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Original Article

Ovulation Induction in Clomiphene Citrate Resistant Patient by Human Menopausal Gonadotrophin

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Abstract

Background :To find out ovulation rates, in Clomiphene citrate (CC) resistance anovulatory infertility, after administration of human menopausal gonadotrophin.

Methods: In this cross sectional study 400 infertile patients of anovulation, bilateral patent fallopian tubes evidenced by HSG, normal husband semen analysis and resistant to Clomiphene citrate therapy and take at least three months consecutive unsuccessful treatment in dose ≥150 mg/day were incorporated. Patients were divided randomly via lottery technique into two groups. Group-A, included those subjects who received Clomiphene citrate (CC) daily from day 2 to 6 of menstrual cycle and Human Menopausal Gonadotrophin 75 IU begun from day 7 onward for 3 days intramuscularly. Group B comprised of those who received Human Menopausal Gonadotrophin alone 75 IU intramuscularly begun from day 2 of menstrual cycle, 5 injections were given on alternate day till 10th day of cycle. Follow up was done by ultrasound for follicle tracking and serum progesterone level on day 21 of the treatment cycle.

Results: Mean age was 30.12±4.8 years and 30.27±4.48 years in both groups respectively without significant difference. Out of 400 patients, ovulation induction was observed in 386 patients of both groups. Among these 386, 15 patients got pregnant, 9(2.25%) from group A and 6(1.5%) from group B. Mild OHSS was seen in 12 (3%) and moderate OHSS was seen 4 (1%).

Conclusion: Clomiphene Citrate with Human Menopausal Gonadotropins have a likely supportive consequences on ovulation rate contrasted to that of Human Menopausal Gonadotropin alone.

Key words: Ovulation Induction, Clomiphene Citrate Resistance, HMG

Introduction

Infertility is the important health issue that has physical and emotional effects, and that affects 8–10% of women and men at reproductive age.[1] Even though infertility itself can not affect physical well-being, it can possibly have a serious influence on the social and mental health of couples as well as can cause social and detrimental consequences for example ostracism and divorce. A worldwide review of infertility from the world fertility analysis and others projected alike proportions of infertility are, 6%, 5%, 4%, and 4% within South Asia, Nepal, Pakistan, Bangladesh, and Sri lanka, respectively.[2]

Infertility represents a rising medical challenge. A progressive reduction in fertility rates (number of live births to the total population of females at reproductive ages) has been indicated since 1955 and that of within the same age group.[3]The decrease in fertility rate is correlated with both the non-medical and medical factors. Female age is a key factor of an average time period needed to conceive among all couples in addition particularly in the couples who have delayed conception until the female reaches her mid-thirties. The greatest live birth rates are among the 20-30 years of age group and drops sharply following 35 years of age. Moreover, the infertility duration plays a role in significant information to approximate the upcoming fertility, since every year of infertility significantly diminishes the chance of birth.[4] In addition, the more the time period of infertility, the higher the probability of the presence of genetic or more severe pathological factors. Ovulatory dysfunction is frequent factor of women infertility, taking place among around 40% of infertile females. Unfortunately still among about 20% of couples, the infertility factor remain unidentified.[1]

Like the rest of the world, treating infertility poses problems in Pakistan also. It is a challenge to the professionals more, because in our social setup an infertile woman has to face many social problems as well.[5] Most of the subjects delay looking for the advice from an expert till they reach their late 30s and 40s. The desire of the children by a normal woman is stronger than self-interest in beauty, figure and the claims of a career. In nearly all cases, the wives are the

first to approach a physician, as there is a false concept that sexual strength of a male is equal to fertility.[5] Being unable to conceive due to ovulation dysfunction causes several females to use ovulation induction treatment to handle their ovulatory infertility. Ovulation induction is the stimulation of ovulation by medication.[6] Ovulation induction treatment is an infertility therapy that lets females to ovulate and achieve a chance to conceive naturally. This therapy stimulates the ovaries to yield a single mature (dominant) follicle, to stimulate ovulation, and to let fertilization and pregnancy takes place via natural intercourse.[6] Approaches to ovulation induction therapy may include ovulation induction drug therapy (alone or in combination with further interventions and/or drug therapies) or surgeries.[6] A treatment plan for infertility requires an understanding of etiology of the disorder and the natural history of the condition to reach a diagnosis and to start treatment. Hormonal treatment is safe, useful, and effective for the treatment of infertility. Various hormonal therapy protocols have been practiced for ovulation induction, in addition to Clomiphene citrate, hMG, GnRH, Insulin sensitizers, Aromatase inhibitor, alone or in combination. This study has been conducted to find out ovulation rates, in Clomiphene citrate (CC) resistance anovulatory infertility, after administration of human menopausal gonadotrophin.

