Pergamon

Psychoneuroendocrinology, Vol. 20, No. 1, pp. 53–63, 1995

0306-4530/95 $6.00 + .00

0306-4530(94)E0041-7

ENDOCRINE AND PSYCHOLOGICAL EVALUATION OF WOMEN WITH RECENT WEIGHT GAIN

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(Received 30 December 1993; in final form 5 March 1994)

SUMMARY

A group of 13 consecutive regularly menstruating women who gained at least 5 kg the previous year (Group I) was compared to a control group of similar age, parity, and social class (Group II). The two groups were similar in estimated and observed food intakes; pre- and postprandial gastrin levels; hourly 24-h profiles of cortisol and insulin; urinary cortisol and 17-hydroxycorticosteroids. Group I had higher serum prolactin concentrations at all times than Group II (mean values 14.60 μg/l vs. 8.84 μg/l; $p = .0121$). Galactorrhea was observed in 5 women from Group I and in none of the women from Group II ($p < .05$). Group I also differed from Group II in a higher incidence of meaningful life-events the year preceding the study, higher prevalence of sexual dysfunction (9/13 vs. 4/13; $p < .01$) and higher indexes ($p < .05$) of several parameters in the MMPI and SCL 90. Median serum cortisol and prolactin concentrations were negatively correlated, both in Group I ($R = -.669$; $p = .012$) and in the whole sample ($R = -.453$; $p = .0298$). It is suggested that the rapid weight gain is part of a neuroendocrine response to environmental stimuli also characterized by hyperprolactinemia. The significant negative correlation between serum prolactin and cortisol indicates that this response differs from, and is possibly an alternative to, the sympathoadrenal "stress" response.

Keywords—Obesity; Prolactin; Psychological stress; Psychosomatic medicine; Psychophysiology; Weight gain.

INTRODUCTION

OBESITY IS USUALLY associated with normal serum prolactin concentrations (Scaglione et al., 1991). Yet, a large population study revealed a positive correlation between serum prolactin and weight (Wang et al., 1987). Hyperprolactinemia and weight gain are associated in two pathologic conditions—prolactinomas and pseudocyesis.

Pseudocyesis is generally viewed as a defensive response to abandon and profound depression characterized by a delusional belief of being pregnant and by specific physical changes. These changes—weight gain, amenorrhea, breast engorgement, and galactorrhea—imply that, somehow, the psychological adjustments that are involved can be

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transduced into a neuroendocrine response. So far, moderate hyperprolactinemia has been the most consistent hormonal abnormality found in pseudocyesis (Sobrinho, 1991).

Rapid weight gain is a common initial symptom in women with pathologic hyperprolactinemia (prolactinoma and idiopathic hyperprolactinemia), along with galactorrhea and menstrual abnormalities (Creemers et al., 1991; Nunes et al,. 1980; Sobrinho, 1991). Psychological factors also appear to play a role in the genesis of prolactinomas. These tumors occur predominantly in women who were brought up in conditions of paternal deprivation (Assies et al., 1992; Nunes et al,. 1980; Sobrinho, 1991). Moreover, the clinical onset of the disease is often preceded by an elevated prevalence of significant life events (Nunes et al,. 1980; Sobrinho, 1991). To reconcile these findings with the presence of a pituitary tumor, we hypothesized that, in women with paternal deprivation during childhood, interactional changes may lead to activation of the lactotrophs. The activated state may predispose to tumor development (Sobrinho, 1991).

The present study was designed to test the hypothesis that rapid weight gain, even without menstrual disturbances, may be an expression of activation of neuroendocrine mechanisms comparable to those that operate in pseudocyesis and in the pretumorous stage of prolactinomas. For this purpose, 24-h serum prolactin profiles and other endocrine and psychological parameters were obtained in a group of 13 consecutive women who presented with a history of recent weight gain at the Endocrine Clinic of the Portuguese Cancer Institute during a 2-year period, as compared to controls with stable weight, matched for age, parity, and social class.

