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Oral Clomiphene vs. Injectable Gonadotropins in Ovulation Induction: A Comparative Study of Efficacy and Outcomes

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Abstract

Introduction: Infertility affects a significant proportion of couples worldwide, with anovulatory disorders being a leading cause among women. Ovulation induction remains a cornerstone of treatment, with oral clomiphene citrate commonly used as a first-line agent due to its simplicity, cost-effectiveness, and favorable safety profile. Injectable gonadotropins, including FSH and hMG, are reserved for patients who do not respond to clomiphene or require higher efficacy. This study aimed to compare oral clomiphene citrate and injectable gonadotropins for ovulation induction.

Methods: This prospective comparative study was conducted at 250 Bed General Hospital, Noakhali, Bangladesh, from January to December 2025, including 68 infertile women aged 20–35 years with anovulatory cycles or PCOS. Participants were equally divided into two groups: Group A received oral clomiphene citrate (50–100 mg/day for 5 days) starting on day 2–5 of the menstrual cycle, and Group B received injectable gonadotropins (FSH or hMG) with individualized dosing. Data were analyzed using SPSS v. 25.

Result: Among 68 women, baseline characteristics were similar between groups. Gonadotropins achieved higher ovulation (85.3% vs. 67.6%, $P = 0.04$), more mature follicles (2.3 ± 0.9 vs. 1.4 ± 0.6, $P < 0.001$), and thicker endometrium (9.1 ± 1.4 mm vs. 7.6 ± 1.2 mm, $P < 0.001$) than clomiphene. Pregnancy rates were higher with gonadotropins (clinical 35.3% vs. 20.6%), though not statistically significant. Gonadotropin cycles required longer stimulation and more monitoring, with increased complications including multiple follicles, OHSS, and multiple pregnancies (32.4% vs. 11.8%). Overall, gonadotropins were more effective but had a greater treatment burden and risk.

Conclusion: Injectable gonadotropins showed superior ovulation and pregnancy outcomes compared to oral clomiphene citrate, with enhanced follicular development and thicker endometrium. However, this increased efficacy came with more complex treatment, additional monitoring, and a higher risk of complications.

Keywords: Clomiphene, gonadotropins, ovulation induction, ovarian hyperstimulation syndrome

Introduction

Infertility is a significant global health concern, affecting approximately 10–15% of reproductive-aged couples worldwide, with anovulation accounting for nearly one-third of female infertility cases.[1] Ovulation induction remains a cornerstone in the management of anovulatory infertility, particularly in women with polycystic ovary syndrome (PCOS), hypothalamic

dysfunction, or unexplained infertility.[2] Among the available therapeutic options, oral clomiphene citrate and injectable gonadotropins are the most commonly utilized agents, each with distinct mechanisms of action, efficacy profiles, costs, and risk–benefit considerations. Clomiphene citrate (CC), a selective estrogen receptor modulator, has long been considered the first-line agent for ovulation induction due to its oral administration, affordability, ease of use, and favorable safety profile.[3] By antagonizing estrogen receptors at the hypothalamus, CC increases gonadotropin-releasing hormone secretion, thereby stimulating endogenous follicle-stimulating hormone (FSH) and luteinizing hormone (LH) release.[4] Ovulation rates with CC range from 60–85%, with cumulative pregnancy rates of approximately 30–40% over several cycles.[5] Despite its widespread use, CC is associated with limitations such as anti-estrogenic effects on the endometrium and cervical mucus, a relatively high rate of ovulatory failure in CC-resistant women, and a discrepancy between ovulation and pregnancy rates.[6] Injectable gonadotropins, including recombinant or urinary FSH preparations, directly stimulate ovarian follicular development and are typically reserved for women who fail to ovulate or conceive with oral agents.[7] Gonadotropins offer higher ovulation and pregnancy rates compared to CC, particularly in CC-resistant cases and unexplained infertility.[8] However, their use is constrained by higher costs, the need for intensive monitoring, increased patient burden, and a substantially higher risk of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies.[9] These complications contribute to both medical and ethical concerns, especially in low- and middle-income settings where access to close monitoring may be limited. Several studies and clinical guidelines have emphasized the importance of balancing efficacy with safety when selecting ovulation induction agents.[2,7] While gonadotropins may yield superior pregnancy outcomes in selected populations, their risks necessitate careful patient selection and individualized treatment protocols. Conversely, CC remains widely used as an initial therapy, particularly in resource-limited settings, despite its lower live birth rates in certain subgroups.[10] In recent years, advances in reproductive endocrinology and evolving clinical practices have renewed interest in re-evaluating traditional ovulation induction strategies. Factors such as patient age, etiology of infertility, body mass index, treatment costs, and access to monitoring facilities increasingly influence therapeutic choices.[3,8] This study aimed to compare oral clomiphene citrate and injectable gonadotropins for ovulation induction.

