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Effect of Laparoscopic Ovarian Drilling on Doppler Pattern in Patients with Clomiphene Citrate_ Resistant Polycystic Ovarian Syndrome

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Polycystic ovarian syndrome (PCOs) is a prevalent endocrine condition affecting women throughout their reproductive years. It is the most common cause of ovulation-related infertility, accounting for around 75% of instances of anovulatory infertility. The goal of this study is to see how laparoscopic ovarian drilling affects the Doppler pattern in patients with clomiphene citrate-resistant polycystic ovarian syndrome.
Methods: 50 patients were included, diagnosed as PCO patients according to Rotterdam criteria, 2003 and were planned for LOD.
Results: This study was done at 50 patients was with mean age 29 year, Mean BMI 27.28 Kg/m^2,Mean duration of infertility 3.71 years. there were statistically significant decrease in ovarian stromal VI ,FI,VFI and PSV postoperatively, But there was statistically significant increase in ovarian stromal RI postoperatively.
Conclusion: ovarian stromal blood flow indices significantly changed after LOD. Our results provide a potential avenue for evaluation of ovarian stromal blood flow changes after LOD.

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Keywords: Drilling; Laparoscopy; clomiphene citrate; polycystic ovarian; syndrome.

1. INTRODUCTION

PCOs is one of the most common endocrine disorders, affecting 5–10 percent of women in their reproductive years. It is the most common cause of ovulation-related infertility, accounting for at least 75% of anovulatory infertility cases [1]. The first line of treatment of such disorder was induction of ovulation using clomiphene citrate (CC) and other members of selective estrogen receptor modulators (SERM).However; 15–40% of patients with CC – resistant PCO patients can be managed either by using gonadotropins or by minimal surgical procedure known as laparoscopic ovarian drilling [2].

Those PCOS patients have considerable difference in the blood flow within the ovarian stroma when compared to females with healthy ovaries. The blood flow within the ovarian stroma is measured by evaluating the vasculature of the ovarian stroma (small arteries within the stroma of the ovary away from the surface of the ovary and the wall of the follicles) [3].

A primary disorder within those ovaries most probably causes significant difference in the blood flow within the ovarian stroma [4]. Those PCOS patients when comparing them with healthy females not suffering from PCOS have an increased blood flow within the ovarian stroma in the early follicular phase of their menstruation [2,4].

2. PATIENTS AND METHODS

This prospective study was carried at the Department of Obstetrics and Gynecology, Tanta University Hospitals the duration was one year from January 2019 to January 2020 on 50 patients were included, diagnosed as PCO patients according to Rotterdam criteria, 2003 and were planned for LOD.

2.1 Inclusion Criteria

- Age between 18-35 years old
- All patients were infertile (primary or secondary infertility)
- All were diagnosed as PCO according to Rotterdam criteria, 2003 (two criteria are sufficient for diagnosis of PCOS):
- They were diagnosed as being clomiphene citrate resistant after they received 50 mg CC in the 1st month for 5 days starting from the 3rd day of the menstrual cycle ,100 mg in the 2nd month and 150 mg for 4 months (they received CC for 6 months) with no evidence of ovulation.
- Absence of any medical disorders.
- Body mass index between 18-35.
- Normal hysterosalpingography.
- Normal semen analysis.

2.2 Exclusion Critera

- Infertile patients due to causes other than PCOs.
- Patients with any organic pelvic disease diagnosed during laparoscopy.
- Patients with previous pelvic surgerye. gappendectomy, ectopic, myomectomy.
- Patients with medical disorders that may affect fertility as diabetes mellitus, liver disease.
- Patients with hyperprolactinemia or other endocrine disorders that may affect fertility e.g thyroid disease.

3. METHODS

All patients were subjected for full detailed history Included menstrual history, medical history, and surgical history, obstetric history, sexual history and any previous investigation done or treatment given.

