Original Research Article

Sequential use of clomiphene citrate and human menopausal gonadotropin in anovulatory infertility

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Abstract

Background: Infertility is a complex disorder with significant medical, psychosocial and economic aspects. Infertility causes great distress to many couples, causing increased numbers of them to seek specialist fertility care.

Objectives: To measure the success rate of combined clomiphene citrate and gonadotropin therapy in anovulatory infertile patients overcoming the drawbacks of clomiphene alone treatment.

Materials and methods: In this observational analytical study, total of 100 anovulatory infertile patients were selected for Combined Clomiphene Citrate and Human Menopausal Gonadotropin (CC – hMG) regime and maximum of three treatment cycle were given.

Results: Out of 100 patients in present study, 46 patients became pregnant. Primary infertility was seen in 81 patients (81%) and secondary infertility in remaining 19(19%) of patients. Polycystic ovary disease (PCOD) was the commonest cause of anovulation seen in 62% of patients. Miscarriage was seen in 3 patients (3%). Multiple pregnancies were observed in 8 patients (8%). Number of patients conceived after 1 cycle was 12 (26%), 2nd cycle was 20 (43.47%), 3rd cycle was 14 (30.43%).

Conclusions: Present study shows the success rate of 46% with CC-HMG combined regimen. Sequential clomiphene/ HMG regimen appears to be an effective protocol for controlled ovarian stimulation in infertile women who are resistant to clomiphene alone which has drawback of poor endometrial quality. It is easy to administer, requires less intense monitoring, fewer medications, and

is cheaper without sacrificing efficacy, in other words it's a cost effective technique in the management of infertile patients.

Key words

Anovulation, Infertility, Clomiphene citrate, Gonadotropin therapy.

Introduction

Infertility is a complex disorder with significant medical, psychosocial and economic aspects [1]. Infertility causes great distress to many couples, causing increased numbers of them to seek specialist fertility care.

Many infertile women seek the most aggressive forms of treatment simply because they offer the greatest chance for success, finding it hard to believe that any treatment could be too successful. Even those committed to avoiding excessive risks can find it very difficult to accept recommendations to cancel a treatment cycle, thereby forfeiting their investment of time and resources [2]. Financial pressures weigh heavily on the minds of even the most risk-averse patients and physicians.

Infertility is defined as 1 year of unprotected intercourse without pregnancy. This condition may be further classified as primary infertility, in which no previous pregnancies have occurred, and secondary infertility, in which a prior pregnancy, although not necessarily a live birth, has occurred.

The main causes of infertility include:

- Male factor
- Decreased ovarian reserve
- Ovulatory disorders (ovulatory factor)
- Tubal injury, blockage, or paratubal adhesions (including endometriosis with evidence of tubal or peritoneal adhesions)
- Uterine factors
- Systemic conditions (including infections , autoimmune conditions or chronic renal failure)
- Cervical and immunologic factors
- Unexplained factors (including endometriosis with no evidence of tubal or peritoneal adhesions)

Relative prevalence of the etiologies of infertility (%)

Male factor 25–40
Both male and female factors 10
Female factor 40–55
Unexplained infertility 10

Approximate prevalence of the causes of infertility in the female (%)

Ovulatory dysfunction 30–40
Tubal or periotoneal factor 30–40
Unexplained infertility 10–15
Miscellaneous causes 10–15

Data from population based studies suggest that 10-15% of couples in world experience infertility [3, 4]. Investigation of couples with infertility results in different diagnostic category each with its own management pathway.

In the WHO classification of ovulatory problems, it is classified into three groups as follows

- Hypothalamo-pituitary failure/ Hypogonadotrophic hypogonadism
- Hypothalamo-pituitary dysfunction/ Normogonadotrophic anovulation
- Premature ovarian failure/ hypergonadotrophic hypogonadism.

