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Indian Fertility Society

SYNAPSES

HYPERPROLACTINEMIA

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Prolactin (PRL) is a single-chain peptide hormone secreted from lactotroph cells of the anterior pituitary gland. It mainly promotes milk secretion from mammary glands during postpartum period.

PROLACTIN SERUM ISOFORMS

Prolactin exists in three major circulating molecular isoforms.-**Monomeric or little PRL** (molecular weight [MW] 23 kDa) - 80–95% of the total prolactin in healthy subjects and those with prolactinomas, **Dimeric or big PRL** (MW 45–60 kDa), **Multimeric / big-big PRL** or macroprolactin (MW > 150 kDa)[1]

REGULATION OF PROLACTIN SECRETION

Prolactin is secreted in pulsatile manner following a circadian rhythm with the highest plasma concentration during sleep and the lowest in the morning about 2–3h after waking up. The predominant regulatory signal is the **inhibition of prolactin secretion by the neurotransmitter, dopamine, from neurons in the hypothalamus** [2,3]

HYPERPROLACTINEMIA

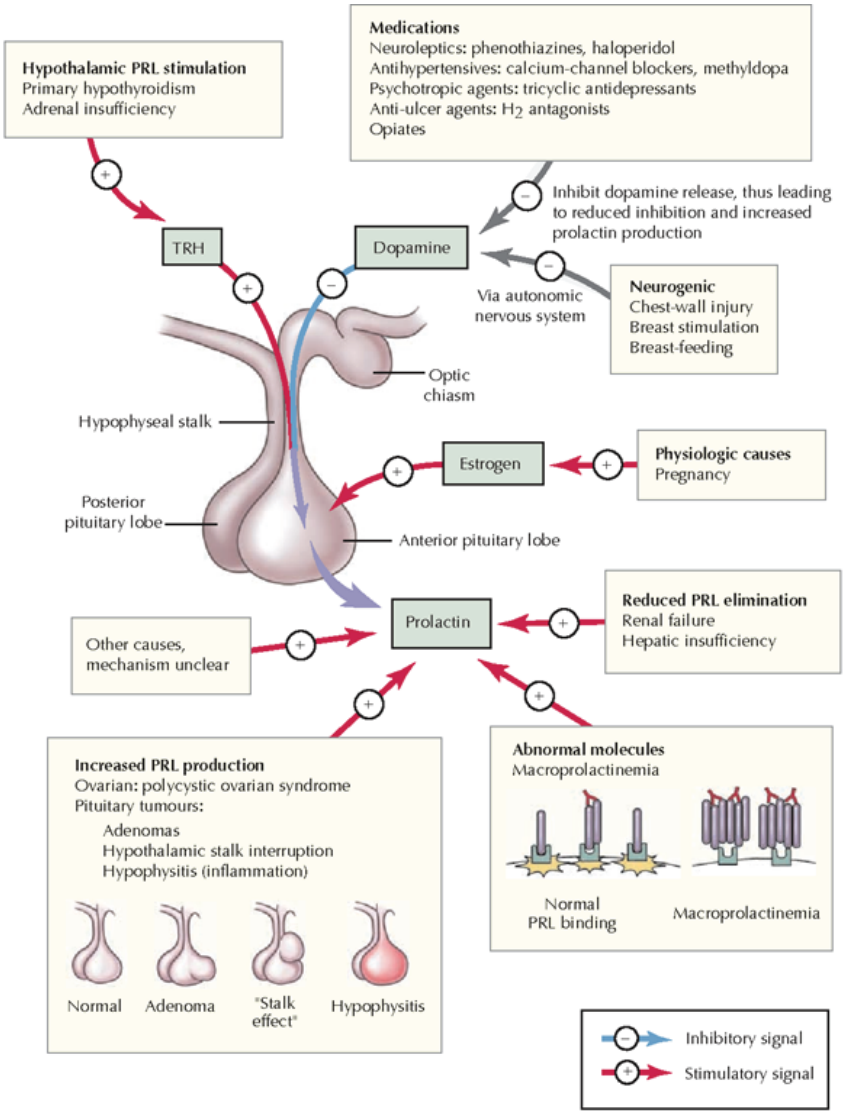
Hyperprolactinemia is defined as the presence of abnormally high level of prolactin in the blood above normal **levels of 10–28 ng/mL in women and 5–10 ng/mL in men**. The prevalence ranges from 0.4% to as high as 9-17% in women with reproductive diseases.

