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INFERTILITY

EFFICACY OF COMBINED CLOMIPHENE CITRATE AND GONADOTROPHIN THERAPY

DR. ROBINA KAUSAR
Assistant Professor Gynae & Obs.
Mohi-ud-Din Islamic Medical College
Mirpur (A.K),

DR. TAHIRA JABBAR
Associate Prof. Gynae/Obst,
Mohi-ud-Din Islamic Medical College,
Mirpur (A.K)

DR. LUBNA YASMEEN
Senior registrar, Obs/Gynae Unit-I
Holy Family Hospital, Rawalpindi.

Dr. Faiqa Imran
Assistant Professor
Central Park Medical College,
Lahore

ABSTRACT... Objective: To measure the success rate of combined clomiphene citrate and gonadotrophin therapy in infertile patients. **Study Design:** Observational analytical study. **Period:** June 2009 to June 2010. **Methods:** In this observational analytical study, total of 100 infertile patients were selected for Combined Clomiphene Citrate and Human Menopausal Gonadotrophin (CC – hMG) regime and maximum of three treatment cycle were given. **Results:** Out of 100 patients in our study, 74% (2/3 rd) patients were less than 30 years of age and 26% (1/3rd) were between 30 – 40 yrs of age. Primary infertility was seen also in 2/3rd of patients (73%) and secondary infertility in remaining 1/3rd (27%) of patients. Polycystic ovary (PCO) was the commonest cause of an ovulation seen in 62% of patients, obesity in 24% of patients and in 14% of patients cause was unknown (unexplained infertility). on average only 4.1 Inj of gonadotrophin were required to get a mature follicle on an average 12th day (12.41 day) of the cycle. As concerned the treatment outcome, 82% of patient reported back after first course of treatment. Urine pregnancy test was positive in 18%. Remaining 64% patent were offered second course of treatment, out of which only 35% agreed for further treatment. After second course of treatment positive urine pregnancy test was seen in only 5% of patients. Remaining 30% of patients were advised third course of treatment. Out of these 30%, 8 patients took gonadotrophin regime, 10 patients agreed on follicle tracking only, 8 % of patients refused further treatment and 4 % did not report back. **Conclusions:** Our study shows the success rate of 23% with CC-HMG combined treatment which is double the CC alone and equal to HMG alone, thereby reducing the cost of treatment without sacrificing efficacy. In other words combined CC-HMG regime is cost effective technique in the management of infertile patients.

Key words: Clomiphene Citrate (CC), Human menopausal gonadotrophin (hMG), Hunman chorionic gonadotrophin (hCG), Follicle stimulating hormone (FSH), Luetinizing hormone (LH), Infertility, Polycystic ovaries (PCO).

INTRODUCTION

Infertility is a complex disorder with significant medical, psychosocial, and economic aspects[1]. Infertility causes great distress to many couples, causing increase numbers of them to seek specialist fertility care. Data from population - based studies suggest that 10-15 % of couples in the world experience infertility[2,3].

In Pakistan 70% of population living in remote area usually have infertility of prolonged duration because of lack of availability of modern techniques Keeping this in mind , we planned a study at a health centre in periphery, "Robina Mubahsar Hospital Mirpur (A.K)" where a consultant gynaecologist was available. At this centre we provided modern and evidence based treatment to women of remote area. In the study the role of gonadotrophin in the ovulation induction was evaluated.

Investigations of Couples with infertility result in different diagnostic category each with its own management pathway. Pregnancy rate is expected in 35 – 40 % in women on Clomiphene Citrate (CC). Approximately 20 – 25 % of women show no response to CC and are considered to be resistant[4]. Treatment with gonadotrophins is contemplated when women either do not respond to clomiphene or fail to conceive after 6 – 12 ovulatory cycles. Preparation in common use include recombinant FSH or purified urinary Human Menopausal Gonadotrophin which contains FSH as well as LH.

Human Menopausal Gonadotrophin (HMG) (Mentotropins) are extracted from the urine of post menopausal females and possess follicle – stimulating hormone (FSH) and luteinizing hormone (LH) activity. HMG is often used as an alternative if clomiphene Citrate (CC) does not work effectively. Like CC, HMG works by controlling and producing FSH and LH in order to induce ovulation. This fertility drug can be helpful for women with low level of Estrogeon, PCO'S, Luteal phase defect and unexplained infertility.

The need for frequent injections and monitoring, the possibility of multiple gestations, and the higher cost compared to Clomiphene Citrate, prevents many clinicians from using Human Menopausal Gonadotrophin (HMG) for ovulation induction. A sequential medication regimen, in which HMG is taken after clomiphene, overcomes these problems[5].

