Original Research Article

Effect of laparoscopic ovarian drilling on Doppler pattern in patients with clomiphene citrate_ resistant polycystic ovarian syndrome

Abstract

Background: Polycystic ovary (PCO) is one of the most common endocrine disorder that affect women in reproductive age group. It is the major cause of ovulation – related infertility and account for about 75% of cases with anovulatory infertility, aim of the work is to assess effect of laparoscopic ovarian drilling on Doppler pattern in patients with clomiphene citrate_ resistant polycystic ovarian syndrome

Methods: The study was done to assess the effect of laparoscopic ovarian drilling on Doppler pattern in patients with clomiphene citrate_ resistant polycystic ovarian syndrome**.** 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.

Comment [g1]: PCOS(Polycystic ovary syndrome)

Comment [g2]: Incomplete and brief. Start with50 patient

Comment [g3]: Delete the 1st sentence

Comment [g4]: Add more data with exact values. Compare the important findings between the groups

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**.**

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

Comment [g5]: Focus mainly on your noticeable findings, in regards to the study aim

Introduction

Comment [g6]: Be more focused on previous relevant studies, which have been published recently. What is the logic behind this study design which has not been reported previously? Any novelty? Please, highlight it clearly. Also, give a good background in support of the aim of this investigation using up-to-date REFs (2019-22).

Comment [g7]: Edit..

Polycystic ovary (PCO) is considered as one of the most common endocrine disorder that occurred in 5–10% of women in reproductive age group. It is the major cause of ovulation – related infertility, accounting for at least75% of cases with anovulatory infertility [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).**

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.

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.

Exclusion critera:

-Infertile patients due to causes other than PCO.

Comment [g8]: ...

-Patients with any organic pelvic disease diagnosed during laparoscopy.

-Patients with previous pelvic surgery e.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.

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-Baseline investigations like:

Complete blood Count, blood sugar profile, HbA1c,urine analysis, liver and kidney function tests, thyroid function tests, viral markers were done for all patients. Husband semen analysis.

-Investigational studies

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. By means of colour and power Doppler flow imaging, colour signals were searched in the

ovarian stroma away from the ovarian surface or near the wall of afollicle. By placing the colour Doppler gate over the ovarian stroma, areas of maximum colour intensity, representing the greatest Doppler frequency shifts, could be visualized, then selected for pulsed Doppler examination. Peak systolic blood flow velocity wave-forms were selected for analysis after angel correction. Then PI and RI were calculated in each selected Doppler wave.

- Areas of maximum color intensity, representing the greatest 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.

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.

Outcome Measures

Primary Outcome Measures:

-Ovarian blood flow

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

Secondary Outcome Measures:

1. **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.

2. **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.

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

The used tests were:

1 - Paired t-test

For normally distributed quantitative variables, to compare between two periods.

2–Wilcoxon signed ranks test

For abnormally distributed quantitative variables, to compare between two periods.

Results

Comment [g9]: Point out the parameters of value in the text briefly

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)

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

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)	

the mean duration of infertility among studied cases was 3.71 years.

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

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 (3):Preoperative and postoperative ovarian stromal VI .

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

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

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

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).

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

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

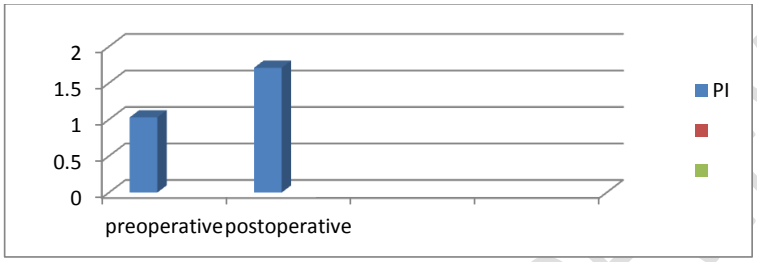
According to **PSV** preoperative and postoperative was 12.85, 10.76 respectively there was statistically significant decrease in PSV postoperative p-value<0.001

Table (6)shows Comparison between preoperative and postoperative according to RI

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

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).



Figure(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

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

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

Discussion

PCOS affects 5%–15% of women of reproductive age and is the first cause of infertility due to anovulation (**5**).The first-line treatment for PCOS-related infertility is medical, using clomiphene citrate (CC) **.**CC induces ovulation in 75%–80% of women. Hyperandrogenism, obesity,

Comment [g10]: Be more specific as how others have reported their data and compare the present findings with others. Discuss the reasons behind setting this study design.

high ovarian volume, and anovulation are predictive factors for the failure of CC. In CC-resistant infertility, there is no gold standard for management (**5).**

The two principal options available are a medical treatment by gonadotropin or a surgical management by ovarian drilling. There is no significant difference in birth rate between these two options. Ovarian drilling leads to a lower risk of multiple pregnancies (OR 0.21, CI 95% 0.08–0.58) and avoids hyperstimulation syndrome (**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)}.

As regard occurrence of natural conception in ovulating group during 6 months of follow up after LOD, 20 cases became pregnant represented 57 % of the ovulating patients (40% of the whole number of cases in the study) and 15 patients did not become pregnant (43% of the ovulating patients) 30% of the whole number of cases in study.**(17).**

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**.**

Refrences

Comment [g11]: Add new relevant REFs (2019-22). The majority of REFs are old, and should be replaced with recent ones.

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The manuscript should be edited by a scientist with English language proficiency!

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