Comparison Between Preovulatory Follicular Pulsed Doppler Indices Under the Effect of Mild Ovarian Stimulation by Clomiphene Citrate vs Letrozole

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Dalia Jasim Mahmood*, Huda Ali Hussaini, Wasan Adnan Abdulhameed

High Institute of Infertility Diagnosis and Assisted Reproductive Technologies, Al Nahrain University, Baghdad, Iraq. *daliad142@yahoo.com

ABSTRACT

It was observed that embryos from oocytes resulting from well-vascularized follicles had a higher implantation rate than those from oocytes developed in poorly vascularized follicles. Neovascularization was recognized as primary in terms of ovulatory follicles growth and selection. Vascular endothelial growth factor serum level has a positive correlation with perifollicular blood flow. The 2D Color and Pulsed Doppler ultrasounds that allow visual observation of the flux of the blood in a limited part of the wall of the preovulatory follicles can be easily measured. To study the preovulatory follicle's blood flow parameters in infertile women undergoing different ovulation induction protocols. 50 infertile female patients who had undergone Intrauterine Insemination (IUI) procedures were classified into two groups which were letrozole or clomiphene citrate groups as induction protocol. Another ultrasound was performed on cycle day 11, 12, or 13 to evaluate growth follicles, also a Doppler study was done to measure perifollicular blood flow and endometrial thickness at the same time blood sample to measure vascular endothelial growth factor were taken. Human chorionic gonadotropin was injected and then after 36-40 hrs. IUI Procedure is done and follows up with the patient to do a pregnancy test after 14 days. The number of dominant follicles, endometrial thickness at HCG trigger, Perifollicular doppler blood flow vascular endothelial growth factor level, pregnancy rates were all measured in both groups. There were significant differences in Perifollicular RI ($p < 0.001$) but there were no significant differences in Perifollicular PI ($p = 0.476$). Regarding pregnancy rate, the letrozole group has a higher although not significant pregnancy rate (32%), if compared with those using CC (20%).

Keywords: Pulsed Doppler; Perifollicular vascularity; Letrozole; Vascular Endothelial growth factor; Clomiphene citrate; Intrauterine insemination.

1. Introduction

The ‘gold standard’ and final proof of uterine receptivity is conception. However, implantation by itself also depends on embryo quality, and the differentiation between these two factors in each case is not always obvious. So, the quality of an oocyte is one of the determining factors of embryo quality. It has become increasingly clear that the follicular microenvironment of a human oocyte is a crucial factor for its developmental competence (*Petro, et al. [1]*). A receptive endometrium, a normal, and functional embryo are necessary for successful implantation (*Singh, et al. [2]*; *Schulte, et al. [3]*). In addition to the endometrium, it was observed that embryos from oocytes resulting from well-vascularized follicles had a higher implantation rate than those from oocytes developed in poorly vascularized follicles (*Naredi, et al. [4]*). Neovascularity, in addition to the subsequent development and function of corpus luteum, may be of utmost importance in the growth and

selection of ovulatory follicles. (*Blankstein, et al. [5]*; *Bassett, D. [6]*). So, the association between perifollicular perfusion and follicular oxygenation, and oocyte maturation does exist which ultimately gets translated to the quality of embryos. If other contributed factors such as endometrial receptivity are controlled, it influences the implantation potential too. At least hypothetically, the quality of an oocyte, a follicle, and its vascular network are correlated, and therefore perifollicular vascularization and VEGF levels may be valid indirect markers of oocyte quality. Serum VEGF levels have a positive correlation with perifollicular blood flow. This can be easily measured by two-dimensional Color and Pulsed Doppler ultrasonography (*Vural, et al. [7]*). Transvaginal color Doppler (TVCD) plays an important role in better understanding the physiology of the menstrual cycle. This technique was intensively studied at the beginning of the 1990s, and many studies proved the usefulness in the detection of vascular changes in the uterus and the