SUBJECTS AND METHODS

All women aged 20–40 years, with monthly menstrual cycles who came to the Endocrine Clinic of the Portuguese Cancer Institute between October 1991 and October 1993, complaining of a weight gain of at least 5 kg (range 6–10 kg) starting in the previous 12 mo or more recently, were considered for the study. Exclusion criteria were: (1) evidence of underlying disease; (2) chronic medications including oral contraceptives and psychoactive drugs; (3) pregnancy or weaning of a child the year before the study; (4) coming off a diet; and (5) changes in physical activity or smoking habits.

Thirteen of the women who met the above criteria agreed to participate in the study (Group I). Another group of 13 women with stable weight attending the same clinic and of similar age, parity, and social class were used as controls (Group II). Informed consent was obtained in all cases.

All subjects were instructed not to take self-prescribed medications the week before admission to the hospital. None of them smoked or drank alcoholic or caffeinated beverages in the eve and day of the study.

Clinical and Nutritional Studies

Besides a general clinical and biological evaluation, the women were interviewed in detail by a dietician about their eating habits, variations of weight, and caloric intake the day prior to admission. During the stay in the hospital, standard meals containing a total of 2.500 kcal/24 h were provided. Free access was allowed to extra food which was taken into account. All food left was subtracted for the estimation of the actual caloric intake.

Endocrine Studies

The studies were performed during the first 5 days of the menstrual cycle. After full discussion of the nature and purposes of the protocol, patients were admitted to the hospital, fasting, at 0800h. An indwelling catheter was inserted into a forearm vein and

connected through a stopcock to an extension tube such that, during sleeping hours, the samples of blood were obtained without disturbing the patient. The patients were allowed free movement. Blood was drawn hourly for 24 h for the measurements of cortisol, prolactin, and insulin. Before each of the two main meals (lunch and dinner) and 30 and 60 min afterwards, samples were also obtained for the measurement of gastrin. Urine was collected during the same 24-h period for the measurement of 17-hydroxycorticosteroids and free cortisol. Serum prolactin, serum and urinary cortisol, insulin, and gastrin were measured with commercial kits, respectively: ELSA-PROL (IRMA, CIS biointernational), sensitivity .29 μg/l; intra-assay coefficient of variation for a mean value of 11.35 μg/l was 6.05%; inter-assay variation for mean values of 38.8, 91.4, and 147.6 μg/l were 9.7, 7.8, and 5.4%, respectively; COAT-A-COUNT cortisol (RIA, DPC), sensitivity .24 μg/dl; intra-assay coefficient of variation for a mean value of 10 μg/dl was 2%; inter-assay variation for mean values of 1.13, 4.68, and 18.8 μg/dl were 7.2, 4.8, and 9.8%, respectively, COAT-A-COUNT insulin (RIA, DPC), sensitivity 1.2 mU/l; intra-assay coefficient of variation for a mean value of 15 mU/l was 5.5%; inter-assay variation for mean values of 7.9, 37.7, and 204.0 mU/l were 12.6, 11.1, and 12.8%, respectively; GASK-PR (RIA, CIS biointernational), sensitivity 15 ng/l; intra-assay coefficient of variation for a mean value of 91 ng/l was 8.0%; inter-assay variation for mean values of 54, 259, and 610 ng/l were 9.9, 7.1, and 5.9%, respectively. 17-hydroxycorticosteroids were measured by the Norimbersky method, sensitivity .6 mg/l; intra-assay coefficient of variation for a mean value of 7.4 mg/l was 4.5%, and inter-assay variation for a mean value of 8.1 mg/l was 9.1%.

Psychological Studies

Semistructured interviews were conducted according to the following model:

1. The patient was allowed time to talk freely about herself. No leading questions were asked but care was taken such that all major areas of life were thoroughly covered.
2. During the interview, a series of possible recent (i.e., during the previous year) life events was considered according to the methodology devised by Paykel (1987) and Paykel and Mangen (1980).
3. All patients and controls were seen by the same interviewer who is an endocrinologist, with training in psychoanalysis and psychometric methodologies (MFF). The interviews were reduced to writing and discussed with the other members of the team who are endocrinologists with training in psychoanalysis (LGS) and in psychometry (JSP). During their stay in the hospital, patients were given the SCL 90 Questionnaire and the MMPI, both validated for the Portuguese population.
4. All psychological and psychometric evaluation was blind to the results of the endocrine studies.

