

الحمد لله رب العالمين





Prolactin-secreting adenomas: pathogenesis, diagnosis, and management

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Lancet Diabetes Endocrinol
2025; 13: 874-90

Published Online
August 25, 2025

[https://doi.org/10.1016/S2213-8587\(25\)00227-X](https://doi.org/10.1016/S2213-8587(25)00227-X)

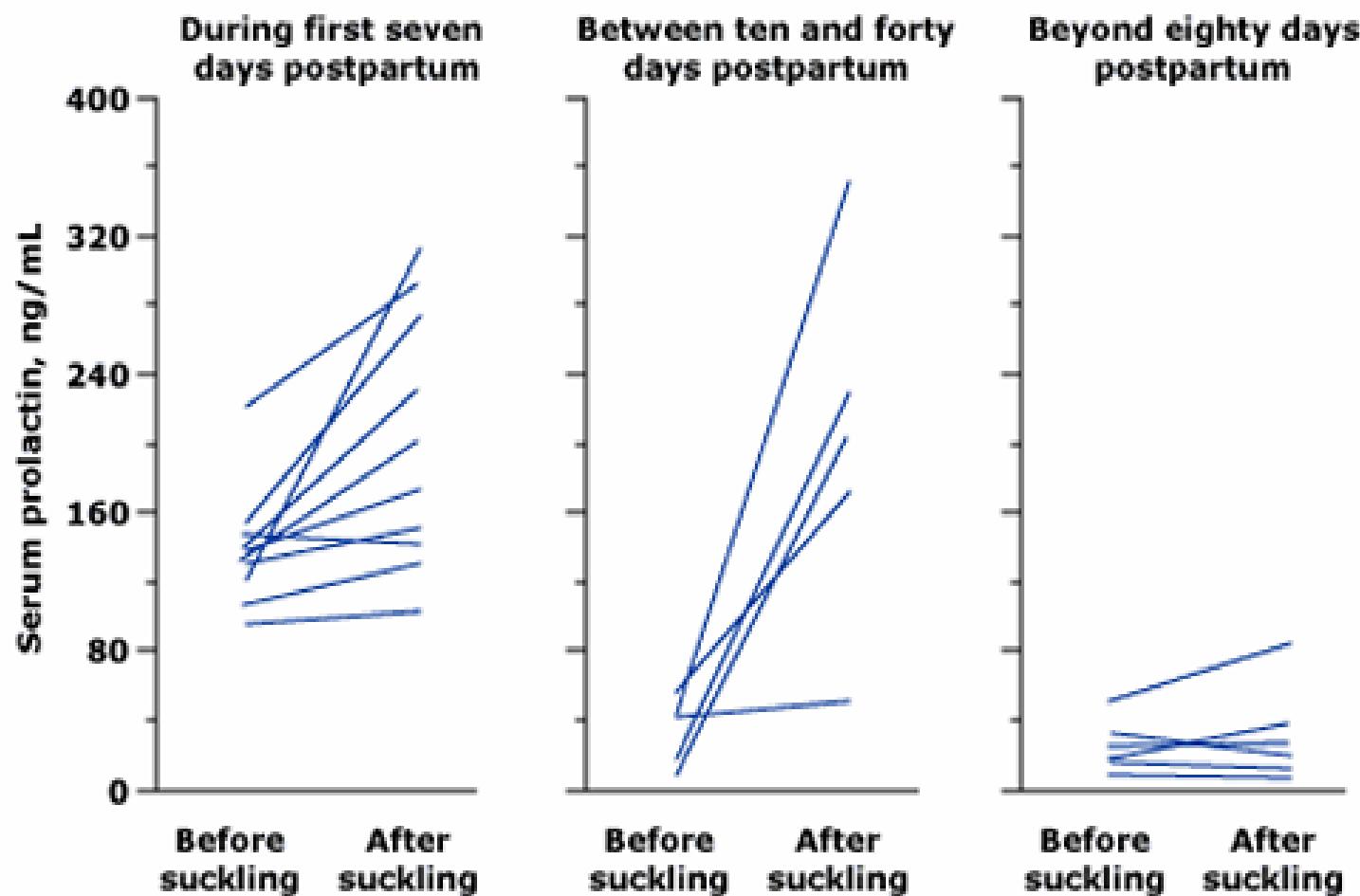
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Hyperprolactinaemia can result from physiological causes, pharmacological agents, or pathological conditions such as prolactin-secreting pituitary adenomas and other pituitary stalk-compressing masses. Sporadic prolactinomas are the most common functioning pituitary adenomas, with a female predominance during reproductive years. In men, these adenomas are usually larger and more aggressive. Prolactinomas are characterised by positive immunostaining for prolactin, pituitary-specific positive transcription factor 1, and oestrogen receptor α . Dopamine agonists, particularly cabergoline, are typically used as primary therapy. Treatment with up to 2.0 mg per week of cabergoline for at least 6 months normalises prolactin concentrations, achieves adenoma shrinkage of at least 30%, and restores gonadal function in most patients. Transsphenoidal surgery is increasingly used as primary therapy for small prolactinomas given a high chance of remission; transsphenoidal surgery is also indicated for patients with dopamine agonist intolerance or resistance. Radiotherapy is reserved for treatment-refractory prolactinomas. Multidisciplinary management and an individualised approach are key to maximising therapeutic responsiveness and optimising outcomes. In this Review, we assess evidence relating to pathogenesis, diagnosis, and management of prolactinomas, and highlight opportunities for future research.

Prolactin

- ▶ PRL, a polypeptide hormone comprising 199 amino acids (molecular weight 23 KD) is structurally similar to GH and placental lactogens.
- ▶ **Reproductive function and lactation:**
 - PRL normalize within a week postpartum if suckling does not occur.
- ▶ **Bone health**
 - PRL increases bone turnover by enhancing resorption and, to a lesser extent, bone formation .
 - This process is mediated through the modulation of the ratio between RANKL and osteoprotegerin
- ▶ **Carbohydrate and lipid metabolism**
 - enhances β -cell proliferation, insulin secretion, and glucose uptake.
 - improves insulin sensitivity
 - maintains adipose tissue homeostasis
 - The concept of homeo-fit-prolactin proposes a functionally homeostatic prolactin range, as very low and very high concentrations are linked to adverse metabolic outcomes.

Serum prolactin and suckling



Serum prolactin concentrations basally and in response to suckling as a function of time after delivery. Within the first week after delivery, the basal value is high relative to the nonpregnant state, and there may be a further increase in response to suckling. Several weeks after delivery, the basal value is close to that of the nonpregnant state, but there is still a pronounced increase in response to suckling. Three months after delivery, the basal value is similar to that of the nonpregnant state, and there is a minimal response to suckling, if any.

Hyperprolactinaemia

- ▶ PRL testing should be done in a **fasting** state under controlled conditions to reduce stress-induced variability and avoid prior nipple stimulation.
- ▶ Assay interference : high **biotin** intake rarely lead to **falsely decreased** PRL in assays that use biotin-streptavidin technology.
- ▶ **Macro-prolactin:**
 - a monomeric PRL complexes with IgG and non-IgG Ab
 - minimal bioactivity
 - 20% of hyperprolactinaemia
 - moderately elevated PRL (<200 µg/L) discordant with clinical findings should be evaluated with the use of PEG precipitation .
- ▶ PRL : 1 µg/L = 21·2 mIU/L
- ▶ **hook effect** : PRL are unexpectedly **low** in the presence of a **large adenoma**, measuring prolactin with a 1:100 dilution will help differentiate between a **NFPA** and a **prolactinoma**

