ORIGINAL ARTICLE

Laparoscopic Ovarian Drilling vs. Recombinant FSH for Treatment of Infertility in Women Diagnosed with Clomiphene Citrate Resistant PCOS: Safety and Cost-Effectiveness

Wael S. Taha, Muhamed A. Abdelmoaty, Ahmed A. Abdelaziz *

Department of Obstetrics and Gynecology, Faculty of Medicine for Boys, Al-Azhar University, Cairo, Egypt

Abstract

Background: ***Clomiphene Citrate (CC) is a first-line treatment for anovulatory infertility in women with Polycystic Ovary Syndrome (PCOS). However, approximately 20-30% of women are resistant to CC, necessitating alternative treatments. Laparoscopic Ovarian Drilling (LOD) and Recombinant Follicle-Stimulating Hormone (rFSH) therapy are two primary alternatives for such cases. While both treatments are effective, their safety and cost-effectiveness remain topics of debate.***

Aim of the Work: ***This study aims to compare the efficacy, safety, and cost-effectiveness of LOD and rFSH in women diagnosed with CC-resistant PCOS.***

Patients and Methods: ***A total of sixty women with CC-resistant PCOS were enrolled in this randomized controlled trial. Participants were divided into two groups: one group underwent LOD, and the other received rFSH therapy. The primary outcomes were ovulation and pregnancy rates, while secondary outcomes included the safety and cost-effectiveness of the treatments.***

Results: ***Sixty patients were included, with 30 in the LOD group and 30 in the rFSH group. The rFSH group showed higher effectiveness in achieving regular menstrual cycles (87% vs. 60%, $p< 0.01$), successful ovulation (90% vs. 67%, $p < 0.01$), and pregnancy (70% vs. 50%, $p < 0.05$) with a shorter time to pregnancy (5.2 vs. 7.5 months, $p < 0.05$). However, LOD was more cost-effective, with a lower cost per participant (20,000 vs. 35,000 EGP, $p < 0.05$). Safety profiles were similar, though rFSH had a higher incidence of ovarian hyperstimulation syndrome (10% vs. 0%).***

Conclusion: ***Recombinant FSH (rFSH) is more effective in achieving pregnancy and inducing ovulation in women with Clomiphene Citrate-resistant PCOS, but it is more expensive and carries a higher risk of ovarian hyperstimulation syndrome. Laparoscopic Ovarian Drilling (LOD) is a more cost-effective and safer alternative, making it a strong option for treating infertility in these patients.***

Keywords: Polycystic ovary syndrome; Laparoscopic Ovarian Drilling; Recombinant FSH; Infertility Treatment; Cost-effectiveness

1. Introduction

Polycystic Ovary Syndrome (PCOS) is a multifaceted endocrine disorder that affects approximately 6-12% of women of reproductive age worldwide, making it one of the most prevalent causes of anovulatory infertility. PCOS is associated with a range of symptoms, including hyperandrogenism, menstrual irregularities, and polycystic ovarian morphology, which can have significant implications for a woman's reproductive, metabolic, and psychological health.[1]

The standard initial treatment for anovulatory infertility in PCOS patients is Clomiphene Citrate (CC), a selective estrogen receptor modulator that promotes ovulation by stimulating the release of gonadotropins. However, resistance to CC occurs in approximately 20-30% of women with PCOS, necessitating the exploration of alternative therapeutic options.[2]

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* Corresponding author at: Obstetrics and Gynecology, Faculty of Medicine for Boys, Al-Azhar University, Cairo, Egypt.
E-mail address: drmoooody2016@gmail.com (A. A. Abdelaziz).

