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Prolactin and human weight disturbances: A puzzling and neglected association

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Abstract
Weight gain at the outset of prolactinomas in many women is well documented. Yet, this symptom is absent from the clinical descriptions of the disease in textbooks and reviews. This omission is almost certainly due to the absence of a physiological explanation for the phenomenon, as prolactin is not a recognized fat promoting hormone. In this review we present the clinical evidence for a relationship between prolactin and fat accumulation and address some possible mechanisms involved. We put forward the hypothesis that prolactin is a component of a neuroendocrine program – maternal subroutine – aimed at optimizing the care of the young through the production of milk, promotion of maternal behavior and increase in the metabolic efficiency of the mother. These adaptations can enable her to face the extraordinary metabolic expenses of pregnancy and nursing, especially during times of suboptimal environmental conditions. We emphasize the uniqueness of prolactin in that it is a hormone that is tonically inhibited and which has its major effects on the regulation of an inter-individual (the mother – offspring dyad), rather than an intra-individual, system. This approach opens a window to consider the possibility of external events as regulators of this system. It also allows addressing a variety of hitherto unexplained findings reported in the literature. Examples include: association of prolactinomas with paternal deprivation and with stressful life events; pseudocyesis; acute life event-driven episodes of galactorrhea; episodes of rapid weight gain following a life event; prolactin surges (without associated cortisol surges) following some psychological stresses.

Keywords Prolactin · Prolactinoma · Pseudocyesis · Fat · Obesity · Weight gain

1 Introduction

Most prolactinomas present clinically with the amenorrhea/galactorrhea syndrome. Other symptoms such as headaches, visual disturbances, etc. may also occur. This description or variants thereof can be found in every textbook or review on the subject. It is striking that another symptom that occurs concomitantly with the onset of menstrual irregularities and galactorrhea in a fair number of cases – rapid weight gain – is seldom mentioned. This symptom had already been listed in the only case described in full in the seminal paper by Forbes and Albright [1] on amenorrhea/galactorrhea syndrome. Their paper also enumerated excess weight in 11/15 cases. Despite consistent evidence that weight gain occurs at the clinical outset of prolactinomas (see below) this symptom did not raise much curiosity in the scientific community and has been largely ignored in conventional descriptions of the disease. One can only speculate on the reasons for this omission. The most likely is the absence of a physiological explanation for the phenomenon. Prolactinomas are benign tumors that overproduce prolactin, but no other hormones. Although prolactinomas occasionally impact on nearby neural structures, this process does not have any relationship with weight gain. The acknowledged cardinal prolactinoma symptoms have obvious explanations - prolactin stimulates the breast to produce milk and feeds back on the hypothalamus stimulating dopaminergic tone and disrupting the gonadal axis. In contrast, weight gain is not a recognized effect of prolactin. Besides, weight gain in prolactinomas is inconsistent and there is no correlation between serum prolactin concentrations and weight gain or BMI [2, 3]. In the following sections of this review we propose to overview the pertinent literature on situations in which prolactin and weight gain or adiposity are somehow related.

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2 Weight gain as an initial symptom in patients with prolactinoma

Besides the already mentioned report by Forbes et al. [1] weight gain at the outset of the other symptoms of prolactinomas also has been sporadically described by others [4, 5]. The association was observed in 19 of the 35 women with prolactinomas reported by Nunes et al. [3] and in 9/14 patients with prolactinomas described by Creemers et al. [6]. Likewise, Greenman et al. [7] reported a marked (8–22 kg) gain of weight as a presenting symptom in 13/42 patients with prolactinomas as compared to 1/36 with non-functioning adenomas ($p = 0.001$). In a review of 219 newly diagnosed patients with pathological hyperprolactinemia Colao et al. [8] found that weight gain had been a presenting symptom in 94% of the women with macroprolactinomas, 59% with microprolactinomas and 53% with non-tumoral hyperprolactinemia. For men the figures were 53% in macroprolactinomas and 19% in microprolactinomas.

3 Overweight in patients with prolactinoma and reversal upon treatment

Consistent with these observations patients with prolactinomas have been found to be overweight as compared to controls in several reported series [1, 3, 6, 9, 10] as summarized in Table 1. Unquantified adiposity was found in 11/16 men with prolactinomas by Cohen et al. [11]. Excess weight has been reported by some authors to be more common in macroprolactinomas and in males [6, 10].

Not all studies were consistent Greenman et al. [7] compared the BMI of 42 patients with prolactinomas (males and females) to 36 patients with non-functioning pituitary adenomas. Males with prolactinomas had higher BMI than the others (31.6 vs 26.5 kg/m^2; $p = 0.002$). For females the reverse was observed (26.1 vs 31.2 kg/m^2; p = n.s.). However, women in the control group were much older than those with prolactinomas (61.7 vs 46.4 years) and the expected age-related increase in weight may have been responsible for the observed results.

