OPEN ACCESS

Scholars International Journal of Obstetrics and Gynecology

Abbreviated Key Title: Sch Int J Obstet Gynec
ISSN 2616-8235 (Print) |ISSN 2617-3492 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Review Article

Hyperprolactinemia and Male Infertility

Erhunmwunse RU[1], Ogbodo EC[2]*

[1]Department of Medical Laboratory Science, Faculty of Allied Health Sciences, Benson Idahosa University, Benin City, Nigeria
[2]Department of Clinical Chemistry, Faculty of Medical Laboratory Science, Nnamdi Azikiwe University, Anambra State, Nigeria

DOI: https://doi.org/10.36348/sijog.2025.v08i07.003 | **Received:** 08.06.2025 | **Accepted:** 16.07.2025 | **Published:** 19.07.2025

***Corresponding author:** Ogbodo EC
Department of Clinical Chemistry, Faculty of Medical Laboratory Science, Nnamdi Azikiwe University, Anambra State, Nigeria

Abstract

Infertility is a prevalent medical disease affecting between 8% and 17.5% of couples globally, with a male factor accounting for nearly half of all cases of infertility among couples. Infertility is a reproductive system disorder characterized by the failure to conceive following at least 12 months of frequent unprotected sexual intercourse. It may be primary or secondary in nature. Most countries still struggle to provide equal and fair access to fertility care, particularly in poor and middle-income countries. Hormonal imbalances such as a high prolactin level otherwise called hyperprolactinemia can induce infertility in males. Hyperprolactinemia is a frequent endocrine illness that can cause severe morbidity. It can be caused by a variety of factors, including drug use, hypothyroidism, and pituitary problems. Depending on the origin and effects of hyperprolactinemia, patients require treatment that takes into account the underlying cause, age, gender, and reproductive status. This study examined the biological and metabolic roles of prolactin, as well as the pathophysiological mechanisms and controls that drive male hyperprolactinaemia, laboratory diagnosis, and treatment.

Keywords: Infertility, Male Infertility, Prolactin, Hyperprolactinaemia, Hormonal Imbalance, Risk Factors, Pathophysiological Mechanisms, Laboratory Diagnosis and Treatment.

1.0. INTRODUCTION

Infertility is a disease of the male or female reproductive system defined by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse (WHO, 2018). In the male reproductive system, infertility is most commonly caused by problems in the ejection of semen, absence or low levels of sperm, or abnormal shape (morphology) and movement (motility) of the sperm (WHO, 2018). In the female reproductive system, infertility may be caused by a range of abnormalities of the ovaries, uterus, fallopian tubes, and the endocrine system, among others. Infertility can be primary or secondary. Primary infertility is when a pregnancy has never been achieved by a person, and secondary infertility is when at least one prior pregnancy has been achieved. Fertility care encompasses the prevention, diagnosis and treatment of infertility. Equal and equitable access to fertility care remains a challenge in most countries; particularly in low and middle-income countries (WHO, 2020). However, hormonal disturbances such as high level of prolactin (hyperprolactinemia) may cause infertility in males.

Prolactin (PRL) is a 23 kDa single chain protein of 199 amino acids synthesized and released principally by lactotrophs in the anterior pituitary gland (Rasmi *et al*., 2023). The secretion is mainly under inhibitory control by hypothalamic dopamine and regulated in a negative feedback manner, with prolactin itself providing the afferent signal: short-loop feedback (Rasmi *et al*., 2023). The main function of prolactin is during pregnancy and lactation in the development of mammary glands, milk synthesis and maintenance of milk secretion. Serum prolactin levels rise rapidly during pregnancy with increase in the size and number of lactotrophs. During lactation suckling induces rapid secretion of prolactin via a neuroendocrine reflex pathway. In the absence of pregnancy, hyperprolactinaemia may present with symptoms of hypogonadotropic hypogonadism including menstrual disturbance and infertility or visual symptoms from a pituitary mass effect by a prolactinoma, the most common pituitary tumor (Saleem *et al*., 2018).

Hyperprolactinemia is a common endocrine disorder that can be associated with significant

morbidity. It can result from a number of causes, including use of medication, hypothyroidism and pituitary disorders. Depending on the cause and consequences of hyperprolactinemia, selected patients require treatment considering the underlying cause, age, sex, and reproductive status (Nazma *et al*., 2020). Zeinab and Stephen, (2017) observed an elevated levels of serum prolactin have a detrimental effect on male reproduction through inhibition of the pulsatile release of gonadotrophins from the anterior pituitary gland, and a direct effect on spermatogenesis. Treatment of confirmed hyperprolactinaemia with dopamine agonists leads to significant improvements in both semen parameters and hormone levels.

1.1. Types of Infertility

1.1. 1 Primary: This is a condition where there has not been any conception after one year of unprotected sexual intercourse.

1.1.2 Secondary: This is a condition where a woman can't get pregnant again after having at least one successful pregnancy.

1.2. Prolactin Synthesis

The anterior pituitary synthesizes and secretes prolactin and dopamine-mediated hypothalamic regulation; however, the central nervous system, the immune system, the uterus, and the mammary glands all are capable of producing prolactin. Nipple stimulation, light, olfaction, and stress can all contribute to the initiation of prolactin synthesis in these tissues. Other factors that stimulate prolactin production include thyrotropin-releasing hormone (TRH), estrogen (pregnancy), and dopamine antagonists (antipsychotics). Males have characteristically low levels of prolactin. Abnormal elevation in males is suggestive of a potential underlying pathological process like a pituitary adenoma or a medication adverse effect, which warrants further evaluation. Prolactin is low in males and non-lactating non-pregnant females (Jin and Fan, 2019).

In humans, prolactin is encoded by a single gene on chromosome 6 which consists of six exons and four intros. Following cleavage of the 28 amino acid signal peptide, the mature 23 kDa protein consists of 199 amino acids. It belongs to the cytokine family of proteins, characterised by a 3D structure comprising four antiparallel α helices, and has strong structural homology with growth hormone and placental lactogen (Salem *et al*., 2018). Numerous variants of the prolactin protein have been identified, many of which result from post-translational modifications of the mature protein including phosphorylation, glycosylation, sulfation and deamidation. In addition to monomeric 23 kDa prolactin, two other major forms are present in the circulation: 'big prolactin' and 'big-big prolactin' (macroprolactin).

