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A Narrative Review on Reproductive Hormones

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Abstract

Reproductive hormones play a crucial role in regulating the reproductive system and maintaining fertility in both males and females. This review provides an overview of the key reproductive hormones, their functions, and interactions in the human body. In females, hormones such as estrogen, progesterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and gonadotropin-releasing hormone (GnRH) govern the menstrual cycle, ovulation, and pregnancy. Estrogen and progesterone prepare the uterus for pregnancy, while FSH and LH stimulate follicular development and ovulation. In males, testosterone, produced by the testes, is essential for sperm production and secondary sexual characteristics. FSH and LH also regulate spermatogenesis by stimulating the testes to produce testosterone. The complex feedback mechanisms of the hypothalamic-pituitary-gonadal (HPG) axis maintain hormonal balance and reproductive health. Disruptions in this axis can lead to reproductive disorders, including infertility, polycystic ovary syndrome (PCOS), and hypogonadism. Hormonal therapies, such as birth control, hormone replacement therapy, and fertility treatments, manipulate reproductive hormones to address various health concerns. Recent advances in reproductive endocrinology have highlighted the role of environmental factors, such as endocrine disruptors, in influencing hormone levels and reproductive health. Overall, understanding the intricacies of reproductive hormones is essential for improving reproductive health outcomes and addressing hormonal disorders.

Keywords: Reproductive Hormones, Spermatogenesis, Hypogonadism, Hormonal Disorders, Hypothalamic-pituitary-gonadal

Introduction

Reproductive physiology has been a topic of speculation since the early ages but the reproductive hormones, their true nature, mechanisms and functions have been understood only fairly recently. The earliest known description was in the Sushruta in 1400 BCE, where menstruation was explained as the impurity of the seven body elements, while pregnancy was the result of

the union of this fiery blood with semen. The same scripture also recommends "testis tissue for impotence". It was not till the 17th century that the physiological processes involved started becoming lucid. Theodor Kerckring (1638–1693), who is famous for his "Spicilegium Anatomicum", stated that the ovum is expelled by the onset of menstruation.

Eugen Steinach, an Austrian physiologist, and his colleagues were the first to study the effects of steroid hormones on sexual behavior in rats – an experiment that gained him the status of the pioneer in reproductive neuro-endocrinology. His discovery of the role of Oestrogens in androgen-activated behavior got him nominated for the Nobel Prize seven times. Their original publication in 1936 was in German, and it was translated into English in 2014 by Sodersten *et al.* [1], who enumerated their major breakthroughs as below 4:

1. Interstitial cells are the main source of gonadal hormones
2. Steroid hormones act on the brain to induce sexual behaviour
3. Chronic gonadal transplants produce physiological and behavioural sexual reversals
4. Sensory stimulation is necessary for testicular stimulation
5. He also developed commercial synthetic hormones for clinical use in humans [Fig 1].

