The Effect of Anti-Gonadotropic Hormone Antibodies on Ovarian Response to Ovulation Induction in Women With PCOS.

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ABSTRACT

Background: PCOS patients often require ovulation induction due to infertility. However, it is observed in practice that some of these patients do not respond despite multiple attempts. Anti-gonadotropin antibodies are believed to be responsible. The goal of this study was to estimate the response of women with PCOS and positive anti-gonadotropin antibodies to the induction of ovulation.

Methodology: A prospective study was conducted at Basra Maternity and Child Hospital from January 2019 to November 2021. The study included 73 women with PCOS. The diagnosis of PCOS was based on amenorrhea, signs of hyperandrogenism, as well as typical sonographic findings in PCOS. The male factor was excluded in all selected cases. Three cycles of parental gonadotropin were administered to all women. Individual blood samples were collected, and ovulation monitoring was performed. Anti-FSH and Anti-LH levels were detected by the ELISA technique. Statistical analysis was carried out using SPSS.

Results: The total number of samples evaluated was 73, with ages ranging from 20 to 36. Based on sonographic evaluation of follicle size, hormonal levels and demographic characteristics, 44 cases were classified as good responders, and 29 cases as poor responders. It seems that age is a significant factor between the two groups. There was a statistically significant difference in the level of FSH and LH between the two groups on day three of the cycle. The duration of infertility and the number of treatment cycles did not affect the outcome in either group. Anti-FSH antibodies were much higher in poor responders compared to good ones, while the level of anti-LH antibodies was marginally significant between the two groups. The level of anti-gonadotropin antibodies in the present study was not significantly influenced by BMI.

Conclusions: The anti- gonadotropin antibodies affect the response to ovulation induction in women with PCOS. It seems that the age as well as the basal level of FSH and LH are significant factors among the good and poor responders. Poor responders have a significantly higher level of anti-FSH, which affects fertility adversely.

Keywords: Anti-Gonadotropic hormone antibodies, ovarian stimulation, polycystic ovarian.

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Introduction

Infertility means being unable to conceive after one year despite unprotected intercourse (1, 2). Polycystic ovary syndrome (PCOS) is defined as a condition characterized by amenorrhea, hirsutism, obesity, and enlarged polycystic ovaries (3). Diagnostic features of PCOS include clinical and/or biochemical signs of hyperandrogenism, oligo-ovulation, or anovulation, following the exclusion of other endocrine disorders. Furthermore, the sonographic finding of polycystic ovaries on ultrasound is also considered a diagnostic criterion.

Autoimmune mechanisms are associated with increased production of autoantibodies of several types (such as anti-gonadotropin antibodies, anti-ovarian antibodies, and anti-thyroglobulin antibodies), which are involved in several disorders that may lead to infertility, such as PCOS (4).

The diagnosis of autoimmune reactions in PCOS has long relied on the detection of anti-ovarian autoantibodies. Some antibodies are thought to be associated with a direct effect on the ovaries, while others do not have the same effects. Anti-FSH antibodies may interfere with either endogenous or exogenous FSH function. They may interact with FSH and form immune complexes, thus provoking its clearance. Also, anti-FSH antibodies could interfere with the binding of FSH to its receptors (5). This study aimed to estimate the

response of women with PCOS and positive anti-gonadotropin antibodies to ovulation induction.

Method

A prospective study was conducted at the Infertility Center in Basra Maternity and Child Hospital from January 1, 2019, to November 1, 2021. A total of 73 infertile women with primary infertility due to PCOS were included in this study. The women were recruited from the outpatient department of the Infertility Center and private gynecological clinics in various areas of Basra, with ages ranging from 20 to 36 years.

The diagnosis of PCOS was based on oligomenorrhea or amenorrhea, biochemical and/or clinical signs of hyperandrogenism, and the appearance of polycystic ovaries on ultrasound examination (6). Inclusion criteria included an age range of 18-36 years, a period of infertility of more than two years, normal serum prolactin levels, thyroid and adrenal function. Hirsutism was diagnosed when the Ferriman and Gallwey score was greater than eight (7). All patients underwent clinical examination, and their weight, height, and body mass index (BMI) were recorded. Transvaginal ultrasound examinations were performed to exclude any pelvic pathology or ectopic pregnancy before treatment. Previous ovulation induction was excluded based on the gynecological history. Blood samples (5 ml) were collected in clot activator tubes, after the separation of serum, and kept frozen at (-20 degrees Celsius) until the time of analysis. The estimation of human anti-FSH and anti-LH antibodies of IgG was performed using a quantitative sandwich ELISA.

