Interference by macroprolactin in assays for prolactin: will the In Vitro Diagnostics Regulation lead to a solution at last?

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Opinion Paper

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Interference by macroprolactin in assays for prolactin: will the *In Vitro* Diagnostics Regulation lead to a solution at last?

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Abstract: Cross reactivity with high molecular weight complexes of prolactin known as macroprolactin is a common cause of positive interference in assays for serum prolactin. All prolactin assays currently available are affected with 5–25% of results indicating hyperprolactinaemia falsely elevated due to macroprolactinaemia – hyperprolactinaemia due to macroprolactin with normal concentrations of bioactive monomeric prolactin. Macroprolactinaemia has no pathological significance but, if it is not recognised as the cause, the apparent hyperprolactinaemia can lead to clinical confusion, unnecessary further investigations, inappropriate treatment and waste of healthcare resources. Macroprolactinaemia cannot be distinguished from true hyperprolactinaemia on clinical grounds alone but can be detected by a simple laboratory test based on the precipitation of macroprolactin with polyethylene glycol. Laboratory screening of all cases of hyperprolactinaemia to exclude macroprolactinaemia has been advised as best practice but has not been implemented universally and reports of clinical confusion caused by macroprolactinaemia continue to appear in the literature. Information provided by manufacturers to users of assays for prolactin regarding interference by macroprolactin is absent or inadequate and does not comply with the European Union Regulation covering *in vitro* diagnostic medical devices (IVDR). As the IVDR is implemented notified bodies should insist that manufacturers of assays for serum prolactin comply with the regulations by informing users that macroprolactin is a source of interference which may have untoward clinical consequences and by providing an estimate of the magnitude of the interference and a means of detecting macroprolactinaemia. Laboratories should institute a policy for excluding macroprolactinaemia in all cases of hyperprolactinaemia.

Keywords: assay manufacturers; *In Vitro* Diagnostics Regulation; interference; macroprolactin; prolactin assay.

A recent review [1] included data on the frequency of reported interferences in immunoassays ranging from 0.4–4.0%. Cross-reactivity is a particular form of assay interference [2] and is a major cause of inaccuracy in immunoassays [3]. Smith et al. [4] report the prevalence of interference in two immunoassays for prolactin as 6.2–24.6%, due to cross reactivity with macroprolactin. This report demonstrates that the prevalence of interference in immunoassays for prolactin is exceptional and is a reminder that interference by macroprolactin in assays for prolactin continues to be a problem for laboratories and manufacturers and can lead to clinical confusion and avoidable morbidity for patients [5]. Assays for prolactin have been used almost exclusively in the diagnosis and management of prolactinoma, the symptoms of which (the hyperprolactinaemic syndrome) are directly related to hyperprolactinaemia resulting from unregulated secretion of prolactin by the pituitary adenoma. The symptoms are common and non-specific and the clinical question underlying a request for prolactin assay is, 'are this patient's symptoms due to hyperprolactinaemia?' To answer this question an immunoassay specific for bioactive prolactin is essential. A radioimmunoassay for the 23 kDa bioactive form of pituitary prolactin was established in 1971 [6] and within a few years gel filtration chromatography of plasma demonstrated cross-reactivity with two higher molecular weight species; 50 kDa big prolactin and >100 kDa big-big prolactin [7]. The report in 1981 of an asymptomatic volunteer with hyperprolactinaemia, in which big-big prolactin was the major circulating immunoreactive species, and the concentration of the 23 kDa form was normal

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[8] raised concerns that big-big prolactin was not bioactive *in vivo* and constituted interference in the prolactin radioimmunoassay. Jackson et al. [9] describing a case with a similar pattern of prolactin immunoreactivity on gel filtration chromatography, introduced the terms macroprolactin, to describe the >100 kDa species (this has largely replaced the term big-big prolactin) and macroprolactinaemia, to describe hyperprolactinaemia in which macroprolactin was the predominant immunoreactive species of prolactin present. It has been argued subsequently [10] that, for clinical purposes, the most useful definition of macroprolactinaemia is hyperprolactinaemia due to the presence of macroprolactin with normal concentrations of 23 kDa monomeric prolactin and we use the term in that sense in this manuscript. Furthermore, we use the term true hyperprolactinaemia to refer to hyperprolactinaemia due solely to elevated concentrations of 23 kDa monomeric prolactin.

