Hormone supply to the pituitary gland: A comprehensive investigation of female-related tumors (Review)

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Abstract. The hypothalamus acts on the pituitary gland after signal integration, thus regulating various physiological functions of the body. The pituitary gland includes the adenohypophysis and neurohypophysis, which differ in structure and function. The hypothalamus-hypophysis axis controls the secretion of adenohypophyseal hormones through the pituitary portal vein system. Thyroid-stimulating hormone, adrenocorticotropic hormone, gonadotropin, growth hormone (GH), and prolactin (PRL) are secreted by the adenohypophysis and regulate the functions of the body in physiological and pathological conditions. The aim of this review was to summarize the functions of female-associated hormones (GH, PRL, luteinizing hormone, and follicle-stimulating hormone) in tumors. Their pathophysiology was described and the mechanisms underlying female hormone-related diseases were investigated.

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Abbreviations: AD, Alzheimer's disease; CAB, cabergoline; CCOC, clear cell carcinoma; COX, cyclooxygenase; DAs, dopamine agonists; EMT, epithelial-mesenchymal transition; FSH, follicle-stimulating hormone; FSHR, FSH receptor; GH, growth hormone; GHD, growth hormone deficiency; GHRs, growth hormone receptors; GHRH, growth hormone-releasing hormone; GnRH, gonadotropin-releasing hormone; GnRH-a, gonadotropin-releasing hormone agonists; GnRH ant, gonadotropin-releasing hormone antagonists; HCC, hepatocellular carcinoma; hGH, human GH; HSC, hematopoietic stem cells; HSL, hormone-sensitive lipase; IGF-1, insulin-like growth factor-1; iNOS, inducible nitric oxide synthase; IVF, *in vitro* fertilization; LC3, light chain 3; LH, luteinizing hormone; LHCGR, luteinizing hormone-choriogonadotropin receptor; LHR, LH receptor; MKRN3, makorin ring-finger protein 3; MMPs, matrix metalloproteinases; OS, oxidative stress; PCOS, polycystic ovary syndrome; PitNET, pituitary neuroendocrine tumor; PKC, protein kinase C; PRL, prolactin; PRLRs, PRL receptors; RANK, receptor activator of nuclear factor-κB; SGA, small for gestational age; SHOX, short stature homeobox; SOC, serous ovarian cancer; SST, somatostatin; SSTR2, somatostatin receptor 2; VEGF, vascular endothelial growth factor

Key words: growth hormone, prolactin, gonadotropin-releasing hormone, luteinizing hormone, follicle-stimulating hormone

Contents

1. Introduction

To systemically study the association between pituitary hormones and female-related tumors, a PubMed search was performed using the key terms ‘growth hormone’, ‘prolactin’, ‘luteinizing hormone’, ‘follicle-stimulating hormone’ or ‘female’, including articles from 2017 to 2021, with some exceptions from the last 10 years. The search strategy included research articles and reviews. In total, 158 studies were included in the present review. The pituitary gland is the most important endocrine gland in the human body, controlling the secretion of key hormones involved in metabolism, growth, development, and reproduction. Six main hormones are secreted by adenohypophyseal cells: growth hormone (GH), prolactin

(PRL), thyroid-stimulating hormone (TSH), gonadotropin [luteinizing hormone (LH) and follicle-stimulating hormone (FSH)], and adrenocorticotropic hormone. In the present review, the association between the GH, gonadotropin-related hormones, and PRL, and the occurrence of associated diseases was summarized, with a focus on tumor development.

2. Growth hormone

The regulation of hypothalamic GH secretion is mediated by the growth hormone-releasing hormone (GHRH), somatostatin (SST), and ghrelin (1). GHRH promotes GH release by interacting with the growth hormone-releasing hormone receptor (GHRHR) in the somatotroph cells of the adenohypophysis through the cyclic adenosine monophosphate (cAMP)-mediated signal transduction pathway (2). SST inhibits GH secretion by binding to SST receptors (2,3). In addition, ghrelin, a hormone-releasing peptide, promotes GH secretion by activating the growth hormone secretagogue receptor (GHS-R) in the hypothalamus and pituitary (3). Growth hormone receptors (GHRs) are widely distributed through the body, including in bones, muscles, heart, brain, kidney, and fat cells (4). GH secretion may vary with age, sex, and nutritional status, peaking at a young age due to increased estrogen or testosterone concentrations (4-6).

Effects of GH on growth and development. GH misregulation is linked to several diseases. Growth hormone deficiency (GHD) incidence is highest in children. It has been reported that children with GHD after birth are often characterized by slow growth and short stature (7,8). Being a positive modulator of growth, GH is used to treat diseases characterized by short statures, such as short stature homeobox (SHOX) deficiency (linked to SHOX gene mutations), Turner syndrome, Prader-Willi syndrome, Noonan syndrome, and small for gestational age (SGA) (9-13). GH regulates human growth by modulating the metabolism of carbohydrates, proteins and lipids (14). Moreover, adults with GHD experience increased total and visceral body fat, low bone and muscle mass, reduced muscle strength, impaired anaerobic performance, poor cardiovascular status, and poor quality of life (15,16). Previous research has shown that GH acts directly in chondrocytes to promote differentiation and chondrocyte proliferation, by stimulating peripheral tissues via upregulation of the insulin-like growth factor-1 (IGF-1), especially in the liver (17). In adults, excessive growth hormone secretion and increased IGF-1 concentration may lead to acromegaly. In children, excessive secretion of GH and IGF-1 leads to gigantism (18,19). Therefore, accurate regulation of GH is crucial to modulate human growth and development at all ages.

