Macroprolactinemia: a mini-review and update on clinical practice

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Hyperprolactinemia is common among infertile patients, with up to 15%–20% of women with oligomenorrhea having hyperprolactinemia. Suppression of the hypothalamic-pituitary-gonadal axis via inhibition of pulsatile gonadotropin releasing hormone because of hyperprolactinemia is a common endocrine etiology of infertility. There are 3 forms of human prolactin (PRL): monomeric PRL, dimeric PRL, and macro-PRL. Also known as big-big PRL, macro-PRL has a molecular weight >150 kDa and normally comprises 5%–10% of circulating PRL. When the predominant form of circulating PRL is macro-PRL, macroprolactinemia is diagnosed. Among patients with hyperprolactinemia, 10%–46% have macroprolactinemia. Patients with macroprolactinemia are at risk of unnecessary pituitary imaging and treatment with dopamine agonists if not correctly diagnosed. Given the high prevalence of macroprolactinemia among patients with elevated PRL levels and the different management of patients with macroprolactinemia vs true monomeric hyperprolactinemia, all patients with persistently elevated PRL levels should be screened for macro-PRL. (Fertil Steril Rep® 2023;4:245–50. ©2023 by American Society for Reproductive Medicine.)

Key Words: Prolactin, macroprolactin, hyperprolactinemia, macroprolactinemia

Prolactin (PRL) is secreted by the anterior pituitary and has 3 forms in circulation, demonstrated in Table 1 (1–3). Monomeric PRL has a molecular weight (MW) of 23 kDa and accounts for 85% of total immunoreactive PRL, dimeric PRL has a MW of 48–56 kDa and comprises 5%–10%, and macro-PRL has a MW >150 kDa and is responsible for 5%–10% of circulating PRL in healthy patients (1–4). The predominant form of PRL in healthy individuals and patients with prolactinomas is monomeric PRL (2, 5, 6). Dimeric PRL consists of glycosylated monomers that form aggregates and are clinically benign (7, 8). Macro-PRL is composed of antigen-antibody complexes of monomeric PRL and immunoglobulin, most commonly IgG (2, 9, 10). Although less common, other nonIgG types of macro-PRL include monomeric PRL complexed with IgA or IgM, highly glycosylated monomeric PRL, or covalently and noncovalently bound monomeric PRL (2). Routine PRL assays are unable to distinguish the 3 forms of circulating PRL (1).

HYPERPROLACTINEMIA ETIOLOGIES AND EVALUATION

Hyperprolactinemia occurs physiologically with pregnancy, lactation, stress, sleep, coitus, nipple stimulation, and exercise (3, 5, 9). Pathologic causes of hyperprolactinemia include PRL secreting pituitary adenomas, hypothalamic tumors (ie, craniopharyngiomas, meningiomas), and infiltrative diseases (ie, sarcoidosis, histiocytosis), pituitary stalk damage, hypothyroidism, chest wall lesions (ie, breast surgery, herpes zoster), hepatorenal disorders, antidopaminergic medications (ie, antipsychotics, prokinetic agents), ectopic prolactin production (ie, renal cell carcinoma, ovarian teratomas), and macroprolactinemia (2, 3, 5, 9). Apart from macroprolactinemia, the predominant form of PRL in circulation is monomeric PRL (2). Among the general population, 0.2%–4.04% of women and 0.0%–4.48% of men have macroprolactinemia, and among patients with hyperprolactinemia, 10%–46% have macroprolactinemia (2–4, 6, 7, 9–16).

Patients should avoid vigorous exercise and nipple stimulation for at least 30 minutes before evaluating serum PRL levels (3). Hyperprolactinemia is diagnosed when serum PRL levels exceed the upper limit of normal (20–25 ng/mL, depending on the laboratory) on two separate occasions (3). Therefore, an elevated PRL level should be repeated at least once (5). However, if PRL levels are elevated >100 ng/mL, then one PRL measurement may be sufficient to diagnose hyperprolactinemia (3).

