Hyperprolactinemia: Effect on Reproduction, Diagnosis, and Management

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Kathleen O'Leary

16.1 Prolactin Physiology

Hyperprolactinemia has many etiologies and is one of the most common causes of amenorrhea, accounting for up to 15–30% of cases. Prolactin (PRL) is encoded by a single gene on chromosome 6 and is a 199-amino acid polypeptide hormone, 23.4 kDa in size, synthesized and secreted mainly by lactotroph cells of the anterior pituitary gland. It comprises five coding exons with 40% homology to growth hormone gene and is also similar to placental lactogen [1]. The prolactin receptors are included as members of the cytokine receptor superfamily, distributed throughout the immune system [2]. Several biologic forms of PRL exist due to various post-translation modifications, including cleavage, phosphorylation, polymerization, glycosylation, and degradation [3]. These include the "little" monomeric form (the most active and non-glycosylated, 85–95%), the low-activity dimeric "big" form (50–60 kDa, 5–15%), and the inactive tetrameric "big-big" form (macroprolactin, 150–170 kDa, <1%) [3–5]. Differences in splicing and protein modification of the PRL hormone create the structural diversity of PRL molecules, and it is assumed that the bigger forms of PRL have diminished bioactivity due to decreasing receptor-binding affinity caused by glycosylation [1]. PRL is expressed in sources other than the pituitary, such as the T lymphocytes, brain, skin fibroblasts, adipose tissue, breast, endometrial decidua, prostate, and even neoplastic cells. Decidual PRL has been proposed to affect the functional changes of the endometrium from the time of implantation to delivery by silencing genes that are detrimental to pregnancy [1, 3]. The majority of circulating PRL is of pituitary origin.

The main role of PRL is stimulation of lactation in the postpartum period, but PRL has many other diverse physiologic functions that include immunomodulation, angiogenesis, growth, synergism with steroid hormones, integumentary functions, and osmoregulation [6]. The secretion of PRL is episodic with an increase of secretion observed 60–90 minutes after sleep begins, increasing during REM sleep with highest concentrations noted between 2:00 and 5:00 a.m. [5]. Normal PRL is regulated by many stimulatory and inhibitory factors. Dopamine (prolactin-inhibiting factor) binding to the D2 receptors of pituitary lactotroph cell membranes is the main inhibitory factor of PRL and is secreted into the portal circulation by the arcuate and paraventricular nuclei of the hypothalamus. Other neuropeptides and hormones act as prolactin-releasing factors, such as thyrotropin-releasing hormone (TRH), estradiol, oxytocin, epidermal growth factor, vasopressin, GnRH, angiotensin II, vasoactive intestinal polypeptide, and dopamine antagonists [3, 7–9]. The amount of prolactin in the serum is also affected by kidney clearance. The factors influencing PRL secretion are listed in Table 16.1.

PRL promotes milk biosynthesis and maintains lactation in the postpartum period. The increased estrogen production during pregnancy causes lactotroph cells to proliferate, increasing PRL secretion starting around 8 weeks' gestation. During pregnancy, prolactin levels rise from the normal level of 10–25 ng/mL to a peak of 200–400 ng/mL at term, a tenfold increase in PRL [8, 10]. The increased PRL with other hormones, such as estradiol, progesterone, placental lactogen, insulin, and cortisol, causes mammary gland growth. While estrogen enhances breast development, it blunts the effects of PRL on lactation during pregnancy. Progesterone also inhibits full lactation during pregnancy [8]. The fall of serum estrogens and progesterone to non-pregnant levels after delivery results in the initiation of lactation [8]. One week postpartum, serum prolactin declines 50% (to about 100 ng/mL) in postpartum breastfeeding women. During breastfeeding, nipple stimulation by the suckling infant causes a short-term twofold rise in PRL production, based on a neuro-humoral mechanism, which is important for milk production [7, 8]. Prolactin levels normalize within 6 months after delivery in breastfeeding mothers and return to normal within a few weeks in non-nursing women.

