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REVIEW

Management of hyperprolactinemic infertility

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Abstract Pathological hyperprolactinemia may cause defective ovulation and reduced fecundability. Abnormal prolactin (PRL) secretion is usually related to an idiopathic hypothalamic dysfunction or to the presence of a pituitary adenoma. The use of medication is the most common cause of functional hyperprolactinemia. Pituitary prolactin secreting adenoma is classified according to size: micro (the vast majority) being smaller than 10 mm in diameter or macroprolactinoma (very few) of larger size.

An excessive PRL secretion decreases the pulsatile release of GnRH impairing the pituitary production of FSH and LH. Furthermore it may directly impair the endocrine activity of ovarian follicles. As a consequence: defective luteal phase, inconstant ovulation and chronic anovulation are conditions frequently observed in young hyperprolactinemic patients. In addition 5% of unselected, asymptomatic infertile women show hyperprolactinemia. In such patients fertility may be promoted with long-term use of dopaminergic drugs. The normalized PRL level induced by the treatment allows the occurrence of spontaneous ovulatory cycles or the normalization of the defective luteal phase. Treatment should be continued for at least one year since half of the pregnancies occurring during dopaminergic therapy start after the first 6 months of drug assumption. An ovarian stimulation with gonadotropin and the pulsatile administration of GnRH may also induce ovulatory cycles and fertility in the infertile hyperprolactinemic patients.

Hyperprolactinemia either, due to hypothalamic dysfunction, as well as the presence of PRL secreting adenoma usually improves after delivery.

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Contents

1. Introduction

1.1. Causes of hyperprolactinemia

In the woman hyperprolactinemia can be defined as the presence of abnormally high level of prolactin in the blood. Normal levels are typically 10–35 ng/ml and 1 ng is equivalent to 21.2 mU/ml (1).

Aside from high levels of prolactin observed during pregnancy and lactation, hyperprolactinemia can present as a pathological condition at any age and this excess of prolactin may result from a variety of causes, which are summarized in Table 1.

Prolactin secretion shows a circadian rhythm with higher concentration during the night and lower circulating level during the day. The regulating mechanism, independent of sleep, depends from an hypothalamic regulator and from the pituitary melatonin secretion (2).

The pronounced PRL elevation after the orgasm has been considered beneficial for decidualization and implantation (3).

A transient elevation in serum prolactin can be produced by the venepuncture stress while mildly elevated hyperprolactinemia is frequently seen in PCOS patients due to the raised circulating estrogen level (4). The raised hypothalamic TRH release observed in patients with primary hypothyroidism almost constantly stimulates prolactin secretion (5).

Table 1 Main causes of pathologic hyperprolactinemia (40).

Dysfunction/disease	Mechanism
Idiopathic	Impaired hypothalamic dopamine secretion
Pituitary tumors: micro- or macroprolactinoma, adenoma, hypothalamic stalk interruption	Disruption of dopamine delivery and/or secretion of prolactin
Acromegaly	Prolactin secretion from a GH adenoma
Empty Sella syndrome	Damage of the pituitary
Primary hypothyroidism	Increased hypothalamic TRH
Polycystic ovary syndrome	Raised estrogen concentration
Renal failure	Reduced PRL clearance
Drugs	Mechanism
Antidopaminergic drugs	
- *Anti-psychotics* (phenothiazines, haloperidol, butyrophenones, risperidone, monoamine, oxidase inhibitors, fluoxetine, sulpiride)	Inhibition of dopamine release
- *Anti-emetics* (metoclopramide, domperidone)	
- *Tricyclic antidepressants*	
Opiates	Stimulation of opioid hypothalamic receptors
Oestrogens	Stimulation of lactotrophs
Verapamil	Unknown

The occurrence of menopause is also associated with a short-living (weeks–months) prolactin secretion (6).

1.1.1. Functional hyperprolactinemia

Prolactin levels lower than 100 ng/ml may be observed with all causes of hyperprolactinemia, while higher levels are usually indicative of a prolactin secreting adenoma (prolactinoma).

Pituitary imaging should be performed in all patients with persistently elevated prolactin levels, as pituitary tumors may be observed even in patients with prolactin levels just exceeding the normal range (7).

As far as natural history hyperprolactinemia is concerned, fewer than 10% of patients with the idiopathic form ultimately are found to harbor a microadenoma and progression from micro to macro is rare (8). The most frequent cause of nontumoral hyperprolactinemia is medications (9).