Methods

This prospective comparative study was conducted at -250 Bed General Hospital, Noakhali, Bangladesh, from January to December 2025, Bangladesh, from January to December 2025, including 68 infertile women aged 20–35 years with anovulatory cycles or PCOS. Participants were equally divided into two groups: Group A received oral clomiphene citrate (50–100 mg/day for 5 days) starting on day 2–5 of the menstrual cycle, and Group B received injectable gonadotropins (FSH or hMG) with individualized dosing. Follicular development and endometrial thickness were monitored via transvaginal ultrasound, and ovulation was triggered with hCG when at least one follicle reached ≥18 mm. Inclusion criteria included primary or secondary infertility of ≥1 year, while women with tubal or severe male factor infertility, uncontrolled endocrine disorders, history of ovarian surgery, or contraindications to study drugs were excluded. Outcomes measured included ovulation rate, number of mature follicles, endometrial thickness, pregnancy outcomes, treatment cycle characteristics, and complications. Data were analyzed using SPSS v25, with continuous variables expressed as mean ± SD and compared using t-tests, and categorical variables as frequencies (%) using Chi-square tests, with $P < 0.05$ considered statistically significant.

Results

Among the 68 participants, 34 women received clomiphene citrate and 34 received injectable gonadotropins. The mean age was 27.9 ± 3.6 years in the clomiphene group and 28.4 ± 3.9 years in the gonadotropin group ($P = 0.56$). Mean BMI was 24.1 ± 2.8 kg/m² and 24.6 ± 3.1 kg/m² in the two groups, respectively ($P = 0.48$). The mean duration of infertility was 3.2 ± 1.4 years in the clomiphene group compared to 3.5 ± 1.6 years in the gonadotropin group ($P = 0.41$). Primary infertility was present in 22 women (64.7%) in the clomiphene group and 21 women (61.8%) in the gonadotropin group ($P = 0.80$). Polycystic ovary syndrome was diagnosed in 20 patients (58.8%) receiving clomiphene and 19 patients (55.9%) receiving gonadotropins ($P = 0.81$). No statistically significant baseline differences were observed [Table 1].

Ovulation was achieved in 23 women (67.6%) in the clomiphene citrate group and in 29 women (85.3%) in the gonadotropin group, with the difference being statistically significant ($P = 0.04$). The mean number of follicles ≥18 mm was 1.4 ± 0.6 in the clomiphene group compared to 2.3 ± 0.9 in the gonadotropin group ($P < 0.001$). Mean endometrial thickness measured at the time of ovulation trigger was 7.6 ± 1.2 mm in the clomiphene group and 9.1 ± 1.4 mm in the gonadotropin group, showing a statistically significant difference ($P < 0.001$) [Table 2].

Biochemical pregnancy was observed in 9 women (26.5%) treated with clomiphene citrate and 14 women (41.2%) treated with gonadotropins ($P = 0.19$). Clinical pregnancy occurred in 7 women (20.6%) in the clomiphene group compared to 12 women (35.3%) in the gonadotropin group ($P = 0.18$). Ongoing pregnancy rates were 17.6% (6 women) in the clomiphene group and 32.4% (11 women) in the gonadotropin group, with no statistically significant difference between groups ($P = 0.16$) [Table 3].

