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# **Role of clomiphene citrate in anovulation and hormonal imbalance of patients with polycystic ovarian syndrome**

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**Abstract**--This study was conducted to see the effects of Clomiphene Citrate on fertility hormones estrogen, progesterone, LH, FSH in patients with infertility associated with polycystic ovary syndrome. For this study fifty infertile patients with PCOS who were given treatment with clomiphene citrate (50–150mg/day for 5 days). For Ovarian response ovulation was monitored by transvaginal ultrasonography and serum levels of FSH, LH, progesterone, estrogen was also estimated by using ELISA methods.

**Keywords**---PCOS, Clomiphene citrate, anovulation.

## Introduction

Infertility is a one of most common diseases and problems which can upset the normal living and social pattern of the people's life. Therefore, it is a very common problem which affects the human race and reached up to 50 to 80 million in the world total [1]. Female reproductive pattern is controlled with a balanced hormonal system. These hormonal regulation works with positive and negative feedback mechanisms [1]. PCOS (Polycystic ovarian syndrome) is the most occurring cause of infertility in women at the age of puberty or at a child bearing stage. [15] Anovulation or absence of egg production is a common cause of infertility in PCOS. Therefore in PCOS patients are treated with clomiphene citrate and it is used very commonly for induction of ovulation in PCOS. This drug is a selective estrogen receptor modulator (SERM). [2,3]

In start it is given in a dose of 50mg/day. This amount can then be increased up to 250mg/day. This drug is given with a combination of other drugs for better results and effects. As in insulin resistance in PCOS this drug is given with insulin lowering drugs. Clomiphene Citrate is also given with some other drugs as exogenous gonadotropins to induce ovulation. [4]

Clomiphene Citrate has better effect and anti infertility properties when used in females for ovulation and its clomiphene drug has better results for induction of pregnancy given in combination. It induces induction of ovulation in females with amenorrhic symptoms and ovulatory women. [5] Clomiphene Citrate has a direct effect on release of GnRH and affects its release. Therefore it affects the production of FSH and LH. As GnRH secretion affects the stimulation and release of FSH and LH. Clomiphene Citrate effects directly on the hypothalamic-pituitary-ovarian axis. There is a rise in levels of FSH and LH with clomiphene citrate. [6] Clomiphene Citrate also increases the levels of estrogen hormone along with LH and this cause induction of ovulation. [7] Clomiphene citrate has 75% to 80% ovulation rates and also 30% to 40 % conception rates. Therefore, Clomiphene Citrate is used preferably as a drug of choice especially in females with PCOS. [8]

Human Reproduction Embryology (ESHRE), the American Society for Reproductive Medicine (ASRM) criteria has proposed points for PCOS diagnosis and detection. According to criteria diagnosis of PCOS made on anovulation, elevated androgens in serum, and presence of cyst in ovaries which lead to morphological changes in them. Normal ovulation is disturbed in PCOS due to imbalance in hormones. These hormones included progesterone, estrogen, FSH and LH. [9]

The prevalence of the polycystic ovarian syndrome

In Pakistan it is about 52%, and it is much higher than the number of patients with PCOS in the UK which is about 20 to 25%. [10] Pakistan is also a populous country in the world. About 2% is its growth rate with infertility rate of 21.9% so one fifth of married people are facing this problem in Pakistan.[11] Studies show

that occurrence of PCOS is more in young females than in older women and percentage of primary infertility is more than secondary infertility. [12] The level of LH and other hormone like FSH, and prolactin are also increased in women with simple infertility with no PCOS. [13] Sometimes patients with clomiphene therapy not respond to the treatment as they are resistant to Clomiphene Citrate, about 25% people are resistant to Clomiphene Citrate. [14] In such patients a combined therapy along with Clomiphene Citrate is used. [15] Therefore hormones are important to regulate reproduction and reproduction is affected by outer environment and also with hormones. [16]

## **Materials and Methods**

### **Objectives of this study**

As reproduction is a basic desire for human instinct. Infertility is one of the major problems faced by a huge population. The main concern and aim of this study was to evaluate the effect and pattern of important reproductive hormones like FSH, LH, Estrogen and Progesterone in infertile women with PCOS. The study was conducted in infertile women who were attending infertility clinic at Service Hospital, Lahore.

This research will help clinicians to demonstrate the benefits of clomiphene and its uses to treat infertility in patients with PCOS and other anovulation conditions.

