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INTEGRATED STUDY MASTER'S THESIS

Hyperprolactinemia and Hypoprolactinemia: Causes and Management

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Summary

Prolactin is also defined as a lactogenic hormone that is secreted by the anterior pituitary gland. It is crucial to note menstrual cycle can be affected by this hormone and spermatogenesis in males. In order for the reproductive system and fertility to be adequate, a normal range of prolactin is crucial. However, there are also effects of excess or lack of prolactin, hyperprolactinemia and hypoprolactinemia on the reproductive and fertility capabilities. Hyperprolactinemia can also be associated with a decrease in libido among people, including men. This condition is also related to prolactinomas which are prolactin secreting tumors. The treatment of this disease includes dopamine that are known to decrease prolactin levels and tumor sizes. Aside from hyperprolactinemia, other forms include low prolactin levels which are not as common for most people. In association with other complications it can result in hormone imbalance, therefore affecting an individual's reproductive health. Other health issues extending from hormone-specific to genetic problems can cause lactation failure in women as well as menstrual irregularity. Due to this effect, these conditions can result in hormone imbalance that can negatively affect reproductive health and diagnostic procedures such as blood tests and imagine examinations are crucial. If not treated, these conditions can cause reproductive tract dysfunction and various health complications.

Due to recent improvements in diagnostic and treatment approaches, there has been significant advancements in diagnosing prolactin related disorders. The ongoing research of the various roles of prolactin in the body are still being carried out to help with more effective treatment methods. Along with investigations of the physiological roles of prolactin and how its fluctuations relate to treatment options for hyper and hypoprolactinemia, this literature review emphasizes the importance of hormone regulation for reproductive health.

Keywords

Prolactin, hyperprolactinemia, hypoprolactinemia, reproductive health, prolactinoma, dopamine agonists, infertility, lactation, pituitary gland, hormone regulation.

List of Abbreviations

CNS - Central Nervous System

CT - Computed Tomography

ED - Erectile Dysfunction

FNA - Fine Needle Aspiration

FSH - Follicle-Stimulating Hormone

GnRH - Gonadotropin-Releasing Hormone

HPG - Hypothalamic-Pituitary-Gonadal

HPT - Hypothalamic-Pituitary-Thyroid

HRT - Hormone Replacement Therapy

LH - Luteinizing Hormone

MRI - Magnetic Resonance Imaging

PCOS - Polycystic Ovary Syndrome

PCT - Prolactin Cell Tumor

PRL - Prolactin

PRLR - Prolactin Receptor

PTSD - Post-Traumatic Stress Disorder

SPRMs - Selective Prolactin Receptor Modulators

TRH - Thyrotropin-Releasing Hormone

1. Introduction

Prolactin is initially recognized as a lactogenic hormone, which facilitates the start and maintains milk production after birth; its role extends beyond lactation. The regulation of the menstrual cycle is influenced by prolactin, particularly by modulation of the secretion of gonadotropin-releasing hormone (GnRH), which affects the release of estrogen and progesterone, which are reproductive hormones. This complex hormonal interplay aids in regulating ovulation and prepares the body for potential pregnancy. In men, it is produced in small amounts but plays a vital role in maintaining healthy sperm release and controlling testosterone. Therefore, the hormone's influence on reproduction is not limited to one gender, highlighting its broader significance in human biology.

Interruptions in prolactin levels can have profound impacts on reproductive health. Excessive prolactin is responsible for irregular menstrual cycles in women and reduced libido and infertility in men. The cause of hyperprolactinemia can vary from including benign pituitary tumors, known as prolactinomas, and using various medications such as antipsychotics. Hypoprolactinemia, although it is less frequent, can be noted due to low prolactin levels, which can cause mothers to fail breastfeeding after giving birth, along with irregular menstrual cycles. It is crucial to well-regulate hormone balance for healthy reproductive function.

This literature review aims to provide insight into prolactin's function in reproductive health by analyzing its physiological roles, the result of abnormal prolactin levels, and the management of related disorders. This review intends to consolidate recent research to give a clear understanding of how prolactin imbalances influence reproductive health and to provide recommendations for treatment strategies.

2. Physiological roles of prolactin

2.1 Synthesis and regulation of prolactin

Prolactin is mainly produced by lactotroph cells that are found in the anterior pituitary gland, a gland in the brain that controls the release of hormones. The anterior pituitary gland is a part of a larger structure called the pituitary gland, which also includes the posterior pituitary gland. The hypothalamus is found above the pituitary and controls its functions through the infundibulum. The anterior pituitary is further divided into three parts, pars tuberalis, pars intermedia, and pars distalis, all of which secrete hormones (Alatzoglou et al.,

2020). Therefore, it is a essential part of the brain that controls the various hormonal functions. The findings done by Dobolyi et al. (2020) indicate that prolactin synthesis and secretion are mainly controlled by dopamine, which is a neurotransmitter that inhibits its secretion. Dopamine, in this case, dopamine serves to prevent high levels of prolactin from occurring in any situation that may occur outside the normal domain. The thyrotropin-releasing hormone is produced and released from the hypothalamus, which stimulates the release of TSH and prolactin from the anterior pituitary. In this case, it affects the volume of prolactin released under certain conditions such as pregnancy and lactation period. The prolactin production must be maintained at a reasonable level. This happens when there is a balance between dopamine and TRH stimulation. Estrogen causes an increase in prolactin level synthesis through the growth of the uterus and the placenta during lactation. Freeman et al. (2000) also indicated that such implants would not be observed where there is the incorrect activity of dopamine or TRH overdrive; in that case, incorrect amounts of prolactin, leading to medical problems such as hyperprolactinemia and hypoprolactinemia.

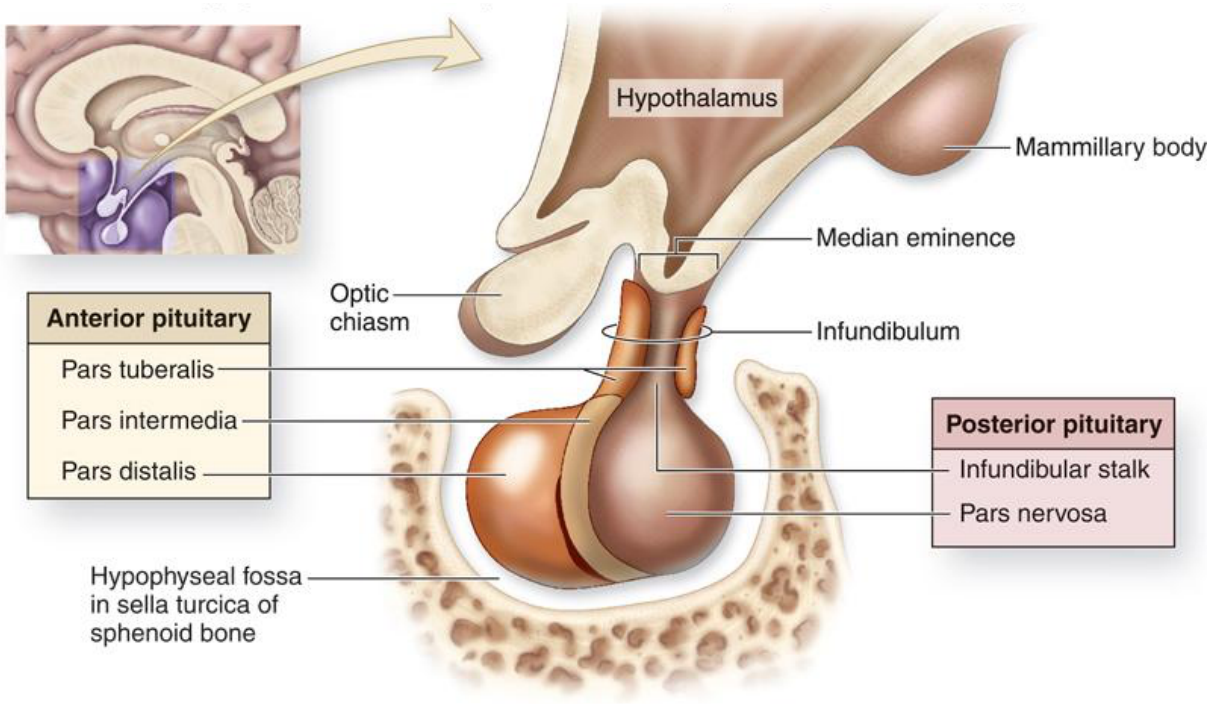

Figure 1: Anatomy of the Hypothalamus and Pituitary Gland

The structure of the hypophysis is presented on the figure. The figure illustrates the hypophysis anatomy and structure. The figure has been adapted from Ismaili, R. (2024). Growth Hormone Secretory Organ—Structure—Mode of Action. ResearchGate. https://www.researchgate.net/figure/Structure-of-the-pituitary-gland-5_fig1_380856338

2.2 Prolactin's role in lactation and reproductive function

2.2.1 Impact on mammary gland development and lactation

Prolactin is widely recognized for its role in lactation, especially in relation to the growth of the mammary gland during pregnancy and milk production after childbirth. Prolactin stimulates the mammary glands' alveolar cells, which produce milk growth throughout pregnancy, preparing for breastfeeding (Alex et al., 2020). Prolactin levels increase significantly following childbirth, triggering the production and secretion of milk to feed the newborn. The release of prolactin is maintained through a feedback loop during breastfeeding, ensuring prolactin continues to be released. When the infant suckles at the breast, it causes the brain to receive sensory signals, which causes the anterior pituitary to release prolactin if breastfeeding is sustained. Without adequate prolactin levels, lactation could be impaired, which makes it challenging for women to breastfeed their infants successfully.

2.2.2 Influence of gonadal function, ovulation, and hormone balance

Prolactin plays a vital role in lactation and in the synthesis and equilibrium of other hormones. Prolactin inhibits the secretion of GnRH from the hypothalamus and, consequently, FSH and LH from the pituitary gland in females (Laoharatchatathanin et al., 2023). It has an essential function in ovulation and regulation of the menstrual cycle. The hypothalamus is a structure of the brain that is situated at the base of the brain. It is closely related to the pituitary gland, a vital endocrine gland that controls hormones. FSH and LH are secreted by the anterior pituitary, while the posterior pituitary releases hormones that are produced by the hypothalamus but stored in the posterior pituitary (Bosch et al., 2021).

