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Nicholas A. Tritos
Anne Klibanski *Editors*

Prolactin Disorders

From Basic Science to Clinical Management

Humana Press

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Series Editor Foreword

To paraphrase Rodney Dangerfield, some hormones get no respect. Although the existence of prolactin in animals has been known since at least the 1930s, the debate about its presence in humans was not settled until the 1970s, when reliable assays that allowed us to distinguish prolactin from growth hormone were developed.

During the last five decades, our knowledge about prolactin has accumulated at a rapid pace. This hormone was found to be associated with some of the most frequently encountered pituitary disorders in women and men. Prolactin excess or, less commonly, deficiency can produce significant symptoms and sometimes may signal a life-threatening condition.

The volume, edited by Nicholas A. Tritos and Anne Klibanski, takes us on a remarkable journey focused on prolactin, starting with its history, then moving to anatomy, physiology in both animals and humans, molecular biology, and clinical aspects of prolactin-related disorders.

An international group of authors produced an extraordinarily well-written monograph, which not only contains the most up-to-date information on its subject, but also is a pleasure to read. This book will be useful to all those interested in pituitary biology, including students of biology and medicine and physicians in multiple specialties.

I hope you enjoy the journey!

New York, NY, USA — Leonid Poretsky, MD

Preface

Our understanding of the role of prolactin in health and disease has continued to expand over the past several decades. In addition to its critical role in reproduction and lactation, animal studies have suggested that prolactin may be involved in a host of metabolic processes, which have yet to be established in humans. Prolactin-secreting pituitary tumors are the most common pituitary tumor phenotype. Prolactin disorders cause substantial morbidity and are quite diverse in etiology and management.

The purpose of this volume is to review our knowledge of both basic and clinical aspects of prolactin and help bridge gaps in existing literature in the field. Leading experts from basic sciences and clinical medicine have contributed a series of outstanding chapters that span the spectrum of prolactin-related literature. As such, the goal of this book is to provide information that should be of interest to a diverse audience, including basic scientists, clinical investigators, and clinicians from several specialties, including specialists in endocrinology, neurosurgery, radiation oncology, and neuro-oncology.

We are deeply indebted to an exceptional cadre of contributors who have authored a series of outstanding chapters in their respective fields. We hope that the present volume will become a valued guide to scientists and physicians, both in training and in practice, who wish to obtain current, in-depth information on this exciting and expanding field.

Boston, MA, USA

Nicholas A. Tritos
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Chapter 1
History of Prolactin Disorders

John AH Wass

Medical Therapy

Medical therapy for prolactinoma began with the dopamine agonist bromocriptine and has now moved on to cabergoline, a longer-acting dopamine agonist. Surgery and radiotherapy are occasionally indicated in the treatment of prolactinoma.

Prolactinoma, besides being the commonest of the pituitary tumours, has a recent and very rich history.

Introduction

Prolactinoma is the most recent of the characterised pituitary tumours to be described in detail. Hippocrates (above) may have been the first to describe prolactinoma. Galen, who was the most important physician of the Greco-Roman period (A.D. 130–200), had an enormous influence on medicine through the middle ages and was both a prolific writer and a keen experimental physiologist but got endocrinology wrong and thought the ductless glands were filters through which the fluid portions of the blood were sieved. Thus, he thought the thyroid lubricated the larynx and that the animal spirit was formed in the brain with the waste products flowing to the base of the brain, down the pituitary stalk and so to the pituitary gland. From this 'phlegmatic glandule', the waste products were passed by ducts through the sphenoid and ethmoid bones to the nasopharynx where they emerged as 'pituita' or nasal mucus. This view of the pituitary was held for 1500 years until the existence

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of communication between the ventricles of the brain and the nasal pharynx was disproved as ‘pituita phlegm’.

This chapter will deal with the history of prolactin and its differentiation from growth hormone and the history of the discovery of its actions, its gene and receptors. It will also deal with assays for prolactin and the regulation of prolactin by the hypothalamus. It will deal with prolactin in males. Furthermore, the history of the clarification of symptoms of prolactinoma in both women and men is set out together with the history of medical treatment for prolactinoma, the effects of medical treatment on pituitary size as well as surgical and radiotherapy treatments of prolactinoma.

Did Mary Tudor of England Have a Prolactinoma? [1]

Mary Tudor (Queen Mary 1 of England) was the eldest child of Henry VIII by his first wife Catherine of Aragon.

In brief, she had a difficult life with paternal deprivation. She had episodes from the age of 19 of amenorrhoea and also complained of headaches. Her vision was impaired. During her two episodes of assumed pregnancy, she, in addition to amenorrhoea, had swelling of the abdomen and mild secretion from the breasts. She died at age 42.

While amenorrhoea and even galactorrhoea can occur with pseudocyesis, severe headaches and impairment of vision do not. It may be that Queen Mary had a prolactinoma, but it is unlikely to be known because she is buried in Westminster Abbey under the tomb of Queen Elizabeth 1, her half-sister, and it is therefore very unlikely for her tomb to be disturbed. It is nevertheless an interesting speculation.

The Discovery of Human Prolactin

Although prolactin was discovered in the early 1930s in sheep, cows and birds, no human form had been found because it was thought to be identical to growth hormone [2]. In fact, prior to 1970, most endocrinologists doubted human prolactin even existed. Attempts to purify prolactin identified only growth hormone. A search was begun for prolactin through protein synthesis studies using pituitaries from pregnant and postpartum monkeys. Proteins obtained in a radioactive peak were similar to, but not identical with, growth hormone by molecular weight and electrophoretic mobility. Evidence was then obtained confirming that in the human, pituitary prolactin and growth hormone synthesis could be distinguished using antibodies to human growth hormone or to sheep prolactin [2]. The final discovery of this hormone has had a major impact in endocrinology and reproductive medicine.

Prolactin is mainly produced by pituitary lactotrophs and is tonically inhibited in the hypothalamus by dopamine. There are multiple extrapituitary sites of prolactin secretion, but its primary function is to enable breast milk production through prolactin receptors which are also found in many other tissues.

The major isoform is 23-kDa prolactin which acts via a membrane receptor, the prolactin receptor, which is a member of the cytokine superfamily. As will be discussed below, it is clear that high levels of prolactin interfere with reproductive function in humans.

In 1915 Gaines demonstrated that the pituitary was important in lactation [3].

In 1928 Stricker and Grueter observed that lactation could be produced in ovariectomised pseudopregnant rabbits by the administration of anterior pituitary extracts [4].

In the late 1920s, it was found that pituitary extracts induce milk secretion. Riddle [5] found that the substance which they called prolactin could be differentiated from the known growth- and gonad-stimulating substances. John Hunter in 1786 had described pigeon's milk secreted by the crops of breeding birds [6]. In these experiments, it was found that prolactin stimulated milk production by guinea pig mammary glands and a milklike substance from the crop sacs of pigeon and doves was produced, thus giving rise to the pigeon crop sac assay for prolactin. Furthermore, it was discovered that hypophysectomy stops lactation [7]. Although in the ensuing years prolactin was characterised in sequence in other species, the high lactogenic activity of even very highly purified preparations of growth hormone was impossible to separate from human prolactin using the relatively crude pigeon crop assay. Several diseases however suggested that the two hormones were separate. Most patients with pituitary tumours in which there was amenorrhoea or galactorrhoea had these cardinal features but not features of acromegaly. Furthermore, patients who had growth hormone deficiency from birth were able to lactate.

David Kleinberg (Fig. 1.1) and Andrew Frantz [8] developed an in vitro bioassay which was highly sensitive. They used unextracted human plasma to look at breast tissue fragments from pregnant mice incubated in organ culture, and the sensitivity of the assay was 5 ng/ml. All 14 of the nursing mothers they studied had elevated levels of circulating prolactin in this assay, and growth hormone was in the low normal range in all of these subjects. They also showed that psychoactive drugs of the phenothiazine series elevated prolactin. Furthermore, when growth hormone antisera to human growth hormone were pre-incubated with plasma from each of these subjects there was no significant inhibition of prolactin activity. They concluded that growth hormone and human prolactin were separate molecules with little if any immunological cross-reactivity. Further, they concluded that there were different physiological mechanisms for their release. Shortly after this, a radioimmunoassay for human prolactin was developed which could measure prolactin levels in normal individuals permitting the entire sequence of human prolactin to be shown. This therefore was the last anterior pituitary hormone to have its sequence described [9]. We know that the composition of the human prolactin is similar to that of bovine prolactin and porcine prolactin. Human prolactin's composition resembles that of growth hormone being rich in acidic and hydrophobic residues.

Fig. 1.1 David Kleinberg

Shortly after the report of the bioassay for prolactin, Noel described the release of prolactin as well as growth hormone during surgery and other conditions of stress [10]. They showed a fivefold increase with major surgery. They also showed significant elevation of prolactin levels after insulin-induced hypoglycaemia as well as a rise in some women though not in men following sexual intercourse.

Cell of Origin

We know that prolactin is made by the pituitary lactotrophs and in a normal human pituitary these comprise 15–25% of the total number of cells. This is similar in both sexes and does not change significantly with age. During pregnancy however and subsequent lactation, lactotroph hyperplasia is observed because of lactotroph proliferation. This hyperplastic process involutes within several months after delivery but breastfeeding retards this progress. This stimulatory effect of pregnancy on the

lactotrophs is also true for prolactinomas, and we know that lactation may induce significant tumour growth in these circumstances.

Prolactin Action

Prolactin has a large number of different actions in many species including fishes, birds and mammals. These are very diverse including osmoregulation, growth, metabolic effects and actions related to reproduction. In humans, clearly, the primary physiological action is the preparation of the breast for lactation in the postpartum period.

Prolactin belongs to the somatotropins/prolactin (PRL) family, a large family of proteins that include growth hormone, placental lactogen and other prolactin-like hormones. The human prolactin gene is located on chromosome 6p22.2-p21.3 and consists of five coding exons, one non-coding exon and four introns. It is believed that prolactin, growth hormone and placental lactogen arose from duplication of a common ancestral gene about 40 million years ago. The entire prolactin locus in humans spans a region of about 10 kb.

The prolactin receptor belongs to the class 1 cytokine receptor superfamily, a family of transmembrane proteins that transduce signals following phosphorylation by cytoplasmic kinases. The human prolactin receptor gene is located on chromosome 5p14-p13.2 and consists of eight or nine coding exons and two non-coding exons.

Neuroendocrine Regulation

Geoffrey Harris (Fig. 1.2) in his influential monograph *Neural Control of the Pituitary Gland* thought that prolactin (lactogenic hormone) was controlled differently to the other adenohypophyseal hormones [11]. He showed that cutting the pituitary stalk did not abolish lactation.

The hypothalamus is the predominant regulator of prolactin secretion by inhibition through prolactin inhibitory factors which reach the pituitary via the hypothalamic portal blood vessels. Dopamine is the major pituitary prolactin-inhibiting factor, and a section or disruption of the stalk therefore leads to moderate increases of prolactin [12].

Dopamine in the 1950s was demonstrated to be the predominant inhibitory factor when pituitaries were transplanted below the renal capsule resulting in an elevation of prolactin, thus demonstrating the predominant inhibitory effect of the hypothalamus on prolactin secretion. The concentration of dopamine in the pituitary stalk plasma was enough to inhibit prolactin release [13]. Work with D2 receptor-deficient mice subsequently showed the development of lactotroph hyperplasia and hyperprolactinaemia [14].

Fig. 1.2 Geoffrey Harris

Thyrotroph-stimulating hormones and prolactin release have been shown to be caused by thyrotropin-releasing hormone (TRH). There are type 1 TRH receptors both in thyrotrophs and lactotrophs. Intravenously TRH causes a rapid rise in prolactin. In hypothyroidism, TRH synthesis is increased which results in hyperprolactinaemia which is corrected once euthyroidism is restored.

Actions of High Levels of Prolactin

Prolactin causes growth and development of the mammary gland, the synthesis of milk and the maintenance of milk secretion. Other hormones besides prolactin are involved. During pregnancy high concentrations of oestradiol and progesterone produced by the placenta together with high levels of prolactin and human placental lactogen promote proliferation of the lobular alveolar epithelium. After parturition, progesterone and oestrogen levels together with those of human placental lactogen decline, whereas prolactin levels rise. Lobular alveolar epithelium converts into secretory acini.

Nonpubertal galactorrhoea may be present in normal women in around 5–10% in whom basal prolactin levels are normal in 90%.

Prolactin affects gonadotrophin secretion and has been shown to suppress LH pulsatility, and the mechanism of this has been recently demonstrated. This is caused by reduced hypothalamic expression of kisspeptin 1, and kisspeptin if given intraperitoneally restores hypothalamic GnRH and gonadotrophin secretion showing that kisspeptin 1 neurones have an importance in hyperprolactinaemic anovulation [15].

In normal men, the role of prolactin is less well defined, but in men with high prolactin levels, there is impotence and lowered libido. Galactorrhoea is reported in 10–20% of men with hyperprolactinaemia. This symptom does not occur in normal men, and around 25% of men with hyperprolactinaemia have impotence or infertility or both. The reason for this is decreased pulsatile gonadotrophin secretion which results in low or low-normal testosterone levels. Sperm counts and motility are also decreased in men with hyperprolactinaemia.

Drugs can interfere with prolactin secretion. Thus, dopamine antagonists result in hyperprolactinaemia, and some antidepressants including selective serotonin reuptake inhibitors may also have the same effect because of the importance of serotonin in neuroregulatory control of prolactin.

Medical Treatment of Hyperprolactinaemia

The first description of the successful treatment of galactorrhoea associated with a high prolactin level was by Besser et al. in 1972 [16]. He described in a small group of patients with inappropriate lactation associated with high prolactin levels as measured by a bioassay, patients in whom a number of characteristic symptoms were present including galactorrhoea and amenorrhoea in women and impotence in men. They used the ergot alkaloid bromo-ergocryptine to suppress prolactin levels. In the patients they described, galactorrhoea ceased, and normal periods resumed, and in men potency returned. S. Franks and Howard Jacobs confirmed the reduction in prolactin in patients with elevated levels of prolactin by bromocriptine [17], and many of these patients were shown to have pituitary tumours and the bromocriptine restored fertility.

Later studies by Thorner et al. in 1974 in a larger group of women and men with galactorrhoea and hypogonadism showed that treatment for between 2 and 28 months was effective and gonadal status became normal on treatment [18].

Earlier work by scientists at the pharmaceutical firm Sandoz following on a series of experiments at the Weizmann Institute of Science in Tel Aviv by Moses Shelesnyak had shown that ergometrine and ergot toxin could adversely affect ovum implantation [19]. The conclusion of the Tel Aviv group was that this was not acting at the level of the uterus but in the hypothalamus where it inhibited prolactin secretion. However, at that stage, there was no assay for plasma prolactin

and the findings were ignored. At Sandoz though, work was done on ergocryptine and ergocornine, and these compounds also proved to be active in the inhibition of implantation of the ovum. In the meantime, the structure of prolactin had been established and sensitivity immunoassays had been developed. Flückiger at Sandoz began the search for an ergot alkaloid that would be active by mouth to specifically inhibit prolactin. Success came in 1965 with the synthesis of an ergoline compound called bromocriptine which acted predominantly as a dopamine agonist without any effects on adrenergic and serotoninergic receptors. Thus, was developed one of the more important compounds to treat patients with prolactin disorders.

Another ergot derivative is cabergoline which is an ergot derivative and selective for D2 receptors and with a long duration of action, because of extensive enterohepatic recycling. In an important paper in 1994, this drug was shown to have less side effects than bromocriptine and greater efficacy [20]. Thus, in 459 patients with hyperprolactinaemia and amenorrhoea, cabergoline (0.5–1.0 mg weekly) was compared to bromocriptine (2.5–5.0 mg daily). Cabergoline vs. bromocriptine achieved normal prolactin levels in 83% vs. 59% of patients. There were also few side effects with cabergoline. Now cabergoline is the preferred drug because of its lower side effects and increased efficacy.

Pituitary Tumour Shrinkage

Pituitary tumour shrinkage with dopamine agonists in patients with prolactinomas was first documented in the late 1970s. It was known that there was an antimitotic effect of bromocriptine. In 1982 a number of reports suggested that tumour regression was due to lactotroph cell size reduction which was a reversible effect after withdrawal [21]. From the clinical point of view, 79% of macroprolactinomas reduced in size by at least 25% and 89% shrank to some degree. The majority of this was shown to occur in the first 3 months of treatment.

Surgery

Historically, surgical resection of prolactinomas was the preferred way of treating them before the advent of dopamine agonists. Nowadays, surgery in the treatment of prolactinoma is not often required except in patients who are resistant to or intolerant of dopamine agonists. This may provide helpful results. Several surgeons have reported their results and around 75% of microadenomas and 30% of macroadenomas are reportedly cured by surgery. Recurrence of hyperprolactinaemia may occur. Complications of transsphenoidal surgery, initially reported as infrequent, show a degree of hypopituitarism partly related, possibly, to the small size of the tumour in a proportion of patients.

Radiotherapy

Because of the excellent responses both to dopamine agonists and surgery, radiotherapy is very rarely indicated in patients with prolactinomas. Sometimes in resistant prolactinomas, radiotherapy may be indicated in patients with large tumours and to control growth in aggressive tumours, when tumour control is important. In the treatment of pure hyperprolactinaemia, only a minority of patients over 2–14 years (32%) are rendered normoprolactinaemic.

Summary

The story of the history of prolactinoma is fascinating. We have moved on from surgical treatment to highly effective medical treatment in the vast majority of patients.

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Chapter 2
Pituitary Anatomy and Development

Ronald M. Lechan, Knarik Arkun, and Roberto Toni

Historical Anatomy

The most ancient suggestion of a pituitary gland in man can be traced to the Tantra Yoga, elaborated by the pre-Aryan, Dravidic culture and Aryan Brahmanic, Ayurvedic medicine of fifteenth to fifth centuries B.C. [1]. Although Vedic medical doctrine prohibited dissection of human cadavers, it recognized an "energy center" in the brain called ājñā chakra in ancient Sanskrit, believed to regulate consciousness and perception of "self." This center was symbolized by two petals of the lotus flower, reminiscent of the two thalamic masses [2], and, possibly, the two lobes of the pituitary gland [1]. According to the Tantric anatomy, this region included numerous efferent channels (nerve fibers) called nadis [3], which we now recognize to contain the hypothalamic tuberoinfundibular system (for historical reviews, see [4–7]).

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The first anatomical description of the pituitary gland on record, however, was during the second century A.D. by Galen of Pergamon. In *Anatomicae Administrationes*, he described a physical connection between the pituitary and infundibulum of the hypothalamic third ventricle and its association with a surrounding vascular network that he called "rete mirabilis." He proposed this unique, arterial structure had a key role in the regulation of body energy, sensation, and impulse, which he referred to as "vital and animal spirits." Galen was influenced by the ancient, Greek anatomist, Herophilus of Alexandria (third century B.C.), however, to whom he credited the discovery of the rete mirabilis [4, 5, 8, 9]. Although absent in humans, the rete mirabilis is a well-developed structure in a number of animal species (*Carnivora*, *Cetacea*, *Edentata*, *and Ungulata*) and equivalent to the suprahypophysial, circuminfundibular, and prechiasmal arteriolar-capillary plexus of man [4–6]. In *De Usu Partium*, the major treatise of Galenic physiology, the pituitary gland is described as a receptacle for brain "waste" in the form of mucus or phlegm (pituita in Latin) that accumulates in the third ventricle as a result of the "metabolism" of "body energy" at the level of the rete mirabilis. This material was proposed to drain along the hypothalamic infundibulum and "filtered" by the pituitary gland before exiting through the nasal cavities [4, 5]. Although now archaic in concept, it is of interest that evidence for brain paravascular channels that drain into sinus-associated dural lymphatics and perivenular lymphatics (so-called glymphatic system) have recently been described [8], re-energizing the Galenic concept of nasopharyngeal extracerebral transport of "metabolic impurities" from the central nervous system.

Galenic concepts dominated for several centuries as indicated by drawings of the pituitary gland and rete mirabilis by Leonardo da Vinci in 1508 (Fig. 2.1a, b), but he also provided the first detailed drawings of the anatomy of the human skull base. These included transverse and sagittal views of the cranial fossa, giving a detailed anatomical depiction of the association between the third ventricle/pituitary stalk and the cranial vault, facial bones, and nasal/oral cavities (Fig. 2.1c–e). During the same period, Johannes de' Ketam published the superficial cranial projection of somatesthesia (Fig. 2.1f) in *Man of Diseases* (1491), corresponding to the frontal area where hyperalgesia occurs with stretching of the diaphragma sellae, as with a pituitary macroadenoma that extends into the suprasellar cistern [9]. In 1511, Michelangelo Buonarroti painted the fresco, *Creation of Adam*, on the ceiling of the Sistine Chapel, believed to be the first depiction of the hypothalamic-pituitary region (Fig. 2.1g, h) [4, 5].

It was not until the sixteenth century, however, that Berengario da Carpi in *Isagoge Breves* first challenged the Galenic concept of the pituitary gland as a basin that filtered cerebral waste products, based on his work with human cadavers, and described the sphenoid sinus as a route to the sella turcica [4, 5]. Shortly thereafter, Andreas Vesalius in *Tabulae anatomicae sex* (1538) described the venous drainage from the cranial vault, which recapitulates what we now recognize as the inferior and superior petrosal and sphenoparietal sinuses (Fig. 2.2a), and although demonstrated that the rete mirabilis originates from the internal carotid artery, surrounds the pituitary fossa, and then widens symmetrically and superiorly to vascularize the

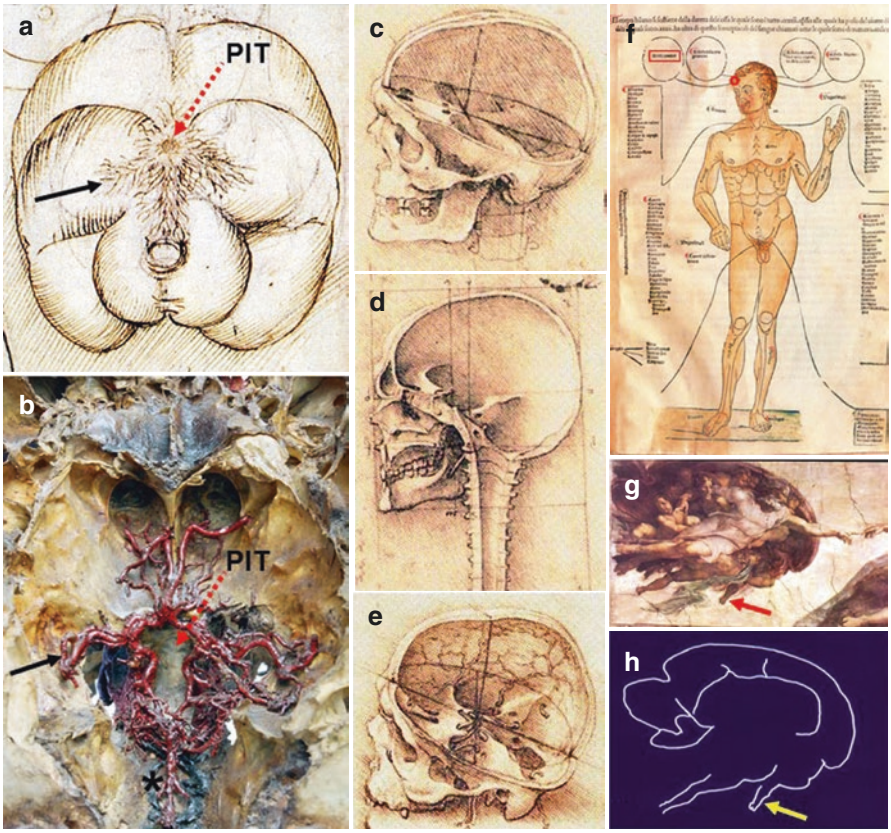

Fig. 2.1 (**a**) Drawing of the base of the brain by Leonardo da Vinci depicting the rete mirabilis (arrow) surrounding the pituitary gland (PIT), likely the oldest image of this anatomical region. Note squat morphology of the temporal lobes and width of the encephalic mass, typical of ox anatomy as opposed to human anatomy where an elongated morphology of brain lobes prevails and the rete mirabilis is absent. (Royal Library at Windsor Castle, Courtesy of the Historical Library of the Museum of Biomedicine – BIOMED, University of Parma, Parma, Italy, partly modified) (**b**) Injection-corrosion cast of the bovine rete mirabilis around the pituitary (PIT) fossa (dotted arrow) and basilar (asterisk) arteries. Note the arrangement of blood vessels around the sella turcica is very similar to that depicted by Leonardo in his drawing. (Courtesy of Prof. Ferdinando Gazza, nineteenth-century collection of the Museum of Veterinary Anatomy, University of Parma, Parma, Italy) (**c**–**e**) Drawings by Leonardo da Vinci of the middle cranial fossa, sella turcica, and their anatomical relationships with the cranial vault and facial bones. These drawings were the oldest anatomical maps inspiring the surgical and later stereotaxic approach to tumors of the hypothalamic-pituitary complex at the end of the nineteenth century. (**c**, **d**) From O'Malley and de C.M. Saunders [157]; (**e**) Royal Library at Windsor Castle, Courtesy of the Historical Library of the Museum of Biomedicine – BIOMED, University of Parma, Parma, Italy (**f**) Johannes de' Ketam's depiction of sensory afferent projections (*sensus communis*, red rectangle) in the median supraorbital, frontal region in *Man of Diseases*. (Modified from Premuda L. Storia dell'Iconografia Anatomica. Ciba Edizioni, Ciba-Geigy, 1993, ISBN 88-7645-107-2, p. 65.) (**g**) Detail from the fresco, Creation of Adam, by Michelangelo Buonarroti. Red arrow points to a limb of one of the angels. (**h**) Contour of fresco in (**g**) is reminiscent of a midline sagittal section of the human brain. Limb of the angel (yellow arrow) represents the pituitary stalk. ((**g**, **h**) Adapted from [158])

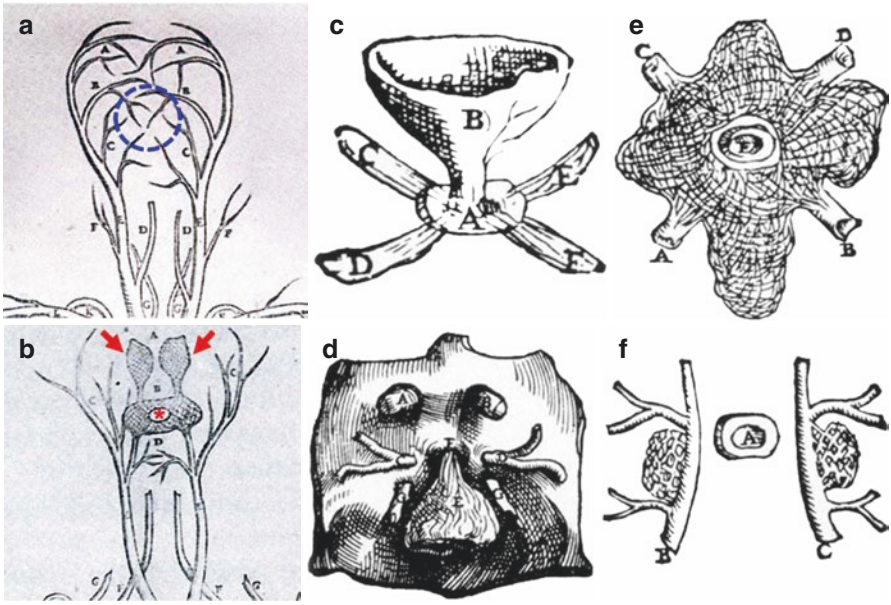

Fig. 2.2 Drawings of Andreas Vesalius. (**a**, **b**) Plates from *Tabulae anatomicae sex* depicting (**a**) anatomy of the venous vertebral and internal jugular systems and the common facial vein. Note the X-shaped, venous pattern at the center of the image (blue dotted circle) fed by six, symmetrical branches of the internal jugular vein reminiscent of the distribution of the inferior and superior petrosal and sphenoparietal sinuses around the cavernous sinus. (**b**) The arterial, vertebral (dorsal vessels) and common carotid (ventral vessels) systems. The rete mirabilis has central opening where the pituitary gland would be located (red asterisk) and fed by the internal carotid artery. Note that the *rete mirabilis* widens symmetrically and superiorly to vascularize the suprahypophysial, hypothalamic area (corresponding to the red arrowheads). (From [5, 9], partly modified.) (**c**–**f**) Plates from the seventh book of *De Humani Corporis Fabrica*. (**c**) Enlarged view of the pituitary (**A**) showing the hypothalamic infundibulum and ducts comprising the foramen lacerum and superior orbital fissure. (**d**) Anatomical relationships between the infundibulum (**e**), dural diaphragma sellae, internal carotid arteries, and oculomotor and optic nerves. (**e**) Enlarged view of the pituitary (**E**) surrounded by the *rete mirabilis* arising from branches of the internal carotid artery. (**f**) Detailed view of the association between the pituitary (**A**), carotid arteries, and rete mirabilis. (Partly modified from [5, 9]) (From the BIOMED Museum, University of Parma)

infundibulum and hypothalamic floor, he erroneously reported that it was present in man (Fig. 2.2b). Subsequently, in *De Humani Corporis Fabrica* (1543), he detailed the anatomical relationships between the pituitary gland and the hypothalamic infundibulum, diaphragma sellae, internal carotid arteries, and oculomotor nerves and, although now denying the presence of the rete mirabilis in man, held fast to the Galenic dogma by describing bony ducts of the cranial base he believed to drain brain mucus (Fig. 2.2c–f). The contemporary of Vesalius, Gabriele Fallopius,

similarly argued against the presence of the *rete mirabilis* in man, but it was not until the seventeenth century that Thomas Willis raised the possibility in *Cerebri Anatome* that "humors" from blood perfusing the ventral surface of the brain are carried to the pituitary gland, unwittingly anticipating current concepts of releasing and inhibiting factors for adenohypophysial regulation [4, 5]. The Galenic idea that the pituitary gland filters brain secretions into the nose was also criticized by Konrad Victor Schneider during the same period in *Liber Primus De Catarrhis* (1660), showing that the cribriform plate of the ethmoid bone was impervious to drainage from the central nervous system, and by Willis' assistant, Richard Lower, in his 1670 *Tractatus de Corde*, observing that the infundibular connection to the pituitary gland was filled with a gelatinous substance that would obstruct the possibility of mucous percolation from the third ventricle into the gland (see [6] for historical review).

Further advances were made in the eighteenth century by the French clinician and anatomist, Joseph Lieutaud, in *Essais Anatomique* (1742), who introduced the term "pituitary stalk" (la tige de la glande pituitaire) and described stalk vessels we now recognize as part of the portal circulation. In 1767, Luigi Galvani in *Disquisitiones Anatomicae Circa Membranam Pituitariam* showed that mucus passing through the nostrils originates from glands in the nasal mucosa and not the pituitary [10], and in 1791 Samuel Thomas von Sömmerring coined the term "hypophysis" in *Hirnlehre und Nervenlehre* [5]. However, it was not until the late in the nineteenth century and throughout the twentieth century that a new renaissance in the understanding the anatomy and importance of the pituitary gland was begun, coincident with the development of new and powerful histochemical and molecular techniques, and continues into the present century. Included was work by Santiago Ramón y Cajal in 1894 using the Golgi's silver impregnation technique to elucidate the connection between the hypothalamus and posterior pituitary (supraoptic-hypophysial tract), the discovery of hypothalamic neurosecretion by Ernst Scharrer in 1928, the finding by Popa and Fielding in 1930 of an interconnection between the pituitary and hypothalamus through the "hypophyseo-portal vessels" (although misinterpreted as blood flowing from the pituitary upward to the hypothalamus), evidence by Harris and Green between 1935 and 1955 that the blood flow in portal vessels was from the hypothalamic median eminence to the pars distalis of the pituitary gland and that electrical stimulation of the hypothalamus was ineffective in eliciting a pituitary response if the pituitary stalk was severed, and descriptions of the neurosecretory nature of the neurohypophysis by Wolfgang Bargmann in 1949 using the Gomori's histochemical method [11] (see also [6] for historical review). Many advancements have been made since, and those relevant to the current understanding of the anatomy of the pituitary gland are alluded to in the following sections. A timeline of major, historical breakthroughs in elucidation of the functional anatomy of the mammalian pituitary gland is summarized in Table 2.1.

Table 2.1 Timeline of major, historical breakthroughs in elucidation of the functional anatomy of the mammalian pituitary gland

1500–500 B.C	Tantric Yoga and Vedic medicine locate an energy center at the level of the thalamic-pituitary area	1791	Sömmerring introduces the term "hypophysis"
II century A.D	Galen describes the *rete mirabilis* around the pituitary considered a filter for brain mucous to the nasal cavities	1894	Santiago Ramón y Cajal describes the supraoptico-hypophysial tract in rats using the Golgi's silver impregnation method
1489–1511	Leonardo da Vinci and Michelangelo Buonarroti paint the pituitary gland, *rete mirabilis*, and possibly a brain section with the pituitary stalk	1928	Ernst Scharrer describes "glandular cells" in the fish hypothalamus (concept of "neurosecretion) using standard histologic techniques
1521–1523	Berengario da Carpi denies the existence of the *rete mirabilis*	1930	Popa and Fielding discover the pituitary portal system
1543	Andreas Vesalius publishes the drawings of the hypothalamic-pituitary unit, *rete mirabilis*, and pituitary venous drainage as currently known for petrosal sampling	1938	Feyrter identifies "clear cells" in the anterior pituitary using the tartaric acid-thionin staining as a marker of the diffuse endocrine system later described by AGE Pearse
1561	Gabriele Fallopius confirms the absence of the pituitary *rete mirabilis* in humans	1935–1955	Harris and Green demonstrate in anesthetized rats that blood in the portal vessels flows to the pituitary, and this vascular link is critical to the hypothalamic control of pituitary secretions
1664	Thomas Willis argues that humors out of the brain base may be carried to the pituitary gland	1949	Wolfgang Bargmann describes the posterior pituitary using the *Gomori's* chrome alum hematoxylin-phloxine *stain*
1660–1670	Schneider and Lower reject the Galenic idea that the pituitary gland filters brain secretions to the nose	1964	János Szentágothai defines the hypothalamic origin of the tuberoinfundibular tract in rats, and Kjell Fuxe shows its entire course using the Falck-Hillarp histochemical technique for monoamines
1742	Lieutaud discovers vessels in the pituitary stalk connected to those of the pituitary gland	1969–1970	Yoshimura et al. show that mice pituitary chromophobes may behave like pituitary stem cells, and Nakane provides ultrastructural bases for paracrine interactions in the pituitary gland
1767	Luigi Galvani shows that mucus passing through the nostrils originates from mucous glands of the human nasal mucosa and not from the pituitary gland	2009	Garcia-Lavandeira et al. identify stem cells/progenitors in the marginal zone of the adult human pituitary gland

Macroscopic Anatomy

Landmarks of the Sellar Region

The pituitary gland lies in the central part of the sella turcica (pituitary fossa), a saddle-shaped groove in the endocranial, superior surface of the sphenoid bone corresponding to the median part of the middle cranial fossa (Fig. 2.3a). On a lateral skull projection, the sella and pituitary lie 5–6 cm anterior to the point of the orthogonal intersection between Frankfurt horizontal plane and a vertical line descending from the vertex of the cranial vault (posterior to the bregma) to the center of the external acoustic meatus (Fig. 2.3b). Bordering the sella turcica is a bony thickening at the apex of its anterior wall, the tuberculum sellae, protruding upward as much as 3 mm to terminate into two, small, bony eminences, the middle clinoid process. Lateral and above are the anterior clinoid processes, forming the tip of the lesser wings of the sphenoid. The tuberculum sellae also forms the posterior wall of the chiasmatic groove into which rests the optic chiasm (Fig. 2.3a, c, d). Just above the optic chiasm are the anterior cerebral and anterior communicating arteries of the circle of Willis, the lamina terminalis, and third ventricle of the hypothalamus (Fig. 2.3d).

Lateral to the sella are the cavernous sinuses (Fig. 2.4a–c), a collection of spaces, loculated by fibrous septa between the outer periosteal and inner meningeal dural sheaths. The outer periosteal dural sheath covers the floor and anterior and posterior walls of the sella. The inner meningeal dura forms the lateral wall and roof of the cavernous sinus, gives rise to a very thin medial meningeal lining that serves as its medial wall and adheres to the capsule of the pituitary gland [12], and fuses with the cerebellar tentorium at the roof and superior aspects of the lateral walls of the sella turcica (Fig. 2.4c). Venous blood from the cavernous sinus (Fig. 2.4a) exits via endocranial tributaries of the internal jugular veins that include the superior and inferior petrosal sinuses and exocranial tributaries of the internal jugular vein, including the ophthalmic and facial veins.

Within the space between the medial and lateral walls of the cavernous sinus (Fig. 2.4a), a loose, reticular, connective tissue membrane envelops the oculomotor (III), trochlear (IV), abducens (VI), ophthalmic (V_1), and maxillary (V_2) branches of the trigeminal nerves and a sympathetic plexus that surrounds the internal carotid artery [12]. The internal carotid artery is separated from the pituitary gland by at least 2 mm but occasionally can indent the pituitary parenchyma. Once in the cavernous sinus, the internal carotid artery courses horizontally and anteriorly for ~2 cm (Fig. 2.4b–d), then forms a genu forward, and is fixed to either the anterior clinoid process by a dural ring (carotid collar) or between the anterior and middle clinoid processes by an osseous ring, the caroticoclinoidal ring.

Posteriorly, the sella turcica is bordered by the dorsum sellae (Fig. 2.3a) and the posterior clinoid processes (Fig. 2.3a). Anterior and caudal to the dorsum sellae, venous lacunae are found between the periosteal linings and the pituitary capsule [13], including the posterior intercavernous sinus and basilar sinus [14]. Connections between the posterior intercavernous sinus and the anterior intercavernous sinus

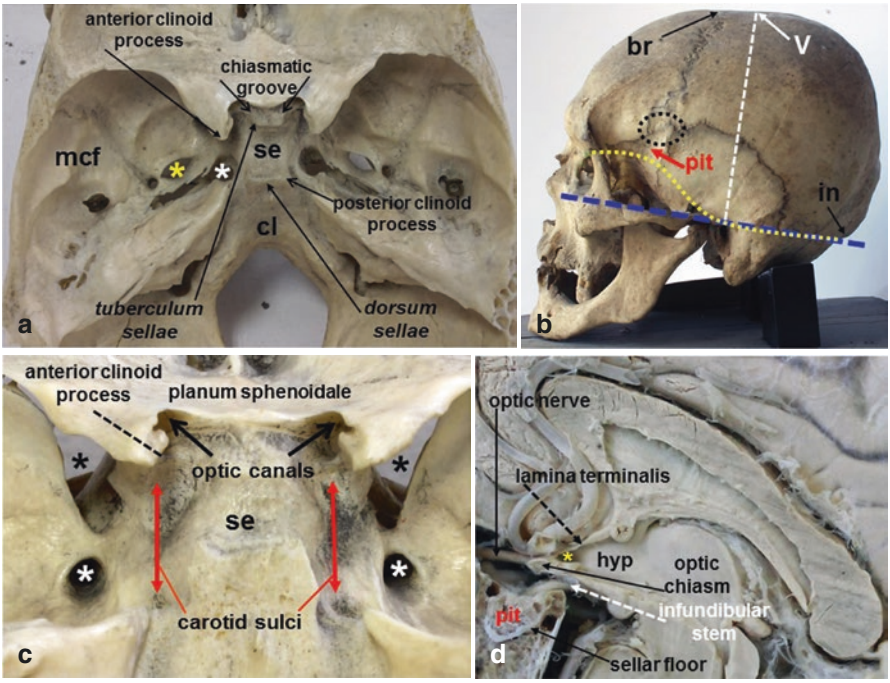

Fig. 2.3 (**a**) Middle cranial fossa (mcf) of an adult human skull showing the location of the sella turcica (se), a saddle-shaped groove in the superior part of the sphenoid in continuity with the dorsum sellae and clivus (cl) of the occipital bone. A number of other bony landmarks relevant to the anatomy of the sellar region are shown; white asterisk, the foramen lacerum allowing the passage of the internal carotid artery; yellow asterisk, the foramen ovale allowing the passage of the mandibular branch of the trigeminal nerve. (**b**) Lateral projection of an adult human skull. The location of the sellar region and pituitary gland (pit) are indicated by the red arrow, just inferior to the pterion (black dotted circle), the area of intersection between the sphenotemporal, sphenoparietal, and sphenofrontal sutures. The pituitary lies some centimeters anterior to the intersection of Frankfurt plane (blue dotted line) and the line connecting the vertex of the cranial vault (V) with the external acoustic meatus. Due to the sinusoidal shape of the cranial base profile (yellow dotted line), however, the pituitary fossa is pushed upward toward the center of the temple; *br* bregma, *in* inion or external occipital protuberance. (**c**) Optic canals (black arrows) allow the passage of the optic nerves and ophthalmic artery and are located anterior to the sella (se) and medially to the superior orbital fissure (black asterisk), where the oculomotor, trochlear, abducens, and ophthalmic branch of the trigeminal nerves and ophthalmic veins course. Below is the foramen rotundum (white asterisk) allowing entry of the maxillary branch of the trigeminal nerve. The internal carotid artery courses laterally and inferiorly to the sella in the carotid sulci (red arrows). (**d**) Sagittal section of an adult, human brain showing the major, neuroanatomical structures lying above the sella turcica and pituitary gland. *pit* pituitary, *hyp* hypothalamus, yellow asterisk = optic recess of the third ventricle. (All images (**a**–**d**) courtesy of the Museum of Biomedicine – BIOMED, University of Parma, Parma, Italy)

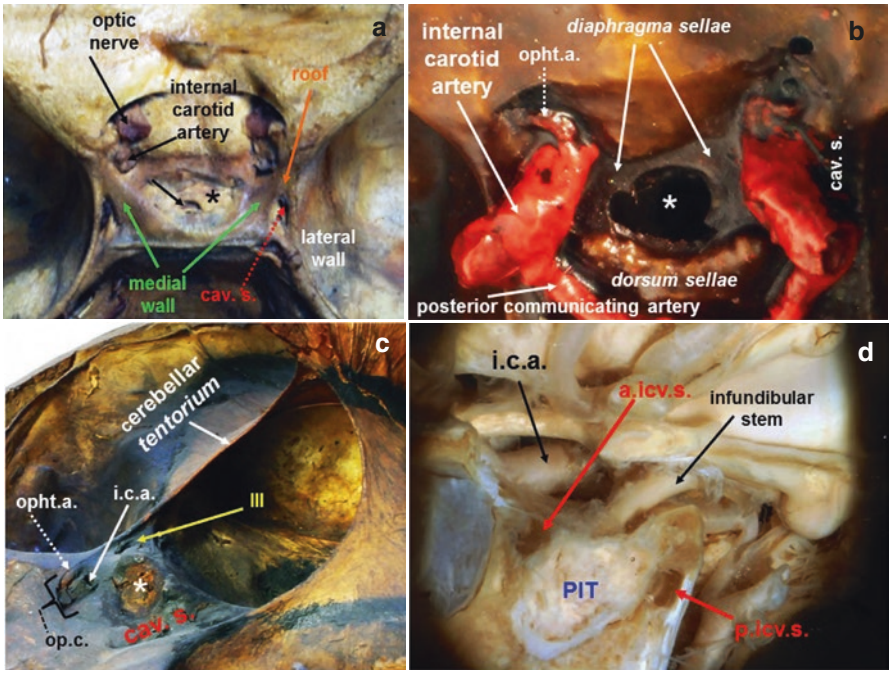

Fig. 2.4 (**a**, **b**) Views from behind and above the human sella turcica (dehydrated preparations); (**a**) Adult subject, (**b**) infant. (**a**) The sella is covered by a meningeal lining (asterisk) and contains a central opening (arrow) through which the pituitary stalk enters the pituitary fossa. The medial walls and roof of the cavernous sinus (cav.s.) circumscribe the pituitary. (**b**) The course of the horizontal segment of the internal carotid artery within the cavernous sinus (cav.s.) and emergence of the ophthalmic artery (opht. a.) is well delineated following injection with colored resin. Note dark, meningeal lining of the roof continuous with the diaphragma sellae. Central opening of diaphragma is denoted by an asterisk. (**c**) View from above and left side of the endocranial surface of the human cranial base (dehydrated preparation, adult subject). The central opening in the diaphragma sellae reveals the underlying pituitary tissue (asterisk). The oculomotor nerve (III) courses within the lateral wall of the cavernous sinus (cav.s.), and the ophthalmic artery (opht.a.) is seen arising from the internal carotid artery (i.c.a.) and to enter the optic canal (op.c.). The meningeal lining of the diaphragma is continuous with the free edge of the meningeal cerebellar tentorium that is fused with the lateral wall of the cavernous sinus. (**d**) Detail of a sagittal section of an adult, human brain. The internal carotid artery (i.c.a.) courses lateral to the pituitary gland (PIT) and surrounded anteriorly and posteriorly by the anterior intercavernous sinus (a.icv.s) and posterior intercavernous sinus (p.icv.s.), respectively. (All images courtesy of the Museum of Biomedicine – BIOMED, University of Parma, Pama, Italy)

(Fig. 2.4d), which run along the anterior wall of the sella, contribute to a ring of venous lacunae around the pituitary called the circular sinus. The basilar sinus collects blood from the superior and inferior petrosal sinuses and is the most consistent, intercavernous connection across the midline [14].

Superiorly, the inner meningeal layer forms the roof of the cavernous sinus (Fig. 2.4a) and expands medially to form the roof of the sella turcica (Fig. 2.4a, b),

called the diaphragma sellae [15]. It is located ~5–10mm below the optic chiasm [16] and, in most instances, extends from the tuberculum sellae to the dorsum sellae measuring 11–13 × 8–10 mm (w × l) to cover the pituitary gland [17]. It has a central, circular opening of ~5 mm to allow the passage of the pituitary stalk (Fig. 2.4a, b). At the level of this orifice, the inner meningeal layer and leptomeninges (arachnoid and pia mater) of the suprasellar arachnoid cisternae (suprachiasmatic, interpeduncular, and lamina terminalis) and base of the brain fuse with the capsule of the pituitary gland [13], preventing the development of subdural and infra-arachnoid spaces within the pituitary fossa. However, in ~50% of normal subjects, an outpouching of arachnoid protrudes into the sella through the central opening and can give rise to an empty sella (see section "Radiologic Anatomy") or, if resected, predispose to the development of a cerebrospinal leak following transsphenoidal surgery [18].

Inferiorly, the floor of the sella turcica is made up of a thin layer of the bone covered by outer periosteal dura, sometimes containing an inferior intercavernous sinus similar to that described above pertaining to the sinuses in the posterior and anterior sellar walls. The sellar floor separates the pituitary fossa from a pneumatic cavity within the body of the sphenoid bone, the sphenoid sinus. This sinus has an average depth of ~2 cm [14] and communicates with the nasal space (Fig. 2.5a) through an ostium that opens superiorly and behind the superior nasal conchae of the ethmoid, corresponding to the sphenoethmoidal recess (Fig. 2.5b). Rarely, the sellar floor connects the pituitary fossa with the posterior part of the nasopharynx through a craniopharyngeal canal, terminating ~1.5 mm behind the posterosuperior angle of the nasal vomer [19–21]. The craniopharyngeal canal, a remnant of the migration pathway taken by the embryonic pituitary to reach the sella turcica (see section "Embryologic Anatomy") and lined by dura mater, may persist in the adults and contain functional pituitary tissue [19].

The sphenoid sinus serves as the primary, anatomical landmark for the transsphenoidal approach to the sella turcica. In ~75% of adults, the sphenoid sinus is entirely pneumatized and located below the floor of the sella turcica, even extending up to the clivus (sellar type) (Fig. 2.5a, b). Otherwise, it terminates at the level of the anterior sellar wall (presellar type) (Fig. 2.5c). In both instances, the sellar floor thickness ranges from 0.1 to 1.5 mm. In young children, however, a pneumatized sphenoid is lacking, and the floor of the sella can be up to 10 mm thick. Most often (~70% of adults), the sphenoid sinus is asymmetrically divided into two, separate spaces by a bony septum (intersphenoid septum) but can contain multiple smaller septa to further loculate each space [14]. The internal carotid artery courses along and external to the lateral walls of the sphenoid sinus, giving rise to a carotid prominence inside the sinus.

Craniometric parameters used to identify and/or predict changes in the macroscopic morphology of the pituitary gland include the sellar length and width. The sellar length is greatest in the anterior-posterior diameter of the pituitary fossa when measured at the level of the tuberculum sellae or below, whereas the sellar width is defined as the distance between the two carotid sulci at the level of the sellar floor (Fig. 2.3c). In most Caucasian adults, the upper limit of normal is 17 × 15 mm [14]. The depth of the sella generally does not exceed 13 mm when the greatest distance between the sellar floor and a perpendicular line connecting the tuberculum and dorsum is measured [14].

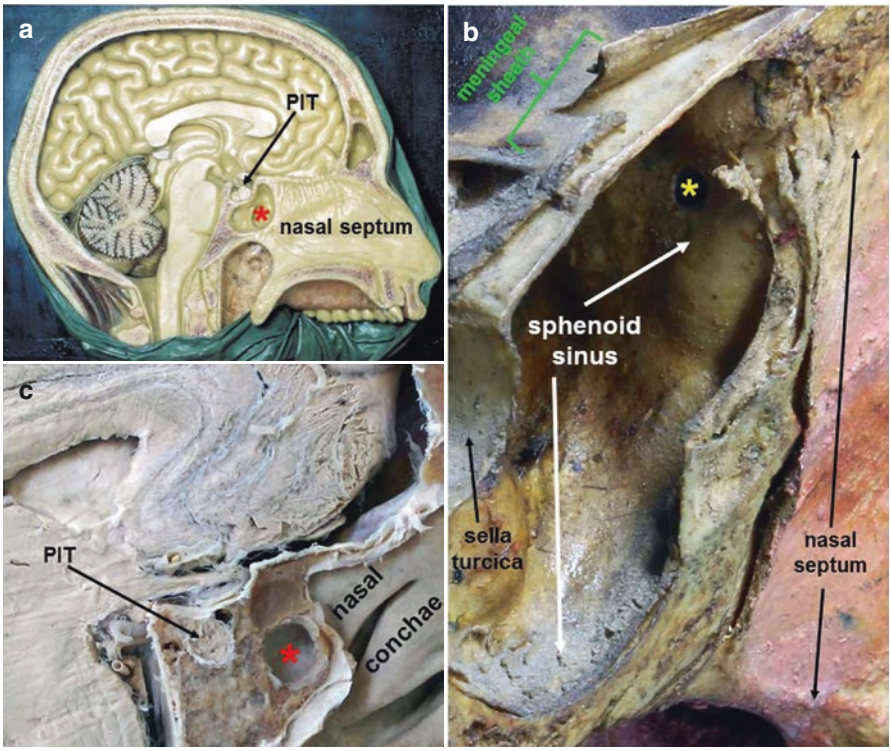

Fig. 2.5 (**a**) Sagittal section of the human head and brain. The sphenoid sinus (sellar type, red asterisk) lies in front of and beneath the sella turcica harboring the pituitary gland (PIT) (nineteenth-century anatomical wax preparation by Cesare Bettini, courtesy of the Collection of Anatomical Waxes "Luigi Cattaneo," University of Bologna, Bologna, Italy). (**b**) Detail and enlargement of a sagittal section of the adult, human sphenoid sinus (dehydrated specimen of the skull and meninges). The sinus opens into the sphenoethmoidal recess through an ostium (yellow asterisk) and communicates with the endonasal space. (**c**) Sagittal section of an adult, human brain showing the sphenoid sinus (presellar type, red asterisk) and its relationship to the pituitary gland (PIT) and nasal conchae. ((**b**, **c**) Courtesy of the Museum of Biomedicine – BIOMED, University of Parma, Parma, Italy)

Pituitary Gland

The pituitary gland is composed of an anterior, epithelial lobe (anterior pituitary or adenohypophysis) and a posterior neural lobe (neurohypophysis) (Fig. 2.6a). In man, the wet weight of the entire gland is proportional to its volume. It increases from ~100 mg at birth to ~500–600mg during the second decade depending upon ethnicity [22, 23] and may even reach 800 mg in males and 900 mg in females [24]. Women generally have a pituitary that is ~20% larger than men [22] and can double its weight during pregnancy and with a progressive increase in multiparity [24]. These changes are confined to the anterior lobe, however, as the size and weight of the posterior lobe remain fairly constant throughout life [22, 25] and it does not display sexual dimorphism [26]. In general, the adult hypophysis measures approximately 10 mm in length, 10–15 mm in width, and 5 mm in height [22].

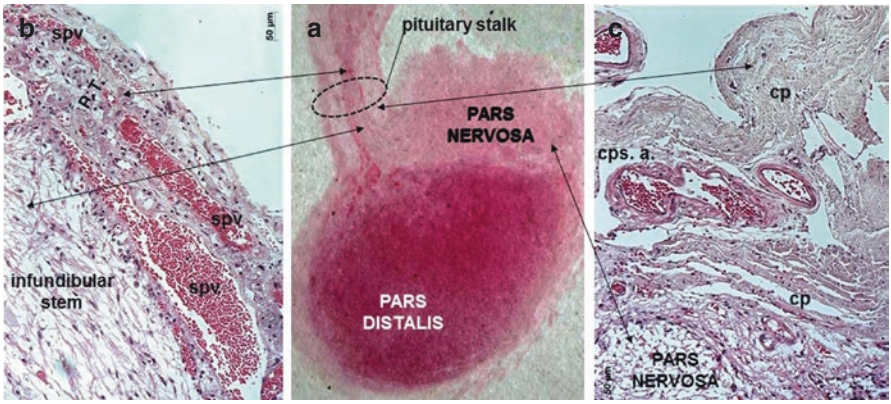

Fig. 2.6 (**a**) Sagittal section (hematoxylin and eosin staining) of the human pituitary gland and pituitary stalk (Courtesy of Cristina Micheloni, Section of Human Anatomy – DIMEC, University of Parma, Parma, Italy). (**b**) The pituitary stalk is shown under higher magnification. The pars tuberalis (P.T.) covers neural tissue of the infundibular stem and contains numerous short portal vessels (spv). (**c**) The posterior pituitary or pars nervosa and infundibular stem are enveloped by a fibrous capsule (cp) enriched by branches of the capsular artery (cps.a.) arising from the inferior hypophysial artery

The entire gland is surrounded by a fibrous capsule organized into two layers (Fig. 2.6c). The first is an inner layer of lamina propria made up of collagen types 1–5 [27] that gives rise to fibrous trabeculae that penetrate the adenohypophysial parenchyma [13] and segments it into three, main territories, a central mucoid wedge (named because of its strong PAS positivity, otherwise known as the pars interloralis, see Figs. 2.15a, e and 2.17b) and two lateral wings [28]. These fibrous trabeculae (called the fibrous core) provide passage for arterial branches that perfuse adenohypophysial parenchyma [29] and described further below. The second is a thicker, external layer made up of collagen types 1, 2, and 4 [13] that forms the lateral walls and roof of the sella [27, 30]. The external layer is a periphypophysial extension of the dural sheath and presumed to be the true pituitary capsule [13]. Since the capsule is loosely attached to the lamina propria through connective fibers that fills a potential space between them, the anterior lobe retains some degree of passive movement, as observed in cases of adenohypophysial displacement to one side of the sella in the presence of an enlarging pituitary adenoma [13]. In contrast, at the level of the neurohypophysis, the two adenohypophysial capsular layers fuse to each other, preventing movement of the posterior pituitary [13].

