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ORGINAL ARTICLE

Effect of Letrozole versus Clomiphene Citrate on Endometrial Receptivity and Perifollicular Vascularity in Infertile Women with Polycystic Ovarian Syndrome

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ABSTRACT

Background: Polycystic ovarian syndrome (PCOS) is the most common endocrine problem in females with an incidence of (6 -10%). The purpose of this study was to make a comparison between the effect of clomiphene citrate versus letrozole on the endometrial receptivity and perifollicular vascularity among infertile patients having PCOS. **Methods:** This randomized comparative clinical study was conducted at infertility clinic of laparoscopy cytogenic unit, Obstetrics and Gynecology Department, Zagazig University, Egypt from June 2019 to June 2020. It included a total of 54 infertile women diagnosed as having PCOS, 27 women received Clomiphene Citrate 100 mg and 27 patients received letrozole 5mg for ovulation induction. Thickness and pattern of the endometrium, uterine and spiral artery Doppler indices were calculated for 3 subsequent cycles on HCG injection day. Either clomiphene citrate or Letrozole was administrated by mouth for 5 days from day 3 of menstrual cycle. **Results:** As regards peri follicular vascularity, highly valuable difference was detected between two tested groups on HCG injection day in the 3 subsequent cycles. Ovulation rates were higher in the letrozole group than in the Clomiphene citrate group, however the discrepancy was not statistically valuable, in letrozole (70%, 74%, 81%) and in clomiphene citrate (63.0%, 67%, 77%) in 3 subsequent cycles. **Conclusions:** Both Clomiphene citrate and letrozole increase perifollicular blood flow with a significant difference in favor to letrozole, in letrozole group, the most of follicles were (grade3) and in Clomiphene citrate group (grade2).

Key words: Polycystic ovary syndrome (PCOS); Clomiphene citrate; Letrozole

INTRODUCTION

Polycystic ovarian disease is the most prevalent endocrine disorder during childhood time. PCOS is a heterogeneous disease of uncertain cause, but there is a good proof that it is considered as a genetic disorder **[1]**. Polycystic ovarian disease causes manifestations in about 5 % to 10 % of women during years of reproduction (12–45 years). It was considered to be one of the commonest causes of female subfertility **[2]**.

Polycystic ovarian disease is characterized by prolonged non ovulation, increasing androgen and multimolecular ovaries. Despite of great trials has been made towards more explaining the mechanism of this condition, it is still uncertain about the exact etiology **[3].** Clomiphene citrate have been used for induction of ovulation 60 years ago. It is considered as a first-choice medication for anovulatory women with PCOS. But nonresponse to clomiphene citrate (15-20 %), decreased endometrial thickness and cervical mucus plug (15-50 %) make it not effective in a lot of cases **[4]**. Letrozole, inhibitor of aromatase, has been proved as a good other medication by several studies, but proof of its action as opposed to clomiphene citrate is not certain **[5].**

Previous studies have discussed some ultrasonic parameters as thickness and pattern of the endometrium, spiral and uterine artery blood flow for evaluation of endometrial receptivity. The most of these studies have reported that adequate uterine blood flow increased the receptivity of the endometrium and incidence of pregnancy **[6]**. So, this study was designed to make comparison between the effect of clomiphene citrate and letrozole on the receptivity of the endometrium and perifollicular vascularity in infertile women with PCOS.

METHODS

Fifty-four infertile women were diagnosed as having PCOS, were recruited in infertility clinic, Obstetrics and Gynecology Department, Zagazig University,

