

ORIGINAL ARTICLE

# Comparison of Clomiphene Citrate Alone with Combination of Clomiphene Citrate Plus Gonadotropin in Achieving Pregnancy with Unexplained Infertility

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## Abstract:

**Background:** Infertility is the most common problem faced by couples now days. According to statistics 2023 approximately 48.5 million couples faced infertility worldwide.

**Objective:** Our study's objective was to examine the effectiveness of clomiphene citrate alone vs a combination of clomiphene citrate and gonadotropin in helping patients with unexplained infertility become pregnant.

**Methods:** A total of seventy-two patients, 20 to 35 years of age with unexplained infertility were included, through a randomized control trial in MCH center of PIMS, Islamabad. Patients with history of taking medicines such dopamine dilators, dopamine receptor blockers, H-2 blockers, and verapamil as well as other reasons of infertility included tubal factors, male factors, and hyperprolactinemia were excluded. All patients were divided into two groups i.e. Group A (clomiphene citrate) & Group B (clomiphene citrate plus gonadotropin). Outcome variables like efficacy i.e. occurrence of pregnancy, were noted.

**Results:** In groups A and B the mean age was 26.73 3.49 and 27.20 3.35, respectively. The average marriage lasted 4.17 ± 2.12 years in group A and 4.39 2.27 years in group B. Group A (the clomiphene citrate group) efficacy was 15 (41%) while Group B (the combination of clomiphene citrate and gonadotropin) efficacy was 28 (77%) with a p-value of 0.005.

**Conclusion:** The conclusion of the study was that efficacy of clomiphene citrate plus gonadotropin combination in achieving pregnancy in patients with unexplained infertility is higher compared to clomiphene citrate only.

**Keywords:** Unexplained Infertility, Occurrence of pregnancy, Gonadotropins, Clomiphene Citrate.

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## Introduction

**10** % to 15% of heterosexual couples experience infertility as a problem. According to estimates, 20% of issues are related to

both partners, or unknown, 40% to both the males and females, and 25% of infertile couples have more than one cause preventing fertility<sup>1</sup>. Undetermined infertility occurs when a couple fails to become pregnant after 12 months of trying to conceive, or after six months in the case of women 35 and older, despite a careful assessment.<sup>2</sup> Up to 30% of couples who initially present with this primary symptom are ultimately diagnosed to have unexplained infertility.<sup>3</sup> Couples who have unexplained infertility are thought to either be part of a patient sub-population that falls towards the lower end of the normal fertility distribution or to be a group of patients who have a fecundity issue that is not identified by the usual infertility evaluation.<sup>4</sup>

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Unknown infertility is a difficult medical condition to treat since it requires a multi-tiered approach to patient treatment. The clinician should, first and foremost, be well-versed on the most frequent etiologies and be able to rule them out, particularly those that can pose significant risks to a patient's immediate health.<sup>5</sup> Treatment methods for unexplained infertility include intrauterine insemination (IUI), intracervical insemination (ICI), and invitro fertilisation (IVF), as well as oral ovarian stimulation drugs (such clomefine citrate, anastrozole, or letrozole).

In a study by Mukherjee Set al<sup>10</sup>, efficacy (pregnancy rate) of clomiphene citrate alone in unexplained infertility was found to be 6.3%. In another study by GibreelAet al<sup>11</sup>, the efficacy (pregnancy rate) of clomiphene citrate plus gonadotrophins in unexplained infertility was found to be 22.49%.

We planned this study to compare the efficacy of clomiphene citrate alone versus clomiphene citrate plus gonadotropin combination in achieving pregnancy in patients with unexplained infertility in our population, in order to provide a more efficacious regimen in unexplained infertility treatment to achieve the greatest number of pregnancies.

**Table-II:** Percentage of patients according to duration of marriage

Age (years)	Group A (n=36)		Group B (n=36)		Total (n=72)	
	Number of patients	Percent Age	Number of patients	Percent Age	Number of patients	Percent Age
20-25	13	36.1	10	27.9	23	31.09
26-30	18	50.0	20	55.5	38	52.75
31-35	05	14.0	6	16.6	11	15.3
Mean $\pm$ SD	26.73 $\pm$ 3.49		27.20 $\pm$ 3.35		26.97 $\pm$ 3.38	

The length of the marriage was  $4.31 \pm 2.23$  years. In group A, the mean marriage lasted  $4.17 \pm 2.12$  years, while in group B, it lasted  $4.39 \pm 2.27$  years. According to Table II, the majority of patients 56 (77%) were married for less than five years

### Methodology

The study was a randomized control trial, carried out in MCH centre Of Pakistan Institute of Medical Sciences Islamabad, from Jan 2016- Dec 2017. A total of 72 patients with unexplained infertility were included in the study, ranging in age from 20 to 35 years. Patients with history of dopamine-depleting, dopamine receptor blocking, H-2 blocker, and verapamil use as well as those with additional reasons of infertility, such as tubal factors, male factors, and hyperprolactinemia, were excluded. Patients were placed into two groups, i.e. Group A (clomiphene citrate) & Group B (clomiphene citrate plus gonatotrophin). Over the first five days (2–6) of the menstrual cycle, clomiphene citrate was administered orally once daily starting at a dose of 50mg to all cases in Group A. In the second cycle, the CC dose was increased to 100 mg, then to 150 mg in the third cycle, 200 mg in the fourth cycle, and 200 mg for the final two cycles. Pregnancy was anticipated for six menstrual cycles following the start of therapy. On day 3,5 of each cycle, CC was administered to group B patients at a dose of 50 mg coupled with one ampoule of Inj HMG 75 IU intramuscularly.

