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Hyperprolactinemia and Woman's Health

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1. Introduction

Background

Hyperprolactinemia (HP) is a real challenge of gynecologic practice. This chapter will cover the following aspects:

Physiologic role of prolactin (PRL) hormone

Galactorrhea

Definition, causes, health problems caused by HP.
Types of prolactin (PRL) hormone.
Estimation of PRL hormone: timing, methodology and factors affecting prolctin level.
Complementary investigations in cases of hyperprolacinemia.

Treatment of HP:

- Health education.
- Pharmacological treatment.
- Herbal preparations.
- New drug delivery systems.
- Choice of a suitable drug for an individual patient.

2. Physiologic role of prolactin (PRL) hormone

The most important of which is to stimulate the mammary glands to produce milk (lactation). Increased serum concentrations of PRL during pregnancy cause enlargement of the mammary glands of the breasts and increases the production of milk. However, the high levels of progesterone during pregnancy act directly on the breasts to stop ejection of milk. It is only when the levels of this hormone fall after childbirth that milk ejection is possible. Sometimes, newborn babies (males as well as females) secrete a milky substance from their nipples. This substance is commonly known as Witch's milk. This is caused by the fetus being affected by PRL circulating in the mother just before birth, and usually stops soon after birth. Another effect is to provide the body with sexual gratification after sexual acts. The hormone represses the effect of dopamine, which is responsible for sexual arousal, thus causing the sexual refractory period. The amount of PRL can be an indicator for the amount of sexual satisfaction and relaxation. On the other hand, high amounts are suspected to be

responsible for impotence and loss of libido. PRL has been found to stimulate proliferation of oligodendrocyte precursor cells. These cells differentiate into oligodendrocytes, the cells responsible for the formation of myelin coating on axons in the CNS (Gregg, et al; 2007). PRL possibly contributes to surfactant synthesis of the fetal lungs at the end of pregnancy and immune tolerance of the fetus by the mother during pregnancy (Snyder and Dekowski, 1992). It decreases normal levels of sex hormones (estrogen in women and testosterone in men). PRL, traditionally named from its lactogenic action (mammogenesis and galactopoiesis included), is now recognized from animal – studies to have over 300 identifiable bioactivities corresponding to the wide distribution of PRL receptors, including osmoregulation, reproduction, behavior modification and immune modulation (Bole-Feysot, et al; 1998). 19 Many of these functions are difficult to discern in man, however, where the reproductive roles of PRL are the most evident in terms of clinical disease.

3. Galactorrhea

It refers to the mammary secretion of a milky fluid, which is non-physiologic in that being inappropriate (not immediately related to pregnancy or the needs of a child), persistent, and sometimes excessive. Although usually white or clear, the color may be yellow or even green. In the latter circumstance, local breast disease should be considered. To elicit breast secretion, pressure should be applied to all sections of the breast beginning at the base of the breast and working up toward the nipple. Hormonally induced secretions usually come from multiple duct openings in contrast to pathologic discharge that usually comes from a single duct. A bloody discharge is more typical of cancer. The quantity of secretion is not an important criterion. Amenorrhea does not necessarily accompany galactorrhea, even in the most serious provocative disorders. Any galactorrhea demands evaluation in a nulliparous woman and if at least 12 months have elapsed since the last pregnancy or weaning in a parous woman. Galactorrhea can involve either breasts or just one breast. This recommendation has evolved empirically, knowing that many women have the persistence of galactorrhea for many months after breastfeeding, and therefore the rule is a soft one. The exact numbers have never been established by appropriate studies. Thus, there is room for clinical judgment with this clinical problem. Galactorrhea is present in about 30–80% women; this may reflect the duration of gonadal dysfunction, because women with long-standing estrogen deficiency are less likely to have galactorrhea.

3.1 Galactorrhea with normal PRL level

Only one-third of women with high PRL levels have galactorrhea, probably because the low estrogen environment associated with the amenorrhea prevents a normal response to PRL. Another possible explanation again focuses on the heterogeneity of peptide hormones. PRL circulates in various forms with structural modifications, which are the result of glycosylation, phosphorylation, deletions, and additions. The various forms are associated with varying bioactivity (manifested by galactorrhea) and immunoreactivity (recognition by immunoassay). The predominant variant is little PRL (80-85%), which also has more biologic activity than the larger variants. Therefore, it is not surprising that big PRLs compose the major form of circulating PRL in women with normal menses and minimal galactorrhea (Jackson, et al; 1985).

Simultaneous measurements of PRL by both bioassay and immunoassay reveal discrepancies. At first, differences in PRL were observed based on size, leading to the use of terms such as little, big and the wonderfully sophisticated term big big PRL. Further chemical studies have revealed structural modifications that include glycosylation, phosphorylation and variations in binding and charge. This heterogeneity is the result of many influences at many levels: transcription, translation and peripheral metabolism (Ben-Jonathan, et al; 1996)

Enzymatic cleavage of the PRL molecule yields fragments that may be capable of biologic activity. PRL that has been glycosylated continues to exert activity; differences in the carbohydrate moities can produce differences in biologic activity and immunoreactivity. However, the nonglycosylated form of PRL is the predominant form of PRL secreted into the circulation (Brue, et al; 1992). Modification of PRL also includes phosphorylation, deamination and sulfation.

Most, if not all, variants of PRL are the result of posttranslational modifications. Little PRL probably represents a splicing variant resulting from the proteolytic deletion of amino acids. Big PRL can result from the failure to remove introns; it has little biologic activity and does not cross-react with antibodies to the major form of PRL. The so-called big big variants of PRL are due to separate molecules of PRL binding to each other, either noncovalently or by interchain disulfide bonding. Some of the apparently larger forms of PRL are PRL molecules complexed to binding proteins. High levels of relatively inactive PRL in the absence of a tumor can be due to the creation of macromolecules of PRL by anti-PRL autoantibodies (Hattori and Inagaki, 1997). Overall, big PRL account for somewhere between 10% and 25% of the hyperprolactinemic reported by commercial assays (Smith, et al; 2002).

At any one point of time, the bioactivity (e.g., galactorrhea) and the immunoreactivity (circulating level by immunoassay) of PRL represent the cumulative effect of the family of structural variants despite that immunoassays do not always reflect the biologic situation (e.g., a normal PRL level in women with galactorrhea). Some authors consider women with galactorrhea without HP to have sensitive breasts to trivial stimuli but no evidence supports this postulation.

High blood level (350-400 ng/mL) of PRL composed predominantly of high molecular weight PRL has been reported in a woman with oligomenorrhea and galactorrhea but with no evidence of a pituitary tumor (Jackson, et al; 1985). Big PRLs can also be secreted by pituitary adenomas (Vallette-Kasic, et al; 2002). High levels of relatively inactive PRL in the absence of a tumor can be due to the creation of macromolecules of PRL by anti-PRL autoantibodies (Cook, et al; 1991). Explanations for clinically illogical situations can be found in the variable molecular heterogeneity of the peptide hormones. At any one point in time, the bioactivity and the immunoreactivity of PRL represent the cumulative effect of the circulating family of structural variants. Another illogical situation occurs with large prolactinomas. When clinical and imaging evidence indicates the presence of a large pituitary tumor and PRL levels are low, serial dilutions can reveal very high levels. The falsely low levels are caused by an effect in the assay known as the high-dose hook effect (an extremely large amount of PRL prevents accurate assessment by the antibody in the assay) (Schofl, et al; 2002).

4. Clinical presentations of hyperprolactinemia (HP)

PRL hormone may increase in some physiologic situations that should be considered firstly. They include pregnancy, breast stimulation, breastfeeding, sexual intercourse, stress, exercise, sleep and postictal state. Pathologic HP typically it may cause oligomenorrhea, amenorrhea, galactorrhea, or infertility (Jones, 1995). In hyperprolactinemic women, the incidence of galactorrhea is up to 80%, depending on the diligence with which galactorrhea is sought (Vance and Thorner, 1987). HP may be found in 30% of women with secondary amenorrhea, and in 75% of women with both amenorrhea and galactorrhea (Schlechte, et al; 1980).

It is postulated that PRL acts on hypothalamo-pituitary–ovarian axis. PRL inhibits pulsatile secretion of GnRH and therefore gonadotrophin secretion and has a direct effect on the ovary itself which is supposed to be responsible for the menstrual disturbances that are seen with HP. The amenorrhoea associated with elevated PRL is due to an inhibition of the pulsatile secretion of GnRH. The pituitary gland in these patients responds normally to GnRH or in augmented fashion (perhaps because of increased stores of gonadotrophins), thus indicating that this mechanism of amenorrhoea is a decrease in GnRH (Sauder, et al; 1984). Short-term administration of an opioid antagonist suggests that inhibition is mediated by increased opioid activity (Cook, et al; 1991). However, chronic administration of naltrexone (a long-acting opioid antagonist) does not restore menstrual function (Matera, et al; 1995). Nevertheless, treatment that lowers PRL restores ovarian responsiveness and menstrual function. This is true whether the treatment consists of removal of PRL-secreting tumor or suppression of PRL secretion.

The increase in PRL levels observed in pathological HP results in effects equivalent to those observed during the postpartum period, namely inhibition of the release of GnRH from the hypothalamus and subsequent inhibition of LH and FSH, suppressed gonadal function and promotion of milk formation; this explains why HP is one of the most frequent causes of anovulation.

4.1 Why some women develop menstrual irregularities up to amenorrhea?

High prolactn bioavilability was recorded in women with HP and irregular cycles as well as women with hyperprolactinomas. biological activity of PRL was detected after polyethylene glycol (PEG) precipitation (Kostrzak et al., 2009). Moreover, Macroprolactin (macroprolactin), present in as many as 25% of serum specimens with elevated serum PRL concentrations, can cause apparent HP in the absence of clinical features and lead to unnecessary clinical, laboratory, and neuroradiological workups. Ultrafiltration as well as gel filtration chromatography are effective methods for the estimation of the monomeric PRL concentration of serum thus eliminating macro-PRL interference from PRL immunoassays (Quinn et al., 2006).

4.2 HP in unexplained infertility

Role of PRL estimation in cases with unexplained infertility may have no role except if associated with luteal phase defect (Glazener et al., 1987). It may have a definite role and commonly associated with hypothyroidism in many cases with unexplained infertility (Avasthi Kumkum et al., 2006). Our protocol of management of unexplained infertility is to search for HP in all cases prior to endoscopic evaluation.

4.3 HP and polycystic ovaries

The increased production of PRL observed in patients with PCO is usually transient and does not require treatment (Milewicz, 1984). PCO may be associated in up to 40%. Laparoscopic ovarian drilling may lead to HP in one small sample sized study (Parsanezhad et al., 2005). It is seen in 40% of polycystic ovarian syndrome (PCOS) patients (Conner and Fried, 1998). PCOS and Prolactinoma may co-exist and may need to be treated independently (Bracero and Zacur, 2001).

4.4 HP and sexual function

HP is a common hormonal disorder in women that may affect the phases of female sexual function (FSD). Kadioglu et al (2005) investigated sexual function in patients with HP. A total of 25 women with primary HP and 16 age matched voluntary healthy women who served as the as control group were evaluated with a detailed medical and sexual history, including a female sexual function index (FSFI) questionnaire and the Beck Depression Inventory. Serum PRL, dehydroepiandrosterone sulfate, free testosterone, androstenedione, 17alpha-hydroxyprogesterone, estradiol, free thyroxin and thyrotropin were measured. These variables were compared statistically between the 2 groups. Except for PRL serum hormone levels in women with HP were not different from those in the control group. The median total FSFI score was 23.40 (IQR 17.70 to 27.30) in the hyperprolactinemic group, whereas healthy women had a median total FSFI score of 31.10 (IQR 27.55 to 32.88, $p < 0.0001$). FSD was diagnosed in 22 of 25 patients (88%), while 4 of 16 healthy women (25%) had FSD ($p = 0.03$). Desire ($p = 0.001$), arousal ($p < 0.0001$), lubrication ($p = 0.001$), orgasm ($p = 0.001$), satisfaction ($p = 0.07$) and pain ($p = 0.003$) domain scores were also significantly lower in women with HP. Total FSFI ($p = 0.009$, $r = -0.405$), desire ($p = 0.001$, $r = -0.512$), arousal ($p = 0.002$, $r = -0.466$), orgasm ($p = 0.026$, $r = 0.348$) and satisfaction ($p = 0.041$, $r = -0.320$) scores negatively correlated with mean PRL but not with the other hormones measured. They concluded that a significant percent of women with HP whom we evaluated had sexual dysfunction. No hormonal changes other than PRL and no depression were found as a cause of FSD. We think that these changes could be attributed to anolvulation with subsequent estrogen deprivation.