When anovulation is the only infertility factor, the prognosis for pregnancy is very good because modern ovulation induction strategies are highly effective. When anovulation can be attributed to a specific treatable cause, ovulation induction can achieve pregnancy. When a specific cause cannot be defined, as in most anovulatory women, ovulation induction becomes intended to

identify the successful treatment regimen associated with the least cost and risk. When treatment fails to achieve ovulation or induces ovulation but fails to achieve pregnancy, more aggressive therapies often succeed, but the associated costs and risks are substantially greater. Ultimately, almost all anovulatory infertile women can be induced to ovulate. Unfortunately, many still do not conceive, for reasons uncertain and vexing.

Anovulation is among the most common causes of infertility, and clinicians caring for infertile couples must have a thorough understanding of the many treatment options, their indications, and their risks.

Clomiphene citrate (CC) continues to be the drug of choice for ovulation induction at the initial stage of management of infertile couples with anovulation (WHO GII) and unexplained infertility [4, 5]. Clomiphene citrate interacts with estrogen receptors at the level of hypothalamus with subsequent elevation in circulating LH and FSH [6]. Pregnancy rate is expected in 35 – 40 % in women on Clomiphene Citrate (CC). However, it is known to have certain disadvantages [7, 8].

Ovulation induction with gonadotrophins should be considered for women who do not respond to clomiphene or fail to conceive after 6 ovulatory cycles [9].

Gonadotropin preparation in common use includes recombinant FSH or purified human menopausal gonadotropin (HMG). HMG are extracted from the urine of post-menopausal females and possess FSH and LH activity and is helpful for women with low level of estrogen, polcystic ovarian disease, luteal phase defect and unexplained infertility.

The regimen of clomiphene citrate and gonadotropins, termed as sequential clomiphene/ HMG regimen was used in ovulation induction in clomiphene resistance with or without intra uterine insemination [10]. The CC/HMG regimen improves response to clomiphene citrate, reduces the HMG dose for optimal stimulation and finally makes it a cost effective method in ovulation induction [11]. This regimen requires less monitoring and leads to satisfactory pregnancy results [12].

Therefore, this study was designed with aim to develop a clomiphene citrate plus HMG regimen convenient to get an improved pregnancy outcome overcoming the drawback of clomiphene on endometrial quality at lower cost and simultaneously avoiding risk of ovarian hyperstimulation commonly associated with continuous gonadotropin therapy [9].

Review of literature

In 1958, Gemzall and his co-workers announced 1st successful induction of ovulation using human pituitary gonadotrophins and first pregnancy in 1960 [13].

In 1960, Greenblatt and his co-workers published in journal of America medical association; the first result achieved by application of clomiphene citrate [14].

In 1963, Lunenfeld succeeded in extracting a potent gonaotropin material from urine of menopausal women [15].

In 1966, Kistner, et al. postulated that sequential CC/ HMG improves ovulation as well as pregnancy rate (i.e. 30%). Postulated that using HMG in addition to CC had the advantages of increased number of pre ovulatory follicles and doubling of implantation rate per follicle [10].

In 1992, Hamilton Fairley, et al. reported that most significant factors that adversely influence pregnancy rate using gonadotropins are age, excess body weight and insulin resistance [16].

In 1993, Dickey, et al. and colleagues concluded that ovulation induction with sequential CC/ HMG results in fecundity double that of clomiphene citrate alone and equal to HMG

alone or concurrent with clomiphene citrate, thereby reducing the requirement for HMG [17].

In 1998, Peter R Brzechffa, suggested that treatment with sequential CC/ HMG with IUI may be an effective therapy for patients who were previously unable to conceive with CC or HMG IUI therapy. Pregnancy rates in patients undergoing ovulation induction with sequential CC/HMG with IUI decline significantly with increasing female partner age [18].

In1999, Nuojua Hettunan S, et al. analysed retrospectively a total of 811 intra uterine insemination cycles in which CC/ HMG was used for ovarian stimulation to identify the prognostic factors regarding treatment outcome and concluded that a multifollicular ovarian response to CC/ HMG resulted in better treatment success than monofollicular response and 97% of pregnancies were obtained in 1st four cycles [19].

