RESEARCH ARTICLE

Comparison between the levels of anti mullerian hormone after treatment with clomid versus letrozole in polycystic women: an experimental study

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Abstract

Objective: To compare the effect of two ovulation induction drugs on anti-Mullerian hormone level in polycystic women.

Method: The experimental cohort study was done at the infertility outpatient clinics of Al-Yarmouk Teaching Hospital, Baghdad, Iraq, from May 2020 to April 2021, and comprised infertile women aged 18-35 years with confirmed diagnosis of polycystic ovarian syndrome. Baseline blood level of anti-Mullerian hormone was tested in all patients. The patients were divided into two groups. Group A patients received clomid 50mg twice daily to a maximum of 200mg for 5 days starting from the third day of the menstrual cycle. Group B patients received letrozole 2.5mg twice daily for 5 days starting from the third day of the menstrual cycle. After ovulation induction on day 12-14, a second sample of serum anti-Mullerian hormone was tested, and intergroup comparisons were done. Data were analysed by using the available statistical package of SPSS-28 (Statistical Packages for Social Sciences- version 28). Students-t-test , Paired-t-test , Pearson correlation , t-test or ANOVA test Statistical significance was considered for P value equal or less than 0.05.

Results: Of the 83 women, 41(49.4%) were in Group A with mean age 26.0±4.9 years, while Group B had 42(50.6%) subjects with mean age 27.0±5.1 years. Post-intervention, the level of anti-Mullerian hormone decreased significantly in both groups ($p<0.05$). The decrease in Group B was more than Group A, but the difference was not significant ($p>0.05$).

Conclusions: Ovulation induction drugs clomid and leterzole decreased the level of anti-Mullerian hormone significantly.

Key Words: Polycystic Ovary, Anti-Mullerian Hormone, Letrozole, Infertility, Ovulation Induction, Ambulatory Care, Menstrual Cycle, Clomiphene

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Introduction

Polycystic ovarian syndrome (PCOS) is a common heterogeneous ovarian endocrine problems affecting 6-8% of women, leading to different complications that affect women's health, such as disturbances in the menstrual cycle, weight-gain, hyper-androgenic features like hirsutism and acne, and metabolic syndrome. Besides, it is considered the most common cause of infertility[1].

In 1935 it was found that PCOS women may complain of amenorrhea, hirsutism and/or obesity[2]. The majority of PCOS patients have infertility as their first major complaint, and clomiphene citrate (CC) has been suggested an effective, low-cost first-line treatment with few side effects, with 60-85% success rate[3]. However, 15-20% of such women show resistance which is diagnosed after 3-6 months of treatment[4].

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The anti-Müllerian hormone (AMH), a member of the transforming growth factor-beta (TGF-β) super family, has been seen to be 2-3-fold higher in PCOS subjects than in healthy women, making it an important PCOS marker[5]. Many studies have found that ovarian response and ovulation in response to ovulation-induction drugs (OIDs) in PCOS women correlate better, depending on serum AMH level[6].

The level of AMH seems to decrease throughout the whole reproductive period[7,8]. In women with PCOS, increased AMH level can be found with a large number of antral follicles[9]. In vitro fertilisation (IVF) seems to depend more on AMH levels, and AMH is also regarded as an important indicator of ovarian reserve[10].

CC has been shown to affect cervical mucus secretion as well as endometrial lining. It affects development of multiple follicles, and about 15% of PCOS patients do not respond to the treatment, becoming CC-resistant[11]. On the other hand, letrozole does not inhibit oestrogen-negative effect on the hypothalamic-pituitary-ovarian (HPO) axis[12].

The current study was planned to compare the effect of two OIDs on AMH level in PCOS women.

Patients and Methods

The experimental cohort study was done at the infertility outpatient clinics of Al-Yarmouk Teaching Hospital, Baghdad, Iraq, from May 2020 to April 2021. After approval from the ethics review committee of the College of Medicine, Mustansiriyah University, Baghdad, the sample was raised. Those included were infertile women aged 18-35 years having body mass index (BMI) <=35kg/m^2. Infertility owing to PCOS was diagnosed based on two of the three elements in the Rotterdam consensus criteria: oligomenorrhea and/or anovulation, hyperandrogenaemia and ultrasound appearance of polycystic ovaries[4]. However, those with marked hyperandrogenaemia were screened for other related causes, such as congenital adrenal hyperplasia and Cushing syndrome as part of their treatment.

