Induction of multifollicular growth in patients non responding to clomiphene citrate and gonadotropins or gonadotropins only

M. TARTAGNI - A. DIAFERIA - P. L. NICASTRI - P. LOIZZI

Summary: Objective: We aimed at inducing multifollicular recruitment in patients with chronic anovulation resistant to Clomiphene Citrate (CC) and/or exogenous gonadotropins. Design: At the II Department of Obstetrics and Gynecology we treated our patients with exogenous gonadotropins and concomitant endogenous gonadotropin suppression obtained by the use of a GnRH analog (Buserelin). Patients: We studied 14 patients with chronic anovulation due to either hypothalamic dysfunction or polycystic ovarian syndrome. Measurements: We monitored the follicular growth ultrasonographically from the eighth day of the menstrual cycle, and assessed E2 and LH daily dosage from the tenth day. Results: With this protocol we obtained 2 or 3 mature follicles, and reached an ovulatory rate of 80.7% and a pregnancy rate of 71.4%. Premature luteinization never occurred, and progesterone increase took place only after human chorionic gonadotropins administration.

Key words: Chronic anovulation; GnRH agonist (Buserelin); Gonadotropins; Ovulation-induction.

INTRODUCTION

Chronic anovulation is quite a common clinical condition. Its most frequent causes can be subdivided into:

- causes due to dysfunction of the hypothalamohypophyseal tract (Hypothalamic Chronic Anovulation) (HCA), (Table 1);
- causes due to anomalies in the feedback system (AN FB), (Table 2).

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Table 1. – Chronic anovulation due to hypothalamohypophyseal tract dysfunction.

1) Dysfunctional (Hypothalamic chronic anovulation)
   A) Psychogenic
   B) Due to malnutrition
      - Anorexia nervosa
      - Simple loss of weight
   C) Associated with physical activity
   D) Hormonal congenital deficiencies
      - Gonadotropin isolated deficit
      - Laurence-Biedl syndrome.

Table 2. – Chronic anovulation due to feed-back system anomalies.

Polycystic ovarian syndrome
   - Cushing's syndrome
   - Addison's syndrome
   - Adrenal delayed congenital hyperplasia
   - Associated with androgenous tumors
   - Associated with thyrohyoid hypo and hyper-function.

1988) shows a common denominator in a reduction of GnRH release, caused by an increase of opiodergic and dopaminergic levels.

In the forms linked to loss of weight, anovulation occurs when the loss is over 15% of the ideal corporeal weight. Ovulation, in fact, seems to be connected with a minimum of adipose tissue, representing 22% of the total corporeal weight.

Basal and dynamic studies on the gonadotropic activity show different situations, ranging from prepuberal hypothalamic regression (prevailing FSH secretion) (anorexia nervosa) to normogonadotropinemia and oestrogenemia (simple loss of weight).

Chronic anovulation from feed-back system anomalies is the consequence of an anomalous secretion and peripheral steroid metabolism.

Acyclic oestrogenic production and the alteration of androgenous metabolism with a frequent reduction of sexual binding steroid globulins (SHBG) interfere with the delicate counterregulation mechanisms governing the ovulatory cycle over the reproductive age.

The commonest cause of chronic anovulation from ANFB is the polycystic ovarian syndrome (PCOS).

The first choice treatment for these pathologic conditions is Clomiphene Citrate (CC), which induces a high ovulatory rate (70%), resulting in an acceptable pregnancy rate; the best conditions for its use are normogonadotropinemia and normoestrogenemia.

The matter becomes more difficult when no response is given to CC. With gonadotropins (hMG, FSH), the pregnancy rate does not rise over 25-30% (Zimmermann et al., 1982; Thompson and Hansen, 1970), and this percentage is also impinged by a large number of abortions. This depends on exogenous gonadotropin interference with endogenous hypophyseal secretion. Exogenous gonadotropins often induce high quantities of plasma estradiol (E$_2$) (before full follicular maturation). By a positive feedback, they cause a premature LH surge with precocious follicular luteinization.

The relation between E$_2$ increase and the diameter of the dominant follicle is, consequently, suddenly interrupted, and an altered quality of oocytes follows (Zimmerman et al., 1982).

Precocious luteinization occurs when progesterone is 1.5 ng/ml 24 hours before the diameter of the dominant follicle reaches 20 mm (Fleming et al., 1986).

This phenomenon can be observed in 33% (Vargyas et al., 1984), 51% (Fleming et al., 1986) of cycles treated with gonadotropins and it is higher than the rate found in patients treated with Clo-miphene Citrate only.