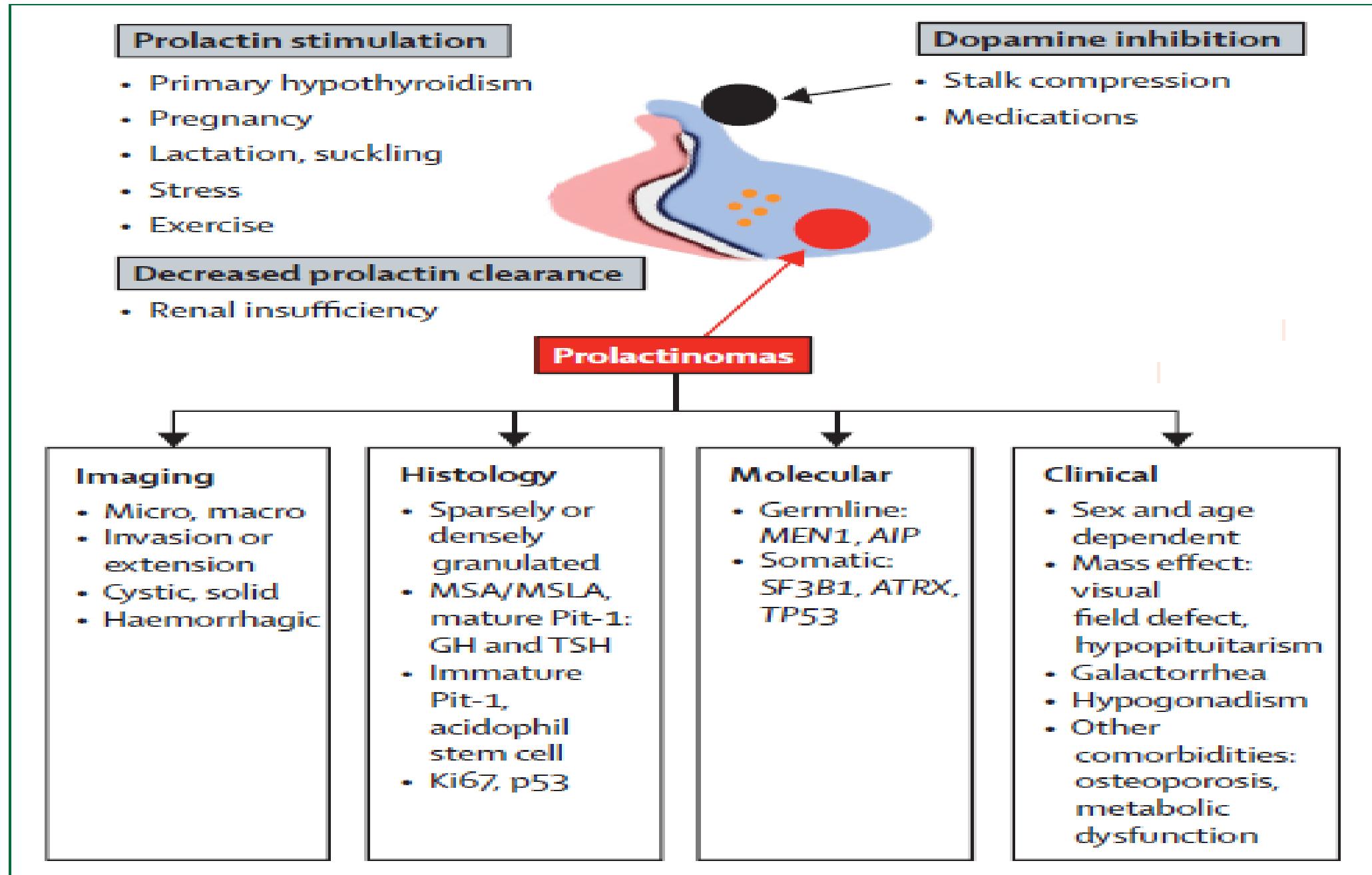
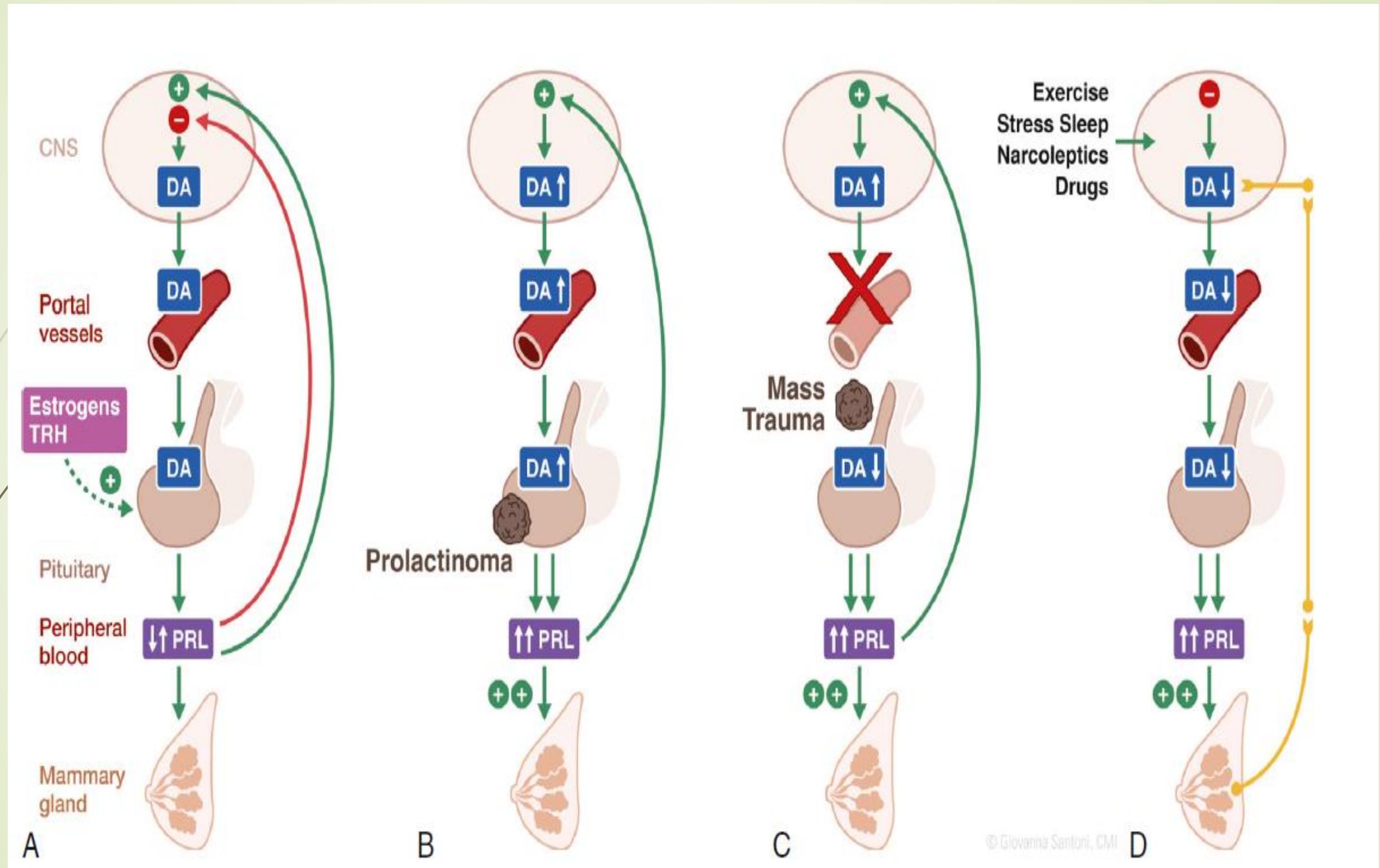
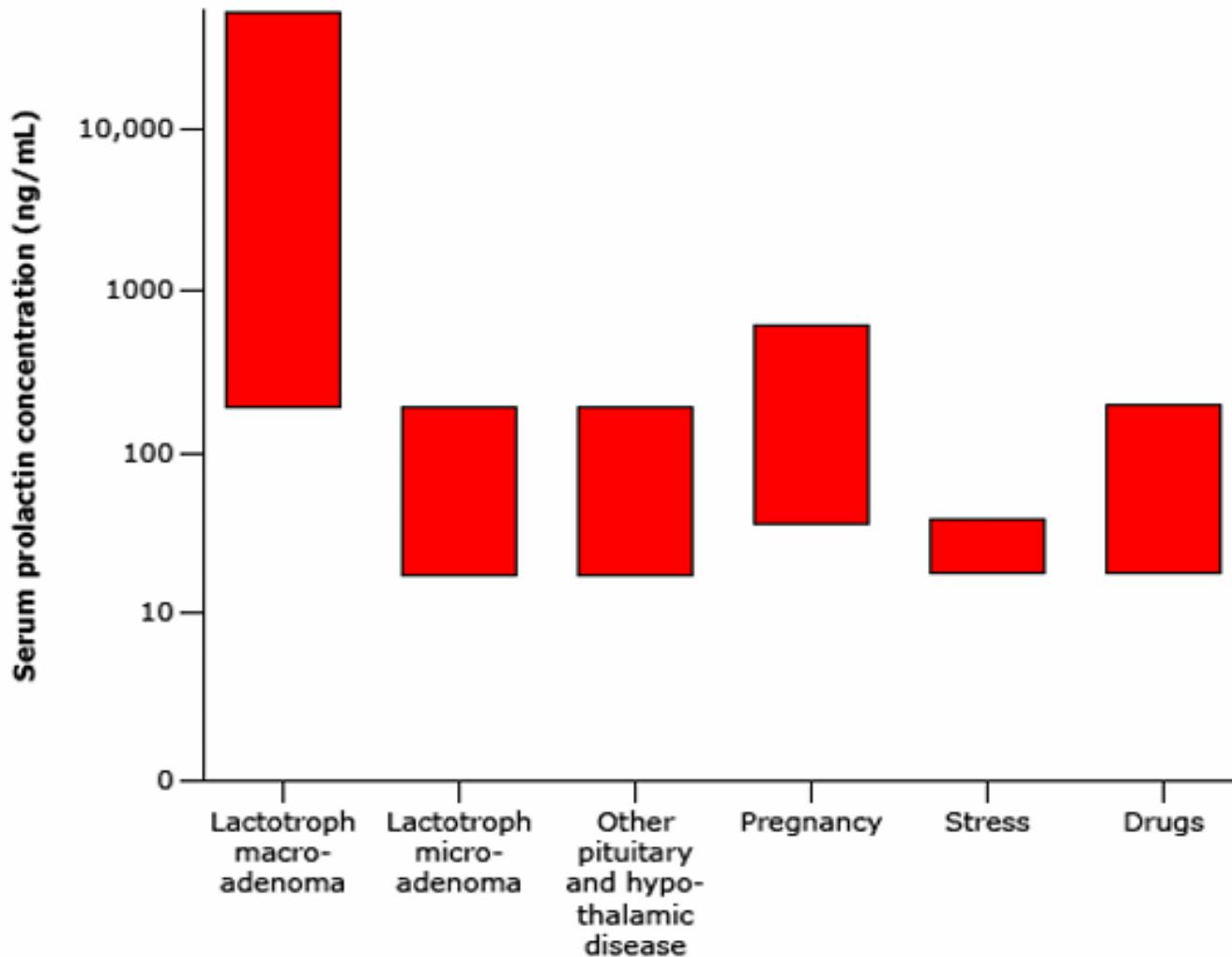


Figure 1: Causes of hyperprolactinaemia



Ranges of serum prolactin concentrations in several causes of hyperprolactinemia



The serum prolactin concentration is much higher in most patients who have lactotroph macroadenoma than in patients with any other cause of hyperprolactinemia. The prolactin concentrations among other causes overlap with each other.

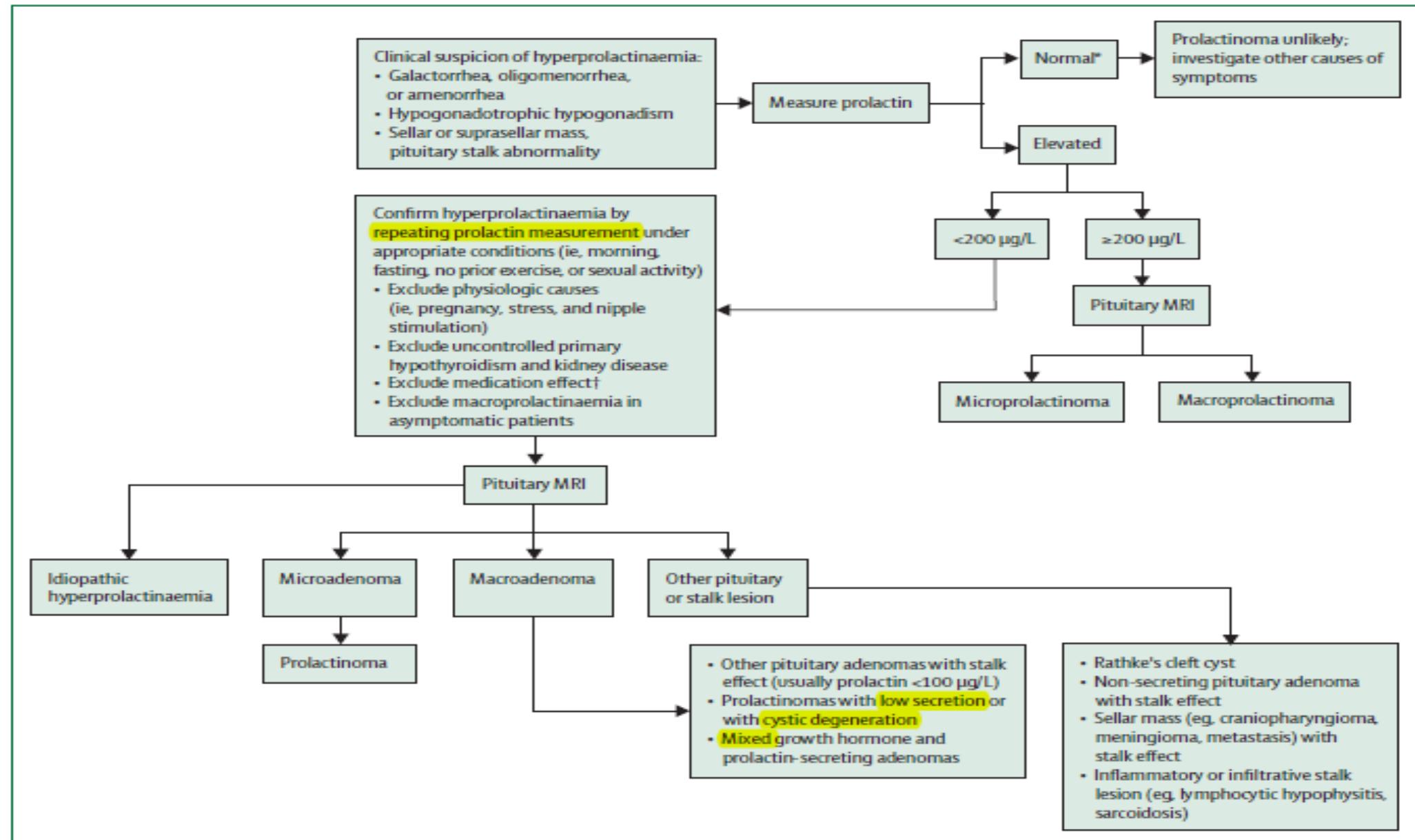


Figure 3: Evaluation of patients with suspected hyperprolactinaemia

*Upper limit of normal differs by laboratory and is usually less than 23–30 µg/L in premenopausal women and less than 15–18 µg/L in men. Laboratory specific ranges should be used when interpreting results. †See figure 2.

