News in the Ovarian Drilling in the Polycystic Ovary Syndrome

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The purpose of the study is to determine the efficiency on the endocrine and clinical parameters of the ovarian laparoscopic drilling in the patients with SOPC and resistant to the therapy with chlomiphene. Were studied the factors that influence the results of the ovarian laparoscopic drilling as method of treatment in women with the syndrome of polycystic ovaries it was studied too the efficiency of the ovarian laparoscopic drilling compared to other methods of treatment and it was identified of a protocol that leads to the increase of the percentage of pregnancy in the patients with SOPC resistant to the treatment with citrate chlomiphene.

Keywords: clinical parameters, laparoscopic drilling, SOPC, chlomiphene

The cuneiform resection of ovary is the first therapy introduced for SOP and represents the excision of half to 3/4 of the ovary medulla by laparotomy (Halbe, 1972). Because of the risks of post-surgery adherences, which transformed the endocrinological sub-fertility into a mechanical one, it was gradually abandoned and replaced with medical therapy (Adashi 1981, Buttram 1975, Stein 1939).

The technique of the cuneiform resection of ovaries, carried out by laparotomy in the past, is currently abandoned. If there are no contraindications, the ovary surgery in cases of SOPC is always done on a minimum invasive way, laparoscopic, either trans-umbilical or trans-vaginal (culdoscopy or fertiloscopy). The relation between the amplitude of the drilling (number, size and depth of sites) and the success of inducing ovulation or duration to maintain the spontaneous ovulation was not precisely identified.

Laparoscopy is the traditional approach and, theoretically, it can be done in any surgery room, with general anaesthesia. It allows carrying out some multiple ovary biopsies and some multiple perforations, by using monopolar electro-coagulation or laser.

The advantage of laparoscopy is that it can be done in any surgery room; it does not require special equipment and allows to examine the whole abdomen cavities. The surgeons who often do laparoscopies by using this method can learn this technique very easily. Laparoscopy can transform the endocrinological sub-fertility into a mechanical one, it was gradually abandoned and replaced with medical therapy (Adashi 1981, Buttram 1975, Stein 1939).

The technique of ovarian laparoscopic drilling was described for the first time by Gjonnaess in 1984. The purpose of the intervention was to destroy as many atretic follicles, without eliminating from the ovarian tissue. He used a monopolar instrument, attached to electricity of 200-300 W. The dimensions of the perforations depend on the thickness of the ovary capsule. Their number in the initial technique was 10-15 on each side.

Stein and Leventhal described for the first time the surgery treatment in 1935, cuneiform resection, to which it was noticed a restoration of the normal menstrual cycle in about 80% of the patients, and the rate of pregnancy of 50%. Because of the appearance of the pelvic adherences, this method was abandoned.

Gjonnaess introduced in 1984 the technique of ovarian laparoscopic drilling for the patients with syndrome of polycystic ovarian resistant to treatment with citrate chlomiphene.

Fernandez et al. published a retrospective study in 2011, creating an image of the technique of ovarian laparoscopic drilling.

In the patients who have the ovarian laparoscopic drilling done, at first there is a pneumoperitoneum with about 4 litres of CO₂ until a pressure in the intra-abdominal cavity of 12-14 mmHg. Using the instruments is done by introducing the electrode by trocars using commonly in the gynaecological laparoscopy. Based on the dimension...
of the ovary, it is done a variable number of points of ovarian drilling between 6-15 in the ovarian capsule. Each of these punctures is of about 3mm in diameter and 4-6mm thickness. The isolated monopolar electrode is of 1.5-2mm in diameter, with a conic peak. The empty tip of the electrode is introduced perpendicularly on the ovary 3-4mm deep, applying 30W for about 4-5 s. There are various studies reporting various data regarding the depth of introducing the needle in the ovarian capsule, the intensity of the electricity, the time to carry out each puncture in the ovarian capsule. The procedure is finished by assuring the presence of adequate haemostasis, and by careful pelvic washing. Even though the surgery access is usually by laparoscopy, the procedure was carried out also by trans-vaginal hydrolaparoscopy. The hydrolaparoscopy is done by introducing the Veress needle in the peritoneum cavity through the sack bottom Douglas. About 300 mL normal salty solution at room temperature is introduced in the peritoneum cavity. Then it is introduced with an operative surgery canal of 5mm calibre through the sack bottom Douglas, a hysterectomy of 2.9 mm with a lens of 30 degrees. It is continued with the examination of the pelvis and a hydro-tubation with contrast substance. Because the fallopian tubes, fimbriae and ovaries can be clearly seen, it can be used a bipolar electrode of 5 (5-French) for the micro-perforation of the ovarian cortex in 5 to 10 points [1, 6]:

- infertility on anovulation reason in SOPC;
- patients with persisting hyper-secretion of LH;
- response to citrate chlomiphene, because DOL reduces the secretion of LH;
- patients who do not have ovulations and have SOPC, and who require surgery intervention to pelvis assessment;
- monitoring continuously during a treatment with gonadotropins.

The groups of indications where patients have an advantage from the laparoscopic operation are not enough defined.

Complications of the ovarian drilling:
- infection of the sub-umbilical incision;
- para-ovarian hematoma.

The risks of the ovarian drilling include the formations of adherences and other relatively minor complications, and rare, such as haemorrhage, infection or thermal affection of the intestine.

The theoretical risks of reducing the ovarian reserve or the appearance of ovarian insufficiency remain to be defined.

The ovarian atrophy after the ovarian drilling is rare, but it was met (Dabirershafi, 1989).

The formation of adherences is frequent, but their majority has a light degree, with a minimum impact on fertility (Gargan, 1992; Naether, 1993).

Comparing with the medical treatment, the ovarian drilling presents a lower risk for the syndrome of ovarian hyper-stimulation and multiple pregnancy (Schorge et al. 2008).

The ovary is raised like a blunt probe. The electrocautery is set at 30-60 W. 3-5 perforations perpendicularly on the capsular surface are done, on the anterior face of the ovary, and cystic follicles characteristic for PCOS are stung. It is avoided the drilling at the level of the lateral surfaces of the ovary and at the level of the hil to minimize the risk of forming adherences, and bleeding respectively (Schorge, 2008).

Experimental part
Materials and methods
The study is retrospective, analytical and descriptive, and it includes 156 patients (28.41%) who addressed in problems of primary infertility of ovulatory reason, with antecedent of medical treatment and who accepted the procedure of ovarian drilling as method of treatment, during a period of 5 years, January 2010 - December 2014.

Treatment of sterility
At the beginning the citrate chlomiphene was used. The citrate chlomiphene (CC) remains the first-choice treatment to induce ovulation in women with anovulatory menstruation and SOPC. The way of administration is oral, with less side effects.

In case of failure, gonadotropins were administrated with action FSH and LH according to the trials set. The treatment with gonadotropins requires extensive monitoring because of high sensitivity of polycystic ovaries at exogenous gonadotropins, with the risk of developing multiple follicles that lead to the appearance of the syndrome of ovarian hyper-stimulation or multiple pregnancy.

The last option was laparoscopic electrocautery of the cysts (ovarian drilling). The drilling can sometimes improve the receptivity to exogenous gonadotropins and it was tried a new treatment with gonadotropins after the surgery.

The diagnostic of SOPC was according to the criteria set at the common meeting of the European Society of Human Reproduction (ESHRE) and the American Society of Reproductive Medicine (ASRM) in Rotterdam in May 2003 (Rotterdam ESHRE/ASRM-Sponsored SOPC Consensus Workshop Group, 2004) with the mention that 2 out of 3 to be present: oligo/anovulation, clinical/biological signs of hyper-androgenism, polycystic ovaries (presence of 12 or more follicles of 2-9 mm in each ovary and/or the increase of the ovarian volume > 10 mL).

It was set the report LH/FSH on the third day of the menstruation ≥ 2 and/or high levels of androgen hormones (testosterone ≥ 0.7 ng/mL, testosterone free ≥ 2pg/mL) in patients with oligomenorrhea or amenorrhea; or image of ovarian stromal hypertrophy and multiple follicles (≥ 10 follicles) of small dimensions (6-8 mm) in the endovaginal ultrasound examination.