1.1.2. Pituitary tumors

Prolactinoma: Is the most frequent type of pituitary neoplasia.

Prolactinomas are classified according to size. Adenomas smaller than 10 mm in diameter, the great majority, are defined as microprolactinomas and larger tumors ($\geqslant$10 mm) are defined as macroprolactinomas.

Patients with non-functioning pituitary tumors can develop hyperprolactinemia because of pituitary stalk compression (9).

Using CAT scan or MRI imaging pituitary adenoma secreting prolactin is preferentially found in women between 25 and 50 years age (Fig. 1). Their prolactin secretion is quite variable.

The differential diagnosis between functional and tumoral hyperprolactinemia relies primarily on basal serum PRL levels and neuroradiologic evaluation by either computed tomography or magnetic resonance imaging (4). PRL levels $>$100 ng/ml are almost always due to prolactinomas: very high levels ($>$500–1.000 ng/ml) are found only in macroprolactinomas; PRL $<$ 50–100 ng/ml in the presence of pituitary or parapituitary macrotumors suggests that the lesion is not a prolactinoma.

1.2. Ovarian function in young hyperprolactinemic women

Hyperprolactinemia decreases the pulsatile secretion of gonadotrophin-releasing hormone impairing the release of LH and FSH.

In addition an excess prolactin can directly influence the steroidogenetic activity of the ovary causing menstrual irregularities.

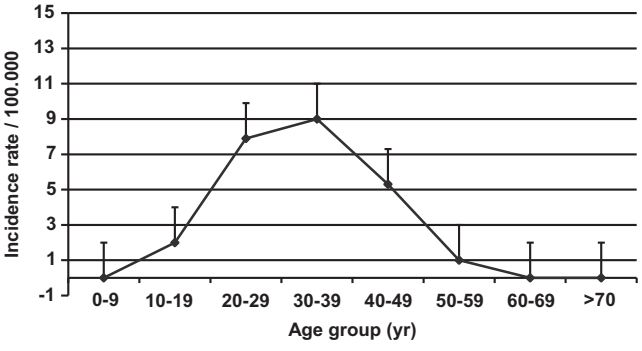

Figure 1 Incidence of PRL-secreting pituitary adenomas in the woman (Northern Finland) (46).

Hyperprolactinemia is a relatively common cause of secondary amenorrhea: 14% of young women between 21 and 30 years, and of abnormal uterine bleeding: 9% of subjects in the same age group (10).

Otherwise hyperprolactinemia is often undiagnosed for the absence of specific symptoms.

1.3. Prevalence of hyperprolactinemia among patients with infertility

Prevalence of hyperprolactinemia in an unselected, asymptomatic population with infertility is approximately 5% and 30% of them suffer from some form of brain lesion or malformation (11). Mild to moderate PRL elevations do not correlate with

- the presence or absence of menstrual irregularities
- the degree of menstrual disturbance and
- the underlying infertility diagnosis (11).

Inconstant ovulation and chronic anovulation are conditions observed in hyperprolactinemic patients as well as the occurrence of frequent luteal phase defects.

Luteal phase insufficiency may lead to a defective endometrial growth with a failure of embryo implantation (12), this mechanism accounts for 3–10% of infertility cases and two-thirds of these patients show elevated prolactin concentration (13).

2. Clinical evaluation of prolactin related infertility

2.1. The impact of "big prolactin" on the diagnosis of hyperprolactinemia

The presence in the blood of the so called big prolactin is a frequent condition leading to a misclassification of approximately 10% of hyperprolactinemic patients (14).

In these subjects, prolactin molecules form irregular high molecular weight polymers (primarily a molecular complex with an antiprolactin antibody). The high molecular mass confines the molecular complex to the vascular system, and is not bio-available in vivo. Macroprolactinemic patients could not be differentiated from true hyperprolactinemic patients on the basis of clinical features alone.

It is therefore important to eliminate before PRL assay the "big prolactin molecules" from blood samples with a polyethylene glycol (PEG) treatment. Table 2 illustrates the changes in circulating PRL concentration observed in a group of normoprolactinemic women after PEG precipitation of "big prolactin".

2.2. Diagnosis of anovulation or defective luteal phase due to an excessive PRL secretion

Table 3 summarizes the diagnostic indices useful for a reliable diagnosis and an effective follow-up of the profertility treatments (15). The morning is the best time for prolactin measurement. Known physiological and pharmacological causes of hyperprolactinemia must be considered and such, a detailed medical history, clinical examination and blood biochemistry, including tests for pregnancy and renal and thyroid function,

Table 2 Macroprolactinemia in normoprolactinemic women: reliable prolactin levels revealed by PEG pretreated serum samples (14).

