Modern management of Hyperprolactinaemia

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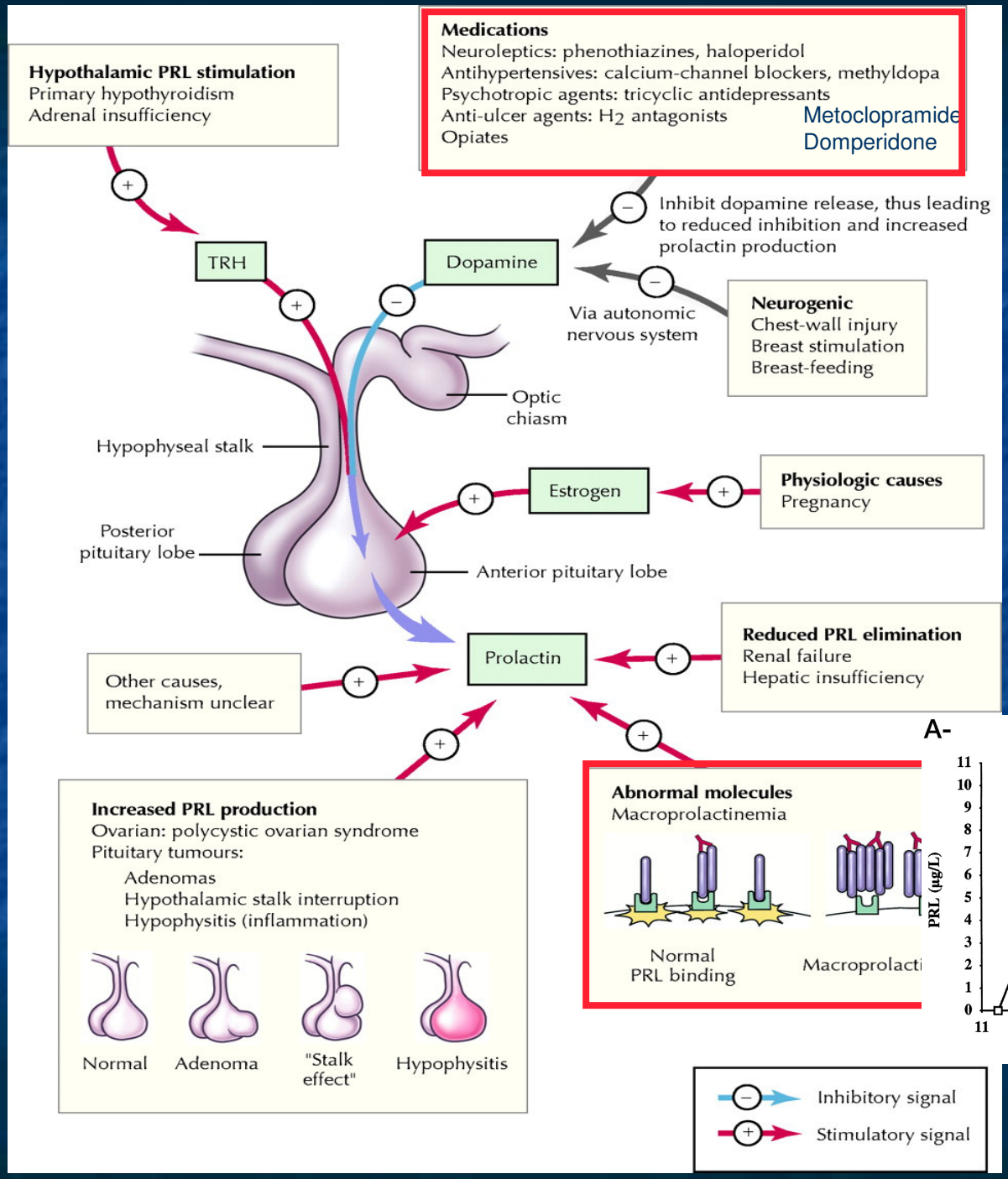
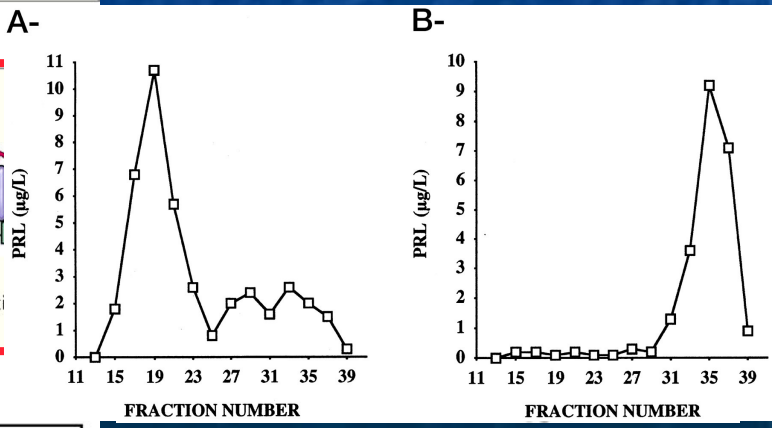
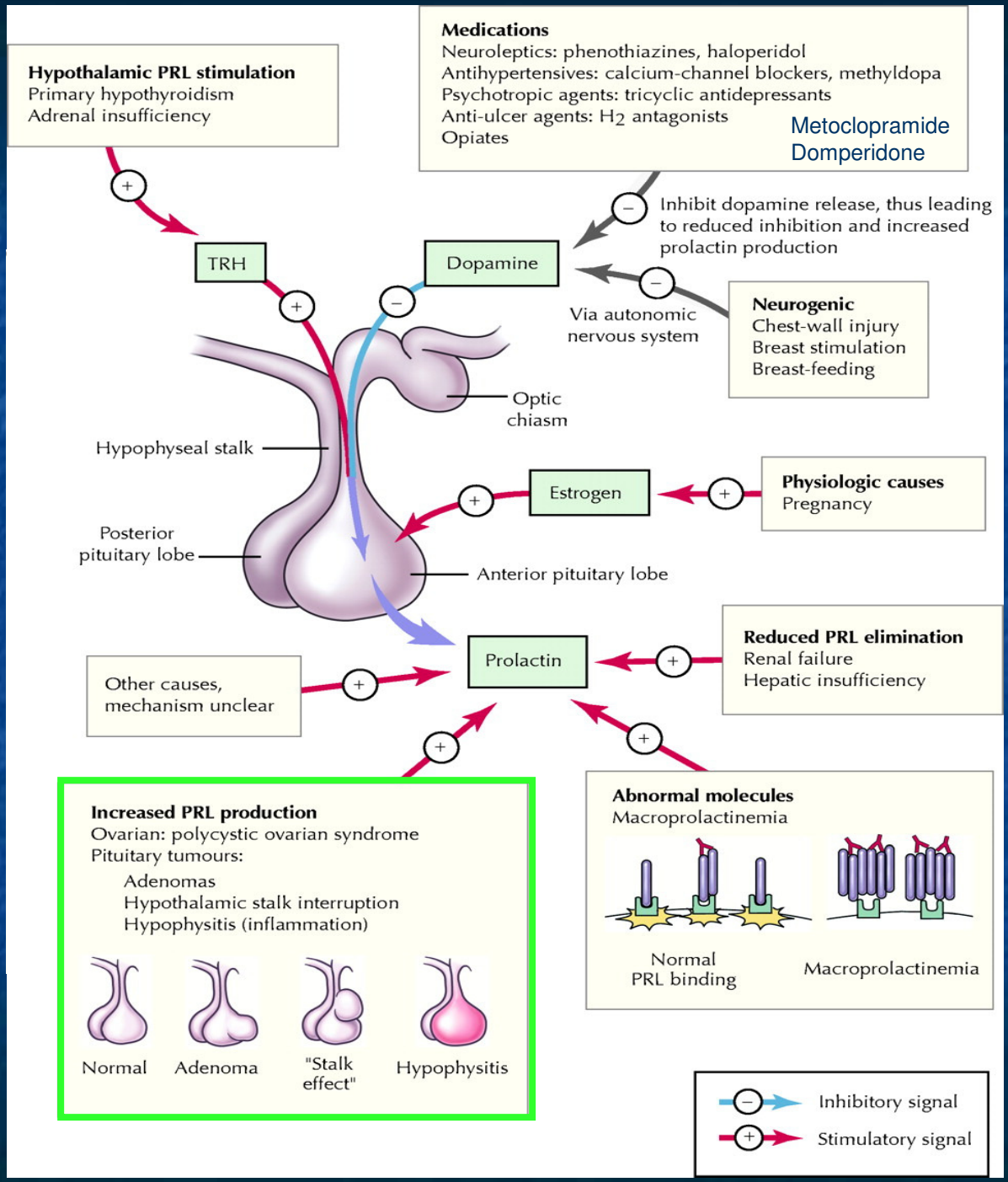
HYPER-PROLACTINAEMIA: the true and the false problems





