

Effects of Exogenous Ethinyl Estradiol on Endometrial Receptivity in Clomiphene Induced Cycles in Infertile Women with Polycystic Ovaries

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Abstract

To compare the effectiveness of clomiphene citrate used alone and in combination with ethinyl estradiol on endometrial receptivity in infertile women with polycystic ovaries (PCO). Color doppler ultrasonographic evaluation of endometrial thickness (ET) and pulsatility index (PI) was done for 27 infertile women with polycystic ovaries. These women were studied for one control unmedicated cycle and randomized to receive clomiphene citrate (CC) alone and CC with ethinyl estradiol (EE) in subsequent 2 cycles. The total duration of follow up of patients was 77 months in which 2 women conceived in control cycle and 1 conceived in CC+EE cycle. On day of HCG injection, mean ET was 6.96 ± 1.63 mm in control cycle, 7.25 ± 1.64 mm in CC and 8.53 ± 1.36 mm in CC + EE cycle, whereas, the mean pulsatility index (PI) of dominant uterine arteries was 4.09 ± 0.97 in control cycle, 3.96 ± 0.95 in CC cycle and 3.75 ± 0.98 in CC + EE cycle. On day of HCG injection, mean PI of non-dominant uterine arteries was 4.06 ± 1.01 in control, 4.00 ± 1.02 in CC and 3.71 ± 0.95 in CC + EE cycles. A statistically significant change ($p < 0.05$) was observed in ET and PI of dominant and non-dominant uterine arteries in control and CC+EE cycle and those in CC and CC+EE cycles. Addition of ethinyl estradiol to clomiphene induced cycles produces a favorable endometrial response in infertile women with PCO.

Key Words

Polycystic ovaries (PCO), Color Doppler, Endometrial thickness (ET), Pulsatility index (PI)

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. The diagnosis of PCOS is based on the presence of two of the following three criteria: (A) PCO on pelvic ultrasound examination, (B) clinical features or biochemical features of hyperandrogenism, and (C) oligo-ovulation or anovulation (1-3). Polycystic ovaries on pelvic ultrasound examination are observed in approximately 22% to 33% of the general population (3,4). In women seeking fertility treatment, prevalence of PCO or PCOS is almost 40% (5).

Clomiphene citrate has been widely used for over 20 years for the induction of ovulation with the pregnancy rate of 25-43%. The antiestrogenic activity of clomiphene citrate on endometrial development may be a factor in the reduced conception rates (6). Exogenous estrogen treatment to alleviate poor cervical mucus in clomiphene citrate treated women is common. The endometrium undergoes well established histological and ultrastructural changes under the influence of estrogen and progesterone during menstrual cycle (7). It is clear that histological and hormone assessments are not reliable predictors of

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endometrial status. It is therefore important to find alternate non-invasive methods of assessing uterine receptivity (8).

Steer et al (9), noted that lowest uterine artery PI was found 9 days after LH peak which is consistent with maximum uterine perfusion at the time of peak luteal function and expected implantation in normally cycling women using transvaginal ultrasonography.

In a study by Nakamura et al, clomiphene citrate (CC) produced less endometrial thickness during the CC cycle than during the control cycle on late proliferative days; but there was no significant difference on midsecretory days (10). Ben et al (11), found that exogenous ethinyl estradiol (EE) does not overcome the CC induced alterations in endometrial thickness. However, Yagel et al (12), demonstrated favorable changes in the endometrium and uterine volume with CC and EE combination therapy. Gerli et al (13), reported ethinyl estradiol to reverse the deleterious effects of clomiphene citrate on endometrial thickness, which may contribute to higher pregnancy rates. Shimoya et al (14), supported that addition of transdermal estrogen to the treatment protocol of the women treated with CC elicited a favorable response of the endometrium. Khanna et al (15), proposed that the exogenous estrogen possibly corrects the negative effects of clomiphene citrate on cervical mucus and endometrium.

We endeavor to compare the effectiveness of clomiphene citrate used alone and in combination with ethinyl estradiol on endometrial receptivity in infertile women with polycystic ovaries (PCO) using transvaginal color doppler ultrasonography.

Material and Methods

This prospective randomized study was conducted in the Department of Obstetrics and Gynaecology and Department of Radiology, Indraprastha Apollo Hospitals after approval by the Hospital's Committee for Ethics on Human Experimentation.

A total of 27 infertile women with polycystic ovaries (PCO), less than 38 years age, non smokers, non tobacco chewers, with no other uterine pathology like fibroid, polyp, adenomyosis as confirmed by USG and having normal husband semen analysis were enrolled in this study. Women with abnormal position of the uterus, history of

previous surgeries on the uterus and history of previous immediate D&C were excluded from this study.

