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Role of Different Ovulation Induction Protocols in Follicular Growth, Estradiol and Pregnancy Rates for Women with Unexplained Infertility and Polycystic Ovary Syndrome Undergoing Intrauterine Insemination

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Authors' contributions

This work was carried out in collaboration between all authors. Author MBMRF designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors SFH and RHE managed the analyses of the study. Author MTM managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: The study aimed to study the effects of ovulation induction programs on the number of pre-ovulatory dominant follicles and endometrial thickness, their effects on pre-ovulatory estradiol 2 levels, and to determine the favored ovulation induction protocol to attain better pregnancy results in polycystic ovary syndrome and unexplained infertility women.
Materials and Methods: Twenty unexplained infertile and thirty polycystic ovary syndrome women subjected to ovulation induction/intrauterine insemination were enrolled in this study. First ovulation induction protocol involved clomiphene citrate only, the second involved Gonal-f only, and the third involved combination of clomiphene citrate and Gonal-f. Immediately before triggering of ovulation, follicular parameters, endometrial thickness, and estradiol 2 mean levels were measured.
Results: Only two (4%) subjected to combination of clomiphene citrate and Gonal-f became pregnant. Combination of clomid and Gonal-f yielded better pre-ovulatory endometrial thickness and higher pre-ovulatory estradiol 2 mean levels for all cases.
Conclusions: Combination of clomid and Gonal-f attained better results.

Keywords: Clomid; Gonal-f; differentiated follicles; endometrial thickness; estradiol 2.

1. INTRODUCTION

Intrauterine insemination (IUI) was first reported by Dickinson in 1921. But it became popular in the 1980s [1]. Intrauterine insemination is considered the first therapeutic step in assisted reproductive technology due to its simplicity, easy management, low cost, and absence of serious complications [2]. Intrauterine insemination is mostly used in the treatment of infertile couples with various causes of infertility, including cervical factor, ovulatory dysfunction, endometriosis, immunological causes, male factor, and unexplained infertility factors [3].

This study aimed to study the effects of ovulation induction programs on the number of pre-ovulatory dominant follicles and endometrial thickness, their effects on estradiol 2 (E2) levels on the day of triggering of ovulation using human chorionic gonadotropin (hCG) administration and to determine the favored ovulation induction program to achieve better pregnancy results in unexplained infertile and polycystic ovarian syndrome women.

2. MATERIALS AND METHODS

2.1 Study Subjects

This study was conducted with study subjects at the consultant clinic of Higher Institute for Infertility Diagnosis and Assisted Reproductive Technologies at AL-Nahrain University in Baghdad/ Iraq during period from April 2015 to February 2016. The study cases involved 20 infertile women with unexplained infertility and 30 infertile women with polycystic ovary syndrome (PCOS) subjected to ovulation induction (OI) and intrauterine insemination (IUI). All study cases were chosen randomly. Their ages ranged from 21-35 years old. For unexplained infertility females, ten (50%) were with primary infertility and with duration of infertility ranged from two to eleven years and ten (50%) were with secondary infertility and with duration of infertility ranged from one to twelve years. For polycystic ovarian syndrome females, eighteen (60%) were with primary infertility and with duration of infertility ranged from two to fourteen years and twelve (40%) were with secondary infertility and with duration of infertility ranged from one to seven years.

The diagnosis of unexplained infertility implied that a couple had normal and timely ovulation, fallopian tube patency, normal integrity of the endometrial cavity, adequate cervical mucus production, timely development of endometrial secretory change, no pelvic endometriosis and adequate sperm production [4]. Unexplained infertility women were with normal levels of follicle-stimulating hormone, luteinizing hormone, prolactin, estradiol 2 and testosterone hormones measured on menstrual cycle day 2.

Inclusion criteria for the study cases with unexplained infertility were as follows: 21-35 years old, primary or secondary infertility, body mass index (BMI)<30 kg/m^2, and with normal hormonal levels on menstrual cycle day 2.

The diagnostic criteria for polycystic ovary syndrome were done according to the Rotterdam criteria [2003 European Society for Human

Reproduction and Embryology and American Society for Reproductive Medicine consensus (2003 ESHRE/ASRM consensus)] [5]. 2003 European Society for Human Reproduction and Embryology and American Society for Reproductive Medicine (2003 ESHRE/ASRM or Rotterdam) Guidelines involve patient with polycystic ovary disease demonstrate two of three criteria:

1- Oligo-or chronic anovulation.
2- Clinical and / or biochemical signs of hyperandrogenism.
3- Polycystic ovaries.