### **Subjects and methods**

The Evaluation of hormonal profile FSH (follicular stimulating hormone), LH (luteinizing hormone), Estrogen and Progesterone was performed at the clinical laboratory of Services Hospital, Lahore. The Levels of these hormones were observed in 60 women with infertility and 50 healthy fertile women as a control group. The levels of hormones were measured by the micro well enzyme linked immunosorbent assay (ELISA) technique based on the noncompetitive sandwich principle for LH, FSH, Estrogen and Progesterone. ELISA kits were used for the measurement of these hormone levels.

### **Population study**

Services Hospital Lahore is one of the major teaching hospitals in Pakistan. We selected 60 infertile patients with PCOS and 50 healthy subjects as control.

### **Exclusion criteria**

Patients having hyperprolactinemia, ovarian hyperstimulation syndrome, diabetic patients, or any thyroid problem.

### **Inclusion criteria**

Patient diagnosed infertile PCOS with tenure of more than one year after marriage.

BMI, a weighting scale is used to measure weight (Lee & Nieman, 2003)

A thorough history of patients was noted on a Questionnaire, the height and weight of the selected patients was noted and finally their blood samples were collected.

## Results

100 patients were included in this study, out of these 50 were infertile with PCOS, and 50 were taken as a control group. The details are given in Table.

In table 1 for LH, the mean level of LH hormone in PCO patients before treatment was  $5.74 \pm 0.939$  while after treatment with CC the mean level of LH was noted  $3.716 \pm 0.513$  which is satisfactory.

In table 2 for FSH, the mean level of FSH hormone in PCO patients before treatment was  $3.804 \pm 1.163$  while after treatment with CC the mean level of FSH was noted  $5.644 \pm 1.1306$  which is satisfactory.

In table 3 for Progesterone, the mean level of Progesterone hormone in PCO patients before treatment was  $2.098 \pm 1.233$  while after treatment with CC the mean level of Progesterone was noted as  $10.704 \pm 2.313$  which is satisfactory.

In table 4 for Estradiol, the mean level of Estradiol hormone in PCO patients before treatment was  $51.458 \pm 7.091$  while after treatment with CC the mean level of Estradiol was noted as  $37.72 \pm 4.969$  which is satisfactory. The P-value for testing means before and after groups for Estradiol we applied Paired T-test and P- value is found to be  $<0.001$  which is less than 0.05, so the difference in mean are significant different which show that there exit the difference in before and after groups which is due to treatment applied.

This table 1 shows the hormonal level in PCOS women before and after the use of Clomiphene citrate drug. There are abnormal LH, FSH, Progesterone, Estradiol levels in women with PCOS. There is an abnormal high level of luteinizing hormone in PCOS and decrease in follicular stimulating hormone in PCOS. In PCOS there is also decrease in progesterone and increase of estradiol serum level. But after the use of the drug Clomiphene citrate there is significant change in the values of PCOS hormonal level.

The value of these hormonal levels obtained is less than 0.001 ( $<0.001$ ) which shows significant change of before and after use of Clomiphene citrate in PCOS. Therefore there is significant change in PCOS patients and their hormonal profile after dose of Clomiphene Citrate drug. There is significant change in the plasma hormonal level after use of Clomiphene citrate.

Table 1: Comparison of LH, FSH, Progesterone and Estradiol in patients before and after treatment with Clomiphene citrate

Hormones	Infertile women with PCOS Before CC (mean $\pm$ SD)	Infertile women with PCOS After CC (mean $\pm$ SD)	P Value (P<0.05)
LH mIU/ml	5.74 $\pm$ 0.939	3.716 $\pm$ 0.513	<0.001
FSH m IU /ml	3.804 $\pm$ 1.163	5.644 $\pm$ 1.1306	<0.001
Peogesterone ng/ml	2.098 $\pm$ 1.233	10.704 $\pm$ 2.313	<0.001
Estradiol Pg/ml	51.458 $\pm$ 7.091	37.72 $\pm$ 4.969	<0.001

Table 2: Comparison of levels of LH, FSH, Progesterone, Estradiol and BMI between control and PCOS Groups

Hormones	Control (mean $\pm$ SD)	PCOS (mean $\pm$ SD)	P value (P<0.05)
LH I U/ml	4.672 $\pm$ 1.0065	5.748 $\pm$ 0.9390	<0.001
FSH I U/ml	6.4 $\pm$ 0.9617	3.804 $\pm$ 1.16320	<0.001
Progesterone mg/ml	11.13 $\pm$ 2.352	2.098 $\pm$ 1.2332	<0.001
Estradiol Pg/ml	30.06 $\pm$ 4.41	51.458 $\pm$ 7.0911	<0.001
BMI	21.772 $\pm$ 2.9604	23.842 $\pm$ 0.6658	<0.001

The table 2 shows the level of plasma serum level of reproductive hormones. The level of luteinizing hormone is increased in PCOS women. While it is normal in Control women. The value of follicular stimulating hormone and progesterone hormone is also decreased in the PCOS women. While hormonal level is normal in Control women. The value of Estradiol hormone is high in PCOS. While its value is normal in Control women.