Egypt from June 2019 to June 2020. According to Rotterdam ESHRE/ASRM, 2004 criteria that is used to diagnose PCOS. Patients have been randomly divided into two groups, (27 patients) received Clomiphene citrate 100mg and (27 patients) received letrozole 5mg. Either Clomiphene citrate or Letrozole was administrated by mouth for 5 days from day 3 of menstrual cycle. Each patient had regimen for 3 subsequent cycles.sample calculated using Epi program, At confidence interval 95% and power of test 80%. A written informed consent was obtained from all cases and the Research Ethics Committee of the Faculty of Medicine, Zagazig University accepted the study, ZUIRB-3854 6\8\2017. The study was done according to the Code of Ethics of the World Medical Association (Declaration Helsinki) for Studies involving humans. Patients included in the current study are those with Polycystic Ovarian disease diagnosed by Rotterdam Criteria, aged 18-40 years, had an infertility duration lasted at least 1 year and Follicle stimulating hormone level <10 mIU/mL on day (2) of the cycle, and presented either with primary or secondary Infertility and semen analysis for the husband is normal according to WHO (2010) **[7]**. Patients who had history of operations in pelvis, endometriosis, inflammatory pelvic disorder, Abnormal tubal patency test, male causes of infertility, endocrinal disorders such as increased prolactin level, congenital adrenal hyperplasia, thyroid disorder and Cushing disease, pathology in the uterus such as fibroid, adenomyosis , polyps , any lesion in uterus seen by ultrasound and hysteroscopy or ovarian cysts as endometriosis, contraindication for induction as medical disorders, ovarian masses, chemotherapy, radiotherapy, drilling of PCO by laparoscope in previous 6 months, or history of induction of ovulation or other medications as metformin in the previous six months were excluded from the study. All patients underwent comprehensive history, general, abdominal, and local examination. Basal hormonal studies on Day 2 of cycle included FSH, LH, PRL and TSH were measured. A transvaginal ultrasound examination was performed by Medisone sono Ace R5 Korea 2013 on day 3 of the cycle to evaluate (thickness and pattern of the endometrium, Doppler of spiral and uterine arteries) before starting induction. Induction by either clomiphene citrate in Group 1 or letrozole in Group 2 for 5 days starting from day 3 of menstrual cycle. Ultrasound per vagina for monitoring of follicular size has been performed from day 10 of the cycle and then day after day to reach at least one follicle with a diameter equal to or greater than 16 mm, HCG 10,000IU was administered to enhance ovulation **[8]**. Endometrial thickness, pattern, uterine and spiral artery Doppler indices were measured by ultrasound on HCG injection day. The endometrial thickness was measured at the maximum diameter vertical to the mid-sagittal plane in the most upper zone, including both endometrial layers **[9]**. A multilayered (pattern I) and a non-multilayered (pattern II) endometrium were found to occur as two types of endometrial pattern. Measurement of uterine artery Doppler flow velocity using color Doppler ultrasound in two dimensional mode , flow velocity waveforms were obtained from the main branch of the uterine artery on both sides of the uterus in the longitudinal plane before entering the uterus, the Doppler gate was placed when a vessel with clear color signals was detected on the screen, the pulsatility index and resistance index of the uterine arteries were determined automatically when obvious wave was achieved. Both uterine artery Doppler indices were measured, and the mean was determined. The color power Doppler signal at the edge of the endometrial line (1–2mm of the endometrial line) was calculated and spiral artery Doppler indices were determined (RI and PI). The dominant follicle was graded using power Doppler depending on a subjective grading system. A comparison between the effect of clomiphene citrate and letrozole on the endometrial thickness, endometrial pattern, Doppler indices of the uterine and spiral arteries and perifollicular blood flow on day of HCG injection for 3 consecutive cycles. pregnancy test (BHCG) is performed after 14 days from expected menses. The outcomes of the study were either primary outcomes as effect on endometrial thickness, pattern, Doppler indices of uterine and spiral arteries, perifollicular blood flow and ovulation rate or secondary outcomes as pregnancy rate and incidence of complications as ovarian hyper stimulation syndrome.

STATISTICAL ANALYSIS

The data were reviewed, entered, and analyzed using SPSS version 23 for processing of data, and expressing it as number and percentage for qualitative data and mean + standard deviation (SD) for quantitative ones and we compare data using the 't' test to compare the mean of two independent classes. The results of the "t" value was reviewed using student "t" table at degree of freedom (df=n1 +n2 – 2) to detect the level of significance (p-value).

Table (1): Comparing endometrial thickness between the two studied groups (basal and on day of HCG administration)

	Clomiphene citrate group (N=27)	letrozole group (N=27)	T	P
Basal Endo thickness (mm)	4.85±1.59	4.97±1.65	0.231	0.818
Endometrial thickness (1st cycle)	9.71±2.83	10.07±1.35	1.263	0.228
Endometrial thickness (2nd cycle)	8.77±2.65	9.07±1.38	1.128	0.237
Endometrial thickness (3rd cycle)	8.88±2.69	9.29±1.35	1.026	0.289

HCG: human chorionic gonadotropin. N: number. T: T-test. P: p-value.

