Hyperprolactinemia, Galactorrhea, and Pituitary Adenomas

Ina S. Irabon, MD, FPOGS, FPSRM, FPSGE
Obstetrics and Gynecology
Reproductive Endocrinology and Infertility

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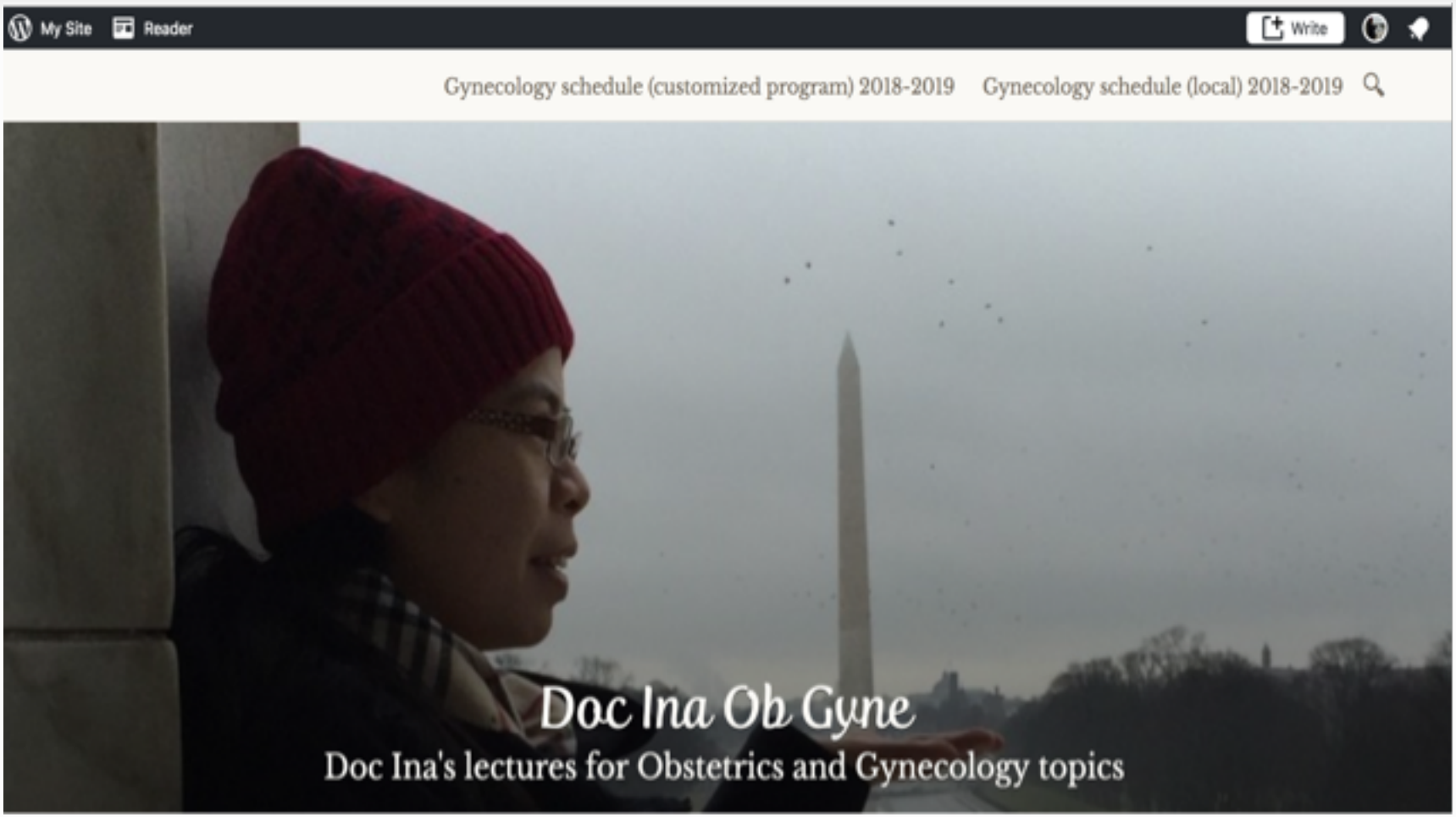

