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Effect Of Anti Mullerian Hormone Levels On Prediction Of Ovulation In Two Different Protocols Of Letrozole In Infertile PCOS Female

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ABS TRAC T

Background: Anti-Müllerian hormone (AMH) reflects ovarian reserve and predicts ovulation induction outcomes. This study evaluates the impact of serum AMH on ovulation induction using conventional and extended letrozole regimens in women with PCOS.
Methods: A prospective randomized study was conducted on 148 infertile PCOS women unresponsive to 2.5 mg letrozole. Group A (conventional) received 5 mg/day from cycle day 2–6, while Group B (extended) received 5 mg/day from day 2–11. Serum AMH levels were compared between ovulatory and non-ovulatory participants.
Results: Mean AMH levels were higher in non-ovulatory women than ovulatory ones. In the conventional group, AMH was 4.00 ± 2.88 ng/mL in non-ovulatory vs2.41 ± 1.48 ng/mL in ovulatory ($P = 0.001$). In the extended group, AMH was5.59 ± 2.31 ng/mL vs 2.29 ± 1.01 ng/mL respectively ($P = 0.001$). Overall, elevated AMH correlated significantly with reduced ovulation rates ($P < 0.001$).
Conclusion: High AMH levels are inversely associated with ovulatory response in both protocols. AMH can guide individualized stimulation strategies for better fertility outcomes in PCOS.

Keywords: AMH(Anti Mullerian Hormone),ovulation induction (OI), letrozole , Extended protocol, Conventional protocol.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women, with an overall prevalence of 5% to 15%, and a frequent cause of infertility[(1)(2)].Currently, the diagnosis is based on the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine criteria, also known as Rotterdam criteria, from 2003.[(3)]Ovulation disorders are the cause of infertility in around 25% of couples and PCOS is the major cause of anovulatory infertility, accounting for approximately 70% of all cases.[(4-6)]

Anti- Mullerian hormone (AMH), a dimeric glycoprotein that is part of the transforming growth factor b family, is produced by granulosa cells of preantral and antral follicles in the ovary [(7).] Although AMH is not currently a diagnostic criterion forPCOS, several studies suggest that AMH could serve as a proxy for AFC [(8-10).] The serum AMH concentration is often noted to be 2–4 times higher in individuals with PCOS but no clearcutoff value has been established because of limited data on the AMH values as well as variation among assays and by age[(11).] Excess AMH may be harmful to the process of folliculogenesis and may be involved in the cessation of follicular growth[(9, 12).]

Treatment response is often influenced by AMH. There is evidence that high AMH concentrations can be associated with resistance to clomiphene and letrozole, for women with PCOS.However, data on this association, as well as the association between the AMH concentrations and pregnancy and live birth rates with OI, remain limited. This study

evaluates whether baseline AMH levels can predict ovulatory response to conventional and extended letrozole regimens. We hypothesized that a higher baseline serum AMH concentration would be associated with reduced odds of ovulation in all treatment groups.

MATERIALS AND METHODS

This interventional randomized controlled trial was conducted in the Department of Obstetrics and Gynaecology, SMS Medical College, Jaipur, to compare the efficacy of extended versus conventional letrozole regimens for ovulation induction in infertile women with polycystic ovary syndrome (PCOS). Following ethical approval, data collection began in October 2023 and continued for one year.

Infertile women aged 18–40 years diagnosed with PCOS (Rotterdam criteria) who had inadequate response to 2.5 mg letrozole were included. Eligibility required at least one patent fallopian tube, a normozoospermic partner, and an active marital life of three to five years.

Women with endometriosis, thyroid or prolactin disorders, or uterine anomalies were excluded. Based on 80% power and a 5% significance level, assuming a 20% improvement in ovulation rate with the extended regimen (reference: Zhu et al., 2023), 74 participants were enrolled per group to account for attrition. After informed consent and baseline evaluation—including clinical history, examination, and day 2–3 transvaginal ultrasonography—participants were randomized into two groups.

Group 1 (Conventional Regimen): Letrozole 5 mg/day from day 2–6 for five days.
Group 2 (Extended Regimen): Letrozole 5 mg/day from day 2–11 for ten days.

Serum AMH values were measured on day 2 of cycle by ELISA. Follicular monitoring started on day 10. When a follicle ≥18 mm and endometrium ≥7 mm was observed, ovulation was triggered with β-hCG (5,000–10,000 IU) followed by intrauterine insemination (IUI) after 36 hours and luteal phase progesterone support. Ovulation was confirmed by follicular rupture on ultrasound and pregnancy by serum β-hCG >50 mIU/mL and fetal cardiac activity on scan.

Data were analysed using SPSS v26. Continuous variables were expressed as mean ± SD and compared using Student's t-test; categorical variables were compared using Chi-square or Fisher's exact test. A p-value<0.05 considered statistically significant.

RESULTS

Among the 148 infertile women with PCOS enrolled in the study, demographic characteristics were broadly comparable between groups. The largest proportion of participants (45.3%) were aged 28–32 years, followed by 30.4% in the 37–40-year range and 24.3% between 33 and 36 years. Most women (69.6%) had a normal body mass index (BMI) of 18.5–22.9 kg/m², while 30.4% were overweight (BMI ≥23 kg/m²). Primary infertility was predominant, reported in 89.9% of cases, whereas 10.1% had secondary infertility. The duration of active marital life (AML) exceeded three years in 70.3% of participants. A smoking history was present in 20.3% of cases, prior oral contraceptive pill (OCP) use in 44.6%, and clinical signs of hyperandrogenism in 22.3% of the study population. In terms of ovulation outcomes, the extended letrozole regimen demonstrated a significantly higher ovulation rate than the conventional regimen. Ovulation occurred in 68 out of 74 participants (91.89%) in the extended group compared with 52 out of 74 (70.27%) in the conventional group, a difference that was statistically significant (p = 0.0005).

