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RESEARCH ARTICLE

To Study the Effect on Fertility Outcome by Gonadotropins *vs* Laparoscopic Ovarian Drilling in Clomiphene-resistant Cases of Polycystic Ovarian Syndrome

[1]Poonam Yadav, [2]Saroj Singh, [3]Richa Singh, [4]Meenal Jain, [5]Sarvesh Awasthi, [6]Pallavi Raj

ABSTRACT

Introduction: The polycystic ovary syndrome (PCOS) is the most common condition associated with chronic anovulation affecting 4 to 6% of reproductive age women.

Aim: To compare the effectiveness of laparoscopic ovarian drilling (LOD) for ovulation induction with gonadotropins in clomiphene-resistant PCOS in terms of ovulation, pregnancy, live birth, abortion, multiple pregnancies, and complication like ovarian hyperstimulation syndrome (OHSS).

Setting and design: A prospective hospital-based randomized trial.

Materials and methods: It was a prospective study, which was carried out from January 2012 to May 2015. Totally, 89 women were evaluated in the study, out of which 44 women were in gonadotropin group and 45 were in LOD group.

Statistical analysis: Standard statistical analysis was done and significance of difference in results was tested by chi-square test.

Results: Ovulation rate in gonadotropin group was 75.0% at 6 months, whereas in LOD group, it was 20% at 3 months and was increased up to 66.66% after addition of clomiphene citrate and gonadotropin. The primary outcome in terms of pregnancy in gonadotropin group was 45.45% after 6 cycles and in LOD group was 11.11% after 3 cycles and 40.00% after 6 cycles with supplementation of clomiphene citrate and gonadotropin.

Conclusion: The ongoing pregnancy rate from ovulation induction with LOD alone was significantly less but if supplemented by clomiphene citrate and gonadotropin, it seems equivalent to ovulation induction with gonadotropin, but the former procedure carries a lower risk of multiple pregnancies.

Keywords: Clomiphene citrate resistance, Laparoscopic ovarian drilling, Polycystic ovary syndrome.

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[1,4,5]Assistant Professor, [2]Professor and Head, [3]Professor [6]Senior Resident

[1-4,6]Department of Obstetrics and Gynecology, Sarojini Naidu Medical College, Agra, Uttar Pradesh, India

[5]Department of Community Medicine, RUHS College of Medical Sciences, Jaipur, Rajasthan, India

Corresponding Author: Poonam Yadav, Assistant Professor Department of Obstetrics and Gynecology, Sarojini Naidu Medical College, Agra, Uttar Pradesh, India, Phone: +919690199138 e-mail: dr.poonamneeraj@gmail.com

INTRODUCTION

The PCOS is the most common condition associated with chronic anovulation affecting 4 to 6% of reproductive age women.[1,2] Several mechanisms contribute to the pathophysiology of anovulation in PCOS, operating at every level of the reproductive system. Therapeutic approaches to chronic anovulation from PCOS are still under debate. The drug of first choice for ovulation induction is clomiphene citrate. However, about 20% of women failed to ovulate in spite of increasing dose of this drug up to 150 mg daily. Clomiphene citrate resistance[3] refers to the failure to ovulate with 150 mg of clomiphene citrate for at least 3 cycles, while clomiphene citrate failure[3] is defined as failure to conceive with clomiphene citrate despite successful regular ovulation for 6 to 9 cycles.

Ovulation induction with gonadotropin is well established in women resistant to clomiphene citrate, but extensive monitoring is necessary because of the risk of multiple follicle developments leading to termination of the cycle, OHSS, or multiple pregnancies. To reduce these complications, various dose regimens have been used. A chronic low-dose setup regimen is probably the most efficient and safest treatment at present.

Recently, laparoscopic electrocautery of the ovaries has been introduced as an alternative treatment for women with the clomiphene citrate-resistant PCOS. This involves a single procedure, which has minimal morbidity and can lead to consecutive ovulations with minimal risks of multiple pregnancies. Women may also respond to clomiphene citrate and/or gonadotropins after this treatment. The disadvantages are the need for surgery under general anesthesia, the unknown long-term effects on ovarian function, and possible adhesion formation.

