was body mass index ≥35 kg/m^2, ovarian surgery and other causes of infertility. Complete history of all the patients such as age, residence, socioeconomic status, education level and the number of ovarian follicles, diameter of follicle, ultrasound of uterine or tubal abnormality, parity and gravidity was noted. Ovulation induction, hormone assays and transvaginal scan was done.

RESULTS

This study included 200 women who were admitted in infertility clinic and having induction of ovulation by gonadotropins. In the present study, both the groups were comparable with respect to the demographic profile as shown in below tables.

Variables	Group A (n=100)	Group B (n=100)	P-Value
Age	30.2 ± 1.9	30.9 ± 2.8	>0.05
Menarche age	11.5 ± 2.5	12.5 ± 2.9	>0.05
Body mass index (kg/m^2)	27.3 ± 3.2	27.8 ± 1.5	>0.05
Duration of infertility (minutes)	8.0 ± 1.8	8.4 ± 2.7	>0.05
Number of developing follicles at insemination	3.2 ± 1.4	3.7 ± 1.2	>0.05
Mean diameter of dominant follicles at insemination	22.3 ± 1.1	21.0 ± 1.8	>0.05

Table 1. Demographic Differences between the Two Groups

As Table 1 shows age of 30.2 ± 1.9 in group A, 30.9 ± 2.8 in group B and the 'p' value was nonsignificant, menarche age of 11.5 ± 2.5 in group A, 12.5 ± 2.9 in group B and the 'p' value was nonsignificant, body mass index in kg/m^2 of 27.3 ± 3.2 in group A, 27.8 ± 1.5 in group B and the 'p' value was nonsignificant. Duration of infertility in minutes of 8.0 ± 1.8 in group A, 8.4 ± 2.7 in group B and the 'p' value was nonsignificant. Number of developing follicles at insemination of 3.2 ± 1.4 in group A, 3.7 ± 1.2 in group B and the 'p' value was nonsignificant, mean diameter of dominant follicles at insemination of 22.3 ± 1.1 in group A, 21.0 ± 1.8 in group B and the 'p' value was nonsignificant.

Variables	Group A (n=100)	Group B (n=100)	P-Value
Mean endometrial thickness	8.3 ± 1.3	8.9 ± 1.5	>0.05
Mean ovarian volume	10.2 ± 1.7	10.9 ± 1.0	>0.05
LH (U/L)	7.3 ± 1.4	7.8 ± 2.1	>0.05
FSH (U/L)	5.0 ± 1.1	5.6 ± 2.8	>0.05
LH/FSH	1.2 ± 1.0	1.5 ± 1.8	>0.05
AMH	4.8 ± 0.8	9.0 ± 1.4	<0.05

Table 2. Demographic Differences between the Two Groups

Table 2 shows mean endometrial thickness of 8.3 ± 1.3 in group A, 8.9 ± 1.5 in group B and the 'p' value was nonsignificant, mean ovarian volume of 10.2 ± 1.7 in group A, 10.9 ± 1.0 in group B and the 'p' value was nonsignificant, LH (U/L) of 7.3 ± 1.4 in group A, 7.8 ± 2.1 in group B and the 'p' value was nonsignificant, FSH (U/L) of 5.0 ± 1.1 in group A, 5.6 ± 2.8 in group B and the 'p' value was nonsignificant, LH/FSH of 1.2 ± 1.0 in group A, 1.5 ± 1.8 in group B and the 'p' value was nonsignificant, AMH of 4.8 ± 0.8 in group A, 9.0 ± 1.4 in group B and the 'p' value was significant.

Table 3 shows that biochemical pregnancy rates were 4411.2 in group A, 3122.5 in group B, clinical pregnancy rates were 3022.8 in group A and 2478.1 in group B, dose of HMG (IU/cycle) was 658 ± 35.8 in group A and 820.9 ± 54.9 in group B.

Pregnancy Rates	Group A (n=100)	Group B (n=100)	P-Value
Biochemical pregnancy	4411.2	3122.5	<0.05 (significant)
Clinical pregnancy	3022.8	2478.1	<0.05 (significant)
Dose of HMG (IU/cycle)	658 ± 35.8	820.9 ± 54.9	<0.05 (significant)

Table 3. Biochemical and Clinical Pregnancy Rates Along with Total Dose of HMG Used per Cycle between the Two Groups

95%, CI	Sensitivity	Specificity	PPV	NPV	Accuracy	Diagnostic OR
AMH	62	90	65	80	71.8	18.25
7.77 ng/mL	40-75	84-92	40-85	75-87	68-89	

Table 4. AMH Sensitivity, Specificity, PPV, NPV, Accuracy and Diagnostic Odd Ratio When Threshold Concentration was 7.5 ng/mL

Table 4 shows that AMH sensitivity, specificity, PPV, NPV, accuracy and diagnostic odd ratio was 62, 90, 65, 80, 71.8 and 18.25 respectively when threshold concentration was 7.77 ng/mL.