Additional functions of GH. Some evidence shows a close association between the neuroendocrine and the immune systems. *In vitro* and *in vivo* studies have demonstrated that GH is involved in immune response, by regulating the proliferation and activity of immune cells, namely the proliferation of leukocyte subsets with expression of GHRs (20). GH-activated protein kinase C (PKC) and ERK-activated hormone-sensitive lipase (HSL) regulate lipolysis and improve sleep efficiency (21,22). Furthermore, it is likely that GH exerts important roles in ovulation and fertility of women (23). Polycystic ovary syndrome (PCOS) is the most common female endocrine disorder, affecting 5-10% of women at reproductive age. Oxidative stress (OS) plays a central role in the pathophysiology of PCOS and other diseases. GH reduces OS-induced apoptosis by activating the PI3K/Akt signaling pathway, which may provide a theoretical basis for PCOS treatment (24). Furthermore, GH administration has been associated with successful *in vitro* fertilization (IVF). Exogenous GH administration alleviates mitochondrial dysfunction and improves oocyte quality in women above 40, and in patients with poor ovarian response. Studies have shown that GH treatment during ovarian stimulation in young women who have failed IVF may increase IVF success rates by improving oocyte quality (25).

Research progress in GH and female GH-related tumors. The incidence of malignant tumors, including breast cancer, is major public health concern in Chinese women. A significant portion of cancers are hormone-dependent, and GH plays key roles in the proliferation and invasion of breast cancer cells (26). Human GH (hGH) promotes body growth via activation of distinct biological processes, including IGF-1 synthesis and secretion in the liver, and activation of JAK2/STAT5 and BRAF/MEK/ERK signaling pathways. GH triggers cell proliferation in breast cancer cells by increasing JAK2 and STAT5 gene expression. Conversely, silencing of GHRs blocks JAK2/STAT5 and BRAF/MEK/ERK signaling pathways, thereby inhibiting the growth of breast cancer cells (27,28). Clinicopathological studies of cases with breast cancer revealed that hGH expression was positively correlated with the presence of metastases, high clinical stage and HER2 positive lymph nodes. It has also been reported that elevated GH levels may induce malignant transformation of mammary epithelial cells, promote proliferation and metastasis via activation of epithelial-mesenchymal transition (EMT), through miR-183-96-182 cluster activation. During EMT, epithelial cells reduce their polarity and intercellular contacts, therefore acquiring migration and motility capacities, enabling them to invade adjacent tissues and distant tissues. EMT is triggered after cells receive microenvironmental signals and it is activated during the pathogenesis of cancer (29-31).

GH promotes the proliferation and invasion of breast cancer cells by promoting EMT. GH-mediated EMT in breast cancer may occur via two distinct mechanisms: i) GH may directly promote EMT, or ii) GH may promote the EMT of breast cancer cells by inducing microRNA clustering and inhibiting the expression of breast cancer metastasis suppressor 1-like (BRMS1L) (32,33). In addition, GH may promote the development of breast cancer cells by downregulating connexin E-cadherin expression and inducing the WNT signaling pathway (32,34). Abnormal secretion of GH is additionally associated with several human diseases. Previous research has revealed that hGH expression is increased in hepatocellular carcinoma (HCC) and is associated with poor survival outcomes in HCC patients. hGH secreted by HCC promotes invasion and cancer stem cell-like properties by inhibiting the expression of the tight junction component CLAUDIN-1. Thus, inhibiting hGH and hGHR signaling pathways may be a potential therapeutic approach to limit HCC progression

and recurrence (35). The specific molecular mechanism is presented in Fig. 1.

Drug treatment of GH-related diseases. Excessive GH secretion is often surgically treated, followed by post-operative adjuvant drug therapy, which may include GHR antagonists, dopamine agonists (DAs), and SST receptor ligands. Pegvisomant is a recombinant GHR antagonist, similar to hGH, that binds and blocks GHR activity (36). Pegvisomant treatment reestablishes normal levels of IGF-1 in patients with acromegaly and relieves symptoms related to excess GH (37). Cabergoline (CAB) is a dopamine agonist that can be used in combination with pegvisomant. CAB is the first-line treatment for hyperprolactinemia, being additionally used to treat acromegaly (38,39). SST is a cyclic-released hormone that functions as an inhibitory peptide. SST receptor ligand drugs, such as octreotide, lanreotide, and pasireotide, are used in the clinic to treat diseases caused by the excessive release of GH. Octreotide and lanreotide are specific for the SST receptor somatostatin receptor 2 (SSTR2), a key regulator of GH secretion (40,41). Acromegaly is characterized by hypersecretion of GH and elevated levels of IGF-1. The reported leading cause of acromegaly is the presence of a GH-secreting pituitary neuroendocrine tumor (PitNET) or GH plus PRL-secreting mixed adenoma. Combination therapy including SST and dopamine inhibit GH and IGF-1 secretion by binding to SSTR2 and dopamine D2 receptor (D2R), thereby inhibiting the acral lesions caused by GH-secreting PitNETs (41-43).

3. Prolactin

PRL is a versatile hormone and serves a wide variety of physiological functions apart from lactation. PRL lactotrophs in the pituitary are released in a circadian pattern depending on the physiological state. PRL content in the human body varies slightly with sex; with women presenting higher levels than men during puberty (44,45). PRL further participates in immune regulation, by binding to PRL receptors (PRLRs) in the surface of monocytes, lymphocytes, and thymic epithelial cells (46,47). PRL secretion is controlled by hypothalamic PRL release factors and PRL release-inhibiting hormones, which include TSH-releasing hormone, vasoactive intestinal peptide, serotonin, PRL release-inhibiting hormone dopamine class material, growth hormone-releasing inhibitory hormone (GHIH), gamma-aminobutyric acid (GABA), and thyroid hormone, among others (48). In addition, PRL regulates luteal function via modulation of LH receptors in the ovaries (49).

Role of PRL in pregnancy. PRL belongs to the family of growth factors that regulate cellular and humoral immunity. During pregnancy, PRL is key for intrauterine homeostasis and normal embryo development. PRL levels in women who have suffered from miscarriage are significantly lower than in women with healthy pregnancies. Moreover, low levels of PRL are associated with low weight at birth and premature birth (50).

