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Original Research Article

Study of the response of PCOS patients to clomiphene citrate based on hormonal Parameters and body mass index

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ABSTRACT

Background: Our study aimed to evaluate the response of polycystic ovarian syndrome patients to clomiphene citrate based on hormonal parameters and body mass index.
Methods: It is a prospective observational study that was carried out on 48 women with PCOS-related infertility. They were treated with an incremental dose of clomiphene citrate starting with 50 mg/day to a maximum of 100 mg. The response was recorded as either the presence or absence of ovulation. Hormonal parameters such as serum FSH, LH, testosterone, fasting insulin, DHEA, prolactin, and body mass index (BMI) were evaluated. The correlation of each of these parameters in predicting non-responsiveness (failure to ovulate with 100 mg clomiphene) was calculated.
Results: Among 48 PCOS patients who were enrolled in the study, 14 patients responded to CC 50 mg, 26 patients responded to CC 100 mg and 8 patients were CC non-responders. We concluded that serum LH, fasting insulin, and BMI were significant predictors of response to ovulation with CC in PCOS patients.
Conclusions: In our study, we concluded that among the hormonal and biochemical parameters we studied serum LH, fasting insulin, and BMI are significant predictors of response of ovulation with CC in women with PCOS-related infertility. This may help physicians to counsel and select the proper infertility treatment for women with PCOS experiencing infertility so that it should be less time-consuming and cost-effective.

Keywords: Anovulation, Body mass index, Clomiphene citrate response, Infertility, Hormonal correlation, Polycystic ovarian syndrome

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies in women, affecting 5 to 10% of women of fertile age group.[1] PCOS was first described by Irving Stein and Michael Leventhal in 1935.[2] This syndrome not only interferes with reproduction but is in many ways a systemic disease. It is a complex hormonal disturbance that affects the entire body and has numerous implications for general health. PCOS is a heterogeneous syndrome and its etiology is still speculative. Over the years it has evolved from a disease to a syndrome. PCOS is diagnosed by the presence of at least two of the three cardinal features - oligo-ovulation, hyperandrogenism, and polycystic ovaries (as per Rotterdam's criteria 2003).[3] It should be noted that the diagnosis of PCOS can only be made when other aetiologies for irregular cycles, such as thyroid dysfunction, acromegaly, or hyperprolactinemia, have been excluded if there is clinical suspicion. One of the common findings in PCOS patients is chronic anovulation which ultimately leads to infertility. Among such infertile patients, 75% will ovulate with clomiphene citrate (CC) and 50% will conceive. So in this study, we evaluated the response of PCOS patients to CC based on hormonal parameters such as serum FSH, LH, testosterone, fasting insulin, DHEA, prolactin, and body

mass index (BMI). So, an attempt was made to analyze various clinical, metabolic, and hormonal parameters in predicting the response to clomiphene. This will help the physicians to counsel and select infertility treatments accordingly for women with PCOS. Aim of this was to study the response of PCOS patients to clomiphene citrate based on hormonal parameters and BMI. Also, to study the correlation between serum FSH, LH, testosterone, DHEA, fasting insulin, and prolactin with the response to ovulation induction done with clomiphene citrate in PCOS patients and to study the correlation between body mass index and the response of ovulation induction done with Clomiphene citrate in PCOS patients.

METHODS

This was a prospective observational study. This study was conducted in the Maternity care and infertility clinic attached to a teaching medical institute- Nowrosjee Wadia Maternity Hospital, Mumbai. The women with PCOS, attending the infertility clinic were included in this study. Systematic random sampling technique was used. This study was conducted for eighteen months from October 2014 to April 2016. Total 48 patients included in the study.

Inclusion criteria

Inclusion criteria were the age <35 years, oligomenorrhea or amenorrhea secondary to PCOS, FSH<10, PCOS with anovulation, normal serum prolactin and TSH concentration.

Exclusion criteria

Exclusion criteria were age >35 years, patient having abnormal serum FSH (FSH >10 or <1, other causes of infertility such as hypothalamic amenorrhea, premature ovarian failure, congenital adrenal hyperplasia, androgen-secreting tumor, Cushing's syndrome, any tubal, or peritoneal factor, and a partner with male infertility.

Study procedure

After obtaining informed consent from the patients, they were included in the study based on inclusion and exclusion criteria. PCOS women attending infertility clinics were selected in the study based on Rotterdam's criteria. Once the women had been recruited, baseline blood investigations were done on day 2 of the menstrual cycle, in the form of serum FSH, serum LH, serum prolactin, serum DHEA, serum testosterone, serum fasting insulin, and body mass index of each one of them was calculated. Women were started on clomiphene citrate 50 mg from day 2 to day 7th of spontaneous or progestin-induced menstrual cycle for 5 days. Follicle size was assessed by transvaginal sonography from day 9th of the cycle. The dose would be increased to a maximum of 100 mg in the next cycle if the dominant follicle was not formed. If there was no growth of the dominant follicle with CC 100 mg till day 16th then the patient was labeled as a non-responders to CC. According to the unit protocol, the maximum clomiphene citrate dose given was 100 mg as CC has relative side effects on cervical mucus and endometrium. Hormonal status and body mass index of such patients were analyzed and correlated thereafter.