The success rate of gonadotrophin therapy depends on the individual patients's clinical problem. For patients who do not ovulate or ovulate infrequently, approximately 100% would be able to ovulate during treatment. The pregnancy rate per fertility drug cycle is 25% and over 60% of patients will become pregnant with in 5-6 cycles. However the success rates will differ, when there are additional factors affecting a couple's fertility as mentioned in above paragraph. Success rates for these patients will range from approximately 10-20% per gonadotrophin treatment cycle.

PATIENTS AND METHODS

In this observational analytical study, a total of 100 cases were included over the period of one year from June 2009 – June 2010.

Patients with infertility were registered at the centre with proper record maintenance and planned follow - up visits. In the study On first booking visit, a detailed history was taken. All women with primary and secondary infertility with age < 40 years, both partners living together, no male infertility factors, patent fallopian tubes (confirmed by Hysterosalpingography (HSG), An-ovulation, resistance to Clomiphene Citrate (CC) therapy alone.and unexplained infertility were included in the study.

All infertile patients with Age > 40 years with pregnancy, primary ovarian failure, male factor infertility, blocked fallopian tubes, husband abroad or living away and women in whom HMG is contraindicated were excluded from the study. HMG is contraindicated in patients with high FSH level indicating primary ovarian failure, abnormal bleeding of undetermined origin, ovarian cysts or enlargement not due to polycystic ovary syndrome, Uncontrolled thyroid and adrenal function, An organic intracranial lesion such as a pituitary tumor and Prior hypersensitivity to menotropins.

All patients selected in study had through clinical examination after detailed history. Routine investigations were carried out which include blood group, blood complete picture (blood C/P), random blood sugar, hepatitis B, C and HIV screening. Specific investigations including serum FSH, LH, thyroid stimulating hormone (TSH), Husband semen analysis (HSA) and Hysterosalpingography (HSG) were advised as first step evaluation. In addition a base line Pelvic scan – trans vaginal scan (TVS) was also done. Later on, TVS was used for tracking of mature follicle.

For second stage evaluation, patient were called on second day of menstrual cycle and tablet Clomiphine citrate was prescribed for next five days. On seventh day of cycle Inj HMG – (75 IU FSH+ 75 IU LH) I/M daily started till mature follicle of 18- 20 mm was found on TVS. Then Inj Human Chorionic Gonadotrophin (hCG) 5000 – 1000 IU was administered IM . It is well known that ovulation would occur approximately 36 – 40 hours after hCG Inj and accordingly the patients were advised intercourse with special instructions.

If more than two mature follicles or ovarian cysts were seen on TVS then Inj hCG was not administered in that cycle. If the cycle was unsuccessful then mensturation occur 14 days from the time of hCG Inj. If they were one week late for menstrual period then we performed pregnancy test otherwise second course was started in case of unsuccessful cycle.

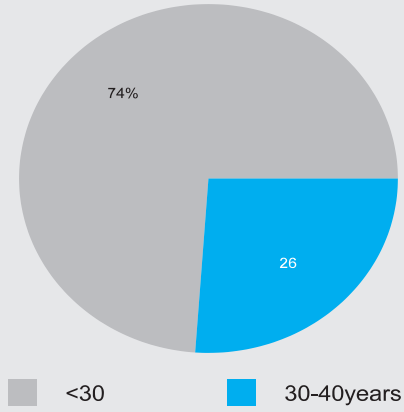
RESULTS

Regarding the general results, out of 100 patients in our study, 74% (2/3 rd) patients were less than 30 years of age and 26% (1/3rd) were between 30 – 40 yrs of age as shown in pie chart (figure 1.1). Primary infertility was seen also in 2/3rd of patients (73%) and secondary infertility in remaining 1/3rd (27%) of patients as shown in pie chart (figure 1.2). .

Regarding causes of an-ovulation, Polycystic ovary (PCO) was the commonest cause in our study seen in