PRL is synthesized in the endometrium during embryo implantation, providing a suitable microenvironment for blastocyst implantation through PRLR, to improve the endometrial receptivity. Precise regulation of PRL concentration is key to promote growth and adhesion of the endometrial cells which are essential for embryo implantation and development (51). The space-temporal regulation of PRLR expression suggests that PRL regulates several functions related to mitosis and differentiation of ovarian tissue. PRL production is positively correlated with the degree of the decidualization of endometrial stromal cells (48). PRL secreted by decidua during pregnancy increases after embryo implantation, reaching the peak around 20-25 weeks of pregnancy (52). PRLR expression has further been detected in the placental trophoblast, and amniotic epithelial cells (53). Thus, PRL should be adequately added as hormone replacement therapy in premature infants (54).

In recent years, the association between human T helper cells (Th1/Th2) in serum, lymphocytes, decidua, and spontaneous abortion has attracted much attention. It is maintained that Th1 cells inhibit embryo development. In contrast, Th2 cells play key roles in maintaining a normal pregnancy. PRL regulates the Th1/Th2 balance, particularly acting on Th1 cells. In addition, PRL decreases natural killer (NK) cells and Th1 activity. PRL and PRLR are abundantly expressed in uterine decidual tissue in early pregnancy (55-57). PRL further stimulates the expression of LH/placental secretory chorionic gonadotropin receptor (CG receptor) in the corpus luteum after fertilization. Moreover, PRLR, coordinates with FSH and LH, thereby regulating cAMP and progesterone synthesis, both of which are essential during pregnancy (58-60). Based on these studies, PRL may regulate the local microenvironment of uterine decidua that controls the synthesis and secretion levels of hormones and factors by autocrine and paracrine pathways. Endogenous or exogenous factors blocking PRL synthesis and secretion may affect the expression of LH/CG receptors in the pregnant corpus luteum of the ovary, which may result in miscarriage. In conclusion, PRL levels during early pregnancy are essential to normal embryo development, acting via luteal maintenance, immune function regulation, and decidual development.

Research progress in PRL and female PRL-related tumors. PRL is an essential growth factor with direct influence on the division and proliferation of somatic cells. Particularly, PRL plays a key role in regulating breast development and terminal differentiation of breast epithelial cells. Epidemiological research has revealed that elevated serum PRL levels are associated with increased risk of breast cancer. PRL and PRLR overexpression is observed in several tumors, including breast cancer, and is associated with increased cell proliferation, reduced apoptosis, and a shorter cell cycle (61).

The association between PRL and breast cancer has been thoroughly studied. Li *et al* determined that the PRL/p-STAT5 pathway induced $HER2^+$ mammary tumorigenesis through oxytocin receptor (62). Another study revealed that two small molecule inhibitors, SMI-1 and SMI-6, abrogated PRL-induced $HER2^+$ breast cancer cell invasion and malignant lymphocyte proliferation by binding the extracellular domain of PRLR (63). Moreover, PRL synergizes with canonical WNT signals and KRAS activation to drive the development of ER^+ mammary tumors, by activating the Notch signaling pathway (64,65). MacDonald *et al* reported that PRL-inducible EDD E3 ubiquitin ligase promotes TORC1 signaling, anti-apoptotic protein expression, and

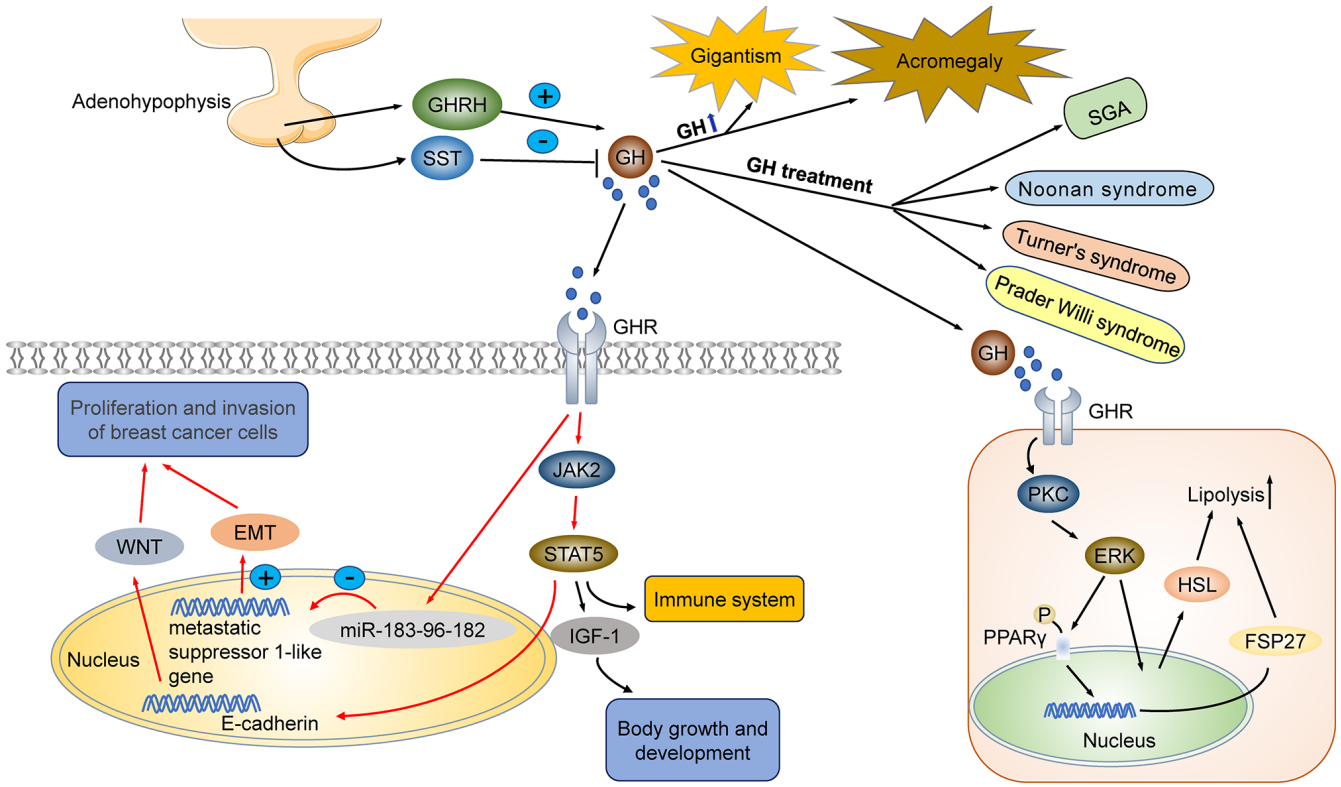

Figure 1. Summary of GH-related molecular mechanisms. GH is regulated by GHRH and SST. GH promotes EMT and induces WNT signaling pathway to promote the proliferation and invasion of breast cancer. In addition, GH also promotes lipolysis through ERK signaling pathways. GH, growth hormone; GHRH, growth hormone-releasing hormone; SST, somatostatin; EMT, epithelial-mesenchymal transition; SGA, small for gestational age; GHR, growth hormone receptor; IGF-1, insulin-like growth factor-1; PKC, protein kinase C; HSL, hormone-sensitive lipase.