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MACROPROLACTIN STRUCTURE

Macro-PRL consists of monomeric PRL complexed with immunoglobulins. Most macro-PRL (87%) is composed of monomeric PRL complexed with IgG (3, 9, 17, 18). Within this category of PRL-IgG complexes, the majority (67%) involve anti-PRL autoantibodies (Fig. 1) (9). It is postulated that a genetic predisposition to posttranslational modifications of monomeric PRL, such as glycosylation and phosphorylation, triggers the production of autoantibodies to the new epitopes (3, 19). There is a significant positive correlation between anti-PRL autoantibody titers and serum PRL levels, which supports anti-PRL autoantibodies being a cause of macroprolactinemia (9, 12). Additionally, macro-PRL has been identified in cord blood from a mother with macroprolactinemia, indicating the passive transfer of PRL-IgG complexes (12).

The hypothalamic-anterior pituitary negative feedback loop does not function normally in patients with macroprolactinemia. Normally, PRL crosses the blood-brain barrier and binds PRL receptors on the tuberoinfundibular cells of the hypothalamus, which secrete dopamine and decrease monomeric PRL secretion from the anterior pituitary (20). However, because PRL-IgG complexes, with their MW >150 kDa, are unable to cross the blood-brain barrier to access PRL receptors on the tuberoinfundibular cells of the hypothalamus, the elevated PRL levels observed in macroprolactinemia do not lead to downregulation of monomeric PRL secretion from the anterior pituitary (9, 11, 12, 20). Rather, in patients with macro-PRL as the predominant form of circulating PRL, monomeric PRL often maintains normal levels (9, 12).

Another consequence of macro-PRL's elevated MW is decreased filtration through glomeruli and, therefore, reduced renal clearance compared with monomeric PRL (2, 3, 12, 19). This leads to higher serum levels of macro-PRL and hence, hyperprolactinemia. The hyperprolactinemia resulting from macroprolactinemia is based on delayed clearance of macro-PRL rather than increased production of PRL (3).

TRUE HYPERPROLACTINEMIA AND MACROPROLACTINEMIA CLINICAL PRESENTATIONS

The classic symptoms associated with monomeric or true hyperprolactinemia in women are amenorrhea, oligomenorrhea, and galactorrhea (4, 11). In men, hyperprolactinemia is associated with reduced libido, erectile dysfunction, and galactorrhea (11). These symptoms result from the inhibitory effect of PRL on the pulsatile secretion of gonadotropin releasing hormone from the hypothalamus via inhibition of kisspeptin neurons which express PRL receptors, and from the stimulatory effect on mammary cell proliferation (2). A study by Thirunavakkarasu et al. (1) demonstrated that patients with macroprolactinemia are less likely than patients with true hyperprolactinemia to experience oligomenorrhea and galactorrhea, 14% vs 46%, $P<.008$ and 5% vs 30%, $P=.01$, respectively (Table 2). These findings of decreased symptomatology in patients with macroprolactinemia, compared with true hyperprolactinemia, have been replicated in other studies (4, 13, 16).

The muted phenotype of patients with macroprolactinemia is based on the low bioavailability of macro-PRL compared with monomeric PRL (3). PRL autoantibodies and PRL receptors bind to similar regions on the PRL molecule (9). Therefore, it has been proposed that PRL autoantibodies present in patients with macroprolactinemia compete with PRL receptors for the binding of free PRL (9). Furthermore, macro-PRL is largely confined to the vascular space by its high MW and is unable to access target organs, such as the pituitary and hypothalamus (2, 3, 12, 18, 19). It is hypothesized that the low rates of oligomenorrhea and galactorrhea experienced by patients with macroprolactinemia are because of temporary dissociation of monomeric PRL from its immunoglobulin and hence a short-term increase in monomeric PRL (2, 19).

