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1401.5.27



# CAUSES & EVALUATION OF HYPERPROLACTINEMIA

# AGENDA

- **Causes of hyperprolactinemia**
- Physiologic causes
- Pathologic causes
  
- **Evaluation of hyperprolactinemia**
- Diagnosis
- Pitfalls in diagnosis
- History
- Physical exam
- Laboratory/imaging tests
- Chronic kidney disease
- Ectopic prolactin secretion

# CAUSES OF HYPERPROLACTINEMIA

## PHYSIOLOGIC CAUSES

- Pregnancy
- Nipple stimulation
- Breast examinations
- Stress

## PATHOLOGIC CAUSES

- Hypothalamic-pituitary disorders
- Decreased dopaminergic inhibition of prolactin secretion
- Drug induced

# PHYSIOLOGIC CAUSES

- Serum prolactin concentrations normally increase substantially :
- During pregnancy
  
- A lesser degree in response to:
- Nipple stimulation during breastfeeding
- Physical exertion
- Stress

# PREGNANCY

- Serum prolactin increases throughout pregnancy, reaching a **peak at delivery**
- The magnitude of the increase, is quite variable **35 to 600** mcg/L
- The probable cause of the hyperprolactinemia is the **increasing serum estradiol** concentrations during pregnancy
- By **six weeks after delivery**, estradiol secretion has decreased, and the **basal serum** prolactin concentration is usually normal ,even when the mother is breastfeeding

## Nipple stimulation and breast examinations

- Nipple stimulation **during breastfeeding** increases serum prolactin concentrations, presumably via a neural pathway
- The magnitude of the increase is directly proportional to the degree of preexisting lactotroph hyperplasia due to estrogen
- In the first weeks postpartum, as an example, the serum prolactin concentration increases up to 300 ng/ml above baseline in response to suckling
- In contrast, several months after delivery, the increase in prolactin in response to suckling in the breastfeeding woman is usually less than 10 ng/ml above baseline

## In nonlactating females and males:

- Nipple stimulation
- Breast imaging (mammography, ultrasound)
- Breast examination

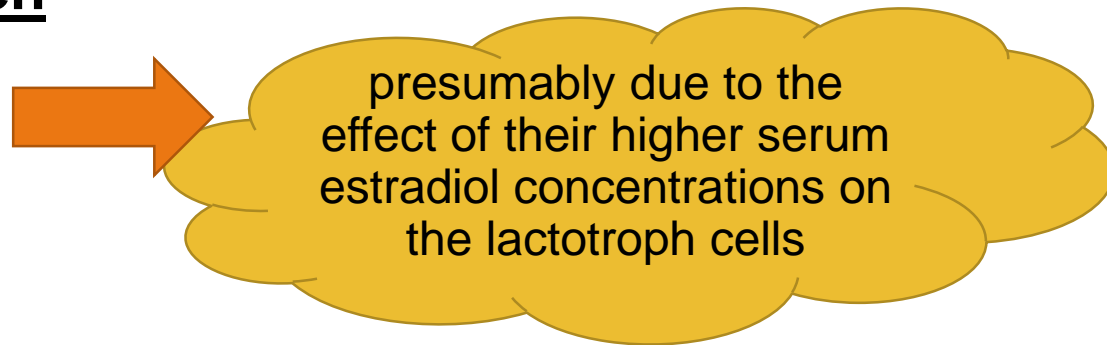
Does not increase prolactin secretion

Therefore, prolactin may be measured after a breast examination



# STRESS

- Stress of any kind, **physical or psychological**, can cause an increase in the serum prolactin concentration
- As with all stimuli of prolactin secretion, women have greater increases than men



- The magnitude of the increase in prolactin in response to stress is small, so the values rarely exceed 40 ng/mL

The background features several flowing, wavy bands of color. At the top, a thick, vibrant red band curves across the frame. Below it, a thinner, more translucent yellow band follows a similar path. In the lower portion, there are more complex, overlapping waves in shades of red and orange, creating a sense of depth and movement. The overall effect is dynamic and modern.