drug resistance in mammary tumors (66). Chen *et al* used hybridoma technology to generate an anti-idiotypic antibody named H53. H53 exhibits biological activity against breast cancer, suggesting that an internal image with anti-idiotypic antibodies may be a candidate strategy to develop PRLR/GHR dual-function antagonists for breast cancer therapy (67). PRL has further been shown to promote pancreatic ductal adenocarcinoma, which, notably, can be reversed by antipsychotic diphenylbutylpiperidines (68). Moreover, blood PRL levels are reduced in rats with diabetes or obesity. In the clinical setting, it has been observed that low circulating levels of PRL are correlated with increased prevalence of diabetes and a higher risk of metabolic alterations, by increasing β-cell loss and pancreatic inflammation (69). PRL misregulation is also associated with glioma, uterine, prostate, renal cell, and pituitary tumors. In uterine cancer, blocking PRLR induces FOXO3a/EIF-4EBP1-mediated cell death (70). In glioma, the therapeutic block of PRLR enhances the response of tumor cells to chemotherapy (71). PRL promotes the expression of inducible nitric oxide synthase (iNOS) in glioma cells, thereby promoting the production of nitric oxide (NO). Furthermore, PRL leads to the accumulation of NO and the expression of iNOS by enhancing IFN-γ. In the prostate, PRL drives tumorigenesis by regulating STAT5a/b (72). The specific molecular mechanism is presented in Fig. 2.

Additional functions of PRL. PRL is involved in several biological processes that include immune response, neuroprotection, and metabolic regulation. PRL participates in immune regulation by interacting with PRLR on the surface of immune cells such as leukocytes, macrophages, lymphocytes, among others (46). PRL misregulation is associated with increased risk of multiple sclerosis and rheumatoid arthritis by regulating the number of circulating lymphocytes (57). PRL has been reported to exert neuroprotective functions. For instance, in a rat glutamate (Glu) injury model, PRL maintained the function of neuronal mitochondria by promoting intracellular calcium release and NF-κB. PRL further regulates nerve regeneration of non-transferrin bound iron (NTBI) by preventing calcium overload (73,74). Finally, PRL maintains physiological homeostasis through the regulation of the level of insulin, liver-related enzyme activity, and intestinal Ca^{2+} absorption (75-77).

Treatment of PRL-related diseases. Excessive secretion of PRL may lead to hyperprolactinemia, which is frequent in hermaphroditism. DAs are used as first-line treatment. Most commonly used drugs are CAB, bromocriptine (BRC), and pergolide (PER) (78-80), all of which act on dopamine receptors in the lactating cell membrane of the pituitary gland to reduce serum levels of PRL (81), thereby relieving the clinical symptoms of patients, and recovering the menstruation and fertility of women. Antipsychotics also increase the level of PRL. Among them, amisulpride, risperidone, and paliperidone significantly increase the levels of PRL, even at low doses (82). PRL dysfunction inhibits the male reproductive system and reduces semen quality (83). The antipsychotic drug aripiprazole (ARI) decreases serum PRL levels in children and adolescents (84). With the increasing research on the molecular