Many patients with macroprolactinemia have serum PRL levels <100 ng/mL (3). However, PRL levels are highly variable, ranging from 20 to 663 ng/mL (mean 61 ± 66 ng/mL) (3). The ranges of PRL levels for macroprolactinomas, microprolactinomas, drug-induced hyperprolactinemia, and primary hypothyroidism overlap (3). A study by Kalsi et al. (16) showed no significant difference in median PRL levels between patients with macroprolactinemia and true hyperprolactinemia (137 ng/mL vs 164 ng/mL, $P=.054$). Given the overlapping symptoms and PRL levels associated with true monomeric hyperprolactinemia and macroprolactinemia, the correct diagnosis cannot be determined based on symptomatology or lab values alone (2, 3, 6, 11, 14). Furthermore, a subset of patients may have macroprolactinemia in conjunction with another cause of hyperprolactinemia (2, 3, 7). Patients with macroprolactinemia who demonstrate neurological signs or symptoms of an intracranial mass should undergo further evaluation with pituitary imaging (3). Up to 26% of patients with macroprolactinemia have concomitant prolactinomas, which are generally associated with elevated monomeric PRL (12, 21).

Correctly identifying the etiology of hyperprolactinemia is paramount because indicated treatments vary significantly. For example, dopamine agonists and/or surgery are used to manage prolactinomas, thyroid hormone supplementation normalizes PRL levels in the setting of primary hypothyroidism, and discontinuation of dopamine antagonists resolves hyperprolactinemia in drug-induced cases (3). Dopamine agonists are often the first-line treatment for patients with hyperprolactinemia (9). However, when administered to

TABLE 1

Forms of circulating prolactin (1–3).

Type of PRL	Molecular Weight (kDa)	Prevalence in Serum (%)
Monomeric	23	80–95
Big (dimeric)	48–56	5–10
Big-big (macro)	>150	5–10

PRL = prolactin.

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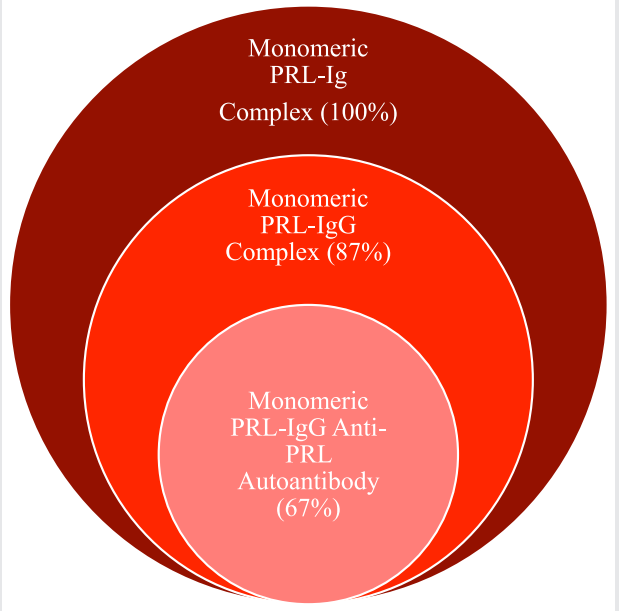
FIGURE 1



Macro-PRL consists of monomeric PRL complexed with IgG and nonIgG antibodies. The majority of macro-PRL (87%) consists of monomeric PRL-IgG complexes. Among the monomeric PRL-IgG complexes, 67% consist of anti-PRL autoantibodies.

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patients with macroprolactinemia, serum PRL concentrations decrease minimally (9). Furthermore, macroprolactinemia usually does not require treatment (2, 3).

