CLINICAL

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FUNCTIONAL AND IATROGENIC SECONDARY CORTICOHYPOTHALAMIC AMENORRHEA IN P.N.E.I. DYNAMICS

SUMMARY

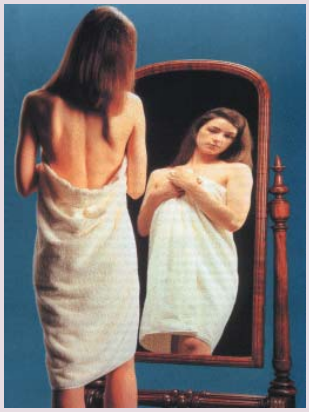
The author reports on the final results of a clinical trial carried out over six years on 13 patients suffering from functional (8 cases) and iatrogenic (5 cases) corticohypothalamic amenorrhea.

Suis organotherapic preparations and homeopathised hormones have primarily been used in treating this disorder. This resulted in the return of the menstrual cycle with evidence of ovulation in 11 cases and pregnancy to full-term in 2 cases.

We should emphasize that there were no negative side effects with the treatment as well as full compliance of all the patients.

KEY WORDS:

HOMEOPATHY, HOMOTOXICOLOGY, CORTICOHYPOTHALAMIC AMENORRHEA, SUIS ORGANOTHERAPIC PREPARATIONS, HOMEOPATHISED HORMONES.



INTRODUCTION

The term *secondary amenorrhea* means that menstruation does not occur for more than **three cycles**, after a period of regular menstruation.

Until very recently, corticohypothalamic amenorrhea was only diagnosed after eliminating other diagnostic possibilities, but recent PNEI findings, particularly advances made in Neuroendocrinology, allow us to make a more satisfactory diagnosis.

With hypothalamic disorder there is a deficiency in the secretion of gonadotropin-releasing hormone (GnRH), which is necessary for the pulsatile secretion of gonadotropins (1).

In men, the pulsatile secretion of GnRH - a synthesised decapeptidic structure in the mediobasal nuclei of the anterior hypothalamus, transported into the portal hypophysary system - is responsible for maintaining gonadotropin pulsatile secretion.

The greatest concentration of GnRH neurons can be found in the *arcuate nucleus* of the mediobasal hypothalamus. Their cell bodies are cast into the *median eminence*. The GnRH from the hypothalamic neurons is carried to the anterior hypophysis from the median eminence via the portal hypophysary capillary network, linking it to the membrane receptors of the gonadotrope cells. Via a mechanism that involves calcium ions, it stimulates the secretion of gonadotropin. The endogenous secretion of GnRH is vital for maintaining the hypophysary concentration of receptors and subsequent gonadotropin secretion.

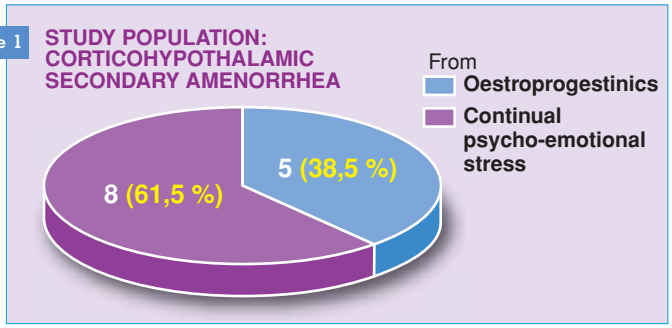
From electrophysiological studies on inferior primates, it has emerged that GnRH neurons depolarise, releasing GnRH every 60 to 120 minutes and stimulating the episodic secretion of luteinising hormones (*Luteinising Hormone - LH*). Studies carried out on humans relating to the pulsatile secretion of LH, show a similar secretion pattern. When the frequency of GnRH-LH secretion occurs outside this *frequency window*, the release of hypophysary gonadotropin alters, causing an interruption in the normal ovulatory cycle.

Alterations in the frequency and amplitude of GnRH pulsatility, therefore, causes the non-pulsatile secretion of LH and FSH or an altered ratio between the two gonadotropins (2).

