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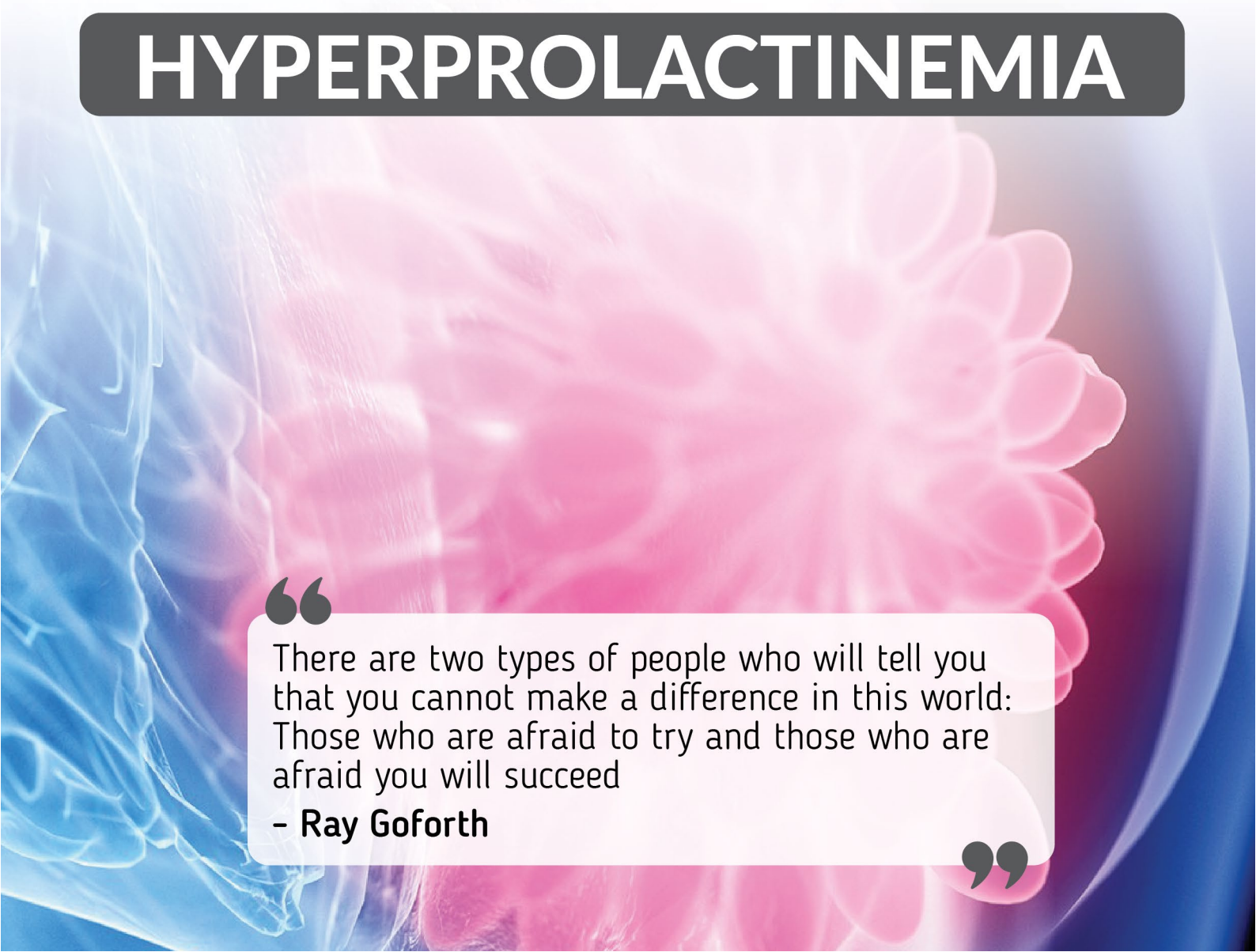
Clinical & Embryology
Academy of ART
Vol: 3/2021

i-Ceat
RESONANCE

TEN COMMANDMENTS SERIES
HYPERPROLACTINEMIA



> There are two types of people who will tell you that you cannot make a difference in this world: Those who are afraid to try and those who are afraid you will succeed
>
> **- Ray Goforth**

Preface

i-Ceat RESONANCE, the monthly bulletin, is the path-breaking academic initiative by Clinical and Embryology Academy of ART. It aims to mentor the budding fertility specialists and embryologists from the very basics to the highest level of clinical expertise.