DIAGNOSING MACROPROLACTINEMIA

Immunoassays

The greatest challenge to diagnosing macroprolactinemia is that immunoassays cannot differentiate monomeric PRL from dimeric PRL, macro-PRL, or PRL fragments (7, 8, 10, 19, 22). This leads to inappropriate diagnosis of hyperprolactinemia, unnecessary pituitary imaging, and unindicated administration of dopamine agonists (7, 18, 19, 22). Therefore, when immunoassays detect elevated PRL, it is essential to screen for the presence of macro-PRL (19). A study of 6 immunoassays for PRL demonstrated discordant PRL levels in patients with macroprolactinemia (22). Additionally, an investigation of the immunoassay purported to be the least reactive with macro-PRL cross-reacted with macro-PRL in half of the patients with macroprolactinemia (10). These studies emphasize that immunoassays cannot consistently differentiate macro-PRL from monomeric PRL. Despite the Endocrine Society's recommendation to screen all patients with hyperprolactinemia for macroprolactinemia, universal testing for macro-PRL has not been implemented (21, 22). In fact, a recent study by Muhtaroglu et al. (17) found that of 5,007 consecutive serum samples evaluated for PRL, 900/5,007 (17.9%) had elevated PRL levels, and providers requested macro-PRL screening for only 171/900 (19.0%) samples. Of the 171 patients who underwent screening for macro-PRL with polyethylene glycol (PEG), 31 were diagnosed with macroprolactinemia (17). This study demonstrates that unless patients with hyperprolactinemia are screened for macroprolactinemia, many patients will be incorrectly diagnosed.

Precipitation with PEG

Precipitation of macro-PRL with PEG is a simple, quick, accessible, and inexpensive method of screening for macro-PRL and is comparable with the gold standard gel filtration chromatography (2, 7, 9, 19). The PEG dehydrates proteins, decreasing their solubility and leading to precipitation (23). When exposed to PEG, immunoglobulins become insoluble, which leads to the precipitation of PRL-IgG complexes and decreased levels of PRL in the supernatant (3, 12, 18). To calculate free PRL precipitation with PEG, a serum sample is mixed with 12.5%–25% PEG and then centrifuged, whereas another serum sample is mixed with water and then centrifuged to determine the total PRL concentration (9, 12). The PRL in the supernatant is then assayed. The percent PEG-precipitated PRL, which represents macro-PRL, is calculated as (total PRL-free PRL)/total PRL $\times$ 100 (9). When the percent of PEG-precipitated PRL is $\geq$60%, indicating recovery of monomeric PRL is $\leq$40%, macroprolactinemia is diagnosed (1, 7, 9, 11, 12, 14). The sensitivity and specificity of precipitation with PEG for diagnosing macroprolactinemia are 100% and 94.4%, respectively (18). When $\leq$40% recovery of monomeric PRL is used as a cutoff, 3.3% of patients are diagnosed with macroprolactinemia, compared with 8.8% of patients when a cutoff of $\leq$60% is used (19). Precipitation with PEG is a screening method, rather than diagnostic, because it lacks specificity for macro-PRL (2). A limitation of this laboratory technique is that PEG causes precipitation of some monomeric PRL, which leads to underestimation of monomeric PRL, particularly in patients with simultaneous macroprolactinemia and supraphysiologic monomeric PRL (2, 19). Concomitant prolactinoma should be suspected when monomeric PRL levels remain elevated despite recoveries $\leq$40% with PEG precipitation (5). Furthermore, PEG only partially precipitates IgA, causing macroprolactinemia involving IgA-PRL complexes to be misdiagnosed (23). Overall, it has been estimated that precipitation with PEG correctly diagnoses macroprolactinemia in 80% of cases (5).

Other Methods

Gel filtration chromatography is the gold standard for measuring macro-PRL; however, it is expensive and

TABLE 2

Presenting symptoms among patients with true hyperprolactinemia and macroprolactinemia (1).

Presenting Symptom	True Hyperprolactinemia (%)	Macroprolactinemia (%)
Oligomenorrhea	46	14
Galactorrhea	30	5
Polycystic ovaries	15	14