# **PATHOLOGIC CAUSES**

## HYPERPROLACTINEMIA DUE TO HYPOTHALAMIC-PITUITARY DISORDERS

- Lactotroph adenomas (prolactinomas), are benign tumors of the lactotroph cell
- Serum prolactin concentrations in patients who have lactotroph adenomas can range from minimally elevated to 50,000 ng/mL
- In hyperprolactinemia due to other causes, the concentrations rarely exceed 200 ng/mL

## Serum prolactin concentrations tend to vary with adenoma size

- Adenomas **<1 cm** in diameter are typically associated with serum prolactin values **below 200** ng/mL
- Those approximately **1.0 to 2.0 cm** in diameter with values between **200 and 1000** ng/mL
- Those **greater than 2.0 cm** in diameter with values **above 1000** ng/mL

## CONDITIONS ASSOCIATED WITH DECREASED DOPAMINERGIC INHIBITION OF PROLACTIN SECRETION

- These include:
  1. Damage to the dopaminergic neurons of the hypothalamus
  2. Pituitary stalk section
  3. Drugs that block dopamine receptors on lactotroph cells

# HYPOTHALAMIC OR PITUITARY DISORDERS

Any disease in or near the hypothalamus or pituitary that interferes with the secretion of dopamine or its delivery to the pituitary can cause hyperprolactinemia

- Tumors of the hypothalamus, both benign (eg, craniopharyngiomas) and malignant (eg, metastatic breast carcinoma)
- Infiltrative diseases of the hypothalamus (eg, sarcoidosis)
- Section of the hypothalamic-pituitary stalk (eg, due to head trauma or surgery)
- Adenomas of the pituitary other than lactotroph adenomas

# DRUG INDUCED

- A number of drugs may cause hyperprolactinemia
- Although drugs can cause hyperprolactinemia, they do not cause lactotroph adenomas
- In medication-induced hyperprolactinemia, serum prolactin concentrations are typically in the 25 to 100 ng/ml range
- One exception is the antipsychotic drug, risperidone, which may be associated with serum prolactin concentrations as high as 200 ng/ml

## Medications that cause hyperprolactinemia

Medication class	Frequency of prolactin elevation*	Mechanism
<b>Antipsychotics, first generation</b>		
Chlorpromazine	Moderate	Dopamine D <sub>2</sub> receptor blockade within hypothalamic tuberoinfundibular system.
Fluphenazine	High	
Haloperidol	High	
Loxapine	Moderate	
Perphenazine	Moderate	
Pimozide	Moderate	
Thiothixene	Moderate	
Trifluoperazine	Moderate	
<b>Antipsychotics, second generation</b>		
Aripiprazole	None or low	Dopamine D <sub>2</sub> receptor blockade.
Asenapine	Moderate	
Clozapine	None or low	
Iloperidone	None or low	
Lurasidone	None or low	
Olanzapine	Low	
Paliperidone	High	
Quetiapine	None or low	
Risperidone	High	
Ziprasidone	Low	



<b>Antidepressants, cyclic</b>		
Amitriptyline	Low	Not well understood. Possibly by GABA stimulation and indirect modulation of prolactin release by serotonin.
Desipramine	Low	
Clomipramine	High	
Nortriptyline	None	
<b>Antidepressants, SSRI</b>		
Citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	None or low (rare reports)	Same as for cyclic antidepressants.
<b>Antidepressants, other</b>		
Bupropion, venlafaxine, mirtazapine, nefazodone, trazodone	None	Not applicable.
<b>Antiemetic and gastrointestinal</b>		
Metoclopramide	High	Dopamine D <sub>2</sub> receptor blockade.
Domperidone (not available in United States)	High	
Prochlorperazine	Low	
<b>Antihypertensives</b>		
Verapamil	Low	Not well understood. Specific to verapamil. May involve calcium influx inhibition within tuberoinfundibular dopaminergic neurons.
Methyldopa	Moderate	Decreased conversion of L-dopa to dopamine; suppression of dopamine synthesis.
Most other antihypertensives (including other calcium channel blockers)	None	Not applicable.
<b>Opioid analgesics</b>		
Methadone, morphine, others	Transient increase for several hours following dose	Potentially an indirect effect of mu opiate receptor activation.

