Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://dx.doi.org/10.21608/zumj.2020.37755.1910 Volume 29, Issue 1, - January 2023, Page (142-148) Supplement Issue

Manuscript ID ZUMJ-2008-1910 (R3)
DOI **10.21608/zumj.2020.37755.1910**

ORIGINAL ARTICLE

The Efficacy of phytoestrogens with Clomiphene Citrate for Ovulation Induction in Women with Polycystic Ovary Syndrome.

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Submit Date 2020-08-06
Revise Date 2020-09-14
Accept Date 2020-11-07

ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is the commonest endocrine disorder in premenopausal women. This study aimed to evaluate the efficacy of isoflavonoids with clomiphene citrate during ovulation induction in PCOS women on the endometrial thickness which has an impact on pregnancy rate.

Patients and methods: A prospective randomized clinical trial study was carried in Gynecology and Obstetrics Department, Zagazig University Hospitals on 160 infertile PCOS patients during the period from January 2019 to November 2019 to assess the effect of isoflavonoids in patients managed by clomiphene ovulation induction, triggered by HCG injection. All patients were divided into two groups: **group I:** included 80 women receiving Clomiphene citrate (CC) plus Isoflavonoids. **Group 2**: included 80 women receiving Clomiphene citrate only.

Results: showed that the days till HCG injection were lower significantly in group I compared to group II which indicate better ovulation. As for the endometrial thickness, it was higher significantly in group I compared to group II. The number of ovulatory follicle(s) as single, two or three showed no statistical significant difference between the studied groups. The number of pregnancies was higher significantly in group I where phytoestrogens were added to CC than group II. On the other hand, there was no statistical significant difference between the studied groups as regard the number of biochemical pregnancies between group I and group II.

Conclusion: current results showed that Phytoestrogen (PE) (Isoflavonoids) with CC induced cycles, improved the endometrial thickness, promoted follicular maturation in a shorter time and also improved clinical pregnancy rates.

Keywords: Human chorionic gonadotropin, clomiphene Citrate, Isoflavonoids, polycystic ovary syndrome.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common cause of anovulatory infertility, affecting approximately 4% to 18% of reproductive-aged females worldwide **[1].**

Anovulatory infertility mostly treated with ovulation stimulating agents such as antiestrogens (clomiphene citrate, tamoxifen) and gonadotrophins (luteinizing hormone LH and follicle stimulating hormone FSH), and aromatase inhibitors **[2].**

Clomiphene citrate (CC) is commonly used as a first-choice treatment for infertility Clomiphene citrate binds with hypothalamic estrogen receptors exerting antiestrogenic effect, the block of receptors simulates the release of gonadotropin-releasing hormone (GnRH) which simulates the anterior pituitary gland for gonadotropin secretion **[3]**.

Clomiphene citrate is successful in ovulation induction in 80% of cases, however the cumulative pregnancy rates reach 30-40% only after its use for a few cycles. The discrepancy between ovulation and cumulative pregnancy rates is due to the antiestrogenic effects of CC on both endometrial lining and the quality of cervical mucus **[4]**.

Phytoestrogens are natural compounds with estrogenic activity that occur in many plants and fungi**.** In general, phytoestrogens such as soy isoflavones, have been thought to have predominant affinity to estrogen receptor beta(ER β) **[5].**

The administration of a high dose of phytoestrogens (500 mg of isoflavones containing genistein, diadzein and glycitein) along with CC significantly increased endometrial thickness and improved both clinical and ongoing pregnancy rates compared with CC treatment alone **[6]**.

This study aimed to evaluate the efficacy of isoflavonoids with clomiphene citrate during ovulation induction in PCOS women on the endometrial thickness which has an impact on pregnancy rate.