Exclusion of other etiologies of androgen excess and anovulatory infertility was necessary [5]. The excluded conditions included thyroid dysfunction, congenital adrenal hyperplasia, hyperprolactinaemia, androgen-secreting tumors, and Cushing's syndrome [6].

Inclusion criteria for the study cases with polycystic ovary syndrome were as follows: 21-35 years old, primary or secondary infertility, and diagnostic criteria according to Rotterdam criteria.

Women with endometriosis, tubal factor infertility, anatomical uterine pathological conditions, male factor infertility, and women with previous implantation failure or recurrent spontaneous abortion history were excluded from this study.

The diagnosis of unexplained infertility and polycystic ovary syndrome (PCOS) and the excluded cases were done by the specialist physician.

2.2 Ovulation Induction

Thirty infertile women with polycystic ovary syndrome and twenty infertile women with unexplained infertility were subjected to one of the following three ovulation induction protocols. First ovulation induction protocol involved the administration of clomiphene citrate (clomid; Patheon France S.A./France). After a spontaneous or progestagen induced withdrawal bleeding, clomid administration was started on day three of the menstrual cycle and continued for five days with a daily dose of 50 mg two times [7]. The starting dose was 50 mg, but if needed the dose could be increased by 50 mg daily during subsequent stimulation. Usually, a daily dose>150 mg was not recommended, as higher doses could compromise endometrial development and pregnancy rates would be very low [8]. Second ovulation induction protocol involved injectable follicle-stimulating hormone (FSH) (Gonal-f; Merck Serono S.A./ Schweiz). This protocol started in a dose of 75IU from day3 of menstrual cycle until the diameter of the leading follicle was ≥17 mm [9]. Third ovulation induction protocol involved combination of clomid and injectable FSH product (Gonal-f) by taking clomid pills daily from day 3 of the menstrual cycle to day 7 of the cycle and injectable FSH product (Gonal-f) started on day 10 at a dose of 75 units per day [10]. Any of the stimulation protocols was cancelled when more than three follicles larger than 12 mm in diameter were present [7]. Ovulation induction protocols were prescribed by the specialist physician.

2.3 Ultrasound Examination

Transvaginal ultrasound scan was performed to measure endometrial thickness and follicular parameters. Transvaginal ultrasound examination was initiated on day 10-12 of the menstrual cycle and then repeated every 1-2 days until one to two or three follicles were with a diameter of 16 to 18 millimeters before triggering of ovulation by hCG administration (OVITRELLE; Merck Serono S.P.A./Italy) [11,12]. On the day of triggering of ovulation by hCG administration, a transvaginal ultrasound scan was performed to measure endometrial thickness and to determine number and size of developing follicles [12]. Measurement of endometrial thickness was made from the outer edge of the endometrial-myometrial interface to the outer edge in the widest part of the endometrium. If two or three layers of endometrium were visible (triple-line pattern), then the required endometrial thickness for intrauterine insemination were obtained [11]. Follicular parameters and endometrial thickness measurements were done by the specialist physician.

2.4 Blood Sampling

Informed and signed consent was obtained at the time of blood sampling from all cases involved in the study. On the day of triggering ovulation immediately before administration of hCG injection (OVITRELLE), peripheral venous blood samples were obtained and centrifuged at 2500 rpm for 15 minutes. Serum E2 was measured using commercially available mini-VIDAS E2 kit (BIOMERIEUX/France).

2.5 Triggering of Ovulation

Trigger of ovulation was done with 10000 units of hCG (OVITRELLE) when one to two or three follicles with a diameter of 16 to 18mm were present [10,12].

2.6 Male Partner Preparation

On day of intrauterine insemination, semen samples were collected after three days of abstinence and collection was done by masturbation [13]. After semen liquification by incubation in the incubator, seminal fluid analysis was done and semen parameters were measured according to 2010WHO reference values [14]. Direct swim-up or simple wash sperm preparation techniques were done. After sperm activation, sample from the re-suspended sperm pellet was taken and sperm quality was measured and if good sperm quality was obtained then the prepared sperm would be used in intrauterine insemination.

2.7 Intrauterine Insemination (IUI)

Intrauterine insemination was carried out 36-40 hours post hCG administration [15]. Bivalent speculum was used to expose the cervix and after cleaning the cervix and vaginal fornices with cotton swabs soaked with physiological saline, intrauterine insemination was performed using an intrauterine catheter (Gynetics/Belgium) with one milliliter syringe. To eliminate dead space problem, intrauterine insemination (IUI) catheter was first attached to syringe and then inseminate was aspirated. The insemination catheter was gently passed through the cervical canal and the sperm suspension (0.5ml) was expelled slowly (over 15 seconds) into the upper part of the uterine cavity which means that the inseminate was deposited at the junction of the ampulla with the tubal isthmus [16,17]. The woman remained supine for 30 minutes after intrauterine insemination. Intrauterine insemination was done by the specialist physician. A two weeks course of daily treatment with progesterone vaginal gel was prescribed for luteal support after intrauterine insemination [18].

