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Determination of prolactin: The macroprolactin problem

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Serum prolactin is frequently measured when investigating patients with reproductive disorders and elevated concentrations are found in up to 17% of such cases. Clinical laboratories rely predominantly on automated analysers to quantify prolactin levels using sandwich immunometric methodologies. Though generally robust and reliable, such immunoassays are susceptible to interference from a high molecular mass prolactin/IgG autoantibody complex termed macroprolactin. While macroprolactin remains reactive to varying degrees in all prolactin immunoassays, it exhibits little if any biological activity in vivo and consequently its presence is considered clinically irrelevant. Macroprolactinaemia, defined as hyperprolactinaemia due to excess macroprolactin with normal concentrations of bioactive monomeric prolactin, may lead to misdiagnosis and mismanagement of hyperprolactinemic patients if not recognised. Current best practice recommends that all sera with elevated total prolactin concentrations are subfractionated using polyethylene glycol precipitation to provide a more meaningful clinical measurement of the bioactive monomeric prolactin content. Manufacturers of prolactin assays should strive to minimise interference from macroprolactin in their assays. Clinical laboratories should introduce screening procedures to exclude macroprolactinaemia in all patients identified as having hyperprolactinaemia. Clinicians should be aware of this potential diagnostic pit fall and insist on PEG screening of all hyperprolactinaemic sera.

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Introduction

In man, prolactin is a 23 kDa peptide hormone, principally secreted by the lactotroph cells of the anterior pituitary gland [1]. Secretion is controlled via a negative feedback loop whereby circulating prolactin stimulates hypothalamic dopamine secretion which inhibits prolactin release by the pituitary gland. The target organ for prolactin is the mammary gland and the principal functions of prolactin are exerted as part of the hormonal changes of pregnancy. During pregnancy, the pituitary gland enlarges, the number of lactotrophs increase and serum prolactin levels rise approximately ten-fold thereby contributing to breast development and lactation. Suckling also stimulates secretion of prolactin via a neuroendocrine reflex pathway. This pathway maintains elevated serum prolactin concentrations after parturition with hyperprolactinaemic suppression of pituitary gonadotrophin secretion leading to amenorrhoea and a period of relative infertility. In the absence of pregnancy, symptoms of galactorrhoea, menstrual disturbance and infertility constitute the hyperprolactinaemic syndrome and may be the result of autonomous secretion of prolactin by a prolactinoma, the most common pituitary tumour [2]. Symptoms of the hyperprolactinaemic syndrome are the most common reason for measurement of serum prolactin and since the symptoms are common and non-specific, considerable reliance is placed on the laboratory result for the diagnosis of prolactinoma and in monitoring the effects of treatment with dopamine agonists or following pituitary surgery. The key principle of a serum prolactin assay in clinical practice relies on the fact that the serum concentration of the hormone, as determined by immunoassay, reflects the in vivo hormonal bioactivity accurately. Macroprolactin disrupts this relationship and therein lies the problem. This chapter will serve to update the reader on current evidence based best practice in the investigation of hyperprolactinaemia and in screening for macroprolactinaemia [3–5].

Measurement of serum prolactin

Prolactin concentrations in sera are easily measured in modern clinical laboratories predominantly with automated immunoassay methodology. Manufacturers of the most widely used analysers are shown in Table 1 [6–8]. Current immunoassays generally employ a two-site immunometric or sandwich principle whereby prolactin is allowed to react with both a capture antibody, which is often immobilised on a solid phase, and a labelled antibody which is used for detection. Following capture of the analyte-antibody sandwich and removal of unreacted reagents by a wash step, the signal generated is directly related to the amount of prolactin present (Fig. 1). Such assays give rapid, precise results, over a wide range of concentrations and show good within-method agreement in external quality assessment schemes [8]. However, despite standardisation of most prolactin immunoassays to the World Health Organisation's third international standard for prolactin, 84/500 (Table 1), which consists exclusively of 23 kDa of monomeric prolactin derived from human pituitaries, agreement between methods is relatively poor and there is no relationship between recovery of the international standard and assay bias [8]. While the concentration of prolactin in serum of normal adult males and females is usually less than 300 mU/L and 500 mU/L respectively, reference ranges are assay dependant and vary

Table 1
Commonly used auto-analysers for serum prolactin, together with international standard in use and relative reactivity towards macroprolactin.

Manufacturer	Instrument	International standard	Relative reactivity towards macroprolactin*
Abbott	Architect	84/500	High
Beckman	Access/DxI	84/500	Low
Ortho	Vitros ECi	84/500	Medium
Roche	Elecsys/E170/Cobas	84/500	Low
Siemens	Centaur	84/500	Low
Siemens	Immulite	84/500	Medium
Tosoh	AIA	83/562	High

* References: [3,9,27,33,87,91,92].