Table (2): Comparing Mean uterine artery(a) and spiral artery (b)Doppler indices between the two studied groups

	Clomiphene group N=27(a)	letrozole group N=27(a)	T(a)	P(a)	Clomiphene group N=27(b)	Letrozole group N=27(b)	T(b)	P(b)
RI Basal	0.83±0.071	0.86±0.13	0.712	0.591	0.86±0.04	0.88±0.04	1.686	0.089
PI Basal	2.27±0.53	2.42±0.38	1.706	0.094	1.29±0.08	1.32±0.15	1.934	0.058
RI on day of HCG administration of 1st cycle	0.80±0.12	0.72±0.08	2.512	0.008*	0.70±0.05	0.69±0.04	0.479	0.634
PI on day of HCG administration of 1st cycle	1.84±0.48	1.82±0.31	.412	0.831	1.173±0.09	1.17±0.17	0.096	0.924
RI on day of HCG administration of 2nd cycle	0.82±0.11	0.73±0.13	2.597	0.007*	0.71±0.05	0.71±0.05	0.616	0.540
PI on day of HCG administration of 2nd cycle	1.88±0.48	1.82±0.31	.841	0.511	1.19±0.11	1.18±0.19	0.111	0.912
RI on day of HCG administration of 3rd cycle	0.84±0.09 (N=26)	0.72±0.08 (N=26)	2.917	0.002*	0.71±0.05 (N=26)	0.71±0.05 (N=26)	0.616	0.540
PI on day of HCG administration 3rd cycle	1.83±0.46 (N=26)	1.81±0.31 (N=26)	.451	0.798	1.19±0.12 (N=26)	1.18±0.19 (N=26)	0.111	0.912

RI: resistance index. PI: pulsatility index. T: t –test. P: p-value

Table (3): Comparing Peri- follicular vascularity between the two studied groups on day of HCG administration.

	Clomiphene citrate group	letrozole group	T	P
Peri follicular blood flow (1st cycle) (in % of follicular circumference)	45.37±5.7(G2) (n=17)	71.29±6.87(G3) (n=19)	15.254	0.00**
Peri follicular blood flow (2nd cycle) (in % of follicular circumference)	45.18±6.7(G2) (n=18)	71.85±7.15(G3) (n=20)	13.998	0.00**
Peri follicular blood flow (3rd cycle) (in % of follicular circumference)	46.48±7.1(G2) (n=20)	70.74±6.75(G3) (n=21)	12.812	0.00**

G: Grade. T:t-test. P: p value

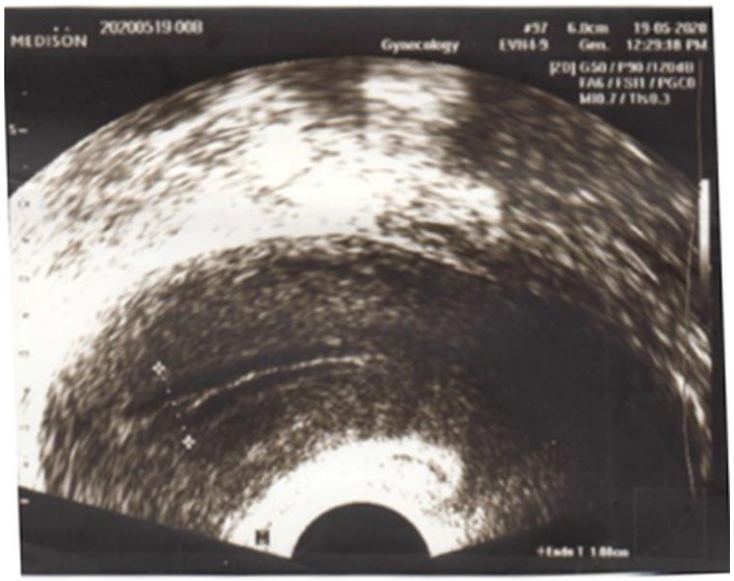

Figure (1) Tri-laminar pattern endometrium after induction by clomiphene citrate.