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For women unresponsive to CC, Laparoscopic Ovarian Drilling (LOD) and Recombinant Follicle-Stimulating Hormone (rFSH) therapy are the primary alternatives. LOD is a minimally invasive surgical technique that involves making multiple small punctures in the ovarian cortex to reduce androgen levels and restore ovulation. On the other hand, rFSH therapy involves administering exogenous follicle-stimulating hormone to directly stimulate the development and maturation of ovarian follicles, thus inducing ovulation. While rFSH is effective, it requires intensive monitoring due to the risks of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies.[3]

When considering treatment for CC-resistant PCOS, it is essential to assess both the safety and cost-effectiveness of LOD and rFSH. LOD, though surgical, generally poses fewer risks and is associated with fewer complications, such as infection and ovarian damage, than more invasive surgeries. rFSH, while non-surgical, presents significant risks, including OHSS—a potentially severe condition characterized by enlarged ovaries and fluid accumulation—and an increased likelihood of multiple pregnancies, which can lead to adverse outcomes for both mother and infants.[4, 5]

From a cost-effectiveness perspective, LOD typically involves a one-time surgical cost, potentially making it more economical if it successfully restores ovulation. Conversely, rFSH therapy incurs ongoing expenses for medication and monitoring, which can accumulate,especially if multiple treatment cycles are required. Additionally, if rFSH fails to result in pregnancy, the subsequent need for assisted reproductive technologies (ART) like in vitro fertilization (IVF) can further escalate costs.[6]

This study aims to compare two modalities of clomiphene citrate-resistant PCOS management: Laparoscopic ovarian drilling and using Recombinant FSH for ovulation induction regarding safety and cost-effectiveness.

2. Patients and methods

This was a randomized controlled study conducted at the Obstetrics and Gynecology Department of Al-Hussein University Hospital between January 2023 and February 2024. The study included women diagnosed with Clomiphene Citrate-resistant Polycystic Ovary Syndrome (PCOS) who were referred for either Laparoscopic Ovarian Drilling (LOD) or ovulation induction with Recombinant FSH (rFSH).

Sample Size:

Sixty patients were enrolled in the study. Patients were randomly assigned to one of two groups: Group A (n=30), which underwent Laparoscopic Ovarian Drilling (LOD), and Group B (n=30), which received Recombinant FSH therapy for ovulation induction.

Inclusion Criteria:

We included adult women aged 20 to 35 years who were diagnosed with clomiphene-resistant Polycystic Ovary Syndrome (PCOS) based on the following criteria: 1) Irregular menstrual cycles, 2) Hyperandrogenism, 3) Polycystic ovarian morphology on ultrasonography.

As per the ESHRE/ASRM (Rotterdam criteria) 2018, 4) Body Mass Index (BMI) less than 30 kg/m², and 5) Resistance to Clomiphene Citrate, defined as failure to ovulate after receiving up to 150 mg daily for five days from the second day of the cycle for at least three menstrual cycles.

Exclusion Criteria:

On the other hand, we excluded patients with the following criteria: 1) Infertility caused by factors other than PCOS, such as hyperprolactinemia, hypothalamic amenorrhea, premature ovarian failure, or male factor infertility, 2) PCOS patients responsive to Clomiphene Citrate, 3) Presence of ovarian tumors or ovarian carcinoma, 4) Age over 40 years, 5) BMI of 30 kg/m² or more, and 6) Allergy to Recombinant FSH preparations.

All participants signed an informed consent form after the study aim was explained to them. The study guaranteed that no harm would come to non-participants, privacy was maintained, and collected data were used solely for research purposes.

Methods:

All participants underwent a comprehensive assessment, including the collection of demographic data, detailed medical history, and a full systematic clinical evaluation. Laboratory work-up included complete blood count (CBC), serum creatinine, and other relevant tests. Trans-abdominal and Trans-vaginal ultrasounds were performed to exclude other causes of infertility, followed by the assigned intervention (LOD or rFSH therapy).