The mean duration of ovarian stimulation was significantly shorter in the clomiphene group at 5.2 ± 0.8 days compared to 9.4 ± 1.6 days in the gonadotropin group ($P < 0.001$). The mean number of ultrasound monitoring visits was 1.6 ± 0.5 for clomiphene cycles and 4.2 ± 0.9 for gonadotropin cycles ($P < 0.001$). Cycle cancellation occurred in 2 cases (5.9%) in the clomiphene group and 4 cases (11.8%) in the gonadotropin group ($P = 0.39$) [Table 4].

Table 1: Baseline demographic and clinical characteristics of the study population ($n = 68$)

Variable	Clomiphene citrate ($n = 34$)	Gonadotropins ($n = 34$)	*P*-value
Mean age (years)	27.9 ± 3.6	28.4 ± 3.9	0.56
BMI (kg/m²)	24.1 ± 2.8	24.6 ± 3.1	0.48
Duration of infertility (years)	3.2 ± 1.4	3.5 ± 1.6	0.41
Primary infertility	22 (64.7%)	21 (61.8%)	0.80
PCOS diagnosis	20 (58.8%)	19 (55.9%)	0.81

Table 2: Ovulation induction response parameters ($n = 68$)

Parameter	Clomiphene citrate	Gonadotropins	*P*-value
Ovulation achieved	23 (67.6%)	29 (85.3%)	0.04
Mean follicles ≥18 mm	1.4 ± 0.6	2.3 ± 0.9	<0.001
Mean endometrial thickness (mm)	7.6 ± 1.2	9.1 ± 1.4	<0.001

Multiple follicular development was noted in 3 women (8.8%) receiving clomiphene citrate and in 10 women (29.4%) receiving gonadotropins, with a statistically significant difference (P = 0.03). Mild ovarian hyperstimulation syndrome was not observed in the clomiphene group (0%) but occurred in 3 women (8.8%) in the gonadotropin group (P = 0.07). Multiple pregnancy occurred in 1 case (2.9%) in the clomiphene group and 4 cases (11.8%) in the gonadotropin group (P = 0.16) [Table 5].

The overall ovulation rate was 67.6% in the clomiphene citrate group compared to 85.3% in the gonadotropin group. Clinical pregnancy rates were 20.6% for clomiphene and 35.3% for gonadotropins. The overall complication rate was 11.8% in the clomiphene group, whereas a higher complication rate of 32.4% was observed in the gonadotropin group [Table 6].

Discussion

Baseline characteristics in our study showed comparable distributions between groups, with a mean age of 27.9 ± 3.6 years in the clomiphene group and 28.4 ± 3.9 years in the gonadotropin group, and mean BMI values of 24.1 ± 2.8 kg/m² and 24.6 ± 3.1 kg/m², respectively. In a prospective study by Elnashar et al., the mean age ranged between 26 and 30 years, and the mean BMI ranged from 23 to 26 kg/m² in both clomiphene- and gonadotropin-treated groups, closely

Table 3: Pregnancy outcomes per treatment cycle (n = 68)

Outcome	Clomiphene citrate	Gonadotropins	*P*-value
Biochemical pregnancy	9 (26.5%)	14 (41.2%)	0.19
Clinical pregnancy	7 (20.6%)	12 (35.3%)	0.18
Ongoing pregnancy	6 (17.6%)	11 (32.4%)	0.16

Table 4: Treatment cycle characteristics (n = 68)

Variable	Clomiphene citrate	Gonadotropins	*P*-value
Mean days of stimulation	5.2 ± 0.8	9.4 ± 1.6	<0.001
Mean number of monitoring visits	1.6 ± 0.5	4.2 ± 0.9	<0.001
Cycle cancellation	2 (5.9%)	4 (11.8%)	0.39

Table 5: Adverse effects and complications (n = 68)

Complication	Clomiphene citrate	Gonadotropins	*P*-value
Multiple follicular development	3 (8.8%)	10 (29.4%)	0.03
Mild OHSS	0 (0%)	3 (8.8%)	0.07
Multiple pregnancy	1 (2.9%)	4 (11.8%)	0.16