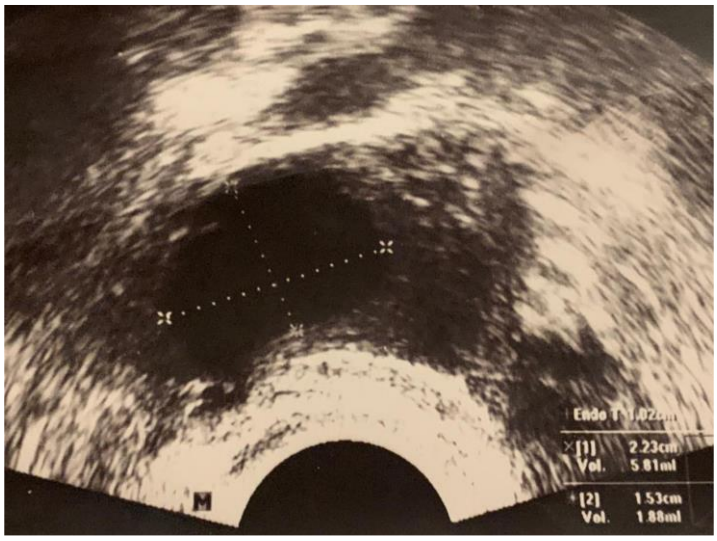

Figure (2) Mean Follicular diameter 19 mm after induction by letrozole

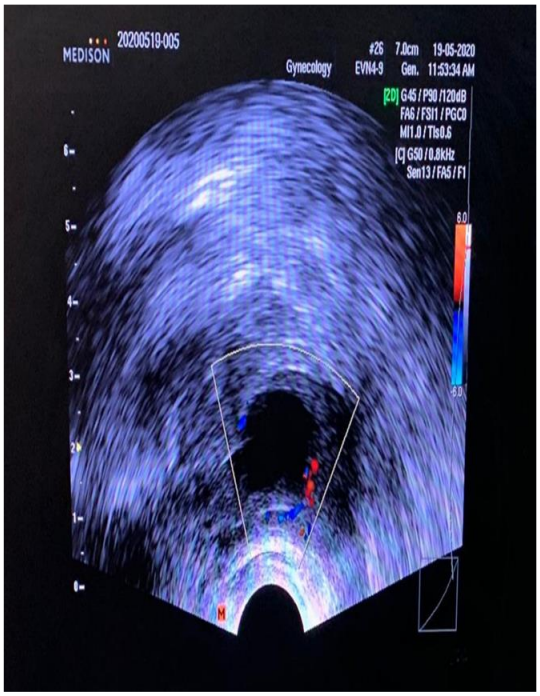

Figure (3) (a) Perifollicular vascularity after induction by clomiphene citrate (Grade2). (b) perifollicular vascularity after induction by letrozole (Grade3).

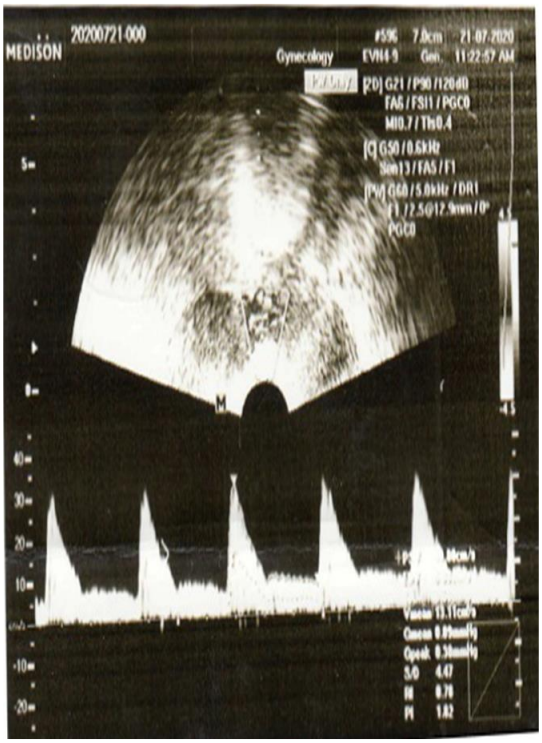

Figure (4) (a) Uterine artery Doppler indices after induction by Letrozole RI=0.78, PI=1.82). (b) spiral artery Doppler indices after induction by clomiphene citrate

RESULTS

The study initially included 58 cases, but 4 cases were excluded due to missed follow up or non-compliance to the drug regimen, thus 54 cases were included and divided into 2 groups, clomiphene

citrate group (27cases) and letrozole group (27cases).