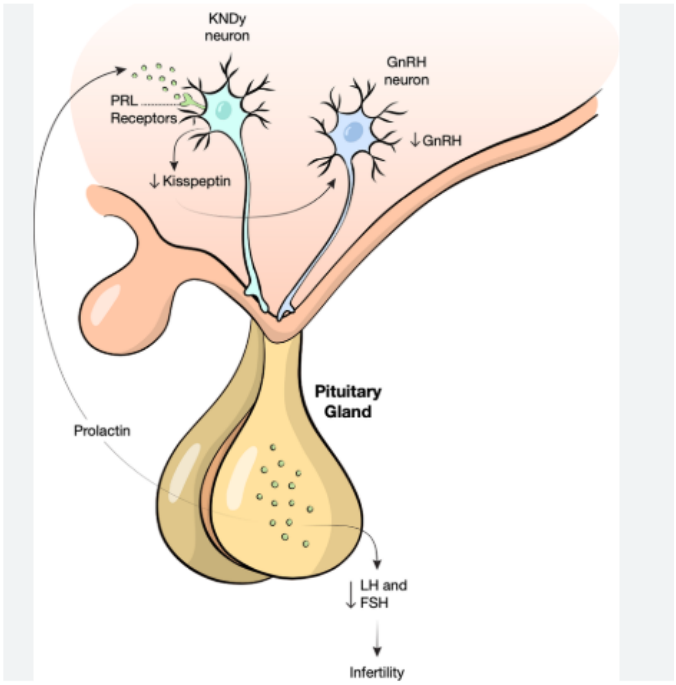

Figure 2: Prolactin's Influence on Reproductive Hormones and Fertility

The infundibulum is located between the hypothalamus and the pituitary gland, as illustrated below, leading to facilitating the two structures to interact. Prolactin levels in blood serum may fluctuate in different physiological conditions and are usually within the range of 4.8-23.3 ng/mL in women and 2.1-17.7 ng/mL in men. This is because hormonal imbalance due to increased or decreased levels of prolactin in the body affects fertility and menstrual cycle.

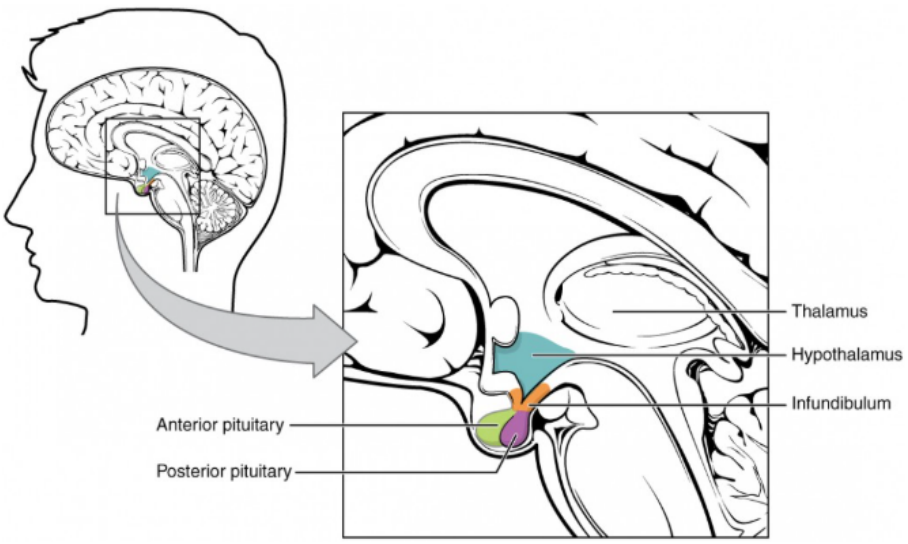

Figure 3: The Pituitary Gland and its Connections with the Hypothalamus

Note. From The pituitary gland and hypothalamus, by Lumen Learning, n.d. (https://courses.lumenlearning.com/suny-ap2/chapter/the-pituitary-gland-and-hypothalamus/).

According to di Filippo et al. (2020), this hormonal imbalance can be caused by hyperprolactinemia, which is a condition that results in high levels of prolactin in the body, this can lead to menstrual irregularities such as amenorrhea or oligomenorrhea. In men, prolactin controls testosterone secretion through the testes. Prolactinemia leads to hypogonadism, which in turn reduces testosterone levels and sexual desire and impairs fertility. Prolactin is a hormone in the regulation of hormones and fertility in both male and female individuals.

2.3 Mechanism of prolactin action

2.3.1 Prolactin receptors and JAK-STAT signaling pathway

Prolactin targets tissues by binding to specific prolactin receptors in various tissues, including the ovaries, breasts, testes, and immune system. Prolactin binds to its receptor, activating a signaling cascade mediated by the Janus kinase-signal transducer and activator of the transcription (JAK-STAT) pathway. Rajakumar and Pugalendhi (2023) state that this pathway is involved in gene regulation by relaying signals from prolactin receptors on the cell membrane to the nucleus. The activation of the JAK-STAT pathway is beneficial in the growth and differentiation of cells, particularly in the mammary glands, as it tries to prepare the breasts for lactation (Rajakumar & Pugalendhi, 2023). These signals also play a role in reproductive tissues, promoting hormone production and aiding in reproductive functions. If disruption occurs in these signaling pathways, it can contribute to abnormal prolactin levels and associated health issues such as reproductive disorders and lactation failure.

2.3.2 Variations in prolactin levels during pregnancy, stress, and other factors

Prolactin levels vary as a natural response to different physiological conditions and external factors. In pregnancy, there is a precise elevation in prolactin levels. Hannan et al. (2023) note that these levels rise steeply as they build up the body for lactation, and this rise is mainly due to a rise in estrogen levels. Beyond pregnancy, other factors such as stress, physical exertion, and sleep can also influence prolactin levels. Stress can cause an increase in prolactin levels in the body, especially when one is under pressure (Ng & Chin, 2021). Stress hormones such as cortisol and adrenaline can indirectly stimulate the pituitary gland to release more prolactin; however, this increase is typically short-lived as the stress factors withdraw. During physical activity, prolactin levels increase as well. However, this is a normal

physiological response to physical activity and is also short-lived. Prolactin levels rise during deep sleep, with its peak concentration occurring in the early morning hours.

Understanding these natural variations in prolactin levels is crucial to differentiate between the normal physiological and pathological changes in hyperprolactinemia or hypoprolactinemia. By understanding prolactin's physiological roles and mechanisms, clinicians can better manage and treat the condition more effectively.

3. Hyperprolactinemia

3.1 Definition

Hyperprolactinemia is characterized by the elevation of prolactin in the blood, according to the research done by Starace et al. (2019). Hyperprolactinemia can be classified into three categories: pathologic, pharmacologic, and physiologic, according to Chutpiboonwat et al. (2020). Prolactin is a hormone in charge of encouraging milk production following childbirth. On the other side, it also regulates both sexes' reproductive processes. Under normal conditions, dopamine inhibits the release of prolactin, keeping its level under control (Chutpiboonwat et al., 2020). This equilibrium is impaired in hyperprolactinemia, resulting in excess prolactin production. Greater levels of prolactin are considered acceptable during pregnancy and lactation; however, outside of these physiological circumstances, they appear questionable as they can result in a variety of reproductive health problems.

3.2 Prevalence

3.2.1 Prevalence in women

Women are the most prone to have hyperprolactinemia, specifically as they reach the reproductive age. Research done by Mancini, Casanueva, & Giustina (2013) suggests that the prevalence of hyperprolactinemia ranges from 0.4% in the unselected adult population and can range up to as high as 9-17% in women with reproductive diseases. In other cases, it was found to be 5% in family planning clinics, in women with adult-onset amenorrhea to be 9%, and among women with polycystic ovary syndrome to be 17%. Women with high prolactin levels can experience anovulation (lack of ovulation), amenorrhea (absence of menstruation), or irregular periods. In clinical situations like these, it is an essential indication to get a further diagnosis.

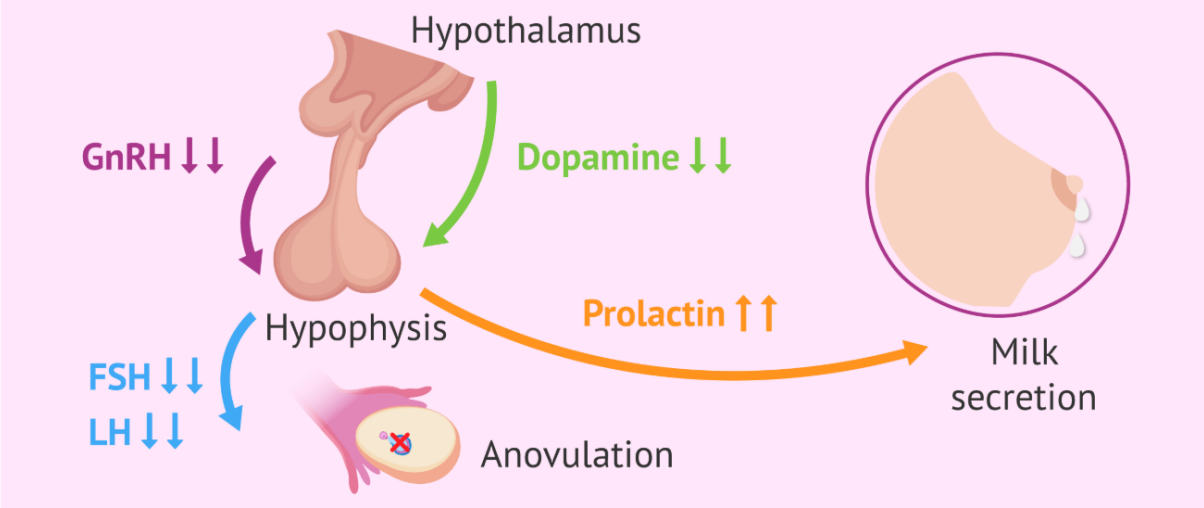

Figure 4: Hyperprolactinemia in women

Note. From "What is hyperprolactinemia?" by inVitra, 2022. (https://www.invitra.com/en/hyperprolactinemia/). © 2022 inVitra.

