

**RELATIONSHIP BETWEEN AMH LEVEL AND OVARIAN RESPONSE TO  
CLOMIPHENE CITRATE IN WOMEN WITH POLYCYSTIC OVARIAN SYNDROME**Sheren Hussien<sup>\*1</sup>, Basel Mohammad<sup>2</sup> and Rajaa Rajab<sup>3</sup><sup>1</sup>M. D, Department of Obstetrics and Gynecology, Tishreen University Hospital, Lattakia, Syria.<sup>2,3</sup>Associate Prof., Department of Obstetrics and Gynecology, Tishreen University Hospital, Lattakia, Syria.**\*Corresponding Author: Dr. Sheren Hussien**

M. D, Department of Obstetrics and Gynecology, Tishreen University Hospital, Lattakia, Syria.

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**ABSTRACT**

**Background:** Polycystic ovary syndrome (PCOS) is a common endocrine disorder of uncertain origin and it is the major cause of anovulatory infertility. The treatment of first choice for induction of ovulation is antiestrogen therapy. Clomiphene citrate stimulates endogenous FSH secretion, leading to development of a dominant follicle and ovulation in approximately 75% of patients. While the exact function of anti mullarian hormone (AMH) is yet to be completely clarified, there is evidence that it counteracts the actions of FSH on aromatase activity and in the development of an ovulatory follicle. Although serum AMH levels are used as a predictive marker of ovarian response during IVF, there are conflicting reports of its predictive value for follicular recruitment in ovulation induction with clomiphene citrate. **Objective:** This study aims to detection the predictive value of AMH for ovarian response to Clomiphene Citrate in PCO patients. **Methods:** A prospective trial conducted 100 patients with PCO syndrome, who have an indication for ovulation induction. After measurement of AMH value, they received tablet clomiphene citrate 100 mg/day starting on 5<sup>th</sup> day of menstrual period, for five days. The association between AMH and ovarian response to clomiphene citrate was studied. **Results:** The mean AMH value in responsive group was (3.11±0.7), while it was (4.57±1.6) in the non-responsive group (p=0.0001). The cut-off value of AMH =4.1, with sensitivity of 96.7% [87 - 99] and specificity of 87.1% [70 - 95]. 39 (60%) cases of regular menstrual period group showed ovarian response to clomiphin citrate compared with 26 (40%)cases in irregular group. Ovarian response was most common in normal weight group41(63.1%) followed by overweight group24(36.9%) with no response noticed in the obesity group0 (0%). **Conclusions:** AMH may be predictive for resistance of ovulation induction with clomiphin citrate.

**KEYWORDS:** AMH, PCO, Clomiphene citrate.**INTRODUCTION**

Polycystic ovary syndrome (PCOS) is a common endocrine disorder of uncertain origin and it is the major cause of anovulatory infertility.<sup>[1]</sup> Using the more recent Rotterdam consensus<sup>[2]</sup>, the prevalence is estimated to be as high as 20-25% in white women in the UK.<sup>[3]</sup> In a recently reported series 83% of women with anovulatory infertility (who complained of irregular periods, oligomenorrhoea, or amenorrhoea) have polycystic ovaries on ultrasound examination.<sup>[4]</sup> Although PCOS is by far the most common cause of anovulation, the precise reason or reasons for the failure of ovulation remain unclear.<sup>[5]</sup> The anovulation in women with polycystic ovary syndrome may due to the endocrine abnormalities include raised concentrations of luteinising hormone (LH; seen in about 40% of women), testosterone, and androstenedione, in association with low or normal concentrations of follicle stimulating hormone (FSH).<sup>[6]</sup> Although insulin resistance is a key pathophysiological abnormality, and women with polycystic ovary

syndrome have increased risk of impaired glucose tolerance, type 2 diabetes mellitus, and the metabolic syndrome.<sup>[7]</sup> Most studies suggested that metformin—when used alone and compared with placebo—significantly lowered serum androgen concentrations and restored menstrual cyclicity. One of these early meta-analyses indicated that metformin can achieve ovulation either alone or when combined with clomiphene.<sup>[8]</sup> The treatment of first choice for induction of ovulation is antiestrogen therapy; the most commonly used agent is clomiphene citrate. Clomiphene is given orally, usually at a starting dose of 50 mg/day for 5 days, generally starting on day 2 or 3 after the onset of spontaneous or progestin-induced menses. The drug stimulates endogenous FSH secretion, leading to development of a dominant follicle and ovulation in approximately 75% of patients. The fecundity rate after clomiphene-induced ovulation (70% of women conceive within 6 cycles) is close to normal.<sup>[9]</sup> Possible problems range from failure to develop a preovulatory follicle to hyperstimulation

syndrome. Predictors of ovulation in response to clomiphene include body weight and free androgen index.<sup>[10]</sup> The AMH expressed by the antral follicles.<sup>[11]</sup> The density of pre-antral and small antral follicles in the polycystic ovary is six times that of the normal ovary.<sup>[12]</sup> It is hence not surprising that serum AMH levels are higher in women with PCOS as compared to those without PCOS.<sup>[13]</sup> While the exact function of AMH is yet to be completely clarified, there is evidence that it counteracts the actions of FSH on aromatase activity and in the development of an ovulatory follicle.<sup>[11]</sup> Although serum AMH levels are used as a predictive marker of ovarian response during IVF, there are conflicting reports of its predictive value for follicular recruitment in ovulation induction with clomiphene citrate. Mahran et al. reported a cut-off value of >3.4 ng/ml, at which clomiphene resistance was more commonly observed. They suggested that higher doses of clomiphene may be required above this threshold.<sup>[14]</sup>