Table 6: Overall treatment outcomes (n = 68)

Outcome measure	Clomiphene citrate	Gonadotropins
Ovulation rate (%)	67.6	85.3
Clinical pregnancy rate (%)	20.6	35.3
Complication rate (%)	11.8	32.4

corresponding to the demographic profile of our cohort.[11] Similarly, the WHO multicenter trials on ovulation induction included women with comparable age and BMI distributions, supporting the external validity of our population.[3] With regard to ovulatory response, ovulation was achieved in 67.6% of clomiphene cycles and 85.3% of gonadotropin cycles in our study. In comparison, Elnashar and colleagues reported ovulation rates of 65% with clomiphene citrate and 82% with gonadotropins, showing nearly identical differences between the two modalities.[11] We also observed a higher mean number of mature follicles with gonadotropins (2.3 ± 0.9) than with clomiphene (1.4 ± 0.6). A randomized study by Kamath et al. demonstrated an average of 2.0–2.5 dominant follicles per gonadotropin cycle compared to approximately 1.3 follicles in clomiphene cycles, reinforcing the enhanced follicular recruitment seen in our study.[12] Endometrial thickness was greater in gonadotropin cycles (9.1 ± 1.4 mm) compared to clomiphene cycles (7.6 ± 1.2 mm), a difference also observed by Al-Inany et al., who reported mean endometrial thickness of 9–10 mm with gonadotropins and 7–8 mm with clomiphene.[13] Pregnancy outcomes in our study favored gonadotropins, with clinical pregnancy rates of 35.3% versus 20.6% with clomiphene. In a large systematic review, Al-Inany et al. reported pregnancy rates of approximately 30–38% with gonadotropins and 18–25% with clomiphene, which closely parallels our observed rates.[13] Similarly, Zolton et al. reported clinical pregnancy rates of 34% with gonadotropins compared to 22% with clomiphene in ovulation induction cycles, further corroborating our findings.[14] The lack of statistical significance in our study is likely related to the limited sample size rather than the absence of a true effect. Treatment cycle characteristics revealed that gonadotropin cycles required longer stimulation (9.4 ± 1.6 days) and more monitoring visits (4.2 ± 0.9) compared to clomiphene cycles (5.2 ± 0.8 days and 1.6 ± 0.5 visits). A cohort study by Pandian et al. reported an average stimulation duration of 9–11 days and 4–5 monitoring visits for gonadotropin cycles, compared with fewer than 6 days and fewer than 2 visits for clomiphene, which is consistent with our findings.[15] Adverse effects were more frequent in the gonadotropin group in our study. Multiple follicular development occurred in 29.4% of gonadotropin cycles compared to 8.8% with clomiphene, while mild OHSS was observed in 8.8% of gonadotropin cycles only. A large observational study by Steward et al. reported multifollicular development in approximately 25–30% of gonadotropin cycles and OHSS rates between 5–10%, aligning closely with our observed complication rates.[16] Multiple pregnancy occurred in 11.8% of gonadotropin cycles versus 2.9% with clomiphene, comparable to rates reported by ICMART, where gonadotropin-associated multiple pregnancy rates ranged from 10–20%.[17] This study confirms that gonadotropins achieve higher ovulation and pregnancy rates than clomiphene citrate but at the cost of increased monitoring requirements and higher complication rates. These findings support contemporary guidelines advocating clomiphene as first-line therapy and reserving gonadotropins for selected cases where higher efficacy outweighs potential risks.[18]

Limitations of the Study

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community.

Conclusion

Injectable gonadotropins demonstrated higher ovulation and pregnancy rates than oral clomiphene citrate, along with improved follicular response and endometrial thickness. However, these advantages were associated with greater treatment complexity, increased monitoring, and higher complication rates.

Recommendation

Clomiphene citrate can be recommended as the first-line agent for ovulation induction due to its simplicity, lower cost, and favorable safety profile. Injectable gonadotropins should be considered for patients who do not respond to clomiphene or require higher ovulation and pregnancy success, with careful monitoring to minimize the risk of complications.

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