

An Imminent Prospective & Randomized Trial Comparing Clomiphene Citrate With Tamoxifen For Ovulation Induction In Women With Polycystic Ovary Syndrome

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Abstract- The aim of the study was to compare in a clinical setting the efficacy of Clomiphene citrate comparing with Tamoxifen as a first line approaches for treating anovulation in infertile PCOS Patients. PCOS is the endocrinological disorder during menstrual cycle initiated, constitutes the major effect of anovulation belongs to infertility contributed up to 95% ovarian factors of infertility. Ovulatory disorder neither anovulation nor oligo-ovulation found a major factor for infertility. This clinical trial study was conducted at Deepam Hospital – west Perungalathur Chennai after approval of the research ethics committee, on 100 patients with P.C.O. The participants were recruited from women attending the outpatient infertility clinic of Deepam Hospital. Patients are classified randomly into 2 groups: Group A: 50 patients (clomiphene Citrate). Group B: 50 patients (Tamoxifen). Ovulation rate & Pregnancy rate was significantly better under Tamoxifen therapy. Number of stimulated follicles was not significantly different between the two drugs. Endometrial thickness was significantly better under Tamoxifen therapy especially in mid-luteal. Adverse effects with the two drugs was non-significant. Endometrial perfusion indices were significantly better in pregnant versus non-pregnant case. Tamoxifen can give similar or even better results than clomiphene citrate in induction of ovulation in women with PCOS. Each of them can be used as a first line option for induction of ovulation in women with PCOS in selected cases.

Keywords- Infertility, Anovulation, polycystic ovarian syndrome, Ovulation induction, Clomiphene, Tamoxifen.

I. INTRODUCTION

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder with an incidence of (4-7%) among reproductive aged women^[1]. It is characterized by chronic anovulation, hyperandrogenism, and is the most frequent endocrinopathy in women. Clomiphene citrate (CC) is a non-

steroidal Selective estrogen receptor modulators (SERM) has both estrogen agonist and antagonist properties^[2,3,4]. It binds with estrogen receptors primarily in the hypothalamus, which interrupts the negative feedback of the increasing estrogen level and results in continued production of FSH, which stimulates follicular growth and maturation. Its anti-estrogenic effect causes long standing estrogen receptor depletion due to its long half-life (2 weeks), so it has adverse effects on the quality and quantity of cervical mucus and negative impact on endometrial development causing its significant thinning, implantation failure and decreased blood flow during the peri-implantation stage^[5].

CC resistance affects approximately 15% to 40% of women with PCOS, perhaps, because of anti-estrogenic effects of CC to the endometrium and cervical mucus, or because of luteinizing hormone hyper secretion. CC resistance is defined as a lack of ovulation after 6 cycles of CC^[6]. Tamoxifen is effective in CC in inducing ovulation in anovulatory women with normal prolactin levels, but it has a much lesser anti-estrogenic effect on the endometrium, cervical mucus, and granulosa cells^[7]. Tamoxifen is a non-steroidal SERM, commonly used today as an adjuvant therapy in treatment of breast cancer. It acts primarily by binding estrogen receptors at the hypothalamus, this competitive inhibition results in a perceived drop in endogenous estrogen levels, eventually leading to increased gonadotropin secretion and subsequent induction of ovulation^[8].

It acts as an agonist on estrogen receptors of endometrium and vaginal mucosa, its half life is short (5-7 days) leading to favorable cervical mucus, better endometrial thickness, and maybe better endometrial blood flow^[9].

AIM:-

The study aimed to compare the efficacy of Clomiphene citrate and Tamoxifen in induction of ovulation in women with polycystic ovary syndrome.

II. PATIENT AND METHODS

This aspect of cohort study was conducted at fertility foundation of Deepam hospital – Perungalathur during from June 2023 to October 2023 on 100 women's recruited from outpatient infertility clinic.

Inclusion criteria:

Primary infertility

Age, Body mass index (BMI) between 25 and 35 Kg/m². Poly cystic ovary syndrome (using ESHRE/ASRM criteria).

Exclusion criteria:

Secondary infertility.

Patients with BMI under 25 or over 35 Kg/m². Hyper or hypothyroidism, or hyperprolactinemia. Current or previous (within the last six months) use of oral contraceptives, glucocorticoids, anti-androgen, anti-diabetic and anti-obesity drugs, or other hormonal drugs. Intention to start a diet or a specific program of physical activity^[10].

Chronic pelvic diseases, Tubal or male factor infertility, Interval of earlier treatment with any of the fertility drugs of less than 6 months before being recruited in the studies. Clomiphene citrate, Tamoxifen, HCG injection^[11]. Participants that seem to be fulfilling all the inclusion and exclusion criteria were recruited, then an informed written consent was taken from every participant before starting the study^[12]. Participants not fulfilling all inclusion and exclusion criteria were dropped from the study and not considered as part of the calculated sample size^[13].