Treatment with dopamine agonists was followed by a significant, but generally modest, weight reduction mainly in patients with macroprolactinomas [6, 12–14] by some, but not all authors [15]. Exceptionally, marked weight loss was obtained, reversible upon reduction of the medication and resumed upon re-introduction of the full dosage of the medication [5]. Factors influencing weight loss were normalization of prolactin levels and long follow-up [13].

4 Normal endocrine states similar to prolactinoma

It is useful to consider the extent to which the pathophysiological state associated with prolactinoma can be related to any normal physiological states. Lactogenic hormones (prolactin or placental lactogens) are never high in normal males. Females are relevant because prolactin activity can be quite high under perfectly normal states. To the extent that placental lactogens and prolactin are functionally similar, pregnancy is characterized by elevated lactogen. However, reproductive steroids (progesterone and estrogens secreted from the placenta) are very high in pregnancy, but their effects on the breast are suppressed by prolactinomas because of the antigonadal effects of prolactin [16]. Lactation, when ovarian steroids are low, is therefore most likely to resemble the physiological status most similar to prolactinoma.

Active lactation is similar to prolactinoma in terms of elevated prolactin and low ovarian steroids. But it is dissimilar because of suckling-induced oxytocin secretion as well as possible other effects associated with the presence of a nursing infant. The transitory condition of milk stasis (accumulation

Table 1 Frequency of Overweight in Patients with Prolactinomas

Author (Ref)	Nr Sex	% overweight	Definition of overweight	Macro/Micro-prolactinoma
Forbes et al. [1]	15 F	9/15. Range 22 to over 60 pounds overweight.	Pounds overweight compared to the norm.	Pre CT scan
Nunes et al. [3]	35 F	Average excess weight 35% v. 11% in controls ($p < 0.01$)	% of excess weight above the norm.	Pre CT scan
Creemers et al. [6]	18 F; 29 M	Nr with BMI= > 25 Kg/m^2: M ($p < 0.001$); F (n.s.).	BMI compared to the average Dutch population	Micro =11 Macro = 36
Wallace et al. [9]	157 F	Ten pounds heavier than controls ($p < 0.05$). Height was similar in both groups.	Pounds overweight compared to age-matched controls	Pre CT scan
Schmid et al. [10]	126 F; 55 M	Macro −25% v. 4,5% Micro – 9.9% v. 4%	BMI = > 30 Kg/m^2 v. controls	Macro = 100 Micro = 81
Cohen et al. [11]	16 M	11/16	"Adiposity" undefined	Pre CT scan

Legend to Table 1 – Nr – Number of subjects; F - Females; M – Males; n.s. - Difference not significant; Pre CT scan – Series reported before CT scan was widely available

of milk in the absence of suckling) is the only normal physiological condition that is closely similar to prolactinoma. During milk stasis the residual effects of prolactin continue to drive lactation. The condition is short-lived if an infant returns to nursing and stimulates milk letdown and milk removal. With weaning the milk stasis persists for up to a few days in the absence of milk letdown. Beyond the general description of high lactogen, low steroids, and absent oxytocin, relatively little is known about physiological regulation during milk stasis.

A productive finding was the discovery of mammary serotonin, which is generally elevated during lactation and greatly increased during milk stasis [17, 18]. Mammary serotonin synthesis is driven by prolactin and inhibited by progesterone through mechanisms that require distension of the mammary alveoli by the presence of secreted milk. Two of the well-documented effects of mammary serotonin are to initiate several involution-related processes [17, 18] and to induce parathyroid hormone-related peptide (PTHrP) secretion [19, 20]. These responses are mediated by different receptors (5HT7 and 5HT2b, respectively), which permits the mammary gland to respond appropriately to changing levels of serotonin production locally. PTHrP drives calcium mobilization and conservation to replace the calcium delivered in the milk. The effect of mammary serotonin in PTHrP and calcium may be related to bone loss in prolactinoma [21, 22].

Prolactin-induced serotonin also is an important element in the pancreatic adaption to pregnancy. Islet ß-cell proliferation is induced indirectly by prolactin (and placental lactogens) via serotonin synthesis in the pancreatic islets in humans and rodents [23]. In mice ß-cell mass declines after parturition [24]. It is possible that ß-cell hyperplasia may be involved in metabolic disturbances in prolactinoma, but there are apparently no studies regarding ß-cell proliferation associated with hyperprolactinemia outside pregnancy.