K. O'Leary (✉)
Institute for Reproductive Health, Cincinnati, OH, USA

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Table 16.1 Factors affecting prolactin secretion

Category	Increase	Decrease
Physiologic	Pregnancy Luteal phase Nipple stimulation Nursing Exercise Sleep Eating High-protein diet Hypoglycemia Seizures Stress Surgery Sex Neonatal	
Endocrine/ autocrine/ paracrine factors	*Prolactin-releasing factors (PRFs):* Estradiol TRH Oxytocin Epidermal growth factor Growth hormone-releasing hormone GnRH Vasoactive intestinal polypeptide Angiotensin II Histidine Serotonin Prolactin-releasing peptide	*Prolactin-inhibiting factors (PIFs)* Dopamine GABA GnRH-associated protein (GAP)
Pharmacologic	Antipsychotics/ neuroleptics Risperidone Phenothiazines Haloperidol Antidepressants Tricyclic antidepressants Monoamine oxidase inhibitors Serotonin reuptake inhibitors Benzodiazepines Amphetamines Opiates/opioid peptides Morphine Heroin Cocaine Dopaminergic blockers Metoclopramide Domperidone Cisapride Antihistamines H2 blockers Intravenous cimetidine Antihypertensives Verapamil Methyldopa Reserpine Licorice	Dopamine agonists Bromocriptine Cabergoline Levodopa Pergolide Apomorphine

Table 16.1 (continued)

Category	Increase	Decrease
Pathologic Pituitary	Prolactinomas Other secretory or non-secretory tumors Acromegaly Lymphocytic hypophysitis Trauma Surgery Radiation Empty sella syndrome Histiocytosis X Cushing's disease	
Hypothalamic	Craniopharyngioma Meningioma Germinoma Sarcoidosis Eosinophilic granuloma Pituitary stalk section Rathke's cleft cyst Metastasis Infiltration Trauma Encephalitis	
Systemic conditions	Chronic renal disease Primary hypothyroidism Polycystic ovary syndrome Cirrhosis Renal cell carcinoma Polycystic kidney disease Bronchogenic carcinoma Addison's disease Epilepsy Chronic uremia Ectopic production	
Neurogenic	Herpes zoster Chest trauma or burns (intercostal nerves stimulation) Post-thoracic surgery Cervical spine lesions Malignant ovarian teratoma	
Idiopathic	Macroprolactinemia Pseudocyesis	

16.2 Effect of Hyperprolactinemia on the Reproductive System

Although PRL does not appear to play a direct physiologic role in the regulation of gonadal function, hyperprolactinemia can cause hypogonadotropic hypogonadism in men and women. The exact mechanism of disruption of gonadal function is not fully defined, but there appears to be altera-

tion of the hypothalamic-pituitary-gonadal axis. In women, pulsatile secretion of FSH and LH is decreased through suppression of GnRH, and the midcycle LH surge is suppressed. The decrease in the amplitude and frequency of the LH pulses and the decrease in FSH concentration affect Graafian follicle development, leading to anovulatory cycles. The suppression of LH secretion also affects the luteal phase by disrupting steroidogenesis in granulosa cells [5]. In addition, hyperprolactinemia has direct effects on the ovary by stimulating expression of type II 3B-hydroxysteroid dehydrogenase, which is the final step in progesterone biosynthesis and increases IGF-II secretion [11]. Hyperprolactinemia indirectly causes an imbalance of lipid metabolism, an increase in ACTH and adrenal androgens, disruptions of insulin secretion, and a decrease in sex hormone-binding globulin [5]. This elevation of androgens affects the developmental competence of the oocyte [5].

Depending on the serum level of prolactin, first there is a shortening of the luteal phase (20–50 ng/mL). This is due to the poor pre-ovulatory follicular development and decreased progesterone secretion and premature regression of the corpus luteum; thus high PRL is considered luteolytic [5, 8, 12]. Anovulation, oligomenorrhea or amenorrhea, and infertility can occur with moderate levels of hyperprolactinemia (50–100 ng/mL). Serum prolactin levels over 100 ng/mL can cause frank hypogonadism by significantly affecting ovarian follicles and causing low estrogen levels and resultant clinical symptoms of vasomotor symptoms, vaginal atrophy, dyspareunia, lowered libido, disturbances of the arousal phase and orgasm, and osteopenia [5]. Other symptoms include hirsutism and acne. Delayed puberty and primary amenorrhea and even growth arrest can occur if hyperprolactinemia occurs before menarche [3]. Only about one-third of women with hyperprolactinemia exhibit galactorrhea. This may be because breast milk production requires estrogen, and hyperprolactinemia often results in anovulation or more severe hypogonadotropic hypogonadism with low serum estrogen levels.

While hyperprolactinemia mostly affects younger women of reproductive age and its incidence decreases with age, menopausal women may have symptoms of hyperprolactinemia, including obesity, lipid abnormalities, or insulin resistance [5]. Bone fractures are more common in women with hyperprolactinemia in menopause due the effects on bone mineralization and osteoblast proliferation [5].