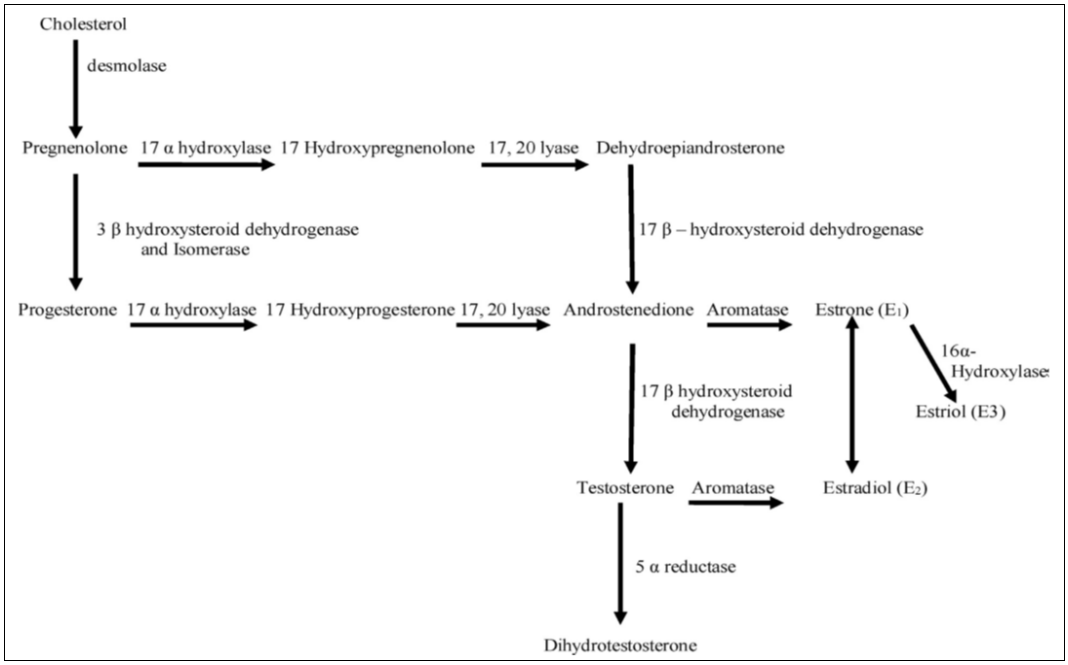

Fig 1: Pathways involved in the biosynthesis of reproductive hormones [2, 3].

Despite this epochal research, another four decades passed before experiments revealed the mechanism of action of the steroid hormones including the sex steroids. It was elucidated that these hormones act through receptors, whereby they alter transcriptional activation of target genes. Also, there is a multitude of interactions and ramifications of these hormones and the physiological processes that they influence. In view of these intricate mechanisms, it is the aim of this review to highlight briefly the physiology, metabolism and the most important clinical aspects of these hormones to facilitate their optimal utilization in clinical practice.

The brain, in particular, has a wide distribution of receptors for hormones like estrogen and testosterone, which allows these sex steroids to affect a multitude of brain circuits, influencing how, where, and when brain cells communicate [Fig 2]. Many researchers hypothesize that sex steroids act as a type of signaling mediator, helping other neurotransmitters and neuropeptides do their job more efficiently. Researchers who study hormones at the molecular level sometimes refer to them as "gate openers," helping cells send out and receive other important neurochemicals. That mediation is important: It may ultimately influence human behavior by helping to direct our attention to specific items in the environment, or making certain stimuli more appealing.

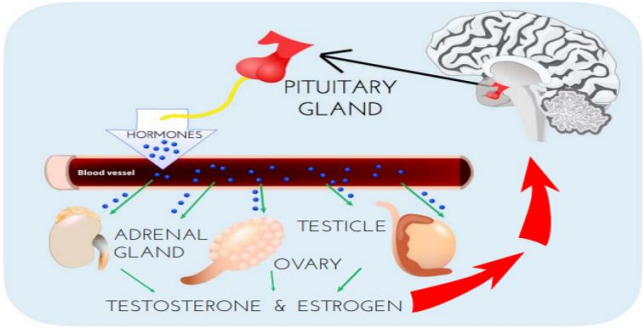

Fig 2: Reproductive hormones and the brain

Hypothalamic-pituitary-gonadal (HPG) axis

The hypothalamic-pituitary-gonadal (HPG) axis is a key hormonal system that regulates reproduction and sexual development in humans and many animals. It involves interactions between three primary components: the hypothalamus, the pituitary gland, and the gonads (ovaries in females, testes in males) [4, 5].

The hypothalamus is region of the brain releases gonadotropin-releasing hormone (GnRH) in a pulsatile manner, signaling the start of the reproductive hormone cascade.

The Pituitary Gland in response to GnRH, the anterior pituitary releases two important hormones: luteinizing

hormone (LH) and follicle-stimulating hormone (FSH). These hormones travel through the bloodstream to the gonads.

The gonads are stimulated by LH and FSH to produce sex hormones (estrogen and progesterone in females, testosterone in males) and regulate the production of gametes (eggs in females, sperm in males). These sex hormones play crucial roles in secondary sexual characteristics, reproductive functions, and feedback regulation.