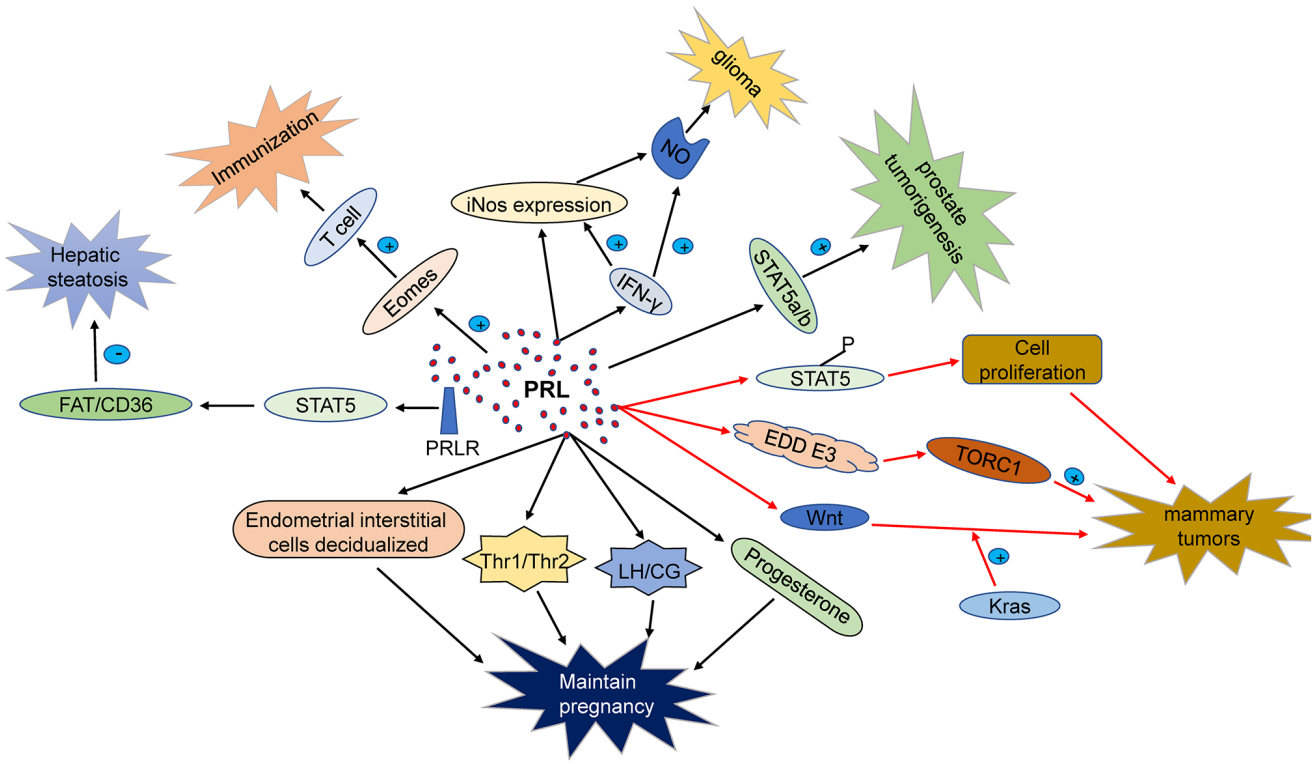

Figure 2. Schematic diagram of PRL involvement in disease. Excessive secretion of PRL is linked to breast cancer, via TORC1, WNT, and STAT5 signaling activation. PRL is also associated with prostate tumor and glioma occurrence. At the therapeutic level, PRL ameliorates liver steatosis and induces cell death in cervical tumor cells through Eomesodermin-mediated inflammatory response. PRL, prolactin; NO, nitric oxide; iNOS, inducible nitric oxide synthase; Eomes, Eomesodermin; PRLR, PRL receptor; LH, luteinizing hormone; GH, growth hormone.

and cellular biology of the pituitary, different target genes and gene transfer methods are under study as therapeutic candidates against PitNET. In the future, gene therapy will likely focus on the treatment of invasive PitNET and residual drug resistance diseases with local invasion following surgery (85). Gene therapy will undoubtedly enlighten the future clinical treatment of infections caused by abnormal PRL secretion.

4. Gonadotropin

Gonadotropin-releasing hormone (GnRH) is a heterodimeric glycoprotein composed of an α subunit and a β subunit (86-88). Gonadotropin, a member of the glycoprotein hormone family, consists of FSH and LH. There are several subtypes of FSH generated by post-translational modifications, all of which affect FSH half-life through the change of carbohydrate pattern (86). FSH participates in follicular development and regulates follicular secretion, maturation, and atresia by modulating granulosa cells. Late follicular stages may induce LH receptor (LHR) synthesis by granulosa cells, thus supporting LHR interaction with LH, resulting in the production of a luteinizing follicle (87). In women, LH stimulates the secretion of estrogen by theca cells, promotes ovulation, and maintains the physiological role of luteinization. In addition, inhibition of the hypothalamus is performed by inhibin A to regulate the menstrual cycle of women. GnRH is a therapeutic drug that stimulates the release of inhibin A, enhances the activity of LH, selectively inhibits the synthesis and secretion of FSH, and promotes the selection of dominant follicles (DF), thereby regulating reproductive function (89-92). Duan *et al* described four luteinizing hormone-choriogonadotropin receptor (LHCGR) structures using cryo-electron microscopy (cryo-EM): Two of the structures were the wild-type receptor in the inactive or in the active states; and the other two structures were the constitutively active mutated receptor. Research has revealed a unique mechanism of receptor activation, providing a rationale for drug discovery in endocrine-related diseases (93,94).

Neuromodulation of gonadotropin. A new action factor, the neuropeptide kisspeptin, which acts upstream of GnRH, has attracted the attention of the scientific community in recent years (95). Other neuropeptides (gonadotropin inhibitory hormone/radiofrequency amide-related peptide and other members of the radiofrequency amide peptide superfamily), and various non-peptide neurotransmitters (glial fibrillary acidic protein, dopamine, neuron-derived neurotrophic factor, and serotonin), also function as regulators of GnRH secretion and synthesis, as well as of LH and FSH secretion (95-98). Kisspeptin/neurokinin B/dynorphin (KNDy) neuron is a GnRH pulse generator that maintains gonadotropin levels and follicular development (99). Nuclear receptors, such as the steroid generation factor 1 and liver receptor homolog 1 (LRH-1), regulate progesterone receptors to control FSH and LH. These are also critical regulators of steroid generation, cell proliferation and migration, and cytoskeleton remodeling (100). Concurrently, makorin ring-finger protein 3 (MKRN3) inhibits the reproductive axis through its role in kisspeptin-expressing neurons involved in a MKRN3-guided ubiquitination mediation mechanism (101,102). A previous study revealed that a high-fat diet (HFD) intake by parents may also be a risk

