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Review Article

# Laboratory and clinical significance of macroprolactinemia in women with hyperprolactinemia

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ABSTRACT

The role of macroprolactinemia in women with hyperprolactinemia is currently controversial and can lead to clinical dilemmas, depending upon the origin of macroprolactin, the presence of hyperprolactinemic symptoms and monomeric prolactin (PRL) levels. Macroprolactinemia is mostly considered an extrapituitary phenomenon of mild and asymptomatic hyperprolactinemia associated with normal concentrations of monomeric PRL and a predominance of macroprolactin confined to the vascular system, which is biologically inactive. Patients can therefore be reassured that macroprolactinemia should be considered a benign clinical condition, resistant to antiprolactinemic drugs, and that no diagnostic investigations or prolonged follow-up should be necessary. However, a significant proportion of macroprolactinemic patients appears to suffer from hyperprolactinemia-related symptoms and radiological pituitary findings commonly associated with true hyperprolactinemia. The symptoms of hyperprolactinemia are correlated to the levels of monomeric PRL excess, which may be explained as coincidental, by dissociation of macroprolactin, or by physiological, pharmacological and pathological causes. The excess of monomeric PRL levels in such cases is of primarily importance and the diagnosis of macroprolactinemia is misleading or inadequate. However, macroprolactinemia of pituitary origin associated with radiological findings of pituitary adenomas may rarely occur with similar hyperprolactinemic manifestations, exclusively due to bioactivity of macroprolactin. Therefore, in such cases with hyperprolactinemic signs and pituitary findings, macroprolactinemia should be considered a pathological biochemical condition of hyperprolactinemia. Accordingly, individualized diagnostic investigations with the introduction of dopamine agonists, or other treatment with prolonged follow-up, should be mandatory. The review analyses the laboratory and clinical significance of macroprolactinemia in hyperprolactinemic women suggesting clinically useful diagnostic and treatment strategies.



## Introduction

Prolactin (PRL) is a globular protein hormone of 199 aminoacids produced by the anterior pituitary lactotrophic cells that acts with other hormones to initiate secretion of milk by the mammary glands. PRL homeostasis is under hypothalamic regulation with the primary control of its secretion being inhibitory rather than stimulatory. The hypothalamic factor that chiefly inhibits PRL secretion at the level of D2 receptors is the neurotransmitter dopamine which is believed to be the principal PRL inhibiting factor (PIF). The PRL-releasing factors include vasoactive intestinal peptide, epidermal growth factor and thyrotrophin-releasing hormone, as the only important clinical manifestation that occurs with hypothyroidism. Heterogeneity in the molecular size of PRL has been described in the majority of serum from normal and hyperprolactinemic individuals and three major variants can be classified including monomeric, dimeric and polymeric isoforms. The monomeric or little PRL (MW 23 kDa) results from a cleaved preprolactin molecule (MW 26 kDa) and it represents the major circulatory isoform (80–95%) of the total PRL in cases with normoprolactinemia and true hyperprolactinemia. The biological

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and immunological activity of PRL may be almost exclusively attributed to the monomeric form [1]. The most common symptoms of monomeric PRL excess in premenopausal women are oligomenorrhea/amenorrhea and galactorrhea, which result from the inhibitory effect on gonadotrophin-releasing hormone (GnRH) secretion and from the stimulatory effect on the proliferation and differentiation of mammary cells during lactation. The predominant physiologic consequence of hyperprolactinemia is hypogonadotrophic hypogonadism due to suppression of pulsatile GnRH. Furthermore, women with hyperprolactinemia can present with various other symptoms including; a short luteal phase, menstrual irregularities, decreased libido or orgasmic dysfunction, anovulation, infertility, chronic hyperandrogenism due to increased dehydroepiandrosterone sulfate secretion from the adrenals, prolonged hypoestrogenism, decreased bone mass and osteopenia [2].