CLINICAL SIGNS AND SYMPTOMS[3]

- It is present in **10% to 25% women with secondary amenorrhea or oligomenorrhea, in 30% of women with galactorrhea or infertility, and in 75% of those with both amenorrhea and galactorrhea**
- Hyperprolactinemia causes hypogonadotropic hypogonadism (HH) which is due to suppression of pulsatile GnRH thus causing anovulation, hypoestrogenism and hence osteoporosis in perimenopausal women.
- When hyperprolactinemia is caused by a prolactinoma, additional pressure symptoms may include headaches, visual field defects and abnormal pituitary function.
- Hyperprolactinemia in men may result in decreased libido, impotence, decreased sperm production, infertility, weight gain and osteoporosis.

ETIOLOGY

Fig. 1. Regulation of prolactin secretion and causes of hyperprolactinemia[3]



Potential causes of hyperprolactinemia.[4]

- **Prolactinomas:** The most frequent cause of persistent hyperprolactinemia is the presence of a micro- (<10 mm diameter) or macro-prolactinoma(>10 mm).These pituitary tumours either may produce an excessive amount of prolactin or disrupt the normal delivery of dopamine from the hypothalamus to the pituitary. Raised prolactin levels can also be caused by pituitary adenomas co-secreting prolactin hormone.
- **Idiopathic hyperprolactinemia** accounts for 30–40% of cases where there is no obvious cause for the disorder and hypothalamic pituitary anatomy is normal.
- **Macroprolactinemia:** Its a condition where more than 60% of circulating PRL is made up of macroprolactin, which has low biologic activity instead of the normal 5-10%. Hyperprolactinemia **due to macroprolactin is because of its lower renal clearance, longer half-life and its lower capability to activate hypothalamic dopaminergic tone,** which negatively regulates the secretion of pituitary prolactin. These patients are usually asymptomatic and no medication or further tests are recommended.

DIAGNOSIS

- Exclude physiological and pharmacological causes on history.
- Evaluate signs of hypothyroidism, hypogonadism, renal failure and visual field defects.
- **Measure Serum Prolactin. Also measure TSH, free T4, and creatinine levels** to rule out primary hypothyroidism and renal failure.[5]
- PRL levels greater than 500ng/mL are commonly seen in macroprolactinoma. PRL levels > 250ng/mL usually indicate the presence of a prolactinoma, however, prolactinoma cannot be excluded in the presence of lower levels and PRL levels >100ng/mL are present in some patients with idiopathic hyperprolactinemia. Several drugs may cause PRL elevations above 200ng/mL.[6]
- Hyperprolactinemia without an identified cause requires imaging of the hypothalamic-pituitary area. Although Computerized axial tomography (CAT) scan can be used, magnetic resonance image (MRI) with gadolinium enhancement provides the best visualization of the sellar area.[6]

Endocrine Society Clinical Practice Guidelines for Diagnosis.[7] See annexe 1 for level of evidence.

To establish the diagnosis of hyperprolactinemia ,a single measurement of fasting serum prolactin is recommended (2-3 hrs after waking up) ;a level above the upper limit of normal confirms the diagnosis as long as the serum sample was obtained without excessive venipuncture stress. Dynamic testing of prolactin secretion for the diagnosis of hyperprolactinemia is not recommended	1|⊕⊕⊕⊕
In patients with asymptomatic hyperprolactinemia, the screening of macroprolactinemia is recommended by polyethyleneglycol- (PEG-) precipitation method, and the confirmative and qualitative examinations include gel chromatography, protein A/G column and 125I-PRL binding studies	2|⊕⊕⊕⊕

When there is a discrepancy between a very large pituitary tumor and a mildly elevated prolactin level, do serial dilution of serum samples to eliminate an artifact that can occur with some immune radiometric assays leading to a falsely low prolactin value ("hook effect")	1|⊕⊕⊕⊕

TREATMENT

Endocrine Society Clinical Practice Guideline for **Management of drug-induced hyperprolactinemia**[7]

Exclude medication use, renal failure, hypothyroidism, and parasellar tumors in patients with symptomatic nonphysiological hyperprolactinemia	1|⊕⊕⊕⊕
In a symptomatic patient with suspected drug-induced hyperprolactinemia, discontinue the medication for 3 days or substitute an alternative drug, followed by re-measurement of serum prolactin	2|⊕⊕⊕⊕
If the drug cannot be discontinued and the onset of the hyperprolactinemia does not coincide with therapy initiation, do a pituitary magnetic resonance image (MRI) to differentiate between medication-induced hyperprolactinemia and symptomatic hyperprolactinemia due to a pituitary or hypothalamic mass	1|⊕⊕⊕⊕
Do not treat patients with asymptomatic medication-induced hyperprolactinemia	2|⊕⊕⊕⊕
Use estrogen or testosterone in patients with long-term hypogonadism (hypogonadal symptoms or low bone mass) related to medication-induced hyperprolactinemia	2|⊕⊕⊕⊕

TREATMENT OF PROLACTINOMAS

Dopamine agonists are the drug of choice.