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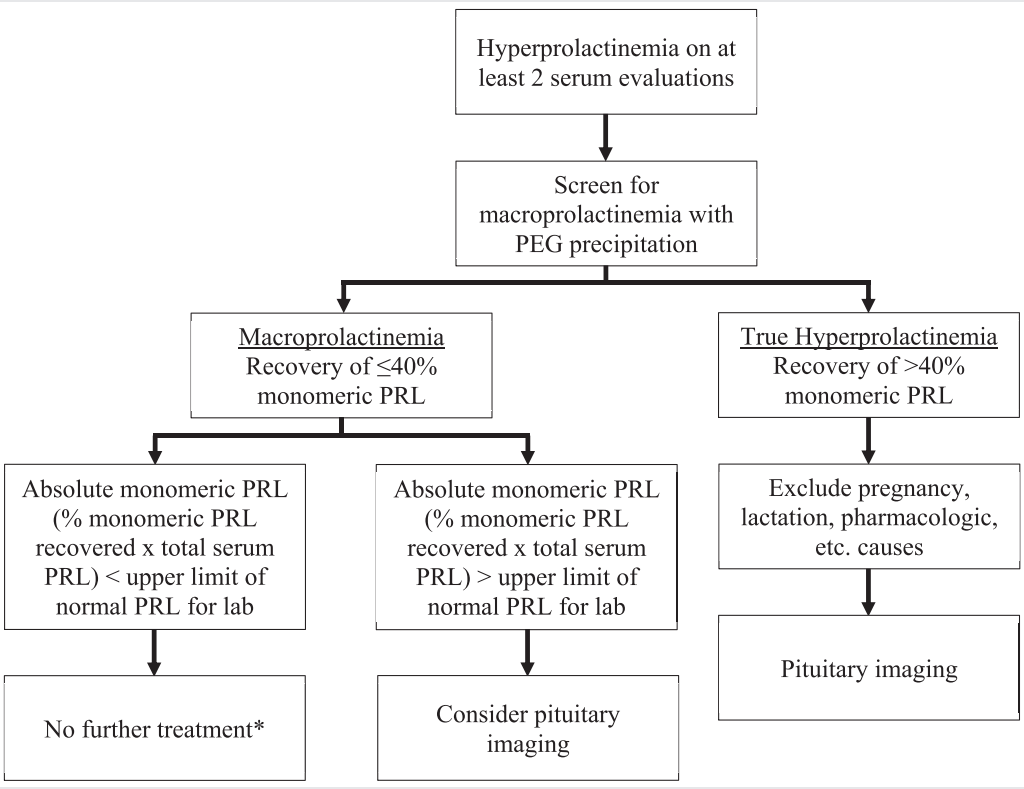
FIGURE 2



All patients with hyperprolactinemia on serum testing should be assessed for macroprolactinemia. PEG = polyethylene glycol, PRL = prolactin. *Unless a patient has clinical presentation suggestive of simultaneous prolactinoma such as amenorrhea/oligomenorrhea and/or galactorrhea

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time-consuming (2, 3, 7, 9, 11, 22). Therefore, this technique is used only to confirm the diagnosis of macroprolactinemia by separating PRL based on molecular size (9). Other methods of confirming macroprolactinemia are protein A/G column and ^{125}I-PRL binding studies (9). Protein A/G column involves protein A binding to the Fc portion of the immunoglobulin in the PRL-immunoglobulin complex, whereas protein G binds only to IgG, the most common immunoglobulin in macro-PRL (9). Although this process can reliably identify PRL-IgG complexes, it is expensive and cannot identify the subset of macro-PRL containing immunoglobulins other than IgG (9). ^{125}I-PRL binding involves mixing a serum sample first with ^{125}I-PRL, then with PEG, followed by centrifugation (9, 12). The gamma radioactivity of the sediment is measured and is able to identify the presence of anti-PRL autoantibodies (9). Although ^{125}I-PRL binding is able to detect a subset of PRL-IgG complexes, those containing anti-PRL autoantibodies, this method cannot detect all macro-PRL (9). Furthermore, this process is time-consuming and requires access to a radioisotope laboratory (9).

MACROPROLACTINEMIA IMPLICATIONS

Thirunavakkarasu et al. (1) demonstrated that 183/1,163 (15.7%) female patients with infertility had hyperprolactinemia, and 21/183 (11.5%) had macroprolactinemia. Meanwhile, 5.8% of patients with polycystic ovarian syndrome were found to have macroprolactinemia (24). Women with macroprolactinemia can conceive, progress through normal pregnancies, deliver healthy neonates, and lactate postpartum without any treatment for hyperprolactinemia (9, 12). It is essential to differentiate macroprolactinemia from true hyperprolactinemia so as to not proceed with unindicated imaging and administration of dopamine agonist therapy in a patient who actually has macroprolactinemia.