PATIENTS AND METHOD

This prospective, randomized clinical trial study has been carried out in Gynecology and Obstetrics Department, Zagazig University Hospitals conducted on one hundred and sixty (160) infertile patients seeking pregnancy to evaluate the effect of follicular phase oral isoflavonoids in patients with PCOS, managed by clomiphene ovulation induction, triggered by HCG injection, in terms of endometrial thickness, follicular maturation and pregnancy rate, during the period from January 2019 to November 2019.

Written informed consent was obtained from all participants and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The st udy was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Inclusion criteria: Patient aged 18- 30 years old with at least two years of infertility or patient aged 30- 35 years old with at least one year of infertility. Diagnosis of PCOS according to Rotterdam criteria [7] demonstrating two of the three criteria (Oligo or anovulation, Clinical and/or biochemical signs of hyperandrogenism, Polycystic ovaries on ultrasonography (12 or more follicles). After exclusion other causes of androgen excess. Primary and secondary infertility. Normal uterus by trans-vaginal ultrasound. Proved patency of at least one fallopian tube diagnosed by hysterosalpingography, sonography and/or laparoscopy. Normal semen analysis according to [8].

Exclusion criteria: Patient whose husband has a male factor of infertility. Hepatic, renal, diabetic, thyroid or cardiovascular disorders. Organic pelvic disease (uterine fibroids or ovarian cysts). Previous pelvic surgery such as laparoscopic ovarian drilling. Abnormality detected by HSG as blocked tubes.

All Patients were subjected to:

Complete history taking (Personal history including: name, age, telephone no and address).

Menstrual history: including age of menarche, menstrual disturbance, dysmenorrhea, related symptoms.

Obstetric history: including parity and mode of delivery.

Present history: of chronic diseases and medication.

Past history of HTN, DM.

Family history of similar condition or diabetes.

History of allergy to any medication.

Surgical history of operation, laparoscopic interference, treatment of hirsutism by laser.

General examination: Evaluation of vital signs. Measurement of weight and height (BMI). Inspection: hyperandrogenic manifestation e.g. hirsutism, acne. Examination of thyroid gland. Breast examination to exclude presence of galactorrhea. Abdominal and local clinical examination for hair distribution, scar of previous operation, mass, tenderness or rigidity, any abdominal or pelvic clinically detectable pathology.

Bimanual pelvic examination of both adnexa, and uterus for detection of any abnormality of female genitalia.

Investigations:

Basal hormonal studies on day 2 of cycle included serum FSH, LH, androgen level, prolactin level and TSH was measured.

Basal transvaginal U/S on day 3 of the cycle to examine each ovary for detecting criteria of PCOS and count number of antral follicle in both ovaries and to measure basal endometrial thickness.

All patients were divided into two groups:

The 1st group (study group): included eighty (80) women, Stimulation began on day 3 with the administration of 100 mg of CC daily for 5 days From day 3 and for 10 days they received phytoestrogen 1500 mg daily [6].

The 2nd group (control group): included eighty (80) women receiving Clomiphene citrate only, at dose (100 mg/day, starting from day 3 to day 7 of the cycle).

Follow up

Technique of trans-vaginal ultrasound: Voluson 730 ProV (Model:AY_15CUK, Korea), each patient is advised to empty bladder before examination, procedure was carried for women in lithotomy position, transducer was covered by gel, introduced into latex condom which was again lubricated with gel before insertion.

Transducer was introduced into posterior vaginal fornix and scanning was done, starting with uterus, next ovaries followed with fallopian tubes.

Endometrial thickness was measured as maximal thickness between the highly reflective interfaces of endometrial myometrial junction.

Follicular monitoring carried out for both groups with transvaginal ultrasound with same technique, started from 9 day of cycle till attaining a mature follicle with a mean diameter of 18-22 mm, number and size of dominant follicle, endometrial thickness and pattern were reported on day of HCG administration. Then single injection of HCG (Pregnyl, Organon, Holland, 10,000 IU, I.M) was given for triggering ovulation.