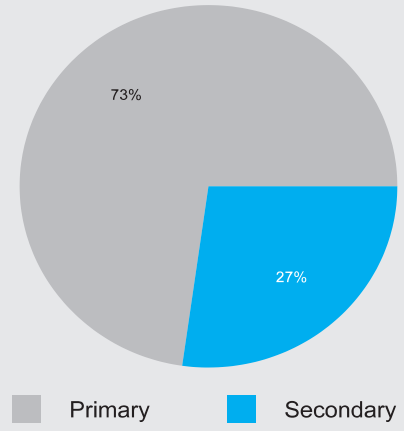
Age	
<30	74%
30-40 years	26%

Fig-1.1. Age



Infertility	
Primary	73%
Secondary	27%

Fig-1.2. Infertility

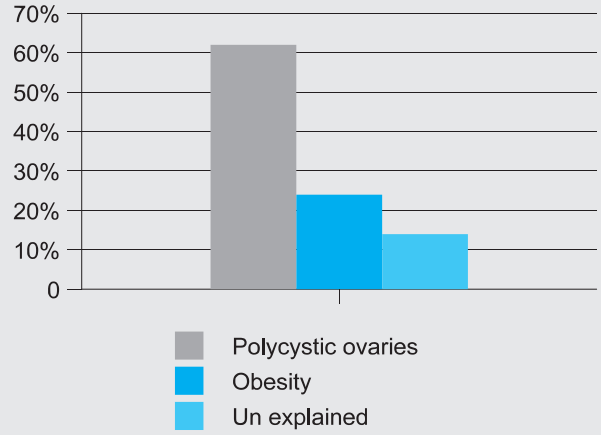


62% of patients, obesity in 24% of patients and in 14% of patients cause was unknown (unexplained infertility) as shown in column chart (figure 1.3).

More specific interesting finding in our study was that, on

An-ovulation	
Polycystic ovaries	62%
Obesity	24%
Un explained	14%

Fig-1.3. An ovulation



average only 4.1 Inj of gonadotrophin were required to get a mature follicle on an average 12th day (12.41 day) of the cycle.

As concerned the treatment outcome, 82% of patient reported back after first course of treatment. Urine pregnancy test was positive in 18% out of these cases Polycystic Ovaries were the cause of an-ovulation in 13 % . Remaining 64% patent were offered second course of treatment, out of which only 35% were agreed for further treatment. After second course of treatment positive urine pregnancy test was seen in only 5% of patients. Remaining 30% of patients were advised third course of treatment. Out of these 30%, 8 patients took gonadotrophin regime, 10 patients agreed on follicle tracking only and 8 % of patients refused further treatment and 4 % did not report back. None of these patients became pregnant and were referred for further assisted reproductive techniques (ART) to specialized centers.

DISCUSSION

In our study 2/3rd of patients with infertility were under 30

years of age which could have positive effect on our results. The timing of initial evaluation of infertility depends on the age of female partner. Women experience a decline in fecundity due to avarian age which correlates with increased chronological age[6,7].

Regarding the type of infertility 73% of patients were with primary infertility and 27% with secondary infertility, showed ovulatory problem as an important cause in both types of infertility.

Evaluating the anovulatory causes, polycystic ovaries were seen to be commonest in our study. Other studies have also shown that Polycystic ovaries account for over 75% of all women with an ovulation,[8] and gonadotrophins have been used more effectively for ovulation induction in these patients[9,10].

Second commonest cause of anovulation in our study was obesity. Many studies have shown that simple weight loss may result in ovulatory cycles and spontaneous conception, that's why the weight reducing drugs are gaining popularity in management of infertile couple.

In these women a loss of 5-10 % of body weight may be enough to restore reproductive functions in 55- 100% of women within 6 months[11].

Cause of infertility in remaining 14% of patients was found to be unexplained, which is another important category. It has been shown that ovarian stimulation in this group of patients increases the pregnancy rate[12,13,14].

Treatment outcome in our study was satisfactory to a great extent, as on average four Injections were needed to get a mature follicle at 12th – 13th day of cycle (12.41).) Richard P et al[5] needed 8 ampules to get mature follicle in his study, the reason might have been that age factor was not controlled in his study.

Most important finding of the study was the pregnancy rate seen in 18 % of patients after first course improving to 23% after second course. Richard P et al also found the pregnancy rate of 22% in his study with combined (CC- hMG) regime. It has been reported that combination of CC – hMG may be superior either CC or hMG alone[15] and may decrease hMG requirements compared with hMG alone. So cost reduction has been achieved without sacrificing efficacy. Lakhbirk et al also found the pregnancy rate of 21% with CC – hMG regime in his study[16].

One important finding in our study was that, not even a single case of ovarian hyperstimulation syndrome (OHSS) was seen with CC-HMG that reduces the monitoring cost and shows the cost effectiveness of the treatment

.

There were few draw backs In our study as well like, we could not measure the ovulation rate by day 21 serum progesterone level but it was due to funding and financial issues. Another drawback in our study was the lack of follow up visits. One reason may be, as a significant amount of population of Mirpur is residing in United Kingdom (UK) and visiting their native city for the short period of time. Second reason could be, the study was observational analytical and was not prospective. So further studies are needed in future to further evaluate the efficacy of assisted reproductive techniques (ART).

CONCLUSIONS

Our study shows the success rate of 23% with CC-HMG combined treatment which is double the CC alone and equal to HMG alone, thereby reducing the cost of treatment without sacrificing efficacy. In other worlds combined CC-HMG regime is cost effective technique in the management of infertile patients.

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Correspondence Address:
Dr. Robina Kausar
Medical Director,
Robina Mubashar Hospital
Plot No. 257-D1, Sector B/5 Kalyal
Near Kalyal Girls High School Mirpur (A.K).
robinamubshar@yahoo.com

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PREVIOUS RELATED STUDIES

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