ORIGINAL STUDY

TREATMENT OF POLYCYSTIC OVARY SINDROME
RETROSPECTIVE STUDY 2004-2010

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ABSTRACT

The aim of the study is the investigation done in the 95 cases of polycystic ovary syndrome, the diagnosis, therapy and posttherapy results. Polycystic ovary syndrome is one of the most frequent endocrine conditions, its frequency is estimated between 1.5 and 20% (the average is 5-8%) in the fertile female population. Polycystic ovary syndrome has a wide etiological spectrum and multiple clinical symptoms and it is considered an exclusion diagnosis. The importance of polycystic ovary syndrome in the medical practice resultes from the fact that is the most common cause of hirsutism and clinical elements of androgenism and the first cause of infertility thru anovulation and with metabolic consequences (insuline resistance, obesity, lipid profile disorder, second degree diabetes with serious cordio – vascular implications). The study follows the clinical features of the group of patients. The analyzed group consists of 95 patients, studied according to the pathological mechanism, the identification of long-term risk factors, the diagnosis and therapy accuracy. The numerous treatment options must be individualized in relation with patients characteristics. Menstrual cycle regulations thru: usage of oral contraceptives in 54 cases; Ciproteron Acetate in 3 cases; Methformin in 11 cases. Four patients have undergone surgical treatment. The ovulation was stimulated in 10 cases by administrating Clomifen. Using diferent schemes of treatment led to pregnancy in 12 cases, which represents 12,63% of total studied cases. The patients were prescribed treatment according to their options: menstrual cycle regulations; pregnancy. The numerous therapeutical options must be individualised in relation with patients characteristics and preferences.

KEYWORDS: POS, secondary amenorheea, obesity, methformin

1. Introduction

Polycystic ovary syndrome is a heterogeneous disorder frequently characterized by a spectrum of anatomic and hormonal elements which vary in point of intensity and implication [1]. Being of uncertain etiology, it may include genetic aspects, environmental factors, reducing activity process and even hypercaloric diets. The diagnosis criteria are [2,3]

- oligoovulation or anovulation
- clinical or biochimical hyperandrogenism on a long term
- polycystic ultrasound aspect
The signs and symptoms may vary from one patient to another over the years. As a result, women with Polycystical ovary syndrome may address to many medical field like: gynecology, internal medicine, endocrinology or dermatology [4]. The particular secretion of gonadotropins: high LH (Luteinizing Hormone) and low FSH (Follicule Stimulating Hormone) are due to the increased GnRH( Gonadotropin Realising Hormone) pulsation freaquency. The increase of GnRH pulsations may be assigned to the opioide hypothalamic inhibition through the chronic lack of progesterone. The increase of GnRH pulsations generates raise in amplitude and LH secretion frequency, in connection with the high levels of estrogens. [5, 6].

2. Material and methods

This study analyses 95 patients diagnosed with Polycystic ovary syndrome in the Ambulatory of the Obstetrics- Gynecology Hospital Galati.

The group of 95 patients was selected from 4833 patients who came to „Buna Vestire” Hospital Galati.

The analysed patients come from: Urban 68, Rural 26

The analysed patients are assigned on age groups:( figure 1, table I)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 20 years old</td>
<td>14.89%</td>
</tr>
<tr>
<td>20-24 years old</td>
<td>25.53 %</td>
</tr>
<tr>
<td>25-29 years old</td>
<td>31.91%</td>
</tr>
<tr>
<td>30-34 years old</td>
<td>14.89%</td>
</tr>
<tr>
<td>35-39 years old</td>
<td>8.51%</td>
</tr>
<tr>
<td>40 and over 40 years old</td>
<td>4.26%</td>
</tr>
</tbody>
</table>

Polycystic ovary syndrome (PCOS), being heterogenous, presents different clinical and biological symptom combinations (7). Many of these symptoms occur immediately after menstruation.(8) At menopause many of them improve.