Timed intercourse was advised from the day of HCG and for 4 days. Clinical pregnancy detected by serum pregnancy test and transvaginal U/S which detect intrauterine gestational sac and fetal pulsation. Follow up of both groups was done for 1 cycle.

Outcome measures:

Primary outcome: Clinical pregnancy rate (defined as the presence of gestational sac containing fetal hearts on ultrasound scan).

Secondary outcome: Endometrial thickness, ovulation rate.

Statistical Analysis: Analysis of data was carried out using statistical package of social science (SPSS version 20). Description of quantitative variables was given as mean, and Standard deviation (SD). Chi square test (χ^2 –test) was used to compare qualitative variables between groups. The t-test was used to compare quantitative variables in parametric data. The Z-test was used for proportions. P-values less than 0.05 will be considered significant and P values less than 0.01 were considered highly significant.

RESULTS

Table (1), showed that there was no statistically significant difference between the two studied groups in age, weight, height and BMI. Table (2), showed that there was no statistical significant difference between the two studied groups in type of infertility with (56.3%) of the isoflavonoids plus clomiphene citrate group was primary infertility type while (51.3%) of clomiphene citrate group only was secondary infertility type. Table (3), showed that the endometrial thickness on day of HCG injection was significantly higher in group I (9.1±0.7) mm than group II (7.5±1.1) mm, however the days till HCG injection were significantly lower in group I (13.8±1.8) days where isoflavonoids were added to CC than group II (14.9±2.1) days where CC was used only. Table (4), showed that there was no statistical significant difference between the two studied groups in number of pre-ovulatory follicles (≥18mm) with (48.7%) of the isoflavonoids plus clomiphene citrate group had two pre-ovulatory follicles (≥18mm) while in clomiphene citrate group only (50.0%) had two pre-ovulatory follicles (≥18mm). Table (5), showed that there was statistically significant difference between the two studied groups in total pregnancies with (43.7%) of the isoflavonoids plus clomiphene citrate group had pregnancies divided into (37.5%) had clinical pregnancies at 6 weeks and (3.7%) had miscarriage while in clomiphene citrate group only (32.5%) had pregnancies divided into (23.8%) had clinical pregnancies at 6 weeks and (5.0%) had miscarriage. Regarding biochemical pregnancies, there was no statistically significant difference between the two studied groups with (2.5%) of the 1st group had biochemical pregnancies while (3.7%) of the 2nd group had biochemical pregnancies.

Table (1): Comparing demographic data between the two studied groups:

Variable	1st group (80) mean ± SD range	2nd group (80) mean ± SD range	t-test	p-value
Age (years)	26.3 ± 3.4 (18-35)	25.8 ± 4.5 (18 -35)	1.3	0.3
Weight (kg)	79.8 ± 8.4 (60-90)	75.6 ± 4.6 (63 -92)	1.5	0.4
Height (cm)	162.3 ± 7.6 (145-178)	159.6 ± 4.8 (143 -179)	0.9	0.7
BMI (kg/M^2)	31.9 ± 4.2 (20-37)	30.6 ± 4.6 (20 -35)	1.2	0.4

Table (2): Comparing type of infertility between the two studied groups:

Type of infertility	1st group		2nd group		χ^2	p-value
	No. (80)	%	No. (80)	%		
Primary	45	56.3	39	48.7	1.8	0.07
Secondary	35	43.7	41	51.3		

Table (3): Comparing days till HCG injection and endometrial thickness at day of HCG injection between the two studied groups

Variable	1st group (80) mean± SD range	2nd group (80) mean± SD range	t-test	p-value
Basal endometrial thickness	3.98±0.5 (3.5-4.5)	4.12±0.6 (3.5-4.7)	0.86	0.3
Endometrial thickness at day of HCG injection	9.1±0.7 (7.3-10.1)	7.5±1.1 (6 -9.1)	6.7	0.001**
Days till HCG injection	13.8±1.8 (11-15)	14.9±2.1 (11 -16)	4.9	0.001**

