

STUDY ON OVULATION INDUCTION WITH CLOMIPHENE CITRATE, METFORMIN, HUMAN CHORIONIC GONADOTROPIN AND HUMAN MENOPAUSAL GONADOTROPIN IN FEMALE INFERTILITY

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ABSTRACT

BACKGROUND

Ovulatory disorders account for about 30-40% of all causes of female infertility. Normal ovulation requires co-ordination of neuro-endocrinal system at all levels. Clomiphene citrate, human chorionic gonadotropin, human menopausal gonadotropin, metformin are the commonly used drugs for ovulation induction. They are used alone or in combination with ultrasound monitoring. Ovulation is characterized by a decrease in the size of a monitored ovarian follicle and by the appearance of fluid in the cul-de sac by ultrasound. We wanted to evaluate the effects of ovulation inducing agents like ovulation rate (by ultrasound monitoring), viable pregnancy rate (≥ 28 weeks), abortion rate and side effects like multiple pregnancies & ovarian hyper stimulation syndrome (OHSS) in a case of primary or secondary infertility.

METHODS

Our study was an interventional study and was done to induce ovulation among 100 infertile women having oligo-ovulation or anovulation with clomiphene citrate alone, with metformin alone, with combination of clomiphene citrate & metformin, with combination of clomiphene citrate & HCG, with combination of clomiphene citrate, HMG & HCG. It was conducted at the department of Obstetrics & Gynecology, Calcutta National Medical College & Hospital, and Kolkata from February 2017 to August 2018.

RESULTS

In this study group of 100 cases of infertility, 80% were primary infertility and 20% were of secondary infertility and maximum number of cases belong to the age group 26-30 years (55%). The maximum number (70%) of cases presented within 7 years of marriage. In our study it was found that ovulatory response is better with combination of clomiphene & metformin (62.5%) than clomiphene alone (53.84%) or metformin alone (48.57%). Regarding pregnancy rate, metformin alone (42.85%) and combination of clomiphene & metformin (43.75%) are almost similar in efficacy but both are superior to clomiphene alone (35.38%). Total rate of ovulation with clomiphene & HCG was 66.66% and total rate of conception was 50%. With clomiphene, HMG & HCG ovulation rate was approximately 50% & conception rate 33.33%. OHSS is an important iatrogenic side effect of ovulation inducing drugs specially clomiphene with HCG & HMG. In our study, the incidence of multiple pregnancies was 4% (4 out of 100 cases, among which 3 were twin and one triplet). 3 cases were found with the use of clomiphene citrate alone and one case was found with the use of combination of clomiphene & metformin. The incidence of pregnancy wastage in my study was 12% (Total 12 abortions in 100 patients).

CONCLUSIONS

Total 70 patients conceived out of total 100 patients studied and out of which 97 patients ovulated. Pregnancy rates were maximum with clomiphene with HCG (50%). Among 70 patients conceived, 12 aborted in early pregnancies during study time & 58 patients gave birth to term babies. Rate of OHSS and pregnancy wastage was 12% each. Multiple pregnancies occurred in 4 patients out of 100 patients. So, if there is a correct evaluation of cases, conveying psychological assurance, taking the couple into confidence and providing them a correct medical therapy, we can help them to become mother and have happy family.

KEY WORDS

Ovulation Induction, Infertility, Clomiphene Citrate, Metformin, Human Chorionic Gonadotropin, Human Menopausal Gonadotropin

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BACKGROUND

Infertility is defined as one year of unprotected intercourse without pregnancy.¹ This condition is further classified as primary infertility and secondary infertility. Normal ovulation requires co-ordination of neuro-endocrinal system at all levels i.e. central hypothalamic-pituitary axis, the feedback signal & local response within the ovary. An ovulatory disorders are commonly due to polycystic ovarian

syndrome, hypogonadotropic hypogonadism hyperprolactinaemia & hypothyroidism.