Whether gonadotropin or electrocautery should be the first treatment of choice in women with the clomiphene citrate-resistant PCOS is still debatable. We conducted a randomized controlled prospective trial to compare the effectiveness of an electrocautery strategy against ovulation induction with recombinant follicle stimulating hormone (FSH) in women who had clomiphene citrate-resistant PCOS.

AIMS AND OBJECTIVES

The aim of this article is to compare the results of LOD with gonadotropins in clomiphene citrate-resistant PCOS women in terms of ovulation and pregnancy. We had also evaluated the secondary outcome of pregnancy in terms of live birth, abortion, multiple pregnancy, and ectopic pregnancy and complications like OHSS.

MATERIALS AND METHODS

Our trial was conducted between January 2012 and May 2015. Women were invited to participate if they had chronic anovulation and polycystic ovaries diagnosed by transvaginal ultrasonography. They had also to be resistant to clomiphene citrate, which is shown by persistent anovulation after taking 150 mg clomiphene citrate daily for 5 days for at least 3 cycles. Women aged between 21 and 35 years were included and women were recruited in study till December 2013. Exclusion criteria were severe male factor subfertility and other causes of infertility like tubal obstruction and extensive adhesion (endometriosis) stages III and IV according to the classification of the American Fertility Society.

All the women were subjected to detailed history, clinical examination, and hormonal evaluation including serum luteinizing hormone (LH), FSH, estradiol, prolactin, serum free testosterone, serum thyroid-stimulating hormone, transvaginal sonography, and preoperative investigations.

Women who gave written informed consent were scheduled for diagnostic laparoscopy and chromopertubation. Secondary exclusion criteria identified during the procedure were tubal obstruction, extensive adhesion of the ovaries or fallopian tubes, and endometriosis stage III or IV. In the absence of any of these, the patients were randomly allocated to either LOD followed by clomiphene citrate and recombinant FSH if anovulation persisted or in the case of ovulation induction with recombinant FSH.

Laparoscopic Ovarian Drilling Strategy

Women underwent preoperative preparation and were given general anesthesia. The woman was placed in steep Trendelenburgs and lithotomy position. Once pneumoperitoneum was created, 10-mm port was introduced into abdominal cavity through the superior crease of the umbilicus for 10-mm telescope. Another two 5-mm ports were introduced into abdominal cavity under vision in each iliac fossa and a diagnostic laparoscopy with chromopertubation for tubal patency was done. An insulated monopolar needle was introduced at 90° angle to the ovarian cortex and a series of puncture sites were created. A cutting current of 100 W was used to initially enter the cortex and was followed by 2 seconds of coagulation current at 40 W. The whole length of the needle was placed into the ovary. Based on ovarian site, anywhere from 4 to 5 puncture sites may be made to adequately destroy ovarian tissue. The surface of the ovary was then irrigated with crystalloid before the trocars were removed.

Women underwent LOD if they failed to ovulate spontaneously at 8 weeks, and were then subsequently added with clomiphene citrate for one cycle followed by gonadotropin.

Gonadotropin Regimen

Women allocated recombinant FSH received 10 mg medroxyprogesterone for 10 days and randomization to induce a withdrawal bleed or if day 2/3 serum LH >7 IU/L, then women were administered combined preparation of ethinyl estradiol 35 µg + cyproterone 2 mg up to three cycles. Ovulation induction was started on cycle day 3 by subcutaneous injection of 37.5/75 IU recombinant FSH daily according to the chronic low-dose stepup regimen. If the diameter of the follicle remained <10 mm, the dose was increased by half an ampoule (37.5 IU) on each of cycle days 16 and 23. If no follicle development (diameter >10 mm) was seen by cycle day 30, the cycle was terminated because of poor response. Cycles were also terminated to prevent hyperstimulation or multiple pregnancies when there were more than six follicles with a diameter of 14 mm or greater, or more than three follicles with a diameter of 16 mm or greater. If one follicle at least 18 mm in diameter and up to two follicles more than 15 mm in diameter were present, then ovulation was induced with 10,000 IU of human chorionic gonadotropin (hCG) subcutaneously or intramuscularly. Women were treated until six treatment cycles were achieved within 12 months. Follicle development was monitored in both treatment arms by transvaginal ultrasonography at weekly intervals and more frequently if indicated by follicle growth. After 48 hours of giving hCG, patients were followed with transvaginal ultrasonography for follicular rupture. They were then called after 17 to 18 days for urine pregnancy test.