Patient no.	Age (yr)	Pituitary imaging	Serum PRL (mU/liter)	
			Before PEG	After PEG
1	15	N	1760	230
2	27	MI	1206	344
3	26	N	2240	192
4	20	MI	1940	378
5	33	N	1288	214
6	29	ND	1360	171
7	22	N	1310	236
8	21	N	819	302
9	38	N	1590	232
10	55	N	1530	224
11	38	N	3390	248
12	40	ND	883	337
13	28	N	1037	24
14	32	N	4021	142
15	33	N	891	194

N = Normal.
MI = Microadenoma.
ND = Not Done.

Table 3 Hyperprolactinemic anovulation: diagnostic workup (15).

1. Women with menses: measure PRL and progesterone in the supposed luteal phase (during at least two cycles)
2. Women with oligomenorrhea: measure FSH and PRL on two different occasions
3. CT or MRI should be performed in all hyperprolactinemic women
4. Measure TSH, T_3 and T_4 (to exclude hypothyroidism)

FSH = follicle-stimulating hormone.
CT = computed tomography.
MRI = magnetic resonance imaging.
TSH = thyroid-stimulating (thyrotropic) hormone.
T_3 = triiodothyronine.
T_4 = thyroxine.

are all important. It is also important to determine serum follicle-stimulating hormone in order to pick-up an unknown primary ovarian insufficiency in these women seeking pregnancy.

For a reliable study of the abnormal luteal phase repeated postovulatory plasma progesterone assays and the precise measurement of the luteal phase length are the key informations.

3. Spontaneous and induced fertility

3.1. Spontaneous pregnancies

Hyperprolactinemia does not preclude fertility, and several spontaneous pregnancies have been reported in untreated series of hyperprolactinemic women.

Table 4 reports 34 spontaneous pregnancies in 31 women with mild to moderate hyperprolactinemia (16). Nevertheless the mean time to pregnancy in this group of patients is longer than normal thus, if an hyperprolactinemic woman complains of infertility, the best treatment to favor conception is to lower prolactin secretion with the administration of dopaminergic drugs.

Table 4 34 spontaneous conceptions in 31 hyperprolactinemic women (4 with radiological evidence of microprolactinoma (16).

Plasma PRL (ng/ml)	24–30	N 7
	31–50	N 18
	31–100	N 6
Normal cycle		N 16
Oligomenorrhea		N 13
Amenorrhea		N 2
Time to pregnancy	1 year	N 11
	3 years	N 16
	Not programmed	N 7

3.2. Dopaminergic treatments

Dopamine agonists are the first choice treatment for both idiopathic hyperprolactinemia and for patients carrying prolactinomas.

Dopamine receptors have been classified into D1 and D2 subtypes, based upon physiological or biochemical responses (17).

Binding of dopamine agonists to dopamine D2 receptors on the surface of lactotrophs reduces adenyl cyclase activity and inhibits prolactin secretion (18). The three dopamine agonist preparations available for the treatment of hyperprolactinemia are illustrated in Table 5.

3.2.1. Bromocriptine

Bromocriptine still the most widely used dopamine agonist, is given orally starting with a low dose. The dose should be increased until prolactin levels are returned to normal. Bromocriptine therapy should start with 1.25 mg at dinner, and gradually increased up to 2.5 mg twice daily with food over one to two weeks to minimize side effects; the drug dose should be increased further if PRL values do not become normal or near normal and ovarian function is not restored (Fig. 2). Bromocriptine treatment normalizes serum prolactin levels in 80% of patients with idiopathic hyperprolactinemia or microprolactinoma with a pregnancy rate of 60–80% provided there are no other infertility factors (19).

In order to induce fertility it is important to maintain the effective PRL lowering dose for 10–12 months since it takes time to reestablish ovulatory cycles and half of the pregnancies occur after the first six months of therapy.

The clinical occurrence of ovulation in women receiving bromocriptine can be monitored by measurements of plasma progesterone.

If ovulation does not occur despite the normalized PRL to increase the success rate a cyclical treatment with clomiphene citrate can be added (20). Not all patients respond to bromocriptine (21) and 65–70% of patients experience side effects although only 5% of patients discontinue treatment for this reason. Moreover bromocriptine due to its short half-life should be administered twice a day.