	Bromocriptine	Cabergoline
Dopamine receptor target sites	D1 and D2	D1 (low affinity) and D2 (high affinity)
Duration of action	8–12 h	7–14 days
Half-life (h)	3.3	65
Available doses	1.0 and 2.5 mg scored tablets; 5 and 10 mg capsules	0.5 mg scored tablets
Typical dose	2.5 mg/day in divided doses	0.5 mg/week or twice-weekly
Dosing regimens, starter packs, dosage	Start on 1.25–2.5 mg/day at bedtime. Gradually increase to a median of 5.0–7.5 mg/day and a maximum of 15–20 mg/day	Start at 0.25–0.5 mg twice-weekly. Adjust by every 2–4 months according to serum prolactin levels
Advantages	Long history of use; does not appear to be teratogenic; inexpensive	Good efficacy; low frequency of adverse events; may be useful in bromocriptine-resistant patients; weekly or twice-weekly dose
Disadvantages	Tolerance; recurrence; resistance; multiple daily dosing	Not yet indicated for use during pregnancy
Common side effects	Nausea, headache, dizziness, abdominal pain, syncope, orthostatic hypotension, fatigue	Milder and less frequent compared with bromocriptine

Table 1. Comparison between Bromocriptine and Carbergoline in the treatment of hyperprolactinemia [8]

Endocrine Society Clinical Practice Guideline for **Management of Prolactinoma**.[7]

Use dopamine agonist therapy to lower prolactin levels, decrease tumor size, and restore gonadal function for patients harbouring symptomatic prolactin-secreting microadenomas or macroadenomas	1|⊕⊕⊕⊕
Cabergoline is preferred to other dopamine agonists because it has higher efficacy in normalizing prolactin levels, as well as a higher frequency of pituitary tumor shrinkage	1|⊕⊕⊕⊕
Do not treat asymptomatic patients harbouring microprolactinomas with dopamine agonists	2|⊕⊕⊕⊕
Treat with dopamine agonist or oral contraceptive in patients with amenorrhea caused by a microadenoma	2|⊕⊕⊕⊕
With careful clinical and biochemical follow-up, therapy may be tapered and perhaps discontinued in patients who have been treated with dopamine agonists for at least 2 years, who no longer have elevated serum prolactin, and who have no visible tumor remnant on MRI	2|⊕⊕⊕⊕

Endocrine Society Clinical Practice Guideline for **Management of Resistant and malignant prolactinoma**[7]

For symptomatic patients who do not achieve normal prolactin levels or show significant reduction in tumor size on standard doses of a dopamine agonist , increase the dose to maximal tolerable doses before referring the patient for surgery	1|⊕⊕⊕⊕
Patients resistant to bromocriptine be switched to cabergoline	1|⊕⊕⊕⊕
Trans-sphenoidal surgical resection of the prolactinoma remains the main option for patients who may refuse or do not respond to long-term pharmacological therapy	2|⊕⊕⊕⊕
Radiotherapy and/or estrogens are also reasonable choices if surgery fails.	2|⊕⊕⊕⊕
Chemotherapy with temozolamide is limited to resistant and malignant prolactinomas	2|⊕⊕⊕⊕