4.5 Common causes of pathologic HP

Hypothalamic and pituitary causes include Pituitary tumors: micro- or macroprolactinoma, craniopharyngioma, meningioma, dysgerminoma, glioma, chordoma, mixed GH-PRL & adrenocorticotrophic hormone-PRL adenomas, non functioning pituitary adenoma, metastases, hypothalamic stalk interruption, hypophysitis (inflammation), Acromegaly, Cushing's syndrome, Empty Sella syndrome, Rathke's cysts or Infiltrative diseases (tuberculosis, sarcoidosis, histiocytosis X). Medications may induce hyperprolctinemia like Anti-psychotics (phenothiazines, haloperidol, butyrophenones, risperidone, monoamine oxidase inhibitors, fluoxetine, sulpiride), Anti-emetics (metoclopramide, domperidone), Antihypertensives (methyldopa, calcium channel blockers, reserpine), Tricyclic antidepressants (amitriptyline, amoxapine, imperamines), Opiates (morphine, methadone), estrogens and antiandrogens, Verapamil, Protease inhibitors, H_2 antagonists (cimetidine , ranitidine), or Cocaine. Chest wall injury (trauma, surgery, herpes zoster) or spinal cord lesions represent common neurogenic causes. Renal failure or hepatic insufficiency are commonly associated with HP due to disturbed PRL elimination (Melmed, 2001).

4.6 Pituitary prolactin-secreting adenomas

Marked increases in PRL are usually caused by a prolactinoma, a functional adenoma of the lactotroph cells. HP is associated with a PRL-secreting adenoma in almost half of all cases. A markedly high level of PRL (>100 ng/mL) confers a greater risk of having a prolactinoma. It is found in 10-20% of the normal population and account for 25-30% of functioning pituitary tumors identified at autopsy and are the most frequent cause of persistent HP (Mah and Webster, 2002). Probably as many as one-third of patients with secondary amenorrhoea have a pituitary adenoma, and if galactorrhea is also present, half have an abnormal sella turcica (Schlechte, et al; 1980). The clinical symptoms do not always correlate with the PRL level, and patients with normal PRL levels can have pituitary tumors (Speroff, et al; 1979). The highest PRL levels, however, are associated with amenorrhoea, with or without galactorrhea. Prolactinoma is less common in men than in women, typically presenting as an incidental finding on a brain computed tomography (CT) scan or MRI, or with symptoms of tumor mass effect (Kaye, 1996). It is usually associated with markedly increased PRL (>100 ng/mL), but nonfunctioning adenomas and other tumors are sometimes seen with mildly increased PRL. Macro HP should be considered when the PRL is very high, clinical symptoms are mild, and there are no evidence of a prolactinoma. An occasional case has been reported where oligomenorrhoea with Galactorrhea presented with high levels of PRL (350–400 ng/ml) composed of predominantly high molecular weight but with no evidence of pituitary tumor (Vallette-Kasic, et al; 2002). These high levels of relatively inactive PRL, in the absence of a tumor may be due to the creation of macromolecules of PRL by anti-PRL antibodies (Hattori, et al; 1992).

Dopamine-agonists are the treatment of choice of PRL-secreting pituitary adenomas (prolactinomas). Their actions on D2 dopamine receptor (DRD2) and the clinical outcome may be affected by polymorphisms. Prolactinomas are well-differentiated endocrine tumors expressing DRD2. DRD2 polymorphisms correlate with neuropsychiatric disorders, in particular alcoholism and schizophrenia. Some DRD2 polymorphisms, particularly TaqIA, TaqIB and NcoI, are associated with different receptor binding in brain areas. One study carried out on patients with prolactinomas found a correlation between NcoI and TaqIA and resistance to CB. In particular, resistant patients had higher prevalence of NcoI-T allele than the responsive patients, while the commonest haplotype (having TaqIA2 allele) was associated with better response. Only one study was carried out to analyze the role of DRD2 polymorphisms in prolactinomas response to CB. Further studies, including pituitary and hypothalamus in vivo determination of DRD2 binding according to DRD2 genotypes, investigation of possible post-receptorial mechanisms involved, as well as population studies in collaboration with psychiatrists and neurologists, are needed (Filopanti et al., 2010).

4.7 Diagnosis of HP

The diagnosis of HP should be included in the differential diagnosis of female patients presenting with oligomenorrhoea, amenorrhoea, Galactorrhea or infertility or for male patients presenting with sexual dysfunction.

History: Women typically present with a history of oligomenorrhoea, amenorrhoea or infertility which generally results from PRL suppression of GnRH. Galactorrhea is due to

the direct physiologic effect of PRL on breast epithelial cells. Pregnancy always should be excluded unless the patient is postmenopausal or has had a hysterectomy. In addition, HP is a normal finding in the postpartum period. Men typically present with complaints of sexual dysfunction, visual problems or headache and are subsequently diagnosed with HP in the evaluation process. PRL suppresses GnRH, causing a decrease in LH and FSH, ultimately leading to decreased serum testosterone levels and hypogonadism (loss of libido, impotence and infertility). Prolactinoma in men also may cause neurological symptoms, particularly visual-field defects. In both sexes, the presence of pituitary tumor may cause visual-field defects, headache, cranial nerve palsies and anterior hypopituitarism (hypoadrenalism and hypothyroidism) especially with macroprolactinomas. Headaches are definitely correlated with the presence of a pituitary adenoma (Strebel, et al; 1986). Although they are usually bifrontal, retro-orbital, or bitemporal, no locations or features are specific for pituitary tumors. Most patients with prolactinoma (the most common type of pituitary adenoma) are women. Most prolactinomas in women are small at the time of diagnosis, and headaches and neurological deficits are rare. Other common conditions to exclude a history of chest wall surgery or trauma, renal failure and cirrhosis (history of alcohol abuse). A drug history is essential because numerous medications have been linked to HP (as mentioned before), usually with PRL levels of less than 100 ng/mL. When drug etiology is suspected, a 1-month trial period off the medicine can be attempted with subsequent remeasurement of serum PRL. Diagnostic challenges can occur in cases when it would be imprudent to stop a medication (i.e., a neuroleptic) and the PRL level is mildly high.

Physical examination: Physical findings most commonly encountered in patients with HP are galactorrhea and occasionally visual-field defects. Visual field Goldman's perimetry is required only in patients in whom tumors are adjacent to or pressing on the optic chiasm, as visualized on MRI. Abdominal examination may give clues for cirrhosis. Generally, HP is discovered in the course of evaluating a patient's presenting complaint (i.e., amenorrhoea, galactorrhea and erectile dysfunction). Typically, the diagnosis is made via the aid of laboratory studies.

4.8 Laboratory serum PRL estimation

In brief, HP is diagnosed when, on more than one occasion under defined conditions, serum levels exceed the upper limit of normal for the particular PRL assay. In the commonly used assays, normal PRL levels in men and women are usually quoted as being <20 µg/L and <25 µg/L, respectively (1 µg/L equivalent to 21.2 mU/L). The defined conditions are a fully awake, fasting individual (for 8-10 hours) with no prior breast or pelvic examination, exercise or sexual activity, in the follicular phase of the menstrual cycle if menses are occurring and is under no significant emotional or physical stress (Zacur, et al; 1997). Plasma levels of PRL demonstrate diurnal variations, where the highest levels are observed during sleep (between 3 am and 9 am) and the lowest levels during waking hours. Thus, PRL secretion is subject to a circadian rhythm and levels should be measured (i.e.; sample should be collected) in the morning (between 9 am and 12 noon) (Biller, et al; 1999). Stress, including nervousness about the blood test can also elevate PRL levels. Mild stress, including the stress of venepuncture, can induce transient elevations in serum PRL, which needs to borne in mind before making a firm diagnosis and proceeding to further investigation. These physiological factors should be taken into consideration in the diagnosis of HP.

Normal levels are typically 10–28 µg/L or <25 µg/L (625 mU/litre) in women and 5–10 µg/L or <20 µg/L (375 mU/litre) in men (1 µg/L equivalent to 21.2 mU/L). However, the reference range for most laboratories is skewed, and a reference range up to 35 µg/L (700 mU/L) may be more appropriate in premenopausal women (Davis, 2004). A mildly increased PRL level (<70 ng/mL) should prompt a repeat test under controlled conditions. Pathological HP should be suspected in patients with a PRL concentration of consistently more than 700–900 mU/litre with no identified physiological or drug cause. PRL levels lower than 100 µg/L may be observed with all causes of HP, while levels exceeding 100 µg/L are usually indicative of a prolactinoma. While the values are certainly not absolute, the recently published guidelines from the Pituitary Society (Casanueva, et al; 2006) suggest that PRL values up to 100 µg/L (2000 mU/L) may be due to psychoactive drugs, estrogens, idiopathic causes or even microprolactinomas, whereas macroprolactinomas are typically associated with levels >25 µg/L (>5000 mU/L). Evidence from a large series suggests that PRL level in non-functioning pituitary adenomas (causing stalk disconnection HP) is almost always <100 µg/L (<2000 mU/L) (Karavitaki, et al; 2006). Levels >1000 ng/ml are associated with locally invasive tumors. Very high PRL levels greater than 2000–3000 ng/ml are probably the result of invasion of cavernous sinuses with release directly into the blood stream. If patients of renal insufficiency take medicines like metoclopramide or methyldopa known to alter the hypothalamic regulation of PRL, PRL levels may rise to over 2000 ng/ml (Hou, et al; 1985). This is based on studies which have shown that levels ≥100 ng/ml are almost diagnostic of PRL microadenoma while the levels between 50 and 100 ng/ml have a 20% risk of having the tumor (Blackwell, et al; 1979). The correct diagnosis can be made using PRL chromatography and polyethylene glycol (PEG) immunoprecipitation (Yuen, et al; 2003). It is more appropriate to employ the PEG precipitation in cases with asymptomatic HP, than repeating measurements of serum PEG level or performing radiological examinations like MRI or CT scan of the pituitary gland as the macroaemia may be the cause but the clinical significance of macroprolactinemia has not been explained yet and is the subject for the future investigations.

Fallacies: Sometimes high levels of relatively inactive PRL in absence of tumor can be due to the creation of macromolecules of PRL by antiPRL autoantibodies (Strachan, et al; 2003). Occasionally in presence of a large pituitary tumor falsely low levels are caused by an effect known as high dose hook effect" where extremely large doses of PRL prevent accurate assessment by antibody assay.

4.9 Other laboratory tests

Pregnancy testing is required unless the patient is post menopausal or has had a hysterectomy. Current TSH assays are very sensitive for detecting hypothyroid conditions. T3, T4 and TSH are done to rule out compensated or primary hypothyroidism. Both of them may be found in cases of HP (elevated TSH with low free T4. Measuring blood urea nitrogen and creatinine is important for detecting renal failure. Patients with macroadenoma should be evaluated for possible hypopituitarism. Initial basal determinations of pituitary and target organ hormones, as well as IGF-1, are measured routinely in order to rule out possible secondary hypoadrenalism and hypothyroidism associated with significant pituitary disease, and to exclude excess GH co-secretion from mammosomatotroph pituitary tumors. Male patients should have testosterone levels checked. Many patients with

acromegaly have PRL co-secreted with GH. Anyone thought to have acromegaly should be evaluated with an IGF-1 level measurement and a GTT for nonsuppressible GH levels if needed.

4.10 Radioimaging

Patients with persistent HP should be investigated for possible structural pathology in the hypothalamo-pituitary region, after other common causes have been excluded.

Cone-down view: With newer accurate imaging techniques, cone down lateral view X-ray of sella turcica is no longer the investigation of choice.

CT scanning: When other causes of HP have been excluded, the diagnosis of Prolactinoma is confirmed by gadolinium-enhanced pituitary MRI, though CT with contrast is an alternative. CT scan can detect microadenomas of 2 mm diameter and presence of any suprasellar extension if thin sections and coronal view are obtained. CT scanning (capable of high-resolution 1.5-mm cuts) is able to evaluate the contents of the sella turcica as well as the suprasellar area; however, total accuracy is not achieved (Teasdale, et al; 1986).