The replacement of the original isotopic assays with a variety of automated, two-site immunometric techniques enabled wider application of prolactin assays but these newer assays also cross react with higher molecular mass forms of prolactin. In 2005 it was conservatively estimated that 10% of all laboratory reports of hyperprolactinaemia from such assays were due to macroprolactinaemia [5]. The report by Smith et al. [4] indicates that the scale of the interference in two widely used assays remains unchanged and we are not aware of an immunoassay for prolactin which does not cross-react with macroprolactin to some degree. It is remarkable that interference by macroprolactin in prolactin immunoassays has been recognised for 50 years and continues to be a cause for concern while the nature and extent of the macroprolactin problem has been thoroughly investigated, is now well understood and is the subject of comprehensive reviews [5, 7, 10, 11]. Macroprolactin is a heterogeneous species but usually a combination of prolactin with IgG and most often exhibits properties consistent with an antigen-autoantibody complex. The complex is formed within the vascular compartment, has a longer half-life in the circulation than monomeric prolactin and the prolactin component cross-reacts in assays for prolactin resulting in macroprolactinaemia. Macroprolactin has low bioactivity in *in vitro* bioassays based on human receptors [11] and there is no evidence of bioactivity *in vivo*, probably because the bound autoantibody prevents the prolactin component binding to cellular prolactin receptors but also, because of its size, the complex is confined to the intravascular space and thus unable to reach tissue receptors. A long-term follow-up study of patients with macroprolactinaemia has shown that it is a persistent but benign condition with no pathological significance [12]. Nevertheless, macroprolactinaemia is of biochemical and clinical significance because if the cause is not recognised the apparent hyperprolactinaemia can lead to misleading laboratory reports and clinical confusion. Gibney et al. [5] reviewed eight case series of female patients with macroprolactinaemia reported between 1992 and 2003. Symptoms and signs of hyperprolactinaemia were common amongst cases in all series. Where pituitary imaging studies were carried out 7–22% were reported as abnormal and 22–87% of cases received treatment with dopamine agonists. Gibney et al. [5] concluded that the misdiagnosis of hyperprolactinaemia in these cases led to patient mismanagement involving inappropriate imaging investigations and treatment, and delay in making a correct diagnosis and instituting appropriate treatment. Furthermore, the clinical confusion resulting from the non-specificity of assays for prolactin may be exacerbated by the poor specificity of pituitary imaging which, when coinciding with macroprolactinaemia, can result in a double diagnostic pitfall [13].

There is a clear consensus of opinion on the need to avoid clinical confusion by excluding macroprolactinaemia as a potential cause in all cases of hyperprolactinaemia [5, 10, 11]. To this end many clinical laboratories have responded by introducing the PEG (polyethylene glycol) precipitation test. PEG precipitates macroprolactin and the prolactin remaining in the supernatant provides a measure of the 23 kDa bioactive species. A PEG precipitation procedure has been validated for the detection of macroprolactinaemia by comparison with the reference gel filtration chromatography technique [14]. However, individual cases of macroprolactinaemia and case series continue to be reported indicating that laboratory testing for macroprolactinaemia is not universal and that interference by macroprolactin in prolactin assays remains a problem and continues to cause clinical confusion [15–17]. It is therefore important to consider what more could be done by all parties involved to solve the problem.

The clinical confusion caused by macroprolactinaemia demonstrates that macroprolactinaemia cannot be distinguished reliably from true hyperprolactinaemia on clinical grounds alone [5] and this is recognised in clinical practice guidelines [18]. Laboratories should make clinical colleagues aware that macroprolactin interferes in their prolactin assay and clinicians should insist that laboratories exclude macroprolactinaemia by providing a measure of bioactive prolactin whenever hyperprolactinaemia is detected.

The problem of assay interference should be a prime concern for manufacturers and the ideal solution to the