 <3 times increase  3–10 times increase  >10 times increase

Antipsychotics

1st generation

 Butaperazine, chlorpromazine, flupentixol, fluphenazine, loxapine, thiordiazine, and thiothixene  Haloperidol  Perphenazine

2nd generation

 Quetiapine, olanzapine  Amisulpride, paliperidone, and sulpiride  Risperidone

Antidepressants

Tricyclic antidepressants

 Clomipramine  Amoxapine

SSRIs

 Citalopram, fluoxetine, and sertraline

SNRIs

 Duloxetine and venlafaxine

MAO inhibitors

 Phenelzine and pargyline

Antihistamines and H₂ blockers

 Cetirizine, cimetidine, and ranitidine

Antihypertensives

 Reserpine and verapamil  Methyldopa

Antiemetics

 Chlorpromazine  Metoclopramide, domperidone

Opioids and other substances

 Heroin, morphine, methadone, marijuana, and cocaine

Hormone therapies

 Oestrogens*  GnRH agonists

Figure 2: Medications commonly causing hyperprolactinaemia

Hyperprolactinaemia

patients treated with antipsychotic:

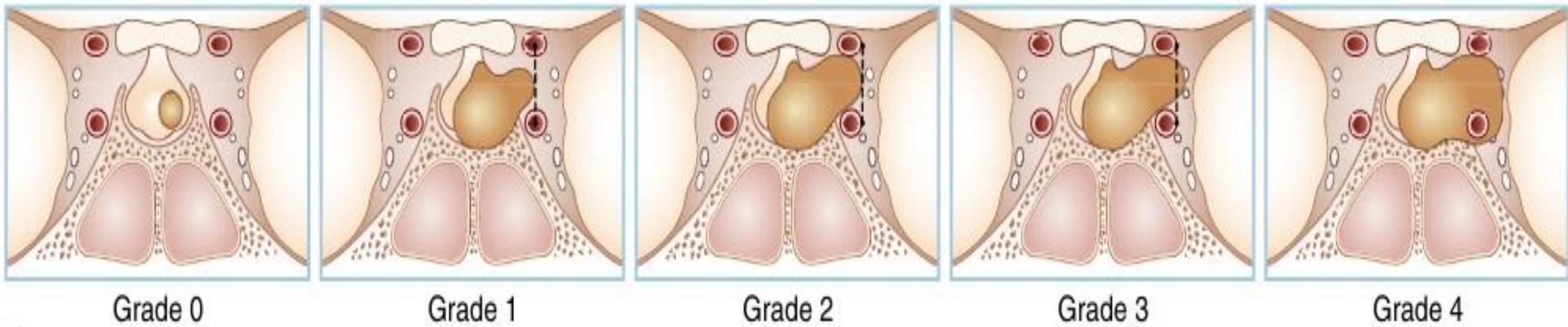
- ▶ PRL measurement before starting therapy.
- ▶ If medications cannot be discontinued, MRI recommended if PRL is **more than 10 times** .
- ▶ dose adjustment or switching to a PRL -sparing antipsychotic that might normalize concentrations.
- ▶ medications with mild or moderate elevations, which resolve with switching to a different medication.
- ▶ As stalk effect due to a large NFPA cannot be excluded when PRL are moderately elevated, MRI could be considered if **mass effect symptoms** or **thyroid or adrenal deficiencies** are present.
- ▶ Routine PRL monitoring : **not recommended** unless there are specific symptoms suggestive of a pituitary adenoma.

Prolactinoma

- ▶ most common pathological cause of hyperprolactinaemia
- ▶ half of pituitary adenomas.
- ▶ aged 20–50 years: ten times more common in women
- ▶ after age of 50 : incidence is similar between sexes.
- ▶ older than 65 years : prevalence of clinically relevant prolactinomas decreases (4–8% of pituitary adenomas)
- ▶ WHO classification describes prolactinomas as lactotroph pituitary NET.
- ▶ Pituitary Society, Endocrine Society, and European Society of Endocrinology determined there was no convincing justification for adopting the lactotroph pituitary NET terminology.

Imaging

- ▶ most prolactinomas are microadenomas.
- ▶ initial mass size is important for planning treatment and follow-up.
- ▶ Modified Knosp classification with cavernous sinus invasion assessment correlates with surgical remission rate.
- ▶ Giant prolactinomas.
- ▶ Cystic prolactinomas: more than 50% of the volume is fluid-filled
- ▶ haemorrhagic prolactinomas are not uncommon



B

KNOSP CLASSIFICATION SYSTEM

• **Fig. 7.25** Classification systems characterizing pituitary adenomas. (A) *Hardy classification system*. Sella turcica adenomas can be noninvasive (grade 0, intact with normal contour; grade I, intact with bulging floor; or grade II, intact, enlarged fossa) or invasive (grade III, localized sellar destruction; or grade IV, diffuse destruction). Suprasellar tumors can be symmetric (grade A, suprasellar cistern only; grade B, recess of the third ventricle; or grade C, whole anterior third ventricle) or asymmetric (grade D, intracranial extradural; or grade E, extracranial extradural [cavernous sinus]). (B) *Knosp classification system* used to quantify invasion of the cavernous sinus, in which only grades 3 and 4 define true invasion of the adenoma into the cavernous sinus. Grade 0, no cavernous sinus involvement; grades 1 and 2, the tumor pushes into the medial wall of the cavernous sinus but does not go beyond a hypothetical line extending between the centers of the two segments of the internal carotid artery (grade 1) or it goes beyond such a line but without passing a line tangent to the lateral margins of the artery itself (grade 2); grade 3, the tumor extends laterally to the internal carotid artery within the cavernous sinus; grade 4, total encasement of the intracavernous carotid artery. (Modified from Di Ieva A, Rotondo F, Syro LV, et al. Aggressive pituitary adenomas: diagnosis and emerging treatments. *Nat Rev Endocrinol*. 2014;10:423–435, used with permission.)

Imaging

- ▶ PRL in microadenomas are $< 200 \mu\text{g/L}$.
- ▶ Macroadenoma :
 - $\text{PRL} > 200 \mu\text{g/L}$
 - $\text{PRL} < 200 \mu\text{g/L}$: hemorrhagic, necrotic, and cystic macroadenomas
- ▶ $\text{PRL} < 100 \mu\text{g/L}$, in the presence of a macroadenoma : stalk effect.
- ▶ **idiopathic hyperprolactinaemia** : pituitary cause for PRL elevation but the adenoma is not visualized on imaging

Imaging

- ▶ Prolactinomas are typically **hypointense** on **T1**-weighted MRI and **mildly hyperintense** on **T2**-weighted MRI
- ▶ Marked T1-weighted hyper intensity without GAD indicate a recent hemorrhage
- ▶ **hypo intense** T1-weighted and **marked hyper intense** T2-weighted signals are often observed in **cystic** adenoma transformation.
- ▶ volumetric MRI sequences, and molecular imaging with ^{11}C -methionine PET used complementary to MRI to localize newly diagnosed or residual prolactinomas when MRI findings are inconclusive

Histology

- ▶ Lactotroph adenomas are characterized by expression of prolactin, PIT-1, and estrogen receptor α .
- ▶ **Sparsely granulated** lactotroph adenomas are most common
- ▶ densely granulated adenomas are usually larger, express high PRL , and show resistance to DA
- ▶ Clinically relevant GH expression :
 - mammosomatotroph cells, secrete both PRL and GH -favorable prognosis
 - mixed somatotroph and lactotroph lineages : higher prolactin concentrations
- ▶ large and more aggressive masses:
 - Immature PIT-1-lineage : clinically silent or cause acromegaly, hyperprolactinaemia, central hyperthyroidism, or all of these disorders
 - acidophil stem cell adenomas :associated with only hyperprolactinaemia.

Genetic

- ▶ Prolactinomas are rarely associated with germline mutations.
- ▶ Screening for **MEN1** mutations :
 - a family history of pituitary adenomas or endocrine neoplasia
 - macroadenomas < 30 years
 - aggressive pituitary tumours
- ▶ Macroadenomas in MEN1 :more aggressive and resistant to medical therapy
- ▶ Genetic screening for Germline mutations **AIP** mutations might be justified in **young** patients with prolactinomas **unresponsive to medical therapy**

Genetic

- ▶ prolactinomas are mostly sporadic and monoclonal.
- ▶ mutation in *SF3B1* :
 - higher PRL
 - larger adenoma size
 - shorter progression-free survival
 - 50% of lactotroph carcinomas
- ▶ Loss-of-function *ATRX* variants:
 - reported in patients with corticotroph adenomas
 - rarely in isolated aggressive prolactinomas
- ▶ Somatic screening, including for *TP53* and *SF3B1*, considered in prolactinomas with unusual proliferation rates