In a feedback loop, high levels of sex hormones inhibit GnRH, LH, and FSH production, ensuring hormonal balance. This axis is essential for puberty, menstrual cycles, sperm production, and maintaining reproductive health [Fig 3]. Any dysfunction in the HPG axis can lead to fertility issues, hormonal imbalances, or disorders like polycystic ovary syndrome (PCOS) and hypogonadism. The HPG axis is also modulated by external factors such as stress, nutrition, and aging.

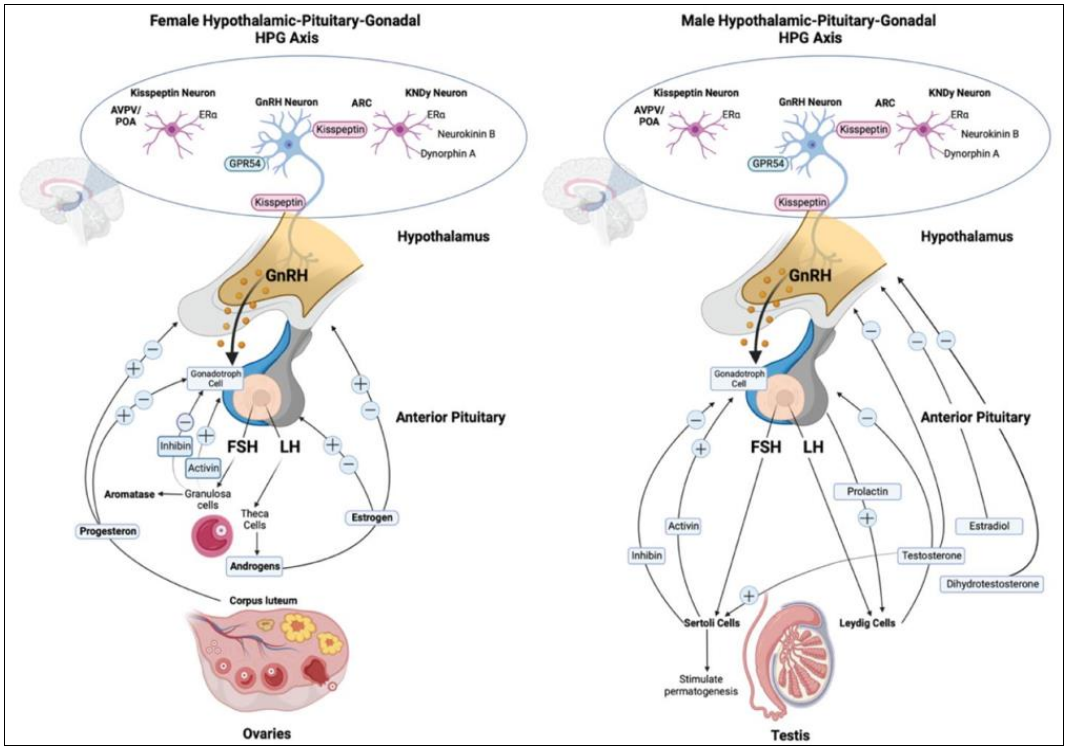

Fig 3: Schematic of the different hormone production pathways of male and female Hypothalamic-pituitary-gonadal (HPG) axis. Kiss 1 neurones in the ARC provide tonic stimulatory input to GnRH neurones, which are adversely affected by sex hormones. AVPV sex steroids stimulate Kiss 1 neurones. Transsynaptic and glial inputs cause GnRH to be released into the hypophysial circulation. GnRH regulates LH and FSH levels, which promote ovarian and testicular development. LH activates theca cells in females, which produce oestrogen, principally estradiol. FSH acts on granulosa cells and regulates aromatase. In the ovary, the corpus luteum produces progesterone, which, along with oestrogen, offers positive and negative feedback to the pituitary and hypothalamus. LH promotes testosterone production in male Leydig cells, which has a detrimental effect on the brain and pituitary glands. Testosterone is further metabolised into dihydrotestosterone and estradiol, which have a detrimental effect on the hypothalamus and pituitary glands. While FSH acts on Sertoli cells to enhance spermatogenesis. Adapted from (Tammasse and Tamrin[6]; Ozawa[7]).