DISCUSSION

This prospective study was conducted in Laxmi Narasimha Hospital, Warangal, Telangana, for a period of 2 years. This study was conducted to evaluate the serum AMH levels in predicting ovarian response in infertile women with PCOS.

Totally, 200 patients were included and were divided into 2 groups as Group A included 100 patients with PCOS having Anti-Mullerian hormone <7.77 mg/dL and Group B, which included 100 patients who were women with PCOS having Anti-Mullerian hormone >7.77 mg/dL.

Anti-Mullerian Hormone (AMH) has an inhibitory role during folliculogenesis, which may contribute to anovulation in Polycystic Ovary Syndrome (PCOS). AMH level has been shown to be a predictor of reproductive response to weight loss and clomiphene citrate in women with PCOS. Women with high AMH levels are considered to predict excessive ovarian response to gonadotropin. Meanwhile, low AMH levels indicative of a diminished ovarian reserve is associated with poor response. In that study, as serum AMH levels increased, an increase in estradiol levels on the day of HCG administration and the number of retrieved oocytes were observed, while the total dose of the gonadotropins was significantly decreased.

Amer SA et al[6] demonstrated the contradiction maybe 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. Kaya et al[7] demonstrated a positive correlation between serum AMH concentrations and ovarian response to gonadotropin 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 gonadotropins.

Elsaid N et al[8] conducted a study in which the outcomes of 300 cycles found that AMH was a useful predictor of gonadotropins ovulation induction in PCOS women having 92% specificity and 65% sensitivity when the threshold AMH concentration was 7.7 ng/mL. Wenyan Xi et al[9] reported that AMH is a useful predictor of ovulation induction by CC in PCOS patients having 92% specificity and 65% sensitivity when the threshold AMH concentration was 7.77 ng/mL. Mohamed S. Sweed et al[10] conducted a study in which 72 women ovulated within 12 to 33 days of the menstrual cycle, while 28 had undetectable ovulation till day 35. The median serum AMH level was significantly higher in women with failed ovulation than in ovulating women. Best cut-off value of AMH for prediction of successful ovulation ≤3.6 ng/mL (sensitivity = 97.2%, specificity = 82.1%). Haiyan Zheng et al[11] conducted a study in which it was reported that the predictive value of Anti-Mullerian Hormone (AMH) in Chinese women undergoing In Vitro Fertilisation (IVF) treatment. The AMH level was positively correlated with the number of oocytes retrieved. Overall, AMH was significantly correlated with risk of cycle cancellation, Poor Ovarian Response (POR, 3 or fewer oocytes retrieved) and high response (>15 oocytes) with an Area Under the Curve (AUC) of 0.83, 0.89, and 0.82, respectively. An AMH cut-off of 0.6 ng/mL had a sensitivity of 54.0% and a specificity of 90.0% for the prediction of cycle cancellation and cut-off of 0.8 ng/mL with a sensitivity of 55.0% and a specificity of 94.0% for the prediction of POR. Homburg R et al[12] conducted a study in which Polycystic Ovary Syndrome (PCOS) is the most common cause of infertility due to anovulation. Confirmed that AMH concentrations present in women with PCOS play an integral role in causing anovulation due to its inhibitory influence on the actions of follicle-stimulating hormone, which normally promotes follicular development from the small antral to the ovulatory stage. Some studies even suggested AMH to be a possible predictor of pregnancy in IVF cycles done for women with PCOS with the women producing relatively lower levels of AMH having the best outcome.

CONCLUSION

Hence, we conclude that PCOS is the most frequent endocrine disorder in women of reproductive age, but its diagnosis remains one of the most challenging issues in endocrinology, gynaecology and reproductive medicine. In outcome prediction, circulating serum AMH level evaluation for anovulatory women suffering from PCOS before undergoing therapy acts as a helpful tool. It can act in predicting ovarian response in inducing gonadotropin therapy. Finding an anti-AMH therapy seems to be the upcoming quest in the management of anovulatory PCOS.

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