Review Article : Gynaecology

Managing Hyperprolactinemia

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Introduction

Prolactin is a polypeptide responsible for milk production, secreted from the anterior lobe of pituitary gland. It is associated with eating, mating and nursing. It is upregulated by several stimulatory factors and downregulated Prolactin Inhibitory Factor.

Hyperprolactinemia is a state, not a disease in itself, in which the total serum level of prolactin rises. It is a common clinical condition which is seen in 9% cases of amenorrhoea, 25% cases of galactorrhoea and in 70% cases of combined amenorrhoea & galactorrhoea. It is also found in 5% cases of infertility or erectile dysfunction in men. Hyperprolactinemia is found to be associated with polycystic ovary syndrome in about 7-30 % of cases. In a study of etiological factors of irregular periods in young Women in a semi urban tertiary care hospital of West Bengal, India, it was found that 57.3% of women with menstrual dysfunction have only polycystic ovary syndrome according to Rotterdam criteria. 22% had normal findings suggesting only anovulation without any known cause, 10.6% had polycystic ovary syndrome with hyperprolactinemia, 2% had only hyperprolactinemia, 2% had subclinical hypothyroidism and 0.66% had premature ovarian insufficiency and hypothyroidism.[1]

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Causes of Hyperprolactinemia:

Physiological

- Pain
- Pregnancy
- Coitus
- Sleep
- Nipple stimulation
- Pelvic examination
- Exercise

Pathological factors

- Hypothalamic factor
- Pituitary factor
- Thyroid dysfunction

Drugs

- Dopamine antagonists
- Dopamine depleting agents
- Narcotics

Idiopathic

Antipsychotics (typical) Phenothiazines Prochlorperazine Clomipramine Thioridazine Fluphenazine Pimozide	Gastrointestinal Metoclopramide Cimetidine
Antipsychotics(atypical) Risperidone Olanzapine Molindone	Antihypertensives Methyldopa Verapamil Reserpine
Antidepressants Clomipramine Desipramine Amitriptyline	Opiates Morphine Codeine
	Monoamine oxidase inhibitors Pargyline Clorgyline

Fig 1: Drugs causing Hyperprolactinemia

Prolactin assay is indicated in certain common conditions mentioned below:

- Secondary amenorrhoea
- Galactorrhoea
- Ovulatory dysfunction
- Unexplained infertility
- Oligospermic men

Not all hyperprolactinemic patients will display galactorrhoea and galactorrhoea can be seen with normal prolactin level.

Blood for serum prolactin should be drawn without multiple venepuncture stress at any time of the day. A single report above the normal levels is generally sufficient to confirm the diagnosis. If any doubt arises, sampling can be repeated on a different day.

Macroprolactin effect:

Monomeric prolactin (PRL) and Immunoglobulin G (IgG) combines to form macroprolactin. It has a longer half-life and is considered biologically inactive. It is responsible for false positivity in most available immunoassays. Polyethylene glycol (PEG) is used to precipitate macroprolactin and thus helps in eliminating unnecessary testing and treatment.

Hook effect: High serum prolactin concentrations saturate antibodies in the two-site immunoradiometric assay which causes a falsely low prolactin value. This is known as "hook effect". Serial dilution of serum samples eliminates such errors. Discrepancy between a very large pituitary tumor and a mildly elevated prolactin level is suggestive of hook effect.

REPORT ON THE EXAMINATION OF BLOOD (SERUM)

SYSTEM : Cobas e 411

METHOD : Electrochemiluminescence

TEST			REFERENCE RANGES
PROLACTIN (native) (ng/ml)	113.0	Female :Non pregnant woman Male :	: 4.79 - 29.5 : 4.04 - 15.2
PROLACTIN (After PEG Precipitation) (ng/ml) (MONOMERIC PROLACTIN) (Biologically active)	98.26	(Recovery :86.95%)	

INTERPRETATION :

A) If Recovery is >60% ----- Sample contains mostly monomeric prolactin.
B) If Recovery is between 40% and 60% -----"grey zone".
In addition to monomeric prolactin, sample also contains macroprolactin and/or oligomeric prolactin. Further assessment is necessary(e.g.gel filtration chromatography).
C) If Recovery is <40% ----- Sample contains mostly macroprolactin and/or oligomeric prolactin.Results need to be correlated with clinical findings.