5 Pseudocyesis

Pseudocyesis is a rare disorder rarely seen in our time in industrialized societies, but abundantly reported in the older literature and still occasionally observed in rural societies. It is characterized by a delusional state of being pregnant, which is unchangeable by logical reasoning. What is peculiar to this condition is the fact that the body follows the delusion: these women cease to menstruate, the breasts become engorged with visible superficial veins and milk discharge and they gain a lot of weight. This set of events is characteristic of normal pregnancy/lactation, and can be referred to as pseudopregnancy (not to be confused of pseudo-pregnancy in some non-human animals). The abnormality lies in the fact that the condition is not triggered by placental hormones. Before going deeper into the analysis of the physiology of pseudopregnancy two words of caution are in order: 1) It is likely that many of the reports in the older literature were prolactinomas. In the absence of hormonal assays and of ultrasonography, a woman does not need to be delusional to believe that she is pregnant when the above symptoms appear; 2) Animal models are of little help. The very definition and, consequently, the physiology of pseudopregnancy are different in women, rodents, bitches and mares [25].

Most reports on pseudocyesis are old and come from agricultural communities. A search on PubMed yielded, since 2000, only one report of pseudocyesis in a woman in whom a prolactin assay was performed [26] and one extensive review but without raw data [27]. In the few cases in which serum prolactin were evaluated nearly half of the values have been found to be within the normal range. Individual values per publication were: Two patients, PRL = 15 and 60 ng/ml [28]; One patient, PRL = 40 ng/ml [29]; Six patients, average 81.1 ng/ml; SEM 17.5 [30]; Two patients 4.1 ng/ml and 13.4 ng/ml [31]; Five patients, average 23.5 ng/ml; SEM 1.3 ng/ml [32]; Two patients, studied with 24 h profiles. Morning values of 4 ng/ml and 17 ng/ml but night peaks of 40 ng/ml and 65 ng/ml [33]; Two patients, PRL = 9 and 14 ng/ml [34]; Five patients. Morning values of 5, 6, 20, 20 and 25 ng/ml but night peaks up to 65 ng/ml [35]; Nine patients, all with morning prolactin within the normal range. Average PRL 8.4 ng/ml SEM 1.5 [36]; One case PRL = 33 ng/ml [26]. It has been postulated, that nighttime hyperprolactinemic surges well above the normal circadian variation might be responsible for the galactorrhea when morning prolactin levels are within the normal range [33, 35]. It is likely that the wide variability in the values reported depends on diagnostic criteria, age, duration of the condition, state of ovarian function and other factors. What is unquestionable is that the exuberant mammary and weight changes characteristic of pseudocyesis can be obtained by prolactin concentrations not far from normality and well within its presumed regulatory range.

6 Serum prolactin levels in obesity

Most publications have not found significant differences in serum prolactin concentrations between lean and obese subjects [37]; for review, see [38]. However, [39] a study of 4550 healthy premenopausal women found a positive correlation between ponderosity and serum prolactin levels. Kok et al. [38] using 10 min blood sampling during 24 h and deconvolution analysis in healthy and obese premenopausal women found out that obese women had higher average 24 h prolactin concentrations (49 ng/ml v. 25 ng/ml; $p = 0{,}001$) than lean controls. The peak amplitude, and peak area were higher in the obese whereas peak frequency was lower. Average prolactin secretion rate was positively correlated with both BMI and amount of visceral fat. Pulsatile prolactin release was reduced in a group of obese women after they were placed on very low calorie diets and lost 50% of their overweight (15% body

weight on average) [40]. The authors suggest that increased dopamine tone due to severe dieting contributed to blunted prolactin release. The fact that prolactin pulse dynamics was affected, and not simply basal levels, suggests a hypothalamic explanation rather than changes in secretion from extrapituitary sources such as adipose tissue [41].

7 Rapid weight gain in women without prolactinomas

Occasionally, a woman presents with the complaint that she had gained an important amount of weight over a short period of time. There are possible causes for this phenomenon. Overeating, recovering from previous weight loss, reduction of physical activity, quit smoking or the intake of some drugs. However, in a few cases none of these causes apply. Ferreira et al. [42] studied a group of 13 such patients with regular periods (Group 1) and compared it with a group of women with stable weight matched for age, parity and social class (Group 2). Group1 differed from group 2 in that:

1. There had been a significant number of meaningful life events in the year preceding the study. The average number of life events was 2.85 ± 1.27 in Group 1 and 1.13 ± 1.25 in Group 2 ($p = 0.004$). The Paykel Life Events score [43] which corresponds to the number of events times intensity of the impact, as assessed by the observer was 9.23 + 5.99 in Group 1 and 4.25 + 5.9 in Group 2 ($p = 0.05$).
2. Group 1 had a significantly higher score than group 2 in a number of parameters in the SCL 90 and MMPI tests.
3. Galactorrhea was observed in 5 women from group 1 and in none from group 2.
4. Hormonal profiles obtained hourly during a 24 h period for insulin, cortisol and gastrin were similar in groups 1 and 2. However, patients in group 1had higher 24 h prolactin concentrations than patients in group 2. Average of hourly values during 24 h was, respectively, 14.6 ng/ml and 8.84 ng/ml ($p = 0.012$).