Long-term follow-up studies have demonstrated that macroprolactinemia persists, but symptoms do not progress (2, 9, 13). A prospective cohort study of 51 patients with macroprolactinemia observed for a median of 9.9 years demonstrated continued macroprolactinemia at follow-up with no progression in symptoms (4). Furthermore, 29/43 patients conceived spontaneously during follow-up (4). A study by Hattori et al. (15) followed 27 macroprolactinemic patients for 4 years and during the study period, total and free PRL levels did not change significantly. Another study by the same group demonstrated that over a median of 4.4 years (range 2–17 years), the ratios of PEG-precipitable PRL, IgG-bound PRL, and anti-PRL autoantibody-bound PRL remained stable (25). This suggests that despite the heterogeneous nature of macro-PRL with IgG and nonIgG bound PRL monomers, the composition of macro-PRL remains stable over

time (25). Prospective follow-up studies suggest that macroprolactinemia is a benign condition that does not require pituitary imaging or dopamine agonist treatment. However, to diagnose macroprolactinemia, it is essential that serum samples with hyperprolactinemia be screened for macro-PRL.

CLINICAL GUIDELINES

Because of the high prevalence of hyperprolactinemia among couples with female factor infertility and 11.5% incidence of macroprolactinemia among this patient population, macro-PRL screening should be routinely performed when a patient is noted to have persistent hyperprolactinemia (1). This is supported by the Endocrine Society's recommendation to assess for macroprolactinemia in patients with asymptomatic hyperprolactinemia (21). When serum PRL is elevated, the level should be repeated in the fasting state with reflexive screening for macro-PRL. Reflexive screening for macro-PRL in all repeat serum samples with elevated PRL levels should be initiated across all laboratories rather than provider-initiated screening for macro-PRL. This would enhance patient safety as a study by Muhtaroglu et al. (17) demonstrated that 77% of serum samples with PRL levels above the reference range were overlooked for macro-PRL screening when left to the ordering provider to request the macro-PRL testing. Universal screening for macro-PRL has been more widely implemented in Europe than in North America (7). Correctly diagnosing macroprolactinemia is essential because patients labeled as having idiopathic hyperprolactinemia are often subjected to repeated computerized tomographies and magnetic resonance imaging scans in an effort to locate a microadenoma of the pituitary, in addition to long-term treatment with a dopamine agonist, and occasionally, unnecessary surgical exploration (8, 12). Therefore, reflexive screening for macro-PRL should be instituted for all repeat serum samples with PRL levels above the upper limit of normal for the laboratory (Fig. 2).

Patients with hyperprolactinemia and a predominance of macro-PRL do not require pituitary imaging or long-term treatment with a dopamine agonist (2). However, when the absolute monomeric PRL remains above the upper limit of normal for the lab after PEG precipitation, we recommend considering pituitary imaging to evaluate for a concurrent pituitary adenoma. Despite an initial increased cost for reflexive macro-PRL testing, routine screening of all women with hyperprolactinemia for macro-PRL is justified financially because it decreases health care costs on imaging and treatment with dopamine agonists (2, 6, 7). A cost analysis involving 1,793 patients with elevated PRL ($\geq$30 ng/mL), of whom 63.5% were diagnosed with true hyperprolactinemia, and 35.6% were diagnosed with macroprolactinemia, demonstrated that continued unnecessary testing in macroprolactinemia patients resulted in bloodwork, imaging, and dopamine agonist therapy that was unindicated and burdensome (6).

CONCLUSION

All patients with persistent hyperprolactinemia should be screened for macroprolactinemia. Reflexive screening for macro-PRL in patients with hyperprolactinemia on routine bloodwork may minimize misdiagnosis, unnecessary imaging, inappropriate treatment, and high levels of stress for patients and providers (23). With its simplicity, correlation with the gold standard of gel filtration chromatography, and high sensitivity and specificity, precipitation with PEG is a reasonable technique for identifying patients with macroprolactinemia whose PRL level is persistently elevated (13).

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