The normal values taken into the consideration 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; testosterone in total, 0.06-0.82 ng/mL; testosterone free, 0.1-4.1 pg/mL.

The administration of citrate chlomiphene was indicated on in the patients with proved ovular dysfunction and who corresponded to the following conditions (criteria): normal hepatic function; endogenous estrogens within physiological limits (estimates through vaginal smear, endometrial biopsy, determination of urinary estrogens, or through bleeding after the administration of progesterone). A low level of estrogens, even if it is less favourable, does not compromise the therapeutic success. The treatment with citrate chlomiphene is not enough in the patients with primary insufficiency in hypophysis or ovaries. It cannot substitute the therapy adequate to other troubles that lead to dysfunctions. It must be done a careful investigation of the patients with abnormal metrorrhagias before starting the treatment with citrate chlomiphene. It is of maximum importance to detect the neoplastic lesions.

The mechanism of action is based on the capacity to occupy the nuclear receptors for estrogens at the level of the hypothalamus and hypophysis, thus impeding the formation of negative estrogens feedback on the secretion of gonadotrophin; there is an increase of the concentration...
of gonadotrophin, having as effect the ovulation stimulation. The secretion of LH and FSH increases. Under the influence of the high values of these hormones, an ovarian follicle appears, followed by ovulation and the formation of the yellow body.

If CC is used to induce the ovulation, the probability of pregnancy is the highest in the first 3 to 6 menstruations, and the therapy after 6 menstruations is not recommended in general. In the patients treated with this conventional regime of gradual increase of the dose of CC, it was be expected a total cumulative percentage of pregnancies of 55%–73%. Aging and the duration of infertility are associated with the failure of the treatment.

The studies are very diverse in the literature in the field, because resistance to citrate chlomiphene is interpreted in various ways and there are no internationally recognized standards. I introduced in the study the patients with SOPC resistant to CC, those who did not present ovulation after 3-6 months of treatment with 2cp/day of CC administrated on the 5th day of the menstruation. Using this criterion of inclusion, I had the possibility to recruit more patients in the lot of study.

51 of the patients included in our study (32.69%), were treated with chlomiphene, before the surgery, with inefficient results, in the doses customized for 3 months.

The ovarian laparoscopic drilling

The polycystic ovaries (of porcelain and/or ivory) appear intra-operatory increased in volume, with shining surface, white-ivory. It is the classical aspect, very suggestive for the diagnostic [7].

During the surgery complications may appear, such as adherences. If the ovarian tissue is destroyed too much, there is a risk of premature ovarian troubles, even though this risk is still in the stage of estimation (Flores JC, 1990, Greespan FS, 2001). In the case of our study, one case (0.64%) required the conversion in laparotomy, to which it was practiced cuneiform resection of ovary, instead of drilling, the patient being obese.

In the period after the ovarian drilling, the patients were instructed to keep evidence of the menstrual cycle. Thus, if within six weeks from the intervention there was menstruation, we carried out the dose, on the third day of menstruation, of the serum concentration of total testosterone, of testosterone free, LH, FSH and glucose, and on the 21st day of the menstruation, the value of the progesterone. The diagnostic of the ovulation was a value of progesterone higher than 8 ng/mL. We also took into account the characters of the menstruation cycles and the number of pregnancies obtained and their evolution.

The surgery technique used supposed the introduction of three trocars: one sub-umbilical and the other two in the septic iliac, bilateral. Through the trocars in the septic iliac were introduced a forceps of grasping type, used at raising the ovary by the means of the utero-ovarian ligament and the dia-thermal needle with which we did the ovarian drilling. The diathermal needle had a length of 7-8 mm and a diameter of 0.5 mm, the monopolar electricity used set at 30W, and the duration of each penetration of the ovarian tissue was \( \approx 1 \) s. We did between 10 and 15 punctures in each ovary, each with a length of 3 mm and a depth between 4 and 6 mm, according to the size of each ovary. After the diathermal puncture, it was used a solution of 0.9% NaCl to irrigate the ovaries [8, 9].
Reasons to visit the doctor:
1. Oligospaniomenorrhea and sterility - 103 patients - 66.02%;
2. Sterility - 30 patients - 19.23%;
4. Primary amenorrhea - 2 patients - 1.28%.