Prolactin is named after its vital role of promoting milk production during lactation, although it has been implicated in multiple functions within the body, including metabolism and energy homeostasis. Prolactin has been hypothesised to play a key role in driving many of the adaptations of the maternal body to allow the mother to meet the physiological demands of both pregnancy and lactation, including the high energetic demands of the growing foetus followed by milk production to support the offspring after birth. Prolactin receptors are found in many tissues involved in metabolism and food intake, such as the pancreas, liver, hypothalamus, small intestine and adipose tissue (Felicitas *et al*., 2020). Over 300 functions have been described for prolactin (PRL), which is classified in six main categories:

i. Water and electrolyte equilibrium,
ii. Growth and development,
iii. Endocrinology and metabolism,
iv. Brain and behavior,
v. Reproduction and maintaining pregnancy, and
vi. Immunoregulation and protection (Costanza *et al*., 2015).

1.3. Regulation of prolactin synthesis

Molecules in the environment, such as cytokines and pathogen-associated molecular patterns (PAMPs) participate in the regulation of PRL effects by inducing or inhibiting its secretion and acting synergistically or antagonistically with PRL, or by inducing expression of different PRLR isoforms (Borba *et al*., 2018; Martínez-Neri *et al*., 2015).

PRL secretion is partly regulated by cytokines in the environment. For example, IL-1, IL-2, and IL-6 stimulate PRL secretion while endothelin 3, transforming growth factor-beta (TGF-β) and IFN-γ inhibit its secretion (Borba *et al*., 2018). TNF-α can stimulate release of PRL, but prolonged exposure of this cytokine can inhibit this action (Rasmi *et al*., 2023). Cytokines not only participate in the regulation of PRL secretion but may also act synergistically with this hormone in the inflammatory response. For example, macrophage cultures treated with both PRL and INF-γ display increased nitric oxide (NO) release and cytotoxic capacity against tumor cells compared to macrophages treated only with either PRL or with INF-γ. Furthermore, IL-12 and PRL can act synergistically to induce differentiation of CD4+ T cells towards a Th1 phenotype, since PRL induces the release of IL-12 by macrophages as a positive feedback mechanism. In the case of NK cells, PRL interacts jointly with IL-2 and IL-12 to increase INF-γ production and with IL-15 to increase proliferation, perforin expression and cytotoxic activity of these cells.

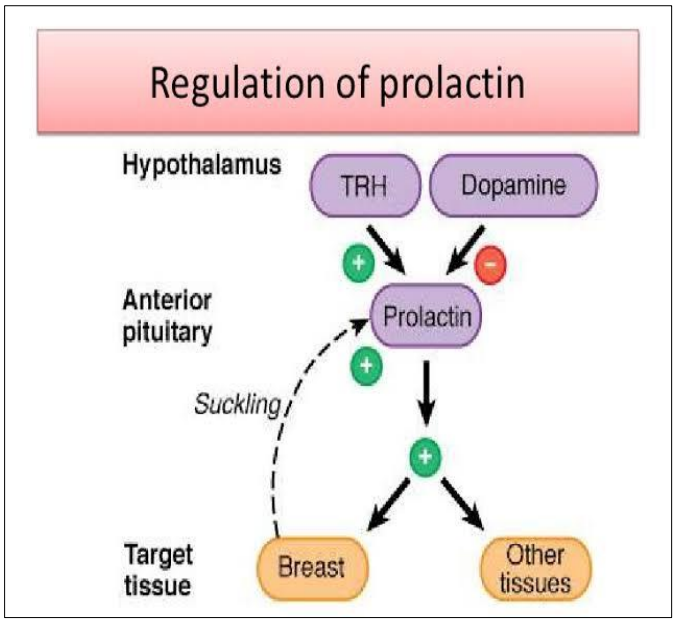

Fig. 1: Regulation of prolactin (Source: Mohamed *et al*., 2018)

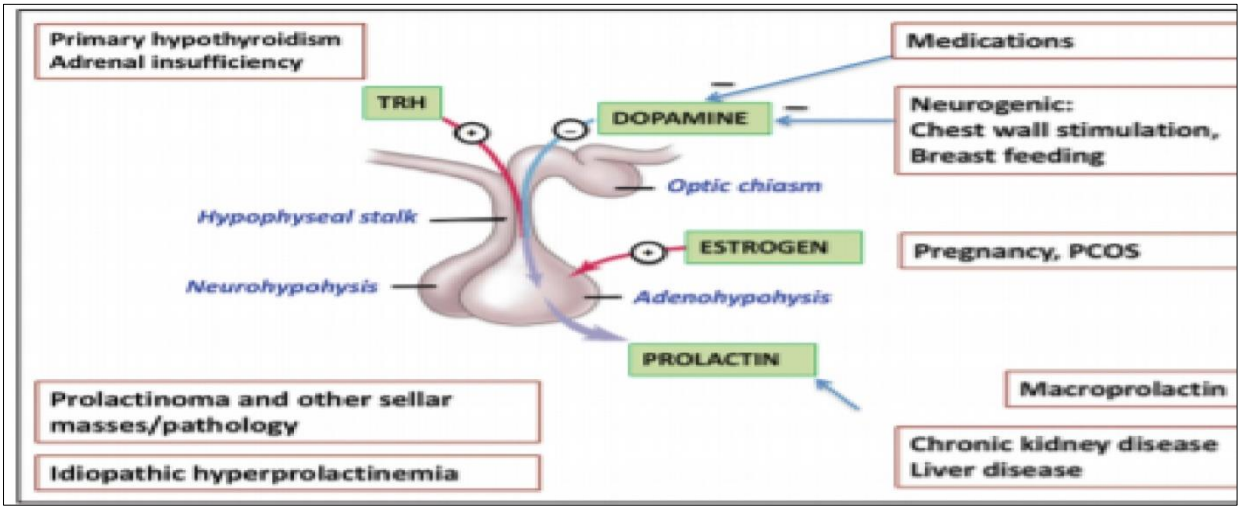

Fig. 2: Regulation of prolactin secretion and mechanisms (Source: Mussa and Salem, 2020)

1.4. Biological Functions/Effects of Prolactin

1.4.1. Lactotrophic Functions

The main role of prolactin is promoting milk synthesis and maintaining lactation postpartum. In pregnant women, increasing oestrogen secretion stimulates proliferation of the lactotrophs, resulting in increased prolactin secretion (Al-Chalabi *et al*., 2023). Prolactin stimulates mammary gland growth and, together with oestradiol, progesterone, placental lactogen, insulin and cortisol prepares the breast for postpartum lactation (Al-Chalabi *et al*., 2023). At the same time, high oestrogen concentrations inhibit the lactotropic effect of prolactin in the mammary gland (Pérez-López *et al*., 2021). The fall in oestrogen levels to non-pregnant levels after delivery results in the initiation of lactation (Saleem *et al*., 2018).