Patients and Methods

This randomized clinical trial was held at the outpatient department of PUMHS, from November 2013 to October 2015. All the women with primary/secondary infertility due to anovulation, bilateral patent fallopian tubes evidence by HSG, normal husband semen analysis and patients with documented anovulation who were resistant to clomiphene citrate therapy and take at least three months consecutive unsuccessful treatment in dose $\geq$150 mg/day were included in the study. All the women with any pelvic pathology like endometriosis, fibroid uterus, and ovarian pathology (Excluding PCOS), tubal pathology/ obstruction, malformation of sexual organ incompatible with pregnancy and hypersensitivity to any trial product were excluded. Women were instructed to bring their husbands along with them. These patients were investigated for routine including husband semen analysis, hysteron-salpingography and ultrasonography. In women who did not have spontaneous menstrual cycle, withdrawal bleeding was induced by administering oral medroxyprogesterone acetate 5 mg twice daily for 5 days. All these women had both ultrasound and endocrine assessment by hormonal assay (LH, FSH, S.Prolactin) done prior to the beginning of treatment. Those patients who had previously failed to conceive or ovulate on clomiphene up to a dose of 150 mg daily for five days were included in the study. Patients were divided by lottery method into two groups according to treatment as:Patient' s of Group A received CC daily from day 2 to 6 days of menstrual cycle with combination Human Menopausal Gonadotrophin 75 IU begun from day 7 onward for 3 days intramuscularly. Women in Group B received Human Menopausal Gonadotrophin 75 IU intramuscularly begun from day 2 of menstrual cycle, 5 injections were given on alternate day till 10th day of cycle. Monitoring was carried out by follicle measurement using TVS on day 12-16 in group A and on alternate day from day 10 – 16 in group B in collaboration with ultrasound department. The stimulating medication was stopped and human chorionic gonadotropin (hCG) was administered intramuscularly to induce ovulation, once the leading follicle was 14-20 mm. All patients were advised to do timed intercourse in between day 10 to 20. Serum progesterone was done on day 21 of the treatment cycle in both groups for the confirmation of ovulation. A urine pregnancy test was performed if the expected menstrual cycle was delayed. All the data was entered in the proforma. Mean $\pm$SD was calculated for quantitative variable like age, duration of marriage, duration of infertility, height, weight, BMI, Hemoglobin, BSR. Chi-square test was applied for comparison categorical variables and t-test was applied for comparison of mean and standard deviation in both groups. P-value$\leq$0.05 was considered as significant.

Results

In this study 400 females with infertility were taken for the purpose of ovulation. Mean age was 30.12±4.8 years and 30.27±4.48 years in both groups respectively (p-value = 0.739;insignificant). In group A the mean duration of marriage was 5.81 ± 3.80 years and in Group B the mean duration of marriage was 5.83 ± 3.06 years(p-value = 0.957;insignificant). Primary infertility was significantly high in group B and secondary infertility was higher in group A(p-value = 0.002). The mean duration of infertility in group A was 4.93 ± 3.13 years and in Group B 5.41 ± 2.97 years. Dysmenorrhea was seen in 40 cases were from group A and 56 were from group B(p-value = 0.07). Breast tenderness was in 34 cases from group A and 42 in group B. In group A, galactorrhea was present in 26

females which was significantly higher from group B (p-value = 0.028).