ovary (*Stadtmauer and Tur-Kaspa* ^[8]) Doppler flow study with its indices such as pulsatility index (PI) and resistance index (RI) provides important information about perfusion and angiogenesis in the ovarian follicles (*Han, et al.* ^[9]). The perifollicular vascularity is a constant challenge for clinicians and researchers. It is known that it correlates well with the level of follicular oxygenation. Oocytes from severe hypoxic follicles are associated with a high frequency of abnormalities in the organization of the chromosomes. Color Doppler analysis of perifollicular blood may provide an indirect sign of the developmental competence of the oocyte (*Huyghe, et al.* ^[10]). In the stimulated cycles, there is a correlation of higher peak systolic velocity (PSV > 10 cm/s) in follicles with subsequently fertilized oocytes. Treatment of infertility has many options and it depends normally on the underlying infertility etiology, age, period of infertility, personal preference, and their general state of health. So, the treatment can be intrauterine insemination (IUI), in

vitro fertilization (IVF), intracytoplasmic sperm injection and others, (IUI) Intrauterine insemination is recognized as effective and cost-effective and has little impact and is less invasive than any other type of ART. and are acceptable to most religious groups (*Tjon-Kon-Fat, et al.* ^[11]). IUI combined with controlled ovarian stimulation (COS) is widely used because of the higher pregnancy rates compared to IUI cycles without COS. Therapy for ovulation induction include

A. Clomiphene Citrate Since its introduction in clinical practice, it has been widely used to treat infertility. (*Bryan, J.* ^[12]). The effects are 60-85% ovulation and 10-20% pregnancy per period. Clomiphene (*Fisher, et al.* ^[13]).

B. Letrozole Aromatase Inhibitors such as letrozole have been introduced as a treatment option for ovulation induction. Inhibition of the aromatase enzyme decreases the aromatization of androgens to estrogens that in turn releases the

hypothalamic-pituitary axis from negative feedback of estrogen. Adverse effects on the endometrium and cervical mucosa are significantly lower than with CC, and there are researches on good pregnancy rates with a lower incidence of multiple pregnancies (*Walker and Tobler* ^[14]).

C. Gonadotropins for clomiphene resistant women, are a long-standing therapy such as Human Menopausal Gonadotropins (HMG), urinary FSH (rec. FSH) and recombinant LH (resec. LH) are several injection medications available, all these have problems related to cost and Multiple pregnancies and hyperstimulation syndrome risks (*Nahuis, et al.* ^[15]).

2. Materials and Methods

This prospective observational study was conducted during the period from (Sep 2019 to March 2020), at the Higher Institute of Infertility Diagnosis and Assisted Reproductive Techniques at Al

Nahrain University also this study was approved by it. Informed consent was obtained from all participants after the nature of the procedures had been fully explained. were randomly selected from those who attended the Higher Institute of Infertility Diagnosis and Assisted Reproductive Technologies, and were treated for IUI 50 women participated in the study. Those female patients had the same inclusion and exclusion criteria. These women were between 18 and 40 years old, more than two years of infertility in this study, had one or bilateral patent tubes confirmed by hysterosalpingography, and excluded patients who have an ovarian cyst or uterine pathology such as leiomyoma, untreated endocrinopathies such as hyperprolactinemia, diabetes. Taking complete history and examination, a hormonal assay (FSH, LH, prolactin, E₂, and TSH) on the 2nd day of the cycle was tested for all patients. Baseline ultrasound on the 2nd or 3rd day of the cycle to measure antral follicular count. 25 Patients were

given letrozole orally 2.5 mg twice daily 12 hours apart from the 3rd day for 5 days of the menstrual cycle. 25 patients were given Clomiphene citrate 50 mg twice daily in two doses 12 hours apart from the 3rd day of menses for 5 days long. Transvaginal ultrasound was done from day 10 of the menstrual cycle and every other day till we reach the optimal size of the follicle where at least one follicle with a mean diameter of more than 18 mm. A recombinant HCG (1-2) ampule of HCG (6,500 – 13,000 IU) was administered subcutaneously to trigger ovulation. On the day of trigger, the ovary was identified and measured size and number of the dominant follicles and Doppler study for Perifollicular blood flow by color signals were used to detect the area with the highest blood flow within the matured follicle then blood flow was identified in the follicular wall of the preovulatory follicle the conventional color Doppler was used to display perifollicular vessels and to determine the area with the highest blood flow. Then a pulsed Doppler range

gate was put over the interested vessels. The direction of the probe was changed to obtain the highest frequency shift signal; the frequency shift was evaluated using the parameter resistance index (RI). The resistance index (RI) was calculated electronically when 3–5 similar, consecutive waveforms of good quality, pulsatility index (PI), and peak systolic velocity (PSV). When at least three cycles with a strong signal were collected, sonograms were analyzed. Index measurement was automatic, using the formulae:

$$PI = (A - B)/M$$

$$RI = (A - B)/A$$

Where A is the peak systolic frequency, B is the peak diastolic frequency and M is the mean value (*Stadtmauer and Tur-Kaspa [8]*), the endometrial thickness and morphology were evaluated at the longitudinal axis of the uterus. The maximum thickness of the endometrium was measured at the thickest point between the two basal layers on the

anterior and posterior uterine walls at the fundal area. Endometrial thickness, measured to the nearest millimeters, included both endometrial layers, together on the day of triggering VEGF was measured and IUI timed (36-40 hr. after hCG injection) was advised. All patients were followed-up by having a blood-based pregnancy test 2 weeks after hCG injection.

3. Statistical Analysis

The data were analyzed using version 22.0 of the Social Sciences Statistical Package (SPSS). The groups were calculated using the Pearson correlation coefficient (r). They were compared by independent samples t, paired sample t-test, and chi-square. When p is less than 0.05, the findings were statistically significant.

4. Results

Patients of both letrozole and CC classes have demographic and hormonal parameters). Their differences were not significant in all parameters between the two groups as shown in *Table (1)*.

Regarding stimulation parameters, *Table (2)* group of letrozole has a substantially lower follicle no. of developing follicles, In addition to lower estradiol levels at hCG days, and thicker endometrium. Concerning pregnancy, the letrozole group is higher in eight patients from 25 (32%) as compared to the pregnancy rates. Utilization of CC in which 5 patients get 25 (20%) pregnancies. *Table (3)* showed that there were significant differences in Perifollicular RI, but there were no significant differences in Perifollicular PI (p=0.476).

5. Discussion

Oocytes are very sensitive to hypoxic damage (*Petro, et al.* ^[1]). In light of the reality that Intrafollicular oxygen levels are controlled by blood supply, growth factors, nutritional factors, gonadotropins, oocyte quality are defined. The supply of blood is essential. The results from this study showed that the average follicle no of the transvaginal ultrasound in the clomiphene citrate was considerably

Table (1): Comparison of demographic parameters and hormones between clomiphene citrate and letrozole groups

<i>Parameter</i>	<i>Letrozole N=25 Mean±SD</i>	<i>CC N=25 Mean±SD</i>	<i>P-value</i>
<i>Age (yr)</i>	29.4±6.35	28.4±5.27	0.548
<i>Duration of infertility (yr)</i>	2.8±1.38	2.36±1.32	0.256
<i>BMI (Kg/m²)</i>	27.2±1.97	28.16±1.79	0.091
<i>Type of infertility</i>			
<i>Primary</i>	16	19	0.355
<i>Secondary</i>	9	6	
<i>S.FSH (mIU/ml)</i>	7.26±2.29	6.31±2.18	0.139
<i>S.LH (mIU/ml)</i>	7.77±1.61	7.30±1.73	0.325
<i>S.TSH (mIU/ml)</i>	2.13±0.739	1.89±0.69	0.237
<i>S.E2 (pg/ ml)</i>	48.2±22.5	42.4±12.5	0.268
<i>S.Progesterone (ng/ml)</i>	0.58±0.22	0.72±0.72	0.385
<i>S.Prolactin (ng/ml)</i>	6.95±3.37	6.53±2.8	0.634

Table (2): Stimulation protocols parameters

<i>Parameter</i>	<i>Letrozole group (Mean±SD)</i>	<i>Clomiphene citrate group (Mean±SD)</i>	<i>P-value</i>
<i>No. of dominant follicles at HCG trigger</i>	1.2 ± 0.41	1.52 ± 0.65	0.043
<i>Size of dominant follicles at HCG trigger (mm)</i>	19.42 ± 1.06	19.35 ± 1.27	0.836
<i>ET at day of HCG trigger (mm)</i>	8.46 ± 0.87	6.45 ± 0.77	< 0.001*
<i>VEGF level (ng/l)</i>	326.84 ± 74.9	245.24 ± 53.1	< 0.001*
<i>Pregnancy rate</i>	8 (32 %)	5 (20 %)	0.333

Table (3): Comparison of perifollicular Doppler blood flow between Letrozole group and Clomiphene citrate group