* Statistically significant difference (P ≤ 0.05)

Table (4): Comparing number of women with mature pre-ovulatory follicles (≥ 18 mm) between the two studied groups:

Variable	1st group		2nd group		χ^2	p-value
	No.(80)	%	No.(80)	%		
Single pre-ovulatory follicles ≥ 18 mm	19	23.7	21	26.3	1.9	0.08
Two pre-ovulatory follicles ≥ 18 mm	39	48.7	40	50.0		
≥ Three pre-ovulatory follicles ≥ 18 mm	22	27.6	19	23.7		

Table (5): Comparing the pregnancy outcome between the two studied groups:

Variable	1st group		2nd group		χ^2	p-value
	No. (80)	%	No. (80)	%		
Clinical pregnancies at 6 weeks NO = (49)	30	37.5	19	23.8	8.9	0.002*
Miscarriage NO = (7)	3	3.7	4	5.0		
Biochemical pregnancies NO =(5)	2	2.5	3	3.7		
Total pregnancies NO = (61)	35	43.7	26	32.5		

* Statistically significant difference (P ≤ 0.05)

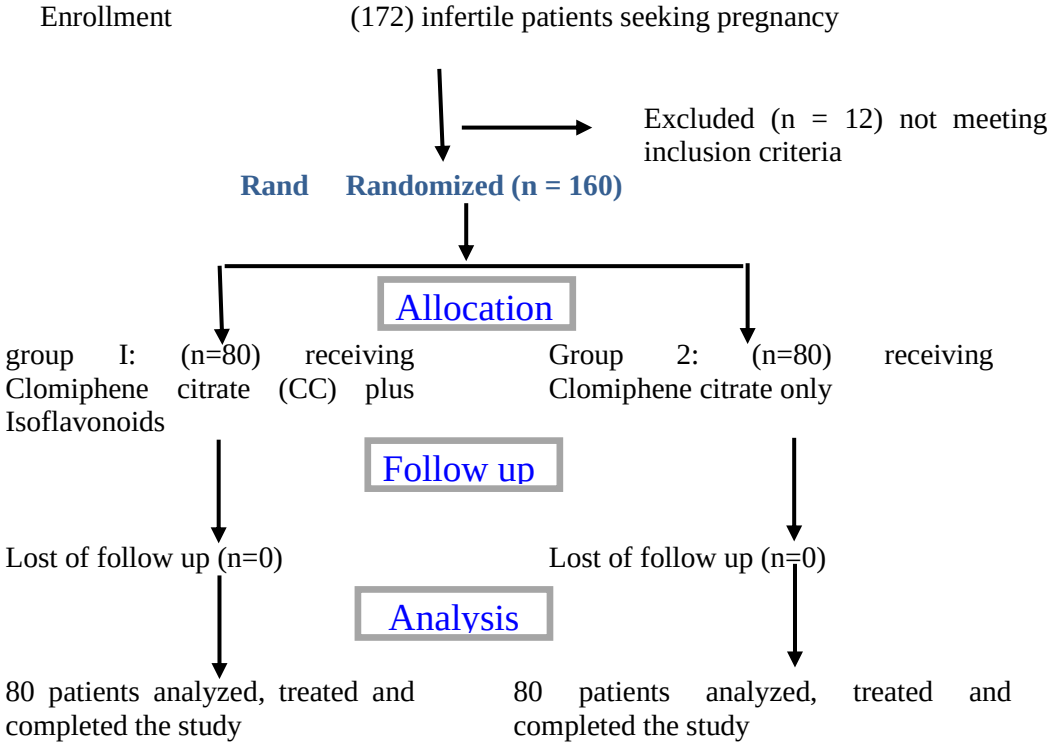

Fig. (1) : Flow chart of patients in the studied group

DISCUSSION

Polycystic ovary syndrome (PCOS) is the most common cause of an-ovulatory infertility. Anovulatory infertility is treated with ovulation stimulating agents as antiestrogens (clomiphene citrate,tamoxifen) and gonadotrophins (follicle stimulating hormone FSH, and luteinizing hormone LH), and aromatase inhibitors [9].