Women with positive antibodies were included in the study. All women were then subjected to a course of induction of ovulation, consisting of 5 days of 75-150 IU/day (1 or 2 ampules of Gonal F, recombinant FSH), followed by measurements of serum estradiol on day 3 of the cycle and ultrasound examination to monitor follicular growth and development (target follicular size 18-25 mm). Follow-up scans were scheduled every other day or every 3 days. The ovulation assessment was observed by assessing follicular size by transvaginal ultrasound and serum progesterone (>10 ng/ml) at day 21. The main outcome measures were hormonal levels in women with PCOS after ovulation induction.

Data are expressed as mean±SD, and the difference in hormone levels was evaluated by the independent sample t-test. The correlation between variables was also evaluated. Statistical analysis was performed using IBM SPSS V21. P-value of < 0.05 was considered statistically significant.

RESULTS

*Note: All tables mentioned in this section are provided at the end of the article.

This was a comparative study that included 73 infertile women with primary infertility due to PCOS who underwent induction of ovulation by parenteral injectable gonadotropin. Based on the demographic characteristics and hormonal levels, the sample was divided into two groups: Group 1, which comprised poor responders (29 cases), and Group 2, which consisted of good responders (44 cases). The basic characteristics of both groups are presented in (table 1). Statistically significant differences were observed in mean age between poor responders and good responders. However, no significant differences were observed in the duration of infertility or patterns of menstrual disturbance between the two groups.

A significant difference between the two groups was noted concerning the levels of FSH and LH after ovulation induction (Table 2). There was a significant difference in terms of anti-FSH antibodies between poor responder PCOS women and the good responder group measured before the induction of ovulation (Table 3). Meanwhile, the level of anti-LH antibodies showed marginal significance between the two groups (Table 3). There were no statistically significant differences in the levels of these antibodies between obese and overweight women with PCOS and non-obese women with PCOS regarding LH antibodies, but marginal significance was observed with respect to FSH antibodies (Table 4). No statistically significant difference in anti-gonadotropin antibodies was observed in PCOS women with an LH/FSH ratio greater than 3 or less than 3 (Figure 1).

Meanwhile, the level of anti-LH antibodies showed marginal significance between the two groups (Table 3). There were no statistically significant differences in the levels of these antibodies between obese and overweight women with PCOS and non-obese women with PCOS regarding LH antibodies, but marginal significance was observed with respect to FSH antibodies

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Discussion

Polycystic ovarian syndrome is one of the endocrine disorders in females, accounting for about 5%-10% of women. It is associated with autoimmune disorders, which lead to some diseases such as thyroid disorder, diabetes mellitus (8-10). The immune system is affected by the estrogen /progesterone ratio (11). There is a high level of serum estrogen and a low level of serum progesterone in women with PCOS due to a defect in ovulation and menstrual disturbance, which leads to antibody formation due to stimulation of the immune system (11). It is well documented that the formation of anti- gonadotropin antibodies against the gonadotropin therapy may lead to a decrease in the drug efficacy. This immunological reaction could be mild and transient or could be severe. It has been shown that β-FSH is an autoantigen in women presenting with ovarian auto antibodies (11,12). In this study, which involved 73 women with primary infertility and PCO, the mean age was (34 + 3.1) years in poor responders and (25+ 3.8) years for good responders, which is statistically significant. It is observed from the result of this study that the poor responder women is older than the good responders which is in agreement with Marshall (13) who found the average age is (27.85 ± 4years) and Yan Yang (14) which was (28.4 ± 3.8years) and comparative to a study done by Elmekkawi which was (31 ± 5years) and higher than what found by Agacayak (mean 26.2±4.0years, 15-16). There are similarities between these studies regarding the age group, as most women with PCOS are diagnosed when their age is between 20-30 years (17). Obesity is the major feature in PCOS women; there is a relation between adiposity and hyperandrogenic status in PCOS (18). In the present study, all the women in both groups are overweight (BMI > 28, Table 1), which is in agreement with the previous studies (15,16,17). The European Society of Human Reproduction and Embryology (ESHRE) working group reported that in order to define a poor response, at least two of the following three features must be present: an advanced maternal age, a previous poor ovarian response, and an abnormal ovarian reserve test. Some researchers classify poor responders into two subgroups; the first includes young age ≤37 years and slim-bodied, weight ≤70 *kg* patients who develop less than five follicles following 9 days of ovarian stimulation and reach follicular size less than 15mm. The second includes patients who are >37 years old and weight >70 *kg,* and their cycles have been cancelled due to the production of less than five follicles following 9 days of ovarian stimulation (18).

Regarding the basal level of FSH &LH, the difference in the level of both hormones was statistically significant between the poor and good responders. Serum level of FSH at day 3 of cycle (≥7 to ≥15 mIU/mL) is one of the criteria of poor responder (20). The difference in the level of anti-FSH antibodies is highly significant between poor responder PCOS women, in contrast to the good responder group. While the level of anti-LH antibodies is marginally significant between the two groups, this agrees with a study done in Iraq (21, 22). The changes in PCOS affect the immune system and may lead to the formation of autoantibodies (23). Study was done by haller et al, concluded that autoantibodies production in the serum of women who used gonadotropin is more in women who their basal level of FSH&LH higher than physiological level, in this study, the poor responder PCOS women had higher level of basal FSH&LH than the other group, which explains the higher levels of antibody production (24).