Medication-induced hyperprolactinemia can cause decreased libido and erectile dysfunction in men and galactorrhea and amenorrhea in women.

# IDIOPATHIC HYPERPROLACTINEMIA

- In a substantial number of patients whose serum prolactin concentration is between 20 and 100 ng/mL , no cause can be found
- Although many of these patients may have microadenomas not visible on imaging studies

In most of them, the serum prolactin concentrations change little during follow-up for several years

# ESTROGEN

- Estrogen increases prolactin secretion proportionate to the degree of estrogenization

The amount of estrogen in hormonal contraceptives generally does not cause hyperprolactinemia

# HYPOTHYROIDISM

- Hypothyroidism predisposes to hyperprolactinemia
- **Basal** serum prolactin concentrations are **normal** in most hypothyroid patients
- only the serum prolactin response to **stimuli**, such as TRH, is **increased**
- The values return to normal when the hypothyroidism is corrected

The mechanism of hyperprolactinemia in hypothyroidism is not known

Both :

- Enhanced hypothalamic synthesis of TRH
- Increased pituitary responsiveness to TRH have been described

# DECREASED CLEARANCE OF PROLACTIN

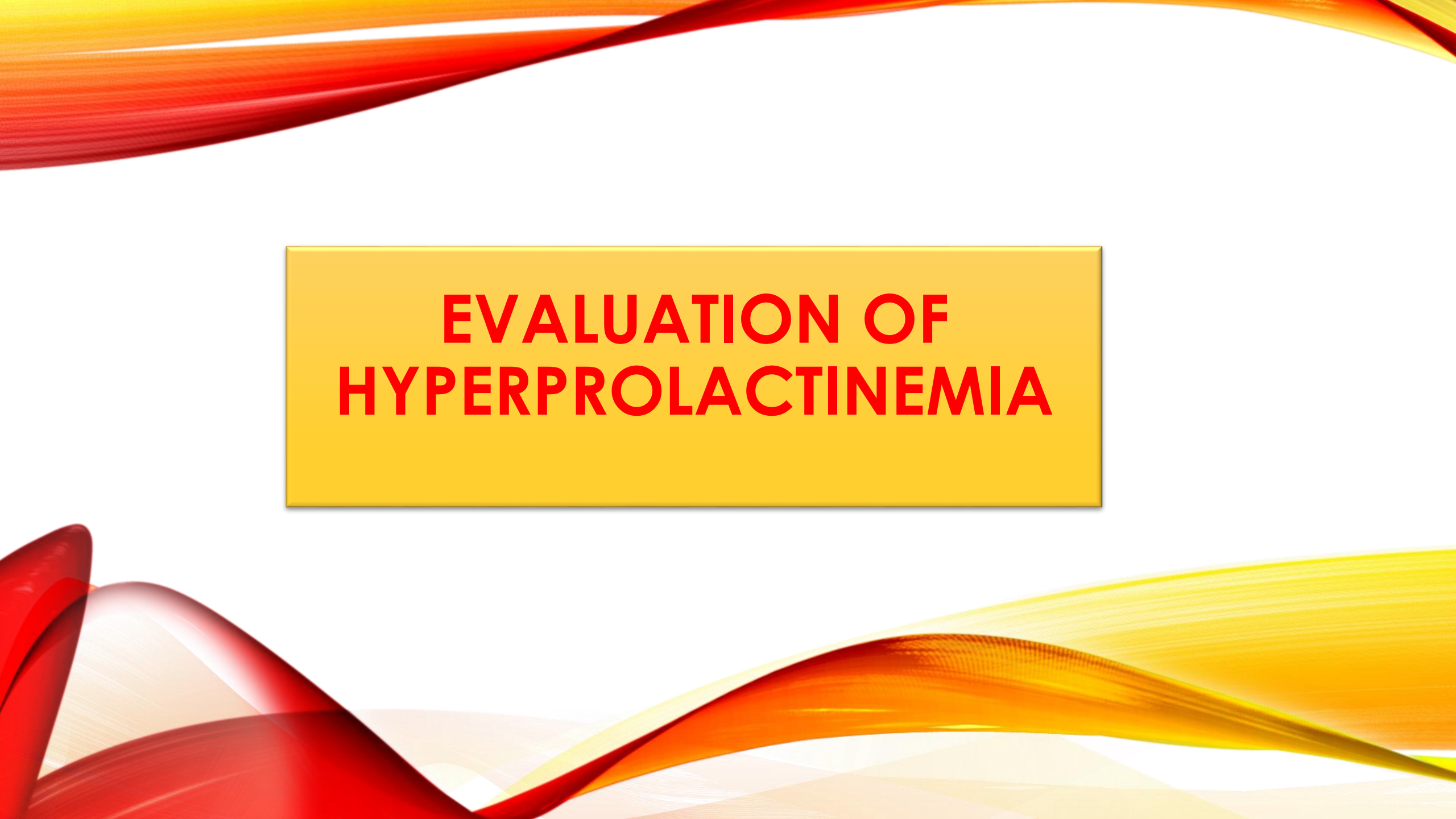
- Two causes of hyperprolactinemia due to decreased clearance of prolactin include :
  1. Chronic renal failure
  2. Macroprolactinemia

