Serum prolactin after laparoscopic ovarian drilling in women with clomiphene citrate resistant anovulation and its correlation with ovulation

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Abstract: Objective: to evaluate changes in serum prolactin after laparoscopic ovarian drilling (LOD) in polycystic ovaries (PCOS) not responding to the drilling. **Methods:** One hundred patients with PCOS were selected from the infertility clinic of Ain shams university hospital, where LOD was done for them during the period from September 2009 to June 2010. All women were infertile due to anovulation because of PCOS. PCOS was diagnosed when at least two of the following three criteria were present: oligo-ovulation or anovulation, clinical and/or biochemical signs of hyperandrogenism, or polycystic ovaries on transvaginal ultrasound. All participants were clomiphene citrate (CC) resistant. **Results:** After LOD 34% of cases remained anovulatory, 36% were ovulatory but were not pregnant, and 30% became pregnant. There was no statistical significance of mean serum prolactin after LOD (9.98 ±3.41ng/dl) when compared to baseline serum level (12.58 ±4.9 ng/dl) in patients who became ovulatory (but not pregnant). There was a statistical significant higher mean serum prolactin after LOD (19.98 ±10.46 ng/dl) when compared to baseline serum level (10.35 ±4.65 ng/dl) in patients who remained anovulatory after LOD (p<0.0001). There was a significant difference in mean serum prolactin between patients who remained anovulatory 19.98 ±10.64 ng/dl and who became ovulatory 9.5 ±3.41 ng/dl (but not pregnant) after LOD (p<0.0001). In multivariate analysis, all studied parameters were not predictors of postoperative hyperprolactinemia. Furthermore, there was no correlation between the duration of operative procedure and postoperative hyperprolactinemia. **Conclusion:** Women who remained anovulatory after ovarian drilling had elevated prolactin levels. Measurement and treatment of hyperprolactinemia LOD after can predict and affect ovulation After LOD. No correlation of pre and post LOD prolactin with age, FSH, type and duration of infertility levels in non-ovulating patients.
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1. Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder in up to 10% of women in the reproductive age. Diagnostic criteria are oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries by ultrasound. At least two out of these three criteria must be present. (1)

Mild hyperprolactinemia occurs in up to 15-30% of women with PCOS but is not a clinical manifestation of PCOS. In one study of women with confirmed PCOS; 16% had hyperprolactinemia. In 69% the prolactin elevation was due to a pituitary tumor, 15% were using oral contraceptives, 8% were taking an antipsychotic agent and 8% had macroprolactinemia. Therefore, PCOS patients with increased prolactin levels must be investigated for other causes of hyperprolactinemia. (2)

Laparoscopic ovarian drilling (LOD) has been used to induce ovulation in PCOS women with clomiphene citrate (CC) resistant anovulation (CRA). However, 20–30% of anovulatory PCOS women fail to respond to LOD. The mechanism of action of LOD is not fully understood and therefore it is not exactly clear why some PCOS patients do not respond to this treatment. (3-5)

The reported ovulation rate after LOD varies between 50% and 90%, the conception rate does not increase in parallel with the increase in ovulation rate. There is also some disparity between hormonal improvement and ovulation rate. Part of disparity may be due to post-operative adhesion formation, post-LOD hyperprolactinemia or any unknown reason. Although many studies concerning the endocrine effects of LOD have been performed, none has emphasized on the cause of disparity between hormonal changes and ovulation. (6-8)

Prolactin concentrations were not altered weeks to years after LOD in the majority of the studies. One study showed a decline in prolactin after the procedure. Another study showed that the majority of the women remaining anovulatory after ovarian surgery were hyperprolactinaemic 6–10 weeks after surgery. (6, 9, 10)

Aim of the Work

The aim of this study was to compare serum prolactin levels in women with polycystic ovary

syndrome remained anovulatory after laparoscopic ovarian drilling with those who ovulated.