In men, most recent data suggest that PRL stimulates testicular functions [6]. PRL increase LH receptors, cellular morphology, steroidogenesis, and androgen function in Leydig cells [6]. PRL increases lipids and spermatocyte-spermatid changes in germ cells [6]. PRL also has a role in sexual responsiveness in men [6]. Hyperprolactinemia can cause decreased testosterone and decreased spermatogenesis. The decreased testosterone may cause decreased libido, impotence (16%), oligospermia (11%), infertility, decreased muscle mass and body hair, anemia, and, rarely, gynecomastia and galactorrhea [6, 13, 14]. Prostate volume is decreased in hyperprolactinemic men, presumably due to decreased testosterone [3].

Decreased bone mineral density can occur in both sexes and occurs in 25% of women diagnosed with hyperprolactinemia [9]. Bone loss and progressive atherosclerosis can also occur in both men and women due to altered body composition with increased body fat and reduced lean mass as well as the indirect decrease in estrogen secretion [7]. Behavioral and mood changes can also occur with chronic hyperprolactinemia [14]. Patients with sellar or parasellar lesions that are the cause of hyperprolactinemia may present with symptoms of headaches or vision loss in addition to the symptoms of hypogonadism.

16.3 Etiologies of Hyperprolactinemia

Hyperprolactinemia can be identified in up to 10% of the population and in 5% of patients who present with infertility [7, 9]. In reproductive-age women 25–34 years, the annual incidence of hyperprolactinemia is reported to be 23.9 per 100,000 person years [9]. There are many conditions that cause hyperprolactinemia (Table 16.1). Physiological etiologies include pregnancy, lactation, intercourse, exercise, stress, and sleep. Pathological causes of hyperprolactinemia include renal disease and hepatic cirrhosis—conditions that decrease clearance of prolactin—renal and lung cancers, and endocrinopathies such as primary hypothyroidism, polycystic ovary syndrome (up to 30%), and primary adrenocortical insufficiency. Hypothyroidism causes hyperprolactinemia by the compensatory increase in the hypothalamic thyrotropin-releasing hormone, which stimulates secretion of prolactin. Neurogenic stimulation caused by chest wall injury or severe burns can also cause hyperprolactinemia. Pharmacologic causes of hyperprolactinemia reduce hypothalamic secretion of dopamine, cause antagonistic effects on D2 receptors, or have an inhibitory effect on the enzyme that converts L-dopa to dopamine [15]. These are mainly antipsychotic medications (such as risperidone) and neuroleptic drugs. Others include antidepressants, antiemetics, opiates, H2-receptor blockers, antihypertensives, and calcium channel blockers. Sellar lesions, such as prolactinomas or other pituitary adenomas and infiltrative conditions, induce hyperprolactinemia by compressing the pituitary stalk and damaging the dopaminergic neurons [16]. Hypothalamic-pituitary stalk damage can also occur with craniopharyngiomas, granulomas, Rathke's cleft cysts, and other tumors.

Pituitary tumors are common and found in 12% of pituitary glands at autopsy. They can have a diverse range of hormonal and growth activity [9]. Prolactinomas are the most

common hormone-secreting pituitary tumors, comprising 40% of all pituitary tumors, and are found in approximately half of patients with hyperprolactinemia. Prolactinomas are composed mainly of lactotrophs, which secrete prolactin and can occasionally secrete other hormones, such as growth hormone, an important clinical distinction as treatment options will differ [16].

Prolactinomas are characterized by size. Microadenomas, found in 1% of women age 20–40, measure less than 10 mm; macroadenomas measure 10 mm or larger in diameter [3]. Most men present with macroadenomas, often with associated neurologic symptoms, which may reflect diagnostic delay [13]. These tumors are usually found in the lateral wings of the anterior pituitary but rarely can infiltrate the surrounding tissue. Because prolactinomas can extend outside of the sella, these tumors cause hyperprolactinemia by interrupting dopamine delivery from the hypothalamus to the pituitary, causing a loss of the tonic inhibitory release of prolactin. A macroadenoma may expand out of the sella to impinge on structures such as the optic chiasm resulting in symptoms such as severe headaches and ophthalmoplegia, due to entrapment of cranial nerves III, IV, V_1 V_2, and V1 [16]. Serum prolactin is usually proportional to tumor burden. Prolactinomas are rarely hereditary but can occur as part of the multiple endocrine neoplasia (MEN) syndrome in 20% of patients diagnosed with MEN type 1 [3, 13]. The incidence of a microadenoma enlarging to a macroadenoma is low, 3–7% [16], and the risk of enlargement during pregnancy is also very low. However, tumor growth of macroadenomas is up to 25% in pregnancy [13].