This elevated or decreased level of hormone in PCOS is due to disturbed hormonal pattern as PCOS presented with abnormal hormonal level. These abnormalities lead to infertility in PCOS. There is also a significant difference in BMI in PCOS and control group.

As increase in weight in PCOS women is also common which also has additional complication which leads to infertility? While hormones in Control groups are within normal range.

## Discussion

Clomiphene Citrate is an anti-estrogenic drug which also decreases the estrogen effect and also decreases the LH serum and it also decrease the premature LH surge. [17] In a cohort study by Branigan et al., the effects of Clomiphene Citrate and Oral Contraceptive Pills (OCP) in preventing hypersecretion of LH in women who were gone under IUI was assessed. Al-Inany et al. assayed the effect of Clomiphene Citrate in reducing LH secretion. Having best anti estrogenic effect, it also increases FSH level and also effects on the 21 day serum

progesterone increase it. [18] Hyper secretion of LH is related to increase miscarriages and decrease pregnancies rate. [19]

It has been observed that present study on 50 women's with PCOS shows significant changes as compare to normal studied women. As polycystic ovarian syndrome is a heterogeneous clinical disease associated with infertility in young women. Increased LH decrease in FSH is hallmark of this disease. Therefore elevated LH and low FSH and progesterone effect the normal induction of ovulation. Due to this decrease level of FSH follicles does not grow in women with PCOS. High levels of LH increase the production of androgen hormones. BMI difference between both PCOS women and control studied women is also significant as weight of PCOS women is slightly high then normal. As these findings are same to other published reports (Rogers and mitchel 1989, Hantz, et al 1995, Bates, G.W, 199) that increase in weight and BMI shows overweight or obesity. Weight of women at reproductive age is important as it also cause the reproductive abnormalities in the women. Many women are diagnosed earlier with endocrine problems, menstrual irregularity and an ovulation. There for women with a low serum level of LH, FSH, and Progesterone indicates that there is problem in the function of hypothalamus or the function of pituitary gland. While an increase in the level of reproductive hormones indicates there is dysfunction in normal production of hormones in the ovaries. As ovaries are main site of production and regulation of female hormones and this endocrine disorder affects the normal mechanism of the ovulation induction and fertility in females. As when there is any type of the defect in the hypothalamus. Then there is effective production of the gonadotropins. As gonadotropins production is effected then they are also not able to stimulate the ovaries. A high serum LH and low serum FSH is an indication of the PCOS.

Progesterone level may also be decreased due to the deficiency of luteal phase defect. Increase in prolactin level called hyper prolectemia is also cause of infertility because high level of the prolactin also decreases ovulation process. Other cause which can affect the fertility and ovulation are like endometriosis and bacterial infection in uterine cavity which complicates the other factors in the normal healthy uterine cavity. Therefore along with hormonal disturbance the reproductive tract infections also lead to complication and cause infertility. But hormonal abnormalities contribute more in fertility problems and reduce the stimulating process of ovulation. So when patient came with complication of infertility then a proper evaluation of hormones should be performed, along with the biopsy of uterine cavity for evaluation of the other diseases. [20]

A complete physical examination and fertility hormonal evaluation including LH, FSH, Progesterone, Estrogen, and Prolactin also other important hormone like Thyroid hormone test should be carried out. Male semen analysis is also important to know the cause of infertility. To diagnose the luteal phase deficiency for low serum level of progesterone is also important and some time there is no cause of infertility and this infertility is unexplained. [21]

## Conclusion

The present study shows the positive effect of clomiphene citrate drug when it was used in women with PCOS. The CC has positive effect on reproductive hormones in women but also induce the ovulation which is abnormally disturbed due to alteration of normal hormonal level. Anovulation is due to many reasons which cause infertility including luteal phase defects and CC has also shows positive impact to address this cause of infertility. Normal levels of prolactin and thyroid hormone are also important for regulation of normal reproduction. So these parameters should also be evaluated. Therefore clomiphene drug can be used in women with PCOS and in other condition which leads to anovulation and hormonal imbalance.

Being an easy availability and low cost medicine, it is affordable to patients and it has minimal side effects on patient's health. The major side effect reported with CC is multiple pregnancies. There are many causes which leads to infertility some are primary and some are related to genetics which affects normal reproduction.