Diagnoses of anovulation was considered confirmed when either cycle length was >6 weeks, or serum progesterone concentration at mid-luteal phase of the menstrual cycle was <10 pmol/L (in women with shorter cycles). Hyperandrogenism was diagnosed either clinically in the form of acne and/or hirsutism with or without biochemical indications that included either testosterone level >2.5nmol/l or free androgen index (FAI) >=5. Ultrasound features of polycystic ovaries were noted if the ovary contained >=12 follicles and their diameter was 2-9mm with ovarian volume >10ml. All participants had patency of at least one fallopian tube on hystrosalpingography (HSG), and their male partners had normal semen analysis as per the World Health Organisation (WHO) criteria[13].

After obtaining informed consent from the subjects, baseline serum AMH level was tested in all patients. The patients were divided into two groups. Group A patients received CC clomid 50mg twice a day to a maximum of 200mg for 5 days starting from day 3 of the menstrual cycle. Group B patients received letrozole 2.5mg twice a day for 5 days starting from the third day of the menstrual cycle. After OI on day 12-14, a second sample of serum AMH was tested, and intergroup comparisons were done.

Data were analysed by using the available statistical package of SPSS-28 (Statistical Packages for Social Sciences- version 28). Students-t-test , Paired-t-test , Pearson correlation , t-test or ANOVA test Statistical significance was considered for P value equal or less than 0.05.

Results

Of the 83 women, 41(49.4%) were in Group A with a mean age of 26.0±4.9 years, while Group B had 42(50.6%) subjects with a mean age of 27.0±5.1 years. Age, BMI, parity and duration of infertility were not significantly different between the groups (Table 1).

Table-1: Demographic data of the study groups

	Group A (n=41)		Group B (n=42)		
	No	%	No	%	
Age (years)					
<20years	5	12.2	5	11.9	0.749
20---24	11	26.8	9	21.4	
25---29	13	31.7	11	26.2	
30---35	12	29.3	17	40.5	
Mean±SD (Range)	26.0±4.9	(18-35)	27.0±5.1	(18-35)	0.355
Parity					
0	15	36.6	16	38.1	0.848
1	18	43.9	15	35.7	
2	4	9.8	6	14.3	
3	4	9.8	5	11.9	
BMI (Kg/m2)					
Normal (18.5-24.9)	13	31.7	15	35.7	0.895
Overweight (25-29.9)	22	53.7	22	52.4	
Obese (=>30)	6	14.6	5	11.9	
Mean±SD (Range)	25.90±3.64 (18.9-30.0)		25.55±3.66 (19.0-30.1)		0.663
Duration of infertility (years)					
<5years	28	68.3	30	71.4	0.756
=>5years	13	31.7	12	28.6	
Mean±SD (Range)	3.8±1.4	(2-7)	3.6±1.6	(2-7)	0.622
Duration of infertility (years)					
2	8	19.5	12	28.6	0.906
3	12	29.3	12	28.6	
4	8	19.5	6	14.3	
5	8	19.5	6	14.3	
6	3	7.3	3	7.1	
7	2	4.9	3	7.1	
Mean±SD (Range)	3.8±1.4	(2-7)	3.6±1.6	(2-7)	0.622

*Significant difference between percentages using Pearson Chi-square test (♩ 2-test) at 0.05 level.
#Significant difference between two independent means using Students-t-test at 0.05 level.
SD: Standard deviation

Table-2: Baseline and post-intervention levels of anti-mullerian hormone (AMH).

Serum AMH (ng/ml)	Type of ovulation induction treatment		P value
	Group A	Group B	
Initial "before" induction	4.46±1.11 (2.00-6.00)	4.51±1.03 (2.00-6.00)	0.813
After induction	4.07±1.08 (2.00-6.00)	3.69±1.05 (2.00-5.30)	0.102
P value	0.001^	0.0001^	

^Significant difference between two dependent means using Paired-t-test at 0.05 level.
#Significant difference between two independent means using Students-t-test at 0.05 level.

