

## AN INTERVENTIONAL STUDY OF LOW DOSE HUMAN MENOPAUSAL GONADOTROPIN WITH CLOMIPHENE CITRATE FOR OVULATION INDUCTION IN CLOMIPHENE RESISTANT POLYCYSTIC OVARIAN SYNDROME WOMEN IN THE DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY, SMS MEDICAL COLLEGE, JAIPUR

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**Article Info:** Received 28 June 2021; Accepted 11 August 2021

**DOI:** <https://doi.org/10.32553/ijmbs.v5i8.2098>

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**Conflict of interest:** No conflict of interest.

### Abstract

#### Background:

**Methods:** The present study is a single arm interventional study done at a tertiary care hospital in a metropolitan city. The study participants were the females who had infertility due to PCOS and resistant to clomiphene citrate, and participants were given HMG in a sequential manner with Clomiphene citrate and ovulation was observed using the TVS.

**Results:** 79% of the study participants ovulated at the end of the study as a final outcome and only 25 participants who constitute 21% of the total had not ovulated. No cases of ovarian hyperstimulation and multiple gestation was reported.

**Conclusion:** The study thus concludes that CC with low dose HMG is an efficient and safe method for induction of ovulation in females with CC resistant PCOS related infertility without the dangers of OHSS and other adverse events, also the presence of normal BMI can help in a better rate of ovulation

**Keywords:** HMG, TVS, Infertility

### Introduction

In PCOS women, as the cause of infertility is anovulation, the purpose of treatment is ovulation induction which means the development of an appropriate size follicle which can ovulate timely and pregnancy can be planned according to her infertile status spontaneously or by IUI or IVF. An estimated 50% of women with PCOS are overweight. Lifestyle factors such as obesity and smoking which could result in reproductive failure should be identified and corrected before initiating treatment.<sup>1</sup>

The treatment of infertility in PCOS includes lifestyle changes (diet and exercise), pharmacological therapies (oral agents such as clomiphene citrate, letrozole or metformin or injectable agents such as gonadotropins), surgical therapy (laparoscopic ovarian surgery) or IVF.<sup>2</sup>

Clomiphene citrate is an antiestrogenic drug with long half-life and accumulates in the body. In anovulatory PCOS women, the use of CC is widely accepted as the first line therapy because of its low cost and easy administration. Its use is associated with a high ovulation rate of 60% - 80%, but with a lower pregnancy rate of about 50% due to a detrimental effect on the endometrial thickness (an estrogen responsive site).<sup>3</sup> With the incidence of increasing resistance of clomiphene citrate other avenues were explored, A widely accepted second line management is gonadotropin and LOD. Need for expertise, invasive procedure, anaesthetic and surgical complications, cortical

damage, decreased ovarian reserve and chances of premature ovarian failure makes LOD secondary to Gonadotropins.<sup>3</sup>

Gonadotropins used for conventional ovulation induction are either urinary or recombinant products. Urinary human menopausal gonadotropins contain a combination of FSH 75 iu and LH 75 iu, while the recombinant preparations usually contain either FSH or LH activity. In women with hypothalamic hypogonadism, recombinant FSH alone stimulates follicular growth, but results in inadequate estrogen production, confirming the need for LH to fulfil the '*two cell, two gonadotropin*' requirement for ovarian steroidogenesis.<sup>4</sup>

Gonadotropins were initially administered at a high starting dose of 150 IU once a day. This conventional protocol resulted in an unacceptable rate of excessive follicle development and increased risk of ovarian hyperstimulation (8.4-23%). Hence, focus shifted to develop **low-dose protocols (37.5–75 IU/day)**, which have essentially replaced the original conventional protocol. Different ovulation induction regimens are used, with either a **low dose step-up or step-down regimen of gonadotropins**. In order to minimise the chances of multifollicular development and thereby to reduce the risks of multiple pregnancy and ovarian hyperstimulation syndrome, low-dose step-up regimens are usually employed.<sup>5</sup>

Monofollicular growth is the ultimate goal of the chronic low dose step up protocol and has lesser incidence of side effects. But used alone is not affordable to major crowd. Thus, there is a need for cost effective treatment regimen with same success rates equivalent to LOD or conventional high dose hMG regimen and significantly lower side effects.