We present before you the third volume of this monthly bulletin. Here we are discussing about the first stepping stone in the field of ART "HYPERPROLACTINEMIA." The ART clinicians face many challenges regarding success of IUI. We have tried to bust all the myths and dilemmas with the following "TEN COMMANDMENTS IN HYPERPROLACTINEMIA."

We sincerely wish that our fraternity is benefitted academically and the knowledge enhances their results.

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> Throw your heart over the fence and the rest will follow
> **- Norman Vincent Peale**

10 COMMANDMENTS IN HYPERPROLACTINEMIA

INTRODUCTION

Hyperprolactinaemia is a common endocrine disorder of hypothalamo-pituitary axis. It is the most common pituitary cause of amenorrhea affecting about 1-17 percent of women of reproductive age.

STRUCTURE

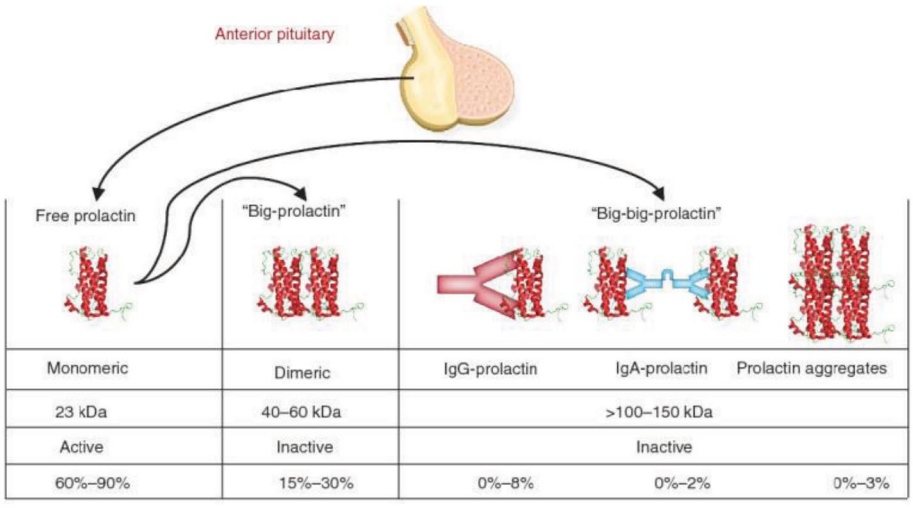
Prolactin is a 199 amino **acid** polypeptide hormone released by the lactotrophs in the anterior pituitary. It shares genetic, structural and binding properties with growth hormone and human placental lactogen. In human genome, a single gene, found on chromosome 6, encodes prolactin. (Freeman et al, Jan 2000)

METABOLISM

Normal adult serum prolactin levels vary between sexes: for women between 10 and 25 µg/L and 10–20 µg/L in men. Like many hormones, prolactin secretion is pulsatile, with maximum secretion during REM sleep, with typical peak between 4 and 6AM. Prolactin is eliminated by the liver and the kidney, and the half life of circulating prolactin is 20–50 minutes. (J.J.Mehmed,2014, L.Ra, Comprehensive Gynaecology, 2016)

CLINICAL CORRELATION

There are three types of prolactin - little, big and big big prolactin of which little prolactin has more biological activity than the bigger forms. These big variants of prolactin molecule are of 50 and 150 kDa (PRL-IgG complexes) also known as 'big prolactin' and the 'big-big prolactin' which have high immunogenic properties, but poor or no biological effect. The 'big prolactin' or macroprolactin represents dimers, trimers, polymers of prolactin, or prolactin-immunoglobulin immune complexes.