The release of GnRH is the result of various neural stimuli that operate via the neurotransmitters - catecholamines are the main neurotransmitters involved.

In addition to the GnRH neurons, there are other neuron networks in the hypothalamic *arcuate nucleus*. These net-

Figure 1 STUDY POPULATION: CORTICOHYPOTHALAMIC SECONDARY AMENORRHEA



works comprise neurons that have the capacity to secrete *beta-endorphin*, *dopamine* and *noradrenaline* (1; 2). As each system enters into synapsis with GnRH neurons, the neurotransmitters can alter the neurosecretion of GnRH.

-*Noradrenaline* has a **stimulatory effect** on the modulation of GnRH release, as it stimulates this release from the *median eminence* terminals, mainly by interacting with the alpha-adrenergic receptor.

-*Dopamine*, on the other hand, has a central **inhibitory action** on the GnRH neuron, via direct neurosecretion in the portal circulation.

Immunohistochemical studies have identified dopaminergic neurons in direct contact with the nervous terminals of *median eminence* GnRH. The secretion of GnRH, therefore, would be induced by an imbalance between noradrenaline's stimulatory action and dopamine's inhibitory action.

Endorphins, peptides with a morphine-like action, are involved in the modulation of gonadotropin secretion with the site of action at hypothalamic level - it has been shown that there are receptors for the opioids in dopamine neurons. The increased activity of the endogenous opioids can directly inhibit the neuronal activity of GnRH, operate indirectly by suppressing the noradrenergic neurons or modulate the release of GnRH at *median eminence* level.

The cyclical variations in *steroid hormones* can also affect antehypophysary function via the synthesis and release of *hypothalamic endorphins*.

In fact, there are higher portal concentrations of endorphins in the luteal phase and they can be further increased by the combined administration of *estradiol* and *progesterone* - this illustrates that endogenous opioids encourage a reduction in gonadotropin pulsatility during the luteal phase (1).

The anterior hypophysary gland comprises cells with the capacity to synthesise and release LH and Follicle-stimulating hormones (FSH). The secretion of the latter requires constant intermittent exposure to GnRH impulses on which the quantities released are dependent.

Low levels of exposure to GnRH, as a result of decreased impulse frequency, cause the preferential transcription of messenger RNA for the FSH beta subunit, with the preferential release of FSH - as occurs during the average puberty - whilst normal impulse frequencies for GnRH stimulate the release of similar quantities of LH and FSH (2).

-**Functional corticohypothalamic secondary amenorrhea** can be defined as *"no menstrual cycle for a period of more than three cycles, in the absence of anatomical or organic anomalies"*.

There are three etiopathogenetic moments: psychogenic or stress-related amenorrhea, nutritional disorders, and intense and prolonged physical exercise (3).

▶ Exposure to **repeated cognitive, non-cognitive, physical or environmental psycho-emotional stress** of sufficient intensity can cause or exacerbate an imbalance in the formation and metabolism of cerebral biogenic amines.

Recent PNEI findings illustrate the primary importance of the Total Stress Load, i.e. all the previous stressful experiences in one.

In the PNEI vision, the Neuroendocrine and Immune Systems act, respectively, as **sense organs** in the management of cognitive and non-cognitive stressors (4; 5).

Experiments on laboratory animals illustrate that acute and chronic stress can increase the formation of cerebral *catecholamines*, stimulating the initial stage of biosynthesis, i.e. the activity of *tyrosine-hydroxylase*.

In the pathogenesis of stress-induced secondary amenorrhea, often one can see an increase in opioid tone - the endogenous opioid peptides modulate the function of the cerebral neurotransmitters, by expanding, reducing or giving the correct *tone* to local synaptic activity (2). Many studies also illustrate the responsibility of endogenous and environmental stressors in the chronic activation of the hypothalamus-hypophysis-adrenal axis.

The response to stress correlates to an increase in adrenocorticotropic (*AdrenoCorticoTropic Hormone - ACTH*) and cortisolic activity, as well as the activity of the hormone that secretes corticotropin (CRH) at hypothalamic level.