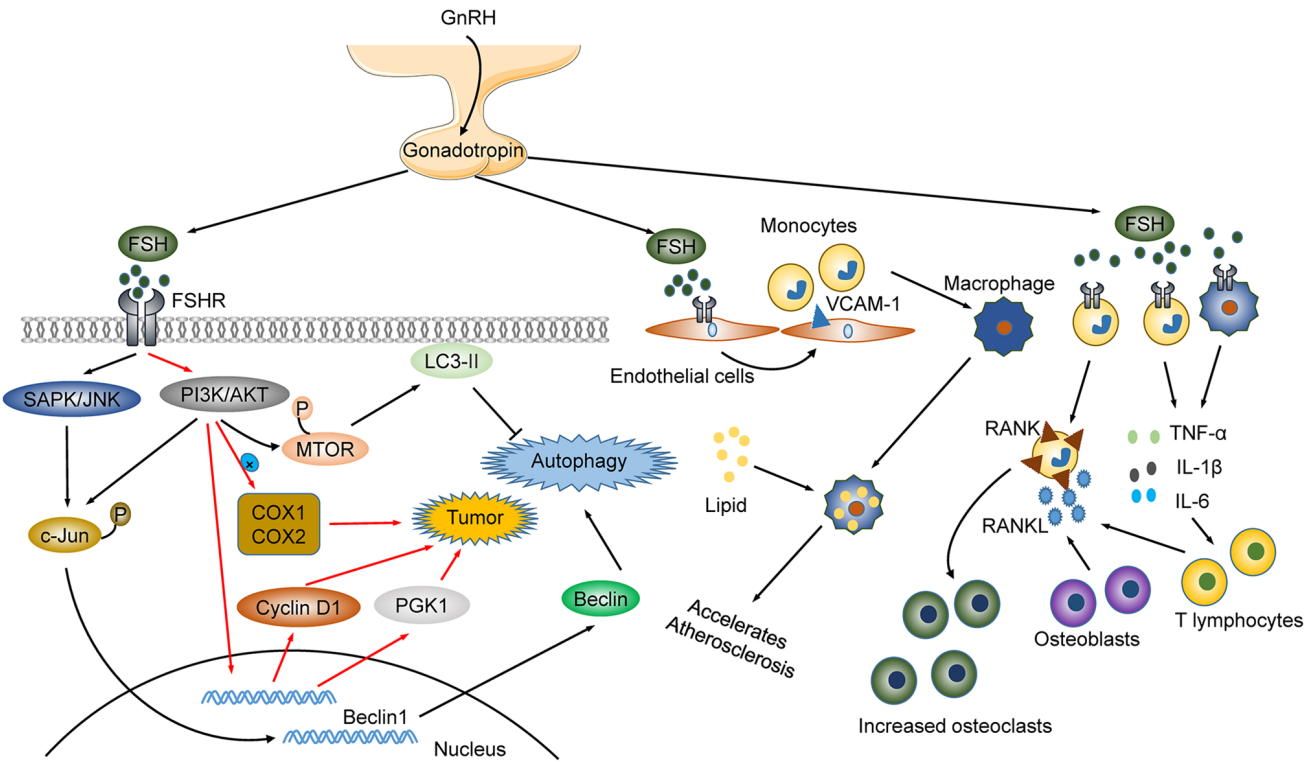

Figure 3. FSH-related molecular mechanisms. GnRH regulates the synthesis of FSH and LH. FSH regulates autophagy through the SAPK/JNK and PI3K/AKT signaling pathways. FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; FSHR, FSH receptor; LC3, light chain 3; COX1, cyclooxygenase-1; COX2, cyclooxygenase-2; RANK, receptor activator of nuclear factor-κB.

factor for prostate hyperplasia and cancer at advanced ages, due to a negative impact on the reproductive system of male offspring (102,103). Thus, it is advised that epidemiological and clinical research on semen quality must include male offspring of overweight and/or obese parents (103,104).

Effect of FSH on reproductive development. Gonadotropin plays a key role in reproduction, and the evaluation of FSH and LH is an index of ovarian reserve. There are several recombinant preparations used to treat gonadotropin deficiency and gonadal dysfunction. Abnormal FSH may lead to abnormal ovarian function, such as follicular development disorder and abnormal follicular atresia (105,106). The combination of urinary follicle-stimulating hormone (uFSH) and recombinant follicle-stimulating hormone (rFSH) improves ovarian stimulation (107). In addition, GnRH upregulates the anti-Mullerian hormone (AMH), which leads to ovulation dysfunction and androgen elevation by causing abnormal follicular growth and abnormal secretion of granulosa cells (108). Furthermore, GnRH affects bone mineral density in postmenopausal women by regulating LH and FSH levels (109). Postmenopausal osteoporosis is a risk factor for bone fracture. It was initially proposed that estrogen decay was responsible for the onset of postmenopausal osteoporosis. However, recent studies have shown that FSH, which increases along with estrogen decreasing, acts on FSH receptor (FSHR) in osteoclasts. FSH promotes osteoclast formation and accelerates bone loss by enhancing the expression of receptor activator of nuclear factor-κB (RANK). This suggests that FSH, along with estrogen, may be linked to the risk of osteoporosis in postmenopausal women (110,111). In addition, LH and FSH are distinctly regulated. For example, LH and FSH reduce nicotine-induced oocyte autophagy in different manners. LH reduces nicotine-induced autophagy by restoring the phosphorylation of adenosine 5'-monophosphate-activated protein kinase α-1. By contrast, FSH reduces autophagy by downregulating the phosphorylation of forkhead box O1 (FoxO1) and light chain 3 (LC3)-II (112,113). Paradoxically, FSH upregulates Beclin1 through the PI3K/JNK/c-Jun pathway to accelerate the degradation of lipid droplets in mammalian follicular granulosa cells, thus enhancing autophagy. FSH affects follicular development, and participates in the regulation of lipid metabolism (such as cholesterol and fat), regulates bone density, and is associated with the onset of cardiovascular diseases, and the occurrence of breast cancer (112). FSH activates liver cholesterol biosynthesis and decreases serum cholesterol through the Gi2α/β-inhibin-2/Akt pathway during menopause (114). Elderly postmenopausal women with higher FSH levels have higher bone marrow obesity rates, lower bone density, fat, and lean meat mass than elderly postmenopausal women with lower FSH levels (115,116). It is also suggested that FSH regulates bone formation and regeneration, and that its dysregulation enhances joint inflammation in rheumatoid arthritis. Mechanistically, FSH triggers pathogenesis through the regulation of activin A or inhibin B in the respiratory system (Fig. 3) (117,118).