The present study delves into the possibility and effectiveness of Clomiphene with Low Dose HMG for induction of ovulation in CC resistant PCOS females as an alternative to approach the effectiveness of standard HMG therapy with a significant economic advantage and markedly lower rate of multiple gestation and Ovarian Hyper Stimulation Syndrome.

### Materials and Methods

**STUDY TYPE:** Descriptive type of observational study

**STUDY DESIGN:** Prospective single arm interventional study

**STUDY SITE:** The study is conducted in Department of Obstetrics & Gynecology, SMS Medical College, Jaipur.

**STUDY POPULATION:** Infertile women diagnosed with PCOS who are clomiphene citrate resistance.

**DURATION OF STUDY:** May 2019 till sample size is achieved

**STUDY UNIVERSE:** Women attending infertility clinic in Department of Obstetrics and Gynaecology, SMS Medical College, Jaipur.

### Inclusion Criteria

- Women between age 21-35 years with diagnosed PCOS and clomiphene citrate resistance as defined by failure to ovulate with at least 3 cycles of clomiphene citrate 100mg or more for 5 days.
- All women with primary and secondary infertility with PCOS.
- TSH and Prolactin within normal limit.

### Exclusion Criteria

- Women who are not giving written and informed consent to participate in this study.
- Any ovarian pathology which leads to decrease ovarian reserve like premature or primary ovarian failure, endometrioma, ovarian enlargement other than PCOS
- Uncontrolled thyroid or adrenal function, organic intracranial lesions like pituitary tumor.
- Women in whom HMG is contraindicated.

Women who are not giving written and informed consent to participate in this study.

### Methodology:

Informed consent will be taken from the patient as well as partner. Patients will be instructed to take 100 mg Clomiphene Citrate daily from day 2nd of menses at same time of day for 5 days than low dose hMG 75 i.u. intramuscular injection was given daily from day 6 for 3 doses (6th to 8th day).

Follicular monitoring will be done by TVS starting from Day 9 and every alternate day thereafter, additional doses of HMG 75 IU were given IM daily till dominant follicle reached 18 mm in size. Ovulation trigger will be given by HCG 5000 IU IM. Ovulation will be confirmed by disappearance of dominant follicle, change in the shape of the follicle or appearance of internal echoes within the follicle or free fluid in the pouch of Douglas.

Data Collection was done using excel and analysis was done in SPSS version 25.

Normal Range of the Bio-chemical and other hormonal markers were taken according to the international standards.

### Results

The mean age of the participants was  $26.7 \pm 2.55$  years with the minimum age of participant being 23 years and oldest being 33 years. The distribution of patient had been done in terms of Kuppaswamy's socio-economic classification. Majority of study participants (58.3%) belonged to the Class III (Lower-Middle) socio-economic status, 27.5 belonged to class II (Upper-Middle class) and 13.3% belong to class IV (upper-lower). Only 1% belonged to I and no participants from class V

**Table 1: Distribution based on Ovulation achieved:**

Ovulation	Number of Participants	Percentage
Present	95	79.2%
Absent	25	20.8%

### Figure: Final Result of Ovulation induction

Majority of study subjects had ovulated at the end of 14<sup>th</sup> day as found out by a TVS. It is clear from the picture above that nearly 79% of the study participants ovulated at the end of the study as a final outcome and only 25 participants who constitute 21% of the total had not ovulated.

**Table 2: Average Follicular Count and Ovulation**

AFC	Ovulation Absent	Ovulation Present	Total
0-10	0	7	7
10-20	13	47	60
More than 20	12	41	53
	25	95	120

**Chi-square value – 1.972, P-value – 0.373**

The above table shows that the 100% of participants who had 1-10 AFC ovulated after treatment however, this was 78.3% in average follicular count between 10-20 and 77.3% in AFC more than 20, the difference between these groups was not found to be significant on applying the statistical test as the P-values was 0.373.

**Table 3: Ovulation induction Cycles and Ovulation**

Number of Ovulation induction Cycles	Ovulation absent	Ovulation Present	Total	Percentage
1.0	13	72	85	76%
2.0	7	14	21	14.7%
3.0	5	9	14	9.4%

**P value = 0.06**

The above table indicates the number of induction cycles given to the participant v/s the number ovulated after each cycle, out of 95 participants who were ovulated 76% i.e. 72 ovulated after the first cycle, nearly 15% i.e. 14 ovulated after 2 cycles of HMG and only 9 people needed 3<sup>rd</sup> cycle of ovulation.