The group of 95 patients presented:
- irregular menstruation- 86 cases (76.7%)
- infertility- 74 cases (66%)
- hirsutism- 25 cases (22.3%)
- hyperandrogenism- 20 cases (17.8%)
- obesity - 20 cases (17.8%)
- acne, seborrhea- 36 cases (32.1%)

Chronic amenorrhea, oligoamenorrhea and prolonged bleeding are specific to this disease. Menstruation that lasts more than 35 days is anovulatory in 50-90% of cases. Women with PCOS frequently suffer from hirsutism, acne and seborrhea. In the diagram below are represented the FSH and LH value frequency for the patients with amenorrhea.(figures 2, 3) The values are assigned almost normal for these two hormones with a small deviation towards the low values.
Comparing the insulin, LH and FSH level, the LH/FSH report and BMI (obesity) in case of women with normal or high level of gonadotropins is shown in the table below. (Table II)

**Table II. LH/FSH report**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PCOS with LH/FSH&gt;2</th>
<th>PCOS with LH/FSH&lt;2</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH mU/ml</td>
<td>13.7</td>
<td>10.1</td>
</tr>
<tr>
<td>LH/FSH</td>
<td>24</td>
<td>45</td>
</tr>
<tr>
<td>BMI (obesity)</td>
<td>25.8</td>
<td>19.7</td>
</tr>
</tbody>
</table>

Determining LH/FSH abnormal report in case of women with PCOS still remains an important problem.

**Table III. LH/FSH report**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PCOS with LH/FSH&gt;2</th>
<th>PCOS with LH/FSH&lt;2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>9</td>
<td>27</td>
</tr>
<tr>
<td>Testosterone</td>
<td>11</td>
<td>53</td>
</tr>
<tr>
<td>LH mU/ml</td>
<td>13.7</td>
<td>10.1</td>
</tr>
<tr>
<td>FSH</td>
<td>4.9</td>
<td>4.4</td>
</tr>
<tr>
<td>LH/FSH</td>
<td>24</td>
<td>45</td>
</tr>
</tbody>
</table>

In this study 45 cases were diagnosed with hyperandrogenism. Insulin resistance is associate with androgenic (abdominal) type of obesity. [7-9]. Most of the patients with high cholesterol levels have BMI>25. In the late 1980s the LH/FSH report was considered a real standard for the PCOS diagnosis. In this study the high report of the gonadotropins was found in 47.87% of the patients. The level of the free testosterone is not related to the LH and insulin value. (Table III)

**Insulin resistance**

Blood sugar level that was determined to the group of 95 patients showed the following values. (10) 71 patients with normal blood sugar, representing 75.53% 
-23 patients with high blood sugar, representing 24.46%

The frequency blood sugar levels shows that this factor is assigned almost following the normal law, around the average of 92.04% and with a standard error of 10.171. (Figure 4)

**Figure 4. Blood sugar frequency**

Blood sugar level was determined and in case of 23 patients who had the value between 105-120 mg/ml, the oral Glucose Tolerance Test (TTGO) was performed. Insulin resistance was associated with obesity. (Table IV)

The tables below show the frequency of TTGO:

**Table IV. TTGO**

<table>
<thead>
<tr>
<th>TTGO</th>
<th>Frequency</th>
<th>Percent</th>
<th>Total percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>23</td>
<td>20.5%</td>
<td>20.5%</td>
</tr>
<tr>
<td>NO</td>
<td>89</td>
<td>79.5%</td>
<td>100%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>112</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

Patients with PCOS were investigate for dyslipidemia to measure the total cholesterol (LDL, HDL), triglycerides. (Table V) Gynecological
ultrasonography is the real standard in the morphological diagnosis of polycystic ovary (figures 5).

