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Original Research Article

Laparoscopic ovarian drilling-plus: a one-stop management approach for PCO-associated infertility

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ABSTRACT

Background: The current study aims to estimate additional values of laparoscopic intervention for diagnosis and treatment of concomitant pelvic pathologies among infertile women with clomiphene-resistant polycystic ovarian syndrome (PCOS) subjected to laparoscopic ovarian drilling (LOD) in comparison to non-PCOS infertile women subjected to diagnostic/therapeutic laparoscopy.
Methods: A prospective cross sectional observational study was carried out in the Endoscopic unit of a tertiary care university hospital. The study included 232 infertile women planned for laparoscopy were divided into a study group A (116 cases) with clomiphene-resistant PCOS and a control group B (116 cases) without PCOS. Each group was further subdivided into two subgroups according to the presence and absence of risk factors (RF) for adhesion formation. Diagnostic/operative laparoscopy was done. The main study outcome was the prevalence of any pelvic abnormalities seen during laparoscopy.
Results: Both groups showed insignificant difference regarding socio-demographic history and basic data. Laparoscopy detected pelvic pathologies in 44 cases (37.9%) and 86 cases (74.1%) in both groups respectively. In group A, we diagnosed pelvic pathologies in 29 (32.6%) and 15 (55.6%) cases with and without RF respectively while in group B they were diagnosed in 76 (84.4%) and 10 (38.5%) cases with and without RF respectively. If compared to women with unexplained infertility, PCO patients without risk factors have an insignificant but higher prevalence of pelvic abnormalities. All concomitant pelvic pathologies in both groups were treated on a one-stop (see and treat) basis.
Conclusions: Detection and proper management of associated pelvic pathologies at laparoscopy is a valuable additional advantage of LOD particularly in women with positive risk factors. LOD plus see and treat associated pathologies is a time saving and prompt management approach for women with PCO–associated infertility.

Keywords: Infertility, Laparoscopy, Ovarian drilling, Polycystic ovarian syndrome

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is the commonest hyperandrogenic disorder in women and one of the most common causes of anovulatory infertility, with an estimated prevalence of 4–7% worldwide.[1] It is an over-diagnosed and disproportionately treated condition. Lifestyle modification, weight loss, and exercise form the first line of treatment in infertile women with PCOS.[2]

The recommended first-line drug for ovulation induction remains clomiphene citrate (CC), while metformin is helpful in cases with glucose intolerance, or those with a BMI >35 kg/m.[3]

The recommended second-line treatment involves gonadotropins or LOD.[2] Despite being equally effective, yet the main benefits of LOD are shorter time to pregnancy, less need to ovulation induction drugs, more comfort, cost-effective and possibility to be performed ambulatory.[4]

In a previous study, we could explain the lower possibility of ovarian hyperstimulation syndrome (OHSS) after LOD.[5] However, still many centers prefer HMG therapy omitting advantages of LOD as supported by recommendations of fertility-interested societies which restrict indications of laparoscopy in infertility to cases with suspected tubal occlusive disease, peritoneal factor or advanced endometriosis.[6] Possible risks of ovarian failure, decrease ovarian reserve and adhesions are definite mares against LOD.[7,8] Studies on associated pelvic pathologies with PCOS are scarce. One study found a significant association between endometriosis and women with PCOS with pelvic pain and/or infertility up to 74%.[9] The majority of endometriotic lesions (76%) were stage I or II. This study aims to estimate additional values of laparoscopic intervention for diagnosis and treatment of concomitant pelvic pathologies among infertile women with CC-PCOS subjected to LOD in comparison to non- PCOS infertile women subjected to diagnostic/therapeutic laparoscopy.

METHODS

This prospective, cross sectional, single-centre, clinical study took place at Woman's Health Hospital, Assiut University from May 2015 to May 2016. The institutional review board (IRB) approved the study. It comprised 232 infertile women attending gynecologic and infertility clinics that were selected for the study.

Sample size was calculated using EPI info 2000 statistical package. The calculation was done using the expected frequencies of different risk factors among cases and controls and or the calculated odds ratio from previous studies using 95% confidence interval and 80% power of the test and taking one control for each case.

Two hundred twenty three infertile women planned for laparoscopy were divided into a study group A (116 cases) with CC-resistant PCOS and a control group B (116 cases) without PCOS respectively. Each group was further subdivided into two subgroups according to the presence and absence of risk factors (RF).