The anterior lobe contains three subdivisions including the pars distalis, pars intermedia, and pars tuberalis. The pars distalis lies adjacent to the pars nervosa but demarcated by an epithelial lamina corresponding to the pars intermedia. Rarely, the pars distalis envelops the pars nervosa or is detached from it, resulting in protrusion of the neurohypophysis into a depression of the dorsum sellae [24]. The pars distalis makes up the bulk of the anterior pituitary and contains all of the hormone-secreting cells of the adenohypophysis (see section "Microscopic Anatomy"). The pars intermedia lies between the pars distalis and the posterior pituitary, representing what

remains of the posterior loop of Rathke's pouch (see section "Embryologic Anatomy"). The pars tuberalis can be subdivided into a superior part attached to the hypothalamic median eminence, and an inferior part that surrounds the infundibular stem (Fig. 2.6b) but separated from it by a fibrovascular lamina (septum tuberalis) that contains the portal vessels [29, 31].

The neurohypophysis is comprised of the posterior pituitary and infundibular stem (the neural component of the pituitary stalk, the latter also including the pars tuberalis) that extends from the floor of the hypothalamus (a protrusion of the hypothalamic tuber cinereum that contains the infundibular recess of the third ventricle) to the posterior pituitary. Where the infundibular stem joins the posterior pituitary, the pars distalis forms two, symmetric groves called the loral groves, into which the loral arteries pass to enter the pars distalis (see section "Vascularization of the Pituitary Gland"). The lower part of the stem forms a genu that displaces adenohypophysial tissue anteriorly and is covered by a continuation of the septum tuberalis (described above) called the genual septum. It is through the genual septum that the portal vessels as well as other pituitary arteries pass into the pars distalis (see section "Vascularization of the Pituitary Gland").

Pituitary tissue can also be present in the nasopharynx, commonly referred to as a pharyngeal pituitary [32]. This structure is a residual of Rathke's pouch during its migration from the oral cavity to the middle cranial fossa (see section "Embryologic Anatomy") and situated in the mucoperiosteum between the sphenoid and vomer bones [33]. Typically, it is observed as a compact, elongated cell group 2–5 × 0.2–0.5 mm (l × w) that contains an incomplete fibrous capsule and occupies a volume ranging from 0.13% to 0.5% of the normal pituitary [34, 35]. All cell types in the pars distalis are also present in the pharyngeal pituitary [34, 36], and because of its connections with the sellar hypophysis via transsphenoidal venous and arterial vessels originating from the vomerosphenoidal fossa, sellar intercavernous sinus, sellar arteries, and possibly stalk portal vessels [37, 38], it can be functional [39].

Vascularization of the Pituitary Gland

The human pituitary gland is a highly vascular structure that receives both direct (arterial) and indirect (sinusoidal) vascularization. Direct vascularization originates from the supracavernous portion of the internal carotid arteries that give rise to lateral and anterior superior hypophysial arteries and the intercavernous portion of the internal carotid artery that gives rise to the inferior hypophysial arteries. The lateral and anterior superior hypophysial arteries give off numerous short branches that course along the long axis of the infundibular stem and terminate in capillary complexes at its upper part. The superior hypophysial artery also gives rise to the loral artery (also known as the middle hypophysial artery or artery of the trabecula) [40, 41]. It enters the superior surface of the anterior lobe at the homolateral loral groove to perfuse the region between the mucoid wedge and the lateral wings of the pars distalis and gives off branches that extend upward onto the surface of the pars

tuberalis to anastomose with long branches of the anterior superior hypophysial artery [40], contributing to the vascularization of the pituitary stalk and a small part of the posterior pituitary [29]. Collectively, therefore, the superior hypophysial artery serves both the stalk and anterior lobe [42].

The inferior hypophysial artery on either side of the pituitary divides into ascending and descending branches running in the groove between the anterior and posterior pituitary lobes and anastomoses with each other, giving rise to an arterial circle that penetrates the posterior lobe or courses along the capsular surface of the neurohypophysis (Fig. 2.6c) to perfuse this tissue [29, 40]. Some vessels also extend over the inferior surface of the pars distalis to penetrate adenohypophysial parenchyma [29]. Collectively, this arrangement indicates that the inferior hypophysial artery primarily serves the posterior lobe and, to a minor extent, the adenohypophysis [42].

The most critical source of the vascularization to the anterior pituitary, however, is the pituitary portal system, originally identified as "portal veins" because its vessels act as a link between the arterial blood of the hypophysial arteries and venous blood of the hypophysial veins [43]. However, technically, the human hypophysial-portal veins are really fenestrated sinusoids originating from the surface of the hypothalamic median eminence and infundibulum [29]. They remain superficial and collect a network of deeper sinusoidal capillaries stemming from the branches of the superior and inferior hypophysial arteries that form capillary tufts (so-called gomitoli) within the neural tissue of the hypothalamic infundibulum, infundibular stem, and neurohypophysial genu [29]. The portal sinusoids include a posterior and anterior group. The posterior group gives rise to the long portal vessels that enter the bulk of the pars distalis, whereas the anterior group is the source of the short portal vessels that form in a region of the infundibular stem beneath the pars tuberalis (septum tuberalis) (Fig. 2.6b) and neurohypophysial genu and terminate in the mucoid wedge and lateral wings of the pars distalis [29].

The venous drainage from the pituitary gland is primarily directed into the cavernous sinuses, although some venous blood also drains into the circular sinus and the inferior sinus. Portal sinusoids within the adenohypophysis join together to form small, collecting channels (the lateral and anteroinferior hypophysial veins) located lateral to the gland before emptying into one of its venous perihypophysial sinuses [40, 44]. Other veins are formed in the superior part of the pars distalis (superior hypophysial veins) and drain into a venous plexus at its dorsal surface. Ultimately, the pituitary blood drains from the cavernous sinuses into the superior and inferior petrosal sinuses. Some authors have also observed drainage from hypophysial stalk sinusoids into the sellar circular sinus [44] and the venous network of the pia mater [40], but this is only minor. Venous efferents from the posterior pituitary run parallel to the inferior hypophysial artery and mainly drain into the posterior hypophysial sinus and a plexus of veins lying posterior to the posterior pituitary (posterior venous network) that drain both the intercavernous/cavernous sinuses and cranial basilar sinus [44].

Embryologic Anatomy

In man, the anterior pituitary derives from a specialization of the embryonic ectoderm bordering the most anterior and ventral portion of the neural tube [45] that in the early, vertebrate embryo corresponds to the preplacodal ectoderm of the neural plate [46]. At the beginning of the 4th week of fetal development, the neural tube closes, but a cranial opening remains, the anterior neuropore, that quickly collapses to become the anterior wall of the proencephalic vesicle. Below the anterior neuropore is the frontotemporal ectoderm of the neural tube that adjoins with the mouth opening or stomodeum inferiorly. At the level of the most ventral and median part of the frontotemporal ectoderm, fusion occurs with ectodermal cells of the surface epithelium (the epidermis), enveloping the entire neural tube and body of the embryo [45]. This "mixed" ectodermal structure (neural tube ectoderm/surface ectoderm) invaginates backward into the stomodeum to line its roof but, at this stage, is not separated from the overlying neural tube by the mesoderm. Only later, the mesoderm interposes to form the sphenoid bone (see below), moving anteriorly from the notochord and terminating behind a temporary closure of the stomodeum, the fenestrated buccopharyngeal membrane. As a result, a "specialized" ectoderm develops anterior to the buccopharyngeal membrane, the adenohypophysial placode, the source of tissue lining the roof of the oral aperture. Whether in man, the adjacent neural crest forming the thickened "lips" of the anterior neuropore contributes to the adenohypophysial placode is not known. By analogy with other vertebrates, however, it is assumed that the preplacodal ectoderm is devoid of neural crest cells [46]. However, it is suggested that the adenohypophysial placode might contain neural crest cells [47], and recent immunocytochemical data in human embryos support this possibility [48, 49].

Around the 4th to 5th weeks of fetal development, the adenohypophysial placode emits a dorsally directed evagination, Rathke's diverticulum, that moves upward throughout the mesoderm that is now interposed between the roof of the buccal cavity and the ventral surface of the proencephalon [50]. This mesoderm, called the prechordal ectomesenchyme (because it is positioned anterior to the notochord), contains neural crest cells arising from the mesencephalic crest [51]. Rathke's diverticulum elongates inside the prechordal ectomesenchyme, forming a pharyngohypophysial stalk that will come in contact with the floor of the diencephalic vesicle which will become the hypothalamic infundibulum. At the same time, the future superior hypophysial artery develops from the ectomesenchyme below the diencephalic vesicle, giving off branches to the primordium of the hypothalamic infundibulum [52]. Around the 6th to 7th weeks of fetal development, the floor of the diencephalic vesicle extrudes a neural diverticulum, the primordium of the infundibular stem, that moves inferiorly toward the tip and posterior surface of Rathke's diverticulum, the latter progressively closing to form a pouch or Rathke's pouch that loses continuity with the oral cavity (Fig. 2.7a). At this stage, the placodal cells of the tip of Rathke's pouch wrap around the primordial infundibular stem to eventu-

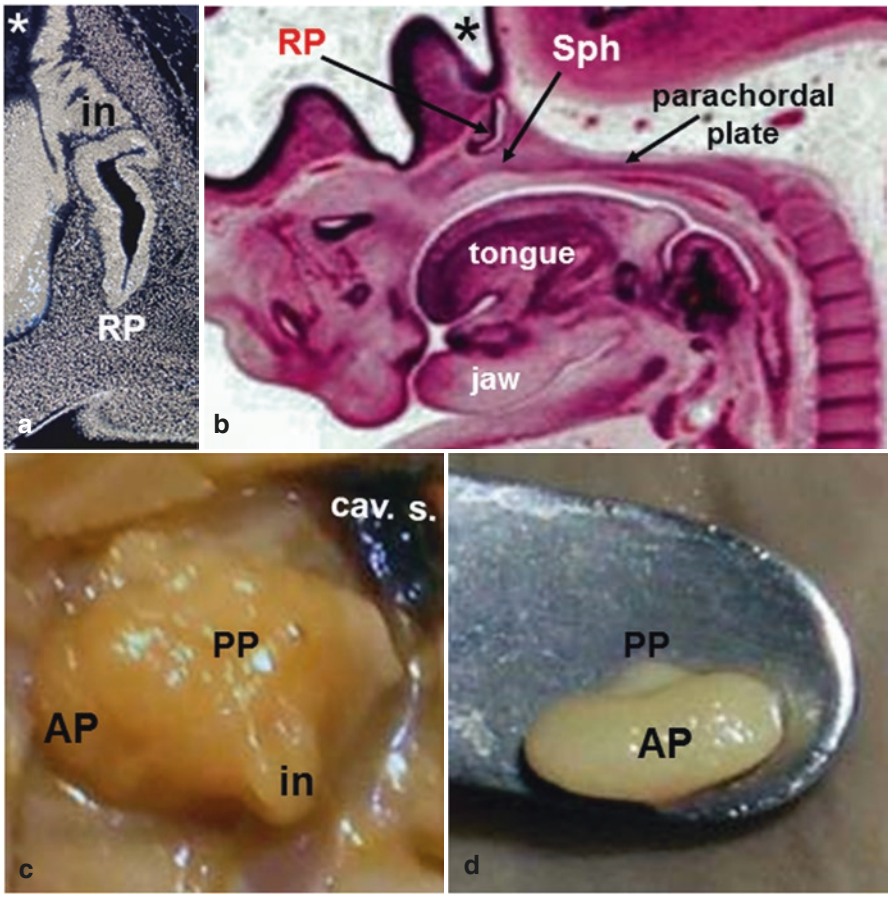

Fig. 2.7 (**a**, **b**) Midsagittal sections of two, human embryos at 6 and 7 fetal weeks, respectively (H&E staining, magnification × 10). (**a**) Rathke's pouch (RP) has just closed and joins with the tip of the primordial infundibular stem (in) extruding from the floor of the third ventricle (asterisk). (**b**) The base of Rathke's pouch is now separated from the buccal floor and located in the primordial sella turcica of the sphenoid bone (Sph) developing in the ectomesenchyme cranial to the parachordal plate of the notochord. Asterisk = third ventricle. (**c**, **d**) Macroscopic dissection of two human fetuses at 17 and 21 fetal weeks, respectively. (**c**) The pituitary gland is in the sella turcica and tilted forward. The posterior pituitary (PP) is well demarcated from the anterior pituitary (AP) and continuous with the infundibular stem (in). Laterally, the right cavernous sinus (cav.s.) is visible. (**d**) The pituitary gland has been removed from the sella turcica. The bulk of the anterior pituitary (AP) is already well formed, and the pars distalis is enlarging laterally, anterior to the posterior pituitary (PP)

ally become the adenohypophysial pars tuberalis (see below) [50]. Rathke's pouch separates from the stomodeal roof due to the development of cartilage of the primordial sphenoid bone (Fig. 2.7b). Only a mesenchyme-filled channel through the sphenoidal cartilage remains, the craniopharyngeal canal, that will later involute, although occasionally remains as a part of a developmental disorder [19]. During

the 8th week of fetal development, sinusoidal connections with the superior hypophysial artery appear in the prechordal ectomesenchyme, invading Rathke's pouch to become the intrapituitary fibrous septa and giving rise the primordial hypophysial-portal vessels that will later proliferate within the pars distalis [52]. During this developmental period, the prechordal ectomesenchyme also proliferates anteriorly and inferiorly to give rise to the so-called nasal trabecula (i.e., the primordium of the nasal septum) [53]. Thus, the cartilage of the nasal septum contains neural crest cells and of the same type believed to contribute to the development of the human pituitary [48, 49].

The ectomesenchymal area of the nasopharynx, at the interphase between the inferior surface of the developing sphenoid and the vomer bones, encases the posterior aspect of the nasal septum where the buccopharyngeal membrane ceases and Rathke's pouch arises in the oral cavity. At this location, between the 8th and 10th weeks of fetal development, an ectodermal pituitary outgrowth, the buccohypophysial stalk, segregates between the external layer of ectomesenchyme (later forming the periosteum of the sphenoid) and the epithelial lining of the pharynx to become the pharyngeal pituitary. By the end of the first trimester of pregnancy, the pharyngeal pituitary is highly vascularized by branches of pharyngeal arteries and by venous conduits originating from intracranial venous sinuses in the region of the future sella turcica and exhibits signs of eosinophilic and basophilic histodifferentiation. However, numerous cells display cytological features of undifferentiated elements [54–56].

The prechordal ectomesenchyme of the sphenoid bone is also believed to be critical for the specification of different adenohypophysial cell types from placodal cells. Between the 8th and 9th weeks of fetal development, Rathke's pouch forms three diverticula, a single median, and two laterals. The upper part of the lateral diverticula gives rise to the pars tuberalis, whereas the median diverticulum provides the epithelial bulk of the mucoid wedge in the fully differentiated gland. Simultaneously, the first corticotrophs and thyrotrophs differentiate in the lower diverticular parts in direct contact with the surrounding ectomesenchyme [50]. During the 13th week of fetal development, somatotrophs and gonadotrophs differentiate in the lower portions of the lateral diverticulum of Rathke's pouch, increasing in number throughout the 21st–29th weeks. At these developmental stages, the neural lobe acquires a well-defined morphology (Fig. 2.7c), and the bulk of the corticotrophs differentiate in the walls of the median diverticulum, including that in contact with the primordial infundibular stem, the pars intermedia. Concurrently, thyrotrophs and gonadotrophs become detectable in the pars tuberalis. Since anencephalic fetuses lack corticotrophs and gonadotrophs, it has been suggested that early contact with the primordial neurohypophysial tissue may have a key role for the histodifferentiation of these two pituitary cell types in man [57]. Finally, starting in the 21st week of fetal development, lactotrophs are identified throughout the primordial pars distalis (Fig. 2.7d) that includes all three diverticula of Rathke's pouch [50].

During the last trimester, pituitary tissue completely surrounds the infundibular stem, and the primordial pars distalis enlarges laterally to give rise to the lateral wings,

Table 2.2 Transcription factors associated with genetic causes for human disorders of pituitary development and secretion

Transcription factor	Anterior pituitary deficiencies	Pituitary appearance by MRI
ARNT2	TSH, ACTH, variable GH, LH, FSH	Hypoplastic anterior pituitary, posterior pituitary can be absent
GLI2	Variable GH, PRL, TSH, LH, FSH, ACTH	Hypoplastic anterior pituitary, posterior pituitary can be ectopic or absent
HESX1	GH, variable PRL, TSH, LH, FSH, ACTH	Nl, hypoplastic or aplastic anterior pituitary, posterior pituitary can be ectopic
LHX3	GH, PRL, TSH, LH, FSH	Nl, hypoplastic or enlarged anterior pituitary
LHX4	GH, TSH, LH, FSH, variable ACTH	Hypoplastic anterior pituitary
OTX2	Variable GH, PRL, TSH, LH, FSH, ACTH	Nl, hypoplastic or ectopic anterior pituitary, posterior pituitary can be ectopic
PAX6	Variable GH, TSH, LH, FSH, ACTH	Nl or hypoplastic anterior pituitary
POU1F1 (PIT-1)	GH, PRL, variable TSH	Nl or hypoplastic anterior pituitary
PROP1[a]	GH, PRL, TSH, variable LH, FSH and ACTH	Nl, hypoplastic or enlarged anterior pituitary
SOX 2/SOX 3	Variable GH, TSH, LH, FSH, ACTH	Hypoplastic or enlarged anterior pituitary, posterior pituitary can be ectopic
TPIT (TBX19)	ACTH	Nl anterior pituitary

Adapted from Di Iorgi et al. [159], Giordano [160], and McCabe and Dattani [62]
[a]Most common genetic cause for combined pituitary hormone deficiency

as in the adult (Fig. 2.7c). Although the cavity of Rathke's pouch is still present, follicular structures are progressively formed in its vicinity as a part of protrusions from its walls, the posterior one becoming the pars intermedia. Due to the strong morphological similarity between folliculostellate cells and the free surface epithelium of Rathke's cavity, it is presumed that the cells that make up the follicular structures are precursors of the human folliculostellate cells [50]. Numerous genes and transcription factors are involved in regulating the various developmental steps of the human pituitary and are extensively reviewed elsewhere [58–63]. A summary of transcription factors relevant to human, pituitary morphogenesis, and histodifferentiation is provided in Table 2.2, based on clinical outcomes when any of these factors are mutated. A schematic summary of the sequential actions of transcription and other morphogenetic factors to induce the different adenohypophysial cell types is shown in Fig. 2.8.

Radiologic Anatomy

The introduction of computed tomography (CT) and magnetic resonance imaging (MRI) into medical practice has provided highly sensitive tools to elucidate the normal anatomy of the pituitary gland and to identify pathology. In particular, by MRI, the anterior and posterior pituitary are well delineated in T1-weighted images by the

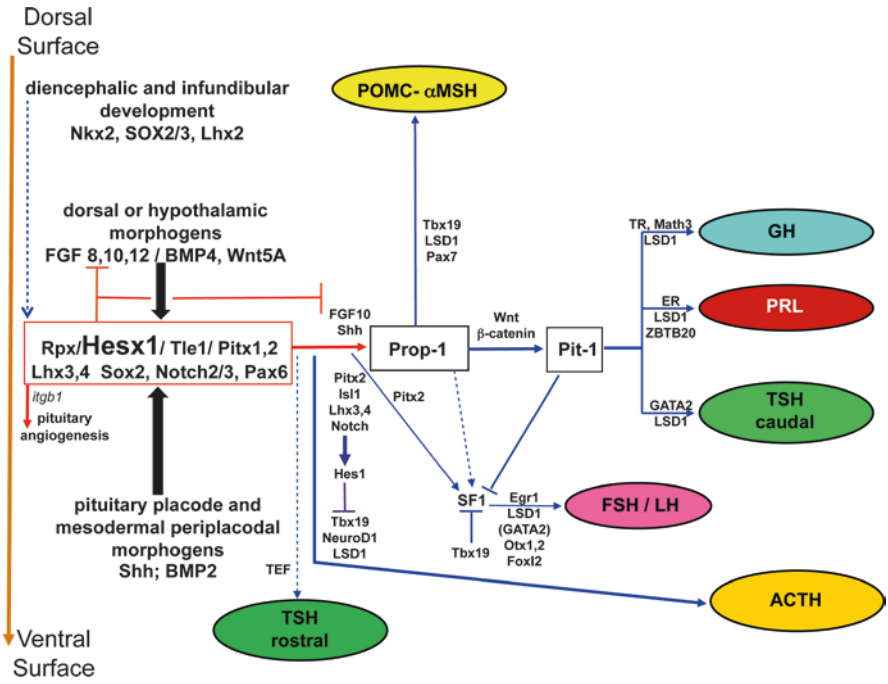

Fig. 2.8 Signaling molecules and transcription factors involved in the development of the anterior pituitary, including its vascularization (based on rodent studies). Anterior lobe somatotrophs, lactotrophs, and caudally placed thyrotrophs derive from a common lineage, determined by Prop-1 and Pit-1. Independent lineages are observed for a rostrally placed group of thyrotrophs, corticotrophs, gonadotrophs, and intermediate lobe melanotrophs. All cell types are committed to a specific lineage through activation of Notch signaling at the placodal stage. Development of the entire pituitary anlagen and related cell types are also dependent on interactions with the diencephalon and infundibular stem, whose morphogenesis is under particular influence by Hesx1. Continuous arrows, direct stimulatory action; dotted arrows, indirect stimulatory action; blocked line, inhibitory action. (Modified from Lechan and Toni [5])

so-called bright spot of the posterior pituitary (Fig. 2.9a), the posterior pituitary being hyperintense relative to gray matter despite the absence of contrast [64]. The bright spot is observed in up to 100% of normal adults, although can be absent in older individuals, possibly due to reduced storage of neurosecretory material. Typically, the bright spot measures between 1.2 and 8.5 mm in its greatest diameter and between 0.4 and 4.4 mm in the axis perpendicular to the longest axis [64]. Anything larger should raise suspicion of the underlying pathology such as a Rathke's cleft cyst (Fig. 2.9b) or hemorrhagic pituitary adenoma. It has been proposed that the bright spot can be a useful diagnostic tool to differentiate central diabetes insipidus from psychogenic polydipsia, as in central diabetes insipidus, the bright spot is absent [65] (Fig. 2.9c), whereas in psychogenic polydipsia, the bright spot is present, perhaps even larger than normal due to increased accumulation of neurosecretory material [66, 67]. The posterior pituitary has tremendous regenerative capacity such

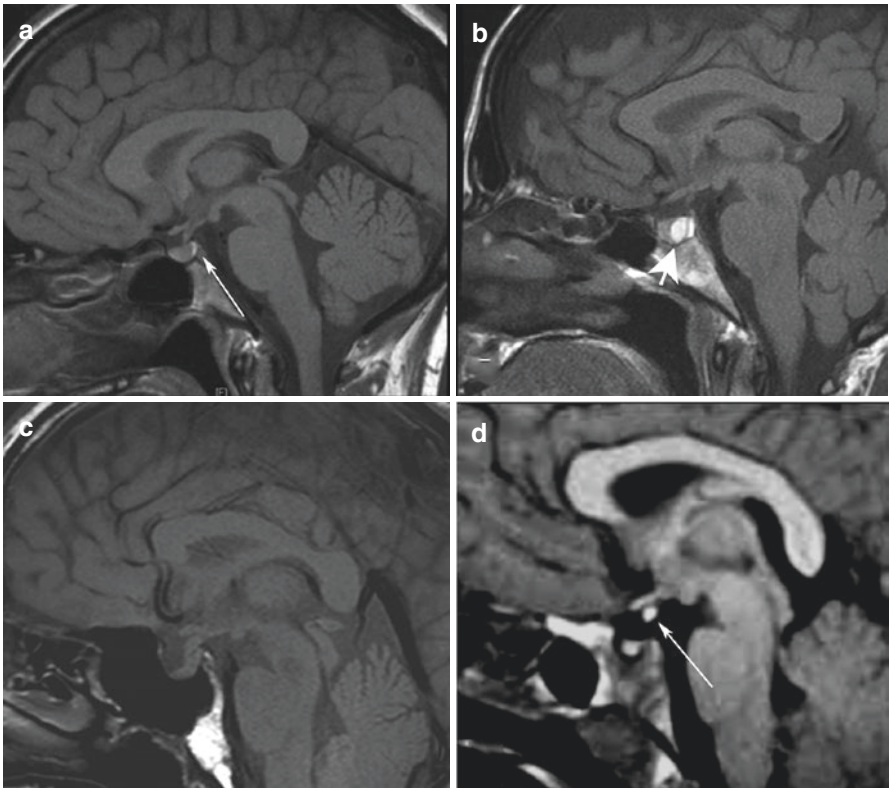

Fig. 2.9 Sagittal views of the adult, human brain by MRI. (**a**) Normal radiologic anatomy of the pituitary gland in a T1-weighted image. Note the flat to slightly concave upper surface of the pituitary and the typical appearance of the "bright spot" (arrow) denoting the posterior pituitary. The pituitary stalk is directed anteriorly and tapers as it enters the pituitary gland, the diameter of the proximal portion being somewhat larger due to invagination of the third ventricle to create the infundibular recess. (**b**) Bright spot of the posterior pituitary should not be confused with pathology such as Rathke's cleft cyst (arrowhead) which can also appear hyperintense on T1-weighted images. (**c**) Absent "bright spot" in a patient with diabetes insipidus secondary to neuroinfundibulitis. Note marked thickening of the pituitary stalk. (**c**) Ectopic posterior pituitary following stalk transection. Note the location of "bright spot" in the suprasellar cistern (arrow), absence of the pituitary stalk, and small size of the anterior pituitary

that with transection of the pituitary stalk, a new, functional posterior pituitary can form, apparent as a bright spot in an ectopic location, generally the suprasellar cistern (Fig. 2.9d).

The anterior pituitary is isointense to gray matter on T1-weighted images and isointense to hypointense on T2-weighted images and generally has a flat or concave superior surface (Fig. 2.9a). In keeping with the macroscopic anatomy (see above), the pituitary volume by MRI shows significant differences between the sexes and with aging [68–71]. In general, the anterior pituitary is small and flattened during most of childhood but enlarges during puberty, somewhat more in girls than

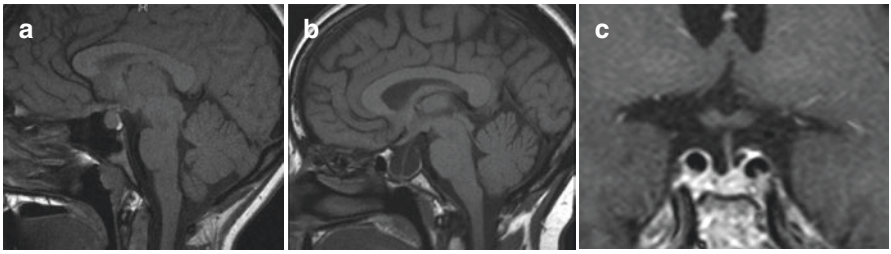

Fig. 2.10 (**a**, **b**) Sagittal and (**c**) coronal views of the adult, human brain by MRI showing normal variations of the pituitary and stalk. (**a**) Enlarged anterior pituitary in a normal, adolescent woman demonstrating convex superior surface extending into the suprasellar cistern. (**b**) Empty sella in an individual with otherwise normal anterior and posterior pituitary function. (**c**) Slight deviation of the stalk to the left in a man with an asymmetric intersphenoid septum

boys, and then decreases in size in the aged [72–74]. In a Croatian study of 199 adults (91 males and 108 females), the mean pituitary volume by MRI in young men (ages 20–29) was 539.2 mm^3 and in females 680 mm^3, whereas in the aged (ages 70–79), it was 450.4 mm^3 in males and 636.3 mm^3 in females [68]. Adolescent women may have a convex superior border to the pituitary gland suggesting anterior pituitary hyperplasia (Fig. 2.10a), but this can be a normal appearance. A similar enlargement of the anterior pituitary by MRI is characteristic of pregnancy due to the proliferation of lactotrophs [75, 76], increasing in volume by as much as 120% by the third trimester, and may extend into the suprasellar cistern. This phenomenon reflects the tremendous plasticity intrinsic to the function of the anterior pituitary, capable of responding to a changing hormonal milieu. Marked enlargement of the anterior pituitary can also be observed in severely hypothyroid individuals due to hyperplasia of anterior pituitary thyrotrophs and in Addison's disease due to corticotroph hyperplasia, fully reversible with replacement of the deficient hormones [77, 78]. Anterior pituitary volume has also been observed to increase in association with anxiety and depression [79], likely secondary to the activation of the hypothalamic-pituitary-adrenal axis.

Occasionally, the anterior pituitary can appear flattened to the base of the sella turcica, commonly described as an "empty sella" (Fig. 2.10b). While this appearance can be indicative of underlying pathology (e.g., a pituitary adenoma that has undergone apoplexy, end stages of anterior pituitary hypophysitis, intracranial hypertension) [80], it may also be a normal variant due to herniation of arachnoid and cerebrospinal fluid into the sella turcica through an incompetent diaphragma sellae (see above, Pituitary Anatomy). Small cystic structures less than 2–3 mm can be observed on occasion in the central portions of the pituitary due to remnants of Rathke's pouch but incidental findings and of no real clinical significance.

The pituitary stalk is well visualized on MRI as a midline structure arising from the base of the hypothalamus coursing through the suprasellar cistern to terminate in the posterior pituitary (Fig. 2.9a). The characteristic tapering of the stalk from superior to inferior is due to the infundibular recess of the hypothalamus that results in an invagination of cerebrospinal fluid into the proximal portion of the stalk as an

extension of the third ventricle. Using high-resolution MRI (3T MR) in 29 healthy volunteers ages 21–43, the stalk diameter at the level of the optic chiasm measured 3.25 ± 0.39 mm, whereas at the pituitary insertion, it was 2.32 ± 0.39 mm [81]. On T2-weighted images in the majority of normal subjects, the central portion of the stalk is hyperintense compared to cerebral white matter due to neurosecretory material en route to the posterior pituitary and surrounded by a peripheral rim of isointensity, thought to represent pars tuberalis. Although stalk deviation often suggests underlying pathology, minor deviation of the stalk can be seen normally, particularly if there is some sloping of the sellar floor due to an eccentric location of the intersphenoid septum [82] (Fig. 2.10c).

The vascular anatomy of the pituitary, namely, that the posterior pituitary receives an arterial supply and the anterior pituitary is primarily (although not exclusively, see above, Vascular Anatomy) fed by sinusoidal blood coming from the portal circulation, can be appreciated with dynamic imaging of the pituitary in which MRI sequences are captured simultaneously with the intravenous administration of gadolinium. As would be anticipated, initial sequences show enhancement of the posterior pituitary and base of the hypothalamus, followed by enhancement of the pituitary stalk and finally the anterior pituitary (Fig. 2.11a–c) [83].

Many of the landmarks around the pituitary gland described above can also be well visualized by MRI, including the optic chiasm and structures in the cavernous sinus. The optic chiasm lies above the pituitary gland and can be central (directly over the pituitary ~65% of cases as shown in Fig. 2.9a), prefixed (more anterior to the pituitary ~25%), or post-fixed (more posterior over the pituitary ~10%). It is separated from the pituitary by the suprasellar cistern, which appears as a pentagonal, cerebrospinal fluid-filled space on coronal images (Fig. 2.12). The cavernous sinuses are located immediately lateral to the pituitary gland and contain vascular and neuronal elements. Most prominent in the cavernous sinus is the internal carotid artery, which appears hypointense on T1-weighted images because of the blood flowing through it (Fig. 2.12a). Cranial nerves III, IV, V_1, and V_2 sometimes can be visualized as hypointense filling defects by MRI, particularly cranial nerve III as shown in Fig. 2.12a. Sympathetic fibers encircle the carotid arteries but are not well visualized.

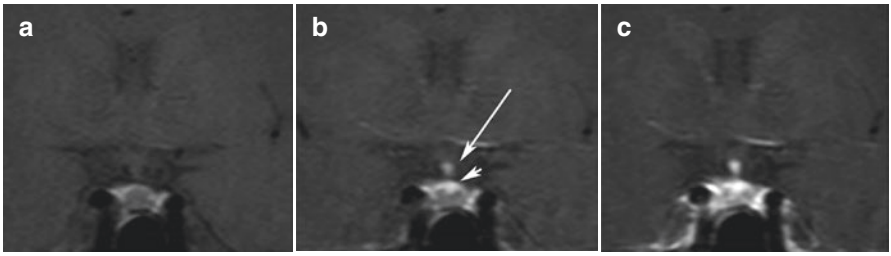

Fig. 2.11 Dynamic MRI in the coronal plane showing the time course of gadolinium filling of the pituitary following iv administration. (**a**) Pre-gadolinium. (**b**) Immediately post-gadolinium. The proximal pituitary stalk (arrow) and posterior pituitary (arrowhead) are the first to fill. (**c**) Gadolinium then fills the anterior pituitary

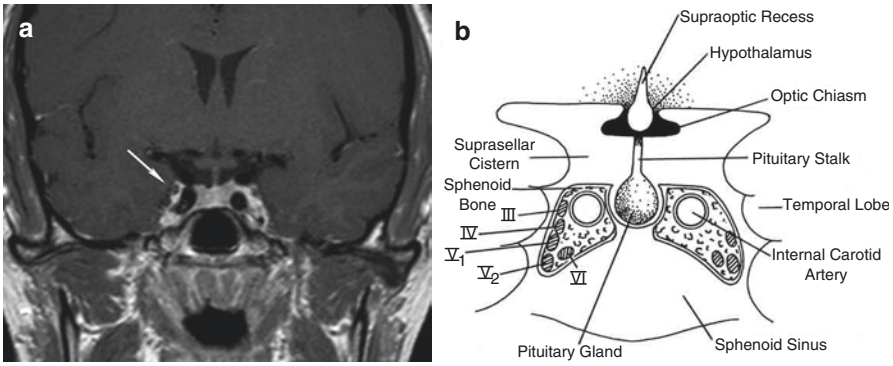

Fig. 2.12 (**a**) MRI and (**b**) schematic image of the pituitary and its anatomic relationships in coronal orientation. The cavernous sinus is situated on either side of the pituitary and contains the internal carotid artery and cranial nerves III, IV, V_1, V_2, and VI. The optic chiasm resides immediately above the pituitary gland and is separated from it by a pentagonal-shaped cerebrospinal fluid-filled space, the suprasellar cistern. Arrow in (**a**) points to cranial nerve III. (**b** from Endocrinol Metab Clin North Am, 16, Lechan RM, p 477, Copyright Elsevier)

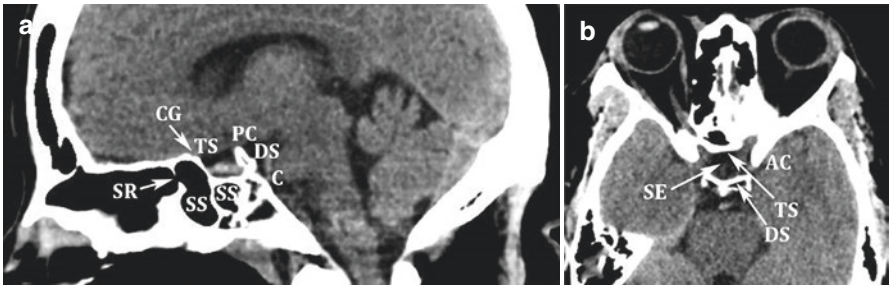

Fig. 2.13 (**a**) Parasagittal and (**b**) horizontal images of the sella turcica by CT. The bony architecture is well delineated. Note septations in the "sellar type" sphenoid sinus (SS). AC anterior clinoid, C clivus, CG chiasmatic groove, DS dorsum sellae, PC posterior clinoid, SE sella turcica, SR ostium of sphenoethmoidal recess, TS tuberculum sellae

MRI has largely replaced CT as the imaging modality of choice to assess the pituitary gland, but the bony architecture of the sella turcica is best seen by CT (Fig. 2.13). The clivus is also well seen as it slopes posteriorly and inferiorly from the dorsum sellae, as is the sphenoid sinus (Fig. 2.13). Mean length and height of the sella turcica by CT tend to be greater in females than in males [84], reflecting that the female gland is larger than the male gland.

Imaging using positron emission tomography (PET) is gaining increasing utility as newer tracers are being developed. ^{68}Ga-DOTATATE, which binds to somatostatin receptors 2 and 5, shows reasonably good uniform uptake throughout the normal, anterior pituitary due to its high expression of somatostatin receptors [85]. In contrast, 18F-FDG PET shows preferential uptake into pituitary adenomas as well

as other inflammatory and infiltrative disorders and little or no uptake into normal pituitary tissue [85], making it feasible to use PET imaging as a tool to identify tiny, functional pituitary adenomas by subtractive analysis.

Microscopic and Functional Anatomy

Anterior Pituitary (Adenohypophysis)

As noted above, the anterior pituitary is made up of three components, the pars distalis, the largest component of the anterior pituitary; pars intermedia, which is vestigial in man; and the pars tuberalis. It is the pars distalis, however, that is the main source of anterior pituitary hormone secretion.

Pars Distalis

The pars distalis is composed of nests or cords of large, epithelial, polygonal cells organized near venous sinusoids lined with a fenestrated epithelium into which secretory products from the anterior pituitary are collected. The nesting pattern is apparent in reticulin preparations that show a delicate, continuous border around acini (Fig. 2.14a), differentiating normal anterior pituitary tissue from adenomatous tissue that have a disrupted reticulin pattern (Fig. 2.14b). The cells of the normal pars distalis contain abundant cytoplasm that stain varyingly. Three cells types, acidophils, basophils, and chromophobes, were classically recognized using standard histological preparations such as hematoxylin and eosin (H&E) in which acidophils are red, basophils purple, and chromophobes light blue and PAS in which basophils are bright purple (Fig. 2.14c, d). A number of other stains have also been used in an attempt to identify specific cell subtypes, as illustrated in Fig. 2.14e, f, such as aldehyde thionine with PAS and orange G and Herlant stain. However, immunocytochemistry, which is now widely used in surgical pathology, best differentiates the five, major, cell types and six, secretory products of the anterior pituitary gland: somatotrophs (growth hormone), lactotrophs (prolactin), corticotrophs (adrenocorticotropic hormone), thyrotrophs (thyroid-stimulating hormone), and gonadotrophs (luteinizing hormone and follicle-stimulating hormone) (Table 2.3). The somatotrophs make up the acidophils (although lactotrophs can also be acidophilic), corticotrophs the basophils (although thyrotrophs can also be basophilic), and gonadotrophs, lactotrophs, and thyrotrophs the chromophobes. In fish, pituitary cell types tend to be highly organized into distinct zones, with lactotrophs more rostral and somatotrophs more caudal in the pars distalis [86]. A topography is also retained in man (Fig. 2.15) with a tendency for somatotrophs to occupy more lateral regions of the pars distalis, lactotrophs the posterolateral region, and corticotrophs

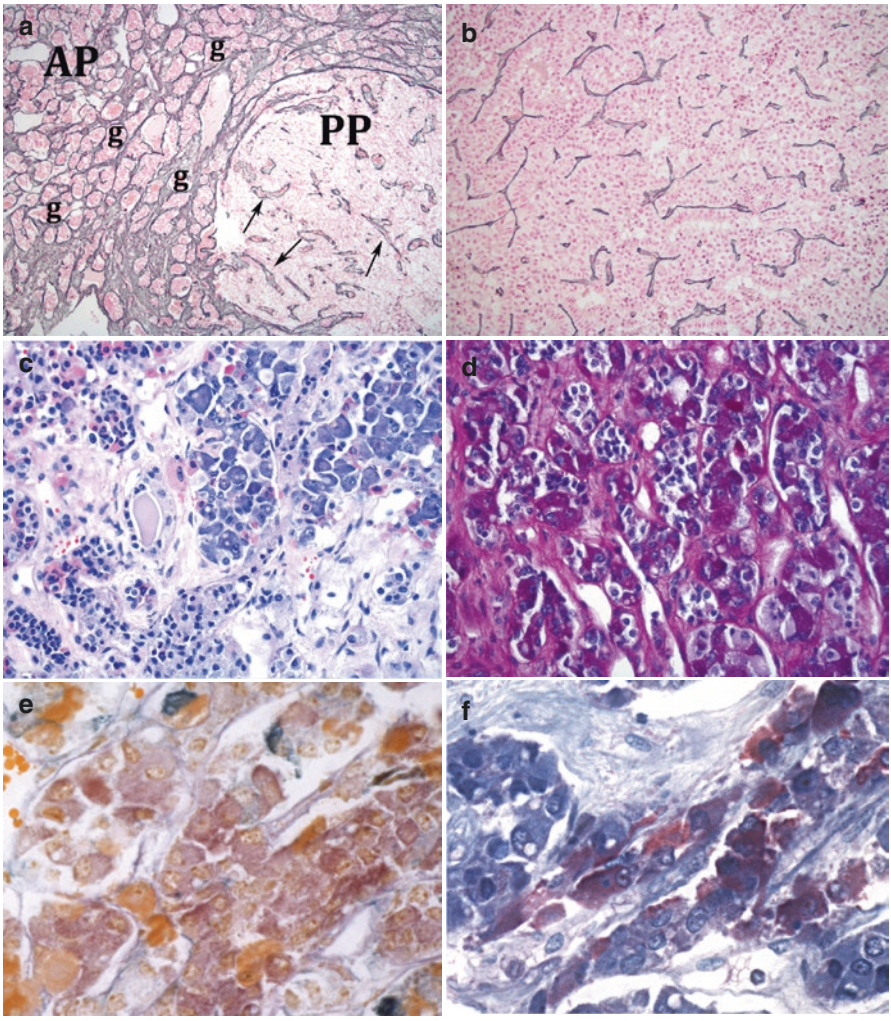

Fig. 2.14 Reticulin special stain of (**a**) normal pituitary and (**b**) pituitary adenoma. In the normal pituitary, reticulin fibers surround glandular (acini) components (g) of the pars distalis (PD) and decorate vessels (arrows) in the posterior pituitary (PP) but are discontinuous in pituitary adenomas with only capillaries picking up black staining. (**c**) H&E, (**d**) PAS, (**e**) PAS with aldehyde thionine orange G, and (**f**) Herlant stains of a normal pituitary. (**c**) Glands show mixed cell population including basophils (dark blue cytoplasm), acidophils (red cytoplasm), and chromophobes (light blue granular cytoplasm). Basophils show single or multiple small clear vacuoles in the cytoplasm, corresponding to enigmatic bodies. Yellow inclusions in some cells due to the presence of lipofuscin. (**d**) Only basophils avidly pick up PAS and appear bright purple. (**e**) Acidophils, which are largely somatotrophs, stain bright orange, gonadotrophs purple, and thyrotrophs dark blue. (**f**) Somatotrophs stain orange, lactotrophs red-purple, corticotrophs dark blue, and thyrotrophs light blue or unstained. Magnification ×200 in (**a**), ×400 in (**b**–**d**) and ×600 (**e**, **f**)

Table 2.3 Classic cell types and secretory products of the anterior pituitary

Cell type	Secretory products	% of cell population
Somatotroph	Growth hormone (GH)	50
Lactotroph	Prolactin	15
Corticotroph	Adrenocorticotropic hormone (ACTH)	15
Thyrotroph	Thyroid-stimulating hormone (TSH)	10
Gonadotroph	Luteinizing hormone (LH)	10
	Follicle-stimulating hormone (FSH)	

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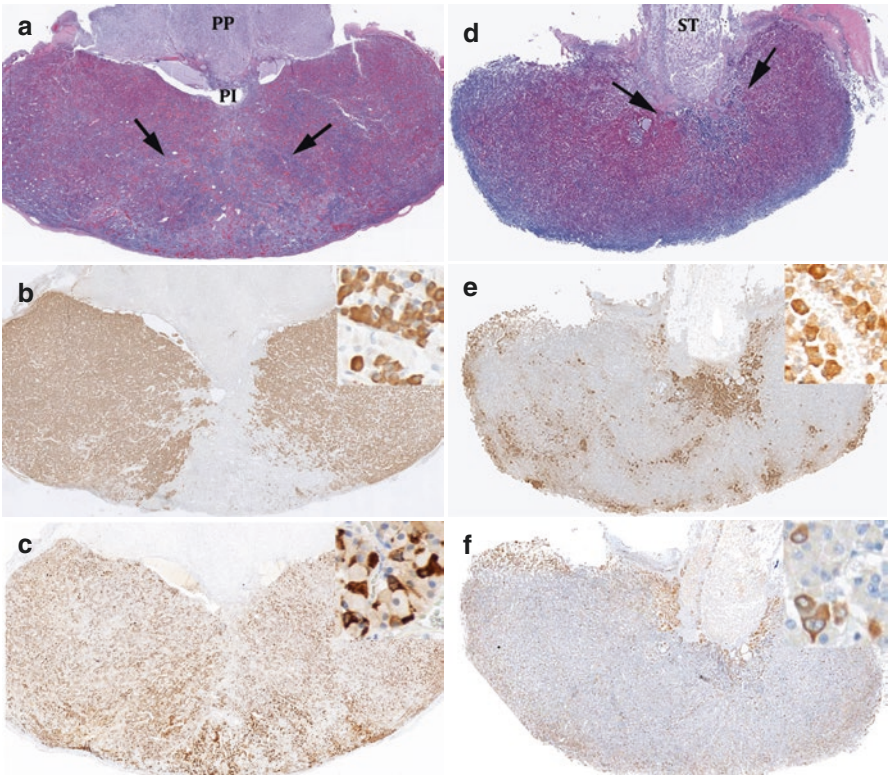

Fig. 2.15 (**a**, **d**) H&E stains of transverse section through an adult male (**a**) and coronal section through a female (**b**) pituitary gland (magnification 15×). Pale staining areas located at the superior surface of the sections correspond to the posterior pituitary (PP) and neural component of the pituitary stalk (ST). Note the high concentration of basophilic cells in the midportion of the pars distalis (below arrows in (**a**, **d**)) comprising the mucoid wedge and in the pars intermedia (PI) in (**a**). (**b**, **c**) Correspond to (**a**) and show the distribution and morphologic appearance of somatotrophs in (**b**) and lactotrophs in (**c**). (**e**, **f**) Correspond to (**d**) and show the distribution and morphologic appearance of corticotrophs (**e**) and gonadotrophs (**f**). Insets ×200. Note tendency for somatotrophs to occupy the lateral wings of the pars distalis and virtual absence from the mucoid wedge, whereas corticotrophs tend to concentrate in the mucoid wedge. A more generalized distribution is seen for lactotrophs and gonadotrophs. Also note particular angularity of lactotrophs compared to other cell types

and thyrotrophs the anteromedial region or mucoid wedge, whereas gonadotrophs are widely dispersed [87]. Each of these cell types is regulated by hypothalamic releasing and inhibitory hormones after they are released into the portal vasculature for conveyance to pars distalis cells (see Lechan and Toni [5] for review).

Corticotrophs are medium-sized cells and contain large, clear, cytoplasmic vacuoles known as "enigmatic bodies" that are lysosomal complexes, easily identified on routine H&E sections. By electron microscopy, numerous secretory granules can be seen along with bundles of intermediate keratin filaments. ACTH immunostaining decorates the cytoplasm of corticotrophs by immunostaining secretory granules, but not keratin filaments or lysosomal bodies [88]. In response to excess glucocorticoids, an accumulation of intermediate filaments results in Crooke's hyaline change in corticotrophs, a pale, pink, glassy, ringlike staining of the cytoplasm on H&E. These changes are readily identified by immunostaining for low-molecular-weight keratins such as CAM5.2 and by demonstrating displacement secretory granules to the cell membrane edges with ACTH antiserum [89]. In cases of extensive Crooke's hyaline change, the keratin filaments will occupy almost the entire cytoplasm, the cells become larger, and the nuclei develop prominent nucleoli.

Somatotrophs comprise the largest cell population of the pars distalis and are round to oval shaped with round nuclei. Immunostaining with GH-directed antibodies shows particularly strong cytoplasmic immunopositivity and the best way to recognize these cells. By electron microscopy, active cells have prominent, lamellar, rough endoplasmic reticulum and large Golgi regions. The entire cytoplasm is filled with dense secretory granules measuring from 150 to 800 nm in diameter, and there is a prominent endoplasmic reticulum that changes with the activity of the cell [90].

Lactotrophs are also well delineated by prolactin antiserum. Ultrastructural morphology identifies cells with both dense and sparse granules, although sparsely granulated cells make up the majority of prolactin-producing cells that actively secrete the hormone. The endoplasmic reticulum is well developed with parallel arrays that can occasionally form concentric structures called the Nebenkern formation. Long cytoplasmic processes can project into the center of acini and wrap around gonadotrophs, providing morphologic evidence suggesting paracrine regulation (see below).

Mammosomatotrophs resemble somatotrophs but produce both growth hormone and prolactin, detected within the same cell by immunohistochemistry and even within the same secretory granule. Two types of mammosomatotrophs have been identified by electron microscopy including cells containing numerous, small electrodense granules (150–400 nm), and cells with large cigar-shaped granules ranging up to 2000 nm with variable density [91].

Thyrotrophs are medium-sized, angulated cells that contain an eccentric nucleus. The cells are filled with small secretory granules that measure 100–200 nm, short rough endoplasmic reticulum and large Golgi complexes.

Gonadotrophs can be bihormonal or contain only one of the gonadotropins. By electron microscopy, round Golgi complexes and numerous granules are characteristic. The size of secretory granules varies in males and females: smaller secretory granules in male and larger secretory granules in females. Gonadotrophs frequently show oncocytic change and squamous metaplasia in older individuals.

Several of the major anterior pituitary cell types can also be detected in the adult pituitary with antiserum directed against transcription factors involved in their embryologic development. Included are TPIT that can be detected in corticotrophs [92], Pit-1 that can be found in somatotrophs, lactotrophs and thyrotrophs [93], steroidogenic factor 1 (SF-1) that is present in gonadotrophs, and GATA-2 in gonadotrophs and thyrotrophs [94]. These transcription factors can be retained in pituitary adenomas, facilitating the identification of their cell type [95]. All anterior pituitary cell types also can be identified with antiserum to the epithelial marker, CAM5.2 (low molecular weight keratin), and to the neuroendocrine marker, synaptophysin. Immunocytochemistry for alpha subunit also identifies cells producing LH, FSH, and TSH, since all are glycoprotein hormones and contain a common alpha subunit.

There are also small populations of other cellular subtypes in the pars distalis. Included are oncocytes that contain abundant mitochondria making the cytoplasm appear eosinophilic and granular by routine H&E stain and become more prominent with aging; null cells that are scattered throughout the pars distalis and, thereby, cannot be classified by hormone production and represent resting or stem cells; and follicular cells that tend to be seen in areas of cell injury or adjacent to tumors, formed from somatotrophs, lactotrophs, and/or corticotrophs that surround damaged cells and become degranulated and dedifferentiated. The folliculostellate cell comprises approximately 5–10% of the pars distalis cell population and is described more fully below.

It is becoming increasingly recognized that the organization of the pars distalis is vastly more complicated than described above. First, there is morphological and physiological evidence for heterogeneity among the classical anterior pituitary cell types including at least three subtypes of somatotrophs (sparsely granulated cell, densely granulated cells, and, as described above, mammosomatotrophs) and functionally different lactotrophs [96–98]. Plurihormonal cells in the human pituitary are also commonly found, particularly for somatotrophs and lactotrophs in which up to 25% of somatotrophs and 15% of lactotrophs co-express FSH [87]. Up to 4% of thyrotrophs co-express FSH, ACTH, or LH [87].

Cell clustering has also been observed for several of the hormonal cell types in the pars distalis and to form networks that can extend distances over the pars distalis [99], presumably as a way to integrate or amplify signals from the hypothalamus. The organization of these networks tends to change with specific phases of development or alterations in physiologic milieu [99, 100], indicative of the plasticity of the pars distalis. For example, during lactation, there is proliferation and reorganization of lactotrophs into a honeycomb-like structure with increased contacts between the cells as a way to coordinate increased output of prolactin [99, 101]. Somatotrophs tend to form clusters that are interconnected by strands of single somatotrophs but become particularly prominent during puberty in association with the growth spurt [100].

In addition to the above, there is strong evidence that the microenvironment of hormonal-secreting cells in the pars distalis is an important component for cell regulation in conjunction with neurosecretion from the hypothalamus. This local, regulatory control mechanism is mediated by paracrine and autocrine secretion of pars distalis hormones utilizing an expanding list of peptides, growth factors, cytokines, binding proteins, gases, and neurotransmitters listed in Table 2.4 (see Denef for

Table 2.4 Nonclassical anterior pituitary substances and cell(s) of origin

Substances	Cell types
Peptides	
Activin B, inhibin, follistatin	F,G
Aldosterone-stimulating factor	UN
Angiotensin II (angiotensinogen, angiotensin I	C,G,L,S
Converting enzyme, cathepsin B, renin)	
Atrial natriuretic peptide	G
AVP	C
Corticotropin-releasing hormone-binding protein	C
Dynorphin	G
Enkephalin	S
Endothelins	L
Galanin	L,S,T
Ghrelin	L,S,T
Gawk (chromogranin B)	G
Growth hormone-releasing hormone	UN
Histidyl-proline diketopiperazine	UN
Motilin	S
Neuromedin B	T
Neuromedin U	C
Neuropeptide Y	S,T
Neurotensin	G,T
Protein 7B2	G,T
Somatostatin 28	UN
Substance P (substance K)	C,L,G,S,T
Thyrotropin-releasing hormone	G,L,S,T
Urocortin	C,L,S
Vasoactive intestinal polypeptide	G,L,T
Growth factors	
Basic fibroblast growth factor	C,F
Chondrocyte growth factor	UN
Epidermal growth factor	G,T
Glial cell-derived neurotrophic factor	F
Insulin-like growth factor I	S,F
Nerve growth factor	L
Pituitary cytotropic factor	UN
Transforming growth factor alpha	l,s,g
Vascular endothelial growth factor	F
Cytokines	
Interleukin-1 beta	T
Interleukin-6	F
Leukemia inhibitory factor	C,F

(continued)

Table 2.4 (continued)

Substances	Cell types
Neurotransmitters	
Acetylcholine	C,L
Nitric oxide	F,G
Other	
Endocannabinoids	C,L,S
Carboxypeptidase E	C,L,S
Carboxypeptidase	D,C
Carboxypeptidase Z	C,G,L,S,T
Leptin	C,F,G,S,T

Modified from Lechan and Toni [5]
C corticotroph, *F* folliculostellate cell, *G* gonadotroph, *L* lactotroph, *S* somatotroph, *T* thyrotroph, *UN* unknown

extensive review [102]). That some gonadotrophs are closely apposed to lactotrophs was first recognized by Nakane [103] and later demonstrated by Denef and Andries [104] that gonadotrophs secrete substances in response to GnRH that stimulate prolactin secretion. Namely, medium from a highly enriched population of gonadotrophs in culture treated with GnRH, when added to a highly enriched population of lactotrophs, induces prolactin secretion [105]. Candidate substances derived from gonadotrophs abound and include pituitary glycoprotein hormone alpha subunit (αGSU), a N-terminal fragment of POMC (POMC 1–74), neurotensin, angiotensin II, PACAP, calcitonin, and CART among a number of other substances [102]. Gonadotrophs may also modulate the secretion from somatotrophs and corticotrophs through paracrine interactions [102]. Autocrine regulation has been recognized for somatotrophs, which express growth hormone receptors [106] that when activated, exert an inhibitory action on its own secretion [106]. Other substances may also contribute to autocrine regulation of somatotrophs including ghrelin, TRH, leptin, enkephalin, NPY, and substance P [102]. Numerous other examples of autocrine control can be found in the literature including evidence that lactotrophs are under autocrine regulation by galanin, VIP may mediate the proliferative response of lactotrophs to estrogen, neuromedin B produced by thyrotrophs exerts an inhibitory effect on TSH secretion, and activin B produced by gonadotrophs selectively induces LH secretion without having an effect on FSH secretion [102].