Ensure that HPRL is really the culprit!

- Require symptoms of HPRL
  - Galactorrhea
  - Clinical and/or biological signs of hypo(normo)gonadotropic hypogonadism
- If not present:
  - Episodic drug consumption
  - Macroprolactinaemia


Medications
Neuroleptics: phenothiazines, haloperidol
Antihypertensives: calcium-channel blockers, methyldopa
Psychotropic agents: tricyclic antidepressants
Anti-ulcer agents: H2 antagonists
Opiates
Metoclopramide
Domperidone
Hypothalamic PRL stimulation
Primary hypothyroidism
Adrenal insufficiency
Inhibit dopamine release, thus leading to reduced inhibition and increased prolactin production
TRH
Dopamine
Via autonomic nervous system
Neurogenic
Chest-wall injury
Breast stimulation
Breast-feeding
Optic chiasm
Hypophyseal stalk
Estrogen
Physiologic causes
Pregnancy
Posterior pituitary lobe
Anterior pituitary lobe
Prolactin
Reduced PRL elimination
Renal failure
Hepatic insufficiency
Other causes, mechanism unclear
Abnormal molecules
Macroprolactinemia
Normal PRL binding
Macroprolactinemia
Increased PRL production
Ovarian: polycystic ovarian syndrome
Pituitary tumours:
Adenomas
Hypothalamic stalk interruption
Hypophysitis (inflammation)
Normal
Adenoma
"Stalk effect"
Hypophysitis
Inhibitory signal
Stimulatory signal

HPRL due to PCOS : *also a false problem!*

Filho RB et al. Gynecol Endocrinol. (2007)

82 PCOS women, 13 (16%) presented high PRL levels (103.9 ± 136.0 µg/l).

- pituitary tumor (responding to cabergoline) in nine cases (69%; PRL range: 28.6 - 538 µg/l)
- oral hormonal contraceptive treatment in two cases (15%; PRL: 46 and 55 µg/l, respectively)
- use of buspirone and tianeptine in one case (8%; PRL: 37.1 µg/l)
- macroprolactinemia in one case (8%; PRL: 34.4 µg/l).

Should dynamic tests be performed?

- Dynamic testing should not be used as a first line test.
- It should not guide the decision to ask for a MRI.
- It can be useful when the MRI is inconclusive or misleading.
- The most commonly used are TRH and metoclopramide tests

Increased PRL production

~~Ovarian: polycystic ovarian syndrome~~

Pituitary tumours:

- Adenomas
- Hypothalamic stalk interruption
- Hypophysitis (inflammation)