Oestrogen

Oestrogen is a primary female sex hormone produced mainly by the ovarian follicles and corpus luteum, and also by the placenta. The three major types of oestrogens are estrone, estradiol and estriol, of which, estradiol is the most potent oestrogen [2.3] Since 17β estradiol is derived almost completely from the ovaries, its measurement is used to evaluate ovarian function.

Physiological function

During the reproductive period, oestrogen is responsible for the follicular phase changes in the uterus. The ovaries secrete very little oestrogen or progesterone in the early follicular phase but a rise in Follicle Stimulating Hormone (FSH) stimulates oestrogen production. This oestrogen stimulates the uterine epithelial cells, growth of blood vessels and development of endometrial glands to increase the endometrial thickness. oestrogen levels peak one day before ovulation, resulting in the Luteinizing Hormone (LH) surge due to a positive feedback system. This starts the luteal phase in which, approximately 36 hours after the LH surge, the ovum is extruded and corpus luteum is formed. This corpus luteum then secretes progesterone which aids embryo implantation. However, if fertilization does not take place, oestrogen and progesterone production gradually decline approximately 14 days after ovula- tion [8].

Metabolism

Estradiol is the most important oestrogen in premenopausal women, while in postmenopausal women, estrone, from peripheral tissues, predominates. Estradiol and estrone are metabolized primarily in the liver, involving irreversible hydroxylations catalyzed by the NADPH-dependent cytochrome P450 (CYP) enzymes, and finally excreted as conjugates in urine [9].

Clinical significance

Oestrogens are responsible for the development of female sex organs and secondary sex characteristics. With progesterone, they regulate the menstrual cycle as well as growth of breast and uterus. They also help to maintain

pregnancy. oestrogens are responsible for the regulation of gonadotropin secretions. In addition, oestrogens have anti-inflammatory properties and play an important preven- tive role in heart disease. They increase lipogenesis in adipose tissue and have a hypocholesterolemic effect. oestrogens have an anabolic effect and also increase concentration of plasma proteins that bind copper and iron. oestrogens decrease bone resorption and accelerate linear bone growth in prepubertal girls, hence, its deficiency results in increased stress fractures and post meno-pausal osteoporosis. The large increase in bone resorption is caused mainly by increased osteoclastic activity [10]. Natural or synthetic oestrogen has been used clinically in a number of conditions like gonadal dysgenesis, excessive height and genital infections in prepubertal females. In the reproductive years, oestrogen is used to treat menstrual disorders, infertility, pregnancy disorders like abortion and suppression of lactation, and skin disorders like acne vulgaris and hirsutism. oestrogen/ progestogen combination pills are used for contraception and postcoital contraception. oestrogens are also used to treat menopausal syndrome as well as genital problems like infection, atropic vaginitis and genital prolapse. In males, the use of oestrogen has been beneficial in the treatment of prostatic carcinoma and sexual problems [11]. Oestrogen is the main cause of hormonal changes associated with menopause and since it is usually administered with progestogen, Freedman had reviewed the use of oestrogen or hormone replacement therapy (ERT/HRT) in menopause and supported its use in treatment of menopausal symptoms [12]. Recent studies have improved our understanding of the role played by oestrogen in the human body significantly. Oestrogens promote proliferation of the normal and the neoplastic breast epithelium and their role as breast carcinogens has long been suspected. However, the mechanism by which they cause cancer needs further research [13].

