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THE NUMBER OF FOLLICLES AND OVARIAN VOLUME IN THE ASSESSMENT OF RESPONSE TO CLOMIPHENE CITRATE TREATMENT IN WOMEN WITH POLYCYSTIC OVARIAN SYNDROME

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Abstract

This prospected follow–up study was carried out over 12 months period (from 1st September 2008 till 30th August 2009) in infertility clinic in Basrah maternity and child hospital to evaluate whether certain criteria assessed during initial screening (number of follicles and ovarian volume) could predict the response to ovulation induction with clomiphene citrate (CC) medication.

Clinical, ultrasonographic and endocrine data were collected and analyzed on 58 women with oligomenorrhoea or secondary amenorrhoea with PCOS and infertility before initiation of CC medication. The ovarian morphology were determined by transvaginal U/S which showed all women had altered ovarian morphology (both ovaries had >10 multiple small cyst of 2-9 mm, mean total follicular number (11.0±2.5) and enlarged ovaries, mean ovarian volume (13.2±4.01). Thirty eight patients (65%) ovulate, the remaining 20 (35%) did not. Age, body mass index (BMI), ovarian volume, number of small follicles, serum LH, testosterone and LH/FSH ratio in CC non responders were all significantly higher than in CC responders (P< 0.05).

Data suggest that patients whose ovarian are less likely to respond to stimulation by CC treatment, can be predicted on the basis of initial screening characteristics, such as: BMI, history (oligomenorrhoea, or secondary amenorrhoea) and number of follicles and mean ovarian volume.

These ultrasonographic features & laboratory assays could be clinically useful for distinguishing better the CC no responders from responders.

These observations may add to ongoing discussion regarding etiological factors involved in ovarian dysfunction in these patients and classification of anovulatory infertile women.

Introduction

Polycystic ovary syndrome (PCOS) is one of the commonest endo-crinopathies affecting women of reproductive age[1]. It is a disorder that affects the reproductive, endocrine and metabolic systems, and it is the most common cause of anovulatory infertility[2]. It has eluded definitive description because of the varied combination of clinical, biochemical and ultrasongraphic features which may occur. The commonest association is of hyperandrogenism and chronic anovulation; recognition of characteristic ovarian ultrasound features together with clinical symptoms of oligomenorrhoea, hyperandrogenism, infertility or obesity is presently the preferred to diagnosis[3].

Historically, detection of the polycystic ovary required visualization of the ovaries at laparotomy and histological confirmation following biopsy (Stein and Leventhal, 1935)[4]. As further studies identified the association of certain

endocrine abnormalities in women with histological evidence of polycystic ovaries, biochemical criteria became the mainstay for diagnosis. Raised serum levels of LH, testosterone and androstenedione, in association with low or normal levels of FSH, described an endocrine profile which many believed to be diagnostic of polycystic ovary syndrome (PCOS)[5]. Whether diagnosis is by ultrasonography or by the traditional clinical & biochemical criteria, an average group of anovulatory women at any one point in time will reveal that approximately 75% have polycystic ovaries[6]. Most of these patients, will respond to ovulation induction with clomiphene citrate (CC) alone or combined with human chorioinic gonadotrophene (HCG)[7]. Ovulation is expected in 80% and pregnancy rate 35-40% approximately 20-25% of women show no response to (CC) and are considered to be resistant, those refractory patient are likely to be more insulin resistant and hyperardrogenic than those who do respond[8]. The purpose of this study is to evaluate the significance of the number of follicles and ovarian volume in response to clomiphene citrate treatment in women with PCOS.

Material and methods

This prospective follow up study was conducted over a 12 months period (from first Sept 2008 till 31th Aug 2009) on 58 women with PCOS attending infertility clinic in Basrah Maternity & Child Hospital. Their ages ranged from 20-38 years with periods of infertility more than two years.

An informed consent was obtained from all patients. After taking a proper history, all patients were thoroughly examined clinically and their finding were recorded. The following information were obtained including name, age, gravidity, party, menstrual disorders, evidence of hyperardrogenism (hirsutism and acne), family and drug history.

All women studies had no other endocrine disorders (Diabetes mellitus, Cushing syndrome, thyroid dysfunction). None of patients received any form of hormonal treatment in the preceding 3 months.