1.4.2. Adaptations to Short-Loop Feedback during Lactation

Normal negative feedback regulation of prolactin secretion dominates until late pregnancy. Placental lactogens produced during pregnancy bind to and activate PRLR stimulating prolactin responsive functions and bypasses the feedback inhibition (Rassie *et al*., 2022; Rasmi *et al*., 2023) although prolactin remains dominant over placental lactogens in human pregnancy. The continued increase in prolactin during human pregnancy is thought to be due to stimulatory effect of oestrogen on TIDA neurons thereby inhibiting dopamine release as well as its stimulatory effect on lactotrophs resulting in hyperplasia (Saleem *et al*., 2018).

In late pregnancy, there is a decrease in activity of the hypothalamic dopamine neurons associated with a nocturnal surge in pituitary prolactin secretion immediately before parturition (Grattan *et al*., 2015).

Hypothalamic dopamine neurons no longer release dopamine in response to prolactin or placental lactogen, rendering the short-loop negative feedback system functionally inactive and this adaptation persists during lactation (Rasmi *et al*., 2023). Although PRLR expression in the dopamine neurons is maintained and acute electrophysiological responses to prolactin persist, there is a change in the cellular response downstream of the PRLR (Grattan, 2015). Phosphorylation of tyrosine hydroxylase is decreased and activation of STAT5b in dopamine neurons is also reduced during lactation (Saleem *et al*., 2018). At the same time, there is an increase in met-enkephalin expression in the dopamine neurons and it seems possible that elevated prolactin may drive this met-enkephalin expression (Yip *et al*., 2019). Hence, the neurons essentially change their phenotype, changing from being dopaminergic to enkephalinergic possibly mediating a completely different function of prolactin in the brain during lactation. There is a highly coordinated release of prolactin during lactation, caused by the suckling stimulus. It has been postulated that a suckling induced 'prolactin-releasing factor' may be involved in stimulating prolactin secretion at this time. It is well established that enkephalin can promote prolactin secretion (Yip *et al*., 2019). While most evidence suggests that this effect is mediated centrally through regulation of TIDA neurons, it can also act in the pituitary gland to antagonise dopaminergic inhibition of lactotrophs (Qi-Lytle *et al*., 2024; Saleem *et al*., 2018; Grattan *et al*., 2015).

1.4.3. Reproductive Effects

The main mechanism by which prolactin influences the gonads is by inhibition of gonadotropin-releasing hormone (GnRH) secretion leading to hypogonadotropic hypogonadism (Marques *et al*., 2024). Although GnRH neurons were thought to be directly regulated by prolactin, it has been demonstrated that only a very small percentage of GnRH neurons express the PRLRs and membrane excitability of GnRH neurons is not acutely modulated by prolactin (Szukiewicz, 2024; Saleem *et al*., 2018; Donato and Frazão, 2016). Recent studies have shown that prolactin may modulate the reproductive axis by acting on a specific population of hypothalamic neurons that express the Kiss1 gene (Xie *et al*., 2022). The Kiss1 gene encodes neuropeptides, known as kisspeptins, that are critically involved in reproduction. Most of these neurons co-express the PRLRs and an acute prolactin stimulus can induce pSTAT5 in Kiss1-expressing neurons (Xie *et al*., 2022; Ogawa and Parhar, 2018). Kisspeptin1 reduces secretion of GnRHI from hypothalamic neurons resulting in reduced LH and FSH secretion and loss of ovarian stimulation, which can result in infertility (Saleem *et al*., 2018). Prolactin also decreases sensitivity of the luteinizing hormone (LH) and of the follicle-stimulating hormone (FSH) receptors in the gonads.

1.4.4. Effects on Other Hormones

Prolactin improves glucose homeostasis by increasing ß-cell mass under certain conditions such as pregnancy, whereas hyperprolactinaemia due to a pituitary gland adenoma exacerbates insulin resistance (Yang *et al*., 2021). In diabetic rats, it was observed that high levels of prolactin exacerbate insulin resistance and impair the insulin-secretory capacity, in contrast to the normal adaptive increases in glucose stimulated insulin secretion and insulin sensitivity realized with moderately increased prolactin levels (Yang *et al*., 2021; Park *et al*., 2011). Prolactin also enhances dihydroepiandrosterone (DHEA), cortisol and aldosterone secretion by the adrenal cortex cells.

1.4.5. Effects on the Immunological System

Prolactin is also produced by lymphocytes and other immune cells. It acts as a cytokine and plays an important role in human immune responses (Rasmi *et al*., 2023; Borba *et al*., 2019). Prolactin effects on immunological systems may depend on concentration, resulting in immunostimulation at modest levels and inhibition at high levels (Legorreta-Haquet *et al*., 2022; Langan, 2024). For example, in many cases of autoimmune diseases, the severity of the disease is lower or even remitted during pregnancy when serum prolactin level is elevated (Saleem *et al*., 2018). On the other hand, there is an association between autoimmune diseases and moderate hyperprolactinaemia suggesting that prolactin is implicated in the initiation of the autoimmune reactions (Borba *et al*., 2018; dos Santos *et al*., 2024).

1.4.6. Other Functions

Prolactin is involved in osmoregulation, acting to increase water and salt absorption in all segments of the bowel and reduce renal Na+ and K+ excretion (Saleem *et al*., 2018). It can also stimulate proliferation, differentiation and migration of neuronal stem cells. It has been observed that prolactin has a proliferative effect on glial progenitors and oligodendrocyte precursor cells, leading to myelination of central nervous system (Saleem *et al*., 2018).

1.5. Causes of Male Infertility

In the male reproductive system, infertility may be caused by:

1. Obstruction of the reproductive tract causing dysfunctionalities in the ejection of semen. This blockage can occur in the tubes that carry semen (such as ejaculatory ducts and seminal vesicles). Blockages are commonly due to injuries or infections of the genital tract.
2. Hormonal disorders leading to abnormalities in hormones produced by the pituitary gland, hypothalamus and testicles. Hormones such as testosterone regulate sperm production. Example of disorders that result in hormonal imbalance include pituitary or testicular cancers.

3. Testicular failure to produce sperm, for example due to varicoceles or medical treatments that impair sperm-producing cells (such as chemotherapy).
4. Abnormal sperm function and quality. Conditions or situations that cause abnormal shape (morphology) and movement (motility) of the sperm negatively affect fertility. For example, the use of anabolic steroids can cause abnormal semen parameters such sperm count and shape (Gore *et al*., 2015).
5. Environmental and lifestyle factors such as smoking, excessive alcohol intake and obesity can affect fertility. In addition, exposure to environmental pollutants and toxins can be directly toxic to gametes (eggs and sperm), resulting in their decreased numbers and poor quality, leading to infertility (Gore *et al*., 2015, Segal and Giudice, 2019)

1.6. Metabolic Functions of Prolactin

Prolactin has a wide variety of effects. Apart from stimulating the mammary glands to produce milk (lactation), increasing serum concentrations of prolactin during pregnancy, causing enlargement of the mammary glands and preparing the mammary glands for milk production; it also has these metabolic functions;

Prolactin plays an important role in maternal behavior.