Table 5 Dopamine agonists commonly used in the treatment of hyperprolactinemia.

	Bromocriptine	Cabergoline	Quinagolide
Duration of action	8–12 h	7–14 days	24 h
Half-life (hours)	3.3	65	22
Available doses	1.0 and 2.5 mg scored tablets 5 and 10 mg capsules	0.5 mg scored tablets	25, 50, 75 and 150 mg tablets
Typical dose	5 mg/day in divided doses	0.5 mg/week or twice-weekly	75 mg/day
Dosing regimens	Start on 1.25–2.5 mg/day at bedtime Gradually increase to a median of 5.0–7.5 mg/day	Start at 0.25–0.5 mg twice-weekly Adjust by 0.25 mg twice-weekly up to 1 mg twice-weekly every 2–4 months	Start at 25 mg/day Increase over 1 week up to 75 mg/day
Advantages	Long history of use Safe for the fetus (41) Inexpensive	High efficacy Useful in bromocriptine-resistant -patients (42) Weekly or twice-weekly dose	Good efficacy and tolerability (30) Once-daily dosing
Disadvantages	Tolerance (43); Resistance Multiple daily dosing	Possible risk of fibrotic valvular heart disease (28)	Increased congenital malformation if used during pregnancy (30)
Side effects	Nausea, headache, dizziness, orthostatic hypotension	Milder and less frequent	Milder and less frequent (44)

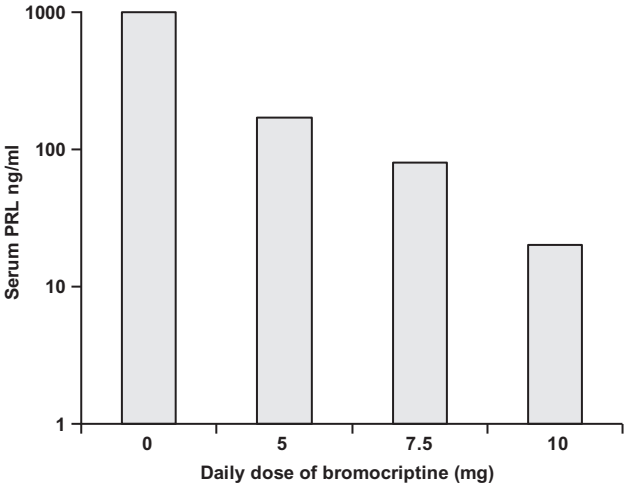

Figure 2 Lowering serum prolactin concentration induced by increased bromocriptine doses in 14 hyperprolactinemic patients.

3.2.2. *Cabergoline*

This drug is probably the most effective dopamine agonist and due to its long-lasting activity can be used on weekly or twice-weekly basis.

Cabergoline effectively treats hyperprolactinemia, micro and macroadenomas with a low incidence of side effects (22–23) and offers an effective therapy for patients who are resistant or intolerant to bromocriptine (Table 6). In the past owing to its long half-life, cabergoline was not approved for treatment of hyperprolactinemia to induce pregnancy now after the observation of hundreds cases in which the drug was taken during early pregnancy without fetal damage its use is considered safe for the fetus (24).

In some studies long-term use of cabergoline was associated with the occurrence of a fibrotic valvular heart disease (25) and despite some reassuring studies (26–27), an active echocardiographic monitoring is still suggested during the treatment (28).

Table 6 Effectiveness of cabergoline in normalizing serum PRL levels in hyperprolactinemic patients during long-term treatment (45).

		Patients with normalized PRL levels	
Final dose (mg/wk)	No. of patients	No.	Cumulative %
0.0625	31	29	5.3
0.5–0.75	145	137	30.3
1.0	288	260	77.7
1.25–1.5	48	26	82.5
1.75–2.0	29	6	83.6
2.25–4.0	7	1	83.8
Total	548	459	83.8

3.2.3. *Quinagolide*

Quinagolide is a non-ergot-derived agent that has a chemical structure similar to apomorphine.

Quinagolide is a specific D2-type receptor agonist very active and with fewer side effects than ergot derivatives.

Quinagolide has a 24-h duration of action and this allows for once-daily dosing, which is a major advantage over the multiple daily dosing of bromocriptine (29).

Quinagolide is associated with an increased rate of congenital malformation and should not be used during gestation (30).

3.3. *Ovarian stimulation*

Pulsatile administration of GnRH also reestablishes normal ovulatory cycles (31).