Social and economic status also affects the reproduction in females in the form of stress. Many women also have lack of awareness about their fertility days. They don't know how to start their treatment for infertility.

## References

1. Ainavi, I. I., 2009. Pattern of Reproductive Hormones in Women with Infertility in Zaria, Northern Nigeria (Doctoral dissertation):1-70.
2. Bhagavath, B. and Carson, S. A., 2012. Ovulation induction in women with polycystic ovary syndrome: an update. *American Journal of Obstetrics & Gynecology*, 206(3), 195-198
3. Y Maximov, P., M Lee, T. and Craig Jordan, V., 2013. The discovery and development of selective estrogen receptor modulators (SERMs) for clinical practice. *Current clinical pharmacology*, 8(2), 135-155.
4. Practice Committee of the American Society for Reproductive Medicine. 2006. Use of clomiphene citrate in women. *Fertility and sterility*, 86(5), S187-S191.
5. Huppert, L. C., 1982. Induction of ovulation with clomiphene citrate: 1.
6. Jacobson, A., Marshall, J. R., Ross, G. T. and Cargille, C. M., 1968. Plasma gonadotropins during clomiphene induced ovulatory cycles. *American journal of obstetrics and gynecology*, 102(2), 284-290
7. Wu, C. H., 1977. Plasma hormones in clomiphene citrate therapy. *Obstetrics and gynecology*, 49(4), 443-448.
8. Elnashar, A., Abdelmageed, E., Fayed, M. and Sharaf, M., 2006. Clomiphene citrate and dexamethazone in treatment of clomiphene citrate-resistant polycystic ovary syndrome: a prospective placebo-controlled study. *Human Reproduction*, 21(7), 1805-1808.
9. Gorry, A., White, D. M. and Franks, S., 2006. Infertility in polycystic ovary syndrome. *Endocrine*, 30(1), 27-33.
10. Shaheen, R., Subhan, F., Sultan, S., Subhan, K. and Tahir, F., 2010. Prevalence of infertility in a cross section of Pakistani population. *Pakistan J Zool*, 42(4), 389-393.

11. Yusuf, L., 2016. Depression, anxiety and stress among female patients of infertility; A case control study. *Pakistan journal of medical sciences*, 32(6), 1340.
12. Spandana, J. C., 2017. A study on the clinical, biochemical and hormonal profile of polycystic ovary syndrome patients attending tertiary care hospital. *International Journal of Reproduction, Contraception, Obstetrics and Gynecology*, 6(5), 1986-1992.
13. Bheem, P., Dinesh, P. and NC, S., 2015. A study on serum FSH, LH and Prolactin Levels Among infertile women. *International Journal of Medical Research and Health Sciences*, 4(4), 876-878.
14. Xi, W., Liu, S., Mao, H., Yang, Y., Xue, X. and Lu, X., 2015. Use of letrozole and clomiphene citrate combined with gonadotropins in clomiphene-resistant infertile women with polycystic ovary syndrome: a prospective study. *Drug design, development and therapy*, 9, 6001
15. Al-Shaikh, S. F., Al-Mukhatar, E. J., Al-Zubaidy, A. A., Al-Rubaie, B. J. and AlKhuzaaee, L., 2017. Use of clomiphene or letrozole for treating women with polycystic ovary syndrome related subfertility in Hilla city. *Middle East Fertility Society Journal*, 22(2), 105110.
16. Ben-Chioma, A. E. and Tamuno-Emine, D. G., 2015. Evaluation of female fertility hormone profile in women with primary and secondary infertility. *International Journal of Science and Research*, 4(10), 1583-1585.
17. Al-Inany, H., Azab, H., El-Khayat, W., Nada, A., El-Khattan, E. and Abou-Setta, A. M., 2010. The effectiveness of clomiphene citrate in LH surge suppression in women undergoing IUI: a randomized controlled trial. *Fertility and sterility*, 94(6), 2167-2171
18. Kawwass, J. F., Loucks, T. L. and Berga, S. L., 2010. An algorithm for treatment of infertile women with polycystic ovary syndrome. *Middle East Fertility Society Journal*, 15(4), 231-239.
19. Meenakumari, K. J., Agarwal, S., Krishna, A. and Pandey, L. K., 2004. Effects of metformin treatment on luteal phase progesterone concentration in polycystic ovary syndrome. *Brazilian journal of medical and biological research*, 37(11), 1637-1644.
20. Emokpae, M. A., Uadia, P. O. and Mohammed, A. Z., 2005. Hormonal evaluations and endometrial biopsy in infertile women in Kano, Northern Nigeria: A comparative study, 100102.