Macroprolactinemia is implicated as a major cause of hyperprolactinemia (in up to 46% of cases of hyperprolactinemia in a retrospective analysis) and occurs in 3.7% of the general population [5, 7]. It is a heterogeneous, benign, and usually asymptomatic condition with many different causes [9]. IgG complexes bind the 23 kDa prolactin molecule, especially anti-PRL autoantibodies, and form a large macroprolactin complex. The resulting molecular mass of over 150 kDA can increase the circulating serum PRL, likely by delayed clearance of prolactin. The complexes are immunologically detectable but not usually biologically active, as the polymer cannot interact with the prolactin receptor. However, a small proportion of patients may have clinical symptoms of hyperprolactinemia such as galactorrhea or oligomenorrhea [9]. This is thought due to intermittent dissociation of monomeric PRL from the low affinity, high capacity IgG antibody [17]. Alternatively, this could be due coincidental findings or another etiology such as polycystic ovary syndrome. In certain instances, a patient may have both hyperprolactinemia and macroprolactinemia [5, 18].

Up to 30% of etiologies of hyperprolactinemia are classified as "idiopathic" because no etiology has been determined [4]. In many cases, small prolactinomas may be present that are too small to be detected radiologically [3]. Long-term follow-up in these patients found that many have normal PRL levels (30%), while 10–15% will develop an increase in PRL over baseline [3].

16.4 Diagnosis of Hyperprolactinemia

In most laboratories, normal serum prolactin levels are less than 25 ng/mL in women and less than 20 ng/mL in men. Slight elevations of less than twofold could reflect a stressful phlebotomy and should be repeated to prevent otherwise costly imaging [8]. Most secondary causes and macroprolactinemia induce mild elevations of prolactin from 25 to 100 ng/mL. Hypothalamic damage or pituitary stalk compression typically causes prolactin levels of 100–150 ng/mL. Prolactin levels often correspond to prolactin size, but symptoms do not correspond well with prolactin levels. A macroadenoma will usually have a prolactin level of over 200 ng/mL [3]. The prolactin level is rarely above 250 ng/mL if a non-prolactin-secreting tumor is present. In cases of large pituitary tumors with only mild hyperprolactinemia, prolactin should be repeated with dilutions to rule out the "hook effect," which artifactually lowers the lab value [3, 16]. Levels higher than 250 ng/ML may suggest a macroadenoma. However some drugs such as risperidone or phenothiazines can induce prolactin to levels higher than 200 ng/ML, indicating overlap between different conditions causing hyperprolactinemia [19].

A thorough medical history may help provide clues for determining whether physiological, pharmacologic, or pathological etiologies are causing hyperprolactinemia. The physical exam should be focused on evidence of hypothyroidism, hypogonadism, systemic disease like renal or hepatic failure, and visual field defects. A thorough history and exam are important, because pituitary incidentaloma can be found in 10% of pituitary MRI in normal patients [15]. Depending on the medical and physical exam, the next step in diagnostic approach is a lab and radiologic evaluation. Because PRL is secreted in a pulsatile fashion, a single elevated value if obtained in the morning, 2–3 hours after awaking and in a fasting state, is recommended, although the Endocrine Society states that an atraumatic venipuncture performed at any time of the day is adequate to diagnose hyperprolactinemia [9]. Since macroprolactinemia can occur in up to 20% of patients with hyperprolactinemia, it should be measured in all asymptomatic patients by precipitation of the sample with polyethylene glycol (PEG) [19]. Macroprolactinemia should also be evaluated if the patient has an atypical clinical picture or conflicting PRL results in distinct assays [15]. Macroprolactinemia is present when the recovery of monomeric PRL following treatment with PEG is less than 40%

[17]. In patients with symptoms of hyperprolactinemia or a known macroadenoma but in which PRL is within the normal range or is only mildly elevated, further evaluation with lab dilutional measurements (1100) of the original sample should be performed to rule out a "hook effect" which is an assay artifact when high serum prolactin levels saturate antibodies in the two-site immunoradiometric assay [9]. This will help distinguish between a large macroadenoma and a large nonfunctioning tumor [19].