TVS was performed on days 10,12, and 14 for tracking of mature follicles. To all patients of both groups, Inj HCG 5000 IU was administered if mature a follicle of 18-22 mm was found on TVS. After the end of each cycle, the outpatient department was contacted to check for pregnancy among all patients in both groups (as peroperational definition). Patients who participated in the study provided monthly updates to the researcher in the OPD for the first six menstrual cycles, which helped to determine the final result.

### Results

We considered 72 patients with unexplained infertility who were between the ages of 20 and 35. In groups A and B the mean age of women was 26.73 3.49 and 27.20 3.35, respectively. Maximum number of the patients 38 (52%) were between 26 to 30 years of age as

**Table III: Comparison of Efficacy between both Groups**

Duration of marriage (years)	Group A (n=36)		Group B (n=36)		Total (n=72)	
	Number of patients	Percent Age	Number of patients	Percent Age	Number of patients	Percent Age
≤ 5 years	42	65.63	41	64.06	83	64.94
>5 years	22	34.37	23	35.9	45	35.1
Mean ± SD	4.17 ± 2.12		4.39 ± 2.27		4.31 ± 2.23	

In Group A efficacy of clomiphene citrate group was 15 (41%) while in Group B (clomiphene citrate plus gonadotropin combination) was 28 (77%) as shown in Table III (p-value = 0.005).

**Table IV: Comparison between Efficacy of both groups according to age**

		Group A (n=36)		Group B (n=36)	
		Number of Patients	Percent Age	Number of Patients	Percent Age
Efficacy	Yes	15	41.6	28	77
	No	21	58.4	8	23

Statistics show that the P value is 0.005, which is significant.

Table IV compares the efficacies of the two groups according to age groups and reveals a substantial difference in efficacy between the two groups between the ages of 20 and 30.

## Discussion

The cost and effectiveness of various infertility treatment options varies greatly. IVF procedures continue to be expensive despite the availability of family income funding sources, public insurance or private insurance. The high expense of infertility treatments in

developing nations may make it more difficult for clients to acquire these services. We conducted this study to compare the efficacy of clomiphene citrate alone compared to clomiphene citrate plus gonadotrophin combination in achieving pregnancy in patients with unexplained infertility.

In our study, the efficacy of Group A (clomiphene citrate group) was 05 (7.81%) while that of Group B (clomiphene citrate plus gonadotropin combination) was 17 (26.56%) with a p-value of 0.005. 1527 infertile women were randomized to one of two groups in a randomised prospective clinical trial. On day three of the menstrual cycle, Group A received just one dosage of uFSH combined with clomiphene. Clomiphene was exclusively administered to Group B to induce ovulation. Pregnancy rates between Group A (11% vs. 6.3%) did not differ statistically significantly. In Groups A and B, respectively, women with PCOS saw miscarriage rates of 8.8% and 9.5%, whereas those with unexplained infertility experienced rates of 14% and 13%.<sup>12</sup> In another study by Gibreel Aet al.<sup>13</sup>, efficacy (pregnancy rate) of clomiphene citrate plus gonatotrophins in unexplained infertility was found to be 22.49%. Several prospective randomised trials have used sequential gonadotrophins, either HMG or FSH, along with CC from days 7 to 9 in order to prevent nondominant follicles to undergo atresia that typically results from the suppression of FSH secretion by rising estrogen concentration produced by the dominant follicle. Some of those trials showed that the pregnancy rates with sequential clomiphene and HMG were nearly identical to those with HMG alone.<sup>14</sup> Clomiphene 50 mg was not successful in treating unexplained infertility in one trial. 18 CC users and 15 healthy controls were contrasted by Fujii et al. Pregnancies occurred in 11 of 51 (21.5%) control cycles (p = 0.04) and 4 of 66 (6.1%) cycles treated with CC 50 mgs.<sup>15</sup>

Kistner et al. first proposed the sequential administration of hMG after CC in 1966 with the goal of increasing ovulation and conception rates. When HMG is given after clomiphene as opposed to clomiphene alone, fecundity is increased. This is because there are more pre-ovulatory follicles present, and because the implantation rate per follicle has doubled. When compared to clomiphene alone, the oestradiol level per follicle for the clomiphene-HMG group substantially doubled.<sup>16</sup>

A review of descriptive and randomised studies revealed that empiric gonadotropin medication, particularly when paired with IUI, was a successful treatment for unexplained infertility. For instance, Welner et al.

found that 97 couples waiting for IVF who received gonadotropins and IUI treatment had improved fecundity compared to 48 control couples

Age of patients (years)	Group A (n=36)		Group B (n=36)		Pvalue
	Efficacy		Efficacy		
	yes	no	yes	no	
20-25	04 (11%)	2(10%)	05 (13.8%)	02 (5.5%)	0.048
26-30	07 (19.4%)	04 (19%)	20 (55%)	04 (11%)	0.036
31-35	04 (11.11%)	15(71%)	03 (8.3%)	02 (5.5%)	0.596

### Conclusion

This study concluded that the combination of clomiphene citrate and gonadotropin is more effective than clomiphene citrate alone in achieving pregnancy in patients with unexplained infertility. In order to achieve the greatest number of pregnancies in situations of unexplained infertility, we thus advise that these specific individuals be treated with gonadotropin+ clomiphene citrate rather than clomiphene citrate alone.

### Conflict of Interest

The authors declared no conflict of interest.

### Funding

No specific fund received.

### Data

Data will be available on request.

### Ethical approval

The study was approved by the institutional board of studies and informed consent was obtained from each participants included in the study.

### Author's contributions

HS was involved in the execution of the project. SBK designed, executed the study and wrote the manuscript. SF and MM helped in organization of data

and writing. M helped in the editing. All named authors have read and approved the final version of the manuscript.

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