Effects of LH on reproductive development. At present, research on LH function is mainly focused on the maturation and development of follicles and the recovery of the hematopoietic system (119,120). LH coordinates the process of oocyte meiosis via the activation of zinc finger protein 36 (ZFP36)

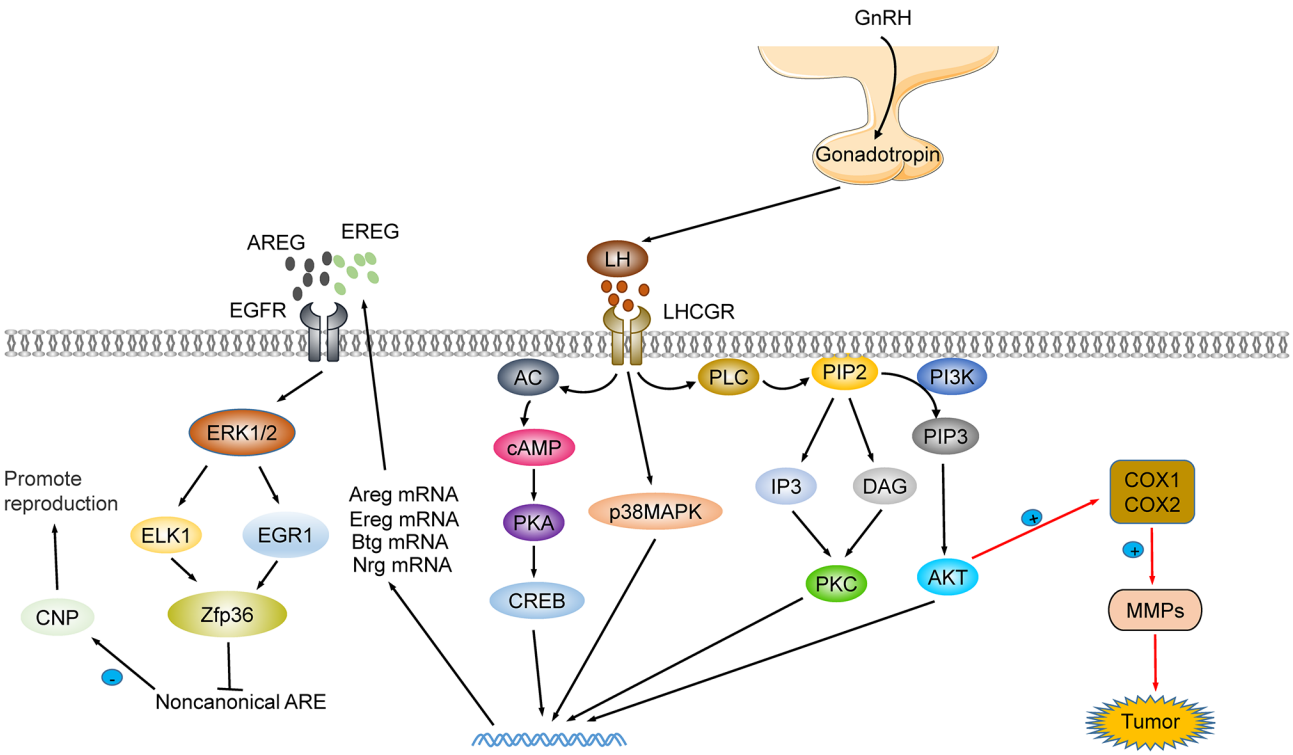

Figure 4. LH-related molecular mechanisms. LH regulates EGF-like factors through PKA, p38MAPK, PKC, and AKT signaling pathways. LH, luteinizing hormone; PKC, protein kinase C; LHCGR, luteinizing hormone-choriogonadotropin receptor; GnRH, gonadotropin-releasing hormone; cAMP, cyclic adenosine monophosphate; COX1, cyclooxygenase-1; COX2, cyclooxygenase-2; MMPs, matrix metalloproteinases.

expression in an EGFR-ERK1/2 dependent pathway (86,121). Moreover, LH participates in the homeostasis of hematopoietic stem cells (HSC). The lack of LHCGR has been revealed to accelerate the development of acute myeloid leukemia in mice (119). The LH blocker leuprorelin improves hematopoietic recovery after radiotherapy or chemotherapy, by protecting LHR-expressing HSCs (122,123). Additionally, LH is an inflammation modulator. During follicular maturation and development, the first responders to the LH wave are granulosa and theca cells, which produce steroids, prostaglandins, chemokines, and cytokines. These mediators activate ovarian cells and resident immune cells in the ovary, and further attract additional immune cells to the ovaries. These jointly regulate the proteolytic pathway to recombine the follicular matrix, destroy the basal layer of granulosa cells and promote the invasion of vascular endothelial cells (124,125). In mice, it was revealed that LH reduced the expression of the apoptosis-promoting protein Tap63, inhibited cisplatin-induced oocyte apoptosis, and protected the reproductive function of female mice following treatment (126). In addition, Li *et al* reported that p62 depletion in the pituitary impairs LH synthesis through mitochondrial OXPHOS signal transduction and leads to female infertility. This provided a new theoretical basis for studying female reproductive dysfunction in gonadotropic cells: The GnRH-p62-oxphos (ndufa2)-Ca^{2+}/ATP-LH pathway (127). Notably, LH has been described as a therapeutic candidate in treating Alzheimer's disease (AD) and recovering from cognitive impairment. The increase in LH has been associated with increased risk of cognitive impairment and AD. Cognitive improvement after LH level reestablishment, and remission of AD symptoms after treatment with specific LHCGR blockers, have been observed (128,129). The precise molecular mechanism is revealed in Fig. 4.

Research progress on gonadotropin-related hormones and female-related tumors. In recent years, the expression of GnRH and its receptor have been found in a variety of gynecological tumors, including uterine fibroids, endometrial cancer, ovarian cancer, and breast cancer. Ovarian cancer is a common reproductive tumor in women. The most frequent subtype is epithelioid ovarian cancer (EOC), which can be further divided in serous ovarian cancer (SOC), endometrioid carcinoma, clear cell carcinoma (CCOC), mucinous carcinoma and other less diagnosed types (130,131).

Previous studies have shown that genetic, hormonal, and reproductive factors affect the incidence of ovarian cancer, but its etiology and pathogenesis remain unclear. The hypothalamus-pituitary ovary axis is an important neuroendocrine system that plays a crucial role in regulating the female reproductive system. Gonadotropin, as the key hub of this axis, plays an important role in ovarian cancer incidence (132). Tumor cell metabolic reprogramming and microenvironmental changes have been linked to the development of ovarian tumors (133-135). In this context, FSH and LH increase the synthesis of cyclooxygenase (COX)1 and COX2 through the PI3K/Akt signaling pathway and the production of prostaglandin E2 (PGE2), which itself is linked to disease progression (hypertension, diabetes, and dyslipidemia) (136-138). PEG2 promotes the progression of ovarian cancer by increasing the production of matrix metalloproteinase (MMP)2 and MMP9 (139,140). In addition, FSH promotes ovarian cancer progression by affecting the

glycolysis process. For instance, FSH promotes glycolysis in ovarian cancer cells and the decrease of pH in the microenvironment by promoting the expression of pyruvate kinase M2 (PKM2) and phosphoglycerate kinase 1 (PGK1) (141,142). Therefore, gonadotropin may be involved in the progression of ovarian cancer by modulating tumor cell metabolism.