The clinical picture is characterized by excessive increases in the circadian levels of *cortisol*, and a delay in or lack of response to ACTH and *cortisol*.

As increased levels of CRH, ACTH and cortisol inhibit the secretion of GnRH and LH, cognitive and non-cognitive stress can cause menstrual disorders and amenorrhea (1; 2).

TABLE 1
Pathological/behavioural typology of the 13 patients included in the study

Oligomenorrhea	Delayed menarche	Sports activities	Athletic activities	CCO	Anorexia	Bulimia
9	3	13	5	4	3	1

▶ **Compulsive disorders in food consumption** are important causal factors in menstrual disorders; in the PNEI vision, in fact, gender is linked to nutrition.
Adipose tissue (or the *adipose organ*) should be regarded as vital from an endocrine viewpoint - a link between the Endocrine and Neuroimmune Systems (4). The discovery that leptin plays a key role in nutritional regulation is an important factor in this context too - this hormone is produced by adipose tissue and provides the cerebral regulatory centres with information. *Leptin's* action on the receptor found at the arcuate nucleus level of the hypothalamus leads to weight stability as it balances stimulation and suppression activity. In fact, food intake is stimulated by low levels of leptin secreted by the adipocytes and vice versa. Nevertheless, the fact that we are able to detect high levels of *leptin* in obese patients leads us to assume that there are leptin-resistant mechanisms in the pathogenesis of some forms of obesity (6).
Abdominal obesity is often associated with menstrual cycle anomalies.
The most common pathology of the nutritional sphere is obesity from a compulsion for carbohydrates (Carbohydrate Craving Obesity - CCO) - this is the most widespread dependency; food is perceived as one of the greatest possible forms of pleasure.
Weight loss can also cause amenorrhea. It is well-known that the critical weight/height ratio affects the onset of menarche, although the percentage of fat out of the total body weight is the main determinant. For menarche to occur, at least **17%** of body weight should be composed of adipose tissue. **22%** is the critical percentage for maintaining a regular cycle after the age of 16; the onset or loss of the cycle is dependent upon this fat index. Women at high risk of amenorrhea present with little body fat (<20%) and a body weight of less than 10% of the ideal weight (2; 3).

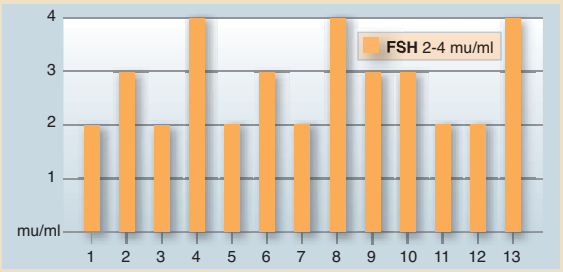
Bulimia and *anorexia* are the most evident example of psychogenic amenorrhea accompanied by significant changes in weight.
Bulimia is a food disorder that is characterised by the sufferer alternating between excessive food consumption and periods of restraint, self-induced vomiting and the excessive use of laxatives and/or diuretics.
Anorexia nervosa is a syndrome that is characterised by extreme weight loss (25% of the ideal body weight), distorted body image, placing abnormal emphasis on the importance of food and nutrition, and obsessive-compulsive behaviour.
Demographically, 90-95% of bulimic/anorexic patients are young white women, belonging to the middle or upper classes. Signs of depression are encountered in these patients, with a suicide rate of between 2 and 5%.
When the patients improve and regain weight, the levels of gonadotropin increase and the response to GnRH returns to normal - nevertheless, despite the recovery of a normal body weight, at least 50% of patients do not begin to ovulate again.
In both bulimic and anorexic patients, one sees *hyperactivation* of the hypothalamo-hypophysis-adrenal axis with persistent hypersecretion of cortisol throughout the day - this can cause inhibition of GnRH and the secretion of *gonadotropin*.
The increased production of *cortisol* does not appear to be linked to peripheral effects or manifestations of hypercortisolism due to the concomitant reduction in intracellular receptors for the glucocorticoids (1; 2).