problem of macroprolactinaemia would be for manufacturers to develop an assay specific for the 23 kDa monomeric form of prolactin. Since the prevalence of macroprolactinaemia in cases of hyperprolactinaemia varies considerably depending on which immunoassay is used [10] it is clear that some assays are more specific than others for monomeric prolactin. One manufacturer (Roche) modified their prolactin assay to minimise reactivity with macroprolactin by using different antibodies and reaction conditions [19] and the prevalence of macroprolactinaemia was reduced from approximately 15% to 6% [4, 10]. It is surprising that this approach has not been taken by other manufacturers whose prolactin assays have a relatively high cross-reactivity with macroprolactin; a prevalence of 14.9% has been reported for the Abbott prolactin assay [20] and 24.6% with the Tosoh assay [4]. The fact that some manufacturers have not reduced, and none have abolished, cross-reactivity with macroprolactin in their prolactin assays may be due to the difficulty of producing specific antibodies which distinguish between free monomeric 23 kDa prolactin and that bound in the macroprolactin complex. It has been postulated that a post-translational change in the prolactin molecule, involving phosphorylation, stimulates anti-prolactin autoantibody production [11]. However, there may be no difference in the composition and structure of prolactin in bioactive, monomeric form and in the bioinactive macroprolactin complex. If it is not possible to produce an immunoassay for prolactin which does not cross-react with macroprolactin it is necessary to test for interference in the clinical laboratory and this should prompt close collaboration between manufacturers and laboratories. Ideal practice for laboratories would be to apply the PEG precipitation test to exclude macroprolactinaemia in all cases of hyperprolactinaemia but PEG precipitation, although simple, is a manual procedure and the additional workload may be difficult to accommodate, especially in highly automated laboratories. As discussed by Smith et al. [4] this has prompted considerable debate on the best laboratory policy to optimise detection of macroprolactinaemia while minimising the associated manual workload. It is remarkable that many laboratories have recognised the need to detect interference by macroprolactin, and have shouldered the burden of correcting this failure in assay performance by introducing a PEG precipitation procedure, without demanding action from the assay manufacturers. Automation of the PEG precipitation procedure, using magnetic separation of the precipitate to avoid the centrifugation step [21] would reduce the burden of manual intervention considerably, especially if this was included on the same analytical platform as the prolactin assay, and manufacturers should investigate this possibility. At present detection of macroprolactinaemia is only possible with a manual procedure and a number of studies have validated techniques based on PEG precipitation and determined reference limits for monomeric prolactin with commercial assays for prolactin [14, 22, 23]. The study by Beltran et al. [14] published in 2008, was encouraged and supported by five major manufacturers of prolactin assays (Abbott, Beckman, Roche, Siemens and Tosoh) but the results have not been incorporated in Information For Use (IFU) documents which are distributed with assay reagents. While all IFUs from these manufacturers include sections on interferences and assay specificity, only that of Roche considers macroprolactin under these headings and in any detail. The IFUs for the Siemens Centaur and the Immulite prolactin assays do not mention macroprolactin at all despite extensive evidence of cross-reactivity with both assays [10] and a conservative estimate of the prevalence of macroprolactinaemia with the Centaur assay of 4% [24]. The IFUs from Abbott, Beckman, and Tosoh contain brief references to macroprolactin under the heading 'Limitations of the procedure'. The Beckman IFU describes interference from macroprolactin in the Access assay as 'minimal' whereas Ellis et al. [22] reported macroprolactinaemia in 7.4% of cases of hyperprolactinaemia with that assay. The Roche IFU advises that both assay antibodies 'show a low reactivity with most forms of macroprolactin'; Smith et al. [4] found that the prevalence of macroprolactinaemia in cases of hyperprolactinaemia with the Roche assay was 6.2%. In all the prolactin IFUs reviewed the paucity of information on interference by macroprolactin contrasts with an abundance of information, often quantitative, on less common causes of interference (haemolysis, icterus, lipaemia, biotin and human anti-mouse antibodies) and rare, and now obsolete sources of potential cross-reactivity (eg. TSH, LH, FSH, hPL, hCG, hGH).

The IFUs from the manufacturers mentioned above fail to provide sufficient and accurate information to make laboratories and their users aware of the degree of interference by macroprolactin. Furthermore, none provides satisfactory advice on how laboratories should detect or mitigate this interference (Roche include a method for PEG precipitation but this does not provide any guidance on interpretation of the results). Thus, despite comprehensive information being readily available regarding interference from macroprolactin in assays for prolactin, and a readily available solution to the problem, appropriate information and guidance from manufacturers in prolactin IFUs is lacking.

In the European Economic Area, Directive 98/79/EC, known as the *In Vitro* Diagnostic Directive (IVDD), specifies that the supply of 'information needed for the control of