Table 1: Patients distribution according to demographic characteristics among study groups (n=400)

	Study Groups		t-test	Chi-square	P-value
	A	B			
Aage (Years)					
Mean ± SD	30.12±4.80	30.27±4.48	0.334		0.739
Residential Area					
Urban	128	139		1.36	0.243
Rural	72	61			
Duration of Marriage					
Mean ± SD	5.81±3.80	5.83±3.06	0.054		0.957
Types of Infertility					
Primary	125	154		9.655	0.002
Secondary	75	46			
Duration of Infertility					
Mean ± SD	4.93±3.13	5.41±2.97	1.594		0.112
Dysmenorrhea Frequency					
Yes	40	56		3.50	0.07
No	160	144			
Breast Tenderness					
Yes	34	42		1.04	0.308
No	166	158			
Galactorrhea					
Yes	26	13		4.80	0.028
No	174	187			
Hirsutism					
Yes	42	53		1.67	0.196
No	158	147			
Body Mass Index					
Under weight	15	14		3.84	0.278
Normal weight	119	106			
Over weight	42	59			
Obese	24	21			

Group A: Clomiphene citrate plus human menopausal gonadotrophin;Group B:Human menopausal gonadotrophin

Hirsutism was seen in 42 females in group A, and 53 females in group B. There were 15 females in group A and 14 females in group B who were under weight, 119 in group A and 106 in group B had normal weight, 101 (42 in group A and 59 in group B) were overweight and 45 (24 in group A and 21 in group B) were obese. In both study groups the status of BMI was statistically insignificant, p-value 0.278 (Table 1).

Table 2: Patients distribution according to investigation among study groups (n=400)

	Study Groups		t-test	Chi-square	P-value
	A	B			
Bimanual Vaginal Examination					
Normal	136	138		0.055	0.793
Normal with other findings	51	49			
Normal with discharge	13	13			
Haemoglobin					
Mean ± Std. Deviation	10.93±1.33	11.14±1.41	0.043		0.118
Ultrasound findings					
Normal	162	143		6.58	0.086
PCO	34	51			
Normal with tubal factor	3	6			
Others	1	0			
Signs and symptoms in PCO cases					
Dysmenorrhea	13	27		3.47	0.082
Breast tenderness	12	19			
Galactorrhea	12	11			
Hirsutism	19	36			
Hoarseness of voice	0	0			
Obese	3	3			
Multiple	4	2			

Group A: Clomiphene citrate plus human menopausal gonadotrophin;Group B:Human menopausal gonadotrophin

According to bimanual vaginal examination, 136 cases of group A and 138 cases from group B had normal findings. On ultrasonography 305 patients had normal findings, in which 162 were from group A and 143 were from group B. PCO was found in 85 females in which 34 were from group A and 51 were from group B. Normal findings with tubal factors were found in 9 patients only (3 were from group A and 6 were from group B). Findings on USG were similar in both study groups(p-value = 0.086) (Table 2).After treatment, 197 out of 200 had ovulation in group A and 189 in group B. There were 11 females in group B and 3 females in group A who did not have ovulation. Group A had significantly more ovulation as compared to group B,

p-value = 0.030. Ovarian hyper stimulation syndrome was not developed in 384 females, 194 from group A and 190 from group B. Mild ovarian hyper stimulation syndrome was in 5 females of group A and 7 of group B, moderate ovarian hyper stimulation syndrome was seen in 4 females only, in which 1 was from group A and 3 were from group B. This ovarian difference was insignificant(p-value = 0.503) (Table 3).Fifteen females achieved pregnancies, 9 female of group A and 6 of group B and frequency of pregnancy in both study group was statistically non-significant, p-value = 0.433 (Table 3).

Table 3: Patient distribution according to outcome among study groups. (n=400)

	Study Groups		Chi-square	P-value
	A	B		
Ovulation				
Yes	197	189	4.73	0.030
No	3	11		
Ovarian hyper stimulation syndrome				
No	194	190	1.375	0.503
Mild	5	7		
Moderate	1	3		
Pregnancy				
Yes	9	6	*0.623*	*0.433*
No	191	194		

Group A: Clomiphene citrate plus human menopausal gonadotrophin;Group B:Human menopausal gonadotrophin