Paracrine regulation and network functioning are also facilitated by a nonhormonal cell type, the folliculostellate cell. The folliculostellate cell is a small, chromophobic, stellate-shaped cell with long, delicate cytoplasmic processes (Fig. 2.16) creating a meshwork in which the glandular cells of the pars distalis reside [107]. Because they are immunopositive for glial fibrillary acidic protein (GFAP), cytokeratin, vimentin, and fibronectin, they are believed to be of glial origin. Folliculostellate cells are also strongly immunopositive for S-100. These cells function as part of an intrapituitary regulatory center, modulating glandular cells of the pars distalis as an excitable network capable of transmitting signals over long distances by electronic coupling to each other through gap junctions and intercellular junctions (zona adherens) [102, 108]. Folliculostellate cells also make contact with

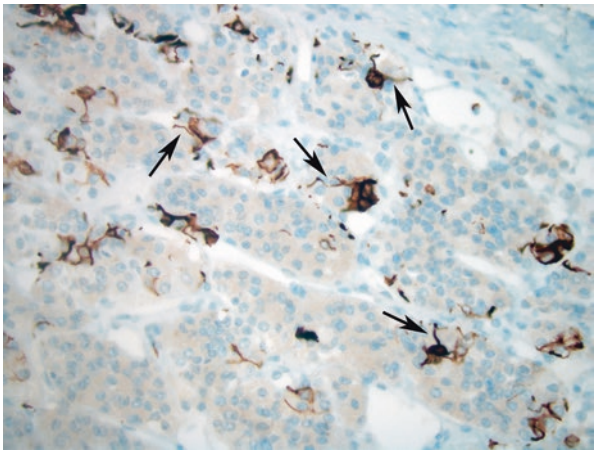

Fig. 2.16 GFAP immunostaining of folliculostellate cells in pars distalis. Note typical stellate appearance highlighted by dark brown cytoplasmic immunopositivity, close association with glandular cells, and long, cytoplasmic processes (arrows) that extend into acini. Magnification ×400

hormonal cells in the pars distalis and, through the release of a variety of substances including cytokines and growth factors listed in Table 2.4, can modify pituitary hormone secretion [100, 102]. Among many examples include a paracrine action of folliculostellate cell-derived IL-6 in response to endotoxin contributing to the increase in ACTH from corticotrophs [109], basic fibroblast growth factor and glial cell-derived neurotrophic factor as permissive for the mitogenic effect of estradiol on lactotrophs [110] and regulation of lactotroph apoptosis [111], respectively, and a role in the luteinizing hormone surge [112]. Folliculostellate cells also contribute to organization of the extracellular matrix surrounding clusters of pars distalis cells by regulating collagen synthesis from pericytes through the release of TGFβ2 [113] and laminin from gonadotrophs [114] and potentially contribute to the stem cell population [115].

Pars Intermedia

The pars intermedia is located between the pars distalis and posterior pituitary, but there is no clearly defined boarder. Although well developed during fetal development in man, it involutes shortly after birth and in the adult consists of clusters of basophil cells (corticotrophs) around colloid-filled cysts in dorsal portions of the mucoid wedge and PAS positive (Figs. 2.15a and 2.17a), but in some cases only scant connective tissue can be found [116]. Here, corticotrophs tend to be smaller than in the pars distalis, have more granules, and are less sensitive to glucocorticoids as they do not develop Crooke's hyaline change and contain fewer keratin filaments. Some of these cells comprise the basophil invasion and extend well into the posterior pituitary (Fig. 2.17b, c), found in approximately 62% of human autopsy series [117]. However, the basophil invasion is more often seen in aging men, although the significance of this phenomenon is unknown and there are no endocrine abnormalities recognized. The pars intermedia is primarily comprised of a

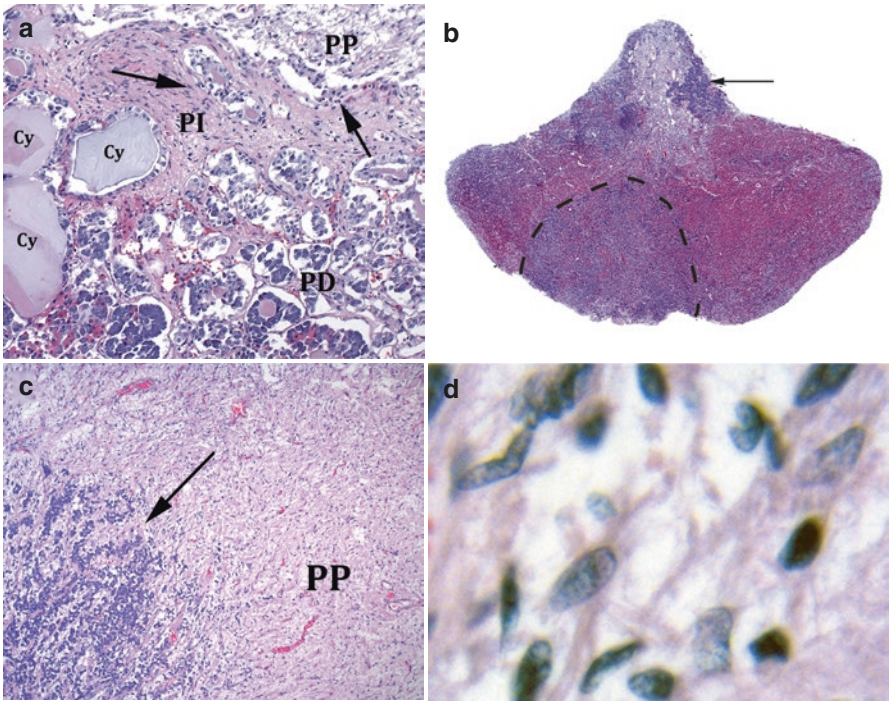

Fig. 2.17 (**a**) H&E stain of the pars intermedia (PI, corresponds to Fig. 2.15a) at the interphase of the pars distalis (PD) and posterior pituitary (PP). The PI contains multiple follicular cysts (Cy) lined with columnar cells and filled with homogeneous, eosinophilic, colloidal material, and areas of basophilic cells (arrows), presumed to be melanotrophs of the PI, interspersed within fibrous tissue. (**b**) H&E stain of an adult male pituitary gland (coronal section) showing the basophil invasion (arrow) into the posterior pituitary. The mucoid wedge is seen below the dotted line and contains mainly basophilic cells. (**c**) Higher magnification of basophil invasion (arrow) and posterior pituitary (PP). The PP is readily recognizable as neural tissue with a fibrillary background and fine capillary network. (**d**) High magnification of a region of the PP shown in (**c**). Note typical appearance of the numerous, spindle-shaped pituicytes. Magnification ×100 in (**a**), ×15 in (**b**), ×200 in (**c**) and ×600 in (**d**)

single cell type that synthesizes pro-opiomelanocortin (POMC), but as opposed to anterior pituitary corticotrophs, these cells do not generally produce ACTH due to extensive processing of the prohormone [118]. Rather, the major peptide contained in pars intermedia cells is α-MSH, and hence, they are commonly referred to as melanotrophs. Extensive processing also results in the production of β-endorphin, but because it is N-acetylated, it does not have opiate activity [118]. Small clusters of ACTH-producing cells have also been identified in the vicinity of the pars intermedia but could also belong to the pars distalis.

As opposed to the pars distalis, the pars intermedia is essentially hypovascular [119, 120], although there is evidence that any secretory products from these cells can reach the peripheral bloodstream via the posterior pituitary vasculature [121]. However, the pars intermedia is directly innervated by axonal fibers originating

from the hypothalamus. Included are dopamine- and serotonin-containing axons [122–124] and TRH-containing axons [125]. Melanotrophs also express dopamine D2 receptors [126] and TRH receptors [125]. The propensity for the pars intermedia to selectively recruit a neuronal innervation may relate to the ability of these cells to express brain-derived neurotrophic factor [127, 128]. While the physiologic significance of this innervation in amphibians is clear, as dopamine inhibits and TRH stimulates the release of α-MSH, allowing α-MSH to regulate pigment dispersion in dermal melanophores [129], the role of the pars intermedia in man is of uncertain physiologic importance. Nevertheless, the common occurrence of the basophil invasion in the posterior pituitary and evidence that these cells also produce α-MSH and have a high proliferative index indicative of active mitosis [117] suggest a potential, functional role for these cells in the adult human brain.

Marginal Zone

Although not considered one of the major subdivisions of the anterior pituitary, the region that comprises the first row of cells from each of the pars distalis and the intermediate lobe is referred to as the marginal zone and is conserved in the human pituitary [130]. The main cell population consists of ciliated epithelial cells that are attached to each other and co-express a variety of stem cell markers such as Sox2, Sox9, Gfra2, RET, Oct 4, SEA4, Prop1, and KLf4 [131]. Tracing experiments indicate that these cells are capable of migrating into the pars distalis and differentiating into mature, hormone-producing cells [132] and may underlie the plasticity of the anterior pituitary in response to physiological changes as discussed previously.

Pars Tuberalis

The pars tuberalis is composed of columns of cells separated by sinuses, very much like the structure of the pars distalis, but encircling the infundibular stem (Fig. 2.6b) and in close contact with the base of the median eminence superiorly and pars distalis inferiorly. The physiological role of the pars tuberalis in man remains somewhat enigmatic, but it is clear that it is part of the photosensing pathway in the CNS and, in some mammals and birds, has an established role in the regulation of seasonal reproduction, sexual behavior, and hibernation (for reviews see Wood and Loudon [133], Korf [134], Azzali et al. [135]). The majority of cells that make up the pars tuberalis (PT-specific cells) are immunoreactive for the common, glycoprotein alpha subunit (CGA) due to the presence of gonadotrophs and thyrotropes [136]. As opposed to thyrotrophs in the pars distalis, however, pars tuberalis thyrotrophs are smaller and lack receptors for TRH [137]. Rather, they express the melatonin MT1 receptor [138, 139], which, in response to melatonin, results in the expression and release of TSH as part of a complex, so-called retrograde pathway

that by increasing type 2 deiodinase activity in third ventricular tanycytes, ultimately leads to the regulation of GnRH secretion in the mediobasal hypothalamus [140, 141]. Melatonin also appears to have an important role in the regulation of clock genes in the pars tuberalis including *Clock*, *Bmal1*, *Per2*, *Cry1*, and *Cry2* [142] that serve to mediate the photoperiodic signal generated by melatonin. Evidence that the pars tuberalis can activate Iκ-Bα in response to endotoxin, indicative of cytokine signaling through the NF-κB pathway, also suggests a role in immune modulation and hypothesized contribute to the mechanism of nonthyroidal illness during infection [143].

The pars tuberalis may also be involved in the seasonal release of prolactin secretion from the pars distalis through an "anterograde pathway" utilizing a variety of other substances including neurokinin A, substance P, and endocannabinoids [134]. In man, the CB1 receptor is most highly expressed in folliculostellate cells and corticotrophs in the pars distalis, however, indicating that any effect of the pars tuberalis on prolactin secretion must be indirect through paracrine regulation in the pars distalis [136]. Given the high expression of CB1 receptors on corticotrophs, the release of endocannabinoids by the pars tuberalis may also contribute to the regulation of the hypothalamic-pituitary-adrenal axis through direct, inhibitory effects in the pars distalis [144, 145].

Posterior Pituitary

The posterior pituitary is the lowest part of a continuous bundle of nerve fibers that extend from the hypothalamic magnocellular neurons that produce vasopressin and oxytocin, pass through the internal layer of the median eminence that forms the base of the hypothalamic infundibulum, and then proceed into the infundibular stem to terminate in the posterior pituitary (see above, Pituitary Anatomy). This bundle is composed of numerous unmyelinated and sparsely myelinated axons and axon terminals containing large neurosecretory vesicles, specialized glial cells called pituicytes, and a rich capillary network (Fig. 2.17c, d). The neurosecretory material is largely made up of the nonapeptides, vasopressin and oxytocin, and their carrier proteins, derived from magnocellular neurons in the hypothalamic paraventricular and supraoptic nuclei, but a variety of other substances are also found in the posterior pituitary, co-contained in vasopressin and oxytocin terminals. Coexisting in vasopressin axon terminals are dynorphin, galanin, pituitary adenylate pituitary cyclase-activating polypeptide (PACAP), secretin, and glutamate and in oxytocin axon terminals, dynorphin and proenkephalin A-derived μ-opioid peptides (see Brown [146] for review). In addition, neurons synthesizing dopamine and norepinephrine originating from the hypothalamus and brainstem, respectively, also innervate the posterior pituitary [147].

The importance of vasopressin as an antidiuretic hormone and oxytocin in uterine contraction and milk letdown is well known. Coexisting substances in vasopressin and oxytocin neurons are presumed to modulate the secretion of vasopressin and

oxytocin from the posterior pituitary and/or their dendritic processes in the hypothalamus [146]. This concept is supported by an inhibitory effect of dynorphin on phasic activity of vasopressin secretion [146] and the existence of kappa opioid receptors, the endogenous ligand for dynorphin, on nerve terminals in the posterior pituitary [148]. However, it is also possible that some substances, such as dopamine, are destined for regulation of the anterior pituitary by way of the short portal vessels [149] that interconnect the capillary beds in the posterior pituitary with the anterior pituitary [150].

Pituicytes comprise approximately 25% of the posterior pituitary and have been classified into parenchymatous and fiber subtypes [151]. Parenchymatous pituicytes are large cells and immunostain with thyroid transcription factor −1 (TTF-1), glial fibrillary acid protein (GFAP), and S100, whereas fibrous pituicytes, the most abundant pituicyte, are small cells and immunostain only with S100 (Fig. 2.17d). The significance of this morphologic distinction is uncertain. However, pituicytes contain processes that interconnect with each other through tight, gap, intermediate, and complex junctions, terminate on blood vessels, and envelop axon terminals containing vasopressin and oxytocin, indicative of an important role in regulating vasopressin and oxytocin secretion [152]. Namely, under basal conditions, pituicytes completely engulf the neurosecretory axon endings and interject their processes between secretory nerve endings and the basal lamina of the fenestrated vasculature. Dehydration, however, results in retraction of pituicyte processes (stellation) from axon terminals and at the vascular surface, favoring increased hormone release into the peripheral bloodstream. Pituicytes are also believed to be osmotic sensors and produce humoral factors such as galanin-like peptide (GALP) in response to hypertonic saline [153], which may contribute to the release of vasopressin and oxytocin from neuronal endings in the posterior pituitary [154]. Conversely, pituicytes release taurine in response to hypotonic conditions, inhibiting hormone release from the posterior pituitary [155]. Thus, as summarized by Rosso and Mienville [156], pituicytes may control neurohormone output by at least two major mechanisms, through structural modifications and by the release of hormone modulators.

Concluding Remarks

The pituitary gland comprises only a tiny fraction of the intracranial volume, yet as apparent from current understanding of its embryologic development, macroscopic and microscopic anatomy, and functionality, it is a highly complicated structure. Particularly exciting is the potential for regeneration of the pars distalis, given evidence for embryonic stem cells in the marginal zone of the pars intermedia and the remarkable plasticity of the adenohypophysis as apparent during adolescent development in women and in association with primary hypothyroidism, pregnancy, and primary hypoadrenalism. Evidence for communication between tanycytes in the hypothalamus and hormonal-producing cells in the pars tuberalis has provided new insights about the functionality of this portion of the anterior pituitary in animal models, but although also

a well-established structure in man, its role is still unknown. While the pituitary has fascinated scientists over the centuries and a vast amount of knowledge has been amassed since the original Galenic concepts, we still have much to learn.

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Chapter 3
Prolactin Assays and Regulation of Secretion: Animal and Human Data

Nadine Binart, Jacques Young, and Philippe Chanson

Prolactin Assays

In humans, the demonstration of hyperprolactinemia is crucial for the etiological diagnosis of acquired hypogonadism and pituitary adenomas.

What Is Measured in Prolactin Assays?

The mature PRL protein in humans (hPRL) is composed of 199 amino acids [1, 2]. The PRL polypeptide is formed of a single chain of amino acids with three highly conserved intramolecular disulfide bonds between six cysteine residues. PRL can undergo posttranslational modifications including glycosylation, phosphorylation, proteolytic cleavage, or polymerization, which have an impact on its receptor binding, biological activity, stability, and measurement.

Phosphorylated forms of PRL have been identified in most species, although it is not known whether these forms occur in the plasma in vivo. In standard bioassays,

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phosphorylated PRL shows reduced potency, and it antagonizes the pro-proliferative action of the predominant unphosphorylated form [2, 3].

Glycosylated PRL has been identified in the pituitary gland, where it forms a highly variable proportion of total PRL (1–60%) [4]. hPRL is N-glycosylated on N31. Glycosylation lowers the biological activity of PRL, reduces its receptor binding, and lowers its metabolic clearance rate. Glycosylated PRL may account for rare cases of mild asymptomatic unexplained hyperprolactinemia [5].

Proteolytic cleavage of the 23 kDa protein generates several PRL variants [6]. The major 16 kDa variant is a product of cleavage that occurs in the interstitial medium outside the cells and in the vicinity of blood capillaries, which implies that tissue-specific mechanisms of regulation exist. The 16 kDa variant includes only the N-terminal section of the mature protein and does not bind the PRL receptor. This variant appears to bind to endothelial cells, and its inherent antiangiogenic properties have led to the use of the term "vasoinhibin" for this protein [7, 8].

PRL circulates in several molecular forms. In healthy individuals the monomeric form of 23 kDa ("little PRL") represents 60–85% of circulating PRL. In addition to forming dimers of 50 kDa ("big PRL"), which represent 10–20% of circulating PRL in serum, PRL can aggregate with immunoglobulin G (autoantibodies), creating high-molecular-weight forms (150 kDa, "big-big PRL"), which normally account for only 5–25% of circulating PRL. These larger forms of PRL have minimal biological activity in vivo and no known pathologic actions [9].

The History of Prolactin Assays

Following the discovery that pituitary extracts induce milk production, a relatively crude bioassay for prolactin (PRL) was devised, based on the stimulation of production of a milk-like substance by the crop sacs of pigeons [10]. However, because even very highly purified preparations of human growth hormone (GH) have high lactogenic activity, it was not possible to differentiate human PRL from GH using this assay.

PRL from a number of species has been characterized and sequenced and specific radioimmunoassays (RIAs) developed for these PRLs [2].

A sensitive in vitro bioassay was developed in the 1970s that was capable of measuring serum PRL levels as low as 5 ng/mL, using staining milk produced by cultured, lactating mouse mammary tissue in response to PRL [11]. For the first time, excess antibody to GH was used to neutralize the potential lactogenic effects of GH. With this assay, PRL levels were measurable in women with puerperal and nonpuerperal galactorrhea, but not in most healthy men and women.

Subsequently an RIA for human PRL was developed which could measure PRL levels in healthy individuals, permitting the entire amino acid sequencing of human PRL [12] and determination of its cDNA sequence, thus opening the way for modern immunoassays.

Measurement of Prolactin Levels

The first competitive immunoradiological assays with polyclonal antibodies were replaced, in the 1980s, by noncompetitive immunometric assays using monoclonal antibodies, which are considered to be more sensitive, more reproducible, and more specific [13]. Although assay kits using radioactive labeling (immunoradiometric assay, IRMA) are still available, most assays are now automated and employ nonradioactive, enzymatic, or chemiluminescent labels (IEMA or ICMA methods, respectively). These assays are based on the sandwich principle in which the PRL molecule reacts with both a capture antibody, immobilized on a solid phase, and a labeled detection antibody, used to detect the PRL. The capture and labeled detection antibodies are each specific for a particular epitope on the PRL molecule. After a wash step to remove unused labeled antibody, the signal generated is proportional to the concentration of PRL in the sample (Fig. 3.1).

Most immunoassays are calibrated against the WHO third International Standard for PRL, IS 84/500, which consists of human 23 kDa monomeric PRL purified from a pituitary extract [14]. Although it is recommended that concentrations of PRL are expressed in mIU/L, they are more frequently reported in μg/L. If IS 84/500 is used, the correspondence is 1 μg/L ≈ 21 mIU/L. The IS standards are calibrated in mIU/L

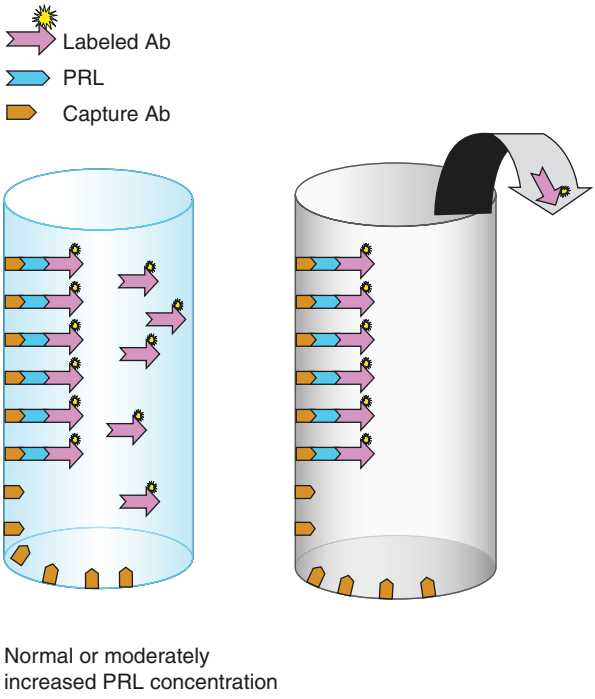

Fig. 3.1 PRL assays are based on the sandwich principle where PRL molecule reacts both with a capture antibody (immobilized on a solid phase) and a labeled antibody (used for detection), each antibody being specific for a particular epitope on the PRL molecule. Following the removal of unused labeled antibody with a wash step, the signal generated is proportional to the concentration of PRL in the sample

using a bioassay: Nb2 cell proliferation assay in which rat lymphoma cells are completely dependent on lactogenic hormones for growth. This assay is extremely sensitive (10 pg/mL) but carries a theoretical risk of inaccuracy due to species differences in PRL receptor responsiveness. Newer bioassays for human lactogens have been developed to address this issue, in addition to analyzing the structure-function relationship of human lactogen analogs, and to assay for the presence of macroprolactin (see below). These employ cell lines that stably express the human PRL receptor (PRLR) alone, as part of a proliferation assay, or in the presence of a luciferase reporter to measure transcriptional activity [15, 16]. However, practical experience with these assays is limited, and testing to determine their validity, accuracy, and reproducibility in larger series of patients is awaited. In experimental mouse models, an ultrasensitive ELISA assay has been developed to detect PRL in very small volumes of whole blood [17].

As stocks of the third IS are becoming exhausted, the WHO Expert Committee on Biological Standardization (ECBS) has recognized the need for a replacement IS. The fourth IS consists of a batch of ampoules, coded 83/573, which contain purified human PRL of pituitary origin. These ampoules of PRL have been calibrated against IS, 84/500 in an international collaborative study [18].

Analytical Pitfalls

The analytical pitfalls inherent in all immunometric assays are the "hook effect" and the interference of heterophilic antibodies. In the case of PRL immunoassays, another major problem is the interference from macroprolactin. Macroprolactin interference is a common issue with the current generation of PRL immunoassays, but interference from heterophilic antibodies is very rare. Moreover, in the case of a glycoprotein hormone such as PRL, where there is heterogeneity of circulating molecular forms, the nonidentity between the PRL contained in the standards and the serum, and the variable recognition of the different molecular forms by the antibodies in each assay kit, causes some variability between the results of different kits.

The "Hook Effect"

PRL immunoassays are highly sensitive and specific, but artefacts may occur due to saturation of the antibodies at excessively high PRL concentrations, preventing antibody-PRL-antibody sandwich formation, the so-called hook effect. The antibodies used in sandwich immunometric assays must be present in a large excess relative to the usual PRL concentration range. Kit calibration ranges and antibody concentrations are adapted to the usual physiological and pathological concentrations. When the PRL concentration of the sample exceeds the highest value in the calibration range, it can saturate the capture antibody bound to the solid phase.

The number of sandwiches formed and, thus, the measured signal reaches a plateau (Fig. 3.2a). If the PRL concentration rises even higher, the labeled signal antibodies may react with PRL molecules that remain in solution. This means that not all the PRL molecules bound to the solid phase are able to form sandwiches and, as a result, the signal gradually decreases as the sample PRL concentration increases leading to the actual concentration of PRL being underestimated.

This problem is only encountered with serum from patients with adenomas that secrete very large amounts of PRL (usually more than 10,000 ng/mL) [19–22]; in such cases the assay will indicate moderately increased (e.g., 38 ng/mL) [20] or normal values [23]. The threshold for this effect varies between different immunoassay kits and laboratories. In a study involving 69 patients with macroadenomas, the hook effect was observed in 5.6% of patients [24].

One means of detecting the hook effect is to dilute the sample [19]: if the hook effect is present, the signal will increase rather than decrease as the dilution factor increases (Fig. 3.2b). Laboratories in hospitals with considerable experience in managing patients with pituitary adenoma with potentially very high PRL concentrations often routinely dilute their plasma samples. Usually, however, the hook effect is too rare to justify diluting every sample, and in practice, a sample will only be diluted if the technician conducting the assay is aware of a likelihood of a very high PRL concentration, e.g., in a male patient with a very large adenoma, or if there is a clinical-biological discrepancy.

Another means to detect the hook effect is to use assays that can measure the kinetics of sandwich formation: rapid kinetics at the very beginning of the reaction can indicate that the concentration of the analyte is very high. This approach is employed by non-isotopic assays in homogeneous phase, such as assays using TRACE® (Time Resolved Amplified Cryptate Emission) technology, which are based on energy transfer luminescence from a donor molecule (europium cryptate) to acceptor molecule (XL665) as a result of the completed immune reaction [25]. As soon as particularly fast kinetics are detected, the device automatically triggers a dilution of the sample. This method, theoretically, will only dilute samples where this is justified to avoid the hook effect.

Another indirect sign of the hook effect is a clear postoperative increase in PRL level in a patient with an apparently nonfunctioning adenoma whose preoperative PRL level was normal or only slightly elevated. This is due to surgical reduction of the tumor mass reducing PRL levels, so that the hook effect does not occur and the assay provides an accurate measure of PRL concentration.

Macroprolactin

High-molecular-weight forms of PRL (150 kDa, big-big PRL) [26] pose a major problem due to their interference with PRL assays. Indeed, when the autoantibody level rises, the concentration of big-big PRL increases, in contrast to that of little (monomeric) PRL, the biologically active and normally regulated form. This creates false hyperprolactinemia that is not, or very rarely, accompanied by the usual signs

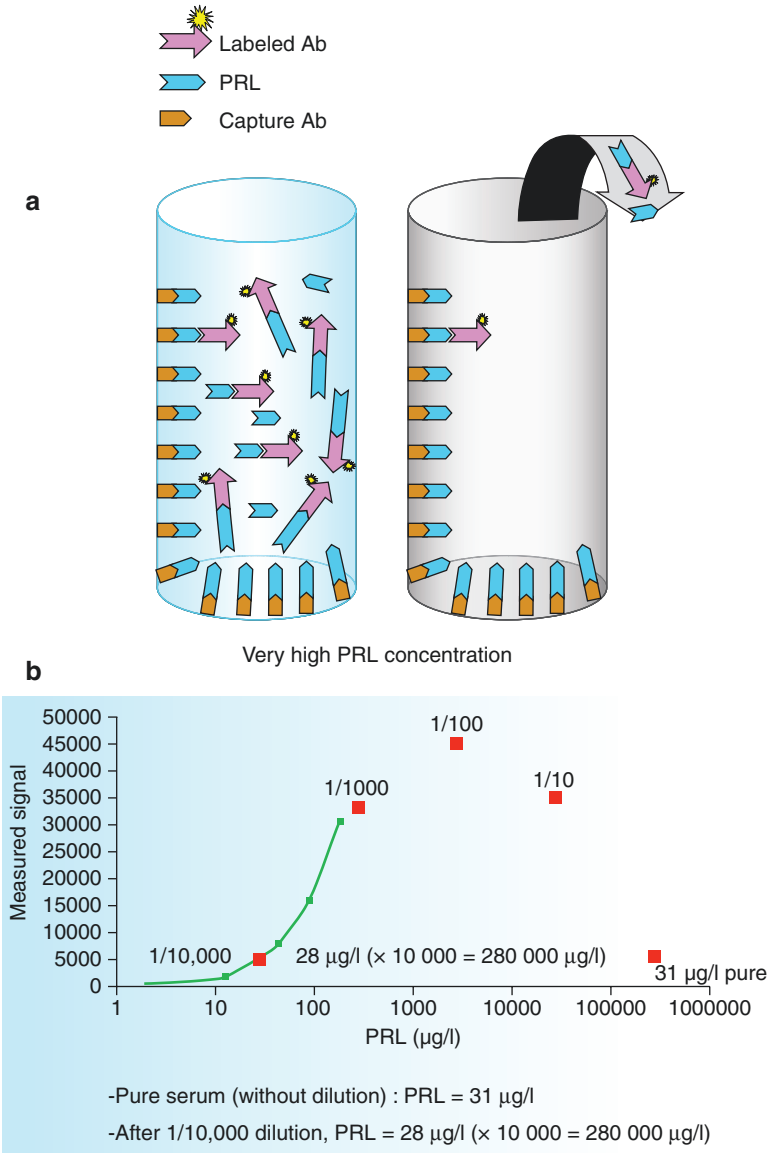

Fig. 3.2 The "hook effect" is an artefact due to saturation of the antibodies at excessively high PRL concentrations preventing antibody-PRL-antibody sandwich formation (**a**). When the sample PRL concentration exceeds the highest value in the calibration range, it can saturate the capture antibody bound to the solid phase. The number of sandwiches formed and, thus, the measured signal reaches a plateau. If the PRL concentration is higher, the labeled detection antibodies may react with PRL molecules remaining in solution. As a result, the signal gradually decreases as the sample concentration increases, until it reaches values within the calibration range. After dilution of the sample, the signal increases rather than decreases with the dilution factor (**b**)

of hyperprolactinemia, i.e., amenorrhea and galactorrhea [13, 27–29]. The first reports of false hyperprolactinemia in patients without pituitary adenomas date back to 1985 [30]. Macroprolactin is recognized by immunoassays for PRL but has no biological activity. High concentrations of macroprolactin appear to be due to reduced clearance of IgG-PRL aggregates [31] and to their interference with reactivity between PRL and the capture and detection antibodies involved in the sandwich reaction of PRL immunoassays [32] (Fig. 3.3). All available immunoassays detect macroprolactin, but what is quite surprising is the variability, with 2.3- to 7.8-fold differences in detection levels [33] (Fig. 3.4). The proximity of the epitopes to which the capture or detection antibodies of the immunoassay are directed relative to the epitope to which the endogenous autoantibody is directed may explain the differences in reactivity of the various commercial immunoassays [32].

A further unresolved issue is the reliable estimation of the bioactivity of macroprolactin, as it is presumed that its presence in serum is not of biologic significance since it is unable to pass through the capillary endothelial barrier and thus remains confined to the intravascular space, presumably because of its high molecular weight [9]. The bioactivity of macroprolactin in vitro, as measured by the rat Nb2 cell proliferation assay, is similar to the bioactivity of monomeric PRL [31, 34–37]. By contrast, when using phosphorylation of signal transducer and activator of transcription (Stat)5 in T47D human breast cancer cells as bioassay, the bioactivity of

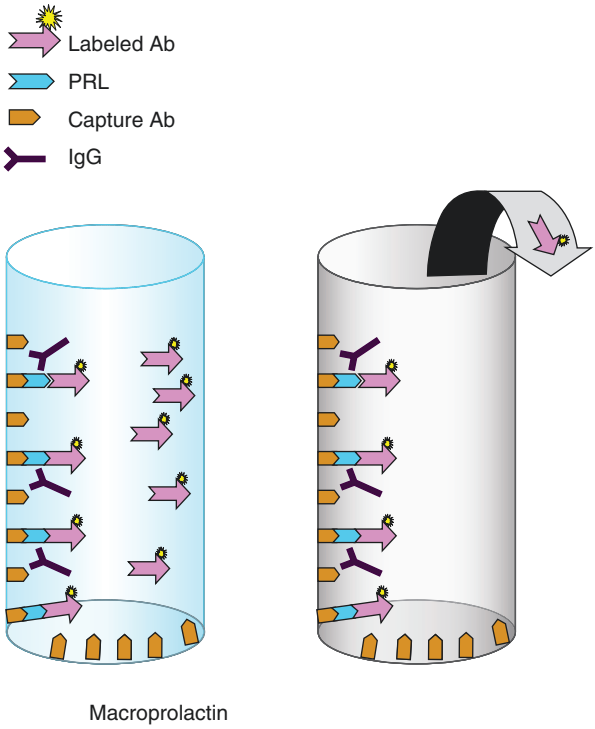

Fig. 3.3 Macroprolactin is an aggregate of monomeric PRL molecule with IgG which probably interferes with reactivity between PRL and antibodies (capture and detection) involved in the sandwich reaction of PRL immunoassays. The proximity of the epitopes to which the capture or detection antibodies of the immunoassay are directed, relative to the epitope to which the endogenous autoantibody is directed, may explain the differences in reactivity of the various commercial immunoassays

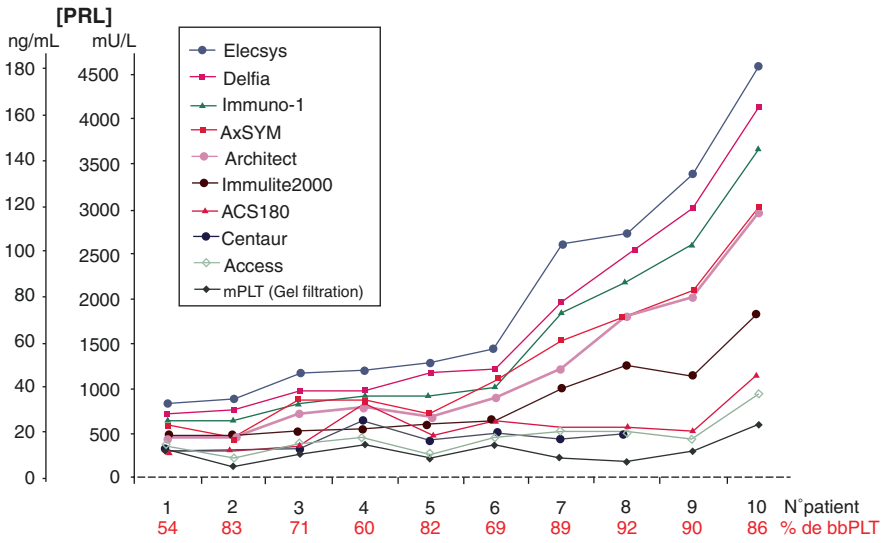

Fig. 3.4 Mean serum PRL levels reported by nine different immunoanalyzer user groups in specimens collected from ten macroprolactinemic subjects. For comparative purposes, the PRL level in each specimen following removal of macroprolactin by gel filtration is shown. (Smith et al. [33])

macroprolactin was found to be low in vivo due to anti-PRL autoantibodies, while monomeric PRL dissociated from the autoantibodies retained full biological activity in patients with macroprolactinemia [36]. Similarly, when bioactivity is measured using human PRLR constructs as tested in Ba/F-3 or human embryonic kidney-derived 293 (HEK-293) cell lines, the bioactivity of macroprolactin is reduced [15, 16]. Technical difficulties could potentially account for the findings in either of these cell-based systems. For example, under the bioassay conditions employed in the Nb2 cell assay, dissociation of macroprolactin into its constituents may liberate monomeric PRL to react, yielding a result suggestive of hormonal activity [38]. On the other hand, transfection conditions used to express exogenous human *PRLR* plasmids could alter the structure or function of the PRL added from the sample.

False hyperprolactinemia related to macroprolactin is an important clinical issue as it may lead to misdiagnosis and mismanagement of patients, including unnecessary pituitary exploration, a waste of healthcare resources, and unnecessary concerns for both patient and clinician [39–46].

Macroprolactinemia is rare in the general population: 0.2% in women and 0.02% in men [47, 48]. However, as PRL assays are now readily available and very simple to perform, they may be used to investigate even the slightest suspicion of a pathology, especially when exploring infertility, vague menstrual disorders, or hirsutism, irrespective of the clinical signs of hyperprolactinemia. The prevalence of macroprolactinemia in hyperprolactinemic samples from clinical practice has been evaluated in different studies and reported to be between 15% and 46% [49]. The nature

of the population studied, the type of PRL immunoassay, and the method used to detect macroprolactin probably explain this high variability [13, 50]. To limit this risk, guidelines have been formulated both for assay kit manufacturers and for clinical laboratories and clinicians. Manufacturers are advised to refine their assay kits if these are excessively prone to interference from IgG-PRL complexes; commercial kits differ markedly in their susceptibility to interference from macroprolactinemia [33]. When hyperprolactinemia is detected in the first assay, clinicians are advised to obtain a control test from another laboratory that uses a different assay kit. If there is a major discrepancy between the two results, particularly if one is normal, then macroprolactinemia is the most likely explanation [13]. The current best practice recommendation for clinical chemistry laboratories, when hyperprolactinemia is detected, is to sub-fractionate the serum, using polyethylene glycol (PEG) 12.5% (w/v). This procedure removes the higher molecular weight forms of PRL by precipitation, leaving the monomeric forms in the supernatant [13], to provide a more accurate measurement of the bioactive monomeric PRL concentration [26, 40, 51]. Normal ranges for sera treated with PEG have been published for several of the most widely used assay systems [52].

However, discrepancies persist concerning the threshold concentration of monomeric PRL at which a hyperprolactinemia in a serum sample should be considered attributable to macroprolactin. Some investigators assert that in a patient with hyperprolactinemia, if residual monomeric PRL following PEG precipitation is less than 40% or 50% of the initial total value, then the hyperprolactinemia is due to macroprolactin [50]. Others suggest that since some macroprolactin is present in normal serum and/or some monomer is precipitated with PEG, the normal reference range should be recalculated from normal samples after PEG treatment; therefore, hyperprolactinemia is attributable to macroprolactin only when the level of non-precipitated PRL is within the normal range [53]. When a serum sample contains high concentrations of PRL, even when the amount of non-precipitated PRL is less than 40% of the total, the residual PRL level still exceeds the normal range.

Residual PRL levels after precipitation with PEG correspond closely to monomeric PRL levels obtained after gel filtration chromatography (GFC), a simple to perform, inexpensive, precise, and reproducible method for removing macroprolactin [54], which is the reference method for fractionating the various isoforms of PRL including macroprolactin, in serum [55–57] (Fig. 3.5). GFC confirms the presence of macroprolactin if the sample contains 30–60% of heavy forms, but GFC is cumbersome and costly. Other methods such as protein A, protein G, human IgG antibody, and ultrafiltration immunoprecipitation tend to overestimate the amount of monomeric PRL [54]. In studies in which patients with suspected macroprolactinemia are treated with dopamine agonists, galactorrhea, when present, generally disappears, but the response of oligomenorrhea or amenorrhea is variable [27]. Long-term follow-up studies of patients diagnosed with macroprolactinemia indicate that PRL levels show considerable instability [27].

In clinical practice, if a patient presents with typical symptoms, such as galactorrhea, amenorrhea, or decreased libido, and is found to have mild hyperprolactinemia, after excluding other common causes (i.e., medications, hypothyroidism,

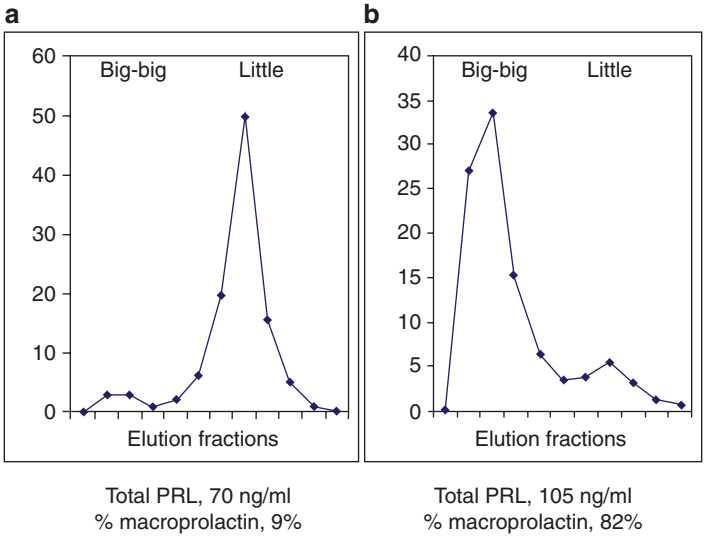

Fig. 3.5 The various isoforms of PRL in serum fractionated by gel filtration chromatography. (**a**) Normal elution profile with large predominance of monomeric PRL. (**b**) Macroprolactin is the predominant form (82%) in this elution profile of a patient with macroprolactinemia

renal failure, or pregnancy), a pituitary magnetic resonance imaging (MRI) scan should be performed to determine if either a prolactinoma, or a large lesion such as a craniopharyngioma, or clinically nonfunctioning adenoma associated with hyperprolactinemia related to pituitary stalk compression is present. Headaches associated with hyperprolactinemia must also lead to perform MRI, while in a patient with hirsutism, it may be helpful to obtain androgen levels for a potential diagnosis of polycystic ovary syndrome. Assessment for macroprolactin, using PEG precipitation, is reasonable in patients with mild hyperprolactinemia and equivocal symptoms, but normal menses and no galactorrhea. It also depends on the assay used to measure prolactin (since different assays may variably detect it, as detailed above). A decision that hyperprolactinemia is due to macroprolactin would then depend on demonstrating an abnormal amount of PRL precipitated by PEG and a residual PRL monomer level that falls within the normal range. Under these circumstances, pituitary imaging may not be indicated, but continued clinical and biochemical assessment of the patient would be warranted.

Interference from Heterophilic Antibodies

Heterophilic antibodies are human immunoglobulins capable of recognizing animal immunoglobulins. Rheumatoid factors, human antihuman immunoglobulin antibodies, can react with animal immunoglobulins and are sometimes considered heterophile antibodies [58]. Heterophilic antibodies can interfere with immunoassays by binding to the assay antibodies (Fig. 3.6).

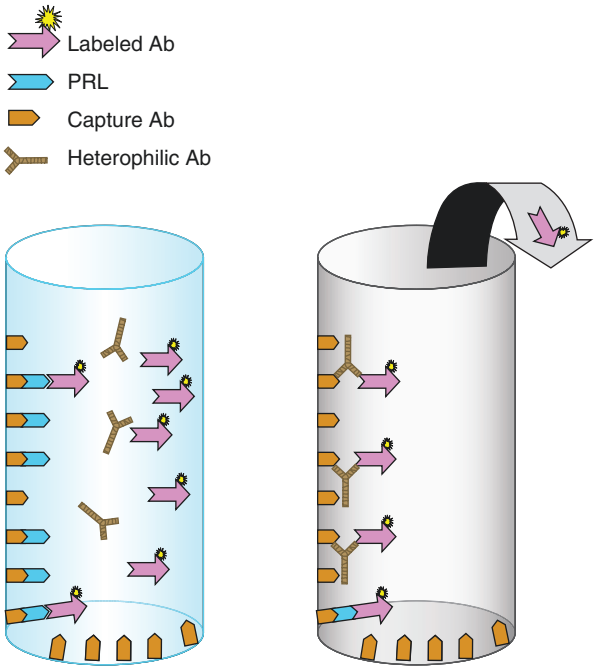

Fig. 3.6 Heterophilic antibodies are human immunoglobulins capable of recognizing animal immunoglobulins which bridge the capture antibody and the labeled antibody and, by mimicking the role of the PRL, induce a false elevation of the result

Heterophilic antibodies are most often IgG or low-affinity IgM naturally present in the serum. Such antibodies can also be induced by an injection of animal immunoglobulins for therapeutic or diagnostic purposes or by animal contact, e.g., with mice in a research laboratory. The induced antibodies, known as anti-animal antibodies, generally have a higher affinity than natural antibodies. Human anti-mouse antibodies (HAMA) are the most common [59]. These heterophilic antibodies bridge the capture antibody and the labeled detection antibody and by mimicking the effect of PRL induce a falsely elevated value for PRL levels. More rarely they react only with one type of assay antibody and by preventing sandwich formation produce a false low result. This interference can be prevented by incorporating a non-specific blocking agent (e.g., animal serum, polyclonal animal IgG, polymerized animal IgG) into the assay reagents to neutralize the heterophilic antibodies: this strategy has been generalized in all immunometric assays [60, 61]. In addition, specific blocking agents containing antibodies directed against certain human immunoglobulins can be used. In PRL assays such additives prevent most heterophilic antibody interference. The relatively frequent interference with the old radioimmunoassays sensitive to anti-rabbit antibodies seems now to have become quite exceptional [62]. Treatment of the patient's serum with specific blocking agents not initially present in the assay reagents has made it possible to unmask the interference and resolve this issue.

Interference with Biotin

Biotin therapy given in some patients with neurological disorders or high dietary amount of biotin may lead to analytical interference in many immunoassays that use streptavidin-biotin capture techniques, yielding skewed results that can mimic various endocrine disorders. This is particularly true for T3, T4, and TSH, mimicking hyperthyroidism [63]. According to two studies where healthy volunteers ingested high amounts of biotin, PRL results do not seem to be importantly affected by this artefact [64, 65].

Interpretation of Hyperprolactinemia

PRL is secreted episodically, and over the course of the day, PRL levels may rise slightly above the upper limit of normal established for a given laboratory. Consequently, a finding of minimally elevated PRL levels in blood requires confirmation in several samples taken at different times of the day.

In the face of increased PRL levels, the clinician has to consider the possibility of an artefact, particularly the presence of macroprolactin. If the clinical picture is not typical, i.e., if amenorrhea and galactorrhea are present in females, or loss of libido and signs of hypopituitarism in males are absent, the increased PRL levels must be confirmed by reassaying the serum after PEG precipitation.

If the clinical picture is typical and/or if macroprolactinemia has been excluded, potential causes of secondary hyperprolactinemia must be investigated: a careful history and physical examination, screening blood chemistry, thyroid function tests, and a pregnancy test will identify virtually all secondary causes, except for hypothalamic-pituitary disease (Fig. 3.7).

When there is no obvious secondary cause of the hyperprolactinemia from routine screening, neuroradiologic evaluation of the hypothalamic-pituitary area is mandatory. MRI with gadolinium enhancement is the preferred technique for pituitary imaging (Fig. 3.7).

It must be emphasized that it is essential to distinguish between a large nonfunctioning tumor causing modest PRL elevations (usually <250 ng/mL) and a PRL-secreting macroadenoma (PRL levels usually >250 ng/mL), as the management approaches to these two entities are different. It is also important to be aware of potential artefacts in PRL measurement that may lead to misdiagnosis. Stimulation and suppression tests using thyrotropin-releasing hormone (TRH), hypoglycemia, chlorpromazine, domperidone, and other medications yield non-specific results and provide no more information than measurement of basal PRL levels. The consensus is that stimulation and suppression tests are not recommended for the differential diagnosis of hyperprolactinemia [66, 67].

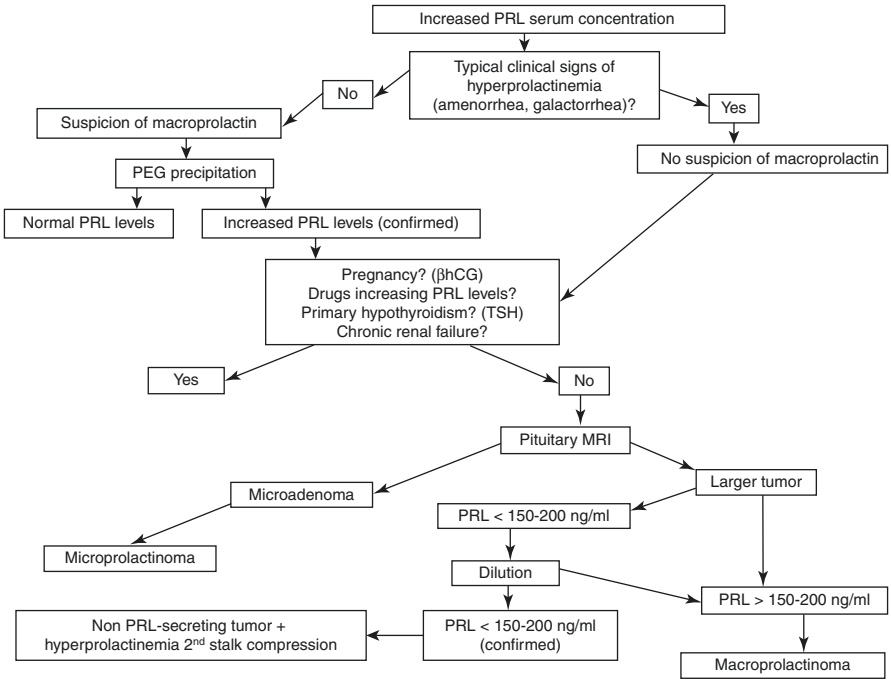

Fig. 3.7 Diagnostic strategy in case of hyperprolactinemia, taking into account potential traps and artefacts of PRL assay

Regulation of Secretion

Modes of Secretion of Prolactin

The existence of two pools of PRL within the rat lactotroph cell, one turning over rapidly and the other turning over slowly, has been demonstrated [68]. Newly synthesized PRL is released preferentially to stored PRL, in response to some stimuli, and constitutes the rapidly turning over pool. These two types of secretion, rapid and slow, are not so much due to differences in the type of stimulation for a given cell, but to the functional heterogeneity of the cells; some cells synthesize and secrete PRL rapidly, while others secrete more slowly [69]. In the pituitary gland, much of the storage pool of PRL appears to exist in a high-molecular-weight, disulfide-bonded, poorly immunoreactive polymeric form that is converted to a releasable, immunoreactive monomeric form within the secretory granule [70].

The hypothalamus exerts a predominantly inhibitory tone on PRL secretion through one or more PRL inhibitory factors that reach the pituitary via the hypothalamic-pituitary portal vessels.

Factors and Hormones Inhibiting the Secretion of Prolactin (Prolactin Inhibitory Factors)

Dopamine: The Major Prolactin Regulatory Hormone

In the 1950s the luteotropic properties of the pituitary were shown to be increased when pituitary glands are transplanted to sites beneath the renal capsule, away from the regulation by the hypothalamus, thus demonstrating that hypothalamic regulation of PRL secretion is predominantly inhibitory [71]. It was subsequently determined that tuberoinfundibular dopamine (TIDA) released into the hypothalamic-pituitary portal vessels in the median eminence was the physiologic inhibitory factor with direct action on the pituitary [72]. Dopamine inhibitory tone is exerted via D2 dopamine receptors (D2R) located on the surface of lactotroph cells. Conversely, PRL provides negative feedback on its own secretion, by stimulating hypothalamic dopamine secretion via PRLR located on TIDA membranes.

Many experiments have definitively established dopamine to be the major, physiologic inhibitory factor for PRL secretion. Dopamine fulfills the Geoffrey Harris criteria for hypothalamic neuroendocrine control of the pituitary: it is secreted from the hypothalamus, released into the portal vessels of the pituitary stalk, and acts on the lactotrophs in the pituitary to inhibit PRL secretion. Dopamine is produced by TIDA neurons; its concentration in the pituitary stalk plasma is largely higher than in the systemic circulation (about 6 ng/mL), which is sufficient to decrease PRL levels in rats. Furthermore, stimuli which produce an acute release of PRL usually also result in an acute decrease in portal vessel dopamine levels [72]. It is likely that for most physiologic circumstances that cause PRL levels to rise, such as lactation, there is a simultaneous fall in dopamine levels sufficient to account for the increased PRL release. It is not clear whether or not this decrease in dopamine is associated with a rise in potential PRL-releasing factors (PRF).

The earlier studies that employed pharmacologic methods or lesioning to assess the actions of dopamine have been confirmed by the analysis of the phenotypes of mice deficient in the D2R or dopamine transporter (DAT). Thus, *D2r*$^{-/-}$ mice develop lactotroph hyperplasia and sustained hyperprolactinemia, followed in aged mice by lactotroph adenomas, demonstrating that a chronic loss of dopamine inhibition promotes a hyperplasia-neoplasia sequence in adenohypophysial lactotrophs [73]. Dopaminergic action within the synapse is terminated by dopamine reuptake by the dopamine-secreting neurons via the DAT. In contrast to the findings with the *D2r*$^{-/-}$, *Dat*$^{-/-}$ mice have increased dopaminergic tone and lactotroph hypoplasia [74]. Although such mice have normal circulating levels of PRL, their PRL levels do not increase in response to stimuli, and they are unable to lactate [74].

While the studies demonstrating dopamine in hypothalamic-pituitary portal vessels and the effects of dopamine on PRL release in vitro were performed in animals,

it is established that dopamine is also the main inhibitory factor for PRL release in humans. Infusion of dopamine causes a rapid suppression of basal PRL levels that can be reversed by metoclopramide, a dopamine receptor blocker [75]. Dopamine also blocks the PRL increments induced by various stimuli. Studies with low-dose dopamine infusions in humans have shown that dopamine blood concentrations similar to those found in rat and monkey hypothalamic-pituitary portal blood are able to suppress PRL secretion [76]. Blockade of endogenous dopamine receptors by various drugs, including phenothiazines, butyrophenones, metoclopramide, and domperidone, causes a rise in PRL [77].

Gonadotropin-Associated Peptide

Other PRL inhibitory factors have been proposed, such as gonadotropin-releasing hormone (GnRH)-associated protein (GAP), but their relevance in rodents and humans is unclear. GAP, a 56 amino acid polypeptide, found in the carboxyterminal region of the precursor to GnRH, was reported to have a PRL-inhibiting ability on rat pituitary cell cultures [78]. However, the GAP amino acid sequences in human and rat have 17 differences, and subsequent studies showed that GAP has no PRL-suppressing activity on human prolactinomas cultured in vitro. Moreover, individuals carrying *GNRH1* homozygous frameshift mutations were found to have normal or even low plasma PRL levels despite lacking the GAP peptide sequence, indicating that in humans GAP does not act on the pituitary gland to regulate PRL secretion [79].

