بسم الله الرحمن الرحيم

PROLACTIN-SECRETING ADENOMAS

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- Prolactinomas are the most frequently secretory pituitary tumors,
- annual incidence of approximately 30 per 100,000
- would be much higher if the estimate included microadenomas discovered in approximately 11% of pituitaries at autopsy, 46% of which immunostain positively for PRL.
- The f/m ratio for microprolactinomas is 20 : 1,
- For macroadenomas the gender ratio is roughly equivalent. Both PRL levels and tumor size generally remain stable

- in some patients, microadenomas may disappear after discontinuing dopamine agonist therapy,
- 7% to 14% of microadenomas continue to grow.
- Smaller prolactinomas may sometimes regress after pregnancy and lactation

- Macroprolactinomas have propensity to grow
- tumor size correlates with serum PRL levels
- PRL level higher than 200 ng/mL is strongly indicative of a PRL-secreting pituitary tumor.
- Prolactinomas are larger in men than in women (26 ± 2 mm vs. 10 ± 1 mm) and more invasive
- Giant prolactinomas have being larger than 4 cm in diameter with a serum PRL of higher than 1000 ng/mL, and they occur more commonly in men.

- PRL levels higher than 200 ng/mL are seen drugs likes risperidol,
- If PRL levels do not normalize or medication withdrawal is not possible, a pituitary MRI should be performed.
- but levels higher than 500 ng/mL are exclusively observed in patients with prolactinomas.
- a PRL concentration of less than 200 ng/mL in a patient harboring a macroadenoma indicates that the tumor is likely not producing PRL,
- hyperprolactinemia may occur as a result of mass pressure on the pituitary stalk or portal circulation
- microprolactinomas can be associated with PRL levels ranging from minimal to hundreds of ng/mL.

Prolactin Function

- PRL is essential for human species survival,
- because it is responsible for
  - *milk production during pregnancy and lactation.*
  - *reproductive and metabolic effects,*
  - *mammary development, freshwater survival, melanin synthesis, molting, and parental behavior*

- Elevated PRL causes sexual dysfunction via a short loop feedback effect on gonadotropin pulsatility, presumably inhibiting GnRH and LH pulse frequency and amplitude.
- High PRL directly inhibits ovarian and testicular function

- Up to 50% of women and 35% of men have galactorrhea
- Bone density may decrease in both men and women as a result of hyperprolactinemia induced sex steroid deficiency

- increase in vertebral fractures detected radiologically has been reported in women

- In Women with prolactinomas
  - *primary or secondary amenorrhea, oligomenorrhea, menorrhagia, delayed menarche, or regular menses with a short luteal phase that may cause infertility.*
  - *changes in libido and vaginal dryness.*

- In men Sexual dysfunction in men usually manifests:
  - *loss or decrease in libido, impotence, premature ejaculation or intracoital erection loss, oligospermia, or azospermia.*

The role of prolactin in central nervous system inflammation

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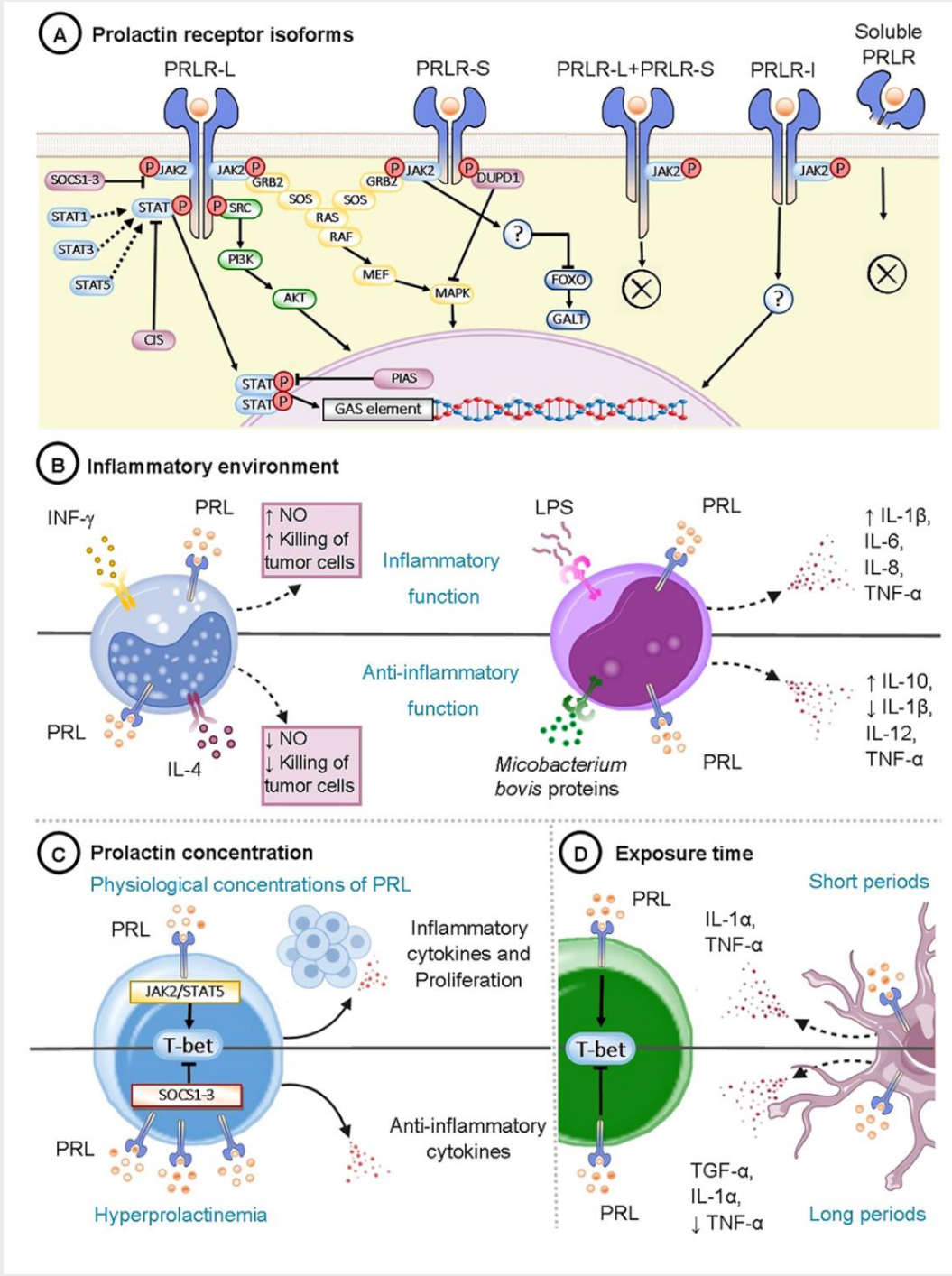
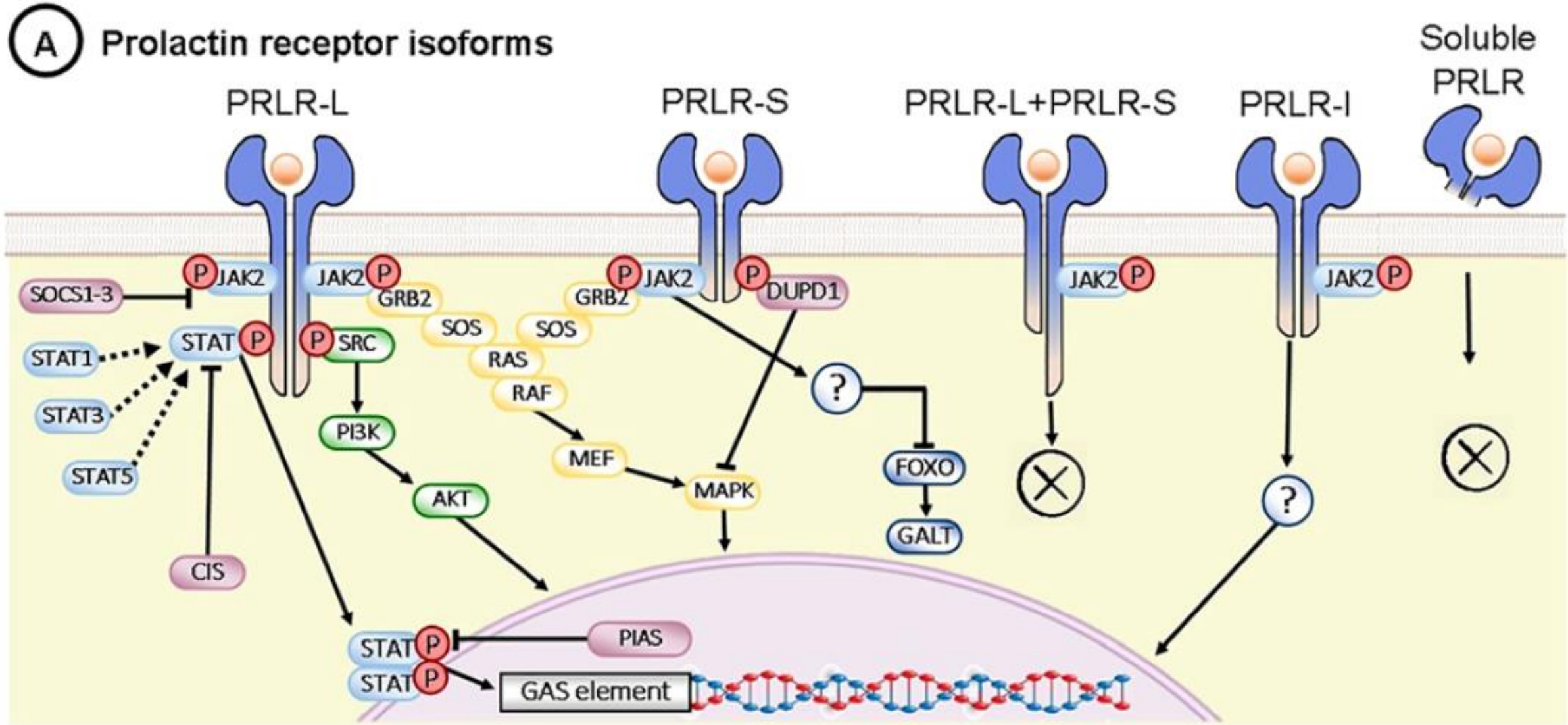
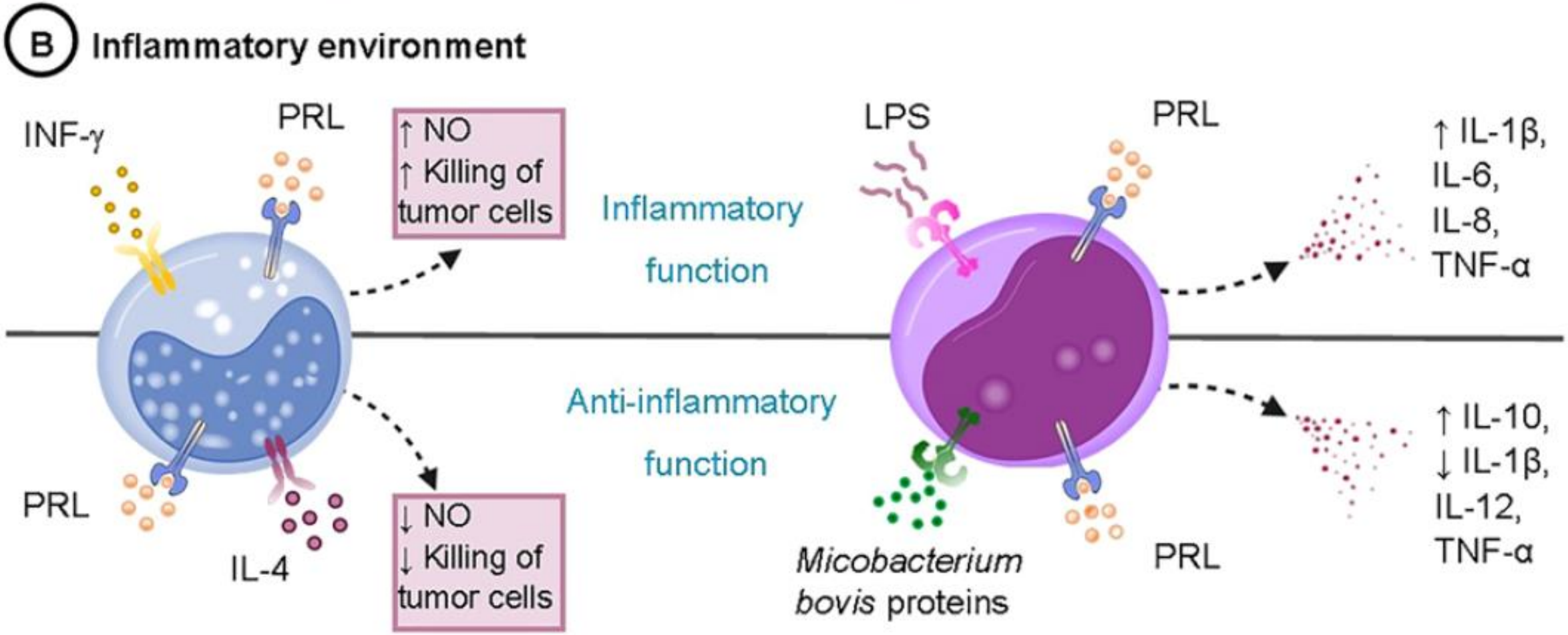
https://doi.org/10.1515/revneuro-2020-0082
Received July 29, 2020; accepted October 25, 2020; published online January 1, 2021


