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Consensus statement

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Diagnosis and management of prolactin-secreting pituitary adenomas: a Pituitary Society international Consensus Statement

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Abstract

This Consensus Statement from an international, multidisciplinary workshop sponsored by the Pituitary Society offers evidence-based graded consensus recommendations and key summary points for clinical practice on the diagnosis and management of prolactinomas. Epidemiology and pathogenesis, clinical presentation of disordered pituitary hormone secretion, assessment of hyperprolactinaemia and biochemical evaluation, optimal use of imaging strategies and disease-related complications are addressed. In-depth discussions present the latest evidence on treatment of prolactinoma, including efficacy, adverse effects and options for withdrawal of dopamine agonist therapy, as well as indications for surgery, preoperative medical therapy and radiation therapy. Management of prolactinoma in special situations is discussed, including cystic lesions, mixed growth hormone-secreting and prolactin-secreting adenomas and giant and aggressive prolactinomas. Furthermore, considerations for pregnancy and fertility are outlined, as well as management of prolactinomas in children and adolescents, patients with an underlying psychiatric disorder, postmenopausal women, transgender individuals and patients with chronic kidney disease. The workshop concluded that, although treatment resistance is rare, there is a need for additional therapeutic options to address clinical challenges in treating these patients and a need to facilitate international registries to enable risk stratification and optimization of therapeutic strategies.

Sections

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Introduction

The Pituitary Society published guidelines on diagnosis and management of prolactin-secreting adenomas (referred to hereafter as prolactinomas) in 2006 (ref. 1) and in conjunction with the Endocrine Society in 2011 (ref. 2). This updated Consensus Statement considers new evidence that has markedly influenced clinical practice, including incorporation of transcription factors into pituitary adenoma classification[3], long-term adverse effects of dopamine agonist therapy[4], outcomes following dopamine agonist withdrawal[5] and advances in surgical tumour resection[6–8]. In addition, management during pregnancy[9–11], effects of hyperprolactinaemia on bone and fracture risk[12], management of cystic and aggressive prolactinomas[13], and prolactinomas in children and transgender patients are covered. Unless otherwise specified, the text refers to ciswomen and cismen, when the terms men and women are used.

Methods

The Pituitary Society hosted a virtual consensus workshop on the diagnosis and management of prolactinoma in January 2022. Workshop co-chairs (S.P., S.M., F.F.C.) and Pituitary Society Programme co-directors (M.F., A.G.) identified topics related to prolactinoma diagnosis and management to be addressed, and 36 experts in the clinical management of pituitary disease representing 13 countries with different health-care systems participated in the workshop. Speakers were selected by the organizers according to their expertise for the specific topic based on their publication record and recognized standing in the field. The speakers summarized key data on their assigned topics in 15-min, fully referenced slide-lecture presentations recorded approximately 1 month prior to the workshop. Speakers and moderators critically reviewed English language PubMed-indexed papers published before January 2022. Search terms included 'prolactinoma', 'prolactin-secreting adenoma' and terms associated with topics for discussion, including 'epidemiology', 'pathogenesis', 'clinical symptoms', 'assessment', 'imaging', 'complications', 'dopamine agonists', 'surgery' and 'radiation therapy'. Lectures were recorded, and a summary of key findings, which workshop participants were invited to review and comment on in advance, was prepared.

During the 2-day meeting, speakers provided 5-min highlight summaries of their assigned topics, participants were divided into breakout groups for extended discussions and then reported their conclusions and comments to the entire group. Recommendations were proposed by each session's chair for majority vote by workshop participants. In cases of dispute or close votes, recommendations were reformulated and proposed again for voting and consensus. After the meeting, consensus recommendations, slide-lecture presentations, summaries and discussion points were collated, and a draft manuscript was prepared by the lead authors (S.P., M.F., S.M.).

Based on principles for grading of evidence for guidelines[14,15], as well as on previously published Consensus Statements from the Pituitary Society[16], consensus recommendations were graded as weak or strong based on the quality of the evidence (Box 1). Recommendations and discussion points were circulated to all participants for review and more recent data (January 2022 to January 2023) identified in literature reviews using the keywords from the original searches were added as appropriate. The draft manuscript was circulated to all authors in three rounds prior to their final approval. Consensus recommendations and key points are presented and additional background discussion and supporting references are included in the Supplementary Information.

Background

Epidemiology

- Microprolactinomas rarely proliferate and are of low concern for persistent long-term adenoma growth (strong).
- Macroprolactinomas, especially in men, have a different clinical prognosis compared with microadenomas and require closer follow-up (strong).

Prolactinomas, which are most commonly benign prolactin-secreting adenomas derived from lactotrophs, account for 50% of all pituitary adenomas in both women and men. At age 25–44 years, prolactinomas predominantly affect women, with a female to male ratio of 5:1 to 10:1, whereas after menopause the ratio equalizes[17]. The standardized incidence rate in women is three times higher than in men. The ratio between macroprolactinomas and microprolactinomas is approximately 1:8 in women and 4:1 in men.

Microprolactinomas (<10 mm in maximal diameter) are the most frequent type of prolactinoma and seldom grow into macroprolactinomas (≥10 mm diameter). Giant prolactinomas (macroprolactinomas >40 mm) are rare[18]. Over the past two decades, studies indicate a higher prevalence of prolactinomas than previously predicted[17]. Incidence and prevalence rates are depicted in Supplementary Table 1 and described in Supplementary Box 1.

Molecular pathogenetic mechanisms

- *MEN1* germline mutation screening could be considered in patients with a family history of pituitary adenomas and in patients aged <30 years old with macroadenomas (weak).
- Somatic mutation screening should not be routinely performed (strong).

Molecular mechanisms for prolactinoma pathogenesis require further elucidation. Prolactinomas are mostly sporadic monoclonal neoplasms[19,20], implying a somatic genetic event that confers a growth advantage. A hotspot somatic mutation in splicing factor 3 subunit B1 (*SF3B1*^{R625H}) was identified in 20% of prolactinomas in one series and was associated with higher serum levels of prolactin and potentially more aggressive behaviour than prolactinomas without this mutation[21]. Prolactinomas are very rarely associated with germline mutations and when these are present, onset of disease usually occurs at a younger age than with somatic mutations. Macroprolactinomas in individuals with multiple endocrine neoplasia type 1 (who have germline mutations in *MEN1*) are more aggressive than in those without these mutations, and prolactinomas with *MEN1* mutations could be resistant to therapy[22,23]. By contrast, microprolactinomas with *MEN1* mutations might be less aggressive than previously thought[24]. As pathogenic *AIP* variants are very rarely detected, screening is not recommended in order to avoid unnecessary testing and cost.

See Supplementary Box 1 for further discussion.

Clinical presentation

Hyperprolactinaemia and hypogonadism

- The presence of a sellar mass on imaging requires evaluation for hyperprolactinaemia (strong).
- Galactorrhoea should trigger investigation for hyperprolactinaemia, except for known physiological reasons (for example, pregnant or lactating women) (strong). Importantly, absence of galactorrhoea does not exclude hyperprolactinaemia (strong).

- Loss of libido and/or infertility, new-onset menstrual irregularities or amenorrhoea in women, as well as erectile dysfunction and/or hypogonadotrophic hypogonadism in men, should trigger investigation for hyperprolactinaemia (strong).
- Prolactin-secreting adenomas have been associated with increased likelihood of obesity and the metabolic syndrome (weak).

Increased prolactin secretion during stress, pregnancy and lactation inhibits hypothalamic kisspeptin neuron function, and consequently reduces gonadotrophin-releasing hormone (GnRH) production[25]. Prolactinoma clinical presentation in part reflects prolactin-induced suppression of the hypothalamic–pituitary–gonadal axis that usually reverts after normalization of prolactin serum levels[26], although hypogonadism can persist, especially in men with macroprolactinoma[27,28].

Hyperprolactinaemia leads to oligomenorrhoea or amenorrhoea with or without galactorrhoea in women and erectile dysfunction in men, while loss of libido and infertility are observed in both sexes[29]. Although obesity is reportedly fourfold more prevalent in individuals with prolactinoma versus those with non-functioning pituitary adenoma[30], this disorder probably occurs secondary to associated hypogonadism (see Supplementary Box 2 for further discussion).

Based on available data, screening for hypogonadotrophic hypogonadism in men and in premenopausal women with microprolactinoma and macroprolactinoma is probably warranted.

Other pituitary hormone deficiencies before and after treatment

- Macroprolactinomas and, less frequently, microprolactinomas can cause growth hormone (GH), thyroid-stimulating hormone (TSH) and adrenocorticotrophic hormone (ACTH) axis deficiencies. Patients should be evaluated for associated clinical features, tested for pituitary hormone deficiencies and appropriately treated per standard guidelines (strong).
- Surgical resection of prolactinomas can resolve hypopituitarism but can also cause new-onset deficiencies. Postoperative retesting is recommended (strong).

Prevalence and clinical course of GH, TSH and/or ACTH deficiencies in patients with prolactinoma are derived largely from retrospective studies and are less well delineated compared with hypogonadism. Hormone deficiencies are more frequently encountered in patients with macroprolactinoma than in those with microprolactinoma[31–33]. In a study in 81 men, prevalence of pretreatment TSH or ACTH deficiency was 6.7% and 0%, respectively, for macroprolactinomas 10–19 mm in size, 17.9% and 6.9%, respectively, for macroprolactinomas 20–39 mm in size and 26.1% and 33.3%, respectively, for giant prolactinomas ≥40 mm in size[34].

As surgery and radiation can each induce hypopituitarism, the post-treatment evaluation timeline should be individualized[35] (see Supplementary Box 2 for further discussion).

Screening for GH, TSH and ACTH deficiencies[35] in all patients with macroadenoma and microadenoma 6–9 mm in size at diagnosis was discussed; the consensus was to retest pituitary function after effective dopamine agonist therapy depending on baseline pituitary deficiencies and mass extension, as well as prolactin and adenoma response. Screening for GH, TSH and ACTH deficiencies was recommended for those undergoing surgical resection and retesting approximately 6–12 weeks after surgery was recommended depending on baseline adenoma size, surgical findings and postoperative symptoms. Some participants concluded that patients with a hormonal deficiency at diagnosis, as well as those with prolactinoma >6 mm in size should all be retested after surgery.