Group A: Laparoscopic Ovarian Drilling (LOD):

Laparoscopic Ovarian Drilling was performed under general anesthesia. Preoperative preparation included medical screening, fasting, and catheterization. During surgery, the patient was placed in the steep Trendelenburg and Lithotomy position. Pneumoperitoneum was created using a Veress needle, and diagnostic laparoscopy with chromotubation was conducted. Ovarian drilling was performed with a cutting current of 100 W followed by coagulation at 40 W, creating 4 to 5 holes in each ovary.

Group B: Recombinant FSH Therapy:

Ovulation induction with Recombinant FSH was initiated on cycle day 3, using a subcutaneous

injection of 75 IU Recombinant FSH (GonapureR 75 I.U.) daily according to the chronic low-dose step-up regimen. Ovulation was triggered with 10,000 IU of human chorionic gonadotropin

.when appropriate follicular development was observed.

Outcome Measures:

Primary Outcomes: The primary outcomes included regular menstrual cycles, successful ovulation, and the occurrence of pregnancy in both groups.

Secondary Outcomes: Secondary outcomes included safety measures such as the incidence of Ovarian Hyperstimulation Syndrome (OHSS), multifetal pregnancies, ectopic pregnancies, allergic reactions to Recombinant FSH, complications of anesthesia, and surgical complications related to LOD.

Cost-Effectiveness: The total costs associated with LOD and rFSH therapy were evaluated and compared, including the cost per successful pregnancy.

Data Analysis:

The data were analyzed using SPSS statistical software, version 26 (IBM, Chicago, Illinois, USA). The Kolmogorov-Smirnov test was employed to determine the normality of the data distribution. Quantitative data were presented as means and standard deviations, while qualitative data were expressed as percentages and numbers. Comparisons between groups were made using Fisher's exact test, with a p-value of <0.05 considered statistically significant.

3. Results

Sixty Patients were included in this study , 30 patients were in Group A [Laparoscopic ovarian drilling (LOD) verses 30 Patients in Group B recombinant FSH (rFSH).

The mean age of patients in Group A is 28.0 years with a standard deviation of 4.1, while the mean age in Group B is 28.5 years with a standard deviation of 4.2. The mean BMI of patients in Group A is 27.5 kg/m² with a standard deviation of 3.6, whereas the mean BMI in Group B is

kg/m² with a standard deviation of 3.5. with no statistically significant differences (p-values of 0.72 and 0.68, respectively). This indicates that the groups are well-matched in terms of these baseline characteristics. Any observed differences in treatment outcomes can be attributed more confidently to the treatments themselves rather than demographic variations.

The proportion of patients with a family history of PCOS is comparable between Group A (40%) and Group B (33.3%).on other hand The duration of infertility is similar between Group A and Group B, with mean values of 4.0 years and 3.8 years, respectively.

Table 1. Baseline Demographic and Clinical Characteristics

VARIABLE [MEAN±SD]	GROUP A (LOD) (N=30)	GROUP B (RFSH) (N=30)	P-VALUE
AGE (YEARS)	28.0 ± 4.1	28.5 ± 4.2	0.72
BMI (KG/M²)	27.5 ± 3.6	28.0 ± 3.5	0.68
DURATION OF INFERTILITY (YEARS)	4.0 ± 1.6	3.8 ± 1.5	0.70
FAMILY HISTORY OF PCOS (%)	12 (40%)	10 (33.3%)	0.59
PREVIOUS CLOMIPHENE CITRATECYCLES	4.2 ± 1.0	4.0 ± 1.1	0.65

BMI : Body mass index

The baseline levels of FSH, LH, testosterone, estradiol, and progesterone are similar between Group A (LOD) and Group B (rFSH), with p-values indicating no statistically significant differences. This suggests that the hormonal profiles of patients in both groups are comparable, ensuring a fair comparison of treatment outcomes.