<i>Parameter</i>	<i>Letrozole group (Mean±SD)</i>	<i>Clomiphene citrate group (Mean±SD)</i>	<i>P-value</i>
<i>Perifollicular (RI)</i>	0.46 ± 0.086	0.59 ± 0.132	< 0.001 *
<i>Perifollicular (PI)</i>	0.67 ± 0.098	0.69 ± 0.073	0.476
<i>PSV (Peak Systolic Velocity)</i>	11.64 ± 2.39	10.56 ± 2.13	0.226

<i>Notations</i>	
<i>Table 1</i>	LH: Luteinizing hormone, FSH: Follicle stimulating hormone, E ₂ : Estradiol, BMI: Body mass index, CC: clomiphene citrate * Data expressed as frequency & percentage
<i>Table 2</i>	ET: Endometrial thickness; VEGF: Vascular endothelial growth factor E ₂ : Estradiol; NO: Number
<i>Table 3</i>	SD: Standard deviation; RI: Resistance index; PI: Pulsatility index

higher than the letrozole groups shown in **Table (2)**. This has been decided by other authors, in the clomiphene citrate group, there have been more follicles ≥ 16 mm (**Pourali, et al. [16]**; **Hussein, et al. [17]**). Another study has shown that the total number of follicles developing in the letrozole and the clomiphene citrate groups did not differ substantially (**Shrivastava, et al. [18]**; **Zeinalzadeh, et al. [19]**). The inhibitors of aromatase increase

follicular affectivity of FSH by the accumulation of intraovarian androgens within the ovary. As the prevalent follicle evolves and estrogens increase, ordinary negative criticism takes place centrally, with the FSH emission and atresia of the littler follicles occurring in single prevailing follicles and mon ovulation occurring (**Franik, et al. [20]**; **Mitwally, et al. [21]**). Another article reveals that its hypoestrogenic state of letrozole did not last until late in the menstrual cycle

follicular stage. Because of its short half-life, mono-follicular growth is more likely to be increased (*Gajjar, et al.* ^[22]; *Hussein, et al.* ^[17]). The present study revealed that the average size of the dominant follicle no critical contrast between the two groups as shown in *Table (2)*. The possible explanation that the mean size of the follicle was determined before hCG administration is agreed by A clinical trial of (*[19]*) who show A higher pregnancy rate was also noted in the letrozole group, on the day of HCG injection, a higher level of estradiol as shown in *Table (2)* in clomiphene citrate community than in letrozole group, by no substantial difference in number and size of mature follicles, which was decided upon in the (*Ray, et al.* ^[23]; *Ganesh, et al.* ^[24]). They found that a significantly higher level of E₂ in the Clomiphene group and this due to the higher number of the follicle in this group than that in a letrozole group. This is why Clomiphene has some detrimental effects on the outcomes of infertility treatment while

reducing estrogen production by an aromatase inhibitor can help to improve this (*Al-Fozan, et al.* ^[25]). The mean thickness of endometrium within that sample was significantly greater in a letrozole than those of clomiphene groups, such results were consistent with other research showing that most patients who received letrozole seemed to have a thicker endometrial lining (*Al-Shoraky, et al.* ^[26]; *Jirge and Patil* ^[27]; *Garg and Vanitha* ^[28]). The antiestrogenic activity and the typically long half-life of clomiphene citrate can be due to these complications (*Behnoud, et al.* ^[29]). In contrast with clomiphene citrate, because of the short half-life, the letrozole is removed from the bloodstream faster; it does not drain estrogen receptors and is not prone to antiestrogenic fringe activity; hence it has no unfavorable effect on endometrial receptivity and cervical fluid consistency (*Pritts, EA.* ^[30]). Surprisingly, another considers uncovered They clarify that in fact, the endometrium is completely denser within the clomiphene

citrate group because the number of follicles develops has increased, and therefore the level of estrogens has been increased (*Al-Shoraky, et al.* ^[26]). On the other hand, another analysis detailed a nonsignificant contrast within the endometrial thickness among the two types of treatment (*Hashim, et al.* ^[31]; *Fisher, et al.* ^[13]). They clarify that due to the little measure of the test (19 ovulatory female volunteers) or may utilize treatment on days 5–9 after menses. **Table (3)** showed that the resistance index (RI) and pulsatility index (PI) was significantly lower in the letrozole group compared to the clomiphene group, this may be explained by vascular endothelial growth factor (VEGF). The development of an adequate capillary network seems to depend at least in part on the action of VEGF which is produced by follicular granulosa, thecal cells (*Monteleone, et al.* ^[32]). In particular, VEGF releases, which are initiated by gonadotropins during folliculogenesis, determine how to structure a vascular organ within the