Elevated levels of prolactin decrease the levels of sex hormones estrogen in women and testosterone in men.

Hysiologic levels of prolactin in males enhance luteinizing hormone-receptors in Leydig cells, resulting in testosterone secretion, which leads to spermatogenesis.

Prolactin also stimulates proliferation of oligodendrocyte precursor cells. These cells differentiate into oligodendrocytes, the cells responsible for the formation of myelin coatings on axons in the central nervous system (Wefak, 2020).

1.7. Spermatogenesis and Hyperprolactinemia

In males, prolactin level imbalances have different clinical implications. Elevated prolactin level in males results in headaches and decreased libido. The decreased libido is associated with decreased spermatogenesis as a result of elevated prolactin affecting the hypothalamus-pituitary reproductive axis (Matalliotakis *et al*., 2019, Auriemma *et al*., 2019).

Prolactin plays a suppressive role in sexual desire. Hyperprolactinaemia is associated with decreased libido yet the mechanism(s) is not entirely clear. It could be acting via prolactin- induced hypogonadism or via effects on the neurotransmitter dopamine which is important for sexual behavior (Nargund, 2015).

1.8. Hyperprolactinemia and Male Infertility

Infertility is a common medical condition affecting between 8% and 17.5% of couples worldwide with a male factor contributing roughly half the cases of infertility amongst couples (Vander Borght and Wyns, 2018; Leslie *et al*., 2024; Choudhary *et al*., 2025). Establishing a precise diagnosis via a thorough history, examination and investigative protocol is essential for optimal male infertility management. During evaluation, the specialist investigates for the presence of endocrine dysfunction that may contribute to a patient's infertility. Current guidelines indicate hormone evaluation of infertile men in the presence of abnormal semen analysis, symptoms of hypogonadism, or other clinical findings suggestive of a specific endocrinopathy, such as gynaecomastia or testicular atrophy (Dabbous and Atkin, 2017).

Hyperprolactinaemia is amongst the endocrine disorders known to influence male infertility. It is a common medical condition present in ~1% of the general population worldwide (Thapa and Bhusal, 2023). Hyperprolactinaemia in men is defined by the presence of a high serum prolactin level of >15 µg/L (Dabbous and Atkin, 2017). It can result from physiological or pathological conditions. Stress and exercise can cause small increases in prolactin levels and are important causes of physiological hyperprolactinemia. Medication-induced hyperprolactinaemia is usually associated with prolactin levels ranging from 25 to 100 µg/L, but metoclopramide, risperidone, and phenothiazines can lead to prolactin levels of >200 µg/L (Dabbous and Atkin, 2017). Prolactinomas (lactotroph adenomas) are the most common pathological cause of hyperprolactinaemia and account for ~40% of pituitary adenomas. The diagnosis is more commonly made in women than men due to the effect of hyperprolactinaemia on the female menstrual cycle giving an earlier indication of hormonal imbalance. Prolactinomas can be microadenomas (<1 cm in diameter) or macroadenomas (>1 cm in diameter), and the level of serum prolactin measured is directly proportional to the size of the adenoma (Yatavelli and Bhusal, 2023; Chen and Burt, 2017). Whilst hyperprolactinaemia is prevalent in up to 11% of infertile males, it is a diagnosis that is often missed because of its subtle clinical manifestations (Dabbous and Atkin, 2017).

1.9. Hypothalamic–Pituitary–Gonadal Axis (HPG)

An understanding of the HPG axis is important for understanding the pathophysiology of pituitary dysfunction in male infertility. Testicular function is regulated by the hypothalamus and pituitary gland. The hypothalamus secretes GnRH, which reaches the anterior pituitary via the hypothalamo-hypophyseal portal circulation to stimulate production of the

glycoprotein hormones LH and FSH (Orlowski and Sarao, 2023; Rawindraraj *et al*., 2023). FSH and LH are consequently secreted into the circulation for their stimulatory actions on the testes. FSH acts on Sertoli cells triggering spermatogenesis and hormone synthesis, primarily inhibin. LH binds to the LH receptors on Leydig cells stimulating steroidogenesis and testosterone production. There is evidence suggesting that FSH may stimulate testosterone production by Leydig cells secondary to the release of activating hormones from Sertoli cells (McQuaid and Tanrikut, 2014). The secretion of GnRH by the hypothalamus is pulsatile in nature triggering a response in LH and consequently testosterone synthesis (Filicori, 2023). This circadian rhythm of hormone release is essential for human health and well-being (Reddy *et al*., 2023).

Testosterone is subsequently aromatised to oestradiol that exerts a negative feedback on the hypothalamus and the pituitary gland, resulting in decreased production of GnRH, FSH and LH, consequently maintaining testosterone in its optimal range (Rohayem *et al*., 2024). Inhibin also exerts negative feedback on the pituitary gland decreasing LH and FSH production (McQuaid and Tanrikut, 2014).

2.0. Pathophysiological Influence of Prolactin on Male Reproduction

Prolactin inhibits pulsatile GnRH secretion and consequently inhibits the pulsatile release of FSH, LH and Testosterone. This results in marked effects on spermatogenesis ranging from alteration in sperm quality to complete spermatogenic arrest. As a result, the patient may present with secondary hypogonadism or male infertility. Furthermore, prolactin may also impact male fertility through a direct effect on spermatogenesis. Studies have identified prolactin receptors on Leydig cells, Sertoli cells and epithelial cells of efferent ducts, suggesting a potential role for prolactin in promoting steroidogenesis, spermatogenesis and secretory/adsorptive functions of male reproductive organs (Dabbous and Atkin, 2017).