Box 1

Grading of evidence and recommendations

Based on principles for grading of evidence for guidelines[14,15] as well as on previously published consensus statements from the Pituitary Society[16].

Evidence

- Very low quality: expert opinion supported by one or a few small uncontrolled studies
- Low quality: supported by large series of small uncontrolled studies
- Moderate quality: supported by one or a few large uncontrolled studies or meta-analyses
- High quality: supported by controlled studies or large series of large uncontrolled studies with sufficiently long follow-up

Recommendations

- Weak: based on very low quality or low quality evidence
- Strong: based on moderate quality or high quality evidence

Initial assessment

Causes of hyperprolactinaemia

- Patients with hyperprolactinaemia but serum levels of prolactin less than five times the upper limit of normal (ULN) should undergo repeat prolactin testing (strong). Cannulated prolactin sampling is recommended if an influence of stress is suspected (strong).
- In general, pituitary adenoma size and serum levels of prolactin correlate; discrepancy should trigger consideration of other possible causes (strong).
- Medication use should be rigorously reviewed to exclude drug-induced hyperprolactinaemia (strong).
- Primary hypothyroidism, renal insufficiency and liver failure should be recognized as causes of mild hyperprolactinaemia (strong).
- Pregnancy should not be overlooked as a cause of hyperprolactinaemia (strong).

Prolactin secretion is under chronic inhibitory control by hypothalamus-derived dopamine[36] (Fig. 1). Dopamine traverses the pituitary stalk and suppresses prolactin production and lactotroph proliferation via D2 receptors (D2R). These inhibitory actions are opposed by oestrogen.

The most common pathological cause of hyperprolactinaemia is excess prolactin production by a prolactinoma[20,37]. However, parasellar or intrasellar masses impinging on the pituitary stalk, including non-secreting pituitary adenomas, can compromise dopamine flow and

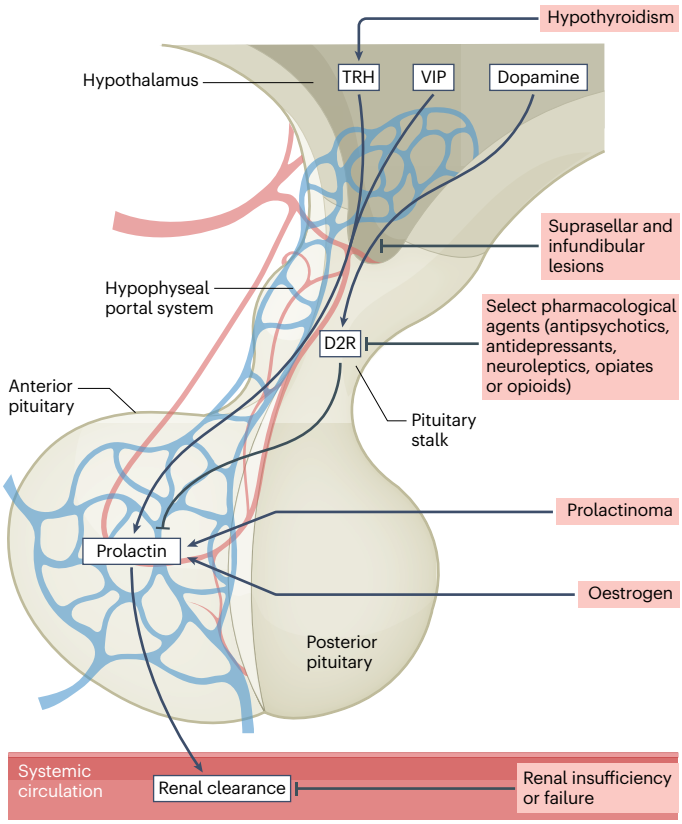

Fig. 1 | Neuroendocrine regulation of prolactin secretion. Dopamine traverses the hypophyseal portal system from the hypothalamus to the anterior pituitary, where it binds the dopamine 2 receptor (D2R) and blocks prolactin secretion. Suprasellar and infundibular lesions involving the stalk and pharmacological agents with antagonist activity at the D2R can result in an increase in prolactin secretion. By contrast, thyrotrophin-releasing hormone (TRH) and vasoactive intestinal peptide (VIP) from the hypothalamus stimulate prolactin secretion in the pituitary, as does oestrogen. Prolactin is systemically cleared by the kidney, so chronic kidney insufficiency can cause elevated serum levels of prolactin.

cause hyperprolactinaemia (Box 2). Hence, elevated serum levels of prolactin (up to six times ULN)[38,39] might reflect a hypothalamic–pituitary lesion or evidence of local trauma, surgery, radiation, skull fracture or internal carotid artery aneurysm[40]. Pituitary adenoma size-adapted cut-offs for prolactin might distinguish true prolactinomas from other pituitary lesions[41].

Oestrogens potently induce hyperprolactinaemia, but the influence of oral contraceptives on prolactinoma development is controversial. In a case–control analysis, there was a mildly increased risk of prolactinoma with menopausal hormone therapy as well as with combined oestrogen–progesterone oral contraceptives, but the risk with oral contraceptives was not present in the prospective cohort analysis[42] (see Supplementary Box 3 for discussion of prolactin excess in pregnancy).

Primary hypothyroidism can present with hyperprolactinaemia, which is reversible with thyroid hormone replacement. Intracranial hypotension can cause hyperprolactinaemia[43]. Stress (for example, due to venipuncture) can induce a twofold to fourfold rise in serum levels of prolactin that lasts for <1 h. Repeated or cannulated prolactin venipuncture sampling for testing is recommended with serum levels of prolactin less than five times ULN or if an influence of stress is suspected[44,45]. Physiological prolactin increases can occur after exercise, high-protein meals and alcohol consumption[46,47]. Patients with polycystic ovary syndrome (PCOS) require further evaluation of elevated serum levels of prolactin, as PCOS per se is rarely associated with hyperprolactinaemia[48].

High prolactin with lymphocytic hypophysitis could reflect either autoimmune cell actions or a stalk effect[49]. Hypophysitis should be considered with apparently idiopathic hyperprolactinaemia[50]. Prolactin co-secretion with GH in acromegaly or with TSH in thyrotrophinoma is due to either plurihormonal adenoma or a stalk effect[51].

Many drugs acting as dopamine antagonists or as serotonin agonists can cause hyperprolactinaemia and galactorrhoea[52–54] (Box 2).

Biochemical evaluation

- In patients with inconsistent symptoms and variable serum levels of prolactin, false-positive or false-negative results should be suspected (strong).
- Standard prolactin assay reference ranges might not be sufficiently validated to recognize mild hyperprolactinaemia (weak).
- Serum samples with prolactin levels above the upper detection limit should be diluted to provide an exact value (strong).
- Macroprolactinaemia should be evaluated in patients with moderately increased serum levels of prolactin (<200 ng/ml), at least in those with discordant clinical or imaging findings (strong).
- With inconsistent symptoms and inconsistent measurement values for prolactin, biotin exposure or heterophilic or human anti-animal antibodies, although rare, should be considered as a cause of erroneous laboratory results (strong).
- In patients with giant adenoma and typical features of hyperprolactinaemia but normal or slightly elevated serum levels of prolactin, samples should be re-measured after 1:100 dilution to exclude a high-dose hook effect (strong).

A correct biochemical diagnosis of hyperprolactinaemia is a prerequisite for further investigation, but can be hampered by potentially overlapping conditions associated with increased measurement values for prolactin[47,55]. Suspicion of an assay artefact should arise in patients whose symptoms and biochemical results are not consistent. Assay errors, macroprolactinaemia and high-dose hook effect are all possible reasons for false-positive or false-negative prolactin measurements (Fig. 2).

Prolactin assays. Prolactin is usually measured by immunoassay, calibrated against the WHO 84/500 international standard containing exclusively 23 kDa monomeric human prolactin. A diagnosis depends on well-established assay-specific and sex-specific reference intervals. However, published upper limits are lower than those presented by most manufacturers[56], normal values are higher in women than in men and different measurement units might be provided (that is, 1 µg/l = 21.2 mIU/l). Stimulation and suppression tests yield non-specific results and have been largely abandoned[2].

Macroprolactinaemia. The major circulating form of prolactin has a molecular weight of 23 kDa, in contrast to 'big' prolactin (40–60 kDa) and 'big-big' prolactin (>150 kDa). In 10–25% of individuals with hyperprolactinaemia, big prolactin and big-big prolactin might be detectable in serum[57]. Anti-prolactin autoantibodies (mostly IgG) bound

to prolactin contribute to big-big prolactin and therefore to macroprolactinaemia. As these variants interfere with prolactin assays but are biologically inactive, most patients with macroprolactinaemia lack typical clinical symptoms of hyperprolactinaemia[58]. Prolactin recovery after polyethylene glycol precipitation can usually distinguish between macroprolactinaemia and true hyperprolactinaemia[59] (see Supplementary Box 3).

Hook effect. In two-site immunoradiometric or chemiluminometric assays, incubation with extremely high concentrations of prolactin saturates both antibodies and prevents sandwich formation, resulting in the so-called hook effect. Thus, patients with very high serum levels of prolactin might show only moderately elevated levels in assay measurements. The hook effect is rarely encountered in current assays, but should be considered when prolactin level is only mildly elevated and clinical suspicion for a macroprolactinoma is high[60].

Imaging

MRI

- MRI should be performed in patients with confirmed hyperprolactinaemia at diagnosis (if no other non-adenomatous causes for hyperprolactinaemia are evident), to demonstrate pituitary adenoma response to medical treatment, and to establish baseline status 3–6 months after surgery (strong). Timing of MRI after medical therapy initiation depends on adenoma size, proximity to the optic chiasm and prolactin response to therapy.
- Follow-up imaging frequency should be based on clinical, biochemical and histological factors, as well as previous imaging results (strong).
- Serial imaging should be performed for treatment-resistant prolactinoma; new onset of symptoms, including visual changes, headaches or galactorrhoea; new-onset pituitary dysfunction; and evidence of a new increase in serum levels of prolactin (strong).

Box 2

Aetiology of hyperprolactinaemia

Physiological
Pregnancy; breast or nipple stimulation; stress; sleep; coitus; exercise.