A Prolactin receptor isoforms
PRLR-L
PRLR-S
PRLR-L+PRLR-S
PRLR-I
Soluble PRLR
SOCS1-3
JAK2
GRB2
SOS
RAS
RAF
MEF
MAPK
STAT1
STAT3
STAT5
STAT
SRC
PI3K
AKT
CIS
DUPD1
FOXO
GALT
PIAS
GAS element
B Inflammatory environment
INF-γ
PRL
↑ NO
↑ Killing of tumor cells
Inflammatory function
LPS
↑ IL-1β, IL-6, IL-8, TNF-α
Anti-inflammatory function
↑ IL-10, ↓ IL-1β, IL-12, TNF-α
IL-4
↓ NO
↓ Killing of tumor cells
Micobacterium bovis proteins
C Prolactin concentration
Physiological concentrations of PRL
JAK2/STAT5
T-bet
SOCS1-3
Inflammatory cytokines and Proliferation
Anti-inflammatory cytokines
Hyperprolactinemia
D Exposure time
Short periods
IL-1α, TNF-α
TGF-α, IL-1α, ↓ TNF-α
Long periods

(A) The image represents some of the signaling pathways activated or inhibited by different PRLR isoforms

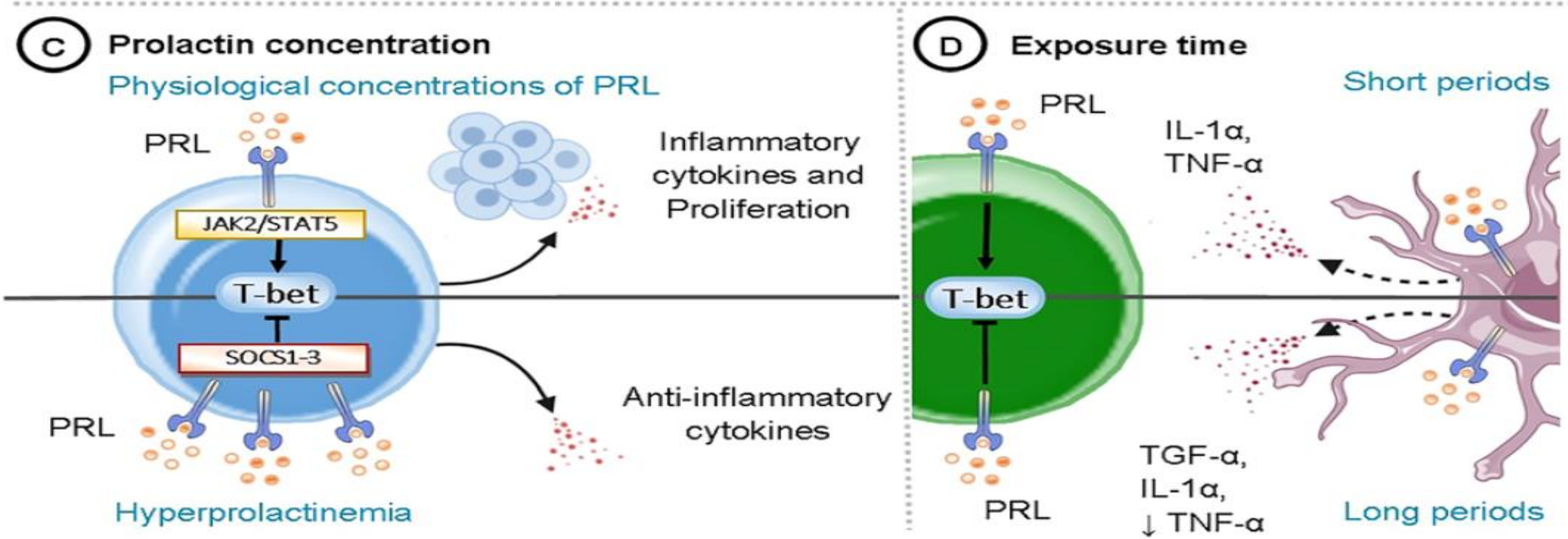


(B) Schematic diagram of the dual function of PRL when it interacts with cytokines and PAMPs. PRL, when acting together with IFN-γ and LPS, favors inflammatory functions in macrophages and monocytes (top).
Illustration of PRL's anti-inflammatory effect by acting alongside IL-4 and M. bovis proteins in these cells (bottom).



(C) The schematic diagram contrasts the effect of PRL at low and high concentrations on transcription factor T-bet expression.

(D) Short periods of exposure to PRL favors T-bet expression in T cells (green) and secretion of inflammatory cytokines in astrocytes (purple) (top). However, prolonged exposure times favor T-bet and TNF-α inhibition (bottom)



- Figure 1: Factors that regulate the function of prolactin.
- (A) The image represents some of the signaling pathways activated or inhibited by different PRLR isoforms (the functions involved in these pathways are described in the text).
- (B) Schematic diagram of the dual function of PRL when it interacts with cytokines and PAMPs. PRL, when acting together with IFN-γ and LPS, favors inflammatory functions in macrophages and monocytes (top). Illustration of PRL's anti-inflammatory effect by acting alongside IL-4 and M. bovis proteins in these cells (bottom).
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- PRL: prolactin, PRLR: prolactin receptor, PRLR-L: long isoform of the
- PRLR, PRLR-I: intermediate isoform of the PRLR, PRLR-S: short isoform of the PRLR, T-bet: T-box transcription factor TBX21, NO: nitric oxide, LPS: lipopolysaccharide, PAMPs: pathogen-associated molecular patterns.

TABLE 9-17

Signs and Symptoms of Prolactinomas

Signs and Symptoms Associated with Tumor Mass	Signs and Symptoms Associated with Hyperprolactinemia
Visual field abnormalities	Amenorrhea, oligomenorrhea, infertility
Blurred vision or decreased visual acuity	Decreased libido, impotence, premature ejaculation, erectile dysfunction, oligospermia
Symptoms of hypopituitarism	Galactorrhea
Headaches	Osteoporosis
Cranial nerve palsies	
Pituitary apoplexy	
Seizures (temporal lobe)	
Hydrocephalus (rare)	
Unilateral exophthalmos (rare)	

Regulation of the hypothalamic-pituitary-prolactin (PRL) axis.

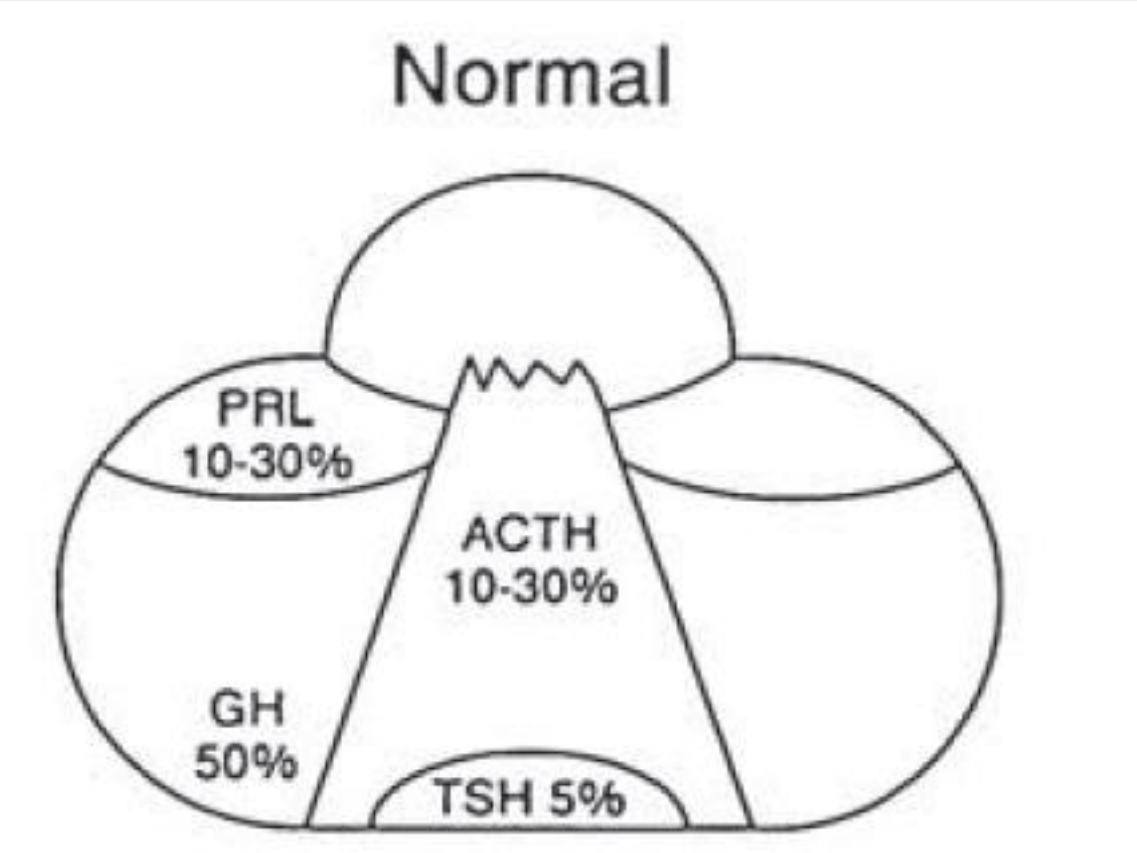
- The predominant effect of the hypothalamus is inhibitory, mediated principally by the tuberohypophyseal dopaminergic neuron
- The dopamine neurons are stimulated by acetylcholine (ACh) and glutamate and inhibited by histamine and opioid peptides.
- One or more prolactin-releasing factors (PRFs) probably mediate acute release of PRL (e.g., in suckling, during stress).
- PRFs, including thyrotropin-releasing hormone (TRH), vasoactive intestinal polypeptide (VIP), and oxytocin.
- PRF neurons are activated by serotonin (5-HT).
- Estrogen sensitizes the pituitary to release PRL,