Likewise, the absence of GAP is associated with a sharp decrease in pituitary PRL content in *Hpg* mouse females lacking the *GnRH1* gene [80, 81] indicating that GnRH and GAP have no major physiologic role in regulating PRL secretion.

γ-Aminobutyric Acid

The presence of γ-aminobutyric acid (GABA) in portal blood has been demonstrated, it has an inhibitory effect on PRL secretion in vivo and in vitro in rats, and high-affinity GABA receptors are present on lactotrophs. A tuberoinfundibular GABAergic system has been described in the arcuate nucleus and nerve endings demonstrated in the median eminence. Studies of the GABA system of widely differing experimental designs in humans or in mouse models have yielded conflicting results [82]. GABA itself causes a modest decrease in PRL levels when given to humans for several days, and activation of the endogenous GABAergic system with sodium valproate causes a suppression in the PRL rise induced by mechanical breast stimulation in puerperal women. The physiologic role of GABA in regulation of PRL release remains to be fully elucidated in humans.

Factors and Hormones Stimulating the Secretion of Prolactin (Prolactin-Releasing Factors): Hypothalamic Prolactin-Releasing Factors

Thyrotropin-Releasing Hormone

TRH binds to the type 1 TRH receptor expressed in both thyrotrophs and lactotrophs. TRH causes a rapid release of PRL from rat pituitary cell cultures and in humans after intravenous injection; however, a number of different experimental approaches have failed to clarify the physiologic role of TRH as a stimulator of PRL secretion. The smallest dose of TRH that releases thyroid-stimulating hormone (TSH) in humans also releases PRL. Immunoneutralization of endogenous TRH with TRH antisera has produced a 50% suppression of basal PRL levels in rats in some studies [83], but not in others. *Trh*$^{-/-}$ mice became hypothyroid with elevated levels of TSH with reduced biological activity, but PRL levels were normal, casting further doubt on TRH having an essential role in PRL regulation [84]. This is reinforced by humans with the *TRH-R* loss of function mutation having normal rather than decreased PRL [85].

If TRH mediates the PRL response to suckling, it ought to be accompanied by an increase in TSH, unless there is a concomitant increase in somatostatin. Studies in humans failed to show any elevations of TSH with suckling. Very small doses of TRH given systemically were effective in releasing PRL and TSH in lactating rats and women; however, it is unlikely that failure to show a rise in TSH was due to an increase in somatostatin.

In hypothyroidism, TRH synthesis is increased, portal vessel TRH levels are increased, and there is an increased number of TRH receptors. In human hypothyroidism, basal TSH and PRL levels are increased as are their responses to injected TRH. Correction of the hypothyroidism with thyroid hormone corrects both the elevated TSH and PRL levels and their responses to TRH. Conversely, in hyperthyroidism in humans, PRL levels are not low basally, but the PRL response to TRH is markedly blunted and returns to normal with correction of the hyperthyroidism.

In conclusion, the TRH receptor does not seem to play a relevant stimulatory physiologic role in PRL secretion, and TRH action is not required for pituitary development, nor is it required for the expression of the *PRL* gene indicating that under normal conditions TRH does not have a major role as a PRL-releasing factor.

Other Potential Prolactin-Releasing Factors

There is currently no convincing evidence for a physiologic PRL-releasing factor [2, 72, 86]. It seems that, as for TRH, most of the factors that are able to stimulate PRL, either in vitro or in vivo, regulate PRL secretion by influencing the secretion of dopamine by hypothalamic dopaminergic neurons. In fact, none of these factors

are really PRL-releasing factors as they do not fulfill the Geoffrey Harris criteria for hypothalamic neuroendocrine control of the pituitary [86]. PRL levels achieved after administration of dopamine antagonists are as high as those normally associated with stimulated PRL release under physiologic conditions, for example, in response to suckling [87], suggesting that maximal stimulation can be achieved by eliminating the normal dopaminergic inhibitory control alone.

Vasoactive intestinal peptide (VIP), an ancestral regulator of PRL secretion, is the major PRL-releasing factor of nonmammalian vertebrates [88] and also stimulates PRL secretion in mammals [89]. However, it is not secreted in the portal system at a higher concentration than in the systemic circulation, nor is it present at high concentrations in the blood when PRL secretion is high. It is probably the same for various other proposed PRL-releasing factors such as TRH, oxytocin, galanin, salsolinol, PRL-releasing peptide, and others [2, 90].

With the administration of domperidone, a potent D2 antagonist, different PRL levels are observed at different times of the day [91], suggesting the presence of an endogenous stimulation rhythm whereby hypothalamic factors, including oxytocin and VIP, promote PRL secretion at specific times [92–94]. Thus, there is evidence for a regulation of PRL secretion independent of dopamine, without any proof that it is mediated by a PRL-releasing factor. The role of a putative PRL-releasing factor produced by a subpopulation of melanotropic cells in the pituitary lobe has been proposed [95, 96] and confirmed by others [87, 97, 98]. However, the identity of this factor has not been defined.

Given the magnitude of PRL release in response to dopamine inhibition [87], decreased dopamine may account for most of the PRL release. Finally, it must be noted that, even after a marked reduction in dopamine secretion during lactation in mice [99], lactation can still regulate PRL secretion suggesting that other regulatory factors must be involved in the physiological regulation of PRL secretion, particularly during lactation, when this is most needed. But these factors remain to be clarified.

Estrogens

The inhibitory action of dopamine on PRL secretion is partially blocked by estrogen administration. This may be largely due to the direct action of estrogen on the estrogen response element located in the *PRL* gene promoter. There may, however, be other mechanisms, with considerable differences between species. Estradiol is able to block the inhibitory action of dopamine on PRL release from rat lactotroph cells in vitro. In humans, the same dose of infused dopamine results in a greater suppression of PRL during the early follicular phase, when estrogen levels are low, compared with the late follicular or periovulatory phases, when estrogen levels are higher. Estrogen administration resulted in a decrease in dopamine receptor abundance in rats, but the dopamine receptor population showed no sex-related differences in a limited number of human pituitaries studied.

Short-Loop Feedback Control of Prolactin Secretion

Considerable evidence in rats suggests that PRL feeds back negatively on its own secretion (short-loop feedback or autofeedback) [100]. Most evidence, which includes direct measurements of dopamine in the portal vessels, suggests that such feedback occurs via augmentation of hypothalamic TIDA turnover. Electrophysiological data have demonstrated rapid actions of PRL on the electrical activity of TIDA in mice [99, 101] or in rats [86, 102]. *Prl*$^{-/-}$ mice show a markedly decreased dopamine turnover in TIDA neurons along with hyperplasia of lactotrophs that do not synthesize PRL [103, 104]. Recently reported data indicate that PRL exerts autocrine or paracrine actions on lactotroph cells in vivo [105]. Conditional deletion of *Prlr* in lactotroph cells of mice led to normal PRL levels. The females did not develop any pituitary lactotroph adenoma, even at 20 months of age, but they displayed an increased dopaminergic inhibitory tone compared with that of control mice, confirming an autocrine/paracrine feedback of PRL on lactotroph cells in vivo, fully compensated by an intact hypothalamic feedback system. Direct evidence for such PRL short-loop feedback in the human has not been demonstrated. During lactation or aging [106–108], physiologic situations where dopamine output is impaired, pituitary autoregulation may be important in minimizing the occurrence of adenomas.

Conclusion

PRL is a major reproductive hormone, and hyperprolactinemia, a pathologic increase in its serum level, is frequently responsible for reproductive diseases. These reproductive diseases are easily treatable if correctly diagnosed, which is achievable by a simple measurement of blood PRL levels. Clinical measurement of blood PRL levels has increased considerably by the availability of simple immunoassays based on the sandwich principle, which are automated, very easy to perform, and extensively used worldwide. However, the flip side to this progress is the potential presence of artefacts, such as the hook effect and false hyperprolactinemia due to macroprolactin, which may lead to misdiagnosis and mismanagement of patients, including unnecessary pituitary exploration, a waste of healthcare resources, and unnecessary concerns for both patient and clinician.

Regulation of PRL secretion is provided mainly, but not only, by dopamine, a PRL inhibiting factor produced by TIDA, released into the portal vessels of pituitary stalk, and which inhibits PRL secretion via dopamine receptors. There is no evidence of a PRL-releasing factor released into the portal circulation that acts directly on lactotrophs. The stimulatory factors seem to act on PRL secretion mainly by regulating the secretion of dopamine at the hypothalamic level.

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Chapter 4
Physiological Actions and Receptors

Nelson D. Horseman

Physiological Actions in Humans and Other Mammals

Our understanding of prolactin (PRL) from the organismic level (physiology and pathophysiology) to the molecular level (receptors, signal transduction, and intracellular responses) has benefited enormously from application of the modern tools of contemporary biology. These tools have allowed us to reconcile the most obvious issues of PRL signaling in laboratory animals and humans [1–3]. PRL actions in nonmammalian vertebrates are still poorly understood. In mammals there are a few particularly nettlesome issues, such as roles of extrapituitary PRL, which are not definitively resolved.

Here we provide a summary of fundamental physiological actions of PRL. This is not intended to exhaustively analyze all of the many claimed PRL actions but rather to focus on reliable knowledge about how PRL functions in the normal life cycle, particularly in humans. In doing so we intend to provide the context for understanding PRL receptors and signaling mechanisms and to establish the concept that normal physiological PRL actions provide the basis for understanding signaling in PRL pathologies.

PRL secretion from the pituitary gland is well understood, both in terms of its association with physiological actions and pathologies [4, 5]. Physiological PRL secretion from the pituitary is higher in females than in males (approximately 20 ng/ml or greater in females and less than 10 ng/ml in males) and highest in lactating females (100 ng/ml and greater). Pathological PRL secretion from the pituitary is generally associated with benign tumors (prolactinomas), although it may occur as a consequence of neuroendocrine causes that interrupt dopamine input to the pituitary gland.

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In humans the PRL gene is expressed in a variety of extrapituitary tissues [6]. The functional roles of extrapituitary PRL are largely a matter of conjecture [6, 7]. This is not for the lack of serious experimental efforts and evidence but results from the underlying heuristic problems associated with distinguishing effects of systemic and local PRL. This is particularly the case because blood levels of PRL or PLs are so very high during the times when PRL actions are most important, i.e., pregnancy and lactation. It is almost certainly true that evolutionary pressures have selected for PRL expression in certain extrapituitary tissues. It is conceivable that the hormone somehow increases reproductive success under stressful environmental conditions. Laboratory conditions and laboratory animals are generally poor contexts for studying evolutionary forces such as these. The problem is even more difficult because selection for expression in one tissue can result in incidental expression in other tissues. Mice in which the PRL gene has been completely humanized express PRL in extrapituitary tissues that emulate human expression patterns [8]. This was possible because the mouse PRL gene had been knocked out and the human PRL gene resides in a large genomic island that includes all the protein-encoding and regulatory regions [8]. Studying environmental stressors using these animals and other similar models could provide clearer proofs for human extrapituitary PRL functions.

Consequences of PRL pathologies in humans correspond very closely with the classically known functions of pituitary PRL. While most humans with a PRL deficiency have multiple pituitary hormone deficits, there are a few examples of isolated PRL deficiency in women. In these cases the women were discovered because they had postpartum alactogenesis (failure of milk secretion) [9–12]. Notably, the women were able to conceive and deliver, and there have been no reports of men with an isolated PRL deficiency. Conversely, the pathophysiology of excess PRL comprises reproductive suppression and mammary stimulation (reviewed elsewhere in this volume). The confirmed physiological and pathophysiological actions of PRL in humans and other mammals serve as the context for reviewing PRL receptors and mechanisms of action.

Mammary Glands

Mammals are vertebrate animals that lactate. PRL is the essential hormone for lactation in all mammals. Isolated examples of secretions that function analogously to mammalian milk are well known (e.g., pigeon crop milk), but mammals are the only class of animals that uniformly secrete milk and suckle their offspring.

The first step in mammary gland development is establishment of a ductal rudiment prenatally. The epithelial rudiment and surrounding stroma grow isometrically in the juvenile female without any need for PRL. At puberty the ductal system grows rapidly under the influence of multiple hormones. Ductal growth is

induced by estrogens, GH, and IGF-1 [13, 14]. Decorating the ductal system, PRL induces small branches and alveolar sacs, referred to lobuloalveoli in rodents [13, 15]. The lobuloalveoli are roughly equivalent to the terminal duct lobular units (TDLU) of the human breast [16]. Progesterone is also necessary for this stage of development of the competent mammary system. Development of alveoli from precursor cells in the ductal epithelium involves both clonal growth from committed precursors [17, 18] and induction of growth and phenotypic changes in cells that are adjacent to specialized "hormone sensing" cells [3].

Under the influence of estrogen, progesterone, and PRL in nonpregnant adolescents, the complexity of the mammary ductal branching increases progressively, and the epithelial cells undergo cyclic changes. During pregnancy the lobuloalveolar or TDLU epithelium undergoes extensive proliferation under the influence of PRL, placental lactogens, and progesterone. These proliferative actions are mediated by RANK-ligand [19, 20] (Fig. 4.1). RANK-ligand knockout mice, like PRL knockouts, fail to develop lobuloalveoli [21]. Because RANK-ligand is a membrane-tethered ligand, it signals to adjacent cells in a juxtacrine manner. IGF2 also supports PRL-induced mammary proliferation, but unlike RANK-ligand it is not essential [22]. PRL is also a survival factor for lobuloalveolar cells during both pregnancy and lactation [23, 24].

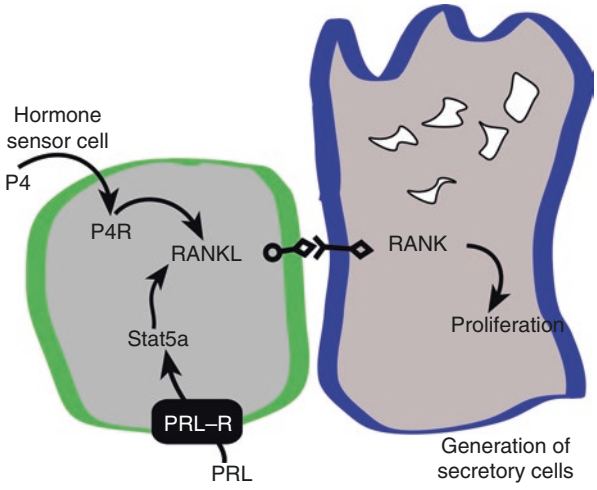

Fig. 4.1 The tissue mechanism by which PRL induces proliferation in the mammary epithelium. Generation of a population of secretory cells requires a synergy between PRL and progesterone (P4) to induce expression of RANK-ligand (RANKL). RANKL is anchored in the membrane and binds to its receptor (RANK) on adjacent cells. Hormone-sensing cells are identified by their expression of receptors for not only PRL but also P4 and estrogen (not shown)

Around the time of parturition, progesterone, estrogen, and placental lactogen levels decrease, and PRL levels increase. This combination of hormone changes allows final functional growth and differentiation of the mammary glands, which has been termed "lactogenesis II" or, among some human mammary biologists, "secretory activation." The timing of this final stage of lactogenesis varies among species. In women it is important that it occurs within about 2 days after parturition [25].

As the epithelium develops its secretory capability, a variety of milk proteins, lactogenic enzymes, milk sugar, milk fats, and complex polysaccharides are synthesized. The exact inventory of milk components depends on the species and supports the reproductive strategy and environmental demands each encounters.

The demand for calcium to support mineralization and growth of the neonatal skeleton poses a major metabolic challenge to the lactating mother. To supply this mammary calcium demand, PRL induces secretion of parathyroid hormone-related protein (PTHrP) during lactation [26–29]. The induction of PTHrP by PRL is mediated by serotonin, which is synthesized and secreted within the mammary gland during lactation [30–32]. Several types of serotonin receptors are present in the mammary epithelium, and the induction of PTHrP secretion is mediated by the -5-HT2B receptor type [31–33].

Involution of the milk secretory system is induced by milk stasis (buildup of milk because of reduced nursing) and declining PRL levels [30]. Even in the presence of high levels of PRL, milk synthesis and secretion are inhibited by a homeostatic feedback system that operates within the gland, completely independent of systemic factors. Involution is an extension of the feedback mechanisms that regulate the amount of milk secretion during lactation. The initial feedback signal that inhibits milk secretion is serotonin [30]. Serotonin synthesis is elevated in the lactating gland, responding to PRL and milk stasis. Milk secretion is suppressed by inhibition of milk protein gene expression and opening of tight junctions [30].

The roles of PRL in mammary gland development, having been inferred from many physiological and cell biology studies, were confirmed by targeted disruption of the PRL gene and reintroduction of the hormone by injection and pituitary transplanting [15, 30, 34]. Disruption of the PRL receptor gene caused the same developmental defects as knocking out PRL [35, 36].

Reproductive Tissues

High levels of PRL inhibit gonadal activity by actions at the hypothalamus, pituitary, and, in females, the ovaries (see other chapters in this volume). These antigonadal effects are manifest during lactation and clinical hyperprolactinemia in humans. The antigonadal effects of PRL are the most broadly conserved physiological actions across all vertebrates, being seen in fishes, amphibians, reptiles, and birds, as well as mammals [37]. Recognizing the fundamental importance of the

antigonadal actions of PRL provides a context for understanding how other actions, such as lactogenesis, could evolve based on the secretion of high levels of PRL during the postmating phase of the reproductive cycle. It also helps to explain the common reproductive pathologies of hyperprolactinemia in both females and males.

PRL is essential to maintain the functional corpus luteum in rodents, but not in humans and other mammals. The rodent estrous cycle has only a brief functional luteal phase, which is not sufficient to support implantation and early pregnancy. Rodents have adapted the PRL system for maintenance of early pregnancy by establishment of surges of PRL that are established after coital stimulation of the cervix. The cervical stimulus drives a hypothalamic reflex that alters the secretion of dopamine and opioids. The diurnal and nocturnal PRL surges in early pregnancy are controlled by somewhat different neuroendocrine factors [38], but the exact circuitry that is responsible for each of the surges is still unknown.

PRL suppresses the hypothalamic drive for pulsatile luteinizing hormone (LH) secretion [39, 40], inhibits ovarian folliculogenesis [41], and inhibits granulosa cell aromatase activity [42, 43]. In sum, these effects result in lower estradiol synthesis. DA levels, which increase in the hypothalamus as part of the feedback response to high PRL levels, also may be involved in suppressing gonadotropic functions. In the rodent ovary, PRL inhibits 20α-hydroxysteroid dehydrogenase activity and thereby increases progesterone secretion by inhibiting its conversion to 20α-hydroxyprogesterone [44, 45].

PRL is implicated in peripartum cardiomyopathy, a rare cause of heart failure. Oxidative stress and cardiac cathepsin D may cause PRL to be cleaved to a 16 k dalton fragment that has antiangiogenic and apoptotic effects on the myocardium [46, 47]. The 16 k dalton PRL fragment and related fragments of PLs were discovered in extracts from tissues other than the heart and may have other functions [48, 49].

In the male high levels of PRL are antigonadotropic as well. However, male PRL knockout mice are completely fertile [15, 50]. Accordingly, PRL is not required for male fertility, but excess PRL inhibits reproduction.

PRL supports pregnancy and lactation with a variety of actions in the digestive system. Bile acid secretion and taurocholate transport in liver are elevated by PRL and PLs [51]. Perhaps most importantly, PRL and PLs induce proliferation of islet β cells during metabolic adaptation to pregnancy and lactation [52–54]. The proliferative effect of PRL on β cells is mediated by induction of local serotonin secretion [55].

Receptors and Signaling

The PRL receptor (PRLR) is a member of the type 1 cytokine receptor family [56]. The GH receptor and various hematopoietic cytokine receptors, such as those for erythropoietin, most interleukins, and granulocyte-macrophage colony-stimulating

factor, are homologous with PRL and GH receptors. A broader superfamily of proteins comprises various cell adhesion proteins, the interferon receptors (type 2 cytokine receptors) and the type 1 cytokine receptors.

The PRLR gene is located on chromosome 5 (5p13.2), comprising 15 exons (gene ID: 5618; https://www.ncbi.nlm.nih.gov/gene/5618). Amplification of the PRL gene is associated with noninvasive lobular neoplasias, but not, apparently, with invasive breast cancer [57].

Type 1 cytokine receptor family members are defined by two signature motifs in the extracellular domain and one in the intracellular domain. Four cysteine residues in the extracellular domain are invariant among all of the type 1 cytokine receptors, and they form two disulfide bridges that are essential for the proper tertiary folding of the ligand-binding domain. A short sequence that includes a tandem repeat of tryptophan-serine interrupted by a single amino acid (the WSXWS motif) is the second signature motif in the extracellular domain. This sequence is highly conserved near the base of the extracellular domain and appears to be involved in receptor dimer formation. The structure of the PRLR extracellular domain, like that of the GH and other cytokine receptors, has been analyzed extensively by x-ray crystallography, as well as by biochemical methods [58]. This domain comprises two 100 amino acid subdomains that are related to the type III repeats of fibronectin. Each of the type III subdomains includes a conserved series of seven β-strands folded into two β-sheets that run in an antiparallel orientation. These type III subdomains are connected by a short, flexible hinge peptide, and residues that contact the ligand span this connector to include amino acids in each of the type III subdomains.

An 8-amino acid proline-rich motif in the intracellular region of the PRL-R is referred to as box 1. This conserved motif interacts directly with the tyrosine kinases that are activated upon ligand binding to the extracellular domain. Mutating box 1 disables PRL-R signaling [59]. Multiple PRL-R isoforms vary based on the length and amino acid sequences in the intracellular domain. The so-called long isoform is present in all species and represents the canonical signal-transducing isoform. The long intracellular domain is about 350 amino acids in length. Short isoforms have been identified in rodents, humans, and various other mammalian species [60]. These short forms are produced by alternative splicing and include the box 1 sequence; but they lack other regions of the intracellular domain that are required for canonical signal transduction. Conserved tyrosine residues in the distal portion of the long receptor isoforms are phosphorylated after ligand binding, and these tyrosines are required for canonical signal transduction.

There is a substantial degree of functional redundancy among the conserved intracellular tyrosine residues. STAT5 activation occurs even if one or more tyrosines are mutated, as long as at least one of the conserved tyrosines is present. However, the most distal tyrosine residue of the PRL-R (Y611 in the human receptor) appears to be important, if not essential, for canonical signaling [60, 61]. A mutant PRL-R isoform in rat Nb2 lymphoma cells has a large deletion between box 1 and the distal conserved tyrosine, and this receptor is able to transduce all of the known signaling functions of the long form and may be hyperfunctional [60].

Multiple short isoforms of the PRL-R have been discovered in a variety of mammalian species. Most of these isoforms do not include the conserved phosphorylatable tyrosines of the long form, so they do not participate in canonical signaling.

The functional significance of the short isoforms is not completely known. Although these could provide for signaling diversity, they are more likely to act as decoy receptors or transport molecules in most circumstances [62]. The best study of functional activity of a short PRL-R showed that exclusive expression of the short form caused an ovarian defect but that this defect was completely absent when the long form was coexpressed [63]. Lactogen levels (PRL and placental lactogens together) can be extremely high during some physiological states, so certain tissues may need to cope with those levels of ligand by expressing decoy receptors.

Canonical PRL-R signal transduction comprises activation of JAK2 tyrosine kinase and phosphorylation of STAT5 (Fig. 4.2). These events lead ultimately to accelerated transcription of specific genes that drive growth and functional differentiation of the target cells.

Ligand binding causes conformational changes of the PRLR to initiate signal transduction. The functional receptor state is a mirror-image dimer with the ligand articulating the two monomeric receptors [64] (Fig. 4.3). The first experiments that

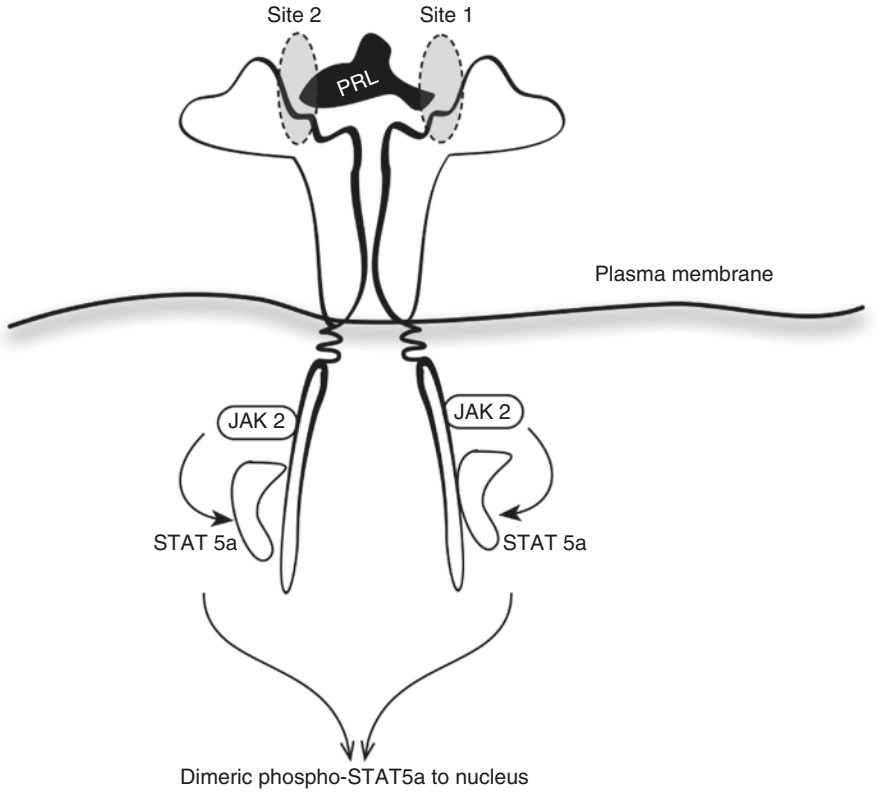

Fig. 4.2 Diagrammatic representation of canonical PRL signaling. Productive signal transduction is activated by PRL binding to the extracellular domains two molecules of transmembrane receptors. The intracellular domains of the receptors bind the tyrosine kinase JAK2 and the transcription factor STAT5. Phosphorylated STAT5 dimers translocate to the nucleus where the alter expression of relevant target genes

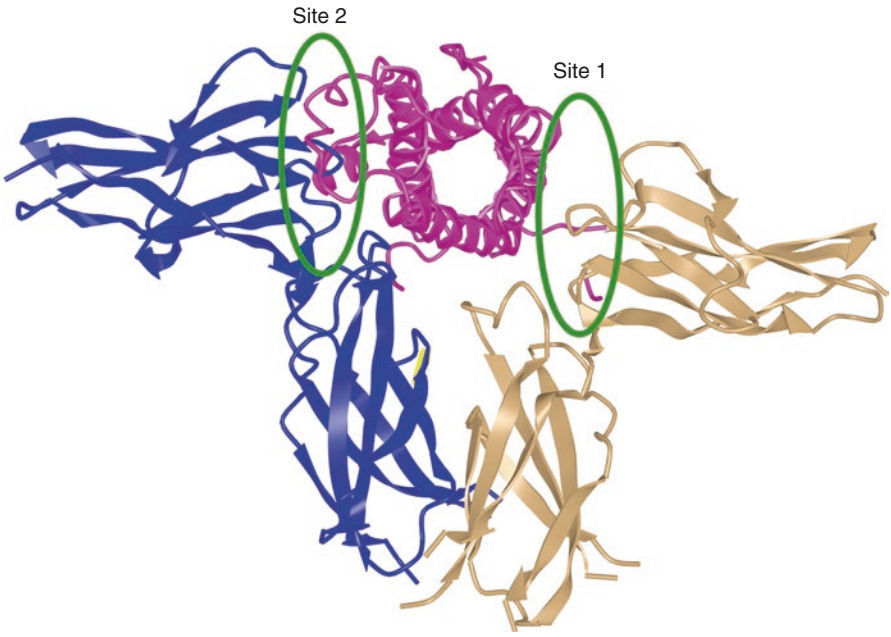

Fig. 4.3 Inferred structure PRL-PRLR complex. The extracellular domain of the human PRLR is crystalized in 2:1 stoichiometric complexes with its natural ligand. Regions corresponding to binding of sites 1 and 2 of the ligand are highlighted. (Adapted from van Agthoven et al. [64])

suggested that the activated functional state is a dimeric receptor complex used antibodies to artificially induce receptor aggregation. The inferences from this creative experimental approach were proven to be correct when hormone-receptor complexes for human GH and PRL receptors were biochemically and crystallographically mapped [59, 65, 66]. The formation of productive 1:2 complexes of the hormone with its receptor appears to be the essential first step in the transmission of the biologic signal within target cells. Transcriptional activation requires homodimerization of the long-form PRL-R. The surface of PRL has two regions (site 1 and site 2) that interact with the PRL-R to tether the receptors in a productive dimeric conformation. Binding of site 1 to its receptor causes major changes in the structure of PRL, when compared with the structure of unbound PRL [67]. This receptor-induced change in PRL conformation provides the configuration needed for productive interaction with a second receptor through site 2. Heterodimers of short and long receptors, or short homodimers, do not mediate normal signal transduction [87]. PRL receptors may exist as preformed dimers that are conformationally activated, or monomers that coalesce into dimers after ligand binding. It seems likely that dimer formation and conformational activation are both stochastic processes that are favored by presence of the ligand. In other words, PRL increases the likelihood of dimer stability and the probability that the receptors will stay locked in a productive signaling configuration. Whether precise quantitative modeling of these processes is possible, or practical, remains to be seen.

The protein tyrosine kinase JAK2 (Janus kinase-2) is associated with the PRL-R through binding to the proline-rich box 1 motif. JAK2 is the essential PRL-regulated protein kinase, as well as essential for signal transduction by a variety of other hormones and cytokines [68–70]. Three other closely related kinases (JAK1, JAK3, and Tyk2) are activated by various cytokine receptors, but not by either PRL or GH receptors [71]. JAK2 activation causes phosphorylation of specific tyrosine residues on the receptor intracellular domain and on residues within the kinase. These phosphotyrosines serve as docking sites for STAT5, which also is phosphorylated by JAK2. The kinases are inactivated by multiple tyrosine phosphatases, which keep the steady-state level of JAK tyrosine phosphorylation at a very low level in the absence of hormonal stimulation. The tyrosine phosphatase short heterodimer partner (SHP)-2 has been shown to be involved in canonical PRL signaling via JAK2-STAT5a [72]. Knockout of SHP-2 in mammary epithelium leads, perhaps paradoxically, to decreased STAT5a signaling. A proposed mechanism for SHP-2 involvement is via suppression of SOCS feedback on JAK2 [73].

A host of noncanonical signaling pathways could be activated when PRL binds to its receptor, and these have been catalogued from the literature [74]. Among these the Src-family kinases could provide numerous downstream activities by virtue of their ability to couple to multiple signaling intermediates. Merely cataloguing all possible pathways in this way is fraught with major problems. First, the map generated in this does not place any relative priorities on different pathways even though it is clear that the JAK2-STAT5 pathway is by far more relevant than others. Second, and perhaps most troubling, is that such a map can imply a mechanism that is clearly wrong. For instance, in the Radhakrishnan et al. [74] map, cell proliferation is labeled as being downstream of a MAP-kinase pathway, but it is clear that PRL-induced mammary cell proliferation is downstream of STAT5a and mediated by RANK-ligand [19].

Although such a wide variety of STAT-independent pathways have been proposed for PRL signaling, it is very unlikely that these mechanisms have any physiologic relevance to PRL actions. It is somewhat more reasonable that some of these mechanisms could be relevant in pathological conditions such as hyperprolactinemia where PRL may be present at extreme levels or in cancer where target cells may be mutated in ways that result in unphysiological signaling. All of the genetic studies in laboratory mammals are consistent with the interpretation that the known physiological actions of PRL can be explained by the JAK2-STAT5 pathway.

One of the actions of PRL that has been suggested to involve STAT-independent signaling is mitogenesis [75]. PRL has legitimate growth-stimulating actions in the mammary gland and in pancreatic islet cells, so these are the tissues that need to be considered when asking how PRL induces cellular proliferation. In both of these tissues, the growth stimulus is not a direct response to PRL but rather is indirectly mediated by local synthesis of mitogens other than PRL. In the normal mammary gland, epithelial proliferation in response to PRL is mediated by secretion of RANK-L. And RANK-L secretion is downstream of the canonical STAT5A pathway and dependent on synergy with progesterone. In pancreatic islet cells, the indirect mediator of proliferation is serotonin [55]. Synthesis and secretion of serotonin by beta cells of the islets are, like RANKL induction in mammary cells, mediated by the canonical JAK2-STAT5 pathway [76].

The only mitogenic effect of PRL in a mammalian cell system that is apparently a direct action is in the rat Nb2 lymphoma cell line [68, 77, 78]. In specific substrains of this cell line, PRL acts as a direct mitogen. But these cells express a mutated or incorrectly spliced form of the PRL-R known as an "intermediate" form. This alternative receptor is missing a large portion of the intracellular domain [79, 80] and therefore may transduce an abnormal or unbalanced set of intracellular signals. Therefore, regardless of how PRL acts in Nb2 cells, it is not an example of PRL signaling in actual PRL target tissues. By the same token, it is an excellent example of how PRL signaling might be subverted in nonphysiological cells, such as some human cancers.

In 1994 it was discovered that PRL-regulated gene promoters include cis-acting elements that bind members of the STAT family of transcription factors [81]. A novel STAT protein (STAT5) was cloned from lactating sheep mammary glands [82]. Mammals synthesize two STAT5 proteins encoded by closely related genes.

Targeted gene disruption in mice made it very clear that STAT5 is responsible for mediating the primary PRL effects in the ovaries and mammary glands. STAT5a is essential in the mammary glands, whereas STAT5b is important in the rodent ovaries [83–85]. It is important to recall that the rodent ovary, unlike the human, requires PRL signaling to maintain the corpus luteum, and therefore molecular signaling by PRL in the human ovary may differ significantly from the rodent. The mouse genetic studies revealed a remarkable degree of concordance in the phenotypes of animals that have disruptions in the genes for the ligand (PRL), its receptor, and the PRL-regulated STAT5 transcription factors [15, 35, 83, 84]. The consistencies in the phenotypes of mice in the various genetic studies convincingly demonstrated that the canonical PRL-R signaling pathway through STAT5 can explain the normal physiologic actions of PRL.

Tyrosine-phosphorylated STAT5 dimerizes through interactions between phosphotyrosines and the Src homology 2 (SH2) domains. The dimeric STAT complexes are imported into the nucleus where they bind to GAS (interferon *g*amma-*a*ctivated *s*ite) elements in the promoters of the PRL-regulated genes. This leads to increased transcription of those genes and the consequent physiological changes.

STAT proteins do not have a conventional NLS (nuclear localization sequence), but instead their translocation into the nucleus is mediated by the alpha helices in the coiled-coil region toward the N-terminus. Although not NLS-mediated, the nuclear membrane importin proteins serve as the pore components for STAT translocation [86]. The details of interactions between STAT proteins and the basal transcription machinery have not been studied in any substantial detail. One nuclear factor that collaborates with STAT5 signaling in the mammary gland is the glucocorticoid receptor (GR) [87]. This synergistic interaction relies on occupancy of the GR by its ligand.

Like other receptors of the type 1 cytokine family, STAT signaling by PRL is controlled by negative feedback mechanisms within the target cells. The feedback inhibitor protein types are the SOCS (suppressors of cytokine signaling; SOCS 1–7) proteins and CIS (cytokine-inducible SH2 protein), which are related structurally to SOCS. These proteins feed back on the receptor complex to inhibit the coupling of

JAK to either the receptor or to the relevant STAT protein [88]. Excellent reviews of SOCS/CIS function have been published [89–91].

Whereas STAT5 appears to be the exclusive mediator of the primary physiologic PRL actions in mammals, other STAT proteins, such as STAT1, may be activated in response to PRL in certain pathophysiologic or pharmacologic conditions. In a rat T lymphoma cell line (Nb2), PRL induces the expression of the interferon response factor-1 (IRF-1) gene. This effect of PRL is mediated by STAT1 and, paradoxically, inhibited by STAT5 [92]. IRF-1 gene regulation is probably not involved in normal functions of PRL, but its induction via STAT1 in Nb2 cells shows one possible type of derangement in PRL signaling that could cause pathologic changes.

Conclusions

PRL is essential for the perpetuation of mammalian species because it drives the development of the mammary glands and stimulates milk synthesis and secretion. In both mammals and non-mammals, PRL excess is antigonadotropic in both females and males, acting on the brain, pituitary, and gonads. PRL acts on non-reproductive tissues that have evolved responses that support the primary roles of PRL in reproduction. For instance, in mammals PRL stimulates growth of the endocrine pancreas to support nutritional and metabolic demands in pregnancy and lactation.

PRL is synthesized primarily in specialized pituitary lactotrophs but also in several extrapituitary cell types. The physiological and pathophysiological roles of these extrapituitary sources of PRL continue to be the subject of necessary experimentation.

The PRL receptor is in a large family of cytokine and hormone receptors that signal via tyrosine phosphorylation and transcription factor activation. The canonical PRL signaling pathway, responsible for most or all proven PRL activities, comprises activation of Janus kinase 2 (JAK2) and the latent transcription factor STAT5. Many functions of PRL are directly mediated by JAK2-STAT5 signaling, whereas others are mediated by expression of secondary regulators, such as serotonin, IGF2, or RANK-ligand.

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Chapter 5
Prolactin Excess and Deficiency: Epidemiology, Causes (Excluding Prolactin-Secreting Pituitary Tumors)

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Introduction

Prolactin is secreted mostly by the lactotroph cells of the pituitary gland, but other organs and tissues also produce prolactin which may act in a paracrine manner, including the hypothalamus, telencephalon, brain stem, spinal cord, choroid plexus, mammary gland, some immune cells, and circumventricular organs [1]. Nevertheless, ectopic production of prolactin in excess is extremely rare, and prolactin excess or deficiency results almost exclusively from diseases that cause hyper- or hyposecretion of prolactin by lactotroph cells [2].

Prolactin excess accounts for the majority of cases of prolactin alterations and is defined as an increase of serum prolactin above the laboratory reference limit, assuming that the serum sample was obtained without excessive venipuncture stress [3].

Prolactin deficiency can be defined as a loss of function of anterior pituitary cells secreting prolactin, with resulting decreased or absent serum levels of prolactin. It can occur either in association with other anterior pituitary hormone defects or in isolation.

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Normal Levels of Prolactin

Several factors affect prolactin levels:

1. Gender: normal serum prolactin concentration varies with gender. Hence, normal prolactin levels for men and women are different (higher in women).
2. Circadian rhythm: serum prolactin also displays pronounced circadian variation with maximal concentrations occurring during sleep, with a peak of up to 30 ng/ml between 4 and 6 am, reaching a nadir during waking hours.
3. Seasonal changes: prolactin levels are also subject to seasonal changes, being higher in the spring and summer.
4. Menstrual cycle: prolactin levels can change during the menstrual cycle, being higher during the mid and second half of the cycle, compared with follicular phase. It also varies significantly between pre- and postmenopausal women. Therefore, specific reference intervals for each phase of the menstrual cycle are needed, and prolactin levels should be measured in the follicular phase, before the mid-cycle.

On the contrary, food does not appear to affect serum prolactin concentrations; and fasting is not necessary when having serum prolactin measured [4].

Prolactin Excess: Epidemiology and Causes

Hyperprolactinemia represents a common problem in endocrine practice. The prevalence and incidence of hyperprolactinemia depend on the study population. In healthy adults, hyperprolactinemia prevalence seems to vary from 1.2% to 4.1%, but in certain clinical settings, it can increase to 3.9–30%, such in female patients with menstrual abnormalities or infertility [5].

In a recent Scottish epidemiological study, all hyperprolactinemia cases between 1988 and 2014 were reviewed. Over this period the prevalence of hyperprolactinemia increased from 22 to 232 per 100,000. The adjusted incidence of all causes for hyperprolactinemia was 13.8 per 100,000, increasing from 9 to 20 per 100,000 over 20 years. This increasing incidence and prevalence over the study period was attributed mostly to an increase in drug-induced cases, but also an increased recognition of macroprolactin and a rise in pituitary diagnosis for men were observed.

Regarding gender distribution, hyperprolactinemia may occur in both males and females, but a female predominance is usually reported. So, in the PROLEARS study, the incidence in women was 3.5 times that was observed in men, but the gender difference was little above the age of 55 years. The highest incidence rate of hyperprolactinemia was found in women aged 25–34 years (49.6 per 100,000 person-years) [5].

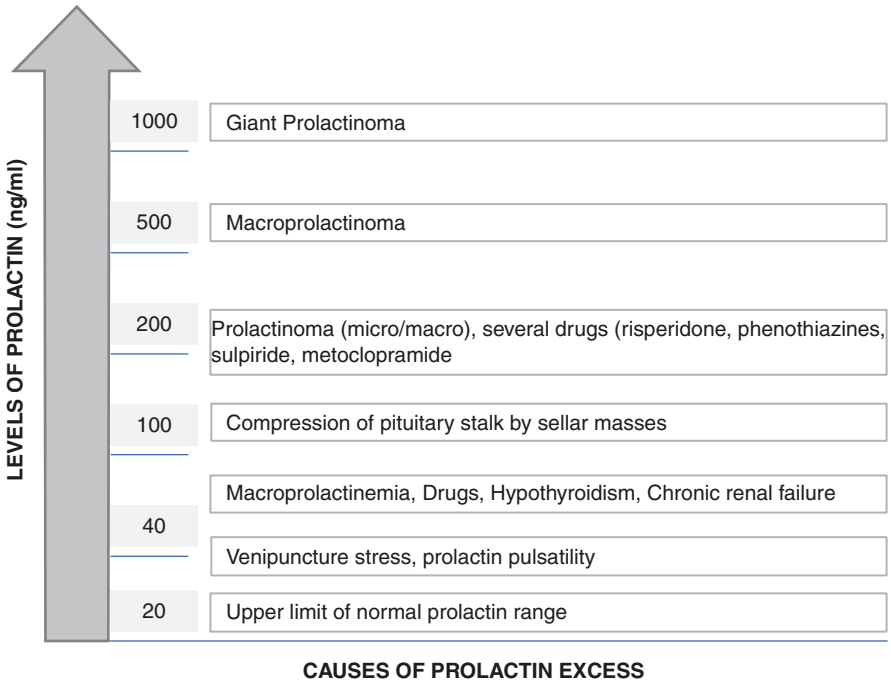

Fig. 5.1 Levels of prolactin and etiologies of hyperprolactinemia

Hyperprolactinemia can be physiological, pathological, or pharmacological [6], but sometimes the cause is unknown (idiopathic hyperprolactinemia). The degree of hyperprolactinemia can help narrow the list of diagnostic possibilities (Fig. 5.1).

Epidemiological data from large clinical series of hyperprolactinemia showed that prolactinomas and other pituitary tumor types are the main cause of hyperprolactinemia (35–70%), followed by idiopathic cases (28–46%). However, the majority of the studies excluded secondary causes of hyperprolactinemia, such us drug-induced hyperprolactinemia. When pharmacological causes are taken into account, they can represent one of the most prevalent etiologies of this condition [7].

Studies addressing pituitary secretion dysfunction following brain injuries have found variable prevalence of hyperprolactinemia in this population. In the first days post-injury, 52–77% of patients may exhibit hyperprolactinemia, but a few months thereafter the prevalence decreases to 3–5.7% [8].

Table 5.1 shows the main causes of hyperprolactinemia registered in epidemiological series [5, 7, 9–14].

Table 5.1 Reported causes of hyperprolactinemia in epidemiological series

Seshadri et al. [9]	Pituitary tumors (35.2%)
n = 71 female patients	Functional hyperprolactinemia (46.4%)
	Drug-induced hyperprolactinemia (7%)
	Hypothyroidism (5.6%)
Sonino et al. [10]	Pituitary adenomas (63.5%)
n = 52 patients (secondary causes of hyperprolactinemia excluded)	Idiopathic hyperprolactinemia (36.5%)
Berinder et al. [11]	Pituitary adenomas (71%)
n = 271 female patients (secondary causes of hyperprolactinemia excluded)	Idiopathic hyperprolactinemia (29%)
Zargar et al. [12]	Pituitary microprolactinoma (35.8%)
n = 187 female patients	Nonfunctioning pituitary adenoma with stalk compression (16%)
	PCOS (12.8%)
	Idiopathic hyperprolactinemia (27.8%)
Vilar et al. [7]	Prolactinomas (56.2%)
n = 1234 patients	Drug-induced hyperprolactinemia (14.5%)
	Macroprolactinemia (9.3%)
	Nonfunctioning pituitary adenomas (6.6%)
	Primary hypothyroidism (6.3%)
	Idiopathic hyperprolactinemia (3.6%)
	Acromegaly (3.2%)
Saejong et al. [13]	Pituitary adenoma 40.2%
n = 139 female patients	Idiopathic hyperprolactinemia 37.1%
Dekkers et al. [14]	Females: pituitary adenoma (70%), idiopathic or drug-associated hyperprolactinemia (30%)
n = 229 patients	
	Males: pituitary macroadenoma (62%)
Soto-Pedre et al. [5]	Drug-induced hyperprolactinemia (45.9%)
n = 1301	Pituitary disorder (25.4%)
	Macroprolactin (7.5%)
	Hypothyroidism (6.1%)
	Idiopathic (15%)

Physiologic Causes

Serum prolactin concentrations normally increase substantially during several physiological situations.

Pregnancy

Throughout pregnancy, the increasing estradiol concentration leads to a prolactin increase, reaching its peak at delivery. The magnitude of the increase is quite variable (ranging from 35 to 600 ng/mL). Estradiol secretion decreases after delivery. Several weeks postpartum, the basal serum prolactin concentration usually normalizes, even when the mother is breastfeeding [15].

Nipple Stimulation and Lactation

Nipple stimulation during breastfeeding transiently increases serum prolactin concentrations, presumably via a neural pathway. This increase is directly proportional to the degree of preexisting lactotroph hyperplasia due to estrogen. In the first weeks postpartum, as an example, the serum prolactin concentration increases up to 300 ng/mL above baseline in response to suckling; in contrast, several months after delivery, the increase in prolactin in response to suckling in the breastfeeding woman is usually less than 10 ng/mL above baseline [15].

In nonlactating women and men, nipple stimulation, breast imaging (mammography, ultrasound), or breast examination may but does not usually increase prolactin secretion.

Stress

Physical or psychological stress can cause hyperprolactinemia. As with all stimuli of prolactin secretion, women have greater increases than men, presumably due to the effect of their higher serum estradiol concentrations on the lactotroph cells. The magnitude of the increase in prolactin in response to stress is small, so the values rarely exceed 40 ng/mL.

Other

Sexual intercourse and acute exercise are also physiological, well-described causes of transient prolactin elevation.

Pathologic Causes

If we exclude lactotroph adenomas, we can identify several causes of pathological prolactin elevations (Fig. 5.2).

Decreased Dopaminergic Inhibition of Prolactin Secretion

Several conditions interfere with normal dopamine inhibition of prolactin secretion. These include any damage to the dopaminergic neurons of the hypothalamus, pituitary stalk section, or any disease in or near the hypothalamus-pituitary area that interferes with the secretion or delivery of dopamine to lactotrophs:

1. Tumors: adenomas of the pituitary other than lactotroph adenomas, craniopharyngiomas, germinomas, meningiomas, or malignant lesions (e.g., metastatic breast carcinoma).
2. Infiltrative diseases of the hypothalamus (e.g., tuberculosis, histiocytosis X, sarcoidosis).

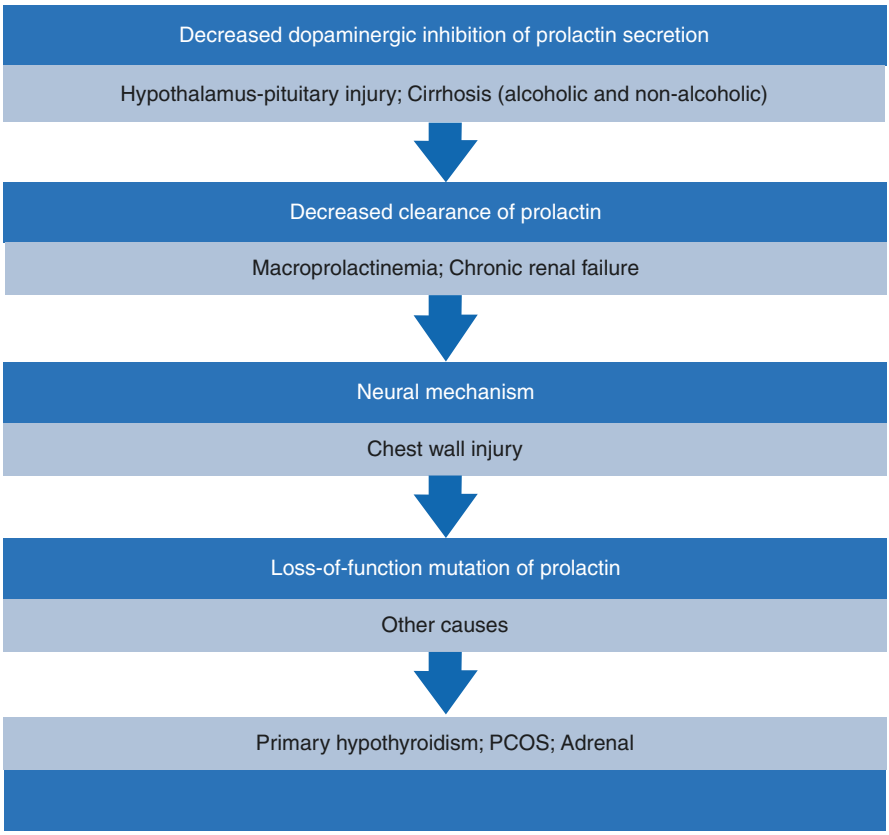

Fig. 5.2 Mechanisms of pathological hyperprolactinemia

3. Section of the hypothalamus-pituitary stalk (e.g., due to head trauma or surgery).
4. Irradiation to hypothalamus-pituitary region.

Alcoholic and nonalcoholic cirrhosis may be associated with elevated basal prolactin levels in 5–20% of these patients, possibly owing to alterations in hypothalamic dopamine generation [16].

Decreased Clearance of Prolactin

Chronic renal failure and macroprolactinemia are two causes of hyperprolactinemia due to decreased clearance of prolactin.

1. Chronic renal failure: the serum prolactin concentration is high in patients who have chronic renal failure and returns to normal after renal transplantation. Although there is a one-third decrease in metabolic clearance rate, a threefold increase in prolactin secretion can also be observed.

2. Macroprolactinemia: macroprolactin results from the formation of prolactin-immunoglobulin complexes that range in size from approximately 150 to 170 kD. These complexes are immunologically detectable, and macroprolactinemia is associated with apparent hyperprolactinemia although not typically associated with clinical features, due to its limited bioavailability and bioactivity. Although this entity is not of clinical significance directly, it is of clinical significance indirectly because it can be misdiagnosed and treated as prolactin hypersecretion. Misdiagnosis can be avoided by asking the laboratory to pretreat the serum with polyethylene glycol to precipitate the macroprolactin before the immunoassay for prolactin.

Prolactin Increase Due to Neural Mechanism

Chest wall injuries, such as severe burns, herpes zoster, trauma, or surgery, can increase prolactin secretion, presumably through stimulation of afferent neural pathways.

Genetic Causes: Germline Loss-of-Function Mutation

High levels of prolactin and prolactin insensitivity can be found in some families with a germline, loss-of-function mutation in the prolactin receptor gene (*PRLR*). The heterozygous mutation in *PRLR* results in an amino acid change from histidine to arginine at codon 188, leading to a loss of downstream signaling by Janus kinase 2 (JAK2) and signal transducer and activator of transcription factor 5 (STAT5). The presence of oligomenorrhea and infertility in these cases suggests that the hyperprolactinemia is having a biologic effect, which in turn suggests that there are functioning prolactin receptors in some tissues [17].

Other Causes

3. Primary hypothyroidism: although prolactin concentrations are normal in most hypothyroid patients, primary hypothyroidism can be a cause of hyperprolactinemia. The mechanism of hyperprolactinemia in hypothyroidism is not known. Both enhanced hypothalamic synthesis of thyrotropin-releasing hormone (TRH) and increased pituitary responsiveness to TRH have been described, and the serum prolactin response to stimuli, such as TRH, is increased. Prolactin values return to normal when hypothyroidism is corrected. It is important to note that severe primary hypothyroidism is a potential cause of an enlarged pituitary gland (due to thyrotroph hyperplasia, lactotroph hyperplasia, or both) and not to confuse this entity with a lactotroph adenoma.
4. Polycystic ovary syndrome (PCOS): PCOS and hyperprolactinemia are usually associated in clinical practice. However, there is no proof of a

pathophysiological link between these two entities [18]. Analysis of the evidence linking PCOS and hyperprolactinemia suggests that these conditions have independent origins and the association seems to be fortuitous. Recent investigations using serial serum sampling have excluded transient elevations of prolactin and have shown a less frequent association between these disorders [19]. PCOS patients with increased prolactin levels must be investigated for other causes of hyperprolactinemia, and in the majority of them, another cause can be found (pituitary adenoma in 69%, pharmacological hyperprolactinemia in 23%, and macroprolactin in 8%) [20].

5. Adrenal insufficiency: hyperprolactinemia has been described in patients with adrenal insufficiency, and cortisol replacement corrects it. This suggests that glucocorticoids modulate prolactin secretion, with a suppressive effect on prolactin gene transcription and prolactin release [21].

Pharmacological Causes

Drugs are a frequent cause of hyperprolactinemia, although they do not cause lactotroph adenomas. In a Brazilian multicenter study of hyperprolactinemia, drug-induced hyperprolactinemia was the second main cause, after prolactinomas, with a prevalence of 14.5% [7]. However, in the recent PROLEARS study, drugs became the leading cause of hyperprolactinemia (45.9%) and tripled during the 20 years of follow-up of the study. Antipsychotic and antidepressant medications were the most frequent etiology, representing 63.5% and 12.7% of the cases of drug-induced hyperprolactinemia, respectively. The increased rate of drug-induced hyperprolactinemia probably reflects a higher use of psychotropic medications over the study period [5].

In medication-induced hyperprolactinemia, serum prolactin concentrations are typically in the 25–100 ng/mL range. One exception is the antipsychotic drug, risperidone, which may be associated with serum prolactin concentrations as high as 200 ng/mL.

Antipsychotics

Antipsychotics are the most common cause of pharmacologically induced hyperprolactinemia, and the association between antipsychotic medication and hyperprolactinemia has been under investigation since at least the 1970s. Some of the antipsychotic drugs are known dopamine D_2 receptor antagonists and raise serum prolactin by that mechanism. Serum prolactin concentrations increase within hours after acute administration of the drug and return to normal within 2–4 days after cessation of chronic therapy.