- Careful general examination, abdominal and pelvic examination.
- Local examination: (per-speculum and pervaginal examination) including cervix, uterine size, position and mobility of uterus, tenderness on uterinemotion and in fornices to exclude other causes of infertility.

3.1 Baseline investigations like

All patients had a complete blood count, blood sugar profile, HbA1c, urine analysis, liver and kidney function tests, thyroid function testing, and viral indicators.

3.2 Investigational Studies

3.2.1 Transvaginal ultrasound

Doppler study: Transvaginal 2D color Doppler is done. A colour Doppler ultrasound machine

(Mindray dc 30, Mindray co Ltd, china) with trasvaginal trandsducer 7.5 mHz was used. baseline 2d TVS was used to examine the uterus for any abnormality and measuring the uterine size and endometrial thickness and then to identify PCO criteria in both ovaries and ovarian volume was measured then color Doppler ultrasound scanning was performed to assess the ovarian stromal blood flow. Color signals were searched in the ovarian stroma away from the ovarian surface or near the afollicle wall using colour and power Doppler flow imaging. Areas of maximal colour intensity, exhibiting the greatest Doppler frequency shifts, might be observed by positioning the colour Doppler gate over the ovarian stroma, and then selected for pulsed Doppler investigation. After angel correction, peak systolic blood flow velocity wave-forms were chosen for investigation. Then, for each Doppler wave, PI and RI were determined. Areas of maximum color intensity, representing thegreatest Doppler frequency shifts, were selected for pulsed Doppler examinations. The resistance index (RI) and pulsatility index (PI) were used as measures of blood flow impedance distal to the point of sampling. All examinations were performed before midday to reduce the effects of diurnal variations in blood flow.

Blood flow assessment (Plasticity index: PI – Resistance index: RI and peak systolic velocity: PSV) were performed once after LOD in the early follicular phase (days 2-4 of the menstrual cycle) of the first post-operative spontaneous menstruation (which occurred within 10 weeks after the operation) .In non-menstruating patients the blood flow assessment was performed by the end of the 10 weeks.

-LOD was done to the all 50 patient by the same technique (under general anathesia the abdomen was inflated with CO2 through abdominal button then surgical punctures from 5 to 10 puncture were performed on the ovarian cortex(both ovaries) and were 4–10 mm deep and 3 mm wide.

3.2.2 Follow up

- Blood flow assessment (PI - RI) were performed again in the early follicular phase (days 2-4 of the menstrual cycle) of the first post-operative spontaneous menstruation (which occurred within 10 weeks after the operation).
- In menstruating patients, the cycle was evaluated for hormonal profile, blood flow within the ovarian stroma and also for ovulation detection.
- Ovulation was assessed by serial transvaginal ultrasound until seeing pre-ovulatory follicle > 15mm. Ovulation was confirmed by visualization of follicle collapse on subsequent transvaginal ultrasound, appearance of fluid in the Douglas pouch and elevated mid-luteal serum progesterone >5 ng/ml. Ovulating group was informed to report the occurance of natural conception for 6 months after LOD.
- Patients who did not menstruate (pregnancy should be excluded) or did not ovulate within 10 weeks after drilling as evidenced by poor follicular growth by serial transvaginal ultrasound folliculometry, and low mid-luteal serum progesterone level less than 5ng/ml were referred to another group of researchers for re-evaluation.

3.3 Outcome Measures

3.3.1 Primary Outcome Measures

-Ovarian blood flow
Ovarian blood flow after laparoscopic ovarian drilling compared with the same pre-operative values.

3.3.2 Secondary Outcome Measures

Ovulation: Ovulation was assessed by serial transvaginal ultrasound until visualization of pre-ovulatory follicle of at least 18 mm. Ovulation was confirmed by seeing follicle collapse on subsequent transvaginal ultrasound, appearance of fluid in the Cul-de-sac and elevated mid-luteal serum progesterone level >5 ng/ml.