Newer aspects of oestrogen signaling were highlighted in a review by Vrta9cnik *et al*., [14] in 2014, that exceeded its classical endocrine regulatory role. They postulated that epigenetic mechanisms augment the intricacy and specificity of oestrogen- mediated transcriptional control. This study of oestrogen regulation has thrown light on the effects of the existing oestrogen receptor modulators, and paved the way for the discovery of newer tissue as well as cell specific compounds [14]. Estradiol is known to play an important role in infertility and attention has been given by researchers to the incorporation of natural estradiol in In-Vitro Fertilization (IVF). Chang *et al* had observed that oestrogen priming through the luteal and stimulation phases, improved ovarian responsiveness, leading to an increase in pregnancy rates [15]. More recently in 2014, Prasad *et al*. [16], assessed the role of estradiol in predicting pregnancy rate in women undergoing controlled ovarian hyperstimulation, and observed estradiol to be an important prognostic marker for the success of IVF treatment [14]. Due to its wide regulatory role, oestrogens now need to be viewed as more than only female sex hormones. They also play an important role in male physiology and sexual function and oestrogen is known to be involved in modulating libido, spermatogenesis and erectile function [3]. A complex balance of testosterone, estradiol, aromatase (converts testosterone to oestrogen), and oestrogen receptors in the testes, penis and brain confirms a highly regulated hormonal interaction of oestrogen in the male. However, more research is required on the effectiveness of estradiol use in the treatment of diminished libido, erectile dysfunction and even oligospermia [17].

Progesterone

Progesterone, a female sex hormone similar to the oestrogens, is an endogenous steroid released by the ovaries and the adrenal glands. Progesterone, in association with oestrogen, helps to regulate the accessory organs during the menstrual cycle [18]. It stimulates and regulates ovulation and plays a major role in maintaining pregnancy. Progesterone is especially important in preparing the uterus for implantation of the blastocyst.

Metabolism

Progesterone metabolism is complex, occurs mainly in the liver and is rapid and extensive. Enzymes that metabolize progesterone are also expressed in the brain, skin and other extrahepatic tissues [19]. Progesterone is transported mainly bound to albumin, and to a lesser extent, to corticosteroid binding globulin and sex hormone binding globulin. In circulation, the half-life of progesterone is approximately five minutes [20]. Progesterone is highly susceptible to enzymatic reduction via reductases and hydrox- ysteroid dehydrogenases, due to the double bond (between the C-4 and C-5 positions) and its two ketones (at C-3 and C-20 positions) [21].

Clinical significance

Progesterone has a myriad of functions in the body. It is a crucial metabolic intermediate in the production of corticosteroids, sex hormones, and other endogenous steroids. Progesterone level above 10ng/ml indicates the occurrence of ovulation. The time right after ovulation until the next menstrual period is called the “corpus luteum phase” or the “luteal phase.” In this phase, under normal circumstances, the lining of uterus thickens to prepare for a possible pregnancy. In case of luteal phase defect, in which the uterine lining fails to develop normally, successful implantation and growth of the embryo is prevented [22]. Progesterone is also known as the “hormone of pregnancy” as increasing progesterone level is indicative of viable pregnancy. This was elucidated by Patel *et al*, who studied the role of progesterone in fetal development and observed that serum concentrations are relatively constant at 8–10 weeks of gestation, unless the pregnancy is failing, which then is signaled by decreasing serum progesterone [23]. After 10–12 weeks, levels increase more rapidly. In their study, they also stated that serum progesterone determinations are not considered useful for diagnosing late pregnancy and found that, with drop in progesterone levels, onset of labor is facilitated. Serial measurement of serum progesterone indicates the presence of a functioning corpus luteum and ovulation.

In addition, progesterone inhibits lactation during pregnancy. Following delivery, a fall in progesterone level triggers milk production. Beyond its role as a reproductive hormone, progesterone is also known as a neurosteroid for its neuromodulatory and neuro- protective effects on the nervous system. Baulieu and Schumacher studied the role of progesterone in the regulation of neurotransmission and mylenation, and explored the role of stimulation of endogenous progesterone in neuroprotection and myelin repair [24].