Pathological

Hypothalamic–pituitary stalk damage
Adenomas; craniopharyngioma; Rathke's cleft cyst; suprasellar pituitary mass extension; meningioma; dysgerminoma; hypothalamic or pituitary metastases; granulomatous disorders; infiltrations; pituitary and/or brain irradiation; intracranial hypotension; trauma (pituitary stalk section, sellar surgery, severe head injury).

Pituitary
Prolactinoma; acromegaly; macroadenoma (compressive); idiopathic; plurihormonal adenoma; lymphocytic hypophysitis; parasellar mass.

Non-pituitary disorders
Ectopic prolactin secretion; primary hypothyroidism; chronic renal failure; cirrhosis; pseudocyesis; epileptic seizures; malnutrition; anorexia nervosa; chest (neurogenic, chest wall trauma, piercings, surgery, herpes zoster).

Genetic
Inactivating mutation in the gene encoding prolactin receptor (*PRLR*).

Pharmacological

Dopamine receptor blockers
Phenothiazines (chlorpromazine, perphenazine); butyrophenones (haloperidol); thioxanthenes; metoclopramide; domperidone; alizapride.

Dopamine synthesis inhibitors
α-Methyldopa.

Catecholamine depleters
Reserpine.

Cholinergic agonists
Physostigmine.

Antihypertensives
Labetalol; reserpine; verapamil.

H_2 antihistamines
Cimetidine; ranitidine.

Oestrogens
Oral contraceptives (controversial, see discussion in text).

Anticonvulsants
Phenytoin.

Neuroleptics
Chlorpromazine; risperidone; promazine; promethazine; trifluoperazine; fluphenazine; butaperazine; perphenazine; thiethylperazine; thioridazine; haloperidol; pimozide; thiothixene; molindone.

Opiates and opiate agonists
Heroin; methadone; apomorphine; morphine.

Antidepressants
Tricyclic antidepressants; selective serotonin reuptake inhibitors.

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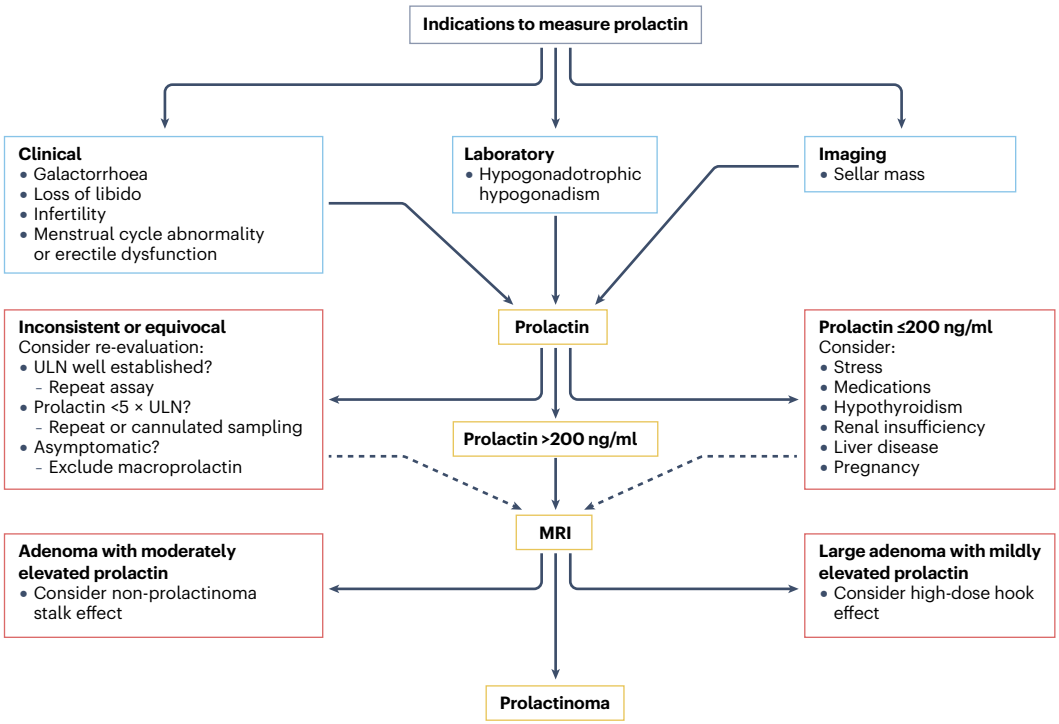

Fig. 2 | Diagnostic algorithm for prolactinoma. Clinical signs and symptoms of hyperprolactinaemia, laboratory findings of hypogonadotrophic hypogonadism or sellar mass on MRI should all trigger evaluation of prolactin. If moderately elevated blood levels are observed (≤200 ng/ml), diagnoses other than prolactinoma should be considered. Equivocal or questionable results inconsistent with clinical findings should prompt further investigation related to diagnostic procedures. If prolactin levels are >200 ng/ml, prolactinoma is more probable than other diagnoses. Imaging results inconsistent with clinical findings should prompt investigation for non-prolactinoma stalk effect, or high-dose hook effect. ULN, upper limit of normal.

- Dynamic gadolinium-based MRI contrast enhancement is important for initial diagnosis of prolactinoma (strong). For follow-up MRIs, gadolinium should be used judiciously; macrocyclic chelates are preferred over linear chelates until further studies clarify possible long-term retention risks (strong).
- Gadolinium should be used with caution in patients with chronic kidney disease (CKD) owing to the risk of nephrogenic systemic fibrosis (strong).
- Patients with pituitary adenoma at high risk of aggressive behaviour require closer surveillance (strong).

MRI is the recommended imaging modality for diagnosing pituitary and parasellar lesions, as well as for follow-up monitoring of treated or untreated pituitary adenomas[2,20]. However, repeat imaging incurs a cost burden and the possible retention of linear gadolinium-based contrast agents has been reported[61,62]; thus, determining the optimal imaging frequency to safely assess treatment response is paramount, but the evidence is sparse. Macroprolactinoma expansion is usually accompanied by biochemical and clinical changes[63,64], and serum levels of prolactin usually correlate with adenoma size, but exceptions occur[63,65]. As microadenomas not treated with dopamine agonists rarely increase in size, MRI (as an adjunct to prolactin monitoring) is typically warranted only with suspected adenoma growth or optic chiasm proximity or to evaluate surgical possibilities[64,66].

Prolactinomas are typically mildly hyperintense on T2-weighted MRI[67]. Men might exhibit a heterogeneous T2 intensity signal that reflects necrosis and haemorrhage and that might be associated with increased serum levels of prolactin and less effective dopamine agonist response compared with a homogeneous adenoma[68,69]. T2 hypointensity in women has been associated with dopamine agonist resistance[70]. Increased T2 hyperintensity occurs with dopamine agonist treatment, although this increase might not be noticeable in haemorrhagic or highly hyperintense adenomas. T2 echo gradient imaging might be useful for diagnosing haemorrhage.

Timing after medical therapy. For macroprolactinomas, MRI should be repeated at 3–6 months after the start of dopamine agonist treatment, as a reduction in size at 3 months after starting cabergoline could predict further long-term response and/or biochemical control[71]. For microprolactinomas, re-scanning depends on clinical and biochemical follow-up, but can be repeated after 1 year, or at least when considering withdrawal of dopamine agonists. As adenoma growth can occur with biochemically resistant prolactinomas treated with dopamine agonists, follow-up imaging should be considered for persistently elevated or rising serum levels of prolactin. If shrinkage is not demonstrated with dopamine agonists and the initial serum level of prolactin is not unequivocally indicative of prolactinoma, a stalk effect due to a non-functioning adenoma should be reconsidered.

For treatment-responsive microprolactinomas and macroprolactinomas, serial imaging beyond 1 year is not necessary unless serum levels of prolactin persistently increase[64,72]. However, partially responsive macroprolactinomas or those close to the optic chiasm

might require periodic annual imaging for the first 3 years and less frequently thereafter[64]. Symptoms suggestive of pituitary apoplexy warrant prompt imaging.

Discordant results showing normalization of prolactin serum levels without substantial mass shrinkage, or notable shrinkage without complete normalization of prolactin serum levels, could be encountered. Although prolactin serum levels often normalize within the first 6 months[73], and substantial mass shrinkage can also occur early, some prolactinomas only slowly decrease in size over several years of dopamine agonist therapy.

When dopamine agonist withdrawal is being considered, an absence of residual adenoma on MRI is a favourable prognostic factor for lack of recurrence[2,74,75]. MRI should be performed after dopamine agonist withdrawal if serum levels of prolactin rise progressively or if headaches, vision changes or pituitary dysfunction develop.

Timing after surgery. MRI should be performed 3–6 months postoperatively to establish a new baseline. Serial imaging might be performed for dopamine agonist-resistant, partially resected adenomas at initial imaging intervals of 6–12 months. Completely resected adenomas should be re-imaged only if serum levels of prolactin rise, or if headaches, vision changes or pituitary dysfunction develop[64]. If surgery is performed as first-line management for microprolactinoma and postoperative normalization of prolactin serum levels is achieved, repeat imaging is required only upon hyperprolactinaemia recurrence.

During pregnancy. Pregnancy is a risk factor for prolactinoma enlargement, especially for macroprolactinomas, and risk is increased in patients without prior surgery[76]. MRI without contrast agent administration should be performed if a pregnant patient with prolactinoma develops headaches of increased severity or different characteristics, or vision changes, typically indicative of adenoma enlargement. As apoplexy during pregnancy has been reported even in those with microprolactinoma[77], imaging is required for concerning symptoms.

Novel imaging strategies

- There is a limited role for novel imaging strategies in routine clinical practice (strong).
- Response to dopamine agonist therapy might be predicted by functional imaging (weak).
- Functional imaging applied with hybrid MRI techniques might improve preoperative prolactinoma localization in selected patients (weak).

In patients undergoing surgery, particularly for a microprolactinoma when the expectation of surgical cure is high[8,78], or in those undergoing stereotactic radiosurgery, accurate adenoma localization could reduce the risk of hypopituitarism. Although dynamic and volumetric MRI sequences are useful in identifying a previously non-visible mass, molecular (functional) imaging could guide targeted intervention[79,80]. Molecular ^{11}C-methionine PET imaging holds promise as an adjunct to MRI for localization of *de novo* and residual prolactinomas when MRI is indeterminate[80,81] (see Supplementary Box 4 for further discussion).