There was no valuable difference in thickness of the endometrium between the two groups tested. (Table 1).

There was no valuable difference between the two groups examined regards basal RI or PI of the uterine artery, but RI was significantly lower at letrozole group on day of HCG injection of the three cycles and no valuable difference regard PI between the two groups tested (Table 2a)**.**

There was no valuable difference between the two groups tested regards spiral artery Doppler indices (RI&PI) (Table 2b).

There was highly valuable difference between the two groups tested on day of HCG injection regards peri- follicular blood flow. Mean peri follicular blood flow is (Grade2) defined as 25% - < 50% of circumference of the dominant follicle has color Doppler blood flow in clomiphene citrate group and (Grade3) defined as 50% - <75% of circumference of the dominant follicle has color Doppler blood flow in letrozole group (Table 3).

There was no valuable difference between the two groups tested as regard to pattern of the endometrium. (Figure 1).

There was no valuable difference as regard to mean follicular diameter between the two groups examined (Figure 2).

There was highly valuable difference between the two groups examined on day of HCG injection as regard to peri- follicular blood flow. Mean peri follicular blood flow is (Grade2) in clomiphene citrate group and (Grade3) in letrozole group (Figure 3). (a&b)

There was no valuable difference between the two groups examined regards basal RI or PI of the uterine artery, but RI was significantly lower at letrozole group on day of HCG injection of the three cycles and no valuable difference regard PI between the two groups tested also there was no valuable difference between the two groups tested regards spiral artery Doppler indices (RI&PI) (Figure 4) (a&b)

DISCUSSIONS

It was detected that there was no valuable difference between letrozole and clomiphene citrate groups regarding basal endometrial thickness (Day3) (4.97±1.65, 4.85±1.59) respectively but there was difference regarding endometrial thickness on day of HCG injection for 3 subsequent cycles. Thicker endometrium was in (letrozole) group compared to clomiphene citrate one (10.07±1.35, 9.07±1.38, 9.29±1.35), (9.71±2.83, 8.77±2.65**,** 8.88±2.69) respectively but the difference was not statistically significant.

This was in agreement with a study that was performed by **[10, 11]**, who found that a higher endometrial thickness on HCG injection day in favor of Letrozole and expected higher pregnancy rate.

This was in contrast with a study that was performed by **[12]** who found that the endometrial thickness with clomiphene citrate was significantly higher than that with letrozole.

It was detected that the percentage of multilayered endometrial pattern on day of HCG administration in letrozole group was higher compared with clomiphene citrate group in 3 subsequent cycles, in letrozole group (62.9%, 66.7%, 70.4%) and clomiphene citrate group (55.6%, 59.3%, 62.9%) but this difference was not statistically significant. It was in agreement with a study that was performed by **[13]** who found that the percentage of multilayered endometrial pattern in letrozole group was increased on HCG injection day relative to the clomiphene citrate group (77.5 % vs. 55.0 %), but this difference was statistically significant

It was noticed that there was no significant difference between the two groups examined as regard to mean follicular diameter and number on HCG injection day of the 3 subsequent cycles. It was in agreement with **[14]** who stated that average size of the largest mature follicle was larger in letrozole group relative to clomiphene citrate group but with no significant difference but these results came in contrast with that of **[15]** who noticed that the number of mature ovarian follicles (greater than 16 mm) during the third cycle was significantly higher in cases who received clomiphene citrate than in those who received letrozole, but it was equal in both groups in first and second cycles.

It was found that there was no significant difference between the two groups examined regarding basal RI of the uterine artery (p value.591) or basal PI of the uterine artery (p value.094), but RI was significantly decreased in letrozole group on HCG injection day of the 3 consecutive cycles (p value 0.008*, 0.006*, 0.002*) but no significant difference regarding PI on HCG injection day of 3 consecutive cycles between both groups (p value 0.276, 0.261,0.245).