Normal | Adenoma | "Stalk effect" | Hypophysitis

MRI

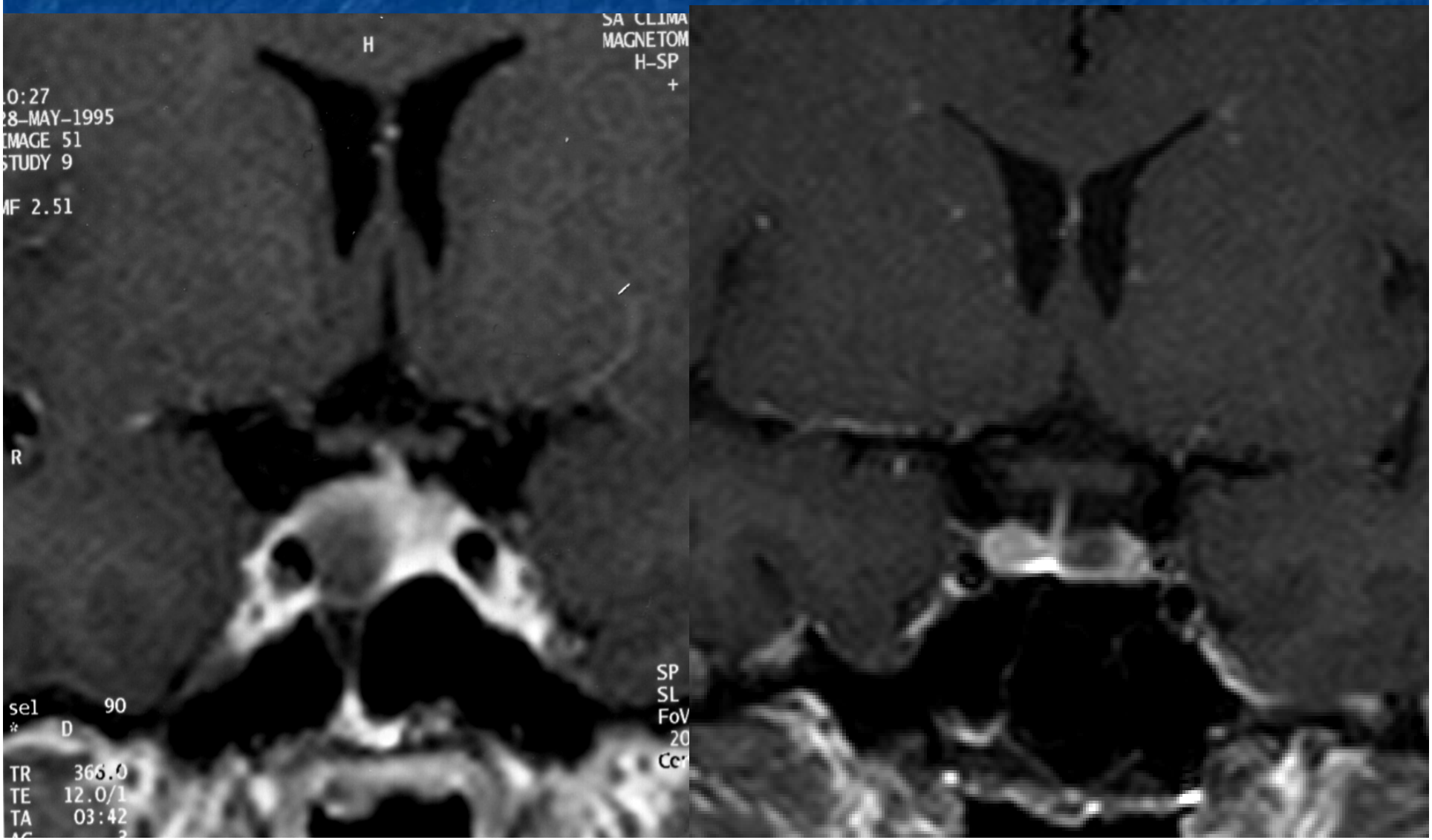
Technique

- Coronal T2 and T1-weighted sections before and after injection are usually enough to identify microadenomas.
- Dynamic MRI with gadolinium injection should give rise to cautious interpretation as it is prone to yielding false positives.
- Sections in the frontal and lateral directions are required in cases of mass syndrome.