Discussion

Infertility is the frequent clinical challenge. It influences 13% to 15% of couples around world. The incidence differs widely, being less within developed nations and more within underdeveloped nations where there are limited resources for treatment and investigation.[7] In current study Human menopausal gonadotrophin and clomiphene citrate were used which are economical and easily available. Human menopausal gonadotrophin alone and Human menopausal gonadotrophin plus Clomiphene citrate were used for ovulation induction. Total 386 patients showed ovulation induction. The ovulation rate was 47.25% in Human menopausal gonadotrophin group and 49.25% in Clomiphene citrate plus Human menopausal gonadotrophin group. Fourteen patients did not show ovulation after treatment. Among those 14 patients 5 were over 35 years of age and remaining 9 had PCO. The average age of the subjects in current study was 30 years. Approximately 35% of the patients had presented at the age 35 years. Since likelihoods of conception decline dramatically following this age, this study reflects the mindfulness of the general population about the importance of age in infertility. Furthermore, the factors of infertility among older females are not similar to those among younger females. The growing age poses an adverse impact on every treatment modality for infertility however noticeably cannot be overcome. Maheshwari A, proved in his study that patients with age of 35 years are almost twofold as likely to present with unexplained infertility than those younger.[8] Sadia S presents this relationship of age and fertility. In her study around 90% of the subjects had presented at the age of 35 years with the complaint of infertility.[9] A study from Auckland, reported that significant impact of the deferral in childbearing is a rise in unexplained infertility associated with natural drop in monthly fecundity rate with age from around 25% at 25 years of age to 16% at the age of 35 years and 6% at the age of 40 years.[9] Whereas woman age is possibly the most significant single cause influencing fertility, maternal weight as well appears to pose a significant effect. Obese females are less fertile with both, by ovulation induction and in natural cycles and have greater rates of miscarriage in contrast to their corresponding person of normal weight, they also need higher dosages of ovulation-inducing agents. [10]

In this study nine patients who did not ovulate during present study period had poly cystic ovaries (PCO), out of those 5 patients were obese and had BMI >25. Overweight and obesity are frequent characters among the PCOS cases and they have several health effects, together with reproductive disorders. Obese PCOS females are further likely to undergo infertility contrasted to normal-weight PCOS cases. Balen AH et al studied relationship of body mass index and fertility in PCOS and found that sterility rate is around 40% greater among females with a BMI >30 contrasted to the females with a BMI <30 in all PCOS patients.[11] Mulders et al presented in his study that patients having further severe PCOS for instance polycystic ovaries, hyperandrogenism and obesity are low responders of treatment, as compared with mild PCOS. [12] The systematic review of Maheshwari et al, looked at the cycle cancellations within overweight and obese females and proposes that the likelihoods of cycle cancellation within females with BMI >25 kg/m^2 was 1.83 as contrasted to females with BMI <25 kg/m^2. [13]

Susanne Hahn reported in his study that significantly higher proportion of females having PCOS were clinically obese, having a raised mean BMI. He

performed his study on 120 women, 33 cases presented with BMI ≤ 24.9 kg/m², 24 cases with BMI from 25 to 29.9 kg/m² and 63 cases with BMI ≥30 kg/m². Serum testosterone, LH/FSH ratio, and mean hirsutism score and parameters resistance were as well substantially raised in cases with PCOS. [14] A higher rate of PCOS case reported at present have an unsatisfied desire to conceive a baby but this is not true in case of present study as there were total 85 PCO patient included in study and only 9 out of them did not show ovulation induction. Gurnee I.L's study supports present study results, which showed that the chances of getting pregnant with PCOS using infertility treatment in the form of gonadotrophin is very good and most of cases with PCOS will be able to have a baby with infertility treatment. [15]

The successful therapy for insulin resistance and obesity has a potential to reverse the deleterious consequences of these complications. Further gonadotrophins are needed to accomplish ovulation within PCOS insulin-resistant females.[16]

In current study the pregnancy rates within group A was noted to be greater than in group B. The clinical pregnancy rates were 3.75% in present study. Shiuli Mukherjee et al[17] also reported that the pregnancy rate in Clomiphene citrate + Human menopausal gonadotrophin was found to be significantly higher. This is highly consistent with few further studies that have contrasted Clomiphene citrate+ hMG with hMG. The pregnancy rates per case in Clomiphene citrate+hMG was considerably higher in their study than in hMG group (46% vs 25.9%) as was the pregnancy rates per therapy cycle (31.3% vs 15.8%).[17]