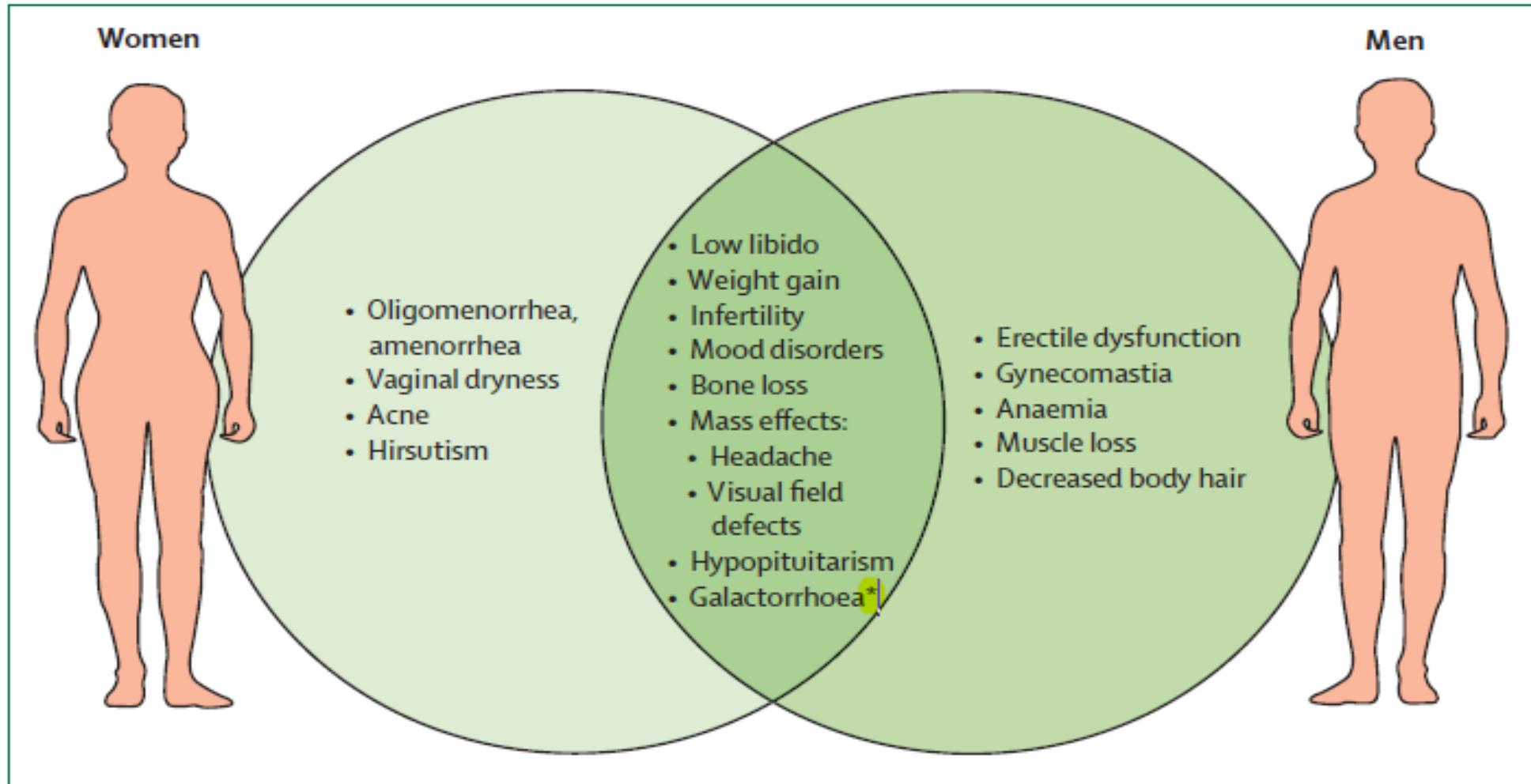


Figure 4: Clinical presentation of hyperprolactinaemia in adults

Clinical features might be different in children and adolescents, which could drive diagnostic workup and influence treatment decisions. *Common presentation in women, extremely rare for men.

TABLE 7.12**Signs and Symptoms of Prolactinomas**

Associated With Tumor Mass	Associated With Hyperprolactinemia
Common	
Visual field abnormalities	Hypogonadism
Blurred vision or decreased visual acuity	Amenorrhea, oligomenorrhea
Symptoms of hypopituitarism	Infertility
Headaches	Oligospermia
Rare	Decreased libido
Cranial nerve palsies	Erectile dysfunction
Pituitary apoplexy	Galactorrhea
Seizures (temporal lobe)	Osteoporosis
Hydrocephalus	
Unilateral exophthalmos	
Cerebrospinal fluid rhinorrhea	
Empty sella	

Clinical

- ▶ adenomas in men are:
 - larger
 - more invasive
 - express higher PRL
 - higher proliferation rates
 - more frequently DA resistant.
- ▶ IGF-1 should be measured at baseline and during follow-up to drive management decisions in mixed GH–PRL pituitary adenomas :
 - larger
 - more invasive
 - hypopituitarism more frequently (than do pure GH -secreting pituitary adenomas)

Clinical

- ▶ excess PRL suppresses GnRH by :
 - reducing kisspeptin
 - Increased opioid tone
- ▶ Galactorrhoea is common in **premenopausal** women but rare after menopause.
- ▶ Increased adrenal androgen production and PCO phenotype.
- ▶ Treatment restores libido, but has a lesser effect on erections
- ▶ In both sexes, hyperprolactinaemia increases appetite, weight, **insulin resistance**, and lipid abnormalities.
- ▶ Bone health is compromised due to:
 - hypogonadism
 - PRL -induced bone resorption
 - reduced muscle mass.

Comorbidities

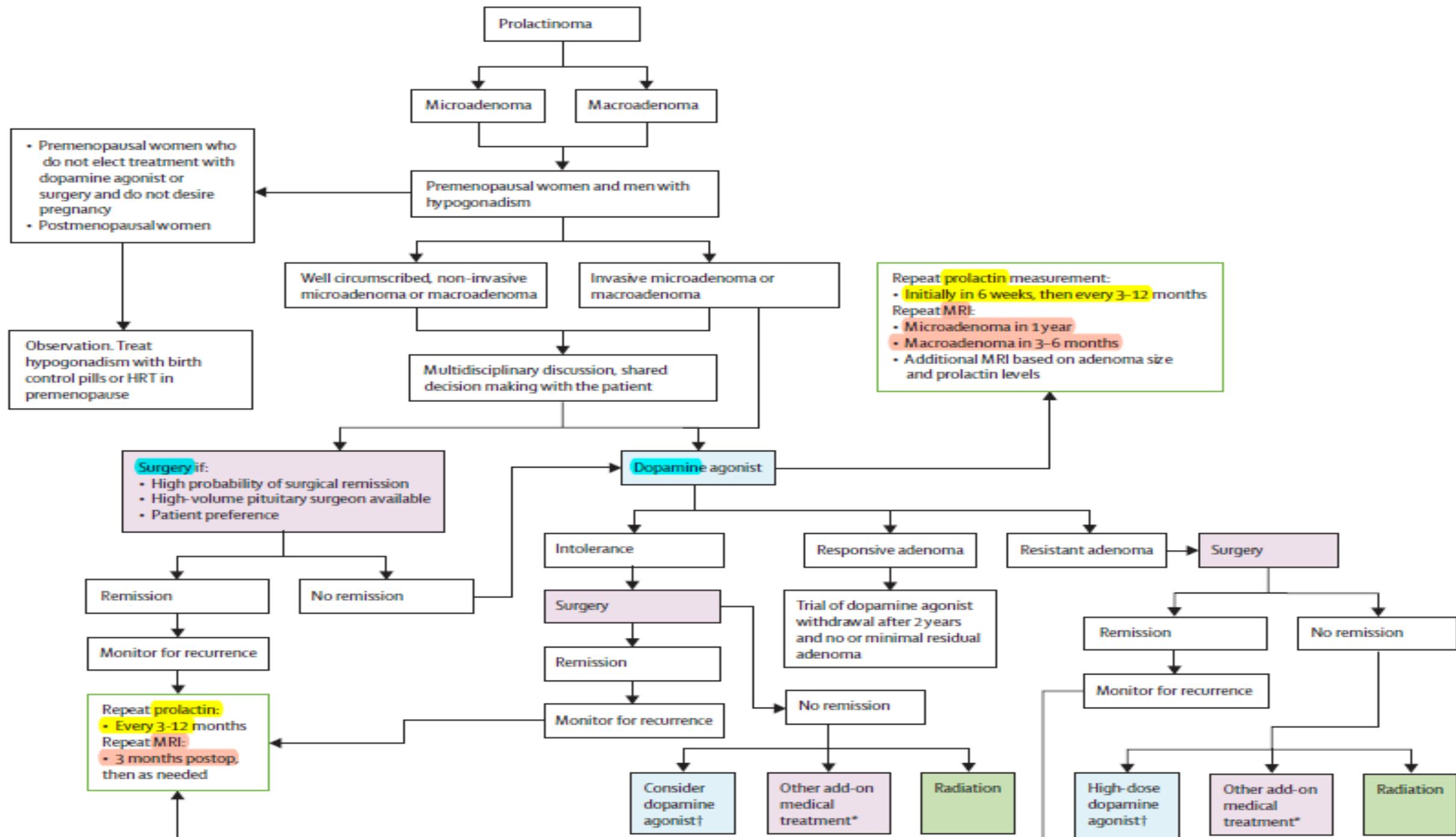
- ▶ Quality of life related to:
 - hyperprolactinaemia
 - treatment side-effects
 - mass effects
 - decreased to a lesser extent in prolactinoma than acromegaly or Cushing's disease
- ▶ prolactinomas controlled on DA or in remission post-surgery :
subtle impairments in
 - memory
 - attention
 - processing speed

Comorbidities

- ▶ DEXA recommended for patients with long-standing hypogonadism (>6 m)
- ▶ Plain radiographs or vertebral fracture assessment are needed in back pain and height loss
- ▶ Cabergoline fracture risk reduction as high as 75%
- ▶ eugonadism restoration and hypogonadism treatment **not be sufficient** for fracture risk reduction.
- ▶ Osteoporotic drugs should be provided in accordance with guidelines.
- ▶ .

Comorbidities

- Both hyperprolactinaemia and hypoprolactinaemia : increase risk of metabolic dysfunction
 - visceral obesity, insulin resistance, T2DM , dyslipidaemia, chronic inflammation, diastolic dysfunction, and sexual dysfunction were all more frequent in patients with both hyperprolactinaemia and hypo prolactinaemia versus individuals with normal PRL
 - screening for glucometabolic disorders considered in prolactinoma who have very low PRL on DA.
 - Presence of a metabolic disorder does not warrant PRL measurement in the absence of galactorrhoea, oligomenorrhoea, amenorrhoea, or hypogonadism
- Baseline pituitary function should be undertaken in all patients regardless of adenoma size