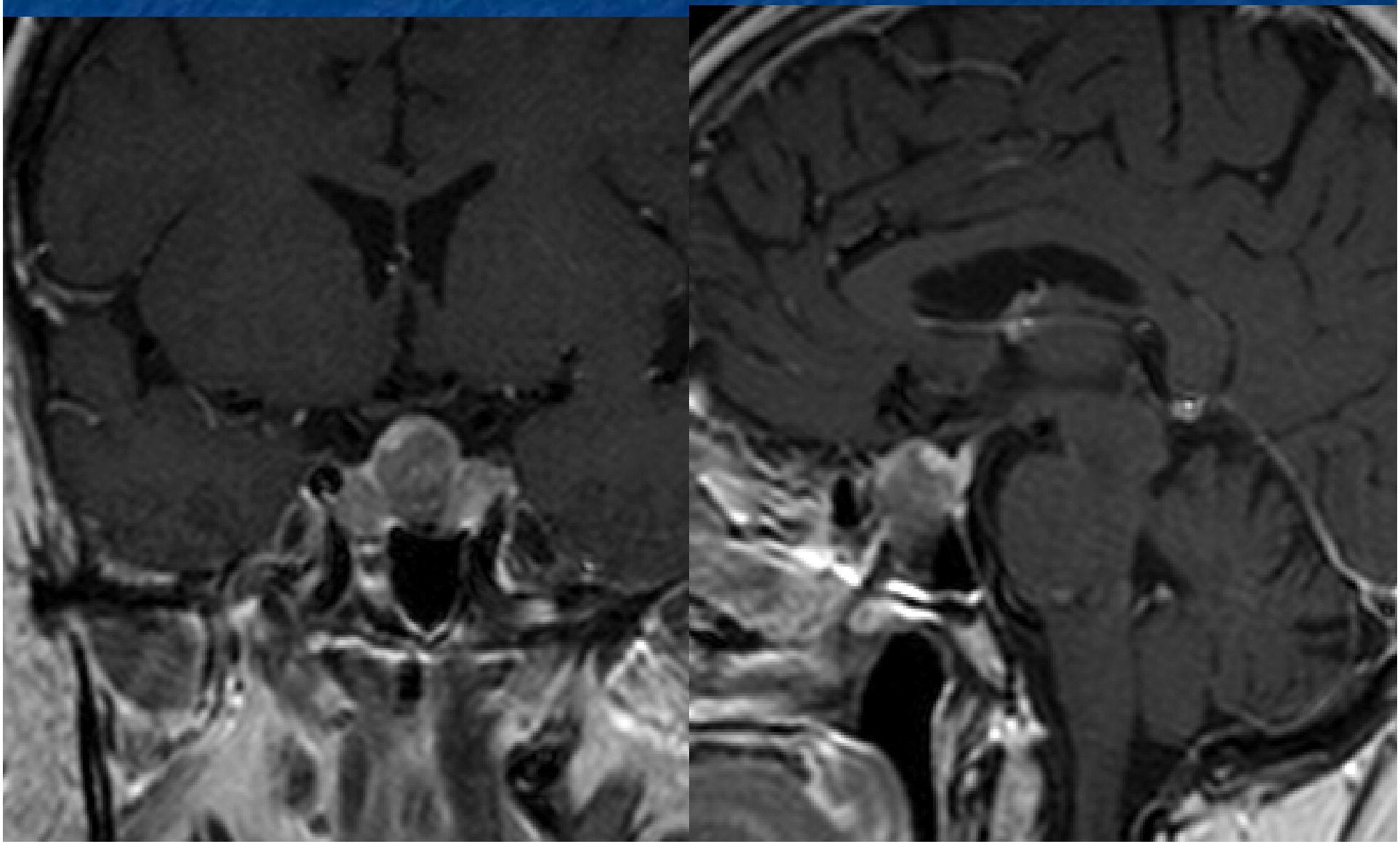
Results

- Microadenoma (<10mm)
- Macroadenoma
- Craniopharyngioma
- Meningioma
- Cysts
- Others…

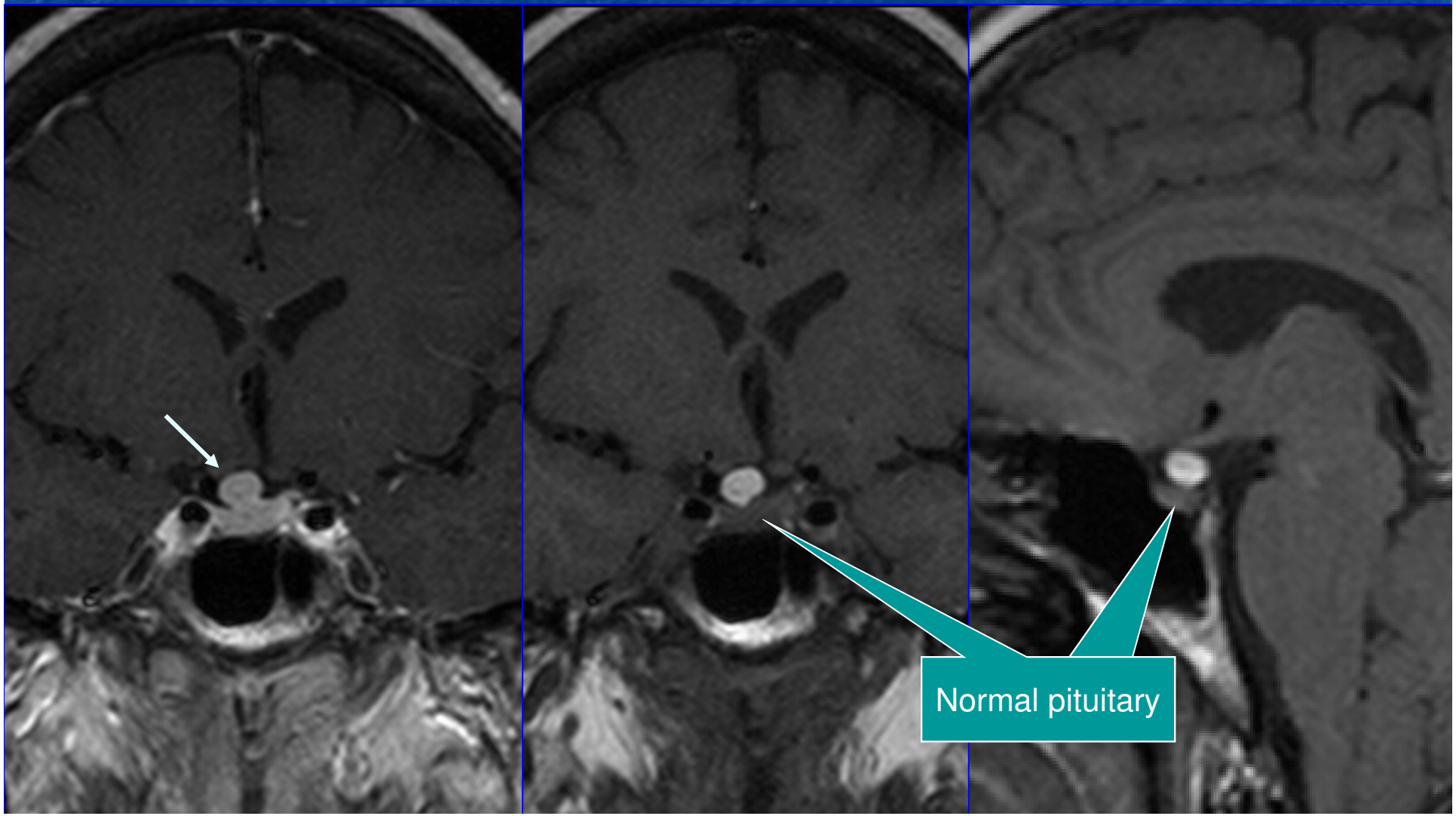
MICROADENOMA (< 10 MM)



