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ORIGINAL ARTICLE

The Effect of Clomiphene Citrate versus Tamoxifen versus Letrozol on Endometrial Thickness and Blood Flow in Ovulation Induction in Women with Polycystic Ovaries

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ABSTRACT

Aim of Work: To compare between the effects of clomiphene citrate, tamoxifen and letrozol as ovulation induction agents on endometrial thickness and blood flow as non-invasive parameters of endometrial receptivity in women with polycystic ovaries.

Patients and Methods: One hundred and fifty cases meeting the selection criteria were prospectively randomized into three groups 1st Group took 100 mg clomiphene citrate, 2nd Group took 5 mg letrozol and 3rd group took 40 mg tamoxifen. Transvaginal ultrasound and Doppler were done to measure endometrial thickness and endometrial blood flow both pulsatility index (PI) and resistance index (RI) at the day of the maximum follicular growth or at day 20 in the absence of the dominant follicle in the three groups.

Results: Significantly thinner endometrium in the clomiphene citrate group as compared to the other two groups and lower impedance in the spiral arteries in both letrozol and tamoxifen groups (P value less than 0.001).

Conclusion: Endometrium was thicker with lower impedance in the spiral arteries in both letrozol and tamoxifen groups as compared to clomiphene citrate group. Ovulation and pregnancy rates were not significantly different. Other studies are needed to measure the cumulative results of six cycles, increasing the dose in non-responders and the incidence of miscarriage.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the commonest form of ovarian causes of infertility representing between 90% and 95% of women with ovarian causes presenting to infertility clinics. PCOS women have normal count of primordial follicles while, there is a significant increase in primary and secondary follicles. However, due to a disturbance in the factors affecting normal follicular development, follicular growth stops when follicles reach a diameter between 4 and 8 mm. Anovulation is due to the lack of development of a dominant follicle.[1,2]

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Clomiphene citrate acts as a partially selective modulator of estrogen receptors. It acts on the level of the hypothalamus by inducing changes in gonadotropin releasing hormone (GnRH) frequency of pulses leading to increased in the release of follicle stimulating hormone (FSH) from the pituitary gland, it's ovulation rate ranges between 70% and 85% in each cycle while, it's cumulative live birth rate is lower ranging between 50% and 60% in treatment for six cycles.[3]

Aromatase inhibitors inhibit the conversion of testosterone to estradiol and of androstenedione to estrone which decreases the estrogenic activity releasing the hypothalamus from its negative feedback leading to an increase in FSH release.[4]

Tamoxifen is a pro-drug converted in the liver to its active metabolites as 4-hydroxytamoxifen and N-desmethyl-4-hydroxytamoxifen. These active metabolites compete with estrogen for its receptors.[5]

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Tamoxifen is used in the treatment of anovulatory infertility with a favorable action on cervical mucus and acting as an estrogen receptor agonist on the endometrium leading to better endometrial thickness and better endometrial blood flow, thus, improving endometrial receptivity and fertility.[6]

Endometrial receptivity is a unique and temporary sequence of factors making the endometrium receptive to embryo implantation.[7] Ultrasonic parameters of endometrial receptivity are endometrial thickness, endometrial volume, endometrial pattern and Doppler study of uterine arteries and the endometrium.[8]

Endometrium thickness of less than 7 mm is a sign of suboptimal implantation potential.[9] Pregnant women had significantly higher mean endometrial thickness than non-pregnant women as shown in a meta-analysis done by.[10]

A good blood supply to the endometrium is an essential factor for normal implantation. Color and power Doppler ultrasound are non-invasive methods to evaluate endometrial blood flow,[11] which is a more important parameter for embryo transplantation than total uterine blood flow.[12]

The aim of our work was to compare between the effects of clomiphene citrate, tamoxifen and letrozol as ovulation induction agents on endometrial thickness and blood flow as non-invasive parameters of endometrial receptivity in women with polycystic ovaries.

PATIENTS AND METHODS

Three hundred and thirty seven infertile women with anovulatory (PCOS) were recruited from the outpatient clinics of both 6th October and Bab Elshaaria University Hospitals from August 2014 and January 2015, of which one hundred and fifty met the inclusion criteria of the study which are: age between 20 and 35 years, body mass index (BMI) between 18 and 30 kg/m^2, normal uterus and patent tubes by hysterosalpingography (H.S.G.), normal semen analysis and normal serum prolactin, while, exclusion criteria included women with endocrinal disturbance, active liver disease, local disease as hydro- or pyosalpinx, and history of previous ovarian surgery. The study was approved by the ethical committee of Al Azhar University.

All patients were subjected to the following: detailed history and physical examination, hormonal profile on day 2-4 (FSH, LH, E2, Prolaction, TSH, free T3 and T4), HSG and semen analysis.

The patients were prospectively randomized into three groups each containing fifty patients by computer allocation method. Each of the three groups received 2 tablets for 5 days sarting from day 3 to day 7 of the cycle. Group 1 received 100 mg (50 mg/tablet) clomiphene citrate, Group 2 5 mg (2.5 mg/tablet) letrozole and Group 3 40 mg (20 mg/tablet) tamoxifen.