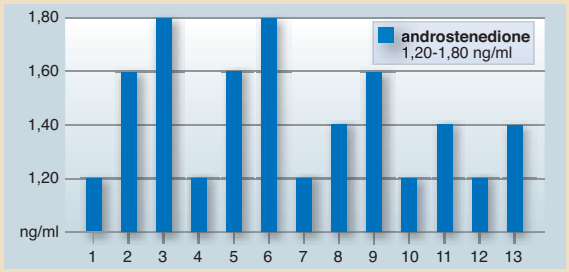
▶ For millions of women **regular physical exercise** - including at high levels - has become an essential way of life; a third of athletes are female. This development has led to an increase in the incidence of menstrual disorders, oligo-ovulation and secondary amenorrhea. Women who participate in gymnastics, dance or middle- and long-distance running - activities that encourage a more lean physique - are particularly vulnerable. Swimmers and cyclists appear to be less susceptible to amenorrhea, despite the similar intensity of effort.
The psychological stress of competing can play a significant role - in fact, the incidence of illness is greater in athletes who take part in athletics.
Women who do intensive sports activities, however, have 50% less fat than others. The conversion of fat weight into lean weight does not necessarily mean significant weight loss (2; 3).
Physical activity is linked to a prolonged increase in *endorphin* levels.
The suppression of the pulsatile secretion of GnRH is a central problem, as a result of the inhibition of the *arcuate nucleus* by the endorphins (1).
The main characteristics of patients who are amenorrhoeic as a result of intensive physical activity are anxiety and *control of one's own body, performance, stress from competition and success*.

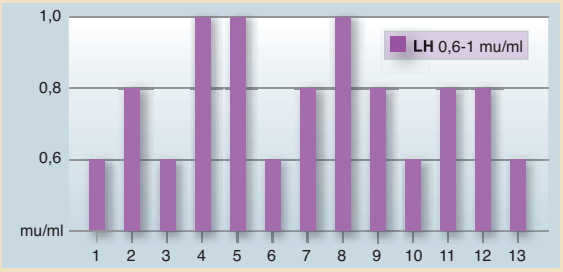
In the case of **post-contraceptive pill iatrogenic amenorrhea**, the hypothalamic blocking of GnRH can be caused by the strengthening of the estrogens' negative feedback, although it can also be the result of endometrial atrophy of the mucosa with fragile and poor glands and fibrous stroma, in patients with weak hormone balance.
With current low-dose contraceptive pills, the estrogen content can be insufficient to stimulate normal endometrial growth - therefore, it is the progestinic effect of the pill that dominates causing endometrial atrophy and amenorrhea (1).
With functional and iatrogenic corticohypothalamic amenorrhea, semeiotics highlights no clinically demonstrable organic changes in the hypophysis-ovary axis or other endocrine functions and no pathologies or anatomical changes that justify the pathology. The objective gynaecological examination is negative or highlights atrophic changes in the genital mucosa.
Ecographic and hormonal diagnostics indicate the absence of ovulation, and normal *androgen*, *cortisol* and *prolattin* values (7; 8).
We should point out that **Phosphoric phenotype** was the most common type in terms of the psychical/biological or emotional/cognitive identity of the pa-

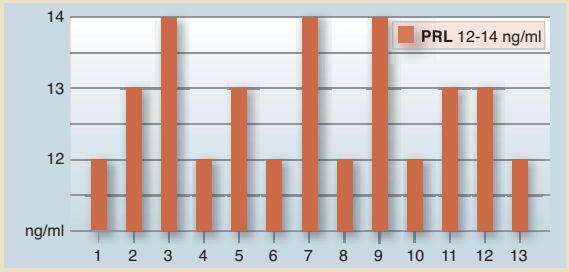
FIGURE 2

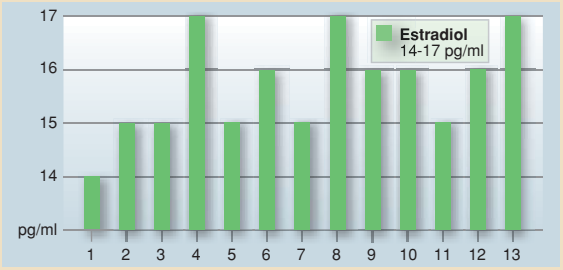
Laboratory parameters examined: values of the 13 patients included. Comparative tables.