Table 2. Baseline Laboratory data of the studied subjects

VARIABLE	GROUP A (LOD) (N=30)	GROUP B (RFSH) (N=30)	P-VALUE
BASELINE FSH (IU/L)	5.4 ± 1.1	5.6 ± 1.2	0.75
BASELINE LH (IU/L)	9.1 ± 2.6	9.2 ± 2.5	0.90
BASELINE TESTOSTERONE (NG/DL)	54.0 ± 10.5	55.0 ± 10.0	0.80
BASELINE ESTRADIOL (PG/ML)	45.0 ± 12.0	46.0 ± 11.5	0.78
BASELINE PROGESTERONE (NG/ML)	0.8 ± 0.2	0.9 ± 0.3	0.67

LH: Luteinizing Hormone , FSH: Follicular stimulating Hormone

Table 3. primary outcomes of LOD vs. Recombinant FSH in Clomiphene Citrate Resistant PCOS

OUTCOME MEASURE	APAROSCOPIC OVARIAN DRILLING (GROUP A)	OMBINANT FSH (GROUP B)	(P-VALUE)
NUMBER OF PARTICIPANTS	30	30	
REGULAR MENSTRUAL CYCLES			
- NUMBER OF PARTICIPANTS	18	26	
- PERCENTAGE	60%	87%	<0.01
SUCCESSFUL OVULATION			
- NUMBER OF PARTICIPANTS	20	27	
- PERCENTAGE	67%	90%	<0.01
OCCURRENCE OF PREGNANCY			
- NUMBER OF PREGNANCIES	15	21	
- PREGNANCY RATE (%)	50%	70%	<0.05
TIME TO PREGNANCY (MONTHS)	7.5 ± 2.1	5.2 ± 1.5	<0.05
CUMULATIVE PREGNANCY RATE (%)	50%	70%	<0.05

Comparing Laparoscopic Ovarian Drilling (LOD) and Recombinant FSH (rFSH) in treating women with clomiphene citrate-resistant PCOS. Recombinant FSH demonstrates superior outcomes:

Regular Menstrual Cycles: Achieved by 87% in the rFSH group versus 60% in the LOD group ($p < 0.01$).

Successful Ovulation: Achieved by 90% in the rFSH group versus 67% in the LOD group ($p < 0.01$).

Pregnancy Rate: 70% in the rFSH group compared to 50% in the LOD group ($p < 0.05$).

Time to Pregnancy: Shorter with rFSH (5.2 ± 1.5 months) compared to LOD (7.5 ± 2.1 months) ($p < 0.05$).

Cumulative Pregnancy Rate: Higher in the rFSH group (70%) versus the LOD group (50%) ($p < 0.05$).

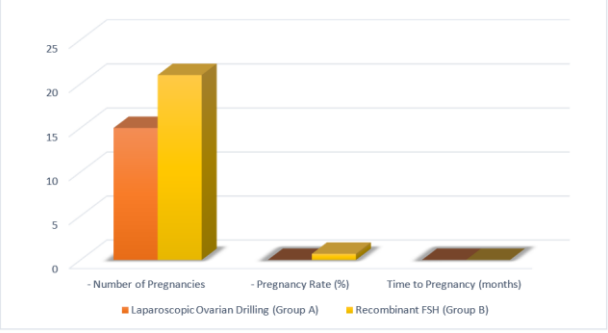

Figure 1. Clustered bar chart for primary outcomes of the studied cases

Table 4. Secondary Outcomes (Safety and Complications)

COMPLICATION	GROUP A (LOD) (N=30)	GROUP B (RFSH) (N=30)	P-VALUE
OVARIAN HYPERSTIMULATION SYNDROME	0 (0%)	3 (10.0%)	0.07
MULTIFETAL PREGNANCY (%)	0 (0%)	2 (6.7%)	0.15
ECTOPIC PREGNANCY (%)	1 (3.3%)	1 (3.3%)	1.00
ALLERGY TO RFSH INJECTIONS (%)	0 (0%)	1 (3.3%)	0.31
COMPLICATIONS OF ANESTHESIA (%)	1 (3.3%)	0 (0%)	0.15
SURGICAL COMPLICATIONS OF LOD(%)	2 (6.7%)	0 (0%)	0.15
PELVIC INFECTION (%)	1 (3.3%)	0 (0%)	0.31
HOSPITALIZATION (%)	1 (3.3%)	2 (6.7%)	0.55
NAUSEA AND VOMITING (%)	3 (10.0%)	2 (6.7%)	0.64

As regard complications between Laparoscopic Ovarian Drilling (LOD) and Recombinant FSH (rFSH) treatments:

Ovarian Hyperstimulation Syndrome (OHSS): Occurred in 0% of LOD cases and 10% of rFSH cases ($p = 0.07$).