Ethical clearance was received from the Institutional Ethics Committee.

Hormone assays

Serum FSH, LH, prolactin, testosterone, DHEA, and fasting insulin, were assessed in patients with clinically significant PCOS, as a part of routine protocol on day 2 of the menstrual cycle.

Clomiphene citrate

Clomiphene citrate (CC is a selective estrogen receptor modulator (SERM).[4] It is used for the induction of ovulation in infertile women with PCOS. However, 20 to 25% of PCOS patients failed to ovulate with incremental doses of CC.[5] The recommended starting dose is 50 mg/day, as almost half of the pregnancies are achieved with this dose.[6] The ovulation rate with CC is 70–90% and the pregnancy rate is 30-40%, which is somewhat on the lower side. Women who do not ovulate with increasing doses of CC are described as being CC-resistant.[7] When pregnancy is not achieved despite ovulation, the term 'clomiphene failure' is used. Clomiphene citrate is cleared through the liver and excreted in the stool. The CC has negative effects on cervical mucus and endometrium.[8]

Statistical analysis

To correlate BMI with follicular induction, the Spearman correlation was used. To study the effect of increasing doses of CC on follicular induction repeated measures ANOVA was used. Descriptive statistical analyses like percentage (%), mean, and standard deviation were carried out.

RESULTS

This was a prospective, observational, study that was conducted in the Department of Maternity Care and Infertility Clinic of Nowrosjee Wadia Maternity Hospital, Mumbai after the approval of the Institutional Ethics Committee with a sample size of 48.

Figure 1 suggests the age-wise distribution of patients who participated in this study. Among 48 patients, 9 (18.8%) patients were in the age group of 20-24 years, 21 (43.8%) patients were in the age group of 25-29 years, and 18 (37.5%) were in the age group of 30-34 years with the mean age of 27.65 years in a study group. Our results state that, 70.8% (34/48) of patients belong to PCOS patients studied mostly belong to primary (1 ry) infertility compared to secondary 29.2% (14/48).

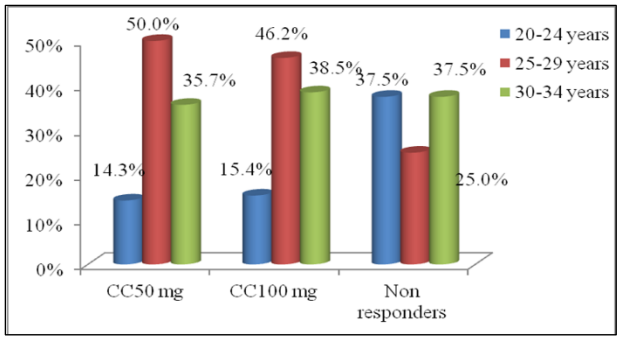

Figure 1- Age-wise response to CC dose.

Table 1 suggests the mean values for serum. FSH- 5.736, serum LH -14.47, serum testosterone-0.74, s.DHEA-4.498, serum prolactin-14.485, S. TSH-2.015, serum fasting insulin -9.217, and BMI is 24.29. The 54.2 % (22) of patients had features of hyperandrogenism and 45.8% (22) patients did not show features of hyperandrogenism. Table 2 shows that response to CC that 29.2% responded to CC 50mg, 54.2% responded to CC 100mg and nonresponders were 16.7%.

Table 3 suggest that, age-wise response of PCOS patients to CC. CC 50 mg responders- there were 2 patients in the age group of 20 to 24 years, 7 patients were in the age group of 25 to 29 years, and 5 patients were in the age group of 30 to 34 years. CC 100 mg, there were 4 patients in the age group of 20 to 24 years, 12 patients in the age group of 25 to 29 years, and 10 patients in the age group of 30 to 34 years. Non-responders included, 3 patients in the age group of 20 to 24 years, 2 patients were in the age group of 25 to 29 years, and 3 patients were in the age group of 30 to 34 years. P value is 0.891 which is statistically insignificant. So, the age factor is statistically insignificant for prognosticating the response of PCOS patients to CC.

Table 1: Hormonal assessment and BMI.

