Middle East Fertility Society Journal (2012) 17, 63–69

Middle East Fertility Society

Middle East Fertility Society Journal

www.mefsjournal.org
www.sciencedirect.com

REVIEW

# Management of hyperprolactinemic infertility

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Received 10 April 2012; accepted 19 April 2012
Available online 31 May 2012

**KEYWORDS**

Hyperprolactinemia;
Anovulation;
Defective luteal phase;
Pituitary adenoma;
Prolactinoma

**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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Peer review under responsibility of Middle East Fertility Society.
http://dx.doi.org/10.1016/j.mefs.2012.04.003

Production and hosting by Elsevier

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## 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 |