Statistics

Differences between groups were evaluated by the two tailed *t*-test and chi-square tests. Correlations between hormonal parameters were calculated by the Spearman's method. Correlations between hormonal and psychological parameters were calculated by ANOVA. Comparisons between the 24-h prolactin profiles of the two groups were made by analysis on cubic trends associated with profile analysis.

TABLE I. RELEVANT CLINICAL AND NUTRITIONAL DATA OF PATIENTS FROM GROUPS I (WEIGHT GAIN) AND II (CONTROLS)

	Group I	Group II
N	13	13
Age (years)	33.8 ± 6.0	31.9 ± 6.1
Parity	10/13	9/13
Galactorrhea	5/13	0/13*
Sexual dysfunction	9/13	4/13*
BMI	28.8 ± 4.4	24.2 ± 3.4**
Weight gain (kg)	7.9 ± 2.8	0†
Cal/day −1	2322 ± 823	2587 ± 621
Cal/day 0	2396 ± 353	2447 ± 790

BMI, body mass index; Weight gain (kg), weight gained the year before the study; Cal/day −1, 24 h caloric intake the day before admission; Cal/day 0, 24 h caloric intake within the hospital.
*Significantly different from Group I ($p < .05$); **significantly different from Group I ($p = .008$); †different from Group I by definition.

RESULTS

Differences Between Groups I and II

Clinical and Nutritional Data. The relevant clinical and nutritional characteristics of both groups are summarized in Table I. None of the women from either group engaged in any physical activity besides the ones inherent to a sedentary job and household activities. There was no evidence of current or past eating disorder in any of the patients. Four of the women from Group I reported an increase in appetite concomitant with the weight gain. Previous episodes of weight gain were reported in the past by 8 of the women in Group I and by 5 in Group II, most of them associated with pregnancies.

There were five smokers in each of the two groups. Nine women from Group I and 4 from Group II ($p < .05$) met the DSM III criteria for sexual dysfunction.

The average caloric intakes the day before admission to the hospital and the day of the study were similar in both groups (2322 kcal/day ± 823 and 2396 kcal/day ± 353 for Group I vs. 2587 kcal/day ± 621 and 2447 kcal/day ± 790 for Group II).

Endocrine Data.

1. Prolactin: Group I had a higher mean serum prolactin concentration than Group II in each of the 26 samples measured during the 24-h period. This difference was significant ($p < .05$) in 12 of the hourly points, including the samples between 0700 and 1500, as represented in Fig. 1. The average circadian rhythm of prolactin levels of both groups fitted to polynomial curves (Group I: $y = 26.727 - 4.109x + .237x^2 - .004x^3$; $\Phi = 14.58$; $\alpha = .0001$; Group II: $y = 42.24 - 3.866x + .333x^2 - .005x^3$; $\Phi = 12.14$; $\alpha = .0015$). There was a significant difference ($p < .05$) in the acrophase of both curves such that the peak value was obtained at 0200 in Group I and at 0400 in Group II. Mean 24-h prolactin concentrations were significantly higher in Group I as