Pregnancy: Ovulating group was informed to report the occurrence of natural conception for 6 months after LOD. Pregnancy was diagnosed by positive pregnancy test with seeing intrauterine gestational sac by transvaginal ultrasound.

3.4 Statistical Methods

Data is statistically represented by the term of range, mean, standard deviation (+SD) and percentages. Accuracy was represented using the terms of sensitivity, specificity, positive predictive value, negative predictive value and

overall accuracy. All statistical calculations were done using computer programs Microsoft Excel.

3.5 The used Tests Were

Paired t-test: For normally distributed quantitative variables, to compare between two periods.

Wilcoxon signed ranks test: For abnormally distributed quantitative variables, to compare between two periods.

4. RESULTS

This is a prospective study was done at the Department of Obstetrics and Gynecology, Tanta University Hospitals the on 50 patients that diagnosed as PCO patients according to Rotterdam criteria, 2003 and were planned for LOD. Regarding to age, 31 patients were less than 30 years and 19 patients were more than 30 years with mean age 29.0 ± 3.11 years. Mean BMI was 27.28 ± 0.83 Kg\m^2 (Table1) the mean duration of infertility among studied cases was 3.71 years.

Table 1. Distribution of the studied cases according to age (years)and BMI

	No.	%
Age (years)		
≤30	31	62.0
>30	19	38.0
Min. – Max.	24.0 – 33.0	
Mean ± SD.	29.0 ± 3.11	
Median (IQR)	29.0 (26.0 – 32.0)	
BMI (kg/m^2)		
Min. – Max.	26.0 – 29.0	
Mean ± SD.	27.28 ± 0.83	
Median (IQR)	27.0 (27.0 – 28.0)	

Table 2. Shows Distribution of the studied cases according to duration of infertility

Duration of infertility	No.	%
≤ 3	19	38.0
>3	31	62.0
Min. – Max.	2.0 – 6.0	
Mean ± SD.	3.71 ± 1.13	
Median (IQR)	3.45 (3.0 – 4.60)	

Table (3) shows that preoperative mean ovarian stromal VI was 4.7+0.38 and postoperative ovarian stromal VI was 2.20+0.34. there was statistically significant decrease in ovarian stromal VI postoperative p-value<0.001.

Table (4) Shows Comparison between preoperative and postoperative according to ovarian stromal FI (n= 50)with Ovarian stromal FI preoperative was 51.5 and postoperative was 43.74, there was statistically significant decrease in Ovarian stromal FI postoperative p-value<0.001.

Regarding to Ovarian stromal VFI, preoperative and postoperative was 2.79, 1.28 respectively, there was statistically significant decrease in Ovarian stromal VFI postoperative p-value<0.001. Table (5).

According to PSV preoperative and postoperative was 12.85, 10.76 respectively there was statistically significant decrease in PSV postoperative p-value<0.001.

This table shows that RI preoperative and postoperative was 0.61, 0.78 respectively there was statistically significant increase in RI postoperative p-value<0.001.

But according to PI, preoperative and postoperative was 1.03, 1.71respectively, there was statistically significant increase in PI postoperative p-value<0.001(Fig1).

Table 3. Preoperative and postoperative ovarian stromal VI

Ovarian stromal VI	Preoperative	Postoperative	t	p
Min. – Max.	3.90 – 5.20	1.80 – 2.80	39.295*	<0.001*
Mean ± SD.	4.71 ± 0.38	2.20 ± 0.34		
Median (IQR)	4.80 (4.60 – 4.98)	2.20 (1.90 – 2.50)		

Table 4. Comparison between preoperative and postoperative according to ovarian stromal FI

Ovarian stromal FI	Preoperative	Postoperative	t	P
Min. – Max.	49.0 – 54.0	41.80 – 46.50	23.016*	<0.001*
Mean ± SD.	51.50 ± 1.69	43.74 ± 1.46		
Median (IQR)	51.50(49.80 – 53.50)	43.50(42.40 – 44.0)		

Table 5. Comparison between preoperative and postoperative according to ovarian stromal VFI