Another study was conducted with different sets of similar subjects containing 17 subjects in each group [44]. Morning basal hormonal values were obtained for cortisol, prolactin, insulin, estradiol, IGF-1, gastrin, cholecystokinin, somatostatin, oxytocin, leptin, thyroxine, triiodothyronine and TSH. After the collection of blood samples the subjects were given 10 mg of domperidone i.v. and serum prolactin concentrations were measured in the following 20, 30 and 60 min. The findings were as follows: There were significantly more life events and a higher Paykel's Life Events Score in group 1 than in Group 2 ($p = 0.01$ and $p = 0.013$, respectively). Galactorrhea was observed in 6/17 subjects from group 1 and in 1/17 subjects from group 2. Prolactin values were significantly higher in group 1 than in group 2 (8.15 ± 4.92 v. 5.29 ± 2.48; $p < 0.05$). However, the distribution of prolactin values in group 1 was markedly skewed to the right. Six of the 17 subjects had serum prolactin concentrations higher than the highest value observed in the subjects from group 2 as shown in Fig. 1. These subjects were considered as a population of outliers. As a consequence, for the purpose of further analysis Group 1 was subdivided in Group 1a (containing de 6 outliers) and Group 1b (containing the remnant 11 subjects). Leptin values were significantly higher in group 1 as compared with group 2 (18.85 ng/ml ± 10.63 v. 10.15 ± 6.38; $p = 0.02$). This difference could be justified by differences in the BMI between the two groups (26.64 + 2.35 kg/m2 v. 23.6 + 2.84; $p < 0{,}01$). No other significant differences were observed between the groups.

1. Prolactin response to domperidone – Group 1a had, by definition, higher basal prolactin levels (13.72 ± 3.69) than either group 1b (5.12 ± 1.81) or Group 2 (5.29 ± 2.48), both similar to each other. The prolactin response to domperidone by subjects from group 1a was significantly lower at all points than that of groups 1b and 2 ($p < 0.02$ and $p < 0.05$, respectively) again, both similar to each other.
2. Overall, these reports support the formulation that unexplained rapid weight gain in women is a phenomenon triggered by an external event, associated with disturbed affect (therefore a "psychosomatic" condition),

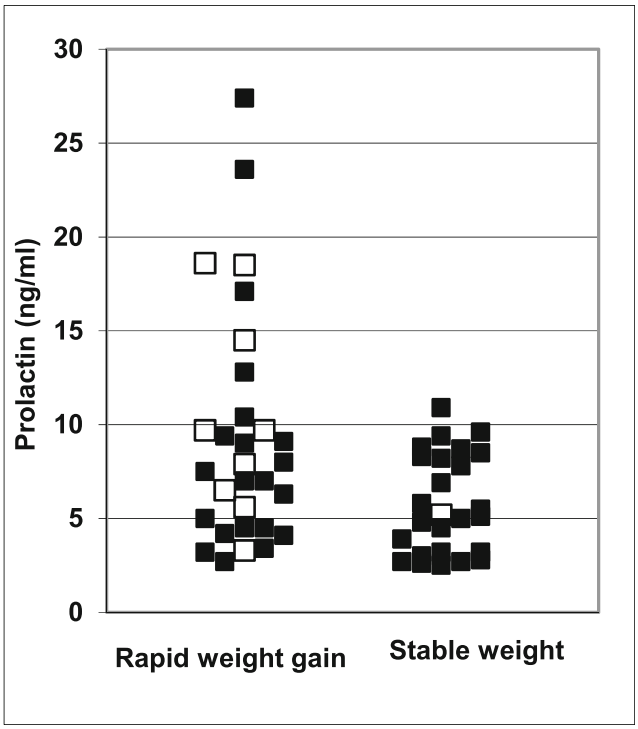

Fig. 1 Morning prolactin levels in 30 women with rapid weight gain (Group 1) and 26 controls with stable weight (Group 2). Galactorrhea was found in women represented by white squares (from [44], used with permission)

galactorrhea and modest, yet significant, hyperprolactinemia. Detailed analysis revealed that the higher average prolactin levels in the group of weight gainers as compared to controls was due to a subgroup of subjects with clearly elevated prolactin values. This subgroup also differed from the others (weight gainers and controls) in having a blunted prolactin response to domperidone, suggesting a reduced hypothalamic dopaminergic tone.

