

OVARIAN DRILLING IN INFERTILITY ASSOCIATED WITH POLYCYSTIC OVARY SYNDROME

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Abstract. About 7-8% of the women of reproductive age are affected by the polycystic ovary syndrome (PCOS), and this is considered to be the main cause of infertility and also the most frequent endocrine illness in women. The study offers an open perspective for the physician who treats the polycystic ovary syndrome, regarding the judicious use of investigations in order to analyse the amplitude of the syndrome objectively, so as the treatment of infertility can become the major objective for the woman diagnosed with this syndrome. The study was a retrospective one, both analytical and descriptive and included 156 patients (28.41%) who addressed the hospital for primary/secondary infertility issues, of ovulatory cause, with previous medical treatment and who accepted ovarian drilling as a method of treatment in the Clinic of Obstetrics-Gynaecology of the Emergency County Hospital Bacău. The values of LH and the ratio LH/FSH are increased for the patients with polycystic ovary syndrome, but the sensitivity and specificity of gonadotropins in defining the syndrome are not certain. There is no correlation between the level of FSH and LH that can have statistical significance, even if the slope of the regression line has an ascending character. In reality, what is important for diagnosing the illness is the ratio between the two pituitary tropes and not the absolute value of each of them. If you consider the pharmaceutical and economical point of view, the laparoscopic ovarian drilling could be the first choice when deciding what treatment to use for the patients with PCOS that are resistant to clomiphene, as it is cheaper than the treatment with gonadotropins. The laparoscopic ovarian drilling, followed by an appropriate stimulation with clomiphene is an efficient method of treatment for the patients with anovulatory infertility.

INTRODUCTION

The cuneiform ovary resection is the first therapy introduced for PCOS and it represents the excision of a half up to three quarters of the ovarian medulla through laparotomy. Because of the risks of postsurgical adhesions that transformed endocrinologic infertility into mechanical infertility, it was abandoned little by little and replaced with medical therapy. Stein and Leventhal described the surgical treatment for the first time in the year 1935 – cuneiform resection – and consequently the menstrual cycle came back to normal for about 80% of the patients and also the pregnancy rate increased to 50% (Stein I. & Leventhal M., 1935). This method was abandoned because it caused pelvic adhesions to appear. Gjonnaess introduced the technique of laparoscopic ovarian drilling in 1984 for the patients with polycystic ovary syndrome who were resistant to clomiphene citrate (Gjonnaess H., 1984).

Fernandez et al. published a retrospective study in 2011 and it was used to create an overview of the laparoscopic ovarian drilling (Fernandez H. et al, 2011). The laparoscopic ovarian drilling (LOD) is the new laparoscopic method, an alternative for the anovulatory patients that are also resistant to the medicine treatment. It consists of electrocoagulation- puncture and laser vaporisation, in order to create multiple perforations on the ovarian surface and the stroma.

The method can reduce the use of ovulation stimulators, expensive drugs that need a long time of treatment. Many authors state that this method obtained very good results on the short term, regarding the percentage of ovulations and pregnancies and re-establishing the normal menstrual cycles (Rossmann W.G., 1991; Farquhar C.M., 2002; Bayram N., et al, 2004; Kaya H., 2005; Madnani N., et al, 2013).

PURPOSE AND OBJECTIVES

The study intends to determine:

- the efficiency of laparoscopic ovarian drilling for the patients with polycystic ovary syndrome (PCOS) that are resistant to the therapy with clomiphene over the improvement of the endocrine and clinical parameters;
- the factors that influence the results of the laparoscopic ovarian drilling (LOD), as a method of treatment for the women with polycystic ovary syndrome;
- the efficiency of the laparoscopic ovarian drilling in comparison with other methods of treatment;

- how to identify a protocol that will lead to an increase in the pregnancy rate for the patients with PCOS that are resistant to the treatment with citrate clomiphene.

MATERIALS AND METHODS

The retrospective study took place in the period of time between January 2010 - December 2014 and it was performed on 156 patients, with a mean age of 30 years old, who were investigated for a mean period of time of 28 months after the procedure.

