

ANTIESTROGENIC EFFECT OF CLOMIPHENE CITRATE IN HYPERSECRETION OF FEMALE GONADAL HORMONES IN POLYCYSTIC OVARIAN SYNDROME WOMEN

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Abstract

Objective: Clomiphene is one of the drugs of choice which is given for the treatment of anovulation. In PCOS anovulation is the main reason for infertility therefore this drug is used along with other medicine therapies. Clomiphene citrate also affects the female gonadal hormones FSH, LH, estrogen and progesterone. As level of these hormones is altered in PCOS. This drug controls the hypersecretion of LH. This study was to evaluate the effects of drugs on female gonadal hormones. Ovarian response for ovulation is observed by serum level of these hormones and ultrasound to monitor the follicle size. 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.

Keywords: PCOS, Clomiphene citrate, anovulation, progestogen, estrogen, luteinizing hormone, follicle stimulating hormone

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) leading to anovulation at the age of conception. [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 one of the main modulators for estrogen receptors known as selective estrogen receptor modulator (SERM). [2, 3]

In start it is given in a dose of 50mg/day. This amount can be then increased up to 250 mg/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 gonadal hormones FSH and LH. As GnRH secretion affects the activation and production of these hormones. 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 this syndrome is 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 PCOS in Pakistan 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 then 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 don't give response 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]

MATERIAL AND METHODS

Infertility is one of the major problems faced by a huge population. In this study the hormonal change in females will be measured. The study was conducted in infertile women who were attending infertility clinics at Service Hospital, Lahore.

The serum estimation of gonadal hormones 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 ELISA technique. ELISA kits were used for the measurement of these hormone levels.

Population study

Total 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 ± 0.939 while after treatment with CC the mean level of LH was noted 3.716 ± 0.513 which is significantly satisfactory.

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

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

In table 4 for Estradiol, the mean level of Estradiol hormone in PCO patients before treatment was 51.458 ± 7.091 while after treatment with CC the mean level of Estradiol was noted as 37.72 ± 4.969 which is significantly 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 and it is less than 0.05, 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 increased level of LH in polycystic syndrome 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 with Clomiphene citrate

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

Table 2: serum levels of LH, FSH, Progesterone, Estradiol, and BMI in control and PCOS Groups

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

As increase in weight in PCOS women is also common which also has additional complications 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 decreases the premature LH serum levels. [17]. Clomiphene Citrate reduces the high serum level of LH by reducing its production Branigan et al|Inany et al. also observe the effect of Clomiphene Citrate in reducing LH serum level and secretion. Having the 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 with PCOS shows significant changes as compared to normal studied women. 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 affect the normal induction of ovulation. Due to this decrease level of FSH follicles does not grow in women with PCOS. BMI difference between both PCOS women and control studied women is also significant as weight of PCOS women is slightly higher than normal. These findings are the same as other published reports (Rogers and Mitchell 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 causes reproductive abnormalities in the women. Many women are diagnosed earlier with endocrine problems, menstrual irregularity and ovulation. Therefore, for women with a low serum level of LH, FSH, and Progesterone indicates that there is a problem in the function of the hypothalamus or the function of the 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 the main site of production and regulation of female hormones, 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 affected 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 hyperprolactinemia is also the cause of infertility because high levels of the prolactin also decrease the ovulation process. Other causes which can affect fertility and ovulation are like endometriosis and bacterial infection in the 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 complications and cause infertility. But hormonal abnormalities contribute more to 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 hormones 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

This study shows that clomiphene citrate causes ovulation induction when it is used in women with PCOS. The CC has a 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 shown 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 drugs can be used in women with PCOS and in other conditions 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 lead 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 a lack of awareness about their fertility days. They don't know how to start their treatment for infertility.

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