In 2000, Zafeirion suggested that in patients with PCOD with poor response to CC, older than 40 years or hypergonadotrophic patients with ovarian failure, urinary HMG is necessary in addition to GNRH analogues in a short or ultra-short protocol as endogenous LH levels are obviously not sufficient for proper steroidogenesis in theca cells of follicles of these patients [20].

In 2002, Roy Homburg an Vaclav insler concluded that, taking into account efficiency, complication rate and cost of treatment, women with hypogonadotrophic hypogonadism or polycystic ovary syndrome should be offered accepted methods of ovulation induction and that couples with `unexplained' or `multifactorial subfertility' should still be exposed to COH with IUI and only after the failure of these therapies, be offered IVF [21].

In 2003, Z. Kilani, and colleagues found that duration of treatment and amount of exogenous gonadotropins needed to achieve comparable levels of folliculogenesis were significantly reduced among patients with highly purified HMG [22].

In 2005, B.H. Rashidi and colleagues reported that for patients undergoing controlled ovarian hyperstimulation with IUI, CC/ HMG protocol yields higher pregnancy rate than one using CC [23].

In 2010, Shiuli Mukerjee, et al. concluded that CC/ HMG regimen has the advantage of controlled ovarian hyperstimulation (COH) at a lower cost and less cycle monitoring [24].

In 2011, Robina Kouser, et al. showed the success rate of 23% with CC-HMG combined treatment which is double the CC alone and equal to HMG alone [25].

In 2013, Ibrahim A concluded that sequential CC/ HMG regimen is effective for ovulation induction and the dose of gonadotropins used was significantly low in CC/HMG group compared to HMG group and pregnancy rate was high in CC/HMG group [11].

Clomiphene citrate

In early clinical trials, 80% of anovulatory women treated with clomiphene achieved ovulation and half of those who ovulated also conceived [14].

Pharmacology of Clomiphene

Clomiphene is a nonsteroidal triphenylethylene derivative with both estrogen agonist and antagonist properties [26]. However, in almost all circumstances, clomiphene acts purely as an antagonist or antiestrogen; its weak estrogenic actions are clinically apparent only when endogenous estrogen levels are very low. Clomiphene is cleared through the liver and excreted in the stool; approximately 85% is eliminated within a week, but traces can remain in the circulation for longer [27].

Clomiphene is a racemic mixture of two different stereoisomers, enclomiphene and zuclomiphene [26] Enclomiphene is the more potent isomer and

the one responsible for its ovulation-inducing actions [26]. The half-life of enclomiphene is relatively short, so serum concentrations rise and fall quickly during and after treatment [26]. Zuclomiphene is cleared much more slowly; serum levels remain detectable for weeks after a single dose and may even gradually accumulate over a series of cycles, but there is no evidence that residual zuclomiphene has any important clinical effects or consequences [28].

Mechanism of Action

Because of its structural similarity to estrogen, clomiphene competes for and binds to nuclear estrogen receptors throughout the reproductive system. Clomiphene remains bound for an extended interval of time and ultimately depletes receptor concentrations by interfering with receptor recycling [26]. Reduced estrogen negative feedback triggers normal compensatory mechanisms that alter the pattern of gonadotropin-releasing hormone (GnRH) secretion and stimulate increased pituitary gonadotropin release, which drives ovarian follicular development.

In anovulatory women with polycystic ovary syndrome in whom the GnRH pulse frequency is already abnormally high, clomiphene increases pulse amplitude and not frequency [29]. Serum levels of both FSH and LH rise during clomiphene treatment and fall again promptly after completion of the typical 5-day course of therapy [18]. In successful treatment cycles, one or more follicles emerge and grow to maturity. In parallel, serum estrogen levels rise progressively, ultimately triggering an LH surge and ovulation. In sum, clomiphene works by stimulating the normal endocrine mechanisms that define the hypothalamicpituitary-ovarian feedback axis.