After the diagnosis of hyperprolactinemia, other labs such as thyroid function tests, liver panel, and kidney function tests should be considered [19]. A pregnancy test should be obtained in all reproductive-age women. In amenorrheic women, follicle-stimulating hormone should be obtained to rule out primary ovarian insufficiency [13]. Testosterone should be measured in men with hyperprolactinemia. Once hyperprolactinemia is diagnosed and secondary causes ruled out, imaging of the pituitary fossa should be performed with T1-weighted MRI with gadolinium to rule out a pituitary tumor, pituitary stalk lesion, hypothalamic tumors, granulomas, or other lesions, especially if there are neurologic symptoms present [18]. Microprolactinomas often appear to be hypointense compared to the bright pituitary gland and usually do not distort the pituitary shape [3]. Often, microadenomas may not be seen on the MRI, suggesting that the lesion is less than 2 mm in diameter or that the patient has lactotroph hyperplasia [18]. Larger macroadenomas have a variable enhancement with gadolinium and appear to cause the inferior portion of the pituitary stalk to be distorted [3]. It is also important to rule out acromegaly. Growth hormone (GH) is a prolactogen, so galactorrhea in a patient with a pituitary adenoma and elevated prolactin could be secondary to a growth hormone-secreting tumor (somatotropinoma); treatment with a dopamine agonist would decrease serum prolactin, but undiagnosed acromegaly could cause irreversible consequences from continued somatotropinoma growth [3, 16]. Importantly, in patients who are found to have a lesion in the pituitary or hypothalamus, it is possible that partial or complete hypopituitarism may be present, and a complete evaluation of the other pituitary hormones and pituitary-adrenal axis may be necessary [18].

In patients with drug-induced hyperprolactinemia, a repeat measurement 72 hours after discontinuation of the drug can be considered unless it is a psychotropic medication [19]. Antipsychotics should only be stopped or changed under the supervision of the psychiatrist. A pituitary MRI should be considered if the drug cannot be discontinued or if the onset of the symptoms does not coincide with initiation of the drug.

Other diagnostic elements to consider are visual field tests or pituitary function tests, especially in the presence of a macroadenoma or if the lesion compresses the optic chiasm [19]. Bone density tests should be considered if long-term hypogonadism has been present. A semen analysis should be obtained in men [6].

16.5 Treatment

Once physiological and pathological causes of hyperprolactinemia have been discerned, treatment options are decided based on the patient's symptoms and treatment goals. Medical therapy is the first line of therapy to achieve eugonadism by restoring ovarian function, normalizing both cyclical estrogen production and ovulation, suppressing lactation, and preventing further reductions in bone mineral density [18]. An important treatment goal is to also control tumor growth in patients with prolactinomas [7]. Dopamine agonists are first-line treatment to reduce prolactin levels and tumor size by absorbing lactotroph cell cytoplasm and limiting cell multiplication, causing tumor shrinkage [3, 10]. Asymptomatic patients or patients with microadenomas do not necessarily need treatment as 93% of microadenomas do not enlarge over a 4- to 6-year period [3].

Cabergoline, an ergot and selective D2 agonist, is the most favorable dopamine agonist due to its long half-life, tolerability, and efficacy. The long duration of action is due to its higher affinity for lactotroph dopamine receptor binding sites, slow elimination from pituitary tissue, and extensive enterohepatic recycling [3, 7, 9]. The starting dose is 0.25–0.5 mg/week, slowly increased to normalize PRL (mean dose 0.5–1 mg/week) [19]. At dose of 0.5 mg per week in 95% of patients with microadenomas and at a dose of 1 mg per week in 80% of patients with macroadenomas, hypogonadism can be reversed and prolactinoma size decreased [7, 9]. A placebo-controlled study showed that cabergoline in doses of 0.125–1 mg twice weekly for 1–2 years resulted in restoration of menses in 82% of patients [9]. Another retrospective study of over 400 patients showed benefit of cabergoline in 92% of patients with either a microadenoma or idiopathic hyperprolactinemia [9]. While there have been no clinical trials directly comparing the tumor shrinkage effects of the different dopamine agonists, various studies show that cabergoline decreases pituitary tumor size by 90% versus 50% with bromocriptine in two-thirds of patients [9].

Bromocriptine, a semisynthetic ergot derivative and a D2-selective dopamine agonist and D1 antagonist, was the first drug introduced to treat hyperprolactinemia. Bromocriptine is an inexpensive and effective alternative to cabergoline, although multiple daily doses may be required to be therapeutic (2.5–15 mg/day) because of its short half-life [7]. Bromocriptine is often associated with gastrointestinal side effects, such as nausea, vomiting, constipation, and reflux [19]. It may also cause nasal congestion, postural

hypotension, and lightheadedness, or dizziness [3, 19]. Higher doses up to 20–30 mg/daily are often not tolerated due to the side effects. Bromocriptine should be taken with a meal and may be used intravaginally if patients are intolerant of taking it orally.

Women with microadenomas causing menstrual disturbances, such as amenorrhea, can be treated with an oral contraceptive pill as an alternative to dopamine agonist or if they do not wish to conceive or if they have minimal galactorrhea and wish to prevent bone loss [7]. Importantly, no randomized controlled trials have compared treatment with a dopamine agonist versus oral contraceptive in this context, but it does not appear that microadenomas increase in size after 2 years of treatment with oral contraceptive treatment [9, 13]. The low incidence of tumor growth during pregnancy (when estrogen levels are elevated) also further supports that oral contraceptive therapy is a safe option. PRL levels should still be checked annually in these women, and caution should be used in women who have macroadenomas [10].