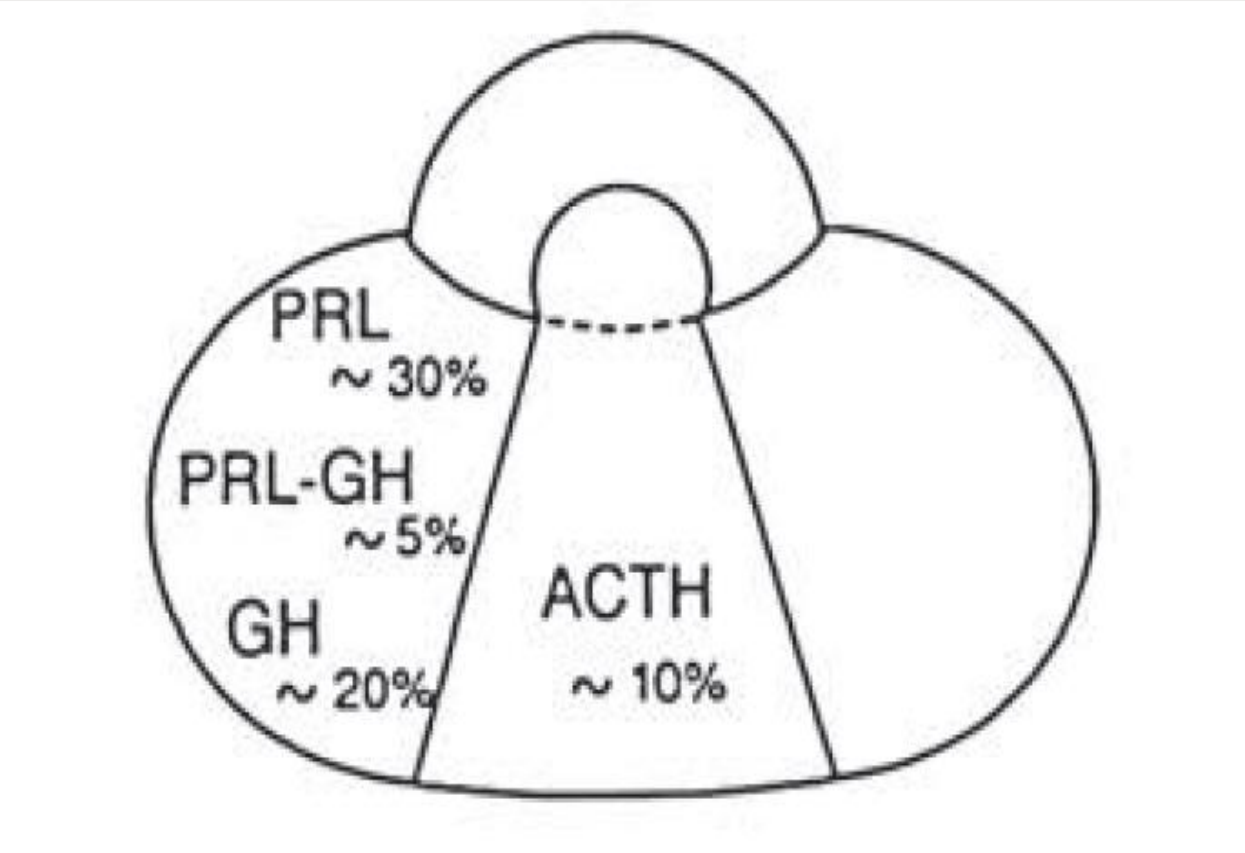
TABLE 9.13 Pituitary Adenoma Prevalence[a]

	Belgium (n = 68)	Finland (n = 164)	Iceland (n = 471)	Malta (n = 316)	Sweden (n = 592)	Switzerland (n = 44)	United Kingdom (n = 63)
Population prevalence	1/1064	1/1471	1/865	1/1321	1/2688	1/1241	1/1289
ACTH secreting, %	6	3	6	2	4	4	2
GH secreting, %	13	8	11	16	9	9	11
PRL secreting, %	66	51	40	46	32	56	57
Nonfunctioning, %	15	37	43	34	54	30	28

[a]Includes three adenomas not classified, nine TSH-secreting adenomas, and one gonadotrophin-secreting adenoma.

Data from Molitch ME. Diagnosis and treatment of pituitary adenomas: a review. *JAMA*. 2017;317:516–524.





Left panels show normal pituitary
Right panels depict adenoma distribution with multiple incidental adenomas shown by arrows.

Etiology of hyperprolactinemia

TABLE 8-3
Etiology of Hyperprolactinemia

Physiologic

Pregnancy
Sucking
Stress
Sleep
Coitus
Exercise

Pathologic

Hypothalamic-Pituitary Stalk Damage
Tumors
Craniopharyngioma
Suprasellar pituitary mass extension
Meningioma
Dysgerminoma
Hypothalamic metastases
Granulomas
Infiltrations
Rathke's cyst
Irradiation
Trauma: pituitary stalk section, sellar surgery, head trauma

Pituitary
Prolactinoma
Acromegaly
Macroadenoma (compressive)
Idiopathic
Plurihormonal adenoma
Lymphocytic hypophysitis
Parasellar mass
Macroprolactinemia

Systemic Disorders
Chronic renal failure
Polycystic ovary syndrome
Cirrhosis
Pseudocyesis
Epileptic seizures
Cranial irradiation
Chest: neurogenic, chest wall trauma, surgery, herpes zoster

Genetic
Inactivating prolactin receptor mutation

Pharmacologic

Neuropeptides
Thyrotropin-releasing hormone

Drug-Induced Hypersecretion
Dopamine Receptor Blockers
Phenothiazines: chlorpromazine, perphenazine
Butyrophenones: haloperidol
Thioxanthenes
Metoclopramide

Dopamine Synthesis Inhibitors
α-Methyldopa

Catecholamine Depleters
Reserpine

Cholinergic Agonists
Physostigmine

Antihypertensives
Labetolol
Reserpine
Verapamil

H_2 Antihistamines
Cimetidine
Ranitidine

Estrogens
Oral contraceptives
Oral contraceptive withdrawal

Anticonvulsants
Phenytoin

Neuroleptics
Chlorpromazine
Risperidone
Promazine
Promethazine
Trifluoperazine
Fluphenazine
Butaperazine
Perphenazine
Thiethylperazine
Thioridazine
Haloperidol
Pimozide
Thiothixene
Molindone

Opiates and Opiate Antagonists
Heroin
Methadone
Apomorphine
Morphine

Antidepressants
Tricyclic antidepressants: chlorimipramine
Selective serotonin reuptake inhibitors: flu

Medications that cause hyperprolactinemia

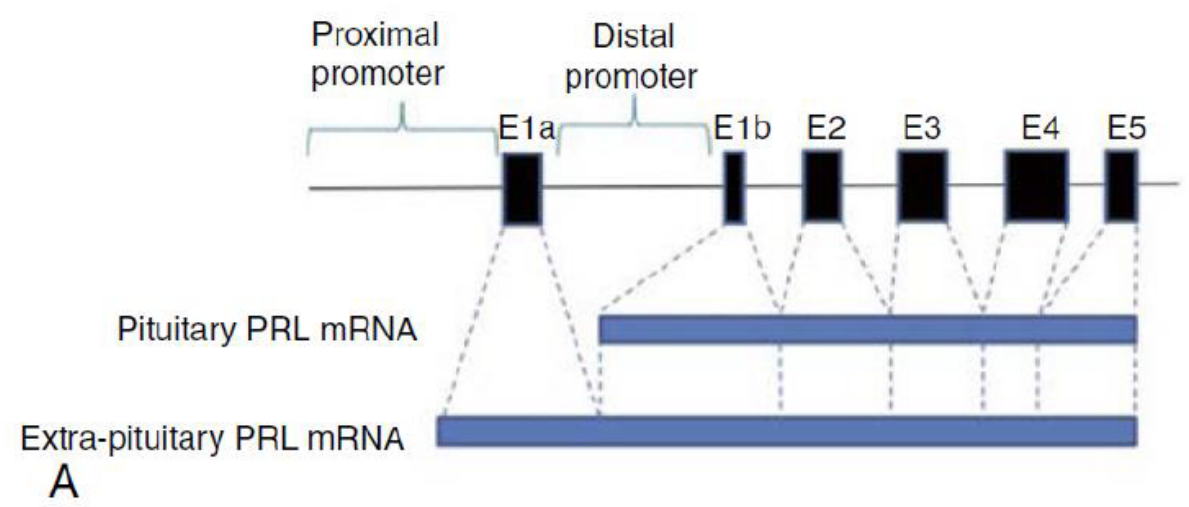
Medication class	Frequency of prolactin elevation*	Mechanism
Antipsychotics, first generation		
Chlorpromazine	Moderate	Dopamine D_2 receptor blockade within hypothalamic tuberoinfundibular system.
Fluphenazine	High	
Haloperidol	High	
Loxapine	Moderate	
Perphenazine	Moderate	
Pimozide	Moderate	
Thiothixene	Moderate	
Trifluoperazine	Moderate	
Antipsychotics, second generation		
Aripiprazole	None or low	Dopamine D_2 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	

Antidepressants, cyclic		
Amitriptyline	Low	Not well understood. Possibly by GABA stimulation and indirect modulation of prolactin release by serotonin.
Desipramine	Low	
Clomipramine	High	
Nortriptyline	None	
Antidepressants, SSRI		
Citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	None or low (rare reports)	Same as for cyclic antidepressants.
Antidepressants, other		
Bupropion, venlafaxine, mirtazapine, nefazodone, trazodone	None	Not applicable.
Antiemetic and gastrointestinal		
Metoclopramide	High	Dopamine D_2 receptor blockade.
Domperidone (not available in United States)	High	
Prochlorperazine	Low	
Antihypertensives		
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.
Opioid analgesics		
Methadone, morphine, others	Transient increase for several hours following dose	Potentially an indirect effect of mu opiate receptor activation.