MR scanning: MRI is even more sensitive than the CT scan, but it is also more expensive, and it requires a lengthy period of time to obtain the images. MRI provides highly accurate assessments without biologic hazard, and it is better for evaluation of extrasellar extensions and the empty sella turcica (Stein, et al; 1989). Most neuroradiologists and neurosurgeons prefer MRI, as do we. The intention of this workup is to be conscious of cost and to isolate those few patients who require sophisticated but expensive imaging. MR scanning is currently the radiological investigation of choice (Rennert and Doerfler, 2007) because it has a resolution of 1mm and is more sensitive than CT, with the use of gadolinium enhancement increasing the detection of microadenomas. If MRI is contra-indicated or inappropriate, a CT scan with intravenous contrast is the best available option, although frequently repeated scans do entail a significant radiation dose, particularly important with regard to the eyes. Patients with macroadenomas that might impinge on the optic apparatus should undergo formal visual field assessment (e.g. by Goldman perimetry or by computerized charting).

The indications for radio-imaging are:

- Serum PRL level > 100 ng/ml (Bayrak, et al; 2005). However, a recent retrospective study of 104 women with HP suggested that pituitary imaging should be performed in all patients with persistently elevated PRL levels, as pituitary tumors may be observed even in patients with PRL levels just exceeding the normal range (Bayrak, et al; 2005).
- Presence of headaches and visual field defects.
- Abnormal X-ray cone down view of the sella turcica.

With increasing use of these modalities, incidental discovery of pituitary microadenomas is seen in 10% of individuals having normal PRL levels. These tumors are called pituitary incidentalomas (Hall, et al; 1994). Macroadenoma by definition is more than 1 cm and imaging techniques now identify suprasellar extensions, compression of optic chiasma and invasion of cavernous sinus. Therefore, the presence of an MR-scan-detected pituitary adenoma in a patient with HP is suggestive but not absolutely diagnostic that the lesion is a Prolactinoma. On the other hand, no demonstrable lesion may be seen in these patients even on high-resolution imaging, suggesting that they either harbour a microadenoma <2 mm in diameter, or that they have lactotroph hyperplasia or idiopathic 'non-tumoral' HP.

5. Treatment of HP

Goals of treatment of HP

- Elimination of symptoms like galactorrhea and amenorrhoea.
- Induction of ovulation.
- Treatment of PRL secreting macroadenomas.

Recognized indications for therapy include hypogonadism (oligo-/amenorrhoea, infertility, impotence, osteoporosis/osteopenia), tumor mass effect, and significant or troublesome Galactorrhea (Colao, et al; 1998).

Prior to any pharmacological intervention, it is essential to exclude potential physiological or pharmacological causes of HP. The preferred treatment for patients with secondary causes of elevated PRL may be to remove the relevant stimuli. For example, this may involve suspension of a particular medication or measures to reduce stress levels (Biller, et al; 1999).

Treatment options of HP

- Expectant management.
- Medical treatment.
- Surgical intervention.
- Radiotherapy.

5.1 Expectant management

Where no tumor is seen on imaging and there is absence of symptoms like galactorrhea, infertility, menstrual disturbance or hypestrogenism one can use the expectant line of management with serial monitoring of PRL levels and a CT scan every 2 years. Asymptomatic patients may not require treatment (Webster, 1999) and periodic observation should then suffice. Studies examining the natural history of untreated microprolactinomas have shown that significant growth of these tumors is uncommon (Whitaker, et al; 1983). Women with HP but normal regular menses are not at risk of osteoporosis and, again, periodic observation should suffice (Davis, 2004).

5.2 Medical treatment

Medical treatment of HP is recommended to restore menses in young, amenorrheic women concerned about bone loss or to initiate ovulation in anovulatory hyperprolactinemic women who desire to conceive. When symptoms are present, medical therapy is the treatment of choice. Medical therapy affords the greatest benefit to risk ratio and is generally considered the primary therapy of choice when some intervention is warranted.

Indications for medical treatment in women who do not wish to become pregnant include induction of normal menstrual cycles and prevention of potential long-term complications, such as bone loss. Normal conception can occur in some patients and HP is not a reliable contraceptive; oral contraceptives can be given safely to women with HP as these agents do not affect the growth of microadenomas (Testa, et al; 1998). Hormone replacement therapy may be considered in patients with HP-induced amenorrhoea as a means to reduce the risk of bone loss (Franks, et al; 1983). Patients on medications that cause HP should have them

withdrawn if possible. Patients with hypothyroidism should be given thyroid hormone replacement therapy. In cases of HP due to psychoactive medications, it is considered unwise to initiate DA therapy for the fear of precipitating a psychotic crisis (Peter, et al; 1993). In most such situations, the exclusion of any significant co-existing hypothalamo-pituitary structural lesion is necessary. Occasionally, psychiatric management can be adjusted and drugs substituted, for example olanzapine, which is said to have a lesser effect on PRL secretion (Karagianis and Baksh, 2003).

The approach to Prolactinomas has changed in the last 25 years, thanks to availability of dopaminergic drugs, characterized by a potent PRL inhibitory effect, a tumor-shrinking effect associated with a satisfactory tolerability. It is considered as the main stay of treatment.

5.2.1 Dopamine treatment

Interestingly, the discovery of a human PRL molecule resulted in the detection of specific reproductive endocrine disorders (e.g., galactorrhea and amenorrhoea), and this event occurred simultaneously with the discovery of a very specific drug capable of lowering PRL levels. From animal experiments performed in the late 1960s and early 1970s, dopamine inhibition of pituitary PRL secretion was suspected (Zacur, et al; 1976). In the 1950s Shelesnyak demonstrated that implantation in the rat could be inhibited by ergot alkaloids, and this action could be reversed with concomitant administration of either progesterone or PRL (Shelesnyak, 1958). It was then shown that this effect could be observed with the ergot alkaloid, ergonovine, and that its action took place at that level of the pituitary gland (Zeilmaker and Carslen, 1962). This resulted in the development by Sandoz Pharmaceuticals (Basel, Switzerland) of 2-Br-alpha-ergocryptine mesylate, also known as CB-154, BC mesylate, or Parlodel. BC was soon found to be effective in the treatment of galactorrhea (Besser, et al; 1972) and to inhibit PRL secretion in men (Del Pozo, et al; 1972).

Dopamine is an endogenous ligand for PRL-secreting cells, binding to cell surface dopamine receptors. Dopamine receptors have been classified into D1 and D2 subtypes, based upon physiological or biochemical responses (Levey, et al; 1993). To date, five dopamine receptor subtypes have been identified, either D1-type (D1 and D5; also known as D1A and D1B) or D2-type (D2, D3 and D4; also known as D2A, D2B and D2C) (Melmed, 1997). Dopamine receptors are located both centrally and peripherally: both D1 and D2 receptors are located in the substantia nigra and striatum, limbic cortex and associated structures (Levey, et al; 1993); D2 receptors are found on the cell surface of lactotroph cells (Schoors, et al; 1991). Peripherally, D1 receptors are located in blood vessels and the proximal tubule cells (Jose, et al; 1998); D2 receptors are found in sympathetic nerve terminals (Mannelli, et al; 1997). The location of specific D1 and D2 receptors has therapeutic implications; selective drugs that act predominantly on one subtype would be anticipated to be associated with fewer side effects than DAs that act on both D1 and D2 receptors. Binding of DAs to dopamine D2 receptors on the surface of lactotroph cells reduces AC activity and inhibits PRL secretion (Melmed, 1997). Several DA therapies are available for the treatment of HP and are outlined in the following table (Hutchinson and Zacur, 1997):

	Bromocriptine (BC)	Cabergoline (Dustinex)	Quinagolide (Norprolac®)
Dopamine receptor target sites	D1 and D2	D1 (low affinity) and D2 (high affinity)	D2
Duration of action	8–12 h	7–14 days	24 h
Half-life (hours)	3.3	65	22
Available doses	1.0 and 2.5 mg scored tablets; 5 and 10 mg capsules	0.5 mg scored tablets	25, 50, 75 and 150 µg tablets
Typical dose	2.5 mg/day in divided doses	0.5 mg/week or twice-weekly	75 µg/day
Dosing regimens, starter packs, dosage	Start on 1.25–2.5 mg/day at bedtime. Gradually increase to a median of 5.0–7.5 mg/day and a maximum of 15–20 mg/day	Start at 0.25–0.5 mg twice-weekly. Adjust by 0.25 mg twice-weekly up to 1 mg twice-weekly every 2–4 months according to serum PRL levels	Start at 25 µg/day. Increase over 1 week up to 75 µg/day. Starter pack (3× 25 µg tablets + 3× 50 µg tablets) allows quick and convenient titration
Advantages	Long history of use; does not appear to be teratogenic (Czeizel, et al; 1989); inexpensive	Good efficacy; low frequency of adverse events; may be useful in BC-resistant patients (Ferrari, et al; 1997); weekly or twice-weekly dose	Good efficacy and tolerability (Webster, 1996); once-daily dosing; simple titration; pituitary selective; use to the time of confirmed pregnancy
Disadvantages	Tolerance; recurrence (Van't Verlaat and Croughs, 1991); resistance; multiple daily dosing	Not yet indicated for use during pregnancy	Not currently available in the USA or Japan
Contraindications	Documented hypersensitivity; ischemic heart disease, uncontrolled hypertension, peripheral vascular disorders; breastfeeding	Documented hypersensitivity; ischemic heart disease, uncontrolled hypertension, peripheral vascular disorders; breastfeeding	Documented hypersensitivity; decreased kidney or liver function
Precautions	Caution in renal or hepatic disease; generally stopped during pregnancy but can be restarted if symptoms recur; perform regular visual-field testing during	Caution in renal or hepatic disease; generally stopped during pregnancy but can be restarted if symptoms recur; perform regular visual-field testing during pregnancy to monitor for	May cause dizziness or hypotension

	Bromocriptine (BC)	Cabergoline (Dustinex)	Quinagolide (Norprolac®)
	pregnancy to monitor for tumor growth; should be given to minimize postural hypotension or nausea	tumor growth; should be given to minimize postural hypotension or nausea	
Interactions	Toxicity may increase with ergot alkaloids; amitriptyline, butyrophenones, impiramine, methyldopa, phenothiazines and reserpine may decrease effects	Toxicity may increase with ergot alkaloids; amitriptyline, butyrophenones, impiramine, methyldopa, phenothiazines and reserpine may decrease effects	Not established
Pregnancy	Usually safe but benefits must outweigh the risks	Usually safe but benefits must outweigh the risks	
Common side effects	Nausea, headache, dizziness, abdominal pain, syncope, orthostatic hypotension, fatigue	Milder and less frequent compared with BC	Milder and less frequent compared with BC (Rohmer, et al; 2000)

DAs play a major role in the management of both idiopathic/non-tumoral and prolactinoma-related PRL excess. These agents act on dopamine D2-type receptors on pituitary lactotroph cells, resulting in a decrease in synthesis and release of PRL (Vallar, et al; 1988). By mechanisms yet to be fully understood, DA therapy is known to cause marked and sometimes dramatic reductions in prolactinoma tumor volume (Webster, 1999).

The majority of medications used to treat PRL disorders are ergot-derived, quinagolide only is not ergot-derived. While all three lower serum PRL on oral administration and also reduce tumor size, they differ in their affinity for D2 receptors and plasma half-life. CAB has the highest affinity and greatest selectivity for D2 receptors. The half-lives of CAB, quinagolide and BC are 65 h (Rains, et al; 1995), approximately 24 h and 8–12 h, respectively, thereby influencing the dosing regimen. A study of 85 patients with macroadenomas, 65 of whom had received previous DA therapy, found that PRL normalized in 61.2%, and a decrease of at least 75% of pretreatment levels was seen in another 28.2% (Ferrari, et al; 1997). Menses resumed in 79.5% of premenopausal patients. Only 4.7% of patients discontinued therapy due to adverse events. Other DAs are lysuride, terguride and metergoline are available.