3.2.2 Prevalence in men

Men with hyperprolactinemia have lower testosterone levels along with a lower total motile sperm count in comparison with men without hyperprolactinemia. According to McCartney, C. R., & Marshall, J. C. (2021), 43.1% of men with hyperprolactinemia were found to have oligospermia in comparison with men without hyperprolactinemia 21.5%. There is a less frequent diagnosis of hyperprolactinemia in men than in women. Hyperprolactinemia may also manifest with other symptoms like low sexual desire, impotence, and reduced muscle mass (Vilar et al., 2019). The awareness of hyperprolactinemia is often delayed as men don't have menstrual irregularities, such as women, to bring attention to their reproductive system, leading to late observation to seek medical attention to receive a diagnosis.

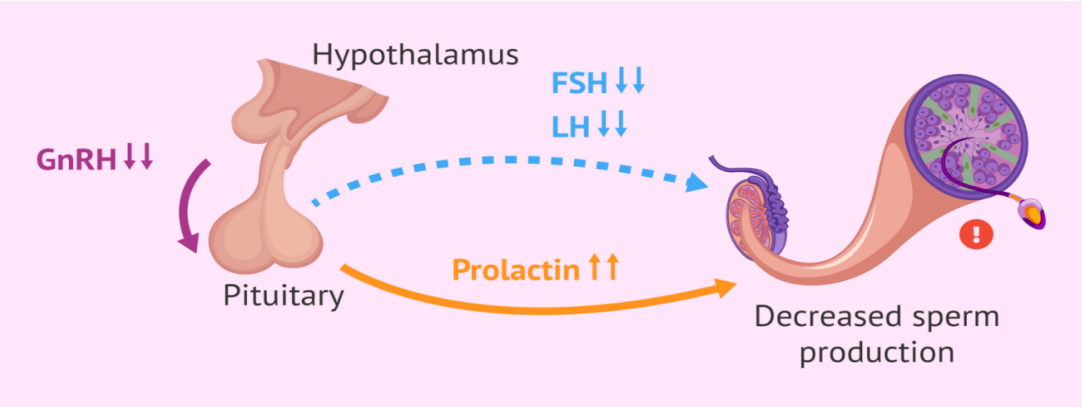

Figure 5: Effect of Hyperprolactinaemia on Male Fertility

Pre-testicular causes of male infertility. Reprinted from Male infertility because of pre-testicular factor, av C. Mestre Ferrer, n.d., inviTRA (https://www.invitra.com/en/male-infertility-because-of-pre-testicular-factor/). Copyright inviTRA.

3.3 Underdiagnosis and diagnostic challenges

Signs and symptoms of hyperprolactinemia may vary from individual to individual and can often appear subtle or unspecific. Research done by Eftimov et al. (2020), symptoms in women can present as mild to moderate menstrual disturbances, and it can be easily mistaken and be associated with factors such as stress or weight changes, causing it to be undiagnosed in women. Not all women with hyperprolactinemia experience clear signs and symptoms such as galactorrhea or menstrual abnormalities. In both sexes presenting with symptoms such as sexual dysfunction or infertility, it does not indicate a direct relation to hormone abnormalities. The temporary rise in prolactin due to stress or drug use can also provide diagnostic problems as it can mask the underlying issue (Raveendran, 2021). Despite its significant effects on reproductive health, hyperprolactinemia can go undiagnosed.

3.4 Impact on fertility

The hypothalamic secretion of GnRH is suppressed by prolactin in women. Koniares et al. (2023) notes that GnRH leads to secretion of luteinizing and follicle-stimulating hormones by the anterior pituitary gland. These hormones have a significant role for ovulation and the menstrual cycle. Koniares et al. (2023) also adds that hyperprolactinemia can suppress GnRH and result in amenorrhea, oligomenorrhea, and other menstrual problems. This may be due to the reduced levels of LH and FSH in women with hyperprolactinemia.

It is also important to note that the endometrium lining can become thin, and fertility levels can be low due to the low estrogen levels. Higher rates of infertility are due to the inability of a fertilized egg to implant in the endometrium. Lim & Khoo (2020) also note that fertility is also greatly affected in men with hyperprolactinemia due to the blocked production of testosterone. Testosterone is required for sperm development and other sexual activities in the body. According to Bendarska-Czerwińska et al. (2023), decreased sperm count or the lack of sperm, oligospermia or azoospermia may be due to hyperprolactinemia, as it interferes with the function of the testes to produce sperm.

3.5 Importance of early diagnosis

Early detection and diagnosis of the etiology of the symptoms are essential to manage the effects of hyperprolactinemia on reproductive health. Early detection of signs and symptoms can prevent its adverse effects on the reproductive system (Melgar et al., 2016). This is necessary to prevent later invasive procedures for conception, reduce psychological distress and enhance the patient's autonomy in making decisions on their reproduction. Early management and treatment can also prevent further advancements of prolactinomas and the likelihood of further complications. As prolactinomas occur in the pituitary gland they can cause headaches, vision disturbances and other neurological symptoms. Iancu et al. (2023) state that standard diagnostic testing can detect these tumors early before they case significant harm. When prolactinomas are detected and diagnosed early, medical professionals can manage them in a variety of ways, including medication, monitoring or, in extreme cases, surgery. Specifically in patients with reproductive or sexual health issues.

3.6 Causes

3.6.1 Physiological Causes

Pregnancy and nursing are the most common physiological causes of hyperprolactinemia (Vilar et al., 2019). The drastic hormonal changes, particularly increased estrogen levels, trigger these symptoms. Alex et al. (2020) explain that elevated estrogen stimulates the anterior pituitary gland to secrete prolactin, preparing the breasts for lactation. This hormonal surge supports breast development and the initiation of milk production after childbirth. Prolactin levels remain elevated throughout the nursing period to ensure continuous milk production. This natural increase in prolactin is a normal physiological response and is not considered a pathological condition in motherhood. On the other hand, temporary hyperprolactinemia can result from physical and emotional stress. During stressful situations, the body releases stress hormones such as cortisol and adrenaline, which indirectly stimulate prolactin secretion by the pituitary gland. Raveendran (2021) notes that in most

cases, this form of hyperprolactinemia is transient and resolves once the stressor is eliminated. Understanding the relationship between stress and prolactin levels is crucial for the early diagnosis and treatment of hyperprolactinemia.

Hyperprolactinemia can also be physiological, occurring due to physical exercise or sleep disorders. Philippou et al. (2017) highlight that prolactin levels fluctuate throughout the day, often peaking during sleep due to the body's circadian rhythm. Testing prolactin levels at specific times can help identify this nocturnal rise, which may cause temporary elevations. Similarly, physical exertion can briefly increase prolactin levels as a normal physiological response to stress. These temporary increases in prolactin are generally harmless and should not be misinterpreted as pathological hyperprolactinemia. Recognizing these physiological factors enables healthcare professionals to diagnose and interpret prolactin levels accurately.

3.6.2 Pharmacological causes

Antipsychotics such as risperidone and haloperidol block the dopamine receptors in the brain, which can be associated with hyperprolactinemia. When dopamine receptors are blocked it can result in increased prolactin levels Lyons et al., 2016). Research done by Lyons et al., 2016). Demonstrates that SSRIs including sertraline and fluoxetine can cause an increase in prolactin by the effect of serotonin levels. Metoclopramide is commonly used to treat nausea and vomiting and stimulates the release of prolactin by antagonizing dopamine receptors (Al-Kuraishy et al., 2022). Also, other antihypertensives specifically those that act on the central nervous system result in hyperprolactinemia development. Drug induced hyperprolactinemia is typically reversible once the medication is discontinued by the patient or substituted with a different alternative that does not impact prolactin secretion. Prolactin levels return then to normal, and symptoms will gradually resolve. However, medical professionals need to evaluate the side effects of these drugs with great attention. Ensuring open communication is required in order to make timely diagnosis and give appropriate treatment recommendations.

3.6.3 Endocrine disorders

Endocrine disorders, specifically those that involve the thyroid or adrenal glands, can also lead to hyperprolactinemia. Low thyroid hormone levels and hypothyroidism trigger the increased release of thyrotropin-releasing hormone (TRH) from the hypothalamus (Simonsen & Rejnmark, 2021). The increase of thyrotropin-releasing hormone stimulates the anterior pituitary gland and thyroid gland to increase the prolactin secretion. Another complication of adrenal insufficiency is hyperprolactinemia due to the disruption of the hormonal feedback

loop (Simonsen & Rejnmark, 2021). The imbalances may worsen the symptoms of hyperprolactinemia and further interfere with the body's reproductive functions.

3.6.4 Pathophysiology and clinical manifestations

3.6.4.1 Inhibition of GnRH

The pathophysiology of hyperprolactinemia is related to the effects of high prolactin levels and the release of GnRH from the hypothalamus. GnRH role is crucial in the reproductive system as it stimulates the release of necessary hormones such as luteinizing and follicle-stimulating hormones. Calik-Ksepka et al., 2022) note that these hormones are essential to maintain normal functioning of the reproductive system. LH and FSH regulate the menstrual cycle in women promoting the growth of ovarian follicles and induce ovulation. In men these hormones support sperm production and regulation of testosterone levels (Sun et al., 2019). Disruption of GnRH secretion through hyperprolactinemia can affect fertility and overall reproductive health.

When prolactin levels increase significantly, they suppress the secretion of GnRH, which results in decreased LH and FSH levels in the blood (Koniares et al., 2023). Suppression of LH and FSH in women can lead to menstrual irregularities, including oligomenorrhea or amenorrhea. Insufficient levels of these hormones disrupt ovulatory process creating difficulties in conceiving. In men, low LH and FSH levels testosterone production is disrupted leading to infertility.

The suppression of GnRH has effects beyond just fertility, in women, prolonged suppression of reproductive hormones can lead to secondary sexual characteristics, such as breast alterations, and decreased libido. In men, decreased LH levels and low testosterone levels can lead to symptoms such as hypogonadism, decreased libido, erectile dysfunction and fatigue (Bendarska-Czerwińska et al., 2023). The intricate relationship between prolactin, GnRH and reproductive hormones is important to understand the implications of hyperprolactinemia on reproductive health.