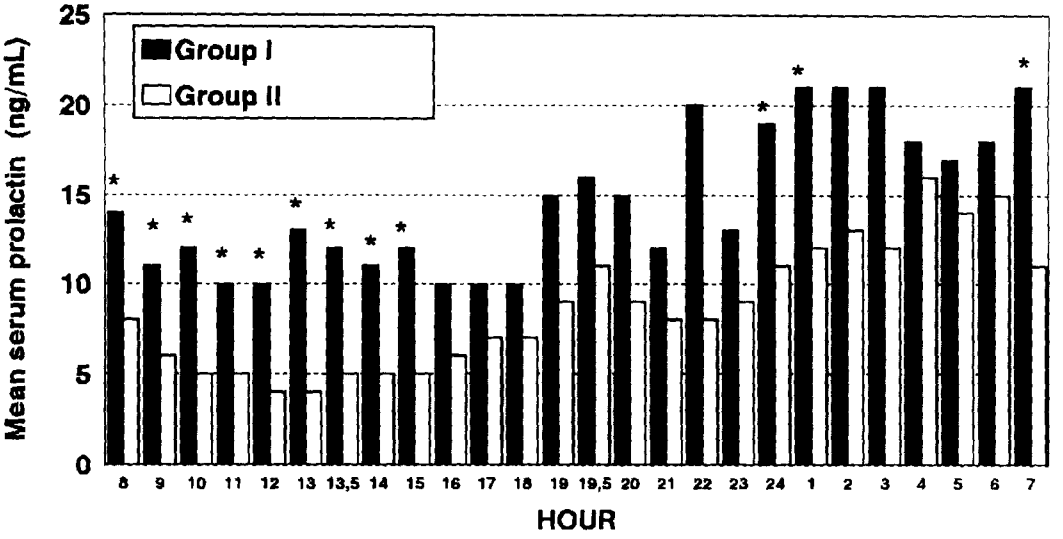

FIG. 1: Twenty-four hour profile of serum prolactin in patients from Groups I and II. *$p < .05$.

compared to Group II (X = 14.60 vs. 8.84 μg/l; p = .0121). In Group I, 5 of the women had mean 24-h prolactin levels higher than the highest value observed in women from Group I (13.15 μg/l).

2. Cortisol: Serum cortisol was similar in the two groups both in hourly values (Fig. 2) and in the average of 24 h (6.96 vs. 7.10 μg/dl; NS). Urinary cortisols (40.0 vs. 41.5 μg/24 h) and 17-hydroxycorticosteroids (7.4 vs. 6.2 mg/24 h) were also similar.
3. Insulin: Serum insulin was similar in both groups of patients in hourly values (Fig.

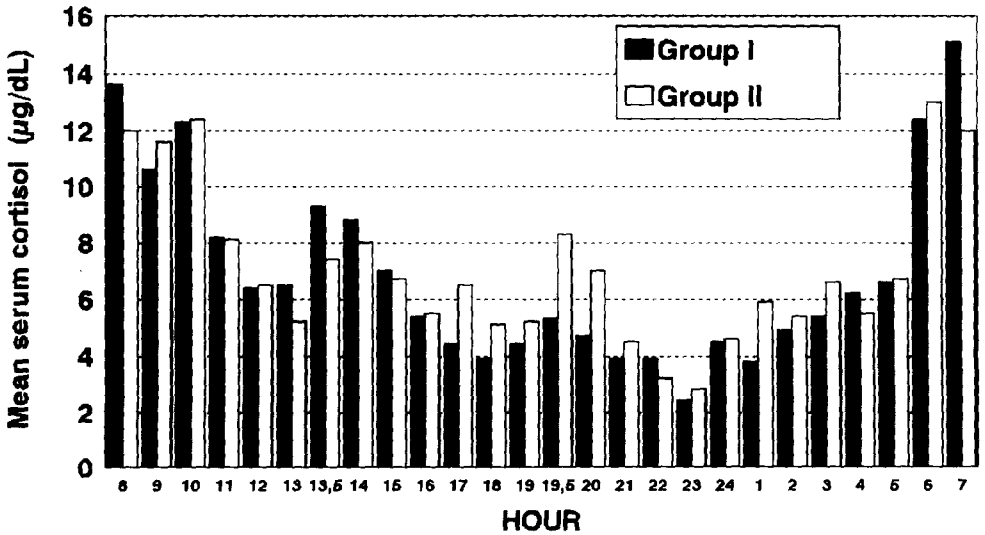

FIG. 2: Twenty-four hour profile of cortisol in patients from Groups I and II.

