

ABSTRACT

Background: Polycystic ovarian syndrome is a common endocrine disorder affecting 6-10% of women of reproductive age and the most common cause of anovulatory infertility.

Objective: The aim of the study was to compare the effectiveness, side effects and outcomes of step-up gonadotrophin protocol versus laparoscopic ovarian diathermy (LOD) in infertile patients with clomiphene citrate resistant polycystic ovary syndrome.

Methods: The sample included women who attended our infertility clinic at Al-Elwiya Maternity Teaching Hospital and Kamal Al-Samarrae for Infertility and IVF Hospital in Baghdad/ Iraq from November 2013 to November 2014. Eighty cases of infertile women with polycystic ovarian syndrome who failed to ovulate with clomiphene citrate for six months were collected, forty women treated with step-up protocol with low dose recombinant FSH gonadotrophin which increased gradually according to ovulation response, another forty women treated with LOD. Ovulation monitoring in each group was done with transvaginal ultrasound to exclude monofollicular, bifollicular ovulation, ovarian hyperstimulation syndrome, multiple pregnancy and pregnancy rate in each cycle for 6 cycles.

Results: Higher unifollicular ovulation and pregnancy rate in LOD than step-up protocol (91.4% & 25% versus 75% & 10%) respectively, while multifollicular and hyperstimulation rate were higher in gonadotrophin group (24.3% & 0.1% versus 8.50% & nil) respectively.

Conclusion: Ovulation induction and pregnancy rate per cycle was higher with LOD group, not time consuming, also there was no risk of hyperstimulation of the ovary or twin pregnancy as compared to the step-up protocol with gonadotrophin.

Keywords: step-up gonadotrophin, laparoscopic ovarian drilling, PCOS

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INTRODUCTION

Polycystic ovary syndrome (PCOS), also called hyper androgenic anovulation or Stein-Leventhal syndrome⁽¹⁾ is one of the most common endocrine disorders among women. According to the Rotterdam criteria, PCOS is characterized by a combination of oligo/amenorrhoea, clinical or endocrine signs of hyperandrogenism and polycystic ovaries.⁽²⁾

Women with PCOS have normogonadotrophic and normo-oestrogenic anovulation (WHO group II) and constitute the largest group of anovulatory women encountered in clinical practice (60-85%).⁽³⁾ The heterogeneity of PCOS is reflected in the varying response exhibited to ovulation induction regimens.⁽⁴⁾

Not all women with PCOS have difficulty becoming pregnant, for those who

do; anovulation is a common cause. The mechanism of this anovulation is uncertain, but there is evidence of arrested antral follicle development, which in turn, may be caused by abnormal interaction of insulin and luteinizing hormone on granulosa cells.⁽⁵⁾

Endocrine disruption may also directly decrease fertility, such as changed levels of gonadotrophin-releasing hormone gonadotrophin⁽⁶⁾ especially an increase in luteinizing hormone^(6,7), hyperandrogenemia and hyperinsulinemia.⁽⁸⁾

Clomiphene citrate (CC), a selective estrogen receptor modulator, is an efficient, inexpensive and well tolerated drug with a well-known safety profile when dosed correctly⁽⁹⁾ and still remains the first line of

treatment for ovulation induction (OI) in PCOS patients. ^(10,11,12,13,14) CC-resistance (CCR) refers to the failure to ovulate with 150 mg of CC for at least 3 cycles, while CC-failure is defined as failure to conceive with CC despite successful regular ovulation for 6-9 cycles. ⁽¹⁵⁾

Gonadotrophin stimulation is usually administered to women who are CCR as an effective second-line treatment, but can be used as first line ⁽¹⁶⁾ and pregnancy rates are higher in low-dose recombinant FSH cycles compared with clomiphene citrate cycles. ^(17,18) As the polycystic ovary may be sensitive to gonadotrophin stimulation, careful dosage adjustment is recommended. ⁽¹⁶⁾ The step-up approach is significantly more successful than the step-down approach in achieving mono-follicular development (68.2% versus 32.0%; $P < 0.0001$) and ovarian hyper stimulation syndrome (OHSS) is less (4.7% versus 36%). ⁽¹⁹⁾

The development of techniques has reawakened interest in surgical laparoscopic treatment for anovulation in those who fail to ovulate with medical therapy. Minimal invasive surgery with laparoscopic ovarian drilling (LOD) could be considered as an alternative treatment in infertile PCOS women characterized by CCR, excessive or uncontrollable reaction to gonadotrophins or previous OHSS. ⁽¹⁸⁾

METHODS

This prospective, observational-follow up study was conducted at Al-Elwiya Maternity Teaching Hospital and Kamal Al-Samarraee for Infertility and IVF Hospital in Baghdad/ Iraq from November 2013 to November 2014.