FSH hormone is responsible for follicular development; therefore, external gonadotropic therapy is used in ovarian induction of ovulation. There is an increase in the development of antibodies against FSH in women with infertility (24). This observation was detected by many studies that demonstrated the relation between poor ovarian response and the function of FSH caused by ovarian autoimmunity, which includes anti-gonadotropin antibodies (24). Although the role of anti-FSH in poor ovarian responders in the induction of ovulation and IVF is still unclear but many studies have proved the pathological role of antibodies on the growing follicles (25).

Conclusion

The anti-gonadotropin antibodies affect the response to ovulation induction in women with PCOS. It seems that the age and the basal level of gonadotropic hormones are significant factors among the good and poor responders in the present study. Poor responders have a significantly higher level of anti-FSH, which adversely affects fertility. We recommend studying the association of anti-FSH antibodies with IVF treatment outcome and evaluate the role of immunosuppressive therapy in cases of repeated IVF.

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Table 1: Demographic characteristics for both groups

Demographic characteristic	Group 1 Poor responder (No=29)	Group 2 Good responder (No =44)	*p* value
Age (year) Mean ± S.D.	34.4 ± 3.1	25.5 ± 3.8	0.002
BMI(Kg/m^2) Mean ± S.D.	28.0 ± 2.5	29.0 ± 3.2	0.60
Duration of infertility (years)	3.4	4.2	0.1
No. of treatment cycles (months)	3-9	3-19	0.12

Table 2: Hormonal levels of the study women on day 3 of the cycle

Variable	Poor responder Mean± SD	Good responder Mean ±SD	*P* value
FSH mlu/ml	6.13 ± 1.7	4.37±1.5	0.04
LH mlu/ml	9.40 ± 2.42	8.8±1.04	0.01
E2(Pg/ml)	62.3±17.1	60.3±17.1	0.12
Prolactin ng/ml	19.34± 3.2	23.96±9.4	0.56
Teststeron nmol/L	1.7± 3.5.	1.6±1.6	0.12

Table 3: Anti-gonadotropin antibody levels in both PCOS women.

Immunological markers	Subjects	Mean ± S.D	Range	*p* value
Anti-LH Ab(ng/ml)	Group 1	125.6 ± 49.9	(11.6 – 271.2)	0.051
	Group 2	79.4 ± 30.1	(74.6 – 231.5)	
Anti-FSH Ab(ng/ml)	Group 1	36.1 ± 3.91	(3.5 - 161.3)	0.012
	Group 2	22.4 ±2.79	(5.9 – 134.4)	

Table 4: The relation between obesity and anti-gonadotropin antibodies levels in PCOS women

Immunological markers	Normal (BMI ≤ 25 Kg/m^2)	Overweight and obese (BMI > 25 Kg/m^2)	*P* value
Anti-LH Ab (ng/ml)	79.8 ± 1.70	101.5 ±1.24	0.553
Anti-FSH Ab (ng/ml)	22.1 ± 68.0	45.9 ± 29.3	0.056

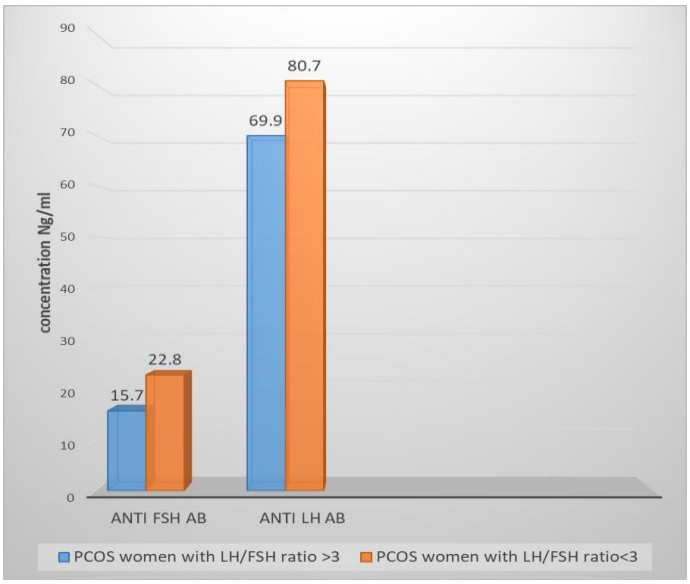

Figure (1): Effect of LH/FSH ratio on anti-gonadotropin antibody levels in both groups of women (poor and good responders)