2. Methods

This study is a prospective study conducted on 100 women with PCOS attended the infertility clinic of Ain shams university maternity hospital. They were candidate for laparoscopic ovarian drilling.

The inclusion criteria included: infertile patients with PCOS (age 20-35years) who were resistant to clomiphene citrate (CC) (ovulation did not occur after 3-4 cycles of CC treatment at the maximum dosage 250 mg/day for 5 days from the second or third day of the menstrual cycle) (11). Diagnosis of PCOS was based on two of those three criteria; menstrual disturbances (Chronic oligoovulation or anovulation), clinical and/or biochemical signs of hyperandrogenism and typical ultrasonographic findings of polycystic ovaries "presence of 12 or more follicles in each ovary measuring 2-9 mm in diameter, and/or increased ovarian volume (> 10 cm^3)"(12).

The exclusion criteria included: age over 35years, patient with regular cycles, women with prolactin level > 20 ng/dl, contraindication to laparoscopy, patient who were receiving any drugs that increase serum prolactin level as sedatives, antiemetic and antihistaminic drugs and other cause of infertility including male factor.

Women who agreed to participate in the study were informed about the nature of the study, the investigations they will undergo and its timing. An informed consent was signed by every participant after approval of ethics and research committee of council of obstetrics and gynecology department, Ain shams university hospital.

Overweight patients were defined as those with body mass index (BMI) 25-29.9 kg/m^2 and obese patients were those with BMI > 30 kg/ m^2. Pre-operative investigations included husband semen analysis to exclude male factor of infertility and hystrosalpingiography to exclude tubal factor of infertility.

In all women, base line blood samples were obtained before laparoscopy (day 2 or 3 of spontaneous or induced menstruation to assess basal Serum prolactin, FSH and LH. Another blood sample was taken in the early follicular phase of first post laparoscopy menstrual cycle (approximately 4 to 10 weeks after operation). Prolactin level was measured in all women. The samples were labeled; sera were separated and frozen until the end of study and were assayed concurrently by the same kit of radioimmunoassay (RIA).As prolactin levels are diurnal and are very variable, samples were obtained in afternoon and patients are instructed to avoid stress, exercise, sexual intercourse and nipple stimulation a day before sampling.

All women were followed for three months sonographically for ovulation and if pregnancy occurred.

Laparoscopic ovarian drilling procedure was done following the standard operating procedures. Both ovaries were fixed in such a position that damage to other pelvic organs was minimized, by grasping the ovarian ligament and then electrocautery was performed using unipolar diathermy probe pressed against the ovarian anti-mesenteric surface performing 4 punctures on each ovary 4-5 mm apart through the ovarian cortex to a depth of 4-5 mm graduated on the specific needle used for the procedure using coagulation current of 40 W. Then the ovaries were immediately cooled by raining with normal saline solution to minimize adhesion formation and to prevent heat trauma to adjacent viscera. At the end of the operation, the saline used was aspirated with suction cannula through the second puncture.

Statistical analysis

For all calculations, SPSS version 15 was used. All baseline characteristics and outcomes were continuous, and Student's t-test was used for comparison between two means. The paired test was used before and after comparison. Results were considered significant at *P*-value <0.05

3. Results

The study included 100 women. Table 1 shows the baseline characteristics of the included patients before LOD classified into 3 groups according the outcome of LOD (after having LOD). After LOD 34% of cases remained anovulatory, 36% were ovulatory but were not pregnant, and 30% became pregnant.

There was no statistical significance of mean serum prolactin after LOD (9.98 ±3.41ng/dl) when compared to baseline serum level (12.58 ±4.9 ng/dl) in patients who became ovulatory (but not pregnant) after LOD.

There was a statistical significant higher mean serum prolactin after LOD (19.98 ±10.46) when compared to baseline serum level (10.35 ±4.65 ng/dl) in patients who remained anovulatory after LOD (p <0.0001).