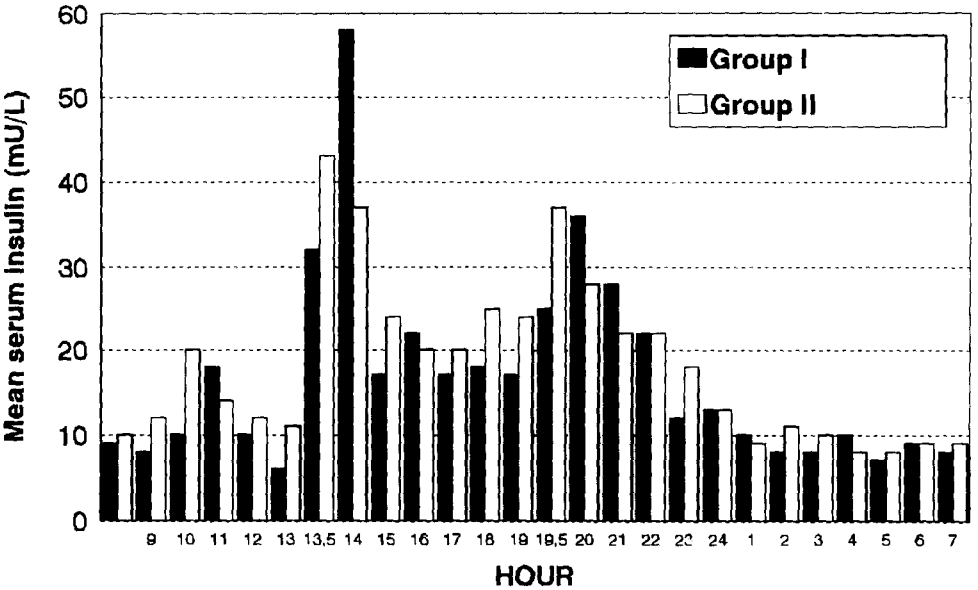

FIG. 3: Twenty-four hour profile of insulin in patients from Groups I and II.

3), means of 24 h (13.0 vs. 16.4 mU/l or means of fasting (0100–0700) samples (9.0 vs. 9.0 mU/l).

4. Gastrin: Mean serum gastrin concentration observed before each of the main meals in Group I was 19.9 ng/l and mean peak response to meals was 73.9 ng/l. These values were not different from the control group (18 and 52.8 ng/l, respectively).

Paykel's Life Events Scale. All patients in Group I had at least one meaningful life event in the year preceding the study, compared with 9 in Group II. The average of the total number of life events per subject was 2.85 ± 1.27 in Group I and 1.13 ± 1.25 in Group II ($p = .004$). The total score (number of events times intensity of the impact, as assessed by the observer) was 9.23 ± 5.99 in Group I vs. 4.25 ± 5.90 ($p = .05$) in Group II. The number of events with negative impact was 1.85 ± 1.29 vs. 1.00 ± 1.31 ($p = .1$). The distribution of categories of events in both groups is shown in Table II.

Psychometric Data. Group I had a significantly higher score than Group II in a number of parameters (Table III).

Correlations

There was a significant negative correlation between median serum prolactin and median serum cortisol in Group I ($r = -.669$, $p = .012$) and in the whole sample ($r = -.453$, $p = .0298$), as shown in Fig. 4. The same trend was observed in Group II ($r = -.255$, NS).

No other significant correlations were found between mean serum prolactin, cortisol, basal or total insulin and body mass index (BMI), neither in separate groups nor when the data were pooled. Mean serum cortisol correlated positively with hostility in the whole sample ($r = .37$, $p < .05$). Mean serum prolactin correlated negatively with hostility

TABLE II. CATEGORIES OF EVENTS*

Type of categorization	Category	Group I	Group II
Changes in social field	Entrances	3	4
	Exits	0	4
Desirability	Desirable	4	1
	Undesirable	1	3
Degree of control by the subject	Controlled	5	5
	Uncontrolled	4	4
Area of activity	Work	8	3
	Health	4	7
	Legal	0	0
	Family	5	1
	Marital	6	4

*Numbers of individuals reporting at least one event in category.

in Group I patients ($r = -.797$, $p < .01$) and in the whole sample ($r = -.467$, $p < .02$) but not in Group II patients ($r = .249$, NS). Mean serum prolactin also correlated negatively with somatization in Group I ($r = -.634$, $p < .02$) and in the pooled sample ($r = -.376$, $p < .05$) but not significantly so in Group II ($r = -.370$, NS). No other significant correlations were observed between endocrine variables and psychological parameters.