Complications

Hypogonadism

- Women with hyperprolactinaemia, microprolactinoma and normal gonadal function can be followed by observation (weak).
- Unless pregnancy is desired, management of premenopausal women with microprolactinoma should include the option of adequate sex hormone replacement without other interventions (strong).
- Combined oral contraceptives can be used in women with hyperprolactinaemia treated with dopamine agonist therapy, but they might reduce efficacy of dopamine agonist therapy and could contribute to persistence of galactorrhoea (weak).
- Postmenopausal women with microprolactinoma, who usually present with mild to moderate prolactin elevation, might not require intervention and can be observed by annual prolactin evaluation (weak).
- Men with ongoing hypogonadism for more than 6 months while being treated for prolactinoma should be considered for testosterone replacement (weak). Caution is needed for large pituitary adenomas due to the potential for adenoma growth (weak). Indication for testosterone replacement should be re-evaluated at 6-month intervals based on serum levels of prolactin, as the gonadotrophic axis could recover and ongoing testosterone replacement might no longer be needed (weak).
- Patients with persistent hypogonadotrophic hypogonadism despite dopamine agonist therapy and normal serum levels of prolactin who desire fertility require gonadotrophin treatment (strong).
- Replacement of oestrogen and testosterone (probably via aromatization to oestradiol) can reduce dopamine agonist efficacy. It is important to monitor effects of such treatment on serum levels of prolactin (weak).

Most participants agreed that evaluation for restoration of gonadal function should be performed at least 6 months after normalization of prolactin serum levels. Recovery usually occurs in about 60% of men[33] but more frequently in women. The presence of complete hypopituitarism reduces the chances of recovery from hypogonadism and could justify earlier hormone supplementation.

After sex hormone replacement is started, serum levels of prolactin might increase[82]. Use of a short-acting testosterone formulation (for example, testosterone gel) is recommended in patients with a large adenoma, as it leads to rapid reversal of adverse effects of combined dopamine agonists and testosterone (for example, irritability or hypersexuality), should they develop. Off-label aromatase inhibitor therapy might be considered[83], although long-term data are limited and there could be additional adverse effects on bone health[84]. Clomiphene has been used as an off-label treatment in men with hypogonadism[85].

Testosterone should not be started when fertility planning is contemplated. Induction of spermatogenesis by human chorionic gonadotropin and recombinant follicle-stimulating hormone can be considered[86]. However, a semen analysis should be performed prior to initiating gonadotrophin treatment, as nearly 50% of men with hypopituitarism treated with testosterone had adequate spermatogenesis for fertility in one series[87] (see Supplementary Box 5 for further discussion).

Bone disease

- Increased fracture risk is recognized as a clinical consequence of prolactinoma (strong).
- Clinicians should initiate morphometric investigation by plain radiograph in patients with prolactinoma and back pain or decrease in height (strong).

- Patients should be evaluated for changes in bone mineral density by dual-energy X-ray absorptiometry (DXA), depending on age, duration of hyperprolactinaemia and hypogonadism, and other risk factors (strong).

Baseline DXA is recommended in all patients with prolactinoma with suspected long-standing (that is, >6 months) hypogonadism or with other risk factors for osteoporosis, including menopause and previous vertebral fracture. Osteoporosis, particularly if complicated by fractures, should be treated with anti-osteoporotic drugs according to general guidelines[88]. In this context, control of hyperprolactinaemia could potentially have a role as suggested by indirect evidence[89], but specific studies are needed to assess the risk to benefit ratio (see Supplementary Box 5 for further discussion).

Treatment

Dopamine agonists: efficacy

- Dopamine agonist therapy is highly effective at lowering serum levels of prolactin, improving clinical consequences of hyperprolactinaemia and reducing adenoma size (strong).
- Cabergoline is the preferred dopamine agonist owing to its long half-life, high efficacy and good tolerability (strong). Bromocriptine and quinagolide are less commonly used, depending on regional approval and availability.
- Cabergoline is used as primary medical therapy in patients with prolactinoma. For microprolactinomas and well-encased macroprolactinomas (Knosp grade 0 and 1), the curative potential and risks of surgery should be discussed with patients in a multidisciplinary setting prior to medical treatment initiation (strong).
- Patients with prolactinoma of Knosp grade ≥2 should be treated with cabergoline (strong).
- Patients with resistance or intolerability to other dopamine agonist therapy should be switched to cabergoline (strong).
- The need for long-term dopamine agonist treatment and the limited chances of permanent cure should be highlighted in patient discussions (strong).
- In women not desiring fertility, mechanical contraception is advised when starting dopamine agonist therapy as pregnancy can occur prior to menses re-initiation (weak).

Dopamine agonists are an effective treatment for prolactinomas, resulting in normalization of prolactin serum levels, adenoma mass reduction and gonadal function restoration[2] (Fig. 3). Cabergoline, bromocriptine and quinagolide control most symptoms[90], but cabergoline has superior efficacy and is the recommended treatment (see Supplementary Box 6). High dopamine agonist efficacy is maintained in patients with a giant prolactinoma, with improved visual fields reported in 97% of patients, normalized serum levels of prolactin in 60% and reduced adenoma volume in 74%[91–93]. Frequently employed cabergoline doses range from 0.5 to 3.5 mg per week (maximum FDA approved dose is 2 mg weekly), bromocriptine doses range from 2.5 to 15 mg per day and quinagolide doses range from 75 to 300 μg per day.

A study on imaging and prolactin level regression during dopamine agonist treatment[73] revealed that the greatest decreases in adenoma size and serum levels of prolactin occurred within 6 months of therapy initiation. Improvement rates diminished considerably during the subsequent 6 months and even further thereafter. Thus, if a prolactinoma does not exhibit a favourable response in the first 3–6 months of treatment, it probably will not respond adequately to dopamine agonist therapy. Normoprolactinaemia and tumour volume reduction of >25% after 3 months of cabergoline predicts long-term response[94]. After 6 months, lower serum levels of prolactin predict long-term normalization of prolactin serum levels (prolactin levels up to ULN, normalization in 100%; up to three times ULN, normalization in 61%; more than three times ULN, normalization in 39%) and mass shrinkage on MRI correlates with long-term adenoma shrinkage[95], but results can depend on dose escalation protocols. Other predictors of long-term (>15 months) dopamine agonist response include low pretreatment prolactin level and small adenoma at diagnosis, as well as normalization of prolactin serum levels with a low dopamine agonist dose (cabergoline, <2 mg per week)[90].

Dopamine agonists: adverse effects

- Patients should be advised before starting treatment about frequent, mild adverse effects of cabergoline, including gastrointestinal symptoms, dizziness and fatigue (strong).
- Adverse effects usually improve with time, but can be ongoing and disabling in individual patients (strong).
- Quality of life remains impaired in some patients despite effective treatment (strong).
- Administration before bedtime and/or with food might improve tolerability (weak).
- Starting with low doses and escalating slowly might improve tolerability (weak).
- In patients with ongoing intolerance to cabergoline, other D2-specific dopamine agonists, such as quinagolide, could be tried with a chance of improvements in tolerance (weak).
- Dopamine agonist therapy can cause neuropsychiatric adverse effects, such as compulsive buying, gambling, aggression, changes in mood and hypersexuality, particularly in men. Although these effects are rarely encountered, if present, dopamine agonist therapy should be discontinued or the dose adjusted (strong).
- Patients should be informed about the potential for the rare adverse effect of cardiac valve changes with long-term and/or high-dose cabergoline treatment (strong). Intervals for screening echocardiography vary in different countries. Baseline and follow-up screening is suggested in patients considered for long-term or high-dose therapy (weak).
- Cerebrospinal fluid (CSF) rhinorrhoea can rarely occur in patients with an invasive macroprolactinoma that is reduced in size with dopamine agonist therapy. If suspected, β_2-transferrrin or β-trace protein should be measured in nasal fluid; if confirmed, surgical repair is required (strong).
- Dopamine agonist-induced apoplexy due to extensive shrinkage of a macroprolactinoma can lead to visual changes. In such cases, surgical repair is probably warranted (strong).

The most frequent adverse effects of cabergoline are gastric discomfort, nausea and vomiting, as well as mild dizziness[96,97]. Intensity of these symptoms depends on individual tolerability, but they are generally mild and rarely impair drug adherence. They mostly appear at treatment initiation and can typically be reduced or eliminated by starting treatment at a low dose and escalating slowly. If intolerance to oral cabergoline persists, patients can switch to a different dopamine agonist such as quinagolide (a more specific D2R agonist), if available; intolerance can also be an indication for re-evaluation for other treatments, including surgical resection[98].