Selection criteria: age between 20 and 30 years old - 115 patients (73.71%); 30-40 years old - 41 patients (26.29%).

The reasons for seeing the doctor: Oligo-spaniomenorrhea and infertility - 103 patients (66.03%); infertility - 30 patients (19.23%); secondary amenorrhea and infertility - 21 patients (13.46%); primary amenorrhea - 2 patients (1.28%).

Indications: anovulatory infertility caused by PCOS; patients with a persistent hypersecretion of luteinizing hormone (LH); trspeonding to citrate clomiphene, because LOD reduces the secretion of LH; patients with no ovulations who have PCOS and who need surgery in order to assess the pelvis, permanent monitoring during the treatment with gonadotropins.

Principles to follow up when treating infertility. The laparoscopic ovarian drilling can be performed through transvaginal hydrolaparoscopy, culdoscopy or fertiloscopy. In the first instance doctors always use citrate clomiphene. In case it doesn't work they associate gonadotropins with follicle-stimulating hormone (FSH) and LH. The last option is the laparoscopic electrocautery of cysts. Sometimes the drilling can improve receptivity to exogenous gonadotropins and the doctor can be tempted to start a new treatment with gonadotropins post operatory (Onofriescu A., et al, 2012).

The diagnostic of PCOS was established based on the Rotterdam criteria (2 out of 3 present): oligo/anovulation, clinical/biological signs of hyperandrogenism, polycystic ovaries (the presence of 12 or more follicles of 2-9 mm in each ovary and/or an increased ovarian volume >10 mL) (The Rotterdam ESHRE/ASRM, 2004).

The ratio LH/FSH was established in the third day of the menstrual cycle ≥ 2 and/or high levels of the androgenic hormones (testosterone ≥ 0.7 ng/ml, free testosterone ≥ 2 pg/ml) for the patients with oligomenorrhea or amenorrhea; there was also an image of ovarian stromal hypertrophia and multiple follicles (≥ 10 follicles) of small dimensions (6-8 mm) that appeared during the ultrasound endovaginal examination.

The normal values of the biochemical parameters tested were as follows: glucose - 76-110 mg/dl; FSH - 3.5-12.5 mUI/ml; LH - 2.4-12.6 mUI/ml; total testosterone - 0.06-0.82 ng/ml; free testosterone - 0.1-4.1 pg/ml.

Citrate clomiphene (CC) remains the first choice treatment for inducing ovulation in the case of the women with anovulatory cycles and PCOS. They are taken orally, with few side effects.

RESULTS AND DISCUSSION

From the paraclinical point of view, out of the 156 patients:

- 141 patients (90.4%) showed suggestive ultrasound aspects for polycystic ovary;
- 15 patients (9.6%) had normal ultrasound scans, but associated suggestive clinical signs of PCOS: hirsutism, menstrual disorders and hormonal changes;
- an increased testosterone value for 98 patients (62.8%);
- 103 patients (66.0%) had an increased BMI above the normal values, the rest being of normal weight;
- a changed ratio FSH/LH for 85 patients (54.5%).

Intraoperative, 47 patients (30.12%) from the total of 156 showed associated pathologies:

- ovarian cysts - 28 patients (59.6%) representing 17.9% from the total;
- adhesences - 12 patients (25.5%) representing 7.7% from the total;
- unilateral tubal obstruction - 5 patients (10.6%) representing 3.2% from the total;
- bilateral tubal obstruction - 2 patients (4.3%) representing 1.3% from the total.

The postoperative monitoring, lasted for an interval of 2-24 months:

- 2 months - 41 patients - 26.28%;
- 2-6 months - 53 patients - 33.97%;
- 6 months - 12 months - 18 patients - 11.53%;
- over 12 months - 9 patients - 5.76.