There was a significant difference between mean serum prolactin in patients who remained anovulatory 19.98 ±10.64 and who became ovulatory 9.5 ±3.41 (but not pregnant) after LOD (p <0.0001).

In multivariate analysis, all studied parameters were not predictors of postoperative hyperprolactinemia. Furthermore, there was no

correlation between the duration of operative procedure and postoperative hyperprolactinemia.

Table 1: Baseline characteristics of the included cohort

	Anovulatory (34)				Ovulatory (not pregnant) (36)				Ovulatory (Pregnant) (30)			
	Mean	SD	Range		Mean	SD	Range		Mean	SD	Range	
Age (years)	25.99	4.97	20.00	35.00	24.85	4.29	20.00	35.00	26.50	4.16	20.00	35.00
Duration of infertility (years)	3.60	2.59	1.00	11.00	4.16	2.83	1.00	14.00	3.92	2.95	1.00	10.00
BMI (kg/m2)	26.83	2.57	22.00	31.93	26.58	2.73	23.30	34.00	24.77	1.47	22.00	28.20
FSH mIU/ml (baseline)	6.36	1.07	4.80	8.20	6.34	1.31	4.40	9.10	6.48	1.10	4.20	8.50
LH mIU/ml (baseline)	11.59	2.92	7.10	18.20	11.90	3.35	5.40	19.00	5.29	1.23	2.60	7.90
Serum Prolactin (baseline) ng/ml	10.35	4.65	3.60	19.50	12.58	4.90	4.30	20.00	10.34	2.84	6.70	19.00

4. Discussion

The outcomes of LOD were similar to those of gonadotropin treatments; however, LOD had a lower risk of multiple pregnancies and development of ovarian hyperstimulation syndrome. (3) Some endocrine effects of LOD have not been well investigated.

In the current study, LOD was used for a cohort of women with CRA to investigate a notorious reported controversial finding of elevated serum prolactin after LOD and if this rise in serum prolactin might be associated with persistent anovulation. The current study was conducted in Ain Shams university maternity hospital between September 2009 & June 2010. It included 100 women who were diagnosed as PCOS patients with CRA and euprolactinemic preoperatively.

Three months following LOD, 34 % of the participants remained anovulatory, 30 % of the participants were pregnant and 36 % were ovulatory but not pregnant. Comparison of baseline prolactin level (before LOD) in ovulating , non-ovulating and those who became pregnant after LOD revealed insignificant difference. In the patients who remained anouvulatory after LOD; their mean prolactin level in sera was (10.35 ± 4.65 ng/dl) and elevated to (mean 19.98 ±10.46 ng/dl) after 2-3 months of LOD. Hyperprolactinemia was found in 64.7 % of them.

In the patients who became ovulatory but not pregnant; their mean serum prolactin level was (12.58 ± 4.9) and slightly decreased to (9.5 ± 3.41) but not enough to cause significant difference. Women who remained anovulatory had significantly higher serum prolactin 3 months after LOD. There was no significant relationship between mean serum prolactin levels before and after LOD in relation to type and duration of infertility, age or FSH level, nor the duration of operative laparoscopy.

This current study confirms previous reports. (5, 6, 10) The possible mechanism of that phenomenon is unclear. It can be speculated that scar formation on the surface of the ovaries and chronic stimulation of ovarian nerves might be the etiology of postoperative hyperprolactinemia. Hyperprolactinemia might be due to the use of general anesthesia, a generalized stress reaction, or the use of postoperative narcotic analgesic.

It is clear that Increase in serum prolactin levels following LOD may adversely affect the potential of ovulation and therefore the chances of pregnancy. It would be prudent not to rely on early hormonal profiles after LOD.

Women who remained anovulatory after ovarian drilling had elevated prolactin levels. After LOD measurement of serum prolactin level and treatment of hyperprolactinemia are recommended. Post LOD

adhesions or scar formation might be responsible for hyperprolactinemia.

5. Conflict of interest

No conflict of interest or supporting agencies**.**

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