2.8 Pregnancy Test

To confirm pregnancy, after 14 days of intrauterine insemination, serum hCG level was measured by using mini-VIDAS HCG kit (BIOMERIEUX/France) [19].

2.9 Statistical Analysis

Statistical analysis was performed using SAS (Statistical Analysis System-version 9.0). Unpaired t-test was used to compare difference between means, while One-way ANOVA and Two-way ANOVA with Least significant difference (LSD) post hoc test were performed when we have multiple comparisons (more than two groups) to assess significant difference among means. Proportions were compared by Chi-square. $P<0.05$ was considered statistically significant [20].

3. RESULTS

Only two out of fifty women (4%) subjected to ovulation induction/intrauterine insemination protocol became pregnant. The two cases became pregnant were subjected to combination of clomiphene citrate and Gonal-f as ovulation induction program before intrauterine insemination.

Results in the Table 1 showed there was significant difference ($P<0.0001$) in the number of pre-ovulatory dominant follicles produced according to the ovulation induction protocols used for unexplained infertility women. Out of 20 women with unexplained infertility, seventeen (85%) produced one pre-ovulatory dominant follicle with diameters ranged from 16mm to 23 mm after ovulation stimulation.

Results in Table 2 revealed no significant difference ($P=0.06$) in the number of pre-ovulatory dominant follicles produced according to ovulation induction protocols used for PCOS women. However, there was notable increase in the number of women produced one dominant follicle after ovulation induction treatment since twenty (66.67%) out of 30 women produced one pre-ovulatory dominant follicle with diameters ranged from 16 mm to 21.1 mm. One of the two women with PCOS became pregnant produced one pre-ovulatory dominant follicle with diameter 17.1 mm and the other woman produced three pre-ovulatory dominant follicles with diameters ranged from 16 mm to 18 mm.

Results in the Table 3 showed no significant effect ($P=0.78$) of drug protocol used for ovulation induction on endometrial thickness for women with unexplained infertility involved in this study. However, seven (77.77%) out of nine women with unexplained infertility subjected to

combination of clomiphene citrate and Gonal-f protocol got preferable pre-ovulatory preferable endometrial thickness more than 7 mm.

Results in the Table 4 showed significant effect (P=0.01) of drug protocol used for ovulation induction on pre-ovulatory endometrial thickness for PCOS women included in this study. Of them, nineteen (95%) out of twenty who subjected to combination of clomiphene citrate and Gonal-f treatment were with preferred pre-ovulatory endometrial thickness more than 7 mm. The two

Table 1. Distribution of women with unexplained infertility according to drug protocol used for ovulation induction and the yielded number of pre-ovulatory dominant follicles

Drug protocol	Number of women yielded one pre-ovulatory D.F. and (%)	Number of women yielded two pre-ovulatory D.F. and (%)	Number of women yielded three pre- ovulatory D.F. and (%)	Total number of women and (%)
Clomid only	8 (40%)	0 (0%)	0 (0%)	8 (40%)
Gonal-f only	3 (15%)	0 (0%)	0 (0%)	3 (15%)
Clomid+Gonal-f	6 (30%)	2 (10%)	1 (5%)	9 (45%)
Total number of women and (%)	17 (85%)	2 (10%)	1 (5%)	20 (100%)
Chi-square test:		40		
P-value:		<0.0001		

D.F.: Differentiated follicle. (%): Percentage. P= Probability, (p<0.05) was designated as significant

Table 2. Distribution of women with polycystic ovary syndrome according to drug protocol used for ovulation induction and the yielded number of pre-ovulatory dominant follicles

Drug protocol	Number of women yielded one pre-ovulatory D.F. and (%)	Number of women yielded two pre-ovulatory D.F. and (%)	Number of women yielded three pre-ovulatory D.F. and (%)	Total number of women and (%)
Clomid only	8 (26.67%)	1 (3.33%)	1 (3.33%)	10 (33.33%)
Clomid+Gonal-f	12 (40%)	5 (16.67%)	3 (10%)	20 (66.67%)
Total number of women and (%)	20 (66.67%)	6 (20%)	4 (13.33%)	30 (100%)
Chi-square test:		5.4		
P-value:		0.06		

D.F.: Differentiated follicle. (%): Percentage. P= Probability, (p<0.05) was designated as significant