On account of all this, there are reasons for using GnRH agonists in multiple ovulation patterns in patients with chronic anovulation HCA and ANFB.
In this study we have used Buserelin associated with gonadotropins (Gn) (FSH-hCG) for ovulation induction in patients non-responding to CC and Gn or Gn only treatment.

MATERIALS AND METHODS

Fourteen women with a mean sterility period of five years due to chronic anovulation were selected for this study. Ten of them had clinical features and hormonal pattern of PCOS, four of HCA.

Tables 3 and 4 show the main clinical and hormonal characteristics of patients with PCOS.

Table 3. – Clinical characteristic of PCOS patients.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age</th>
<th>Sterility period years</th>
<th>Menstrual cycle</th>
<th>Previous cycles of treatment No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>3</td>
<td>ameno</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>4</td>
<td>ameno</td>
<td>6</td>
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<td>3</td>
<td>24</td>
<td>2</td>
<td>ameno</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>8</td>
<td>oligo</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>36</td>
<td>6</td>
<td>oligo</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>27</td>
<td>4</td>
<td>ameno</td>
<td>8</td>
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<td>7</td>
<td>34</td>
<td>6</td>
<td>oligo</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>32</td>
<td>4</td>
<td>oligo</td>
<td>11</td>
</tr>
<tr>
<td>9</td>
<td>31</td>
<td>3</td>
<td>ameno</td>
<td>9</td>
</tr>
<tr>
<td>10</td>
<td>26</td>
<td>4</td>
<td>ameno</td>
<td>10</td>
</tr>
</tbody>
</table>

They were aged 29.5 on the average, and had been previously treated with a daily 100-150 mg CC dose for five days and/or with individual patterns of gonadotropins for six cycles at least.

The sterility period ranged from 2 to 8 years. Six women were amenorrhoeic, the ones left had oligomenorrhoeic cycles. All the patients with amenorrhoea responded to medroxyprogesterone acetate test (MAP test), showing a satisfactory endogenous estrogen level. Prolactin (PRL) was normal in all cases. Plasma androgen values had increased as well as LH/FSH ratio, which was always >2. Reaction to luteinizing hormone releasing hormone test (LHRH test) was always considerable.

Table 5 shows the characteristics of HCA patients. They were 27.5 years old on the average; the infertility period ranged from 3 to 3 years; 3 of them were amenorrhoeas, and one was oligomenorrhoeal. Even these amenorrhoeal patients responded to MAP test showing a satisfactory endogenous estrogen level.

Our therapy protocol consisted of Buserelin (Suprefact Hoechst Spray) associated with human gonadotropins (Gn) (Metrodin and Profasi Serono).

The agonist was administered 4 times a day (200 g each time) by inhalation (IN) from the first day of a menstruation which could be either spontaneous or induced with MAP test.

The Gn posology pattern provided for a pure FSH administration (150 IU/die), on the first and second day of the cycle in order to have, with the agonist “flare-up” effect, the follicular recruitment. Successively patients were given 75 IU/die pure FSH for six more days. From the eighth day, an individual pattern in relation

Table 4. – Hormonal characteristics of PCOS patients.

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>PRL ng/ml</th>
<th>A ng/ml</th>
<th>FT ng/ml</th>
<th>FSH mIU/ml</th>
<th>LH mIU/ml</th>
<th>LH after GNRH test</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>6</td>
<td>3.8</td>
<td>4</td>
<td>18</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>4.4</td>
<td>2.5</td>
<td>5</td>
<td>12.6</td>
<td>50.4</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>3.5</td>
<td>4</td>
<td>3</td>
<td>9</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>2.8</td>
<td>4.1</td>
<td>6</td>
<td>16</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>14</td>
<td>7.1</td>
<td>3.6</td>
<td>5</td>
<td>20</td>
<td>120</td>
</tr>
<tr>
<td>6</td>
<td>18</td>
<td>3</td>
<td>3.4</td>
<td>2</td>
<td>9</td>
<td>51</td>
</tr>
<tr>
<td>7</td>
<td>12</td>
<td>6.2</td>
<td>5.6</td>
<td>6</td>
<td>30</td>
<td>105</td>
</tr>
<tr>
<td>8</td>
<td>14</td>
<td>7.2</td>
<td>4</td>
<td>4</td>
<td>26</td>
<td>85</td>
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<td>16</td>
<td>2.9</td>
<td>3.6</td>
<td>5</td>
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<td>80</td>
</tr>
<tr>
<td>10</td>
<td>12</td>
<td>6.5</td>
<td>4.6</td>
<td>3</td>
<td>14</td>
<td>60</td>
</tr>
</tbody>
</table>

Normal hormones values (RIA); PRL<24.8 NG/ML; A<3.1 NG/ML; FT<3.2 PG/ML.
to follicular maturation and plasmatic estradiol was followed. From the same day follicular growth was followed by means of transabdominal ultrasonography with a 3.5 MHz convex explorer, while plasmatic estradiol level was daily monitored from the tenth day. From the same day also plasmatic LH level was assayed daily every four hours. When the ultrasonographic test showed 2 or more follicles with a diameter ≥16 mm and plasmatic estradiol >300 pg/ml per follicle ≥16 mm, but with a total value ≤2200 pg/ml, according to the ovarian diameter 5,000-10,000 IU hCG were given (O day) and the agonist was interrupted.