(Macroprolactin has reduced bioactivity in comparison to monomeric prolactin. Hence, all samples with increased prolactin should be screened for macroprolactin to distinguish between true hyperprolactinaemia and apparent hyperprolactinaemia due to macroprolactinaemia.)

Suggested clinical correlation

Drawn sample received

Fig 2: Prolactin level after PEG precipitation

Agonist	Nature	Dose	Maintenance
Bromocriptine	Ergot derivatives	2.5 – 10 mg/day	7.5 mg/day
Lisuride	Ergot derivatives	0.1-0.2 mg/day	0.1 mg/day
Quinagolide	Ergot derivatives	25-300 microgram/ day	75 microgram/day
Cabergoline	Ergot derivatives	0.25-1 mg twice a week	1 mg/weekly

Fig 3. Drugs used for hyperprolactinemia

Imaging in Hyperprolactinemia: If prolactin level is 250ng/ml or more, Magnetic resonance Imaging of brain should be done to look for pituitary tumors. Computerized axial Tomography scan is not preferred as it fails to detect small lesions and also large lesions with isodense surrounding structure.

Treatment of Hyperprolactinemia:

Main stay of therapy is use of dopamine agonists. This group of drugs have undergone several decades of clinical use and gradually evolved over the years. Commonly used bromocriptine is largely replaced by user friendly cabergoline.

Bromocriptine vs. Cabergoline:

Bromocriptine has good efficacy with longest track record but has high side effects like nausea, vomiting and postural hypotension.

Cabergoline has high efficacy with low adverse effects and low discontinuation rate.

A meta-analysis of normalization of serum prolactin levels and menstruation with return of ovulatory cycle showed a significant difference in favour of Cabergoline group (RR 0.67 [CI 95% 0.57, 0.80]).[2]

A retrospective study of 100 pregnancies treated with Cabergoline at the time of conception and follow-up of the 88 newborn children shows Cabergoline to be safe for both the pregnancy and the neonate.[3]

Cabergoline use and cardiac valve problems:

Low dose Cabergoline in hyperprolactinemia appears to be associated with an increased prevalence of tricuspid regurgitation. The clinical significance of this is unclear and requires further investigation.[4]

Recurrence of hyperprolactinemia:

In a study comprising of 200 patients of hyperprolactinemia with 25 patients of idiopathic hyperprolactinemia followed up for 2 to 5 years, a recurrence rate of 24% was observed.[5]

Management of hyperprolactinemia in pregnancy:

In idiopathic hyperprolactinemia and in cases of microprolactinoma treatment should be stopped. In cases of macroprolactinoma (size > 1 cm) treatment should be continued. Formal visual field testing should only be done in symptomatic patients and cases of macroadenoma.

In cases of drug induced hyperprolactinemia, the offending drug should be stopped or changed or continued as per the desired outcome.

Take home message:

- Prolactin assay – single assay; macroprolactinemia to be considered.
- Drug history important; Stop, change, continue.
- MRI in select cases; preferable to CT scan.
- If hypothyroid – treatment first.
- Cabergoline – high efficacy and tolerability.
- Long term use of cabergoline – to be done with caution.
- Bromocriptine – used in small number of cases.
- Microadenoma and macroadenoma - satisfactorily managed with dopamine agonists.
- Surgery – indicated in selected cases.
- Pregnancy - should be planned and monitored carefully.
- Idiopathic hyperprolactinemia – recurrence common
- Follow up – necessary

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