Mood changes or impulse control disorders can occur with dopamine agonist therapy use in patients with no previous psychiatric disorder[99]. Changes in impulsivity are more common in men but occur in both men and women and are not dose-related. Such changes might lead to gambling, aggressiveness, compulsive spending of money, depression or mania[100]. Hypersexuality is more frequent in men with

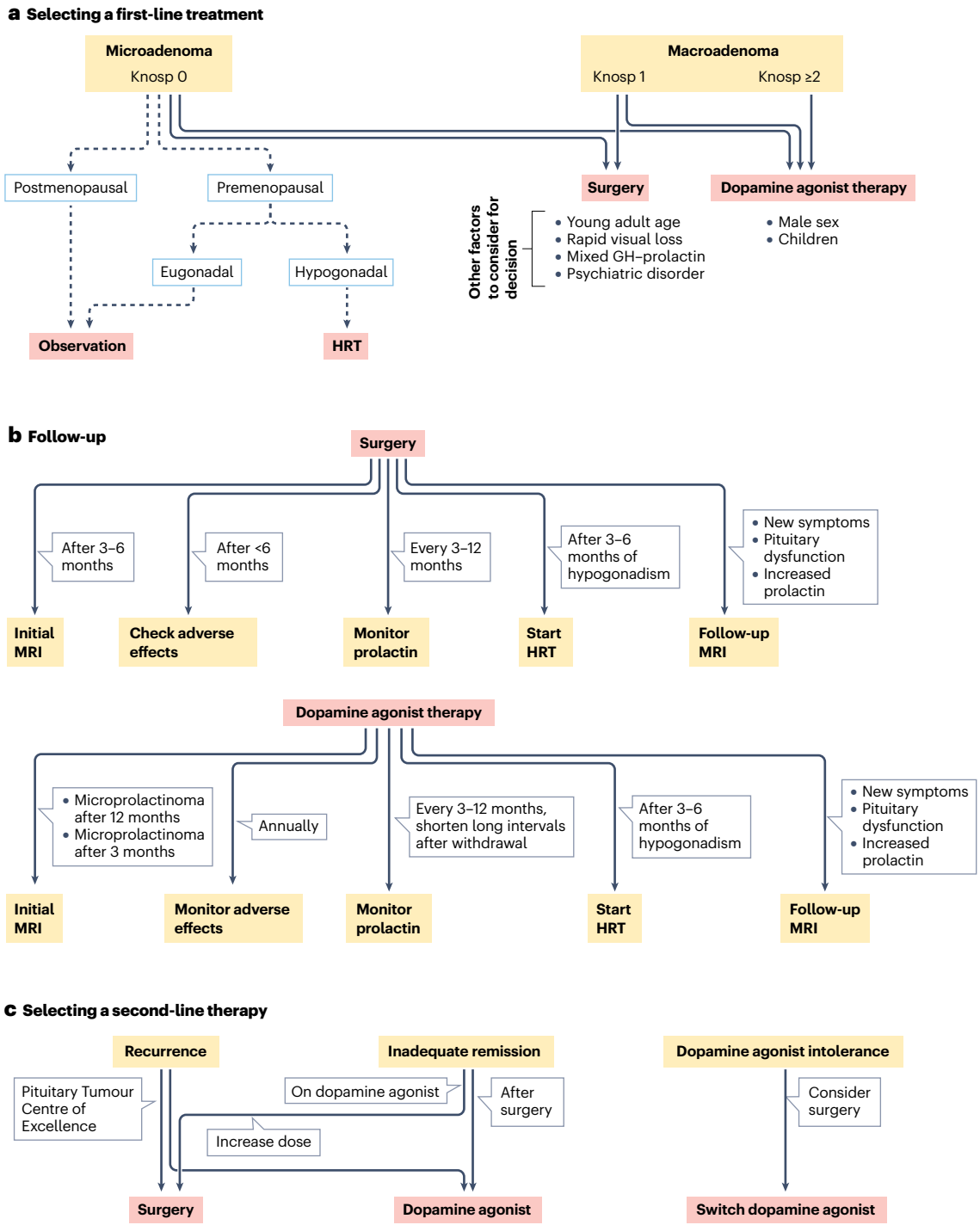

Fig. 3 | Treatment algorithm for prolactinoma. a, Prolactinomas are treated with surgery or dopamine agonists depending on adenoma size, clinical factors and patient preference. In microadenomas, patient preference for observation or HRT can also be considered depending on menopausal and gonadal status (dashed lines). **b**, Follow-up should consider serum levels of prolactin, changes on MRI, need for HRT, complications or adverse effects and potential for dopamine agonist withdrawal. **c**, Recurrence or lack of remission should prompt dopamine agonist dose increase or consideration for surgery; intolerability can be addressed by switching to a different dopamine agonist or consideration for surgery. In all of these cases, management at Pituitary Tumour Centres of Excellence is recommended. GH, growth hormone; HRT, hormone replacement therapy.

prior prolactin-mediated hypogonadism, possibly because of the brisk rebound testosterone surge that occurs with restoration of gonadal function upon starting dopamine agonist therapy[99]. In general, these effects are reversible when the dopamine agonist is discontinued and often ameliorated with dose reduction. Screening for mood changes and impulse control disorders with the Patient Health Questionnaire 9 and Barratt Impulsiveness Scale is useful[101]. It is important to discuss these symptoms with the patient's partner and family members, as the patient might hide behaviours such as impulsive gambling, with potentially ruinous outcomes.

CSF rhinorrhoea due to medication-induced adenoma mass shrinkage should be managed surgically[102]. The diagnosis is made by finding elevated nasal fluid levels of β_2-transferrrin or β-trace protein. Dose reduction and observation could be considered if CSF leakage flow is modest. However, operative repair is eventually required in 90% of patients with a CSF leak[103].

Dopamine agonists: cardiac valvulopathy

- If long-term treatment with high-dose (>2.0 mg per week) cabergoline is anticipated, perform baseline echocardiography to detect any pre-existing valve alterations. Baseline evaluation can be performed before starting cabergoline therapy or during the first few months of treatment (weak).
- Repeat echocardiography every 2–3 years in patients treated with >2.0 mg per week of cabergoline (weak). Most workshop participants believed that annual cardiac examination is unnecessary (weak).
- Perform echocardiography after 5–6 years in patients treated with ≤2.0 mg per week of cabergoline. Some workshop participants believed that these repeat examinations are not necessary in patients treated with <1.0 mg per week and who have no clinical signs of valvular dysfunction (weak).
- Detection of a heart murmur in patients treated with cabergoline should prompt echocardiography (weak).

The discussion of valvular disease screening was based on guidelines jointly developed by the British Society of Echocardiography, the British Heart Valve Society and the Society for Endocrinology[104]. Importantly, these consensus statements diverge somewhat from previously published recommendations (see Supplementary Box 6).

Dopamine agonists: treatment withdrawal

- As approximately one-fifth of patients can remain in remission after discontinuing cabergoline, patients should be evaluated for favourable predictors, and dose reduction or treatment withdrawal should be considered at regular intervals (strong).
- Favourable predictors of successful withdrawal include low maintenance doses of cabergoline, treatment duration >2 years and substantial adenoma size reduction (strong).
- Patients successfully withdrawn from cabergoline should have lifelong evaluations of serum levels of prolactin (annually or more frequently if symptoms recur) and be informed about potential symptoms of recurrence (strong).
- Patients who have recurrence of hyperprolactinaemia after cabergoline withdrawal can usually be successfully treated with dopamine agonist rechallenge (strong).
- Patients with long-term normalized serum levels of prolactin after cabergoline rechallenge could be re-evaluated for another withdrawal trial (weak).
- The chances of permanent resolution of autonomous lactotroph cell growth increase with menopause or after pregnancy; therefore, these patients could undergo a trial of withdrawal (weak).

Owing to potential long-term adverse effects with chronic use of dopamine agonists, and the cost of long-term medical treatment and poor adherence in some patients, withdrawal of therapy can be considered under well-defined conditions in patients with a reasonable chance of persistent remission of hyperprolactinaemia (see Supplementary Box 6).

Careful selection of patients is critical (see Supplementary Table 2). The highest likelihood of persistent remission after withdrawal occurs in patients with a non-invasive and small adenoma with a normal serum level of prolactin and a notable reduction in tumour size after at least 2 years of low-dose cabergoline (0.25–0.50 mg per week)[75,105]. Although only one-third of treated patients are likely to meet these criteria[5], in this subgroup, nearly 55% of those with microprolactinoma and 43% of those with macroprolactinoma will achieve ongoing remission after treatment withdrawal[17]. Thus, under such conditions and in the absence of a visible mass on MRI, patients should be encouraged to withdraw treatment. Alternatively, dopamine agonists could be tapered by serial dose decreases and increasing the dosing interval until the minimal effective dose required to maintain a normal serum level of prolactin level is established[106].

If dopamine agonist therapy withdrawal is attempted, serum levels of prolactin should be measured every 3 months in the first year and annually thereafter. Pituitary MRI can be repeated if hyperprolactinaemia reoccurs. In those who have recurrence of hyperprolactinaemia after withdrawal that requires treatment reinstatement, a second attempt at cabergoline withdrawal can be successful after an additional 2–3 years of therapy. Such an approach might be particularly useful in patients with low serum levels of prolactin while on treatment who have no visible mass on pituitary MRI[107,108].

Studies of dopamine agonist withdrawal in limited series of menopausal women with prolactinomas showed a favourable outcome, with remission rates higher than those observed in premenopausal women[109].

Surgery

- Surgical resection of microprolactinomas and well-circumscribed macroprolactinomas (Knosp grade 0 and 1) by an experienced neurosurgeon offers a high chance of cure, is cost-effective and avoids long-term dopamine agonist treatment. Surgery by an expert pituitary neurosurgeon should therefore be discussed alongside dopamine agonist treatment as a first-line option in this subgroup of patients (strong).
- Medical treatment is the preferred first-line treatment option in patients with a low chance of surgical remission (Knosp grade ≥2) (strong).
- Surgery could be recommended over medical treatment in patients with rapidly progressive vision loss due to a sellar mass effect or apoplexy (weak).
- Surgery could be offered to patients who have intolerance or resistance to long-term dopamine agonist therapy (weak).
- Young age in women could favour a choice of surgical treatment to avoid the need for dopamine agonist therapy over many decades (weak).
- Debulking surgery of a macroprolactinoma is an alternative to dopamine agonist therapy in patients who desire pregnancy, as it

reduces the risk of symptomatic mass enlargement during future pregnancy (weak).
- Surgical repair should be performed in case of spontaneous CSF rhinorrhoea (strong).

Indications for surgery. Transsphenoidal surgery (TSS) performed by an experienced neurosurgeon can achieve initial normoprolactinaemia in up to 93% of individuals with microprolactinomas and 75% of those with selected macroprolactinomas[6,8]. Our review of the literature between 2005 and 2021 showed lower normoprolactinaemia rates of 82% in unselected microprolactinomas and 44%, in unselected macroadenomas (see Supplementary Table 3). However, these remissions might be short-lived, and a recurrence rate of hyperprolactinaemia of ~20% is observed following surgical normalization of prolactin serum levels[110,111], ranging from 10% recurrence in patients with microprolactinoma to 25% in unselected patients with macroprolactinoma (see Supplementary Table 3). Improved remission and low complication rates warrant reappraisal of the role of surgery as a viable alternative to first-line dopamine agonist treatment of prolactinomas in selected patients.