The start of menses (spontaneous or after progesterone withdrawal) was designated as day 1 of the control or study cycle. On day 2 of the cycle serum FSH, serum LH, serum estradiol, serum prolactin, serum DHEAS, serum 17-hydroxyprogesterone, serum testosterone, serum TSH, serum insulin fasting, blood sugar fasting and transvaginal pelvic ultrasound with color doppler were done. Color doppler ultrasonographic evaluation was done using HDI 3000 color doppler system. The ultrasound examinations were performed by a single experienced ultrasonographer between 2 P.M. to 4 P.M. on all occasions to eliminate circadian rhythm affecting pulsatility index measurements.

The endometrial thickness was measured on a sagittal section of the uterus. The distance from the hyperechogenic interface between the endometrium and the myometrium to the opposite interface including the midline echo(endometrial interface) was measured. Uterine blood flow was assessed by the pulsatility index (PI) of the main ascending branch of the uterine arteries for both dominant and nondominant uterine arteries. Dominant uterine artery is the uterine artery of the side on which the dominant follicle grows while the contralateral uterine artery is the nondominant uterine artery.

These women were studied for one control cycle without administering any medicine and randomized to receive subsequent 2 study cycles with clomiphene citrate (CC) alone (regimen 1) and clomiphene citrate in combination with ethinyl estradiol (EE) (regimen 2). The study group comprised of patients of control group A, who did not conceive.

In control group A, 27 PCO women were studied for one cycle without administering any medicine. Follicular monitoring was done from day 2 of cycle along with color doppler ultrasound. The patients were then monitored from day 7 of the cycle daily. At each visit, transvaginal pelvic ultrasonography and color doppler was done to chart the ET and PI of dominant and nondominant uterine arteries. Injection HCG (Profasi) 10,000 I.U. was given intramuscularly when the size of the leading follicle was approximately >17 mm. Confirmation of the extrusion of the dominant follicle was done using transvaginal

ultrasonography. The couple was advised for timed intercourse successively for 3 days, 36 hours after the administration of Injection profasi. Tablet uterone (natural micronised progesterone) 200 mg was given orally twice daily from 2 days after extrusion of dominant follicle for 2 weeks. Confirmation of pregnancy was done 3 days after the patient missed a period. 2 women out of 27 who were studied in the unmedicated control cycle conceived and were therefore not studied in the subsequent study cycles.

In study group B, 25 infertile PCO women of control group A, who did not conceive were studied. Clomiphene citrate (Tab Fertomid) 50mg one tablet once daily was given from the second day of the cycle for 5 consecutive days for ovulation induction. Rests of the interventions were similar to those in the control cycle A.

In study group C, 25 infertile PCO women of study group B who did not conceive were studied. Clomiphene citrate (Tab fertomid) 50mg one tablet once daily was given from the second day of the cycle for 5 consecutive days for ovulation induction. Tab. ethinyl estradiol (Tab progynova) 2mg was given twice daily from the eighth day of the cycle till the day of HCG administration. Rest of the interventions were similar to the control cycle A.

Statistical Analysis was performed with the SPSS Statistical Package. The Paired 't' test was used and results are expressed as Mean+SD. Statistical significance was defined as $P < 0.05$.

Results

The total duration of follow up of the patients recruited in the study was 77 months during the period of study in which 2 women conceived in first control cycle and 1 conceived in study cycle C (CC+EE) (Table 1). Two of these women delivered by full term LSCS while one had full term vaginal delivery. However, the remaining 25 women were followed up for a period of one more year in which 5 of them conceived. 3 of them have delivered already by full term LSCS while 2 of them had ectopic tubal pregnancy.

Table. 1 Distribution of patients with infertility and Polycystic ovaries into Control Group A and Study Groups B and C

	Control Group A (Unmedicated)	Study Group B (CC)	Study Group C (CC+EE)
No. of Patients	27	25	25

All 27 patients presented with infertility and amenorrhea or oligomenorrhea. Five had galactorrhea on clinical examination. None of the patients had clinical features of hyperandrogenism such as acne, hirsutism and crown pattern baldness (Table 2). The mean ages of the patients recruited in the study were 29.78 ± 0.65 years (mean+SE). The mean duration of infertility was 4.07 ± 0.49 years (mean+SE) (Table 3).