DISCUSSION

An interesting finding in this study of women who gained an important amount of weight over a short period of time was the absence of any evidence of changes in their eating patterns or in physical activity. Also, Groups I and II did not significantly differ neither in their estimated caloric intakes the day before admission nor in their observed intakes in the hospital. If anything, Group I women ate less (although not significantly

TABLE III. RESULTS OF THE SCL 90 AND MMPI TESTS

	Group I	Group II	Comparison (p =)
SCL 90			
Phobia	.924 ± .744	.401 ± .393	.009
Anxiety	1.533 ± .503	1.063 ± .487	.020
Depression	1.596 ± .427	1.024 ± .384	.0004
Psychoticism	.862 ± .666	.513 ± .217	.022
MMPI			
Depression	67.9 ± 6.35	59.6 ± 9.72	.022
Psychasthenia	59.0 ± 8.76	53.1 ± 7.08	.026
"Femininity"	50.8 ± 5.31	42.5 ± 8.38	.014
Schizoidy	66.2 ± 13.2	57.4 ± 4.66	.011

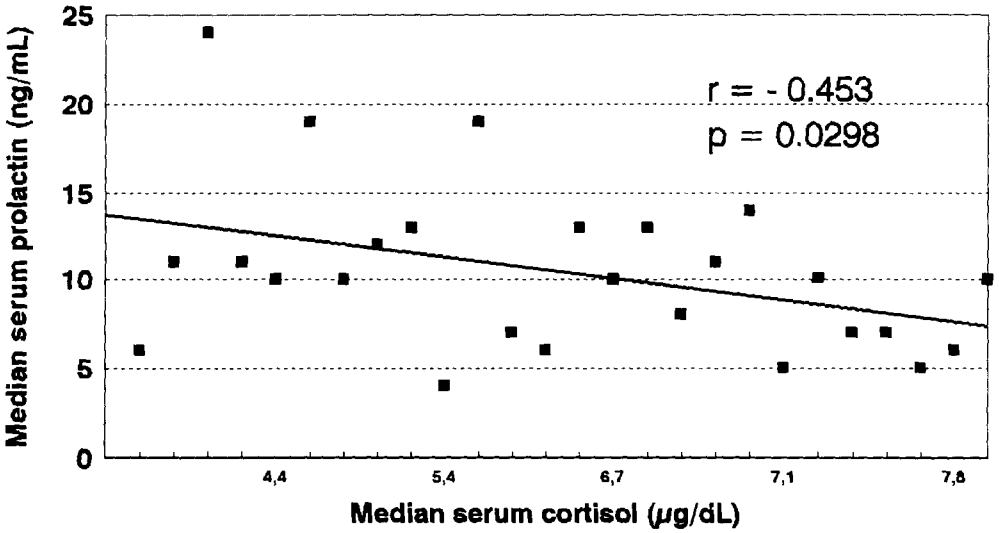

FIG. 4: Correlations between serum prolactin and serum cortisol (medians of 24-h samples) in Group I.

so) than the others. Within the limitations of the protocol used and with the caveat that self reported caloric intakes and physical activity may be misleading in some instances (Lightman et al., 1992), our results suggest that the weight gain in the patients studied was not primarily due to overeating.

From an endocrine point of view, Group I differed from Group II in its significantly higher serum prolactin concentrations observed in hourly samples and in the mean of 24 h. As a clinical counterpart of the above findings, five of the women from Group I, but none from Group II, presented with galactorrhea ($p < .05$). A 24-h circadian rhythm of prolactin secretion was observed in both groups, but Group I peaked significantly earlier than Group II (0200 and 0400, respectively). Other endocrine differences potentially associated with increased metabolic efficiency and deposition of fat were ruled out, namely in the concentrations of insulin, cortisol and gastrin.

It is possible that the increased prolactin concentrations in these women play a role in their weight gain. Prolactin is a powerful promoter of fat deposition (Cincotta & Meier, 1989). Its mechanisms of action and the possible contribution of its insulin antagonism (Cabrera et al., 1988) are unclear. It cannot be excluded that differences in prolactin concentrations between the two groups were secondary to their differences in the BMI. However, this difference, although significant, was small—28.8 vs. 24.2—to the point of not affecting serum concentrations of insulin which were similar in both groups. Also, no correlation was found between BMI and mean 24-h prolactin concentrations in the whole population ($r = .0742$) suggesting that prolactin is not a function of BMI. Obesity per se is not usually associated with increased prolactin concentrations (Scaglione et al., 1991) although, in a large population study, a weak, yet significant, correlation between serum prolactin and weight was described (Wang et al., 1987).