Main reference

- Comprehensive Gynecology 7th edition, 2017 (Lobo RA, Gershenson DM, Lentz GM, Valea FA *editors);* chapter 39, Hyperprolactinemia, Galactorrhea,and Pituitary Adenomas

PROLACTIN

- **Prolactin** (PRL) is a polypeptide hormone containing 198 amino acids and with a molecular weight (MW) of 22 kDa.
- PRL is synthesized and stored in the pituitary gland in chromophobe cells called *lactotrophs,* which are located mainly in the lateral areas of the gland
- the *major stimulating factor is thyroid-releasing hormone (TRH),* and the *major inhibiting factor is dopamine*, which has been suggested to be the prolactin-inhibiting factor (PIF).
- Estrogen also improves PRL secretion by enhancing the effects of TRH and inhibiting the effects of dopamine.

PROLACTIN

- the principal receptor with which dopamine interacts is **D2,** which is the target for various dopamine agonists used in the treatment of hyperprolactinemia.
- PRL is also synthesized in decidualized stroma of endometrial tissue.
  - From these tissues, PRL is secreted into the circulation and, in the event of pregnancy, into the amniotic fluid.
  - the control of decidual PRL is different from that of the pituitary and does not respond to dopamine.

PROLACTIN

- PRL is normally present in measurable amounts in serum, with mean levels of approximately 8 ng/mL in adult women.
- It circulates in an unbound form, has a 20-minute half-life, and is cleared by the liver and kidney.
- *the main function of PRL is to stimulate the growth of mammary tissue as well as to produce and secrete milk into the alveoli;*
  - it has mammogenic and lactogenic functions.

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Physiology

- serotonin and thyrotropin- releasing factor (TRF) stimulate PRL release.
- the rise in PRL levels during sleep appears to be controlled by serotonin.
- PRL is secreted episodically and serum levels fluctuate throughout the day and throughout the menstrual cycle, with *peak levels occurring at midcycle*.
- estrogen stimulates PRL production and release.
  - PRL levels increase in females at the time of puberty; there is a slight decline in levels after menopause.

Physiology

- During pregnancy, as estrogen levels increase, there is a concomitant hypertrophy and hyperplasia of the lactotrophs.
- the maternal increase in PRL levels occurs soon after implantation, concomitant with the increase in circulating estrogen → may reach approximately 200 ng/mL in the third trimester;
- the rise is directly related to the increase in circulating levels of estrogen.

Physiology

- Despite the elevated PRL levels during pregnancy, lactation does not occur because estrogen inhibits the action of PRL on the breast, most likely blocking PRL's interaction with its receptor.
- A day or two following delivery of the placenta, estrogen and PRL levels decline rapidly and lactation is initiated.
- PRL levels reach basal levels in nonnursing women in 2 to 3 weeks.
- Although basal levels of circulating PRL decline to the nonpregnant range approximately 6 months after parturition in nursing women, following each act of suckling, PRL levels increase markedly and stimulate milk production for the next feeding.

Physiology

- Nipple and breast stimulation also increase PRL levels in the nonpregnant female, as does trauma to the chest wall, exercise, sleep, and stress.
- PRL levels normally rise following ingestion of the midday meal.
- PRL levels normally fluctuate throughout the day, with maximal levels observed during the night while asleep and a smaller increase occurring in the early afternoon.
  - *the optimal time to obtain a blood sample for assay to diagnose hyperprolactinemia is in the fasting state and, ideally, during the mid-morning hours.*
- When the amount measured in the circulation in the nonpregnant woman exceeds a certain level, usually 20 to 25 ng/ mL, the condition is called *hyperprolactinemia*.

Physiology

- Increases in PRL levels above the normal range can occur without a pathologic condition if the serum sample is drawn from a woman who has recently awakened, has exercised, or has had recent breast stimulation (such as breast palpation) during a physical examination.

physiology

- Hyperprolactinemia can produce disorders of gonadotropin sex steroid function, resulting in menstrual cycle derangement (oligomenorrhea and amenorrhea) and anovulation, as well as inappropriate lactation, or
- the mechanism whereby elevated PRL levels interfere with gonadotropin release appears to be related to abnormal gonadotropin-releasing hormone (GnRH) release. Women with hyperprolactinemia have abnormalities in the frequency and amplitude of LH pulsations, with a normal or increased gonadotropin response following GnRH infusion.