3.6.4.2 Menstrual disorders and infertility

LH and FSH are key regulators for the development of ovarian follicles and ovulation. Clinical manifestations of hyperprolactinemia cause inhibition of these hormones and lead to anovulation and menstrual disturbances (Fachi et al., 2021). When ovulations do not occur,

mature ova are not released from the ovaries resulting in failure to conceive. In addition, hyperprolactinemia can cause luteal phase defects. The luteal phase occurs after ovulation and is essential for sustaining and establishing a pregnancy.

According to Eftimov et al. (2020), during this phase, progesterone is produced which prepares the uterine lining for implantation. However, since LH stimulates progesterone production, the suppression of prolactin- induced LH can impair this process. As a result, this creates a less favorable environment and does not support implantation, increasing the risk of early miscarriage in case of conception. These factors emphasize the need for early diagnosis and proper management strategies to reduce the impact of hyperprolactinemia on women's reproductive health (Raveendran, 2021).

3.6.4.3 Galactorrhea and Hypogonadism

Galactorrhea is the spontaneous secretion of milk from the breasts. It is a symptom of hyperprolactinemia which affects both men and women due to overstimulation of mammary glands. Tritos and Miller (2023) define galactorrhea as a spontaneous secretion of milk from the breasts. In women prolactin is routinely secreted during pregnancy and lactation in order to stimulate the production of milk (Fang et al., 2024). In case of hyperprolactinemia galactorrhea may occur even in the absence of pregnancy and lactation. This spontaneous milk discharge can be worrying for individuals and create phycological distress, which usually is associated with underlying hormonal imbalance.

In men, increased prolactin levels can suppress secretion of LH is crucial for testosterone production in the testes (Al-Kuraishy et al., 2022). Low levels of testosterone include various symptoms such as, decreased libido, decreased muscle mass, fatigue and erectile function all which cause a significant impact on their quality of life.

Women with hyperprolactinemia can have reduced estrogen levels, which have a range of different symptoms. estrogen is important in the body for various reproductive functions which include, bone density, mood, and cholesterol balance which is increased with HDL and decreased with LDL (Gleeson et al., 2016). Other symptoms such as vaginal dryness can cause pain during sexual intercourse can also be experienced in women when prolactin levels are high, and estrogen levels are low. Other symptoms that are commonly linked with vaginal dryness include hot flashes, mood swings and sleep disturbances (Starace et al 2019).

3.6.5 Neurological symptoms

When hyperprolactinemia is caused by prolactinoma, the patients may experience neurological symptoms due to the pressure exerted by the tumor on surrounding structures in the brain (Koller & Abad-Santos, 2020). Macroprolactinomas, also known as large prolactinomas, can compress the optic chiasm and cause visual disturbances, such as blurred vision or loss of peripheral vision. Patients with large prolactinomas can also experience symptoms such as headaches. The severity of the neurological symptoms often depends on the size of the tumor, with larger tumors having a more significant impact and discomfort.

3.7 Diagnosis and management

3.7.1 Diagnosis

Hyperprolactinemia diagnosis involves blood tets to measure serum prolactin levels, Dobolyi et al. (2020) indicate that this initial test can determine wether the prolactin levels are within normal range or above. Normal blood serum prolactin concentration are between are 4.8-23.3 ng/mL in women and 2.1-17.7 ng/mL in men. It is imporantent to highlight that hyperprolactinemia is not always accurate and can be caused by other factors than pituitary adenomas. In some cases high prolactin levels can be due to macroprolactinemia. Macroprolactinemia is defined by the presense of prolactin in large molecular forms like the big prolactin or big-big prolactin (Glezer & Bronstein, 2022). Prolactin in these large forms can be measured in the blood but are not active biologically and do not cause symptoms of true hyperprolactinemia. Tests such as polyethylene glycol (PEG) are used to differentiate between macroprolactinemia and true hyperprolactinemia and is done by separating the large prolactin complexes from the smaller, active monomeric prolactin (Hu et al., 2021). Clinicans can therefor avoid treating these patients with macroprolactinemia. as they present with elevated prolactin levels due to these large prolactin forms.

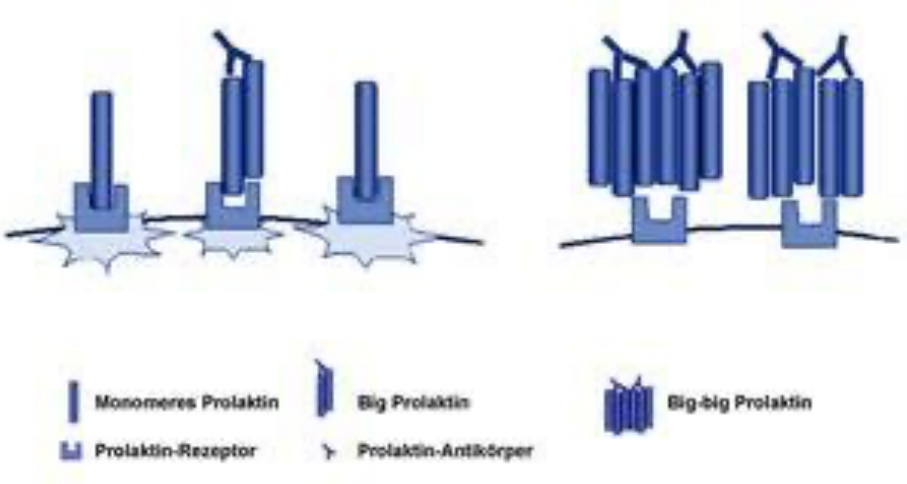

Figure 6: Prolactin Isoforms and Their Receptor Binding

Illustration of how hyperprolactinemia affects reproductive function. Adapted from "Hyperprolactinemia and Reproduction: New Concepts" by J. Young, 2012, Journal für Reproduktionsmedizin und Endokrinologie, 9(3), pp. 157-162 (https://www.kup.at/journals/abbildungen/5438.html). Copyright 2012 by Krause & Pachernegg GmbH.

3.7.2 Dopamine Agonists

The first-line pharmacological therapy for hyperprolactinemia is dopamine agonists, which include cabergoline and bromocriptine. Choi and Horner (2023) state that these drugs target dopamine receptors in the brain, and they help suppress the release of prolactin from the pituitary gland. These drugs work by mimicking the action of dopamine and can also reduce prolactin levels and even shrink the size of the prolactinomas, which are the benign tumors that cause most cases of hyperprolactinemia (Koller & Abad-Santos, 2020). Dopamine agonists are safe and effective with high efficacy rates, which makes them the first-line treatment for this condition. Most patients report a marked improvement in their symptoms, including the return to normal prolactin levels and alleviation of related reproductive disorders. The primary treatment for elevated prolactin levels is dopamine agonists such as quinagolide, cabergoline, and bromocriptine. By interacting with the brain's dopamine D2 receptors, these medications help reduce prolactin. Additionally, they can reduce tiny tumors that raise prolactin levels. Because it has fewer negative effects and lasts longer, cabergoline is recommended. In the UK, quinagolide, commonly known as Norprolac, is used to treat breast pain.

3.7.3 Surgical Intervention

In some cases, when prolactinomas are large and compressing the surrounding structures (macroprolactinomas) or when medical management is ineffective, surgery may be required. Transsphenoidal surgery is the most frequently used technique to perform the resection of prolactinomas (Fukuhara et al., 2022). This is a less invasive surgery that enables surgeons to operate on the tumor through the nostrils without having to open the skull. The aim of the surgery is not only to excise the tumor but also to relieve the pressure that it may be exerting on the surrounding structures like the optic nerves, which may cause vision problems and headaches.

Surgical intervention is most appropriate for patients who have side effects from medications or those who do not respond well to dopamine agonists. Transsphenoidal surgery is considered safe and effective, particularly for macroprolactinomas; most patients have been reported to have low prolactin levels and clinical improvement after the surgery (Dobolyi et al., 2020). However, surgery has its own risks, which include bleeding, infection, and damage to the surrounding tissues. It is usually used in certain circumstances where the advantages of surgery outweigh the disadvantages mentioned above. It is, therefore, important to have regular follow-up and monitoring of prolactin levels after surgery to ensure that the condition does not reoccur, and that any residual tumor tissue is dealt with.

4. Hypoprolactinemia

4.1 Definition

Hypoprolactinemia is a condition in which the levels of prolactin hormone in the body fall below the normal range, and this hormone is produced in the pituitary gland (Kelestimur & Ioachimescu, 2024). This hormone plays a key role in regulating reproductive functions like lactation after birth and menses. When the levels of prolactin are low, these functions are disrupted, and this affects the reproductive health. Although hypoprolactinemia is not as frequent as hyperprolactinemia, it is said to be clinically relevant in terms of fertility, contraceptive intentions, and sexual functions. This condition can affect both male and female individuals, but the symptoms and causes may vary between the two sexes. In men and women, hypoprolactinemia can be due to pituitary gland dysfunction, the presence of certain medications, or any other diseases.

4.2 Prevalence

4.2.1 Prevalence in Women

While hypoprolactinemia is not as prevalent in women as other hormonal disorders, it is still clinically significant even when it is not very frequent. Mahzari et al. (2022) state that women of childbearing age potential are at a higher risk, especially if they have a pituitary gland disease such as a tumor or an inflammation. In addition, dopamine agonists can induce hypoprolactinemia as it suppresses prolactin secretion. SSRIs are commonly used to treat depression; this may lead to low prolactin levels by altering dopamine regulation. Other situations, such as intense exercise and chronic stress, can cause hormonal imbalances and reduced prolactin levels. Breastfeeding problems, infertility, and severe menstrual cycle disturbances are the most significant features of the female population (Mahzari et al., 2022). However, most women with hypoprolactinemia can spend years without being diagnosed since the symptoms are often mistaken for those of other reproductive diseases.

Iancu et al. (2023) suggest that women who experience infertility or recurrent pregnancy losses may have imbalances of prolactin, including hypoprolactinemia. In addition, due to the effects of vaginal dryness and reduced sexual desire, this illness can also affect sexual dysfunction, which may complicate sexual relationships. Because the disorder is so rare, physicians often diagnose it later in life and focus more on other reproductive issues, such as PCOS or thyroid issues. However, women with unexplained infertility or those who are trying to conceive may experience disruptions in ovulation due to abnormal prolactin levels. In this case, enhancing the health status of the affected females involves raising awareness among patients and healthcare providers about this condition (Iancu et al., 2023).