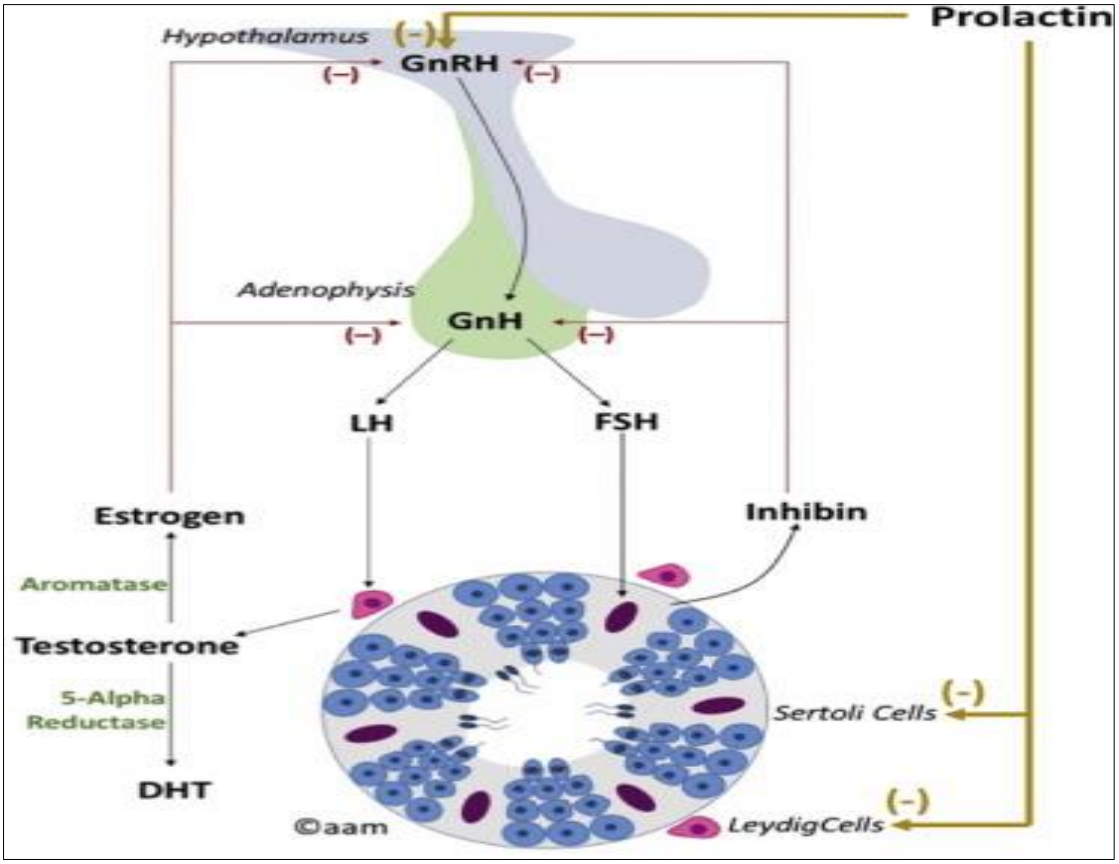

Fig. 3: Hypothalamic–pituitary–gonadal axis (HPG) (Source: Zeinab and Stephen, 2018)

2.1. Etiology

Causes of hyperprolactinemia usually fall into three categories physiologic, pharmacologic, and pathologic.

2.1.1. Recognized Physiological States

These include; exercise, diet, stress, neurogenic stimulation such as chest wall stimulation and nipple stimulation, sexual intercourse, or pregnancy, can cause various degrees of serum prolactin elevation. Another important cause is the intake of some medications. Hyperprolactinemia has been recognized in association with several classes and individual pharmacological agents. Medications that block the central dopaminergic system can potentially increase prolactin levels. These include a group of drugs that antagonize the dopamine

receptor on lactotrophs (risperidone, metoclopramide, haloperidol), inhibit dopamine reuptake (serotonin reuptake inhibitors, monoamine oxidase inhibitors, tricyclic antidepressants), deplete dopamine (reserpine, methyldopa), or increase transcription of the prolactin gene (estrogens) (Mussa *et al*., 2020).

2.1.2. Pathological Causes of Hyperprolactinemia

These include a wide range of disorders. Naturally, the most important cause is a prolactin-secreting pituitary adenoma (prolactinoma), which accounts for 30%–40% of all pituitary tumors. Furthermore, any pathology in the hypothalamic-pituitary region such as craniopharyngiomas, granulomatous infiltration of the hypothalamus, and other hypothalamic tumors can cause hyperprolactinemia through interference with the normal dopaminergic inhibitory effect on prolactin secretion stalk effect.

2.1.3. Chronic Illness

Chronic illnesses such as chronic renal failure and liver cirrhosis can increase circulating prolactin levels due to decreased clearance. Hypothyroidism can cause moderate hyperprolactinemia by the enhanced release of thyrotropin-releasing hormone (TSH) and reduced prolactin clearance. It is more frequent in overt than subclinical hypothyroidism (Mussa *et al*., 2020).

2.2. Epidemiology of Male Infertility

It is estimated that infertility affects 8–12% of couples globally, with a male factor being a primary or contributing cause in approximately 50% of couples. Causes of male subfertility vary highly, but can be related to congenital, acquired, or idiopathic factors that impair spermatogenesis. Many health conditions can affect male fertility, which underscores the need for a thorough evaluation of patients to identify treatable or reversible lifestyle factors or medical conditions. Although semen analysis remains the cornerstone for evaluating male infertility, advanced diagnostic tests to investigate sperm quality and function have been developed to improve diagnosis and management (Agarwal *et al*., 2021).

2.3. Risk Factors for Male Infertility

1. Enlarged veins (varicocele) in the scrotum, the sac that holds the testicles.
2. Genetic disorders, such as cystic fibrosis.
3. High heat exposure to testicles from tight clothing or frequent use of hot tubs and saunas.
4. Injury to the scrotum or testicles.
5. Low sperm count or low testosterone (hypogonadism).
6. Misuse of anabolic steroids.
7. Premature ejaculation or retrograde ejaculation (semen flows back into the bladder).
8. Testicular cancer and treatments.
9. Undescended testicls (cryptorchidism)
10. Hyperprolactinemia (leading to reduced Testosterone level)

2.4. Laboratory Investigation of Prolactin (Architect system)

The Architect system for Prolactin assay is a Chemiluminescent Microparticle Immunoassay (CMIA) for the quantitative determination of prolactin in human serum and plasma

2.4.1. Summary

Human prolactin (hPRL) is a single chain polypeptide of 199 amino acids and a molecular weight of approximately 23,000 daltons. Its existence as a distinct chemical entity, separate from growth hormone, was established through a series of studies between 1965 and 1971. Prolactin is produced by the anterior pituitary and its secretion is regulated physiologically by inhibitory and releasing factors of the hypothalamus. Prolactin appears in the blood promptly after administration of thyrotropin-releasing hormone (TRH). The major physiologic action of prolactin is the initiation and maintenance of lactation in women.

Hyperprolactinemia has been established as a common cause of infertility and gonadal disorders in men and women. Prolactin has been shown to inhibit the secretion of ovarian steroids and to interfere with follicle maturation and the secretion of LH and FSH in the human female. Measurement of elevated serum prolactin levels may provide the first quantitative evidence of pituitary dysfunction. Quantitation of prolactin levels is also of interest in the evaluation and management of patients with amenorrhea and galactorrhea.10Various factors other than disease states have been found to influence prolactin levels. Factors which increase prolactin concentrations include: pregnancy, breast stimulation, stress, coitus, administration of estrogens, progesterone, androgens, some psychotropic and antihypertensive drugs, and TRH. Factors which decrease prolactin concentrations include the administration of L-dopa and bromocriptine.