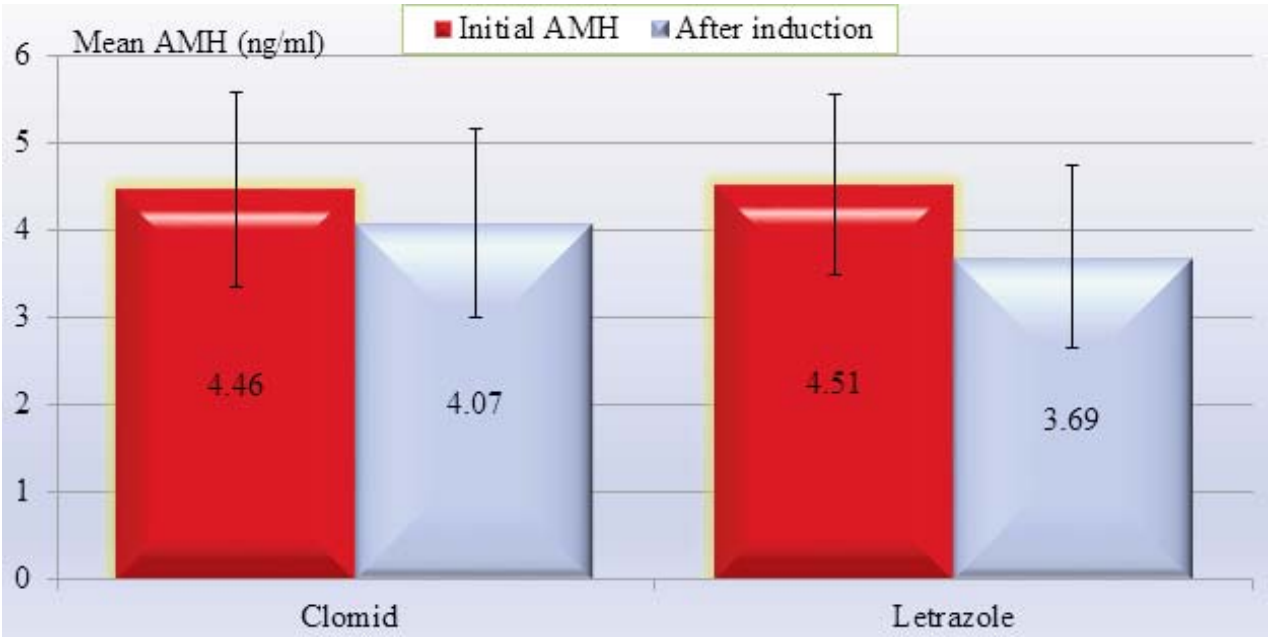

Figure: Decrease of mean anti-mullerian hormone (AMH) level post-intervention.

Post-intervention, the level of AMH decreased significantly in both groups ($p<0.05$). The decrease in Group B was more than in Group A, but the difference was not significant ($p>0.05$) (Table 2, Figure).

Discussion

The pathophysiology of AMH on PCOS patients is still not fully understood. Its seems clear that the main factor that affect the process of folliculogenesis and anovulation disorder is the excess autocrine action of AMH found within the granulosa cells.[5]

Nayereh et al. compare the level of AMH before and after OIDs (letrozole and gonodatrophin), and found that AMH was not a predictor of ovarian response in PCOS patients, but its level seemed to decease after OID treatment.[14] The current findings endorsed the earlier results.

A study showed that women with high AMH levels, regardless of PCOS status, had lower effect on the ovulation process when using CC or letrozole compared to women with normal AMH level.[15] In the current study, the level of AMH decreased after letrozole and CC treatment, and this was probably due to the direct inhibitory effect of AMH on granulosa cells as well as decreased follicle-stimulating hormone (FSH) response.

In 2021 a study found that PCOS patients with high AMH levels had decreased ovulation response when using oral OIDs, and needed different strategies of treatment as per the PCOS criteria.[16]

A study showed that increased levels of AMH may require increase clomiphene or letrozole dose to achieve good ovarian response.[17] The current study had similar findings.

Conclusion

AMH serum level could be useful clinically to identify PCOS women more likely to respond to either clomid or letrozole OID.

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