5.2.2 Bromocriptine

BC ((2-bromo-α-ergocryptine) mesylate) was developed in the 1970s as the first of the DAs to be introduced for pituitary disease, and there is a wealth of data regarding its safety and efficacy (Molitch, et al; 1985) in addition to clinical experience. It is a lysergic acid derivative with a bromine substitute at position 2 (Vance, et al; 1984). The ergot-derivative, BC, stimulates D2-type dopamine receptors on lactotroph cells of the anterior pituitary to reduce PRL secretion (Factor, 1999). However, BC is also able to both antagonize and stimulate D1-

type receptors, resulting in mild adrenal side effects (Bankowski and Zacur, 2003). BC has the longest history of use for the treatment of HP and is well established as a safe and effective therapy (Essais, et al; 2002). Its serum levels peak after 3 h of administration and nadir is at 7 h with very little BC detectable in the circulation after 11–14 h (Molitch, 2001). The biological activity parallels the serum level, but there is continued biological effect even with undetectable serum level. PRL-secreting tumors do not have inactivating mutations in the dopamine receptor gene; thus, DAs can bind and exert inhibitory activity (Friedman, et al; 1994). The oral dose that suppresses PRL is 10 times lower than that which improves the symptoms of Parkinson's disease.

Dosage:

1. Orally:
- Therapy is begun at a low dose (1.25 mg) at bed time with a snack then the dose is typically increased (Brue, et al; 1992).
- It is available as the methane-sulfonate (mesylate) in 2.5 mg tablets. Tablet of 2.5 mg given in a twice daily dose over the course of several weeks as half-life is 8-12 hours. It can be increased to 10 mg/day.
- Slow release oral preparation is also available to be given once a day in a dose of 5 to 15 mg/day and is equally effective with the same side effects, severity and prevalence (Brue, et al; 1992). It is slowly absorbed by the gastrointestinal tract due to the creation of a special capsule. A single oral dose of this preparation can suppress PRL levels for 24 hours (Weingrill, et al; 1992).
2. Long acting depot intravenous injection:
    They are made by embedding glucose initiated polyglycolide microspherules and have a maximum degradation time of 3 months (Espinos, et al; 1994). They are given in a dose of 50 to 75 mg/month. Since response to these injections is rapid they are useful in large tumors with visual field impairment (Beckers, et al; 1992). It has the same severity of side effects as the oral preparation (Brue, et al; 1992).
3. Intravaginal
    It is given in a similar dose of 5 to 10 mg/day. Since it avoids direct contact with the intestinal mucosa it has lesser side effects than oral administration although it provides excellent clinical results (Katz, et al; 1989). So it can be tried when side effects are not tolerated (Ricci, et al; 2001). The levels are sustained for a longer time as it escapes the liver first pass effect when given vaginally and therapeutic results are achieved at a lower dose.

A challenging clinical situation arises when a macroadenoma undergoes symptomatic enlargement during pregnancy. The rationale for using BC during pregnancy for a symptomatic macroadenoma is that:

1. BC shrinks macroadenomas in nonpregnant patients and,
2. The fetal and maternal risks of BC are probably less than the risks of transsphenoidal surgery.

The evidence to support the use of BC for a symptomatic macroadenoma is limited to case reports. The manufacturer of BC collected a series of case reports (Weil, 1986) in which BC was reinstituted after a macroadenoma became symptomatic or used continuously throughout pregnancy. BC was effective at controlling symptoms and preventing the need

for surgery in 44 of 46 patients in whom it was restarted for increasing symptoms attributable to a macroadenoma.

Results

There is no question that macroadenomas will regress with BC treatment (Essais, et al; 2002). In 22 clinical trials with BC, in addition to ameliorating the clinical symptoms of HP (amenorrhoea, Galactorrhea or hypogonadism) in 80% of patients with HP but no demonstrable tumors (Cuellar, 1980), these patients had restored menses. The average treatment time to the initiation of menses was 5.7 weeks. BC is known to normalize PRL levels in 80–90% of patients with microprolactinomas (Jeffcoate, et al; 1996) and nearly 70% of those with macroprolactinomas, together with tumor shrinkage (Bevan, et al; 1992).

The availability of BC to reduce tumor size in humans was initially reported by Corenblum and his colleagues (Corenblum, et al; 1975). Since then, of 248 patients reported in 21 series, 76% had some tumor size decrease in response to BC with period of observation ranging from 6 weeks to more than 10 years (Molitch, 2001). Eight series totaling 112 patients quantified the tumor size reduction as well as finding that 45 patients (40.2%) had a greater than 50% reduction in tumor size, 32 (28.6%) a 25–50% reduction in tumor size, 14 (12.5%) a less than 25% reduction, and 21 (18.7%) no evidence of any reduction in tumors.

In a multicentre study of 29 patients with macroprolactinomas, BC successfully normalized serum PRL levels in 27 patients over a mean period of 6 months and reduced tumor size by more than half in 62% of patients (Essais, et al; 2002). In a study investigating the treatment of PRL-secreting microprolactinomas, BC treatment reduced PRL levels in all of the 36 female patients (Moriondo, et al; 1985). A retrospective study that evaluated the long-term effects of BC on PRL levels and pituitary size concluded that BC treatment of mild HP was effective after 9 years of follow up (Touraine, et al; 2001). Since it is highly genericized, BC is an inexpensive treatment for HP. BC causes regression of macroadenomas. In some shrinkage is seen even with low dose (5-7.5 mg/day) while in others large doses and prolonged duration may be required. Usually a dose of more than 10 mg is ineffective (Mori, et al; 1985). Visual improvement occurs within days and tumor shrinkage occurs in several days to 6 weeks, but in some cases it is not observed until 6 months or more. In most cases, reduction in tumor size can take place in several days to 6 weeks, rapid shrinkage occurs rapidly in first 3 months of therapy followed by slower reduction but in some cases it is not observed until 6 months or more (up to 2-3 years) (Mori, et al; 1985). Locally invasive tumors with levels of BC more than 1000 ng/ml show a good response to medical treatment. Problem with treatment of the tumor with this drug is that it has to be taken indefinitely. Indeed, surgical results with invasive tumors are so poor that long-term control with a DA is recommended. After 2 years therapy 75% of microadenomas and 80 to 90% of macroadenomas regress. On discontinuation of drug after 5 years only 25% patients remained normoprolactinemic (Webster, 2000).

Although tumor shrinkage is always preceded by a decrease in PRL levels, the overall response cannot be predicted by basal PRL levels, the absolute relative fall in PRL or even the attainment of normal PRL levels. Visual impairment improves rapidly, but maximal effect may take several months. However, a PRL level non-responder will be a tumor size non-responder. The response of macroadenomas to BC is impressive and a most compelling

reason in favour of its use is that it has been successful when previous surgery or radiation has failed (Corenblum, et al; 1975). BC causes not only a reduction in size of individual cells but also necrosis of the cells with replacement fibrosis (Mori, et al; 1985). Although improvement in sellar imaging occurs in some cases, however, the occurrence of spontaneous regression of PRL-secreting tumors makes it impossible to attribute cures to BC. There was 75% reduction in breast secretion by 6.4 weeks and galactorrhea was suppressed in 50-60% of patients by 12.7 weeks. It is important to advise patients that the cessation of galactorrhea is a slower and less certain response than restoration of ovulation and menses. Ovulation was restored within 5 to 6 weeks. Studies have shown successful ovulation induction and pregnancy with BC in the absence of galactorrhea or HP in previous nonresponders to clomiphin (Porcile, et al; 1990). Pregnancies that result from BC therapy do not appear to be at increased teratogenic risk (Czeizel, et al; 1989), even though BC crosses the placenta and lowers fetal PRL concentrations (Bigazzi, et al; 1979). Nevertheless, it is recommended that BC treatment be stopped when pregnancy is diagnosed to avoid potential risks to fetal neural development. Cessation of BC use during early pregnancy does not appear to increase the risk for spontaneous abortions (Turkalj, et al; 1982).

Side effects

However, while BC has been shown to be effective in the treatment of both micro- and macroprolactinomas, approximately 12% of patients experience adverse events even at low doses of BC; these patients are considered BC intolerant (Webster, et al; 1994). However, nearly 60% of patients develop side-effects (Ho and Thorner, 1988), mainly gastrointestinal (nausea, dyspepsia, abdominal pain). Other common problems include postural hypotension, dizziness, headache and faintness. The faintness is due to orthostatic hypotension which can be attributed to relaxation of smooth muscles in the splanchnic and renal bed as well as inhibition of transmitter release at noradrenergic nerve endings and central inhibition of sympathetic activity. Neuropsychiatric symptoms, occasionally with hallucinations, occur in less than 1% of patients. This may be due to hydrolysis of the lysergic acid part of the molecule. 10% patients show these intolerable side effects:

- Immediate effects:
  Nausea, headache, fatigue, dizziness, orthostatic hypotension, nasal congestion, vomiting, abdominal cramps and hallucinations.
- Long term effects (Soule and Jacob, 1995):
  Raynaud's phenomenon, constipation and psychiatric changes specially aggression.

To minimize these side effects we have to build tolerance by slowly increasing the dose (2.5 mg) at weekly intervals, instruct the patients to take the drug at bedtime, individualize the dosage schedule and use intravaginal route. It may help to take the tablet with a glass of milk and snack. The peak levels are achieved after 2 hours and the biologic half-life is about 3 hours. If intolerance occurs with this initial dose, then the tablet should be cut in half, and an even slower program should be followed. Usually a week after the initial dose, the second 2.5 mg dose can be added at breakfast or lunch. Patients who are extremely sensitive to the drug should be instructed to divide the tablets and to devise their own schedule of increasing dosage in order to achieve tolerance. A very small percentage of patients cannot tolerate any dosage.

One 2.5-mg tablet is inserted high into the vagina at bedtime. This dose provides excellent clinical results and few side effects (Ginsburg, et al; 1992). In contrast to oral BC, which is not absorbed completely and that which is absorbed is largely metabolized in the first pass through the liver, vaginal absorption is nearly complete, and avoidance of the liver first-pass effect (with longer maintenance of systemic levels) allows achievement of therapeutic results at a lower dose.

Because many patients with hyperprolactinemic anovulation require treatment to become pregnant, there is a large body of evidence on the fetal effect of first-trimester exposure to BC. There are two BC treatment methods to follow in those patients seeking pregnancy. The first is simply daily administration of 2.5 mg twice daily until the patient is pregnant as judged by the basal body temperature chart. In the second method, BC is administered during the follicular phase, and the drug is stopped when a basal body temperature rise indicates that ovulation has occurred, thus avoiding high drug levels early in pregnancy. The drug is resumed at menses when it is apparent the patient is not pregnant. No comparative study has been performed to tell us whether the follicular phase only method is as effective as the daily method. Furthermore, there has been no evidence that BC ingestion during early pregnancy is harmful to the fetus (Weil, 1986).

No adverse effect of BC has as yet been seen in early pregnancy (Turkalj, et al; 1982). They reported on the results of a surveillance project conducted by manufacturer of BC. Information was gathered on 1410 pregnancies in 1335 women. BC was stopped when the pregnancy was recognized, which typically occurred before 8 weeks of gestation. The incidence rates of spontaneous abortions (11.1%), ectopic pregnancies (0.9%), minor malformations (2.5%) and major malformations (1.0%) were low and not different from the expected complication rate in an unselected population.

The safety of BC exposure in utero has been evaluated by extensive monitoring including multi-centre study of 2587 pregnancies in 2437 women exposed to BC during part or all of gestation, with examination of offspring up to the age of 9 years. Although BC treatment profoundly lowers the maternal and foetal blood levels of PRL (Molitch, 1985), the drug does not appear to be associated with any increase in the risk of spontaneous abortion, congenital abnormalities, or multiple pregnancies and no adverse effects on postnatal development have been detected (Webster, 1996). Long-term follow-up studies of 64 children between the age of 6 months and 9 years, whose mothers took BC in this fashion, have shown no ill effect (Molitch, 2001). Although experience is limited to just over 100 women, no abnormalities were noted with the use of BC through out gestation except in one infant with an undescended testicle and one with talipes deformity (Molitch, 2001).

Nevertheless, because these data are relatively sparse as compared to data in over 6000 pregnancies with BC, BC is favored when fertility is the major reason for treatment. If BC is used to achieve pregnancy, it is stopped when pregnancy is confirmed. With this protocol, the risk of fetal malformation is no higher than the background risk. Patients using BC for infertility should undergo frequent evaluation for pregnancy to minimize fetal exposure to BC. Interestingly, some women restore cyclic menses after pregnancy. This spontaneous improvement may be due to tumor infarction brought about by the expansion and shrinkage during and after pregnancy and there may be a correction of hypothalamic dysfunction followed by disappearance of the associated pituitary hyperplasia.