Raine-Fenning *et al*., studied the role of Oestrogen and progesterone receptors in skin and found that at menopause

and thereafter, decreased levels of female sex hormones resulted in atrophy, thinning and increased wrinkling of the skin with a reduction in skin elasticity, firmness and strength [25]. They also studied the effect of HRT in postmenopausal women and postulated that progestogen should be included as a part of HRT, as it counteracted the elevated risk of Oestrogen-induced proliferation of human mammary epithelial cells and endometrial hyperplasia [25]. In HRT, progestin is added with Oestrogen to protect against the risk of hyperplasia and adenocarcinoma of the endometrium. Even low doses of unopposed Oestrogens are associated with increased endometrial cancer risk. Addition of a progestin in adequate dosage reduces that risk. Fournier *et al* studied the association of various Oestrogen–progestogen combinations with breast cancer risk and found that it varied significantly according to the type of progestagen used. They postulated that some progesterone compounds had a higher association with risk of breast cancer, and suggested that it would probably be safer to use progesterone or dydrogesterone [26].

Follicle stimulating hormone

Follicle Stimulating Hormone (FSH) is made up of two non-identical, covalently-associated glycoprotein subunits, alpha and beta. The alpha subunit is similar in structure for FSH, hCG, LH, and TSH, while the beta subunit contains two asparagine-linked carbohydrate chains. It is difference in the beta subunit of these glycoproteins which contributes to its immunological and physiological specificity [27].

Physiological function

FSH plays a vital role in ovulation by stimulating follicular growth and Oestrogen secretion in synchrony with LH. Following ovulation, FSH converts the ruptured follicle to corpus luteum as well as stimulates the secretion of progesterone by the luteal cells [28].

Metabolism

Gonadotropin Releasing Hormone (GnRH), secreted from the medial basal hypothalamus, stimulates anterior lobe of the pituitary gland to secrete FSH. Both FSH and LH are secreted in a pulsatile nature; however, this is less noticeable for FSH, because of its long half life. Levels of circulating FSH vary in response to estradiol and progesterone. In a normal menstrual cycle, a slight peak of FSH is observed toward the end of the luteal phase, which is most likely triggered by a fall in estradiol and progesterone levels. This begins the growth and maturation of ovarian follicles. FSH levels then fall, and remain low throughout the follicular phase (due to negative feedback from estradiol and progesterone produced by the developing follicles).

Clinical significance

GnRH is known to trigger a mid-cycle rise in FSH. The function of this mid-cycle peak is unknown, however, following this rise, FSH is suppressed during the luteal phase by negative feedback from estradiol. Near the end of the menstrual cycle, a small rise in FSH triggers the follicular maturation of the next cycle. In the menopausal female, FSH levels are high due to decrease in Oestrogen and progesterone, hence menstrual cycles decrease and finally cease. In certain conditions like premature ovarian failure, premature menopause, poor ovarian reserve and gonadal dysgenesis, FSH levels have been found to be high. In Polycystic Ovarian Syndrome (PCOS) 37, there is derangement of FSH/LH ratio from a normal of 2:1 [29, 30]. FSH also plays an important role in the treatment of infertility, mainly in ovarian hyperstimulation and reversal of anovulation [31].

Luteinizing hormone

Luteinizing Hormone (LH) also consists of two non-identical, non-covalently joined glycoprotein subunits, alpha and beta. The molecule contains two N-linked carbohydrate chains on the alpha subunit and one asparagine-linked oligosaccharide on the beta subunit. As mentioned earlier, it is this difference in the beta subunit of these glycoproteins that contributes to its immunologi-cal and physiological specificity [27].

Physiological function

LH plays a vital role in follicular maturation, rupture and ovulation. In support, Hillier and Ross demonstrated the role of LH in oocyte maturation through regulation of steroidogenesis [32].

Metabolism

In a normal menstrual cycle, raised estradiol levels stimulate the release of GnRH, leading initially to LH surge and then to ovulation. In the luteal phase, negative feedback by progester- one and estradiol suppresses LH [33]. In menopausal females, due to low oOestrogen and progesterone, LH levels are high, which removes the negative feedback on pituitary gland, leading to a decrease in duration of the menstrual cycle. LH is also known to stimulate Leydig cells of the testes in males to secrete testosterone [34].