# CHRONIC RENAL FAILURE

- The serum prolactin concentration is high in patients who have chronic renal failure
- **The major mechanism is :**
- Threefold increase in **prolactin secretion**
- One-third decrease in metabolic **clearance rate**
- Serum prolactin concentration **returns to normal after renal transplantation**
- Hyperprolactinemia persists, **during dialysis**

# CHEST WALL INJURY

- Chest wall injuries, such as:
- Severe burns increase prolactin **secretion**, presumably due to a neural mechanism similar to that of suckling



# **EVALUATION OF HYPERPROLACTINEMIA**



# DIAGNOSIS

- The usual normal range for serum prolactin is approximately 5 to 20 ng/mL
- The diagnosis of hyperprolactinemia is made by:
- Serum prolactin concentration that is well above the normal range:
- **>20 ng/mL** in men and postmenopausal women
- **>30 ng/mL** in premenopausal women

# SERUM PROLACTIN MEASUREMENT

Since usual daily activities have little effect on prolactin secretion

The measurement can be performed at **any time**

Serum prolactin concentrations may increase slightly during:

- Sleep
- Strenuous exercise
- Emotional or physical stress (Occasionally )
- Intense breast stimulation
- High-protein meals

If an initial prolactin level is only **borderline high**, the test should be repeated

- The upper normal value for serum prolactin in most laboratories is approximately **20 ng/mL**
- **Meals** may stimulate prolactin secretion slightly
- If the prolactin concentration is only slightly high (up to **40 ng/mL** in **males** and **postmenopausal** females and up to **50 ng/mL** in **premenopausal** females)



It should be repeated on a **fasting** sample before the patient is considered to have hyperprolactinemia



# **PITFALLS IN DIAGNOSIS**

# HOOK EFFECT

- Caution should be exercised in interpreting serum prolactin concentrations:
- **Between 20 and 200 ng/mL** in the presence of a **macroadenoma** because of possible artifactually **low** values due to the "hook effect"
- This effect occurs when a very high serum prolactin, eg, 5000 ng/mL saturates both the capture and signal antibodies used in immunoradiometric and chemiluminescent assays, **preventing the binding of the two in a "sandwich."**
- The result is an apparent prolactin concentration that is only modestly elevated, suggesting that the macroadenoma is clinically **nonfunctioning**
- The artifact can be avoided by repeating the assay using a **1:100 dilution of serum**

# MACROPROLACTIN

- The most common form of native prolactin in serum is **23 kD** in size
- Macroprolactin causes hyperprolactinemia through **decreased prolactin clearance**
- Macroprolactin is native prolactin that is bound to immunoglobulin G (**IgG**) and is usually 150 to 170 kDa in size

# MACROPROLACTINEMIA

- These complexes(native prolactin that is bound to IgG) are **immunologically detectable but not biologically active**, so they appear to cause no clinical abnormality
- Misdiagnosis can be avoided by asking the laboratory to pretreat the serum with polyethylene glycol to precipitate the macroprolactin before the immunoassay for prolactin