Disadvantages of BC

- Recurrence:

Recurrence of symptoms occurred in 75% of patients with prolactinomas within 4 to 6 weeks on stopping of the drug. Amenorrhoea recurred in 41% of the patients within an average of 4.4 weeks of discontinuing treatment; galactorrhea recurred in 69% at an average of 6 weeks. Hence these drugs are used only for short-term purpose of achieving pregnancy, curing galactorrhea or reducing tumor mass (Hawkins, 2004).

- Resistance:
  5 to 18% of patients do not tolerate BC or are resistant to it due to decreased dopamine receptor on lactotroph cell membrane. In these cases other drugs can be tried.
- Perivascular fibrosis:
- It may cause perivascular fibrosis in tumors if given for a long time making surgery difficult.

BC has a short half-life (3.3 h), necessitating multiple daily dosing in order to reduce PRL levels. Numerous studies have demonstrated that the less frequent the dosing regimen, the higher the compliance; frequent dosing schedules have been found to reduce patient compliance (Moyle, 2003). Indeed, several studies have demonstrated that compliance with a once-daily dosing regimen can be approximately 73–79%, 69–70% with a twice-daily regimen, 52–65% for a three or 42–51% for a four-times daily regimen (Claxton, et al; 2001). Thus, therapies that offer patients a once-daily dosing regimen would be anticipated to improve patient compliance over therapies such as BC, which require more frequent dosing. In the past 20 years, agents with better side-effect profiles have been developed, notably CAB and quinagolide. Side effects and intolerance with one of these drugs is often solved by using another. A patient who fails to respond to one DA may respond to another.

Although a PRL level nonresponder will be a tumor size nonresponder, about 10% of patients will lower their PRL levels but fail to shrink their tumors (Bevan, et al; 1992). In some cases, the absence of shrinkage is due to cyst formation or tumor infarction. The response of macroadenomas to BC is impressive, and a most compelling reason in favor of its use is that it has been successful when previous surgery or radiation has failed (Bevan, et al; 1992). The problem, however, is that it must be taken indefinitely, because there is yet to be a convincing report of complete disappearance and resolution of tumor that can be attributed to drug therapy and not spontaneous resolution.

Light and electron microscopic, immunohistochemical, and morphometric analyses all indicate that BC causes not only a reduction in the size of individual cells but also necrosis of the cells with replacement fibrosis (Mori, et al; 1985). Nevertheless, PRL levels generally return to an elevated state after discontinuation of the drug. There are cases of improvement in sellar imaging; however, the occurrence of spontaneous regression of PRL-secreting tumors makes it impossible to attribute to BC. Recurrence of HP has been observed after as long as 4-8 years of treatment.

Assiut innovation

During the last decade, we were interested in improving the delivery mode of BC to overcome the common side effects and to increase its efficacy.

Previous work on vaginal BC

In the recent years, research has focused on the vaginal placement of commercial tablets as a logic alternative for patients who cannot tolerate oral treatment. Many studies have demonstrated the superiority of the vaginal over the oral route in terms of dramatic minimization of general and gastrointestinal side effects (Ginsburg et al., 1992, Merola et al., 1991, Merola et al., 1996, Katz et al., 1989). In practice, however, patients find placing orally designed tablets inside the vagina to be inconvenient, a source of local irritation, and a potential hindrance to sexual intercourse.

First innovation: Pluronic-BC combination (Darwish et al., 2005)

In, 2005 we succeeded to add a pluronic to BC to increase its absorption. The aims of this study were to create new formulations of bromocriptine vaginal suppositories that have improved pharmaceutical features and to test their clinical effectiveness and tolerability among hyperprolactinemic patients in comparison with vaginally inserted, commercial bromocriptine tablets. This study had two phases. The pharmaceutical phase was carried out at the Department of Pharmaceutics, Faculty of Pharmacy, Assiut University between May 2001 and August 2002. First, the preparation of vaginal suppositories incorporated 2.5 mg of bromocriptine mesylate (raw material supplied by Novartis Pharma Co., Cairo, Egypt) using a fusion method under ultraclean laboratory conditions. The suppositories were cone shaped, and weighed 1 gram; they were 20 mm in length and 424 mm3 in size. Second, the physical characteristics the suppositories were tested: weight variation, content uniformity, hardness, melting point, liquification time, and disintegration time. Third, in vitro release studies were performed to examine the type of base, partition coefficient of the drug, melting point of the base, hydroxyl number of the base, presence of additives, and concentration of additives. Last, we explored the interaction between the drug and suppository base using differential scanning calorimetry (DSC), and x-ray differactometer infrared spectroscopy (IR). Formulation A included the drug and a base (80% propylene glycol plus 20% polyethylene glycol 20000). Formulation B included Formulation A with solid dispersion with Pluronic F127, prepared by solvent evaporation method. The clinical phase was conducted at the outpatient infertility clinic of Assiut University hospital from September 2002 to August 2003. Fifty-four hyperprolactinemic patients were randomly divided into three groups using 2.5 mg of bromocriptine once daily for 1 month. Formulation A was used by 15 patients (group A), and formulation B was used by 20 patients (group B); commercial vaginal bromocriptine tablets (2.5 mg, Parlodel; Novartis Pharm Co., Cairo, Egypt) were used by 19 patients (group C). The pharmaceutical phase of the study showed an increased dissolution rate of bromocriptine/Pluronic F127 that was 39-fold greater than that of the pure drug alone. First-order release kinetic mechanisms were assessed for formulations A and B. Formula B exhibited a higher release rate constant (k _ 0.51 min_1) than formula A (k _0.048 min_1). The occurrence of in vitro and in vivo agreement can be explained by the presence of non-ion surfactant Pluronic F127. Clinically, most patients entered this study because of intolerance to the oral route (A: 11, 73.4%; B: 17, 85%; and C: 15, 79%, respectively). It was concluded that BC vaginal suppositories containing Pluronic F127 proved to be effective in lowering serum PRL (SP), were well tolerated by most of the patients, had minimal local irritative vaginal effects, and were more convenient for vaginal use than the tablet form.

Second innovation: Rectal approach of BC (Darwish et al., 2007)

Comparison of the rectal and the vaginal administration of the commercial bromocriptine tablets are not published so far. Rectal and vaginal lisuride hydrogen maleates were equally effective in lowering SP if compared with oral administration in a pilot study (Darwish et al., 2005). The pharmaceutical phase revealed that the release pattern of the rectal suppository of bromocriptine mesylate in phosphate buffer pH(7.4) was similar to that of the same formula in citrate buffer (pH 4) which created previously for vaginal use, their release rate constants were 0.60 min-1 and 0.51 min-1 respectively (4). The clinical part of the study comprised 42 female patients with definite high pretreatment SP levels who were randomly classified into two groups. Most of the patients accepted to enter this study due to intolerance to oral route (11(50%) vs. 17(85%)). it is concluded that the approached bromocriptine suppositories containing pluronic F127 were proved to be effective in lowering SP whether used vaginally or rectally. Rectal approach is more effective, has minimal side effects, more convenient for patients who don't accept to manipulate the vagina especially virgins, others fail to use the drug during menstruation, and those patients who believe that the drug may affect their fertility by interfering with sexual relationship. Furthermore, it can be used by intolerant hyperprolactinemic males.

Third innovation: Bioadhesive technology for BC (Darwish et al., 2008)

Transmucosal delivery of therapeutic agents is a popular method because mucous membranes are relatively permeable, allowing for the rapid uptake of a drug into the systemic circulation and avoiding the first pass metabolism. This efficient uptake offers several benefits over other methods of delivery and allows drugs to circumvent some of the body's natural defence mechanisms. Mucoadhesive drug delivery systems are being studied from different angles, including development of novel mucoadhesives, design of the device, mechanisms of mucoadhesion and permeation enhancement. With the influx of a large number of new drug molecules from drug discovery, mucoadhesive drug delivery will play an even more important role in delivering these molecules. We constructed a preliminary study which had two phases. A pharmaceutical phase, which was carried out at the departments of Pharmaceutics, Faculties of Pharmacy, El-Minia and Assiut Universities. It included formulation and evaluation of bioadhesive buccal and vaginal discs containing bromocriptine mesylate 2.5 mg as solid dispersion with pluronic F127 under ultra-clean laboratory conditions. Formulation of Bromocriptine mesylate/Pluronic F-127 solid dispersion passed through the same stages as previously described (7). The row material of bromocriptine mesylate 2.5 mg was kindly supplied by Memphis Co. for Pharm. and Chem. industry, Cairo, Egypt. A unidirectional bilayered buccoadhesive discs were formulated by mixing bromocriptine mesylate/Pluronic F-127 solid dispersion (which is equivalent to 2.5 mg of free bromocriptine mesylate) with bioadhesive polymers carbopol 974P, chitosan and the rest was lactose as a diluent. The mucoadhesive drug-polymer mixture (100 mg) was directly compressed on a previously obtained backing layer of Ethylcellulose (100 mg) using 13 mm diameter die by a hydraulic press machine. A compression force of 2 tones, for 30 sec was found to be satisfactory. The disc is called "unidirectional" because it contains a drug-free backing layer which modifies bromocriptine release towards the mucosa and a drug mucoadhesive layer containing a combination of bioadhesive polymers and bromocriptine mesylate. The prepared discs were of 200 mg total weight, 13 mm in diameter and average thickness of 2 mm. The swelling index, bioadhesion force, surface pH, in-vitro drug release and residence time of the prepared discs were evaluated. These buccoadhesive discs were

evaluated for release pattern, swelling capacity, surface pH, mucoadhesion performance, and in vitro permeation of bromocriptine mesylate through buccal membranes. In vivo testing of mucoadhesion time, strength of adhesion, irritation, bitterness due to drug swallowing and disc disintegration in the buccal cavity were performed. On the other hand, vaginal bioadhesive discs of bromocriptine mesylate (single layered) were formed by mixing bromocriptine mesylate/Pluronic F-127 solid dispersion (which is equivalent to 2.5 mg of free bromocriptine mesylate) with bioadhesive polymers including caobopol 974P, chitosan and the rest was lactose as a diluent. The mucoadhesive drug-polymer mixture (100 mg) was directly compressed using 7 mm diameter die by single punch tablet machine. The prepared discs were of 100 mg total weight, 7 mm in diameter and average thickness of 4 mm. The produced discs were evaluated for their swelling behavior, bioadhesion force, in-vitro drug release.   The clinical phase was conducted at the out-patient Infertility clinic of Women's Health hospital, Assiut University, from April 2004 to March 2007. Institutional Review Board (IRB) approval was obtained. All patients gave a written consent to participate in this study. In this study, we included all patients with pathologic HP who expressed intolerance or resistance to oral bromocriptine. We excluded patients who received oral PRL-normalizing drugs within at least 2 weeks before the pretreatment blood sample for PRL assay (SP) to ensure complete wash out of the drug. Search for HP was carried out by screening for serum PRL among infertile women with evident galactorrhea, amenorrhea or hypomenorrhea, patients with mastodynea, or infertile patients with sonographic suggestion of HP. Hyperprolactinemic patients (SP more than 20 ng/ml) were randomly divided into 2 groups. Randomization was done by means of a computer program using simple random sample. Neither the subjects nor clinicians involved in the study knew which study treatment was being administered to any given subject. Pharmaceutically, the studied buccal formula gave adequate comfort and compliance during at least 6 hrs. Likewise, tests for swelling, surface pH, in-vitro and in-vivo bioadhesion and in-vitro release expressed satisfactory results. Moreover, it has been shown that mucoadheisve discs containing Chitosan 10% and bromocriptine mesylate/pluronic F-127 solid dispersion expressed a relatively weak in-vivo adhesion (residence time) but when used in combination with Cp 974P (5% w/w) the overall in-vitro and in-vivo adhesions were improved. For vaginal discs, there was no change in the swelling behavior of the discs in pH 4.5 when compared to its swelling in pH 6.8 whereas the release is increased due to rapid disintegration of CS in acidic media. The in-vitro release of bromocriptine from the discs is increased in media pH 4.5 due to the rapid disintegration of chitosan. From this study, we concluded that introduction of bioadhesive technology for bromocriptine mysylate/pluronic F127 administration is valuable in achieving prominent serum PRL reduction in hyperprolactinemic patients in a relatively short duration of therapy. Both buccoadhesive and vaginoadhesive discs are of equal efficacy. Buccoadhesive discs have the advantage of being gender non-specific (i.e. could be used by males), avoidance of manipulating the vagina which is not convenient to some patients like virgins, independence on cyclic estrogen level, and could be used easily during menstruation.