4.2.2 Prevalence in Men

It is also necessary to mention the psychological aspects as well because even though hypoprolactinemia is not necessarily only exclusive to women, it is more frequently diagnosed in women due to its impact on fertility and the menstrual cycle. In men, it is often overlooked, leading to underdiagnosis. Corona et al. (2024) state that in men, prolactin has an important role in regulating the hypothalamic-pituitary-gonadal axis; the HPG axis affects testosterone production and, therefore, has a negative impact on the libido, spermatogenesis, and low prolactin levels. Men with hypoprolactinemia experience a range of signs and symptoms, including low libido, erectile dysfunction (ED), and fatigue, but these are often

overlooked or misdiagnosed. Such symptoms are usually attributed to stress, age, or other diseases, which may lead to a wait for a definite diagnosis and treatment (Corona et al., 2024).

Petersenn et al. (2023), however, note that dopamine agonists and opioids, in particular, reduce prolactin levels in men even further, which is detrimental to their reproductive health. Other causes of hypoprolactinemia include chronic stress, usage of PTSD-related medications, and pituitary tumors that can disrupt hormonal balance. Low sperm count or poor sperm quality is another reason why some men with fertility issues may opt for prolactin assays to determine whether hypoprolactinemia is a factor. Increased awareness about the negative impacts of low prolactin in men could improve the management of the condition (Petersenn et al., 2023). Hypoprolactinemia receives little attention, causing a great impact on male reproductive health. Therefore, further research and discussion are crucial for better management.

4.3 Underdiagnosis and Diagnostic Challenges

Even though hypoprolactinemia is not considered a severe disease due to its mild symptoms, it can become challenging due to low awareness and underdiagnosis. Unlike in hyperprolactinemia, the symptoms can appear very distinct, such as galactorrhea; in hypoprolactinemia the symptoms are often nonspecific and vague. This can include headaches, dizziness, hot flushes, night sweats, heavy bleeding, irregular periods, fatigue, and loss of libido, which are often attributed to one or another common disease, which results in a higher number of misdiagnoses or no treatment at all (Krysiak et al., 2024). Prolactin is not normally included in standard hormonal testing unless there is a clinical suspicion of pituitary dysfunction or reproductive axis dysfunction.

Rastrelli et al. (2015) also pointed out that another challenge is that most patients do not present themselves to be treated for diseases they consider to be biopsychosocial transformations. For instance, men consider low sexual desire as age, while women consider missed periods as a sign of stress. The lack of routine prolactin screening in the general population and in those without access to specialized care can further exacerbate the problem. Doctors may first diagnose and manage easily manageable diseases such as thyroid or low testosterone when the patient presents with fertility problems and, therefore, do not diagnose low prolactin levels for a longer time (Rastrelli et al., 2015). This ~~type of~~ diagnostic error underlines the need to expand the knowledge about hypoprolactinemia and enhance the diagnostic process.

4.4 Impact on Fertility

Because of natural conditions, patients with hypoprolactinemia are unable to conceive. Iancu et al. (2023) also pointed out that women with irregular menstrual cycles may have low prolactin levels, leading to irregular ovulation or anovulation. In this regard, the low frequency of ovulation reduces the chances of conception and, pregnancy (Iancu et al., 2023). Also, hypoprolactinemia in women may lead to luteal phase defects, which are likely to lead to early pregnancy loss because a specific lining of the uterus is not provided for implantation. The chances of miscarriage rise when one conceives despite low prolactin, which makes it hard to carry a pregnancy to full term.

Grande et al. (2022) have stated that prolactin plays a role in modulating testosterone in males, which is important for sperm production and sexual activity. Low prolactin levels can also be a factor in male infertility as it reduces sperm count and quality. Besides erectile dysfunction and low sexual desire, Krysiak et al. (2022) add that hypoprolactinemia also affect the ability of a man to have regular intercourse that is necessary for conception. Since it has been established that increasing prolactin levels may help a couple conceive, prolactin testing should be included in the examination of infertile couples (Grande et al., 2022). This is why it is important to diagnose hypoprolactinemia and treat it as early as possible, as it affects fertility.

4.5 Importance of Early Diagnosis

It is, therefore, very crucial to diagnose hypoprolactinemia as early as possible to prevent future problems and enhance their reproductive capabilities. If such conditions are diagnosed at an early stage, the primary conditions, such as pituitary dysfunction or some drug effects, can be managed early, and proper management can be initiated. For women who want to conceive, it is advisable to take medication or hormone therapy to reduce the prolactin level to normal so that ovulation can occur. It could be the same with hypoprolactinemic men who may be able to use testosterone replacement to produce more sperm and enhance their sexual prowess to increase their chances of fathering a child.

This agrees with the findings of Sharma & Shrivastava (2022), where early diagnosis is also deemed useful to the individual in reducing emotional or psychological stress arising from infertility. Infertility issues that couples who have been attempting to conceive may experience include chronic stress, anxiety, and strained relationships, which makes the process of conception even more challenging. If hypoprolactinaemia is diagnosed and treated

early, the emotional stress that the couple undergoes would be reduced, and they would be able to focus on the actualization of their family expansion goals. Urhan and Karaca (2022) note that it also eliminates many other health complications associated with hormones, such as osteoporosis or metabolic diseases that low prolactin levels in the body may cause.

4.6 Causes

4.6.1 Primary Causes

The primary causes of hypoprolactinemia are when there is a problem with the pituitary gland that leads to low levels of prolactin, which is a reproductive hormone. Low prolactin levels may also be seen at birth due to congenital underdevelopment of the gland and hypopituitarism. As Saadeh et al., 2024 mentioned, other important genetic mutations interfere with the normal secretion of prolactin, but these are rare. Benign pituitary tumors may be responsible for hyperprolactinemia states, but when such tumors grow large enough to destroy hormone-secreting cells, they may also be responsible for hypoprolactinemic states (Abdusalomov et al., 2023). Both of them affect reproduction: hypoprolactinemia leads to menstrual irregularities in women and decreased sexual desire and/or impaired fertility in men. The continued presence of these factors further compromises the fertility outcome in such circumstances; therefore, identifying the primary factors is crucial.

4.6.2 Secondary Causes

Secondary hypoprolactinemia is caused by diseases that interfere with prolactin production and its role in reproduction. Huang & Molitch (2021) argue that diseases such as liver or kidney failure are chronic, which affects hormones and, in this case, reduces the levels of prolactin, hence causing infertility. Thyroid disorders, particularly hypothyroidism, can be a cause of low prolactin levels, and this would affect women's menstrual and ovulatory cycles. For instance, in autoimmune diseases such as lymphocytic hypophysis, the pituitary gland is affected, resulting in hormonal imbalances that affect reproduction. However, any injury to the pituitary gland or surgery in that area may affect the levels of prolactin, fertility, and sexual dysfunction (Huang & Molitch, 2021). These diseases explain the complex relationship between overall health and reproductive health.

4.6.3 Iatrogenic Causes

Other causes of hypoprolactinemia, which impacts reproductive health, are associated with medical treatments and drugs. According to Wang et al. (2012), dopamine agonists like cabergoline or bromocriptine are commonly used to treat hyperprolactinemia with the aim of

reducing prolactin levels. Still, there is a possibility of palliative overdose that may suppress prolactin secretion. Other drugs that can influence the levels of prolactin include some antidepressants, some antipsychotics, and hormone therapies that may lead to infertility and sexual dysfunction. These treatments, however, are necessary for the treatment of some diseases, and as Wang et al. (2012) opine, these should be administered with precaution since they have negative impacts on reproductive health. Sometimes, it is necessary to alter the dose or the drug in order to bring prolactin back and, consequently, fertility.

Other causes of hypoprolactinemia include surgery of the pituitary gland and brain radiotherapy for brain tumors. In general, the destructive processes resulting from these manipulations of the pituitary or even the hypothalamus are reflected in the fact that these patients have hormonal deficiencies in sexual hormones that affect menses, ovulation, and libido (Attia et al., 2023). In other cases, long-term hormone replacement therapy may be used to bring hormonal balance, and this may lead to infertility as a result of these surgeries. Such patients require follow-up in order to diagnose hypoprolactinaemia and treat it appropriately. Reproductive health is one of the areas where physicians can intervene by preventing the negative impact of these medical treatments on fertility and sexual life.

4.6.7 Combined Effects and Overlapping Factors

In majority of patients the causes of reproductive health problems are multiple different factors such as hyperprolactinemia and hypoprolactinemia. For instance, a patient with pituitary tumor may initially present with hyperprolactinemia and after the tumor grows and compresses some of the health surrounding tissue it can result in hypoprolactinemia (Fukuhara et al., 2022). Similarly, a patient who has undergone some procedure, such as surgery or radiation to the brain may present with hypoprolactinemia due to the effects of the procedure and the use of other drugs (Fukuhara et al., 2022). When such overlapping factors are present, hormonal imbalance in the gonads are not rare, and infertility accompanied by other reproductive issues become a reality (Vannuccini et al., 2015).

When it comes to the impact of the two conditions, hyperprolactinemia, and hypoprolactinemia on reproductive health age, sex and general health are not different. In some women may experience severe symptoms such as irregular cycles which should not be the case, while men may have low libido or abnormality in sperm deposition. Age is another factor of concern as older people take longer time to regain normal function after disruption in hormonal equilibrium (Biagetti & Puig-Domingo, 2023). However, it is important to note that

for integrated treatment, all possible causes should be considered, including normal effect of drugs, stress and local and systemic diseases. Hormonal screening enables early treatment, which can improve fertility and reproductive health (Wani et al., 2023).

5. Approach

5.1 Pathophysiology of Prolactin Disorders

According to Auriemma et al. (2020), prolactin plays a vital role in regulating reproductive health by influencing lactation and reproductive hormones.