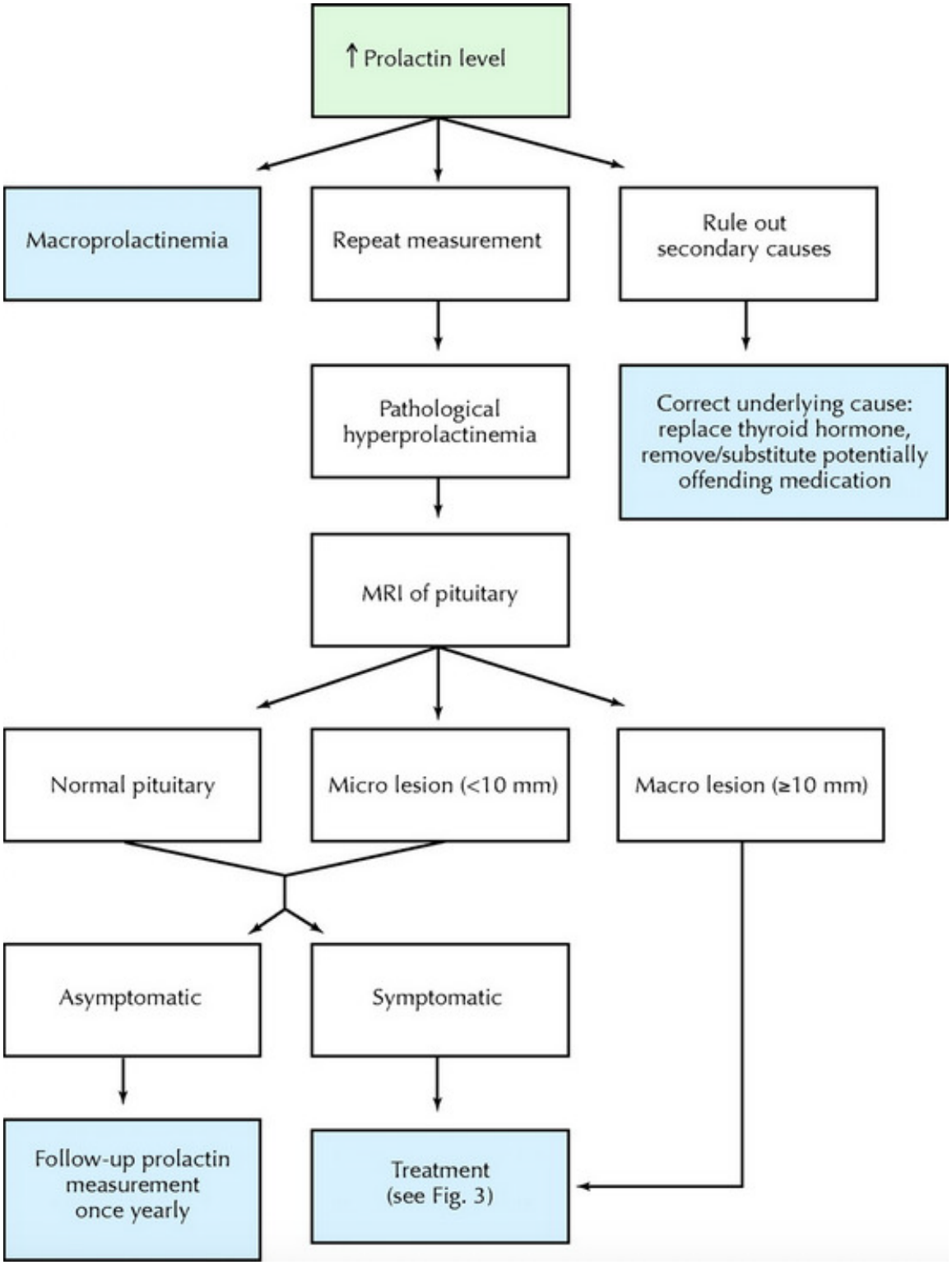


Fig. 2 -Management of Hyperprolactinemia [4]

TREATMENT OF PROLACTINOMAS

During normal pregnancy, serum prolactin rises progressively to around 200-500 ng/mL.
The Endocrine Society clinical guidelines for the **diagnosis and treatment of hyperprolactinemia during pregnancy**[7]

Women with prolactinomas be instructed to discontinue dopamine agonist therapy as soon as they discover that they are pregnant	1|⊕⊕⊕⊕
In selected patients with macroadenomas who became pregnant on dopaminergic therapy and who have not had prior surgical or radiation therapy, it may be prudent to continue dopaminergic therapy throughout the pregnancy, especially if the tumor is invasive or is abutting the optic chiasma	1|⊕⊕⊕⊕
In pregnant patients with prolactinomas, do not perform serum prolactin measurements during pregnancy	1|⊕⊕⊕⊕
Pituitary MRI during pregnancy in patients with microadenomas or intrasellar macroadenomas is not recommended unless there is clinical evidence of tumor growth such as visual field compromise	1|⊕⊕⊕⊕
Women with macroprolactinomas who do not experience pituitary tumor shrinkage during dopamine agonist therapy or who cannot tolerate bromocriptine or cabergoline be counseled regarding potential benefits of surgical resection before attempting pregnancy	1|⊕⊕⊕⊕
Visual field assessment followed by MRI without gadolinium in pregnant women with prolactinomas is recommended who experience severe headaches and/or visual field changes	1|⊕⊕⊕⊕
Bromocriptine therapy is recommended in patients who experience symptomatic growth of a prolactinoma during pregnancy	1|⊕⊕⊕⊕