known relevant interferences' is an essential requirement of manufacturers [25]. Compliance with the IVDD became mandatory in 2003 and was in force when Gibney et al. [5] reviewed the series of cases of macroprolactinaemia and concluded that it was a common diagnostic pitfall. A further essential requirement of the IVDD is that *in vitro* diagnostic medical devices are 'designed and manufactured in such a way that, when used under the conditions and for the purposes intended, they will not compromise, directly or indirectly, the clinical condition or the safety of the patients' [26]. It is clear that prolactin assays do not comply with either of these two essential requirements of the IVDD and, as far as we are aware, appropriate action has not been taken by regulatory bodies. This longstanding failure is due to an inherent weakness in the IVDD which allowed self-certification by manufacturers of the majority of IVDs without reference to regulatory bodies. In May 2022, following a transitional period of 5 years, the IVDD was replaced by the IVDR (Regulation (EU) 2017/746). The essential requirements of the IVDD discussed above remain but, in addition, the IVDR will require that manufacturers provide evidence on the clinical performance of their assays and the Medical Devices Coordination Group have issued guidance to IVD manufacturers on general principles of clinical evidence required for IVDs [27]. Table 1 [27] of this guidance provides examples of events leading to harm including that of cross reaction resulting in falsely elevated results leading to inappropriate medical treatment; a sequence of events that has been well documented in the case of macroprolactinaemia. A further requirement of the IVDR is that certification of the majority of assays will be subject to approval of independent conformity assessment authorities (Notified Bodies). It is surprising to note that five of the IFUs for prolactin assays discussed above were updated within the transition period, yet continue to provide inadequate information on macroprolactin interference and how to overcome it. This suggests that manufacturers still do not consider that the impending IVDR necessitates further revision of their IFUs to address this deficiency.

All immunoassays for prolactin are affected by interference from macroprolactin which renders their overall clinical performance unsatisfactory. This problem would be resolved if manufacturers complied with the requirements of the IVDR. Laboratories should bring the problem to the attention of Notified Bodies which should compel manufacturers to include in IFUs for prolactin assays information on the nature, mechanism and scale of macroprolactin interference and information on the potential adverse clinical consequences if macroprolactinaemia is not distinguished from true hyperprolactinaemia. Manufacturers should also be compelled to provide a practical solution to the problem of interference by macroprolactin and this should be required by Notified Bodies as a condition of certifying the assay for marketing. Under the IVDR the PEG precipitation procedures used currently by laboratories for detecting macroprolactinaemia will be classified as in house IVDs (IH-IVDs). How the IVDR will be applied to IH-IVDs is a matter of considerable concern and uncertainty [28]. In the case of PEG precipitation the situation is complicated by the fact that while the precipitation procedure, manufactured by a Health Institution, may be classified as an IH-IVD it is applied to commercial prolactin assays which are undoubtedly subject to the IVDR and this raises the question of which organisation, Health Institution or manufacturer of the prolactin assay, is legally responsible for the IVD. Due to the unpreparedness of the EU regulatory infrastructure [29] the timetable for implementation of the IVDR has been revised allowing time for clarification of how the provisions will be applied to IH-IVDs [30] but, in any case, if PEG precipitation in user's laboratories is necessary to detect interference by macroprolactin and ensure satisfactory performance of a prolactin assay, the manufacturer should provide a protocol, reagents and control materials for the PEG precipitation procedure as an integral part of a certified prolactin assay. This would have the additional benefits of encouraging wider implementation of testing for macroprolactinaemia and harmonising of testing procedures. Furthermore, the cost of testing for macroprolactinaemia would become an integral part of the cost of prolactin assay which, when considered together with quantitative data on cross-reactivity with macroprolactin, would enable laboratories to make an informed choice of a prolactin assay.

Current estimates of cross-reactivity with macroprolactin, based on the prevalence of macroprolactinaemia amongst cases of hyperprolactinaemia have led to an approximate classification of assays as 'high, medium or low' reacting [10]. Differences in methodology in these studies do not justify a more rigorous comparison based on quantitative data because prevalence of macroprolactinaemia is affected by factors other than the assay used; i.e. the definition of macroprolactinaemia, the composition of the population tested (higher in specialist referral centres [5]) and the reference limits applied both for screening for macroprolactin and how the post-PEG prolactin results are interpreted. Many reports of prevalence are based on studies of patients with prolactin considerably above the upper reference limit, often >700 mU/L [20, 24], and are likely to be underestimates. The prevalence of macroprolactinaemia with the Tosoh (24.6%) and Roche (6.2%) assays reported by Smith et al. [4] is a valid quantitative comparison since the prevalence was determined

with both assays in the same population and reference limits for both assays were also determined in a common population. This may be a model for further studies to provide comparable, quantitative data for other assays and the data would encourage manufacturers to formulate assays which minimise interference from macroprolactin.

Given adequate information from manufacturers and the means to detect macroprolactinamia the responsibility for formulating and introducing a policy on testing for macroprolactinaemia in cases of hyperprolactinaemia would rest with laboratories. In the present circumstances all involved with the manufacture, provision and use of assays for prolactin should be aware that, since interference by macroprolactin and the adverse clinical consequences which can result are well recognised, and a method to avoid this is readily available, failure to detect macroprolactinaemia leading to undesirable patient outcomes may have medico-legal implications [31].

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