Table. 2 Clinical Presentation of patients enrolled in the study (n=27)

Clinical Presentation	Number of patients
Primary Infertility	17
Secondary Infertility	10
Amenorrhea	8
Oligomenorrhea	19
Acne	0
Hirsutism	0
Galactorrea	5
Crown Pattern Baldness	0
Ultrasound picture of Polycystic Ovaries	27

Table. 3 Clinical and hormonal parameters of patients recruited in the study (n=27)

Parameter	Mean +Standard Error (Mean +SE)	Standard Deviation
Age (years)	29.78 ± 0.65	3.37
Duration of Infertility (Years)	4.07 ± 0.49	2.55
Weight (Kg)	62.11 ± 2.33	12.12
Height (Meters)	1.57 ± 0.01	0.04
Body Mass Index (BMI in (Kg/M ²))	25.12 ± 0.86	4.47
Serum LH (miu/ml)	6.57 ± 0.67	3.48
Serum FSH (miu/ml)	3.85 ± 0.58	3.00
LH/FSH	3.35 ± 0.75	3.88
Serum Prolactin (µg/L)	12.45 ± 1.04	5.41
Serum Testosterone (Ng/dl)	39.49 ± 3.68	19.14
Serum 17 Hydroxyprogesterone (ng/ml)	0.64 ± 0.05	0.26
Serum Estradiol (pg/ml)	15.90 ± 1.34	6.98
Serum DHEAS	149.39 ± 8.27	42.96
Serum TSH (miu/ml)	2.66 ± 0.21	1.07
Blood Sugar Fasting (mg/dl)	90.33 ± 1.51	7.83
Serum Insulin Fasting (µinsulin/ml)	8.89 ± 0.61	3.16
Blood Sugar Fasting/ Serum Insulin Fasting	11.42 ± 1.07	5.54

On the day of HCG injection mean endometrial thickness was 6.96 + 1.63 mm in control group A, 7.25 + 1.64 mm in study group B (CC) and 8.53 + 1.36 mm in study group C (CC + EE) (Table 4). On the day of HCG injection the mean PI of dominant uterine artery in group A was 4.09 + 0.97, 3.96 + 0.95 in the CC cycle and 3.75 + 0.98 in the CC+EE cycle (Table 5). On the day of HCG injection the mean PI of nondominant uterine artery in group A was 4.06 + 1.01, 4.00 + 1.02 in CC cycle and 3.71 + 0.95 in CC+EE cycle (Table 6). On the basis of above observations it can be concluded that in the present study the mean PI of non dominant uterine artery was higher in CC cycle as compared to the dominant uterine artery.

Table. 4 Comparison of Endometrial Thickness (ET in mm) in Control Group A (unmedicated) and Study Groups B (CC) and C (CC+EE) on various days of the cycle

Day of Cycle	GROUP A Mean+SD	GROUP B Mean+SD	GROUP C Mean+SD
D2	1.91+0.45	1.97+0.40	2.07+0.40
D7	2.91+0.89	2.87+0.85	3.02+1.01
D8	3.23+1.04	3.18+1.00	3.39+1.04
D9	3.87+1.18	3.70+1.23	4.19+1.11
D10	4.68+1.50	4.34+1.57	4.24+1.29
D11	5.10+1.64	4.99+1.66	6.02+1.47
D12	5.83+1.56	5.69+1.67	6.80+1.29
D13	6.46+1.89	6.56+1.81	7.42+1.33
D14 (hCG)	6.96+1.63	7.25+1.64	8.53+1.36
D15	7.56+1.64	8.04+1.56	9.30+1.38
D16	8.08+1.65	8.91+1.60	10.04+0.83

Table. 5 Comparison of Pulsatility Index (PI) of Dominant Uterine Artery in Control Group A (unmedicated) and Study Groups B (CC) and C (CC+EE) on various days of the cycle

Day of Cycle	GROUP A Mean+SD	GROUP B Mean+SD	GROUP C Mean+SD
D2	3.92+1.03	3.99+1.09	3.71+0.91
D7	2.91+1.04	4.04+1.08	3.75+0.92
D8	4.00+0.93	3.98+0.91	3.82+0.91
D9	4.02+1.03	4.14+1.07	3.84+0.91
D10	4.08+0.93	4.07+0.91	3.90+0.91
D11	4.08+1.04	4.23+1.07	3.92+0.91
D12	4.11+0.94	4.11+0.93	3.93+0.93
D13	4.09+1.06	4.17+1.10	3.85+0.95
D14 (hCG)	4.09+0.97	3.96+0.95	3.75+0.98
D15	4.10+1.01	3.98+1.08	3.64+1.01
D16	4.40+0.85	3.88+1.12	4.36+1.39

Table. 6 Comparison Of Pulsatility Index (PI) of Nondominant Uterine Artery in Control Group A (unmedicated) and Study Groups B (CC) and C (CC+EE) on various days of the cycle.