**Table 4: Additional Dose of HMG and Ovulation**

Additional HMG	Ovulation Absent	Ovulation Present	Total
Not Given	8	39	47
Given	17	56	73
Total	25	95	120

**P = 0.923**

As shown in above table additional dose of HMG was given to 73 participants with total 6 doses in one cycle. Out of 95 participants who ovulated nearly 59% i.e 56 females were given additional Dose of HMG.

**Table 5: LH/ FSH ration in Ovulated Patients**

LH/FSH Ratio	No. of Patients	Percent
<2	88	92.6%
≥2	7	7.4%
Total	95	100%

The LH/FSH ratio in the Ovulated and Non-ovulated females is significantly different with Chi-Square values of **12.4 and P value of 0.0001** which is less than 0.05.

Figure: LH/FSH ratio in patients and ovulation

**Table 6: Ovulation and BMI**

BMI Category	Ovulation Absent	Ovulation Present
Normal	2	15
Obesity	13	23
Pre-Obese	10	57
Total	25	95

**Chi Square value of 7.3 and P value of 0.025**

The above table shows the ovulation in the study subjects based on their BMI category, it can be inferred that the ovulation in the normal BMI category 88.2% of females ovulated, while in Obese and Pre-obese class this percentage was 63.8% and 85% respectively suggesting that the females who had obesity ovulated lesser than normal weight and pre-obese females, this difference was found to be significant with **Chi Square value of 7.3 and P value of 0.025**.

## Discussion

The study was done with the aim to find out the efficacy of treatment by Low Dose HMG in addition to CC in the patients who were resistant to CC, the study was an interventional study and took place at a tertiary care hospital by recruiting patients who were infertile with history of PCOS diagnosed by symptoms as well as investigations.

In ovulation induction, the aim should be to achieve the ovulation of a single follicle and hence to reduce the risks of OHSS and multiple pregnancies in women with PCOS. In our study rate of the number of follicles on the day of HMG administration for ovulation trigger was found that, maximum 47(39%) patients showing monofollicular growth, 38(31.7%) patients showing 2 larger follicle, 13(10.8%) patients was showing 3 follicle on TVS examination. Mean size of follicle was  $1.6 \pm 1$ . In the study of *Ghanem et al*<sup>6</sup> the mean size of larger follicles (16mm) was  $1.6 +_1.03$  and  $1.5 +_1.5$  in uFSH + CC and uFSH alone group respectively which was comparable to our study. In another study by *Basil Mathew*<sup>7</sup> monofollicular cycle rate was present in 56.7% of study population which corresponds to mean number of follicle equal to 1. *Xi et al*<sup>8</sup> reported 65.3% of monofollicular rate. As such low dose HMG with CC for ovulation induction in PCOS females results in fewer number of dominant follicle thus reducing risk of OHSS and multiple gestation.

In the present study the total number of cycles of induction in our study participants were 169 and maximum of three ovulation induction cycle was given to the study participants. The result of the study was encouraging as 79.2% of the total 120 participants achieved ovulation and out of 95 participants who were ovulated 76% i.e. 72 ovulated after the first cycle, nearly 15% i.e. 14 ovulated after 2 cycles of HMG and only 9% i.e. 9 people needed 3<sup>rd</sup> cycle of ovulation. In the study by *Basil Mathews*<sup>6</sup> the ovulation rate of the regimen was 92.3% and 58% respectively. Additional doses of HMG was given to 73 participants with total 6 doses in one cycle. Out of 95 participants 39% nearly 1/3<sup>rd</sup> ovulated without any additional and nearly 2/3<sup>rd</sup> 59% i.e. 56 females were given additional Dose of HMG similar to that found in the study of *Basil Mathew*<sup>7</sup> 33% ovulated with three doses of HMG whereas 59.3% of cases required additional doses.

The current regimen is comparable in its success rate and efficacy to the existing previous studies mention in the review, also not only success rate the efficacy of the current regimen in induction of ovulation but also the low rate of adverse events in the participant's underlines the safety profile of the regimen

## Conclusion

The study thus concludes that CC with low dose HMG is an efficient and safe method for induction of ovulation in females with CC resistant PCOS related infertility without the dangers of OHSS and other adverse events, also the presence of normal BMI can help in a better rate of ovulation

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