Table 3. Distribution of women with unexplained infertility according to drug protocol used for ovulation induction and the yielded pre-ovulatory endometrial thickness

Drug protocol	Number of Women with pre-ovulatory 6≤ET≤7 mm and (%)	Number of Women with pre-ovulatory ET>7 mm and (%)	Total number of women and (%)
Clomid only	3 (15%)	5 (25%)	8 (40%)
Gonal-f only	1 (5%)	2 (10%)	3 (15%)
Clomid+Gonal-f	2 (10%)	7 (35%)	9 (45%)
Total number of women and (%)	6 (30%)	14 (70%)	20 (100%)
Chi-square test:		0.48	
P-value:		0.78	

ET: Endometrial thickness. (%): Percentage. P= Probability, (p<0.05) was designated as significant

women with polycystic ovary syndrome became pregnant were subjected to combination of clomiphene citrate and Gonal-f protocol and produced better mean pre-ovulatory endometrial thickness (8.3±0.2) with diameters ranged from 8.1 mm to 8.5 mm.

Results in the Table 5 appeared significant effect (P<0.05) of drug protocols on levels of serum E2 on the day of triggering of ovulation by hCG administration for women with unexplained infertility subjected to OI/IUI treatment.

Results in the Table 6 exhibited no significant difference (P=0.27) in levels of serum E2 according to drug protocols measured on day of triggering of ovulation by hCG administration for women with PCOS subjected to OI/IUI treatment. However, there was notable increase in the serum E2 levels in PCOS women subjected to combination of clomiphene citrate and Gonal-f treatment. The two cases with PCOS became pregnant showed mean serum E2 levels (325.03±224.07) pg/ml and ranged from 101.0 pg/ml to 549.06 pg/ml.

Table 4. Distribution of women with polycystic ovary syndrome according to drug protocol used for ovulation induction and the yielded pre-ovulatory endometrial thickness

Drug protocol	Number of women with pre-ovulatory 6≤ET≤7 mm and (%)	Number of women with pre-ovulatory ET>7 mm and (%)	Total number of women and (%)
Clomid only	5 (16.67%)	5 (16.67%)	10 (33.33%)
Clomid+Gonal-f	1 (3.33%)	19 (63.33%)	20 (66.67%)
Total number of women and (%)	6 (20%)	24 (80%)	30 (100%)
Chi-square test:		8.43	
P-value:		0.01	

ET: Endometrial thickness. (%): Percentage. P= Probability, (p<0.05) was designated as significant

Table 5. Estradiol 2 levels on the day of triggering of ovulation by hCG administration according to ovulation induction protocol used for women with unexplained infertility

Drug protocol	E2 on hCG day (Mean±SE) (pg/ml)	Number of women and (%)
Clomid only	162.51±28.65 [b]	8 (40%)
Gonal-f only	178.6±37.72 [b]	3 (15%)
Clomid + Gonal-f	368.91±51.49 [a]	9 (45%)
Total number of women and (%)	-	20 (100%)
LSD test:	46.78	
P-value:	<0.05	

E2: Estradiol 2. hCG: Human chorionic gonadotropin. P= Probability, (p<0.05) was designated as significant. Value: Mean±Standard error

Table 6. Serum estradiol 2 levels on the day of triggering of ovulation by hCG administration according to ovulation induction protocol used for women with polycystic ovary syndrome

Drug protocol	E2 on hCG day (Mean±SE) pg/ml	Number of women and (%)
Clomid only	268.75±38.18	10 (33.33%)
Clomid + Gonal-f	325.6±34.22	20 (66.67%)
Total number of women and (%)	-	30 (100%)
Unpaired t-test:	NS	
P-value:	0.27	

E2: Estradiol 2. hCG: Human chorionic gonadotropin. (%): Percentage. P= Probability, (p<0.05) was designated as significant. Value: Mean±Standard error