Induction of ovulation is indicated in –

1. Anovulatory infertile women (commonest cause)
2. Timing of ovulation in irregularly ovulating women
3. Oocyte maturation for in-vitro fertilization
4. As a test of pituitary or ovarian function. Clomiphene citrate, human chorionic gonadotropin (HCG), human

menopausal gonadotropin (HMG), metformin are the commonly used drugs for ovulation induction. They are used alone or in combination with ultrasound monitoring. Ovulation is documented by monitoring the development of a dominant follicle by ultrasound until ovulation takes place. Ovulation is characterized by a decrease in the size of a monitored ovarian follicle and by the appearance of fluid in the cul-de sac.^{2,3}

Commercially available kits for documenting the LH surge are generally accurate, quick convenient and relatively inexpensive.⁴ The least expensive method of confirming ovulation is for the patient to her temperature each morning on a basal body temperature chart. The oral or rectal temperature should be determined before the patient arises, eats or drinks.

METHODS

Our study was a Interventional study and was done to induce ovulation among 100 infertile women (Sample size taken as per convenience) having oligo-ovulation or anovulation. It was conducted at the department of Obstetrics & Gynaecology, Calcutta National Medical College & Hospital, Kolkata from February 2017 to August 2018. The study population was selected from the couples attending the out-patient department. Cases were also selected from those admitted in the in-patient department for evaluation of their infertility status. Infertility status of all couples was evaluated by history from both partners; clinical examination and different routine and specific tests for infertility, so that the cause of their infertility could be detected. Only those couples were undertaken for this study in whom oligo-ovulation or anovulation was suspected. Ovulation was detected by ultrasonography.

Inclusion Criteria

1. Woman who failed to conceive after staying with her husband at least for 1 year without any contraception
2. Both partner in fertile age group.

Exclusion Criteria

1. Abnormal semen analysis of the husband
2. Uterus is not morphologically normal and any of the fallopian tubes is not patent by hystero-salpingography or laparoscopic chromopertubation.
3. Patients with functional ovarian cyst, neoplastic ovarian cyst or ovarian failure.
4. Patients with liver disorders, Visual disturbances (blurred or double vision, scotoma and light sensitivity)
5. Patients with hyperprolactinaemia, hypothyroidism, diabetes mellitus.

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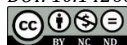
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6. Patients treated with ovulation inducing drugs in last 3 months.

Aims and Objectives

To evaluate the following effects of ovulation inducing agents in a case of primary or secondary infertility-

1. Ovulation rate by ultrasound monitoring.
2. Viable pregnancy rate (≥ 28 weeks).
3. Abortion rate.
4. Side effects like multiple pregnancies & ovarian hyper stimulation syndrome (OHSS)

RESULTS

Out of the 100 couples studied, primary infertility was found in 80% and secondary infertility in 20%. Incidence of primary infertility was 4 times than that of secondary infertility.

Most of the cases (80%) in our study presented at a younger age group (i.e. 20-30 years). Maximum number of cases were between 26-30 years of age (55 Cases) and next between 20-25 years of age (25 Cases).

In our study the duration of infertility ranged from 2 years to 20 years and it was observed that 70% of the cases presented within 7 years of infertility.

In 65% cases, therapy for ovulation induction used was clomiphene alone. In 35% cases, metformin was given alone. 48% patients were given clomiphene with metformin in whom ovulation did not occur with clomiphene alone or metformin alone. Clomiphene with HCG was given in 18% patients in whom ovulation fails to occur with clomiphene with metformin. Rest 6% were given clomiphene with HCG & HMG in whom ovulation did not occur with clomiphene with HCG.

Table I shows that 65 patients were started with 50 mg clomiphene; in whom ovulation did not occur (48 Patients), they were given 100 mg clomiphene. 150 mg clomiphene given in those (38 Patients) who did not ovulate with 100 mg dose.

Total ovulation rate with clomiphene were 53.84% and pregnancy rate were 35.38%.