Clomiphene Treatment Regimens

Clomiphene is administered orally, typically beginning on the third to fifth day after the onset of a spontaneous or progestin-induced menses. In amenorrheic women, treatment can begin immediately if pregnancy has been excluded. Treatment usually starts with a single 50-mg tablet daily for a 5-day interval and increases, by 50 mg increments, in subsequent cycles until ovulation is achieved.

Most women who respond to clomiphene do so at either the 50 mg (52%) or 100 mg (22%) dose level [30]. Lower doses (12.5–25 mg daily) warrant consideration in women who prove exquisitely sensitive to the drug or develop large ovarian cysts that prevent continued treatment [31].

Monitoring Clomiphene Treatment

In clomiphene-induced ovulatory cycles in anovulatory women, the LH surge typically occurs 5–12 days after treatment ends, most often on cycle day 16 or 17 when clomiphene is administered on days 5–9.

In couples with unexplained infertility under combined treatment with clomiphene and IUI, transvaginal ultrasound examinations may help to determine whether treatment has succeeded in promoting the development of more than a single mature preovulatory follicle.

Results of Clomiphene Treatment

Clomiphene will successfully induce ovulation in approximately 80% of properly selected women [7]. The likelihood of response decreases with age, body mass index, and the extent of any associated hyperandrogenemia in anovulatory women.

Cumulative pregnancy rates of 70–75% can be expected over 6–9 cycles of treatment [32].

Because biologic fertility declines progressively with increasing age, prolonged treatment with clomiphene is inappropriate in women over age 35. When pregnancy is not achieved within 3–6 clomiphene-induced ovulatory cycles, the infertility investigation should be expanded to specifically exclude any other infertility factors not yet evaluated or to change the overall treatment strategy if evaluation is already complete.

However, it is known to have certain disadvantages [14].

- About 20-25 % of the patients do not respond to clomiphene citrate.
- There is a marked discrepancy in ovulation (60-85%) and pregnancy (10-20 %) rates [33]
- There is also increased risk of miscarriage
- The anti-estrogenic effect of CC causes a decrease in endometrial quality and thickness, which has an effect on the implantation of the embryo [34].
- There is also decrease in the secretion of cervical mucus, which has a role in facilitating the movement of spermatozoa [33].

To overcome these drawbacks and to improve the results, many other drugs have been tried, either singly or in combination. Ovulation induction with gonadotrophins should be considered for women who do not respond to clomiphene or fail to conceive after 6-12 ovulatory cycles [10].

Induction of Ovulation with Exogenous Gonadotropins

Exogenous gonadotropins have been used for more than 40 years to induce ovulation in gonadotropin deficient women and those who fail to respond to other, less complicated forms of treatment. Consequently, exogenous gonadotropins should be used only by clinicians having the training and experience necessary to provide safe and effective treatment.

Gonadotropin Preparations

Preparations of exogenous gonadotropins used for ovulation induction come in three different varieties -

- Urinary
- Purified urinary
- Recombinant formulations

Urinary

For almost 30 years, the only exogenous gonadotropins available were human menopausal gonadotropins (hMG, menotropins), an extract prepared from the urine of postmenopausal women containing equivalent amounts (75 IU) of FSH and LH per ampule or vial and requiring intramuscular injection [35].

Purified

Contemporary hMG preparations are more highly purified than in the past and can be administered subcutaneously [36]. Beginning about 20 years ago, more purified urinary FSH preparations were developed by removing LH from urinary extracts using immunoaffinity columns containing anti-hCG antibodies.

Recombinant

Just over 10 years ago, the *in vitro* production of recombinant human FSH was achieved through genetic engineering. Recombinant FSH preparations contain less acidic FSH isoforms that have a shorter half-life than those derived from human urine but stimulate estrogen secretion as or even more efficiently [37].