General examination including built, hair distribution, thyroid and breast examination, body weight and height were recorded for determination of body mass index (BMI) measured by weight (kg)/height (squared meters), normal BMI range (19-25 kg/m2)[9,10], hirsutism was staged according to established criteria of (Ferryman and Gallway scor)[11].

Ovarian volume and follicular number and were assessed by transvaginal ultrasound examination on day 3 of the cycle on the same day as basal hormonal measurement were taken. Ovarian volume was calculated by the formula (DIx D2 X D3) X 0.52 where D1, D2 & D3 represented the largest ovarian length, width &depth ovarian volume larger than 10cm3 was considered increase[12].

An ovary can be defined as polycystic if ≥ 10 cysts, usually 2-9mm in diameter arranged peripherally or scattered throughout an echo dense stroma are seen in one section and the volume of the stroma is increased[12].

In those women with oligomnorrhoea and secondary amenorrhoea, withdrawal bleeding had been induced by 5mg twice daily oral medroxyprogesterone acetate (provera) for 7 consequtive days[13].

Basal serum testosterone level, LH, FSH, estradiol and prolactin. Serum was obtained. A raised serum testosterone level, LH level, FSH level and prolactin were defined as > 0.9 ng/mL, >8 miu/mL, >12 miu/mL, >20 ng/mL respectively.

LH/FSH ratio was estimated and raised ratio was defined a >2[14].

The criteria for inclusion of a case having PCOS in the study were based on clinical finding such as chronic anovulation (oligomenorrhoae or amenorrhoae), hyperandrogenism and ultrasonography (enlarge ovarian volume & multiple small

follicles appearing in the cortical layer of both ovaries).

Additional inclusion criteria were obesity[9], elevated serum LH/FSH ratio and spontaneous or positive bleeding response to progesterone withdrawal[13].

Clinical, ultrasonographic and endocrine screening took place before initiation of clomiphene citrate medication 50mg on day 2 for 6 consecutive days.

Ovulation was confirmed by serum progesterone level measurement on day 21 of the cycle, and by trans-vaginal ultrasound monitoring of follicular growth started from day 9 of the cycle every another day. Ovulation was considered satisfactory when serum progesterone measurements, were>30 nmol/L in two successive cycle[14].

In case of absent response, daily doses were increased by 50mg in the next cycle. First ovulation was used as the end point and the duration of follow up was three treatment cycles. CC responders were defined as patients who ovulate during CC therapy independent of the dose administered. The number of treated cycles and number CC dose in which the first ovulation occurred were recorded.

Non responders were patients who did not ovulate despite receiving maximum CC dose of 200ml/ day.

Comparisons of clinical, ultrasound and biochemical data were done between women who responded to CC medications and those who did not in order to evaluate whether there are any significant chance in evaluating the response to clomiphene citrate treatment in infertile women with polycystic ovary syndrome (PCOS).

Statistical methodology

The result was reported as number, percentages and mean±SD for the categorical variables, the Chi-Square (X2) test was used to analyze the difference among the groups. The difference was considered statistically significant if P-value < 0.05.

Results

Fifty eight women were included in this study. The demographic distribution and clinical presentation of women with PCOS are shown in table I.

The mean age was 27-28±4.4 .It was found that (37.9%) were illiterate and most women with PCOS were housewives (72.4%). All women had a history of menstrual dysfunction, including oligomenorrhoea in 35 (60.3%) and secondary amenorrhoea in 23 (39.7%), within 3-7 days after completing the progestational agent course; all patients had a withdrawal bled. Fourty eight women (80%) were found to have primary infertility, 10 women (20%) were found to have secondary infertility, hirsuitism was recorded in 23 (39.7%), acne was present in 22 (38%).

Obesity (BMI ≥ 26 kg/m2) was recorded in 28(48.3%),while 30 (51.7%) women were found to have normal BMI (19-25kg/m2).

As shown in table II, there was no statistical difference between mean total ovarian volume and total number of follicles of right and left ovaries were obtained in all groups.

The number of patients who did or did not ovulate after CC medication in increasing doses of 50, 100, 150 and 200mg depicted. Only 21 out of 58 patients (36.2%) ovulate after 50mg CC/day. Twenty one (72.4%) out of 29 women ovulates after 150mg CC medication /day. Twenty women out of 21(95.2%) remaining unovulated after 200mg CC medication /day as shown in the figure.