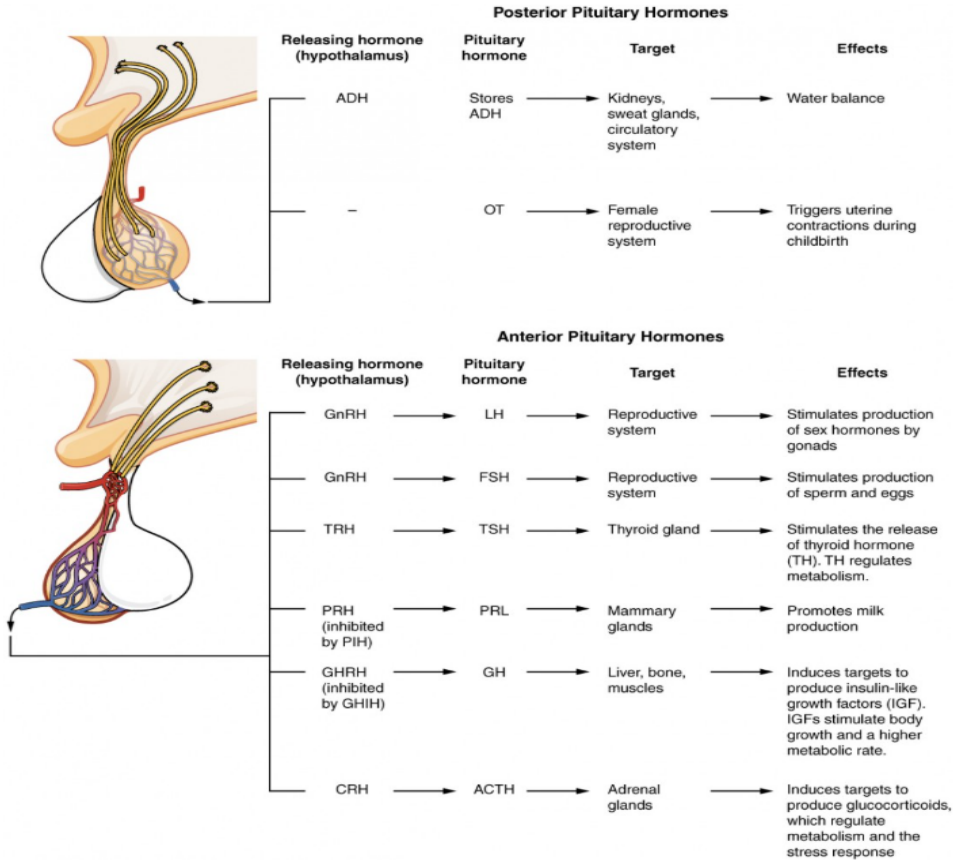

Figure 7: Regulation of Pituitary Hormones by the Hypothalamus

Illustration of the hypothalamus-pituitary complex and its function as the command center of the endocrine system. Adapted from “The Pituitary Gland and Hypothalamus” in Anatomy & Physiology by OpenStax, 2013, published on eCampusOntario Pressbooks (https://ecampusontario.pressbooks.pub/hhnp4/chapter/17-3-the-pituitary-gland-and-hypothalamus/). Licensed under CC BY 3.0.

It is secreted by the anterior pituitary gland and is mainly involved in the promotion of lactation after childbirth. In normal circumstances, prolactin levels rise during pregnancy and breastfeeding, while they are low during other periods to regulate fertility. When the levels of prolactin in the blood are high (hyperprolactinemia) or low (hypoprolactinemia), this balance is upset, and this causes various problems with fertility. Prolactin also has an influence on GnRH, LH, and FSH hormones that are involved in ovulation and testosterone synthesis (Auriemma et al., 2020). These hormonal pathways can be disrupted by either high or low prolactin levels, which can lead to reproductive issues in both sexes.

In hyperprolactinemia, prolactin suppresses the release of GnRH, which in turn decreases the levels of LH and FSH. This suppression hinders normal ovulation in women and reduces testosterone levels in men, causing infertility. The primary reason for hyperprolactinemia is prolactinoma, which is a benign tumor of the pituitary gland that produces prolactin.

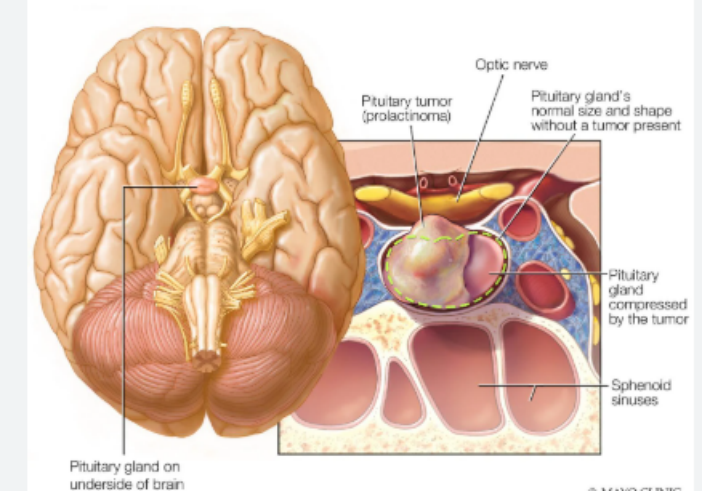

Figure 8: Pituitary Tumor (Prolactinoma) and Its Effects on the Pituitary Gland

Illustration of a pituitary tumor (prolactinoma) and its effects on the pituitary gland. Adapted from "Prolactinoma - Symptoms & Causes" by Mayo Clinic, 2023, Mayo Clinic (https://www.mayoclinic.org/diseases-conditions/prolactinoma/symptoms-causes/syc-20376958). Copyright 2023 by Mayo Foundation for Medical Education and Research (MFMER).

Other causes include hypothyroidism, chronic stress, and some medications that decrease dopamine levels. On the other hand, hypoprolactinemia is caused by pituitary disorders, head injuries, or hypothalamic diseases, which lead to low prolactin levels that affect lactation and fertility (Krogh, 2024). These disruptions demonstrate the intricate hormonal processes that are required for fertility and reproductive health.

Hypoprolactinemia can be postpartum due to pituitary infarction, Sheehan's syndrome, which is caused by blood loss during childbirth affecting the pituitary gland (Karaca et al., 2024). It may also be due to the use of dopamine agonists like bromocriptine, which inhibits prolactin secretion. This condition hinders the ability to produce enough breast milk during breastfeeding and may also interfere with the menstrual cycle by failing to support the luteal phase. It also reduces the levels of prolactin, which in turn affects estrogen levels, which are crucial in ovulation and pregnancy. These physiological changes show how delicate the regulation of prolactin has to be in order to maintain reproductive health.

In both hyperprolactinemia and hypoprolactinemia, the other reproductive hormones are also imbalanced, which has a great impact on health. Estrogen and progesterone are especially influenced by prolactin, and changes in the menstrual cycle and fertility may occur. Mastnak et al. (2023) explain that any disruption in the normal hormonal balance may lead to long-term consequences, including PCOS or endometrial disorders. In men, prolactin dysregulation is associated with low sexual desire, low sperm quality, and erectile dysfunction (Mastnak et al., 2023). In both cases, it is crucial to treat these imbalances as soon as possible to avoid further problems in fertility and sexual function.

5.2 Clinical Manifestations of Prolactin Disorders

The signs of prolactin disorders depend on whether the level is high or low, but both conditions impact fertility. Hyperprolactinemia is characterized by irregular or absent menstrual cycles, decreased fertility, and galactorrhea, which is the secretion of milk not related to pregnancy. Many women with this condition also report low libido, vaginal dryness, and mood disturbances. Chronic hyperprolactinemia results in estrogen deficiency and predisposes the patient to osteoporosis in the long run. In men, hyperprolactinemia leads to erectile dysfunction, gynecomastia, low sexual desire, and infertility because of low sperm count.

Hypoprolactinemia is less dramatic but can also have a profound impact on reproductive function. In women, the most common sign is the lack of breast milk production or insufficient production after childbirth, which makes breastfeeding difficult. They may also have fertility problems because of luteal phase defects, which are a failure to implant a fertilized egg. Hypoprolactinemia in men is characterized by low energy levels, low testosterone levels, and poor sperm quality leading to infertility (Corona et al., 2024). This is

because hypoprolactinemia is not easily diagnosed because it has mild signs and symptoms and is only detected when patients have fertility issues or problems with breastfeeding.

Hyperprolactinemia and hypoprolactinemia also affect mental health since hormonal imbalances lead to depression, anxiety, and mood swings. Stress arising from infertility, sexual dysfunction, and breastfeeding issues can also worsen these diseases. Most patients are frustrated because they are diagnosed with prolactin disorders late, and symptoms are often dismissed as stress or thyroid problems. This is why it is crucial to assess and monitor the hormonal levels to ensure accurate diagnosis and treatment.

Another aspect of the effects of prolactin disorders is the sexual health aspect. In women, hyperprolactinemia leads to anovulation, which makes it difficult for women to conceive and may lead to miscarriages (Cortasa et al., 2025). Low levels of prolactin in men can lead to impotence, low sperm mobility, and erectile dysfunction, which are all factors that cause infertility. Treatment of these symptoms with the right hormonal therapy can lead to the restoration of fertility, a better quality of life, and an improved psychological state.

5.3 Diagnostic Approach to Prolactin Disorders

The diagnosis of prolactin disorders involves taking a detailed history of the patient and blood tests to determine the serum prolactin level. In hyperprolactinemia, the prolactin level is higher than the normal level and may warrant further evaluation through imaging studies. MRI is the most common imaging technique used to diagnose pituitary adenomas or any other pathology in the hypothalamic-pituitary axis (Eisenhut et al., 2022). Thyroid function tests are also required to exclude hypothyroidism, which is known to increase prolactin levels. Also, pregnancy and medication use should be considered as they are other causes of hyperprolactinemia that are not related to a pathological condition.

In hypoprolactinemia, the diagnostic process includes low prolactin levels and other pituitary hormones to determine the gland's function. Possible causes include a history of head trauma, pituitary surgery, or the use of dopamine agonists. MRI scans are employed to identify structural abnormalities or tumors in the pituitary gland (Eisenhut et al., 2022). The main problem in diagnosing hypoprolactinemia is that the symptoms are not very apparent and may only be noticed after a careful examination. Women with postpartum lactation failure or unexplained infertility should be screened for prolactin deficiency to avoid delay.

Other functional tests, like the TRH stimulation test, may also be used to evaluate the ability of the pituitary gland to secrete prolactin. This test entails the use of Thyrotropin-

Releasing Hormone (TRH) and prolactin to assess the hypothalamic-pituitary axis abnormality. In men, further tests may include hormonal profile, specifically testosterone levels, and semen analysis to determine the effects of prolactin disorders on fertility. It is crucial to diagnose the condition properly to determine the right course of action since untreated prolactin disorders can cause long-term reproductive and metabolic disorders.