The direct stimulation of the ovary with the use of gonadotropin preparation is associated with excellent pregnancy rates but in these cases the risk of multiple pregnancy is a frequent problem and the effect of direct or indirect ovarian stimulation is limited to the treated cycle.

In any case when pregnancy does not occur after 6–8 ovulatory cycles, the patient must be reinvestigated carefully looking for other causes of infertility.

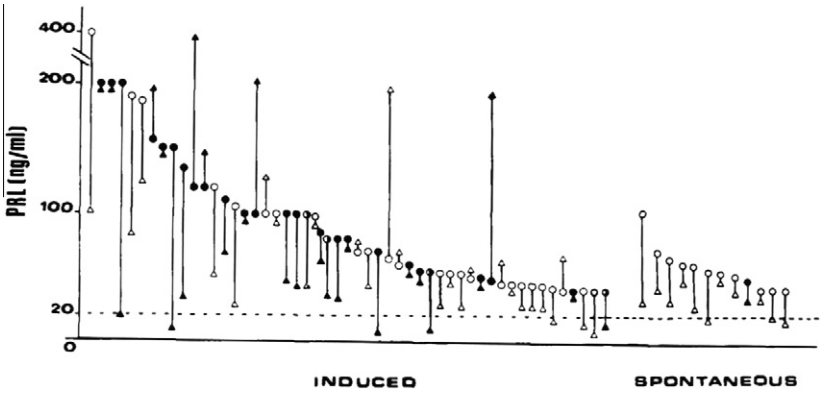

Figure 3 Individual prolactin values before and after gestation for 12 spontaneous (12 patients) and 52 induced pregnancies (46 patients). Circles: prolactin before pregnancy; triangles: prolactin after pregnancy. The presence of adenoma is indicated by black symbols (15).

3.4. Surgery

Could be the alternative treatment for a very few patients intolerant and resistant to dopaminergic drugs or refusing ovarian stimulation.

4. Outcome and pregnancy complications

Data from large series (19,32) did not show any increase in spontaneous abortions, multiple pregnancies or congenital abnormalities associated with the gestations induced by the use of bromocriptine. All these figures compare favorably with those of pregnancies achieved after treatment with antiestrogens, pulsatile GnRH and human menopausal gonadotropin, for both abortion and multiple pregnancy rates. Similar results were reported for the pregnancies induced by cabergoline (24). For the few women treated continuously throughout gestation, inhibition of PRL secretion does not appear to have had any effect on placental function that might adversely influence the course of pregnancy, breast-feeding or child development (33).

The risk of clinically significant adenoma growth during pregnancy is small except in women with macroadenoma (34): 31% of the patients with macroadenoma who did not undergo surgery or irradiation before pregnancy experienced the tumor enlargement during gestation (35).

The onset of headache or a change in the vision acuity suggests the urgent need for visual field testing and a pituitary MRI (9). The symptomatic suprasellar growth of a prolactinoma during pregnancy otherwise can be quickly suppressed with bromocriptine administration (36–38). Visual field evaluation is a good indicator of possible suprasellar tumor growth and should be done regularly in the second part of the pregnancy.

5. The role of pregnancy in the natural history of hyperprolactinemia

Pregnancy may be beneficial to hyperprolactinemic women, since post-partum PRL levels are in general lower than before pregnancy. In a series (15) of 64 pregnancies observed in 54 women with functional hyperprolactinemia or microprolactinoma, the PRL concentrations were lower 12 months after delivery or at the end of lactation (median value 43 versus 67.5 ng/ml). Fig. 3 shows the PRL levels before and after pregnancy in these women. Pregnancy by itself normalized plasma PRL in 11 patients (17%) and five of 11 PRL normalizations occurred in women with radiologic evidence of microadenomas. In addition, spontaneous menstrual cyclicity started in five of the 28 previously amenorrheic patients (18%).

Similar remission rate (17–30%) of hyperprolactinemia after delivery, has been reported by Jeffcoate et al. in 1996 (39). It is still unknown the mechanism of this improvement.

6. Conclusions

A spontaneous conception occurs frequently in hyperprolactinemic women although quite often time to pregnancy appears longer than normal.

Hyperprolactinemia is a frequent finding in young subfertility women.

Dopamine agonists' administration restores normal ovarian function and is the first line treatment for most patients wishing to conceive.

After each spontaneous or induced pregnancy prolactin secretion often appears reduced and eventually normalized after 2–3 gestations.

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