Statistical Analysis and Study Design

The primary endpoint was ongoing pregnancy within 12 months, defined as a viable pregnancy of at least

12 weeks. Secondary endpoints were ovulation, miscarriage, ectopic pregnancy, multiple pregnancies, and live birth. The effectiveness of the ovarian drilling strategy was compared with recombinant FSH.

It was a prospective hospital-based randomized trial carried with the approval of ethical committee. The study was done on 89 women of age group between 21 and 35 years, which was divided into two groups of 45 and 44 in number. Each woman was willing to participate if she had polycystic ovaries with clomiphene resistance.

The sample size was calculated using the appropriate formula Z^2PQ/d^2, where P and Q were 0.5 to get the maximum sample size with 10% permissible error and 10% nonresponse rate with 85% confidence interval. The data were entered in MS Excel and analyzed using Statistical Software for the Social Sciences version 18. Standard statistical techniques were applied according to the suitability of data. The significance of the difference in the outcome variable between groups was tested by using Chi-square test; p-value less than 0.05 was considered statistically significant.

RESULTS

A total of 109 women were eligible to participate in the study after evaluating the exclusion criteria. Out of 109 women, 8 women were further excluded after diagnostic laparoscopy because of the presence of endometriosis and adhesions. Totally 12 women did not complete the study protocol. So the results of remaining 89 women were analyzed. Out of 89 women, 44 women were of gonadotropin group and 45 women were of LOD group (Flow Chart 1).

The mean age of women was 26.23 ± 2.9 years in gonadotropin group and 26.11 ± 2.7 years in ovarian drilling group (p = 0.997), which was statistically not significant. All women of ovarian drilling group were of primary infertility, while only one patient in gonadotropin group was of secondary infertility who had a history of one missed abortion (p = 0.49). The two groups were comparable regarding baseline characteristics and hormonal profile (Table 1).

Flow Chart 1: Complete selection progress

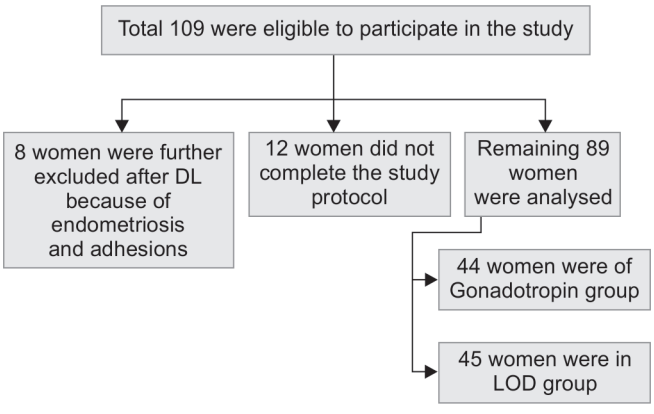

Table 1: Comparison of baseline characteristics of subjects in two groups

	Mean ± Standard deviation		
Baseline characters	*Gonadotropin group (n = 44)*	*LOD group (n = 45)*	*p-value*
Age (years)	26.23 ± 2.9	26.11 ± 2.7	0.997
BMI (kg/m^2)	24.94 ± 2.8	25 ± 2.35	–
Duration of infertility (years)	4.5 ± 2.24	4.62 ± 2.36	0.853
FSH (IU/L)	5.32 ± 0.81	5.14 ± 0.72	0.274
LH (IU/L)	8.65 ± 1.60	10.92 ± 2.96	0.001
Estradiol (pg/mL)	55.33 ± 6.90	56.04 ± 7.24	0
Fasting insulin (μU/mL)	13.79 ± 3.04	14.03 ± 2.53	0.42

Table 2: Use of mean FSH (IU) per patient/cycle and mean duration of induction (days)

	Gonadotropin group	*LOD group*	*p-value*
Doses of FSH (IU)	750–900	600–750	0.001
Duration of induction (days)	12–13	12–14	–