Table 1 shows mean AMH value ofConventional group which is 4 ng/dL in thosewho do not ovulate with standard deviation of 2.88.and 2.41 with standard deviation of 1.48 in those who ovulated. Whereas, in Extended group mean AMH was 5.59 with standard deviation of 2.31 in those who do not ovulate and mean of 2.29 with standard deviation of 1.01 in those who ovulated.AMH levels were significantly higher among non-ovulatory participants in both groups, demonstrating an inverse correlation between AMH and ovulatory response.Treatment group was not a significant effect modifier of theassociation between the baseline AMH concentration and ovulation.

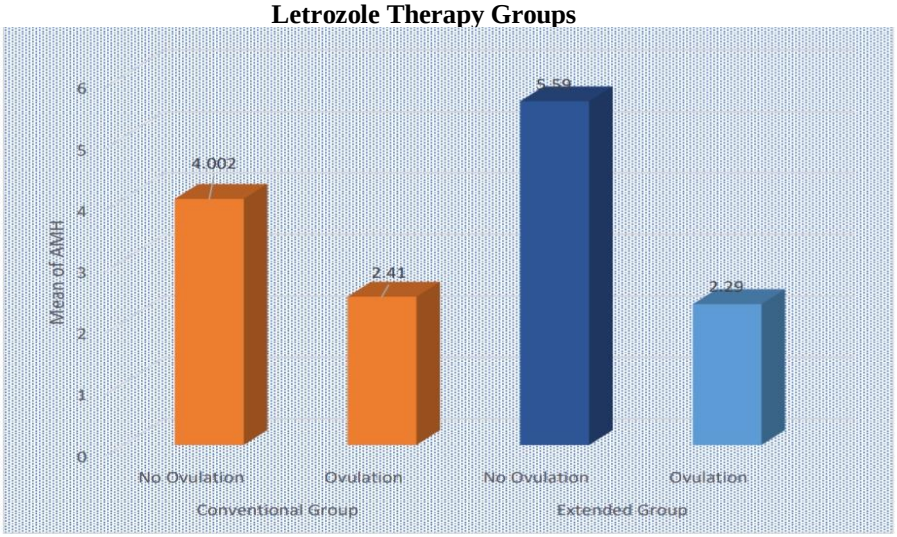
Table 1:Association of Serum AMHLevels with Ovulation Outcomes inConventional and Extended Letrozole Therapy Groups

	Conventional Group				Extended Group			
	No Ovulation		Ovulation		No Ovulation		Ovulation	
Parameter	Mean	SD	Mean	SD	Mean	SD	Mean	SD
AMH	4.002	2.88	2.41	1.48	5.59	2.31	2.29	1.006
P-Value	0.001				0.001			
Overall P-	<0.001							

Table 2: Association of AMH Value with Ovulation Outcomes

Statistic	Value
Chi-square (χ^2)	9.91
p-value	0.0016
Odds Ratio (OR)	0.21
95% CI (Haldane correction)	0.08-0.55
Interpretation	Strong inverse association between AMH and ovulation in both treatment groups.

Fig. 1: Graphical Association of Serum AMH Levels with Ovulation Outcomes in Conventional and Extended Letrozole Therapy Groups



DISCUSSION

In women with anovulatory infertility and PCOS, we found that a higher baseline AMH concentration was associated with reduced odds of ovulation with Ovulation Induction treatment, regardless of letrozole induction protocol. Women with an AMH concentration of >8 ng/mL were significantly less likely to ovulate compared with those with a normal AMH concentration of <4 ng/mL.This study demonstrates that higher AMH levels are strongly associated with poor ovulatory response, irrespective of the letrozole regimen. The extended protocol achieved higher ovulation rates overall, yet women with elevated AMH (> 4 ng/mL) continued to show reduced responsiveness. These findings align with reports by Mumford et al. (2016) and Komorowski et al. (2024), which identified AMH as a negative predictor of ovulation induction success [13,14]. Our findings are generally consistent with the previous studies of OI treatment among women with PCOS. Mumfordet al. [13] conducted a secondary analysis of data from thePPCOS II randomized clinical trial of 748

women and found the lower mean AMH concentration among women who ovulated with OI with clomiphene or letrozole. In their analysis, each unit increase in AMH concentration was associated with a 6% reduction in odds of ovulation which was comparable with our findings. The pathophysiological explanation lies in the inhibitory role of AMH on FSH sensitivity, resulting in delayed or absent follicular maturation. Clinically, AMH can thus serve as a predictive biomarker to tailor stimulation protocols—patients with high AMH may benefit from higher letrozole doses or adjuvant agents likemetformin.Interpretation of the AMH results will be an increasingly important skill for clinicians, and ultra-high AMH concentrations should prompt a referral to specialists in reproductive endocrinology.

CONCLUSION

AMH levels exhibit a significant inverse relationship with ovulatory success in both conventional and extended letrozole regimens. Extended letrozole treatment improves overall ovulation rates but does not fully overcome the inhibitory effect of elevated AMH.

Hence, serum AMH measurement before induction can aid in individualized treatment planning for PCOS-related infertility.This Signiantfinding will guide counseling for women with PCOS-related infertility regarding their odds oftreatment success with OI. Finally, our findings shouldencourage early referral to reproductive endocrinology inwomen with very high AMH values and in women forwhom initial attempts at low-dose OI are unsuccessful.

Abbreviations

PCOS-polycystic ovarian syndrome, OI-ovulation Induction, AMH-Anti mullerian Hormone.

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