Transvaginal ultrasound was done on day 3 then on day 10 of the cycle then every other day until a single follicle of at least 18 mm. in diameter was detected, if no follicle by this size was detected by day 20 it is considered as failure. Endometrial thickness and endometrial blood flow both pulsatility index (PI) and resistance index (RI) were measured at the day of the maximum follicular growth (18 mm. or more) or at day 20 in the absence of the dominant follicle.

The primary outcomes of the study were endometrial thickness and endometrial blood flow (PI and RI), while the secondary outcomes were the development and number of follicles, and the pregnancy rate.

Statistical Methods

Statistical analysis was done using IBM© SPSS © Statistics version 21 (IBM© Corp., Armonk, NY) and MedCalc© version 12.5 13 (MedCalc© software bvba, Ostend, Belgium).

RESULTS

As regards the type of infertility in the three groups it was as follows: group 1 38 (76%) had primary infertility and 12 (24%) had secondary infertility, group 2 36 (72%) had primary infertility and 14 (28%) had secondary infertility, and group 3 37 (74%) had primary infertility and 13 (26%) had secondary infertility. This was statistically insignificant as the P-value was 0.785.

As regards the mean duration of infertility in the three groups it was as follows: Group 1 1.9 with an SD of +/- 0.7, group 2 1.9 +/- an SD of +/- 0.7, and group 3 2.2 with an SD of +/- 0.7. This was statistically insignificant as the P-value was 0.146.

The rate of ovulation (at least one follicle with a diameter 18 m or more) in the three groups was as follows: Group 1 33 (66%), group 2 36 (72%) and group 3 34 (68%). The P-value was not statistically significant P-value more than 0.05.

The number of follicles per ovulating patient in the three groups are as follows: Group 1 median 2 (ranging between 0 and 4 follicles) and mean 2* +/- SD 0.9, group 2 median 1 (ranging between 0 and 2 follicles) and mean 1.2 +/- SD 0.4, and group 3 median 1 (ranging between 0 and 2 follicles)

and mean 1.2 +/- SD 0.4. The P-value was statistically significant with a value of less than 0.001. Clomiphene citrate group showed development of more number of follicles as compared to letrozol and tamoxifen.

The current study revealed a highly significant negative correlation coefficient between endometrial thickness and Doppler indices i.e. as endometrial thickness decreases Doppler indices (PI and RI) increase (Table 3) this was evident in the clomiphene citrate group as compared to the other two groups. This result was similar to the result found by[19] who concluded that endometrial thickness and pattern were impaired in PCO women taking clomiphene citrate. These results suggest that endometrial receptivity parameters might have been worse in patients taking clomiphene citrate with consequently lower implantation and pregnancy rates.

DISCUSSION

Ovulation induction drugs are one of the main lines of treatment of anovulation due to polycystic ovaries. Clomiphene citrate (CC) has been used as the first line for ovulation induction since 1961. Although clomiphene citrate has higher ovulation rates ranging between 50 and 90% pregnancy rates are much lower ranging between 20 and 40%,[13] such difference may be due to the peripheral anti-estrogenic effect on the cervical mucus and the endometrium.[14] Clomiphene citrate is believed to slow down the uterine blood flow in early luteal phase and around the time of implantation. Some authors stated that clomiphene citrate may have a direct effect on both ovarian and uterine blood flow.[15] The above mentioned actions of clomiphene citrate have a negative impact on endometrial receptivity which is a possible explanation for the big discrepancy between ovulation and pregnancy rates with this medication, furthermore, the development of clomiphene citrate resistant patients led several authors to investigate alternative medications as the study done by[16] who reported a thirty percent pregnancy rate in those patients after using 40 mg tamoxifen per day for 5 successive days starting from day 3 of the cycle and suggested that tamoxifen may be a proper alternative in those patients before starting treatment with gonadotrophins.

There was neither a significant difference as regards age and BMI (Table 1 and Figure 1) nor a significant difference as regards the type and duration of infertility in the studied groups.

The current study investigated the effect of clomiphene citrate, letrozol and tamoxifen on both endometrial thickness and endometrial blood flow as non-invasive parameters in the assessment of endometrial receptivity and showed a significantly thinner endometrium in the clomiphene citrate group as compared to the other two groups (P value less than 0.001) (Table 2) and the same high significance for Doppler indices measuring endometrial blood flow (Table 2 and Figure 2). Pregnancy rate was slightly lower in the clomiphene citrate group compared to the other two groups, however, this result was statistically insignificant (P value = 0.413) (Table 4). Selim and Borg[17] studied 200 anovulatory women and reached the same conclusion as regards endometrial thickness and endometrial blood flow when comparing clomiphene citrate to letrozol with higher pregnancy rate in the letrozol group. However, Badawy and co-workers[18] reached different results when comparing clomiphene citrate to letrozol as they had higher endometrial thickness, ovulation and pregnancy rates and in the clomiphene citrate group.