FSH affects the expression of progranulin (PGRN) in CCOC, through activation of the PI3K/Akt pathway via FSHR, thereby supporting the development of ovarian cancer. Nevertheless, FSH regulates different molecular mechanisms via PKC modulation in different subtypes of ovarian cancer including SOC (143). FSH increases the expression of Gankyrin through the PI3K/Akt pathway, and promotes the proliferation of ovarian cancer cells by regulating cyclin D1 (144). In addition, the specific expression of FSH in the reproductive system supports the hypothesis that FSH may be a candidate therapeutic target in ovarian cancer (145-147). LH also regulates the PI3K/Akt pathway by upregulating vascular endothelial growth factor (VEGF) and Slit2 (148). VEGF can be used as a gonadotropin to promote the progression of advanced ovarian cancer (149). In conclusion, gonadotropin is closely related to the occurrence and development of ovarian cancer, and may provide insights for targeted treatment.

Treatment of gonadotropin-related diseases. The treatment of gonadotropin-associated disorders is performed by gonadotropin-releasing hormone agonists (GnRH-a), gonadotropin-releasing hormone antagonists (GnRH ant), estrogen receptor modulators, aromatase inhibitors, and hormone analogs. GnRH-a promotes the release of gonadotropin. However, the long-term use of the GnRH-a leuprorelin results in decreased bone mineral density (150,151). The GnRH ant, cetrorelix inhibits the synthesis and secretion of gonadotropin by competing with GnRH receptor on the surface of pituitary cells to block GnRH secretion (152-154). In addition, clomiphene citrate, an estrogen receptor regulator, increases the secretion of GnRH in the hypothalamus by inhibiting the negative feedback regulation of estrogen. In addition to treating female ovulation dysfunction, clomiphene citrate also improves the levels of testosterone and GnRH in men (155-157). Aromatase inhibitors, which are estrogen receptor regulators, promote the release of GnRH by modulating estrogen levels. Furthermore, gonadotropin drugs are used to replace endogenous hormones. For example, human chorionic gonadotropin (hCG) is used as a LH substitute to induce ovulation (158). Hormone administration is often more effective than oral administration, however at the cost of the occurrence of side effects, such as increasing the risk of multiple births and ovarian hyperstimulation syndrome (OHSS).

5. Conclusions

In recent years, major progress in our knowledge concerning the mechanisms of action of the three pituitary hormones (GH, gonadotropin-related hormones, and PRL) and their roles in human health and diseases has advanced significantly, particularly their involvement in growth and development. GH promotes body growth and development, and its abnormal secretion is associated with a variety of diseases. GH is involved in breast cancer through dysregulation of the JAK2/STAT5 pathway and promotion of EMT. PRL is involved in distinct biological processes: It promotes milk secretion and gonad development, and is essential for metabolism, immunity, and fetal growth and development. In addition, PRL misregulation is linked to human diseases including breast and liver diseases, as well as autoimmune and endocrine diseases. PRL-based therapy is used to manage pain, particularly migraines in women. Moreover, PRL-based treatments are applied in the context of different cancers, including, but not limited to, pancreatic ductal carcinoma, glioma, breast cancer, uterine cancer, and prostate cancer. Dysregulation of LH and FSH hormones is associated with diseases of reproductive development in both men and women. In this context, an accurate FSH-LH balance is critical to seminiferous tubular development in early sexual maturation. The increase of FSH has been observed in primary amenorrhea, congenital ovarian hypoplasia, and primary hyper reproductive function. During the menstrual cycle, an increase in FSH is observed during the fertile period. Elevated FSH levels in the follicular phase are a marker of decreased ovarian function, which in turn leads to secondary decreases in ovarian estrogen and progesterone secretion. LH induces testosterone synthesis, thus supporting the production of mature sperm. Therefore, reduced LH levels are associated with a decrease in fertility, and ultimately with infertility.

The exact role of pituitary hormones in metabolic homeostasis remains to be fully elucidated, with recently described functions expanding further than the standard roles of these hormones. GH plays a unique biological role in various stages of human development through GHRs which are expressed in different organs. Lack of GH in childhood leads to slow growth and development, and to dwarfism in extreme cases. In adults, lack of GH leads to increased fat content and a high risk of cardiovascular disease. Moreover, GH impacts fertilization by affecting egg quality, and alleviates PCOS by reducing OS. An excessive gonadotropin level in adults is an indicator of premature ovarian failure, whereas its excessive levels confer a higher risk for bone loss and cognitive impairment during the perimenopausal period. Similarly, PRL functions are timely regulated. PRL promotes lactation in women, and its accurate regulation is fundamental for the development of healthy pregnancies. Thus, data indicate that these hormones play indispensable roles in different growth stages of the human body.

Overall, hormone regulation of the pituitary function is extremely complex and integrates multiple regulatory levels, ranging from subcellular to extracellular processes. Hormonal recombination agents are more effective than oral drugs. Although hormonal recombination agents are used to treat developmental abnormalities and reproductive disorders, the therapeutic effects come at the expense of several side effects, such as the increased risk of multiple births, in cases where gonadotropins are used to treat infertility. The use of hormonal therapy, using single or multiple agents requires further research, in order to limit the currently observed side effects of such treatment approaches. The present review integrated recent research results, aiming to provide new guidelines for future treatment strategies for clinical management and further drug development.

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Authors' contributions

ZW performed the data collection. HQ performed the data curation. HW wrote the manuscript. WT and SQ prepared the figures. JD and PW revised the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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