5.4 Impact on Lactation and Reproductive Health

Prolactin is crucial in lactation after childbirth, and any imbalance in the hormone impacts breastfeeding. In hyperprolactinemia, there is the production of milk at a time when it is not required, such as after childbirth; this is socially embarrassing and distressing. On the other hand, hypoprolactinemia can cause lactation failure, whereby mothers are unable to produce adequate breast milk to feed their babies, which is a problem in breastfeeding (Karaca et al., 2024). These issues can cause problems in the bond between the mother and the infant, and lactation support may be needed at an early age. These challenges can be managed through hormonal therapy and breastfeeding support programs.

Prolactin disorders have a significant impact on fertility, particularly in women. Hyperprolactinemia disrupts ovulation and results in irregular menstrual cycles, amenorrhea, and infertility. Luteal phase defects are also a result of hypoprolactinemia, which makes it difficult to sustain a pregnancy. In men, prolactin has an impact on testosterone levels, which leads to poor sperm quality and impotence. Hormonal regulation is important for couples who are planning to conceive, and this can be done through the help of a doctor.

Treatment of prolactin disorders is beneficial not only for the reproductive system but also for the psychological state of a woman. Infertility due to hyperprolactinemia leads to anxiety, depression, and stress, which are factors that can also affect fertility. These problems should be detected and addressed as early as possible to avoid their occurrence and maintain good health. These disorders can be managed through hormonal therapies, lifestyle changes, and psychological support.

5.5 Management Options for Hypoprolactinemia

5.5.1 Hormone Replacement Therapy (HRT)

In the study conducted by Langer et al. (2021), they noted that in the management of hypoprolactinemia, HRT is usually recommended as the primary treatment, which aims at replacing the normal hormonal levels that are crucial in fertility and breastfeeding. Low levels

of prolactin can interfere with the normal functioning of the body concerning fertility and lactation, especially estrogen and progesterone in women and testosterone in men. Estrogen and progesterone therapy for women can help to regulate the menstrual cycle, improve fertility, and maintain the health of the endometrium, which is vital for pregnancy. Lincoff et al. (2023) argue that testosterone replacement therapy in men not only helps to increase sexual desire and sperm count but also helps to treat the symptoms of hypogonadism that are caused by low levels of testosterone, including muscle loss, fatigue, and low mood. HRT for both genders also helps in alleviating symptoms that are not necessarily related to fertility, as hormonal balance is important for mental health and brain function (Langer et al., 2021).

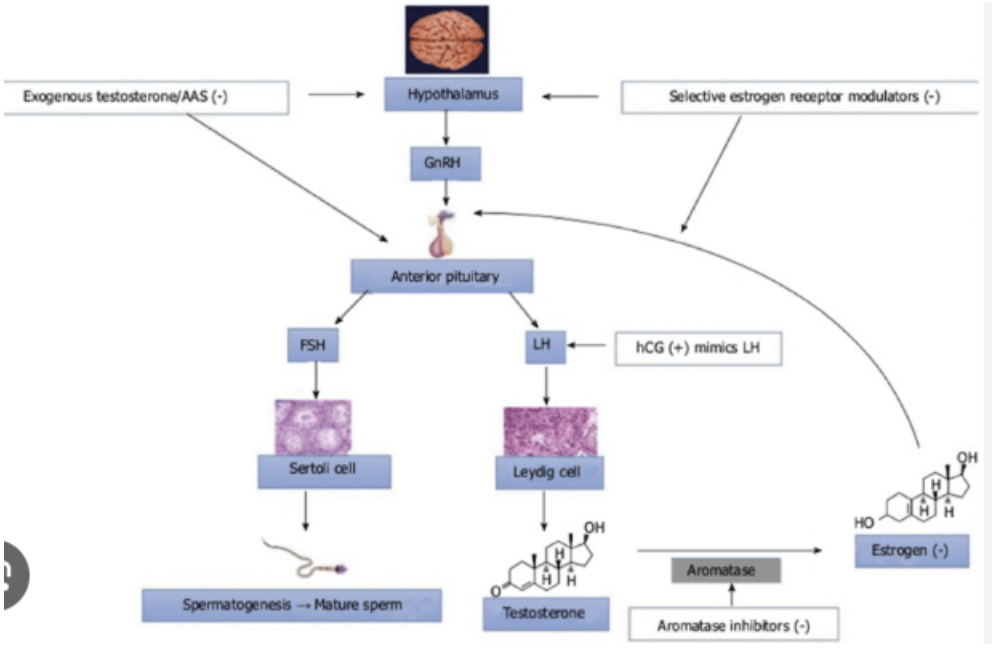

Figure 9: Impact of Exogenous Testosterone and Selective Estrogen Receptor Modulators on Spermatogenesis and Hormonal Pathways

Illustration of Exogenous Testosterone and SERMs' Effect on Spermatogenesis and Hormones. Tilpasset fra “Male Factor Infertility” av N. Rama, H. Lescay og O. Raheem, 2023, Obstetrics and Gynecology Clinics, 50(3), s. [sidetall]. https://doi.org/10.1016/j.ogc.2023.05.008. Copyright 2023 av Elsevier Inc.

Hormone therapy is a complex process that should be tailored to the needs of the patient to be effective. Since the efficacy of HRT is based on the attainment of the right hormone levels, constant assessment and evaluation are crucial throughout the process (Langer et al., 2021). It is common to change the dosages of hormones to maintain the levels within the desired range because hormones have systemic effects that require fine-tuning to

prevent adverse effects. For instance, estrogen or testosterone used in HRT may lead to the development of other complications like cardiovascular diseases or liver problems (Langer et al., 2021). Follow-up care is important because it enables the healthcare providers to adjust the therapy to make it safe and effective for the patient. It is common for patients to report any changes in symptoms to the healthcare team since these may require changes in the HRT regimen.

As stated by Langer et al. (2021), HRT is not only beneficial for reproductive and lactation purposes but also for bone health, which is affected in cases of hormonal dysfunctions for a long time. Prolactin is indirectly involved in bone metabolism, and deficiency of this hormone can lead to increased bone density loss and, result in osteoporosis. Estrogen in women and testosterone in men is essential for bone health, and HRT can prevent bone loss, which is vital for the long-term health of the patient, especially as they age (Langer et al., 2021). HRT helps to prevent fractures and other bone-related complications that low prolactin levels may cause. HRT users are advised to take calcium and vitamin D supplements, which also improve bone health among the patients.

Another advantage of HRT is the improvement of the general psychological state of a woman, as hormonal fluctuations can affect her mood and cognitive abilities. Low levels of prolactin are linked to mood disorders, anxiety, and poor stress coping, which can be uncomfortable for patients (Baker et al., 2021). Through HRT, hormone levels are brought back to normal, and this greatly enhances the emotional stability of the person and enables him or her to effectively deal with the day-to-day challenges of managing the condition. HRT helps the whole person, not only the physical aspect but also the psychological consequences of hypoprolactinemia. The positive effects of HRT on mental health can also translate to better adherence to other aspects of treatment, including lifestyle changes and supportive therapies.

However, there are drawbacks to HRT, and treatment success depends on patient compliance. In the case of HRT, patients may find it inconvenient to follow certain prescription regimens and follow-up appointments (Baker et al., 2021). Weight gain, migraines, breast soreness or tenderness, spotting or bleeding in between periods, and changes in cycles are some of the other adverse effects. A modest increase in the risk of breast cancer and blood clots has also been linked to HRT. To keep an eye on these possible side effects, patients should maintain regular communication with their healthcare professionals. Healthcare professionals must determine whether a patient is contraindicated for HRT before writing a prescription. Patients who are well-informed are aware of the potential side effects

of hormone replacement therapy as well as its benefits and risks. This will enhance the patient's overall experience with hormone replacement treatment by allowing any concerns to be aired and addressed.

5.5.2 Supportive Treatments

Therapeutic interventions are crucial in the management of hypoprolactinemia, especially when fertility issues and breastfeeding complications are evident. For women who experience difficulties in breastfeeding because of low levels of prolactin, there are lactation consultants who can help them with the correct breastfeeding positions and how to induce milk production (Urhan & Karaca, 2024). It may also provide information on how to achieve a good latch, the best breastfeeding positions, and how to feed your baby even if your hormones are not ideal. Also, support groups for breastfeeding enable women to find support from other mothers who are going through the same process, and this helps reduce the isolation that is usually experienced when facing some challenges in the process of breastfeeding.

Counseling and stress management are also important for those who experience the psychological effects of hypoprolactinemia, particularly infertility. Infertility causes much stress, which may impact self-esteem, relationships, and the general well-being of the affected individuals. Counseling services help patients positively deal with these emotions and, better cope with the psychological impact of the disease (Urhan & Karaca, 2024). Cognitive behavioral therapy, relaxation training, and mindfulness exercises effectively enhance emotional resilience. In the case of infertility, joint counseling can be helpful for the couple to discuss their concerns as a team, which strengthens the couple's connection and relationship.

Support groups provide a platform where individuals can freely express themselves on matters concerning reproductive health, mental health, and treatment. Such environments help to eliminate feelings of loneliness that are characteristic of women experiencing fertility or lactation problems and create a sense of togetherness and support (Sharma & Shrivastava, 2022). In the long run, such supportive networks can help build up psychological capital, which in turn allows patients to have a better attitude towards their condition.

6. Discussion

6.1 Common Challenges in Diagnosis and Treatment

6.1.1 Challenge 1: Diagnostic Overlap with Other Hormonal Disorders

The diagnosis of prolactin disorders can be quite challenging because the symptoms are often similar to those of other hormonal or reproductive disorders (Mastnak et al., 2023). For instance, hyperprolactinemia may manifest with symptoms such as irregular menstruation, infertility, and galactorrhea, which are also signs of PCOS and thyroid disorders. This overlap can result in misdiagnosis or delay in the correct diagnosis of prolactin as the cause of the problem. Hypoprolactinemia, although less frequent, has similar symptoms to other endocrine disorders that affect sexual desire, menstrual cycle, and lactation, which increases the likelihood of its diagnosis being missed or mistaken. The standard hormonal assays may not always capture the fluctuations in prolactin levels, which makes the diagnosis even more challenging.