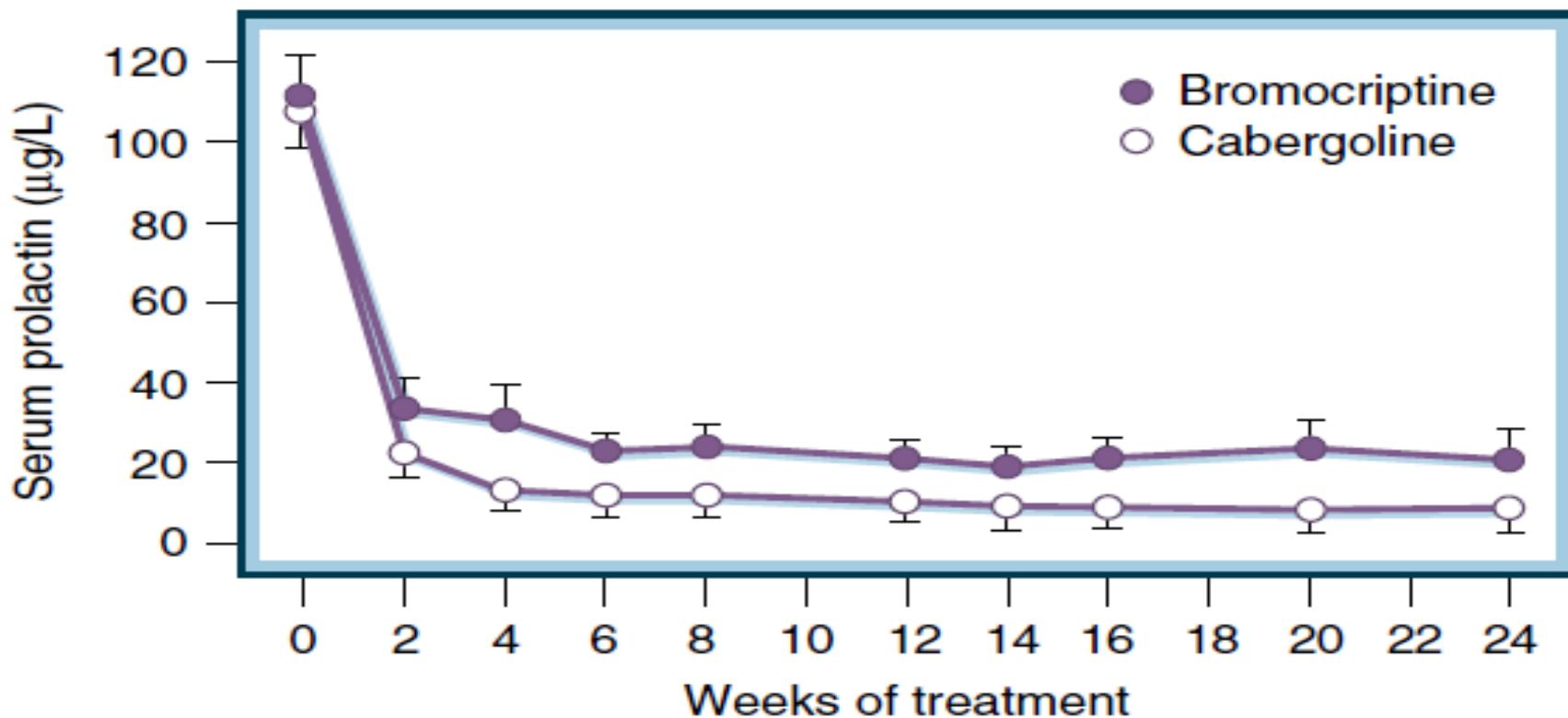


Management: observation

- ▶ Microprolactinomas rarely increase in size and some shrink spontaneously .
- ▶ PRL usually change in parallel with enlargement and a marker of adenoma growth .
- ▶ **baseline PRL and mass size** can **not predict** the likelihood of adenoma growth.
- ▶ Observation : **micro adenomas** and only **mild-to-moderate elevation PRL**
 - premenopausal women with normal gonadal function
 - postmenopausal women
- ▶ Hypogonadal women with microadenomas who decline or are not candidates for surgery or DA should be recommended:
 - sex hormone replacement
 - periodic biochemical and imaging evaluation
- ▶ Risk of microadenoma growth due to lactotroph estrogen stimulation appears small.
- ▶ Women taking OCP for 2–6 y appear not to show prolactinoma growth (in some cases, decreased in size).

Management: dopamine agonists

- ▶ DA :mainstay of prolactinoma treatment
 - PRL normalization
 - adenoma volume reduction
 - recovery of gonadal function
- ▶ Cabergoline, bromocriptine, and quinagolide bind to DR on the pituitary adenoma, inhibit PRL secretion, and induce neoplastic lactotroph apoptosis along with fibrotic changes.
- ▶ **cabergoline** :
 - PRL normalizes: 90% of microprolactinomas ,83% of macroprolactinomas
 - adenoma shrinkage :71% (microadenomas and macroadenomas)
- ▶ **Bromocriptine** : less efficacious, particularly for **macroadenoma shrinkage**
- ▶ Giant prolactinomas respond well to conventional DA doses, with somewhat lower rates of PRL normalization (50–60%) and shrinkage (88–93%).



• **Fig. 7.28** Comparison of bromocriptine and cabergoline in suppressing prolactin levels in women with hyperprolactinemia. (From Webster J, Piscitelli G, Polli A, et al. A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. *N Engl J Med*. 1994;331:904–909.)

TABLE 7.13**Dopamine Agonist Treatment of Prolactinomas**

	Bromocriptine (2.5–7.5 mg/day)	Cabergoline (0.5–1 mg twice weekly)
Prolactin Normalized (range, 40%–100%)		
Macroadenomas	70	80
Microadenomas	65	70
Menses Resumed (range, 40%–100%)		
Macroadenomas	70	80
Microadenomas	85	80
Mass Shrinkage (range, 20%–100%)		
None	20	20
Up to 50%	40	55
50% or more	40	25
Visual Field Improvement (range, 33%–100%)		
Drug Intolerance	15	5

Long-acting cabergoline has superior patient compliance and fewer gastrointestinal side effects. Values shown indicate percentage of patients.

Data from Webster J, Piscatelli G, Polli A, et al. A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. Cabergoline Comparative Study Group. *N Engl J Med*. 1994;331:904–909; Verhelst J, Abs R, Maiter D, et al. Cabergoline in the treatment of hyperprolactinemia: a study in 455 patients. *J Clin Endocrinol Metab*. 1999;84:2518–2522; Melmed S, Casanueva FF, Hoffman AR, et al. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96:273–288.

Management: dopamine agonists

- ▶ Response to DA is rapid, within **3 months**, and within 2–4 weeks in very sensitive adenomas
- ▶ **Predictors** of response to cabergoline within the first year include:
 - normalization or near-normalization of PRL within 3–6 months
 - adenoma volume reduction of 45%.
- ▶ **Cystic prolactinomas** : DA-sensitive, with median cyst volume reduction of 83·5%
- ▶ initiation :
 - cabergoline **0·5–1·0 mg/week**
 - bromocriptine **2·5–5·0 mg daily**
- ▶ The dose is escalated in a stepwise manner **every 1–3 months**
- ▶ maintenance doses :
 - **0·5–2·0 mg/week** for cabergoline
 - **2·5–15/d mg** for bromocriptine

Management: dopamine agonists

- ▶ rapid cabergoline dose escalation in large/giant prolactinomas ↑ increase the risk of CSF leak and apoplexy.
- ▶ DA resistance : an absence of **PRL normalization** with or without relevant mass shrinkage ($\geq 30\%$ volume reduction in maximum diameter) when treated with standard DA doses for **at least 6 m**
 - resistance to bromocriptine : switching to cabergoline is recommended.
 - resistance to cabergoline : increasing doses, up to 7–12 mg/week (side-effects, individualized)
- ▶ After adenoma shrinkage and normal-to-low PRL , dose de-escalation can be attempted.
- ▶ de-escalation has not been associated with mass regrowth in DA -sensitive or partially resistant **macroprolactinomas**

Management: dopamine agonists

- ▶ DA withdrawal : after a minimum of 2 years in individuals with normal PRL **and** maximal shrinkage.
- ▶ among those who meet the criteria for discontinuation, long-term remission :
 - 44% : macroadenoma
 - 57% : microadenoma
- ▶ Second withdrawal has been attempted in selected patients after another 2 years of cabergoline

Table 2. Dose Recommendations and Side-Effect Profiles for Dopamine Agonists Approved for Use in the United States.

Medication	Dose*	Side Effects of Both Drugs†
Bromocriptine	Initial: 0.625 to 1.25 mg daily; usual range for maintenance dose: 2.5–10.0 mg daily	Common: nausea, headaches, dizziness (postural hypotension), nasal congestion, constipation Infrequent: fatigue, anxiety, depression, alcohol intolerance
Cabergoline	Initial: 0.25–0.5 mg weekly; usual range for maintenance dose: 0.25–3.0 mg weekly	Rare: cold-sensitive vasospasm, psychosis Possible: cardiac-valve abnormalities

* Doses are increased until limited by side effects, with prolactin levels generally measured every 4 weeks for patients receiving bromocriptine and every 8 weeks for patients receiving cabergoline, so that the lowest effective dose is used. Doses are increased until prolactin levels are within the normal range, gonadal function returns, or a plateau effect is reached, depending on the indication for treatment. A typical dose-adjustment strategy involves increasing the daily dose on a weekly basis, with the daily dose of bromocriptine increased by 1.25 to 2.5 mg and the weekly dose of cabergoline increased by 0.25 to 0.5 mg. Symptoms of mass effect or visual loss require more rapid escalation (e.g., doubling of the dose every 3 to 5 days, until limited by side effects) until an optimal dose is reached. Maximum doses usually do not exceed 10 mg of bromocriptine per day and 3 mg of cabergoline per week.

† Side effects may occur with all dopamine agonists but are less common with cabergoline than with bromocriptine and can be minimized by starting with a very low dose and directing the patient to take the drug with food before going to sleep at night. Bromocriptine can be prescribed in daily divided doses and cabergoline in weekly divided doses as needed to improve tolerability.

Management: dopamine agonists

- ▶ Recovery of visual impairment : 67% (similar visual recovery is seen with surgery).
- ▶ Hypopituitarism improvement :
 - 44–83% for hypogonadism
 - 17–64% for ACTH deficiency
 - 25–29% for TSH deficiency.
- pituitary function worsening occur due to DA induced adenoma haemorrhage or infarction
- ▶ In one large series: Testosterone < 7.4 nmol/L at 6 month independently **predicted lack of recovery** at 12 months (91% :men and 94% :women)
(7.4 nmol/L=200 ng/dl)

Side-effects and complications

- ▶ Nausea, dizziness, and headache : one-third
- ▶ drowsiness, paresthesia, and dyspnea: less commonly
- ▶ Initiating a low dose, escalating gradually, and administering at **night with food** can minimise side-effects for most patients.
- ▶ Cabergoline better tolerated than oral bromocriptine.
- ▶ Patients who cannot tolerate DA should consider surgical management.
- ▶ **Neuropsychiatric** side-effects:
 - psychosis, mood changes, and impulse control disorders, such as hypersexuality and compulsive gambling, compulsive shopping, or eating.
 - vary from as low as 5–10% to as high as 46–61%.
 - more likely in patients with pre-existing psychiatric disorders
 - **not dose-dependent**.
 - There is a need to specifically inquire about impulse control disorder

Side-effects and complications

Cardiac valvulopathy

- ▶ in patients with Parkinson's disease treated with high doses of cabergoline (3–4 mg/day)
- ▶ Bromocriptine : less frequently
- ▶ no reports with quinagolid
- ▶ A meta-analysis showed:
 - higher odds of TR in patients treated with low-dose DA versus controls .
 - valvulopathy was diagnosed by **screening echocardiography** and not by clinical symptoms
 - no increased risk of HF or cardiac valve surgery in patients treated with DA .
- ▶ baseline echocardiogram is helpful if exposure to higher doses (**>2 mg/week** of cabergoline)
- ▶ periodic echocardiogram **every 2–3 years** can assess cumulative effect from long-term treatment

Side-effects and complications

- ▶ rare complications ; CSF leak, pituitary apoplexy, visual loss with optic chiasmopexy, and vasospasm
- ▶ CSF leak
 - Large invasive prolactinomas more prone to CSF leak
 - DA dose decrease or cessation could lead to improved symptoms while the patient is awaiting care of an expert surgeon, or if surgery is contraindicated.
 - Continuation of cabergoline after successful surgical repair is safe and does not typically result in CSF leakage recurrence.
 - Anti-pneumococcal and anti-haemophilus vaccination
- ▶ Cerebral vasospasm reported with bromocriptine use, mostly peripartum.
- ▶ stroke in DA-treated patients with hyper prolactinaemia seems to be slightly more frequent versus matched controls (HR=1.24)