Paraclinical among the 156 patients:
- 141 patients (90.38%) presented suggestive ultrasound aspects for polycystic ovary;
- 15 patients (9.62%) had normal ultrasound, but associated suggestive clinic signs for SOPK: hirsutism, menstruation troubles, and hormonal modifications;
- Testosterone increased in 98 patients (62.82%);
- 103 patients (66.02%) had IMC increased over normal, the rest being of normal weight;
- Modification report FSH/LH in 85 patients (54.48%).

Intraoperator:
- 47 patients (30.12%) of the total of 156 presented associated pathologies:
  1. Ovarian cysts - 28 patients (17.94%);
  2. Adherences - 12 patients (7.69%);
  3. Unilateral tube obstructive - 5 patients (3.20%);
  4. Obstructive tube bilateral - 2 patients (1.28%).

Complications:
1 case (0.64%) required the conversion in laparotomy, to which we practised cuneiform resection of ovary, instead of drilling, the patient being obese.

Post-operatory monitoring 2-24 months:
- 1.2 months - 41 patients - 26.28%;
- 2-6 month - 53 patients - 33.97%;
- 6 months-1 year - 18 patients - 11.53%;
- over 1 year - 9 patients - 5.76%.
35 of the total did not return.

During the period of survey, the patients were instructed to monitor their menstruation. In the case where the menstruation did not install within 6 weeks from the intervention, there was treatment with progesterone 200mg/day, 10 days. In all the cases where it was used the probe at progesterone, the menstruation reappeared 2-3 days after finishing the administration. We gathered analyses on the third day of the menstruation to determine the serum concentrations of LH, FSH, AMH and testosterone. On the 21st day of the same cycle, it was measured the serum concentration of progesterone. The ovulation was diagnostic for a level of progesterone e" 30nmol/l or by ultrasound monitoring of one or more follicles.

80% of them had regular menstruation, being reached a percentage of spontaneous pregnancies obtained by 36.6%. After the laparoscopic ovarian drilling, the average duration after which the first pregnancy appeared was 3.6 months. The weight and index of body mass were not modified significantly after the procedure (table V.2).

The clinical and hormonal profiles of the patients were recorded before and after the procedure. We recorded significant differences regarding the serum values of FSH, LH, proportion LH/FSH and testosterone.

In this study, we evaluated the impact of the various clinical and biochemical characteristics of DOL in 156 patients with SOPC. Even though the chronic anovulation in women with SOPC is usually associated with irregular menstrual cycles, many studies reported that 16-24% of these women apparently have regular menstrual cycles. Numerous patients with SOPC ovulate occasionally and a part of them can have regular menstrual cycles during periods of time that vary, which explains why certain patients with SOPC anovulatory conceive spontaneously, while being investigated for infertility or expect treatment.

The serum level of LH increases immediately after surgery, and then it decreases. In our study, the serum level of LH one year after the intervention decreased significantly from 5.63 mUI/ml before the surgery to 4.43 mUI/ml one year after the ovarian drilling. The frequency of the pulsations of LH is not modified, but after DOL the amplitude of the pulsations of LH is significantly reduced.

The serum concentrations of LH represent the best factor of prognostic regarding the efficiency of DOL. The patients with SOPC and serum concentrations of LH over 10U/l respond much better after DOL comparing with the patients who have serum levels before surgery lower and

<table>
<thead>
<tr>
<th>Age</th>
<th>Before</th>
<th>After</th>
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<tbody>
<tr>
<td>28.8</td>
<td>39.5</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.5</td>
<td>70.4</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.62</td>
<td>1.62</td>
</tr>
<tr>
<td>Index weight (kg/m²)</td>
<td>26.9</td>
<td>26.8</td>
</tr>
</tbody>
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Table 1
GENERAL DATA FOR THE PATIENTS IN THE STUDY
after surgery present levels of LH and testosterone much more reduced.