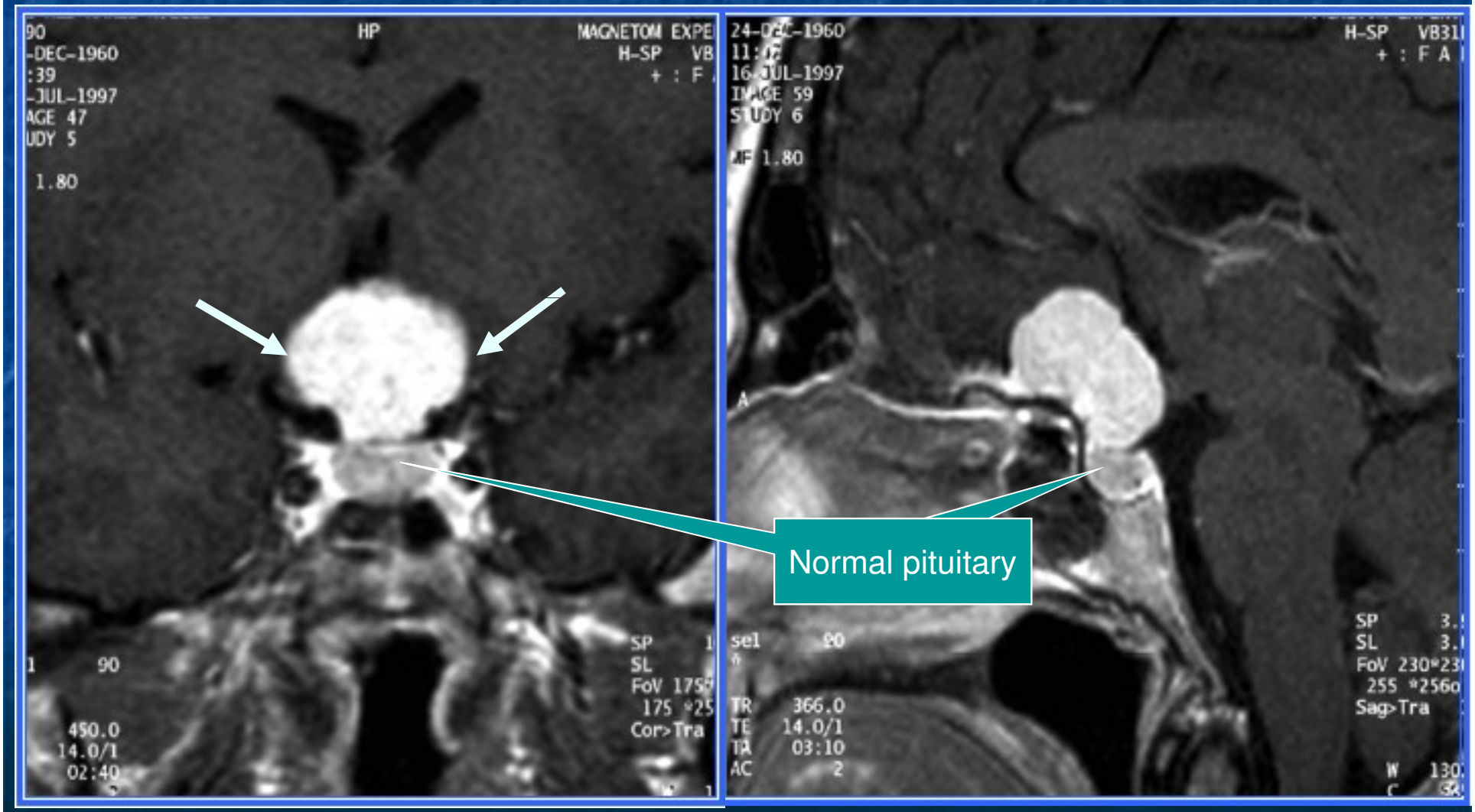
MACROADENOMA (> 10 mm)



CRANIOPHARYNGIOMA



MENINGIOMA

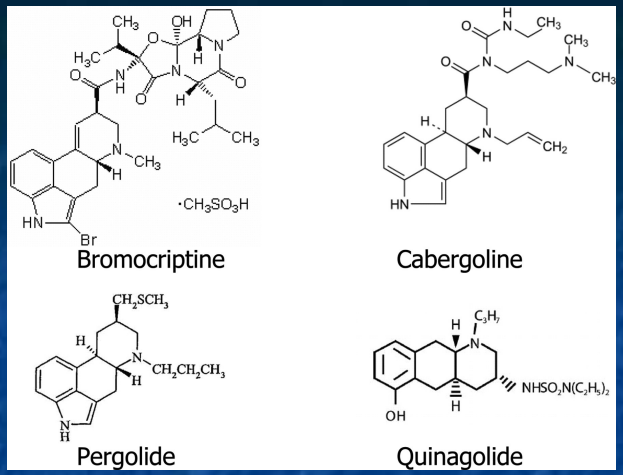


What is your diagnosis?

- 28 y.o. infertile patient
- Oligomenorrhea
- FSH=5.4 UI/L
- LH=6.1 UI/L
- PRL=68 ng/mL
- MRI: intra-sellar 8 mm lesion

Therapeutic management of Microprolactinomas and non extensive Macroprolactinomas

- Dopamine agonists is the first line treatment
- Selective adenomectomy only if:
  - Resistance to treatment (rare: approximately 5-10%)
  - persistent intolerance to dopamine agonists (low blood pressure, digestive disorders, etc.)
  - refuse long-term treatment, has a pregnancy project, expresses anxiety over living with a tumor in his/her head or the uncertainty of tumor progression during pregnancy
  - mixed secreting microadenomas such as prolactin and GH.



DOPAMINE AGONISTS

- BROMOCRIPTINE
  - 2.5 mg tablets
  - Twice a day
- QUINAGOLIDE
  - 0.075 & 0.15 mg tablets
  - Once a day
- CABERGOLINE
  - 0.5 mg tablets
  - Once a week

- Secondary effects
  - digestive (nausea, vomiting)
  - Drowsiness or orthostatic hypotension
- Efficacy
  - 90%
  - Immediate
  - Prescribe contraception!