Management: surgical resection

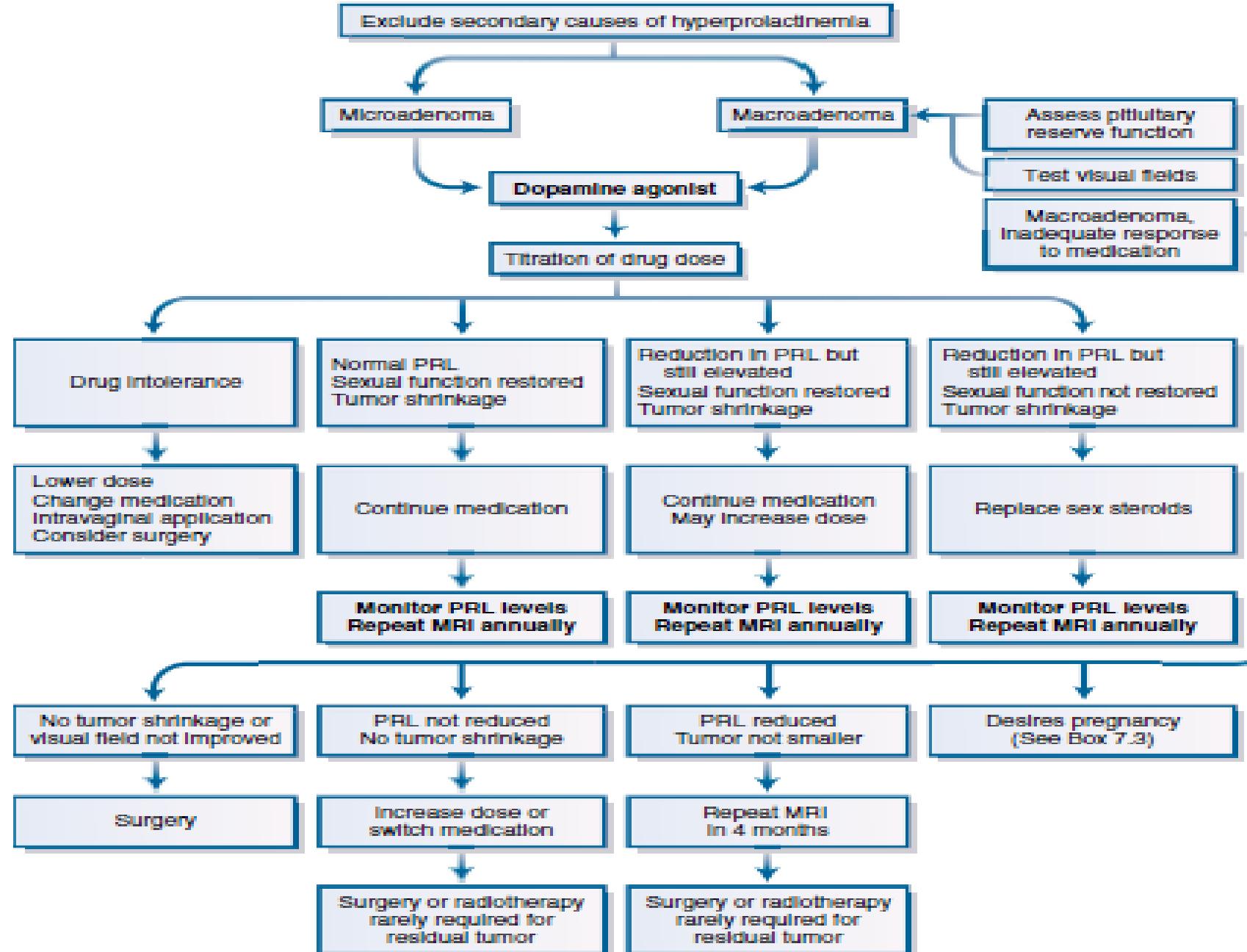
- ▶ TSS
 - DA intolerance or resistance
 - symptomatic pituitary apoplexy
 - CSF leak
 - alternative option for microprolactinomas and well circumscribed macroprolactinomas (Knosp grade 0–1)
 - macroprolactinoma and rapidly progressive vision loss
 - as a strategy for debulking in women desiring pregnancy to reduce the risk of symptomatic enlargement during pregnancy
 - Multidisciplinary care discussions should take into account the unique clinical situation, likelihood of remission with medical therapy, risk of complications, and patient preference, preferably at a Pituitary Centre of Excellence
- ▶ early remission rates: 79% in microadenomas and 44% in surgically treated macroadenomas

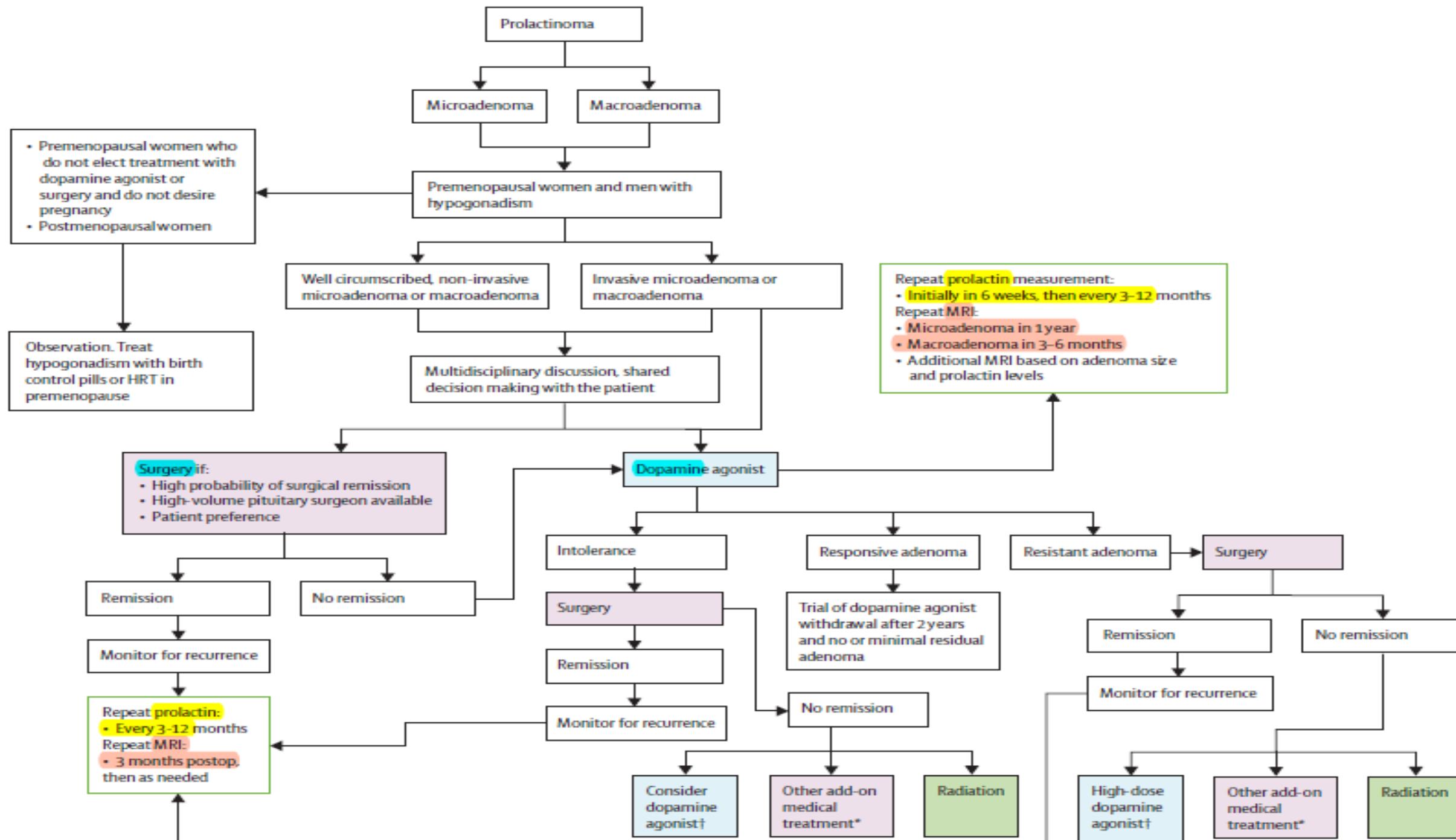
Management: surgical resection

- ▶ Prolactinomas Knops 4 almost never achieve surgical remission.
- ▶ **negative predictors of remission :**
 - preoperative PRL $>200 \mu\text{g/L}$ in a microadenoma
 - male sex
 - Knops 4
- ▶ overall long-term remission rate of only 67%.
- ▶ Low immediate postoperative PRL ($<10 \mu\text{g/L}$) predict long-term remission for both microadenomas and macroadenomas.
- ▶ Few studies with the use of DA before surgery have suggested lower remission.
- ▶ DA are thought to induce adenoma fibrosis, leading to difficulty in tissue removal and a greater potential for injury to nearby structures.
- adenoma fibrosis has been linked to bromocriptine use, but reported fibrosis in cabergoline-treated adenomas seems to be less common.
- Surgical complications in DA versus untreated patients seem similar
(due to fibrosis in small non-invasive adenomas being less relevant to surgical outcome, in the hands of an experienced surgeon)

Management: radiation therapy

- ▶ RT:
 - enlarging or recurrent prolactinomas despite medical and surgical treatment
 - medically resistant prolactinomas that cannot be surgically removed or if surgery is contraindicated
 - lactotroph carcinomas
- ▶ Stereotactic radiotherapy techniques standard-of-care where available.
- ▶ Choice between conventional and stereotactic radiotherapy depends on the prolactinoma size and its proximity to the optic chiasm.
- ▶ Stereotactic radiotherapy is preferred for smaller volume lesions sufficiently distant from the optic chiasm (usually $>3-5$ mm)
- ▶ PRL normalisation is achieved only in about one-third of patients at 4–5 years of follow-up
- ▶ DA cessation pre-radiation is not recommended.
- ▶ Hypopituitarism is the most common complication of radiotherapy(26%)





Long-term monitoring

Biochemical evaluation

► DA :

- PRL : annually in patients treated with DA
- Incomplete PRL normalization **or** an absence of adenoma shrinkage (in cases of mass effect) by **1 year** indicate a need for additional treatment.
- Pituitary function should be periodically reassessed for recovery from deficiencies after adenoma shrinkage
- Microprolactinomas : DA for at least 2 years, with a longer duration for macroadenomas.

Long-term monitoring

- Persistently low or **normal PRL** on $0.25\text{--}0.50 \text{ mg / week}$ cabergoline and **no visible adenoma** on MRI suggests DA withdrawal could be attempted.
- In such a case PRL is measured every 3 months during first year and annually thereafter.
- recurrence occurs in 50% after a median of 4.5 years after DA withdrawal.
- DA is reinitiated if hyperprolactinaemia recurs and treatment continued for another 2–3 years before another withdrawal attempt.

► **Observation** :PRL should be measured annually or if symptoms worsen.