The current study showed a statistically significant mean number of follicles in the clomiphene citrate group as

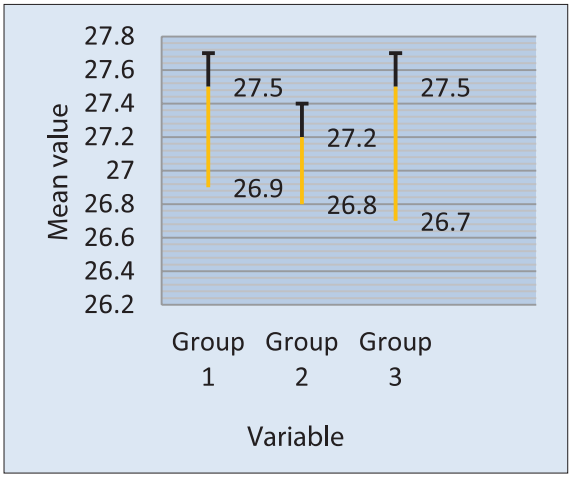

Figure 1: Shows the patients' characteristics in the three group

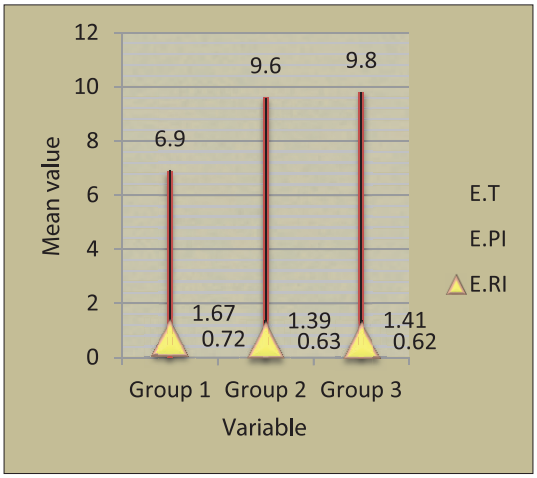

Figure 2: Showed a statistically difference as regards endometrial thickness and Doppler indices (PI and RI) in the studied groups

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Table 1: The patients' characteristics in the three group (no statistically significant difference)

Variable	Mean±SD (N=50)			F (df=2,156)	P value
	Group 1	Group 2	Group 3		
Age (years)	27.5±4.1	27.2±3.9	27.5±4.1	0.076	0.927
BMI (kg/m^2)	26.9±1.7	26.8±1.7	26.7±1.5	0.185	0.832

Table 2: A highly statistically significant difference as regards endometrial thickness and Doppler indices (PI and RI) in the studied groups as the P value was less than 0.001

Variable	Mean±SD			F (df=2,156)	P value
	Group 1	Group 2	Group 3		
Endometrial thickness (mm)	6.9*±1.2	9.6±1.6	9.8±1.7	56.720	Less than 0.001
Endometrial PI	1.67*±0.21	1.39±0.16	1.41±0.14	40.791	Less than 0.001
Endometrial RI	0.72*±0.03	0.63±0.03	0.62±0.03157	157.010	Less than 0.001

Group 1 Clomiphene citrate showed highly significant lower endometrial thickness and higher Doppler indices (PI and RI) as compared to the other two groups

Table 3: Highly statistically significant negative correlation coefficient between endometrial thickness and Doppler indices in the studied groups

	Endometrial PI		Endometrial RI	
	Correlation coefficient (r)	P value	Correlation coefficient (r)	P value
Endometrial thickness (mm)				
All study population	−0.850	Less than 0.0001	−0.837	Less than 0.0001
Group 1	−0.695	Less than 0.0001	−0.58	Less than 0.0001
Group 2	−0.776	Less than 0.0001	−0.716	Less than 0.0001
Group 3	−0.927	Less than 0.0001	−0.818	Less than 0.0001

The relation is inversely proportional, as endometrial thickness increases, the Doppler indices decrease and vice versa

Table 4: Statistically insignificant difference as regards pregnancy rate in the three groups, however, the highest pregnancy rate was in group 2 (letrozol group)

Variable	n=50 (N (%))			X^2	Df	P value
	Group 1	Group 2	Group 3			
Pregnancy						
Negative	42 (84)	36 (72)	38 (76)	1.767	2	0.413
Positive	8 (16)	14 (28)	12 (24)			

X^2=Chi square

compared to the other two groups (P value less than 0.001), however, both ovulation and pregnancy rates were higher in the other two groups although those differences were statistically insignificant. Roy and co-workers,[20] reached the same results when they compared between clomiphene citrate and letrozol, however, pregnancy rate was significantly higher in the letrozol group in their study. Pant[21] had no significant difference as regards ovulation and pregnancy rate when comparing clomiphene citrate with tamoxifen, however, a significant difference was detected as regards endometrial thickness in favor of the tamoxifen group.

CONCLUSION

The current study concluded that endometrium was thicker with lower impedance in the spiral arteries in both letrozol and tamoxifen groups as compared to clomiphene citrate group. Ovulation and pregnancy rates were not significantly different among the three groups, however, certain issues were not addressed in this study which, need to be addressed in other studies as the cumulative results of six cycles, increasing the dose in non-responders and the incidence of miscarriage.

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