**Table V. Obesity**

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>Percent</th>
<th>Total percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>89</td>
<td>79.5%</td>
<td>79.5%</td>
</tr>
<tr>
<td>NO</td>
<td>23</td>
<td>20.5%</td>
<td>100%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>112</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

Figure 5. Polycystic ovary

Therapy aims are focused on two aspects:
- symptoms improving: irregular menstruation, acne and hirsutism, and preventing or minimizing long-term complications which may occur, HTA, diabetes, hyperlipemia, cardio-vascular complications.[10-12]
- As the polycystic ovary disease is physiological by nature, the treatment must be applied for a long-term (table VI). The patients have been informed and advised on the importance of a close follow-up. The first measures to be taken are diet and hygiene. These measures are considered important for overweight female patients as it may cause a decrease in insulin resistance. The study on the allotted group proved that 23 female patients(8%) had obesity problems [13,14]. These patients have been monitored in order to reduce the calory ratio by decreasing the lipid uptake followed by an increase in fiber uptake [15,16]. The demonstrated effects are a decrease in hyper insulinism and hyper androgenism. [17-19]. Another suggested method was that of increasing the physical activity which leads to an improvement in the peripherical use of glucose and also in insulin resistance.

3. Results and discussions

A female patient lost 17 kg after the diet and hygiene treatment had been applied while also increasing her physical activity. This led to resuming both menstrual cycles and ovulation. The pregnancy climaxed into a 37 week vaginal delivery.

The treatment of hyperandrogeny symptoms

This treatment must associate both mechanical means and hormonal treatments. Out of the total number of patients diagnosed with polycystic ovary disease, the following showed symptoms of hyper androgeny:
- hirsutism 27 (9%)
- acne 37 (12%)
- seborrhea 38 (13%)

The mechanical means such as electric epilation were used with 10 of the patients. Mijloacele mecanice cum ar fi: epilarea electrică au fost folosite la 10 dintre paciente. If physical and paraclinical tests led to the diagnosis of POS, the selected treatment implies the interruption of hypothalamic-hypophysis axis by an estro-progestative relation. In addition, an increase in SHNG may be observed which may lead to a decrease in free testosterone or the active form of androgens.

Diane 35 represents the selective treatment for women with POS and acne. The effects of oral drospinerone contraceptives were fast: the improvement in clinical hyperandrogenism symptoms have also been demonstrated by the development of biochemical markers: the value of of total plasmatic testosterone dropped significantly. Reevaluation by
means of an ecograph proved a decrease in size and
improvement in nature in 50% of all cases.

54 patients have been treated, this
representing 57,45%. The treatment has been well
tolerated, side effects being rare: mastodynias,
cephalalgia and mood disorder that dissipated after
the first three stages of treatment.

It was noticed a slight tendency to gain
weight, caused especially by food irregularities.

A number of 5 cases representing 5,31% have
been treated with cyproteron acetate , an anti
androgen and also an effective progestative in the
treatment of hirsutism cases. Clinically, it is used
periodically alongside ethinylestradiol in order to
prevent dismenorrhea when the administration of
cyproterone is stopped. Oral contraceptives are
usually associated with this treatment.

The treated patients did not want to get
pregnant. All treated patients improved their
menstrual cycles that become regular.

The treatment of progestative deficiency
applied to 10 patients consisted of Duphastone 20 mg
beginning from the sixteenth day of the menstrual
cycle until the twenty fifth in association with
clophemone citrate, maximum dosage of 150mg per
day from the third day of the menstrual cycle until
the seventh.

Improving luteal deficiency

The chronic anovulation leads to superfluous
secretion of estrogens devoided of luteal phase. When
estrogen secretion is not counterbalanced by a
progesteron secretion, there is the risk of endometrial
hyperplasia and thus endometrial cancer.

A number of 15 cases, that is 15,95% of
oligomenorrhea without hyperandrogeny have been
treated for 10 days a month with a derivate of natural
progesterone. Duphastone 20 mg form the sixteenth
day of the menstrual cycle up to the twenty fifth. The
level of progesterone has been determined with these
patients since the twenty first or twenty second day of
the menstrual cycle.