The clinical features of the over all studied groups and separately for patients who did and did not ovulate after CC medication were presented in Table III.

Comparison between polycystic ovarian women who respond to CC medication versus those who do not, showed that the mean age, obesity were found significantly higher in CC non responders than those in responders group, the values

were 25.7±4.3 and 33±0.4 versus 20.05±6.6 and 25.6±4.1 respectively.

The frequency of hirsutism was significantly higher in non-responders (75%) than in responders (44.7%) P<0.05. On the other hand, percentage of acne was found among 15 (26%) non-responders women in comparison with responders 16(27.5%). This difference was statistically non significant.

Twenty seven women (71%) and 12(60%) out of 20 non-responders was found to have oligomenorrhoea and secondary amenorrhoea compared with 8(40%), 11(28.9%) of CC responders respectively. The difference was statistically significant (P< 0.05).

Table IV, shows the ultrasound characteristic of over all studied groups and separately for patients who did or did not ovulate after CC medication.

The ovaries showed altered ovarian morphology in all women with clinical diagnosis of PCOS. The mean total ovarian volume 13.2±4.01 and the mean total follicular number were 11.6±2.5.

The mean ovarian volume and mean total number of follicles in non responders (13.4±3.8 and 11.7±1.3) were significantly higher than those in responders (11.6±3.8 and 9.9±0.3) respectively.

Table V, shows endocrine parameters of the over all study group and separately for patients who did or did not ovulate after CC medication. The mean serum LH Level, testosterone level and LH/FSH ratio among CC non responders were significantly higher than responders.

The values were (11.2 ± 0.6, 1.7 ± 0.8 & 3.2 ± 0.9) versus (6.8 ± 6.1, 1.1 ± 0.2 & 2.6 ± 1.7) respectively.

Discussion

Polycystic ovary syndrome (PCOS), usually referred to as chronic hyperandrogenic anovulation. Thirty –five years after its first clinical introduction CC still remains the first line treatment strategy in normogonadotrophic anovulatory patients, significant proportion of treated women do not respond[15].

The present study was designed to investigate whether ovarian response after CC medication could be predicted in anovulatory infertility, if patients remaining anovulatory despite CC therapy could be identified, ineffective and time – consuming CC treatment could be prevented. This may be helpful particularly for women in advanced reproductive age.

The first line of anovulaltory infertility treatment is clomiphene citrate. The minimum ovulatory dose is employed, in order to avoid multiple follicle development without single dominant follicle. Several investigators tried to demonstrate the ovarian responsiveness to CC in patients with PCOS.

but ovulation Therefore cannot be induced by CC in approximately 20% of them[8], evaluating sonographic ovarian features and predicting CC in patients responsiveness before initiation of therapy with PCOS are useful in selecting therapy and shortening the treatment period for patients with CC non responsiveness.

In our study we found that altered ovarian morphology occur in all women with clinical diagnosis of PCOS, our findings are close to Carmina et al[16]. After calculation of the ovarian size, we found all women had increased ovarian size ,our results are in contrast to Hann[17] and Puzigaca[18] findings. This may be explained by our small sized sample. Also we found that the total mean of follicles in non responders are significantly higher than in responders, this is in agreement to that recorded by Jonard et al[19].

In our study, the clinical features in women with PCOS were evaluated and we found all women with PCOS presented with anovulatory infertility. Our findings are higher than that of Kousta[14]. This certainly may be due to that all women who were evaluated in our study recruited from the infertility clinic.

Another finding in our study, obesity has been proven to be common clinical finding, it was presented in 48.3%,this result is in contrast to that of Michelmore et al[20].A higher significant relationship of obesity was found in CC non responders in comparison to CC responders. Our result is in agreement to that of Imani et al[15]. Also we found, hirsuitism were present in 75% in non responders, our result are higher than that of Pache et al[21]. Menstrual disorder is another main clinical presentation, was also evaluated in our study. Approximately 60% of patients presented with oligomenorrhoea. Our result is similar to that of Abdel-Gadier et al[22] The prevalence of oligomenorrhoea was higher among CC resistant women compared with CC responders (table 3). The difference was statistically significant and in agreement with other studies[15,23]. Secondary amenorrhea was presented in 39.7%, our finding is higher than that of Ahmed[24]. In this study a significant higher percentage of secondary amenorrhea was found among CC non responders (60%) in comparison to CC responders (28.9%) ,our results is in agreement to that of Imani et al[23].