physiology

- this abnormality of GnRH cyclicity thus inhibits gonadotropin release but not its synthesis.
- the reason for this abnormal secretion of GnRH is an inhibitory effect of dopamine and opioid peptides at the level of the hypothalamus.
- elevated PRL levels have been shown to interfere with the positive estrogen effect on midcycle LH release.
- It has also been shown that elevated levels of PRL directly inhibit basal and gonadotropin-stimulated ovarian secretion of estradiol and progesterone.
- However, this mechanism is probably not the primary cause of anovulation, because women with hyperprolactinemia can have ovulation induced with various agents, including pulsatile GnRH.

physiology

- the clinician should measure serum PRL levels in all women with galactorrhea, as well as those with oligomenorrhea and amenorrhea not explained by another reason such as ovarian failure (elevated level of follicle-stimulating hormone [FSH]).
- Hyperprolactinemia has been reported to be present in 15% to 20% of women who present with menstrual disturbances.

SPECIAL CASES IN THE MEASUREMENT OF PROLACTIN

- Because of possible aggregation of molecular forms of PRL when levels are high, if a tumor (adenoma) is suspected and values of PRL are only mildly elevated, the test should be repeated in a diluted sample.
  - this has been called the “hook” effect and is explained by high endogenous levels of PRL binding up all the assay antibody, leaving an inadequate quantity for the assay
- PRL levels may be elevated in a woman who is normal clinically.
  - this is due to “clumping” of glycosylated PRL with immunoglobulin and can be corrected by gel electrophoresis or merely by adding polyethylene glycol to the serum, which precipitates the abnormal forms

GALACTORRHEA

- Galactorrhea is defined as the nonpuerperal secretion of watery or milky fluid from the breast that contains neither pus nor blood. The fluid may appear spontaneously or after palpation.
- To determine whether galactorrhea is present, the clinician should palpate the breast, moving from the periphery toward the nipple in an attempt to express any secretion.
- diagnosis of galactorrhea can be confirmed by observing multiple fat droplets in the fluid when examined under low-power magni-cation
- Unless there has been continued breast stimulation after a pregnancy, the presence of galactorrhea serves as a biologic indicator that the PRL level is abnormally elevated.

Causes of hyperprolactinemia

- Pathologic causes of hyperprolactinemia, in addition to a PRL- secreting pituitary adenoma (**prolactinoma**) and other pituitary tumors that produce acromegaly and Cushing disease, include hypothalamic disease, various pharmacologic agents, hypothyroidism, chronic renal disease, or any chronic type of breast nerve stimulation, such as may occur with thoracic operation, herpes zoster, or chest trauma.

Box 39.1 Causes of Hyperprolactinemia

Pituitary Disease
Prolactinomas
Acromegaly
Empty sella syndrome
Lymphocytic hypophysitis
Cushing disease

Hypothalamic Disease
Craniopharyngiomas
Meningiomas
Dysgerminomas
Nonsecreting pituitary adenomas
Other tumors
Sarcoidosis
Eosinophilic granuloma
Neuraxis irradiation
Vascular
Pituitary stalk section

Medications
See Box 39.2.

Neurogenic
Chest wall lesions
Spinal cord lesions
Breast stimulation

Other
Pregnancy
Hypothyroidism
Chronic renal failure
Cirrhosis
Pseudocyesis
Adrenal insufficiency
Ectopic
Polycystic ovary syndrome
Idiopathic

From Molitch ME. Prolactinoma. In: Melmed S, ed. *The Pituitary.* 2nd ed. Malden, MA: Blackwell; 2002:455-495.

Box 39.2 Pharmacologic Agents Affecting Prolactin Concentrations

Stimulators
Anesthetics, including cocaine
Psychoactive drugs
Phenothiazines
Tricyclic antidepressants
Opiates
Chlordiazepoxide
Amphetamines
Diazepam
Haloperidol
Fluphenazine
Chlorpromazine
SSRIs

Hormones
Estrogen
Oral-steroid contraceptives
Thyrotropin-releasing hormone

Antihypertensives
α-Methyldopa
Reserpine
Verapamil

Dopamine receptor antagonists
Metoclopramide

Antiemetics
Sulpiride
Promazine
Perphenazine

Others
Cimetidine
Cyproheptadine
Protease inhibitors

Inhibitors
L-Dopa
Dopamine
Bromocriptine
Pergolide
Cabergoline
Depot bromocriptine

From Shoupe D, Mishell DR Jr. Hyperprolactinemia: diagnosis and treatment. In: Lobo RA, Mishell DR Jr, Paulson RJ, Shoupe D, eds. *Mishell's Textbook of Infertility, Contraception and Reproductive Endocrinology.* 4th ed. Cambridge, MA: Blackwell Scientific; 1997.
SSRIs, Selective serotonin reuptake inhibitors.