This was in agreement with a study that was performed by **[16]** who stated that RI of the uterine artery decreased after induction by either clomiphene citrate or letrozole compared to control group but with no significant difference as regard PI in letrozole, clomiphene citrate and control group in

that order. but these results came in contrast with a study that was done by **[17]** who reported that there was no significant difference in uterine artery Doppler pulsatility index (PI) and resistance index (RI) between the Clomiphene citrate group and the Letrozole one.

There was no significant difference between the two groups examined regards both basal spiral artery Doppler indices RI (p value .089), PI (p value .058) and on HCG injection day of the 3 consecutive cycles (p value for RI 0.634, 0.540, 0.540) and p value for PI (0.924, 0.912, 0.912) for clomiphene citrate and letrozole groups.

This agreed with a study that was performed by **[18]** who reported that there were no major variations between letrozole and clomiphene citrate groups in the Doppler flow indices of spiral artery on the day of the LH surge and in the luteal process. But these results came in contrast with **[19, 20, 21]**, who found that there was significant difference in the spiral artery Doppler indices (RI, PI) between clomiphene citrate group and letrozole group.

There was a highly significant difference between the two groups regards peri-follicular vascularity on day of HCG administration in the 3 consecutive cycles with mean peri-follicular blood flow was in (Grade2) in clomiphene citrate group and was in (Grade3) in letrozole group (p value 0.00**).

This agreed with [**22**] who reported that Perifollicular blood flow is important inoocyte quality, implantation success and embryo quality and higher pregnancy rates in letrozolethan clomiphenecitrate caused by higher grade perifollicular blood flow in letrozole group. These results appeared in contrast with a study that was performed by **[23**] who reported that the highest ranking of perifollicular blood flow and the number of patients with high-grade perifollicular blood flow were found to be similar in both groups.

There was no significant difference regarding incidence of OHSS between the two studied groups (2 cases in clomiphene citrate group (7.4%) and1 case in letrozole group (3.7%) This was in contrast with a study that was performed by **[24]** who found that the incidence of OHSS was significantly lower in theletrozole group compared with clomiphene citrate group but was in agreement with **[25]** who stated that OHSS rates are similar with letrozole and clomiphene citrate groups.

CONCLUSIONS

Both Clomiphene citrate and letrozole increase perifollicular blood flow with a significant difference in favor to letrozole, in letrozole group most of follicles were (grade3) and in Clomiphene citrate group were (grade2).

REFERENCES

[1] **Escobar-Morreale HF.** Polycystic ovary syndrome: definition, aetiology, diagnosis and treatment. Nat Rev Endocrinol. 2018; 14(5): 270.

[2] **Kabel AM.** Polycystic ovarian syndrome: insights into pathogenesis, diagnosis, prognosis, pharmacological and non-pharmacological treatment. J Pharma Reports. 2016; 1(103): 2.

[3] **Carmina E, Azziz R.** Diagnosis, phenotype, and prevalence of polycystic ovary syndrome. Fertil Steril. 2006; 86, S7–S8.

[4] **Costello M, Garad R, Hart R, Homer H, Johnson L, Jordan C, et al.** A review of first line infertility treatments and supporting evidence in women with polycystic ovary syndrome. Med Sci. 2019; 7(9): 95.

[5] **Kamath MS, George K.** Letrozole or clomiphene citrate as first line for anovulatory infertility: a debate. Reprod. Biology and Endocrinology. 2011; 9(1):1–4.

[6] **Chien LW, Lee WS, Au HK, Tzeng CR.** Assessment of changes in utero-ovarian arterial impedance during the peri-implantation period by Doppler sonography in women undergoing assisted reproduction. Ultrasound in Obstetrics and Gynecology: Ultrasound Obstet Gynecol. 2004; 23 (5): 496–500.

[7] **Cooper TG, Noonan E, Von Eckardstein S, Auger J, Baker HW, Behre HM, et al.** World Health Organization reference values for human semen characteristics. Hum Reprod Update. 2010;16 (3), 231–45.

[8] **Badawy A, Aal IA, Abulatta M.** Clomiphene citrate or letrozole for ovulation induction in women with polycystic ovarian syndrome: a prospective randomized trial. Fertil Steril, 2009; 92(3): 849–52.