4. DISCUSSION

Clomiphene citrate is a non-steroidal triphenyl ethylene derivative that demonstrates both estrogen agonist and antagonist properties. Antagonist properties predominate except at very low estrogen levels [8]. Clomiphene citrate acts as a competitive antagonist of 17β-estradiol at the level of the cytoplasmic nuclear receptor complex in the hypothalamus, pituitary and elsewhere. Blockade of estrogen receptors in the hypothalamic arcuate nucleus leads to an increase in gonadotropin-releasing hormone (GnRH) and to an increase in LH, and presumably FSH, pulse frequency but not in pulse amplitude. Additionally, clomiphene citrate increase pituitary sensitivity to GnRH in a fashion similar to estradiol. As a result of these actions, serum concentrations of FSH and LH secretions are increased three-to four folds during clomiphene administration. The increased FSH stimulates folliculogenesis whereas LH stimulates steroidogenesis. In clomiphene cycles unlike gonadotropin cycles, mono-follicular development is facilitated and multiple follicular development is attenuated because FSH is down-regulated by negative feedback of estradiol during the follicular phase. Clomiphene citrate is ineffective if started too soon, before estradiol levels are 45-60 pg/ml. Follicle sizes are 6mm or greater when estradiol is in this stage [21]. Gonal-f is recombinant (synthetic) human FSH (rhFSH) available without LH and is used for ovulation induction [22]. We mainly use r-FSH as it has been reported to reduce the possibility of developing ovarian cysts associated with LH concentration, and also to increase the probability of more consistent, effective and efficient response [23]. Gonal-f treatment direct stimulation of follicle growth in the ovary [7]. To obtain a single mature follicle, FSH should reach but not exceed the threshold FSH, as otherwise the response will be multi-follicular, resulting in a higher rate of cycle cancellation, and increased risk of multiple pregnancy [24]. Low dose FSH is successful in maintaining the multiple pregnancy rate at minimum [25]. Gonal-f can be administered when clomiphene citrate is ineffective or do not lead to pregnancy after repeated attempts. Minimal stimulation using combination of both clomiphene citrate and gonal-f protocol could reduce the risk of multiple pregnancies and achieve the main objective is to obtain a few dominant follicles (up to three dominant follicles) with less complications i.e. ovarian hyperstimulation syndrome (OHSS) [15].

The goal of ovulation induction is to restore mono-ovulatory intrauterine insemination cycles. But it was recognized that the pregnancy rates with only one pre-ovulatory dominant follicle ≥16 mm in diameter was lower compared to cycles with more and up to three pre-ovulatory dominant follicles ≥16 mm in diameter [15,26]. This indicated that if ovulation induction program was directed towards getting more than one and up to three pre-ovulatory differentiated follicles with ≥16 mm in diameter better chances of getting pregnancy might be attained.

The least pregnancy rate was obtained when clomiphene citrate only was used for ovulation induction [27]. Ovulation rates with clomiphene citrate are high but pregnancy rates are low. The difference between the high ovulation rates and low pregnancy rates is most likely due to the antiestrogenic effects of clomiphene citrate on the periphery, most prominently at the level of the endometrium [8]. Clomiphene citrate causes poor endometrial development [11]. The endometrial antiestrogenic properties of clomiphene citrate have been used as an explanation for low pregnancy rates after clomiphene citrate despite high ovulation rates [28]. Classical clomiphene citrate stimulation leads to a delayed histological dating and might lead to a reduction of pinopod formation in the mid-luteal phase [29]. Moreover, the glandular density is reduced and the number of vacuolated cells increase with clomiphene citrate treatment [30]. So all these could explain why no pregnancy attained with the use of clomiphene citrate alone despite all cycles were ovulatory.

It was dedicated that fertility was improved in intrauterine insemination cycles when clomiphene citrate was combined with gonadotropins as ovulation induction program [31]. This was the same as our results since the two women became pregnant were subjected to combination of clomiphene citrate and Gonal-f as ovulation induction program.

The pregnancy rate after intrauterine insemination treatment has a significant relation with pre-ovulatory endometrial thickness equal to or more than 7 mm [32]. Reuter et al. [33] concluded that endometrial thickness of at least 8 mm was correlated with a higher rate of pregnancy following ovulation stimulation. Later, Habibzadeh et al. [12] documented similar results. Our results indicated that combination of

clomiphene citrate and Gonal-f protocol produced better pre-ovulatory endometrial thickness than the other protocols.

High E2 levels on ovulation induction day were found in pregnant patients [34]. It was found that higher pregnancy rates during intrauterine insemination cycles were for women who had higher E2 levels on the day of hCG administration [35]. Merviel et al. [19] demonstrated that higher pregnancy rates were significantly associated with high E2 levels on hCG administration day. These results almost agreed with ours.

5. CONCLUSIONS

Obtaining more than one and up to three preovulatory dominant follicles could result in better pregnancy results. Combination of clomiphene citrate and r-FSH (Gonal-f) as ovulation induction program yielded better pre-ovulatory endometrial thickness and better pre-ovulatory E2 mean levels. The two cases became pregnant after IUI were subjected to combination of clomiphene citrate and r-FSH (Gonal-f) as ovulation induction program and this indicted that this program led to better results.

ETHICAL APPROVAL

Informed consent, protection of privacy, and other human rights are further criteria against which the manuscript will be judged. The authors have obtained all necessary ethical approval from suitable International Committee.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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