If they are surgically resected, prolactinomas can be further classified according to their cell lineage and based on the WHO classification of pituitary tumours[3], which requires assessment of specific pituitary hormones and transcription factors (they are pituitary-specific positive transcription factor 1 (PIT1) and oestrogen receptor-α for prolactin-expressing adenomas). Pure lactotroph adenomas are subtyped as sparsely or densely granulated. These are distinguished from plurihormonal mammosomatotroph adenomas, mature plurihormonal PIT1-lineage adenomas and mixed somatotroph–lactotroph adenomas, as well as from two precursor entities, acidophil stem cell adenomas and immature PIT1-lineage adenomas, which might co-express other pituitary hormones and/or demonstrate a more aggressive behaviour[76].

In centres with experienced multidisciplinary teams and expert pituitary surgeons, the possibility of surgical remission versus long-term dopamine agonist therapy should be discussed with patients, with mass morphology favouring surgical success (discussed below), while also acknowledging patient preference[112,113]. The classical indication of 'resistance and intolerance to dopamine agonists' for surgical treatment of prolactinomas remains valid and is the prevailing indication for surgery in patients with macroprolactinoma[6] (see Supplementary Box 6).

In a 2021 single-centre study, patient preference was the main indication for TSS for microprolactinoma in 42% of patients, followed by intolerance of dopamine agonists (27%), resistance to dopamine agonists (20%) and combined intolerance and resistance (12%)[6]. In another study, remission rates were 71–93% following microscopic TSS and 81–100% following endoscopic surgery[113]. Perioperative and postoperative complication rates were low; that is, neurosurgical complications were seen in <2% of patients and mortality was 0%[113].

Preoperative serum levels of prolactin correlate negatively with microprolactinoma remission rates[114], such that a remission rate of 92% was seen with a preoperative prolactin serum level of ≤200 ng/ml versus only 40% with preoperative prolactin serum level of >200 ng/ml[8]. Furthermore, remission of fully centrally encased small microprolactinomas was 87% versus 45% for those that were lateral and adjacent to the cavernous sinus wall[115]. Early postoperative serum levels of prolactin in the low–normal range predicts long-term remission with low recurrence rates. New-onset anterior and posterior pituitary hormone deficiencies are rarely encountered with microprolactinomas resected by experienced neurosurgeons[6,112,113].

Not surprisingly, surgical remission rates in patients with macroprolactinoma are inferior to remission rates in those with microprolactinoma[116,117], and decrease considerably with invasiveness, increased adenoma size and notably high preoperative serum levels of prolactin[6,91,112,117–119]. For example, the surgical remission rate in one study was 70.4% among patients with non-invasive macroprolactinoma versus 23.5% among those with invasive macroprolactinomas[6]. In addition, a second study limited to women found a surgical remission rate of 95% among those with enclosed macroprolactinoma and only 25% among those with invasive macroprolactinoma[120]. Remission is less likely in patients with suprasellar extension[112,117] and in those with a prolactin serum level of >282 ng/ml (>346 ng/ml, if Knosp grade <3)[119]; male sex is also a negative predictor of postoperative remission[117].

Staging according to the Knosp classification seems to offer a better discrimination for surgical success than does dividing microprolactinomas from macroprolactinomas only (see Supplementary Table 3). Whereas some studies suggest better outcomes for prolactinomas of Knosp grade 0–1 than for those of Knosp grade 2–4 (refs. 6,121), others suggest higher remission rates for prolactinomas of Knosp grade 0–2 than for those of Knosp grade 3–4 (refs. 122,123).

Invasive macroprolactinomas or giant prolactinomas are usually treated with first-line dopamine agonist therapy[91] and surgery is reserved for spontaneous or dopamine agonist-induced CSF rhinorrhoea[91,102,103]. However, surgery could be preferred in the context of rapid or progressive vision loss with large prolactinomas, or in those with large cystic or haemorrhagic components to ensure immediate decompression of visual pathways[124]. Furthermore, debulking surgery could be considered in patients who are resistant to dopamine agonists to improve the outcome of subsequent medical treatment[111,125].

Women desiring pregnancy might also prefer immediate surgery, as fertility is usually restored following adenoma resection[6,118]. In those with macroprolactinomas, prepregnancy adenoma debulking could avoid symptoms from enlargement during pregnancy. If TSS is performed prior to pregnancy, the risk of symptomatic macroprolactinoma enlargement is reduced from 21% to 4.7%[11].

Preoperative medical therapy. Whether to use preoperative medical therapy remains controversial. A 2021 meta-analysis showed preoperative dopamine agonist use in a median of 59% of patients across 13 studies, with lower remission rates in studies reporting preoperative therapy use above the median than in those below the median (although the difference was statistically insignificant in sensitivity analyses)[117]. These findings potentially support the use of first-line surgery with no preoperative medical therapy in appropriate patients. Adenoma fibrosis was found in most patients undergoing surgery after preoperative bromocriptine treatment for >1 month, but the effect was much less pronounced for cabergoline[126].

Radiation therapy

- Radiation therapy should be reserved for patients who show poor mass shrinkage in response to dopamine agonists and have either non-resectable residual adenoma tissue after surgery or contraindications for surgery (strong).
- Stereotactic radiotherapy techniques yield improved outcomes and have now become standard of care where available (strong).
- Patients should be advised that response to radiotherapy can take several years (strong).

- Patients should be informed about potential adverse effects occurring even many years after treatment and should be followed lifelong to detect hypopituitarism, optic neuropathy, cranial nerve palsy or second brain tumours (strong).

Radiation therapy is the least used management approach for prolactinoma and is mainly offered when medical and surgical treatments have not been successful, usually in patients with size-progressing, aggressive prolactinoma or prolactin-secreting malignancies. Expected outcomes are described in Supplementary Box 6.

Special situations

Cystic prolactinomas

- Cystic prolactinomas might respond to dopamine agonist therapy, which should be considered a viable option, particularly in patients without urgent need of optic chiasm decompression (strong).
- The diagnostic evaluation should exclude pituitary cystic lesions with hyperprolactinaemia caused by stalk compression (strong), which are unlikely to respond to dopamine agonist therapy (weak).
- In the absence of visual deficits, an MRI follow-up interval of 6 months is probably appropriate (weak).

The presence of a cystic component is not uncommon in all pituitary adenomas and should be distinguished from predominantly cystic prolactinomas, in which usually more than 50% of the volume is fluid-filled[127]. This distinction also does not include prolactinomas that undergo cystic degeneration as a result of dopamine agonist therapy[128]. Cystic macroprolactinomas can pose a diagnostic challenge, as serum levels of prolactin in cystic prolactinomas (50–150 ng/ml) are lower than in similarly sized solid prolactinomas. This peculiarity makes it difficult to differentiate between a cystic prolactinoma and a non-functioning cystic lesion causing hyperprolactinaemia by stalk compression. The rate at which prolactin declines after dopamine agonist therapy initiation is not always helpful in differentiating the two scenarios[129]. Dopamine agonist therapy demonstrated high efficacy in cyst reduction[130] and should therefore be considered, particularly in patients with no urgent need of chiasmatic decompression[124]. However, it is important to also consider other pituitary cystic lesions with hyperprolactinaemia that would not shrink with dopamine agonist therapy.

Prolactinomas in men

- Men with hypogonadotrophic hypogonadism presenting with gynaecomastia, loss of libido, erectile dysfunction and infertility or with galactorrhoea should be evaluated for hyperprolactinaemia and a prolactin-secreting adenoma (strong).
- Macroprolactinomas in men are more aggressive and show lower response rates to dopamine agonist therapy than in women (strong). Multimodal treatment with dopamine agonist therapy, surgery and/or radiation therapy is frequently required for management, with a need for close follow-up (strong).
- Dopamine agonist adverse effects of impulse control disorders are more frequently observed in men than in women and an informative discussion with patients and their partners and families is needed before initiating treatment (strong).

Prolactinomas in men can be large and invasive, sometimes giant, and present with hypogonadism and mass effects, including vision damage and hypopituitarism[131]. Serum levels of prolactin are typically high, and are associated with low testosterone and osteoporosis if left untreated[132,133]. Diagnosis of hyperprolactinaemia is often delayed in older men, as decreased libido and erectile dysfunction develop gradually, are not specific, and might be attributed to ageing or are under-reported[134]. Prolactinomas are generally more aggressive in men than in women, with higher proliferation (assessed by Ki-67), cellular atypia, angiogenic and proliferative features, and greater invasiveness[135–138].

Treatment with dopamine agonists is preferred regardless of size or invasion. Among men with macroprolactinoma, 80–85% will demonstrate normalization of prolactin serum levels and 90% substantial mass shrinkage[33]. After dopamine agonist therapy, improvement in visual fields occurs in 85–95% of men with macroprolactinoma and vision damage.

Mixed GH–prolactin pituitary adenomas

- Hyperprolactinaemia in patients with pituitary adenoma that occurs in combination with excess GH secretion warrants a different therapeutic approach (strong).
- In patients with acromegaly and hyperprolactinaemia, stalk effect should be distinguished from adenoma co-production, considering adenoma size and follow-up (strong).
- Pure somatotroph adenomas should be distinguished histologically from mammosomatotroph adenomas (combined secretion of prolactin and GH from the same single cell) and somatotroph–lactotroph adenomas (presence of both cell types) (strong). A correct diagnosis is important, as prognosis differs between these types (weak).
- Aggressive prolactinomas should be evaluated for markers of acidophil stem cell adenomas and co-secretion of GH (weak).
- Patients with hyperprolactinaemia should be evaluated at baseline for autonomous GH secretion by screening serum levels of insulin-like growth factor 1 (IGF1), as clinical features of acromegaly could be masked or occur over time. Demonstration of autonomous GH secretion will alter treatment strategy, which should follow current guidelines on acromegaly (strong).
- If IGF1 levels increase above ULN during follow-up and there are no vision changes due to adenoma mass, dopamine agonist therapy should be stopped for 4 weeks to assess for GH hypersecretion (strong).

As mammosomatotroph progenitors differentiate into lactotrophs and somatotrophs, mixed cell-type adenomas comprising GH-secreting and prolactin-secreting cells might be seen[51,139] (see Supplementary Box 7).

Giant prolactinomas

- Giant prolactinomas are rare and are predominantly observed in men; as they usually respond well to dopamine agonist therapy, they should be managed medically (strong).
- Due to increased risk of morbidity and mortality, surgical resection of these large prolactinomas should be restricted to those with apoplexy or CSF leakage or to patients with progressive mass growth despite optimal treatment (strong).