Clomiphen citrate represents the first choice
in treating BOP. These are tablets of 50 mg.(20). It
functions as an estrogen at the level of hypotalamus
and hypophysis and may induce the secretion of FSH.
This increase in the estrogen level allows for the
recruitment of a high number of folicules. The
therapeutic schemata resides in administring 50-
100mg a day for 5 days; from th third day of the
menstrual cycle up to the seventh.

An ultrasound monitoring is required
beginning with the tenth and the twelfth day of the
menstrual cycle in order to highlight the folicules.
This therapeutic schemata has been used with 10
patients that is 11,11%. The dosage of clomiphemone
citrate has been adapted to the ovary response, the
maximum dosage being of 150mg per day.

After this therapeutic schemata has been
applied, 5 pregnancies have been obtained out of
which one has stopped developing at 7-8 weeks. A
case presented a syndrome of slight ovarian
overstimulation that was though spontaneously
remitted as the treatment was well tolerated.

The treatment of metabolically dysfunction

The metformin – is an oral antidiabetic
pertaining to the class of brigandines; it leads to a
decrease in the glucose produced by the liver and also
to an improvement of insulin-sensitivity followed by
weight loss [21].

Several studies emphasize its effectiveness in
resuming ovulation. The positive effect of metformin
demonstrates the role of hyperinsulinism over
hyperandrogeny in POS [22]. The effectiveness of the
metformin treatment resides in inducing ovulation in
POS patients imune to clomiphene citrate treatment. A
number of 11 patients, that is, 11,70% have been
treated with metformin, the dosage being of 1500mg
a day.[23,24]

The treatment of metabolical disfunction
The follow-up treatment with metformin 1500mg per day led to 4 pregnancies.

Surgical treatment

The surgical technique used nowadays is the ovarian drilling [25]. Also called ovarian multiperforation resides in performing 6 up to 12 perforations in the ovarian area by means of either electric or laser power [26,27]

More recently, other laparoscopic techniques have been introduced among which CO2, Argon and ND ZAG laser therapy and also ovarian criotherapy.

Table VI. Treatment schemata suggested for POS:

<table>
<thead>
<tr>
<th>Anovulation Infertility</th>
<th>Hirsutism (Alopecia)</th>
<th>Menstrual imbalance</th>
<th>Obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in lifestyle</td>
<td></td>
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<tr>
<td>Obesity surgery</td>
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<tr>
<td>Metformin</td>
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<tr>
<td>Tiazolidine</td>
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<tr>
<td>Surgical treatment</td>
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<tr>
<td>Analogous to GnRH</td>
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<tr>
<td>CO</td>
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<tr>
<td>Dexametazone steroids</td>
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<tr>
<td>Progestative</td>
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<tr>
<td>Statine</td>
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<tr>
<td>Letrozol</td>
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<tr>
<td>Clomiphene</td>
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<tr>
<td>Gonadotropine</td>
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<tr>
<td>IUD</td>
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<td></td>
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<tr>
<td>Uterine surgery</td>
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<tr>
<td>Eflornithine HCL cream</td>
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<tr>
<td>Spironolactone</td>
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<tr>
<td>Flutamid</td>
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<tr>
<td>Finasteride</td>
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<tr>
<td>Mechanical/ Laser therapy</td>
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</table>
4. Conclusions

54 patients with oligo amenorrhea have been treated with oral contraceptives. Cyprothromone acetate has been used in the treatment of 3 cases. The treatment with metformin has been used with 11 patients. The clomiphene stimulation of the ovulation has been used with 10 patients. Surgical treatment, ovarian drilling has been used with 4 patients. BOP determines important clinical consequences: irregularities of the menstrual cycle up to amenorrhea, infertility, diabetes, hirsutism, endometrial cancer and cardiovascular disease. Anamnesis, physical examination and hormonal dosage allow for a diagnosis and ethiopathogenic treatment. Several therapeutic options must be personalized according to the preferences and peculiarities of the patients.

References

23. Strowitzki T., Clomiphene stimulation of the ovulation treatment increases plasma levels of adiponectin and decreases levels of resistin in overweight women with PCOS, Eur. J. Endocrinol., 2007156, 263-269.