Clinical significance of LH/FSH ratio

LH and FSH estimation is of prime importance in disorders of menstrual cycle, fertility and pubertal developmental abnormali-ties. The ratio of the two hormones is used in PCOS diagnosis. As stated by Deshmukh *et al*, abnormal LH/ FSH ratio is the major cause for continuation of the anovulatory state in PCOS subjects. According to Shoham *et al*, estimation of serum FSH is frequently used in assisted reproductive technology [35]. In pituitary failure, levels of LH and FSH fall whereas their levels rise in gonadal failure. In males, both LH and FSH are required for normal maturation of spermatozoa [36].

Prolactin

Prolactin (PRL) is a single chain polypeptide, composed of 198 amino acids with three inter-chain disulfide bonds. Prolactin secretion is regulated by Prolactin Inhibiting Factor (dopamine) and Prolactin Releasing Factor (serotonin) while it is stimulated by Thyrotropin Releasing Hormone (TRH) [37].

Physiological function

PRL stimulates and maintains lactation in women. During the menstrual cycle, its serum levels are variable and exhibit slight elevation during mid-cycle. PRL levels are also elevated in sleep, exercise, nipple stimulation, sexual intercourse, hypoglycemia, pregnancy as well as surgical stress. It is also raised in post-partum females and newborns [38]. Diurnal variation has been observed in serum PRL levels, with nocturnal peaks late at night and in early morning. Since this variation can lead to spurious hyperprolacti- naemia, it is suggested that PRL be tested around mid-morning [39].

Metabolism

Prolactin is secreted from the anterior pituitary gland, decidua, myometrium, breast, lymphocytes, leukocytes and prostate and is secreted in pulses. Dopamine is released

from arcuate nucleus and inhibits PRL secretion via its action on D2 receptors of lacto-trophs [40].

Clinical significance

Hyperprolactinemia has been observed in PRL secreting pituitary adenomas, functional and organic diseases of the hypothalamus, hypothyroidism, renal failure, and ectopic tumors. Prolactinomas are the commonest hormone-secreting pituitary tumors, and constitute about 60% of primary pituitary tumors. Mindermann *et al* observed that the frequency of pituitary tumors was greater in women than in men, and more than 70% of women suffering from hyperprolactenemia had pituitary tumours [41]. Melmed *et al* in their study stated that tumor size caused variations in female / male ratio, with 20:1 for microprolactinomas and 1:1 for macroprolactinomas Elevated levels of PRL have been observed in primary hypothyroidism due to increased secretion of TRH, which then stimulates thyroid stimulating hormone (TSH) and PRL secretion [42]. Yamada *et al* also showed a positive correlation between serum levels of TSH and increased size of sella turcica [43]. Davis *et al* investigated the effects of 3,5,30 tri-iodothyronine (T_3) supple-mentation on prolactin release and gene transcription on cultured rat pituitary cells, and postulated that reduced thyroid hormone levels increased PRL synthesis [44]. Eckstein *et al* studied the effect of serum prolactin levels on ovarian steroidogenesis, and suggested that chronic hyperprolactinemia reduced the steroidogenetic potential of ovaries when exogenous gonadotropin stimulation was done [45]. Various drugs affect PRL levels. L-dopa and Bromocriptine inhibit PRL secretion and have been used in the treatment of amenorrhea and galactorrhea due to hyperprolactinemia. Psycho- tropic drugs (phenothiazines), anti-hypertensive drugs (reser-pine), and TRH increase PRL secretion. Oestrogen therapy is also known to elevate serum PRL levels [46].

Anti-Müllerian hormone

Anti-Müllerian Hormone (AMH) belonging to the transforming growth factor-β (TGF- β), is formed of two monomeric units, linked by disulfide bridges. Each monomer consists of an N and C terminal domain, also known as "pro region" and "mature region" respectively, with the C-terminal domain as the biologically active form of the molecule [47].