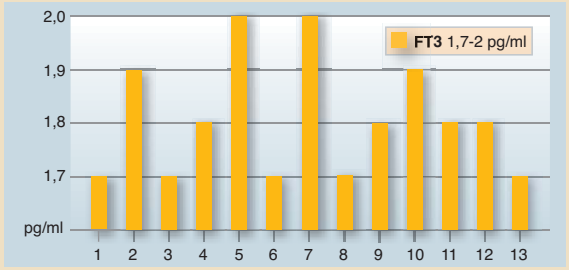


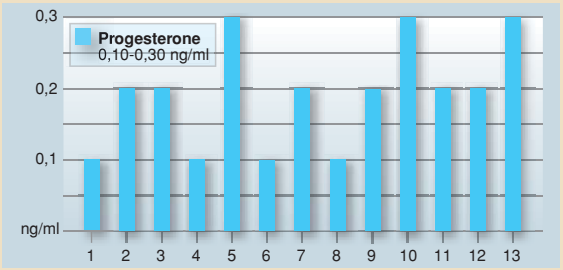


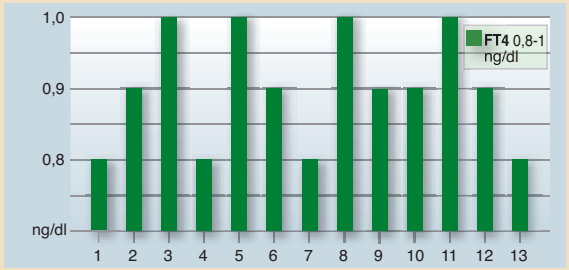


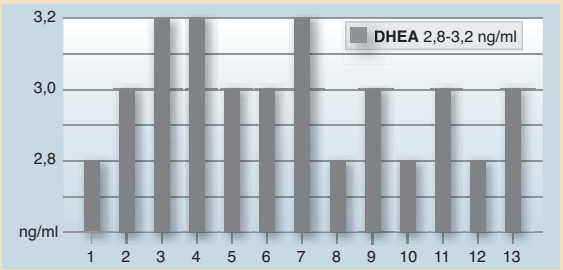


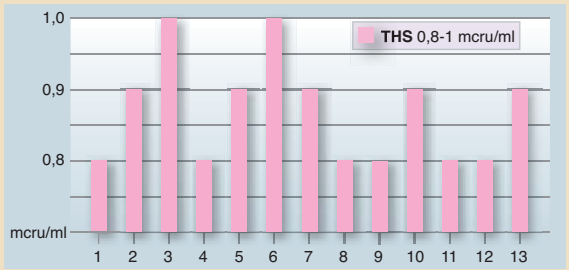


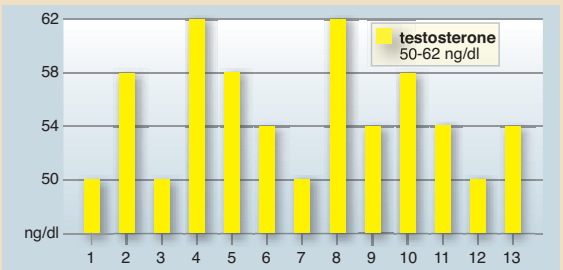


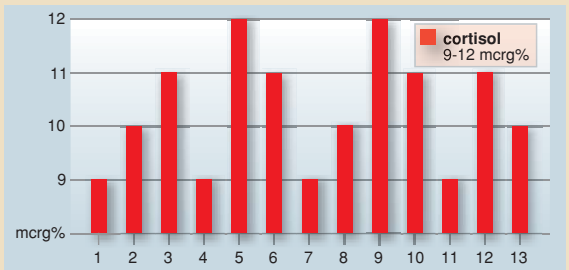












tients suffering from functional and iatrogenic corticohypothalamic secondary amenorrhea.