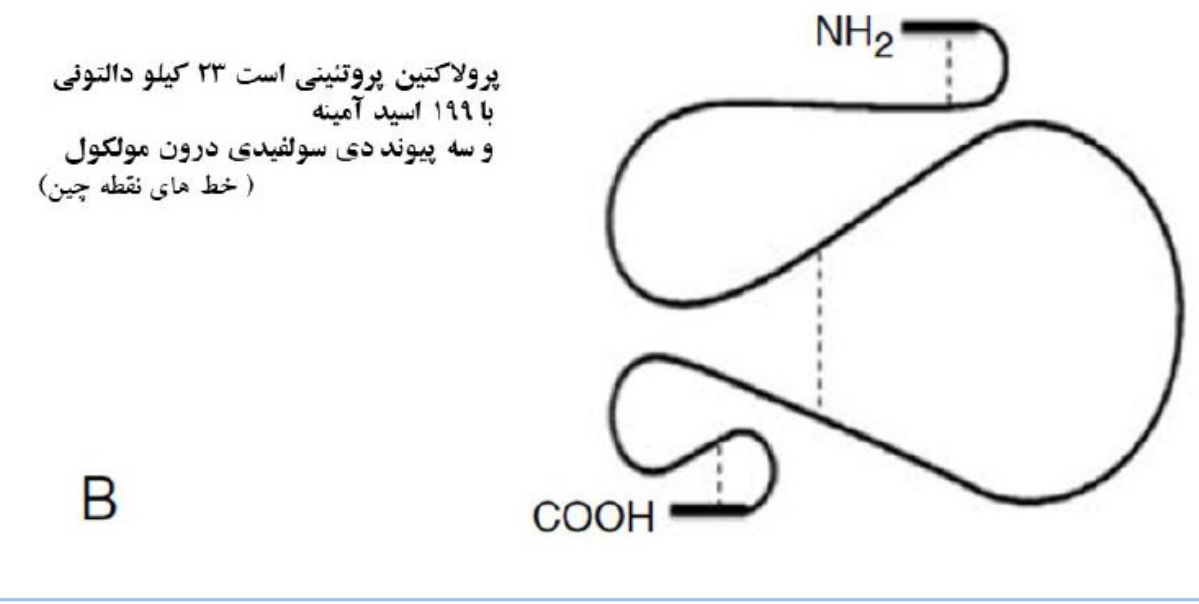
Prolactin Assays

- The main PRL is 23-kDa monomer
- A proportion may be glycosylated (25 kDa) which can facilitate aggregation of monomers to form "**big prolactin**" (10-20% of circulating forms), which is 50 to 60 kDa and likely is clinically silent
- larger molecular weight forms have also been reported due to glycosylation, aggregation, covalent and noncovalent bonding.

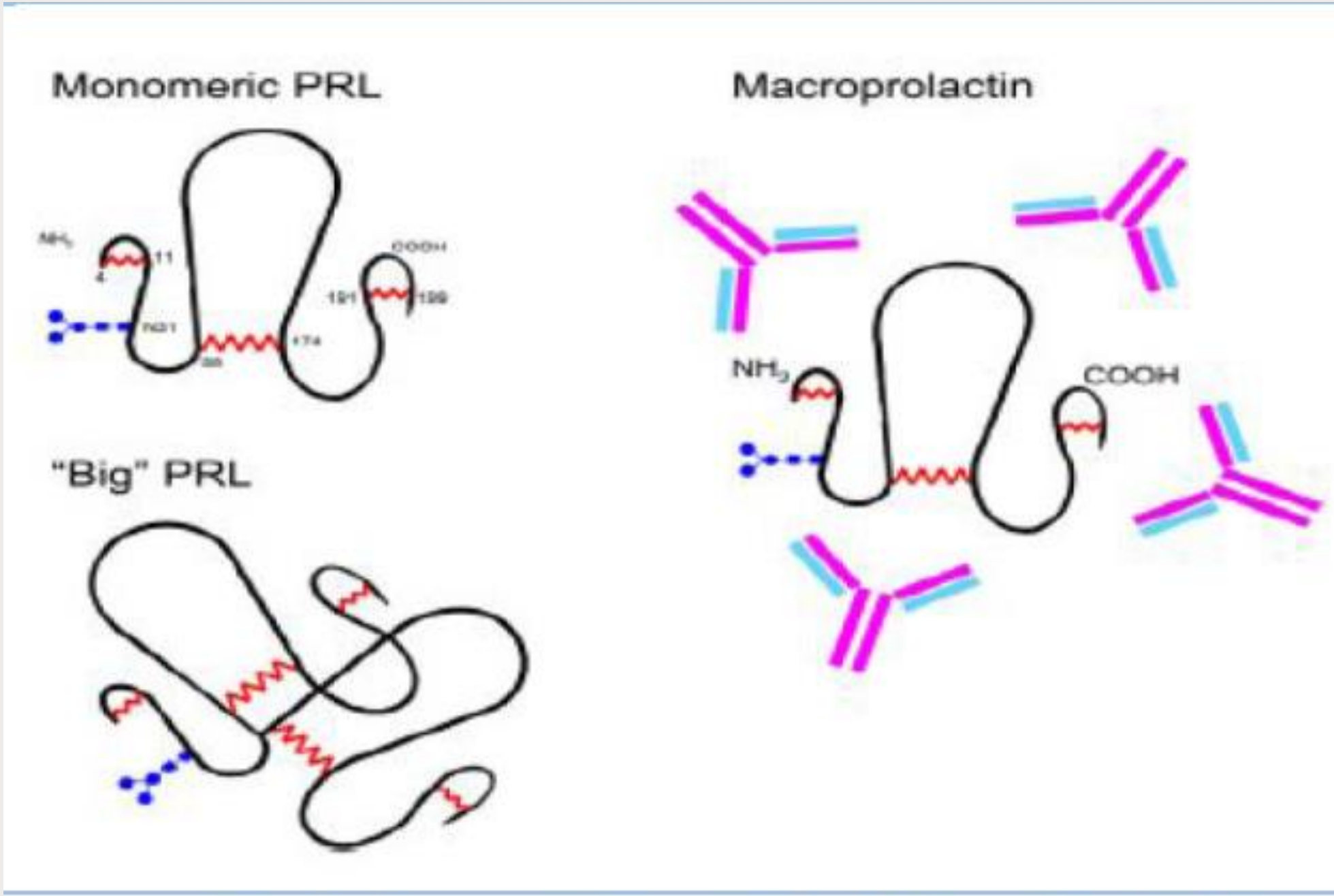
- MacroPRL is a large protein complex of 150 kDa or more
- macroPRL is considered to be significant if <40% of immunoreactive PRL is monomeric
- (IgG) was the predominant immunoglobulin subclass and PRL-specific
- MacroPRL has a slower clearance rate leading to accumulation in the circulation and thus, elevated immunoreactive PRL levels
- it has poor bioavailability;
- it is confined to the intravascular compartment and is unable to pass through capillary walls to interact with target tissues
- anti-PRL antibodies can be responsible for macroPRL, the association with autoimmune disease



رونویسی ژن پرولاکتین از دو "ناحیه پروموتور جایگزین" (E1 تا E5) انجام می شود.



شکل ۸-۲- نمائی از ژن و مولکول پرولاکتین.



شکل ۸ – ۳– سه شکل مختلف پرولاکتین در گردش خون.

Pitfalls in diagnosis

- Hook effect
- Macroprolactin

Hook effect

- — Caution should be exercised in interpreting serum prolactin concentrations between 20 and 200 ng/mL (20 to 200 mcg/L SI units) in the presence of a macroadenoma because of "**hook effect**"
- This effect occurs when a very high serum prolactin, eg, 5000 ng/mL (5000 mcg/L SI units),
- 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 suggesting that the macroadenoma is clinicall nonfunctioning.
- The artifact can be avoided by repeating the assay using a 1:100 dilution of serum

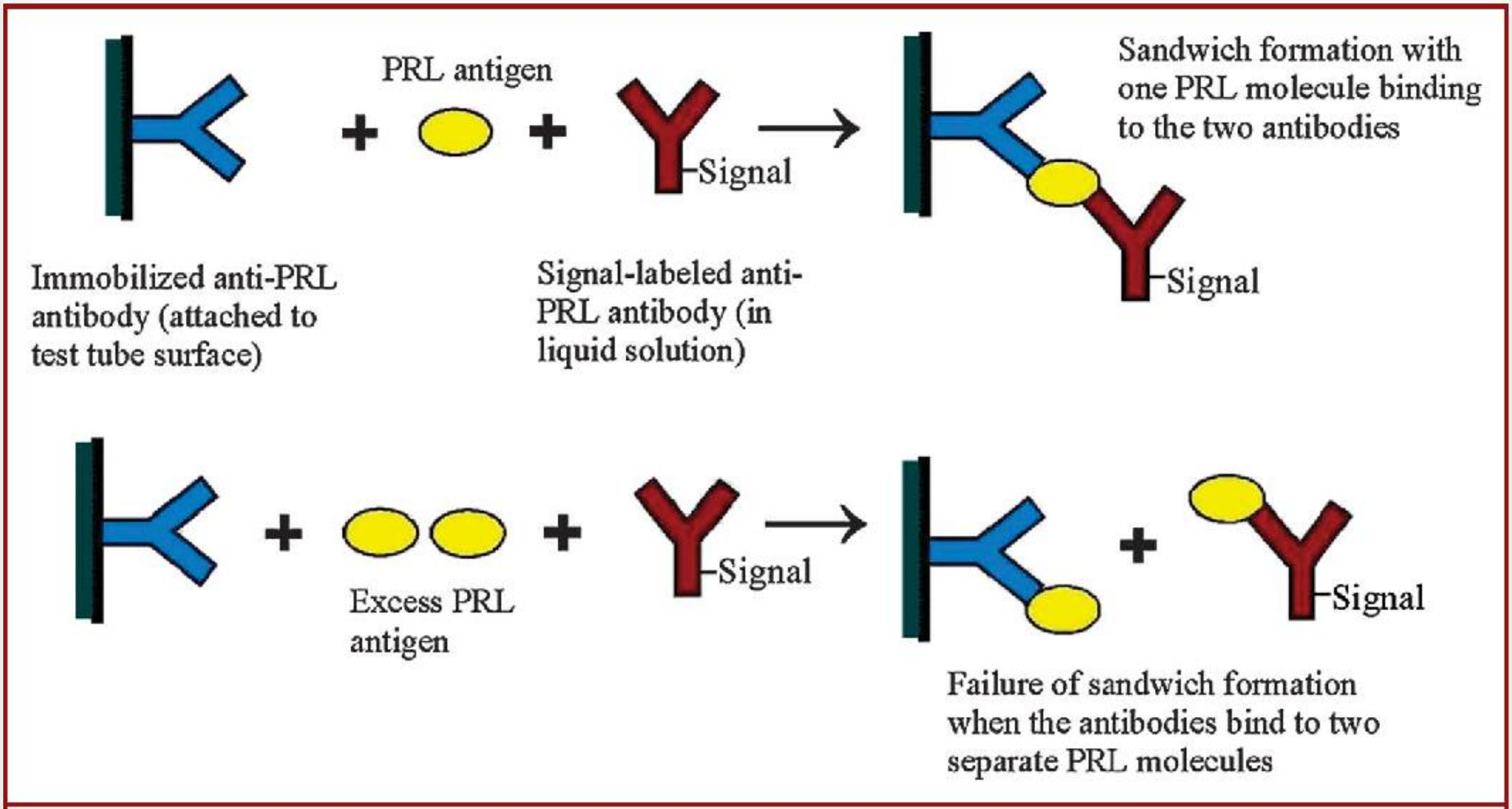
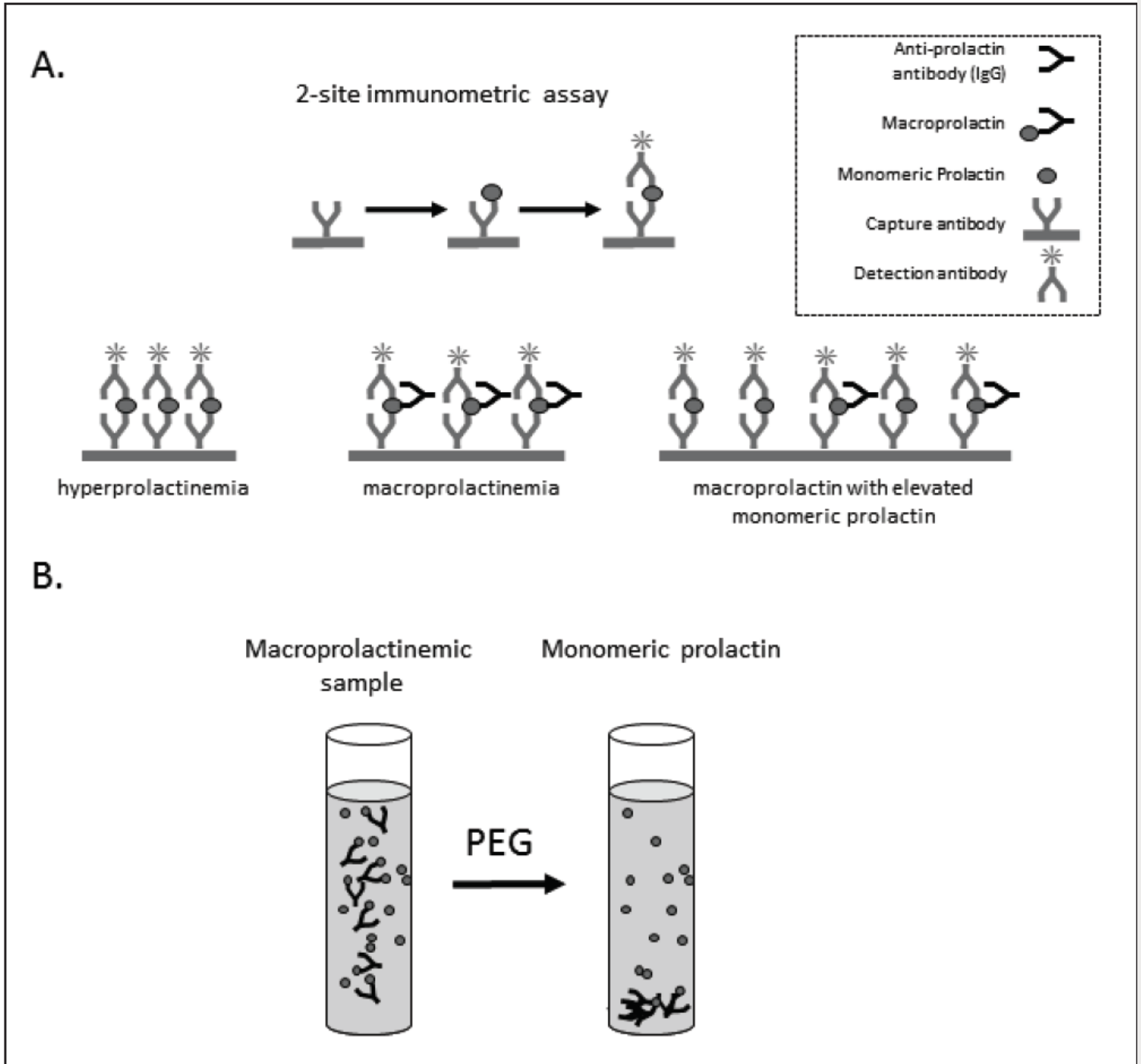