Fourth innovation: Bioadhesive and pluronic F-126 (Darwish et al., 2007)

This study follows the WHO instruction for clinical trials design. The dose of vaginal application is settled in literature as 2.5 mg daily since a long time. This study was preceded by formulation of the drug in a suppository form containing Bromocriptine mesylate 2.87

mg (corresponding to 2.5 mg bromocriptine base) with pluronic F-126 in a special concentration to increase the absorption as a penetration enhancer. Adding Polycarbophil Bioadhasive gel was done which is a polymer that swells in the presence of water. Overall it has a slightly negative ionic charge which produces temporary adhesion to cell surface of the vaginal epithelium. In this study, we included all patients with pathologic HP we expressed intolerance or resistance to oral bromocriptine. We excluded patients who received oral bromocriptine within at least 2 weeks before the pretreatment blood sample for PRL assay to ensure complete wash out of the drug. A pilot phase was carried out on volunteers selected according to strict criteria. The primary endpoints are to assess the effectiveness of the new drug formulation, to investigate the safety including its side effects, and to study the dose-response relationship. It comprised 32 hyperprolactinemic patients who all gave written consent to participate in this study. The study was conducted from March 2004 to August 2004. Search for HP was carried out by screening for serum PRL among infertile women with evident galactorrhea, amenorrhea or hypomenorrhea, patients with mastodynea, or infertile patients with sonographic suggestion of HP. Hyperprolactinemic patients (SP more than 20 ng/ml) were randomly divided into 2 groups. Randomization was done by means of a computer program using simple random sample. Neither the subjects nor clinicians involved in the study know which study treatment is being administered to any given subject. Group A comprised 16 patients who used the new vaginal suppositories once daily for one month. Insertion of the suppository was done by the patient at night before sleep. Group B included 16 patients who used commercial bromocriptine tablets (Parlodel, Novartis Pharma, Egypt) inserted high in the vagina while lying on the back at the bed time once daily for one month. All patients had high pretreatment baseline SP and were advised to take the drug regularly in a fixed time. The patients were instructed to minimize touching nipples and to avoid eating various fowl which contain PRL-releasing factors during the course of therapy. Blood samples were drained from all cases at the start of treatment then every 2 hours thereafter till 16 hours from the start of therapy. Samples were tested for PRL using ELISA method as well as bromocriptine levels using high-performance liquid chromatographic assay of bromocriptine in plasma. Another sample was obtained from all patients at the end of one month of therapy to test for PRL level. Patients were asked to assess their experience with either approach of therapy. In both groups, there was a significant decline of the serum PRL. However, it was more significant in group A. Patient convenience was more evident and local side effects were less in group A than group B in the clinical phase. we conclude that the introduction of bioadhesive technology for bromocriptine mesylate/pluronic F-126 administration is valuable in achieving prominent serum PRL reduction in hyperprolactinemic patients in a relatively short duration of therapy. The formulated vaginal suppositories expressed better convenience with minimal local side effects if compared to vaginally administered commercial bromocriptine tablets. Due to the above demonstrated results, we safely recommend non-use of the commercial bromocriptine tablets for vaginal application.

5.2.3 Cabergoline

CAB is a more recent DA that has a better side effect profile (the most common side effect being headache) with a clinical efficacy similar to that of BC (Colao, et al; 2000). It is an ergot-derived DA (Espinos, et al; 1994) with high affinity for the D2 dopamine receptor (Ferrari, et al; 1986) and, while it can also act upon D1 receptors, it has only a low affinity for

these receptors. It is marketed in the US under the trade name Dostinex and received FDA approval in 1996 for the treatment of HP. CAB is a long-acting agonist capable of inhibiting pituitary PRL secretion for at least 7 days after single oral dosing (Cannavò, et al; 1999). Colao and others (Colao, et al; 2003) reported that in 26 patients with macroadenomas, normoprolactinemia was achieved 1 to 6 months after therapy in 21 individuals and after 24 months of therapy in the remaining 5 individuals.

This long-acting agent has a half-life of 65 h, meaning that dosing is performed on a weekly or twice-weekly basis. CAB is dispensed in 0.5 mg scored tablets. It is given in a dose of 0.5 to 3 mg once a week orally or vaginally, usually starting with a lower dose (half a tablet) at bed time with a snack of food. It was given at a dose of 0.25 mg once weekly for the first week, twice weekly during the second week and then 0.5 mg twice weekly. In clinical practice twice-weekly dosing using 0.25 mg is often effective in normalizing the PRL concentration (Verhelst, et al; 1999). CAB dosage in the majority of patients ranged from a total dose of 0.5 to 1.5 mg/wk given in two doses. For patients whose PRL concentrations did not rapidly decline, the dosage range was 1.5 to 7 mg/wk. Dosage changes were made every 2 to 3 months until PRL levels stabilized. After 2 months of treatment, increased doses of CAB were given to normalize PRL levels until a maximum dose of 3.5 mg per week (0.5 mg/day) was reached. In another recent study by Di sarno and his colleges (Di Sarno, et al; 2001) CAB, given up to a maximal dose of 7 mg/wk for 2 years, normalized serum PRL levels in 82% of patients with a macroadenoma and 90% of patients with a microadenoma within 6 months of initiating treatment. Normalization of PRL occurred in 64% of macroadenoma patients and 56% of microadenoma patients treated with BC for 2 years. Pituitary tumor shrinkage correlated with PRL normalization and on average occurred in 80-95% of patients whose PRL levels were normalized. CAB has been found to be better tolerated than BC, and more efficient in normalizing PRL level, improving gonadal function and achieving comparable tumor shrinkage (Di Sarno, et al; 2001). However, it is much more expensive. It normalized PRL and significantly reduced tumor size in the vast majority of patients (Biller, et al; 1996). CAB has been shown in men and women to effectively treat idiopathic HP, microadenomas and macroadenomas that are native to DAs with minimal side effects (Pontikides, et al; 2000). But it is less commonly used in women being treated for hyperPRLaemic infertility, although small case series do not suggest adverse pregnancy outcome (Robert, et al; 1996), despite the fact that this DA has demonstrated a good safety record in the small number (approximately 300) of cases in which it was taken during early pregnancy (Verhelst, et al; 1999). It is useful in BC resistant cases and is more effective in reducing tumor size and PRL levels than BC or quinagolide (Pontikides, et al; 2000).

The low rate of side effects and the once weekly dosage make CAB an attractive choice for initial treatment, replacing BC. Recent data demonstrate that CAB is also effective in treating HP in patients who have failed or were intolerant to treatment with BC (Webster, et al; 1994), which may be explained in part by the longer half-life of CAB, which results in fewer changes in drug concentration in the blood. A multicentre Belgian chart review including 102 males and 353 females with HP treated with CAB demonstrated that CAB normalized PRL levels in 86% of all patients (77% with macroadenomas and 91% with microadenomas or idiopathic HP). Of, these patients, 292 had been treated previously with BC; of these 140 were intolerant and 58 resistant. Tumor shrinkage was seen in 67% and visual fields normalized in 70%. Although 13% of patients experienced side effects only 3.9%

discontinued treatment because of these side effects. To achieve successful results, patients with macroadenomas were found to require higher doses of CAB (1.0 mg/wk vs. 0.5 mg/wk for patients with microadenomas). After CAB, the effects on micro- and macroProlactinomas showed PRL reduction of 95.6% and 87.5% and more than 80% tumor shrinkage in 30.4% and 31.2%, respectively. CAB shrank the microadenomas significantly more than quinagolide (48.6% vs. 26.7%, P = 0.046), but the results are statistically different for macroadenomas (47.0% vs. 26.8%, P = 0.2). In the BC-resistant patients, PRL normalized in 70% compared with 84% of patients with BC intolerance. CAB can also be administered vaginally for the rare patient who cannot tolerate it orally (Motta, et al; 1996).

BC vs. CAB: An evidence based comparison (Nunes et al., 2011)

Cabergoline and bromocriptine are the most used drugs in the treatment of HP, they are able to normalize the PRL levels, restore gonadal function and promote tumor reduction in the majority of patients. A meta-analysis of randomized controlled trials was undertook to compare cabergoline versus bromocriptine in the treatment of patients with idiopathic HP and prolactinomas. The data sources were: Embase, Pubmed, Lilacs and Cochrane Central. The outcome measures were: normalization of PRL secretion, restoration of gonadal function, reduction of tumoral volume, quality of life and adverse drug effects. The meta-analysis of normalization of serum PRL levels and menstruation with return of ovulatory cycle showed a significant difference in favor of cabergoline group (RR 0.67 [CI 95% 0.57, 0.80]) e (RR 0.74 [CI 95% 0.67, 0.83]), respectively. The number of adverse effects was significantly higher in the bromocriptine number than in cabergoline group (RR 1.43 [CI 95% 1.03, 1.98]). The meta-analysis showed new evidence favoring the use of cabergoline in comparison with bromocriptine for the treatment of prolactinomas and idiopathic HP.

Superiority of cabergoline over oral bromocriptine has been proved in many large sample sized studies. A multicentric study on 455 cases done in Belgium proved the high efficacy and tolerability of cabergoline (Vehelst et al., 1999). Nevertheless, this was a non comparative retrospective study of little clinical significance. CSF rhinorrhea has been reported with both bromocreptine and cabergoline since a long time (Bronstein et al., 2000, Hewage et al., 2000, Netea-Maier et al., 2006).

5.2.4 Quinagolide

Quinagolide (CV205-502) is the other second-generation DA but, unlike either BC or CAB, quinagolide is a non-ergot derived DA with a chemical structure similar to apomorphine. It also provides a safe therapeutic option and higher affinity for the dopamine receptor, so it is efficacious in patients with BC intolerance/resistance (Schultz, et al; 2000). Because it does not act as a D1 receptor antagonist as BC does, it causes fewer side effects and is a better specific D2 DA (Nordmann, et al; 1988). It has a half-life that is intermediate between BC and CAB (22 hours) and is administered daily at bedtime at dosage of 75 to 150 µg/d (Webster, 1996). The dose may be increased up to 300 µg/d.

Although clinically tested in the US, the process of obtaining FDA approval was never completed, so the drug is not available in the US. It is, however, licensed for the treatment of PRL disorders in Europe, where it has been used extensively. Patients in clinical studies who were unable to tolerate BC were better able to tolerate quinagolide treatment (Glasser, et al; 1994).

In women with HP, quinagolide has resulted in an improvement in PRL levels following once-daily treatment with quinagolide with good tolerability (Homburg, et al; 1990) and is effective in reducing pituitary adenoma size and restoring gonadal function and fertility in patients with prolactinomas resistant to treatment with BC (Schultz, et al; 2000). Quinagolide is also effective in decreasing the size of pituitary adenomas (Van der Lely, et al; 1991) and has antidepressant properties (Lappohn, et al; 1992). In an open, randomized crossover trial, quinagolide given as 75 µg daily was compared with CAB given as a 0.5 mg dose twice weekly (Giusti, et al; 1994). CAB users had fewer side effects and PRL levels were suppressed for a longer period of time after cessation of therapy. As a non-ergot derivative, quinagolide is unlikely to cause side effects such as peripheral vasospasm, erythromyalgia, and pleuropulmonary or retroperitoneal fibrosis that occasionally occur with ergot derivatives (Brooks, 2000).

In a study in which 20 women with BC-resistant prolactinomas were treated with quinagolide, normal PRL levels and gonadal function were restored in eight women after 1 year of treatment (Morange, et al; 1996). During a 3-year follow-up period, nine pregnancies were observed in seven women within 1.8 ± 1.5 years (Morange, et al; 1996). Quinagolide therapy was interrupted once pregnancy was confirmed in these women, but was recommended in two women to control symptoms or tumor growth and was continued throughout pregnancy. All pregnancies led to normal deliveries with no abnormalities noted in the babies (Morange, et al; 1996). In addition, quinagolide has been shown to be more effective and better tolerated than BC (Schultz, et al; 2000).