Reevaluation

- ✓ 35 from the total did not come back;
- ✓ 91 patients had ovulatory cycles - 58.34%;
- ✓ 34 patients had pregnancies - 21.79%;
- ✓ 31 patients did not answer - 19.87%

The clinical and hormonal profiles of the patients were recorded before and after the procedure. There were significant differences in the serum values of FSH ($p=0.048$), LH ($p=0.059$), LH/FSH ratio ($p=0.05$) and testosterone ($p=0.025$).

Table I. Hormonal profiles of the patients with PCOS before and after treatment

Hormonal profile	Before drilling	After drilling	p
FSH (mUI /ml)	3.87	4.61	0.048
LH (mUI /ml)	5.63	4.43	0.049
LH /FSH	1.59	1.01	0.050
Testosterone (ng/ml)	0.71	0.63	0.025
Free testosterone (pg /ml)	2.03	1.70	0.049
Glucose (mg /dl)	83.1	83.8	0.999
Regular cycles (%)	16%	80%	0.001

Ovarian laparoscopic drilling, followed by an appropriate stimulation with clomiphene is an efficient method of treatment for the patients with anovulatory infertility. The stimulation of follicular maturation by using Citrate clomiphene, which increases the endogenous secretion of FSH, or exogenous FSH administration, resulted in a complete follicular maturation and ovulation (Onofriescu A., et al, 2013).

In our study, the ovulation rate was 80% and the pregnancy rate 36.6%.

The distribution of pregnancies depending on the clomiphene dose used was as follows: for 50 mg there were 10 pregnancies (41.66%) out of the total of 24 patients; for the dose of 100 mg there were 18 pregnancies (51.42%) out of the 35 patients; and for the dose of 150 mg there were 9 pregnancies (47.36%) out of the 19 patients.

Hormonal and ultrasound monitoring are compulsory during the protocols of ovarian stimulation in order to control the risk of ovarian hyper stimulation syndrome.

Based on the cases studied, ROC curve is drawn in order to highlight the efficiency of the treatment method used for infertility and it shows a better accuracy for the patients who had ovarian drilling, in comparison with the group of patients for which they used citrate clomiphene (CC).

Table II. LOD efficiency in comparison with the classical treatment of infertility

Method	VPP (%)	VPN (%)	Sensibility (%)	Specificity (%)	Accuracy	p
Drilling	84.6	0	85.0	75.0	80.0	0.002
Classic	86.7	0	65.0	47.5	56.3	0.007

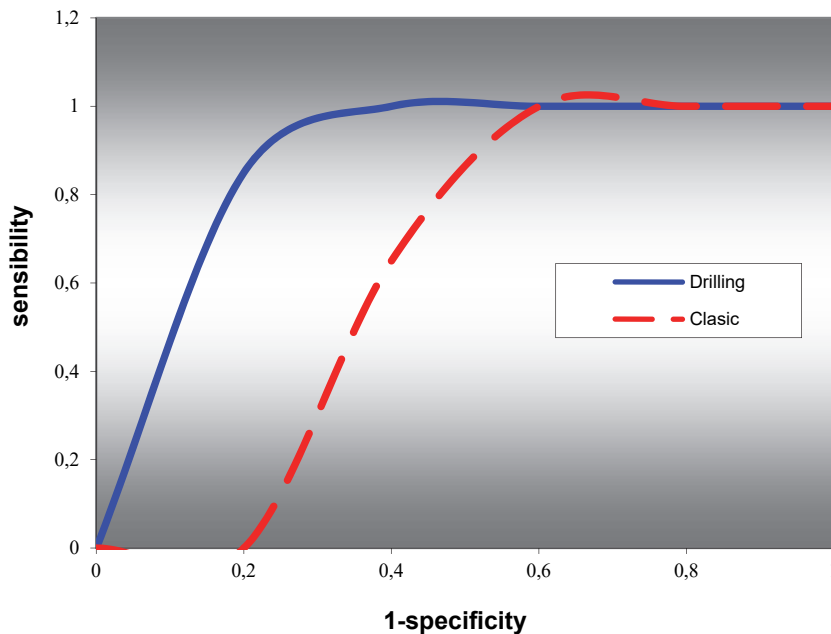


Fig. 1. ROC curve for the effectiveness of infertility treatment

Laparoscopic ovarian drilling through diathermy or laser is actually another option of treatment for women with anovulatory infertility associated with PCOS. This laparoscopic version of the ovarian resection uses electric monopolar coagulation or ovarian puncture with laser in 4-6 places, at a depth of 4-10 mm on each ovary (Liguori G., 1996; Mencaglia L., 2003).