FIGURE 5. *Illustration of the radioimmunoassay for prolactin (PRL). In the top images, the antibodies and antigen form the*

Macroprolactin

- 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, compared with 23 kDa for monomeric prolactin
- polyethylene glycol to precipitate the macroprolactin before the immunoassay
- macroprolactinemia can also occur in patients with pituitary tumors
- Pituitary adenomas are diagnosed in approximately 20% of patientswith macroprolactinemia


A.
2-site immunometric assay
Anti-prolactin antibody (IgG)
Macroprolactin
Monomeric Prolactin
Capture antibody
Detection antibody
hyperprolactinemia
macroprolactinemia
macroprolactin with elevated monomeric prolactin
B.
Macroprolactinemic sample
Monomeric prolactin
PEG

- Prolactin complexed as macroprolactin is still able to interact with the capture antibody of immunometric assays and is detected by the detection antibody.
- There is wide variability among assays for detection of complexed prolactin

B, Illustration of PEG precipitation of macroprolactin forms. *PEG* = polyethylene glycol.

We recommend screening for macroprolactin

- (1) asymptomatic patients,
- (2) patients with atypical clinical picture,
- (3) patients with conflicting PRL results in distinct assays,
- (4) patients with lack of decline of serum PRL levels with DA,

Italian Association of Clinical Endocrinologists (AME) and International Chapter of Clinical Endocrinology (ICCE). Position statement for clinical practice: prolactin-secreting tumors

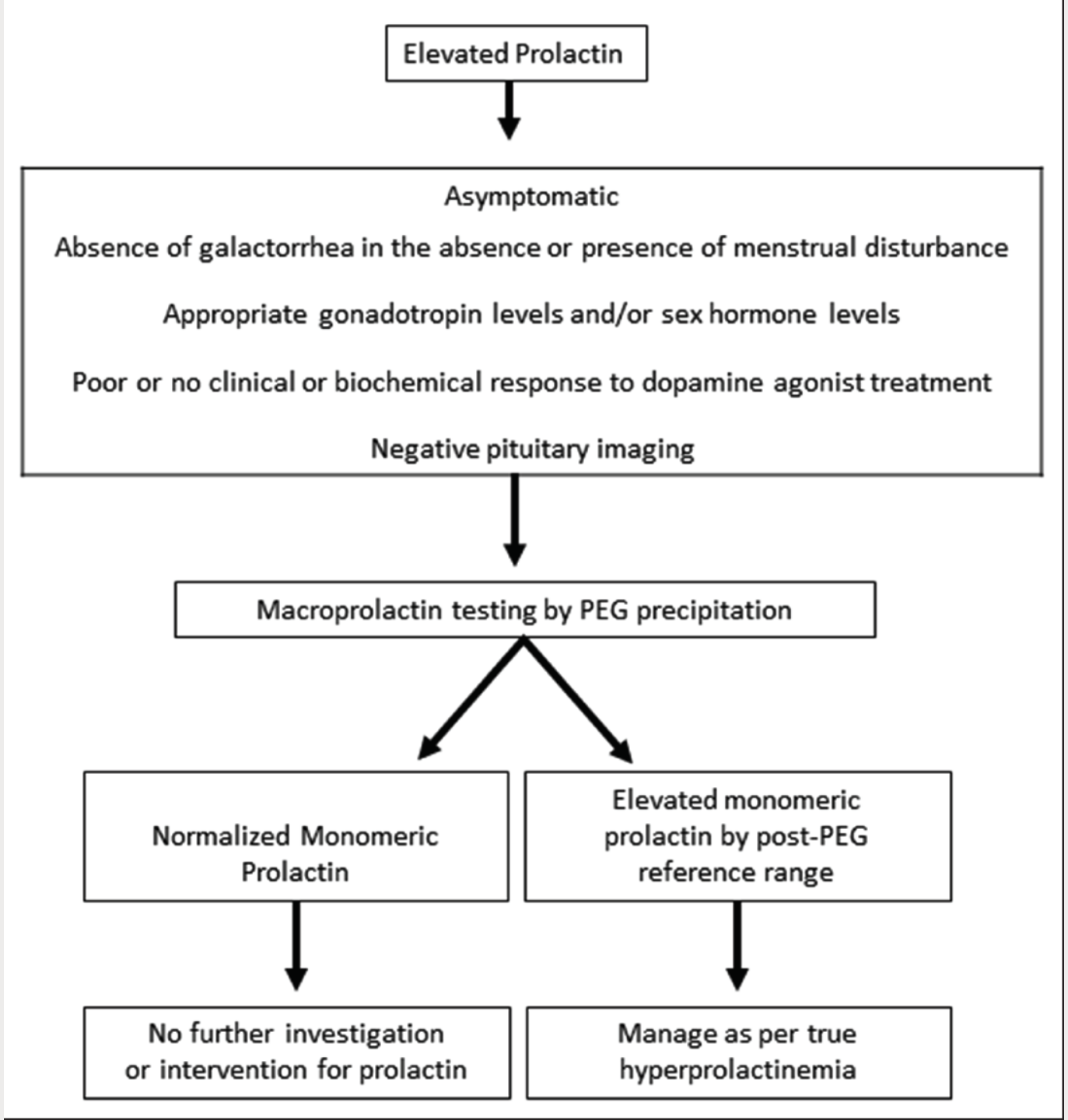
- We recommend confirming the finding of randomly elevated PRL level with the insertion of an i.v. catheter and saline infusion for 15–20 min before blood sampling for PRL assay, unless PRL is clearly elevated (>80–100 ng/mL)

- We recommend that in cases of large pituitary adenomas (i.e. >3 cm) associated with normal or mildly elevated PRL levels, PRL levels should be measured after serial sample dilution to rule out hook effect
- PRL levels >200–250 ng/mL are almost always due to a macroprolactinoma
- We recommend screening of hypopituitarism at diagnosis :
  - *In all patients with MP,*
  - *In microP only if there is a clinical suspicion.*
- We suggest evaluating insulin-like growth factor I (IGF-I) levels in all PRL-secreting tumors at diagnosis

- We recommend MRI control within 3–6 months for MP and suggest it within 1 year for microP after DA initiation.
- Earlier follow-up should be considered in case of non-responders or new symptoms
- We suggest limiting the use of Gd during follow-up (especially in MPs)
- We recommend that a genetic basis for prolactinoma should be suspected based on:
  - *family history, early onset of the adenoma (i.e. before 20 years) and aggressive behavior (i.e. uncontrolled tumor growth despite appropriate treatment), and concomitant other endocrine diseases*

- We suggest periodic cardiac auscultation and ultrasonography in patients with a murmur or consuming more than 2 mg per week of Cab, without overlooking extra-endocrine causes of valvular involvement

- We suggest DA withdrawal in MP only in patients showing:
  - *complete disappearance of tumor mass (or at least a 50% decrease in tumor size) and persistence of low-normal PRL levels after progressive down titration of DA during chronic treatment, with a careful quarterly follow-up of PRL levels and gonadal status*


Elevated Prolactin
Asymptomatic
Absence of galactorrhea in the absence or presence of menstrual disturbance
Appropriate gonadotropin levels and/or sex hormone levels
Poor or no clinical or biochemical response to dopamine agonist treatment
Negative pituitary imaging
Macroprolactin testing by PEG precipitation
Normalized Monomeric Prolactin
Elevated monomeric prolactin by post-PEG reference range
No further investigation or intervention for prolactin
Manage as per true hyperprolactinemia

Evaluation

Even minimal to moderate PRL elevations are important to investigate

- Hyperprolactinemia is made by a serum prolactin:
  - *>20 ng/mL [20 mcg/L] in men and postmenopausal women*
  - *>30 ng/mL in premenopausal women.*
- meals may stimulate prolactin secretion slightly

- A careful history will often unmask symptoms or signs of a space-related mass
  - *visual field abnormalities,*
  - *impaired visual acuity,*
  - *blurred or double vision,*
  - *CSF rhinorrhea,*
  - *headaches, diabetes insipidus, and hypopituitarism.*
  - *PRL is also elevated in up to 50% of patients with acromegaly.*

- Because the human GH molecule has similar lactogenic properties similar to those of PRL, signs and symptoms of a prolactinoma may be mimicked by a purely GH-secreting tumor, and serum IGF-1 should be measured.
- Elevated PRL levels are occasionally encountered in patients with TSH-secreting tumors.
- pituitary hormone functions should be ascertained to determine the presence of hypopituitarism.
- An MRI is required to establish a definitive diagnosis of prolactinoma.

An MRI is required to establish a definitive diagnosis of prolactinoma

Treatment

- Optimal treatment outcomes for a prolactinoma include
  - *normalization of PRL levels (and associated signs and symptoms)*
  - *complete tumor removal or shrinkage with a reversal of tumor-mass effects*

previously abnormal sexual function and fertility should be restored, galactorrhea stopped, impaired bone density improved, tumor eliminated or reduced in size without impairing pituitary or hypothalamic function, and vision normalized, if impaired.