It is conceivable that some of the patients had ceased to accumulate fat at the time of the study. This source of error was impossible to eliminate as no patient accepted to withhold treatment until progression of the weight gain could be documented. Such patients would, presumably, present with hormonal profiles similar to those of the con-

trols. Therefore, this error would blunt the magnitude of any endocrine abnormalities present during the active phase of accumulation of fat and cannot be responsible for the observed differences between the groups.

Prolactin and weight gain appear associated in pseudopregnancy, a well-known psychiatric disorder, and at the clinical outset of prolactinomas when acute weight gain, menstrual disturbances, and galactorrhea are often concomitant (Creemers et al., 1991; Nunes et al,. 1980; Sobrinho, 1991). Prolactinomas have an important psychosomatic component characterized by an abnormal performance on personality tests with a predominance of depressive traits, sexual dysfunction, paternal deprivation during chilhdood and an unusual number of external events preceding the symptoms (Nunes et al,. 1980; Sobrinho, 1991).

In the present study, Group I had a significantly higher prevalence of sexual dysfunction and presented with higher scores for depression, anxiety, phobia, psychoticism, schizoidy, psychastenia, and "femininity," in the SCL 90 and MMPI tests than did Group II. The higher mean scores observed in Group I were still within the normal range. Whether the observed psychometric differences reflect predisposing personality traits, response to higher exposure to life events, consequence of hyperprolactinemia, or any combination of these factors is a matter of speculation. Weight gain (associated with increased appetite) is a feature of atypical depression (Gold et al., 1988). To our knowledge prolactin concentrations in this condition have not been studied. Depressive states are characteristic of pseudopregnancy and pathologic hyperprolactinemia and significantly ameliorate upon normalization of prolactin levels (Sobrinho, 1991), suggesting a role of prolactin in mood changes. In rodents (Drago et al., 1989) and humans (Seki et al., 1986), there is evidence that prolactin acts upon the central nervous system and increases the opioidergic tone. Also in favor of some relation between prolactin and psychometric scoring were the significant negative correlations between prolactin, hostility, and somatization. As these parameters did not discriminate between the groups, it is difficult to speculate further on the possible meaning of the observed correlations .

Women from Group I reported a significantly higher frequency of life events in the year preceding the study (and preceding the weight gain) than the others. The Paykel's life events inventory, used in the present study, is a rather thorough instrument for the assessment of important events occuring during a predefined time period. In the present study, the number of events and total score were significantly higher in Group I than in Group II but the number of events with negative impact was not. Although the sample is small, this may be due to more than a type II statistical error. More women from Group I reported "desirable" events while more control women from Group II reported "undesirable" events and "exits." Life events scales have been used primarily to investigate the influence of stressful events. Undesirable events, events with negative impact and exits have been reported to be significantly more common than in controls in patients with depression, suicide attempts (Paykel et al., 1975) and Cushing's disease (Sonino et al., 1993a). Our observations suggest that the nature of the events preceding, and presumably causally associated with, weight gain need not always be felt as "negative" or regarded by an external observer as "undesirable." A typical example was marriage which preceded weight gain in 3/13 of our patients and in 15/101 of patients with pathologic hyperprolactinemia reported in another study (Nunes et al,. 1980). In the same line, in a recent study of life-events preceding Graves' disease, Sonino et al. (1993b) found a larger number of events in patients than in controls. This was true predominantly for undesirable and negative events, but also for desirable and positive ones.

Taken together our observations provide evidence that acute weight gain is a condition triggered by environmental factors. It is associated with a moderate degree of hyperprolactinemia, galactorrhea and specific psychological characteristics, namely sexual dysfunction and a depressive state. This type of psychoendocrine response to external events is similar to the one observed in pseudocyesis, except for the absence of the delusional component.

The sympathoadrenal "stress" response to external events has been recognized for years. The present findings strongly corroborate the hypothesis that a few women react to environmental changes by activating a different neuroendocrine response characterized by increased prolactin secretion, galactorrhea and weight gain (Sobrinho, 1991). Detailed descriptions of the environmental determinants and psychological and behavioral findings associated with this neuroendocrine response in humans and animals are provided elsewhere (Sobrinho, 1991; Sobrinho & Almeida-Costa, 1992). The finding that median 24-h serum prolactin and cortisol serum concentrations correlate negatively both in Group I patients and in the pooled population confirms that this response is an alternative, and not a complement, to the sympathoadrenal "stress" response.

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