Ovulation during administration of clomiphene citrate 50mg daily, is monitored by serial ultrasonography and midluteal phase progesterone concentration[25], the dose is increased to 200mg, however there is no evidence that with higher doses resistance will be overcome[15]. Clomiphene resistant cases respond better to low dose human menopausal gonadotrophene (HMG), purified urinary or recombinant FSH, with or without gonadotrophene-releasing hormone agents.

As a first step we focused on the clinical screening parameters of the studied group, age and BMI were significantly higher in CC non-responders, this is in agreement with previous studies[15,26]. BMI had a good predictive power for anovulation.

Anovulatory women who do not respond to CC treatment are usually more obese CC responders in patients with PCOS, suggesting that obesity increases CC resistance[27].

The correlation between BMI and ovarian response after CC suggests that much emphasis should be focused on weight reduction.

On the other hand, it was stated that hirsutism is uncommon, despite raised testosterone concentration in patients with PCOS[23], but in our study the frequency of hirsutism in the CC non-responders was (50%) with a significant difference from the CC responders (31.6%). This is in agreement with other studies[15,23].

Therefore our data indicate that hyperandrogenism may be strongly associated with CC responsiveness in women with PCOS.

The use of pelvic ultrasonography, especially trans-vaginal ultrasonography, to demonstrate ovarian appearance in patients with PCOS has been widely accepted in gynecologic practice.

Concerning the ultrasonographic screening characteristics, ovarian volume was significantly increased in non responders similar findings were reported in previous studies[15,23].

Endocrine parameters potentially related to ovarian dysfunction in PCOS women, were also assessed in our study. Serum level of LH, testosterone and LH/FSH ratio were significantly higher in CC non-responders. This is in agreement with other study[26]. The current study also suggest that LH/FSH ratio is implemented in ovarian dysfunction in PCOS. This agree with previous study[26]. However others contradict this findings[28].

Conclusion

Data suggest that obesity, hyper-androgenism & increased number of small follicles are crucial factors involved in ovarian dysfunction that associated with lack CC response in PCOS women .

Recommendations

These observation may add to ongoing discussion regarding etiological factors involved in ovarian dysfunction in these patients and classification of anovulatory infertile women.

Table I: Demographic distribution and clinical presentation of women with PCOS.

Characteristics	Total number:(58)
Age in(years)	27-28±4.4
Education	
Illitrate	22 (37.9%)
Primary	10 (17.24%)
Secondary	18 (31%)
Higher	8(13.7%)
Occupation	
Housewives	42(72.4%)
Employer	16(27.58%)
Primary infertility	48(80%)
Secondary infertility	10(20%)
Hirsutism	23(39.7%)
Moderate Acne	22 (38%)
Oligomenorrhoea	35 (60.3%
Secondary amenorrhoea	23(39.7%)
BMI ≥ 26(kg/m2) 19-25 (kg/m2)	 28 (48.3%) 30 (51.7%)