Once a dopamine agonist is initiated, the patient should be followed with repeat prolactin measurements starting 1 month after therapy to help guide dosing adjustments to achieve normoprolactinemia and resolution of hypogonadism symptoms. An MRI should be repeated in 1 year if prolactin levels continue to increase despite therapy or if new symptoms develop (or sooner, at 3 months, if there is a known macroadenoma) [9]. Visual field testing is recommended for patients with macroadenomas that may impinge the optic chiasm [9]. MRIs should be performed annually in patients with macroprolactinomas. Bone mineral density tests should be repeated if the baseline tests showed osteopenia.

Patients who do not tolerate or respond to medications may need transsphenoidal surgical resection of a prolactinoma. Patients have a 75% cure rate for surgical removal of microadenomas but only a 26% long-term success rate for macroadenomas [3]. Surgical results depend on the initial tumor size, prolactin levels, and experience of the surgeon [3, 19]. Most recurrences occur within 3 years [19]. Dopamine agonists are not definitive therapy for nonfunctioning pituitary adenomas. Adenomas that secrete both growth hormone and prolactin should be treated with transsphenoidal surgery or a long-acting somatostatin analog [16].

Dopamine agonist therapy provides effective improvement of clinical symptoms in most patients. Eighty percent of macroadenomas may decrease in size with treatment [18]. However, recurrence of symptoms or regrowth can occur within months of stopping dopamine agonists, ranging from 26 to 69% [9]. The higher the level of prolactin and the larger the pituitary tumor at the time of diagnosis correlates with the risk of recurrence [9]. Dopamine agonist treatment can be decreased after 2–3 years of normal prolactin levels and no evidence of residual tumor on MRI and may be stopped if serum prolactin has been normal after a period of 1 year at the reduced dose. If dopamine agonists are stopped, monitoring for symptoms of recurrence and prolactin levels should be checked monthly for 3 months for the first year and annually afterward for at least 5 years, especially if a patient has a macroadenoma [9, 19]. If prolactin levels again increase above normal range, an MRI may be indicated. Even without tumor regrowth, up to 28% of patients may develop symptoms of hypogonadism, which suggests the importance of long-term monitoring [9]. It is reasonable to discontinue therapy after a patient has reached menopause in women with microadenomas or idiopathic hyperprolactinemia since the protection of ovarian function is no longer needed [3, 5]. Estrogen hormone therapy can be considered if bone mineral density is a concern as long as PRL level and pituitary adenoma size is monitored [18].

Because men often have a more indolent course, many present to clinicians with large macroadenomas and very elevated prolactin levels, which may affect treatment. Men often already have compression symptoms such as diplopia or vision loss or significant hypogonadism, including erectile dysfunction. Sperm counts can be affected if the patient has gone for several years without treatment. However, sperm count and motility and normal sexual function has resulted after 6 months of treatment with cabergoline in some studies [6, 9].

Men respond well to dopamine agonists, unless hypogonadism has occurred for many years. While the restoration of ovarian function occurs in almost 90% of women, the testicular function in males may be less completely restored, with up to 50% of patients requiring testosterone replacement therapy despite an adequate reduction of serum prolactin [18]. Further, sperm counts that do not improve with dopamine agonists may require human chorionic gonadotropin for fertility. Sexual problems, such as erectile dysfunction, may not fully improve with a dopamine agonist and testosterone until the prolactin level has returned to the normal range [3].

In a small subset of patients and for reasons not entirely known (possibly due to a decreased number of D2 receptors on lactotroph cells), standard doses of dopamine agonists do not result in tumor shrinkage or normoprolactinemia. If maximum doses of dopamine agonists are used and not successful in reducing the tumor by 50%, the patient is noted to have a dopamine agonist-resistant prolactinoma [9]. Macroadenomas and males are more likely to be resistant to treatment [9]. Resistance to dopamine agonist therapy at standard doses may also be reflected in continued infertility. Caution must be used if increasing cabergoline to maximal doses (such as 11 mg/week), as there have been incidences of cardiac valvular regurgitation at doses higher than 3 mg daily as in Parkinson's patients [9]. The valvular disease appears to be due to serotonin receptor agonism leading to

fibromyoblast proliferation by cabergoline [3, 13]. Monitoring patients with periodic echocardiography is recommended if using high-dose cabergoline (over 2 mg/week) or after 5 years of treatment [9, 19, 20]. Referral to an experienced pituitary surgeon for transsphenoidal surgery in symptomatic patients who are resistant or intolerant to maximum doses of dopamine agonists is recommended. Postoperative risks include hypopituitarism, cerebrospinal fluid leak, and diabetes insipidus [9]. Surgically treated dopamine agonist-resistant tumors may recur in 7–50% of patients [3, 9]. Radiotherapy is another option for malignant or medically resistant prolactinomas but may take decades for tumors to respond to treatment [9].