Ovarian stromal VFI	Preoperative	Postoperative	t	p
Min. – Max.	2.30 – 3.10	0.90 – 1.70	28.884*	<0.001*
Mean ± SD.	2.79 ± 0.24	1.28 ± 0.24		
Median (IQR)	2.74 (2.67 – 3.0)	1.20 (1.12 – 1.40)		

Table 6. Comparison between preoperative and postoperative according to RI

RI	preoperative	postoperative	t	p
Min. – Max.	0.45 – 0.99	0.66 – 1.03	14.732*	<0.001*
Mean ± SD.	0.61 ± 0.14	0.78 ± 0.10		
Median (IQR)	0.56 (0.45 – 0.67)	0.77 (0.67 – 0.84)		

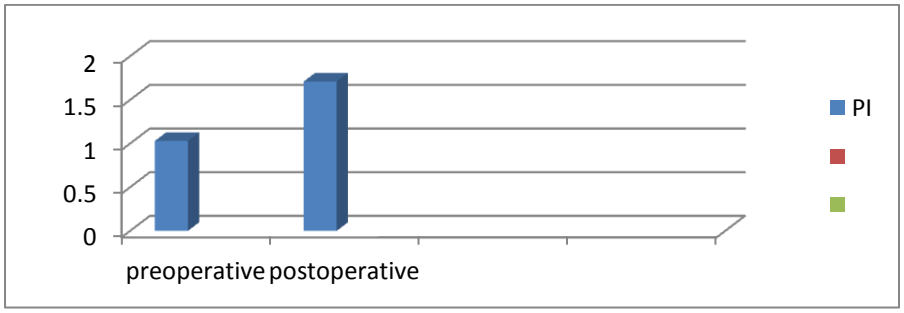

Fig. 1. Comparison between preoperative and postoperative according to PI

Table (7) Shows Distribution of the studied cases according to ovulating and pregnant with ovulation rate was 54% and 14% of patients got pregnant

Table 7. Distribution of the studied cases according to ovulating and pregnancy

	No.	%
Ovulating		
No	23	46.0
Yes	27	54.0
Pregnant		
No	43	86.0
Yes	7	14.0

5. DISCUSSION

PCOS affects 5%–15% of reproductive-age women and is the leading cause of infertility owing to anovulation [5]. Medical treatment with clomiphene citrate (CC) is the first-line treatment for PCOS-related infertility. In 75–80 percent of women, CC triggers ovulation. Anovulation, hyperandrogenism, obesity, and a large ovarian volume are all risk factors for CC failure. In CC-resistant infertility, there is no gold standard for management [5].

Medical treatment with gonadotropin or surgical management with ovarian drilling are the two main alternatives. The birth rate does not differ significantly between these two possibilities. Multiple pregnancies are reduced (OR 0.21, CI 95 percent 0.08–0.58) and hyperstimulation syndrome is avoided by ovarian drilling [6].

In this study we aimed to assess the effect of laparoscopic ovarian drilling on Doppler pattern in 50 patients with clomiphene citrate resistant polycystic ovarian syndrome 50 patients.

In the current study we found that there as significant decrease in ovarian stromal VI postoperative p-value<0.001. In agreement with our result Salem et al showed that there was significant decrease in ovarian Vascularization index postoperative p-value 0.01,also in study by Ashraf et al whose results showed significant reduction in ovarian stromal blood flow, where the VI decreased from 4.8 ± 1.3 pre-LOD to be 2.4 ± 0.75 after LOD [7].

In the current study we found that there was significant decrease in Ovarian stromal FI postoperative p-value<0.001.This agree with Ashraf et al result as found that there was significant decrease in ovarian Flow index

postoperative p-value 0.01 also Ashraf IE et al showed that FI decreased from 52.4 ± 4.3 pre-LOD to 44.3 ± 2.5 after LOD [7].