CONCLUSIONS

- Hyperprolactinemia is a common pituitary hormone disorder usually found in both sexes with abnormal sexual and/or reproductive function or with galactorrhea.
- Asymptomatic patients with microprolactinemia do not require any treatment.
- **Cabergoline is the drug of choice**, however in pregnancy Bromocriptine is preferred.
- **Persistent Hyperprolactinemia** without an identified cause **requires imaging of the hypothalamic-pituitary area.**
- Giant or aggressive prolactinomas may require multiple approach involving surgery, radiotherapy or both.

Annexe: 1

QUALITY OF EVIDENCE		High Quality	Moderate Quality	Low Quality	Very Low Quality
Description of Evidence		• *Well-performed RCTs* • *Very strong evidence from unbiased observation-al studies*	• *RCTs with some limitations* • *Strong evidence from unbiased observation-al studies*	• *RCTs with serious flaws* • *Some evidence from observatio-nal studies*	• *Unsystematic clinical observations* • *Very indirect evidence observation-al studies*
STRENGTH OF RECOMMENDATION	**Strong (1): "We recommend..."** *Benefits clearly outweigh harms and burdens, or vice versa*	1|⊕⊕⊕⊕	1|⊕⊕⊕O	1|⊕⊕OO	1|⊕OOO
	Conditional (2): "We suggest..." *Benefits closely balanced with harms and burdens*	2|⊕⊕⊕⊕	2|⊕⊕⊕O	2|⊕⊕OO	2|⊕OOO

Table 2 -Grade Classification of Guideline Recommendatons[7]

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INDIAN FERTILITY SOCIETY

15th Annual Congress of Indian Fertility Society

FERTIVISION 2019

6-8 December

The Leela Ambience Hotel, Gurugram
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Theme: Beyond Tomorrow

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Invitation

Welcome to *FERTIVISION 2019*

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Dr. Pankaj Talwar
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Dear Friends,

On behalf of the Indian Fertility Society (IFS), we are extremely pleased to announce and cordially invite you to the much awaited academic event – the **15th National Annual Conference - Fertivision 2019**, to be held on **6th, 7th & 8th December 2019** at Hotel **The Leela Ambience, Gurugram, New Delhi / NCR, India**.

This conference is aimed to provide the most comprehensive academic platform in the field of Infertility and Assisted Reproductive Technology (ART)" befitting the theme of the meeting "Beyond Tomorrow"

Renowned and leading expert faculty from around the world would gather and deliver talks in our cutting edge scientific program which will not only enrich your current knowledge and clear all doubts faced in day-to-day clinical practice, but will also enlighten you about the latest innovations and ongoing research.

A large number of renowned international faculties have already confirmed their participations till date. The pre-congress workshops on 6th December are specially designed for informal in-depth training with hands on sessions on simulators and live, where ever feasible. There will be 4 simultaneous running streams on 7th & 8th December covering a wide variety of topics, enabling you to choose the deliberations specific to your area of interest and clinical practice. We are having a dedicated hall for the esteemed embryologist friends.

The best oral and poster presenters under various categories and the quiz winners will be honored with special awards and prizes. Do join us in large numbers and update your knowledge with most updated current standards in clinical practice, as well as get inspired to innovate further to overcome remaining enigmatic issues!

The three days of scientific program will encompass didactic lectures, keynote presentations, panel discussions and orations. There will be 9 Pre-conference workshops based on Ovulation Induction, Ultrasound, Andrology, Embryology, Hands on Embryo Transfer, Ovum Pickup and PGS and more. These workshops will be in addition to the special state of the art workshops by the faculty from IFFS and ESHRE. We expect delegates across India, Sri lanka, Bangladesh, Nepal, Middle - East Countries and African Nations and the arrangements are being made to accommodate more than 2500 delegates.

The exhibition area will be one of the highlights of the conference. Exhibiting provides tremendous benefits to both participating industry and the society. Tea, coffee and lunch will be served confluent with the trade area to allow optimal interaction between the trade companies and delegates during beverage and lunch breaks.

We invite you to participate in the Fertivision 2019 and exchange your expertise with more than 2500 specialists in the field of Assisted Reproduction.

We look forward to your active participation and suggestions for successful conduct of the conference.

With Our Best Regards

and All Executive Committee of Current IFS team

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