With clomiphene, viable pregnancy rate was 29.23% (19 cases), spontaneous abortion rate were 06.15% (4 cases), rate of multiple pregnancy were 04.61% (3 cases) & rate of OHSS were 06.15% (4 cases).

Only metformin was given to 35 patients for one month; in whom ovulation did not occur metformin was continued for one more month and it was continued for three months in those who did not ovulate after two months of the drug. Total ovulation rate was 48.57% and pregnancy rate was 42.85% (Table II)

With metformin alone the viable pregnancy rate was 34.28% (12 cases); rate of spontaneous abortion was 08.57% (3 cases); no cases of multiple pregnancy and OHSS found.

Out of 48 patients treated with clomiphene and metformin, 30 patients ovulated & 21 patients conceived. Maximum number of ovulations occurred in 3rd cycle. (Table III). The viable pregnancy rate was 37.50% (18 cases); spontaneous abortion rate was 06.25% (3 cases); rate of multiple pregnancy and OHSS were 02.08% (1 case) and 04.16% (2 cases) respectively.

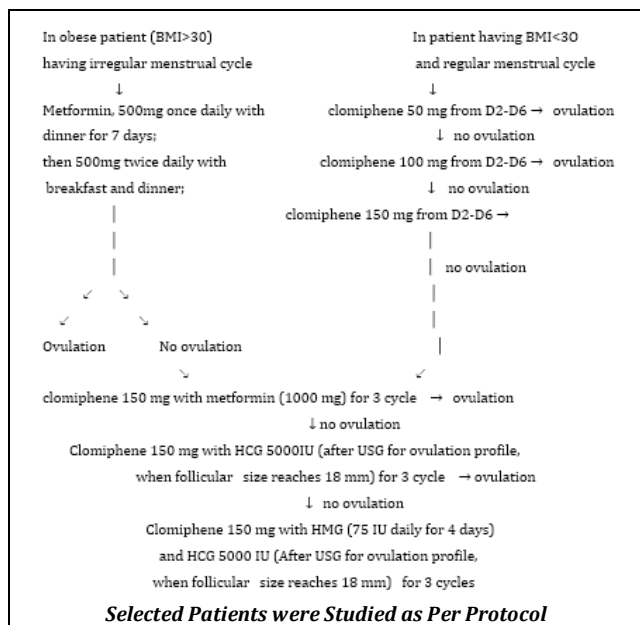
Ovulation & conception rate was highest in 2nd cycle where 150 mg clomiphene was used from 2nd day of

menstruation for 5 days & USG done for ovulation profile on 10th day onwards till the follicular size was of 18 mm & then Inj HCG (5, 000 IU) given IM.

With clomiphene & HCG total rate of ovulation were 66.66% and total rate of conception were 50% (Table IV). With clomiphene & HCG rate of viable pregnancy were 38.88% (7 cases), rate of spontaneous abortion were 11.11% (2 cases), rate of OHSS were 22.22% (4 cases). No case of multiple pregnancies found.

Clomiphene, HCG and HMG were prescribed only in 6 cases and for three cycles as it was cost effective to monitor the cases. Out of these patients 3 ovulated & 2 conceived. (Table V). Rate of viable pregnancy were 33.33% (2 cases) & rate of OHSS were 33.33% (2 cases). No case of multiple pregnancy and spontaneous abortion found.

Efficacy and complications of different ovulation inducing agents is summarized in table VI.