Example of a Clinical case: A 26 year old African lady came to the clinic complaining that she had gained about 8 kg in the last 6 months. She was accompanied by her twin sister who was 6 months pregnant. The patient had had a stable weight until recently, denied any change in eating habits (in fact, she was now eating less to control her situation), physical activity, had never smoked and was not taking any medications. She denied any meaningful change in her personal or professional life. The following dialog ensued:

Doctor (D) – At least there was a change, your sister got pregnant.
Patient (P) – Do you think that had any relation with my problem?
D – I don't know. But it certainly was a meaningful event and there was a coincidence in time. How would you feel about getting pregnant yourself?
P – Not easy. I am single.
D – One thing are the practicalities, another are the deep feelings and yearnings.
P – As a matter of fact I am looking forward to becoming an aunt and helping in the care of the baby. Do you think this is why I gained weight?
D – Honestly I do, but I am not sure. Maybe your body is expressing a deep desire to have a baby of your own.
P and sister – Do you mind if we call in our mother who is in the waiting room? She would love to hear that.

The mother came in and, after some changes of words, said: You know, in the culture we come from, when a twin girl is asked in marriage the bridegroom writes to her, and to her sister, asking permission to court them both. And, until the day of the marriage, he is supposed to treat both equally as brides.

8 Drug induced weight gain and hyperprolactinemia

Treatment with psychotropic drugs with dopamine type 2 receptor antagonistic activity is associated with hyperprolactinemia and weight gain [2] primarily in women but also in men if given enough time of treatment [45]. At the start of the treatment of therapeutically naïve patients the increase in prolactin levels correlates with the increase in weight in some [46] but not all studies [47].

In rats, simultaneous administration of bromocriptine and sulpiride prevents weight gain and hyperprolactinemia, suggesting a close relationship between weight gain and antagonism to D2 dopamine receptors [48] although this relation does not appear to be the same for all medications. Olanzepine is one of the most powerful drugs in promoting weight gain, yet is less potent in increasing serum prolactin levels than paliperidone or risperidone [49]. It appears that olanzepine has an intense orexigenic effect through targeting the Type 2C serotonin receptor [50].

It has been proposed that weight gain promoted by (at least some) psychotropic drugs depends exclusively on increased appetite since it has been observed in patients on a free diet but not in patients under strict dietary control [45]. Likewise stable weight when caloric intake is kept constant has been reported in a group of sulpiride treated female rats while an increase in weight was observed in a similarly medicated group given free access to food. Serum prolactin concentrations were similar in both groups [51]. It should be borne in mind that these drugs act at different receptors and pathways in the nervous system, are different from each other and the regulation of fuel storage is a very complex one. It is likely that prolactin plays a role in the accumulation of fat but the nature and extent of this role is, at the moment, unclear.

9 Prolactin as an anabolic hormone

The very close relationships between prolactin and growth hormone in terms of evolution, structure, and signal transduction suggests that these hormones might share some physiological effects on metabolism. Growth hormone is understood to not only have broad stimulatory effects on somatic growth via the IGF-1 system, but also to cause metabolic adjustments via actions on many tissues [52]. Chronically elevated growth hormone causes insulin resistance, increased insulin secretion, and elevated blood glucose levels. Despite causing insulin resistance, elevated growth hormone does not lead to obesity because of counteracting effects on nutrient utilization by muscle, adipose and liver tissues such that nutrients are directed to growth rather than storage in fat depots. Physiological elevation of growth hormone secretion redirects nutrients to somatic growth and fuel use efficiency, but pathological growth hormone elevation leads to gigantism and Type 2 diabetes associated with lean body mass [52]. It is important to appreciate that only modest shifts in nutrient utilization are needed to support growth (normal or pathological) because the vast majority of nutrient is used for normal metabolism (basal and activity-related).

Growth hormone stimulates islet ß-cell proliferation, reduces ß-cell apoptosis, and increases insulin secretion. Correspondingly, defective growth hormone signaling results in reduced ß-cell mass [53].

The anabolic effects of prolactin are similar to those of growth hormone. Prolactin's effects are not as obvious as those of growth hormone because prolactin actions are normally limited to pregnancy and lactation. In males insulin resistance is positively correlated with serum prolactin [54]. Placental lactogen and growth hormone are secreted by the placenta during pregnancy. Presumably both placental lactogen and placental growth hormone contribute to ß-cell proliferation and insulin secretion, and to a degree of insulin resistance that is normally adaptive for supporting growth of the placenta, fetus, and mammary glands.