All participants were subjected to the following:

(I) History: A careful and detailed history was taken including name, age, occupation, residence, socio-economic status, special habits of medical importance, history suggestive of PCOS (infertility, hirsutism, obesity and anovulation), menstrual history, obstetric history, sexual history, family history, past history of medical disorders, history of medications or allergy and surgical history Previous surgery or Previous laparotomies^[14].

(ii) Examination: (A) General examination: Maternal body weight, height and BMI. Presence of petechiae or ecchymosis of the skin to exclude presence of coagulation defect or blood disease. Cardiac, chest examination, vital data, Presence of pallor or jaundice, Breast examination. (B) Pelvic-abdominal examination: Uterine or adnexal masses, Scar of previous operations.

(iii) Investigations: Hormonal profile on day 2-3 of the cycle. Semen analysis to rule out male factor. Hysterosalpingography (HSG) to confirm tubal patency. Trans-vaginal ultrasound to detect anatomical uterine or adnexal abnormalities.

Patients are classified randomly into 2 groups:

Group A: 50 patients (clomiphene Group).

Group B: 50 patients (Tamoxifen Group).

Start treatment from 2nd day of cycle by:

Group A: 1 tablet clomiphene 50 mg taken Twice daily For Five Days.

Group B: 1 tablet Tamoxifen 10 mg taken Twice daily For Five Days.

Primary outcome: Rate of ovulation.

Secondary outcome:

Endometrial perfusion by using 3D- power Doppler (GE Medical system voluson E6, 5-7 MHz) in the mid luteal day of the cycle to assess endometrial receptivity.

Endometrial thickness and quality in the pre-ovulatory and mid luteal period. Number of growing follicles detected by trans-vaginal ultrasound, Patient compliance, adverse effects such as headache, nausea, vomiting, breast tenderness, blurred vision, and ovarian enlargement or hyper-stimulation.

Statistical Methods:

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 16 (SPSS Inc., Chicago, IL, USA) and subjected to descriptive analysis, i.e., number, percentage. Chi-square test was applied to categorical variables. Significance of the obtained results was judged at the 5% level. P-value < 0.05 was considered statistically significant.

III. RESULT

Table 1: Comparison between Group A (Clomiphene Citrate) and Group B (Tamoxifen) as Regard Ovulation Rate:

Ovulation rate	Clomiphene citrate (n=50)		Tamoxifen (n=50)		Chi square Test	P value
NO	23	53%	20	37%	1.576	0.173
YES	27	45%	30	53%		

**P-value < 0.05 was considered statistically significant.

Table 2: Comparison between Group A (Clomiphene Citrate) and Group B (Tamoxifen) as Regard No & Diameter of follicles, Endometrial Perfusion volume and midluteal serum Progesterone

Parameter	Clomiphene citrate	Tamoxifen	Chi square	P value
No -of Follicles	5.23±0.48**	6.01±0.57*	3.214	0.189
Diameter of follicles(mm)	21.58±0.23**	23.57±0.23*	2.145	0.123
Endometrial Perfusion Volume(ml)	24.85±0.23**	26.78±0.32*	3.458	0.145
Serum Progesterone (mg/ml)	10.23±56**	13.25±0.89*	1.254	0.125

***P-value < 0.05 was considered statistically significant.

IV. DISCUSSION

Anti-estrogens are effective for induction of ovulation in women with PCOS, this study was done to compare the efficacy of induction of ovulation in women with PCOS with Clomiphene citrate versus Tamoxifen. Not only the ovulation rates, but also the number of dominant follicles, peak serum Progesterone levels, endometrial thickness, and pregnancy rates per treatment cycle were compared studied and presented below.

Ovulation rate 45% for CC 100mg, and 53% for Tamoxifen20mg, but there was statistical significant difference between the two groups, his evaluation for ovulation was according to the development of adequate follicular size (21-23 mm), and endometrial perfusion volume (24- 26 ml). Serum Progesterone level was found to be (10-13ng/ml) respectively. Collectively, these data demonstrate that Tamoxifen is a safe and effective agent, and it is a suitable alternative to clomiphene citrate for anovulatory infertility in women with PCOS.

V. CONCLUSION

In the present study, women with PCOS, ovulation induction with Tamoxifen resulted in better dominant follicles, effective endometrial thickness and similar ovulation and pregnancy rates when compared to clomiphene citrate. Thus Tamoxifen can give similar or even better results than clomiphene citrate in induction of ovulation in women with PCOS. Each of them can be used as a first line option for induction of ovulation in women with PCOS "in selected cases". 3D Power Doppler endometrial perfusion is a good method for assessment of endometrial receptivity in cases of induction of ovulation.

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Conflict of Interest

There is no conflict of interest to disclose.

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