► **Postoperative:**

- PRL is measured on day 1, PRL $<10 \mu\text{g/L}$ predict long-term remission.
- every 3–6 months during the first year and annually thereafter

Long-term monitoring

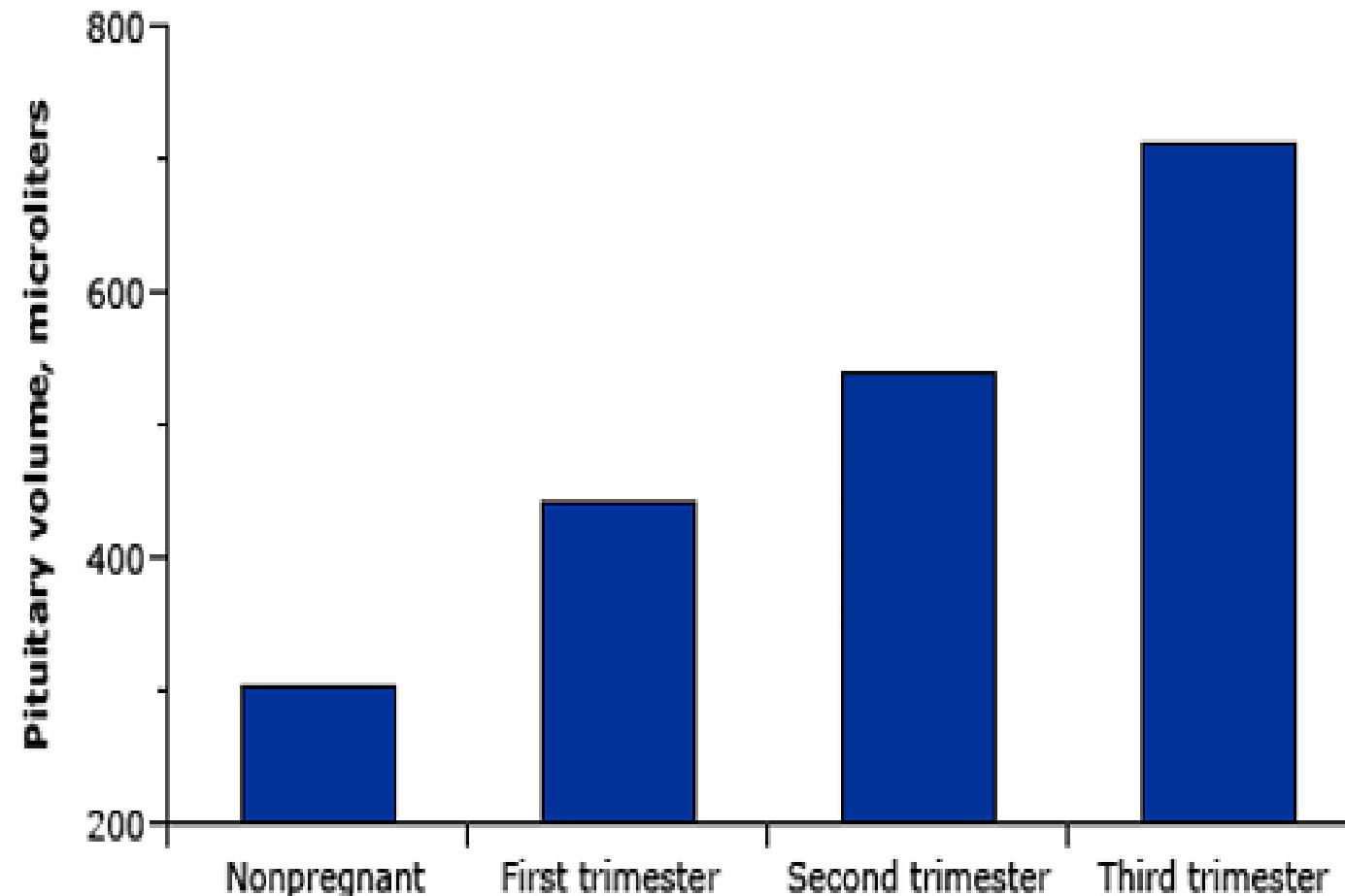
Imaging

- untreated microprolactinomas: MRI repeated at 1 year and subsequent imaging frequency depends on mass stability and PRL
- DA : MRI is repeated after 1 year for microprolactinomas , 3–6 months for macroadenomas. Further imaging is then individualised based on adenoma size, optic chiasm proximity, PRL.
- Decreased PRL correlate with adenoma shrinkage.
- normalization without substantial shrinkage might also occur.
- In DA -responsive adenomas, most shrinkage occurs in the first 6 months, followed by a slow continued size reduction over the subsequent 4 years.

Long-term monitoring

- ▶ In both microadenomas and macroadenomas, if adequate adenoma shrinkage is documented on follow-up MRI, further imaging might not be necessary if prolactin remains normal and the patient remains asymptomatic.
- ▶ any new PRL elevation, mass effect symptoms, or apoplexy should prompt an MRI
- ▶ In case DA withdrawal is attempted, MRI repeated if hyperprolactinaemia occurs.

Pregnancy increases pituitary volume



Pituitary volume, as assessed by magnetic resonance imaging (MRI), in the nonpregnant state and during pregnancy in 19- to 23-year-old normal women. There is a progressive increase in pituitary volume during pregnancy.

• **BOX 7.3**

Management of Pregnancy-Associated Prolactinomas

Prolactinoma management in fertile women

During fertile years, cabergoline treatment is indicated

Macroadenoma mass should be reduced as much as possible before conception

Risks and benefits of surgical resection should be discussed with the patient before and after conception

Planned pregnancy

Barrier contraception should be initiated concomitant with DA treatment

Allow 2–3 normal menses to occur

Stop contraception and perform periodic hCG testing

Upon positive hCG test, discontinue DA

Spontaneous pregnancy

DA should be discontinued as soon as pregnancy confirmed

Expansion risk is <5% for microprolactinoma and is ~50% for macroprolactinoma

If headache or visual disturbances arise, perform visual field tests

If symptoms are worrisome, pituitary MRI without gadolinium is indicated

If adenoma expansion is of concern during second or third trimester, DA should be restarted

Risks and benefits of surgical adenoma resection should be offered to the patient

Vaginal delivery may proceed, but the rare possibility of pituitary apoplexy should be discussed with the obstetrician