Although hyperprolactinemia can be found with all antipsychotic medications, the magnitude of the elevation varies among drugs. First-generation antipsychotics,

like haloperidol or sulpiride, induce a significant rise in serum prolactin, two or three times above the reference values. It has been suggested that patients receiving long-term neuroleptic treatment may develop tolerance, with normalization of prolactin with continued treatment. However, this is not clear and other studies reported that tolerance does not occur.

Several second-generation antipsychotics cause a lesser elevation of the prolactin plasma levels than first-generation ones. Their greater specificity, resulting in a lesser blockade of the dopaminergic receptor but also their stronger blockade of serotonin receptors, may explain the limited elevation of prolactin. As exceptions, amisulpride, risperidone, and paliperidone are associated with higher levels of hyperprolactinemia. On the contrary, clozapine, quetiapine, olanzapine, ziprasidone, and aripiprazole are considered "prolactin-sparing antipsychotics," but prolactin excess can occur in association with their use, too [4].

Prolactin increase with antipsychotic medication has no clinical relevance in most patients, and generally no treatment is needed (unless hypogonadism or bothersome galactorrhea result). It is usually greater in females than in males, probably due to priming by estrogen. Also, prolactin levels are significantly lower in current and ex-cigarette smokers on antipsychotic medications, compared with nonsmokers. Smoking may reduce serum concentration of some antipsychotic drugs due to induction of the hepatic cytochrome P450 1A2 enzyme, and this can lead to a reduction in prolactin levels [22].

Antidepressants

Tricyclic agents and monoamine oxidase inhibitors are a common cause of hyperprolactinemia.

Selective serotonin reuptake inhibitors can cause little, if any, increase in the serum prolactin concentration, and they do not appear to cause clinically significant hyperprolactinemia in most patients.

Gastric Motility Drugs

Metoclopramide and domperidone are dopamine D2 receptor antagonists and can raise serum prolactin.

Antihypertensive Drugs

Methyldopa, which is a not commonly used antihypertensive drug, increases prolactin secretion by an inhibition of dopamine synthesis.

Verapamil is the only calcium channel blocker associated with a rise in prolactin levels, but the mechanism is not known. It can affect 8.5% of drug users and in most cases prolactin levels return to normal after drug cessation [23].

Estrogens

Estrogens have the ability to elevate prolactin and enhance responsiveness to prolactin-releasing stimuli. The mechanism by which estrogen stimulates prolactin secretion appears to involve binding of estrogen to the estrogen receptor, which then binds to an estrogen response element on the prolactin gene in the lactotroph cell. Estrogens increase the number of lactotroph cells of the anterior pituitary and act on the hypothalamus to decrease dopamine content [24].

Nevertheless, the amount of estrogen in hormonal contraceptives generally does not cause significant hyperprolactinemia.

Opioids

Opioids, like morphine or methadone, may both inhibit gonadal function and cause hyperprolactinemia [25].

Other Drugs

1. Cocaine use seems to influence prolactin levels (higher values in cocaine- dependent patients than controls) [26].
2. Cimetidine, an H2 antagonist, produces robust, transient increase in plasma prolactin levels in man following intravenous administration. This effect has been attributed, in part, to indirect central serotonergic mechanisms involving 5-HT2 receptors in the hypothalamus, but the evidence is inconclusive [27].

Idiopathic Hyperprolactinemia

In a substantial number of patients with hyperprolactinemia, no cause can be found, and they are classified as idiopathic. In these cases, serum prolactin concentration usually ranges between 20 and 100 ng/mL. Although many of these patients may have microadenomas not visible on imaging studies, in most of them, the serum prolactin concentrations change little during follow-up for several years.

Idiopathic hyperprolactinemia was one of the most reported etiologies in the past (28–46% of causes) [10–14], but in the recent study PROLEARS, it represented only 15%, maybe due to a better recognition of pathological causes [5].

Prolactin Deficiency: Epidemiology and Causes

Prolactin has a role in breast growth, lactogenesis during pregnancy, and the initiation and maintenance of lactation after delivery. Hypoprolactinemia has been reported to adversely affect fertility. In women, the luteal phase of the menstrual

cycle can be altered in the context of prolactin deficiency [28]. Some authors have concluded that a minimal amount of prolactin is necessary for normal ovulatory function. However, the role of prolactin in human ovulation is not clear, and there are reports of women who, despite undetectable prolactin levels, conceived without any medical assistance. In men, low PRL has been associated with reduced ejaculate and seminal vesicle volume in infertile subjects. In addition, among men consulting for sexual dysfunction, hypoprolactinemia has been associated with erectile dysfunction and premature ejaculation, findings further confirmed in the general European population and infertile men [29].

Hypoprolactinemia may appear in the context of several pathological conditions or pharmacological treatments. Isolated prolactin deficiency is rare; most patients with acquired prolactin deficiency have evidence of other pituitary hormone deficiencies [30]. In fact, the incidence of acquired hypoprolactinemia increases with the number of other anterior pituitary defects and should be considered a marker of extensive pituitary damage.

According to a Spanish epidemiological study, the prevalence of hypopituitarism was 29 of 100,000 in 1992, and it increased to 45.5 of 100,000 in 1999, with an average annual incidence of 4.2 cases of 100,000 (similar for men and women). The most frequent causes included pituitary tumor (61%), non-pituitary tumor (9%), and a nontumor cause (30%). With regard to the type of hormonal deficiencies, LH/FSH defect was the most prevalent, and it was present in 87% of the cases, while prolactin deficiency was the least frequent (17%) [31]. However, epidemiological data of prolactin deficiency are scarce in literature. Most studies of hypopituitarism do not report prolactin deficiency, and this may be the result of a perceived lack of significance relative to other pituitary hormones.

Pathological Causes

Any disease involving the hypothalamus-pituitary area can affect the secretion of one or more of pituitary hormones, including prolactin. The most recognized causes of hypopituitarism are summarized in Table 5.2 [32].

One of the most relevant and identified etiologies of hypoprolactinemia is Sheehan's syndrome, due to its presentation with alactogenesis.

Sheehan's Syndrome

Sheehan's syndrome is a postpartum pituitary necrosis, usually precipitated by massive uterine hemorrhage during the peripartum or postpartum period. It is a leading cause of hypopituitarism in underdeveloped or developing countries but is rare in developed countries, due to improvements in obstetrical care. A recent Turkish study showed that this syndrome was present in 13.8% of patients with hypopituitarism, compared with 3.1% in developed countries.

Table 5.2 Causes of hypopituitarism

Neoplastic	Pituitary and non-pituitary tumors
	Metastases
	Hematological malignancy
Iatrogenic	Surgery in the hypothalamus-pituitary area
	Cranial irradiation
Head trauma	Traumatic brain damage
Infiltrative/inflammatory	Sarcoidosis
	Langerhans cell histiocytosis
	Amyloidosis
	Hemochromatosis
	Lymphocytic hypophysitis
	Wegener's granulomatosis
Infectious	Tuberculosis
	Meningitis
	Syphilis
	Bacterial, viral, parasitic, or fungal infections
	Pituitary abscess
Vascular	Sheehan's syndrome
	Pituitary apoplexy
	Ischemic stroke
	Aneurysm
	Subarachnoid hemorrhage
	Snake bites (Russell's viper bites)
Congenital	Isolated or multiple pituitary hormone deficiencies
Other	Primary empty sella
	Congenital chronic hydrocephalus

The onset of hypopituitarism is usually insidious, with nonspecific symptoms, and there is often a delay in diagnosis of several years or even decades. A history of postpartum hemorrhage so severe as to cause hypotension and require blood transfusion may be crucial to establish the etiology of hypopituitarism.

In severe cases, the presentation can be acute, with lethargy and anorexia. In mild cases, the inability to breastfeed due to prolactin deficiency is a frequent symptom, along with the absence of menses after delivery, loss of sexual hair, fatigue, anorexia, or weight loss. An evaluation of pituitary function should be done after a delivery associated with heavy blood loss, especially the adrenal axis, and initiate replacement treatment as needed. The value of measuring prolactin shortly after postpartum hemorrhage to predict the ability to breastfeed has not been studied. Hypopituitarism is progressive, with no recovery of the pituitary function. In the chronic phase, the MRI may reveal a complete or partial empty sella [32].

Genetic Causes

There are some genetic mutations that cause prolactin deficiency, most of them in combination with other hormone defects.

1. Multiple anterior pituitary hormone deficits (MPHD): familial occurrence of MPHD is unusual and has been described as being transmitted in an autosomal recessive, autosomal dominant, or X-linked recessive manner.

HESX1, LHX3, and LHX4 transcription factors are important for pituitary organogenesis and early differentiation of several types of pituitary cells. Mutations in the genes encoding these factors cause combined pituitary hormone deficiency (GH, prolactin, TSH, LH, and FSH) [33].

PROP-1 is necessary for the differentiation of a cell type that is a precursor to somatotroph, lactotroph, thyrotroph, and gonadotroph cells. Mutations in *PROP-1* appear to be the most common cause of both familial and sporadic congenital combined pituitary hormone deficiency (gonadotropin deficiency in addition to GH, TSH, and prolactin deficiency) [34–35].

PIT-1 (called POU1F1 in the human) acts temporally just after PROP-1 and is necessary for the differentiation of a cell type that is a precursor of somatotroph, lactotroph, and, to a lesser degree, thyrotroph cells. Both dominant and recessive mutations of the gene that encodes PIT-1 lead to congenital deficiencies of GH, prolactin, and sometimes TSH. The secretion of ACTH, FSH, and LH is preserved. Circulating anti-PIT-1 antibodies may also result in hypopituitarism.

Combined prolactin deficiency has also been reported in genetic defects of G proteins underlying the resistance to PTH (pseudohypoparathyroidism), although an associated autoimmune process is hypothesized as being responsible for the prolactin deficiency [36].

2. Isolated prolactin deficiency: an isolated prolactin deficiency without a pharmacological, pathological, or iatrogenic cause is a rare entity of which only a few cases have been reported, usually presenting as puerperal alactogenesis [37, 38]. In these patients, breast milk production does not respond to stimulation with antidopaminergic drugs (domperidone) but is restored with recombinant human prolactin. The lack of response to antidopaminergic drugs, as well as the restoration of milk production upon recombinant human prolactin administration, indicate the existence of a specific defect in lactotroph cells, due to genetic or autoimmune causes. A genetic basis is possible, because in one of these cases a familial occurrence of alactogenesis was reported [38]. Maybe minor or partial mutations of the *PIT1* or *PROP1* genes may be associated with the occurrence of prolactin deficiency. However, in another case, a mutation in the coding region of prolactin gene and its putative releasing hormone or receptor or in other genes related to MPHD could not be demonstrated. Instead, the authors demonstrated the presence of circulating autoantibodies recognizing some antigens in prolactin-secreting cells but not the hormone itself or any other pituitary cells or hormones, suggesting an autoimmune etiology [39].

Pharmacological

Dopamine Agonists

Dopamine agonists are used in high doses in patients with Parkinson's disease. They can cause isolated prolactin suppression in a significant percentage of individuals (44%), especially those with a high rate of exposure to newer dopamine agonists [40].

Aripiprazole

Aripiprazole is a non-prolactin-raising antipsychotic which has been proposed as an alternate option to treat risperidone-associated hyperprolactinemia. However, doses higher than 5 mg can reduce prolactin levels to lower than 3 ng/mL, causing prolactin deficiency [41].

Conclusion

Prolactin disorders are common in clinical practice, especially hyperprolactinemia. An increasing incidence and prevalence is being reported, and it has been attributed mostly to a rise in drug-induced cases but also increased recognition of other causes of prolactin alteration, including genetic causes.

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Chapter 6
Prolactin-Secreting Pituitary Adenomas: Epidemiology and Natural History

Lisa L. Morselli and Janet A. Schlechte

Prolactin-secreting pituitary adenomas are the most common functioning pituitary tumors and may arise sporadically or may be part of a genetic syndrome [1]. The initial estimates of tumor prevalence obtained from cancer registries suggested that these tumors are uncommon; however they are likely underreported in registries because the majority are benign [2]. Conversely, autopsy studies demonstrated a high prevalence of pituitary adenomas, suggesting that many never become clinically significant. In a systematic meta-analysis of imaging and autopsy methods to estimate prevalence, Ezzat et al. found pituitary adenomas in 22.5% and 14% of patients, respectively [3]. Among the autopsy specimens that were subjected to immunohistochemical analysis in this study, 25–41% stained positively for prolactin [1].

In this chapter, we will first discuss the epidemiology and natural history of sporadic prolactinomas and then review the available information on familial prolactinomas.

Epidemiology of Sporadic Prolactinomas

Population Studies

The prevalence of pituitary adenomas derived from multiple cross-sectional population-based cohort studies is shown in Table 6.1 [2–8]. Among cases referred to endocrinologists in a stable catchment area of one million inhabitants in England,

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Table 6.1 Epidemiology of prolactin-secreting adenomas: population study results

Author (year)	Ref.	Country	Catchment period	Total population (*n*)	Prolactinomas		Prevalence (per 100 K)	Incidence (per 100 K per year)
					M (*n*)	F (*n*)		
Davis (2001)	[2]	UK	1988–1998	1,000,000	n/a	n/a	6–10	0.6–1
Daly (2006)	[3]	Belgium	–	72,000	9	36	62	–
Fernandez (2010)	[4]	UK	–	81,500	4	32	44.4	–
Raappana (2010)	[7]	Finland	1992–2007	730,000	16	48	–	2.2
Gruppetta (2013)	[5]	Malta	2000–2011	418,000	45	63	35	2.5
Tjornstrand (2014)	[8]	Sweden	2001–2011	1,600,000	62	125	–	1.6
Agustsson (2015)	[6]	Iceland	1955–2012	330,000	190	281	54.4	F 3.6 M 1.4

– Data not reported

the prevalence of pituitary adenomas was estimated at 6–10 per 10^5 [2]. More recently, much higher rates have been described in Belgium (62 per 10^5) [3], the United Kingdom (44 per 10^5) [4], Malta (35 per 10^5) [5], and Iceland (54 per 10^5) [6]. The estimates in all of these population-based studies were derived by reviewing general practitioner databases, tumor registries, and/or chart review of clinical and hospital records [4–8]. In all more recent population studies, prolactinomas represented the most commonly diagnosed pituitary adenoma (66% of all cases in the Belgian cohort, 57% in the British cohort, 46% in the Maltese cohort, and 40% in the Icelandic cohort).

Fewer studies have specifically assessed incidence rates of prolactinomas. Initial reported incidence rates ranged from 0.6 to 1 per 10^5 [2], but similar to prevalence estimates, more recent population studies report higher values. In the Maltese cohort, incidence was estimated at 2.5 per 10^5 per year from 2000 to 2011 [5], while a Finnish population study reported incidence rates of 2.2 per 10^5 per year from 1992 to 2007 [7], and a Swedish cohort had an incidence of 1.6 per 10^5 per year from 2001 to 2011 [8]. Overall, prolactin-secreting adenomas of 1 cm or more in diameter were reported to represent from 20% to 36% of cases. The increase in prevalence and incidence rates in recent years is likely due to improved diagnostic techniques, especially the availability of magnetic resonance imaging, as well as increased awareness and clinical suspicion [4].

Sex Differences in Tumor Size

Figure 6.1 represents the age-specific incidence of prolactinomas in a Swedish population cohort, illustrating that women are diagnosed at a younger age than men [8]. The median age at diagnosis ranges from 30 to 37.5 years in women compared to 38.5–47.5 years in men [5–9]. Table 6.2 represents the difference in tumor size by sex and the preponderance of large tumors in men [3–8]. The reported proportion of women with macroprolactinomas ranged from 9% to 27% of cases, while 50–75% of men had a tumor larger than 1 cm at diagnosis [3, 5–7]. In a study focused only on macroprolactinomas, Gruppetta et al. [9] reported a prevalence of 12.7 per 10^5 in men and 7.5 per 10^5 in women, with an incidence of 0.66 and 0.47 per 10^5 per year, respectively.

There continues to be controversy as to why a greater proportion of men have macroadenomas compared to women. Do men ignore hypogonadal symptoms and delay treatment allowing the tumor to increase in size, or are there gender-specific differences in tumor behavior? Table 6.3 summarizes the sex differences in indices of cell proliferation in patients with prolactinomas who underwent adenoma resection [10–16]. All of the studies examined positivity of MIB-1, an antibody to the proliferation marker Ki-67 antigen [17], while some also analyzed mitotic indices and other markers of proliferation [11, 13–15]. Of note, because these were surgical series, the prevalence of macroadenomas was higher than is generally seen in non-selected cohorts. The majority of studies have demonstrated higher proliferation

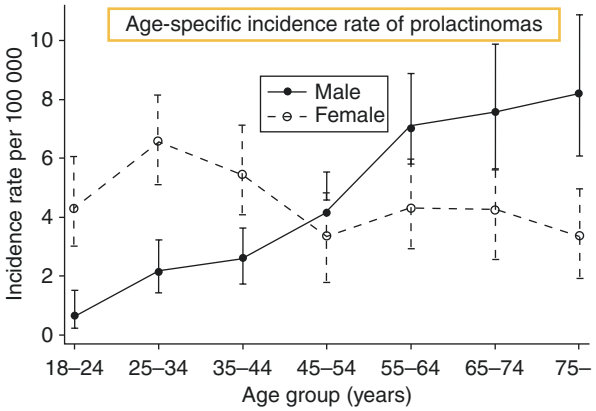

Fig. 6.1 Age-specific incidence rate of prolactinoma in a Swedish population study. (From [8], with permission; copyright 2014, European Journal of Endocrinology)

Table 6.2 Sex differences in prolactinoma size and patient age at diagnosis: epidemiologic studies

Author (year)	Ref.	*n*	M (*n*)	F (*n*)	Macroadenoma (%)		Median age at diagnosis (years)	
					M	F	M	F
Daly (2006)	[3]	43	8	35	50	17	38.5	33
Fernandez (2010)	[4]	36	4	32	–	–	41.5	30.5
Raappana (2010)	[7]	64	16	48	75	23	47.5	32
Gruppetta (2013)	[5]	108	45	63	63	9	47	37.5
Tjornstrand (2014)	[8]	187	62	125	–	–	–	–
Agustsson (2015)	[6]	188	47	141	64	27	47	32

– Data not reported

Table 6.3 Sex differences in proliferation indices in patients with prolactinoma

Author (year)	Ref.	Patients s/p pituitary surgery (n)	M (*n*)	F (*n*)	Macroadenoma (%)		DA before surgery	Proliferation indices in M vs F
					M	F		
Delgrange (1997)	[10]	33	17	16	94	56	Yes	↑*
Calle-Rodrigue (1998)	[11]	72	20	52	75	52	No	↑
Nishioka (2003)	[12]	43	16	27	–	–	Yes	↑
Schaller (2005)	[13]	26	7	19	100	58	Yes	↑
Delgrange (2005)	[14]	72	36	38	97	34	Yes	↑
Scheithauer (2006)	[15]	25	9	16	100	56	Yes	=
Fainstein (2010)	[16]	18	11	7	100	100	Yes	↑

Reported proliferation indices include mitotic index, MIB-1/Ki 67, and others
DA dopamine agonists
*$p = 0.08$
– Data not reported

indices in men compared to women [9, 11–14, 16], while one [10] reported a trend in this direction, and one [15] found no sex difference in any of the indices. Two series reported lower proliferation indices in younger women [11] or no difference by age [15], while one [11] observed no difference in proliferation indices between men with micro- and macroprolactinomas. Complicating the picture is the fact that all but one cohort [11] included patients previously treated with dopamine agonists. Of those who specifically examined the impact of prior treatment with a dopamine agonist, one group [15] found lower proliferation indices, and another [13] reported no impact of dopamine agonist treatment. Fainstein et al. [16] directly compared the characteristics of macroprolactinomas in both sexes and observed lower proliferation indices in women vs men, while Delgrange et al. [10] only reported a trend for higher indices. In these reports, macroprolactinomas were smaller in women than in men. Nishioka et al. [12] and Delgrange et al. [14] found a positive correlation between proliferation indices and tumor size as a continuous variable. Other authors did not observe this result, possibly because they considered tumor size as a categorical variable (i.e., macroadenoma vs microadenoma). While proliferative activity and tumor aggressiveness appear to be greater in men, the mechanism(s) responsible for these observations have not been elucidated.

Effect of Menopause

There may also be an effect of menopause on tumor size. Shimon et al. [18] retrospectively identified 14 women diagnosed with prolactinoma in the postmenopausal period and reported 93% with macroprolactinomas. Similarly, a more recent report found 94% of macroprolactinomas in a cohort of women diagnosed with prolactinoma after age 50 [19]. This striking difference with the presentation of prolactinomas in premenopausal women may be due to the absence of menstrual irregularities preventing early diagnosis. In the report by Calle-Rodrigue et al. [11], indices of cellular proliferation were lower in younger women than in older women (respectively, under and over 40 years old), but the difference was not statistically significant. However the group of older women included both pre- and postmenopausal patients, which precludes drawing conclusions as to the growth potential of prolactinomas in the postmenopausal state.

Giant Prolactinomas

Various criteria have been used to define giant prolactinomas, but all rely on an arbitrary size cutoff of 4 cm or greater, which usually results in extrasellar extension [20]. Furthermore, many authors associate a minimum prolactin level (usually over 1000 μg/dl [20], although a cutoff of 200 [21] or 250 [22] μg/dl was also used).

Table 6.4 Epidemiology of giant prolactinomas

Author (year)	Ref.	*n*	M (*n*)	F (*n*)	Mean age at diagnosis ± SD (years)
Davis (1990)	[23]	10	9	1	43 ± 17
Van der Lely (1992)	[24]	4	3	1	58 ± 8
Grebe (1992)	[25]	4	4	0	40 ± 7
Petakov (1998)	[26]	4	3	1	39 ± 13
Saeki (1998)	[27]	10	7	3	36 ± 14
Shrivastava (2002)	[28]	10	10	0	46 ± 8
Corsello (2003)	[29]	10	10	0	45 ± 13
Wu (2006)	[22]	20	16	4	32 ± 12
Shimon (2007)	[30]	12	12	0	39 ± 10
Cho (2009)	[31]	10	10	0	37 ± 11
Acharya (2010)	[32]	10	5	5	36 ± 10
Madsen (2011)	[33]	5	5	0	45 ± 18
Yang (2011)	[34]	12	10	2	46 ± 11
Yarman (2012)	[35]	4	4	0	31 ± 10
Delgrange (2014)	[36]	15	0	15	49 ± 24
Espinosa (2016)	[37]	47	42	5	44 ± 14
Gruppetta (2016)	[9]	15	10	5	63 (52–74)[a]
Shimon (2016)	[38]	18	16	2	36 ± 13
Total		220	176	44	
Percentage			86%[b]	14%[b]	

Adapted from [20]

[a]Median (interquartile range)

[b]Delgrange et al. [36] not included in calculations due to specific focus on women

Although these tumors are large and usually cause mass effect, they may respond to treatment with dopamine agonists [20]. To date, 220 cases of giant prolactinoma are described in the literature (Table 6.4) [9, 20, 22–38]. Of these, only 14% occurred in women, and the mean age at diagnosis was 41 years. Gruppetta et al. [9] estimated the incidence of giant prolactinomas at 0.07 per 10^5 persons per year. On the other hand, in the Belgian population study by Daly et al. [3], no giant prolactinomas were reported as the largest prolactinoma had a diameter of 35 mm.

Delgrange et al. [36] focused on the characteristics of giant prolactinomas in women. In this multicenter retrospective study, 15 women with giant prolactinoma were identified. The authors also reported another 19 cases in women and 112 cases in men from the literature. Women with giant prolactinomas were on average older than men in this series. Incidence in women showed a bimodal age distribution, with highest numbers in the third and fifth decades, while the highest incidence in men was seen in the fourth decade. Among premenopausal women with secondary amenorrhea, symptoms had been present from 2 to 31 years prior to diagnosis, and all but one patient was diagnosed because of symptoms of mass effect. The reasons for this delay in diagnosis are unclear, but amenorrhea may have been masked by oral contraceptive use in a subset of patients.

Malignant Prolactinomas

The exact incidence of malignant prolactinomas is unclear, but they likely account for <0.5% of symptomatic pituitary tumors. Clinically, malignant prolactinomas appear very similar to invasive benign macroadenomas, and the diagnosis can only be confirmed in the presence of metastases. When surgical or medical therapy is effective, in some tumors there may be a long latency before recurrence [39].

Prolactinomas in Children

Prolactinomas are uncommon in children and adolescents [40]. Only two patients younger than 20 years were reported in the Maltese population cohort [5], and three patients in the British population cohort [4]. In the Finnish cohort, the incidence was estimated at two per 10^5 per year [7]. The majority of pituitary tumors identified in children are prolactinomas, which represent up to 68% of pituitary adenomas and 2.6% of intracranial tumors arising in that age range [41]. As in the adult population, prolactinomas present more commonly as microadenomas in girls and macroadenomas in boys [41]. In some older reports, there is a disproportionately large number of patients presenting with macroadenomas (64%), but this may be a manifestation of reports generated from neurosurgical units [42]. It has also been suggested that the number of patients resistant to dopamine agonists is higher in children [43]. A detailed discussion of prolactinomas in children and adolescents is provided in Chap. 10 "Prolactinomas in Children and Adolescents."

Prolactinomas in the Elderly

Minimal information is available about epidemiology of prolactinomas in elderly individuals. In autopsy series, Kovacs demonstrated prolactin-staining microadenomas in 13% of patients over 80 years of age, but clinical series showed that prolactinomas represent only 4–8% of all pituitary adenomas [44, 45].

Natural History of Sporadic Prolactinomas

Studies examining the natural history of prolactinomas (Table 6.5) [46–53] were mostly conducted before dopamine agonists were widely available and focused on microadenomas, since active treatment (surgery, radiation, and/or bromocriptine) was utilized for macroprolactinomas. These studies only included women, except for one series with one man [50]. Of note, pituitary imaging at the time was essentially limited to polytomography of the sella. It was not until the late l980s that computerized tomography (CT) began to be widely used.

Table 6.5 Studies examining the natural history of prolactinomas

Author (year)	Ref.	Type of study	Follow-up (years)	*n* (M/F)	Type of imaging	Adenoma on baseline imaging %	Progression of adenoma on imaging *n* (%)	Macro-adenoma n	Progression of macro-adenoma on imaging *n* (%)	Stable or decreased PRL at follow-up *n* (%)
March (1981)	[46]	R	3–20	43 (0/43)	XR, ST, CT	100	2 (5)	0	–	41 (95)
Rjosk (1982)	[47]	R	2–6	72 (0/72)	XR, ST, CT	57	2 (3)	4	1 (25)	70 (97)
Weiss (1983)	[51]	P	5–6	27 (0/27)	ST, CT	100	3 (11)	0	–	24 (89)
Johnston (1983)	[48]	R	1–6	9 (0/9)	XR	0	0	0	–	7 (78)
Koppelman (1984)	[49]	R	11	25 (0/25)	XR, ST, CT	52	1 (4)	7	0	22 (88)
Martin (1985)	[50]	R	2–11	41 (1/40)	XR, CT	0	0	0	–	34 (82)
Sisam (1987)	[52]	P	4	38 (0/38)	CT	38	0	0	–	26 (68)
Schlechte (1989)	[53]	P	3–7	27 (0/27)	XR, CT	43	6 (22)	0	–	24 (80)
Total				285 (1/284)			14 (5)	11	1 (9)	248 (87)

R retrospective, *P* prospective, *XR* X-ray, *ST* sellar tomography, *CT* computerized tomography

In retrospective studies [46–50], biochemical evidence of a tumor at presentation was noted in 38–57% of patients, but only 2–5% of patients showed radiographic evidence of tumor growth. None of the patients who had negative imaging at baseline developed radiographic evidence of tumor. Those subjects with initial negative imaging presumably had a microadenoma that was below the threshold for radiological detection. Two retrospective series [47, 49] included patients with macroadenomas, and, out of 11 patients, only 1 showed tumor growth after 4 years [47]. In all of the above-cited studies, over a follow-up ranging from 2 to 20 years, prolactin levels remained stable or improved in over 80% of cases.

Three prospective studies have examined the natural history of prolactinomas. Weiss et al. [51] followed 27 women with untreated microprolactinoma for 5–6 years, using sellar tomography and CT. Only three patients showed tumor enlargement over time, of which one progressed to a macroadenoma. Eighty-nine percent of patients had stable or improved prolactin levels by the end of follow-up. Sisam et al. [52] followed 38 women with untreated microprolactinomas for an average of 4 years. None of the patients showed evidence of prolactinoma growth by high resolution CT, while 68% had stable or decreased prolactin concentrations. Finally, Schlechte et al. [53] enrolled 30 women with hyperprolactinemia and followed them for 3–7 years. At baseline, 43% had abnormal imaging (as shown by polytomography before 1980, head CT after that) consistent with pituitary tumor. Over the course of follow-up, 22% showed tumor growth on imaging, but none of the patients developed signs of compression or compromised pituitary function. The higher number of cases with tumor growth in this study compared to other series is likely due to improved resolution of the imaging techniques used at follow-up. Consistent with earlier studies, prolactin levels remained stable or improved over time in the majority of patients (80%).

Thus it appears that microadenomas are unlikely to grow significantly over time if left untreated. Furthermore, prolactin concentrations appear to remain stable or decrease in the great majority of untreated patients (Table 6.5). This however should not lead to the conclusion that pituitary microadenomas do not need to be treated, especially in premenopausal women, given the negative consequences of hyperprolactinemia on reproductive and bone health. Furthermore, careful monitoring is necessary, as a small proportion of tumors (5%, Table 6.5) will grow. Precise data about the natural history of macroadenomas is scant, since these tumors are usually treated either medically or (less frequently) surgically, but, given their larger size at diagnosis, they are likely more prone to growth.

Impact of Pregnancy on Prolactinoma Growth

Estrogen stimulates synthesis and secretion of prolactin, and the high estrogen levels of pregnancy lead to physiologic lactotroph hyperplasia. Indeed, lactotroph hyperplasia is observed in pregnant women without prolactinoma, and several reports of pituitary enlargement visible on MRI during pregnancy have been published [reviewed in [54]].

In the last 25 years, multiple studies have examined the impact of pregnancy on prolactinoma growth [55–65]. All were retrospective except two [55, 63]. In these cohorts, the majority of patients had received dopamine agonists, and a small number had undergone pituitary surgery with persistence of hyperprolactinemia, prior to conception. Dopamine agonists were discontinued once pregnancy was diagnosed. The proportion of macroprolactinomas included in these series ranged from 1% to 39% of cases. All but one [65] of the retrospective studies reported some degree of tumor growth during pregnancy, which manifested with onset of visual field defects and/or headaches, in the postpartum period. Despite evidence of tumor growth, up to 40% of patients included in these retrospective studies were found to have spontaneous remission of hyperprolactinemia after pregnancy [56–58, 61]. In the two prospective studies [55, 63], no symptoms suggestive of tumor growth were noted after cabergoline discontinuation, and postpartum MRI showed disappearance of one third of macroadenomas and half of microadenomas [63]. Furthermore, in one series, two thirds of patients had normal prolactin levels off dopamine agonists at the end of follow-up [55].

It is clear now that symptomatic tumor enlargement in pregnant women is uncommon. As summarized by Molitch [66], the risk is 2.2% for women with microadenomas, 27.9% for women with macroadenomas, and 4.3% for women with macroadenomas treated prior to pregnancy. Therefore, despite pregnancy being a hyperestrogenic state, it does not appear to promote clinically significant adenoma expansion in most women and may actually induce remission of hyperprolactinemia in a proportion of patients.

Impact of Menopause on Prolactinoma Growth

The current clinical practice is to stop dopamine agonists in women with microprolactinoma diagnosed during their fertile years, once they reach menopause, while continuing to monitor them over time [40]. Two groups have focused on the natural history of prolactinomas in women undergoing menopause. Karunakaran et al. [67] reported spontaneous remission of hyperprolactinemia in 45% of patients. Unfortunately the authors do not provide details about length of follow-up. Mallea-Gil et al. [68], on the other hand, observed normalization of prolactin in 93% of patients followed for 2 years after discontinuation of dopamine agonist treatment. Furthermore, prolactinomas disappeared over time in over two thirds of patients, including almost two thirds of macroprolactinomas. These results need to be confirmed in larger cohorts, and periodic surveillance of postmenopausal women of dopamine agonists is recommended.

Prolactin-Secreting Adenomas in Genetic Syndromes

Hereditary pituitary adenomas are estimated to represent about 3–5% of all pituitary adenomas [69, 70] and are described in multiple endocrine neoplasia syndrome type 1 (MEN1), Carney complex, and familial isolated pituitary adenoma (FIPA)

syndrome [69]. Prolactinomas are mostly reported in patients with multiple endocrine neoplasia syndrome type 1 (MEN1) and familial isolated pituitary adenoma (FIPA) syndrome, while hyperprolactinemia without evidence of pituitary adenoma has been described in Carney complex patients [71].

MEN-1

MEN-1 is an autosomal dominant syndrome secondary to mutations in the *MEN1* gene and classically characterized by primary hyperparathyroidism, pituitary adenoma, and enteropancreatic neuroendocrine tumors [72]. The penetrance of pituitary adenomas by age 50 is 30–40% [73]. Prolactinomas are the predominant pituitary adenoma in MEN-1 patients [74, 75]. In the largest retrospective study focused on pituitary adenomas in MEN-1 patients to date [75], prolactinomas represented 62% of pituitary adenomas. Mean age at diagnosis was significantly younger than for other types of pituitary adenomas. In this cohort, macroadenomas represented 84% of cases, a significantly higher rate than observed in a cohort of carefully matched sporadic prolactinoma patients, suggesting a more aggressive behavior of prolactinomas in MEN-1. More recently, in a large cohort including 90% of MEN-1 cases in the Dutch population [74], prolactinomas represented 73% of pituitary adenomas. However, only 38% were macroprolactinomas. In this cohort, one third of patients remained untreated for up to 6 years without significant tumor progression. Unfortunately the authors did not provide details about the size of these untreated prolactinomas, but these observations suggest that the clinical behavior of prolactinomas in MEN-1 patients may not be different from that of sporadic prolactinomas. The authors hypothesize that the difference in results could be due to inclusion of cases diagnosed by screening in their cohort, while earlier studies relied on cases diagnosed when patients were symptomatic [74].

A few MEN-1 kindreds with a particularly high prevalence of prolactinoma have been reported. They cluster in the Burin Peninsula in Newfoundland, Canada, and share the same MEN-1 mutation, suggesting a founder effect. Pituitary adenomas were diagnosed in 40% of family members and were exclusively prolactinomas [76, 77]. However, except in these rare cases, to date, no phenotype-genotype correlation has been identified in patients with MEN-1 who harbor a pituitary adenoma [74].

FIPA

The term FIPA, coined by the Beckers group in Belgium, describes families in which two or more members have pituitary adenomas of any type that are unrelated to MEN-1 or Carney complex [78]. FIPA kindreds can be divided into homogeneous, in which all affected members have the same kind of pituitary adenoma, and heterogeneous, in which several types of pituitary adenoma are found. About 20% of FIPA patients have been reported to carry mutations in the aryl hydrocarbon receptor interacting protein (*AIP)* gene [70]. Retrospective data indicates that

prolactinomas comprise about 40% of pituitary adenomas that occur in the setting of FIPA [78], a lower prevalence than that reported in MEN-1 patients. They do not appear to differ from sporadic tumors in terms of male to female ratio, age at diagnosis, and proportion of microadenomas [69]. However, they seem to be more aggressive when they occur in heterogeneous FIPA kindreds. Indeed, in these families, suprasellar extension and cavernous sinus invasion were observed significantly more frequently than in sporadic prolactinomas [79], and one patient from a heterogeneous FIPA kindred developed a malignant prolactinoma [39].

Conclusion

The prevalence and incidence of prolactinomas have increased in recent years, possibly due to improved awareness and diagnostic methods. A greater proportion of macroadenomas, including giant prolactinomas, are reported in men, who are usually diagnosed at an older age compared to women. Untreated microprolactinomas seem to have limited growth potential in women, while no data is available on the natural history of these tumors in men, likely due to their larger size prompting active treatment. Pregnancy, despite being a hyperestrogenic state, does not appear to promote tumor growth in most patients, despite discontinuation of dopamine agonists. Menopause may lead to spontaneous remission of hyperprolactinemia in patients diagnosed in their premenopausal years. Prolactinomas are generally thought to be more aggressive in patients with MEN-1 and FIPA. However a recent retrospective study suggests that their clinical behavior in MEN-1 may actually be similar to that of sporadic prolactinomas.

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Chapter 7
Prolactin-Secreting Pituitary Adenomas: Pathology, Clinical Manifestations, and Diagnosis

Andrea Glezer and Marcello D. Bronstein

Pathogenesis

Similar to other subtypes of pituitary tumors, tumorigenesis of prolactinomas involves oncogenes and tumors suppressor genes, as well as other factors, as growth factors and hormones. Nevertheless, even with progress in the field, the mechanisms leading to prolactinoma development need further investigation. The pituitary tumor-transforming gene (PTTG) [1] and the heparin-binding secretory transforming gene (HST) [2] seem to play a role by inducing angiogenesis mediated by fibroblast growth factors (FGF-2 and FGF-4) [1, 2]. The well-known estrogen-induced prolactinoma enlargement is inhibited by estrogen receptor modulator drugs, such as tamoxifen and raloxifene, and by the estrogen receptor antagonist ICI-182780 by halting the PTTG expression in prolactinomas in vitro and their growth in vivo (Fig. 7.1) [3]. The overexpression of bone morphogenetic protein 4 [4] is also involved in prolactinoma tumorigenesis. In addition, Fukuoka et al. demonstrated that HER2/ErbB2 plays a role in prolactinoma hormone regulation and cell proliferation [5].

As the neurotransmitter dopamine, ligand of the D2 receptor (D2R) in pituitary lactotrophs, is the main inhibitor of prolactin secretion, impairment of dopaminergic tone may contribute, as a permissive factor, to prolactinoma progress. As a matter of fact, mice with D2R knockout have developed prolactinomas, with a positive relationship between their aggressiveness in females and estrogen-treated mice [6]. However, no spontaneous mutations were described in the D2R gene, to date [7].

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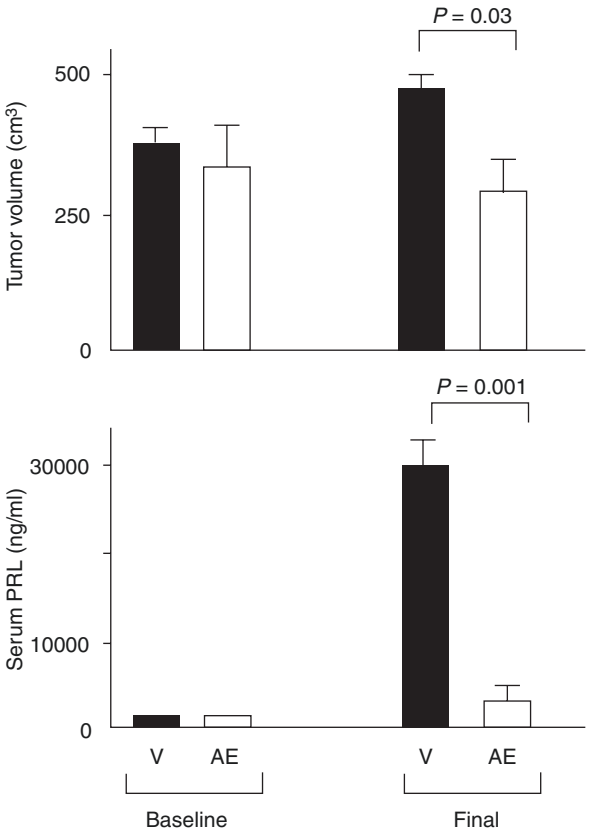

Fig. 7.1 Tumor size and serum prolactin levels before (baseline) and after treatment with the selective antiestrogen IC1-182780 (0.5 mcg per day) or vehicle in female Wistar-Furth rats harboring subcutaneous pituitary tumors. Each bar represents mean ± SEM for ten animals per group. * $P = 0.03$ ** $P < 0.001$. (From Heaney et al. [3])

As far as familial pituitary adenomas are concerned, prolactinomas are the most prevalent subtype in the context of multiple endocrine neoplasia (MEN) 1 characterized by inactivating mutations in the tumor suppressor gene *menin* associated with loss of heterozygosity in locus. Prolactinomas associated with MEN-1 tend to be more aggressive than sporadic tumors. Inactivation mutations of the gene encoding aryl hydrocarbon receptor-interacting protein (AIP) were described in familial isolated pituitary adenomas (FIPA), but mainly in acromegaly and in mixed GH-/PRL-secreting tumors [8].

Pituitary carcinomas, including prolactin (PRL)-secreting ones, are exceedingly rare. Mutations in the proto-oncogene *ras* and in the tumor suppressor gene TP53 are among the events linked to their development [9].

Pathology

Prolactin-secreting pituitary tumors with ≤1 cm and >1 cm are termed microprolactinomas and macroprolactinomas, respectively [10, 11]. Microprolactinomas are more common in women of reproductive age. In older patients, no difference in

prevalence is seen between genders [12]. Although usually enclosed, they also can show invasiveness [11, 13]. Macroprolactinomas may be located into the sellar boundaries, but frequently expand to the suprachiasmatic region or invade structures such as the cavernous sinus or sphenoid sinus [11, 13]. Histologically, there are no differences between microprolactinomas and macroprolactinomas. In the old classification based on hematoxylin-eosin staining, they were generally included in the chromophobic group, but can also be acidophilic. Therefore, before the routine use of PRL radioimmunoassay, some tumors classified as nonsecretory were in fact prolactinomas. Electron microscopy characterized the chromophobic prolactinomas as sparsely granulated: oval and slightly irregular nuclei, complex rough endoplasmic reticulum, large Golgi complexes, and sparse spherical or pleomorphic secretory granules, measuring 130–500 nm [14]. The less common, densely granulated prolactinomas are acidophilic with diffuse immunostaining for PRL in the cytoplasm. They present with less prominent rough endoplasmic reticulum and bigger (500–700 nm) secretory granules, which are more abundant than in the sparsely granulated prolactinoma [14]. Interestingly enough, prolactinomas, as well as normal pituitary lactotrophs, present a unique feature, the so-called misplaced exocytosis, represented by the extrusion of secretory granules in the lateral cell border.

The development of immunohistochemistry, more practical and routinely available, replaced electron microscopy. This technique usually differentiates prolactinomas from the so-called clinically nonfunctioning pituitary adenomas, which can be associated with hyperprolactinemia due to hypothalamus-pituitary disconnection (pseudoprolactinomas) [15]. Nevertheless, 27% of 120 unselected necropsies presented pituitary microincidentalomas, 40% of them immunostaining for PRL [16]. The role of this finding in the natural history of prolactinomas remains to be established.

Clinical Features

The main clinical impact of hyperprolactinemia, including prolactinomas, is related to the impairment of the gonadotroph axis, leading to hypogonadotropic hypogonadism [17]. The main physiopathological mechanism involves the impairment of the pulsatile release of GnRH, probably via kisspeptin [18] (Fig. 7.2).

Clinical manifestations of hypogonadism include menstrual irregularity and amenorrhea (hyperprolactinemia is present in about 20% of women with secondary amenorrhea) as well as loss of libido, erectile dysfunction, fertility impairment, and osteopenia/osteoporosis in both genders. Galactorrhea is not a specific signal, and can be absent in the context of high serum PRL associated with low estrogen levels, as in patients harboring macroprolactinomas, and may be present in parous female individuals with normal PRL levels [19]. As a matter of fact, Kleinberg et al. [20], in a study encompassing a large cohort of patients with galactorrhea, showed that PRL was normal in 86% of women with idiopathic galactorrhea without amenorrhea. Fertility impairment in hyperprolactinemic patients is mainly due to short

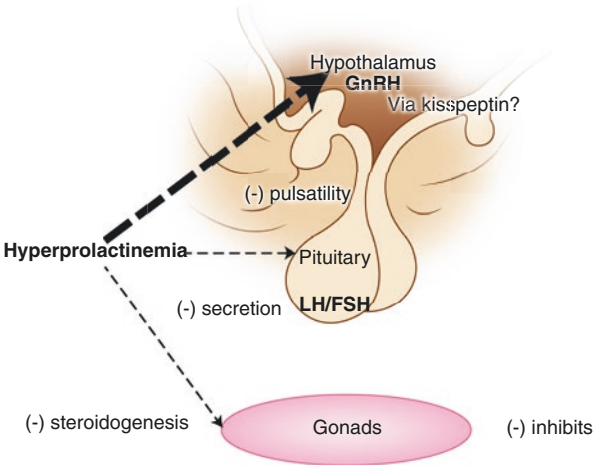

Fig. 7.2 Multiple physiopathological mechanisms involved in hyperprolactinemia-induced hypogonadism

luteal phase; anovulatory cycles, leading to oligomenorrhea and amenorrhea in women; and changes in viability and quantity of sperm in men [19, 21]. Besides its effects on the gonadotrophic axis, hyperprolactinemia may reduce libido independently on testosterone levels. The reduction of sex hormones makes patients with hyperprolactinemia prone to low bone mineral density [22] with the consequent increase of fracture risk in both genders.

Besides the clinical features linked to hyperprolactinemic hypogonadism, patients bearing macroprolactinomas are prone to symptoms related to tumor mass effect as headache, decreased visual acuity and peripheral vision loss, oculomotor impairment, hydrocephalus, seizures, and psychiatric disturbances, each of them depending on tumor size, invasiveness, and location. Additionally, deficiency of pituitary functions other than hypogonadism may occur as a result of compression of the pituitary stalk and/or destruction of normal pituitary gland [23].

Diagnosis

In patients with hyperprolactinemia-related symptomatology, a careful and complete clinical evaluation should be performed in order to rule out other cases of prolactin excess as drugs, uremia, and primary hypothyroidism, among others (please refer to Chap. 5, "Prolactin Excess and Deficiency: Epidemiology, Causes (Excluding Prolactin-Secreting Pituitary Tumors")). Serum PRL assessment is then the next step. Usually, in prolactinomas, PRL levels correlate with tumor size:

usually 50–300 ng/mL in microprolactinomas and 200–5000 ng/mL (or more) in macroprolactinomas. Nevertheless, discordance between serum PRL levels and tumor mass may occur in cystic prolactinomas and giant/invasive prolactinomas due to "hook effect" phenomenon (see below). Provocative tests as TRH and metoclopramide, used in the past for the differential diagnosis of hyperprolactinemia, do not provide any additional information and were discontinued [24]. In pituitary tumors other than prolactinomas, as well as in other tumoral or inflammatory masses of the sellar region, pituitary stalk disconnection may lead to inhibition of dopamine delivery to the normal lactotrophs, resulting in hyperprolactinemia. Nonetheless, PRL levels in those situations seldom exceed 100 ng/mL [25]. It must be stressed that the differential diagnosis between prolactinomas and the so-called pseudoprolactinomas is crucial for the correct treatment selection, usually medical therapy for prolactinomas and surgery for other tumors, such as the clinically nonfunctioning adenomas.

Giant prolactinomas generally present with very high PRL levels, usually above 4000 ng/mL [26], which, due to the excessive concentration of PRL as the antigen, can lead to a laboratorial artifact in PRL serum assessment by two-sided immunometric assays with consequent underestimation of the true value, a phenomenon known as "hook effect." Serum dilution with prolactin reevaluation will disclose this laboratory pitfall [27–29] (Fig. 7.3).

Another important laboratory pitfall is the so-called macroprolactinemia. The main circulating PRL isoforms, named based on molecular weight, are the monomeric (little PRL), dimeric (big PRL), and macroprolactin (big-big PRL). Usually the monomeric PRL is considered biologically active. Monomeric PRL normally accounts for the majority of circulating PRL, whereas macroprolactin represents less than 5% of the total serum PRL. Nevertheless, big-big PRL represents the major circulating isoform in 10% to 25% of patients with hyperprolactinemia, a condition known as macroprolactinemia [30]. Macroprolactin, mostly resulting from a complex of IgG bound to PRL, has a low biological activity [31], and therefore individuals with such a condition do not present with clinical symptoms despite the presence of elevated serum PRL levels. However, the presence of macroprolactinemia does not rule out symptomatic hyperprolactinemia, as it can be associated with elevated serum levels of monomeric PRL [32] secondary to a prolactinoma or other cases of hyperprolactinemia. The gold-standard evaluation of macroprolactinemia is gel filtration chromatography. Nevertheless, this method is expensive and time-consuming, being routinely replaced by the assessment of serum PRL recovery after treatment with polyethylene glycol, a macromolecule that precipitates the high molecular PRL isoforms leaving the monomeric one in the supernatant (Fig. 7.4).

Magnetic resonance imaging (MRI) is the gold-standard method to image the pituitary in patients with hyperprolactinemia and is indicated after excluding pregnancy, breastfeeding, pharmacological causes, primary hypothyroidism, and renal

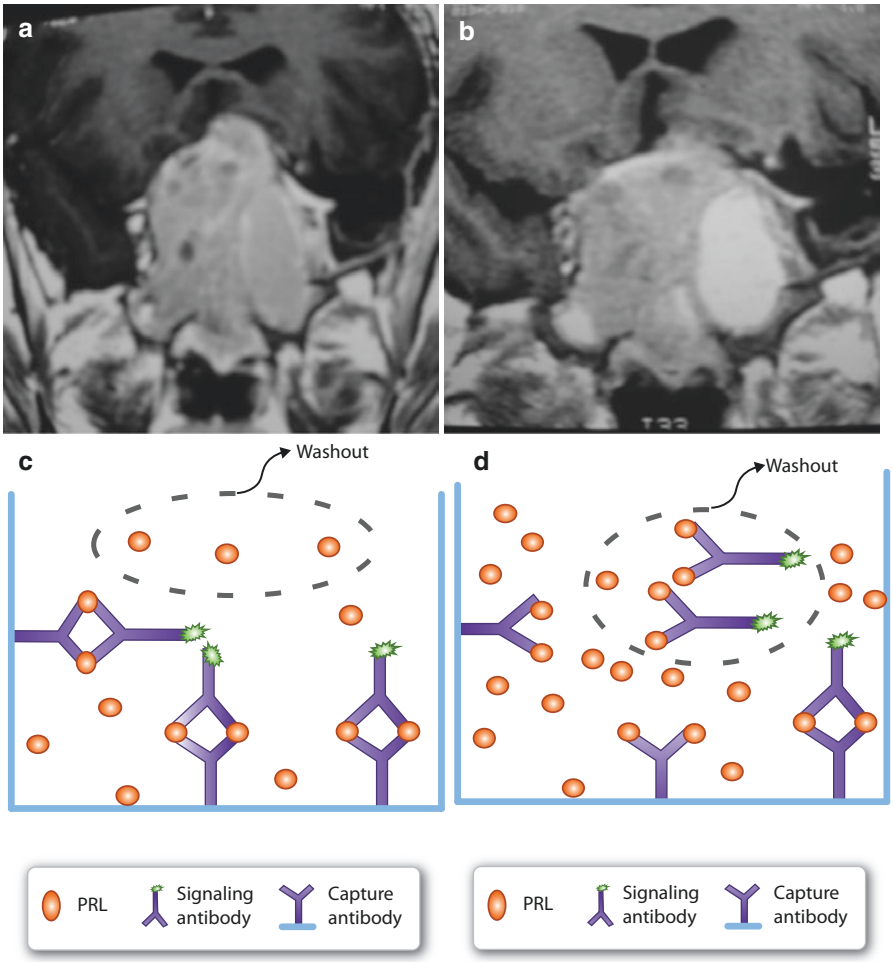

Fig. 7.3 A 28-year-old man complained of visual deficiency, headache, and sexual dysfunction. He presented galactorrhea. Coronal pituitary MRI after gadolinium enhancement (**a**) depicted a giant sellar mass which shrunk (**b**) under bromocriptine treatment. Basal serum prolactin was 97 ng/mL and 30,000 ng/mL after serum dilution, pointing to prolactinoma diagnosis. In contrast with normal or elevated serum prolactin levels (**c**), excessively high prolactin levels (usually >5000 ng/mL) interfere with two-sided immunometric assays, underestimating the true value (hook effect) (**d**). (From Musolino et al. [29])

and hepatic impairment [33]. MRI will detect a micro (<1 cm)- or a macroprolactinoma (>1 cm), indicating in the last one the degree of expansion/invasiveness out of the sellar boundaries (Fig. 7.5). Giant prolactinomas are defined when the maximal diameter is greater than 4 cm, but may assume much larger dimensions [11, 12]. In symptomatic ophthalmologic impairment or in cases in

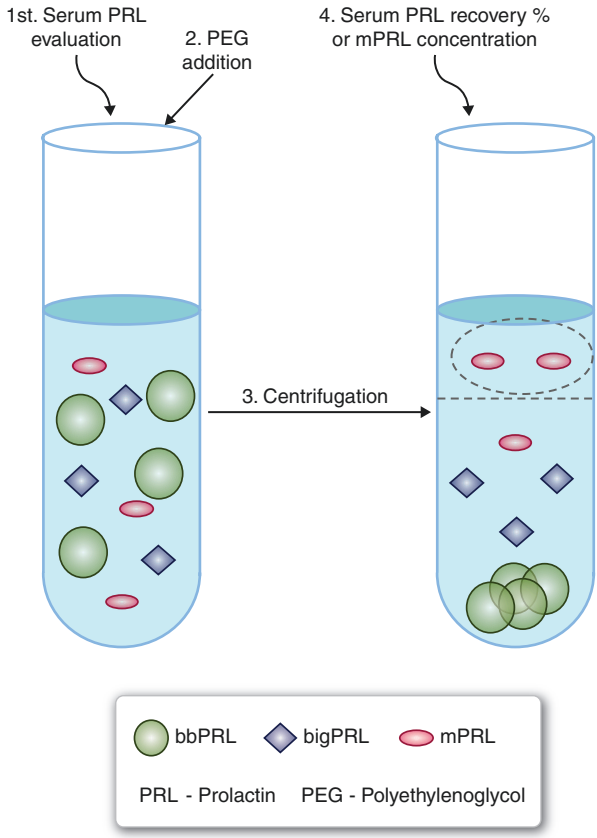

Fig. 7.4 Macroprolactinemia screening with polyethylene glycol (PEG) precipitation

which the tumors approach or impinge on the optic chiasm, a neuro-ophthalmologic evaluation is indicated. One important issue is the presence of a pituitary incidentaloma, which may coexist with a laboratory scenario of macroprolactinemia, leading to a double diagnostic pitfall in an otherwise asymptomatic individual [34]. The performance of bone densitometry is indicated in order to evaluate the bone mineral density status.

Additional pituitary function should be assessed, especially in macroprolactinomas, including IGF-1 measurements to evaluate the possibility of GH co-secretion by the tumor. Serum gonadotropin levels may be normal or suppressed, reflecting hypogonadotropic hypogonadism. In patients with prolactinomas with hypercalcemia, screening for MEN-1 is also recommended [35]. As the issue of valvular heart disease associated with the use of dopamine agonists for prolactinomas is still an open question, we recommend performing a transthoracic echocardiogram before the initiation and periodically thereafter, depending on the dose and duration of treatment.