Another level of complexity is added by the fact that prolactin levels may vary throughout the day due to stress, sleep, and some medications. Kirsch et al. (2022) have pointed out that these factors can lead to short-term fluctuations in prolactin levels that may be mistaken for pathological hyperprolactinemia and, therefore, warrant treatment. However, it is also important to note that prolactin levels are influenced by the menstrual cycle and pregnancy in women. Clinicians should also take into account the patient's history of stress and medication use to distinguish between transient elevations and chronic conditions (Urhan & Karaca, 2024). This often has to be done repeatedly over a period of time, which poses both practical and financial difficulties for the patient and the healthcare facilities.

6.1.2 Challenge 2: Managing Medication Side Effects in Hyperprolactinemia

Bromocriptine and cabergoline are the first-line drugs for the treatment of hyperprolactinemia because they effectively lower prolactin levels and shrink tumors. However, these medications have side effects such as nausea, headaches, dizziness, and hypotension that may deter patients from taking them. These side effects are significant enough to interfere with the patient's quality of life, which makes long-term treatment difficult. Patient compliance is crucial in managing prolactin disorders, but side effects make it difficult for patients to adhere to the recommended dosages, which may compromise the effectiveness of the treatment.

Also, dopamine agonists are not well tolerated in all patients, some of whom develop severe side effects that require dose reduction or withdrawal. When high doses are needed to suppress prolactin levels, patients experience more severe side effects, which, in turn, contribute to higher rates of treatment dropout (Nunes-Nogueira et al., 2018). Clinicians often have to try different dosages or switch between medications to achieve the desired therapeutic effect with minimal side effects, which may take time to achieve control of hyperprolactinemia.

The presence of other treatment options for the cases that do not respond to dopamine, for instance, surgery or radiotherapy, poses other issues. Both surgery and radiation have side effects such as damage to the surrounding pituitary tissue that may cause hypopituitarism (Fukuhara et al., 2022). This risk makes these options less desirable, especially for young patients. Therefore, for patients who cannot take dopamine agonists, there are few treatment options available, which is why new drugs with fewer side effects are needed.

6.1.3 Challenge 3: Risk of Hypopituitarism Post-Surgery or Radiation

As stated by Fukuhara et al., (2022), surgery and radiation therapy are the second-line treatment for hyperprolactinemia, especially when the prolactinoma is large and unresponsive to medication. However, these treatments are not without their dangers, and hypopituitarism is one of the most dangerous side effects. Surgical or radiation injury to the pituitary gland can affect the secretion of other hormones and result in a chain of endocrine disorders. These procedures may necessitate lifelong hormone replacement therapy, which not only affects the quality of life but also leads to other health issues like adrenal insufficiency and hypothyroidism.

Yeliosof and Gangat (2019) also expound that hypopituitarism is a risk of surgical and radiation treatments, especially for young patients with fertility desires. However, when hypopituitarism is present, it can worsen fertility and pregnancy since hormone levels need to be regulated. The long-term use of hormones has its own problems, such as the risks of serious side effects, necessity of constant check-ups, dosage changes, and the use of medications that may be unavailable at times.

However, hypopituitarism is not only limited to the reproductive system but also has an impact on the metabolism, cardiovascular system, and mental health of the patient (Yeliosof & Gangat, 2019). This broad impact means that patients with surgically or radiation-induced hypopituitarism need to be managed by endocrinologists, fertility specialists, and

general practitioners. The coordination of care for these patients is not easy and is expensive, making the management of prolactin disorders even more difficult.

6.2 Recent Advances in Understanding and Management

New developments in diagnostic methods and treatment approaches are gradually enhancing the management of prolactin abnormalities. Eisenhut et al. (2022) state that new imaging methods like high-resolution MRI have helped in better identification and localization of pituitary adenomas, which helps in diagnosis. This has made it possible to intervene early and evaluate the treatment's effectiveness as it progresses. In addition, new and more accurate assays that distinguish between bioactive and immunoreactive prolactin reduce the likelihood of misdiagnosis resulting from temporary increases in prolactin levels, providing a more accurate picture of a patient's prolactin levels and the effects on their reproductive system.

As stated by Islam et al. (2020), Other therapeutic strategies that are being explored include selective prolactin receptor modulators (SPRMs). These modulators are designed to act only on prolactin receptors, as a result minimizing the chances of side effects. Although in the experimental phase, SPRMs are a potential future therapy that may change the approach to the treatment of hyperprolactinemia and other disorders associated with prolactin (Islam et al., 2020). New knowledge about the genetic background of some forms of hyperprolactinemia, especially in familial prolactinomas, may also lead to the concept of pharmacogenomics, where treatment is based on the patient's genetic makeup, which would be more efficient.

Figure 10 shows how sleep, sex hormones, orgasm, stress, and suckling influence the secretion of prolactin. It depicts the circular relationship between the dopaminergic neurons in the hypothalamus and the anterior pituitary gland. The diagram shows the pathway in which the secretion of the hormone prolactin, which is needed for lactation, is regulated.

7. Conclusion

In conclusion, this literature review shows that prolactin has multiple functions in reproductive health and that the levels of prolactin should be balanced in both men and women. It is not only involved in lactation but also in ovulation, hormonal balance, and sexual activity. Both hyperprolactinemia and hypoprolactinemia interfere with this balance and lead to various reproductive issues. Hyperprolactinemia leads to menstrual irregularities, infertility, and low sexual desire in both sexes due to prolactinomas or medications. On the other hand, low levels of prolactin are also known to have negative impacts on reproductive functions, especially in lactation and hormonal balance, affecting fertility and reproductive health.

hyperprolactinemia, which is associated with more pronounced symptoms such as galactorrhea and menstrual irregularities, should be investigated using biochemical tests and MRI scans to identify pituitary tumors. The mainstay of therapy is dopamine agonists that decrease prolactin levels and shrink the tumor; however, side effects may compromise patient compliance with long-term medications. For patients who cannot take these drugs, surgical and radiation therapies are other options that come with other risks, such as hypopituitarism, hence the need for safer therapies. New studies on SPRMs show that they may be a future treatment that is less invasive than dopamine agonists and may help to reduce prolactin levels without the side effects.

Hypoprolactinemia is challenging to diagnose because of its non-specific symptoms, and therefore, patients may present late for treatment. Conditions such as low sexual desire, low sperm count in men, and failure of lactation in women are often overlooked or attributed to other hormonal imbalances. Educating the healthcare providers about hypoprolactinemia and integrating prolactin level tests into fertility assessments are ways to enhance the diagnosis. This is especially important because early diagnosis enables the patient to receive treatment that will help regulate prolactin levels before the development of other reproductive issues that may harm the quality of life.

In conclusion, this review emphasizes the significance of prolactin homeostasis and the need for further research to enhance the understanding of the diagnosis and treatment of prolactin dysregulation. New developments in genetic testing and molecular medicine may lead to targeted therapies that are more effective and less toxic to the patient. This is because

both hyperprolactinemia and hypoprolactinemia require a multidisciplinary approach to the diagnosis and management of reproductive health outcomes.

Appendices

Appendix A

Figure 10 shows how sleep, sex hormones, orgasm, stress, and suckling influence the secretion of prolactin. It depicts the circular relationship between the dopaminergic neurons in the hypothalamus and the anterior pituitary gland. The diagram shows the pathway in which the secretion of the hormone prolactin, which is needed for lactation, is regulated.

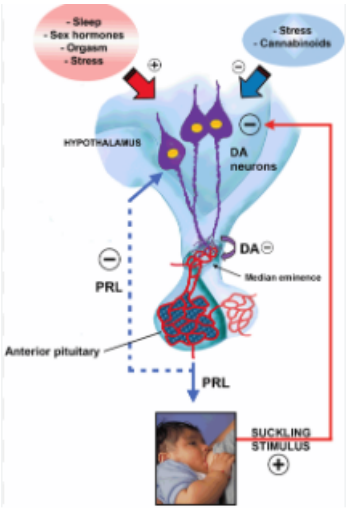

Figure 10: Regulation of prolactin secretion

Illustration of the regulation of prolactin secretion. Adapted from "Hypothalamic Regulation of Prolactin Secretion" by A. J. MacGregor, in Clinical Neuroendocrinology (M. Wilkinson & S. M. Shalet, Eds.), 1st edition, p. 36, 1998, Cambridge University Press. https://doi.org/10.1017/CBO9780511544413.007. Copyright 1998 by Cambridge University Press.

Appendix B

Figure 11 illustrates how (PRLR) prolactin binds to its receptor, by activating signaling pathways such as JAK-STAT, MAPK and PI3K-AKT. Regulation of these pathways, cell survival and hypothalamic-pituitary-gonadal axis for reproductive health.

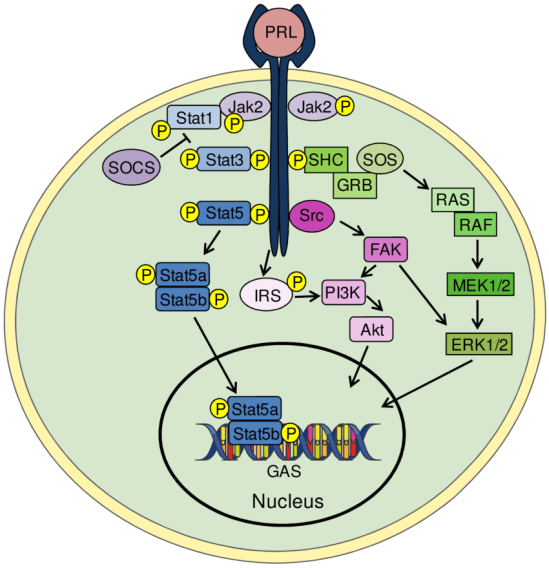

Figure 11: Prolactin Signaling Pathway

Prolactin signaling pathways. Adapted from "Diagram of prolactin (PRL) signaling pathways" by N. Ben-Jonathan, W. Ip, D. D. Alessio, et al., 2009, ResearchGate. Retrieved from https://www.researchgate.net/figure/Diagram-of-prolactin-PRL-signaling-pathways-Binding-of-PRL-induces-PRL-receptor-PRLR_fig1_228607554

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