2.4.2. Principle of the Procedure

The ARCHITECT Prolactin assay is a two-step immunoassay to determine the presence of prolactin in human serum and plasma using Chemiluminescent Microparticle Immunoassay (CMIA) technology with flexible assay protocols, referred to as Chemiflex. In the first step, sample and anti-prolactin (mouse, monoclonal) coated paramagnetic microparticles are combined. Prolactin present in the sample binds to the anti-prolactin (mouse, monoclonal) coated microparticles. After washing, anti-prolactin (mouse, monoclonal) acridinium labeled conjugate is added in the second step. Pre-Trigger and Trigger Solutions are then added to the reaction mixture; the resulting chemiluminescent reaction is measured as relative light units (RLUs). A direct relationship exists between the amount of

prolactin in the sample and the RLUs detected by the ARCHITECT optical system.

2.4.3. Specimen Collection and Preparation for Analysis

- Human serum (including serum collected in serum separator tubes) or plasma collected in sodium heparin, lithium heparin, or potassium EDTA may be used in the ARCHITECT Prolactin assay. Other anticoagulants have not been validated for use with the ARCHITECT Prolactin assay. Follow manufacturer's processing instructions for serum or plasma collection tubes.
- The ARCHITECT System does not provide the capability to verify specimen type. It is the responsibility of the operator to verify the correct specimen types are used in the ARCHITECT Prolactin assay.
- Use caution when handling patient specimens to prevent cross contamination. Use of disposable pipettes or pipette tips is recommended.
- For optimal results, inspect all samples for bubbles. Remove bubbles with an applicator stick prior to analysis. Use a new applicator stick for each sample to prevent cross contamination.
- For optimal results, serum and plasma specimens should be free of fibrin, red blood cells or other particulate matter.
- Ensure that complete clot formation in serum specimens has taken place prior to centrifugation. Some specimens, especially those from patients receiving anticoagulant or thrombolytic therapy may exhibit increased clotting time. If the specimen is centrifuged before a complete clot forms, the presence of fibrin may cause erroneous results.
- If testing will be delayed more than 24 hours, remove serum or plasma from the clot, serum separator or red blood cells. Specimens may be stored for up to 7 days at 2-8°C prior to being tested. If testing will be delayed more than 7 days, specimens should be frozen at -10°C or colder. Specimens stored frozen at -10°C or colder for 12 months showed no performance differences.
- Multiple freeze-thaw cycles of specimens should be avoided. Specimens must be mixed THOROUGHLY after thawing, by LOW speed vortexing or by gently inverting, and centrifuged prior to use to remove red blood cells or particulate matter to ensure consistency in the results.
- When shipped, specimens must be packaged and labeled in compliance with applicable state, federal and international regulations covering the transport of clinical specimens and infectious substances. Specimens must be shipped frozen (dry ice). Prior to shipment, it is recommended that specimens be removed from the clot, serum separator or red blood cells.

2.4.4. Assay Procedure

- Before loading the ARCHITECT Prolactin Reagent Kit on the system for the first time, the microparticle bottle requires mixing to resuspend microparticles that have settled during shipment:
- Invert the microparticle bottle 30 times.
- Visually inspect the bottle to ensure microparticles are resuspended. If microparticles are still adhered to the bottle, continue to invert the bottle until the microparticles have been completely resuspended.
- Once the microparticles have been resuspended, remove and discard the cap. Wearing clean gloves, remove a septum from the bag. Carefully snap the septum onto the top of the bottle.

➢ **Order Tests**

- Load the ARCHITECT Prolactin Reagent Kit on the ARCHITECT System. Verify that all necessary assay reagents are present. Ensure that septums are present on all reagent bottles.
- The minimum sample cup volume is calculated by the system and is printed on the Orderlist report. No more than 10 replicates may be sampled from the same sample cup. To minimize the effects of evaporation verify adequate sample cup volume is present prior to running the test.
- Priority: 80 µL for the first Prolactin test plus 30 µL for each additional Prolactin test from the same sample cup
  ≤ 3 hours onboard: 150 µL for the first Prolactin test plus 30 µL for each additional Prolactin test from the same sample cup
- 3 hours onboard: additional sample volume is required. Refer to the ARCHITECT System Operations Manual, Section 5 for information on sample evaporation and volumes.
- If using primary or aliquot tubes, use the sample gauge to ensure sufficient patient specimen is present.
- ARCHITECT Prolactin Calibrators and Controls should be mixed by gentle inversion prior to use.
- To obtain the recommended volume requirements for the ARCHITECT Prolactin Calibrators and Controls, hold the bottles vertically and dispense 4 drops of each calibrator or 3 drops of each control into each respective sample cup.

❖ **Load Samples**

- Press RUN. The Architect System performs the following function:
- Moves the sample to the aspiration point
- Loads a reaction vessel (RV) into the process path
- Aspirates and transfers sample into the RV
- Advances the RV one position and transfers microparticles into the RV
- Mixes, incubates and washes the reaction mixture
- Adds conjugate to the RV
- Mixes, incubates and washes the reaction mixture
- Adds Pre-Trigger and Trigger Solutions
- Measures chemiluminescent emission to determine the quantity of prolactin in the sample
- Aspirates contents of RV to liquid waste and unloads RV to solid waste
- Calculates the result.

2.4.5. Reference Range

Male: 3.46-19.40
Female: 5.18-26.53

2.5. Treatment of Hyperprolactinemia

The objectives of treatment of hyperprolactinemia are to normalize PRL concentrations and resolve symptoms. If a tumor is present, the goals of therapy also include reduction in tumor mass, preservation of residual pituitary function, and prevention of disease progression or recurrence.

2.5.1. Medical Therapy

Dopamine agonists are the agents of choice for the treatment of hyperprolactinemia, even in the setting of a prolactin-secreting adenoma. These agents bind to dopamine receptors on the surface of the lactotroph, inhibiting PRL synthesis and release. In most patients, these agents reduce tumor volume and normalize PRL concentrations. Two dopamine agonists, cabergoline and bromocriptine, are currently approved in the United States for the treatment of hyperprolactinemia. Pergolide, although not approved by the US Food and Drug Administration (FDA), has been used for the treatment of hyperprolactinemia. Bromocriptine requires twice-daily administration, whereas cabergoline, which has a longer duration of action, is administered once or twice weekly.