Day of Cycle	GROUP A Mean+SD	GROUP B Mean+SD	GROUP C Mean+SD
D2	3.94+1.18	3.98+1.03	3.72+0.92
D7	3.97+1.19	4.02+1.03	3.77+0.92
D8	3.94+0.98	3.96+0.96	3.82+0.88
D9	4.06+1.18	4.11+1.03	3.86+0.92
D10	4.05+0.98	4.09+0.97	3.87+0.90
D11	4.12+1.18	4.20+1.03	3.93+0.91
D12	4.05+0.99	4.15+0.99	3.91+0.91
D13	4.12+1.20	4.16+1.06	3.86+0.94
D14 (hCG)	4.06+1.01	4.00+1.02	3.71+0.95
D15	4.24+1.12	4.02+1.02	3.63+1.01
D16	4.50+1.03	3.95+1.02	3.69+0.94

On the day of HCG injection mean PI of dominant uterine artery was 4.09 + 0.97 and was 4.06 + 1.01 in nondominant uterine artery in Control group A which showed no significant change (Table 7). On the day of HCG injection mean PI of dominant uterine artery was 3.96 + 0.95 and that of non dominant uterine was 4.00 + 1.02 in CC cycle which was higher than the dominant uterine artery (Table 8). On the day of HCG injection mean PI of dominant uterine artery was 3.76 + 0.98 and that of non dominant uterine was 3.71 + 0.95 in CC+EE cycle which showed no significant change (Table 9).

Table. 7 Comparison of Pulsatility Index (PI) of Dominant and Nondominant Uterine Arteries in Control Group A (unmedicated) on various days Of the cycle

Day of Cycle	DOMINANT UA-PI Mean+SD	NONDOMINANT UA-PI Mean+SD
D2	3.92+1.03	3.94+1.18
D7	2.91+1.04	3.97+1.19
D8	4.00+0.93	3.94+0.98
D9	4.02+1.03	4.06+1.18
D10	4.08+0.93	4.05+0.98
D11	4.08+1.04	4.12+1.18
D12	4.11+0.94	4.05+0.99
D13	4.09+1.06	4.12+1.20
D14 (hCG)	4.09+0.97	4.06+1.01
D15	4.10+1.01	4.24+1.12
D16	4.40+0.85	4.50+1.03

Table. 8 Comparison of Pulsatility Index (PI) Of Dominant And Nondominant Uterine Arteries in Study Group B (CC) on various days of the cycle

Day of Cycle	DOMINANT UA-PI Mean+SD	NONDOMINANT UA-PI Mean+SD
D2	3.99+1.09	3.98+1.03
D7	4.04+1.08	4.02+1.03
D8	3.98+0.91	3.96+0.96
D9	4.14+1.07	4.11+1.03
D10	4.07+0.91	4.09+0.97
D11	4.23+1.07	4.20+1.03
D12	4.11+0.93	4.15+0.99
D13	4.17+1.10	4.16+1.06
D14 (hCG)	3.96+0.95	4.00+1.02
D15	3.98+1.08	4.02+1.02
D16	3.88+1.12	3.95+1.02

Table. 9 Comparison of Pulsatility Index (PI) Of Dominant and Nondominant Uterine Arteries in Study Group C (CC+EE) on various days of the cycle

Day of Cycle	DOMINANT UA-PI Mean+SD	NONDOMINANT UA-PI Mean+SD
D2	3.71+0.91	3.72+0.92
D7	3.75+0.92	3.77+0.92
D8	3.82+0.91	3.82+0.88
D9	3.84+0.91	3.86+0.92
D10	3.90+0.91	3.87+0.90
D11	3.92+0.91	3.93+0.91
D12	3.93+0.93	3.91+0.91
D13	3.85+0.95	3.86+0.94
D14 (hCG)	3.75+0.98	3.71+0.95
D15	3.64+1.01	3.63+1.01
D16	4.36+1.39	3.69+0.94

There was no statistical significant change ($p > 0.05$) in endometrial thickness and pulsatility index of dominant and non dominant uterine arteries of patients in control group A and study group B (Table 10). There was a statistical significant change ($p < 0.05$) in endometrial thickness and pulsatility index of dominant and non dominant uterine arteries of patients in control group A and study group C (Table 11). There was a statistical significant change ($p < 0.05$) in endometrial thickness and pulsatility index of dominant and non dominant uterine arteries of patients in study group B and study group C (Table 12).