Indications for Exogenous Gonadotropin Treatment

Hypogonadotropic Hypogonadism

Women with hypogonadotropic hypogonadism (hypothalamic amenorrhea, WHO Group I) are the most obvious candidates for ovulation induction with exogenous gonadotropins. They generally respond to relatively low doses of gonadotropin stimulation although treatment must nonetheless be carefully monitored and adjusted as indicated by the response.

Clomiphene-Resistant Anovulation

When clomiphene treatment fails to achieve ovulation, exogenous gonadotropins are an obvious option. Serum gonadotropin concentrations in clomiphene-resistant anovulatory women with polycystic ovary syndrome (WHO Group II) are normal; in many, LH levels are relatively high. In this population of women, treatment superimposes boluses of

exogenous gonadotropins on a background of erratic endogenous FSH and LH secretion.

Luteal-phase support is seldom necessary after gonadotropin-induced ovulation in women with polycystic ovary syndrome because endogenous LH levels typically are more than sufficient to support normal luteal function. Considering the higher risk of ovarian hyperstimulation syndrome associated with hCG, progesterone therapy is preferable when treatment is needed [38].

Unexplained Infertility

Exogenous gonadotropins can be used intentionally to stimulate the development and ovulation of more than one mature ovum in efforts to increase cycle fecundity in older subfertile women and those with otherwise unexplained infertility; superovulation is most effective when combined with timely IUI.

AIMS AND OBJECTIVES

- To develop a cost effective regimen convenient to get an improved pregnancy outcome using sequential clomiphene citrate/ HMG regimen overcoming the drawbacks of clomiphene alone treatment.
- To evaluate the success rate of sequential clomiphene citrate/ HMG for ovulation induction in anovulatory infertility cases**.**

Materials and methods

Study Design: Prospective observational study in women with anovulatory infertility.

Study Setting: Muslim Mternity and Zanana Hospital, Hyderabad, Telangana State.

Study Population: All the women attending our infertility centre in home complete infertility work up was done and were diagnosed to have anovulatory infertility. Majority of them belong to Muslim community. 80% of them belong to middle and lower socio economic status from urban background**.**

Study Period: 12 Months

Sample Size: All the women attending the infertility clinic with anovulatory infertility during the period of our study.

The sample size was calculated using the following formula: n = z2pq/d2.

where Z was the standard value at 95% CI, p was the prevalence of conception with cc/hmg regimen which was 20 % , q is 1-p ie 19, d was the relative precision 20%. Sample size came as 91. A round figure of hundred (100) cases were taken.

Methodology

Data collection

Patients attending infertility OPD at Muslim Maternity Hospital in whom complete infertility work up has been done. Infertility work up included: pelvic ultrasound, TSH, prolactin, HSG, semen analysis.

Inclusion Criteria

- All the women with primary and secondary infertility with age <40 years.
- Both partners living together.
- No male factor infertility.
- Patent fallopian tubes (confirmed by HSG).
- Anovulatory infertility
- Unexplained infertility
- TSH and prolactin within normal limits

The patients in whom these findings were normal, were then included in the study if they satisfied the following criteria

- Those who did not ovulate with 100mg and higher doses of CC as standalone treatment
- Those patients who did not conceive despite ovulation with CC

Exclusion Criteria

- All infertile patients with age >40 years.
- Primary ovarian failure.
- Male factor infertility.
- Blocked fallopian tube.
- Husband abroad /living away.

- Women in whom HMG is contraindicated (high FSH i.e. primary ovarian failure; abnormal bleeding of undetermined origin; ovarian cysts or enlargement not due to PCOS, uncontrolled thyroid and adrenal function; organic intracranial lesion like pituitary tumor; prior hypersensitivity to menotrophins).

All patients selected in study had thorough clinical examination after detailed history followed by infertility work up and routine investigations. After satisfying the inclusion criteria, accordingly the patients were advised intercourse with special instructions.

If the cycle was unsuccessful then menstruation occurs 14 days from the time of hCG Inj. If the patient showed no follicular response after three doses of 150 units of HMG, no more doses were given but the patients were kept on follow up to look for late response or to try another regime in the next cycle.