In some cases there was evidence of greater susceptibility to stressors, particularly from affectivity. In fact, we are dealing with individuals who are chronically stressed, unresponsive, immunodepressed, with delayed puberty (as a result of epiphyseal activity and an increase in opioid tone) and previous oligomenorrhoeic cycles, with the possible appearance of pathologies of the nutritional sphere, particularly during periods of excitement or depression.

For the purposes of inclusion in the Table of Homotoxicology, functional and iatrogenic corticohypothalamic amenorrhea can be classified under the **Impregnation Phase**.

PATIENTS AND METHODS

Over 6 consecutive years, **13 patients** were treated - the patients were aged between 20 and 29, had been suffering from amenorrhea for 4 - 8 months and had no concomitant pathology. In 8 cases this was caused by exposure to psycho-emotional stress (61.5%) (romantic disappointment, marital break-up, financial difficulties and starting a new job) and nutritional stress (improper diet) and in 5 cases (38.5%) it was a result of taking estroprogestinics for a period of 1-2 years (7) (FIGURE 1).
Nine of the 13 patients (69%) reported previous oligomenorrhoeic and hypomenorrhoeic cycles; 3 of these (33%) presented with delayed menarche.

All the patients regularly took part in athletics; 5 at the competitive level (3 gymnasts; 2 runners).

Four patients (30.7%) suffered from *CCO*, 3 had suffered from anorexia at the age of 15-16, and 1 of purging bulimia at the age of 18 (TABLE 1).

The genital examination was normal for all the cases, without ovulatory expression; in 5 cases there were initial atrophic changes in the genital mucosa.

The ecographic examination was normal in all cases with a reduced endometrial echopattern (between 2 and 4 mm), without signs of follicular activation.

The laboratory analyses produced results within normal limits: FSH between 2 and 4 mu/ml, LH between 0.6 and 1 mu/ml, estradiol between 14 and 17 pg/ml, progesterone between 0.10 and 0.30 ng/dl, DHEA between 2.8 and 3.2 ng/ml, testosterone between 50 and 62 ng/dl, androstenedione between 1.20 and 1.80 ng/ml, PRL between 12 and 14 ng/ml, FT3 between 1.7 and 2 pg/ml, FT4 between 0.8 and 1 ng/dl, TSH between 0.8 and 1 mcru/ml, cortisol between 9 and 12 mcrg% (FIGURE 2).

The therapeutic strategy was applied as follows:
- constitutional biotypology therapy on the basis of the psychobiological or emotional/cognitive identity;
- emunctorial drainage therapy to stimulate excretory activity;
- suis organotherapic preparations, used according to the principle of regulation that, via subliminal immunological mechanisms, stimulate the immune response of the target organ;
- homeopathised hormones with a stimulating action according to the Arndt-Schulz law on the physiological function of homologous hormones (9; 10; 11);
- a CH dilution of *Melatonin* for modulating epiphysary activity and therefore the suppressive effect on the production of GnRH and gonadotropins (12);
- An LM dilution of *Ignatia* with rising potency according to Kent for the predominant mental aspect.

The 13 patients began the therapy with:
- **Calcarea phosphorica 200 C**, 1 dosing tube/month x 3 consecutive months;
- **Lycopodium compositum**, 1 vial twice a week per os (only for 5 cases who had taken estroprogestinics);
- **Melatonin 4C**, 8 drops in the evening;
- **Ignatia 0.6-0.30 LM**, 1 tablet every evening, in progression (for 6 cases with repeated cognitive/non-cognitive stress);
- **Hypothalamus suis-Injeel**, 1 vial twice a week per os;
- **Hypophysis suis-Injeel**, 1 vial twice a week per os;
- **Ovarium suis-Injeel**, 1 vial twice a week per os;
- **Estriadol 6X**, 8 drops from the 5th to the 20th day of the month;
- **Progesterone 6X**, 8 drops from the 10th to the 24th day of the month.

The treatment was suspended for a week on reappearance of the menstrual cycle and was offered again in 4-week cycles and suspended on any subsequent appearance of the cycle.