Table. 10 Statistical Significance of Endometrial Thickness(ET) and Pulsatility Index(PI) of Dominant(D) and Nondominant(N) Uterine Arteries(UA) of patients in control Group A (unmedicated) and Study Group B (CC only)

	Group A (n=27) MEAN+SD	Group B (n=25) MEAN+SD	P Value
ET (mm)	5.14+2.39	5.13+2.42	$P > 0.05$
PI-UA D	4.08+0.97	4.04+0.98	$P > 0.05$
PI-UA N	4.09+1.09	4.06+0.96	$P > 0.05$

Statistical Analysis was performed with the SPSS Statistical Package. The Paired 't' test was used and results are expressed as Mean+SD. Statistical significance was defined as $P < 0.05$.

Table. 11 Statistical Significance of Endometrial Thickness(ET) and Pulsatility Index(PI) of Dominant(D) and Nondominant(N) Uterine Arteries(UA) of patients in Control Group A (unmedicated) and Study Group C (CC+EE)

	Group A (n=27) MEAN+SD	Group B (n=25) MEAN+SD	P Value
ET (mm)	5.14+2.39	6.09+2.81	$P < 0.05$
PI-UA D	4.08+0.97	3.87+0.96	$P < 0.05$
PI-UA N	4.09+1.09	3.79+0.88	$P < 0.05$

Statistical Analysis was performed with the SPSS Statistical Package. The Paired 't' test was used and results are expressed as Mean+SD. Statistical significance was defined as $P < 0.05$.

Table. 12 Statistical Significance of Endometrial Thickness(ET) and Pulsatility Index(PI) of Dominant(D) and Nondominant(N) Uterine Arteries(UA) of patients in Group B (CC Only) and Study Group C (CC+EE)

	Group B (n=25) MEAN+SD	Group C (n=25) MEAN+SD	P Value
ET (mm)	5.13+2.42	6.09+2.81	$P < 0.05$
PI-UA D	4.05+0.98	3.87+0.96	$P < 0.05$
PI-UA N	4.06+0.96	3.79+0.88	$P < 0.05$

Statistical Analysis was performed with the SPSS Statistical Package. The Paired 't' test was used and results are expressed as Mean+SD. Statistical significance was defined as $P < 0.05$.

Discussion

In this study we endeavored to compare the effectiveness of clomiphene citrate used alone and in combination with ethinyl estradiol on endometrial receptivity in infertile women with polycystic ovaries (PCO) using transvaginal color doppler ultrasonography.

A substantial group of authors found significant differences in uterine arteries resistance between cycles with or without pregnancy, yet another important group does not observe this difference. These contradictory results are due to clear methodological differences such as the ovarian stimulation protocol used, the cycle day that the doppler study was carried out or the sonographic examination route.

We consider the transvaginal approach with a high frequency transducer to have several advantages over the transabdominal route. It enables very detailed visualization of the uterine cavity and accurate measurements of small changes in endometrial thickness during the cycle with no concerns that a distended bladder may distort the shape of the uterine cavity.

The present study was conducted on small number of patients (n=27) and was planned for a limited amount of time (3 cycles for each patient i.e. 81 months of follow up). However, to eliminate bias in the present study transvaginal scans were performed by a single ultrasonographer, the co-author of the present study between 3-4 PM daily along with color doppler studies on all days of the cycle. During the present study, in agreement with other studies by Yagel et al. 1992 (14), Gerli et al (15) & Shimoya et al. 1999 (16) and disagreement with the study by Ben Ami et al (13), it was observed that there was no statistical significance in the endometrial thickness and pulsatility index of dominant and nondominant uterine arteries between control and CC cycle. However, in the present study, a statistical significance was observed in endometrial thickness and pulsatility index of dominant and nondominant uterine arteries between control and CC+EE cycle and CC and CC+EE cycle.

In most of the studies, which have compared endometrial thickness and pulsatility index in patients after giving CC and CC + EE, the patients did not serve as their own control. The measurements of the endometrial thickness were performed only during the proliferative phase and the dosage used was different from our study. Small sample size and the use of different protocols make discrepancies between studies difficult to evaluate.

Conclusion

We finally believe that there is a normal appearance to the 'Normal' mid cycle which is ascertainable, the recognition of which can benefit all infertility patients by improving pregnancy rates and reducing mental agony.

Non-invasive color doppler technique offers great potential in the assessment of the physiology of hemodynamic regulation of spontaneous and induced cycles. The clinical impact of color doppler on daily practice must be investigated in larger series.

Addition of ethinyl estradiol to treatment protocols that include clomiphene citrate produce a favorable endometrial response. Adding exogenous estrogen to

clomiphene citrate in ovulation induction regimens is a good strategy for maximizing pregnancy rates while reducing costs associated with serum hormone measurements, ultrasound examinations and repeated HCG injections.

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