Causes of hyperprolactinemia

- One of the most frequent causes of galactorrhea and hyperprolactinemia is the ingestion of pharmacologic agents, particularly tranquilizers, narcotics, and antihypertensive agents (Box 39.2). Of the tranquilizers, the phenothiazines and diazepam can produce hyperprolactinemia by depleting the hypothalamic circulation of dopamine or by blocking its binding sites and thus decreasing dopamine action.

Causes of hyperprolactinemia

- tricyclic antidepressants block dopamine uptake and propranolol, haloperidol, phentolamine, and cyproheptadine block hypothalamic dopamine receptors.
- antihypertensive agent reserpine depletes catecholamines, and methyldopa blocks the conversion of tyrosine to dihydroxyphenylalanine (dopa).
- Ingestion of oral contraceptive steroids can also mildly increase PRL levels, with a greater incidence of hyperprolactinemia occurring with older higher estrogen formulations.
  - Nevertheless, galactorrhea does not usually occur during oral contraceptive ingestion because the exogenous estrogen blocks the binding of PRL to its receptors.

Causes of hyperprolactinemia

- Women who develop galactorrhea while any of the drugs listed in Box 39.2 should ideally discontinue the medication, and the PRL level should be measured 1 month thereafter to determine if the level has returned to normal.
  - If the medication cannot be discontinued, the PRL level should be measured and, if elevated above 100 ng/mL, imaging of the sella turcica should be performed to determine whether a **macroadenoma** is present.
- Primary hypothyroidism can also produce hyperprolactinemia and galactorrhea because of decreased negative feedback of thyroxine (T4) on the hypothalamic-pituitary axis.

Causes of hyperprolactinemia

- the resulting increase in TRH stimulates PRL secretion and thyroid-stimulating hormone (TSH) secretion from the pituitary.
- Approximately 3% to 5% of individuals with hyperprolactinemia have hypothyroidism.
  - therefore TSH, the most sensitive indicator of hypothyroidism, should be measured in all individuals with hyperprolactinemia.
  - If the TSH level is elevated, triiodothyronine (T3) and T4 should be measured to confirm the diagnosis of primary hypothyroidism, because a TSH-secreting pituitary adenoma will occasionally be present.
  - Treatment with appropriate thyroid replacement usually returns the TSH and PRL levels to normal within a short time.
- Hyperprolactinemia can occur in those with abnormal renal disease resulting from decreased metabolic clearance and increased production rate.

Causes of hyperprolactinemia

- Mild hyperprolactinemia (30 to 50 ng/mL) may occur in women with polycystic ovary syndrome (PCOS). is occurs in up to 30% of women and may be related to the chronic state of unopposed estrogen stimulation.

CENTRAL NERVOUS SYSTEM DISORDERS
Hypothalamic Causes

- Diseases of the hypothalamus that produce alterations in the normal portal circulation of dopamine can result in hyperprolactinemia.
  - these include **craniopharyngioma (**most common) and infiltration of the hypothalamus by sarcoidosis, histiocytosis, leukemia, or carcinoma.
  - these tumors arise from remnants of Rathke's pouch along the pituitary stalk.
  - most frequently diagnosed during the second and third decades of life and usually result in impairment of secretion of several pituitary hormones.