Clomiphene citrate (CC) is most commonly used as a first-line treatment of infertility **[10].** It is an estrogen analog that was first used in induction of ovulation in 1961, and clinically approved in the United States in 1967, Clomiphene exerts both estrogen agonist effects and antagonist effects [4].

Phytoestrogens are natural compounds with estrogenic activity that occur in many plants and fungi. In general, phytoestrogens such as soy isoflavones, have been thought to have predominant affinity to estrogen receptor beta(ER β) [11].

The current study showed that both groups were matched with no statistically significant difference between them in age, weight, height and BMI (groups). Their age was (26.3±3.4 VS 25.8±4.5) years, their weight was (79.8±8.4 VS 75.6±4.6) kg, their height was (162.3±7.6 VS 159.6±4.8) cm and their BMI was (31.9±4.2 VS 30.6±4.6) (kg/M2) in 1st and 2nd group respectively**,** which in agreement with the study conducted of **Unfer et al., [6]** whose study included 134 women divided into two groups 1st group consisted of 65 women who received clomiphene citrate plus phytoestrogens and 2nd group consisted of 69 women who received clomiphene citrate only with no statistically significant difference between both groups in age (28±5.6 VS 26 ± 4.2) years in 1st and 2nd group respectively. Also in agreement with **Shahin et al., [11]** who found no statistically significant difference between clomiphene citrate plus phytoestrogens and clomiphene citrate only groups in age (25.3±3.4 VS 25.3±3.1) years and in BMI (27 ± 2.1VS 26 ± 1.4) in 1st and 2nd group respectively in a study contained 147 women.

The same results were reported by **Maged and Deeb [4]** whose study included 150 women with PCOS were randomly into 3 groups clomiphene citrate plus phytoestrogens, Clomiphene citrate plus estradiol and Clomiphene citrate only groups with no statistically significant difference between the three studied groups in age, BMI, type and duration of infertility.

The current study that there was no statistical significant difference between the two studied groups in type of infertility with (56.3%) of the isoflavonoids plus clomiphene citrate group had primary infertility type while (48.7%) of clomiphene citrate group only had primary infertility type, this was in agreement with the study of **Shahin et al., [11]** where (28.3%) of the phytoestrogen plus clomiphene citrate group had primary infertility type while (25.4%) of clomiphene citrate group only had primary

infertility type with no statistically significant difference between the two groups.

The current study showed that the days till HCG injection were significantly lower in group I (13.8±1.8) than group II (14.9 ±2.1) which indicate better ovulation, these results were in agreement with a study of **Shahin et al., [5]** who concluded that the days till HCG injection were significantly lower in the group where phytoestrogen was added to CC than the second group where CC was used with ethinyl estradiol**.**

Also, according to **Shahin and Mohammed [12]**, who concluded that women in (PE plus CC) group needed significantly shorter time to reach adequate maturation of follicles than in (CC only) group.

The present study showed that there was highly statistically significant difference between 1st and 2nd group patients in endometrial thickness at day of HCG injection which was higher in the first group (9.1±0.7)mm than second group (7.5±1.1)mm**,** this was in agreement with study of **Unfer et al. [6]** who found a statistically significant difference between the 2 groups regarding endometrial thickness it was thicker in group 2, also the study of **Shahin et al. [11]** whose study showed highly statistically significant increase in endometrial thickness in clomiphene citrate and phytoestrogen group than clomiphene citrate only (8.9 ± 1.4 mm versus 7.5 ± 1.3 mm respectively P < 0.001).