Risk factors for pelvic abnormalities included abnormal HSG, history suggestive of pelvic endometriosis, history of pelvic inflammatory disease or appendicitis, history of previous ovarian cystectomy, myomectomy, appendectomy, cesarean section or other pelvic operations.

Exclusion criteria included previous LOD, patients with contraindication to laparoscopy e.g. hemodynamic instability, gynecologic malignancy, patients with contraindication to anesthesia or male factor of infertility.

Clinical work-up

All cases were subjected to a detailed history and a thorough clinical examination. All patients were assessed clinically (to determine menstrual pattern, body mass index, hirsutism, abdominal scar in addition to general examination), sonographically (to measure ovarian volume, antral follicle count at time of ovarian quiescence or adnexal or uterine masses) and laboratory (to measure day 3 to 5 serum LH, FSH, LH/FSH ratio, total testosterone and estradiol).

Serum concentration of E2, FSH and LH were measured by chemiluminescent immuno-assay provided by Diagnostic products, and interpretation of assays was performed according to manufacturer recommendations.[10] Pregnancy was ruled out by pregnancy test in all cases with oligo or amenorrhea.

Group A included PCO patients who received CC at maximal dose of 200 mg daily from day 2 for 5 days for 6 successive cycles with proved anovulation using day 21 serum progesterone. The diagnosis of PCO patients was based on the Rotterdam European Society of Human Reproduction/American Society for Reproductive Medicine Sponsored PCOS Consensus Workshop Group with the existence of two of the following three criteria to make the diagnosis of PCOS: oligo-ovulation/anovulation, clinical or biochemical signs of hyperandrogenism and polycystic ovaries by ultrasound.[11]

LOD was performed in the follicular phase of natural cycle via three ports of entry after insufflations of the peritoneal cavity by electronic high-flow pneumoperitoneum insufflator with CO2 gas. Prior to drilling, the pelvis and abdomen were meticulously explored searching for a concomitant pathology that may affect fertility and recorded. LOD was performed using an insulated monopolar electrocautery needle electrode inserted into the antimesentric ovarian surface as close to perpendicularly as possible after proper grasping of the ovarian ligament. Tubal patency and mobility were confirmed by flushing of the tubes with methylene blue.

After drilling, the ovary was allowed to cool in a pole of saline to prevent excessive heat trauma. Any associated fertility-related pelvic pathology was promptly treated at the same session. After exploration of the upper abdomen, the peritoneal cavity was rinsed with 500 cc lactated Ringer's solution.

Group B comprised women with primary or secondary infertility without clinical, sonographic or laboratory evidence of PCOS and planned for diagnostic/operative laparoscopy. Likewise, any associated fertility-related pelvic pathology was reported and promptly treated. The

main outcome of the study was the prevalence of laparoscopic abnormalities. The endpoint of this study was short follow-up period after operative laparoscopy till complete cure of the patient. Any complication was recorded.

Statistical analysis

The data were tested for normality using the Anderson-Darling test and for homogeneity variances prior to further statistical analysis. Statistical analysis was performed with the IBM SPSS 20.0 software (SPSS, Inc., Chicago, IL). Data were presented using descriptive statistics in the form of frequencies and percentages for qualitative variables, and ranges, means and SDs, medians and quartiles for quantitative variables. The comparability of baseline characteristics according to outcome was ascertained by Student t test for continuous variables and Mann-Whitney U test when appropriate and Chi-square test for categorical variables. Values were considered significant if p ≤05.

RESULTS

In this study, 232 infertile patients (PCOS and non PCOS infertile patients) were recruited and allocated as group A and B respectively. They were classified into two subgroups according to RF. Group A included 89 (76.7%) and 27 (23.3%) while group B included 90 (77.6%) and 26 (22.4%) cases with positive and negative RF respectively.

Both groups showed insignificant difference regarding sociodemographic history including age, residence, type and duration of infertility. BMI was significantly higher in group A (32.39±5.81 Kg/m^2) than group B (27.91±3.70 Kg/m^2) (P=0.000).

Table 1: Basic preoperative hormonal profile of both groups.