follicle's thecal cell layer. (*Lam and Haines* ^[33]; *Gordon, et al.* ^[34]) VEGF is recognizable in ovarian follicular liquid (*Kudsy, et al.* ^[35]). As appeared in **Table (2)** the pregnancy rate for Clomiphene Citrate has historically spoken, been lower than for the letrozole group, with a pregnancy rate of 20% for Clomiphene Citrate, and of 32% for the letrozole group, the pregnancy rate after ovulation is generally effective from 9% to 25% (*Teede, et al.* ^[36]). The ‘gold standard’ and final proof of uterine receptivity is conception. However, implantation by itself also depends on embryo quality, and the differentiation between these two factors in each case is not always obvious. So, a likely explanation for the mechanism underlying the lower rate of pregnancy in the Clomiphene Citrate group was Clomiphene citrate is an anti-estrogen with a 60%-80% ovulation rate and a 10%-20% pregnancy rate. Vascularization was the primary essential step in follicular growth, and the follicular micro-environment is a primary oocyte growth

factor (*Teede, et al.* ^[36]; *Fortune, et al.* ^[37]). In oocyte competencies, embryo viability and implantation potential perifollicular perfusion are important (*Naredi, et al.* ^[4]; *Bhal, et al.* ^[38]). Of these markers, the computation of follicular bloodstream utilizing color Doppler imaging was explained to be a valuable indicator of ovarian reaction and expected outcomes of treatment (*Oyesanya, et al.* ^[39]).

6. Conclusions

The perifollicular resistance index (RI) was significantly lower in the letrozole group and shows better endometrial thickness and higher VEGF level than the clomiphene citrate group, letrozole group had a higher pregnancy rate compared to the clomiphene citrate group with 32% and 20% respectively although not significant.

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Author Contribution

Mahmood, DJ, performed the study, examined and reviewed results, and manuscript writing with the help and supervision of Hussaini, HA, and Abdulhameed, WA.

Conflict of Interest

The author declares no conflict of interest.

Ethical Clearance

The study was approved by the Ethical Approval Committee.

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Authors Biography

Dr. Dalia Jasim Mahmood

She received the M.B.CH.B. from the College of Medicine, Al-Mustansiriya University in 2007. She occupied the position of rotator house officer in Al-Yarmouk Teaching Hospital from 2008-2009. She worked in Baghdad during her permanency in obstetrics and gynecology 2011-2012. She started the residency program in 2013 at Al-Yarmouk Teaching Hospital and graduated as a specialist in Obstetrics and Gynecology in 2017 with F.I.C.O.G of Obst. & Gyne. She worked as a specialist in Al-Zaafranea General Hospital from 2017-2018. From 2018-2020 graduated as a specialist in infertility with Ph.D. from Al Nahrain University, the High Institute for Infertility Diagnosis and Assisted Reproductive Technologies.

Dr. Huda Ali Hussaini

She received the M.B.Ch.B: Babylon University, College of Medicine, in 2000. The diploma in Radiology from the University of Baghdad in 2007. She is a fellow of the Iraqi Board for Medical Specialization, Council of Radiology since 2008. Currently, she is an assistant professor. Al Nahrain University, College of Medicine, department of surgery (specialist radiologist). She is a Member of staff in the high Institute of infertility diagnosis and ARTS. Including the ultrasound department in the institute since 2018. She has Participations in a lot of annual meetings, medical conferences. Seminars, continuous learning, and thesis discussion. She is a member of the Iraqi medical association, the Iraqi Society of Radiologists and medical imaging, the Iraqi Journal of Embryos infertility researches, European Society for Hybrid, Molecular, and translation imaging. She published more than 15 articles and has supervised many students.

Dr. Wasan A. Abdulhameed

She received M.B.CH.B. from the University of Baghdad, College of medicine in 1992, the diploma and the Arab Board in Gyn. and Obs. from Medical City, Baghdad in 1998. She worked at Al Sharjah University, UAE. She earned a laparoscopic surgery certificate from India in 2009. She was a Lactation consultant in Australia in 2010. She occupied many administrative positions She attended more than 20 academic congresses internationally.

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