For patients with pharmacologic-induced hyperprolactinemia who are symptomatic, the recommendation is assessment of the advantages and disadvantages of continuing the medication. If possible, discontinuation of the medication or substitution of another drug with less dopamine agonist properties can be attempted. Antipsychotic drugs should not be stopped without consultation and supervision by the treating physician. A dopamine agonist should only be added to antipsychotic-induced hyperprolactinemia with extreme caution as exacerbation of the underlying psychiatric disorder can occur [9]. Asymptomatic patients with drug-induced hyperprolactinemia do not need treatment, but there are reports of women with decreased bone density who have antipsychotic-induced hyperprolactinemia [9]. In symptomatic patients where the medication cannot be stopped, women can be treated with estrogens and men with testosterone to prevent long-term effects of hypogonadism [19].

For women trying to conceive, hyperprolactinemia occurs in 30–40% and has been shown to act as an aromatase inhibitor and can affect follicular fluid steroid metabolism [12, 17]. High PRL disrupts follicular maturation and corpus luteum function and may even reduce fertilization [12]. Some have suggested that hyperprolactinemia can affect the immune system and has opened the door to many studies investigating the neuroendocrine-immune axis (such as the role of natural killer cells) and primary infertility or recurrent pregnancy loss [2]. Further high-quality studies are needed to determine the relationship between hyperprolactinemia and recurrent loss [21]. However, dopamine agonists remain the first line of treatment in women hoping to conceive. Ovulation rates achieved by dopamine agonist treatment only are about 80–90% if hyperprolactinemia is the only cause for anovulation [21, 22]. There is question over management of infertile patients who have elevated levels of PRL who are otherwise asymptomatic, a condition termed "asymptomatic incidental hyperprolactinemia" [12]. Little is known about the initiation of dopamine agonists during ovarian stimulation in in vitro fertilization (IVF) in this situation, but neither cabergoline nor bromocriptine seems to have a deleterious effect on IVF outcomes [12] and may even improve responses in women considered poor responders [12]. If reproductive hormone levels remain low with persistent hyperprolactinemia even after maximal doses of dopamine agonists, injectable gonadotropins replacement therapy may be needed to treat the hypogonadism symptoms [13]. Women with microadenomas can be cycled on and off dopamine agonists to allow for subsequent pregnancies [3].

16.6 Hyperprolactinemia and Pregnancy

While there is no evidence of increased adverse outcomes, such as miscarriage, ectopic pregnancy, trophoblastic disease, birth defects, multiples, or preterm delivery, associated with dopamine agonists in pregnancy, pregnant women with microadenomas should stop bromocriptine or cabergoline, because the risk of tumor expansion is low (less than 3%) and the drugs do cross the placenta [9, 10, 22]. However, the growth of a macroadenoma in pregnancy is possible in up to 31% of patients, so continued use of bromocriptine (which has been studied more extensively than cabergoline in pregnancy) is advised or reinitiation of bromocriptine if previously discontinued [9, 11]. If clinical evidence for tumor growth, such as visual field defects or worsening headaches, develops while a patient is on bromocriptine, MRI without gadolinium is recommended with possible referral for possible pituitary surgery [11]. Preconception counseling for patients with macroadenomas that have not responded to dopamine agonist therapy should include consideration of surgical resection before pregnancy [9], which has shown to limit macroadenoma growth to about 5% [10]. However, patients should be informed that post-procedural risks include hypopituitarism with resulting pituitary hormone deficiencies necessitating fertility treatment with injectable gonadotropins to conceive [9].

Patients with prolactinomas should be clinically assessed every trimester during pregnancy, but formal visual testing is not needed in the absence of compressive symptoms unless a known macroadenoma is present. Obtaining serum prolactin levels during pregnancy is not recommended because prolactin levels increase tenfold by term [3, 9, 10]. Also, physiologic changes to the pituitary gland during pregnancy includes lactotroph hyperplasia and volume increase due to estrogen stimulation from the placenta. The increase in prolactin levels does not accurately correspond with activity or size of prolactinoma [9]. Routine MRIs should not be obtained during pregnancy with microadenomas or macroadenomas unless compressive symptoms develop. If mass effect symptoms develop during pregnancy, dopamine agonist therapy with bromocriptine can be initiated or referral for surgical treatment. There are no studies comparing dopamine agonist therapy to surgical resection in this circumstance in pregnancy.