Monomeric	Dimeric	IgG-prolactin	IgA-prolactin	Prolactin aggregates
23 kDa	40–60 kDa	>100–150 kDa		
Active	Inactive	Inactive		
60%–90%	15%–30%	0%–8%	0%–2%	0%–3%

Structure of monomeric prolactin, "big-prolactin" and "big-big prolactin.(Clin Biochem Rev, 2018 Feb)

Problem in diagnosing and treating hyperprolactinemia is the occurrence of the 'big big molecule of prolactin' that is biologically inactive (called macroprolactinemia), but detected by the same radioimmunoassay as the biologically active prolactin. This may explain many cases of very high prolactin levels sometimes found in normally ovulating women and do not require any treatment.In these situations even though tests determines high levels of circulating prolactin hormone the biological prolactin is normal and thus the lack of clinical symptoms. As macroprolactinemia is a common cause of hyperprolactinemia, routine screening for macroprolactinemia could eliminate unnecessary diagnostic testing as well as treatment. Investigation for macroprolactin should always be done in cases of asymptomatic hyperprolactinemic subjects. Many commercial assays do not detect macroprolactin. Polyethylene glycol precipitation is an inexpensive way to detect the presence of macroprolactin in the serum.

CAUSES

PHYSIOLOGICAL	PATHOLOGICAL	DRUG INDUCED
Pain	Idiopathic	Dopamine antagonist and depleting drugs
Nipple stimulation	Prolactinomas	Narcotics
Sleep	Other hypothalamic pituitary disorders	Estrogen
Exercise	Hypothyroidism	Methyldopa
Pregnancy	Renal failure	Phenothiazines
P/v		Cimetidine
Stress		OCPs etc

FEMALES

- It acts on ovarian steroidogenesis by action on aromatase enzyme
- In follicular phase - disrupts normal follicular growth, causes atresia of follicle and ovulation inhibition.
- In luteal phase - inhibits P4 synthesis and disrupts corpus luteum function.

MALES

PRL

- Reduces testosterone
- Inhibits pulsatile LH secretion
- Inhibits 5- alpha reductase activity

MANIFESTATIONS

FEMALES	MALES
Infertility	Impotence
Galactorrhoea	Erectile Dysfunction
Oligoanovulation	Oligospermia
Headache	Gynaecomastia
Visual disturbances	Headache
Coexisting hypothyroidism	Osteoporosis
H/o drug intake	Decreased libido

DIAGNOSIS AND INVESTIGATIONS

- S. prolactin
- LFT,RFT
- CT/MRI
- Visual field testing

10 COMMANDMENTS IN HYPERPROLACTINEMIA

1. **Prolactin** is the only hormone whose control is mainly inhibitory by dopamine released the hypothalamus.

2. Its secretion follows a circadian rhythm with maximum secretion 5 to 8 hours after the onset of sleep. Its release is pulsatile with frequency of pulses becoming maximum mid-cycle and declining in the luteal phase. Breast examination also increases prolactin secretion. So collection of sample is best on day two after 2 hrs of waking up and fasting, preferably before breast examination. When the results are doubtful (mild prolactin elevations e.g. due to stress) or inconsistent with the clinical picture, the measurement may be repeated on another day with 2-3 samples taken at 15-20 min intervals to minimise the effect of pulsatility.

3. **Normal prolactin** level is generally less than 30ng/ml.100-250ng/ml suggests microadenoma. >250ng/ml suggests macroadenoma. (A-C Paepegaey et al. Gynaecol Obstet Fertil 2016 March)

4. There is no regular consensus when **CT/MRI** should be done.Some say it should be done in all while others say it should be done if prolactin levels are more than 100ng/ml or signs of the intracranial lesion are present. On CT/MRI radiologically a prolactinoma is considered to be microadenoma if <10mm and macroadenoma if >10mm (Dr. Bahman Rasuli and Assoc Prof Frank Gaillard et al.)

5. In **hypothyroid patients**, correction of thyroid problem automatically corrects related hyperprolactinemia. About 30% of patients with PCOS have hyperprolactinemia .Hyperprolactinemia in PCOS requires treatment for both PCOS and hyperprolactinemia .Before 2000 it was considered that hyperprolactinemia was due to hyperestrogenism, so found in PCOS ,but recent studies say they are two separate entities and have to be treated independently.