## METHODS AND MATERIALS

This prospective study has been conducted in gynecology clinic at Tishreen University Hospital from 2023 to 2024.

It enrolled 100 patients with PCO syndrome, who have an indication for ovulation induction.

Patients with hepatic disorders, uncontrolled endocrine diseases, history of chemotherapy or radiotherapy and previous ovarian surgery were excluded. After patients' agreement, a detailed history and a complete clinical examination were done. AMH was measured and vaginal ultrasound was done on the second/third day of menstrual period.

After complete evaluation patients were prescribed to take clomiphene citrate 100 mg/day starting on 5<sup>th</sup> day of menstrual period, for five days. The development follicle counts, follicle diameter and endometrial thickness were measured on the 11<sup>th</sup> day of menstrual period, 13<sup>th</sup> day of menstrual period, 48 hours and 72 hours after at least one follicular development to 18 mm diameter. TVS was performed by the same experienced operator using (SIEMENS ACUSON 150) model ultrasonography machine.

## RESULTS

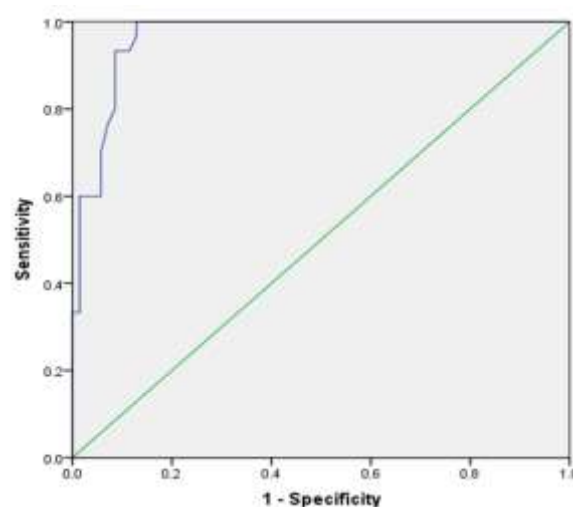
Total 100 cases were enrolled for study. Baseline characteristics are shown in Table 1. Irregular menstrual period was more common than regular menstrual period reported by 53(53%) cases and 46(46%) cases respectively. At enrollment, the BMI classification was normal, overweight and obesity in 42 (42%), 39 (39%) and 19 (19%) of women respectively.

**Table 2: Characteristics of study population.**

Parameters	Value
Age(years)	24.92±3.2
BMI(kg/m2)	25.2±3.1

The mean AMH value in responsive group was (3.11±0.7), while it was (4.57±1.6) in the non-responsive group (p=0.0001). The cut-off value of AMH =4.1, with sensitivity of 96.7% [87 - 99] and specificity of 87.1% [70 - 95], as shown in figure 1.

39 (60%) cases of regular menstrual period group showed ovarian response to clomiphene citrate compared with 26 (40%) cases in irregular group, compared with failure response in 8(22.9%), and 27 (77.1%) respectively (p=0.005). Ovarian response was most common in normal weight group 41(63.1%) followed by overweight group 24(36.9%) with no response noticed in the obesity group 0 (0%), compared with failure response in 1(2.9%), 15 (42.8%) and 19 (54.3%) respectively (p=0.0001).



**Figure 1: AMH values and ovarian response.**

## DISCUSSION

Poly cystic ovary (PCO) is one of the most common endocrinal disorders related to obesity<sup>[15]</sup>, that's why we found (58%) either overweight or obesity. The irregular menstrual periods were more common than regular ones. This irregularity may due to hormonal disturbances observed in PCO syndrome (insulin resistance, high levels of androgens and increasing LH to FSH ratio).<sup>[16]</sup> AMH leads to decreasing of aromatase enzyme and FSH receptors expression, due to AMH affects granular cells in ovary.<sup>[17],[18]</sup> AMH was higher in non-responsive patients. The high values of AMH may be associated with an elevated threshold for ovarian response when PCO patients are inducted with clomiphin citrate. Obesity, hyperandrogenism and insulin resistance may be the responsible factors for the resistance of clomiphin citrate. Several studies reported that chronic inflammatory response in PCO patients (TNF- $\alpha$ , adiponectin) may be the responsible factor for the resistance of clomiphin citrate.

## CONCLUSIONS

AMH may be predictive for resistance of ovulation induction with clomiphin citrate.

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