Dose of Clomiphene (mg)	No. of Pts. Given	No. of pts. Ovulated	% of Total Ovulated Patients	No. of Patient Conceived	% of Total Patient Conceived
50	65	17	26.15 (17/65)	12	18.48 (12/65)
100	48 (65-17)	10	20.83 (10/48)	06	12.50 (06/48)
150	38 (48-10)	08	21.05 (08/38)	05	13.15 (05/38)
Total	65	35	53.84 (35/65)	23	35.38 (23/65)

Table I. Summary of Efficacy of Clomiphene Citrate

No. of Months Given Metformin	No. of Patient Given	No. of Patient Ovulation	% of Total Ovulation Patient	No. of Patient Conceived	% of Total Patient Conceived
1	35	08	22.85 (08/35)	06	17.14 (06/35)
2	27 (35-08)	05	18.51 (05/27)	05	18.51 (05/27)
3	22 (27-05)	04	18.18 (04/22)	04	18.18 (04/22)
Total	35	17	48.57 (17/35)	15	42.85 (15/35)

Table II. Summary of Efficacy of Metformin

Cycles of Clomiphene and Metformin	No. of Patients Given	No. of Patients Ovulated	% of Total Ovulated Patients	No. of Patients Conceived	% Total Patients Conceived
1 st	48	08	16.66 (08/48)	05	10.41 (05/48)
2 nd	40 (48-08)	08	20.00 (08/40)	06	15.00 (06/40)
3 rd	32 (40-08)	14	43.75 (14/32)	10	31.25 (10/32)
Total	48	30	62.50 (30/48)	21	43.75 (21/48)

Table III. Summary of Efficacy of Clomiphene with Metformin.

Cycles of cc + HCG	No. of Pts. Given	No. of Pts. Ovulated	% of Total Ovulated	No. of Pts. Conceived	% of Total Patients Conceived
1 st	18	05	27.77 (05/18)	03	16.66 (03/18)
2 nd	13 (18-05)	05	38.46 (05/13)	04	30.76 (04/13)
3 rd	08 (13-05)	02	25.00 (02/08)	02	25.00 (02/18)
Total	18	12	66.66 (12/18)	09	50.00 (09/18)

Table IV. Summary of Efficacy of Clomiphene with HCG

Cycles of Clomiphene + HCG + HMG	No. of Patients Given	No. of Patients Ovulation	% of Total Ovulation Patients	No. of Patients Conceived	% of Total Patients Conceived
1 st	06	00	00	00	00
2 nd	06 (06-00)	01	16.66 (01/06)	00	00
3 rd	05 (06-01)	02	40.00 (02/05)	02	40 (02/05)
Total	06	03	50.00 (03/06)	02	33.33 (02/06)

Table V. Summary of Efficacy of Clomiphene, HMG & HCG.

	Clomiphene	Metformin	Clomiphene with Metformin	Clomiphene with HCG	Clomiphene with HCG & HMG
	%	%	%	%	%
No. of patient given	65 65 (65/100)	35 35 (35/100)	48 (30+18) 48 (48/100)	18 18 (18/100)	06 06 (06/100)
Ovulation	35 53.84 (35/65)	17 48.57 (17/35)	30 62.50 (30/48)	12 66.66 (12/18)	03 50.00 (03/100)
Conception	23 35.38 (23/65)	15 42.85 (15/35)	21 43.75 (21/48)	09 50.00 (09/18)	02 33.33 (02/06)
VP (>28 wks.)	19 29.23 (19/65)	12 34.28 (12/35)	18 37.50 (18/48)	07 38.88 (07/18)	02 33.33 (02/06)
Complications					
OHSS	04 06.15 (04/65)	NIL	02 04.16 (02/48)	04 22.22 (04/18)	02 33.33 (02/06)
MP	03 04.61 (03/65)	NIL	01 02.08 (01/48)	NIL	NIL
SA	04 06.15 (04/65)	03 08.57 (03/35)	03 06.25 (03/48)	02 11.11 (02/100)	NIL

Table VI. Summary of Efficacy & Complications of Different Ovulation Inducing Agents.

BMI= Body mass index, CC= Clomiphene citrate, HCG= Human chorionic gonadotropin, HMG= Human menopausal gonadotropin, VP= Viable Pregnancy, OHSS= Ovarian Hyper stimulation Syndrome, MP= Multiple Pregnancy, SA= Spontaneous Abortion

DISCUSSION

In this study group of 100 cases of infertility 80% were primary infertility and 20% were of secondary infertility and maximum number of cases belong to the age group 26-30 years (55%). We are well acquainted with the social customs of our country which favour early marriage & quick childbearing. These accounts for the high number of cases were in young age group.