In present study the pregnancy rate was1.5% in hMG group and 2.25% in Clomiphene citrate plus hMG group. In this study, pregnancy rate per cycle Clomiphene citrate +hMG (2.25%) was lower, compared to those stated by Ransom et al. (9.1%).[18] Mulders A.G.M.G.J., showed successful outcome after gonadotrophin treatment of ovulation induction, the pregnancy rates were 15% per cycle as well as 41% per case. [19] Clomiphene citrate indirectly induces GnRH secretion that escalates the both LH and FSH release. This rise in LH, whose basal level is frequently already high among females with PCOS, can possibly settle pregnancy rates among those getting Clomiphene citrate .Addition of gonadotrophin with Clomiphene citrate can invalidate the detrimental influence of LH on pregnancy as well as miscarriage, and thus raises the pregnancy rates among PCOS females. Our examination has made the both ends meet by elevating the rates of pregnancy upto 12.7% and diminishing the miscarriage rates though not significant. Ziadeh et al shared his experience in terms of pregnancy loss, which in Group A(Human menopausal gonadotrophin + clomiphene citrate) was lower than in Group B(Human menopausal gonadotrophin) (17% vs 33.3%).[19]

In current study we have found optimal pregnancy rates. Those patients who respond to treatment were monitored with Progesterone levels and successful conceptions usually occurred early in the treatment cycles as shown in result. Fifteen females achieved their pregnancy, five pregnancies went to term uneventfully and the healthy alive babies were delivered. Four patients had ectopic tubal pregnancies, three out of these four were ruptured and one had intact tubal pregnancy and presented in emergency with pain these patients underwent salpingectomy. Five patients had incomplete abortion at first trimester. These patients presented in emergency with heavy bleeding per vagina. On their per vaginal examination product of conception was found, evacuation and curettage was done. The product of conception was confirmed on histopathology of the specimen. . The primary objective of ovulation induction is to support the maturation, recruitment, and development of just one or two pre-ovulatory follicles. Cases with a polycystic-ovary presentation have a raised inclination to hyper-respond to gonadotrophin therapy. Iatrogenic multiple gestation and ovarian hyperstimulation syndrome are one of the utmost serious risk factors correlated with gonadotrophin.In current study there was no case of multiple gestations. This can possibly be because of the fact that cycles beside excessive ovarian response were held as well as no hCG administration was carried out. In present study OHSS was noted only in 16 patients, in which 12 had mild and 4 had moderate form .No case of severe form was noted. Present results are consistent with the above mentioned references also showed relatively small percentage of complications. Homburg and Hawles 1999 observed in a review of 1391 cycles 69% uni-ovulatory with a relatively low prevalence of OHSS (1.4%) and multiple pregnancy rates of only 5.7%. Franks and Whilie 2002 obtained alike results within a single center together with 1117 treatment cycles.[21] Another study concluded that hMG in a low dosage protocol result in a good pregnancy rates per treated cycle with a low prevalence of multiple pregnancy as well as a low risk for OHSS. [22]

We did not expect that our treatment would be so much effective however, it caused a modest pregnancy and ovulation rates. Least side effects were seen. This therapy appears to offer safety, efficacy, and economic advantages and it is worth trying prior to moving towards further sophisticated or expensive alternatives. It is evident that with potent therapy

modalities, and according to the habits and needs of a society of accomplishment continually reformed by mass media, the therapy of infertility should be well-strategic, efficient and offer outcomes within a satisfactory time.

Conclusion

1. Clomiphene Citrate with Human Menopausal Gonadotropins have a likely supportive consequences on ovulation rate contrasted to that of Human Menopausal Gonadotropin alone.
2. Ovulation induction with gonadotropin has turned out to be a standard element for physicians treating females with ovulatory dysfunction. Accordingly there is a chance of replacing Clomiphene Citrate + Human Menopausal Gonadotropin as first-line therapy for an-ovulatory infertility instead of Clomiphene Citrate therapy alone.

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