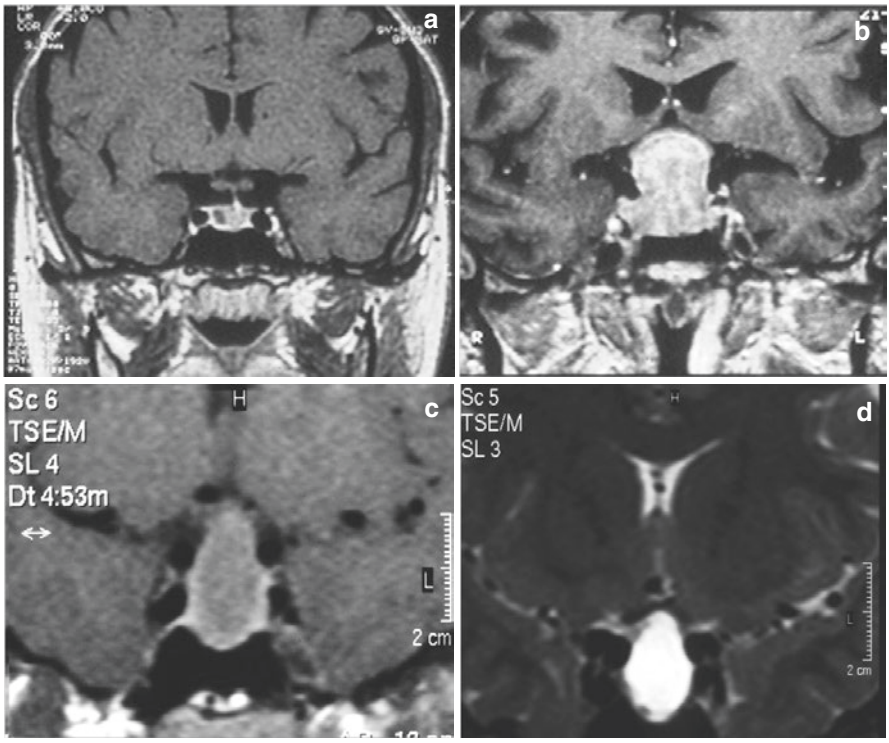

Fig. 7.5 Coronal pituitary MRI after gadolinium enhancement: patients harboring microprolactinoma with serum PRL 120 ng/mL (**a**) and a macroprolactinoma with serum PRL 1350 ng/mL (**b**). Coronal pituitary MRI after gadolinium enhancement of a patient (serum PRL 179 mg/mL) with cystic macroprolactinoma (**c**) depicting high intensity in T2-weighted image (**d**)

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Chapter 8
Prolactin-Secreting Pituitary Adenomas: Clinical Management

Alexander Faje, Marcus A. Zachariah, and Brooke Swearingen

Prolactinomas account for approximately 40% of pituitary adenomas and are the most common type of secretory pituitary tumor in adults and children [1–3]. Biochemical suppression of the hypothalamic-pituitary-gonadal axis by elevated prolactin levels can produce signs and symptoms including oligo-amenorrhea, galactorrhea, infertility, reduced libido, gynecomastia, and erectile dysfunction. Acne or hirsutism can also occur in women, in part by stimulation of adrenal dehydroepiandrosterone sulfate production [4, 5]. Mass effect from larger prolactinomas may result in other pituitary hormone deficiencies or visual compromise from compression of the optic apparatus. Observation may be reasonable in asymptomatic patients with stable microprolactinomas [6]; symptomatic hyperprolactinemia and larger tumor size (macroadenomas) or enlarging lesions are general indications for treatment. Therapeutic modalities include medication, surgery, and radiation therapy.

Medical Therapy

Medical therapy represents the mainstay of treatment for the majority of patients with prolactinomas. Dopamine released by the hypothalamus binds to D2 receptors on lactotrophs and tonically inhibits prolactin secretion by the pituitary [7–9]. Dopamine agonists (DA) are potent inhibitors of prolactin release and also reduce prolactinoma size by causing decreasing tumor cell volume and causing necrosis/

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fibrosis [10]. The oral ergot-derived medications bromocriptine and cabergoline are approved for the treatment of hyperprolactinemia in the United States, and quinagolide (a non-ergot-derived DA) is also utilized in other countries. Bromocriptine (and quinagolide) is typically administered daily or sometimes twice daily at higher doses. Cabergoline can be taken once weekly as a consequence of its longer half-life, though more frequent administration schedules may be utilized for higher doses to minimize side effects when present.

Although both medications lower prolactin levels and induce tumor shrinkage in a majority of patients, cabergoline has a higher binding affinity for the D2 receptor and greater clinical efficacy. This was demonstrated in two early randomized controlled trials which showed higher rates of prolactin normalization and symptom resolution [11, 12] and later by meta-analyses of randomized and non-randomized studies [13, 14]. The side effect profile of the two medications is similar, though cabergoline is typically better tolerated [11–14]. Common side effects can include nausea, headache, dizziness, fatigue, constipation, and abdominal discomfort. Retrospective studies also demonstrate greater tumor volume reduction following treatment with cabergoline compared to bromocriptine [15, 16]. A meta-analysis did not identify a significant difference in efficacy between bromocriptine and quinagolide [14].

DA treatment is often successful even in very large prolactinomas, including patients with visual compromise [17–19]. Tumor shrinkage can occur rapidly; some adenomas have been reported to decrease in size within 2 weeks of treatment initiation [20–22] (Fig. 8.1). Although the majority of tumor reduction often occurs in the 1st year of therapy, additional decline in tumor size can take place in subsequent years, or treatment response may be delayed [23]. Visual symptoms may improve rapidly prior to radiographic changes and before prolactin normalization [19, 20, 22]. Although tumor reduction normally corresponds to significant decreases in prolactin levels, the two outcomes are not absolutely linked [24] (Fig. 8.2). DA treatment in very large prolactinomas can rarely be complicated by cerebrospinal fluid (CSF) leakage, apoplexy, or optic chiasm herniation [25, 26]. Although formal comparisons of dosing strategies are lacking, some physicians begin treatment in these patients with lower doses of DAs to potentially reduce the risk of these complications and to minimize side effects. Hypopituitarism may also improve following treatment with DAs and tumor volume reduction. Recovery rates vary in published series [27].

The topic of prolactinomas and pregnancy is discussed in greater detail in the dedicated chapter of this book. In brief, DAs are generally held during pregnancy, usually due to a lack of necessity for continued treatment, and to limit potential fetal drug exposure [28, 29]. Available pregnancy outcome data from women who conceived while taking bromocriptine or cabergoline are reassuring. Experience is more limited for women taking these DAs throughout pregnancy, though there does not appear to be an increased risk of fetal malformations or other adverse outcome [29]. Conversely, quinagolide does not appear safe to use in the context of pregnancy [30]. Microprolactinomas rarely exhibit clinically significant growth during pregnancy, but this may occur in approximately one-fourth of patients with macroprolactinomas who have not received prior radiation therapy or undergone surgery. Such patients may be

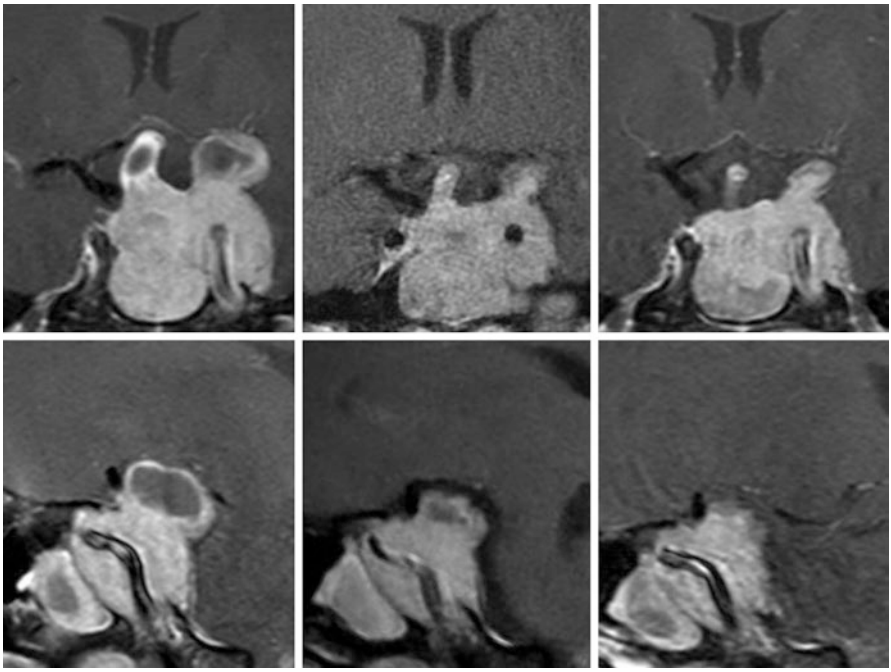

Fig. 8.1 Rapid response of a macroprolactinoma to cabergoline with decompression of the optic chiasm and reduction of the cystic portion of the tumor. (Panel **a**) Baseline, serum prolactin 9387 ng/ml. (Panel **b**) Following 3 weeks of treatment with 0.5 mg once weekly cabergoline, serum prolactin 1988 ng/ml. (Panel **c**) Following 4 weeks of treatment, on 1 mg/week cabergoline, serum prolactin 541.7 ng/ml

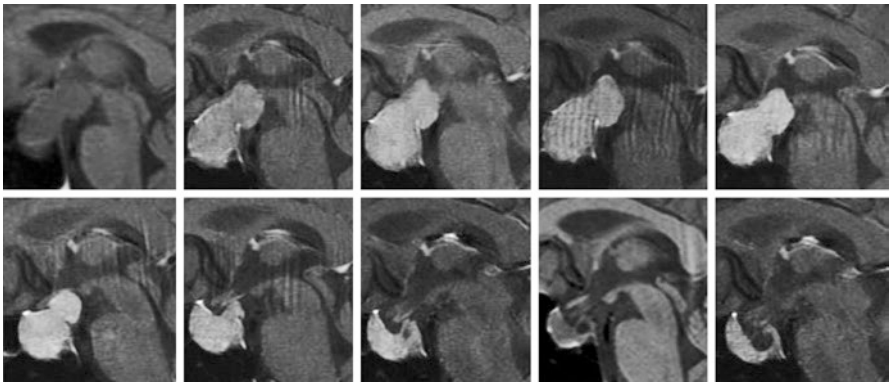

Fig. 8.2 Delayed radiographic response to cabergoline but rapid normalization of serum prolactin levels. A baseline prolactin was 819 ng/ml and decreased to 3.8 ng/ml within a month of cabergoline initiation. Subsequent levels all remained below 5 ng/ml on continuous therapy with cabergoline doses ranging between 1 and 2 mg per week. Panels show images from MRIs taken at baseline, 3, 7, 19, 33, 45, 58, 72, 76, and 84 months after treatment was begun

monitored for tumor progression by periodic visual field examinations during pregnancy and non-contrast magnetic resonance imaging (MRI) if an abnormality is detected. Reinitiation of DAs during pregnancy may be considered if significant growth occurs. Some patients with larger tumors may undergo surgery prior to pregnancy [29]. DAs are typically held during breastfeeding since such medications would impair lactation and, when lactation suppression is not complete, may appear in breast milk. Breastfeeding does not appear to be associated with tumor enlargement [31].

Intratumoral cystic degeneration may occur following DA treatment. Uncommonly, a prolactinoma may have a predominant primary cystic component at presentation. Traditionally, such tumors were thought to be resistant to DA treatment, in terms of volume reduction [32]. Several case reports [33–35] and a recent study [36], however, suggest that DA therapy may be effective in a majority of patients with cystic prolactinomas, though transsphenoidal surgery should be considered in cases with significant visual compromise.

Definitions and criteria for DA resistance vary, but the designation generally refers to a failure to normalize prolactin levels and/or achieve significant prolactinoma size reduction on standard doses of these medications (e.g., up to 3.5 mg of cabergoline per week). Primary DA resistance is uncommon; acquired or secondary resistance is rarely encountered and can (but not necessarily) be associated with malignant transformation [37]. DA resistance is more frequently observed in larger invasive tumors [38–41] and appears to occur more frequently in males in some [38, 42, 43] but not all studies [44]. Germline mutations (including those involving menin and aryl hydrocarbon receptor-interacting protein) may be present in some patients with DA resistance [40, 41]. Decreased expression of the D2 receptor [45, 46] and alterations in posttranscriptional splicing [47], filamin A expression [48], and downstream signaling [49] may confer resistance to DAs. One study suggested that D2 receptor polymorphisms may also contribute to DA resistance [50], but other studies did not find such an association [51, 52]. Resistance to bromocriptine can often be surmounted by transition to quinagolide or cabergoline [16, 23, 53, 54]. Patients with tumors resistant to standard doses of cabergoline will often respond following dose escalation [38, 40]. Dosages as high as 21 mg per week have been reported [55]. Similar to experiences in other types of secretory pituitary adenomas, surgical debulking can enhance the effectiveness of medical therapy in prolactinomas [56].

Surgical Therapy

Indications for Surgery

The endocrine and pituitary societies have issued guidelines on the indications for surgery for prolactinomas; medical therapy is considered first-line treatment [28, 32]. Failure of medical therapy represents the major indication for surgical management. Failure of therapy includes increasing tumor size despite therapy, ongoing intolerable symptoms (including galactorrhea, irregular menstruation, infertility,

decreased libido, and visual changes resulting from chiasm compression), and inadequate biochemical control. Twenty-five percent of patients treated with bromocriptine and 10–15% of patients treated with cabergoline fail to normalize prolactin levels [57]. Additionally, one third of patients treated with bromocriptine and 10–15% of patients treated with cabergoline fail to achieve at least a 50% reduction in tumor volume [57]. These are not absolute indications for surgery, since stable tumor size or stable persistently elevated prolactin levels do not necessarily mandate surgery if symptoms are tolerable.

Intolerance of medical therapy represents another potential indication for surgery. Some patients develop intolerable side effects, usually gastrointestinal, most commonly nausea, constipation, and dry mouth. These symptoms are typically more common with bromocriptine than with cabergoline. Patients may report intractable headache or cognitive difficulties. Pre-existing psychiatric conditions (including schizophrenia and other psychotic disorders) may preclude the use of dopamine agonists, or new psychiatric side effects, especially impulse control and mood disorders, may develop after initiating dopamine agonist therapy. High-dose cabergoline or pergolide treatment of Parkinson's disease has been associated with an increased risk of cardiac valvular disorders, but the risk of valvular heart disease in prolactinoma patients treated with cabergoline may not be as high as was once thought [58].

Other potential indications for surgery include patient preference, prolactinoma hemorrhage leading to apoplexy after instituting medical therapy, CSF leak resulting from tumor shrinkage as a result of medical therapy, and desire for pregnancy in women with large tumors in close proximity to the chiasm [59]. While not explicitly recommended by established guidelines, surgery was reported to be advised to women with prolactinomas seeking pregnancy by 50% of surgeons in the setting of a macroprolactinoma and by 26% of surgeons in the setting of a macroprolactinoma [60]. Patients presenting with apoplexy and significant neurological symptoms (visual loss or other cranial neuropathy) generally require urgent surgery; postoperative DA therapy may be required, but immediate surgical decompression is necessary.

A case series from the Mayo Clinic evaluated the indications for surgery for prolactinomas in the current era [61]. Among microadenomas, the most common indications reported were medication intolerance (37%), medication failure (33%), and patient preference (26%). The most common symptom associated with medication intolerance was nausea (70% of intolerant patients). The mean maximum dose attempted for patients who failed therapy was 2.7 ± 1.2 mg per week of cabergoline and 7.5 ± 4 mg per day of bromocriptine. The most common indications for surgery with macroadenomas were medication failure (31%), clinical and/or radiologic evidence of chiasm compression (21%), and patient preference (16%). With giant prolactinomas (in this series defined as greater than 4 cm in maximum diameter), indications included visual compromise in 67%, medication failure in 17%, and CSF leak in 17%.

A German group reported on indications for surgery in a consecutive series of 212 patients [62]. Indications included medication intolerance (20.0%), failure of

medication to achieve normoprolactinemia (14.2%), failure of medication to achieve adequate tumor shrinkage (27.4%), patient preference (12.1%), and cystic nature of prolactinoma (26.3%). Over the course of the study, the proportion of patients undergoing surgery for classical indications (including medication intolerance and biochemical/radiological failure) decreased, while the fraction of patients undergoing surgery as a result of patient preference or the presence of cystic tumor increased.

In another recent case series [63], indications for surgery for prolactinomas (both microadenomas and macroadenomas) included medication intolerance (28.8%), medication failure (28.7%), misdiagnosis (hyperprolactinemia incorrectly presumed to be stalk effect) (16.7%), combined medication intolerance and failure (15.1%), apoplexy (3%), patient preference in a pregnant patient (1.5%), patient preference in a nonpregnant patient (1.5%), and dopamine agonist contraindication in a patient with schizophrenia (1.5%).

Cystic and giant prolactinomas merit specific consideration. While some have considered the presence of a cystic prolactinoma an indication for surgery, a recent series showed that 20 of 22 patients achieved a persistent decrease in cyst volume following dopaminergic therapy alone. However, 50% of the patients in this series eventually underwent surgery due to medication intolerance, inadequate cyst shrinkage, or patient preference [36]. Another series of five patients with cystic prolactinomas treated surgically reported that three patients achieved biochemical control with surgery alone and two achieved control with the addition of postoperative dopaminergic therapy [64]. Four out of four patients with visual symptoms achieved resolution of symptoms, and all five patients achieved resolution of hypogonadism.

Two recent series have examined a combined approach (including medical, surgical, and radiation therapy) for giant prolactinomas [65, 66]. In one series [65], 11 of 16 patients with giant prolactinomas underwent surgery (5 as first-line therapy and 6 as second-line therapy after dopamine agonists). All patients except for one required postoperative dopaminergic therapy. Prolactin normalized in 7 of 16 patients. Tumor volume decreased on average by 93.8%, and three patients are now tumor free. Another study [66] examined 18 patients with giant prolactinomas; nine out of 18 patients required surgery. Surgery alone was not able to achieve biochemical cure in any of the patients. Eleven of 18 patients eventually achieved normoprolactinemia with combined therapy. These series suggest that a multimodal approach may sometimes be useful for giant prolactinomas.

Efficacy of Surgery

Surgical efficacy varies as a function of tumor size. For microprolactinomas, a recent series [61] reported early remission (defined as prolactin normalization) in 78% and long-term remission (with median follow-up of 12 months) in 72%. For macroprolactinomas, early remission was achieved in 36% and long-term remission in 20%. When tumors with cavernous sinus invasion were excluded, long-term

remission improved to 32%. Of six patients with preoperative visual field defects, three improved, one suffered a persistent defect, and two did not undergo postoperative formal field testing. For patients with giant prolactinomas (greater than 4 centimeters in maximum diameter), all patients (6/6) had persistent disease postoperatively. Nearly all patients (5/6) were placed on dopaminergic therapy postoperatively, and half (3/6) underwent radiotherapy.

Another case series examined outcomes as a function of the indication for surgery [63]. In patients with medication intolerance, at the 6-month postoperative visit, 66.7% had achieved normoprolactinemia without any dopamine agonist therapy, 17.2% required a dopamine agonist to normalize prolactin levels, and 20.6% had moderately elevated prolactin levels and were not taking dopamine agonists. In patients presenting with medication failure, 35.7% of patients had normal prolactin levels without dopaminergic therapy, 25% were receiving a dopamine agonist with a normal prolactin, 28.6% had supraphysiologic prolactin levels but were not on a dopamine agonist, and 10.7% remained hyperprolactinemic despite postoperative dopaminergic therapy.

A large multicenter report reported 212 surgical cases [62], subdivided by tumor size. Overall remission was 48.1% overall. For tumors with only intrasellar involvement, the initial remission rate was higher at 78**.**1%. Surgery was less effective in tumors with suprasellar involvement, with (13.5%) or without (59.4%) clinical evidence of chiasm compression. The surgical remission rate among giant (>4 cm) adenomas was 0%.

The likelihood of surgical remission was decreased in men (odds ratio, 3.98; CI, 1.6–10.8), with higher prolactin levels ($p = 0.003$), with atypia as indicated by elevated Ki-67 ($p = 0.0008$), and with larger tumor size ($p <= 0.001$) [61]. Recurrence was more frequent with macroadenomas and with elevated Ki-67. In another series, males were more likely to have a subtotal compared to gross total resection ($p = 0.0035$) and require continued medical therapy postoperatively ($p = 0.0196$) [67].

A Japanese case series [68] examined surgery for prolactinoma in 138 women under the age of 40. Biochemical cure was achieved in 0% (0/1) and 90% (18/20) of microadenomas with and without cavernous sinus invasion, respectively. Cure was achieved in 25% (9/36) of invasive and 95% (77/81) of noninvasive macroadenomas. Cure was more likely in noninvasive compared to invasive tumors ($p < 0.001$).

A recent case-control series [69] compared primary medical vs. surgical therapy in Swiss men with prolactinomas. Patients were not pre-treated with dopamine agonist therapy prior to study entry. Long-term dependence on dopamine agonists was lower in the primary surgical group (53%) compared to the primary medical group (90%) ($p = 0.02$). The same group presented similar data [70] in a cohort of women, lower long-term dependence on dopamine agonist therapy in the primary surgical group (32%) compared to the primary medical group (64%) ($p = 0.003$).

One of the reasons that salvage surgical therapy after failure of medical treatment may be less effective than de novo surgical therapy is that dopamine agonist treatment may make the adenoma more fibrotic, complicating surgical resection. A pathological analysis of DA-treated tumors showed a significant increase in fibrosis with bromocriptine pre-treatment, as opposed to cabergoline or untreated tumors [71].

Complications

Any potential benefit of surgery needs to be weighed against the risk of complications, especially since modern medical treatment carries minimal morbidity. In the German study, new postoperative anterior pituitary insufficiency occurred in 7% of cases, all with giant or macroadenomas, while pituitary function (excluding hyperprolactinemia) actually improved in 14.6% of cases overall. Surgical mortality in this series was zero, with morbidity of 3.8% (including epistaxis (1), meningitis (2), deep venous thrombosis (DVT) (1), sinusitis (2), and cerebrospinal fluid (CSF) leak (3)) [61]. In the Mayo Clinic series, complications were more common with macroas opposed to microadenomas, with an overall risk of permanent diabetes insipidus (DI) of 5%, CSF leak 8%, infection 1%, and new pituitary insufficiency of 8%. The mortality risk was zero [60].

Cost Analysis

A few studies have analyzed the relative cost effectiveness of medical vs. surgical therapy for prolactinomas. Using a decision tree model, Jetthwa et al., using data abstracted from the literature, found that both microsurgical and endoscopic tumor resection were more cost effective than medical treatment with bromocriptine or cabergoline at 5 and 10 years [72]. A single center study from UCSF found a lower lifetime cost of surgical as opposed to medical treatment in a 40-year-old patient [73]. These cost benefit analyses are obviously a function of the relative cost of the various treatments, the age of the patient, and total time of treatment and presume the availability of an experienced pituitary surgeon with low morbidity and high remission rates.

Radiation Therapy

Due to the high rates of success with medical and/or surgical therapy, radiation therapy is utilized infrequently for patients with prolactinomas and often employed for aggressive or malignant tumors that cannot be adequately controlled by medical therapy and surgery. Data for radiotherapy in prolactinomas are more limited than other pituitary adenoma subtypes, and outcome assessment is complicated by the aforementioned selection bias. Rates of biochemical remission of hyperprolactinemia can also be affected by hypothalamic or infundibular damage from radiation, which may raise prolactin levels. Prolactin normalization therefore appears to occur in a minority of prolactinoma patients treated with radiotherapy. Similar to studies in other pituitary adenoma subtypes, some authors contend that concurrent use of DAs may negatively affect the efficacy of radiotherapy and recommend

temporary withdrawal of these agents prior to radiation treatment [74–76]. Comparison of fractionated radiotherapy and stereotactic radiosurgery is limited by variable radiographic and biochemical outcome measures and confounded by differences in medical and surgical treatments in study patients. It is not clear that either modality is superior, and treatment choice is more often determined by proximity to the optic apparatus and tumor size [77, 78].

Emerging Therapies and Areas of Research

Somatostatin receptor (SSTR) subtypes 1 and 5 appear to be preferentially expressed by prolactinomas [79]. First-generation somatostatin analogues, which preferentially bind to type 2 receptors, have limited efficacy [80, 81] though cases with positive responses have been reported in strongly pentetreotide-avid (which primarily binds SSTR 2 and 5) tumors [82, 83]. Pasireotide, which binds SSTRs 1,2,3 and 5 with strong affinity for the type 5 receptor [84], inhibited prolactin secretion by human prolactinoma cells in vitro more strongly than octreotide [85] though less effectively than cabergoline [86]. Whether the in vitro experiments would accurately reflect in vivo tumor behavior and treatment response is unclear. Notably, in those experiments serum prolactin measurements in patients did not correlate with baseline hormone secretion in vitro [85]. Experiments did not show additive effects of SSTR agonists to treatment with DAs, and the response to SSTRs was attenuated in tumor cells which were resistant to DAs [79, 86]. Clinical studies assessing pasireotide in prolactinomas are lacking. Chimeric somatostatin-dopamine agonist compounds were recently developed but did not appear to have higher efficacy than DAs alone in vitro [86, 87]. Clinical trials for one of these compounds, BIM23A760, were suspended several years ago following disappointing results in patients with acromegaly. Peptide receptor radionuclide therapy with labelled somatostatin analogues has been utilized in a small number of patients with aggressive pituitary tumors, including a patient with a prolactinoma, with variable success [88–90].

Temozolomide is a well-tolerated oral alkylating chemotherapy agent first reported in the treatment of pituitary tumors in 2006 [91–93] and has since become a widely accepted therapy for aggressive adenomas and pituitary carcinomas [94–96]. Treatment regimens and durations have varied widely in published series, though typically the medication is administered on a monthly cycle. Combination therapy with other agents (pasireotide, capecitabine, bevacizumab, and thalidomide) has been reported in a small number of cases, but it is unclear whether such strategies provide additional benefit [97–100]. Some groups suggest that sensitive tumors should exhibit a response to temozolomide within 3 or 4 months [101, 102]. Although complete tumor responses are rare, sustained remission can occur in some patients [101, 103–105]. Temozolomide resistance can be primary or acquired. Temozolomide functions by creating DNA damage which activates mismatch repair (MMR) pathways and induces apoptosis. DNA damage is created by the formation O^6-methylguanine adducts in DNA, which are repaired by O^6-methylguanine-DNA

methyl transferase (MGMT) [106, 107]. High MGMT levels and/or defects in MMR can therefore potentially reduce apoptosis and reduce tumor sensitivity to temozolomide. This phenomenon has been observed in glioblastomas [108, 109] and also appears to be relevant in pituitary adenomas [95, 101, 104, 110]. By the nature of its mechanism of action, temozolomide can potentially promote acquired resistance by de novo mutation of genes related to MMR and the subsequent generation of a hypermutated tumor phenotype [110, 111]. Data regarding retreatment of pituitary tumors with temozolomide are very limited but appear less promising [94]. Concurrent radiation therapy may increase tumor sensitivity to temozolomide [112–114]. Potential temozolomide-sensitizing agents are being studied further [115, 116].

Everolimus has been trialed in a very small number of patients with pituitary carcinoma but did not yield successful results [117, 118]. Anti-vascular endothelial growth factor therapy with bevacizumab has been used as monotherapy in a couple of patients [119, 120] or in combination with temozolomide. Lapatinib, a tyrosine kinase inhibitor that targets epidermal growth factor receptors ErbB1 and ErbB2, is being studied in patients with prolactinomas. ErbB receptors, especially ErbB2, are expressed by prolactinomas, and the activation of these receptors promotes prolactin secretion and tumor cell proliferation. Two patients with aggressive prolactinomas were treated with lapatinib and experienced a decline in serum prolactin levels, plus tumor reduction in one individual [121]. An active study is currently evaluating the efficacy of lapatinib in patients with aggressive prolactinomas and other pituitary tumor subtypes (ClinicalTrials.gov identifier: NCT00939523).

An anti-prolactin receptor monoclonal antibody was recently developed and evaluated in prolactin receptor-positive metastatic breast cancer and castration-resistant prostate cancer [122]. The medication has not been utilized clinically in patients with hyperprolactinemia or prolactinomas. Although the antibody did not have apparent antitumor efficacy in cancer patients [122], it theoretically could have an application for the treatment of symptoms resulting from persistent hyperprolactinemia in patients unable to be successfully managed with standard medical therapies and/or surgery.

Active Surveillance of Prolactinomas and Dopamine Agonists: Safety, Monitoring, and Special Considerations

Direct antitumor therapy is not a necessity for all patients with prolactinomas, and radiographic observation is appropriate for microprolactinomas in asymptomatic individuals or patients who are not good candidates for treatment (due to medication intolerance, other comorbidities, or poor surgical candidacy) [6]. Significant tumor growth rarely occurs in untreated patients with microprolactinomas [123–126]. Gonadal steroid replacement is an alternative therapy in many of these patients, particularly those seeking contraception or poorly tolerant of dopamine agonists, although it will not alleviate galactorrhea or restore fertility. Fertility therapy

(including assisted reproductive technologies) can also be pursued potentially without prolactin normalization when this is not feasible.

Normoprolactinemia can be maintained in some patients following DA withdrawal. Numerous studies have been published on the topic, including three meta-analyses in recent years [127–129]. The reported rates of recurrent hyperprolactinemia vary widely in no large part due to significant study heterogeneity. Recurrence rates appear to be lower in more recent studies which tend to have stricter criteria for medication withdrawal and higher percentages of patients treated with cabergoline. Taken together, studies suggest that the risk of recurrence may be lower in patients treated at least 2 years with cabergoline (versus bromocriptine) who demonstrate significant tumor reduction and are taking a low maintenance dose. When hyperprolactinemia does recur, it typically is observed within a year of treatment cessation. Although DA withdrawal is not advisable in patients with residual tumor approaching the optic apparatus, the precise identification of optimal candidates for DA withdrawal may not be critically important, since DA treatment can simply be reinitiated if hyperprolactinemia recurs. A second attempt at withdrawal can also be trialed at a future date [130, 131].

Side effects may limit the utilization of DAs in some patients. Side effects are often temporary but can be persistent in some individuals. In order to improve patient tolerance, DAs are typically administered at nighttime with a snack to delay absorption. Doses may also be divided into smaller amounts taken at more frequent intervals. Maintenance dose requirements are often lower than the initial doses utilized to achieve normoprolactinemia [53]. Tumor reduction and growth prevention may also be achieved with DA doses below those required to normalize prolactin levels. Bromocriptine and cabergoline can be administered intravaginally, which may lessen gastrointestinal symptoms by avoiding hepatic first pass effect, but this route of administration does not appear to reduce centrally mediated side effects and is generally not acceptable to patients for chronic administration [132–134]. The use of bromocriptine buccoadhesive discs and rectal suppositories has also been described [135, 136].

Behavioral side effects from DAs can include impulse control disorders, and frank psychosis has even been reported [137–140]. Fortunately, these occurrences are rare and more frequently observed with higher dosages utilized to treat patients with Parkinson's disease [141, 142]. DAs are generally avoided in patients with severe psychiatric disease or those treated with antipsychotic medications (most of which function as D2 receptor antagonists) due to the risk of exacerbation of their underlying disorder [143, 144]. Aripiprazole is unique among antipsychotic agents and exhibits partial agonist activity at the D2 receptor [145]. A recent case report described the successful use of aripiprazole in a patient with a probable microprolactinoma and psychotic symptoms. Prolactin levels normalized on treatment, and the tumor decreased in size [146]. Treatment with aripiprazole normalized prolactin in two other patients with pituitary adenomas, though it is unclear if these tumors were prolactin-secreting. Adjunctive treatment with aripiprazole may also be useful for the treatment of antipsychotic-induced hyperprolactinemia [147–149].

High doses of cabergoline or pergolide, but not bromocriptine, have been associated with an increased risk of cardiac valve disease in patients with Parkinson's disease [150–152]. This finding has been attributed to the higher binding affinity of cabergoline to 5-HT_{2B} receptors on valvular interstitial cells [153, 154]. Chronic activation of these receptors induces cell proliferation and fibroblast differentiation leading to heart valve thickening and stiffness with resultant dysfunction and valvular regurgitation [155–157]. With the exception of one analysis [158], numerous studies in patients taking cabergoline (or bromocriptine) for the treatment of hyperprolactinemia have not shown an increased risk of clinically significant cardiac valve abnormalities. Most of the published studies in hyperprolactinemic patients are case-control designs. Longitudinal and prospective data for prolactinoma patients, especially regarding long-term use of higher doses of cabergoline, remain somewhat limited, but recent studies continue to accumulate reassuring results [159–162]. One meta-analysis of case-control studies reported an increased risk of mild to moderate tricuspid regurgitation (TR) in hyperprolactinemic patients treated with cabergoline, but mild TR would not generally be considered clinically significant [163]. A more recent comprehensive review utilized a stricter definition of cabergoline-associated valvulopathy (defined as moderate to severe regurgitation in the presence of a restricted and thickened valve) and found only 2 cases among 1811 patients receiving cabergoline for the treatment of prolactinomas [164]. Cumulative doses of cabergoline in Parkinson's disease studies far exceed the values described in prolactinoma patients [165]. According to the adage, "The dose makes the poison." Significant differences in cumulative dosages and dose density likely underpin the dissimilar observations in Parkinson's disease and prolactinoma patients. Prior to recently published studies, the Food and Drug Administration and European Medicines Agency issued recommendations for all patients starting cabergoline which included a baseline echocardiogram and routine follow-up studies every 6–12 months. Endocrine Society guidelines from 2011 included more measured remarks for the consideration of echocardiography in patients with resistant prolactinomas requiring high doses of DAs for prolonged periods of time [28]. The latter strategy appears more reasonable in the context of currently available data. The American Association of Clinical Endocrinologists/American College of Endocrinology issued similar statements recommending to reserve echocardiographic screening for higher-risk patients (those older than 50 years of age or with a diagnosis of hypertension) or individuals requiring high doses of cabergoline [165].

The role of prolactin in other pathologies, including thrombosis, autoimmune disease, and malignancies (particularly breast cancer) has been studied and produced mixed results. Currently, these comorbidities are not considered formal indications for the treatment of hyperprolactinemia nor reason to modify therapeutic strategies. Inconsistent findings have been published regarding the role of prolactin in platelet aggregation [166, 167], and higher prolactin levels (in normal individuals or patients with prolactinomas) do not appear to confer an increased risk of thrombosis [168, 169]. Higher levels of prolactin may have an association with some autoimmune pathologies, but clinical data are extremely limited for the use of DAs

in these conditions [170, 171]. Prolactin and the prolactin receptor (which can also bind growth hormone) have been implicated in tumorigenesis [172, 173]. Women with hyperprolactinemia, however, do not appear to have an increased risk of breast cancer [174, 175], and analyses performed on women with normal prolactin levels from the Nurses' Health Study and Nurses' Health Study II have design and methodologic limitations [6]. Notably, DAs have not shown significant efficacy in breast cancer [176, 177]. Extrapituitary prolactin is not regulated by dopamine [178, 179], and it was postulated that targeting the prolactin receptor would yield greater antitumor activity. As previously noted, a phase I trial of an anti-prolactin receptor monoclonal antibody failed to demonstrate significant antitumor effects [122].

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Chapter 9
Prolactin and Pregnancy

Mark E. Molitch

Prolactin and Fertility

Prolactinomas are the most common type of pituitary adenoma [1]. Women with prolactinomas and hyperprolactinemia usually present with symptoms of galactorrhea, amenorrhea, and infertility, although mass effects may also occur with larger macroadenomas [1]. Hyperprolactinemia decreases luteinizing hormone (LH) pulse amplitude and frequency through suppression of the pulsatile release of gonadotropin-releasing hormone (GnRH) [2, 3]. This effect appears to be mediated by an earlier step of suppressing the generation of kisspeptin, which is made in the arcuate and periventricular nuclei of the hypothalamus and stimulates GnRH release [4, 5]. Hyperprolactinemia results in loss of the positive estrogen feedback on gonadotropin secretion at mid-cycle [6], but it is not known whether this effect is mediated through kisspeptin.

In ovarian granulosa cells, prolactin (PRL) stimulates the expression of Type II 3β-hydroxysteroid dehydrogenase, the enzyme responsible for the final step in progesterone biosynthesis, and IGF-II production [7, 8]. PRL also directly suppresses progesterone and estrogen secretion from human ovaries [9] and inhibits estrogen formation by antagonizing the stimulatory effects of FSH on aromatase activity [10] and directly inhibiting aromatase synthesis itself [11]. Although low amounts of PRL are required for progesterone production by granulosa cell cultures, at the higher concentrations found with hyperprolactinemia, PRL inhibits progesterone production [12].

A shortened luteal phase is the earliest abnormality in the menstrual cycle caused by hyperprolactinemia [13]. When gonadotropin levels are suppressed with anovulation, infertility results. Of 367 women studied for infertility, one-third were found

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to be hyperprolactinemic; most also had amenorrhea and galactorrhea [14]. Interestingly, hyperprolactinemia was found in 5.6% of women with regular menses and no galactorrhea in 1 series of 1705 cases of infertility, implying that they had ovulatory cycles; it should be noted that these blood samples were not assessed for macroprolactin [15]. The role of hyperprolactinemia in such a patient is uncertain but, in one series, treatment of similar patients with bromocriptine restored fertility [16]. Transient hyperprolactinemia lasting for only 1–2 days during the menstrual cycle has been documented in some infertile women, and some of these women have responded to dopamine agonists with increased progesterone during the luteal phase and improved fertility [17].

Pregnancy in Women with Prolactinomas

Dopamine agonists are the standard treatment for women with hyperprolactinemia, as they have been documented to correct the hyperprolactinemia and restore ovulation in over 90% of women with amenorrhea and anovulation [18–20]. For a variety of reasons, a minority of women with microadenomas or intrasellar macroadenomas may choose transsphenoidal surgery [18–23]. For women with prolactinomas as the cause of their hyperprolactinemia, there are two important issues that arise with regard to pregnancy: (1) the effects of the dopamine agonist on early fetal development and (2) the effect of the high circulating levels of estrogen on prolactinoma size [24].

Effects of Dopamine Agonists on the Developing Fetus

For all medications taken by the mother, it is generally advised to limit the time of exposure of the developing fetus. Since most women are amenorrheic when they start dopamine agonists, it is helpful to know what the normal menstrual cycle timing is once menses begin. The use of mechanical contraception for the first two to three cycles will give the intermenstrual interval, and thus the woman will know when she has missed a menstrual period and can have a pregnancy test performed quickly. In this way, the dopamine agonist is stopped if pregnancy is confirmed, limiting the fetal exposure to only about 3–4 weeks of the gestation [24]. Bromocriptine has been shown to cross the placenta in human studies [25]; cabergoline has been shown to do so in animal studies, but such data are lacking in humans. It should be mentioned, however, that the long half-life of cabergoline means several more days of fetal exposure after the drug has been stopped.

With such short-term exposure of generally less than 6 weeks in over 6000 pregnancies, bromocriptine has not been found to cause any increase in spontaneous abortions, ectopic pregnancies, trophoblastic disease, multiple pregnancies, or congenital malformations (Table 9.1) [26, 27]. A long-term follow-up study of 64 children between the ages of 6 months and 9 years whose mothers

Table 9.1 Pregnancy outcomes summarized for women who became pregnant while taking bromocriptine or cabergoline, compared to what is expected in the normal population

	Bromocriptine (N)	Bromocriptine (%)	Cabergoline (N)	Cabergoline (%)	Normal (%)
Pregnancies	6.239	100	1016	100	100
Spontaneous abortions	620	9.9	77	7.6	10–15
Terminations	75	1.2	66[a]	6.5	20
Ectopic	31	0.5	3	0.3	1.0–1.5
Hydatidiform moles	11	0.2	1	0.1	0.1–0.15
Deliveries (known duration)	4139	100	746	100	100
At term (>37 weeks)	3620	87.5	672[b]	90.1	87.3
Preterm (<37 weeks)	519	12.5	74	9.9	12.7
Deliveries (known outcome)	5120	100	670	100	100
Single births	5031	98.3	655	97.8	96.8
Multiple births	89	1.7	15	2.2	3.2
Babies (known details)	5213	100	863	100	100
Normal	5030	98.2	842	97.6	97
With malformations	93	1.8	21	2.4	3.0

Data for Bromocriptine from Refs. [26, 27]
Data for cabergoline from Refs. [24, 28]
Data for normal births from Refs. [29–31]
[a]Fourteen of these terminations were for malformations
[b]Seven of these births were stillbirths

took bromocriptine in this fashion showed no ill effects of this exposure on their development [32]. Bromocriptine has been used throughout gestation in only a little over 100 women, with no abnormalities noted in the infants except for one with an undescended testicle and another with a talipes deformity [27, 33–35].

Experience with the use of cabergoline in early pregnancy is more limited, with just over 1000 cases being reported (Table 9.1). As with bromocriptine, such use has similarly not shown an increased percentage of spontaneous abortion, premature delivery, or multiple births (Table 9.1) [24, 28]. Outcome data with respect to malformations were available for 863 pregnancies with only 2.4% major malformations found [24, 28].

Follow-up studies of up to 12 years following exposure to cabergoline during gestation in 3 series totalling 232 children showed a slight retardation in verbal fluency in two (0.8%), difficulty in achieving complete continence in 1 by age 4 (0.4%), seizures in two (0.8%), and "pervasive developmental disorder," an autism spectrum disorder, in two (0.8%) [36–38]. A summary of 15 reports of the use of cabergoline throughout gestation indicated that healthy infants were delivered at

term in 13 and at 36 weeks in one but one had an intrauterine death at 34 weeks when the mother had severe preeclampsia [39]. What is expected in the general population in the USA is also shown in in Table 9.1 [29–31]. Overall, there do not appear to be any increases in adverse pregnancy outcomes with either drug compared to the general population.

In a review of 176 pregnancies, in which quinagolide (not available in the USA) was maintained for a median duration of 37 days into the gestations, Webster reported 24 spontaneous abortions, 1 ectopic pregnancy, and 1 stillbirth at 31 weeks of gestation [40]. Nine fetal malformations were reported, including spina bifida, Trisomy 13, Down syndrome, talipes, cleft lip, arrhinencephaly, and Zellweger syndrome [40]. Thus, quinagolide does not appear to be safe for the fetus if used when pregnancy is desired.

In contrast to the above reassuring information regarding cabergoline and bromocriptine, Hurault-Delarue et al. reported some adverse outcomes of dopamine agonist use in an analysis of data from a French database (EFEMERIS, Evaluation chez la Femme Enceinte des Medicaments et de leur RISque) in which all pregnant women covered by the French Health Insurance Service are registered [41]. Of the 57,408 mother-baby outcome pairs, 183 (0.3%) had received dopamine agonists (bromocriptine 64.5%, cabergoline 20.2%, quinagolide 9.8%) at some time during their pregnancy (75% in the first trimester), and their data was compared to a control group twice that number after matching for age and time of the pregnancy [41]. Their analysis showed that dopamine agonist exposure was associated with an increased frequency of preterm birth (14.3% vs. 5.2%, $p = 0.001$), an increased rate of early pregnancy loss (reasons not known for most – 14.8% vs. 5.7%, $p = 0.0006$), and an insignificant increase in fetal malformations (3.9% vs. 2.6%, $p = 0.2$) [41]. There were no differences shown between the dopamine agonists with respect to these outcomes. Assessment of psychomotor development at ages 9 and 24 months showed no differences between the two groups [41].

Bromocriptine clearly has the largest safety database and has a proven safety record for pregnancy, the recent French data notwithstanding. The database for the use of cabergoline in pregnancy is smaller, but there is no evidence at present indicating that it exerts deleterious effects on the developing fetus. The risk of malformations with either drug is not greater than that what is found in the general population.

Effect of Pregnancy on Prolactinoma Size

The increasing amount of estrogen produced by the placenta stimulates lactotroph hyperplasia and a progressive increase in PRL levels over the course of pregnancy, preparing the breast for lactation [42–45]. In normal women, MRI scans show a gradual increase in pituitary volume over the course of gestation, beginning by the 2nd month and peaking the 1st week postpartum with a final height reaching 12 mm [46, 47].

Prolactinomas can enlarge during pregnancy (Fig. 9.1) as a result of both the stimulatory effect of the high estrogen levels produced by the placenta as well as the discontinuation of the dopamine agonist that might have caused tumor shrinkage. In a previous review, I analyzed the risk of symptomatic tumor enlargement in pregnant women with prolactinomas, divided according to their status as micro- or macroprolactinomas [24], and those data are given again here plus data from on additional study [28] (Table 9.2). The reports included in that review date back to the 1970s when CT scans were just starting to be used. Although some early case reports and small series were included in earlier summaries that were in that review [50, 51], the reports after 1985 were included only if they had five or more cases [36–38, 52–60]. In these series, clinically significant tumor enlargement criteria generally consisted of progressive, severe headaches and/or visual field defects. Asymptomatic increases in tumor size without visual field defects found on scans were not counted. Furthermore, in some series some pregnancies did not go to term,

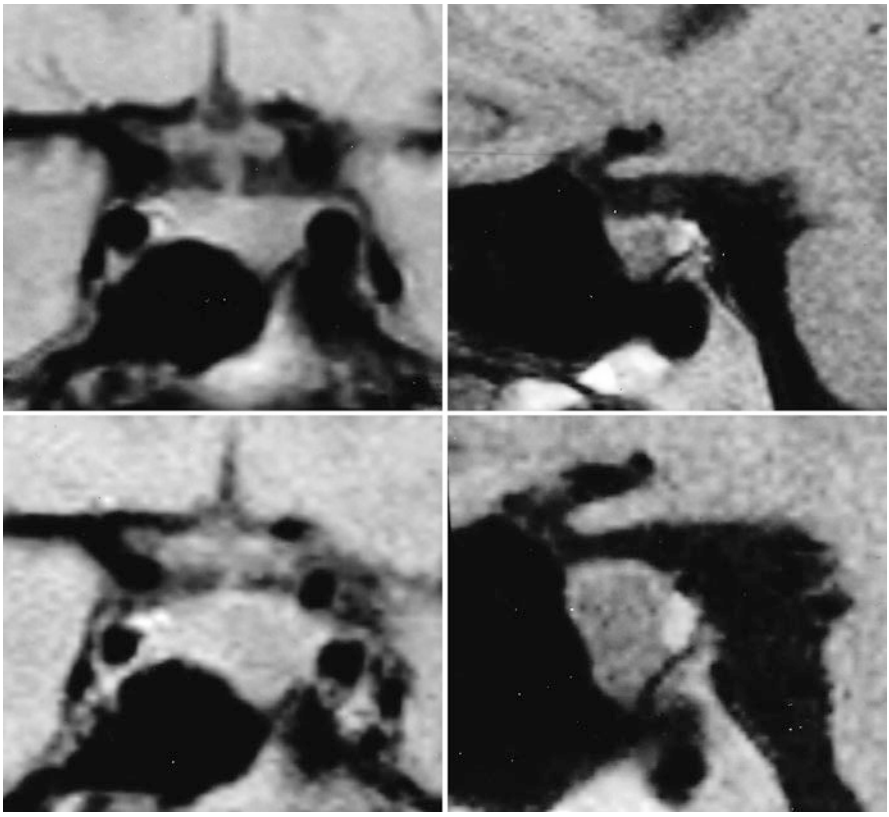

Fig. 9.1 Coronal (left) and sagittal (right) MRI scans of an intrasellar prolactin-secreting macroadenoma in a woman prior to conception (above) and at 7 months of gestation (below). Note the marked tumor enlargement at the latter point, at which time the patient was complaining of headaches. (From Molitch [48, 49]. With permission from Elsevier)

Table 9.2 Enlargement of prolactinomas during pregnancy

Series	Ref. No	Year	Microadenomas			Macroadenomas			Macroadenomas		
						No prior treatment			Prior treatment		
			Total	#Enlarged		Total	#Enlarged		Total	#Enlarged	
Gemzell and Wang	48	1979	85	5		46	20		70	5	
Molitch	49	1985	246	4		45	7		46	2	
Holgrem et al.	50	1986	26	3		4	2		5	0	
Ampudia et al.	51	1992	8	1		1	0		4	0	
Kuppersmith et al.	52	1994	54	0		4	4		0	0	
Rossi et al.	53	1995	22	2		3	1		2	0	
Badawy et al.	54	1997	16	0		0	0		0	0	
Mallmann et al.	55	2002	5	0		3	1		0	0	
Bronstien et al.	56	2002	48	1		30	11		21	0	
Ono et al.	33	2010	56	0		29	0		0	0	
Lebbe et al.	34	2010	45	2		15	3		0	0	
Stalldecker et al.	35	2010	47	0		34	0		0	0	
Auriemma et al.	57	2013	76	0		10	0		0	0	
Domingue et al.[a]	58	2014	30	0		14	1		0	0	
Rastogi et al.	32	2016	0	0		33	0		0	0	
Total			**764**	**18**	**(2.4%)**	**304**	**50**	**(16.4%)**	**148**	**7**	**(4.7%)**

[a]Analysis of tumor growth from this series – personal communication from D. Maite

and how tumor progression in such patients was counted was not clear. Table 9.2, therefore, is a summary of these data, but the limitations of these numbers based on the information outlined above should be recognized. The risk of symptomatic tumor enlargement for microadenomas was 2.4% (18/764), for macroadenomas that had not had prior surgery or irradiation was 16.4% (50/238), and for macroadenomas with prior surgery/irradiation was 4.7% (7/148). Another caveat regarding these numbers is that in a small proportion of those cases, the tumor enlargement reflected tumor apoplexy. There are a number of additional case reports of pituitary apoplexy occurring in women with both micro- and macroprolactinomas during pregnancy [61, 62], so it is difficult to know the true incidence of apoplexy in women with prolactinomas who get pregnant.

We also have information from one study on MRI scans done routinely between 24 and 32 weeks of gestation in 34 women in whom the cabergoline had been stopped shortly after the pregnancy was diagnosed [37]. Compared to prepregnancy scans, of the 12 with macroadenomas, 5 had no change in tumor size, none had a decrease in tumor size, 3 had an increase of <5 mm, and 4 had an increase of >5 mm in size; of the 22 with microadenomas, 9 had no change in tumor size, 3 had a decrease in tumor size, 8 had an increase of <5 mm in size, and 2 had an increase of >5 mm in size [37]. In many cases with tumor enlargement, reintroduction of the dopamine agonist, usually bromocriptine, was successful in reversing the problem, and surgery was very rarely required; others were managed conservatively without medication or surgery. Cabergoline was restarted in six of the patients because of symptomatic headaches and/or vision-threatening increases in size of the adenomas [37, 60].

Postpartum PRL levels and tumor sizes are often actually reduced as compared with values before pregnancy [63], but this has not been observed in all series [64]. Dominguez et al. reported that of 56 hyperprolactinemic women, 23 had normal PRL levels postpartum and of the 33 with persistent hyperprolactinemia, 31% had levels that had decreased by more than 50% [60]. Therefore, a woman may have a significant lowering of the PRL postpartum, may be ovulatory, and may not need resumption of a dopamine agonist. In a study of PRL levels postpartum and nursing in women with prolactinomas, Ikegami et al. [65] found that no nursing patient showed a sharp increase of PRL levels or complained of symptoms suggestive of tumor enlargement, such as headaches or visual disturbances [65]. Thus there is no reason women with prolactinomas cannot breast-feed. However, reinstitution of dopamine agonist has to await the cessation of breast-feeding and should only be done if the woman remains hyperprolactinemic and anovulatory. An alternative for an anovulatory woman who does not wish immediate fertility would be estrogen/progesterone replacement to avoid prolonged estrogen deficiency and potential osteoporosis.

Recommendations for Management of Pregnancy

In women with PRL-secreting microadenomas who are anovulatory, the choice to restore fertility is the use of dopamine agonists or transsphenoidal selective adenoma resection. Dopamine agonists would seem to be the best primary treatment for

such patients because of their efficacy in restoring ovulation and very low (2.4%) risk of clinically serious tumor enlargement. The accumulating data for cabergoline suggest that its safety record is equal to that of bromocriptine, and generally it is better tolerated and more efficacious. Transsphenoidal surgery causes a permanent reduction of PRL levels in only 60–70% of cases and entails morbidity and mortality, albeit at low rates [18, 21, 66]. Pregnancy can generally be achieved in over 85% of patients with dopamine agonists or surgery [20, 24, 36, 64]. Rare patients who do not respond to either modality may need additional treatments to facilitate ovulation, such as clomiphene citrate or human chorionic gonadotropin [67, 68] or in vitro fertilization (IVF). Radiotherapy is not warranted for patients with microadenomas whose levels do not normalize with medication or surgery, as the risk of tumor enlargement without radiotherapy is much lower than the risk of known, long-term sequelae of pituitary radiotherapy, especially hypopituitarism [1].

A patient with a microadenoma who had been treated only with a dopamine agonist needs only to be followed clinically throughout gestation. PRL levels do not always rise during pregnancy in women with prolactinomas, as they do in normal women [69]. Usually PRL levels rise over the first 6–10 weeks after stopping the dopamine agonist and then do not increase further [70]. PRL levels may also not rise with tumor enlargement [69]. Therefore, periodic checking of PRL levels is not recommended [20], as it is of no diagnostic benefit, and may be both misleading and the cause of unnecessary worry on the part of the patient and obstetrician. Because of the low incidence of tumor enlargement, routine, periodic visual field testing is not cost effective. Visual field testing and MRI scanning are performed only in patients who become symptomatic and when intervention is being considered. There are no data documenting harm to the developing fetus from either MRI scans or gadolinium [71–75]; nonetheless, many neuroradiology departments are reluctant to do any MRI scan and even more reluctant to give gadolinium to a pregnant patient. However, in the face of symptoms of headaches that may be nonspecific, it is important to document a significant increase in tumor size before instituting an intervention, such as restarting a dopamine agonist or surgery. If the headache is sudden, it may be caused by pituitary apoplexy, which may require an entirely different management course, including hormone replacement if there is sudden onset of hypopituitarism [61, 62]. MRI may be very helpful in distinguishing between hemorrhage into a tumor and simple tumor enlargement [61]. When obtaining an MRI in a pregnant patient, it is important to work with the neuroradiologist in considering the best radiologic approach [75].

The patient with a small intrasellar or inferiorly extending macroadenoma can probably be managed as those with microadenomas, i.e., with dopamine agonists. The risk that such a tumor will enlarge sufficiently to cause clinically serious complications is probably only marginally higher than the risk in patients with microadenomas.