The study protocol was approved by the Authority of Hospital Administration. The study sample was 80 obese patients with polycystic ovary syndrome (WHO group II) who failed to ovulate after 6 months of treatment with clomiphene citrate, all of them had patent tubes

on hysterosalpingography and normal seminal fluid analysis for their husbands.

The study sample was divided to two groups: 40 of them were treated with gonadotrophin (GnT) considered as group one, and the second group treated by laparoscopic drilling. Consent was obtained from all patients included in the study. Data were collected in special questionnaire and each group was followed for 140 cycles.

Detailed history for each woman included: age, parity & previous treatment.

General and gynecological examination has been done for all patients including weight, height measurement, and BMI calculation with detailed abdominal and vaginal examination.

This study involved two groups:

1st group treated with step-up protocol using Gonal F (follitropin alpha) which is preparation of follicle stimulating hormone produced by genetically engineered Chinese Hamster Ovary cells, produced by Serono Drug Corporation.

Ovulation induction had been started with Gonal F with starting dose of 50 IU/1 given at day 3 of the cycle daily for 7 days in each cycle except in the first cycle, during which the dose of 50IU daily of continued for 14 days instead of only 7 days. Transvaginal ultrasound has been done using Siemens Sonoline versa machine with 3.5MHZ transducer, at the first day or on the third day thereafter during the study period depending on the size and number of the ovarian follicles.

If the follicle size was 12 mm or less at day 8 day, the dose of Gonal F increased by 25 IU. This treatment schedule has been applied to each patient for minimum of 1 cycle and maximum of 6 cycles. At any ultrasound control, if the follicle was 14 mm or more, ultrasound examination was daily, if 1-3 follicle reach the size of 18-20 mm, HCG in dose of 10,000 IU had been given intramuscularly to induce ovulation. If more than 3 follicles reached the size of 16mm or more, ovulation induction with HCG was canceled and the use of barrier contraceptive advised in order to prevent multiple pregnancies and ovarian hyper stimulation. Measurements of serum oestradiol; preovulatory concentration far above the normal range (14-40 ng/dl or 500-1500 pmol) also predicted ovarian hyper stimulation.

2nd group of patients were treated with laparoscopic ovarian drilling with 4 punctures per ovary of 4mm depth for 4seconds, a specially designed monopolar electrocautery probe (ovarian diathermy needle Rocket of London) was used to penetrate the ovarian capsule with monopolar coagulation electricity current activated for 4 s with a power setting of 30W. Patients were followed for 6 cycles to assess ovulatory rate by ultrasound monitoring, pregnancy & ovarian hyper-stimulation rate.

Statistical analysis

All patients' data entered using computerized statistical software; Statistical Package for Social Sciences (SPSS) version 21 was used. Descriptive statistics presented as (mean ± standard deviation) and frequencies as percentages. Multiple contingency tables conducted and appropriate statistical tests performed, Chi-square used for categorical variables (Fishers exact test was used when expected variable was less than 20% of total) and t-test was used to compare between two means. One-way ANOVA analysis was used to compare between more than two means. In all statistical analysis, level of significance (p value) set at ≤ 0.05 and the result presented as tables and/or graphs.

RESULTS

This study had enrolled 80 patients with polycystic ovary, their age ranged between 18 - 37 years (27.1± 4.6 years). 72.5% of the sample were younger than 30 years old, as shown in table1.

Their body mass index ranged between 24.6-33.2 kg/m² (28.5± 7.2 kg/m²)

Table-1: Age distribution of the sample

Age (year-old)	No.	%
<20	2	2.50%
20 – 29	56	70%
30 – 39	22	27.50%
Total	80	100%
Range (years)	18 - 37	
Mean ± SD (years)	27.1 ± 4.6	

All the patients were enrolled in the first treatment cycle, but not all of them continued their treatment throughout all the study period.

Table 2 and figure 1 shows the number of patients included in each of the 6th treatment cycles.