Quinagolide and BC have been compared in three randomized double-blind studies of 24 to 26 weeks in length with 81 hyperprolactinemic patients. Compiled results demonstrate that 82% of quinagolide-treated patients achieved normal PRL levels, compared with 71% of those who received BC. Only 7% stopped quinagolide for side effects, compared with 23% with BC (Webster, 1996). A randomized controlled crossover trial examined 20 patients treated with either CAB or quinagolide, followed by a washout period with placebo and subsequent treatment with the other of the two drugs (Di Sarno, et al; 2000). Eight of the patients had microadenomas, six empty sella syndromes and six idiopathic HP. In one study, after 12 weeks of the second treatment, a higher percentage of patients (90% of patients) on CAB had normal PRL levels compared with 75% on quinagolide. However, clinical efficacy was similar between treatments in terms of improvements in amenorrhoea, oligomenorrhoea and Galactorrhea. The side effect profiles were not significantly different (De Luis, et al; 2000). Another study reported the treatment of 40 patients with HP or Prolactinomas with quinagolide over 6 years (Nordmann, et al; 1988). Ninety percent of the patients were female, 11 had microadenomas, 12 had macroadenomas and 17 had no radiologic evidence of tumor. Reduction in PRL levels was seen with normalization in 73%, 67% and 82% respectively. The size of the tumor on follow-up imaging was reduced in 55% of the microadenomas and 75% of the macroadenomas. The side effects profile of nausea, vomiting, dizziness and drowsiness was decreased by 75% with quinagolide over BC.

A retrospective evaluation of 11 quinagolide-treated micro- and macroprolactinomas in patients resistant to or intolerant of BC demonstrated an average volume reduction of 46% and 57% respectively (Ilkko, et al; 2002). The average PRL decrease was 65% and 73% respectively. The effectiveness of quinagolide in achieving normal PRL levels in women

with macroprolactinomas and HP has been demonstrated to persist after 24 months of treatment (Rasmussen, et al; 1991).

Quinagolide has a 24-h duration of action and this allows for once-daily dosing, which is a major advantage over the multiple daily dosing of BC (Moyle, 2003) and which could offer advantages over twice-weekly CAB in terms of limiting the risk of forgetfulness associated with intermittent dosing regimens. In addition, the 22-h half-life of quinagolide allows this DA to be used until the point of confirmed pregnancy, allowing patients who wish to become pregnant to continue therapy for HP whilst trying to conceive. After the quinagolide treatment, 100% of patients with microprolactinomas had normal PRL levels, as did 87.5% of patients with macroprolactinomas, while tumor volume reduction of greater than 80% was documented in 21.7% of microadenomas and 25% of macroadenomas.

5.2.5 Other DA

5.2.5.1 Pergolide

Pergolide mesylate is another ergot-derived DA that is more potent, longer acting, better tolerated, one-fifth the cost of BC (because it requires only once-daily dosing) and useful in BC resistant patients (Freda, et al; 2000). In one clinical study performed in Europe, once-daily administration of pergolide was shown to be as safe and effective as two- to four-times-daily ingestion of BC (Lamberts and Quik, 1991). This study involved 61 patients (60 women and 1 man) with HP without a pituitary lesion and 96 patients (59 women and 37 men) with pituitary lesions exceeding 5 mm.

Pergolide is given in a single daily dose of 50-150 µg. It was started as a 25 µg dose taken orally with the evening meal for the first 3 days. Dosage was advanced in 25 µg increments every 3 to 4 days until a total dose of 300 µg per day was reached. BC was begun at a 1.25 mg/day oral dose with the evening meal and increased every fourth day in 1.25 to 2.5 mg increments given in divided doses (three per day) in total dosage that did not exceed 20 mg per day and 30 mg per day for the non-pituitary tumor and pituitary tumor groups, respectively. Both drugs were equally effective in lowering PRL levels and were equally effective in shrinking pituitary lesions.

In another study with pergolide, 22 consecutive patients with macroprolactinomas were followed prospectively; an 88% reduction in PRL levels was found with 15 of the 22 normalizing. Mean tumor shrinkage was 50% or greater in 77% of patients and 75% or greater in 45% of patients. Visual abnormalities were reversible after pergolide therapy in all but 1 of 12 patients with abnormal testing (Orrego, et al; 2000). If continued treatment with a DA is needed, another DA should be substituted for Pergolide (Valdemarsson, 2004).

5.2.5.2 Lisuride

It is a dopamine and serotonin receptor partial agonist. It has a high affinity for the dopamine D2, D3 and D4 receptors, as well as serotonin 5-HT1A and 5-HT2A/C receptors. It is used since the 1980s for its prolactin-lowering and anti-Parkinson activity.

It is very effective PRL-normalizing drug with relatively less serious complications if compared to other groups. Unfortunately, oral intolerance is frequently seen among patients up to the level of discontinuation of the drug due to systemic and GIT complications. Its

current oral tablet form requires dramatic modification to restore the high tolerability rate. Despite its common side effects, it is superior to other prolactin normalizing drugs in being extremely potent 5-HT(2B) antagonist. Drug-induced cardiac valvulopathies are always related to a stimulatory drug effect on trophic 5-HT(2B) receptors. As lisuride is devoid of such an effect, but on the contrary is an extremely potent 5-HT(2B) antagonist, an association of lisuride therapy with cardiac valvulopathies seems to be highly unlikely. All ergot-derived drugs and especially DA receptor agonists with some chemical similarity to the ergot structure will cause or facilitate cardiac valvulopathies as observed with pergolide (Hofmann et al., 2006).

5.2.5.3 Hydergeine

Hydergeine (ergaloid mesylate) is a mixed ergot alkaloid that has been shown to increase cognitive function in selected patients with neurologic disorders. It is approved only for this purpose in the US. It has, however, been used to treat HP and has been found to lower PRL levels only if serum PRL levels are less than 100 ng/ml. It is well tolerated by patients and should be used in cases where BC fails resulting in pregnancy in some patients (Tamura, et al; 1989).

5.2.5.4 Pramipexole

Pramipexole is a non-ergot DA. It is a derivative of aminobenzathiazole which primarily affects the D2 subfamily of dopamine receptors. Studies investigating the effects of this new DA on PRL secretion in humans are limited. In one small study performed in 1992, pramipexole decreased serum PRL levels in a dose-dependent manner, with a maximum effect after 2 to 4 hours (Schilling, et al; 1992). Side effects from this DA are frequent and similar to those encountered after the use of other DAs and include nausea, insomnia, constipation and orthostatic hypotension.

Response monitoring

Response to therapy should be monitored by checking fasting serum PRL levels and checking tumor size with MRI. Most women (approximately 90%) regain cyclic menstruation and achieve resolution of galactorrhea. Testosterone levels in men increase but may remain below normal. Therapy should be continued for approximately 12-24 months (depending on the degree of symptoms or tumor size) and then withdrawn if PRL levels have returned to the normal range. After withdrawal, approximately one sixth of patients maintain normal PRL levels. Normalization of visual fields is observed in as many as 90% of patients. A failure to improve within 1-3 months is an indication for surgery. Tumors usually shrink to 50% of their original size in approximately 90% of patients treated for macroadenomas for 1 year. In patients with nonProlactinoma tumors (masses that are compressing the pituitary stalk), medical treatment reduces serum PRL levels but does not reduce tumor size. CAB is somewhat more effective than BC in terms of tumor shrinkage (Wilson, 1998).

Compliance

Often, poor patient compliance may mimic apparent primary resistance (Webster, 1996). Non-compliance, defined as any deviation by the patient from a physician's instructions, is associated with treatment failure, resulting in inefficient use of time for the physician and

patient and in increased costs of health management (Rizzo and Simons, 1997). Compliance with DAs is important to ensure optimal treatment success. However, BC is associated with features that may reduce compliance, namely a poor side effect profile owing to its non-selective mechanism of action, and a short duration of action that necessitates multiple daily dosing. Approximately 5% of patients terminated treatment because of adverse reactions. The problem is that PRL returns to elevated levels in 75% of patients after discontinuation of treatment with DAs, and there is no clinical or laboratory assessment that can predict those patients who will have a beneficial long-term result (Hawkins, 2004). This is the major reason we use DA treatment only to achieve a specific purpose: pregnancy, suppression of bothersome galactorrhea, or reduction in tumor mass. Both quinagolide and CAB offer patients an improved side effect profile over BC, as well as an improved dosing regimen. Additionally, quinagolide can be used until pregnancy is confirmed and may therefore result in improve compliance in females wishing to become pregnant.

Resistance to DAs

Resistance to DAs in prolactinomas, defined as failure to normalize serum PRL levels and failure to reduce tumor size, is thought to relate to a low density of membrane D2 receptors on some lactotroph tumors (Pellegrini, et al; 1989). A complete lack of response to pharmacotherapy is a rare occurrence, with partial response occurring more frequently. A range of 10–20% of patients does not achieve reductions in PRL levels or tumor size after treatment with DAs, even at high doses (Di Sarno, et al; 2001). There is no consensus on the criteria to define resistance, but some proposed definitions for BC resistance include the following:

- The absence of normalized PRL levels after treatment with 15 µg/day BC for 3 months (Hawkins, 2004).
- A less than 50% reduction in serum PRL levels despite treatment with 15 µg/day BC (Luque, et al; 1986).

Resistance to DAs may be due to reduced number of cell surface dopamine receptors, abnormal post-translational processing of receptors, or abnormal intracellular signaling pathways. Lactotrope heterogeneity, as defined by the difference in response to dopamine by different cell populations of lactotropes, may explain this phenomenon (Luque, et al; 1986). The failure of a tumor to shrink significantly in size despite a normalization of PRL levels can be consistent with a nonfunctioning tumor that is interrupting the supply of dopamine to the pituitary by stalk compression. Early surgery is indicated. A tumor that continues to grow despite DA treatment can be a rare carcinoma.

The cross-tolerability of DAs is unpredictable. Evidence suggests that fewer patients show resistance to CAB compared with BC (Di Sarno, et al; 2001). Ninety-seven percent of patients intolerant to BC tolerated CAB. This proportion is no different from the general population (Webster, 1996). Additionally, quinagolide has shown efficacy in patients resistant to or unable to tolerate BC therapy (Di Sarno, et al; 2000). Thus, both quinagolide and CAB may be used to treat patients with prolactinomas who are resistant or intolerant to treatment with BC (Rohmer, et al; 2000).

Management of DA resistance currently includes progressive increase in the DA dosage, changing the DA, and resorting to trans-sphenoidal pituitary surgery if necessary. A novel

class of compounds called PRL resistance antagonists, akin to the GH-receptor antagonist pegvisomant used in acromegaly may have a future therapeutic role in DA-resistant prolactinomas (Goffin, et al; 2006).

Recurrence

Recurrence of HP and re-expansion of previously shrunken pituitary adenomas is a well-known phenomenon after cessation of DA therapy. Few systematic clinical studies have been performed to provide guidance in this area. A comparative study examined 23 patients with microprolactinomas and 16 with macroprolactinomas, all previously intolerant of BC (Hawkins, 2004). Five patients with macroadenomas had also undergone surgery, and one with a microadenoma. All patients received quinagolide for 1 year followed by CAB for 1 year. A washout period after each treatment is performed to evaluate recurrence of HP.

All patients had recurrence of HP within 15 to 60 days of withdrawal of therapy, but post-quinagolide/pre-CAB levels were significantly lower than initial levels in both groups. Withdrawal of CAB led to recurrence of HP in 15 of 23 microprolactinomas and all macroprolactinomas within 30 days. Both drugs were well tolerated. In another study using CAB to treat patient with microadenomas for 12 months, normoprolactinemia was maintained in 4 of 26 patients (18%) 2 months after drug treatment was stopped (Muratori, et al; 1997).

In a more recent study by Passos and his colleges (Passos, et al, 2002) 131 patients (62 with microprolactinoma and 69 with macroprolactinoma) were treated with BC for a median time of 47 months, during which time normalization of PRL levels was observed. After cessation of treatment, normoprolactinemia remained in 26% of the microprolactinoma group when studied and 16% in the macroprolactinoma group for a median time of 44 months. These results are in agreement with other studies that have suggested that the longer the duration of DA therapy, the greater is the chance that normoprolactinemia will be sustained. Long-term DA treatment has been associated with perivascular fibrosis of pituitary adenoma tumor cells (Landolt and Osterwalder, 1984). Subclinical pituitary apoplexy has been observed after pregnancy in women with macroadenomas and during BC therapy.

Dopamine agonists and pregnancy

HP is a frequent cause of anovulatory infertility and luteal phase defect. Dopaminergic treatment is the first line of treatment and is very effective in both idiopathic HP and prolactinoma, with a 60 to 80% pregnancy rate. DAs are normally stopped following confirmation of pregnancy in order to avoid any possible teratogenic risk and so as not to prevent lactation at term. Even when DAs are discontinued early, the fetus is probably exposed to these drugs for up to 3–4 weeks of gestation; however, no adverse outcome has been reported during pregnancy (Krupp and Monka, 1987) or childhood (Raymon, et al; 1985). Whereas BC has a proven safety record in pregnancy (Molitch, 1999), the data on CAB and quinagolide are still limited. DAs impair lactation and hence are avoided in the postpartum period when breastfeeding is desired by the patient.