Giant prolactinomas are defined as those with a diameter >40 mm with notable extrasellar extension, very high serum levels of prolactin (usually >1,000 μg/l) and no concomitant GH or ACTH secretion[92]. They have a male-to-female ratio of approximately 9:1. The diagnosis

is usually delayed until neurological complications arise from massive extension into surrounding structures, leading to cranial nerve palsies, hydrocephalus, temporal epilepsy or exophthalmos. Despite their aggressive appearance, these adenomas are mostly benign and respond well to cabergoline[18,91–93]. Neurological symptoms improve in most patients with a notable mass size reduction, and prolactin serum levels normalize in up to 70% of patients[92]. These lesions are usually not completely resectable.

Aggressive prolactinomas and therapy resistance

- Aggressive prolactinomas are defined as invasive adenomas with an unusually rapid growth rate or adenomas with clinically relevant growth despite maximal tolerated dopamine agonist doses (strong).
- Increasing serum levels of prolactin in an individual with prolactinoma previously well controlled by cabergoline could indicate development of an aggressive adenoma and, very rarely, a carcinoma (weak).
- Rarely encountered patients with prolactinoma and site-specific symptoms (including neurological deficits or back pain), as well as patients with obvious discordance between serum levels of prolactin and pituitary mass, should be evaluated for metastases, which would define a carcinoma (strong).
- Imaging signs of invasiveness coupled with histological markers of proliferation likely predict prolactinoma behaviour (strong).
- In patients with aggressive prolactinomas and documented persistent adenoma growth despite exhausting all treatment modalities, the chemotherapeutic agent temozolomide is recommended (strong).
- Response to temozolomide should be evaluated after 3 months and treatment continued for at least 6 months in responsive patients (strong) or for as long as responses are observed (weak).
- The use of immune-checkpoint inhibitors could be a viable option for aggressive prolactinomas after temozolomide failure (weak).

Definitions. Most patients with prolactinoma respond well to dopamine agonists, showing both normalization of prolactin serum levels and mass shrinkage. However, variable degrees of therapy resistance are encountered, which could indicate specific underlying pathophysiology. The consensus was to define 'resistance' as lack of normalization of prolactin serum levels or lack of relevant mass shrinkage (≥30% reduction in maximum diameter) when treated with standard dopamine agonist doses (7.5–10 mg per day of bromocriptine or 2.0 mg per week of cabergoline) for at least 6 months. Importantly, not all patients with resistance require a change in treatment; dopamine agonist continuation is a good option, for example, in patients without mass effects, in whom tumour shrinkage is not required due to location, or in patients with macroprolactinomas, in whom the adenoma is controlled, but hypogonadism persists due to persistent hyperprolactinaemia and is managed by sex hormone replacement.

If prolactin is not controlled even by dose escalation to maximally tolerated doses of dopamine agonists and surgery is considered for debulking, the term suggested is 'refractory' prolactinoma. Furthermore, refractoriness should be distinguished from 'aggressiveness', which should be reserved for patients with ongoing adenoma proliferation despite treatment with maximally tolerated doses of dopamine agonists.

Distant metastases can occur, which define the prolactinomas as carcinomas[140]. Although extremely rare overall, carcinomas of lactotroph origin represent 30% of all pituitary carcinomas and are the most common type[76,141].

Prognosis. Most studies of prognostic markers focus on predictive markers of dopamine agonist resistance and do not specifically focus on aggressiveness or malignancy. Male sex, young age and invasiveness are associated with increased risk of dopamine agonist resistance. A combined clinicopathological classification that takes into account invasion (based on MRI, surgical and histological findings) and proliferation (Ki-67 index ≥3%, mitotic count more than two out of ten high-power fields and positive p53 staining) could predict potential aggressive behaviour of pituitary adenomas[141].

Treatment. Escalation to maximally tolerated cabergoline dose is the first step for large residual or growing adenomas that do not respond to lower doses; surgical debulking could improve postoperative medical control, and adjuvant radiotherapy could also be considered[142]. When these therapies fail, the alkylating chemotherapeutic agent temozolomide is currently the best option[143], with approximately 40% of treated pituitary adenomas showing at least partial remission[13,144]. Longer duration (>6 months) of temozolomide treatment, its early use and its combination with radiation therapy might improve outcomes[141,144–147]. In prolactin-secreting carcinomas, immunotherapy with the checkpoint inhibitors ipilimumab and nivolumab induced responses, including mass shrinkage, suggesting that these drugs could be an option if temozolomide fails in aggressive prolactinoma[148–150]. Other options that have been studied in patients with aggressive prolactinomas include targeted oncological agents, such as everolimus, bevacizumab and lapatinib[151,152], as well as the oestrogen receptor modulator tamoxifen[153] and peptide receptor radionuclide treatment[154].

Management is discussed in detail in the current European Society of Endocrinology clinical practice guidelines[143]. Patients should be followed in multidisciplinary Pituitary Tumours Centres of Excellence[155].

Pregnancy and fertility

- Patients with prolactinoma considering pregnancy should be informed about both medical and surgical options (strong).
- A comprehensive examination performed shortly before pregnancy provides baseline information on serum levels of prolactin, visual fields and adenoma size (weak).
- Patients desiring fertility and undergoing pituitary surgery before pregnancy should be informed of the potential risk of hypopituitarism and its impact on fertility (strong).
- Mechanical contraception should be used instead of hormonal forms of contraception to confirm treatment efficacy before pregnancy and establish the menstrual interval (weak).
- To reduce exposure of the developing fetus to dopamine agonist therapy, dopamine agonists should be discontinued as soon as pregnancy is confirmed (strong).
- In patients with large macroprolactinomas, maintenance of dopamine agonist therapy during pregnancy is also an option (strong).
- Although bromocriptine might reduce fetal exposure due to its shorter half-life, cabergoline is now preferred by the majority of centres owing to increasing safety data (weak).
- In patients with macroprolactinoma, adenoma response to dopamine agonist therapy should be confirmed prior to conception (strong). In those without mass response, surgery should be considered prior to conception (strong).

- Pregnancy in patients with microprolactinomas is usually uneventful, and patients should be followed clinically every 3 months (strong).
- Patients with macroprolactinoma have a risk of clinically relevant adenoma expansion and apoplexy during pregnancy. Patients should be seen monthly during pregnancy and questioned about local mass effects, and should undergo visual field evaluation every 3 months (strong).
- Patients with suspicion of clinically relevant adenoma growth during pregnancy should undergo MRI without gadolinium (strong).
- Re-initiation of dopamine agonist therapy that was discontinued at conception should be considered in patients with clinically relevant adenoma growth (strong).
- In patients with an enlarged adenoma that does not respond to re-initiation of dopamine agonist therapy, consideration should be given to pituitary surgery or delivery if the pregnancy is sufficiently advanced (strong).
- Serum levels of prolactin should not be used to assess for adenoma growth during pregnancy (strong).

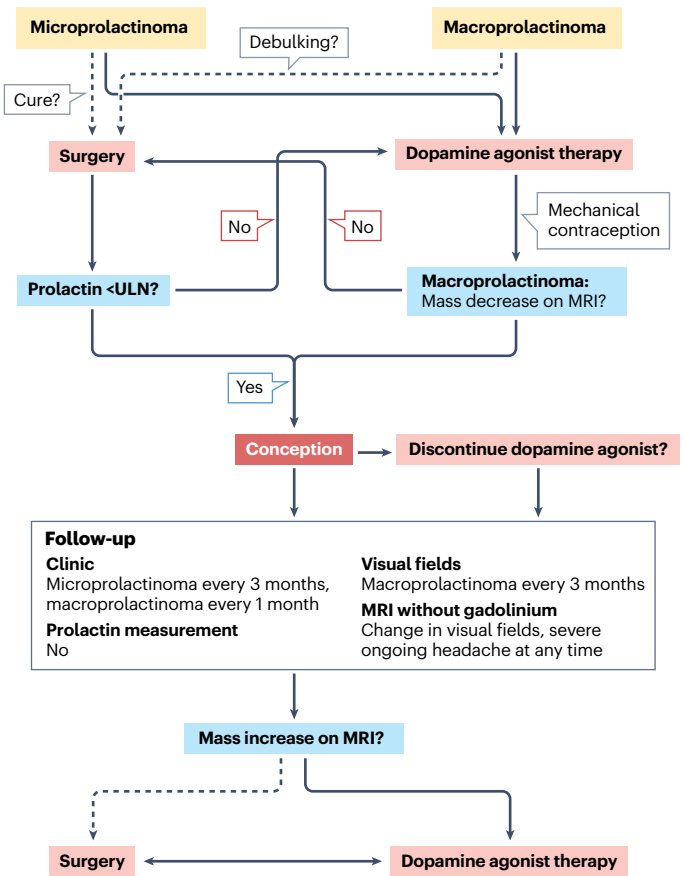

Fig. 4 | Prolactinoma management considerations for pregnancy and fertility. In patients desiring pregnancy, surgery by an experienced surgeon might be considered if cure is likely (dashed line). In patients treated with dopamine agonists, mechanical contraception should be used until mass shrinkage is observed on MRI. During pregnancy, patients should be closely followed for signs of mass increase; MRI should be used without gadolinium contrast. Serum levels of prolactin should not be tested. If the mass increases in size, restart dopamine agonists if previously discontinued and/or consider surgery in second trimester if absolutely necessary. ULN, upper limit of normal.

- Breastfeeding is usually not contraindicated and could be allowed for a period depending on whether treatment reintroduction is needed for mass control (strong).

Most workshop participants recommended medical treatment with dopamine agonists as the first choice of therapy for women with prolactinoma desiring pregnancy (Fig. 4; see Supplementary Box 7). However, surgery for non-invasive microprolactinomas by an experienced pituitary surgeon was also considered reasonable. Risk of postoperative hypopituitarism in microprolactinomas is very low if surgery is performed by an experienced pituitary surgeon[6,113]. By contrast, in patients with macroprolactinoma, most recommend surgery only if the adenoma is not responsive to dopamine agonists and/or if it is close to optic structures. In such cases, management by a multidisciplinary team comprising expert neurosurgeons, obstetricians, ophthalmologists and endocrinologists is recommended[156]. Patients who had prior surgery have very little risk of adenoma growth during pregnancy[11].

