Original Article

Ovarian antral follicle number and the amount of gonadotropin used in ovarian stimulation in polycystic ovarian patients.

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Summary:

Background: Polycystic ovary syndrome is the most common cause of anovulation, and the number of antral follicles is of great importance in determining ovarian reserve, so identification of patients with diminished ovarian reserve help in choosing individualized and well managed ovulation induction protocol. The aim of the study is to find out if the number of ovarian antral follicles could affect the amount of gonadotropins used in ovarian stimulation in polycystic ovarian patients.

Patients and methods: Ninty four infertile polycystic ovaries women, attending the infertility clinic at Baghdad teaching hospital, during the period of November 2005 to October 2006, were compared to 62 control group women who have unexplained infertility. After exact history and examination, ultrasound was done to both groups at cycle day 3 for antral follicle counting. Then ovarian stimulation was started with gonadotropins, and another ultrasound was done on cycle day 13 for mature follicles confirmation.

Results: Antral follicle number was found to be significantly higher in patients than control groups (9.98 ± 2.09 vs 5.40±2.02). Age was found to be negatively correlated with antral follicle size and number in patient and control groups. After measuring the number of mature follicles at cycle day 13 it was observed that the antral follicle number was correlating positively and significantly with the number of follicles at cycle day 13, but negatively with the amount of gonadotropin used for ovarian stimulation in patients and control groups.

Conclusion: Antral follicles number is significantly higher in polycystic ovary patients and they correlate negatively with age. Antral follicle number is a good predictor of the number of gonadotropin ampouls used for ovarian stimulation.

Keywords: PCO, antral follicles, gonadotropins

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Introduction:

Polycystic ovary syndrome is an extremely common heterogeneous disorder of ovarian cyclicity (1). The prevalence of this condition in women in reproductive age has been estimated to be around 5-10 % (2). Typical ovarian ultrasonographic features were suggested, that consisted of more than 10 discrete follicles of less than 10mm diameter, which are usually arranged peripherally around an increased central stroma occupying more than 25% of the ovarian volume. While the so called pearl neck-lace sign is present in about three quarters of women with anovulatory infertility (1).This sign is called also a string of black pearls around white neck (3). Patients who desired to conceive are usually offered ovulation induction treatment, which is particularly challenging in patients with PCOS (4).

The response of polycystic ovary to ovulation induction varies significantly from that of normal ovaries, because of the over responding of the PCOS patients to the treatment. More follicles will grow with larger sizes (5).

Clomiphene citrate is most often applied as a first line therapy (6). If no response to 150 mg/day CC, the addition of gonadotropins is needed (7). FSH preparations and hMG have both been used successfully in PCOS patients (8). The high levels of LH in PCO patients lead to poor oocyte quality reduced rate of fertilization and pregnancy and increased rates of early abortion (9).

As woman ages, her supply of eggs gradually declines over time until menopause. Although we expect the ovary to age in a certain way, it does not behave as predicted. That's why screening for ovarian reserve is one of the initial evaluation for infertility patients of any age. Low ovarian reserve greatly reduces patient's chance for conception (10, 11). Menstrual cycles that occur near the end of ovarian lifetime are associated with eggs of poorer quality (11).

Diminished ovarian reserve means that fewer follicles are available for stimulation and recruitment by fertility drugs. (12). The aim of the work is to study the effect of the number of antral follicles on the amount of gonadotropin used in ovarian stimulation in polycystic ovarian patients and its correlation with age.

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Patients and methods:

The subjects enrolled in this study were 94 infertile polycystic ovaries women, attending the infertility clinic at Baghdad teaching hospital, during the period of November 2005 to October 2006.

Patients were compared with 62 control group women who have unexplained infertility. The age range for control group was between 22 and 46 (mean 33.45 ± 7.91),and for the patients group was between 20 and 45 (mean 31.48 ± 7.48).Exact history was obtained from all patients in addition to that careful examination was done .

The patient was asked also about contraceptives which were used, their types, the time of its usage and the duration of using them, or any complications happened.

Drug history in general especially drugs used for ovulation –induction type amount and duration of their administration, also when was the last time of their usage.

Patients were diagnosed as having polycystic ovaries according to the European society of human reproduction and embryology and American society for reproductive medicine criteria, which include:

1- Menstrual dysfunction.

2- Clinical or biochemical hyperandrogenemia (total testosterone level and the presence of acne and hirsutisim).

3- Presence of polycystic ovaries on ultrasound examination, which include the presence of big ovaries (more than normal size 3.5cm x 2cm x 1cm) with 8 or more follicles measuring 2-10 mm in diameter located peripherally around a thick stroma (13).

Patients with sever hyperprolactinemia , or patients with hormonal therapy or any medications known to interfere with follicular development or hormonal levels under the study for last 3 months of sample aspiration were excluded

While the control group who are the unexplained infertility women are diagnosed after full investigations which include: Normal seminal fluid analysis, normal hormonal assay for the female, including midluteal progesterone assurance of ovulation and normal uterus and tubes by doing hystrosalpingiography (HSG) or laparoscopy.

The ultrasonic device used in this study (transvaginal ultrasound), is (Sonolayer L, SAL-778 with a transvaginal 5mHz probe, Toshiba, Japan).

The ultrasound examination was done at cycle day 3 for the purpose of evaluation of, the number and size of the antral follicles, or any other abnormality, also to see the features of polycystic ovaries. Then the patients and control groups were given gonadotropin injections with serial ultrasounds, until cycle day 13 of the cycle, to evaluate the number and size of the dominant mature follicles (>or = 16 mm in diameter).

The diameter of the follicles were measured from the mean of 2 diameters (longitudinal and anteroposterior diameter), and the ovary was scanned from the inner to the outer margin.