The hypophysis response to the stimulation by GnRH decreases significantly with the decrease of serum concentrations of testosterone, which suggests that the destruction of the ovarian stroma has an indirect modulator effect on the axis hypophysis-ovary. Our study confirmed the statistically significant decrease after DOL of the serum concentrations of testosterone from 2.03nmol/L before surgery to 1.7nmol/L after surgery.

If it is obvious that the serum level of LH decreases after DOL, the effect of the surgery intervention on the serum level of FSH varies or is very little affected. In our studies, the concentrations of FSH modified insignificantly, statistically, one year after the ovarian drilling. Before DOL, the values of serum FSH were 3.87 mUI/mL and 4.61 mUI/mL one year after the surgery. The monthly menstruation variations of FSH become normal with the normal periodicity of the menstruation. The increase of FSH values determines the normalization of the proportion LH/FSH, with the recruitment of new groups of follicles and the appearance of ovulation.

Also, the menstrual irregularities – the most frequent symptom – improved in about 80% of the patients.

1 - 91 patients presented ovulatory menstruation – 58.34%;
2 - 34 patients were pregnant – 21.79%;
3 - 31 did not respond – 19.87%

These results were most often found in the verification after 6 months, 83 patients presenting pregnancy or ovulation cycle, and only 8 patients at more than 6 months.

<p>| Table 2  | THE HORMONAL PROFILES OF TEH PATIENTS WITH SOPC BEFORE AND AFTER THE TREATMENT |
|---------------------------------|---------------------------------|---------------------------------|</p>
<table>
<thead>
<tr>
<th>FSH(mU/l ml)</th>
<th>Before drilling</th>
<th>After drilling</th>
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<tbody>
<tr>
<td>LH (mU/l ml)</td>
<td>3.87</td>
<td>4.61</td>
</tr>
<tr>
<td>LH /FSH</td>
<td>5.63</td>
<td>4.43</td>
</tr>
<tr>
<td>Testosterone (ng /ml)</td>
<td>1.59</td>
<td>1.01</td>
</tr>
<tr>
<td>Testosterone free (pg /ml)</td>
<td>0.71</td>
<td>0.63</td>
</tr>
<tr>
<td>Glucose (mg /dl)</td>
<td>2.03</td>
<td>1.7</td>
</tr>
<tr>
<td>Regular cycles (%)</td>
<td>83.1</td>
<td>83.8</td>
</tr>
<tr>
<td>Statistical significance</td>
<td>After drilling</td>
<td>Before drilling</td>
</tr>
</tbody>
</table>
Conclusions

In our opinion, from the pharmaceutical-economic point of view, the ovarian laparoscopic drilling could be used as treatment of first intention with patients with SOPC resistant to clomiphene. It is cheaper comparing with the treatment with gonadotropins.

The ovarian laparoscopic drilling, followed by a corresponding stimulation with clomiphene in association with metformin is an efficient method of treatment for patients with infertility of anovulator type.

The reduction of androgens after ovarian surgery determines a decrease of peripheral aromatization in estrogens and restores the feedback at hypothalamus and hypophysis.

As for the safety of DOL, few complications are recorded (intra-operative haemorrhage, intestine perforations), adherences after surgery and precocious menopause.

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

The costs of the procedure can recommend it as second-line therapy in the cases that do not respond within six months to the therapy with only citrate clomiphene. It can successfully replace the therapy with gonadotropins.

The costs of the ovarian laparoscopic drilling are lower than the treatment with gonadotropins used in the treatment of infertility in the patients with SOPC.

In order to practice DOL, several types of intervention can be used: cuneiform resection, electrocautery, vapour with laser, multiple ovarian biopsies, procedures that lead to the modification of the endocrine profile.

By the ovarian laparoscopic drilling, the incidence of multiple pregnancies is reduced, as well as the risk of syndrome of ovarian hyper-stimulation.

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