After the laparoscopic ovarian drilling, the ovary volume increases transiently, followed by a decrease in the ovary volume (Rossmanith W.G., 1991).

It is not known exactly why some patients with PCOS do not respond to this treatment. A plausible explanation could be the fact that the destroyed ovarian tissue is not enough to produce the expected effect for some patients or the presence of an inherent resistance of the ovary to the drilling effect (Amer S., et al, 2007).

Efficiency. For about 50% of the women treated with laparoscopic ovarian drilling (LOD) an additional therapy was also necessary. For these women, the additional CC can be considered after 12 weeks, if ovulation did not appear. The additional FSH must be considered after 6 months (Bayram N., et al, 2004).

Five random controlled clinical studies, that compared the efficiency of laparoscopic ovarian drilling (LOD) with that of gonadotropins in women with PCOS who are resistant to CC, did not show any difference regarding the rate for keeping the pregnancy or the birth rate. In one of the clinical studies, if there was no ovulatory cycle 8 weeks after surgery or if the patient became anovulatory again, then she was administered CC in increasing doses. The rate of the multiple pregnancies was significantly higher for the group who were administered gonadotropins during the five clinical trials in comparison with LOS (relative risk [RR] 0.13; confidence interval [CI] of 95%, 0.03-0.98). On the other hand, there were no differences regarding the abortion rate between

the group with LOD and the group of women treated with gonadotropins (RR 0.61; CI de 95%, 0.17-2.16). There were no cases of SHSO in either of the recent studies (Farquhar C.M., 2001; Kaya H., 2005).

Safety. The immediate complications of the surgical intervention are rare. From the total number of 778 cases of LOD, only two cases of haemorrhage were reported as they needed laparotomy and also one case showed an intestine lesion. The long term incidents can include formation of adhesions and early menopause. Premature ovarian failure is a risk of ovarian drilling, especially when it is used with a big number of punctions (Amer S., et al 2002). The risks of surgery are those of anaesthesia, of damage to some abdominal organs, the occurrence of postoperative adhesions. The adherence rate is considered to be 25%. Some people proposed a laparoscopic second-look to lyse any adhesions formed. Apparently when a part of the ovarian tissue is destroyed that does not cause a more rapid start of menopause; but there is a risk of some premature ovarian disorders, although this risk is still being estimated (Hamilton-Fairley D. and Taylor A., 2003).

In comparison, ovarian drilling has the same success rate as the use of gonadotropins. But the multiple pregnancy rates seem to be more reduced. Followed on a period of time of 25 years, the partial ovary resection continues to get the best results. The cumulative rate of pregnancies was 76%, but if we add those induced by medication it goes up to 88%. The cumulative rate of pregnancies was 78%. The only method used in the present that is comparative as results is the laparoscopic cauterise (Hashim H., et al, 2013).

CONCLUSIONS

Laparoscopic ovarian drilling, followed by an appropriate stimulation with clomiphene associated with metformin is an effective method of treatment for the patients with anovulatory infertility.

In our study, the ovulation rate was 80%, and the pregnancy rate was 36.6%.

When talking about LOD safety, there are few complications recorded (haemorrhage during surgery, intestinal perforation), postoperative adhesions and early menopause.

The results are more favourable when the biochemical profile of the patients before surgery is less deteriorated.

The costs of the procedure can recommend it as second-line therapy for the cases that do not respond for a period of 6 months to citrate clomiphene therapy alone, being able to successfully replace the therapy with gonadotropins.

When performing LOD many types of intervention can be used: cuneiform resection, electrocautery, laser vaporization, multiple ovarian biopsies, procedures that lead to an endocrine profile change.

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