Also **Kamel [13]** who performed a study to evaluate the effects of a phytoestrogen in induction of ovulation in 100 patients with PCOS. He randomized them into two equal groups the first group received 100 mg of CC per day for 5 days while the second group were subjected to 20 mg of Cimicifuga racimosa extract (Klimadynon) for 10 successive days. The two study groups showed no significant differences regarding demographic data as age or clinically presenting symptoms or hormonal profile measured before the start of the medications. The women in the second group had a significant thicker endometrium was found in phytoestrogen group (p=0.0004).

Shahin and Mohamed [12] also had higher endometrial thickness in clomiphene citrate and phytoestrogen group than in clomiphene citrate only (12.5 ± 1.9 VS 8.5 ± 1.9 p < 0.001) mm and the same was found by **Elkhateeb [1]** endometrial thickness was greater in the clomiphene citrate and phytoestrogen group compared with clomiphene citrate only (10.3± 1.1 versus 8.2 ± 0.9).

Our study showed that there was no statistically significant difference between the two studied groups in number of pre-ovulatory follicles (≥ 18 mm) with (48.7%) of the isoflavonoids plus clomiphene citrate group had two pre-ovulatory follicles (≥ 18 mm) while in clomiphene citrate group only (50.0%) had two pre-ovulatory follicles (≥ 18 mm)**,** this was in agreement with the study of **Elkhateeb [1]** where higher but not statistically significant difference in number of pre-ovulatory follicles (≥ 17 mm) was present (3.7 ± 0.5 VS 3.2 ± 0.8) in the clomiphene citrate with phytoestrogen group compared and clomiphene citrate only respectively. The same results were proposed by some studies as the single, two and three pre-ovulatory follicles showed no significant difference between the studied groups either having CC alone or CC with phytoestrogen.

The present study showed that there was statistically significant difference between the two studied groups in total pregnancies with (43.7%) of the isoflavonoids plus clomiphene citrate group had pregnancies divided into (37.5%) had clinical pregnancies at 6 weeks, (3.7%) had miscarriage and (2.5%) had biochemical pregnancies while in clomiphene citrate group only (32.5%) had pregnancies divided into (23.8%) had clinical pregnancies at 6 weeks, (5.0%) had miscarriage and (3.7%) had biochemical pregnancies. this was in consistent with the study of **Unfer et al., [6]** who found that the miscarriage rate was 3.1% in the group treated with CC in combination with PE compared with 8.7% in the group treated with CC alone and the difference was statistically significant. At the same time, the percentage of the ongoing pregnancies was higher in the group treated with CC in combination with PE (20.0% VS4.4%; P < .05) than in the group treated with CC alone.

Also similar to **Shahin et al., [11]** the clinical pregnancy rate were significantly higher in CC in combination with PE compared with CC alone (36.7% versus 13.6%, P < 0.01, respectively).

Also **Elkhateeb [1]** study showed cumulative pregnancy rate in women received CC alone was lower than pregnancy rate in women received CC and phytoestrogens (34.2% versus 20.8%). But in contrary with **Kamel [13]** who found higher but clinically insignificant pregnancy rate between two groups (14.0% versus 21.1%).

CONCLUSION:

our results showed that phytoestrogen (PE) (Isoflavonoids) with CC induced cycles, improved the endometrial thickness, promoted follicular maturation in a shorter time and also, improved clinical pregnancy rates.

RECOMMENDATION:

Adding high dose of phytoestrogens to CC in peri-ovulatory period is recommended in patients with PCOS and had unexplained infertility. Further studies are needed to define the appropriate dose,

duration and type of phytoestrogen which prove most successful in improving pregnancy rate.

No Conflict of Interest

No financial disclosure

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How to cite

Albasri, F., Sarhan, A., abdo, A., Abdelrhman, A. The Efficacy of phytoestrogens with Clomiphene Citrate for Ovulation Induction in Women with Polycystic Ovary Syndrome. Zagazig University Medical Journal, 2023; (142-148): -. doi: 10.21608/zumj.2020.37755.1910