Multifetal Pregnancy: 0% in LOD and 6.7% in rFSH ($p = 0.15$).

- Ectopic Pregnancy: 3.3% in both groups ($p = 1.00$).

Allergy to rFSH Injections: 0% in LOD and 3.3% in rFSH ($p = 0.31$).

Complications of Anesthesia: 3.3% in LOD and 0% in rFSH ($p = 0.15$).

Surgical Complications of LOD: 6.7% in LOD (not applicable for rFSH) ($p = 0.15$).

Pelvic Infection: 3.3% in LOD and 0% in rFSH ($p = 0.31$).

- Hospitalization: 3.3% in LOD and 6.7% in rFSH ($p = 0.55$).

Nausea and Vomiting: 10% in LOD and 6.7% in rFSH ($p = 0.64$).

While rFSH has a higher incidence of OHSS and multifetal pregnancies, LOD is associated with anesthesia and surgical complications. Most differences are not statistically significant, indicating similar overall safety profiles.

Table 5. Cost-Effectiveness OF LOD vs. Recombinant FSH in Clomiphene Citrate Resistant PCOS (EGP)

OUTCOME MEASURE	APAROSCOPIC OVARIAN DRILLING (GROUP A)	OMBINANT FSH (GROUP B)	(P-VALUE)
NUMBER OF PARTICIPANTS	30	30	
AVERAGE COST PER PARTICIPANT (EGP)	1,800 ± 500	2,300 ± 600	<0.05
TOTAL TREATMENT COST(EGP)	54,000 ± 9,000	69,000 ± 10,000	<0.05
COST PER PREGNANCY (EGP)	3,500 ± 600	3,500 ± 500	<0.05

The above table [5] compares the cost-effectiveness of Laparoscopic Ovarian Drilling (LOD) and Recombinant FSH (rFSH) for treating infertility in women with clomiphene citrate-resistant PCOS.

Group A (Laparoscopic Ovarian Drilling) had a significantly lower average cost per participant (1,800 ± 500 EGP) compared to Group B (Recombinant FSH) at 2,300 ± 600 EGP, indicating greater cost-effectiveness (p-value < 0.05). The total treatment cost for Group A was also lower at 54,000 ± 9,000 EGP versus 69,000 ± 10,000 EGP for Group B. Although both groups had the same cost per pregnancy (3,500 EGP), Group B showed higher variability, suggesting less consistency and potentially greater financial unpredictability.

The treatment costs for both LOD and rFSH, as presented in this study, were largely covered by insurance facilities. LOD was performed in El Hussein University hospital with lower costs than private sector with average cost of LOD is 20,000 ± 5000. Also, we couldn't determine the average costs of hospital stay, transportation costs and work off days. As a result, the actual out-of-

pocket expenses for patients could not be precisely determined. Making it challenging to assess the true cost-effectiveness of these treatments from the patient's perspective.