CENTRAL NERVOUS SYSTEM DISORDERS
Pituitary Causes

- Various types of pituitary tumors, lactotroph hyperplasia, and the **empty sella syndrome**
- as many as 80% of all pituitary adenomas secrete PRL.
  - the most common pituitary tumor associated with hyperprolactinemia is the prolactinoma, arbitrarily defined as a **microadenoma** if its diameter is less than 1 cm and as a macroadenoma if it is larger
- *Functional hyperprolactinemia* is the term used for the clinical diagnosis of cases of elevated PRL levels without imaging evidence of an adenoma.
- *primary empty sella syndrome* describes a clinical situation in which an intrasellar extension of the subarachnoid space results in compression of the pituitary gland and an enlarged sella turcica.
  - believed to result from a congenital or acquired (by radiation or surgery) defect in the sella diaphragm that allows the subarachnoid membrane to herniate into the sella turcica

PROLACTINOMAS

- more than 10% of those in the general population have an undiagnosed prolactinoma.
- there is an approximate positive correlation between the size of the adenoma and the PRL level.
- majority of prolactinomas in women are microadenomas (<1 cm).
- it is now believed that adenomas arise from single cell mutations, with clonal proliferation occurring subsequently.
- It is also important to note that prolactinomas may also secrete other hormones with GH being the most common
- Long-term studies have demonstrated that many of these tumors regress spontaneously.
- natural progression from micro- to macroadenoma has been estimated to be less than 7%.

Diagnostic studies

IMAGING STUDIES

- Current recommended techniques are to obtain a CT scan with intravenous contrast or an MRI with gadolinium enhancement.
- MRI provides better soft tissue definition, without radiation (23 rad; 0.03 Gy), and the CT scan is principally beneficial for bony structural abnormalities.
- MRI provides 1-mm resolution and thus should be able to detect all microadenomas; it is currently the recommended imaging study to obtain.

RECOMMENDED DIAGNOSTIC EVALUATION

- It is recommended that PRL levels be measured in all women with galactorrhea, oligomenorrhea, or amenorrhea who do not have an elevated FSH level.
- PRL is also frequently measured in the workup of infertility.
- If the PRL level is elevated, a TSH assay should be performed to rule out the presence of primary hypothyroidism.
  - If the TSH level is elevated, T3 and T4 should be measured to rule out the rare possibility of a TSH-secreting pituitary adenoma.
  - If the TSH level is elevated and hypothyroidism is present, appropriate thyroid replacement should begin and the PRL level will usually return to normal.
  - If the TSH level is normal and the woman has a normal PRL level with galactorrhea, no further tests are necessary if she has regular menses.

RECOMMENDED DIAGNOSTIC EVALUATION

- If PRL levels are elevated and the TSH level is normal, an MRI (preferably) or CT scan should be obtained to detect a microadenoma or macroadenoma.
  - Macroadenomas are uncommon and rarely present with a PRL level less than 100 ng/mL.
  - If the PRL level is more than 100 ng/mL or the woman complains of headaches or visual changes, the likelihood of a tumor extending beyond the sella turcica is increased.
  - Microadenomas are a common cause of hyperprolactinemia and remain stable in most cases.
  - Neither pregnancy, oral contraceptives, nor hormone therapy stimulates the growth of these small tumors;
  - therapy is unnecessary unless ovulation induction is desired or hypoestrogenism is present.

RECOMMENDED DIAGNOSTIC EVALUATION

- Routine visual field testing and measurements of ACTH, GH, and thyroid function are not necessary unless warranted clinically.
- These evaluations, particularly visual field testing, should be performed in women with macroadenomas because suprasellar extension of the tumor may exert pressure on the optic chiasm, resulting in bitemporal visual field defects and interference with vision.
- The size of these tumors may also affect other aspects of pituitary function. With a macroadenoma, dynamic tests of pituitary function should be performed.

Treatment

EXPECTANT TREATMENT

- Women with radiologic evidence of a microadenoma or functional hyperprolactinemia who do not wish to conceive may be followed without treatment by measuring PRL levels once annually.
- However, if estrogen is deficient, low estrogen levels in combination with hyperprolactinemia has been shown to be associated with the early onset of osteoporosis
  - exogenous estrogen should be administered.
  - Hormonal therapy, as is used for postmenopausal women, or oral contraceptives may be used.
  - oral contraception use in a group of women with hyperprolactinemia with microadenoma did not alter the size of the adenoma

EXPECTANT TREATMENT

- Because side effects and cost are less and compliance is better with exogenous estrogen than with dopamine agonist therapy, it is not necessary to use the latter unless ovulation and pregnancy are desired

- those with hyperprolactinemia, with or without microadenomas, who have adequate estrogen levels and who do not wish to conceive should be treated with periodic progestogen withdrawal (e.g., medroxyprogesterone acetate, 5 to 10 mg/day for 10 days each month) or with combination oral contraceptives to prevent endometrial hyperplasia.