The most common other forms of PRL with lower biological activity include the dimeric (big PRL, MW 48–56 kDa) and the polymeric isoform or macroprolactin (big–big PRL, MW > 150 kDa), that account for less than 10% and 1%, respectively, of the total PRL levels in normal sera. Macroprolactinemia represents a state of hyperprolactinemia characterized by the predominance of big–big PRL and it is mainly suspected in asymptomatic individuals or those without the typical hyperprolactinemia-related symptoms. Among the three most common causes of hyperprolactinemia, in addition to prolactinomas and neuroleptics/antipsychotic drugs, macroprolactinemia can also be included. Although the nature of macroprolactin is heterogenous it is mainly recognized as an antigen–antibody complex of high stability consisting primarily of monomeric PRL and immunoglobulin (Ig) G isotype. Furthermore, in cases with slightly elevated PRL levels, non-IgG-bound forms of macroprolactin including complexes with IgA or IgM, highly glycosylated monomeric PRL, covalent or noncovalent aggregates of monomeric PRL, have rarely been demonstrated. Macroprolactin is confined to the vascular system owing to its high molecular size and therefore its access to the PRL receptors of target organs in the periphery and centrally is prevented. Accordingly, the absence of macroprolactin in extravascular spaces and the pituitary may be proceeded by the loss of hyperprolactinemia-related symptoms [3]. It seems that asymptomatic macroprolactinemia in women with hyperprolactinemia might be a stable and long-lasting condition for up to 10-years [4]. In patients with macroprolactinemia and normal concentrations of monomeric PRL no symptomatic progression was noted during a 10-year clinical follow-up, macroprolactinemia therefore may be considered a benign variant of hyperprolactinemia. Such patients have been reassured that no pituitary imaging investigations and dopamine agonist treatments were necessary [5]. Consequently, routine diagnostic screening of all hyperprolactinemic women for macroprolactin has been recommended as financially justified due to reduced use of imaging and dopamine agonist treatment in such patients [6]. Although patients with macroprolactinemia are usually asymptomatic and have normal menstrual cycles with spontaneous conceptions, there are a number of women with macroprolactinemia presenting hyperprolactinemic clinical symptoms due to the rise in the levels of monomeric PRL, that cannot be differentiated from the patients with true hyperprolactinemia [7–11]. Since in patients with macroprolactinemia at least one of these symptoms may be found, no clinical feature can reliably distinguish macroprolactinemic from true hyperprolactinemic individuals [7]. Unfortunately, no laboratory investigations and hyperprolactinemia related symptoms are useful in differentiating patients with monomeric hyperprolactinemia from those individuals with macroprolactinemia [8]. Furthermore, a comparison of different immunoassays for the detection of macroprolactin in hyperprolactinemic patients demonstrated no difference in the incidence of hyperprolactinemia-related symptoms, including abnormal menses, galactorrhea, or abnormal pituitary imaging without regard to considering the presence of macroprolactin [9]. Since oligomenorrhea and galactorrhea occur in 57% and 29% of patients with macroprolactinemia, hyperprolactinemia was a significant cause of frequent misdiagnosis and mismanagement before the introduction of macroprolactin screening by the use of appropriate laboratory immunoassays [10]. Consequently, it is essential for clinical laboratories to introduce screening methods to analyze blood samples in hyperprolactinemic patients and to determine the presence of macroprolactin and the monomeric PRL component of all hyperprolactinemic sera [11]. Although the presence of macroprolactinemia is suspected mainly in cases of mild hyperprolactinemia without pathological pituitary findings, a few cases of macroprolactinemia with prolactinomas and typical hyperprolactinemic symptoms have been recently reported. Since the symptoms of hyperprolactinemia disappeared after treatment with dopamine agonists, biological activity of the high-molecular isoform has been suggested similar to that of elevated monomeric PRL levels. Consequently, in these rare cases of macroprolactinemia pituitary diagnostic imaging, medical treatment, and prolonged follow-up may be required [12]. The review aims to asses the laboratory and clinical significance of macroprolactinemia in women with hyperprolactinemia, and pathophysiologic mechanisms of macroprolactinemia, suggesting different approaches which may be useful in diagnostic evaluation and adequate treatment in clinical settings of such patients.

## Prevalence

Although the proportion of macroprolactinemia has earlier been reported less commonly in men (0.02%) than in women (0.2%), according to more recent data it may be more common with a general prevalence of 3.7% with no difference between the sexes [13,14]. However, in hyperprolactinemic populations the mean proportion of macroprolactinemia is 25% and varies between 15 and 35% [8,12,13]. A higher incidence of macroprolactinemia of 46% reported by a study center which received samples sent from other laboratories where the possible diagnosis of macroprolactinemia was raised, may reflect selection bias [15].

## Clinical features

According to earlier reports macroprolactinemia appeared in isolated cases of asymptomatic women or healthy volunteers, with normal concentration of monomeric PRL and between 85 and 90% of serum PRL big–big PRL. Limited bioactivity *in vivo* without the symptoms of hyperprolactinemia has been supported by an explanation that the big–big PRL complex is confined to the vasculature due to its high molecular mass preventing its approach to the target cells [16,17]. Consequently, the new term “macroprolactinemia” was used for the first time in 1985 for such cases of hyperprolactinemia whose PRL mainly consisted of big–big PRL, to characterize a nonprogressive state and a novel cause of hyperprolactinemia [18].

However, later investigations in patients with macroprolactinemia revealed a lower incidence of hyperprolactinemia-related clinical symptoms and abnormal imaging findings in the pituitary gland compared with patients exhibiting true hyperprolactinemia [5,10,15,19–23]. In a cohort of 51 patients with macroprolactinemia, headache was present in twelve patients (24%), oligomenorrhea in five (10%) and galactorrhea in two cases (4%), without symptomatic progression during prolonged follow-up. Therefore, such patients with macroprolactinemia and normal concentrations of monomeric prolactin can be reassured, and