This regime was repeated for further two cycles, if there was ovulation in the first cycle with no pregnancy. If the patient conceived after successful induction they were followed until tiffa scan for pregnancy outcome.

Statistical Analysis

Data was entered in Microsoft excel and analysis was done using SPSS version 20. Descriptive statistical analysis was done. Results on continuous measurements are presented as Mean and Standard Deviation. Results on categorical measurements are presented as Percentages. Significance is assessed at 5% level of significance. T test has been used to find out the significance of study parameters.

Results

Table - 1 shows distribution of pregnancy rate according among different age categories. Out of a total 100 patients earmarked for study 2 (2%) were in the category of <20 years with pregnancy seen none in them, 39 (39%) were in the category of 21-25 year age group with pregnancy in 23, 44 (44%) were in the category of 26-30 years with pregnancy occurring in 20, 15 (15%) were in the age category of >30 year and pregnancy occurred in 3 of them.

Table - 1: Distribution of age and pregnancy rate in various age categories.

Age categories in years	Frequency (%)	Pregnant
<20	2	0
21-25	39	23
26-30	44	20
>30	15	3

(T test value=1.851; p=0.067 not significant)

Table - 2 shows frequency distribution of patients according to their BMI .Out of a total 100 patients earmarked for study 15 (15%) were in the category of <18.5 out of which 13 became pregnant, 50 (50%) were in the category of 25-29.9 out of which 31 became pregnant, 35 (35%) were in the category of >30 out of which 2 became pregnant.

Table – 2: Distribution of patients according to their BMI and pregnancy.

BMI	FREQUENCY (%)	NO CONCEIVED
<18.5	15	13
25-29.9	50	31
>30	35	2

(t test value=6.329, p value=0.0001 significant)

Out of the total 100, 29% belonged to 2 martial life years, 32% belonged to 3 martial life years, 19% belonged to 4 martial life years, 7% belonged to 5 martial life years, 6% belonged to 6 martial life years (**Table – 3**).

Among of total 100, 81% were primary and 36 among them conceived and 19% were secondary and 10 among them conceived (**Table – 4**).

Out of the total 100, 95% were bilateral patent and 46% were significant and 5% are u/l block and none of them conceived (**Table – 5**).

TABLE - 3: DISTRIBUTION OF MARTIAL LIFE IN YEARS.

MARRIED LIFE IN YEARS	FREQUENCY
2	29
3	32
4	19
5	7
6	6
7	3
8	3
9	1

(T TEST VALUE=0.042; P=0.967 NOT SIGNIFICANT)

TABLE - 4: DIFFERENT TYPES OF INFERTILITY.

TYPE	FREQUENCY	NO CONCEIVED
PRIMARY	81	36
SECONDARY	19	10

(T TEST=0.073, P=0.001 SIGNIFICANT)

TABLE - 5: DISTRIBUTION OF HSG RESULTS AND CONCEPTION AMONG THEM.

PATENCY	FALLOPIAN TUBE	NO OF PREGNANT
B/L PATENT	95	46
U/L BLOCK	5	0

(T=2.145, P=0.034 NO SIGNIFICANT)

Out of the total 100, 62% were PCOS and 29 among them conceived, 37% were normal study and 17 among them conceived and 1 % was fibroid and they did not conceive (**Table – 6**).

Out of the total 100, 17% were previously induced with 2 cycles and 83% were induced with >2 cycles (**Table – 7**).

Out of the total 100, 17 (17%) underwent 1 cycle induction among which 12 conceived, 22 (22%) underwent 2 cycles induction out of which 20 conceived and 61(61%) underwent 3 cycles out of which 24 conceived (**Table – 8**).

TABLE - 6: USG FINDINGS.

FINDINGS	FREQUENCY	NO CONCEIVED
PCOS	62	29
FIBROI D	1	17
NORMAL STUDY	37	0

(T TEST=3.915, P=0.001 SIGNIFICANT)

TABLE - 7: PREVIOUS INDUCTION CYCLES WITH CC.