A woman with a larger macroadenoma, especially one with suprasellar extension, has a 16.4% risk of clinically significant tumor enlargement during pregnancy when only dopamine agonists are used. It is helpful to have an MRI scan just prior to pregnancy, so as to assess any size change during pregnancy. There is no best

therapeutic approach in such a patient, and this has to be a highly individualized decision that the patient and endocrinologist have to make after a clear, documented discussion of the various therapeutic alternatives. The most common approach is to stop the dopamine agonist after pregnancy is diagnosed, as in the patient with microadenoma. Another approach is to debulk the tumor via transsphenoidal surgery, being careful to spare the normal pituitary. This reduces the risk of serious tumor enlargement, but cases of tumor expansion during pregnancy after such surgery have been reported [75]. After surgical debulking, a dopamine agonist will generally be required to normalize PRL levels and allow ovulation. A third approach, that of giving the dopamine agonist continuously throughout gestation, has been used, but data of effects on the fetus are quite meager (see above); therefore, such treatment cannot be recommended without reservation. On the other hand, should pregnancy at an advanced stage be discovered in a woman taking bromocriptine or cabergoline, the data that exist are reassuring and would not justify therapeutic abortion. A special case might be a patient with a very large tumor in whom the growth rate of that tumor was slow and any effects of pressure on surrounding brain structures or the optic chiasm were very gradual and of no consequence. If there was substantial tumor shrinkage with the dopamine agonist, then stopping the drug abruptly might cause a sudden enlargement of the tumor with potential pressure on surrounding structures. In such a case, the wisest course could be to continue the dopamine agonist.

For patients with macroadenomas treated with a dopamine agonist alone or after surgery, careful follow-up with 1–3 monthly formal visual field testing is warranted. Repeat MRI scanning is reserved for patients with symptoms of tumor enlargement and/or evidence of a developing visual field defect or both as outlined above for patients with microadenomas. Repeat MRI scanning after delivery to detect asymptomatic tumor enlargement may be useful as well.

Should symptomatic tumor enlargement occur with any of these approaches, reinstitution of the dopamine agonist is probably less harmful to the mother and child than surgery. There have been a number of cases reported where such reinstitution of the dopamine agonist has worked quite satisfactorily, causing rapid tumor size reduction with no adverse effects on the infant (see above). Any type of surgery during pregnancy results in a 1.5-fold increase in fetal loss in the first trimester and a fivefold increase in fetal loss in the second trimester, although there is no risk of congenital malformations from such surgery [76, 77]. In addition, pregnant (compared to nonpregnant) women have significantly increased risks of postoperative complications, including infections and even mortality [78]. Thus, dopamine agonist reinstitution would appear to be preferable to surgical intervention. However, such medical therapy must be very closely monitored, and transsphenoidal surgery or delivery (if the pregnancy is far enough advanced) should be performed if there is no response to the dopamine agonist and vision is progressively worsening.

It is interesting to note how these general recommendations for management during pregnancy are actually carried out in practice. Ahlmalki et al. collected responses to three theoretical cases with either (1) microadenoma, (2) macroadenoma, or (3) large macroadenoma (2.9 cm) from 34 endocrinologists in practice in

several provinces in Canada [79]. Discontinuation of the dopamine agonist when pregnancy was diagnosed was done for 94% of patients with microadenomas but for only 65% of patients with macroadenomas and only 18% of those with "large" macroadenomas. Regular monitoring of visual fields with formal testing was carried in 32% of patients with microadenomas, 60% of those with macroadenomas, and 94% of those with large macroadenomas. Regular monitoring with MRI scans was carried for 30% of those with macroadenomas and 49% of those with large macroadenomas. In a survey in Brazil, Vilar et al. found that a dopamine agonist would be discontinued during pregnancy by only 70% of 721 respondents in women with microadenomas and by only 58% in those with macroadenomas [80]. In a third similar survey of 468 endocrinologists in the Middle East and North Africa, Beshyah et al. found that they would discontinue the dopamine agonists in only 65% of women with microadenomas and 38% of those with macroadenomas who became pregnant [81].

Conclusions

Treatment with dopamine agonists usually restores ovulation and fertility with cabergoline generally being preferred to bromocriptine because of its higher therapeutic efficacy/adverse effects ratio. Experience with both drugs shows no increase in spontaneous abortions, preterm deliveries, multiple births, or congenital malformations, compared to what is expected in the normal population, the French report [41] notwithstanding. Clinically significant tumor growth may occur in 2.4% of women with microadenomas and 16.4% of those with macroadenomas without prior ablative treatment. Patients with macroadenomas should have visual fields assessed periodically during gestation, and an MRI is indicated for either visual field defects or progressive headaches to confirm that it is tumor growth causing these issues. Should symptomatic tumor growth be documented, reinstitution of the dopamine agonist is usually successful in shrinking the tumor, and transsphenoidal debulking is rarely necessary. If the pregnancy is sufficiently advanced, delivery is also an option.

However, there are still several remaining questions about women with prolactinomas who wish to become pregnant. About 18% of patients are resistant to cabergoline and require larger than conventional doses to achieve normal PRL levels and to ovulate [36]. Additional safety information for mother and baby are needed when cabergoline is given in larger than conventional doses. A large macroadenoma that has been greatly reduced in size by dopamine agonists represents a particular safety issue if the dopamine agonist is stopped abruptly at the same time as estrogen levels are increasing; reports of any patients who may have had abrupt adverse consequences in that setting would be of interest. Additional safety information is also needed for doing MRIs and for administering gadolinium during pregnancy in patients with pituitary tumors.

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Chapter 10
Prolactinomas in Children and Adolescents

Takara L. Stanley and Madhusmita Misra

Introduction

Pituitary adenomas represent only 2–3% of brain tumors in the pediatric age group [1]. In prepubertal children, corticotropinomas are the most common adenoma, whereas in peri- and postpubertal children, at least 50% of all pituitary tumors are prolactinomas [2–7]. As in adults, females are more likely to present with prolactinomas than are males, and males with prolactinoma are much more likely to present with macroadenomas [3, 6–8]. Boys may also present at a relatively younger age than girls [8]. In contrast to adults, children are more likely to present with macroprolactinomas and are more likely to have an identifiable genetic etiology [9]. Presentation of prolactinomas in children includes signs and symptoms found in adults as well as age-specific symptoms including growth failure and delayed puberty.

Hyperprolactinemia in Children

Infants have a prolactin surge at the time of delivery, with peak prolactin concentrations of 200–300 ng/mL in the first few hours of life [10, 11]. Levels drop very quickly in the postpartum period and continue to decline during the 1st year of life. Between ages 1 month and 1 year, age-appropriate reference ranges should be used [12, 13]. Levels up to 100 ng/mL may be seen in the first few months of life, whereas levels approach adult normal ranges between 6 and 12 months of age [12, 13]. The

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use of adult norms for prolactin is appropriate starting at 1 year of age [11, 12]. Prolactin has a diurnal rhythm in children, as in adults, and prolactin levels between 11 PM and 5 AM may be two to four times higher than daytime values [14].

The process for evaluation of hyperprolactinemia begins with consideration of a differential diagnosis that includes pregnancy and lactation, stress, the postprandial state [15], primary hypothyroidism, renal insufficiency, and medication use. Our practice is to repeat mildly to moderately elevated prolactin levels ideally in the morning in the fasting state. If stress from phlebotomy is suspected to be the cause of prolactin elevation, an intravenous catheter should be placed and the child allowed to rest for 30–120 min before blood sampling through the catheter.

Medication use is a common cause of hyperprolactinemia in the pediatric age group. The atypical antipsychotics risperidone, olanzapine, and ziprasidone may cause prolactin elevation, with the most significant elevations caused by risperidone. Over 45% of children treated with risperidone have hyperprolactinemia, with elevations as high as 125 ng/mL reported in children [16–18]. Quetiapine is expected to be neutral to prolactin levels, whereas aripiprazole is a partial dopamine agonist that may lower prolactin and is described as an adjunctive therapy to normalize hyperprolactinemia induced by other antipsychotics [19–23]. Typical antipsychotics, metoclopramide, and domperidone may cause substantial elevations in prolactin [24–26], whereas antidepressants, cocaine, opiates, and verapamil may cause milder elevations, typically ≤50 ng/mL [24, 27–32]. Estrogen also increases prolactin, and standard doses of oral contraceptive medication containing ethinyl estradiol may cause mild hyperprolactinemia [24, 33, 34]. In children with mild to moderate elevations in prolactin who are taking a medication expected to increase prolactin levels, we generally do not perform further investigation if there is documentation of a normal prolactin level before treatment. For patients without such documentation, medication should be discontinued for a short period if possible, or the patient should be switched to a similar medication that does not cause hyperprolactinemia, so that prolactin can be remeasured. Withdrawal or change of medication is not always safe, particularly for antipsychotics. If documentation of a normal prolactin level off medication is not available, we recommend proceeding with an MRI of the brain [22]. Additionally, we recommend a pituitary MRI for patients with hyperprolactinemia above the level expected for the given medication, or for patients with a prolactin level ≥100 ng/mL even in the context of medications such as risperidone that may cause such elevations.

Macroprolactinemia, which is an elevation in measured serum prolactin due to increased circulating "big big prolactin" that lacks meaningful biological activity, occurs in children [35, 36], but the prevalence is not known. We do not routinely test children with hyperprolactinemia for the presence of macroprolactin, but testing may be advisable in asymptomatic patients, especially those with a normal pituitary MRI [22]. Another important laboratory consideration is the "hook effect," which is an artifact of the immunometric assay typically used to measure prolactin, with a solid-phase capture antibody and a detection antibody that must both bind prolactin in order to produce the "signal." In the setting of very high prolactin levels, the excess prolactin may saturate the detection antibody in the

liquid phase, such that it is washed away rather than measured, leading to a falsely low prolactin level [37]. Two strategies to prevent falsely low readings due to the hook effect are to perform prolactin assays with serial dilution or to perform a "washout" step after prolactin has bound to the capture antibody and before the detection antibody is added. When a patient with a large pituitary lesion has an unexpectedly modest elevation in prolactin, one of these strategies should be requested. For further information related to prolactin assays, please see Chap. 3, "Prolactin Assays and Regulation of Secretion: Animal and Human Data." Another consideration (as in adults) is prolactin elevation from compression of the pituitary stalk from tumors or cysts in the region of the pituitary and hypothalamus (such as a craniopharyngioma, non-functioning and other pituitary adenomas, rarely large Rathke Cleft cysts), or an infiltrative disorder of the pituitary stalk (such as a germinoma, Langerhans cell histiocytosis, autoimmune hypophysitis, rarely sarcoidosis or tuberculosis).

Signs and Symptoms of Prolactinoma in Children and Adolescents

The signs and symptoms of a prolactinoma can be divided into those caused by hyperprolactinemia itself and those caused by mass effect from the tumor. Microadenomas usually present with symptoms or signs of hyperprolactinemia, whereas macroprolactinomas present with signs and symptoms due to hyperprolactinemia and/or mass effect. To our knowledge incidentally discovered prolactinomas are rare in the pediatric population [38]. Although incidental discovery of a prolactinoma is a possibility, pediatric prolactinomas generally present with one or more of the symptoms described below.

Symptoms of hyperprolactinemia are related to hypogonadotropic hypogonadism and/or the actions of prolactin on breast tissue. Menstrual disturbance is very common in female adolescents with a prolactinoma, as in adult women [3, 6, 7]. Menorrhagia may also rarely occur. In children who develop a prolactinoma before completion of puberty, delayed puberty or primary amenorrhea are common, occurring in up to one-fifth of children with microprolactinomas and up to three-fourths of children with macroprolactinomas [3, 6, 7]. Galactorrhea is reported in 27–67% of children with microprolactinomas and 51–91% of those with macroprolactinomas [3, 6, 7, 9]. In boys, gynecomastia may also be present [7, 9], but this may be difficult to distinguish from normal peri-pubertal gynecomastia.

Symptoms of mass effect include headache and visual disturbances, which occur in 40–90% and 15–50%, respectively, of patients with a macroprolactinoma [3, 6, 7, 9]. Insufficiency of other pituitary hormones may also occur [2, 9], and growth delay may be a presenting sign in a minority of patients who have not yet completed statural growth [3, 6, 7]. Accelerated growth or signs of acromegaly may occur if patients have tumors that co-secrete growth hormone [2].

Evaluation of Suspected Prolactinoma in Children

Laboratory Evaluation

Additional laboratory investigation in children with hyperprolactinemia should include evaluation of other possible causes of hyperprolactinemia as well as possible sequelae of a prolactinoma. In girls of reproductive age, ruling out pregnancy with a serum beta-HCG or a urine HCG is an important initial step. Thyroid-stimulating hormone (TSH) and free thyroxine (free T4) should be tested as significant untreated primary hypothyroidism can cause hyperprolactinemia from elevations in thyrotropin-releasing hormone (TRH). In addition, chronic hypothyroidism can stimulate thyrotrophs and lactotrophs, leading to pituitary hyperplasia that mimics the appearance of pituitary adenoma [22]. Serum creatinine and liver function tests can rule out renal failure and liver disease as causes of hyperprolactinemia. Regular assessment of gonadal steroids should be performed in all boys with prolactinoma and in amenorrhoeic girls to assess for hypogonadotropic hypogonadism. This should be accompanied by careful assessment of sexual function in older adolescents and menstrual history in females. Patients with a macroprolactinoma should have initial and periodic evaluation for hypopituitarism. Insulin-like growth factor 1 (IGF-1) levels are important to rule out an adenoma co-secreting prolactin and growth hormone or a growth hormone-secreting tumor with hyperprolactinemia due to stalk compression.

Pituitary MRI

Children or adolescents with confirmed hyperprolactinemia should have a pituitary protocol brain MRI. Conscious sedation is typically needed for younger children, and children with braces should have these removed prior to MRI. The incidence of pituitary "incidentalomas" is not well-defined in children but is known to be approximately 10% in adults [39, 40]. Thus, a very small pituitary lesion in the presence of modest hyperprolactinemia is not always indicative of a prolactinoma, but an adenoma in the context of persistent hyperprolactinemia is highly suggestive of prolactinoma. As in adults, microprolactinomas in children may be accompanied by hyperprolactinemia ranging from mild to significant, whereas macroprolactinomas are generally accompanied by prolactin >250 ng/mL. When a sellar lesion ≥10 mm is not accompanied by prolactin >250 ng/mL, we recommend consulting radiology and neurosurgery to consider the possibility of other sellar masses. In this age group, the most prevalent sellar mass is craniopharyngioma. Germinomas, nonfunctioning adenomas, lymphomas, hamartomas, meningiomas, and granulomatous processes such as Langerhans cell histiocytosis should also be considered. Prolactinomas that are highly cystic or are poorly differentiated can also present with prolactin levels that are lower than expected for tumor size. Of note, the prevalence of "aggressive"

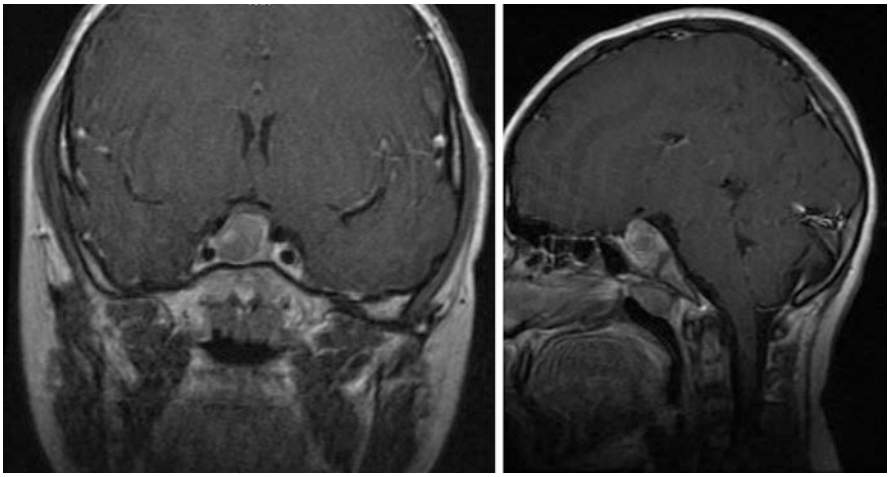

Fig. 10.1 T1-weighted post-gadolinium coronal and sagittal images of a 1.5 × 1.6 × 1.2 cm cystic macroprolactinoma found in an 8-year-old male with prolactin levels in the 200–300 ng/mL range

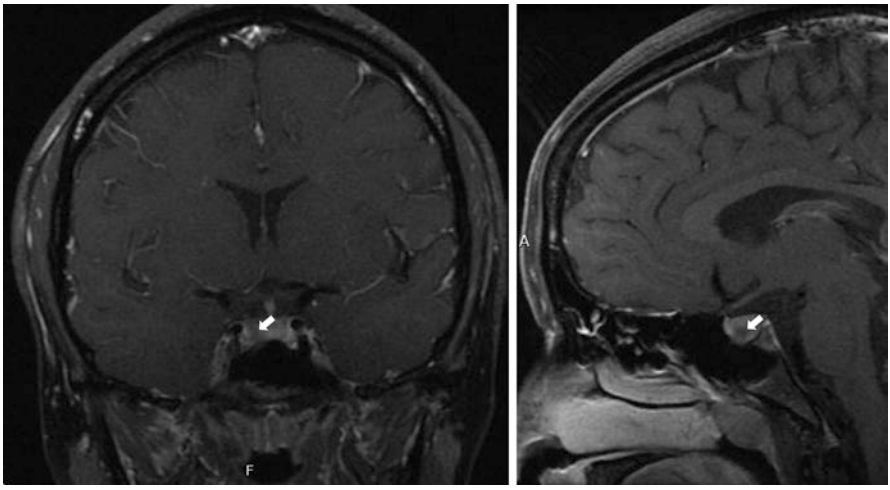

Fig. 10.2 T1-weighted post-gadolinium coronal and sagittal images of a right-sided microprolactinoma (white arrows) in an 18-year-old female with prolactin levels 100–200 ng/mL

prolactinomas and pituitary carcinoma are not well-defined in the pediatric age group, but both are rare.

MRI findings in two children with a prolactinoma are shown in Figs. 10.1 and 10.2. Figure 10.1 shows a 1.5 × 1.6 × 1.2 cm cystic macroprolactinoma found in an 8-year-old male with prolactin levels in the 200–300 ng/mL range. Figure 10.2 shows a right-sided microprolactinoma in an 18-year-old female with prolactin levels between 100 and 200 ng/mL.

Consideration of Genetic Testing

A genetic etiology should be considered for children with prolactinoma. Although primary hyperparathyroidism is the most common presenting symptom of MEN1, about 15% of individuals present with a pituitary adenoma [41], and MEN1 testing should be performed in children with prolactinoma and a family history of hyperparathyroidism or pituitary adenoma. Children with a prolactinoma and a history of familial pituitary adenomas should have testing for *AIP* mutations, which most commonly lead to somatotropinomas, prolactinomas, or mammosomatotropinomas (co-secreting GH and prolactin) [42, 43].

Even in the absence of known family history, genetic testing should be considered in children with macroadenomas. Recent literature suggests that 10–20% of children with apparently sporadic macroprolactinomas may have germline *MEN1* or *AIP* mutations. In a cohort of 77 children with macroprolactinomas, 14% had mutations in *MEN1* or *AIP* [9]. In a separate cohort of 30 children with macroprolactinomas, 3 had *MEN1* mutations and 2 had *AIP* mutations [44]. McCune-Albright syndrome (MAS) should also be considered in patients with mammosomatotropinomas, as these have been described in a few cases of children with MAS [5, 45]. Café-au-lait macules, polyostotic fibrous dysplasia, and other endocrine manifestations such as precocious puberty and hyperthyroidism are classic signs of MAS but are not invariably present. We do not routinely perform genetic testing on children with microprolactinomas who have a negative family history, but we do often send serum calcium levels in these children to rule out hyperparathyroidism that may be consistent with MEN1.

Other Evaluation

We recommend dual x-ray absorptiometry (DXA) scanning for assessment of bone mineral density in patients with chronic hyperprolactinemia, due to the potential adverse effects of persistent hypogonadism on bone density. Additionally, ophthalmologic referral for visual field testing is important for patients with a prolactinoma that may be abutting the optic chiasm. Neurosurgery should be consulted if visual impairment is present, although dopamine agonists remain first-line therapy unless visual impairment is rapidly progressing.

Management

The management of prolactinomas in children and adolescents is very similar to that in adults (see Chap. 11, “Prolactinomas in Men”). The goals of therapy are to reduce prolactin ideally to normal, or at least to a degree that permits normal gonadal

function, and in patients with macroprolactinomas, to also decrease tumor size. This is typically achieved with dopamine agonists, although some patients will require a combination of pharmacotherapy, surgery, and potentially radiation therapy.

Observation Without Treatment

Adult data suggest that hyperprolactinemia resolves without treatment approximately one-third of the time and that microprolactinomas do not act aggressively [22, 46]. Based on these data, asymptomatic patients with normal gonadal function and stable microprolactinomas may not necessarily require dopamine agonist therapy. Similarly, patients with stable microprolactinomas whose only symptom is hypogonadotropic hypogonadism could reasonably be treated with gonadal steroid replacement rather than dopamine agonists. There are not adequate data in the pediatric population, however, to assess the outcomes of either of these strategies compared to the use of dopamine agonists. Patients who are being followed without dopamine agonist treatment should have prolactin measured at least annually, with repeat MRI if prolactin increases [22]. Patients with macroprolactinoma should be treated with dopamine agonists and, if refractory to medical therapy, additional methodologies as described below.

Dopamine Agonist Therapy

Of the two commonly used dopamine agonists, bromocriptine and cabergoline, adult data demonstrate that cabergoline is better tolerated and more effective than bromocriptine [22, 47–52]. Although prescribing information for cabergoline describes that safety is not established in children <18 years of age, multiple case series describe cabergoline use in children [6–9, 53, 54], and cabergoline is generally used as first-line therapy for children at our center. Usual doses of cabergoline are 0.25–3 mg weekly, although case studies in children suggest that higher doses are occasionally effective for tumors resistant to lower doses [8, 9, 54].

After initiation of dopamine agonist therapy, prolactin should be checked in 1 month and then as appropriate to guide dose adjustment [22]. For patients who have macroprolactinomas, MRI should be repeated in the first 3 months and then as clinically indicated [51]. Visual field testing should be repeated as needed based on the proximity of the lesion to the optic chiasm. Most children will achieve reduction in prolactin and tumor control with dopamine agonists. Two recent case studies in children, most of whom received cabergoline as the first-line dopamine agonist, suggest that medication is sufficient to control prolactin levels and tumor growth in approximately three-quarters of children [8, 9]. In a cohort of 77 children with macroprolactinoma, Salenave et al. report that *MEN1* mutations, younger age at presentation, higher prolactin levels, and larger tumor size were associated with resistance to dopamine agonists. Children

without near-normalization of prolactin and/or reduction in tumor volume should be referred to a center with neurosurgical expertise for consideration of surgery.

Adult guidelines suggest a gradual taper of dopamine agonist in patients with normal prolactin and resolution of adenoma after 2 years or more of dopamine agonist therapy [22]. Hoffman et al. recently reported successful discontinuation of dopamine agonist therapy in one child in their cohort, but, to our knowledge, outcomes of dopamine agonist tapering are not yet well-described in the pediatric population.

The side effect profile of dopamine agonists is similar in children and adults and includes nausea, dizziness, headache, fatigue, and postural hypotension. Less common but serious side effects include pituitary apoplexy [55], cerebrospinal fluid rhinorrhea [56], and behaviors consistent with mania or psychosis (per reports in adults) [57–59], and sometimes depression and even suicidal ideation (personal experience). Other less common side effects include constipation, asthenia, insomnia, and edema [60]. Patients intolerant of one dopamine agonist should generally be tried on other available dopamine agonists before abandoning the possibility of medical therapy. Clinician judgment should be used if the initial side effect was severe, however, such as substantial psychiatric disturbance. Patients who cannot tolerate bromocriptine may have milder side effects on cabergoline. Additionally, ergot-derived dopamine agonists are known to increase the risk of valvular heart disease in Parkinson's disease [61, 62], but data thus far have been reassuring in prolactinoma patients, who generally require much lower doses [63–67]. In patients with pre-existing heart disease or patients who may require prolonged therapy with relatively high doses of cabergoline, we obtain baseline and follow-up echocardiograms.

Surgical Therapy

Surgery should be considered immediately for children with pituitary apoplexy or cerebrospinal fluid leak. In other children, dopamine agonist therapy is typically tried first, with referral to surgery if dopamine agonists are not successful in achieving control of prolactin and tumor growth or if patients demonstrate intolerance to multiple dopamine agonists. A macroprolactinoma abutting the optic chiasm or even associated with visual compromise may be treated with dopamine agonists first with close monitoring of visual fields and tumor size; surgery becomes necessary if the adenoma does not shrink with therapy or if visual field deficits persist or worsen. Children should ideally be referred to a highly experienced pituitary surgeon in a center with pediatric anesthesia expertise in order to optimize outcome. Even when complete tumor removal is not possible, debulking along with subsequent dopamine agonist therapy may achieve adequate control [9]. Large pediatric series of surgical outcomes are not available, but a series of over 200 adolescents and adults who underwent surgery for prolactinoma reported remission in 84.8% of those with microprolactinomas, 80% of those with cystic prolactinomas, and 72.5% of those with other intrasellar tumors [68]. Pediatric case series suggest that surgery achieves cure and resolution of hyperprolactinemia in a minority of cases, whereas most patients require continued therapy with dopamine agonists postsurgically [3, 6–8].

Other Treatments

For aggressive or malignant prolactinomas refractory to medical and surgical treatment, radiation therapy should be considered. Successful outcomes of radiation therapy have been reported in the pediatric age group [9]. If a combination of dopamine agonists, surgery, and radiotherapy is unsuccessful, an oncologic agent such as temozolomide could be considered with the help of experienced oncologists [69–71]; data on temozolomide in the pediatric population are limited to case reports.

Outcomes

Three recent case series in children and adolescents demonstrate highly favorable outcomes for pediatric prolactinomas. Dopamine agonists are generally well tolerated and are adequate as stand-alone therapy in three-fourths of children with macroadenomas [8, 9]. In children who require additional treatment, surgery with or, less often, without resumption of dopamine agonists will achieve adequate control of prolactin and tumor growth in the majority, with radiation required only in a minority of patients with refractory macroprolactinomas [6, 8, 9]. Patients requiring extensive surgery and/or radiotherapy are at a higher risk for hypopituitarism, whereas patients who achieve tumor control with dopamine agonists may have recovery of pituitary function [6, 8, 9]. Outcomes for children with microprolactinoma are presumably even better than those for children with macroprolactinomas, with dopamine agonists expected to provide sufficient treatment in nearly all patients. However, microprolactinoma outcomes in children are not well-described in the literature.

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Chapter 11
Prolactinomas in Men

Dominique Maiter

Introduction

Although prolactinomas are the most common pituitary tumors, they arise much less frequently in men than in women [1–5]. Based on several recent epidemiological studies, the estimated prevalence of prolactin-secreting tumors is around 10–15/100,000 men (1 in 7000), while it is about fivefold higher in women (60–70/100,000 women or 1 in 1500) (Table 11.1) [6–10]. Likewise, reported standardized incidence ratios (SIR) of prolactinoma are 3–4/100,000/year in women but only 0.8–1/100,000/year in men [10, 11].

While most female PRL-secreting tumors (90%) are microadenomas, men harbor macroadenomas in up to three-quarters of the cases [12, 13], so that the prevalence of macroprolactinomas (8–10/100,000) is roughly similar in both sexes [14–16]. Autopsy studies have however revealed a similar high prevalence of silent prolactin-containing microadenomas in men and women [17, 18], thus indicating that prolactinomas are diagnosed much less frequently in men than in women. This might be related to a lower awareness of related symptoms in males (such as altered libido and erection disorders which are often attributed to other causes) and/or to a lower sensitivity of the gonadotropic axis to hyperprolactinemia in males. Altogether, there is very likely an underestimation of the true prevalence of male microadenomas.

Although rare, male prolactinomas which come to medical attention have several distinct features that will be reviewed in the present chapter.

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Table 11.1 Estimated prevalence of prolactinoma in the whole population, in the male population only, and of macroprolactinoma in the male population, as calculated from several recent epidemiological European studies

	Belgium (Liège)	UK (Banbury)	Malta (whole island)	Iceland (whole island)	Finland (Oulu)
Study population (number)	71,972	81,149	400,000	321,857	245,000
Nb of prolactinomas (% of all pit adenomas)	45 (66%)	36 (57%)	146 (46%)	188 (40%)	84 (55%)
Prevalence of prolactinomas	$63/10^5$	$44/10^5$	$35/10^5$	$54/10^5$	$63/10^5$
Nb of prolactinomas in males (% of total)	9 (20%)	4 (11%)	27 (19%)	47 (25%)	16 (19%)
Prevalence of prolactinomas in males	$18/10^5$	$10/10^5$	$13/10^5$	$13/10^5$	$13/10^5$
Nb of macroprolactinomas in males (%)	5 (56%)	NA	17 (63%)	30 (65%)	12 (75%)
Prevalence of macroprolactinomas in males	$10/10^5$	NA	$8/10^5$	$8/10^5$	$10/10^5$
Reference	[6]	[7]	[8]	[9]	[10]

Nb number, *pit* pituitary

General Characteristics of Prolactinomas in Males

Differences in the general characteristics of prolactinomas between genders have been examined in several studies [16, 19–26], and some of the main data are summarized in Table 11.2. As already mentioned, the ratio between PRL-secreting microadenomas and macroadenomas is about 1:3 in males, whereas it is inverted (9:1) in females. This is also well illustrated in Fig. 11.1a, which shows the total numbers of men and women harboring microprolactinomas, macroprolactinomas, and giant prolactinomas (defined as tumors with a diameter ≥40 mm) in our own cohort of 490 patients diagnosed and followed in our institution for a 20-year period (July 1997–June 2017; *our unpublished data*). Also, the mean or median age at diagnosis is usually greater by 10 years in men than in women [7, 9, 10, 16, 19, 21–26] (Table 11.2 and Fig. 11.1b), likely reflecting a lower clinical alert threshold for diagnosis and not necessarily a later occurrence of the tumor in the male gender.

Not only are macroprolactinomas more frequent in men but they are also larger, more frequently invasive, and more often aggressive than in women [19, 22–27] (Table 11.2 and Fig. 11.2a). This larger tumor size in men has been for a long time attributed to a greater delay in diagnosis [14, 28]. Though this factor may indeed contribute to prolonged asymptomatic expansion of pituitary macroprolactinomas in men, important gender-related differences in tumor behavior have been now well established.

Higher rates of proliferation markers, such as the Ki-67 labeling index or the mitotic count, are found in surgically resected macroadenomas from males compared to similar tumors from females [19, 22–25]. Also, according to the prognos-

Table 11.2 Comparison of the main characteristics of prolactinomas at diagnosis between men and women

	Delgrange et al. [19]		Colao et al. [20]		Papegaey et al. [21][a]		Khare et al. [16][a]	
	Males	Females	Males	Females	Males	Females	Males	Females
Reference	(*n* = 45)	(*n* = 51)	(*n* = 74)	(*n* = 130)	(*n* = 135)	(*n* = 125)	(*n* = 44)	(*n* = 56)
Age (years)								
Mean ± SD	42 ± 2	28 ± 1	35 ± 14	32 ± 12	42 ± 19	31 ± 15	35 ± 10	30 ± 10
Range	[17–73]	[16–66]	NA	NA	[14–79]	[11–83]	[18–68]	[15–59]
Prolactin (μg/L)								
Mean ± SD	2789 ± 573	292 ± 7	188 ± 52 (m)	135 ± 60 (m)	3100 ± 5472	934 ± 2305	7927 ± 16,748	3094 ± 6863
			2848 ± 2954 (M)	1132 ± 2351 (M)				
Range	[62–16,550]	[36–2080]			[6–38,000]	[25–20,000]	[239–90,000]	[201–43,165]
Tumor diameter(mm)								
Mean ± SD	26 ± 2	10 ± 1	8 ± 1 (m)	7 ± 2 (m)	28 ± 13	19 ± 13	39 ± 15	25 ± 15
			26 ± 12 (M)	17 ± 7 (M)				
Range	NA	NA			[10–67]	[10–110]	[13–78]	[10–72]
Micro-/macroadenomas	5/40	36/15	16/58	81/49	0/135	0/125	0/44	0/56
Invasive macroadenomas (%)	21/40 (53%)	4/15 (27%)	NA	NA	67/135 (50%)	32/125 (26%)	35/44 (80%)	15/56 (27%)
Giant adenomas (%)	8 (18%)	0 (0%)	NA	NA	NA	NA	18 (41%)	7 (13%)
Hypogonadism (%)	40 (89%)	50 (98%)	62 (84%)	110 (85%)	NA	NA	32 (76%)	54 (96%)
Visual impairment (%)	19 (42%)	NA	28 (38%)	18 (14%)	51 (38%)	17 (14%)	17 (39%)	7 (13%)

m microadenomas, *M* macroadenomas, *NA* information not available

[a]These studies included only macroprolactinomas

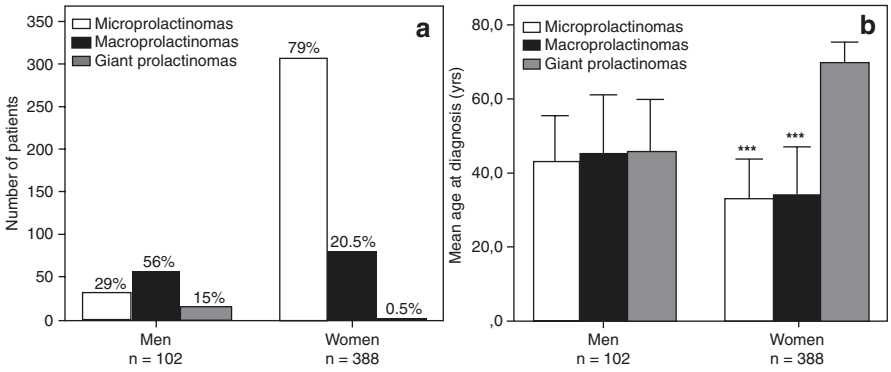

Fig. 11.1 (**a**) Total numbers and percentages and (**b**) mean age at diagnosis (+ standard deviation) in 102 men and 388 women harboring either a microprolactinoma (white bars), a macroprolactinoma (black bars), or a giant prolactinoma (defined as a tumor with a diameter ≥40 mm and a prolactin concentration ≥1000 μg/L; gray bars). Data are calculated from our own cohort of 490 patients diagnosed and followed for a prolactinoma in our institution during a 20-year period (July 1997–June 2017; *unpublished data*). ***: $P < 0.001$ vs males with the same tumor size category

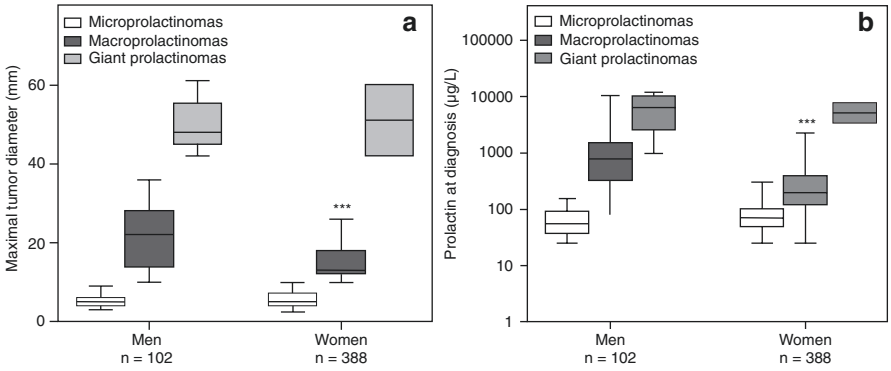

Fig. 11.2 (**a**) Maximal tumor diameter (in mm) and (**b**) prolactin concentrations at diagnosis (in μg/L) in 102 men and 388 women harboring either a microprolactinoma (white bars), a macroprolactinoma (black bars), or a giant prolactinoma (defined as a tumor with a diameter ≥40 mm and a prolactin concentration ≥1000 μg/L; gray bars). Data are calculated from our own cohort of 490 patients diagnosed and followed for a prolactinoma in our institution during a 20-year period (July 1997–June 2017; *unpublished data*). The box and whisker plots represent medians, interquartile ranges, and [P5–P95] intervals, respectively. ***: $P < 0.001$ vs males with the same tumor size category

tic clinicopathological classification proposed by Trouillas et al. [29], men have higher-grade (2b and 3) tumors than women. For example, of the 64 malignant prolactinomas (grade 3 tumors) reported in the English literature between 1981 and 2015, 40 were observed in men and 24 in women [5].

The preponderance of large tumors in males is also largely independent of age [19], and a higher prevalence of macroprolactinomas is seen in boys compared to

girls [30–32]. As shown in Fig. 11.1a, giant prolactinomas are mainly observed among males [33, 34], being found in boys as young as 7 years old [35, 36], and the median age at diagnosis of these very large and invasive PRL tumors is greater by almost 10 years in women compared to men [37]. Finally, most women of childbearing age still exhibit small intrasellar tumors, even after a long duration of symptoms [19], and studies of the natural history of such microadenomas have shown little or no evolution [5]. It is worth mentioning here that the natural history of microprolactinomas is unknown in men, probably because of their rare discovery and the fear of a more aggressive course of disease leading to early treatment. However, they may also remain small, as a long history of impotence is still consistent with the finding of a small PRL-secreting microadenoma [19].

Regarding prolactin concentrations at diagnosis, significantly higher levels are constantly observed in men as compared to women (Table 11.2). However, while Colao and colleagues found higher male PRL concentrations for both micro- and macroadenomas [20], we could only observe such a sex difference in the case of macroprolactinomas ([19]; Fig. 11.2b). Interestingly, higher prolactin levels in male macroprolactinomas are not only related to a larger tumor size but also to a higher secretion rate per tumoral size unit, at least for tumor diameters between 10 and 25 mm, as illustrated in Fig. 11.3. This sex difference in tumoral PRL secretion rate might partly be due to the presence of cystic and/or hemorrhagic changes which seem to occur more frequently in female macroprolactinomas [38–40].

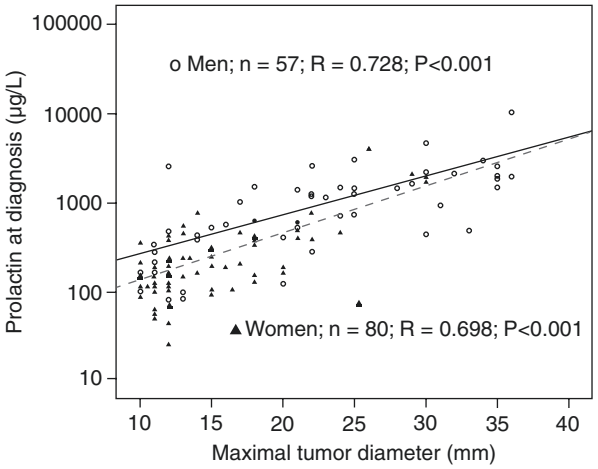

Fig. 11.3 Correlations between maximal tumor diameter (in mm) and prolactin concentration (in µg/L on a log scale) in men (open circles and solid regression line; $n = 57$) and in women (close triangles and dashed regression line; $n = 80$) with a prolactinoma size between 10 and 40 mm. Data are calculated from a cohort of 137 patients diagnosed and followed for a macroprolactinoma in our institution during a 20-year period (July 1997–June 2017; *unpublished data*) and with both parameters available at diagnosis

Why Are Male Prolactinomas Different from Female Prolactinomas?

The reasons for a more aggressive course of prolactinomas in men remain poorly understood. Some clinical data indeed suggest that estrogens could halt PRL tumor progression. A bimodal age distribution of giant prolactinomas is observed in women, with a very low occurrence in childbearing-aged women [37, 41–43]. The proliferative activity of PRL tumors is higher in men and in women older than 40 compared to young women [19, 23]. Delgrange and colleagues also reported recently that a lower expression of estrogen receptor alpha (ERα) is more frequently observed in male prolactinomas and is associated with higher proliferation rates, resistance to dopamine agonists, and progression despite multimodal therapy [26]. They made the hypothesis that, as observed in breast cancer, the loss of ERα might be a sign of tumor dedifferentiation and poorer prognosis.

These observations may seem counterintuitive, as estrogens are known to promote pituitary tumorigenesis and angiogenesis, via induction of pituitary tumor transforming gene (PTTG), in turn leading to increased production in the pituitary gland of basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) [44]. In fact, estrogens appear to differentially influence PRL cell proliferation and PRL secretion [45]. Thus, although there is some evidence of estrogen stimulation of PRL secretion by prolactinoma cells in pregnant women [46] and men [47], no association has been reported between estrogen exposure and development or growth of prolactinoma in women treated with oral contraceptives [48] or in male-to-female transsexuals [49].

The mechanisms by which a higher expression of ERα in female prolactinomas is associated with an inhibition of tumor growth are still unknown. They might involve estrogen-mediated activation of dopaminergic pathways and subsequent dopamine-induced antiproliferative and pro-apoptotic effects [50]. Transforming growth factor-beta1 (TGF-b1) could be another potential player, as it is a known inhibitor of lactotroph proliferation and it is positively regulated by dopamine and negatively by estradiol. Pituitary expression of active TGF-b1 and of putative TGF-b1 activators is higher in normal male mice compared to female mice, and it is postulated that this higher expression TGF-b1 system in male animals could protect them against the development of prolactin tumors [51, 52]. This protection could be lost by down-regulation of the TGF-b1 system in the human male prolactinomas. However, such a mechanism is purely speculative at this time and remains yet to be demonstrated.

Clinical Presentation

Striking differences also exist in the clinical presentation of prolactinoma between sexes. While most women with a prolactinoma come to medical attention during their reproductive period because of oligomenorrhea or amenorrhea, infertility, and/

or galactorrhea [4, 5, 53, 54], more than half of men present initially with symptoms of mass effects [12, 16, 19–21]. Reviewing 16 studies involving 444 males, Gillam et al. reported the presence of visual field defects in 37%, hypopituitarism in 34%, and headaches in 29% [4]. These figures are much lower in women, as illustrated in Table 11.2 for the occurrence of visual field defects.

Although present in the majority of men with a prolactinoma [19, 55–57], symptoms of male hypogonadism, such as loss of libido, erectile dysfunction, gynecomastia, altered sperm features, and infertility or osteopenia, are often unrecognized for a long period of time, or they are attributed to other causes such as age, drugs, or depression. Thus, endocrine symptoms are less frequently the reason to seek medical advice for men with a prolactinoma [5]. On the other hand, galactorrhea is rare in men, as it requires both a fall in testosterone levels and an estrogen excess which is not the rule in case of hyperprolactinemia [4, 5].

Interestingly, the male reproductive axis also seems to be more resistant to chronic prolactin excess than the female axis. Indeed, while in women menstrual dysfunction or galactorrhea is commonly seen with minimal PRL elevations [5], normal testosterone levels may still be observed in many patients with mild hyperprolactinemia [58] and in 20–30% of patients with a micro- or a macroprolactinoma [13, 19, 59, 60]. Likewise, semen quality is significantly altered in only half of men with prolactinoma, and nearly all of them retain some sperm production capacity [56, 57]. The reasons for this differential sensitivity of the male reproductive axis are not fully elucidated. These patients with an apparently preserved gonadal function have usually smaller and less aggressive tumors causing no permanent damage to the gonadotrophs. Moreover, when these men are treated effectively with a dopamine agonist, testosterone levels increase further to higher concentrations within the normal range, and this is often associated with an improvement of sexual function [59, 60], suggesting that baseline testosterone concentrations were likely lower than the optimal values for those individuals.

Other symptoms and signs may be related to hypopituitarism (apart from hypogonadism), which is exceptional in the case of microadenomas, but present in about 30–50% of men with a macroprolactinoma [13, 20, 54, 61, 62]. Central hypothyroidism (present in 18–41%) seems to be more prevalent than ACTH deficiency (12–33%), all deficits are more prevalent among patients with larger adenomas, and recovery of normal hormonal axes occurs in only half of the cases [61]. The exact prevalence of growth hormone (GH) deficiency is not known but likely higher than those of TSH and ACTH deficits. Limited data indicate that GH secretion may recover following successful medical treatment of hyperprolactinemia in most but not all subjects with a macroprolactinoma [63]. In any case, all men with a macroprolactinoma should be carefully evaluated for possible deficits in pituitary function.

Quite intriguingly, two recent retrospective studies have demonstrated an increased risk for cardiovascular disease (CVD) in men but not in women with hyperprolactinemia. The first study included individuals with hyperprolactinemia irrespective of its primary etiology, and the authors reported a higher risk for cardiovascular and all-cause mortality in men as compared to women [64]. In the second

population-based cohort study of more than 12,000 subjects, incident CVD was increased only in men with prolactinoma, with an incidence risk ratio of 1.72 over a 6-year period [65]. Long-standing hyperprolactinemia and its metabolic consequences, such as concomitant insulin resistance and hypercoagulable state, as well as hypopituitarism and its management, were proposed as the underlying mechanisms, without however a clear explanation for sex specificity, except for the known differences in tumor size and invasiveness between men and women. Further studies are clearly needed to confirm and better characterize these findings.

Diagnosis

The diagnosis of prolactinoma in men should rely on the same criteria as in women [4, 5, 53], namely, (i) the repeated observation of elevated prolactin concentrations, (ii) exclusion of other causes that might account entirely for hyperprolactinemia (such as macroprolactin), (iii) unequivocal finding of a pituitary adenoma, and (iv) exclusion of a mixed GH-PRL adenoma with acromegaly. Noteworthily, prolactin concentrations (2–15 μg/L) are lower in healthy men than in normal women, and this is also true for most causes of hyperprolactinemia other than prolactinomas. As an example, the maximal level of hyperprolactinemia related to a pituitary stalk effect caused by a non-lactotrope tumor of the sellar region is lower in men than in women [66].

In men as in women, prolactin levels correlate well with prolactinoma size, especially in the case of macroprolactinomas (Fig. 11.3). Most microprolactinomas have levels between 50 and 150 μg/L [4, 5]. Virtually all macroprolactinomas have levels above 100 μg/l, and patients with large adenomas have PRL levels well above 250 μg/l. Nevertheless, it is always wise to rule out one of the many other disorders which may be responsible for hyperprolactinemia, before making the diagnosis of prolactinoma, and this in men as in women [5].

Regarding magnetic resonance imaging (MRI) findings, some gender differences have been reported between male and female prolactinomas [67]. In addition to being smaller and less frequently invasive, most prolactinomas in women appear to be hyperintense on T2-weighted sequences, while the presentation in men is more heterogeneous. Most male PRL adenomas are iso-intense on T2 images, and 15% of them have a peculiar low T2 signal intensity which might correspond to the presence of spherical amyloid deposits.

As reviewed elsewhere [33], the diagnosis of a giant prolactinoma may sometimes be very challenging and delayed in some men, as the mode of presentation may be atypical for a pituitary tumor while more specific symptoms are neglected. In addition, in such cases, patients with extremely high PRL levels may appear to have only moderate PRL elevation, due to the so-called hook effect [5, 33], and the prolactinoma may be misclassified as a clinically nonfunctioning macroadenoma.

Treatment

A similar therapeutic strategy should be used for male and female prolactinomas. Medical management with dopamine agonists (DA) is considered as the first-line therapy as it is highly effective and safe in men as in women, including those men bearing large or even giant macroprolactinomas [5, 53]. Transsphenoidal surgery should be reserved for patients who are either intolerant or resistant to DAs [68], and most of these operated males will still require a DA to control prolactin hypersecretion [54]. Radiation therapy or radiosurgery should rarely be employed and only to control the growth of aggressive tumors which do not respond to conventional treatment [69].

Dopamine Agonists

Few retrospective studies have carefully compared the hormonal and tumoral responses to dopamine agonists between men and women with a prolactinoma [16, 19–21], and discordant results have been reported (Table 11.3). While Delgrange et al. reported a significantly better response to bromocriptine in women than in men with resistance rates of 5% and 30%, respectively [19], other authors did not find any sex difference in the sensitivity to cabergoline, when tumors were matched for size [16, 20, 21]. Likewise, Verhelst et al. showed that male patients were less likely to achieve normal PRL levels on cabergoline treatment than females [70]. However, when considering the fact that more males had a macroprolactinoma, gender had no longer an independent influence on the hormonal control rate. Although no direct comparison was made with a female population, a very good efficacy of medical treatment was also reported for male prolactinomas by Pinzone et al. [12] and by Iglesias et al. [13], with little difference in the hormonal response rates (65–80%) between micro- and macroprolactinomas.

These results must be challenged against the observations that male gender is usually prevalent among patients exhibiting full resistance to cabergoline [19, 26, 27, 71], that most prolactin-secreting carcinomas arise in men [5], that the dose of cabergoline required to control hyperprolactinemia is often higher in men than in women with a macroprolactinoma [16, 20, 26, 70], and that in at least one study, male gender was associated with resistance to cabergoline, independent of tumor size or invasiveness [27]. Altogether, it seems fair to say that based on current knowledge, prolactinomas are more resistant to medical treatment in men than in women but that this difference is mostly, but perhaps not entirely, due to the greater proportion of large and invasive tumors in the male gender.

Importantly, restoring normal prolactin concentrations with a dopamine agonist allows the restoration of normal gonadal function (including normal semen quality) in most men with prolactinoma [56, 57, 60] and preserves other pituitary functions much better than do surgery or radiotherapy [13, 54]. Symptomatic hypogonadism

Table 11.3 Comparison of the response to dopamine agonists between men and women with prolactinoma

	Delgrange et al. [19]		Colao et al. [20]		Papegaey et al. [21][a]		Khare et al. [16][a]	
	Males	Females	Males	Females	Males	Females	Males	Females
Reference	($n = 45$)	($n = 51$)	($n = 74$)	($n = 130$)	($n = 135$)	($n = 125$)	($n = 44$)	($n = 56$)
Micro-/macroadenomas	5/40	36/15	16/58	81/49	0/135	0/125	0/44	0/56
Type of DA	BRC	BRC	CAB	CAB	CAB	CAB	CAB	CAB
Median dose of DA (mg/week)	NA	NA	1.0 (m)	1.0 (m)	NA	NA	1.5	1.0
			1.5 (M)	1.0 (M)				
Nb of patients with PRL normalization (%)	26/37 (70%)	35/37** (95%)	51/74 (69%)	91/130 (70%)	73/96[b] (76%)	62/83[b] (75%)	22/34 (65%)	39/54 (72%)
Maximal tumor decrease (%; mean ± SD)	NA	NA	38±29 (m)	44±31 (m)	NA	NA	51±22	42±24
			52±23 (M)	45±25 (M)				

m microadenomas, *M* macroadenomas, *NA* information not available

[a]These studies included only macroprolactinomas

[b]These data represent the numbers of patients normalizing prolactin with a dose of cabergoline ≤2.0 mg/week

may however persist in a significant subset of these patients, even when PRL levels are normalized [5, 12, 14], and testosterone supplementation is therefore often required. This testosterone treatment may sometimes be associated with a secondary elevation in PRL levels and with resistance to dopamine agonists. In such cases, combination of a dopamine agonist and an aromatase inhibitor may be helpful [47]. Medical treatment also quickly alleviates acute symptoms due to compression of neighboring structures by very large and invasive prolactinomas in men [5, 33]. Thus, dopamine agonists remain the first therapeutic option also in patients with large or giant prolactinomas, resulting in marked and rapid reductions of prolactin concentrations and tumor size in 80% of cases. Interestingly enough, the proportion of men is similar (around 75%) between good responders and non-responders [33].

Another final gender difference regarding medical treatment concerns the rate of remission observed after withdrawal of dopamine agonists. Based on the latest Endocrine Society guidelines [53], therapy with dopamine agonists might be discontinued in prolactinoma patients who have been treated for at least 2 years, who have normal prolactin concentrations with a low dose of the dopamine agonist, and who have demonstrated a clear reduction of tumor size on treatment (ideally tumor disappearance on MRI). Using such criteria to support the decision of drug withdrawal, Colao et al. reported that the recurrence rate was markedly higher in men than in women (63% vs 32%, respectively) [72]. This finding was however not confirmed in other studies, which usually identified size of the tumor remnant and PRL nadir as the two main factors predicting long-term remission [73, 74]. Very recently, Texeira and colleagues [75] observed that DA withdrawal was in fact more frequently attempted in women (45/115, 39%) than in men with prolactinoma (5/27, 19%) but that once the conditions for withdrawal were met, the recurrence rate was similar between sexes.

Surgery

Although not the primary treatment, transsphenoidal microsurgery may still be required for a number of men with prolactinomas, who are intolerant or resistant to any available dopamine agonist or who elect to undergo surgical excision of their adenoma [4, 5, 53]. Several studies including mixed cohorts of male and female patients did not demonstrate any influence of gender on the surgical outcome [76, 77]. Preoperative PRL level, tumor size, and extension are usually the main predictors of postoperative remission. Raverot et al. reported that persistently elevated prolactin levels after surgery were associated with male sex by univariate analysis, but not by multivariate analysis. Only invasion and pathological classification were independently associated with negative surgical outcome [78].

In specialized centers, the overall efficacy of pituitary surgery is reasonably good in men with prolactinoma (around 60%). Postoperative initial remission is clearly better for microprolactinomas (80–90%) than for macroprolactinomas (40–50%) [68, 76–80], and the remission rate is further dramatically reduced when the tumor is invasive, as it is often the case in males [24]. Moreover, relapse of hyperprolac-

tinemia is frequent, occurring in 20% of the initially cured patient's recurrences [5, 68]. Thus, in most cases, adjunctive medical treatment will still be required to control persistent postoperative hyperprolactinemia.

The treatment of aggressive and malignant prolactin-secreting tumors, which are fortunately rare but more prevalent in men than in women, will be discussed in a separate chapter.

Conclusions

The prevalence of clinically significant prolactinomas is clearly lower in men than in women. However, male prolactin-secreting pituitary tumors have several distinct features that should raise medical interest. They are larger, more frequently invasive, and more often aggressive than in women, and these characteristics are largely due to sex differences in tumor behavior. Significantly higher prolactin concentrations are observed in men as compared to women, especially in the case of macroprolactinoma. Striking sex differences also exist in the clinical presentation of prolactinoma. Most women will present with oligomenorrhea, infertility, and/or galactorrhea, while more than half of men initially complain from symptoms of mass effects. Male hypogonadism is often present but neglected, and the male reproductive axis is also less sensitive to hyperprolactinemia than the female one.

The diagnosis of prolactinoma in men should rely on the same criteria as in women, and prolactin levels correlate well with prolactinoma size, especially in the case of macroprolactinoma, Likewise, a similar therapeutic strategy should be used for male and female prolactinomas. Medical management with dopamine agonists (DA) is highly effective and should always be considered as the first-line therapy, also in men bearing very large and compressive tumors. Transsphenoidal surgery should be reserved for patients who are either intolerant or resistant to dopamine agonists or who elect to undergo surgery. However, most male patients will still require a DA to control prolactin hypersecretion after surgery for a macroprolactinoma.

The reasons for a more aggressive course of prolactinomas in men remain poorly understood but might be related to differential and gender-related effects of estrogens on tumor growth and prolactin secretion. In any case, male prolactinomas offer a unique opportunity to further elucidate some mechanisms responsible for invasive and aggressive behavior of pituitary tumors.