Postpartum MRI should be performed after 6 weeks

Lactation is not contraindicated if the patient is not being treated with DA

Follow-up 6 and 12 months after delivery

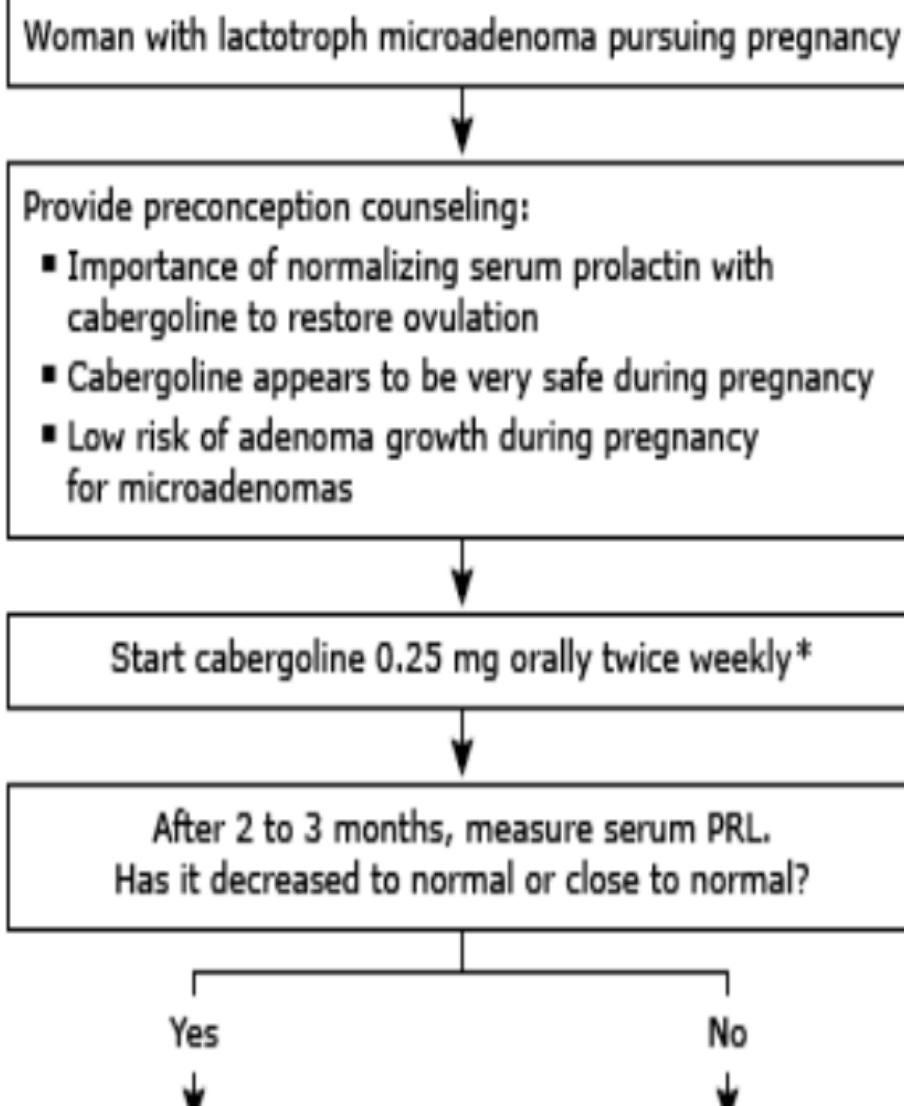
Prolactinoma during pregnancy

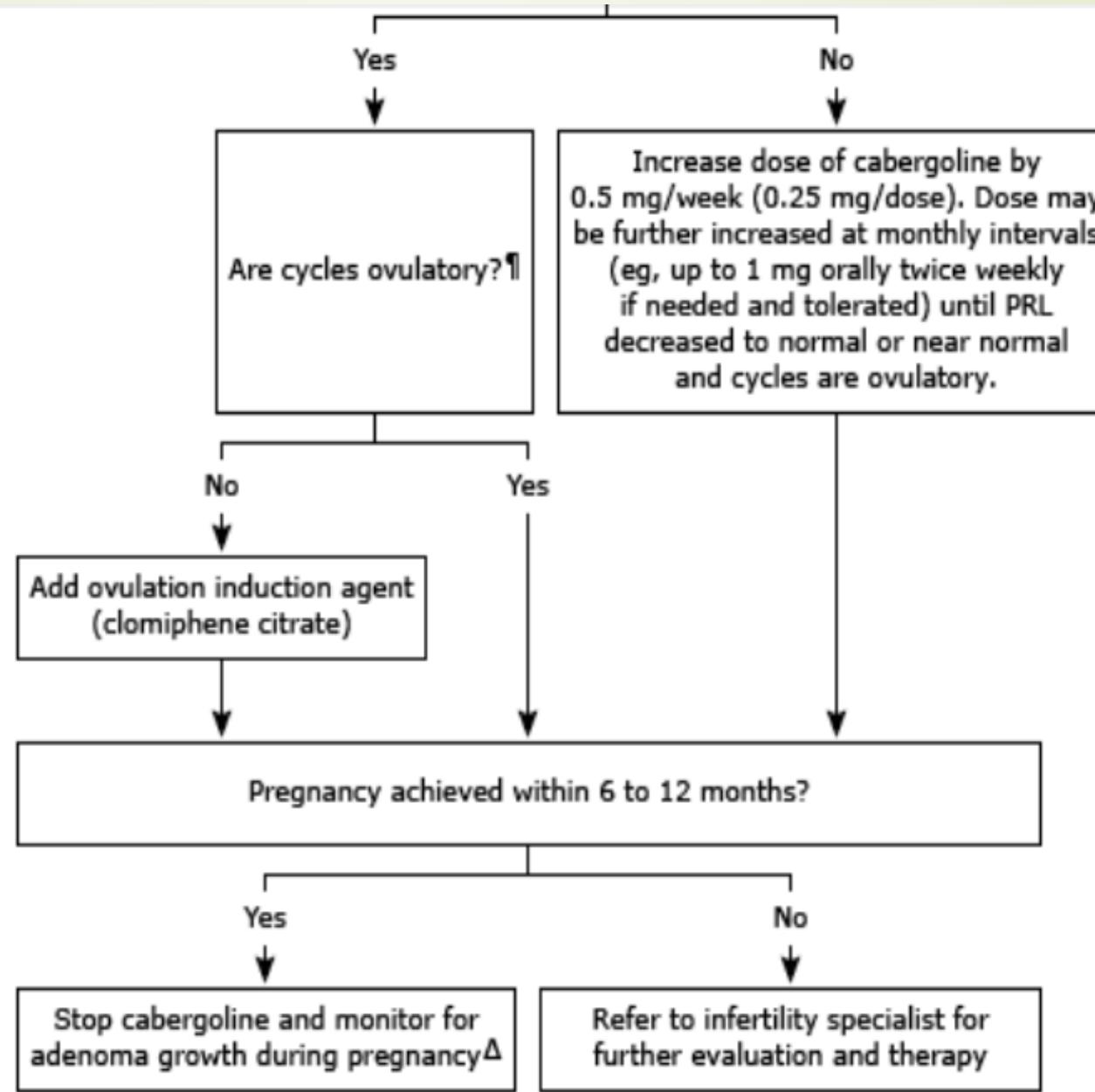
- ▶ Normalizing PRL in prolactinoma is important for optimizing ovulatory function and embryo implantation.
- ▶ before conception, **macroprolactinomas** :
 - should be managed with DA to confirm adenoma regression and PRL normalization
 - Baseline visual field test
- ▶ larger adenomas, surgery before conception:
 - reduces the risk of symptomatic progression
 - increases hypopituitarism risk
- ▶ higher risk of GDM has been linked to low PRL before pregnancy
- ▶ Discontinuation of cabergoline in early pregnancy is recommended

Prolactinoma during pregnancy

- ▶ combination of DA interruption, high estrogen , and physiological pituitary enlargement increase adenoma growth rate.
- ▶ Risk of adenoma progression : 2·4% for microadenomas , 21% for macroadenomas.
- ▶ many women have had successful pregnancies when being treated with cabergoline
- ▶ close follow-up for headaches and visual field defects
- ▶ recurring symptoms or signs of mass effects : re-initiation of cabergoline at the lowest effective dose
- ▶ If cabergoline is not effective in reducing prolactinoma size, surgical debulking or delivery recommended.
- ▶ As hyperprolactinaemia resolve after pregnancy, repeat PRL should be undertaken after delivery before restarting treatment.

Treatment of lactotroph microadenomas in women pursuing pregnancy





Prolactinoma after menopause

- ▶ Estrogen decline after menopause affect prolactinoma behavior by decreasing PRL and lessening lactotroph cell stimulation.
- ▶ prolactinoma prognosis is more favorable
- ▶ remission rates : 90%
- ▶ cabergoline discontinuation :a two-to-three times increase in remission after menopause.
- ▶ DA withdrawal after menopause is often safe, especially in **microprolactinomas**
- ▶ discontinuation could be attempted for menopausal patients with well controlled microprolactinomas

Prolactinoma after menopause

- ▶ annual PRL detect a potential early recurrence.
- ▶ In postmenopausal women with **macroprolactinomas**, DA continuation is encouraged to prevent regrowth.
- ▶ Newly diagnosed prolactinomas after menopause:
 - larger(macroadenomas)
 - mass effect symptoms : common presenting features.
 - DA resulted in normalized PRL (86%)
- ▶ secondary hypogonadism is less of a concern after menopause, adverse bone effects of hyperprolactinaemia can occur.
- ▶ In postmenopausal women with persistent hyperprolactinaemia, osteoporosis prevention and management is advised, with optimisation of calcium and vitamin D intake.

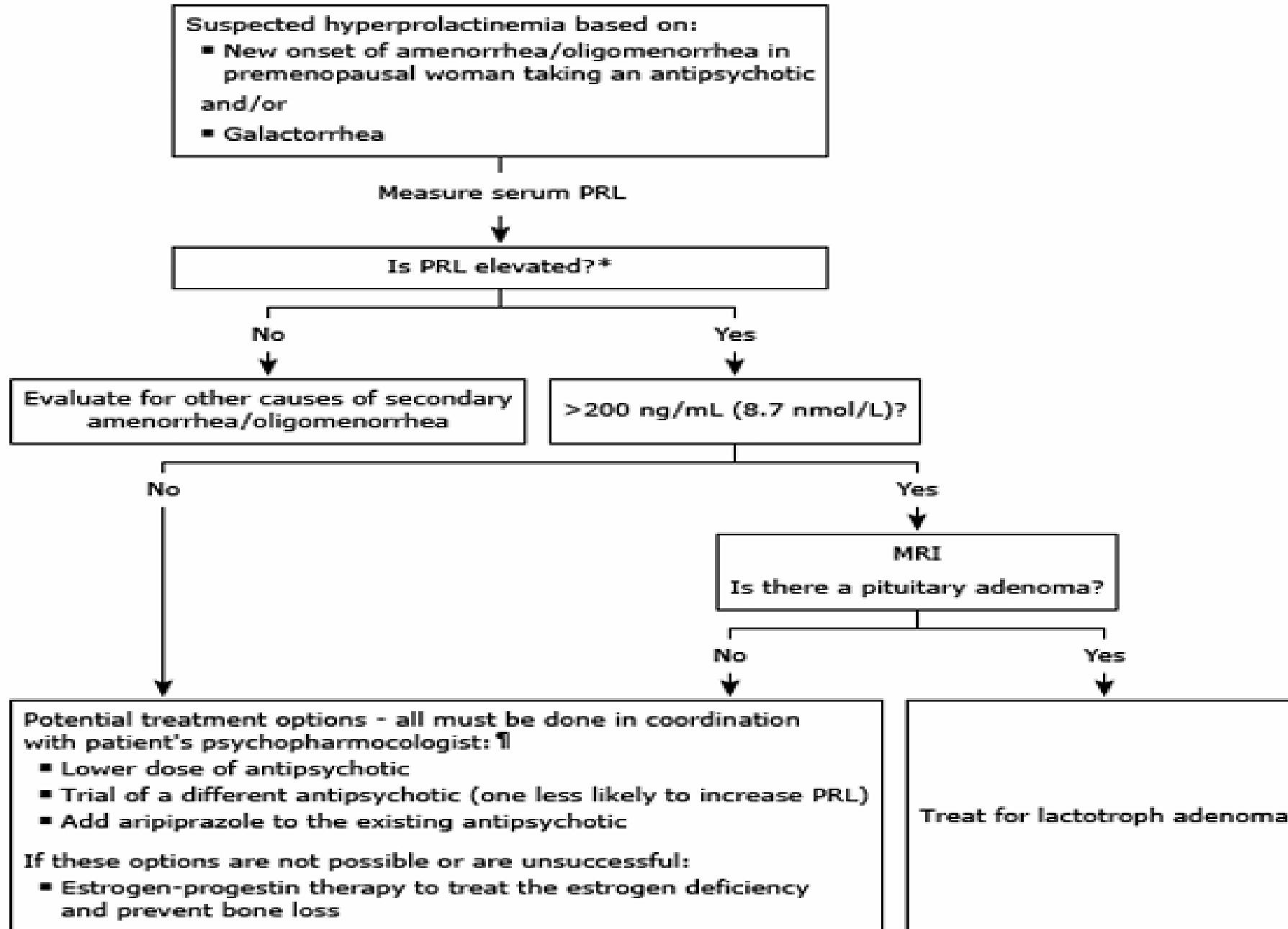
Hyperprolactinaemia and psychiatric disorders

- ▶ antipsychotic medications elevate PRL
- ▶ women taking antipsychotics are at risk of amenorrhea, menstrual irregularities, and infertility
- ▶ men might experience gonadal dysfunction and infertility.
- ▶ Measuring PRL before initiating antipsychotics avoid unnecessary subsequent investigations.
- ▶ PRL >10 times ULN is rare in drug-induced hyperprolactinaemia and should raise suspicion for a prolactinoma, warranting MRI evaluation.
- ▶ Stalk effect due to a large NFPA cannot be excluded even with more moderate PRL elevations. should be made to reduce dosing or switch medications and follow-up
- ▶ A prolactin-sparing antipsychotic, such as aripiprazole, can normalize PRL and help differentiate between drug effects and prolactinoma.

Hyperprolactinaemia and psychiatric disorders

- ▶ drug-induced hyperprolactinaemia t resolves within 48–96 h.
- ▶ Management of **prolactinomas in psychiatric** conditions can be challenging :
 - neuropsychiatric side-effects of DA and symptom exacerbation
 - require higher DA doses to achieve biochemical control and prolactinoma shrinkage.
 - Aripiprazole co-administration allow for lower DA dosing or even discontinuation
 - DA intolerance or refractory prolactinomas, pituitary surgery is an alternative approach

Evaluation of suspected hyperprolactinemia in premenopausal woman taking an antipsychotic



Aggressive prolactinoma

- ▶ Prolactinomas are the second most prevalent aggressive pituitary tumours after corticotroph tumours.
- ▶ defined by both persistent hyperprolactinaemia and adenoma growth.
- ▶ 10–20% of prolactinomas are DA resistant (cabergoline doses up to 2 mg /week).
- ▶ refractory prolactinomas cannot be controlled after use of maximally tolerated DA doses
- ▶ factors associated with DA resistance:
 - Invasion of the cavernous sinus or adjacent bone
 - decreased D2 R expression
 - low expression of ER a.
 - Abnormal cholesterol metabolism reducing DRD2 membrane localization
 - altered signaling of TGF β and bradykinin-receptor type 2
 - overexpression of EGF and VEGF

Aggressive prolactinoma and lactotroph carcinoma

► Aggressive prolactinoma

- 2% of prolactinomas
- rapid growth or invasion
- more frequently in men, (at a younger age)
- surgical pathology exhibit Ki67 >3% , p53 expression, and faint PRL staining.
- **Mass invasiveness** alone or **mass size** should not be equated with aggressive behaviour, as giant prolactinomas shrink with DA

► Pituitary carcinomas

- <0.1% of all pituitary tumours
- lactotroph carcinomas : one-third of reported pituitary carcinomas.
- Multimodal therapy is required in aggressive prolactinomas
- Temozolomide : recommended for clinically relevant prolactinoma progression or invasion after DA is determined ineffective, and especially after radiation therapy.



THANK YOU FOR ATTENTION