# EVALUATION OF HYPERPROLACTINEMIA

- Because **meals** may stimulate prolactin secretion **slightly**:
  - I. If an initial serum prolactin concentration is only **slightly elevated (21 to 40 ng/mL )**, the test should be repeated on a **fasting sample** before the patient is considered to have hyperprolactinemia
  - II. If serum prolactin is elevated on the second sample, hyperprolactinemia is confirmed, and the next step is to **determine the cause**





The  
evaluation  
is aimed  
at



- (1) Exclusion of **pharmacologic** causes of hyperprolactinemia and
- (2) Exclusion of **extrapituitary** causes of hyperprolactinemia and
- (3) Neuroradiologic evaluation of the **hypothalamic-pituitary** region

# HISTORY

- A search for the cause of the hyperprolactinemia should begin with the history
- One should inquire about Pregnancy (physiologic hyperprolactinemia)
- Medications that can cause hyperprolactinemia (such as estrogens, risperidone, metoclopramide, antidepressant drugs, cimetidine, methyldopa, and verapamil)
- One should also inquire about headache, visual symptoms
- symptoms of hypothyroidism, and a history of renal disease

# PHYSICAL EXAMINATION

- The physical examination should be directed toward :
  - I. Testing for a chiasmal syndrome (eg, bitemporal field loss)
  - II. Looking for chest wall injury
  - III. Signs of hypothyroidism
  - IV. Signs of hypogonadism


# LABORATORY

- Studies should be performed to test for :
  - a. Hypopituitarism
  - b. Primary hypothyroidism
  - c. Renal insufficiency

# IMAGING TESTS

- **MRI of the pituitary ±contrast** should be performed in a patient with any degree of hyperprolactinemia to look for a mass lesion in the hypothalamic-pituitary region

- **Unless the patient:**
  - Is taking a **medication** known to cause hyperprolactinemia or
  - Has marked **renal** impairment

- 
- If a mass lesion is found in the region of the sella turcica, secretion of other pituitary hormones should also be evaluated
  - If the MRI shows a normal hypothalamic-pituitary region and there are no obvious causes of hyperprolactinemia, the diagnosis is **idiopathic hyperprolactinemia**
  - Idiopathic hyperprolactinemia may, in some patients, be due to **microadenomas** that are too small to be seen on imaging

# MRI IN DRUG-INDUCED HYPERPROLACTINEMIA

- Most drugs do not cause an elevation to over 100 ng/mL, but the antipsychotic drug **risperidone** can cause an elevation up to 300 or even 400 ng/mL

- Recommend ordering **MRI**: if the serum prolactin concentration is **>100 ng/mL** in patients taking a **drug** known to elevate the prolactin concentration but
  - **>300** ng/mL in those taking **risperidone**

# CHRONIC KIDNEY DISEASE

- Hyperprolactinemia in CKD is due to **decreased clearance of prolactin**
- It is unclear at which threshold of kidney dysfunction prolactin begins to rise
- Serum prolactin concentrations are typically elevated to as much as **10-fold normal** in patients with ESRD requiring dialysis
- Prolactin levels of this magnitude in the setting of end-stage kidney disease (eg, CKD 4 or 5) :
  - a. In the absence of other pituitary hormone abnormalities or
  - b. Symptoms suggestive of pituitary tumor (eg, visual loss) typically need **no further pituitary evaluation**



## The decision to obtain an MRI of the pituitary in ESRD is based on:

- The magnitude of the prolactin elevation
- The degree of renal impairment
- On other findings, such as visual impairment
- Other pituitary hormone abnormalities



- MRI for a patient with any degree of renal impairment should be ordered **without gadolinium**

# ECTOPIC PROLACTIN SECRETION

- Secretion of prolactin from an ectopic source is uncommon but has been reported from several types of tumors
- An ectopic source should be suspected in a patient who has:
  - Hyperprolactinemia that is not associated with a large sellar mass and
  - Is completely resistant to cabergoline

با تشکر از توجه شما