Serum hormones	PCO group (n= 116)	Non-PCO group (n= 116)	P-value
LH (mean±SD) mIU/ml	10.77±4.76	3.69±1.50	0.000*
FSH (mean±SD) mIU/ml	4.79±1.91	6.29±3.75	0.000*
Prolactin (mean±SD) ng/ml	27.43±21.00	14.34±8.06	0.000*
Total testosterone (mean±SD)	0.787±0.30	0.458±0.11	0.000*
Prolactin level			
Normal	78 (67.2%)	109 (94.0%)	0.000*
Increased	38 (32.8%)	7 (6.0%)	
FSH/ LH ratio			
Normal	40 (34.5%)	99 (85.3%)	0.000*
Reversed	76 (65.5%)	17 (14.7%)	

Student-T-test was used for comparing means, Chi-square test was used for comparing frequencies, * Statistically significant difference (p<0.05)

Table 2: Laparoscopic findings in both groups.

Laparoscopic findings	PCO +ve RF (Group A)		Non-PCO +ve RF (Group C)		PCO -ve RF (Group B)		Non-PCO -ve RF (Group D)		P-value[1]	P-value[2]
	No.	%	No.	%	No.	%	No.	%		
Normal laparoscopic findings	0	0	14	15.6	0	0	16	61.5	0.000*	0.000*
Congenital anomalies	4	4.5	10	11.6	0	0	1	3.8	0.082	0.985
Multiple pathology	23	25.8	43	47.8	10	37.0	2	7.7	0.002*	0.011*
Fibroid	5	5.6	13	14.4	2	7.4	0	0	0.050*	0.488
Ovarian findings										
PCOS	89	100	0	0.0	27	100	0	0		
Simple cyst	0	0	9	10.0	1	3.7	0	0	0.007*	0.322
Endometrioma	0	0	4	4.4	0	0.0	0	0		
Dermoid cyst	1	1.1	0	0.0	0	0.0	0	0	0.996	--
Tubal occlusion										
Bilateral tubal block	5	5.6	10	11.1	1	3.7	1	3.8	0.185	0.978
Unilateral tubal block	3	3.4	10	11.1	3	11.1	0	0	0.046*	0.248
Hydrosalpinx										
Bilateral	0	0	5	5.6	0	0	0	0	0.072	--
Unilateral	1	1.1	4	4.4	0	0	0	0	0.371	--
Other tubal pathology	3	3.4	2	2.2	0	0	0	0	0.990	--
PID	0	0	7	7.8	0	0	0	0	0.022*	--
Endometriosis	1	1.1	17	18.9	3	11.1	6	23.1	0.000*	0.427
Adhesions	6	6.7	45	50.0	5	18.5	4	15.4	0.000*	0.761

RF; risk factor, PCO, polycystic ovary; Chi-square test used for comparison between frequencies; * Statistically significant difference (p<0.05); [1]refers to p-value of PCOS +ve risk factors and non PCOS +ve risk factors; [2]refers to p-value of PCOS -ve risk factors and non PCOS -ve risk factors.

Moreover, menstrual irregularities and positive family history of PCOS were significantly higher in group A. Clinical manifestations of hyperandrogenism showed a significant higher hirsutism (79, 68.1% versus 1(0.9%) but not acne 59 (50.1%) versus 51 (44%) in group A than group B respectively. Basic preoperative hormonal profile was significantly different in both groups (Table 1).

Table 3. Summary of laparoscopic findings.

	+ve RF					-ve RF									
	PCO +ve RF (Group A)		Non-PCO +ve RF (Group C)		P-value[1]	PCO -ve RF (Group B)		Non-PCO -ve RF (Group D)		P-value[2]	PCOS		Non PCOS		P-value[3]
	No.	%	No.	%		No.	%	No.	%		No.	%	No.	%	
Total	89	76.7	90	77.6		27	23.3	26	22.4		116	100	116	100	
Pelvic pathology	29	32.6	76	84.4	0.000*	15	55.6	10	38.5	0.213	44	37.9	86	74.1	0.000*

RF; risk factor, PCO, polycystic ovary; Chi-square test used for comparison between frequencies; *Statistically significant difference ($p<0.05$); [1]refers to p-value of PCOS +ve risk factors and non PCOS +ve risk factors. [2]refers to p-value of PCOS -ve risk factors and non PCOS -ve risk factors. [3]refers to p-value of all PCOS patients and all non PCOS patients.

Table 4: See and treat of pelvic pathologies at laparoscopy.