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Chapter 12
Plurihormonal Adenomas

Artak Labadzhyan and Shlomo Melmed

Introduction

Plurihormonal or mixed anterior pituitary adenomas are derived from a single (monomorphous) or mixed cell (polymorphous) lineage and are characterized by expression of two or more pituitary hormones. These adenomas comprise approximately 10–30% of resected adenomas and most commonly immunostain positively for growth hormone (GH) and prolactin (PRL). Expression of other anterior pituitary hormones, including adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH), may also occur.

Since some pituitary tumors may be silent, clinical signs, symptoms, or elevated hormone levels can be absent. Management of plurihormonal adenomas is guided by clinical presentation, the degree and expression of pituitary hormones, and local mass effects.

Classification

The 2017 World Health Organization classification of pituitary tumors recognizes multiple multihormonal adenoma subtypes [1] (Table 12.1). Up to 30 different possible combinations of pituitary hormone and subunit immunostaining have been reported, but GH and PRL combinations are most common [2]. Such adenomas are classified as mammosomatotroph (MSA), mixed somatotroph and lactotroph (MSLA), or acidophilic stem cell (ASC) depending on cellular expression and

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Table 12.1 Classification of multihormonal adenomas [2, 28, 40, 51]

Classification	Immunohistochemistry	Cell type
Mammosomatotroph	GH and PRL	Monomorphous
Mixed somatotroph and lactotroph	GH and PRL	Polymorphous
Acidophilic stem cell adenomas	PRL and GH	Polymorphous
Plurihormonal Pit-1-positive tumors	TSH, GH, PRL	Monomorphous
Plurihormonal silent adenomas	TSH, GH, PRL, ACTH	Varies

ACTH adrenocorticotropic hormone, *GH* growth hormone, *PRL* prolactin, *TSH* thyroid-stimulating hormone

predominance of GH versus PRL. In MSA, GH and PRL are co-expressed in the same cell, but in MSLA, these hormones are expressed individually in different cells [1].

ASC adenomas are rare, comprising immature cells that predominantly express PRL and scattered GH-expressing cells. Adenomas that express GH, PRL, TSH, and the POU1F1 transcription factor pituitary-specific positive transcription factor 1 (Pit-1) are classified as plurihormonal Pit-1-positive tumors (PP1T) [1]. Plurihormonal silent adenomas (PSA) often weakly express PRL or ACTH. PSA represent the nonfunctional equivalents of PP1T, ASC, MSA, MSLA, or silent corticotroph adenomas that express a rare combination of PRL and ACTH [3, 4].

Pathogenesis

Pituitary tumorigenesis involves a cascade of mitotic and apoptotic changes driven by mutations and factors that regulate signal transduction, tumor suppression, cytokine action, chromosomal instability, and epigenetic events [5, 6]. These factors can lead to monoclonal expansion of either progenitor cells or differentiated cells into functional hormone-secreting or silent adenomas.

GH-, PRL-, and TSH-expressing cells are derived from the Pit-1-expressing cell lineage, whereas ACTH-expressing cells are derived from a T-box transcription factor TBX19 (Tpit)-expressing lineage [7]. Shared or overlapping lineage of pituitary cell types may explain hormonal co-expression in plurihormonal adenomas. For example, bone morphogenetic protein-4 (BMP-4), a tumor necrosis factor superfamily secretory peptide expressed predominantly in somatotrophs, is also overexpressed in animal prolactinoma models [8, 9].

Other mechanisms for MSA pathogenesis include chromosomal alterations leading to changes in nuclear proteins such as high-mobility group A1 (HMGA1), which have been implicated in pathogenesis of murine MSA [10]. Normal or nontransformed plurihormonal pituitary cells may also serve as precursors for development of plurihormonal adenomas [11]. Pituitary cells co-expressing GH and PRL have been identified as cells of origin for PRL-secreting cells in the fetal pituitary [12]. Shift in adenoma type may rarely involve a gain of GH expression in a

previously prolactinoma-only adenoma, with de novo appearance of GNAS gene mutation [13]. Overexpression of stimulatory G protein alpha-subunit (Gs alpha) may also play a role in MSA pathogenesis [14].

Hypothalamic signaling likely also plays a role in plurihormonal tumorigenesis as illustrated by development of mammosomatotroph hyperplasia in animal models exposed to continued growth hormone-releasing hormone (GHRH) stimulation [15, 16]. The GHRH source can be hypothalamic or ectopic, leading to acromegaly or, in rare cases, mammosomatotroph hyperplasia [17–19]. Interestingly, ectopic GHRH is associated with a higher frequency of hyperprolactinemia than is pituitary-derived acromegaly, likely due to GHRH stimulation of lactotrophs in mixed and mammosomatotroph normal pituitary cell subsets [20].

PP1T and ASC adenomas tend to be more aggressive, but genetic or transcriptional alterations specific to this feature are not clear. PP1T have more aneuploidy, but the correlation of this finding with tumor aggressiveness is questionable [21]. Genetic mutations or alterations in p53, pituitary tumor-transforming gene (PTTG), and chromosome 11p are important for cell cycle disruptions [22–24], but traditional proliferative markers Ki-67 and p53 have been unreliable in rigorously predicting aggressiveness [25].

Programmed death ligand 1 (PD-L1), an important mediator of immunity and a target for cancer immunotherapy, has also been reported in plurihormonal adenomas. However, its significance in pathogenesis and use as a potential treatment target is not yet known [26, 27].

Mammosomatotroph Adenomas (MSA)

The true incidence of MSA is not well documented. Relative frequency of MSA in patients presenting with acromegaly can be as high as 56% based on pathologic examination with electron microscopy [28], but such technology is not commonly used. An epidemiological study of 1055 adenohypophysial tumors found an overall 2.2% incidence of MSA [29].

Mammosomatotrophs may be difficult to differentiate from somatotrophs by histology. On immunohistochemistry, MSA tissue is reactive to GH, PRL, and the transcription factors estrogen receptor (ER) alpha and Pit-1 [2, 29]. Cell surface receptors include dopamine D2 receptor (D2R) and somatostatin receptor subtypes (SSTR1-5), most notably SSTR5 [28, 30]. On electron microscopy, cells resemble densely granulated somatotrophs, with variable size and irregular-shaped secretory granules. Ultrastructural analysis often reveals localization of GH and PRL within the same granule [28, 31, 32].

Patients with MSA present with signs and symptoms primarily related to GH excess, including gigantism and acromegaly (Table 12.2). Elevated PRL levels can be mild to moderate and lead to infertility, amenorrhea, hypogonadism, galactorrhea, or breast tenderness [5]. Management of MSA is generally the same as for somatotroph adenomas. Transsphenoidal surgery is the recommended primary

Table 12.2 Clinical presentation, diagnosis, and management of plurihormonal adenomas [29, 33, 35, 39, 40, 46, 47, 59]

Classification	Relative frequency	Biochemical findings	Endocrine signs and symptoms	Management
Mammosomatotroph	2.2%	↑↑GH, IGF-I	Acromegaly	Surgery
				SRL
				GRA
				Radiation
		Mild ↑PRL	Galactorrhea	DA
			Hypogonadism/ hypopituitarism	Hormone replacement
Mixed somatotroph and lactotroph	5%	↑↑GH, IGF-I	Acromegaly	Surgery
				SRL
				GRA
				Radiation
		Mild ↑PRL	Galactorrhea	DA
			Hypogonadism/ hypopituitarism	Hormone replacement
Acidophilic stem cell adenomas	0.2–2%	↑↑PRL	Galactorrhea	Surgery
				DA
				Radiation
				Temozolomide
				Monitoring
		↑GH, IGF-I	Acromegaly	SRL/GRA
			Hypogonadism/ hypopituitarism	Hormone replacement
Plurihormonal Pit-1-positive tumors	3.2%	↑ Free T4, normal or ↑ TSH	Hyperthyroidism	Surgery
				SRL
				Radiation
				Temozolomide
				Monitoring
		↑GH, IGF-I	Acromegaly	SRL/GRA
		↑PRL	Galactorrhea	DA
			Hypogonadism/ hypopituitarism	Hormone replacement
Plurihormonal silent adenomas	Varies	Mild ↑PRL	Hypogonadism/ hypopituitarism	Surgery
		Mild ↑ACTH?		Hormone replacement
				Close monitoring
			Transformation to CD	Surgery
				Medical management of CD

ACTH adrenocorticotropic hormone, *CD* Cushing disease, *DA* dopamine agonist, *GH* growth hormone, *GRA* growth hormone antagonist, *IGF-I* insulin-like growth factor I, *PRL* prolactin, *SRL* somatostatin receptor ligand, *TSH* thyroid-stimulating hormone

therapy in most circumstances [33]. In a series of 57 acromegaly patients who underwent transsphenoidal surgery as initial therapy, those with mammosomatotroph adenomas had lower remission rates despite a moderate incidence of dural invasion [34]. Radiation therapy is reserved for patients with aggressive tumors or for residual mass that is not responsive or amenable to repeat surgery or medical therapy.

Medical therapy options include somatostatin receptor ligands (SRL), dopamine agonists (DA), and the growth hormone antagonist pegvisomant [35]. Theoretically, the presence of both GH and PRL should make MSA more responsive to combination treatment with SRL and DA, but neither serum co-elevation nor immunohistochemistry positivity of GH and PRL correlates with combination therapy responsiveness [36, 37].

Mixed Somatotroph and Lactotroph Adenomas (MSLA)

Up to 5% of pituitary adenomas immunostain positively for mixed GH and PRL cells [5]. Although most silent somatotroph adenomas exhibit mixed GH/PRL staining, this pattern is less commonly observed in functional somatotrophs [38]. Thus, in patients who present with acromegaly, a mixed GH/PRL adenoma is present in 20–25% of surgically resected samples [39]. Of note, most MSLA are macroadenomas, and 31% are invasive [40].

As in MSA, individual somatotroph and lactotroph cells in MSLA are immunoreactive to GH, PRL, ER-alpha, and Pit-1 [2, 29]. Electron microscopy reveals densely granulated somatotrophs and sparsely granulated lactotrophs. Densely granulated somatotroph cells are acidophilic with strong cytoplasmic GH reactivity that stain positive for perinuclear keratin and focal fibrous bodies [29]. Sparsely granulated lactotrophs contain scattered secretory PRL granules [41].

Biochemical and clinical presentation of functional MSLA is indistinguishable from MSA (Table 12.2). Patients typically show signs, symptoms, and sequelae of acromegaly or hyperprolactinemia, and hypopituitarism or compressive effects of the tumor may also be seen [33].

The primary approach to management of MSLA is surgical resection of the tumor. However, medical management may be the preferred initial approach for patients with acromegaly sequelae that may make surgery difficult, including severe pharyngeal thickness, sleep apnea, or high-output heart failure [33]. The results of treatment response to medical therapy are variable, and mixed tumors may be more resistant to SRL [28]. Acromegaly patients with mixed adenomas are more likely to experience discordant normal GH values with elevated IGF-I levels after surgery [42].

Observed differences in response to treatment are likely not related to cell surface receptor expression as MSLA express all SSTRs, including SSTR2 and SSTR5, which are targeted by SRL [43, 44].

Acidophilic Stem Cell (ASC) Adenomas

ASC adenomas are rare, with a reported relative frequency of 0.2% of pituitary adenomas, and comprise monomorphous expression of PRL and GH. Unlike MSA, ASC adenomas predominantly express PRL [40]. Immunohistochemistry shows strong PRL expression and weak GH immunopositivity within the same cells. Microscopy reveals secretory granules measuring 50–300 nm and containing predominantly PRL. Giant and abundant mitochondria reaching the size of the nucleus are a distinguishing feature. As observed with densely granulated somatotroph cells, fibrous bodies consisting of keratin are also present [40, 41].

The biochemical profile of ACA adenomas includes increased PRL levels that are more pronounced than the mild hyperprolactinemia observed in MSA or MSLA but lower than observed with pure prolactinomas; elevations in GH and IGF-I are milder than observed with MSA or MSLA [39, 40, 45].

Patients with ASC adenomas present with signs and symptoms related to hyperprolactinemia, including amenorrhea, hypogonadism, or galactorrhea (Table 12.2). Signs and symptoms of acromegaly may also be present but are usually mild and rarely overt [39, 40].

Although ASC adenomas are aggressive, invasive tumors with a high risk of recurrence [39, 40], the initial management approach is typically medical therapy due to the clinical presentation usually mimicking an aggressive prolactinoma.

For unresponsive, recurrent, or, rarely, malignant tumors, treatment options include repeat surgery, radiation, or temozolomide therapy [46].

Plurihormonal Pit-1-Positive Tumors (PP1T)

PP1T are aggressive adenomas previously categorized as silent adenoma subtype 3 but have been renamed due to recognition of associated hormonal hyper-functionality [1]. They have a reported incidence of 3.2% of pituitary adenomas [47], but the true incidence of PP1T may be higher, as immunopositivity for multiple hormones has been reported in 42–100% of thyrotropinomas [48–50], which, in retrospect, may be consistent with the diagnostic criteria for PP1T.

The diagnosis of PP1T relies on histological and ultrastructural findings. Immunohistochemistry shows diffuse reactivity to Pit-1, focal ER, and two or more hormones of Pit-1 lineage cells, including GH, PRL, and TSH [47, 51, 52]. Histochemical diagnosis may be difficult to differentiate from densely granulated mammosomatotrophs that rarely may also express TSH. Differentiating factors in such cases are that, in PP1T tumors, intensity of GH expression is focal or patchy, while immunoreactivity of TSH is stronger and more diffuse [53]. Characteristic findings on electron microscopy include monomorphous populations of poorly differentiated cells that are polygonal or elongated and show nuclear spheridia. The cytoplasm contains both rough and smooth surfaced endoplasmic reticulum as well as numerous small secretory granules [47, 51, 52]. As aggressiveness of these

tumors and elevated PRL levels may resemble ASC adenomas, immunohistochemistry and electron microscopy findings are important in distinguishing the diagnosis [39, 40].

Examination of 31 PP1T tumors showed that all were macroadenomas and that the most common presenting symptom was related to mass effect, including headache and vision loss. Nearly one third of patients had hyperthyroidism, followed less frequently by clinical presentation of acromegaly and hyperprolactinemia [47]. Although PRL is commonly expressed, clinically significant hyperprolactinemia is present in only 4–11% of these patients [47, 54]. Hyperprolactinemia may also occur as a result of stalk effect.

Given the aggressive nature of PP1T, close follow-up and a proactive treatment approach is required (Table 12.2). Patients with PP1T typically will undergo medical treatment after surgery, and, given the high likelihood of cavernous sinus invasion, most will have residual disease after surgery, further increasing the likelihood for repeat surgery due to progression or disease recurrence. Indeed, progression was reported in more than 50% of these patients over a 4-year follow-up period [47].

Medical management is focused on treating presenting hormone hypersecretion, as well as hypopituitarism if present. Hyperprolactinemia should be treated with a DA with uptitration [46]. For patients presenting with hyperthyroidism or acromegaly/gigantism, surgery is the recommended first treatment option [33]. If hormonal hyperfunction recurs or persists after surgery, SRL are useful in an attempt to biochemically control tumor GH or TSH hypersecretion [55]. Radiation treatment should be a consideration for resistant tumors; however, tumors may still recur and even increase in size after radiation [56]. Repeat radiation and/or chemotherapy may be necessary for especially resistant or aggressive tumors. Temozolomide therapy can be considered for aggressive PP1T.

Interestingly, PP1T were shown to have upregulation of genes that encode ARG2 and SEMA3A, which regulate T-cell proliferation and function within the tumor microenvironment. Upregulation of such genes raises the possibility of immune evasion contributing to the aggressiveness of PP1T. Given the success of immunotherapy in cancer treatment, these findings suggest this may also be a treatment option to explore for aggressive or resistant PP1T [57].

Plurihormonal Silent Adenomas (PSA)

Silent adenomas are defined as pituitary adenomas that do not secrete biologically active hormones nor cause sequelae related to hypersecretion (Table 12.2). PP1T, ASC, MSA, and MSLA may all be silent.

Diagnosis of a PSA is made retrospectively after immunohistochemistry of surgically resected tumors reveals multihormone immunopositivity without biochemical hormone elevation in patients presenting with tumor mass effects (headache and vision changes) or a pituitary tumor discovered incidentally in an otherwise asymptomatic patient.

Most silent somatotroph adenomas are immunopositive for GH and PRL and at proportions that are greater than co-staining observed in functional somatotroph adenomas [38]. Although clinical significance of multihormonal staining in silent adenomas is not clear, multihormonal staining in silent somatotrophs may be associated with smaller tumor size, less invasion, and less recurrence [58]. Silent tumors of other subtypes, such as PP1T, are similarly aggressive as their functional counterparts [47].

Plurihormonal silent corticotroph adenomas (PSCA) are rare, with an incidence of 3–4% of all pituitary adenomas. PSCA exhibit immunoreactivity for ACTH with one or more combinations of Tpit, FSH, LH, prolactin, and GH [59, 60]. Hyperprolactinemia is observed in about 45% of silent corticotroph adenomas (SCA), most likely representing stalk effect given that a much smaller proportion of SCA are immunoreactive for PRL. Patients may present with headache, vision loss, hypogonadism, or acute apoplexy; SCA are less likely to be incidentalomas compared to ACTH-negative adenomas [59, 60].

SCA are more aggressive than functional ACTH-secreting adenomas, with up to 40% of patients developing cavernous sinus invasion, tumor recurrence, and hypopituitarism. Risk for transformation to Cushing disease or, rarely, carcinoma also warrants close monitoring [61].

Plurihormonality and Pituitary Carcinoma

Pituitary carcinoma is extremely rare and is rigorously defined by the presence of extracranial metastasis. Gain of plurihormonal function has been reported in adenomas that transformed to carcinomas. For example, gain of TSH expression along with PRL co-staining may occur [62, 63]. Although rare, these observations suggest that silent tumors that later become functional should be evaluated more closely for possible subsequent transformation to malignancy.

Syndromic/Special Populations

Multiple Endocrine Neoplasia Type 1

Pituitary adenomas occur in approximately 40% of multiple endocrine neoplasia type 1 (MEN1) patients [64, 65]. Prolactinomas are most frequently encountered, and up to 10% are plurihormonal. Most commonly, these tumors co-secrete PRL and GH [64], and other combinations with ACTH and LH may occur [66]. Aggressive plurihormonal subtypes, such as PP1T, have also been reported in association with MEN1 [47].

Interestingly, compared with non-MEN1 sporadic pituitary tumors, plurihormonal GH adenomas and plurihormonal PRL adenomas are more frequently encountered among MEN1-associated pituitary tumors. Plurihormonal GH adenomas most commonly express GH-PRL-ACTH or GH-PRL-LH-FSH, and plurihormonal PRL adenomas most commonly express PRL-ACTH [67].

McCune–Albright Syndrome

McCune–Albright syndrome is a rare, sporadic condition characterized by fibrous dysplasia, cafe au lait macules, and functioning endocrinopathies. Relative to other endocrinopathies, pituitary adenomas in this syndrome are rare but are often plurihormonal. These are usually MSAs or mixed GH/PRL adenomas, leading to elevated GH and PRL levels [68, 69].

Carney Complex

Carney complex is a rare familial disorder characterized by abnormal cutaneous spots, cardiac and cutaneous myxoma, schwannomas of the peripheral nerves, Sertoli cell tumors, and endocrine abnormalities, including pituitary adenomas. In most cases, Carney complex is caused by a mutation in the PRKAR1A gene, which codes for the regulatory subunit of protein kinase A [70]. The majority of these patients present with asymptomatic elevation of GH, IGF-I, and PRL and tumors are usually not detectable on MRI at diagnosis. However, patients are at risk for developing pituitary adenomas, with a 10–12% prevalence of acromegaly. When present, tumors typically exhibit mammosomatotroph hyperplasia or adenoma [70, 71].

Summary

Plurihormonal adenomas express various combinations of anterior pituitary hormones and are most commonly derived from the Pit-1 cell lineage. GH and PRL expression is the most common multihormonal pattern, and adenomas may be clinically silent or may lead to clinical presentation of acromegaly and hyperprolactinemia. PP1T and ASC adenomas are aggressive subtypes that require close attention given the propensity for invasion, recurrence, or persistent disease. Management includes surgery, SRL, or DA to achieve biochemical control, and radiation or chemotherapeutic agents may be required for resistant tumors.

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Chapter 13
Aggressive Prolactin-Secreting Pituitary Adenomas and Carcinomas

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Introduction

Pituitary adenomas are common and account for approximately 10–15% of all primary brain tumors [1]. Prolactinomas (PRL-omas) make up ~50% of all pituitary adenomas, occur in both genders, and cause galactorrhea, amenorrhea, and subfertility in females and loss of libido and sexual dysfunction in males [2]. Although infrequent molecular abnormalities have been demonstrated across the transition from benign to PRL-omas to PRL-secreting carcinoma, no consistent collection of molecular events has been characterized that might predict this occurrence. Nonetheless it is generally acknowledged that an accumulation of aberrant intrinsic and extrinsic proliferative and secretory signals most likely caused by environmental epigenetic dysregulation, in some cases compounded by underlying familial genetic mutations predisposing to pituitary tumors, leads to the cellular changes transiting a benign PRL-secreting adenoma to an aggressive tumor and ultimately to a carcinoma (Fig. 13.1).

PRL secretion in normal lactotrophs is under tonic inhibitory control by hypothalamic-derived dopamine, which binds the G-protein-coupled dopamine receptor D2 (D_2R). This ligand-receptor complex then associates with Giα to inhibit adenylyl cyclase (AC) thereby blocking cAMP formation to inhibit PRL secretion [3]. Most PRL-omas retain the dopaminergic inhibitory response, and in the vast

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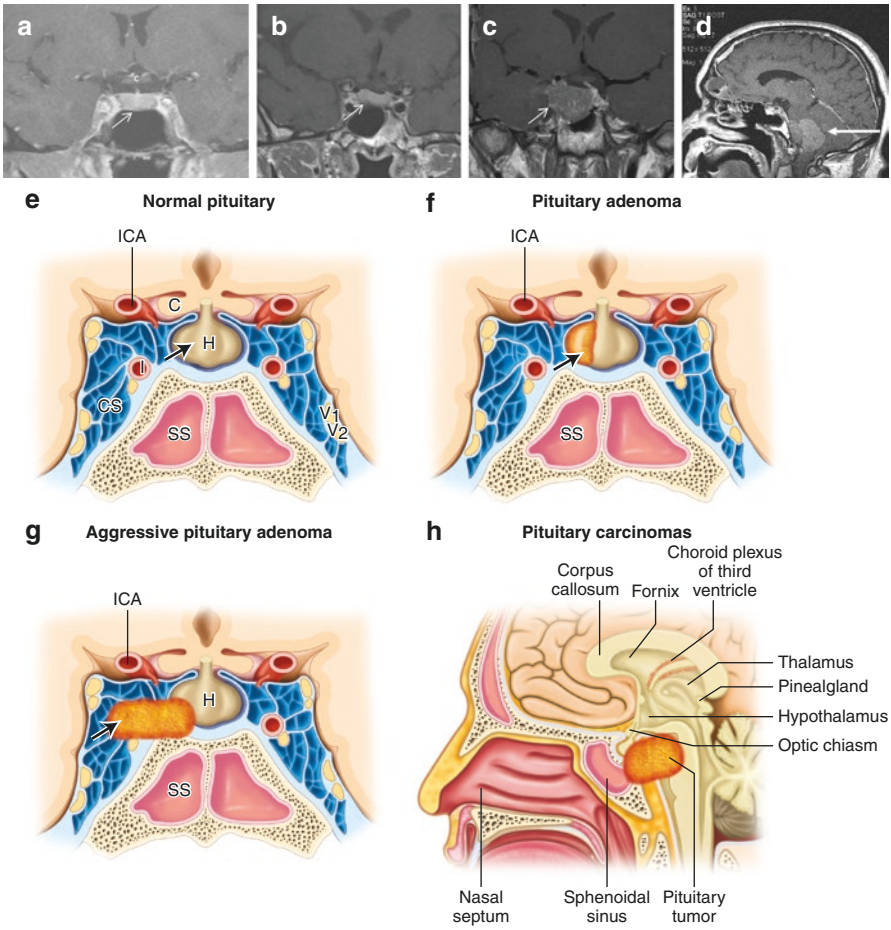

Fig. 13.1 A current model of pituitary tumor pathogenesis from normal pituitary lactotroph cell to adenoma to "aggressive" locally invasive recurrent tumor to carcinoma invokes accumulation of aberrant cellular proliferative and secretory signals caused by environmentally induced epigenetic changes in some cases on a backdrop of inherited genetic mutations. Top panel (from left to right): coronal images of pituitary region showing normal gland (**a**), pituitary microadenoma (**b**), locally invasive pituitary macroadenoma growing despite maximal standard therapy (aggressive tumor, **c**), and pituitary carcinoma (**d**). Lower panel: cartoon depicting schematically the changes seen on MRI series (**e**–**h**). *C* optic chiasm, *CS* cavernous sinus, *ICA* internal carotid artery, *H* hypophysis, *SS* sphenoid sinus (**d** modified from Heaney [13]; **e**–**g** modified from Tubbs et al. [89]; **h** modified from Heaney and Melmed [90])

majority of PRL-omas (~90%), serum PRL level and tumor size are effectively controlled by dopamine agonists, such as bromocriptine and cabergoline [2].

Identification of Aggressive PRL-omas

An all-encompassing broadly accepted definition of an aggressive PRL-oma remains elusive. Ultimately, this descriptive and clinically very useful term is made up of several components. From a histological standpoint, the 2004 WHO classification of a so-called "atypical" pituitary adenoma based on histological features and proliferative markers such as the Ki-67 [4] was vague and has been eliminated in the 2017 edition [5]. The 2017 WHO classification emphasizes tumor proliferation and invasion; however tumor imaging assessment for either tumor growth or stability or clinical response to therapy (lack thereof, or reduced response/resistance) is not reflected for aggressive PRL-oma in the new WHO criteria [5].

Radiologically (usually by MRI) PRL-omas are conventionally classified as microadenomas (maximal diameter <10 mm), macroadenomas (≥10 mm), or giant adenomas (≥40 mm) [6]. Microadenomas are most common in women of childbearing age and are usually associated with PRL levels between 100 and 200 μg/dL. Macroadenomas account for ~20% of PRL-omas and are more commonly observed in men and postmenopausal women and usually associated with more elevated serum PRL levels >200 μg/dL. In the 1–4% of PRL-omas that are ≥40 mm (giant adenomas), PRL levels are typically >1000 μg/dL [7]. Patients harboring these large PRL-omas may experience mass effect symptoms, such as headache, visual disturbances, cranial nerve palsies, hypopituitarism, and obstructive hydrocephalus due to extrasellar tumor mass extension [7]. Importantly, however tumor size at presentation is not of itself an indicator of disease aggressiveness as some giant PRL-omas can exhibit marked responsiveness to dopamine agonist therapy [8], whereas microadenomas can grow quite quickly and invade adjacent sellar structures [9].

Similarly, although proliferation markers such as Ki-67 or nuclear immunoreactivity for the tumor suppressor p53 may correlate with potential for pituitary tumor growth in some cases [10], the use of these biomarkers prospectively to classify PRL-omas aggressiveness is not validated. Whereas it is true that (i) most pituitary adenomas exhibit a Ki-67 LI of 1–2%, (ii) a tumor with Ki-67 LI >3% is unusual [11, 12], and (iii) some retrospective studies have reported higher Ki-67 LI in pituitary carcinomas (Mean±SD, 11.9% ± 3.4%) compared to adenomas (Mean±SD, 1.4% ± 0.15%) [13], no prospective studies have defined a specific Ki-67 LI cutoff that reliably predicts subsequent aggressive tumor behavior [14]. Similarly, although immunohistochemical (IHC) accumulation of the p53 nuclear phosphoprotein (indicating a mutated nonfunctional p53) is an unfavorable prognostic marker in

pituitary tumors [10], a reliable method for p53 IHC quantification in clinical practice has not been widely adopted [14].

As noted in the introduction, the majority of PRL-omas retain responsivity to D2 agonist therapy, but ~10% to 15% of PRL-omas exhibit varying degrees of partial or complete biochemical and/or radiological resistance to dopamine agonists, defined as failure to normalize serum PRL level and failure to decrease tumor size by ≥50%. It must be emphasized that this group is distinct from the patients who are responsive to high dopamine agonist doses but side effects such as headache, nausea, postural hypotension, and fatigue may limit their longer-term effective use [5]. The mechanisms of D2 agonist resistance are not fully understood. The human DRD2 gene is located on chromosome 11 (11q23.2), comprises eight exons [20], and gives rise to two major transcripts, a long isoform (D_2L, NM_000795) and a short isoform (D_2S, NM_016574). Several studies have demonstrated altered post-transcriptional splicing of the dopamine receptor D2 (DRD2) genes [15–18] such as decreased expression of D_2S with reduced D_2S/D_2L mRNA ratio [15, 21] or reduced density of dopaminergic binding sites [19] in D2 agonist-resistant PRL-omas. Other genotypic analyses have revealed an association between the NcoI C/T polymorphism of DRD2 and cabergoline resistance in PRL-oma patients [22]. A further factor implicated in D2 agonist resistance involves transforming growth factor-beta1 (TGFβ1), which is upregulated by dopamine and serves to mediate dopamine's inhibition of normal lactotroph proliferation and PRL secretion [17, 23]. Reduced TGFβ1 expression and Smad2/3 signaling has been reported in bromocriptine-resistant PRL-omas, suggesting that loss of the TGFβ1 inhibitory effect may contribute to D2 agonist resistance in PRL-omas [24].

The D2 agonist-resistant PRL-oma can manifest in several ways. Firstly, tumors may be unresponsive to therapy (~3 mg cabergoline/week or 15 mg bromocriptine daily) from onset with a fall in serum PRL that is typically <10% of the baseline PRL value. More commonly, there is an initial response with sometimes dramatic fall in serum PRL, perhaps from 10, 000 to 500 μg/dL, but thereafter despite increasing drug dosing, serum PRL remains largely unresponsive. The third scenario is a tumor that has been responsive for several months or years, but then serum PRL progressively elevates, and tumor growth escapes from control despite compliance with escalating dopamine agonist therapy. The last two scenarios can occasionally be seen in male patients in whom androgen replacement has been initiated during dopamine agonist treatment, and restoration of dopamine agonist responsiveness can sometimes be attained by concomitant administration of an aromatase inhibitor to block a proposed estrogen mitogenic tumor action [8]. Several studies have demonstrated responses with cabergoline in bromocriptine-resistant patients, and change in therapy should be considered [25, 26]. In any of these situations of D2 agonist resistance that cannot be resolved medically, surgical debulking followed by radiation therapy is typically offered in addition to medical treatment with the ultimate goal of achieving hormonal and tumor growth control [11].

However, in spite of these multiple treatment steps, a small subset of PRL-omas progress (or recur if full resolution was attained at some point), encroaching on surrounding sellar structures including the optic chiasm, carotid artery, and sphenoid and

Table 13.1 Potential predictors of risk of aggressive PRL-omas according to disease pathogenic features and treatment responses

Epidemiological features	Relevance
Gender (male)	+
Age (young)	+
Inherited genetic aberration	++
Pathological characteristics	
Proliferative index (Ki-67 LI)	+/++
Radiological factors	
Tumor size	+
Location/invasiveness	++
Progression despite of standard care therapy	+++
Medical treatment response	
Sustained response	–
Initial response followed by escape	+
No response	++
Surgical resection response	
Remission after complete resection	–
Recurrence after complete resection	++
Regrowth after partial resection	+
Radiation neurosurgery response	
Tumor growth control	–
Recurrence	++
Chemotherapy response	
Tumor growth control	–
Recurrence locally	+++
Craniospinal or systemic metastasis	+++

+ weak, ++ moderate, +++ strong predictive indicator

invading the cavernous sinus [14]. These are the cases which define themselves by their behavior and lack of response to therapy as "aggressive" tumors. In rare instances, these aggressive PRL-omas progress further to carcinoma, with development of either local craniospinal metastases or systemic metastases to the lung, liver, lymph nodes, and bone, but this occurs in only 0.2% of all pituitary tumors [27–29].

In summary, information on radiologic assessment of tumor growth in combination with treatment responses or lack thereof along with histological features (if available) may offer the best current available method to assess the potential for PRL-oma aggressiveness (Table 13.1).

Risk Factors for Aggressive PRL-omas and Carcinomas

Although PRL-omas overall are more frequently observed in females with a 10:1 female incidence before aged 50 years, aggressive PRL-omas are encountered more often in males with a 1.5-fold higher frequency before 50 years and 3.7-fold higher

thereafter [11]. The reason for this male preponderance for aggressive PRL-omas is unclear; a previously proposed role for tumor-derived estrogen-promoting PRL-oma growth was not firmly supported by more recent data showing reduced PRL-oma ER expression in male patients [30].

Most PRL-omas occur sporadically [31], but some familial pituitary adenoma syndromes exist including those where the cell cycle regulators menin-1 (MEN-1) or cyclin-dependent kinase inhibitor 1B (CDKN1B, also known as $p27^{Kip1}$) are dysfunctional. Additionally, mutations in the aryl hydrocarbon receptor-interacting protein (AIP) and growth factor signaling pathway regulators, such as the cAMP pathway activator GNAS1 and protein kinase A regulatory subunit alpha PRKAR1A, can also occur [32]. Although it has not been studied in a rigorous prospective fashion, loss of heterozygosity on chromosome 11q13, the loci where MEN-1 resides, has been observed in invasive pituitary adenomas, and MEN-1-associated PRL-omas are reported in some (but not all) small case series to be more aggressive compared with sporadic tumors [33, 34].

Management of Aggressive PRL-omas and Carcinomas

Surgical Resection

As noted previously, dopamine agonists are first-line therapy for PRL-omas unless "emergent" mass effect, marked hemorrhaging, or apoplexy requiring urgent decompression is present. They offer excellent responses in the majority of cases and lead to normalization of serum PRL and at least 50% tumor shrinkage in more than 85% of patients. However, a minority of tumors exhibit resistance to dopamine agonist therapy as described previously. In these situations where tumor growth occurs despite adequate dopamine agonist therapy (defined somewhat arbitrarily as cabergoline doses >3 mg/week, bromocriptine doses >15 mg/day), surgical debulking is typically the next option to try and achieve tumor growth control, symptom relief, and reduction in serum PRL. Recent advances in transsphenoidal surgery using endoscopy have facilitated direct tumor visualization and enabled more extensive surgical resection in tumors that extend significantly into the suprasellar and cavernous sinus regions. Although near-total surgical resection can be achieved in some cases by expert surgeons, aggressive PRL-omas tend to be extensive and infiltrate structures adjacent to the sella, such as the cavernous sinus, and encase the internal carotid artery, making complete resection extremely challenging if not unattainable [35]. Nonetheless, even though postoperative PRL normalization is not readily achieved in these tumors, surgical treatment is a mainstay of therapy to relieve mass effects and significantly reduce tumor bulk. In some cases, after significant tumor debulking, it has been observed that response to dopamine agonists can be restored to ultimately achieve control of hyperprolactinemia and tumor growth [36]. In some aggressive PRL-omas where additional regrowth or recurrence is seen, multiple

surgeries may be needed over several years but are often associated with increased surgery complications such as optic nerve injury, anterior pituitary deficiencies, and diabetes insipidus [37].

Radiation Therapy

A further therapeutic option for PRL-omas that either exhibit growth or recur quickly after medical treatment or surgery is radiation therapy, which can be administered either as a single stereotactic dose or multiple fractionated doses [38]. Traditionally, some institutions have used radiation as a conventional adjuvant therapy to prevent tumor regrowth in all cases where complete resection has not been achieved. However this strategy exposes many patients to unnecessary risk of radiation-induced complications for tumors that might not have regrown or recurred if they had been left untreated. Single high-dose stereotactic radiation (12–14 Gy, max 16 Gy) is typically used when a sellar tumor target <3 cm in diameter is visible and situated at least 3–5 mm distant from the optic chiasm [39]. Alternatively, if surrounding normal tissues cannot easily be spared from the radiation treatment, low-dose fractionated radiation is employed, usually 25 Gy in 5 fractions over a period of 4–6 weeks. Although radiosurgery in general can provide good tumor control, it is not very effective in offering biochemical control, and PRL normalization can take a significant interval to achieve (up to 10–20 years) in ~1/3 of irradiated patients [7]. Furthermore, there is a dose limitation to the amount of radiation therapy that can safely be given due to the risk of temporal lobe necrosis resulting in neurocognitive impairment, hypopituitarism, and rare instance of radiotherapy-induced secondary neoplasia [40].

Chemotherapy

Response of pituitary tumors of any type, including aggressive PRL-omas or carcinomas, to systemic chemotherapy has not been prospectively studied due to the relative rarity of these tumors [41]. In comparison to other cancers, pituitary tumors, even when demonstrated to be aggressive (as previously described) or carcinomas, often do not exhibit high rates of cell division, so their response to many chemotherapy agents typically used in solid tumors is poor [41]. The orally administered alkylating agent temozolomide (TMZ) has emerged as first-line chemotherapy for aggressive PRL-omas and carcinomas [42]. The most recent European Society of Endocrinology (ESE) guideline reported a 37% efficacy in 156 patients with “aggressive” pituitary tumors or carcinomas following TMZ monotherapy although it must be acknowledged that some of these patients had not been irradiated prior to TMZ treatment [39]. TMZ is spontaneously converted to methyl-triazeno-imidazole-carboxamide (MTIC) at physiological pH, releasing methyldiazonium ion that methylates DNA at

N^7-guanine (60–80%), N^3-adenine (10–20%), and O^6-guanine (5–10%) sites [43]. As tumor cells have impaired DNA repair capability, the erroneous DNA is recognized during genomic replication and triggers cell cycle arrest and induction of tumor cell apoptosis. Given this, TMZ cytotoxicity correlates with repair enzyme activity, whereby low O^6-methylguanine-DNA methyltransferase (MGMT) expression has been shown in some studies to correlate with TMZ responsiveness, making MGMT a potential biomarker predicting TMZ sensitivity [44]. The standard TMZ therapy regimen is treatment cycles of 150–200 mg/m^2 per day for 5 of 28 days, across which hematological and liver function test monitoring should be obtained on day 22 of each cycle [39]. The recent guideline suggests that if an initial response is achieved after the first three TMZ cycles, therapy should be continued for a total of 6 months. Extended TMZ treatment should be considered if a sustained therapeutic benefit is observed with minimal adverse effects [39]. Alternatively, if radiological progression is observed after the initial 3-month TMZ trial, it has been recommended that TMZ monotherapy should either cease, be replaced, or be supplemented with another systemic cytotoxic therapy or radiotherapy offered [39]. Some authors, based on a small case series, have advocated that combination therapy where capecitabine is administered before TMZ may be more efficacious than TMZ monotherapy, but this and other TMZ combinations (cisplatin, procarbazine, lomustine, and vincristine) have not been compared in a randomized fashion [45, 46].

In summary, an individualized multimodal treatment regimen that may include mono or combinatory medical, surgical, repeated surgical, and radiotherapeutics options needs to be created by a multidisciplinary team to achieve individualized and carefully defined therapeutic goals. A suggested algorithm of currently available therapies is depicted in Fig. 13.2.

Emerging Therapies for Aggressive PRL-omas and Carcinomas

Peptide Receptor Radionuclide Therapy

Peptide receptor radionuclide therapy (PRRT) comprises a radionuclide linked by a chelator to a somatostatin receptor ligand (SRL) that can bind cell surface somatostatin receptors (SSTRs). The SRL-radionuclide conjugate penetrates tumor cells to break double-strand DNA causing cell death and has emerged as an effective treatment option in carcinoid and other neuroendocrine tumors (NETs) [47, 48]. Although no clinical trial or prospective evaluation of PRRT has been conducted in pituitary tumors, to date several radionuclides have been evaluated in single case studies of pituitary tumors [49]. ^{111}In-DTPA-octreotide, an Auger-emitting radionuclide with a shallow penetration (0.02–10 μm) [49], induces significant tumor shrinkage and clinical improvement when administrated to a single patient with a recurrent resistant giant PRL-oma [50]. Furthermore, treatment with the SRL-targeted radionuclides ^{177}Lutetium-DOTATOC and ^{90}Yttrium-DOTATATE has also

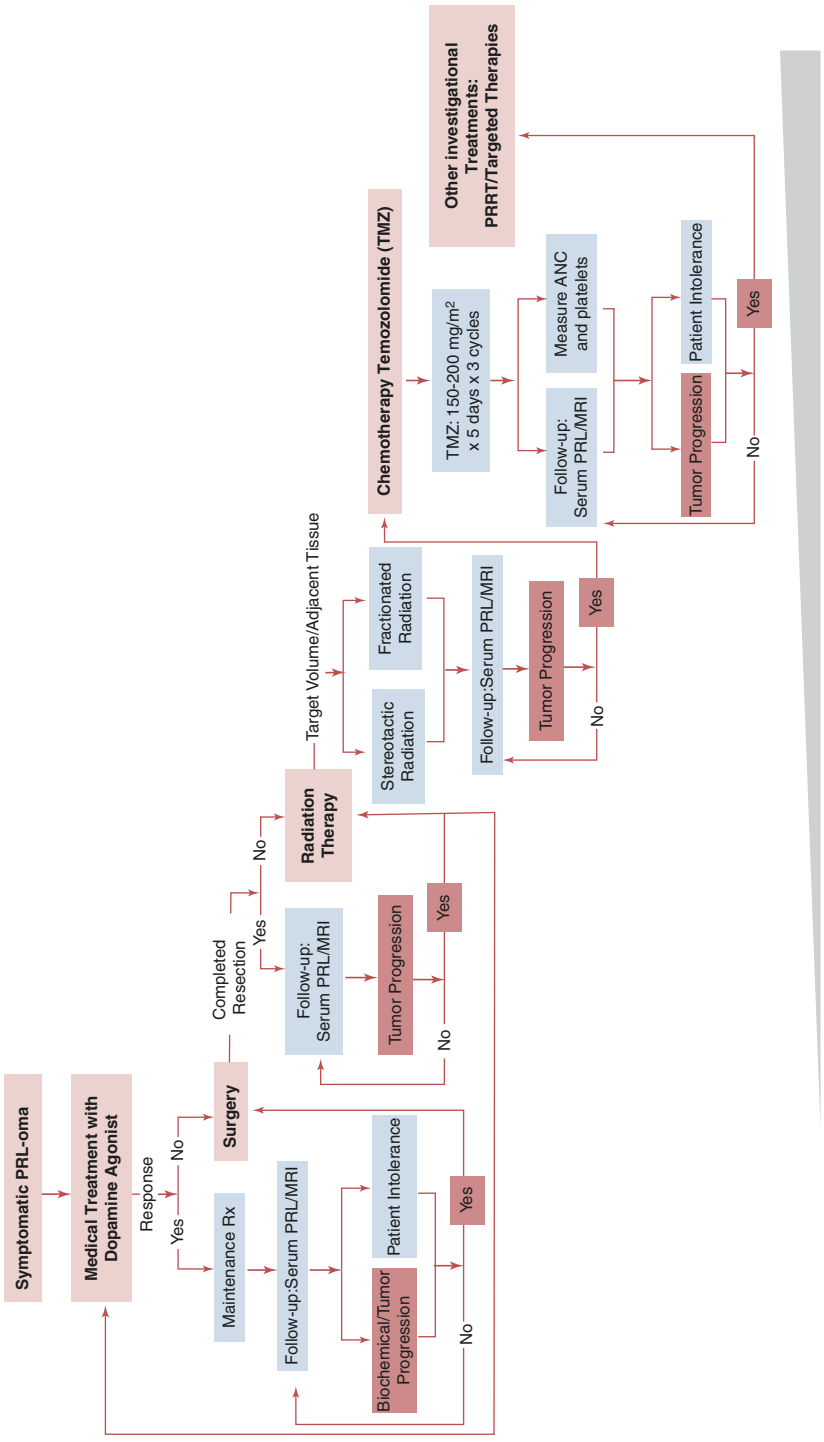

Fig. 13.2 Standard management algorithm for prolactinoma, which highlights some of the features that are often encountered in aggressive PRL-omas

resulted in tumor growth control in refractory nonfunctioning and GH-secreting pituitary tumor patients, respectively [51, 52], but disease progression has been observed in other similarly treated patients [53]. The utility of this novel therapeutic modality in treatment of aggressive pituitary adenomas, including PRL-omas, needs further evaluation ideally in randomized prospective multicenter studies.

Clinically Utilized Novel Medical Therapies

Significant advances in the management of many tumors have been enabled by the development of targeted therapies to control tumor growth and improve disease management, several of which are summarized in Fig. 13.3. For example, epidermal growth factor (EGF) is a local growth factor that modulates cell proliferation and PRL transcription [54]. 76.5% of PRL-omas express some of the four subtypes of

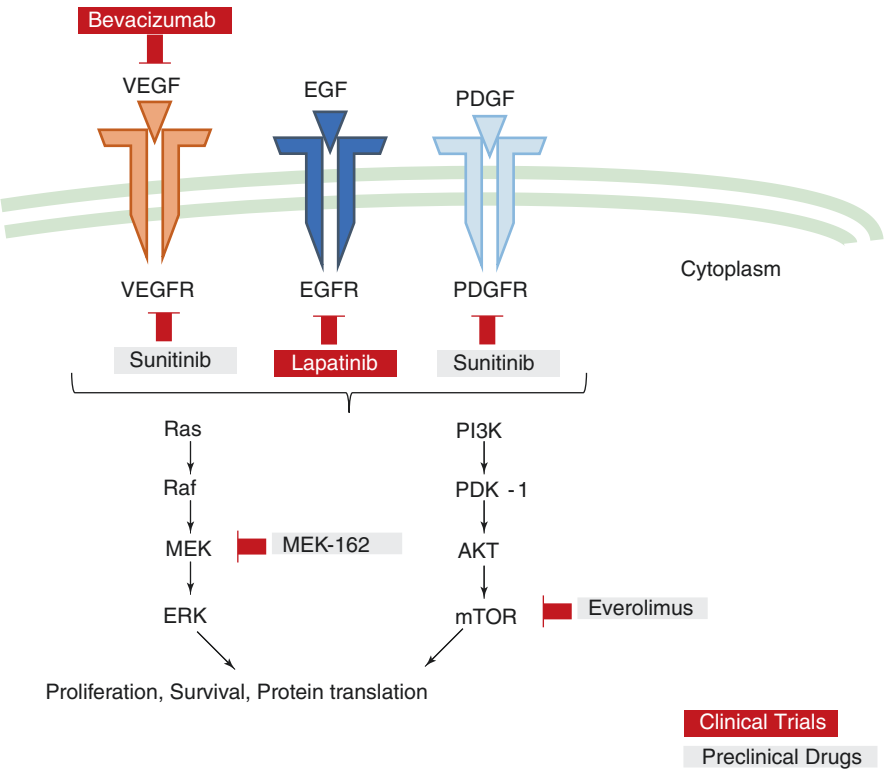

Fig. 13.3 Cartoon depiction of some of the cellular proliferative and metabolic pathways implicated in the pathogenesis of PRL-omas highlighting several targeted drug therapies that have either been used clinically in single or small case series in patients (highlighted in red box) or have been tested in preclinical animal in vivo or tumor cells in vitro studies (highlighted in gray box)

EGF receptors, namely, EGFR (ErbB1, HER1), p185her2/neu (ErbB2, HER2), ErbB3 (HER3), and ErbB4 (HER4) [55]. Furthermore, aggressive pituitary adenomas (including PRL-omas) exhibit higher EGFR and HER2 protein expression, with 40% of invasive adenomas staining positive for HER2 compared with 1.2% of noninvasive adenomas [56]. Additionally, transgenic mice expressing human EGFR and HER2 under the control of a PRL promoter/enhancer developed hyperprolactinemia and PRL-omas. Additionally, these tumors responded to lapatinib, an orally administered small molecule dual EGFR/HER2 kinase inhibitor approved for the treatment of HER2-overexpressing metastatic breast cancer in postmenopausal women [57–59]. Lapatinib is well tolerated with mild side effects of diarrhea, nausea, and fatigue and causes lower cardiac toxicity, which has been a limiting side effect of other tyrosine kinase inhibitors such as trastuzumab [59]. To date, two aggressive PRL-omas have been treated with lapatinib for a duration of 6 months, one demonstrated normalization of serum PRL level, and a reduction of 42% in serum PRL was reported in the second patient [60]. Tumor shrinkage of 22% was seen in one of these patients [60]. These initial results are encouraging, but additional clinical trials are needed to demonstrate a role for lapatinib therapy in patients with aggressive PRL-omas.

The normal pituitary is a highly vascularized organ where abundant highly permeable blood vessels enable the swift exchange of peptide hormone and hormone release signals between the peripheral blood stream and hypophyseal portal veins to regulate the endocrine system. Some studies have reported higher vascularity in invasive pituitary PRL-omas compared to noninvasive tumors [61]. Many angiogenic factors, including vascular endothelial growth factor-A (VEGF-A or VEGF), basic fibroblast growth factor-2 (basic FGF, or FGF2) and FGF4, and their corresponding receptors, have been shown to be involved in pituitary tumor development [61]. In one series of 56 surgically resected pituitary adenomas, higher VEGF protein expression was reported in dopamine agonist-resistant PRL-omas compared to nonfunctioning, corticotroph and somatotroph adenomas, although other studies did not observe increased human pituitary tumor VEGF expression in comparison to the normal pituitary gland [62, 63]. A D_2R knockout ($Drd2^{-/-}$) experimental mouse model of dopamine agonist-resistant PRL-oma exhibited elevated VEGF expression in the hyperplastic lactotrophs [64, 65], and intraperitoneal injection of the anti-VEGF monoclonal antibody Mab G6-31 resulted in reduced tumor size, vessel density, and circulating prolactin levels [66]. Mab G6-31 administration also inhibited tumor growth and reduced PRL levels in tumor-bearing MEN-1 heterozygous deletion mice ($MEN\text{-}1^{+/-}$) [67]. Bevacizumab (Avastin) is a humanized monoclonal antibody that binds to and inhibits the activity of VEGF and has been used clinically to treat several human malignances including glioblastoma, cervical, colorectal, renal cell, ovarian epithelial, and non-small cell lung cancers as a single agent or in combination with cytotoxic chemotherapies [68]. A study examining potential synergism of bevacizumab with the topoisomerase I inhibitor irinotecan in 52 patients with progressive recurrent malignant brain tumors included one patient with malignant PRL-oma [69]. This PRL-oma patient experienced a partial response with a 50% reduction in contrast-enhancing tumor on MRI imaging [69].

Preclinical Studies of Novel Therapies for PRL-omas

VEGF binds to two related receptors VEGFR1 (Flt-1) and VEGFR2 (Flk-1, KDR), of which VEGFR2 is the major mediator of VEGF effects in endothelial cells [70]. VEGF receptor mRNA and protein expression has been demonstrated in normal human pituitary tissue and pituitary adenomas with VEGFR-1 detected in endocrine cells and VEGFR2 exclusively expressed in endothelial cells [63]. Additional functional studies have shown VEGFR1 ligands significantly stimulate proliferation of VEGFR1-positive murine lacto-somatotroph MtT-S cells [63]. Sunitinib is a multi-tyrosine kinase inhibitor that blocks VEGFR1-VEGFR3 activation, has shown efficacy in renal cell, breast, and non-small cell lung cancers, and is approved to treat pancreatic NETs [71]. Although these preclinical studies and its approval for use on other NETs may point to its potential use in aggressive PRL-omas, sunitinib has not been tested clinically in pituitary adenomas.

The FGF family consists of 22 heparin-binding polypeptides (FGF1-22) with diverse biological activities including modulation of proliferation and differentiation in various cells of mesenchymal and neuroectodermal origin [72, 73]. FGF2 was initially purified from bovine pituitary [74], is mainly produced by pituitary follicle-stellate cells [75], and stimulates PRL secretion in a paracrine manner [76]. Multiple selective FGFR inhibitors are in phase II clinical trials in several malignant solid cancers [77], and given the role of FGF/FGFR in lactotroph regulation, they may warrant evaluation in PRL-secreting and potentially other pituitary adenomas.

Although no clear molecular targets have been identified as "driver" signals in aggressive PRL-omas and pituitary carcinomas, many growth factor-regulated kinase pathways have been demonstrated to be over activated, including the phosphoinositide 3-kinase (PI3K)/AKT/mTOR pathway. PI3K is a lipid kinase, comprising four subtypes based on lipid substrate specificity and component structures, and the class IA PI3Ks are the most frequently mutant subtypes in cancer [78]. The activated enzymes catalyze the conversion of the bilayer lipid membrane component phosphatidylinositol (4,5)-bisphosphate (PIP_2) to phosphatidylinositol (3,4,5)-trisphosphate (PIP_3). PIP_3 then further recruits the kinases PDK1 and AKT to the plasma membrane, leading to activation of AKT and a spectrum of downstream kinases, including mTOR, RSK, MAPK, and GSKs that are involved in metabolism, translation, apoptosis, and proliferation [79]. mTOR forms two distinct functional complexes. $mTORC_1$ comprises mTOR, raptor, and mLST8. $mTORC_2$ is made up of mTOR, rictor, and mLST8. Antiproliferative effects of the mTOR inhibitor everolimus have been demonstrated in human pituitary tumor primary cultures as a single treatment and in murine lacto-somatotroph tumor GH3 and SMtT cells, but surprisingly the effects of mTOR inhibition on PRL secretion have not been evaluated [80–82]. Furthermore, a synergistic action of rapamycin with the SRL octreotide was reported in GH3 cells [83], pointing to potential promising actions of combinatory or sequential multimodal medical treatment with these agents, but this has not been systemically tested. To date, one patient with a corticotroph pituitary carcinoma has been treated with everolimus, but this patient failed to respond

[84]. Recently NVP-BKM120 (also known as buparlisib), a pan-PI3K inhibitor, has been demonstrated to inhibit tumor growth and PRL secretion in the rat SmtTW PRL-oma model (5 mg/kg/d for 4 weeks) *in vivo*, although its actions *in vitro* were modest [85]. Other pathways that may be worth further exploration in PRL-omas and have shown promise in other pituitary subtypes include the MEK/ERK pathway [86–88].

Conclusion

Most PRL-secreting tumors respond well to dopamine agonist monotherapy, but aggressive PRL-omas and carcinomas constitute a major challenge for clinical management. This minority of PRL-omas responds poorly to currently available treatments and shows an overall poor prognosis. Diagnostic criteria of this entity remain vague and unstandardized, which impedes early identification of disease aggressiveness and prompt initiation of more intensive treatments to reduce overall morbidity and potential mortality. Current treatment comprises a combination of high-dose dopamine agonist, surgery, radiation therapy, and chemotherapy, which need to be offered in stepwise fashion on an individualized basis depending on the goals of therapy. This subgroup of patients requires careful frequent monitoring as they often exhibit escape from therapy over time and may ultimately succumb to their disease. Future treatments may include PRRT and/or some form of targeted therapy although the optimal molecular targets and therapeutic agents are as yet undefined. Advances in both the diagnostic tools and therapeutic options for these tumors are needed to significantly alter the outcome for these rare but inadequately controlled patients.

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Index

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