[9] **Gallos ID, Khairy M, Chu J, Rajkhowa M, Tobias A, Campbell A, et al.** Optimal endometrial thickness to maximize live births and minimize pregnancy losses: Analysis of 25,767 fresh embryo transfers. Reprod Biomed Online. 2018; 37:542–8.

[10] **Begum RM, Ferdous J, Begam A, Quadir E.** Comparison of efficacy of aromatase inhibitor and clomiphene citrate in polycystic syndrome. Fertil Steril. 2009; 92(3);85: 853–7.

[11] **Zhang H, Li L, Li Q.** Effects of letrozole versus clomiphene citrate on endometrial receptivity in mouse. Reproduction and contraception-shanghal-institute of planned parenthood research. 2007; 27(4), 251.

[12] **Garg N, Vanitha VG.** A Comparative Study of Letrozole Vs Clomiphene Citrate as First Line for

Anovulatory Infertility–An Institutional Experience. Asian Res J Gynaecol Obstet. 2019; 11:1–8.

[13] Zhao J, Zhang Q, Wang Y, Li Y. Endometrial pattern, thickness and growth in predicting pregnancy outcome following 3319 IVF cycle. Reprod Biomed Online. 2014; 29(3): 291–8.

[14] Brown, J, Farquhar C. Clomiphene and other antioestrogens for ovulation induction in polycystic ovarian syndrome. Cochrane Database Syst Rev., 12 (2016).

[15] Palihawadana T, Wijesinghe P, Seneviratne H. A comparison of endometrial thickness following augmentation of ovulation with clomifene citrate or letrozole in women with ovulatory infertility. Ceylon Med. 2015; 60 (2): 48–52.

[16] Kupesic S, Bekavac I and Kurjak A. Assessment of endometrial receptivity by transvaginal color Doppler and three dimentional power Doppler ultrasonography in patients undergoing in vitro fertilization procedures J ultrasound Med. 2001; 20(2): 125–134.

[17] Chien LW, Lee WS, Au HK, Tzeng CR. Assessment of changes in utero-ovarian arterial impedance during the peri-implantation period by Doppler sonography in women undergoing assisted reproduction. Ultrasound Obstet Gynecol. 2004; 23(5):496-500. PMID: 15133803

[18] Ng EHY, Chan CCW, Tang OS, Yeung WSB, Ho PC. Endometrial and sub endometrial blood flow measured during early luteal phase by three-dimensional power Doppler ultrasound in excessive ovarian responders. Hum Reprod. 2004; 19:924–31**.**

[19] Schild RL, Knobloch C, Dorn C, Fimmers R, Van Der Ven H, Hansmann M. Endometrial receptivity in an in vitro fertilization program as assessed by spiral artery blood flow, endometrial thickness, endometrial volume, and uterine artery blood flow. Fertil Steril, 2001; 75(2), 361–366.

[20] Zhao M, Chang C, Liu Z, Chen LM, Chen Q. Treatment with low-dose aspirin increased the level LIF and integrin beta3 expression in mice during the implantation window. Placenta. 2010; 31(12):1101–5.

[21] Chen XY, Chen J, Wang ZY, Yu XH, Wei BX, Wu XH. Effects of modified Shoutaiwai recipe on integrin β3 and leukemia-inhibitory factor in endometrium of controlled ovarian hyperstimulation mice during the implantation window. Genet Mol Res. 2015; 14(2): 2970–7.

[22] Van Blerkom J. Intrafollicular influences on human oocyte developmental competence: perifollicular vascularity, oocyte metabolism and mitochondrial function. Hum Reprod. 2000;15 Suppl 2:173-88. doi: 10.1093/humrep/15.suppl_2.173. PMID: 11041523**.**

[23] Palomba S, Russo T, Falbo A, Orio Jr F, Manguso F, Nelaj E, et al. Clinical use of the perifollicular vascularity assessment in IVF cycles:a pilot study. Hum Reprod. 2006; 21:1055–61

[24] Humaidan P, Nelson SM, Devroey P. Ovarian hyperstimulation syndrome: review and new classification criteria for reporting in clinical trials. Hum Reprod. 2016; 31(9).

[25] PAK A, Rozenberg S. Epidemiology and prevention of ovarian hyperstimulation syndrome (OHSS): a review. Hum Reprod Update, 2002; 8(6): 559–577

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