In order to sustain the luteal phase, 2,000 IU hCG were given four times every three days, or 100 mg intramuscular (IM)/die of natural progesterone for 12 days. Even in this case our choice was made following the stage of ovarian stimulation ultrasonographically determined on the O day.

RESULTS

Tables 6 and 7 summarize the characteristics of the cycles of patients with PCOS and HCA treated with Buserelin+Gn.

Twenty-six treatment cycles altogether were carried out: 13 for the PCOS and 8 for the HCA patients respectively.
Table 7. - Cycles’ characteristics of HCA patients treated with Buserelin+GN.

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Cycle</th>
<th>Ampoules of Gn</th>
<th>Days of Gn treatment</th>
<th>Number of follicles 16 mm</th>
<th>E₂ HCG</th>
<th>Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1° cycle</td>
<td>15</td>
<td>13</td>
<td>2</td>
<td>1000</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>2° cycle</td>
<td>20</td>
<td>15</td>
<td>3</td>
<td>1400</td>
<td>Successful pregnancy</td>
</tr>
<tr>
<td>2</td>
<td>1° cycle</td>
<td>21</td>
<td>13</td>
<td>2</td>
<td>720</td>
<td>Abortion at 6 weeks</td>
</tr>
<tr>
<td></td>
<td>2° cycle</td>
<td>28</td>
<td>18</td>
<td>2</td>
<td>840</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>1° cycle</td>
<td>12</td>
<td>11</td>
<td>2</td>
<td>1650</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>2° cycle</td>
<td>20</td>
<td>13</td>
<td>4</td>
<td>2000</td>
<td>Bigeminal pregnancy</td>
</tr>
<tr>
<td>4</td>
<td>1° cycle</td>
<td>20</td>
<td>15</td>
<td>–</td>
<td>210</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>2° cycle</td>
<td>28</td>
<td>19</td>
<td>–</td>
<td>89</td>
<td>–</td>
</tr>
</tbody>
</table>

The mean number of Gn ampoules used for each cycle was 20. There was a wide range in the number of Gn ampoules used for the ovulation induction (12-30), even for different cycles of the same patient. In five cases no ovulation was induced. The ovulatory rate was 80.7% while the pregnancy rate was 71.4 with an outcome of 10 pregnancies.

No statistically significant difference was observed in the parameters taken for PCOS and HCA patients.

We had 8 cases of mild ovarian hyperstimulation and one of moderate hyperstimulation among the PCOS patients. We never observed premature luteinization of the follicle.

DISCUSSION

If no response is given to CC, GnRH pulsatile pump and Gn are also disappointing.

This might depend on the interference either between exogenous pulsatile GnRH and endogenous GnRH pulses or between endogenous and exogenous gonadotropins.

Furthermore, the use of the drugs mentioned above (CC, GnRH pulsatile, Gn) is likely to induce a high (51%) premature LH surge rate, with following precocious luteinization and low quality of the oocytes.

In administering 800 μg/die of Buserelin, we did not observe any premature LH surge. On the other hand, we had previously noticed that 600 μg/die still allowed some premature LH surges.

GnRH agonists, after a starting flare-up, suppress endogenous LH, FSH estradiol, and ovarian androgen secretions and cause hypogonadotropic hypogonadism, favourable to exogenous gonadotropins which do not interfere with endogenous gonadotropins (Fleming et al., 1987; Fleming et al., 1988).

These characteristics improve the ovulatory and pregnancy rates in patients with chronic anovulation and confirm our satisfactory results (ovulatory rate 80.7%; pregnancy rate 71.4%).

Our choice for short stimulation cycles depends on the fact that they are better tolerated by patients. They require less effort compared with common stimulation patterns, where deposit from agonists are provided for.

It must be also added that in our cases, not intended for fertilization in vitro embryo transfer (Fivet) massive multiple ovulation was not as necessary as high quality oocytes.

This also explains the relative low quantities of Gn used and the relative low rate of ovarian hyperstimulation.
GnRH agonists can thus be considered a good alternative in ovulation induction in patients who have given no response to traditional therapies; they can also provide the first choice treatment for some selected patients.

REFERENCES


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