As described above, prolactin-induced ß-cell proliferation and insulin secretion are at least partly mediated by induction of local serotonin synthesis and secretion in the islets [23, 24]. It is unknown whether growth hormone-induced ß-cell adaptations could also be mediated by serotonin.

Prolactin may increase the metabolic efficiency for lactation, much like growth hormone increases metabolic efficiency for growth. In nursing women there is a reduction in the caloric response to a meal and to the infusion of norepinephrine even though the basal metabolic rate is unchanged [55]. Prolactin appears to be sensitive to the nutritional status of the lactating mother. Abundant nutrition during lactation is associated with rapid reduction of prolactin levels towards normal pre-pregnancy values in women. Undernutrition, on the other hand, maintains high prolactin levels (and anovulation) for a much longer period of time [56] as illustrated in Fig. 2.

10 Prolactin and adipose tissue

Prolactin is synthesized in a variety of extrapituitary tissues and uterine prolactin has been convincingly shown to play multiple roles in successful gestation [57, 58]. In other tissues the evidence is less clear and there are major species differences. Evidence for extrapituitary prolactin synthesis in rodent tissues other than the uterus is inconsistent. On the other hand, primates (humans) express prolactin in many tissues and levels of expression are sufficient to suggest they are physiologically meaningful. Humans employ an alternative promoter (unique from rodents) to drive prolactin in most, if not all, non-pituitary tissues. To replicate the human pattern of prolactin expression a large region encompassing both promoters and the structural gene of human prolactin was cloned into prolactin knockout mice [57]. The pattern of prolactin expression in non-pituitary tissues closely replicated the known pattern in humans.

Adipose tissue appears to be one example of an extrapituitary source of prolactin. Although levels of prolactin secretion are minuscule compared with the pituitary, the larger number of cells might make the adipose a meaningful source of hormone [41]. Direct effects of prolactin on adipose tissues have been studied experimentally, and the results have been complex. Prolactin (and growth hormone) have positive effects on the induction of adipogenesis, but effects on lipogenesis and lipolysis are inconsistent [41].

Rather than having direct effects on adipose tissue, current knowledge favors indirect effects such as alterations in the endocrine pancreas and insulin sensitivity (see above), and central leptin resistance [59].

11 Psychogenic factors

It has been reported that patients with prolactinomas had been brought up under conditions of absent or violent fathers, significantly more so than control populations [3, 60–63]. Life events also often precede the clinical onset of prolactinomas [3, 64]. These observations, taken together, support the hypothesis that exposure, early in life, to paternal deprivation may predispose some persons to, later, react to external stimuli developing a prolactinoma. The mechanisms potentially involved in the process are mind boggling. Prolactinomas have been consistently demonstrated to be monoclonal [65]. It seems very unlikely that a psychologically driven neuroendocrine mechanism could induce a genetic/epigenetic change in a single pituitary cell. However, autopsy studies have consistently revealed the presence of clinically unsuspected adenomas in the pituitary in roughly 11% - 17% of corpses 40% of which stain positively for prolactin [66–68]. Therefore, it is reasonable to assume that some neuroendocrine mechanisms operate at the promotion to functional activity of a preexisting, but hitherto inactive, prolactinoma. It is well known that overstimulated endocrine glands can become hyperplastic and, eventually, develop nodularity. This evolution is common in the thyroid (nodular goiters) and parathyroid in humans (tertiary hyperparathyroidism). Even in the human pituitary, adenomas producing ACTH and gonadotropins have been described in the course of long term Addison's disease [69] and primary hypogonadisms [70, 71]. In mice prolactinomas have been obtained following knock out of prolactin, [72] the prolactin receptor [73] or the dopamine receptor DR2 [74]. However, in all these models, intense and prolonged stimulation is required. The clinical onset of prolactinomas often develops over a relatively short period of time. This is especially obvious when there is a temporal relationship between a life event and appearance of the symptoms. Therefore, although, in principle, a psychologically driven neuroendocrine stimulation might promote the development of a prolactinoma, the known models above described fall short of providing a satisfactory explanation for the natural history of the disease.