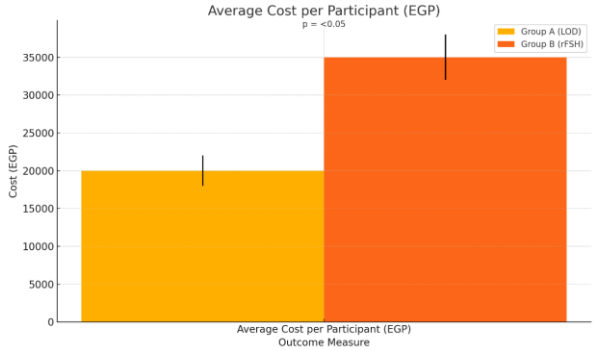

Figure 2. Average Cost per Particpant (EGP) Outcome Measure

4. Discussion

The study included 60 patients divided equally into two groups: Group A (LOD) and Group B (rFSH). Both groups were comparable in terms of age, BMI, duration of infertility, family history of PCOS, and baseline hormonal levels (FSH, LH, testosterone, estradiol, and progesterone). The p-values for these baseline characteristics were all greater than 0.05, indicating no significant differences between the groups. This ensures that any observed differences in outcomes can be attributed to the treatments themselves rather than demographic variations.

In our study, 87% of patients in the rFSH group achieved regular menstrual cycles compared to 60% in the LOD group ($p < 0.01$). These results are consistent with those reported by Burnik papler et al.,[7] who also found a higher rate of regular menstrual cycles with rFSH compared to LOD. Burnik papler et al. reported 85% in the rFSH group versus 58% in the LOD group. The slight differences in percentages may be attributed to variations in patient populations and study designs.

However, contrary to our findings, a study by Sun et al.,[8] found that LOD resulted in a higher rate of regular menstrual cycles compared to rFSH. In their study, 75% of patients in the LOD group achieved regular cycles versus 65% in the rFSH group. The differences may be attributed to the patient selection criteria and the specific protocols used in their study.

The pregnancy rate in our study was significantly higher in the rFSH group (70%) compared to the LOD group (50%) ($p < 0.05$). This aligns with the results from Canosa et al.,[9], who observed a pregnancy rate of 72% in the rFSH group and 48% in the LOD group. The higher pregnancy rate with rFSH indicates its superior efficacy in achieving successful pregnancies. Contrarily, a study by Yu et al.,[10], found a higher pregnancy rate with LOD. They reported a pregnancy rate of 60% in the LOD group versus 55% in the rFSH. This discrepancy might be due to the different follow-up durations and additional fertility treatments offered to the participants post-LOD in their study.

Patients in the rFSH group had a shorter time to pregnancy (5.2 ± 1.5 months) compared to those in the LOD group (7.5 ± 2.1 months) ($p < 0.05$). Similar results were noted by Jia et al.,[11] who reported a time to pregnancy of 5.1 months for rFSH and 7.4 months for LOD. The shorter time to pregnancy with rFSH can be advantageous for couples seeking quicker conception.

The cumulative pregnancy rate was higher in the rFSH group (70%) compared to the LOD group (50%) ($p < 0.05$). This finding is consistent with the study by Yang et al.,[12], which also found a cumulative pregnancy rate of 68% for rFSH and 52% for LOD. The higher cumulative pregnancy rate with rFSH highlights its long-term effectiveness in treating infertility in PCOS patients.

The average cost per participant for LOD was 1,800 ± 500 EGP, while for rFSH, it was 2,300 ± 600 EGP ($p < 0.05$). The total treatment cost for LOD was also lower, at 54,000 ± 9,000 EGP, compared to 69,000 ± 10,000 EGP for rFSH ($p < 0.05$). This further supports the economic advantage of LOD, consistent with studies like that of Farquhar et al.,[13], which also highlighted the cost-effectiveness of LOD in similar patient populations.

Limitations include the small sample size and lack of long-term follow-up, which suggest that further research is needed.

4. Conclusion

This study demonstrates that both Laparoscopic Ovarian Drilling (LOD) and recombinant FSH (rFSH) are effective treatments for women with Clomiphene Citrate-resistant PCOS, with each method having its unique benefits and risks. While rFSH may offer higher pregnancy rates, LOD presents a more cost-effective and safer alternative in many cases. The choice of treatment should be tailored to individual patient needs, considering both clinical outcomes and patient preferences.

Disclosure

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