Dopamine Agonists

- Bromocriptine.
- Cabergoline
- Pergolid
- quinagolide

Dopamine Agonist Treatment of Prolactinomas

	Bromocriptine† (2.5-7.5 mg/day)	Cabergoline† (0.5-1 mg twice weekly)
Microadenomas		
PRL normalized	70	80
Menses resumed	70	80
Macroadenomas		
PRL normalized	65	70
Menses resumed	85	80
Tumor Shrinkage		
None	20	20
Up to 50%	40	55
50% or more	40	25
Visual Field Improvement	90	70
Drug Intolerance	15	5

Bromocriptine

- semisynthetic ergot alkaloid dopamine agonist, lowers elevated PRL levels, restores abnormal menstrual function in 80% to 90% of patients,

- Drug withdrawal can result in rapid tumor expansion.
- Occasionally, tumors that shrink during bromocriptine therapy do not enlarge following drug withdrawal.
- Very occasionally, bromocriptine lowers PRL levels despite continued tumor expansion, although when tumors grow during dopamine agonist therapy there is usually a simultaneous PRL elevation.

- Bromocriptine shrinks prolactinomas by:
  - *shrinking tumor cell size, including cytoplasmic, nuclear, and nucleolar areas.*
- Perivascular fibrosis observed in prolactinomas derived from patients treated with bromocriptine has been attributed to difficulty in tumor removal
- no effect of prior treatment with bromocriptine on surgical success rates,
- bromocriptine was a helpful adjunct to transsphenoidal microsurgery for macroprolactinomas.

Once positive effects on tumor size and amenorrhea and galactorrhea are established, some patients can be satisfactorily maintained with lower doses

Cabergoline

- Administered once or twice weekly,
- the first-line therapeutic choice for most patients, unless pregnancy is desired.
- Cabergoline was also more effective than bromocriptine in restoring ovulatory cycles and fertility
- Cabergoline also may result in dramatic improvement of prolactinoma-associated headache.
- Most “resistant” patients have only partial resistance (i.e., tumors shrink and PRL levels are lowered but do not normalize).

Administration

- Usual starting doses are 1.25 mg bromocriptine (daily) or 0.25 mg cabergoline (weekly).
- Doses of medication are either increased gradually, as tolerated, or decreased depending on tolerability and should be initiated with a small dose with food before bedtime.
- Patients should initially avoid activities that cause peripheral vasodilatation (e.g., hot baths),

thereby decreasing the risk of postural hypotension.

- If side effects are troublesome, the subsequent dose should be halved, and doses increased gradually thereafter to achieve effective levels.
- Switching from one medication to another may be beneficial.
- Application of intravaginal bromocriptine administration has been advocated to alleviate adverse gastrointestinal events.

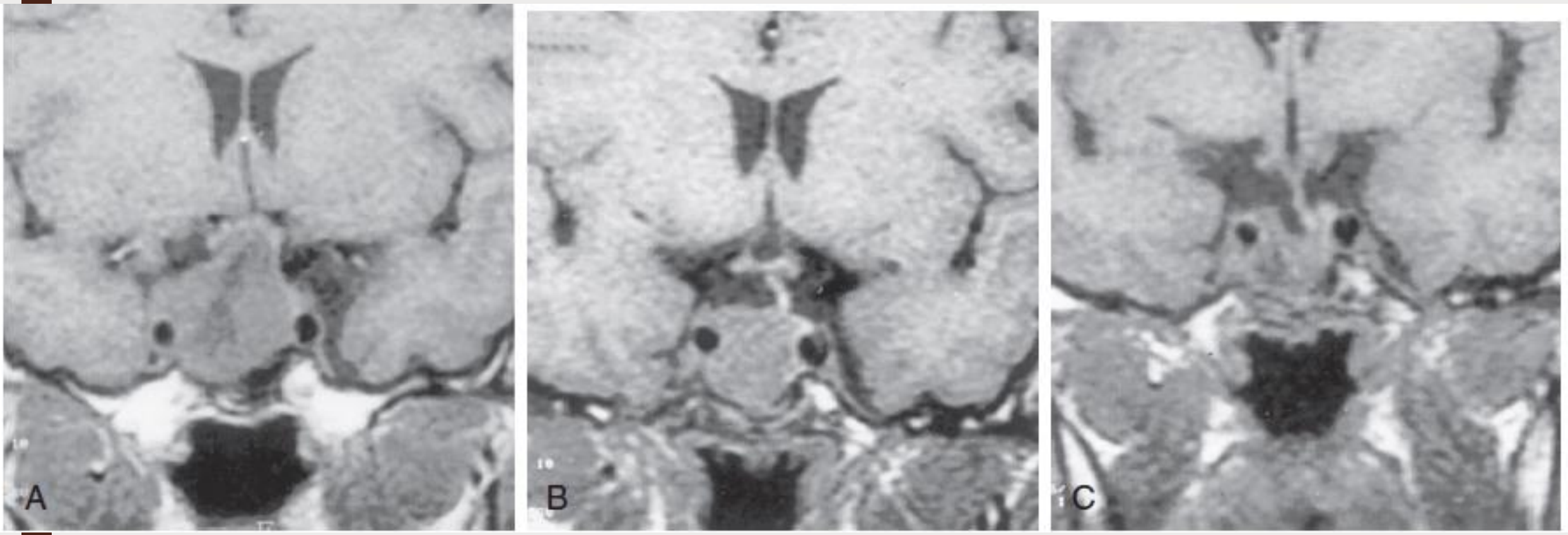
Adverse Effects of Dopamine Agonists.

- Nausea occurs in up to 50%
- nasal stuffiness, depression, and digital vasospasm occur, the latter more frequently with higher doses,
- Postural hypotension can cause loss of consciousness
- Signs and symptoms of psychosis or exacerbation of preexisting psychosis can be

encountered in up to 1.3% of patients receiving bromocriptine.

- If psychosis occurs in a patient in whom dopamine agonists are clearly the treatment of choice, the judicious combination of this agent and antipsychotic medication can be effective.
- A neuroleptic that is not a potent PRL stimulator, such as olanzapine, is preferred.
- CSF rhinorrhea occurs during dopamine agonist treatment in up to 6.1% of patients with macroadenomas, some of which are more resistant to dopamine agonists.
- Other rarely reported serious side effects include:
  - *hepatic dysfunction and cardiac arrythmias. Retroperitoneal fibrosis, pleural effusions and thickening, and restrictive mitral regurgitation have been reported in patients taking high doses of bromocriptine*

- In patients treated with dopamine agonists for at least a year an increased prevalence in valvular calcification with no change in valvular function was observed.
- Increased subclinical cardiac valve fibrosis was also noted in patients receiving cabergoline.



Shrinkage of macroadenoma by cabergoline in a woman harboring a macroadenoma at 22 weeks of gestation (**A**),
when prolactin was 488 μg/L(**B**),
and further reduction at 3 weeks postpartum (**C**)

Withdrawal of dopamine agonists

decreasing gradually and then discontinuing the dopamine agonist in the following situations:

- A patient who had idiopathic hyperprolactinemia (no pituitary mass at baseline) and whose serum prolactin decreased to low normal in response to dopamine agonist treatment. We suggest gradually decreasing the dose, as long as the prolactin remains within the normal range.
- If a patient has a normal prolactin for two years while taking a low dose (eg, 0.25 mg twice a week) of cabergoline, we suggest a trial of discontinuation of the drug.
- A patient who had hyperprolactinemia and a microadenoma prior to treatment in whom prolactin fell to normal and who has not had evidence of an adenoma by MRI for at least two years.
- A patient had a macroadenoma prior to treatment, as long as the serum prolactin has been normal and no adenoma has been detectable by MRI for at least two years.

- If the drug is discontinued, prolactin should be measured after three months and yearly thereafter.
- If the prolactin increases substantially (eg, to >100 ng/mL), especially in a patient who originally had a macroadenoma, an MRI should be performed.
- not stopping the dopamine agonist if the prolactin increases above normal while gradually decreasing the drug.

Menopause

- After menopause, the drug can be discontinued and the serum prolactin concentration can be allowed to rise.
- Imaging should be performed if the value rises above 200 ng/mL to determine if the adenoma has increased to a clinically important size.
- If so, drug therapy should be resumed.

MACROADENOMAS

- **Titration of dose and monitoring** — The serum prolactin should be measured and the cabergoline dose should be increased every one to three months, until the serum prolactin concentration becomes normal
- If vision was abnormal before therapy, it should be reassessed within one month, although improvement may occur within a few days.
- (MRI) should be repeated in 6 to 12 months to determine if the size of the adenoma has decreased
- If the clinical picture is stable (no evidence of adenoma growth on MRI and no symptoms such as headaches or visual symptoms), serum prolactin should be measured in six months, and if normal, it should then be measured yearly.

Candidates for stopping therapy

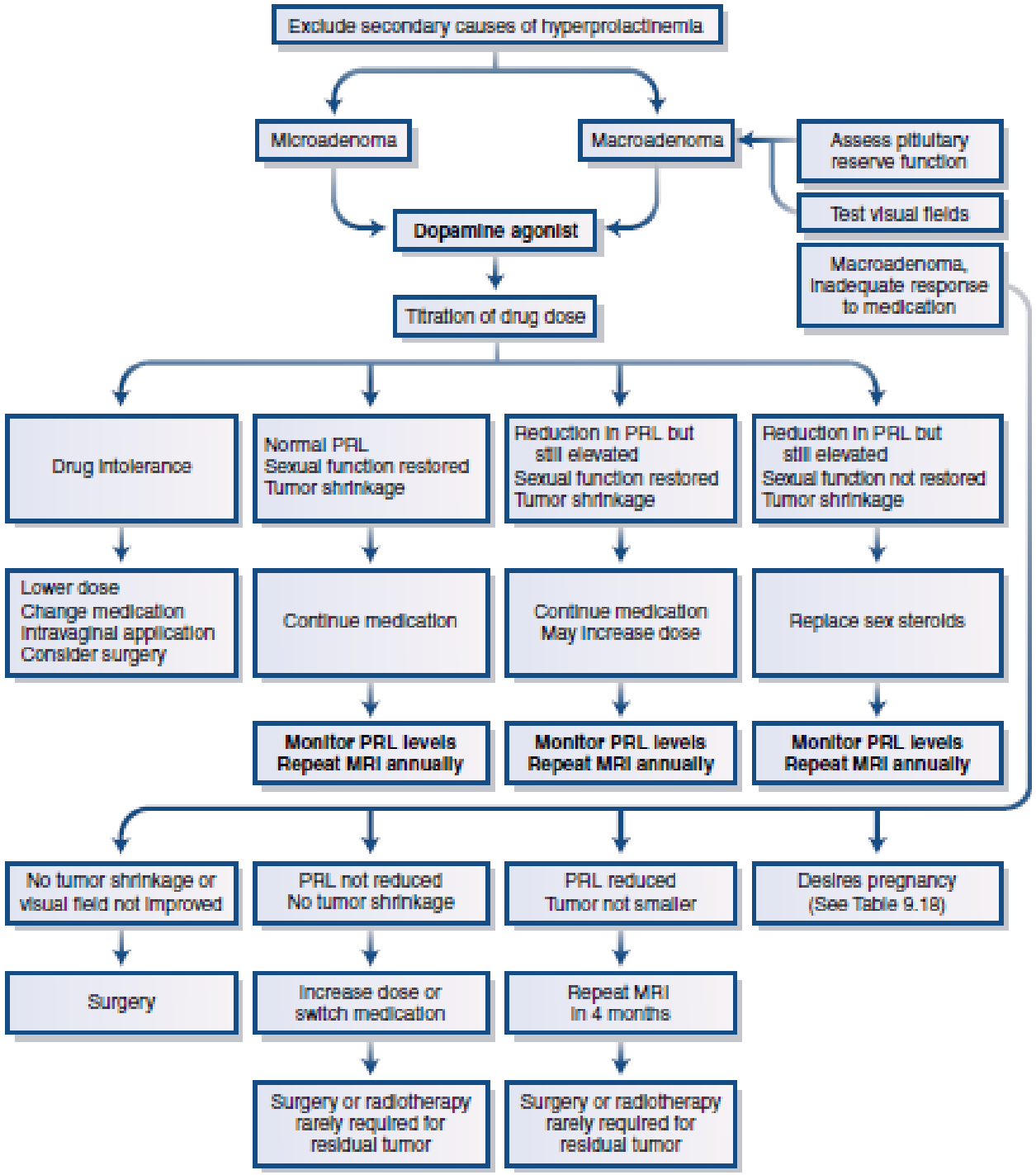
- — If the serum prolactin concentration has been normal for at least one year and the adenoma has decreased markedly in size, the dose of the dopamine agonist can be decreased gradually, as long as the serum prolactin remains normal
- Discontinuation can be considered in those patients who had macroadenomas of modest size (eg, 1.0 to 1.5 cm), whose serum prolactin concentrations have been normal for more than two years, and whose adenomas can no longer be visualized by MRI for more than two years.
- If the drug is discontinued, the prolactin concentration and the size of the adenoma by MRI must be monitored.