NO OF CYCLES	FREQ
2	17
>2	83

TABLE - 8: DIFFERENT INDUCTION CYCLES.

CYCLES	NO	NOP
1	17	12
2	22	20
3	61	24

TABLE - 9: ENDOMETRIAL THICKNESS IN MM BEFORE TREATMENT.

ET IN MM BEFORE	FREQUENCY
4	18
4.5	0
5	30
5.5	2
6	31
6.5	2
7	17

(T=6.192, p=0.0001 significant)

TABLE – 10: ENDOMETRIAL THICKNESS IN MM AFTER TREATMENT.

ENDOMETRIAL THICKNESS AFTER TREATMENT	FREQUENCY
5	6
6	20
7	10
8	33
9	27
10	3
11	1

Out of the total 18% belonged to 4, 0% belonged to 4.5, 30% belonged to 5, 2% belonged to 5.5, 31% belonged to 6, 2%

belonged to 6.5, 17% belonged to 7 (**Table – 9**).

Out of the total 6% belong to 5, 20% belonged to 6, 10% belonged to 7, 33% belonged to 8, 27% belonged to 9, 3% belonged to 10, 1% belonged to 11 (**Table – 10**).

TABLE - 11: NO OF HMG DOSES AND NO OF PREGNANCIES.

HMG DOSES	FREQUENCY	NOP
1	2	2
2	13	8
3	7	6
4	20	16
5	10	6
6	32	8
7	12	0
8	4	0

(T=6.080, P=0.001 SIGNIFICANT)

TABLE – 12: OVULATION.

OVULATED	FREQUENCY	NOP
YES	58	46
NO	42	0

(T=9.816, P=0.001 SIGNIFICANT)

TABLE – 13: DISTRIBUTION OF GESTATION.

GESTATION	FREQUENCY
SINGLE	38
TWIN	6
TRIPLET	2

Out of the total 100, 2% received 1 HMG dose, 13% received 2 HMG doses, 7% received 3 HMG doses, 20% received 4 HMG doses, 10% received 5 HMG doses, 32% received 6 HMG doses, 12% received 7 HMG doses and 4% received 8 HMG doses (**Table – 11**).

Out of the total 100, 42 (42%) were not ovulated and 58 (58%) were ovulated among which 46 conceived (**Table – 12**).

Out of the total 100, 46 (46%) conceived and 56 (56%) not conceived (**Table – 13**).

Discussion

Infertility is a complex disorder with significant medical, psychosocial and economic aspects. Infertility causes great distress to many couples, causing increased numbers of them to seek specialist fertility care.

Sequential clomiphene/ HMG regimen appears to be an effective protocol for controlled ovarian stimulation in infertile women. It is easy to administer, requires less intense monitoring, fewer medications, and is cheaper without sacrificing efficacy. In other words it's a cost effective technique.

Some studies are quoted as per **Table - 14** on comparison of various aspects of sequential clomiphene/HMG regimen in infertility patients in comparison with present study.

TABLE - 14: Comparison of Pregnancy Rate.

STUDY	%
Kistner, et al. [10]	28.7%
Dickey, et al. [17] 1993	22%
Peter Brzechffa, et al. [18] 1998	14.2%
Shiuli Mukherjee, et al. [24] 2010	17%
Robina Kouser, et al. [25] 2011	23%
Ibrahim A Hanan, et al. [11] 2013	26.7%
Present study	46%

In the present series the conception rate was 46% which is highest compared to all other studies. The least rate of conception amongst all the studies was in Peter brzechffa, et al. [18] study which was 14.2%.

The miscarriage rate in our study was 6.5 %, with the highest being reported by Shiuli Mukerjee, et al. [24] which is 11% and the least by Peter Brzechffa, et al. [18] which was 2% (**Table – 15**).

The conception rate among PCOS patients was observed at 46.77% in our study which was more than the observed rate in Shiuli Mukerjee, et al. [24] study which was 11% (**Table – 16**).