The maximum number (70%) of cases presented within 7 years of marriage. Mean duration of infertility was 5 years whereas in cases of secondary infertility the duration was more. Study by WHO (Dec. 1980 to Sept. 1983 in the university clinic of Kandang Kerban Hospital) reported 3.2 years was the duration of infertility which is less than our study group. This can be explained with reference to the social custom & beliefs of the society.

So, in our study it was found that ovulatory response is better with combination of clomiphene & metformin than clomiphene alone or metformin alone which is similar to the result of the study done by Zain MM et al in 2009⁵. We found that the ovulatory response was least with metformin alone.

Regarding pregnancy rate, metformin alone and combination of clomiphene & metformin are almost similar in efficacy but both are superior to clomiphene alone.

In our study 18 patients were treated with clomiphene with HCG (In whom ovulation failed to occur even with clomiphene with metformin.) Total rate of ovulation with clomiphene & HCG were 66.66% and total rate of conception were 50%. Ovulation & conception rate was highest in 2nd cycle where 150 mg clomiphene was used.

In our study 6 patients were treated with clomiphene with HMG & HCG and ovulation rate was approximately 50% & conception rate 33.33 %. OHSS is an important iatrogenic side effect of ovulation inducing drugs specially clomiphene, HCG & HMG.

The reported incidence of OHSS is highly variable according to different studies because various classifications are used. Furthermore, these studies relate to very different clinical situations such ovulation induction using gonadotrophins or clomiphene citrate, or ovarian stimulation during IVF, which are not comparable in terms of therapeutic goals and strategies. ESHRE report on ART in Europe in 2004 found an incidence of OHSS of 1.2% of all stimulated cycles, using register data from 25/29 countries. UK contributed 635 cases from 32, 632 cycles (1.94%).⁶ In our study the total rate of OHSS is 12% (Total 12 cases among 100 patients). 4 cases found in clomiphene only treated patient, 2 cases found in patients who received clomiphene with metformin, 2 cases found in patients treated with clomiphene with HMG with HCG. Maximum incidence found in patients receiving clomiphene with HCG (4 out of 18).

The administration of drugs that induce ovulation to treat infertile couples has become more frequent in the last decade. Such drugs enhance the probability of multiple pregnancy and have been considered responsible for the increase in multiple births observed in recent years in some countries. In our study the incidence of multiple pregnancies was 4% (4 out of 100 cases, among which 3 were twin and one triplet). 3 cases found with the use of clomiphene citrate alone and one case found with the use of combination of clomiphene &

metformin. This incidence was lower than other available studies⁷

The incidence of pregnancy wastage in my study was 12% (Total 12 abortions in 100 patients) which was much lower than other reported incidences.⁸⁻¹¹ This may be due to better evaluation of infertility cases.

CONCLUSIONS

Total 70 patients conceived out of total 100 patients studied and out of which 97 patients ovulated. Pregnancy rates were maximum with clomiphene with HCG (50%).

Among 70 patients conceived, 12 aborted in early pregnancies during study time. 58 patients gave birth to term babies. So, out of 100 patients studied, the viable pregnancy rates were 58%.

Among the complications of ovulation inducing drugs in my study, maximum evidence were both OHSS and pregnancy wastage; rate of each was 12%. The other is multiple pregnancies which occurred in 4 patients out of 100 patients (4%). The commonest type of multiple pregnancy was twin pregnancy (3 out of 4). Only one case of triplet pregnancy was found. Out of 12 cases of OHSS, 11 were mild cases and one was severe for which she was kept hospitalised for careful observation and treated with conservative management.

So, if there is correct evaluation of cases, by conveying psychological assurance, taking the couple into confidence and providing them a correct medical therapy, we can help them to become mothers and have happy families.

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