- Discontinuation should probably **not** be considered if the adenoma was initially >2 cm, if it can still be visualized by MRI during treatment, or if the prolactin has not become normal during treatment.

- The DA should not be discontinued entirely, even after menopause, because hyperprolactinemia will probably recur and the adenoma may increase in size

Inadequate response or drug intolerance

- If bromocriptine was tried first and the patient cannot tolerate it or the adenoma does not respond to it, cabergoline should be tried.
- If the patient cannot tolerate or the adenoma does not respond to agonist therapy, transsphenoidal surgery should be performed,
- and if a significant amount of adenoma tissue remains after surgery, radiation therapy should be administered
- Surgery can also be considered for the woman who has a giant adenoma and is contemplating pregnancy.


Exclude secondary causes of hyperprolactinemia
Microadenoma
Macroadenoma
Assess pituitary reserve function
Test visual fields
Dopamine agonist
Macroadenoma, inadequate response to medication
Titration of drug dose
Drug intolerance
Normal PRL
Sexual function restored
Tumor shrinkage
Reduction in PRL but still elevated
Sexual function restored
Tumor shrinkage
Reduction in PRL but still elevated
Sexual function not restored
Tumor shrinkage
Lower dose
Change medication
Intravaginal application
Consider surgery
Continue medication
Continue medication
May increase dose
Replace sex steroids
Monitor PRL levels
Repeat MRI annually
Monitor PRL levels
Repeat MRI annually
Monitor PRL levels
Repeat MRI annually
No tumor shrinkage or visual field not improved
PRL not reduced
No tumor shrinkage
PRL reduced
Tumor not smaller
Desires pregnancy
(See Table 9.18)
Surgery
Increase dose or switch medication
Repeat MRI in 4 months
Surgery or radiotherapy rarely required for residual tumor
Surgery or radiotherapy rarely required for residual tumor

Radiation Therapy

- Linear accelerator radiotherapy is effective in controlling or reducing the size of prolactinomas.
- recommended radiation dose is 4500 to 4600 centigray (cGy),
- normalization of PRL was achieved in 18 of 36 patients at a mean of 7.3 years after treatment.
- Hypopituitarism occurs as a side effect of radiation.

- Gamma knife stereotactic radiosurgery is often effective in treating prolactinomas resistant to or intolerant of dopamine agonists.

Surgery

- The success rate of pituitary surgery correlates inversely with tumor size and serum PRL concentrations.

- complete resection of macroprolactinomas, especially large invasive tumors, is difficult to achieve, and postoperative serum PRL level is normalized in only 32% of patients with a 19% recurrence rate

Surgery was traditionally indicated as a second-line treatment in 14–38% of prolactinoma patients , fitting certain conditions such as:

- resistance or escape to DA,
- intolerance to DA,
- in some psychiatric disorders worsened by DA treatment,
- spontaneous or DA-induced CSF leakage,
- patient’s preference.

Surgery indication

- who are resistant to dopamine agonist therapy are particularly well suited for surgery.
- If tumor removal is only partial, adjunctive radiation therapy should be considered.
- Prophylactic transsphenoidal surgery should considered in women whose prolactinomas are large enough to potentially threaten vision during pregnancy.
- patients cannot tolerate available dopamine agonists,
- Whose prefer surgery and refuse medication.
- Endoscopic endonasal transsphenoidal surgery has been used to resect prolactinomas.

Chemotherapy

- Temozolomide, an alkylating agent that induces DNA damage to disrupt gene transcription, has been used to treat aggressive pituitary tumors in patients who have failed to respond to other therapies or who have evidence of pituitary carcinoma.
- O^6-methylguanine- DNA methyltransferase (MGMT) may interfere with drug efficacy, assessing MGMT expression in pituitary tumor samples has been reported to have variable use
- Temozolomide, readily crosses the blood-brain barrier, may control tumor growth in individual patients.
- The response to temozolomide may sometimes be predicted by low tumor staining for MGMT but this approach is not uniformly accepted

Pregnancy

- The normal pituitary enlarges during pregnancy and prolactinomas may also increase in size during pregnancy.
- The incidence of pregnancy-associated tumor enlargement, occur in 1.4% of women with microadenomas and 16% of women with macroadenomas.
- In other reports, the risk for macroadenoma enlargement has 36%
- In a prospective analysis in which 57 patients with microprolactinomas none developed visual disturbances.

- dopamine agonists have been used during pregnancy to prevent tumor growth
- It is recommended that AFTER DRUG WITHDRAWAL menstrual periods be allowed to occur naturally for a period of time (3-4 months) long enough to predict that a missed period might be a result of pregnancy
- Barrier contraception is recommended during this period.
- Within several days to a week of obtaining a positive hCG test, medication should be discontinued
- Of 6239 pregnancies managed in this manner, bromocriptine therapy was not associated with increased abortions or terminations, prematurity, multiple births, or infant malformations above that expected in the control population

- pregnancy exposure to the other agonist forms are less comprehensively documented.
- whose vision becomes impaired during pregnancy :
  - *administering bromocriptine during pregnancy,*
  - *high-dose steroids,*
  - *surgical resection.*

- To avoid neurologic complications of tumor enlargement during pregnancy, it is recommended that women with prolactinomas be tested for sensitivity to dopamine agonists before pregnancy.
- If tumors are insensitive to dopamine agonist–related tumor shrinkage, prophylactic surgery could be appropriate.
- If the tumor is a macroadenoma approximating the optic chiasm, the likelihood of visual difficulties is greater and therefore undertaking surgery prior to pregnancy could be prudent

TABLE 9-19

Management of Patients with Prolactinomas Planning Pregnancies

Microadenoma	Macroadenoma
Discontinue dopamine agonist when pregnancy test is positive Periodic visual field examinations during pregnancy Postpartum magnetic resonance imaging (MRI) after 6 weeks*	Consider surgery before pregnancy Ensure bromocriptine sensitivity before pregnancy Monitor visual fields expectantly and frequently Administer bromocriptine if vision becomes compromised Or continue bromocriptine throughout pregnancy if tumor previously affected vision Consider high-dose steroids or surgery during pregnancy if vision is threatened or adenoma hemorrhage occurs Postpartum MRI after 6 weeks

- We recommend DA treatment (preferably Cab for better tolerability) while seeking pregnancy and its discontinuation at confirmation of pregnancy
- We recommend only clinical follow-up throughout gestation in patients with microP or a small intrasellar remnant of MP
- We recommend clinical and pituitary function evaluation and neuro-ophthalmologic evaluation in patients with MP during pregnancy in each trimester
- We recommend against pituitary MRI scan during uneventful pregnancy and in the early postpartum period
- We recommend neuro-ophthalmologic evaluation, MRI without Gd, and pituitary function evaluation in patients who develop mass effect symptoms during pregnancy
- We recommend reinstitution of DA during pregnancy (preferably Cab) in symptomatic patients with MP, to obtain a rapid remission of symptoms and to be maintained even after delivery
- We suggest vaginal delivery in microP (unless otherwise indicated by the obstetrician) and a case-by-case evaluation in MP

- We recommend that women with prolactinomas be allowed to breastfeed, provided that pregnancy was uneventful, postponing the possible restart of DA
- We suggest adopting nonhormonal contraceptive measures after delivery or after the cessation of breastfeeding in order to evaluate PRL levels at 3–6 months in all women and subsequent MRI in MP
- We recommend reinstitution of DA in women with relapsing symptomatic hyperprolactinemia after delivery

MRI is the gold standard for the radiological diagnosis of prolactinoma

- Only those patients with absolute contraindications to MRI will undergo CT scan.
- CT scan will demonstrate prolactinomas just like MRI but its accuracy in case of microadenomas is definitely lower.
- CT scan is usually performed, after MRI, before transsphenoidal pituitary surgery (TSS) to assess the anatomy of the sinuses.
- In one study, 80% of prolactinomas were reported to be hyperintense on T2-weighted MRI sequences when compared to the normal gray matter . Small cysts and hemorrhagic foci are common. Fluid–fluid levels can be present.

When to suspect and how to screen for genetic diseases

- Most prolactinomas are sporadic as the other types of pituitary adenomas.
- Nevertheless, 1.5–3% of cases have a familial basis
- All patients with prolactinoma need a careful family and personal medical history considering the suspect of a hereditary form.
- Early onset of the adenoma and aggressive behavior are additional elements to suspect a genetic form.

- Multiple endocrine neoplasia (MEN) type 1 (MEN-1) is an autosomal dominant syndrome with high penetrance in which prolactinoma is the most frequent pituitary adenoma,
- Familial isolated pituitary adenoma is characterized by the presence of only pituitary adenomas in affected members.
  - *Aryl hydrocarbon receptor interacting protein (AIP) is the most frequently involved gene.*
  - *Transmission is autosomal dominant with relatively low penetrance.*
  - *Prolactinomas along with somatotropinomas are the most frequent type of adenomas and show an aggressive behavior*
- In Carney complex and in X-linked acrogigantism (X-LAG) syndrome, PRL is frequently increased but the clinical characteristics are those of somatotropinomas due to GH excess.

Resistance to treatment and aggressive disease from definition to multimodal treatment

- *a failure to normalize PRL on maximally tolerated doses of DA and a failure to achieve at least 50% tumor size reduction*
- *The maximally tolerated doses vary among patients: doses up to 12 mg weekly and 30 mg daily were anecdotally reported for Cab and Br,*
- *In common clinical practice, the mean maximum dose of Cab is around 4 mg per week*
- *Even though no agreement exists about the minimum duration of treatment to define resistance, it was suggested at least 6 months on the highest tolerated DA dose*

- Resistance is more frequent in cases of MP,
- invasive tumors, and male patients.
- Other factors are very young age, cystic, hemorrhagic and/or necrotic components (before the start of pharmacological treatment) inside the tumor, and genetic predisposition to develop pituitary tumors such MEN-1 or AIP mutations

- Very preliminary data support that in some patients with DA-resistant MP, the addition of octreotide LAR or pasireotide LAR to ongoing Cab therapy may result in significant reductions in tumor volume and PRL levels
- chemotherapy with the alkylating agent temozolomide.