Women can breastfeed their infant postpartum, but if she plans to do this, treatment with dopamine agonists is not recommended since the resulting decrease in PRL would disrupt lactation. There is no evidence that breastfeeding causes pituitary tumor enlargement [3]. Pregnancy may have a favorable effect on a prolactinoma in that PRL levels are lower after delivery and remission of hyperprolactinemia has been reported in up to 37% of women [3, 10]. However, a woman with a macroadenoma should restart dopamine agonist therapy after pregnancy, unless breastfeeding is planned.

References

1. Nawroth F. Hyperprolactinaemia and the regular menstrual cycle in asymptomatic women: should it be treated during therapy for infertility? Reprod Biomed Online. 2005;11(5):581–8.
2. Triggianese P, Perricone C, Perricone R, De Carolis C. Prolactin and natural killer cells: evaluating the neuroendocrine-immune axis in women with primary infertility and recurrent spontaneous abortion. Am J Reprod Immunol. 2015;73:56–65.
3. Strauss JF, Barbieri RL. Yen and Jaffe's reproductive endocrinology: Physiology, pathophysiology, and clinical management. Philadelphia, PA: Saunders/Elsevier; 2009.
4. Lu C, Hsieh C. The importance of measuring macroprolactin in the differential diagnosis of hyperprolactinemic patients. Kaohsiung J Med Sci. 2012;28:94–9.
5. Palubska S, Adamiak-Godlewska A, Winkler I, Romanek-Piva K, Rechberger T, Gogacz M. Hyperprolactinemia-a problem in patients from the reproductive period to the menopause. Menopause Rev. 2017;16(1):1–7.
6. Bolyakov A, Paduch DA. Prolactin in men's health and disease. Curr Opin Urol. 2011;21:527–34.
7. Capozzi A, Scambia G, Pontecorvi A, Lello A. Hyperprolactinemia: pathophysiology and therapeutic approach. Gyncol Endocrinol. 2015;31(7):506–10.
8. Fritz MA, Speroff L. Clinical gynecologic endocrinology and infertility. 8th ed. Philadelphia: Lippincott Williams and Wilkins; 2011.
9. Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, Wass JAH. Diagnosis and treatment of hyperprolactinemia: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(2):273–88.
10. Shibli-Rahhal A, Schlechte J. Hyperprolactinemia and infertility. Endocrinol Metab Clin N Am. 2011;40:837–46.
11. Molitch ME. Prolactinoma in pregnancy. Best Pract Res Clin Endocrinol Metab. 2011;25:885–96.
12. Bahceci M, Sismanoglu A, Ulug U. Comparison of cabergoline and bromocriptine in patients with asymptomatic incidental hyperprolactinemia undergoing ICSI-ET. Gynecol Endocrinol. 2010;26(7):505–8.
13. Klibanski A. Clinical practice. Prolactinomas. N Eng J Med. 2010;362:1219–26.
14. Wong-Anuchit C. Clinical management of antipsychotic-induced hyperprolactinemia. Perspect Psychiatr Care. 2016;52:145–52.
15. Glezer A, Bronstein MD. Approach to the patient with persistent hyperprolactinemia and negative sellar imaging. J Clin Endocrinol Metab. 2012;97(7):2211–6.
16. Gardner DG, Shoback D. Greenspan's basic and clinical endocrinology. 8th ed. New York: McGraw-Hill; 2007.
17. Thirunavakkarasu K, Dutta P, Sridhar S, Dhaliwal L, Prashad GRV, Gainder S, Sachdva N, Bhansali A. Macroprolactinemia in hyperprolactinemic infertile women. Encocrine. 2013;44:750–5.
18. Davis JR. Prolactin and reproductive medicine. Curr Opin Obstet Gynecol. 2004;16:331–7.
19. Rabinovich IH, Gomez RC, Mouriz MG, Garcia-Agullo DO. Clinical guidelines for diagnosis and treatment of prolactinoma and hyperprolactinemia. Endocrinol Nutr. 2013;60(6):308–19.
20. Nachtigall LB. Cabergoline for hyperprolactinemia: getting to the heart of it. Endocrine. 2017;57:3.
21. Chen H, Fu J, Huang W. Dopamine agonists for preventing future miscarriage in women with idiopathic hyperprolactinemia and recurrent miscarriage history. Cochrane Database Syst Rev. 2016;7:1–25.
22. Berinder K, Hulting A, Granath F, Hirschberg AL, Akre O. Parity, pregnancy and neonatal outcomes in women treated for hyperprolactinemia compared with a control group. Clin Endocrinol. 2007;67:393–7.