Operative report	PCO +ve RF (Group A)		Non-PCO +ve RF (Group C)		PCO -ve RF (Group B)		Non-PCO -ve RF (Group D)		P-value[1]	P-value[2]
	No.	%	No.	%	No.	%	No.	%		
Myomectomy	1	1.1	2	2.2	0	0.0	0	0.0	0.657	--
LOD										
Bilateral LOD	72	80.9	0	0.0	22	81.5	0	0.0	0.000*	0.000*
Unilateral LOD	3	3.4	0	0.0	2	7.4	0	0.0	0.240	0.488
Drilling of multicystic ovary	0	0.0	1	1.1	0	0.0	0	0.0	0.319	--
Cystectomy	1	1.1	6	6.7	0	0.0	0	0.0	0.127	--
Excision of endometrioma	0	0.0	2	2.2	0	0.0	0	0.0	0.482	--
Puncture of cyst	3	3.4	8	8.9	1	3.7	0	0.0	0.124	0.322
Successful tubal canulation	4	4.5	8	8.9	1	3.7	0	0.0	0.240	0.322
Failed cannulation	6	6.7	14	15.6	3	11.1	1	3.8	0.061	0.631
Neosalpingostomy	2	2.2	1	1.1	1	3.7	0	0.0	0.992	0.322
Salpingolysis	0	0.0	4	4.4	0	0.0	0	0.0	0.132	--
Salpingectomy	0	0.0	4	4.4	0	0.0	0	0.0	0.132	--
Adhesiolysis	4	4.5	22	24.4	3	11.1	2	7.7	0.000*	0.670
Removal of endometriotic lesion	1	1.1	11	12.2	3	11.1	2	7.7	0.003*	0.670

RF; risk factor, PCO, polycystic ovary; Chi-square test used for comparison between frequencies; *Statistically significant difference ($p<0.05$). 1refers to p-value of PCOS +ve risk factors and non PCOS +ve risk factors. 2refers to p-value of PCOS -ve risk factors and non PCOS -ve risk factors.

Laparoscopy detected pelvic pathologies in 44 cases (37.9%) and 86 cases (74.1%) in both groups respectively. In group A, we diagnosed pelvic pathologies in 29 (32.6%) and 15 (55.6%) cases with and without RF respectively while in group B they were diagnosed in 76 (84.4%) and 10 (38.5%) cases with and without RF respectively as shown in Table 2.

Table 3 summaries laparoscopic diagnosis of pelvic pathologies in both groups. All concomitant pelvic pathologies in both groups were treated on a one-stop (see and treat) basis (Table 4).

DISCUSSION

PCOS is a medical disorder that principally should be medically treated. Failure of CC even on maximal dose as a first line therapy for PCOS represents a real challenge for gynecologists.[12] Many studies tried to combine another drug to CC to increase its efficacy.[13] Others replaced it by an alternative medical or surgical treatment. Gonadotrophins therapy (GTs) is considered the best second line as it doesn't affect ovarian reserve and carries no risks of peritubal or periovarian adhesions.

Moreover, failed ovulation after LOD will ultimately require GTs, so it is logic to use GTs from the start omitting the risks of LOD. Nevertheless, with GTs there is a possibility of life-threatening situations with high ICU admissions. The estimated fatality rates of GTs are 1 per 400,000-500,000 stimulated cycles due to OHSS.[14] Despite weak evidence, many observers have worried that the use of fertility drugs including GTs could lead to an increased risk of cancer—in particular, breast, ovarian, and uterine (including endometrial) cancers.[15]

Contrarily, LOD is proved to be as effective as GTs and is not associated with increased risks of multiple pregnancy or OHSS.[10,11] As reported by our team, LOD was found to cause decline of already increased serum levels of serum vascular endothelial growth factor, and insulin-like growth factor-1 which may explain increased vascularity demonstrated by Doppler blood flow measurements in PCOS.[5] These changes are accused to be associated with OHSS.

Maximal benefit is expected when LOD is associated with concomitant hysteroscopy. Previously, we highlighted the importance of combined laparoscopy and hysteroscopy in infertility even unexplained case.[16] One study detected and simultaneously treated uterine abnormalities in 18 (28%) of 74 PCOS patients using concomitant hysteroscopy.[17]

To cut short this dilemma, it is essential to stratify cases and to restrict LOD to highly selected well-chosen anovulatory CC-resistant PCOS cases who are of young age, raised LH levels, normal body mass index, exaggerated response to gonadotropins, non-compliance or non-feasibility with frequent, intensive monitoring or needing laparoscopic assessment of the pelvis.[18]

In this study, more than 50% of PCO patients were obese which illustrates that obesity is a risk factor for PCOS. In fact, approximately 50% of PCOS women are overweight or obese and the history of the weight gain frequently precedes the onset of oligomenorrhea and hyperandrogenism, suggesting a pathogenic role of obesity in the subsequent development of the syndrome.[19]

As we detected hirsutism in (68.1%) of PCOS infertile patients, and the current indication for LOD is infertility so far no studies recommended LOD for hirsutism thus we recommend more studies to investigate whether those patients would improve after LOD or not.