Therapeutic strategy possible shift to surgery as first-line option

- **Are the Invasive Prolactinomas, Aggressive Prolactinomas, Malignant Prolactinomas, and Pituitary Carcinomas Different Entities?**

- Anatomy and Immunohistopathology **Invasive prolactinomas** are prolactin secreting tumors invading adjacent anatomical structures,
- while **aggressivity** determines not only the invasion but also medical treatment-resistance and high tendency for recurrence.
- In general, invasiveness is mostly a radiological and aggressiveness a clinical definition

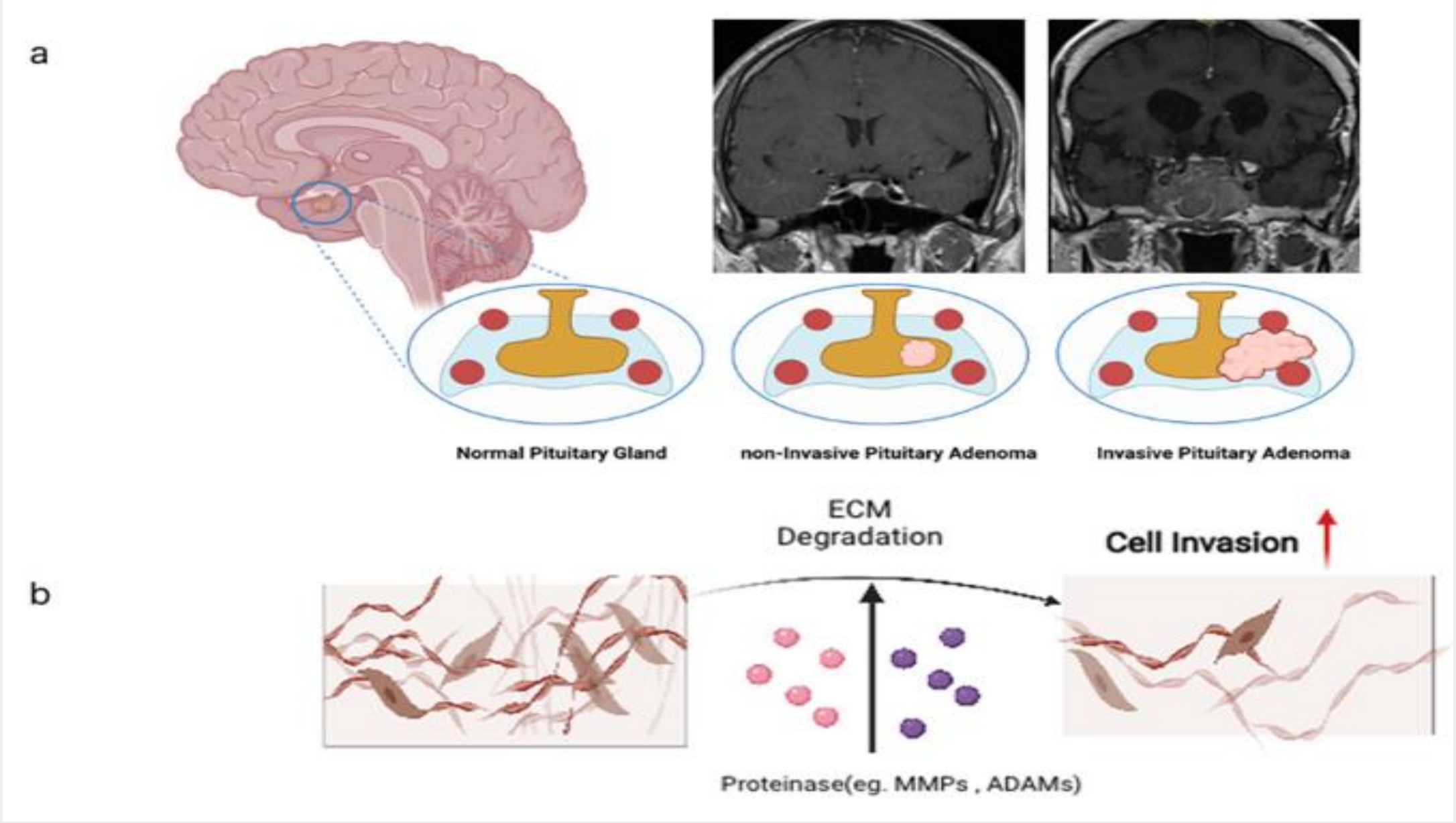
- A relatively recent study demonstrated that prolactinomas constitute most invasive

pituitary tumors

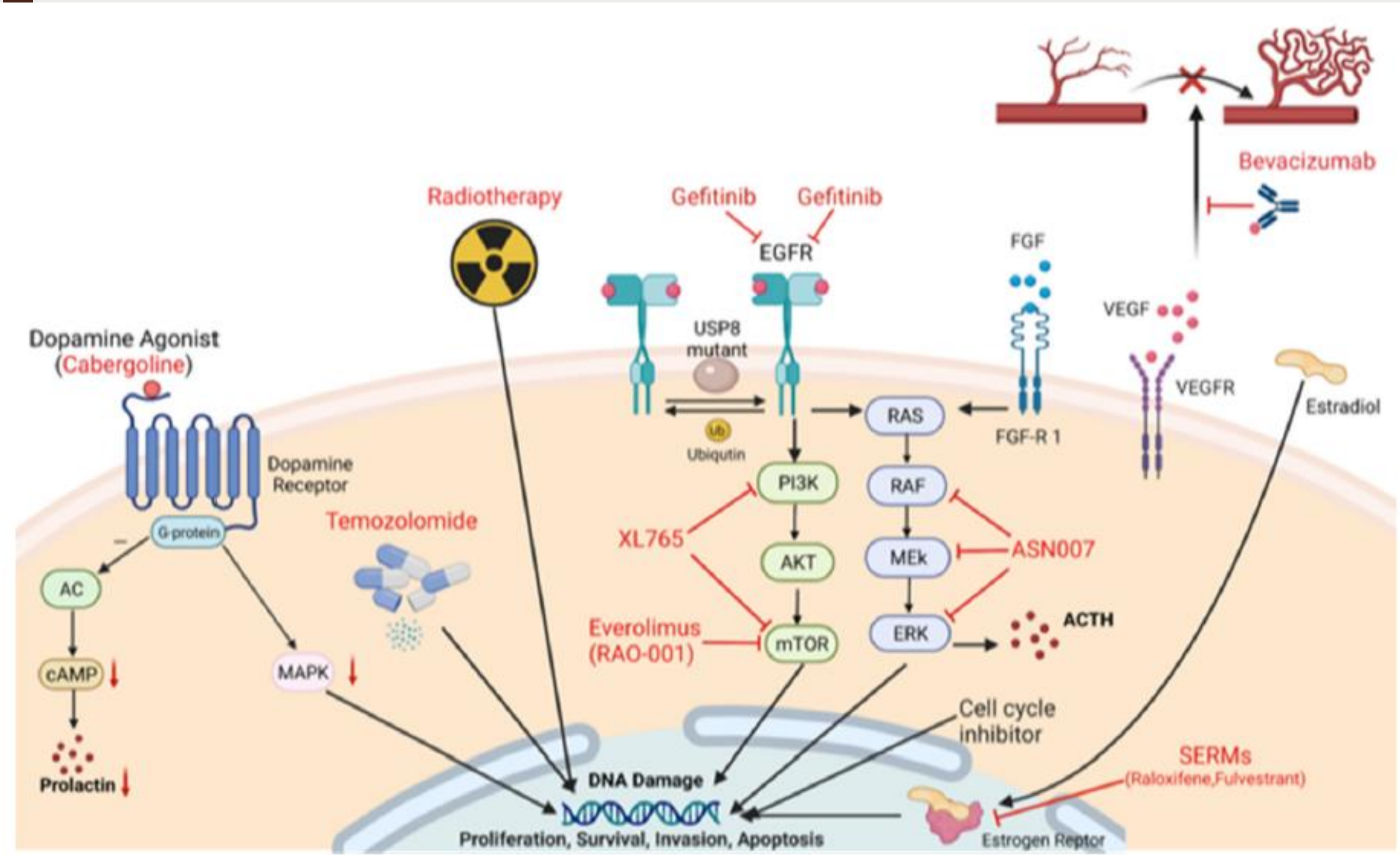
- (WHO) recent criteria (2016), increased mitotic index, Ki67 labeling index greater than 3 % percent and robust p53 expression indicate the aggressivity of pituitary adenomas

Classical Treatment Modalities of Dopamine Agonist-Resistant Prolactinomas

- Surgical Treatment
- Radiotherapy
- Temozolomide
- Peptide Receptor Radionuclide Therapy
  - *Little data exists on peptide receptor radionuclide therapy (PRRT) for the management of aggressive pituitary tumors*



Cellular mode of invasion into the brain tissue depends on degradation of extracellular matrix (ECM) molecules by proteinases of the metzincin family, namely MMPs and ADAMs


Bevacizumab
Radiotherapy
Gefitinib
Gefitinib
EGFR
FGF
VEGF
VEGFR
Estradiol
Dopamine Agonist
(Cabergoline)
USP8
mutant
Ubiqutin
FGF-R 1
RAS
RAF
MEk
ERK
ACTH
PI3K
AKT
mTOR
XL765
Everolimus
(RAO-001)
ASN007
Dopamine
Receptor
G-protein
AC
cAMP
Prolactin
MAPK
Temozolomide
Cell cycle
inhibitor
SERMs
(Raloxifene,Fulvestrant)
DNA Damage
Proliferation, Survival, Invasion, Apoptosis
Estrogen Reptor

- Schematic overview of target proteins and pathways related to the treatment of pituitary adenomas.
- As general therapeutic approaches, VEGF inhibition with Bevacizumab, EGFR inhibition with gefitinib, the Raf/MEK/ERK pathway inhibition pathway by inhibitors such as ASN007, mTOR pathway inhibition with Everolimus and XL-765 as well as chemotherapy with radiation or temozolomide are discussed.
- As a more specialized therapy, application of dopamine agonists such as Cabergoline and antiestrogens is the subject of intense research.

Features of aggressive prolactinoma

Suggestive elements:

- Extremely high serum prolactin
- Large size (>4 cm)
- Imaging with invasion profile
- Male sex
- Early age at diagnosis (<20 years)
- Genetic predisposition (MEM, MP, SDHx mutations)
- Histological report with invasive profile
- Mitotic count >2
- Ki-67 proliferation index 3%

Management:

- Dopamine agonist resistance
- Need for neurosurgery
- Need for radiotherapy 4111
- Early post-operatory relapse
- Lack of serum prolactin control and tumor growth despite multimodal therapy
- IV-line therapy: temozolomide

Alternatives:

- Somatostatin analogues (pasireotide)
- Checkpoint inhibitors (ipilimumab, nivolumab)
- Tyrosine kinase inhibitors (lapatinib)
- mTOR inhibitors (everolimus)

Potential useful assessments:

- E-cadherin
- Matrix metalloproteinase 9
- Vascular endothelial growth factor

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- Review **Targeting Aggressive Pituitary Adenomas at the Molecular Level—A Review**
  - ***Benjamin Voellger 1,* , Zhuo Zhang 1,2, Julia Benzel 1,3, Junwen Wang 1,2, Ting Lei 2, Christopher Nimsky 1 and Jörg-Walter Bartsch 1*** J. Clin. Med. **2022**, 11, 124. https://doi.org/10.3390/jcm11010124

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THANKS FOR YOUR ATTENTION