Table 3: Rate of ovulation in both groups

	Gonadotropin group (%)	*LOD group (%)*
At 3 months	33 (75.0%)	9 (20%)
At 6 months	33 (75.0%)	30 (66.66%)
After adding clomiphene citrate + FSH in LOD group		

Table 1 shows mean of basal serum FSH (5.32 ± 0.81) in gonadotropin group and in LOD group (5.14 ± 0.72; p = 0.274), while mean basal serum LH level was 8.65 ± 1.60 in gonadotropin group and 10.92 ± 2.96 in LOD group (p = 0.001), which was statistically significant. In gonadotropin group, mean of basal serum estradiol was 55.33 ± 6.90 and in LOD group was 56.04 ± 7.24 (p = 0.00), which was statistically significant.

Table 2 depicts the use of mean serum FSH (IU) per patient per cycle. In gonadotropin group, it was 750 to 900 IU per cycle and in LOD group it was 600 to 750 IU per cycle and (p = 0.001) was statistically significant. The duration of induction in gonadotropin was 12 to 13 days and 12 to 14 days for ovarian drilling group (Table 2).

Table 3 shows the rate of ovulation in both the groups at 3 and 6 months. In gonadotropin group, the rate of ovulation was same at 3 and 6 months, whereas in ovarian drilling group, it increased from 20% at 3 months to 66.66% at 6 months after addition of clomiphene citrate or gonadotropin. After ovarian drilling, the rate of spontaneous ovulation was 20%, which increased by 6.66% after adding clomiphene citrate and further increased up to 40% after addition of gonadotropin.

Table 4: Pregnancy rates in both groups (positive urine pregnancy test)

	Gonadotropin group (%)	*LOD group (%)*
After 3 cycles	17 (38.68%)	5 (11.11%)
After 6 cycles	20 (45.45%)	18 (40.00%)

Table 5: Various outcome of pregnancy in both groups

Pregnancy outcome	*Gonadotropin group*	*Pregnancy outcome/ total (%)*	*LOD group*	*Pregnancy outcome/ total (%)*
Live births				
Preterm	5	11.36	3	6.66
Full term	10	22.72	8	17.77
Net	15	34.08	11	24.43
Abortion				
1st trimester	5	11.36	6	13.33
2nd trimester	–	–	–	–
Ectopic	–	–	1	2.22
Multiple pregnancies				
Twin	5	11.36	2	4.44
Triplet	1	2.27	–	–
>3	–	–	–	–
Net	6	13.63	2	4.44

The primary outcome in the form of positive urine pregnancy test in gonadotropin group was 38.68% after 3 cycles and 45.45% after 6 cycles, while in ovarian drilling group, it was 11.11% after 3 cycles and 40% after 6 cycles (after addition of clomiphene citrate or gonadotropin) (Table 4).

The secondary outcome in gonadotropin group is that 11.36% pregnancies landed up in first-trimester abortion, 11.36% were preterm deliveries, and 22.72% were full-term deliveries. On the contrary, in LOD group, 13.33% were first-trimester abortion, 6.66% preterm deliveries, 17.77% full-term deliveries, and 2.22% ectopic pregnancies. The incidence of multiple pregnancies was 13.63% in gonadotropin group, out of which 11.36% were twin gestation and 2.27% were triplets, whereas it was 4.44% in ovarian drilling group and all of them were twin pregnancies (Table 5).

There was no case of OHSS reported in both groups.

DISCUSSION

After analyzing the results statistically, there was no significant difference in age, type of infertility, duration of infertility, body mass index (BMI), and ultrasonographic findings in both groups.

The requirement of a mean dose of gonadotropin was significantly higher in gonadotropin group than in subgroup that required gonadotropin after ovarian drilling, which shows an increase in sensitivity to ovulation induction drugs after ovarian drilling. However, the mean duration of induction was not different in both groups.

In gonadotropin group, 75% women ovulated after 3 cycles, which is comparable to Bayram et al[4] who documented 69% ovulatory cycles in gonadotropin group.