In the current study we found that there was significant decrease in Ovarian stromal VFI postoperative p-value<0.001. In consistent with our result Salem MN et al found that there was significant decrease in ovarian Vascularization flow index postoperative p-value 0.01 [8]. Similarly Ashraf et al found that VFI also decreased from 2.9 ± 0.43 to 1.2 ± 0.59 pre and after LOD respectively [7].

In this study we found that there was significant decrease in PSV postoperative p-value<0.001,this agree with Parsanezhad et al as showed that PSV was significantly lower (P = 0.001) postoperative [9].

This proved by El Behery et al as showed that the ovarian stroma flow indices decreased after LOD, as demonstrated by using 3D power Doppler, suggesting that stromal blood flow had been corrected. Such a decrease in ovarian vascularization and blood flow may reduce the occurrence of OHSS [10].

Similarly Al-Rab et al study has reported a significant reduction in the 3-D power Doppler indices after LOD. These results are in agreement with many previous reports [11].

In contrast, Vizer and co-workers [12] reported an increased intraovarian blood flow after the procedure.

The mechanism of action of LOD is unclear and its beneficial effect is apparently due to the destruction of the androgen producing ovarian stroma with subsequent decrease in ovarian stromal blood flow, decreased serum levels of VEGF and IGFI which are significantly higher in PCOS [13].

In a study by AbouSekkein et al. PSV decreased significantly from (15.19 + 1.76) before LOD to (8.68 + 0.74) after LOD. however PI increased insignificantly from (0.85 + 0.11) before LOD to (0.9 + 0.14) after LOD [14]. In the current study we found that there was significant increase in RI and PI postoperative p-value<0.001.In agreement with our result, Parsanezhad et al showed that the mean 6 SD of PI and RI (6±10 weeks after operation) were significantly higher than those in pre-operation values (P = 0.001) [9]. In a study by Safdarian et al PI increased significantly from (2.01 ± 0.64) before LOD to (2.89 ± 0.57) after LOD. As regard RI, it increased significantly from (0.76 ± 0.11) before LOD to (0.84 ± 0.08) after LOD [15].

The only study that proved that ovarian stromal blood flow increases after LOD was done by Vizer and co-workers , In this study LOD was done on both ovaries (40Watts monopolar coagulating current), and 15–20 cautery points were performed at a depth of 5–7 mm and threedimensional sonography was used to assess the intraovarian blood flow. The defect in this study was the small sample size (10 patients), so this study cannot be used to evaluate the relationship between ovarian stromal blood flow changes and ovulation [12].

In the current study we found that during study period ovulation rate was 54% and 14% of patients got pregnant. Higher percentage founded by Debras et al as one hundred and thirty-seven women (61.4%) achieved at least one pregnancy after drilling (71 were spontaneous [51.8%]), and 48 women (16.6%) achieved at least two (27 were spontaneous [56.3%]).this may due to longer follow up s The mean follow-up period was 28.4 months (25.3–31.5) [5]. Poujade et al. who did their research on 74 patients with CC resistant PCO and found occurrence of pregnancy 47/74 (63%) of patients but within 11 month after LOD [16]. Another study by Ismail et al showed that after LOD 35 cases (70%) showed ovulation as evidenced by folliculometry (leading follicular diameter > 18 mm followed by seeing follicle collapse on subsequent transvaginal ultrasound, appearance of fluid in Douglas pouch) and elevated mid luteal serum progesterone level (>5 ng/ml).

They found 15 cases (30%) did not show ovulation as evidenced by poor follicular growth by serial transvaginal ultrasound folliculometry, (they also reported 5 cases menstruated during the follow up period but did not ovulate) and low mid-luteal serum progesterone level (<5 ng/ml), or lack of menstruation {10 cases (5 patients were belonging to the secondary amenorrhea group and the other 5 patients were belonging to the oligomenorrheagroup).

6. CONCLUSION

After LOD, the ovarian stromal blood flow indicators changed considerably. Our findings suggest a method for assessing changes in ovarian stromal blood flow following LOD.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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