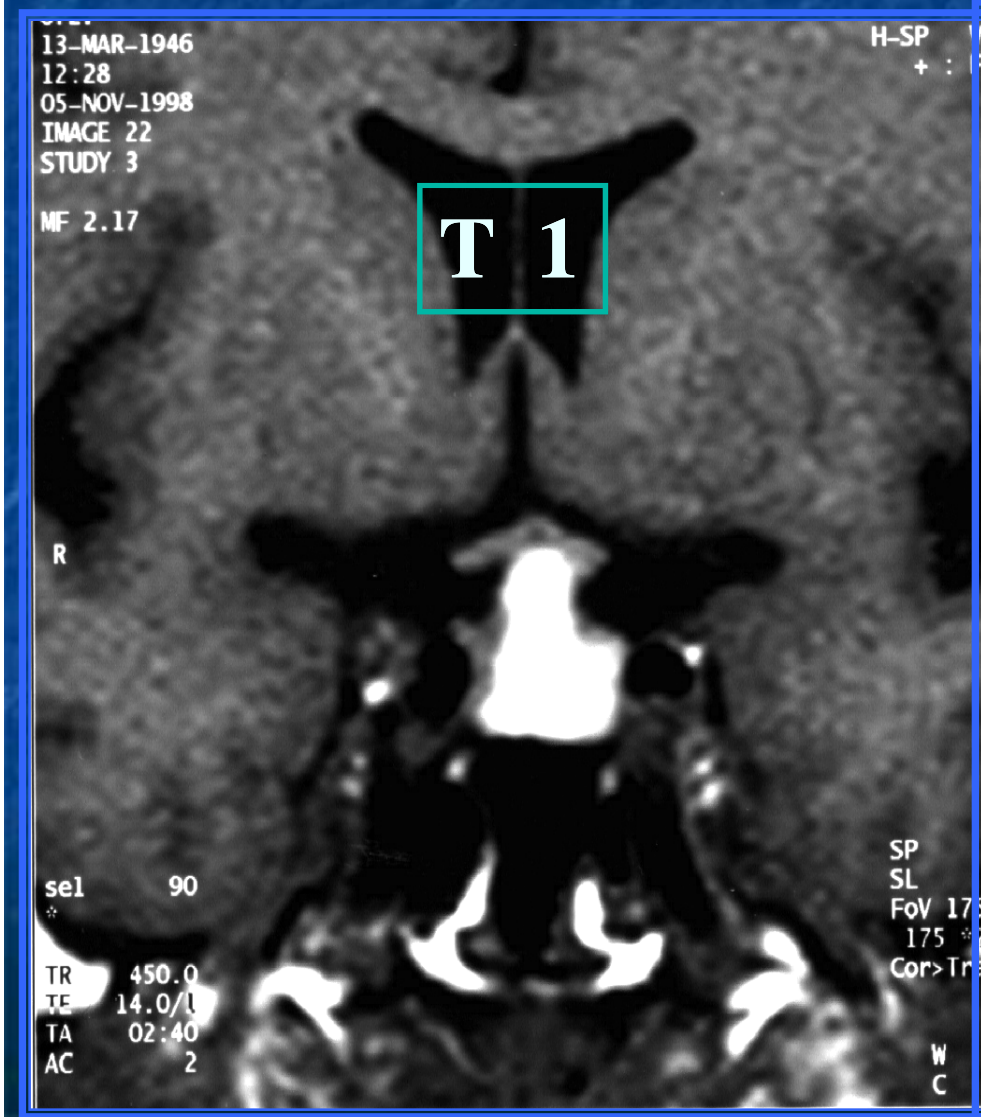
Selective adenomectomy for Microprolactinomas and non extensive Macroprolactinomas

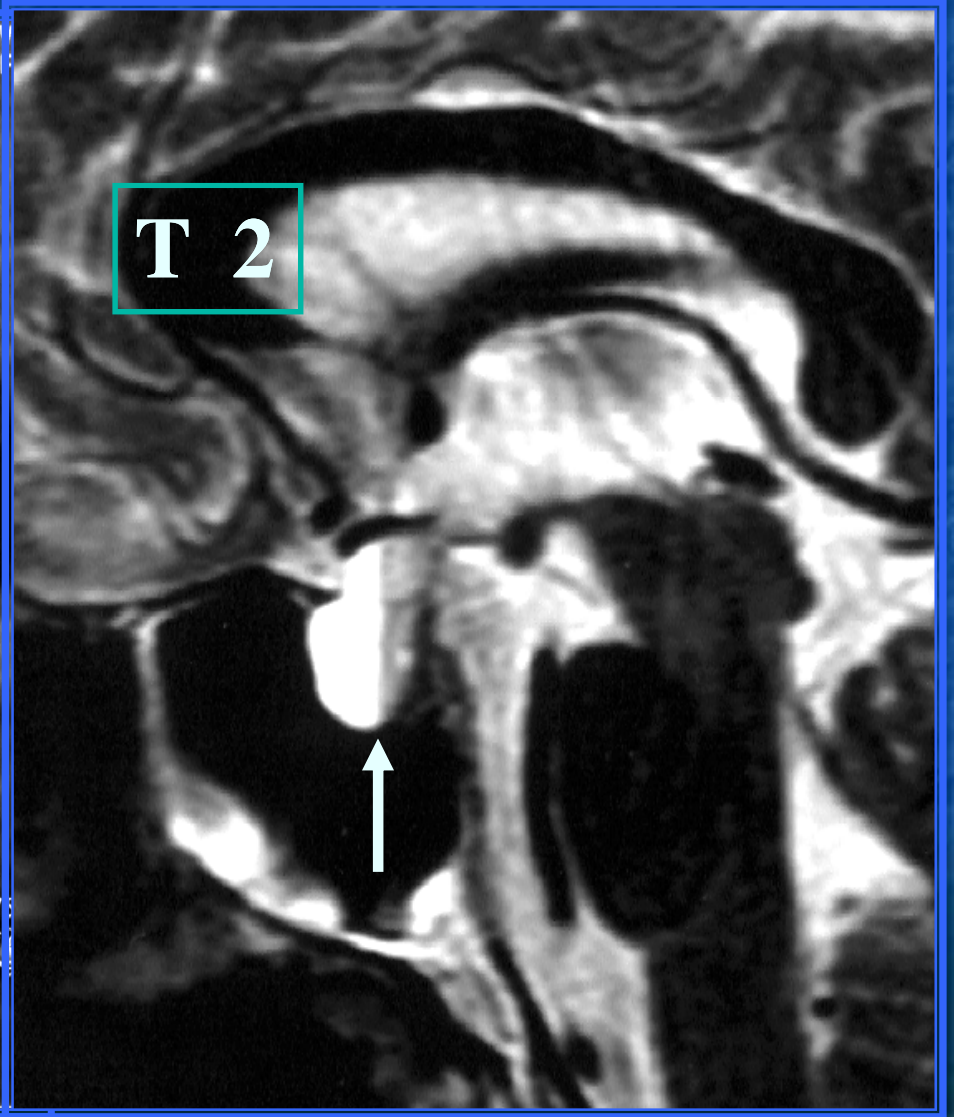
- Surgery should be performed by experienced hands, with regular practice of pituitary procedures.
- Tumors are transsphenoidally removed by a sublabial or direct endonasal approach
- 75 to 90% immediate post-operative normalization can be expected
- Fertility is restored in over 80% of cases
- Transient diabetes insipidus can occur, but it only persists exceptionally
- Hyperprolactinemia recurs in 15-20% of cases