Table-2: Number of patients included in both treatment cycles

Treatment cycles	Number of patients in both groups
1 st	80
2 nd	74
3 rd	48
4 th	42
5 th	26
6 th	10
Total number of cycles during the period of the study	280

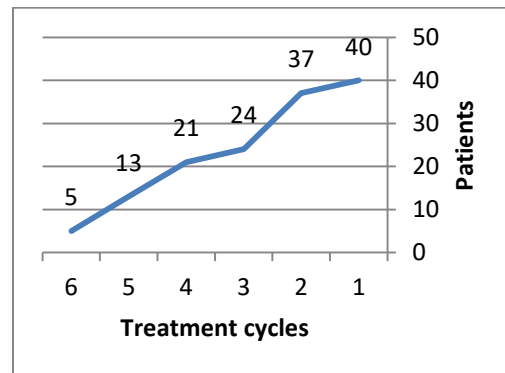


Figure-1: number of patients included in each treatment cycles

Table 3 shows the duration of treatment cycles of gonadotrophin group with first treatment cycle continued for 14.05 days in average, while the 6th treatment cycle continued for 9.5 days.

Table-3: Duration of treatment in gonadotrophin (r-FSH) cycle

Treatment cycles	No. of patients	Range (days)	Mean (days)	± SD
1 st	40	8-22	14.05	3.4
2 nd	37	8-19	12.6	3.2
3 rd	24	7-18	12	3.1
4 th	21	7-16	11	2.6
5 th	13	7-14	10.4	2.3
6 th	5	8-11	9.5	1.7

During this prospective study, 140 cycles had been evaluated for each study group, 75% of the patients who were treated by gonadotrophin were having uni-or monofollicular cycles while only 1 cycle showed 3 follicles. Table 4 shows the number of ovarian follicles observed in the

evaluated cycles for patients who were treated by gonadotrophin.

Table-4: Number of ovarian follicles observed in the gonadotrophin (r-FSH) cycles

Number of follicles/cycle	No.	%
Unifollicular cycle	105	75%
Bifollicular cycle	34	24.30%
3 follicles	1	0.70%
Total	140	100%

For the first treatment cycle, the average total dose of recombinant FSH was 739.4 IU, and it was decreased to 605 IU at the 6th treatment cycle. Table 5 shows the total dose of recombinant FSH used in each cycle.

Table-5: Patients distribution according to the total dose of r-FSH used in each cycle

Treatment cycles	No. of patients	Range of Gnt dose (IU)	Mean (IU)	±SD
1 st	40	400-1325	739.4	225.7
2 nd	37	425-1375	793.2	270.7
3 rd	24	350-1275	737.5	254.7
4 th	21	350-1075	653.6	203.9
5 th	13	350-875	609.6	172.2
6 th	5	425-800	605	136.2

Only four patients of those treated by r-FSH succeeded to conceive: one during the second cycle and the other three during the 3rd cycle both with a total dose of r-FSH of 716.2 ± 20.4 IU and a mean daily dose of 60.4 ± 3.5 IU/day. Five cases of mild hyper-stimulation syndrome and one case of multiple pregnancies were detected among the patients included in this group of study.

Table 6 shows treatment results with laparoscopic ovarian drilling. 128 cycles

(91.4%) were unifollicular while only 12 cycles (8.5%) were bifollicular. No cycle with more than 3 follicles or hyperstimulation. Ten patients of those who were treated by ovarian drilling conceived (all of them singleton pregnancy).

Table-6: number of ovarian follicles observed in the evaluated cycles with LOD

Number of follicle per cycle	No.	%
unifollicular	128	91.40%
bifollicular	12	8.50%
> 3 follicles	nil	0.1
Pregnancy Rate	10	25%

Table 7 shows a comparison between results of gonadotrophin group & LOD group with higher unifollicular ovulation and pregnancy rate in LOD (91.4% versus 75%) and (25% versus 10%) respectively while multifollicular and hyperstimulation rate were higher in gonadotrophin group (25% versus 8.50%) & (0.1% versus nil) respectively.

Table-7 Comparison between the outcomes of step-up protocol gonadotrophin versus laparoscopic ovarian drilling

Outcomes	1 st group	2 nd group
Unifollicular cycles	75%	91.40%
Bifollicular cycles	24.30%	8.50%
Trifollicular cycles	0.70%	nil
Pregnancy rate	10%	25%
Ovarian hyperstimulation	0.1	nil
Twining	3.50%	nil

DISCUSSION

Ovulation induction to reverse the anovulation is the principal treatment used to help infertility in PCOS. Letrozole and clomiphene citrate are the first-line treatment in subfertile anovulatory patients with PCOS.⁽²⁰⁾ There appeared to be no difference between letrozole and laparoscopic ovarian drilling.⁽²¹⁾ Gonadotrophins such as follicle-stimulating hormone (FSH) are, in addition to surgery, second-line treatments.⁽²²⁾