Rather than routinely switching all women desiring pregnancy from cabergoline to bromocriptine, the majority of workshop participants favoured using cabergoline at the lowest effective dose. This strategy is particularly relevant for patients already well controlled on cabergoline, as there were concerns that switching to bromocriptine could result in loss of control of serum levels of prolactin and could negatively affect fertility. In addition, the potential for increased adverse effects after switching to bromocriptine could affect adherence and the need for dose adjustments and thereby also adversely affect fertility. In one retrospective study, continued use of cabergoline during pregnancy was associated with a higher miscarriage rate than in pregnancies in which cabergoline was discontinued, with little additional data available[157].

There was a strong consensus against recommending measurements of prolactin during pregnancy. Rather, evaluation of clinically relevant pituitary mass expansion during pregnancy should be based on symptoms, and imaging should be performed if symptoms or signs of adenoma expansion occur[10].

Prolactinomas in children and adolescents

- In addition to the clinical signs and symptoms present in adults (that is, secondary amenorrhoea and galactorrhoea), delayed puberty due to hypogonadotrophic hypogonadism should trigger evaluation for hyperprolactinaemia in children (strong).
- As apoplexy and aggressive prolactinoma behaviour are more common in children than in adults, high clinical suspicion warrants prompt investigation (strong).
- Children with macroprolactinoma should undergo genetic testing for *MEN1* and *AIP* germline mutations (strong).
- Dopamine agonist therapy is initiated at low doses (for example, 0.25 mg per week of cabergoline) (weak), with slow dose increases due to increased probability of adverse effects in children (strong).
- Surgery should be considered in patients in whom vision is threatened, if severe neurological symptoms or CSF leakage is present, or if the mass is resistant to dopamine agonist therapy (strong).
- Surgery could be considered in children with microprolactinoma to avoid long-term medical treatment (weak).
- Radiation therapy should be limited to patients with an aggressive adenoma that is unresponsive to dopamine agonist therapy and surgery (weak).

Prolactinoma in a paediatric patient should raise suspicion for the presence of germline *MEN1* and *AIP* mutations[158]. Pituitary adenomas with these mutations could have a more aggressive behaviour than those without[159] (see Supplementary Box 7).

Dopamine agonists are first-line therapy, starting at a low dose and individualizing dose adjustments due to the potentially increased susceptibility to adverse effects in children[160,161]. Surgery should be considered in children with threatened vision[162].

Pituitary haemorrhage resulting in apoplexy could be more common within prolactinomas in children than in adults. The level of suspicion for potential apoplexy in children with prolactinoma and new headache, visual loss or other sudden symptoms should be high[163,164]. In microprolactinomas, paediatric surgical series have shown remission rates around 80%[165].

Patients with an underlying psychiatric disorder

- Management of prolactinoma in patients with an underlying psychiatric disorder requires collaboration between the endocrinologist, neurosurgeon and psychiatrist (strong).
- Initiation of dopamine agonist treatment in patients with an underlying psychiatric illness is probably safe but requires caution and psychiatric consultation (weak).
- Prolactin should be measured prior to initiation of an antipsychotic drug (strong).
- Serum levels of prolactin more than ten times ULN are uncommon in antipsychotic-mediated hyperprolactinaemia and should trigger suspicion for a prolactinoma (strong).
- Dose reduction or switching to a second-generation antipsychotic that does not cause hyperprolactinaemia, such as aripiprazole, distinguishes prolactinoma from drug-induced hyperprolactinaemia in most patients (strong). MRI might exclude a large lesion with stalk effect (weak).
- Dopamine agonist therapy efficacy might be reduced in patients treated with antipsychotics, requiring higher doses (weak).
- Prolactin-sparing antipsychotics alone or in combination with established antipsychotic therapy could enable dopamine agonist dose reduction (weak).
- Alternative treatment modalities for prolactinomas, including sex hormone replacement in patients with microprolactinoma or surgery, might be considered in patients requiring treatment with antipsychotics (weak).

Management of prolactinoma in patients with a psychiatric disorder is challenging and requires collaboration between the endocrinologist, neurosurgeon and psychiatrist[166]. Hyperprolactinaemia resulting from antagonism of D2R occurs in 30–75% of individuals receiving antipsychotics[167] within the first 3 months of treatment, and elevations up to ten times ULN have been described[168].

Prolactin measurements prior to initiation of an antipsychotic drug could avoid unnecessary investigation and concern for an underlying prolactinoma. MRI should be performed in patients on antipsychotic drugs with serum levels of prolactin more than ten times ULN, mass effect symptoms such as headache or visual disturbance, or pituitary hormone deficiencies other than the gonadal axis. Antipsychotic dose reduction or switching to a prolactin-sparing antipsychotic with subsequent reduction in serum levels of prolactin is useful[168]. When antipsychotics are withdrawn, drug-induced hyperprolactinaemia resolves within 48–96 h.

Dopamine agonist therapy could contribute to exacerbation of underlying psychiatric illness, although this effect seems to be uncommon and is subject to publication bias[169]. Dopamine agonist treatment is effective to treat prolactinoma in patients receiving antipsychotics, with higher dopamine agonist doses than normally used required to achieve biochemical control and reduce adenoma size, although improvement in visual fields occurs in most patients prescribed first-line dopamine agonist therapy[170] (see Supplementary Box 7). Switching to a prolactin-sparing antipsychotic such as aripiprazole could enable lower doses of dopamine agonist therapy, or even cessation, although this finding is not consistently evident[170]. The addition of aripiprazole to an established antipsychotic therapy is utilized for antipsychotic-mediated hyperprolactinaemia[171]. Pituitary surgery should be considered in patients with prolactinoma and psychiatric illness if there is concern for dopamine agonist intolerance or poor effectiveness.

Prolactinomas and menopause

- Women with well-controlled microprolactinoma entering menopause should undergo a trial of dopamine agonist withdrawal (strong).
- In postmenopausal women with macroprolactinoma, treatment should be targeted to controlling adenoma growth (strong).
- Normalization of serum levels of prolactin in postmenopausal women with microprolactinoma is not indicated to improve metabolic parameters, decrease breast cancer risk or improve bone density (weak).

Menopause is associated with a physiological decrease in circulating levels of prolactin[172]. Normalization of serum prolactin levels occurs in 45% of untreated women with microprolactinoma entering menopause[173]. Furthermore, serum levels of prolactin remained normal in 52–71% of postmenopausal women with prolactinoma (mostly microadenoma) after withdrawal of dopamine agonist treatment, irrespective of serum levels of prolactin prior to treatment discontinuation[174,175]. The prevalence of newly diagnosed postmenopausal prolactinomas cannot be accurately determined as microprolactinomas or small macroprolactinomas not causing mass effects might remain unrecognized in the absence of endocrine manifestations. Among 37 women in three reports diagnosed with prolactinoma after menopause[176–178], the majority had macroprolactinoma (73%) or giant prolactinoma (18.9%) and many were discovered incidentally following head imaging[109]. Normalization of serum prolactin levels and mass shrinkage were achieved with dopamine agonist therapy in most patients.

Current evidence does not support microprolactinoma treatment in asymptomatic postmenopausal women. Macroprolactinomas should be treated according to standard practice. Breast cancer risk was not increased in postmenopausal women with prolactinoma[179,180].

Transgender individuals

- In transgender women, combined treatment with oestradiol and cyproterone acetate usually causes mild and asymptomatic hyperprolactinaemia (strong).
- A diagnosis of prolactinoma should be considered when prolactin increases markedly or with symptoms of mass effect or galactorrhoea (weak).
- There is no evidence for increased incidence of prolactinomas in transgender women receiving gender-affirming hormone therapy (weak).

Hyperprolactinaemia related to feminizing hormone treatment occurs in up to 20% of transwomen and is usually mild and

asymptomatic[181]. Serum levels of prolactin up to two times ULN were observed following initiation of oestradiol combined with cyproterone acetate, but levels remained within the normal range in most patients[182]. Marked or symptomatic prolactin elevations resulting in galactorrhoea should prompt further investigations[183,184].

Prolactinomas have been reported in transgender women receiving feminizing hormone treatment[182,184] (see Supplementary Box 7). However, there is no definitive link between gender-affirming hormone treatment and prolactinoma.

Hyperprolactinaemia and renal failure

- Assessment for hyperprolactinaemia in patients with CKD should be individualized depending on symptoms and presence of hypogonadism (weak).
- Treatment of hypogonadism and underlying hyperprolactinaemia by dopamine agonist therapy or sex hormone replacement might be considered in patients with CKD, depending on clinical symptoms (weak).

Serum levels of prolactin are elevated in patients with CKD. In one study, 23% of patients with CKD and serum levels of creatinine <6.8 mg/dl had hyperprolactinaemia; the proportion increased to 77% of those with creatinine levels >6.8 mg/dl and 78% of those on haemodialysis[185]. Elevated prolactin was reported in patients with serum levels of creatinine as low as 2.0 mg/dl[186]. Most of the prolactin in these patients is monomeric and not due to accumulated macroprolactin[187]. Hyperprolactinaemia is caused by delayed circulating prolactin clearance as well as increased prolactin production[188]. Hyperprolactinaemia is not influenced by intensification of dialysis[189], but is reversed by renal transplantation.

Bromocriptine effectively lowers serum levels of prolactin, increases levels of testosterone and restores sexual potency in men with CKD and hyperprolactinaemia[190]. Interestingly, treatment of patients with CKD on haemodialysis with recombinant erythropoietin could result in normalization of serum prolactin levels[191].

Conclusions

In most patients, dopamine agonists are highly effective at normalizing serum levels of prolactin and shrinking prolactinomas. Cabergoline resistance rarely occurs. Nevertheless, due to adverse effects of long-term dopamine agonist therapy, an exploration of alternative strategies to medical therapy is warranted, such as surgery. There is also an unmet need for additional treatments to address clinical challenges in treating patients with refractory prolactinoma.

A need exists to facilitate international registries of patients to enable risk stratification and optimization of therapeutic strategies. Standardizing the treatment response could enable comparison of results across series, which is critically important for a rare disease such as prolactinoma.

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