Therapeutic management of extensive and invasive Macroprolactinomas

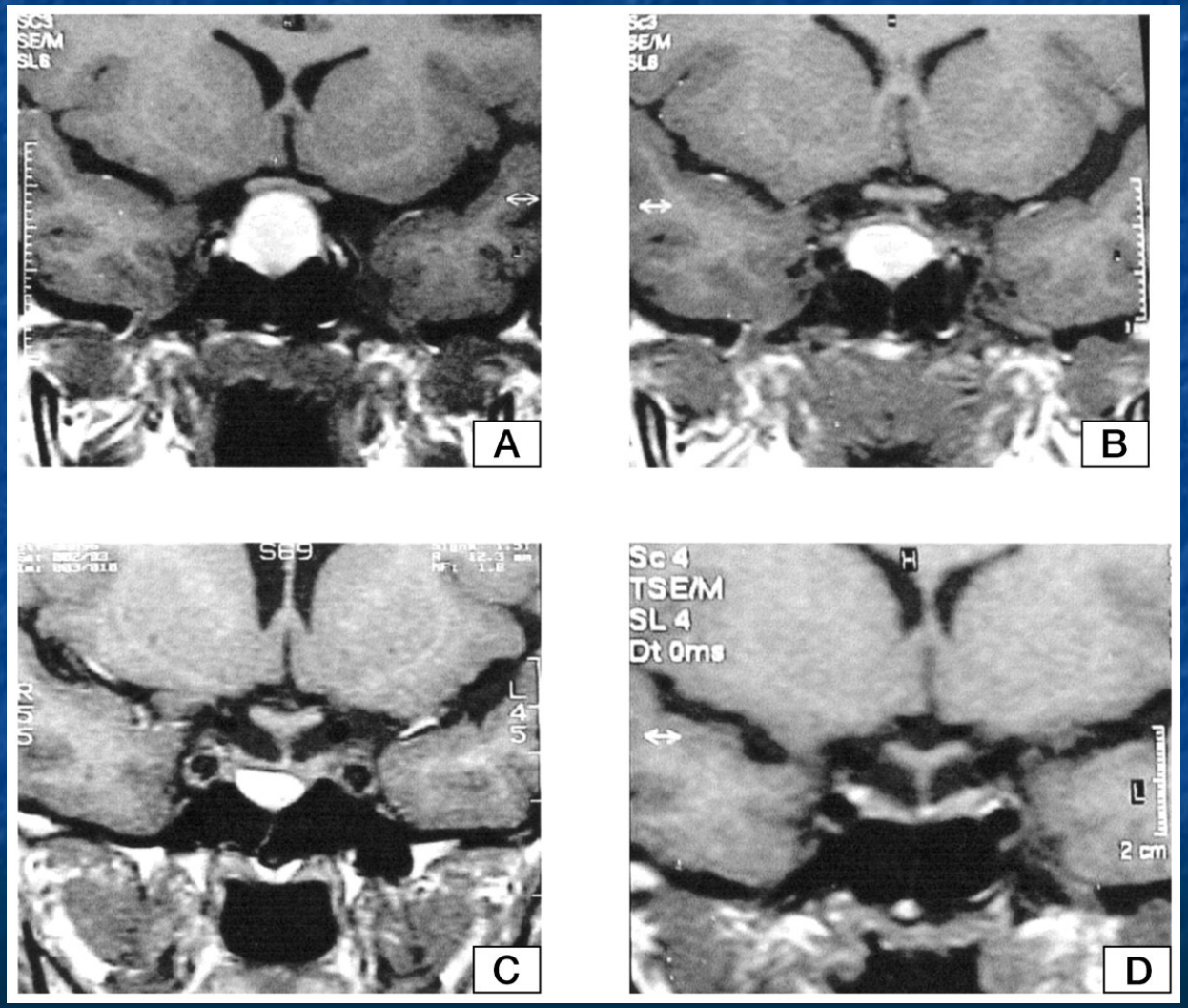
- Dopamine agonists as first line treatment, even if visual disorders
- Partial surgical removal if:
  - No visual improvement under close follow-up
  - Resistance to treatment (10% of cases) and/or with recurring elevation of prolactin levels.
  - Rhinorrhea due to cerebrospinal fluid leaking through a meningeal breach: medical treatment reduces tumor size, uncovering a preexisting breach
  - Uncertain diagnosis
  - Pituitary apoplexy during treatment