MEDICAL TREATMENT

- the initial treatment for women with macroadenomas, as well as for those women with hyperprolactinemia who are anovulatory and wish to conceive, should be the administration of a dopamine receptor agonist.

- Cabergoline, **bromocriptine**, and pergolide have been used successfully;

- pergolide is currently not available.

Bromocriptine

- semisynthetic ergot alkaloid was developed in 1967 to inhibit PRL secretion.
- directly stimulates dopamine 2 receptors and, as a dopamine receptor agonist, it inhibits PRL secretion in vitro and in vivo.
- After ingestion, bromocriptine is rapidly absorbed, with blood levels reaching a peak 1 to 3 hours later.
- Serum PRL levels remain depressed for approximately 14 hours after ingestion of a single dose, after which time the drug is not detectable in the circulation.
- usually given at least twice daily, with initial therapy being started at half of the 2.5-mg tablet to minimize side effects.

Bromocriptine

- the most frequent side effects are orthostatic hypotension(may manifest as fainting and dizziness, as well as nausea and vomiting.
  - To minimize these symptoms, the initial dose should be taken in bed and with food at night.
- Less frequent adverse symptoms include headache, nasal congestion, fatigue, constipation, and diarrhea.
- To reduce the adverse symptoms, the dose should be gradually increased every 1 to 2 weeks until PRL levels fall to normal.
  - May also be administered vaginally
- the greatest decrease in PRL occurs in the first 2 to 4 weeks.
- Preferred over cabergoline for pregnant patients

Cabergoline

- long-acting dopamine receptor agonist and is currently preferred over bromocriptine for primary therapy, because of greater efficacy and fewer side effects
- directly inhibits pituitary lactotrophs, thereby decreasing PRL secretion.
- It is given orally in doses of 0.25 to 1 mg twice weekly.
- the initial dose is half a 0.5- mg tablet twice a week.
- Peak plasma levels occur in 2 to 3 hours, and the drug has a half-life of 65 hours.
  - Its slow elimination and long half-life produce a prolonged PRL-lowering effect.

Cabergoline

- A potential concern with cabergoline and pergolide (now not available) is the development of cardiac valvular lesions.
  - this has only been observed with large doses, as used for Parkinson disease, and has not been reported with lower doses
  - It has been suggested that cardiac ultrasound be performed every 2 years in patients on chronic therapy of cabergoline at doses of less than 2 mg per week.

OPERATIVE APPROACHES FOR PROLACTINOMA

- Trans-sphenoidal microsurgical resection of prolactinoma has been widely used for therapy - mortality of less than 0.5%.
  - the risk of temporary postoperative diabetes insipidus is 10% to 40%, but the risk of permanent diabetes insipidus and iatrogenic hypopituitarism is less than 2%.
  - initial cure rate, with normalization of PRL levels and return of ovulation, is relatively high for microadenomas (65% to 85%) but less so with macroadenomas (20% to 40%).
- the initial cure rate is related to the pretreatment PRL levels:
  - those tumors with PRL levels less than 100 ng/mL have an excellent prognosis (85%), and those with levels higher than 200 ng/ mL have a poor prognosis (35%).

OPERATIVE APPROACHES FOR PROLACTINOMA

- Because of the good results with medical therapy, surgery is recommended only for women with macroadenoma who fail to respond to medical therapy or have poor compliance with this regimen.
- It is best to reduce the size of macroadenomas maximally with bromocriptine before surgical removal of these extrasellar tumors.

RADIATION THERAPY FOR MACROADENOMAS

- External radiation with cobalt, proton beam, or heavy particle therapy and brachytherapy with yttrium-90 rods implanted in the pituitary have all been used to treat macroadenomas but are not the primary mode of treatment.
- the current method of choice is probably the gamma knife and linear accelerator.
- damage to normal pituitary tissue may occur, leading to abnormal anterior pituitary function and diabetes insipidus.
- radiation therapy should be used only as adjunctive management following incomplete operative removal of large tumors.

Thank you!

youtube channel: Ina Irabon
www.wordpress.com: Doc Ina OB Gyne