	S. FSH (mIU/ml)	S.LH (mIU/ml)	S. testosterone (ng/ml)	S. DHEA (ng/ml)	S. prolactin (ng/ml)	S. TSH (IU/ml)	S. fasting insulin (uU/ml)	BMI
N	48	48	48	48	48	48	48	48
Mean	5.736	14.474	0.747	4.498	14.485	2.015	9.217	24.29
Median	5.650	15.850	0.600	4.240	14.200	2.150	8.300	24.20
Mode	4.5	12.0	0.3	3.3	18.0	2.1	8.4	22
Std. deviation	1.4462	5.0523	0.7597	1.6674	3.6723	0.7600	4.4045	2.269
Min.	3.2	4.2	0.1	1.8	5.8	0.2	3.3	20
Max.	9.7	23.0	4.9	8.3	19.8	3.3	21.4	30

Table 2: Response of CC.

		Patients	N %
Outcome	CC50 mg responder	14	29.2
	CC100 mg responder	26	54.2
	Non responders	8	16.7
	Total	48	100.0

Table 4 suggests that the mean level of serum FSH in 50 cc responder patients was 5.496. In 100 CC responders, it was 5.892, and in non-responders, it was 5.649, concluding that serum FSH is not a prognostic factor determining the response of PCOS patients to CC. Table 5 suggests that the mean level of serum LH in CC 50 mg responder patients was 11.061. In CC 100 mg responders it was 14.842 and in nonresponders, it was 19.250. It proves that serum LH level is significantly related to the response of PCOS patients to CC (p value-0.0001).

Table 6 states that the mean level of serum testosterone was 0.607 in 50 mg CC responder patients. It was 0.675 in 100 CC responder patients and it was 1.225 in non-responder patients. It concludes that serum Testosterone is not statistically significant for prognosticating the response of PCOS patients to CC.

Table 3: Age wise response to CC.

		Response to CC					
		CC 50 mg responders		CC100 mg responders		Non responders	
		Patients	N %	Patients	N %	Patients	N %
Age	20-24 years	2	14.3	4	15.4	3	37.5
	25-29 years	7	50.0	12	46.2	2	25.0
	30-34 years	5	35.7	10	38.5	3	37.5
	Total	14	100.0	26	100.0	8	100.0

Table 4: S. FSH and CC response relationship.

S.FSH (mIU/ml)	N	Mean	Std. deviation	Minimum	Maximum	P value
CC50 mg	14	5.496	1.3007	3.5	8.0	0.708
CC100 mg	26	5.892	1.5523	3.2	9.7	
Non responders	8	5.649	1.4429	4.2	8.1	
Total	48	5.736	1.4462	3.2	9.7	

Table 5: Onaway ANOVA for S. LH and CC response.

S.LH (mIU/ml)	N	Mean	Std. Deviation	Minimum	Maximum	P value
CC50 mg	14	11.061	5.9151	4.2	23.0	0.0001
CC100 mg	26	14.842	3.8057	4.6	19.7	
Non responders	8	19.250	2.1928	16.2	23.0	
Total	48	14.474	5.0523	4.2	23.0	

Table 6: Oneway ANOVA for S. testesterone and CC response.

s.Testosterone (ng/ml)	N	Mean	Std. deviation	Minimum	Maximum	P value
CC50 mg	14	0.607	0.3792	0.2	1.2	0.144
CC100 mg	26	0.675	0.9577	0.1	4.9	
Non responders	8	1.225	0.1165	1.0	1.4	
Total	48	0.747	0.7597	0.1	4.9	

Table 7: Oneway ANOVA relation of S. prolactin and CC response.

S. prolactin (ng/ml)	N	Mean	Std. deviation	Minimum	Maximum	P value
CC50 mg	14	14.226	4.0815	5.8	19.8	0.944
CC100 mg	26	14.538	3.3348	7.5	19.6	
Non responders	8	14.762	4.4343	6.8	19.0	
Total	48	14.485	3.6723	5.8	19.8	

Table 8: Oneway ANOVA for S. TSH and CC response.

s.TSH (IU/ml)	N	Mean	Std. deviation	Minimum	Maximum	P value
CC50 mg	14	2.286	0.6443	1.2	3.2	0.283
CC100 mg	26	1.920	0.7939	0.2	3.0	
Non-responders	8	1.849	0.8026	0.8	3.3	
Total	48	2.015	0.7600	0.2	3.3	

Table 9: Oneway ANOVA for S. fasting insulin and CC response.

S. fasting insulin (uU/ml)	N	Mean	Std. deviation	Minimum	Maximum	P value
CC50 mg	14	6.786	2.0103	3.3	11.1	0.0001
CC100 mg	26	8.638	3.2904	5.4	20.0	
Non-responders	8	15.350	5.2945	9.5	21.4	
Total	48	9.217	4.4045	3.3	21.4	

The mean level of serum DHEA in patients responding to CC 50 mg was 5.186, in patients who responded to 100 CC it was 4.284 and in nonresponders, it was 3.991. This proves that serum DHEA is not statistically significant for prognosticating the response of PCOS patients to CC.