PITUITARY APOPLEXY





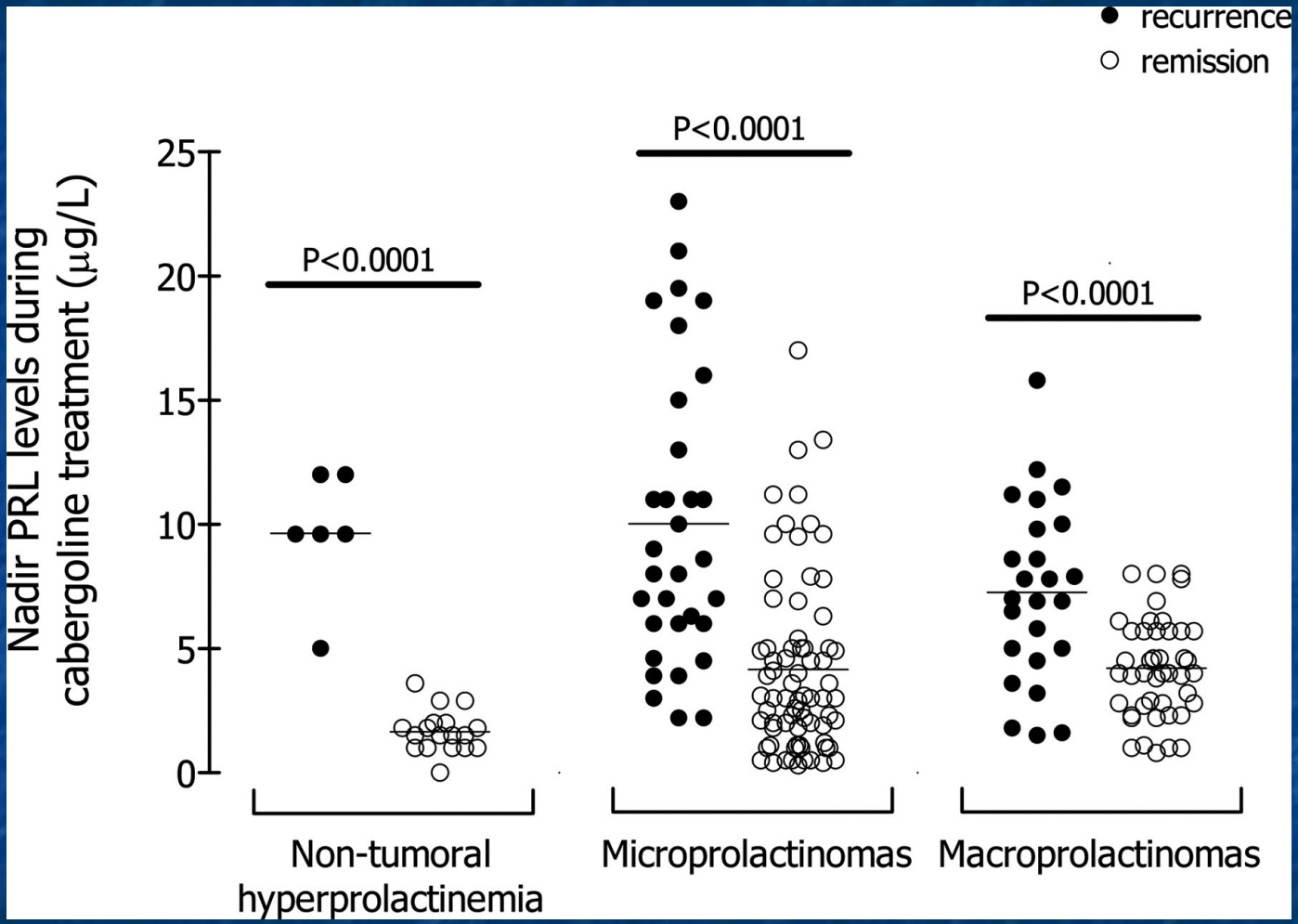
ADENOMA SHRINKAGE



Long Term Follow Up

- Once prolactin levels have normalized, maintain normal prolactin levels with the lowest possible drug doses
- Repeat MRIs are not useful in prolactin-secreting microadenomas where prolactin levels are normal.
- In macroadenomas, control MRI at 3 months with yearly repeats as long as the anti-tumoral effect persists. MRIs can be spaced out thereafter (every 5 years for example).
- There is no reported detrimental effect of long-term treatment
- Prolactin levels are normal out of treatment after 5 years in 30 to 50% of cases in microadenomas and less often in macroprolactinomas

Nadir PRL levels achieved during treatment with cabergoline predicts recurrence of hyperprolactinemia after treatment withdrawal



Gillam, M. P. et al. Endocr Rev 2006;27:485-534

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Prolactinoma and Pregnancy

1- Microadenomas

- Complications due to enlarging microprolactinomas are exceptional during pregnancy (0.5-2%).
- Consequently dopamine agonist treatments can be interrupted as soon as pregnancy is diagnosed
- There is no need for measuring prolactin during pregnancy nor scheduling systematic visual field tests or MRIs unless there are headaches or visual defects.

Prolactinoma and Pregnancy

2- Macroadenomas

- Macroprolactinomas expand in 15 to 30% of cases during pregnancy.
- Dopamine agonists should be continued during pregnancy.
- Bromocriptine is the dopaminergic agonist that has been the most used during pregnancy. It does not carry any known risks for the fetus or the mother.
- Quinagolide and cabergoline can be used when there is a pregnancy project if the benefit in terms of efficiency and tolerance is deemed important
- Visual field should be tested every 2-to-3 months, and an MRI without injection performed if tumoral signs appear (to be avoided during the first trimester). Patients should be followed by a specialist (endocrinologist), along with a general practitioner and an obstetrician.
- Breast-feeding is contraindicated if the agonist treatment is continued or needs to be resumed quickly

Contraception and Prolactinoma

- Oral estroprogestative contraceptives does not seem to modify prolactin levels or imaging *(Davis JR. Curr Opin Obstet Gynecol 2004;16:331).*
- A contraceptive pill containing less than 35 µg of ethynil estradiol can be prescribed to certain patients with a prolactin microadenoma if they are followed more closely.
- Estroprogestative tolerance should be assessed by measuring prolactin levels before and 3 months after beginning the treatment.
- Some authors suggest that the size of the adenoma should also be checked with an MRI within the first year of treatment to ensure that it does not cause tumoral growth.

Main sources

- Advances in the treatment of prolactinomas. *Gillam MP, Molitch ME, Lombardi G, Colao A.* Endocr Rev. 2006;27:485-534.
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- Long-term management of prolactinomas. *Schlechte JA.* J Clin Endocrinol Metab. 2007;92:2861-5

MENINGIOMA