In this study, we found association between raised LH to FSH ratio in (65.5%) of PCOS infertile patients. However, ESHRE/ASRM consensus considered raised LH to FSH ratio as a supportive but not basic item for diagnosis of PCOS.[11]

In this study, hyperprolactinemia was detected in (32.8%) of PCOS infertile patients. Hyperprolactinemia does not seem to be more frequent in PCOS women than in healthy subjects and it should not be considered as characteristic feature of PCOS - both are distinct clinical entities. Prolactin concentrations should be assessed in each woman with PCOS suspicion because of similarity in causing oligo or hypomenorrhea and defective ovulation. Every woman diagnosed with PCOS and hyperprolactinemia should further be examined in terms of its actual causes because the coexistence of these two disease entities is possible.

Even if all criteria of PCOS are present, the question is why to consider PCOS the sole cause of infertility. The scope of infertility specialists should be widened to be able to promptly manage PCOS patients in a short duration. Recently, we outlined a one-stop infertility evaluation unit principle to cut short lengthy infertility management protocols.[20]

Practically, we face a lot of PCOS cases treated by repeated high-dose courses of induction of ovulation and later on proved to have a missed cause of infertility like pelvic endometriosis, tiny peritubal factors like paratubal cysts, lipomesosalpnix or fine adhesions in the pouch of Douglas.

This study highlights the importance of endoscopic intervention in cases of PCOS particularly if the case is associated with a risk factor for a concomitant infertility cause. In this study, out of 232 infertile women subjected to laparoscopy, 37.9% of PCOS infertile patients had pelvic pathology other than PCO and 74.1% of non PCOS infertile patients were diagnosed with pelvic pathology. Likewise, others detected pelvic pathology in 72.6% of infertile patients who subjected to laparoscopy.[21]

These findings and similar studies may call for reconsideration of the fundamental role of laparoscopy in infertility evaluation. We always recommend inclusion of laparoscopy and hysteroscopy in infertility evaluation protocols.[16] This concept is supported by our findings of abnormal pelvic pathologies including endometriosis in non-PCO patients without RF (UI) in this study which illustrates the important role of laparoscopy in diagnosis and management of hidden pelvic pathology.

In this study, the presence of different pathologic findings in (19%) of PCOS infertile patients and in (38.8%) of non PCOS infertile patients by HSG illustrates the important role of HSG as a diagnostic tool for infertile women. ASRM still relies on HSG as a first tool for diagnosis of tubal patency and tubal pathology.[6]

Regarding endometriosis, collectively it was diagnosed in 4 cases with PCO (3.4%) and 23 cases without PCO (19.8%). Detection of endometriosis in each group highlights the valuable role of laparoscopy in infertility even with normal HSG. It was detected in 46 (80.7%) of infertile patients with normal HSG in one study.[22]

In this study, we detected a plethora of pelvic pathologies that may be infertility inducers (in 28.4% and 38.8% of PCOS and non-PCO infertile patients respectively) like adhesions, tubal hydrosalpnix, peritubal adhesions, tubal occlusion and liomyoma nearby or compressing tubal ostia. Moreover, concomitant laparoscopic correction of these fertility-compromising factors was promptly done in the same session like adhesiolysis, salpinogostomy, salpingoneostomy, or myomectomy.

In addition to fertility-enhancing advantages of these concomitant laparoscopic procedures aiming at increasing chances of spontaneous pregnancy, see and treat concept can be covered by health insurance companies in contrast to GTs and ART procedures that are not covered by the Ministry of Health or insurance companies in many countries. From this study, it is concluded that detection and proper management of associated pelvic pathologies at laparoscopy is a valuable additional advantage of LOD particularly in women with positive risk factors. LOD plus see and treat associated pathologies is a time saving and prompt management approach for women with PCO–associated infertility.

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