2.5.2. Surgery

Surgery is second-line therapy for prolactinomas and is used when patients cannot tolerate dopamine agonist therapy or when the tumor is resistant to medical therapy. Preoperative PRL concentration, tumor size, and tumor invasiveness are factors that influence the outcome of surgical intervention. Several studies have shown that the surgical cure rate is inversely proportional to serum PRL concentration. In patients with macroadenoma treated with transsphenoidal surgery, the success rate is poor (<40%), the frequency of postoperative hypopituitarism is relatively high, and adjunctive therapy is necessary in most cases.

2.6. CONCLUSION

Infertility is the inability to conceive within 12 months of involving in unprotected sexual intercourse by a couple. Infertility can be primary or secondary. Many factors can contribute to infertility in both males and females. One the causes in males are hyperprolactinemia.

Prolactin (PRL) is a 23 kDa single chain protein of 199 amino acids synthesised and released principally by lactotrophs in the anterior pituitary gland. The secretion is mainly under inhibitory control by hypothalamic dopamine and regulated in a negative feedback manner, with prolactin itself providing the afferent signal: short-loop feedback. The main function of prolactin is during pregnancy and lactation in the development of mammary glands, milk synthesis and maintenance of milk secretion. Serum prolactin levels rise rapidly during pregnancy with increase in the size and number of lactotrophs. Hyperprolactinemia is a common endocrine disorder that can be associated with significant morbidity. It can result from a number of causes, including use of medication, hypothyroidism and pituitary disorders. Depending on the cause and consequences of hyperprolactinemia, selected patients require treatment considering the underlying cause, age, sex, and reproductive status. Hyperprolactinemia is treatable provided the root cause is detected.

2.7. RECOMMENDATION

Hyperprolactinemia as one of the causes of infertility has been missed by many health care providers because of its subtlety. Unlike in females where an elevated prolactin level will have a very pronounced effect on the reproductive cycle affecting maybe ovulation or menstruation, it does not have this kind of effect on males. It is recommended that hormonal screening be included as part of the tests to be conducted for every intending couple. This will help to reduce the incidence of infertility and/ provide an avenue for early detection and hence management of such challenge.

REFERENCES

- Agarwal, A., Baskaran, S., Parekh, N., Cho, C., Henkel, R., & Vij, R. (2021). Male infertility. *The Lancet*, 397(10271), 319-333.
- Al-Chalabi, M., Bass, A.N., & Alsalman, I. (2023). Physiology, Prolactin. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK507829/
- Auriemma, R. S., Pirchio, R., De Alcubierre, D., Pivonello, R., & Colao, A. (2019). Dopamine Agonists: From the 1970s to Today. *Journal of Neuroendocrinology*, 109(1), 34-41.

- Borba, V.V., Zandman-Goddard, G., & Shoenfeld, Y. (2018). Prolactin and Autoimmunity. *Frontiers in Immunology*, *9*, 73. https://doi.org/10.3389/fimmu.2018.00073
- Borba, V.V., Zandman-Goddard, G., Shoenfeld, Y. (2019). Prolactin and autoimmunity: The hormone as an inflammatory cytokine. *Best Practice & Research Clinical Endocrinology & Metabolism,* 33(6), 101324. https://doi.org/10.1016/j.beem.2019.101324
- Chen, A.X., & Burt, M.G. (2017). Hyperprolactinaemia. *Australia Prescriber*, 40, 220-224. https://doi.org/10.18773/austprescr.2017.060
- Choudhary, P., Dogra, P. & Sharma, K. (2025). Infertility and lifestyle factors: how habits shape reproductive health. *Middle East Fertility Society Journal,* 30, 14. https://doi.org/10.1186/s43043-025-00228-7
- Costanza, M., Binart, N., Steinman, L., & Pedotti, R. (2015). Prolactin: a versatile regulator of inflammation and autoimmune pathology. *Autoimmune Reviews*, 14, 223–230.
- Dabbous, Z., & Atkin, S. L. (2017). Hyperprolactinaemia in male infertility: Clinical case scenarios. *Arab Journal of Urology*, 16(1), 44–52. https://doi.org/10.1016/j.aju.2017.10.002
- Donato, J., Jr, & Frazão, R. (2016). Interactions between prolactin and kisspeptin to control reproduction. *Archives of Endocrinology and Metabolism*, 60(6), 587–595. https://doi.org/10.1590/2359-3997000000230
- dos Santos, Á.A., de Castro, L.F., de Lima, C.L., Casulari da Motta, L.D., Roxo da Motta, L.A.C., & Amato, A.A. (2024). Circulating prolactin levels and the effect of dopaminergic agonists in systemic lupus erythematosus: a systematic review and meta-analysis. *Scientific Reports,* 14, 30143. https://doi.org/10.1038/s41598-024-74749-y
- Eunice, K.S. (2020). National Institute of Child Health and Human Development. What Are Some Possible Causes of Infertility? Cleveland Clinic, Pp. 1-6.
- Felicitas, L., Catalina, D.E., Winne, B.B., Eleonora, S., Sharon, R., & Lady man, Damasia, B. (2020). Metabolic functions of prolactin: Physiological and pathological aspects. *Journal of Neuro endocrinology*, 32(11), 12888.
- Filicori M. (2023). Pulsatile gonadotropin-releasing hormone: clinical applications of a physiologic paradigm. *F&S reports*, 4(2 Suppl), 20–26. https://doi.org/10.1016/j.xfre.2023.01.007
- Gore, A.C., Chappell, V.A., & Fenton, S.E. (2015). EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. *Endocrine Reviews,* 36(6), 1-150.
- Grattan D.R. (2015). 60 Years of Neuroendocrinology: The hypothalamo-prolactin axis. *The Journal of Endocrinology*, 226(2), T101–T122. https://doi.org/10.1530/JOE-15-0213
- Jin, Y., & Fan, M. (2019). Treatment of gynecomastia with prednisone: case report and literature review. *Journal of Internal Medicine Research*, 47(5), 2288-2295.
- Langan, E.A. (2024). Prolactin: A Mammalian Stress Hormone and Its Role in Cutaneous Pathophysiology. *International Journal of Molecular Sciences*, *25*(13), 7100. https://doi.org/10.3390/ijms25137100
- Legorreta-Haquet, M.V., Santana-Sanchez, P., Chavez-Sanchez, L., Chavez-Rueda, A.K. (2022). The effect of prolactin on immune cell subsets involved in SLE pathogenesis. Frontiers in Immunology, 13. https://doi.org/10.3389/fimmu.2022.1016427
- Leslie, S.W., Soon-Sutton, T.L., Khan, M.A.B. (2024). Male Infertility. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK562258/
- Marques, P., De Sousa, L.A., Skorupskaite, K., Rozario, K.S., Anderson, R.A., & George, J.T. (2024). Physiology of GnRH and Gonadotrophin Secretion. [Updated 2024 Oct 15]. In: Feingold, K.R., Ahmed, S.F., Anawalt, B., et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279070/
- Martínez-Neri, P.A., López-Rincón, G., Mancilla-Jiménez, R., del Toro-Arreola, S., Muñoz-Valle, J.F., Fafutis-Morris, M., Bueno-Topete, M.R., Estrada-Chávez, C., & Pereira-Suárez, A.L. (2015). Prolactin modulates cytokine production induced by culture filtrate proteins of M. bovis through different signaling mechanisms in THP1 cells. *Cytokine*, 71, 38–44.
- Matalliotakis, M., Koliarakis, I., Matalliotaki, C., Trivli, A., & Hatzidaki, E. (2019). Clinical manifestations, evaluation and management of hyperprolactinemia in adolescent and young girls: a brief review. *Acta Biomedical Journal*, 90(1), 149-157.
- McQuaid, J.W., & Tanrikut, C. (2014). Physiology of testosterone. In: Mulhall JP, Hsiao W, editors. Men's sexual health and fertility. A Clinician's guide. New York: Springer Science and Business Media; 1-10.
- Mussa, H.A., & Salem, A.B. (2020). A Rational Approach to the Evaluation and Management of Patients with Hyperprolactinemia. Available on Research Gate. www.researchgate.net Pp. 1-5.
- Nargund, V.H. (2015). Effects of psychological stress on male fertility. *Nature Reviews Urology*, 12(**7**), 373–382.
- Nazma, A., Nazmul, K.Q., & Tangera, A. (2018). Hyperprolactinemia: A Systematic Review of