Owing to the accumulated evidence suggesting that BC does not evoke teratogenic or embryopathic effects in humans, continuation of BC therapy during pregnancy may be considered in cases of macroprolactinoma or where there is evidence of tumor expansion

The therapeutic strategy for pregnant women with macroprolactinomas should be individualized for each patient, considering both the potential effects of a therapy on foetal development and the effects of pregnancy on the prolactinoma. If DA therapy is continued throughout pregnancy, careful follow-up is required, with monthly visual-field examinations and MRI for patients who develop symptoms of tumor enlargement of visual field defects.

As a general principle, fetal exposure to DA should be limited to as short a period as possible. Mechanical contraception should be used until the first two to three cycles have occurred so that an intermenstrual period can be established and the woman will know when she has missed a menstrual period. The DA can be stopped after being given for only 3–4 weeks of gestation. When used in this fashion, BC has not been found to cause any increase in spontaneous abortions, ectopic pregnancies, trophoblastic disease, multiple pregnancies or congenital malformation (Molitch, 2001).

Gradual withdrawal

DA agents are the treatment of choice for macroadenomas, utilizing as low a dose as possible. Once shrinkage has occurred, the daily dose should be progressively reduced until the lowest maintenance dose is achieved. The serum PRL level can be utilized as a marker, checking levels every 3 months until stable. In many (but not all) patients, control of tumor growth correlates with maintenance of a baseline PRL level and can be achieved in some patients with as little as one-quarter of a BC tablet (0.625 mg) daily (Liuzzi, et al; 1985).

Withdrawal of the drug can be associated with regrowth or reexpansion of the tumor, and, therefore, treatment must be at least for several years, many tumors (70-80%) do not regrow (Colao, et al; 2003). If there is a good response in PRL levels, and if present, visual field defects, the MRI should be repeated after 1 year of treatment to establish size reduction of the tumor. If clinician and patient need reassurance regarding tumor size, imaging intervals can be prolonged if the tumor is stable; e.g., at 1 year, 2 years, 4 years, 8 years. It should be noted that progressively increasing PRL levels have been observed without associated tumor growth of a microadenoma (Sisam, et al; 1986). Some patients prefer surgery rather than long-term medical treatment, and it is certainly a legitimate option. In view of better results claimed in more recent times, this choice should be presented to the patient.

Estrogen replacement therapy

When a woman with raised PRL does not wish to become pregnant, intolerant to various DAs or the tumor is small but is producing significant hypestrogenism, estrogen replacement therapy should be given for protection of the bones and vascular system (Jeffcoate, et al; 1996). It is may be warranted to prevent osteoporosis or to improve libido. Hypogonadal women with microprolactinomas may therefore be treated for their hypogonadism with combined oral contraceptive agents (Molitch, 1999) when galactorrhea is not a major problem. When contraception is needed they can be put on low dose contraceptive pills. There is no risk of tumor expansion due to estrogens since the level given is only enough to raise levels up to those in natural cycle (Losa, et al; 2002). While published data on patients with prolactinomas who are treated with oral contraceptives for hypogonadism have not shown any substantial risk for tumor enlargement (Corenblum and

Donovan, 1993), it is advisable to monitor patients who use oral contraceptives carefully with periodic measurement of PRL levels (Garcia and Kapcala, 1995). If ovulation still does not occur in patients with HP following treatment with a DA, attempts can be made to induce ovulation with anti-estrogens, gonadotrophins or pulsatile GnRH administration. If pregnancy does not occur after 6–8 months of ovulatory cycles, the patient must be reinvestigated. Patients who do not wish to conceive should be advised to use contraception, as return of fertility may not be immediately apparent.

5.2.6 Chaste tree berry

Chaste tree (Vitex agnus-castus), also known as monk's pepper, is used in Germany for irregular periods, pre-menstrual pain, and feelings of tension and swelling in the breasts. The purpose of this study was to evaluate the chaste tree berry as a treatment for mild HP and mastalgia and to compare its efficacy with BC, a conventional therapy.

A group of women with cyclic mastalgia (n=40) and a group of women with mild HP (n=40) participated in this prospective, randomized, comparative study. (This Brief Communication does not give additional methodological details.) In each group the patients were randomized to receive either BC (Parlodel® 2.5 mg twice daily, Novartis, Turkey) or chaste tree berry (Agnucaston®, 40 mg daily, Bimeks, Germany) for 3 months. Serum PRL and breast pain were evaluated preand post-treatment.

PRL levels were significantly reduced by both treatments (P<0.0001). There was no significant difference in the size of the effect between treatments. Breast pain was significantly less after both treatments (P<0.0001), and there was no significant difference between treatments in regard to breast pain. No adverse events associated with chaste tree berry were reported. Thirteen percent of the patients taking BC reported nausea and vomiting.

The results show that chaste tree berry has PRL and breast pain reducing abilities similar to BC. However, chaste tree berry has better patient compliance and lower cost. The authors recommend chaste tree berry as a first-line treatment for cyclic mastalgia and mild HP. Although these results are promising, the group sizes were small and the study should be reconfirmed with a larger number of patients. Furthermore, this trial did not contain a placebo group; therefore, it is not possible to ascertain the magnitude of the placebo effect in this intervention. The lack of a placebo group is additionally problematic given the study design. It is assumed that the mechanism of action for the reduction of mastalgia is the lowering of PRL (via binding dopamine receptors on the pituitary by either agent); however this association is not clarified. The reduction of PRL in both the hyperprolatinaemia group and the cyclic mastlagia group, with the additional reduction in pain in the mastalgia group, while significant, does not prove the association between lowered PRL and decreased mastalgia. The decreased mastalgia could be due to placebo or other unidentified effects. This study has clinical relevance in that the mechanism could elucidate other indications and contraindications to this therapy. Nonetheless, the trial is a compelling look at the effect of chaste tree berry as a treatment alternative for mastalgia (Kilicdag, et al; 2004).

5.3 Surgical intervention

The efficacy of medical treatment in restoring a normoprolactinemic state without the risk of pituitary insufficiency has limited the indications for surgical resection of prolactinomas.

Surgery may achieve a long-term cure, but remission rates are no better than 60% (Colao, et al; 2003). Nowadays, surgery is usually reserved for cases of intolerance/resistance to medical therapy, persistent tumor mass effect despite maximal DA treatment, and considered in patients who are dependent on antipsychotic medication.

Indications for surgery

Transsphenoidal surgery in pregnancy is indicated in certain circumstances. General indications for pituitary surgery include:

- Patient unwilling for long-term drug therapy.
- Intolerable side effects of drugs.
- Tumors resistant to medical therapy.
- Patients who have persistent visual-field defects in spite of medical treatment.
- Patients with large cystic or hemorrhagic tumors.
- Nonfunctioning tumors where PRL levels are not very high. These tumors may expand with invasion into cavernous sinus, compression of optic chiasma and hemorrhage causing pituitary apoplexy.
- Suprasellar extension not regressing with drug therapy.

5.4 Radiotherapy

Because tumor recurrence after surgery is high, radiotherapy should be considered (Tsagarakis, et al; 1991). It is not the primary choice of treatment and may be tried if medical management or surgery fails. It has a role for macroprolactinomas that are not responsive to other modes of treatment, or when medical and/or surgical therapies are contra-indicated/felt to be inappropriate. Irradiation should be reserved as adjunctive therapy for controlling postoperative persistence or regrowth of large tumors and shrinking large tumors that are unresponsive to medical treatment. It is given using linear cobalt or proton mode. Conventional radiation therapy over a period of 5–6 weeks has been observed to decrease tumor size and PRL secretion (Tsang, et al; 1996). More modern radiotherapy strategies, namely gamma knife and focal radiation surgeries have been designed to reduce the radiation exposure of brain structures outside the target area and deliver a higher dose of radiation to the target area to provide more effective therapy in a single treatment session (Tsang, et al; 1996). However, experience with these techniques remains limited at this time and may increase the risk of hypopituitarism.

Clinical conditions deserve special attention

Lymphocytic hypophysitis

It is a rare, autoimmune, inflammatory disorder that is most often associated with pregnancy and can be present in a fashion similar to that of a pituitary adenoma. The etiology of lymphocytic hypophysitis is unknown but is associated with other autoimmune disorders (Feigenbaum, et al; 1991). Histologic features include lymphocytic infiltration of the anterior pituitary with associated destruction and fibrosis of the gland. Radiographic features are non specific and the appearance mimics that of a pituitary adenoma. The clinical symptoms are attributable to a mass effect on adjoining structures: headache, visual disturbances or pituitary dysfunction. There is no unique endocrinologic profile associated with lymphocytic hypophysitis. It can present with HP, diabetes insipidus or

hypopituitarism. The diagnosis is made by transsphenoidal biopsy and steroids are the first-line therapy (Kerrison and Lee, 1997).

Empty sella syndrome

A patient may have an abnormal sella turcica, but rather than a tumor, she can have the empty sella syndrome. In this condition, there is a congenital incompleteness of the sellar diaphragm that allows an extension of the subarachnoid space into the pituitary fossa. The pituitary gland is separated from the hypothalamus and is flattened. The empty sella syndrome may develop secondary to surgery, radiotherapy, or infarction of a pituitary tumor. An empty sella is found in approximately 5% of autopsies, and approximately 85% are in women, previously thought to be concentrated in middle-aged and obese women (Hodgson, et al; 1972). A closer look at the sella turcica, brought about by our pursuit of elevated PRL levels, has revealed an incidence of empty sella in 4-16% of patients who present with amenorrhoea/galactorrhea (Schlechte, et al; 1980). Galactorrhea and elevated PRL levels can be seen with an empty sella, and there may be a coexisting PRL-secreting adenoma. This suggests that the empty sella in these patients may have arisen because of tumor infarction. This condition is benign; it does not progress to pituitary failure. The chief hazard to the patient is inadvertent treatment for a pituitary tumor. Because of the possibility of a coexisting adenoma, patients with elevated PRL levels or galactorrhea and an empty sella should undergo annual surveillance (PRL assay and imaging) for a few years to detect tumor growth. It is totally safe and appropriate to offer hormone treatment or induction of ovulation.

Pituitary apoplexy

Hemorrhage or necrosis of a pituitary adenoma is an endocrine emergency. The classic, acute syndrome presents over 1-2 days and is characterized by headache, meningeal signs, visual disturbances and neurologic dysfunction. Recent improvements in MRI technology have revealed a subclinical form of pituitary apoplexy in which a small pituitary hemorrhage causes few symptoms. Patients with pituitary apoplexy require intensive support and treatment for hypopituitarism. Worsening visual disturbances or signs of pituitary compression are indications for transsphenoidal decompression.

Keynote points

- Clinical attention towards hyperprolactinemia starts by proper examination of breasts.
- Think of physiologic causes and medications.
- Hyperprolactinemia may affect women's health indifferent ways.
- Dopamine agonists are highly effective for treating hyperprolactinemic amenorrhea and infertility.
- Bromocriptine is the treatment of choice when pregnancy is the goal.
- Alternative bromocriptine delivery approaches are interesting promising modifications that would minimize side effects and increase efficacy.
- Cabergoline is better tolerated and is effective in patients resistant to bromocriptine, but more studies are needed before it can be recommended as first-line treatment for HP in women wishing to conceive.
- Because microadenomas do not grow progressively larger, long-term treatment isn't necessary to prevent tumor growth.

- In carefully selected women with small tumors, consider prescribing an oral contraceptive instead of a dopamine agonist, when fertility is not an issue (Schlechte J, Goldner W,2004).

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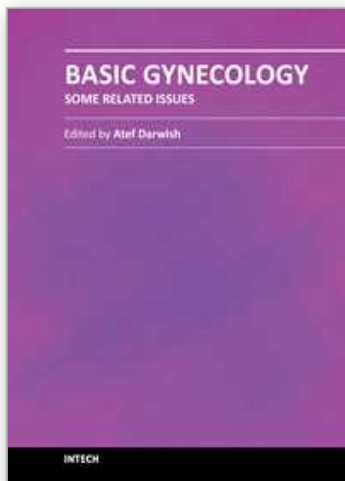
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