-The treatment was continued for 4

FIGURE 3

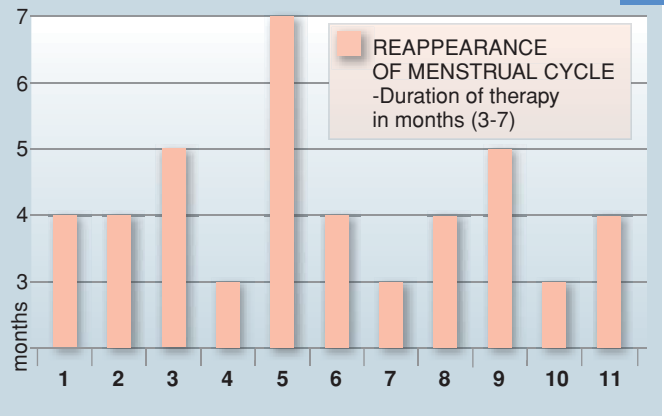
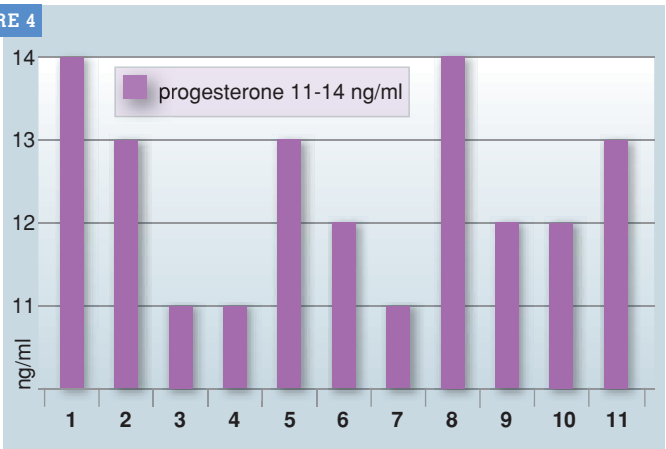


FIGURE 4



months after the reappearance of the menstrual cycle; the drops therapy was continued for a further 2 months (7; 8).

RESULTS

In **11** of the **13** patients included in the trial (84.6%), a reappearance of the menstrual cycle was observed after a therapy period of between 3 and 7 months (after 4 months on average) (FIGURE 3). In these cases the dosage of plasmatic progesterone recorded values of between 11 and 14 ng/ml, was compatible with the occurrence of ovulation (FIGURE 4). The ecographic examinations had also shown post-ovulatory reliefs.
During the course of treatment, 2 patients had monofetal pregnancies that duly went to full-term.

CONCLUSIONS

The homotoxicological therapy used in this study led to the reappearance of the menstrual cycle with the occurrence of ovulation, to the full satisfaction of all the patients.
For the same clinical picture, the corresponding allopathic treatment provides for the use of *estroprogestinics* with sequential or combined administration, or ovulation inductors such as *clomiphene, human menopausal gonadotropin (hMG) or pulsatile GnRH*. With estroprogestinics, in addition to the clear contraindications (previous thromboembolic episodes, clotting disorders, cardiovascular and hepatic episodes, smoking etc.) and related contraindications (cephalea, hypertension, diabetes), there are often specific local (intermenstrual spotting) and systemic (nausea, vomiting, cephalea, irritability, weight increase, reduced libido, breast tenderness) side effects. There are also specific effects on the glycidic and lipidic metabolism, and the risk of thromboembolic diseases and neoplastic pathology, particularly mammary pathology.
With regard to ovulation inductors, more serious complications have to be mentioned - in addition to vasomotor and gastroenteric disorders, and mastodinia - such as ovarian hyperstimulation to various degrees of severity and possible multiple pregnancies (1; 2; 3).

No contraindications, negative collateral effects or allergic reactions were noted in the homotoxicological therapeutic protocol; the compliance of the patients was the best possible. ■

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The photograph on the first page was taken from the website: http://www.psicoactiva.com/anorexia.gif

-The text was drawn up and updated using the content of the Author's thesis towards a Diploma from the Triennial School of Biological Medicine and Integrated Disciplines - Rome, June 2005 (Lecturer: Prof. M. Corgna).

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