Table 7, shows that serum Prolactin level in patients responding to CC 50 mg was 14.226, in 100 CC responders it was14.538, and in patients who are non-responders it was14.768, suggesting that serum prolactin was not statistically significant for the prognosticating response of PCOS patient to CC.

Table 8, shows that serum TSH level in patients responding to CC 50 mg was 2.286, in 100 CC responders it was 1.920, and in patients who are non-responders it was 1.849, suggesting that serum TSH is not statistically significant for prognosticating response of PCOS patient to CC.

Table 9 suggests that serum fasting insulin is statistically significant for prognosticating the response of PCOS patients to CC. Patients responding to CC 50 mg have a mean serum Fasting insulin of 6.786, and those who responded to CC 100 mg have a fasting insulin level of 8.638. And non-responder patient has 15.350. The mean difference is significant at the 0.05 level.

Our study results suggests that patients who responded to CC 50 mg had a mean BMI of 23.26. Those who responded to CC 100 mg had a mean BMI of 23.92. And the patients who do not respond to CC have a BMI of mean 27.28. BMI is statistically significant for prognosticating the response of PCOS patients to CC (p-0.05). The mean difference is significant at the 0.05 level.

DISCUSSION

Several studies have investigated the use of a multivariate model for predicting the value of clinical and endocrine screening parameters for a response to CC. The objective of our study is to evaluate the correlation between serum FSH, LH, prolactin, testosterone, DHEA, fasting insulin, and BMI in PCOS patients experiencing infertility, in whom, ovulation induction is done with clomiphene citrate. In our study, among 48 patients studied, 14 patients responded to CC 50 mg (29.2%), 26 patients responded to 100 mg cc (54.2%), and 8 (16.7%) patients were labelled as non-responders. We concluded that serum LH, fasting insulin, and BMI were significant predictors of response to ovulation with CC in PCOS patients. Serum LH, fasting insulin, and BMI were significantly higher in the non-responders group with mean values of 19.250miu/ml, 15.350ulU/ml, and 27.2kg/m^2 respectively.

Amen et al studied the evaluation of sonographic and biochemical markers of CC resistance in polycystic ovary syndrome, they concluded that the mean age was comparable while the BMI was significantly higher in the CC-resistant group.[9] Total testosterone, serum LH, fasting serum insulin, and HOMA-RI were significantly higher in the CC-resistant group (P values were 0.000), and they said that the resistance of PCOS patients to CC may be affected by multiple metabolic and vascular factors. The results were similar to our study.

Ellakwa et al studied predictors of patient responses to ovulation induction with CC in patients with PCOS experiencing infertility and they concluded that a combination of amenorrhea, BMI, total testosterone, anti-Mullerian hormone, ovarian volume, ovarian stromal artery pulsatility index, and visceral fat area could be used to predict CC treatment response in patients with PCOS experiencing infertility.[10]

Imani et al identified a nomogram to determine the chance of ovulation with CC therapy based on the age of the patient, FAI, BMI, and whether the patient was oligomenorrheic or amenorrheic, this study demonstrates that it is possible to predict patients remaining anovulatory during CC induction of ovulation using criteria that are directly associated with PCOS, predominantly obesity and hyperandrogenemia.[11]

Kousta et al studied the clomiphene citrate response in PCOS patients and concluded that basal hormone concentrations do not predict the outcome.[12] An increased body mass index is the only factor that is consistently associated with a decreased response to clomiphene citrate. This is partly contradictory to our study in which hormonal levels especially serum LH and fasting insulin are two important ones that were statistically significant to prognosticate the response of PCOS patients to CC.

Imani et al also suggest that that LH concentrations do not predict ovarian response after CC medication however in our study serum LH is a strong predictor of CC response in PCOS patients.[11]

Sachdeva et al evaluated the role of clinical, metabolic, hormonal, and ultrasound features of women with PCOS in predicting the response to clomiphene citrate in the treatment of infertility and they concluded that Ferriman-Gallwey score, androstenedione levels, and lipid profile are clinically useful parameters to predict which groups of PCOS women are unlikely to respond to clomiphene.[13]

The limitations of the study can be findings from a specific population may not be easily generalized to other populations. The response to clomiphene citrate and the influence of hormonal parameters and BMI may vary among different ethnicities, cultural backgrounds, or geographical locations.

CONCLUSION

In our study of 48 PCOS patients, responses to clomiphene citrate (CC) varied: 29.1% to 50 mg, 54.1% to 100 mg, and 16.6% were non-responders. We identified serum LH, fasting insulin, and BMI as significant predictors of CC-induced ovulation response. The discernment of these influential factors provides valuable insights for clinicians, enabling them to make informed decisions and offer tailored counselling to women with PCOS seeking infertility treatments. Our conclusions contribute to the advancement of personalized and effective therapeutic approaches for this specific patient population.

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