The gonadotropin used was Follitropin alfa (r-hFSH) , (75 IU/ ampoule, Serono company, Bari, Italy) from cycle day 2 -5 and serial ultrasound used until reaching the favorite follicular size. This protocol was used in 2 ways either in step up or step down (randomly chosen) i.e. either starting by one injection for several days then increasing the dose according to the follicular development or by starting with 2 injections then decreasing the dose .

The patients and control were compared for the number and size of antral follicles and their correlation with age and the amount of gonadotropin used.

Analysis of data was performed using the SPSS software package, spss version 10.1, The P value given are 2- sided and 0.05 was considered the limit of statistical significance.

Differences between patients groups were tested using the students T test.

Results:

After measuring the number of antral follicles in patients and control groups it is demonstrated that there is significant difference between them as in table 1

Table (1): Antral follicle number in patients and control groups (values are in mean ± SEM).

	Patients	Control	P
Antral follicle number	9.98 ± 2.09 (N= 94)	5.40±2.02* (N= 62)	‹0.005

***< 0.05 patient group is significantly different from control group.**

The correlation between age and antral follicle size and number measured at cycle day 3 was shown to be negative and was significant with the follicle number in patients group (table 2 and 3).

Table (2): Correlation coefficient between age and antral follicular size and number in patient group.

	age	
	r	p
Antral follicle size	-0.023	0.833
Antral follicle number	-0.213	0.039*

*** Correlation is significant at 0.05 level.**

Table (3):Correlation coefficient between age and antral follicular size and number in control group.

	age	
	r	p
Antral follicle size	-0.007	0.959
Antral follicle number	-0.095	0.465

Correlating the number of antral follicles at cycle day 3 and those at cycle day 13, it was observed that there is significant positive correlation between them in patients and control groups. The antral follicle count correlated also with the gonadotropin number of ampouls and it was a significant negative one (table 4 and 5).

Table (4):Correlation coefficient between follicular number at cycle day 13 and antral follicular number at cycle day in patients group.

	Antral follicle number	
	r	p
Follicular number cycle day 13	0.273	0.008**
Gonadotropin number	-0.787	0.0001**

**** Correlation is significant at 0.05 level.**

Table (5):Correlation coefficient between follicular number at cycle day 13 and antral follicular number at cycle day 3 in control group.

	Antral follicle number	
	r	p
Follicular number cycle day 13	0.357	0.004**
Gonadotropin ampoule number	-0.069	0.692

****Correlation is significant at 0.05 level.**

Discussion:

It was observed in this study that the number of antral follicles is significantly higher than in control. Which was recorded also by other researchers who found that the antral follicle number /ovary was significantly higher in PCOS than control (14).

Mariet and co- workers, also observed that PCOS patients developed a significantly higher number of stimulated follicles than control patients (15).

Women with pregnancy loss had a lower antral follicle count than those with healthy deliveries. In addition to that, the number of small follicles at the beginning of the cycle may be more representative of the actual function of ovarian reserve than age, and it may be useful tool for predicting pregnancy loss in IVF pregnancies (16).

The total follicle number of > or = 10mm in PCOS were significantly different from that in control and there is a trend towards higher number of follicles (15).

The intraovaroian hyperandrogenism may promote early follicular growth leading to excess of 2-5mm follicles which then will be arrested. The hypothesis explaining follicular arrest is the premature LH action on granulose cells of selectable follicles, also the hyperinsulinemia and insulin resistance act as a second hit worsening the follicular arrest either through amplification of intraovarian hyperandrogenemia or through deregulation of granulose cells (17).Other theory suggested that the arrest of follicular development is due to relative lack of or resistance to FSH (18). Age correlated negatively with follicular number and size. As the age increases, the number and size of follicles decrease which goes well with Burger and his associates (19). Antral follicle count had the best correlation with age of female followed by FSH and ovarian volume and decrease linearly at a rate of 3-8% / year. This decreasing fertility with increasing age is due to decreasing number of primordial follicles (20). Which was found also by other researchers (22, 23, 25).

It was concluded that the number of antral follicles has the best association with the chronological age in normal females with proven fertility (21).So age and number of oocytes retrieved are the strongest predictors of success (26).

If we correlate the number of follicles measured at the beginning of the cycle (CD3), and the number of follicles measured at CD 13 after the treatment, we found the correlation between them was significantly positive. In fact the potential follicular development of the ovary is associated with final follicular number (24).

When there is an average or high number of antral follicles, we get good number of eggs. This agrees with Daniel and co-workers, Pohl and associates, who found that early antral follicular number is positively correlates with the total and mature oocyte number after gonadotropin stimulation and is linked to androgen and insulin action in predicting ovarian follicular recruitment by gonadotropins (28,23). Also Elder and associates observed that the crucial parameter determining the number of oocytes retrieved is the extent of cohort of recruited healthy very small follicles(27). The size of this cohort may change from cycle to cycle especially in elderly people. So the more follicles we have, the large number of oocytes during the treatment cycle (29).

Women with fewer antral follicles needed longer duration and higher dosage of gonadotropins during the stimulation. Even with these higher doses of medications, the number of eggs obtained was significantly less as compared to what was obtained in women with more antral follicles (30).

With higher antral follicle count the ovarian response to gonadotropien improves. So antral follicles are helpful in predicting patients who may be good or poorer cycle responders, and it is important in determining initial gonadotropin doses (31).

Conclusion:

Polycystic ovary patients have significantly higher number of ovarian antral follicles than control group

and this number correlates negatively with the age of the patient, and as there is great number of antral follicles, less number of gonadotropin ampoules used for ovarian stimulation which makes them good predictors of the amount of gonadotropin needed.

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