The problem of achieving the desire for mono or

unifollicular ovulation is particularly difficult. The reason of this is probably due to the fact that polycystic ovaries contain twice the number of available FSH sensitive antral follicles compared with normal ovary. Any dose of FSH overstepping the threshold of the polycystic ovary will therefore produce multifollicular development and impending danger of multiple pregnancy and ovarian hyper stimulation syndrome thus gonadotrophin use requires extensive monitoring.^(23,24)

Laparoscopic ovarian drilling, on the other hand, involves a single procedure that has minimal morbidity and can lead to consecutive ovulations with minimal risks of multiple pregnancies.⁽²⁵⁾ Adnexal adhesions and reduced ovarian reserve are considered two probable hazards of LOD.⁽²⁶⁾

This study had evaluated 140 cycles during 6 treatment cycles with recombinant FSH and another 140 cycles post laparoscopic ovarian drilling.

Total dose of recombinant FSH gonadotropins was 750 IU in a study of Coelingh Bennink HJ et al⁽²⁷⁾ which is close to our total starting dose (739.4 IU) and to the study of Leader A (887 IU)⁽²⁸⁾. The level of unifollicular development observed with gonadotrophin group in our study (75%) is close to that observed in the study done by Alsina⁽²⁹⁾ et al that used step-up protocol (61.3%). Total pregnancy rate was 18 % in the study of Robert Streda et al⁽³⁰⁾ which is close to that of our study (10%) but less than that of Alsina et al⁽²⁹⁾ (53.1%), which can be related to the fact that Alsina et al used intrauterine insemination. Alsina et al showed 6.0% multiple pregnancy rate as compared to 3.5% in our study.⁽²⁹⁾

The study of Amer SA et al⁽³¹⁾ suggests that LOD may be more effective in CC-resistant PCOS women than in women without previous knowledge of their response to CC.

Our study on laparoscopic ovarian drilling shows spontaneous conception rate of 25% while Rama Singh Chundawat and Arun Gupta⁽³²⁾ showed a rate of 48% because their study continued for 2 years and Zahra Moazami et al⁽³³⁾ showed no evidence of a significant difference in rates of clinical pregnancy in women with clomiphene citrate-resistant PCOS undergoing LOD compared to the gonadotropin arm.

The study of Farquhar C et al⁽³⁴⁾ gave multiple pregnancy rate of 10% in LOD, which is significantly lower than gonadotropins, similar to the results of Zahra Moazami⁽³³⁾ thus making LOD an attractive option for CC-resistant PCOS. No difference in the incidence of OHSS is seen between LOD and other medical treatments in Farquhar C et al⁽³⁴⁾ study as with our results. Fortunately, all five cases of hyper stimulation syndrome were mild and treated conservatively and only one case of twin pregnancy was detected in our study with gonadotrophin group;

a finding that can be supported by the high frequency of unifollicular cycles due to close monitoring in our study. Similar advantages of inducing monofollicular stimulation was detected by Rama Singh Chundawat et al and Arun Gupta⁽³²⁾ thus avoiding the risk of multiple pregnancy and OHSS and cost effective as intensive monitoring is not required.

Lastly, we agree with Subarna Mitra et al⁽³⁵⁾ that laparoscopic ovarian drilling is currently recommended as a safe, efficacious and cost-effective alternative to gonadotropins for OI in infertile, anovulatory, CC-resistant PCOS women without the risks of OHSS or multiple gestation. Despite its advantages, LOD is neither the first-line therapy in PCOS nor the treatment of choice in CC-resistant due to surgically-related complications as adhesion formation and destruction of some ovarian tissue.⁽³³⁾ Rather, it should be reserved to well-chosen anovulatory CC-resistant PCOS cases - Those with young age, raised LH levels, exaggerated response to gonadotropins, noncompliance or nonfeasibility with frequent, intensive monitoring or needing laparoscopic assessment of the pelvis. Importantly, reproductive specialists should remember that it is only an alternative, not the ultimate in management of PCOS.⁽³⁵⁾

CONCLUSION

The low dose regimen of r-FSH is less effective in inducing mono- follicular development in WHO group II anovulatory women when compared with laparoscopic ovarian drilling which is superior to gonadotrophin in cumulative pregnancy rate and avoiding ovarian hyperstimulation syndrome and twin pregnancy. Step-up protocol needs intensive follow up & ovulatory monitoring, which is not the case in laparoscopic ovarian drilling group.

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