6. **Medical therapy** is the mainstay therapy in hyperprolactinemia.Bromocriptine and Cabergoline are drugs of choices with better compliance, tolerance and control in cabergoline with lesser side-effects. Serum prolactin levels should be assessed once in 3 to 4 wks of initiating therapy. Once levels have normalized evaluation may be done once in 6 to 12 months. Bromocriptine is started with 1.25mg/day and gradually increased by 1.25mg to maximum 40mg in divided doses. Cabergoline is given as 0.25mg twice a week and can be increased to 2mg twice a week. It is contraindicated in hypertension and valvular heart disease.

7. **Hyperprolactinemia without any symptoms** may be because of big prolactin and it does not require any treatment. **Patients with isolated galactorrhoea and normal prolactin levels** do not require treatment if they are not bothered about galactorrhoea, have no menstrual irregularity, do not wish to conceive and do not show hypogonadism or reduced bone density. Only follow up is required in those cases. But if patient is having other manifestations along with galactorrhoea like irregular menses or infertility then treatment must be given with normal prolactin levels. (J Hum Reprod Sci. 2010 May-August;3(2):111-112.

8. Microadenoma does not generally require surgery.Surgery is done in macroadenomas in persistent, resistant or intolerant to medical treatment cases or in recurrent prolactinomas or in large hemorrhagic tumors. Trans-sphenoidal surgical resection is the best route of surgery. Radiation is given only in the presence of persistent disease following surgery and in rapidly growing tumors.

9. Achieving a normalization of PRL levels and a tumor size <10mm is recommended before conception. When the first menstrual period is missed and a pregnancy test is positive, we recommend the discontinuation of bromocriptine to prevent fetal exposure. During normal pregnancy, PRL levels increase more than 10 times, 40 and treatment decisions in women with prolactinoma should therefore be taken based on their symptoms and signs, rather than on plasma PRL levels. It has been reported that the use of bromocriptine did not increase the

risk of fetal malformations in more than 2500 pregnancies. Experience with cabergoline is more limited, but the data appear to be similar However, some recent findings suggest the need for larger series assessing and monitoring the subsequent neurological development of children exposed in utero to cabergoline.

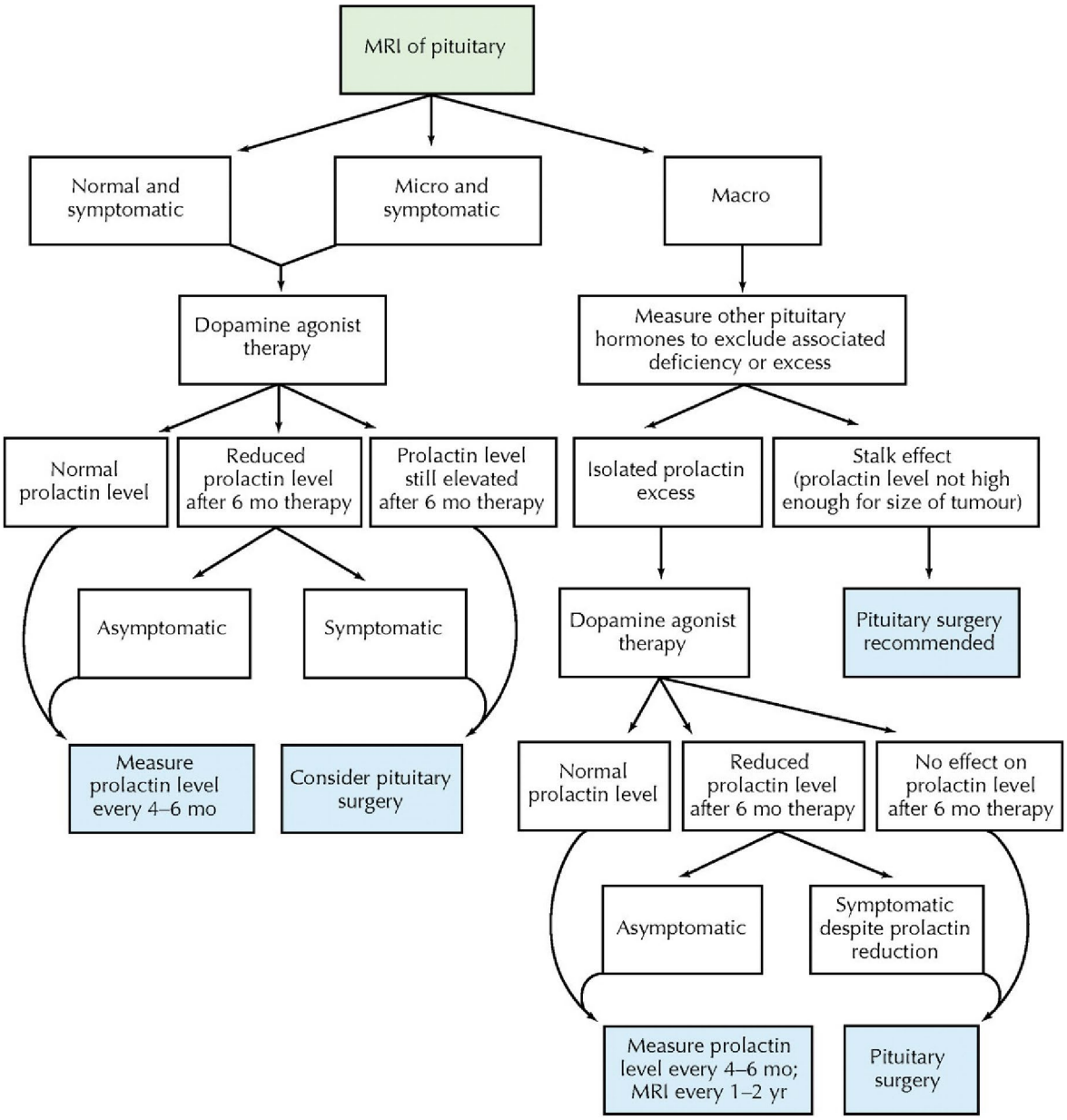
Microadenomas:

- Complications due to enlarging microprolactinomas are exceptional during pregnancy (0.5-2%).
- Consequently dopamine agonist treatments can be interrupted 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.

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 MRI without contrast 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 need to be resumed quickly. (ESHRE guidelines)

10. **Transient hyperprolactinemia** needs to be treated. This is observed in normal prolactinemic patients with luteal insufficiency. These transitory elevations in prolactin to 27-70ng/ml lasts in preovulatory estradiol peak. So Bromocriptine in such cases is given 1.25mg BD from day 5 till ovulation and pregnancy rates are found to be increased from 1% to 40%. (M.Ben David et al J Clin Endocrinol Metab. 1983 Aug)



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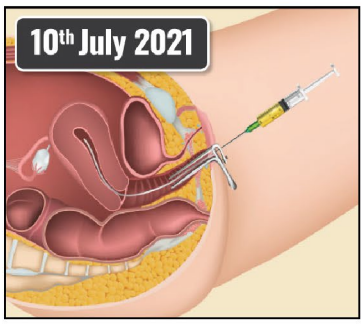

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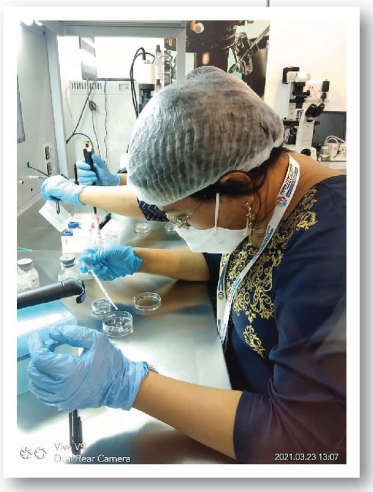

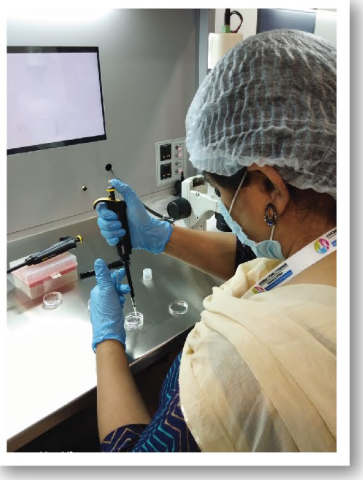

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