Data presented in % and mean ± SD

Table II: Ultrasound features of studied women with PCOS

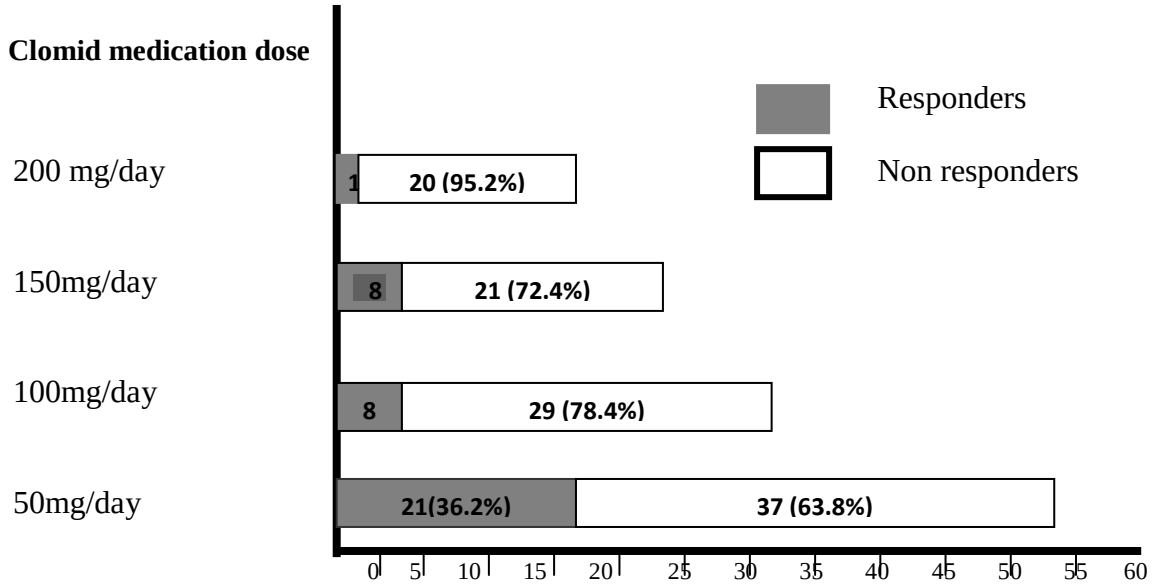
Variables	Total No: (58)
Total Ovarian volume	13.2±4.0
RT ovary	13.5 ± 4.0
LT ovary	13.3 ± 4.4
P value	N.S
Total Follicular number	11.6 ±2.5
RT ovary	11.6 ±0.7
LT ovary	10 ± 1.6
P value	N.S

Data presented in mean±SD, NS: non significant.

Table III: Characteristic in 58 anovul. infert. women subjected to CC medication

Variables	Overall group Total No(58)	CC responders No:38 (65%)	CC non-responders No:20 (35%)	P-value
Age (in years)	29 (20-38) 27.28 ± 4.4	20.05 ± 6.6	25.7 ± 4.3	0.01S.
BMI ≥ 26(kg/m2)	28 (48.3%) 29.3 ± 2.2	10 (26.3%) 25.6 ± 4.1	18 (90%) 33 ± 0.4	< 0.001S.
Hirsutism	32 (58%)	17 (44.7%)	15 (75%)	0.04S.
Moderate acne	31 (53.5%)	16 (27.5%)	15 (26%)	0.06N.S.
Oligomenorrhoea	35 (60.3%)	8 (40%)	27 (71%)	0.04S.
Secondary amenorrhoea	23 (39.7%)	11 (28.9%)	12 (60%)	0.05S.

Data presented in % and mean ± SD. P-value was determined by (X2) test. S: significant. NS: non significant



Distribution of normogonadotrophic oligomnorrhoic or amenorrhoic infertile women who did & did not ovulate after Clomid induction of ovulation in incremental daily doses of 50, 100, 150mg & 200mg for 5 subsequent days.

Table IV: Ultrasound charact. in 58 anovul. infert. women subjected to CC med.

Variables	Overall group Total No:(58)	CC responders No: 38 (65%)	CC non-responders No: 20 (35%)	P-value
Total ovarian volume	13.2 ± 4.01	11.6 ± 3.8	13.4 ± 3.8	0.012S.
Total Follicular number	11.0 ± 2.5	9.9 ± 0.3	11.7 ± 1.3	0.012S.

Data presented in mean ± SD. S: significant

Table V: Endocrine features of patients with PCOS with regard to condition of response to CC.

Variables	Total No: 58	CC responder No: 38	CC resistant No: 20	P. value
FSH (MIU/mL)	3.5 ± 0.6	3.9 ± 0.8	3.0 ± 0.3	0.8(NS)
LH (MIU/mL)	8.6 ± 3.4	6.8 ± 6.1	11.2 ± 0.6	0.002(HS)
LH / FSH ratio	3.0 ± 1.1	2.6 ± 1.7	3.2 ± 0.9	0.001(HS)
Testosterone (ng /ml)	1.5± 0.6	1.1 ± 0.2	1.7 ± 0.8	0.001(HS)

Data presented in % and mean ± SD. P-value was determined by (X2) test
HS: Highly Significant. NS: Non significant

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