In our study, spontaneous ovulation after ovarian drilling was 20% after 3 cycles but subsequently increased up to 66.66% after 6 months by adding either clomiphene citrate or gonadotropin, which was inconsistent with the finding of 86% by Armar and Lachelin.[5] Al-Ojami[6] reported 70% spontaneous ovulation rate and 98.3% cumulative ovulation rate in his study. It can be because of significantly high basal day 2/3 serum LH and E2 level in ovarian drilling group than gonadotropin group.

The rate of pregnancy after 6 cycles in gonadotropin group was 45.45% and the cumulative pregnancy rate was 40.0% in LOD group. A study by Mehrabian and Eessaei[7] documented 71% pregnancy rate with gonadotropins. The findings by Farquhar et al[8] are consistent with our study with cumulative pregnancy rates of 28% at 6 months for ovarian drilling and 33% for 3 cycles of ovulation induction with gonadotropins. Srivastava et al[9] documented 48% pregnancy rate and additional 14% with inducing agents in women treated with ovarian drilling. Bayram et al[4] reported 37.34% pregnancy rate in LOD group and 75.29% with gonadotropin group, which was consistent with our study. A study by Mehrabian and Eessaei[7] also documented results that were consisted to our study that was 34.61% with LOD and 71.15% with gonadotropin group.

One ectopic pregnancy in ovarian drilling group might be because of tubal adhesions after drilling. The abortion rate is little higher in ovarian drilling group to 13.33% than 11.36% in gonadotropin group. Farquhar et al[8] also documented similar miscarriage rate of 1.37 and 1.42% between ovarian drilling and gonadotropin respectively, while Ghafarnegad et al[10] showed pregnancy and abortion rates were more in FSH group, but the difference was not statistically significant. Srivastava et al[9] claimed 6% miscarriage rate in LOD group. Mehrabian and Eessaei[7] stated a similar result that was 9.61% with ovarian drilling group and 11.53% with gonadotropin group.

Out of 20 pregnancies, gonadotropin group had 34.08% live birth and LOD group had 24.43% live birth. Cochrane Database System Review shows[11] 34% live births in LOD group. A recent Cochrane Database System Review of 9 randomized controlled trials and 16 trials concluded that there was no evidence of a significant difference in rates of clinical pregnancy (39.7 *vs* 40.5%) or live birth (34 *vs* 38%) in clomiphene citrate-resistant cases of PCOS undergoing LOD compared with other medical treatment.

By comparing live birth rate (24.43%) with LOD and 34.08% in gonadotropin group, the study by Bayram et al[4] stated 33.73% with LOD and 59.30% with gonadotropin

group and study by Farquhar et al[8] documented 24.69% with LOD and 42.30% with gonadotropin, which is consistent with our study.

The rate of multiple pregnancies in gonadotropin group was 13.63% and LOD group was 4.44% and a study by Mehrabian and Eessaei[7] documented 1.92% with LOD and 9.61% with gonadotropin group, which is consistent with our study.

Totally, 56.81% women in gonadotropin group and 60% women in LOD failed to ovulate or achieve pregnancy despite ovulation and were referred for *in vitro* fertilization (IVF); probably they required higher doses of gonadotropin and more intensive monitoring for OHSS.

CONCLUSION

In our study, it appears that LOD alone is not much effective in inducing ovulation until it was supplemented further with clomiphene citrate or gonadotropin. The advantage of ovarian drilling appears that patient then requires fewer doses of FSH, so it reduces the cost of treatment. The LOD leads to monofollicular development by which risk of multiple pregnancy and OHSS will be reduced. However, the potential risk of periovarian adhesions and premature ovarian failure needs further evaluation of this procedure. As we followed the low-dose stepup protocol for FSH, the risk of OHSS and multiple pregnancies is minimal and appears to achieve higher ovulation and pregnancy rates.

Since LOD improves ovarian responsiveness to clomiphene citrate and gonadotropins, these may be considered after LOD failure before proceeding to the last resort, i.e., IVF. Despite its advantages, LOD is neither the first-line therapy in PCOS nor the treatment of choice in clomiphene citrate-resistant PCOS owing to the advent of a multitude of safe and efficacious oral alternatives and wider acceptance of relatively safe low-dose stepup regimen of gonadotropin therapy.

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