One can speculate that the above described situations of acute weight gain associated with moderately elevated prolactinemia

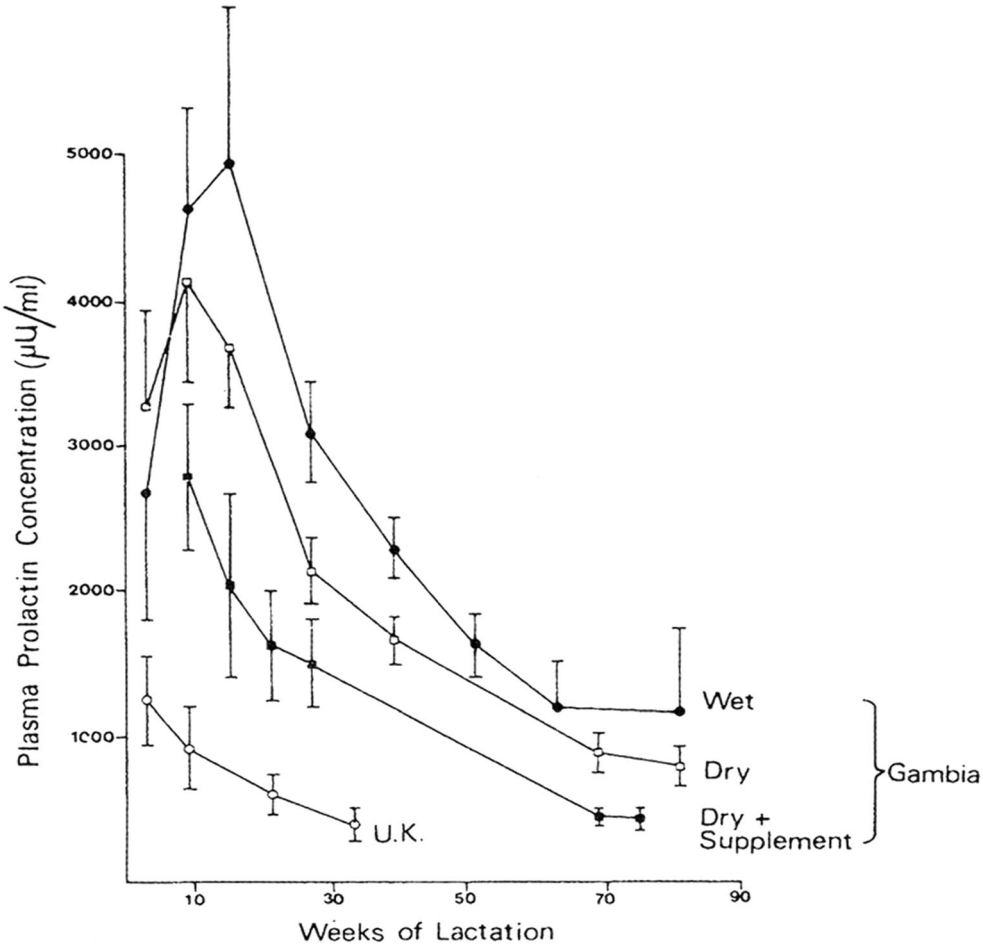

Fig. 2 - Plasma prolactin concentrations in lactating mothers in the U.K. and in The Gambia. Notice that during the wet (Wet) season there is less access to food than during the dry (Dry) season (from [56], used with permission)

and/or galactorrhea following a life event may involve mechanisms similar to those of prolactinomas, the difference being that there was no subclinical adenoma to be promoted.

Unanswered questions are the nature of this hypothetical neuroendocrine mechanism and of the stimuli that activate it. As for the first question we just have no answer. As for the second question there are some contributions. Prolactin is a stress hormone [75]. A report by Sobrinho's group [76] may add some insights into the nature of the prolactin response to psychological stress. The "psychological stress" consisted of a session of about one hour of free associations during an induced hypnoidal state. Twenty five women were observed for a total of 55 sessions. Each session consisted of an interview, induction of the hypnoidal state, free associations during this state, return to a fully conscious state and a debriefing. The whole procedure lasted for about three hours during which the subjects were monitored for heart rate, EKG and skin conductance. Blood was drawn every 15 min for the assay of cortisol, prolactin and growth hormone. Twelve of the women had previously been through the same protocol with the difference that a state of relaxation only was induced, without free associations, to inform on the baseline of spontaneous hormonal secretory bursts. Anyway, each session had its own control consisting on the hormonal activity during the interview and relaxation phase, preceding the free associations. Intense emotional states during the free associations were often observed clinically and documented by changes in the heart rate and skin conductance.

It was found that, as expected, the most responsive hormone to stress was cortisol. On the total of 55 sessions the number of hormonal surges during the initial phase and during the free associations was: cortisol 3 v. 32 ($p < 0.001$), prolactin 3 v. 18 ($p < 0.001$) growth hormone 18 v. 28 ($p < 0.1$). The unexpected finding was a negative association between cortisol and prolactin surges. In standard laboratory tests of psychological stress, prolactin and cortisol responses are positively correlated [77]. In the above described protocol, sessions in which there was a cortisol surge seldom had a prolactin surge, and vice versa. Emotions were equally intense in both situations but the feelings differed. Cortisol surges were predominantly associated with conditions of shock and intimidation while prolactin surges were predominantly associated with rage at the evocation of humiliating experiences. It therefore appears that the neuroendocrinology of "psychological stress" is not restricted to the activation of the CRH-ACTH-cortisol system but there is, at least, an alternative neuroendocrine

response in which the secretion of prolactin, but not of cortisol, is activated. On the clinical side, acute galactorrhea and engorgement of the breasts following intense stress is an uncommon, but recognized, entity [25, 78].