TABLE - 15: Miscarriage rate.

STUDY	%
Peter Brzechffa, et al. [18] 1998	2%
Shiuli Mukerjee, et al. [24] 2010	11%
Present Study	6.5%

TABLE - 16: Pregnancy rate in PCOS patients.

STUDY	%
Shiuli Mukerjee, et al. [24] 2010	11%
Present Study	46.77%

TABLE - 17: Pregnancy rate in patients with unexplained infertility.

STUDY	%
Shiuli Mukerjee, et al. [24] 2010	11%
Present Study	45.94%

TABLE - 18: Ovarian hyperstimulation.

STUDY	%
Kistner, et al. [10] 1976	Nil
Peter Brzechffa, et al. [18] 1998	0.2%
Present Study	Nil

TABLE - 19: Multiple pregnancy rates.

STUDY	%
Kistner, et al. [10] 1976	2.5%
Peter Brzechffa, et al. [18] 1998	7.6%
Present Study	8%

The pregnancy rate among patients with unexplained infertility was observed at 45.94% in our study which was higher than the observed rate in Shiuli Mukerjee, et al. [24] study which was 11% (**Table – 17**).

Not a single case of ovarian hyper stimulation was reported in our study which was corroborating with the study done by Kistner, et al. [10] who similarly reported no case of ovarian hyperstimulation (**Table – 18**).

Multiple pregnancy rates observed in our study was highest which was 8% which was almost in accordance with studies of Peter, et al. [18] 7.6%. The least multiple pregnancy rate was reported in Kistner, et al. [10] study which was 2.5% (**Table – 19**).

Summary

- The pregnancy rate among patients of anovulatory infertility during the study period for 12 months was 46%.
- Majority of them belonged to the age group of 26-30 (44%).
- Majority of them belonged to the BMI grop of 25-29.9 (50%) in whom the success rate was 62%, with success rate highest among patients with BMI<18.5 (86.66%).
- Majority of the cases were in the primary infertility group 81% and 19% in secondary infertility category.
- Endometrial thickness <7 mm was observed in 83% and >7 mm in 74% of patients before this regimen and ET <7 mm was seen in 26% and ET >7 mm was seen in 74% of patients after this regimen. The disadvantages of clomiphene on endometrial quality was overcome by this regimen.
- Number of patients of PCOS were 62% with a conception rate of 62% in that group and 37% belonged to unexplained infertility category.
- Majority of patients underwent 3 induction cycles with CC/HMG regimen which is 61%, 2 cycles in 22%,1 cycle in 17%.pregnancy rate as maximum in patients who underwent 2 cycles (90.99%).
- No of patients who ovulated were 58% with pregnancy rate of 79.31% among those who ovulated.
- Miscarriage occurred in 3.(6.5%).cases.
- Majority of them were singleton pregnancies 38 (82.6%), with twin pregnancy were 6 (13.04%), triplet pregnancy 2 (4.3%).
- No case of ovarian hyperstimulation was reported.

Conclusion

The effect of clomiphene on poor endometrial quality was overcome by this Sequential

clomiphene/hmg regimen.it appears to be an effective protocol for controlled ovarian stimulation in infertile women. It is easy to administer, requires less intense monitoring, fewer medications, and is cheaper without sacrificing efficacy in other words it's a cost effective technique.

Increasing the dose of clomiphene citrate alone resulted in comparatively poor endometrial quality and less conception rates compared to the number of ovulatory cycles. These factors make clomiphene/hmg stimulation protocol a reasonable therapeutic option even incidence of multiple pregnancy, ovarian hyper-stimulation syndrome are less with this regimen.

Present study showed conception rate of 46% which was highest among the studies. Addition of hmg does have a potential supportive effect on pregnancy rate compared to that of CC alone. Thus, the possibility of replacing CC as first-line treatment particularly for anovulatory infertility with CC+hmg therapy needs to be substantiated. We need more RCTs throughout the countries to come to a conclusion on achieving the best outcome on infertility cases.

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