Diagnosis and Management. *Delta Medical College Journal,* 6(2), 90–101.

- Ogawa, S., & Parhar, I.S. (2018). Biological Significance of Kisspeptin–Kiss 1 Receptor Signaling in the Habenula of Teleost Species. Frontiers in Endocrinology, 9. https://doi.org/10.3389/fendo.2018.00222
- Orlowski, M., & Sarao, M.S. (2023). Physiology, Follicle Stimulating Hormone. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK535442/
- Park, S., Kim, D. S., Daily, J. W., & Kim, S. H. (2011). Serum prolactin concentrations determine whether they improve or impair β-cell function and insulin sensitivity in diabetic rats. *Diabetes/metabolism research and reviews*, *27*(6), 564–574. https://doi.org/10.1002/dmrr.1215
- Pérez-López, F.R., López-Baena, M.T., & Pérez-Roncero, G.R. (2021). Prolactin secretion in women: narrative review. *Gynecology and Pelvic Medicine*, 4, 20. https://doi.org.10.21037/gpm-21-4
- Qi-Lytle, X., Sayers, S., & Wagner, E. J. (2024). Current Review of the Function and Regulation of Tuberoinfundibular Dopamine Neurons. *International Journal of Molecular Sciences*, *25*(1), 110. https://doi.org/10.3390/ijms25010110
- Rasmi, Y., Jalali, L., Khalid, S., Shokati, A., Tyagi, P., Ozturk, A., & Nasimfar, A. (2023). The effects of prolactin on the immune system, its relationship with the severity of COVID-19, and its potential immunomodulatory therapeutic effect. *Cytokine*, 169, 156253. https://doi.org/10.1016/j.cyto.2023.156253
- Rassie, K., Giri, R., Joham, A. E., Teede, H., & Mousa, A. (2022). Human Placental Lactogen in Relation to Maternal Metabolic Health and Fetal Outcomes: A Systematic Review and Meta-Analysis. *International Journal of Molecular Sciences*, *23*(24), 15621. https://doi.org/10.3390/ijms232415621
- Rawindraraj, A.D., Basit, H., & Jialal, I. (2023). Physiology, Anterior Pituitary. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499898/
- Reddy, S., Reddy, V., & Sharma, S. (2023). Physiology, Circadian Rhythm. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519507/
- Rohayem, J., Alexander, E.C., Heger, S., Nordenström, A., Howard, S.R. (2024). Mini-Puberty, Physiological and Disordered: Consequences, and Potential for Therapeutic Replacement, *Endocrine Reviews*, 45(4), 460–492, https://doi.org/10.1210/endrev/bnae003
- Saleem, M., Martin, H., & Coates, P. (2018). Prolactin Biology and Laboratory Measurement: An Update on Physiology and Current Analytical Issues. *The Clinical Biochemist. Reviews*, *39*(1), 3–16.
- Segal, T.R., & Giudice, L.C. (2019). Before the beginning: environmental exposures and reproductive and obstetrical outcomes. *Fertility and Sterility,* 112(4), 613-621.
- Szukiewicz, D. (2024). Current Insights in Prolactin Signaling and Ovulatory Function. *International Journal of Molecular Sciences*, *25*(4), 1976. https://doi.org/10.3390/ijms25041976
- Thapa, S., & Bhusal, K. (2023). Hyperprolactinemia. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537331/
- Vander Borght, M., & Wyns, C. (2018). Fertility and infertility: Definition and epidemiology. *Clinical Biochemistry*, 62, 2-10. https://doi.org/10.1016/j.clinbiochem.2018.03.012
- Wefak, J.A. (2020). Prolactin. Available on Research Gate. www.researchgate.net. Pp. 1-15.
- World Health Organization (WHO). (2018). International Classification of Diseases, 11th Revision (ICD-11) Geneva.
- World Health Organization (WHO). (2020). Infertility, Pp. 1-5.
- Xie, Q., Kang, Y., Zhang, C., Xie, Y., Wang, C., Liu, J., Yu, C., Zhao, H., & Huang, D. (2022). The Role of Kisspeptin in the Control of the Hypothalamic-Pituitary-Gonadal Axis and Reproduction. *Frontiers in Endocrinology*, 13. https://doi.org/10.3389/fendo.2022.925206
- Yang, H., Lin, J., Li, H., Liu, Z., Chen, X., & Chen, Q. (2021). Prolactin Is Associated With Insulin Resistance and Beta-Cell Dysfunction in Infertile Women With Polycystic Ovary Syndrome. *Frontiers in Endocrinology*, 12, 571229. https://doi.org/10.3389/fendo.2021.571229
- Yatavelli, R.K.R., & Bhusal, K. (2023). Prolactinoma. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459347/
- Yip, S.H., Romanò, N., Gustafson, P., Hodson, D.J., Williams, E.J., Kokay, I.C., Martin, A.O., Mollard, P., Grattan, D.R., & Bunn, S.J. (2019). Elevated Prolactin during Pregnancy Drives a Phenotypic Switch in Mouse Hypothalamic Dopaminergic Neurons. Cell Reports, 26(7), 1787-1799.e5. https://doi.org/10.1016/j.celrep.2019.01.067