12 Hyperprolactinemia, lactation and weight gain. An integrated view

In this review we presented several clinical conditions in which hyperprolactinemia and weight accrual were associated. The most impressive is weight gain at the outset of prolactinomas, not only because the evidence of the association is overwhelming but because prolactinomas represent what appears to be a simple model wherein there is a single primary abnormality – the hypersecretion of prolactin. The inference that there may be some causal relationship between prolactin and accumulation of fat is supported by some experimental data, but this relationship is far from simple. Not only is weight gain in prolactinomas inconstant, but there is no evidence of a dose response curve between prolactin concentrations and effects on weight. In cases of pseudocyesis the accumulation of a considerable amount of fat over a short period of time occurs despite prolactin levels that are moderately elevated or even within the normal range. This pattern also occurs in women with rapid weight gain after a life event. Modest levels of prolactin are sufficient for a mammary lactogenic response (galactorrhea) in the absence of inhibitory levels of progesterone. In the presence of modestly increased prolactin, neural feedback from the mammary glands to the brain, and/or endocrine factors secreted from the mammary glands could be sufficient to affect metabolism. Under normal, non-pregnancy-associated, conditions, prolactin secretion is regulated around a set point that is somewhat higher in women than in men. Assuming a set point of around 10 ng/ml, its regulatory range may be between zero and 30 ng/ml. Certain physiological effects may be obtained within this range. What are these effects? We do not know. Do these effects include galactorrhea and some action on the complex network that regulates energetic metabolism? Possibly yes. To account for the clinically conspicuous effects of quasi normal prolactin levels as well as for other phenomena – non parental nursing in women and animals [79, 80], for instance – we proposed that prolactin is a component of a neuroendocrine program aimed at optimizing the care of the young with the triple purpose of producing milk, promoting maternal behavior and increasing the metabolic efficiency of females so that they could face the extraordinary demands of pregnancy and lactation. We dubbed this program "maternal subroutine" [25, 76]. Such a program is vital for the survival of the species and, as such, must be of considerable complexity. Besides prolactin, other hormones and the autonomic nervous system are certainly involved in the maternal subroutine but their roles are mostly unknown. We speculate that the activation of the maternal subroutine precedes and promotes the development of, at least, some prolactinomas. That would explain both the temporal relationship between life events and the clinical onset of the disease ([5, 64] and the relative independence between prolactin values and the amount of weight gained.

Prolactin has the unique property of being tonically inhibited. Maybe the whole maternal subroutine is likewise dormant only to be activated when needed. There is another peculiarity in this subroutine that makes it different from most other regulatory systems. The system it regulates is not intra individual but a community. Caring for the young is not necessary for the survival of individuals but is essential for the survival of the species. Therefore, regulatory signals include those involved in inter individual communication. This opens the door to accepting a role for psychological factors and life events in the physiopathology of hyperprolactinemic syndromes. Activation of the maternal subroutine is normally triggered by the placental hormones. But, under particular circumstances it may be conditioned to other stimuli. Consider the following scenario: In a small tribe a woman dies after giving birth, a common event. There may or may not be a wet nurse available. It has been observed that, in this setting, another woman, often the grandmother puts the child to the breast and nurses him [79, 80]. In the intense atmosphere of mourning and the perception of the urgent need to carry on with the care of the child, some women may feel "recruited" and become metabolically enabled to assume the role of the deceased mother. If we accept this scenario as having had evolutionary pressure we will be better prepared to understand how prolactin surges can be elicited by negative, violent, emotions [76, 81, 82], why some women respond to aggressions with acute galactorrhea [25, 78], why pseudocyesis follows abandonment, and why some women suddenly gain weight after a life event [42, 44]. This last condition is not rare and may be an ideal model for further studies. We are aware that the maternal subroutine hypothesis is highly speculative. But it has the heuristic value of providing a frame of reference that allows the incorporation of several hitherto overlooked associations and of "orphan" reports scattered in the medical literature. This hypothesis, whatever its limitations may, hopefully, prompt clinicians and physiologists to be more curious about the environmental and physiological mechanisms involved in the process of moving the fuel stores of a person from one level to another whether or not associated with blatant hyperprolactinemia.

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