Physiological function

AMH plays an important role in fetal sex differentiation with gonads as the target organs in both sexes. AMH is the earliest hormone secreted in males from Sertoli cells and is an important indicator of Sertoli cell function [48]. It is expressed in the granulosa cells of ovaries after 36 weeks of intrauterine life. The main physiological role of AMH is prevention of early depletion of follicular reserve, by targeting the inhibition of primordial follicle recruitment [49].

Metabolism

AMH acts through a serine–threonine kinase receptor complex. It activates ligand-specific type I receptors and type II receptors, which in turn activate receptor complex phosphorylation. This leads to activation of cytoplasmic Smad proteins that affect gene expression [50].

Clinical significance

Role in ovarian reserve

Dewailly *et al* observed that serum levels of AMH were directly proportional to the number of developing ovarian follicles. Hence, AMH is a useful indicator of ovarian aging throughout reproductive life [51]. Broer *et al* too demonstrated that AMH is the most recent and valuable measure of ovarian reserve for evaluating reproduc- tive life span, ovarian dysfunctions like PCOS, IVF treatment and ovarian surgery [52]. In another study, Bentzen *et al* observed that after 21years of age, there was a progressive decline of approx 5.6% in AMH levels [53]. This was probably due to a direct relationship between the prevalence of large follicles and advancement in age [53]. Also human ovarian tissue studies by immunohistochemistry confirmed that AMH expression was the highest in primary, secondary, pre-antral and early antral (<4 mm diameter) follicles [54]. AMH levels are not affected by pregnancy, treatment with GnRH agonists or oral contraceptives. Therefore, AMH estimation is an ideal test for assessing ovarian reserves with the advantage that it can be assessed anytime during the menstrual cycle [55].

Role in PCOS

Due to increased number of antral follicles and also because of the intrinsic characteristics of granulosa cells, high levels of AMH have been observed in PCOS. Skalba *et al* observed women with and without PCOS, and found a significant positive correlation of AMH with free testosterone in women with PCOS [56]. Weenen *et al* demonstrated raised serum AMH levels in obese and non obese women with PCOS, with the increase being more significant in non-obese PCOS women [54]. In another meta-analysis, the specificity and sensitivity of AMH, at a cut off of 4.7 ng/mL, were 79.4 % and 82.8 % respectively for diagnosing PCOS [57].

Role in IVF

Recent data has shown a significant positive correlation existing between basal AMH levels and the number of retrieved oocytes in women undergoing IVF. In another study, Nasr *et al* observed that in women having poor response to controlled ovarian stimulation with human gonadotropins, AMH presented a negative linear correlation with basal FSH levels [58]. Fanchin *et al* elucidated that follicular fluid AMH levels were strongly associated with pregnancy rates in IVF cycles [58]. Toner *et al* suggested the general guidelines for reporting of serum AMH level <0.5 ng/mL as a predictor of poor ovarian reserve and levels >3.5 ng/mL depicting good response to ovarian stimulation [59].

Role in Gynaecological Tumours

It has been observed that 76–93% of women suffering from granulosa cell tumors have raised levels of AMH, hence, AMH can be used as a marker for these tumours [60]. Anti-Müllerian hormone can be used to access ovarian function after chemotherapy and radiotherapy in young women. This was proved in a study which reported a fall in AMH and no difference in serum FSH and inhibin B levels in women with childhood cancer as compared to the control group [61].

Role of AMH in Males

AMH levels are helpful in diagnosing cryptochidism and delayed growth and puberty [62].

Human chorionic gonadotropin

A glycoprotein consisting of two different units, alpha and beta, human chorionic gonadotropin (hCG) has enabled the early detection of pregnancy through its urinary excretion.

Physiology & metabolism

The alpha (α) subunit is the smaller of the two and is common to several of the gonadotropins – LH and FSH, and

also to the thyroid stimulating hormone (TSH). The beta (β) subunit, however, is unique to hCG with an antigenically distinct carboxy terminal. At the same time, there is extensive homology between the β subunits of hCG and LH. Only a fraction of the circulating hormone is excreted directly through urine, the remaining being taken up by and metabolised in various tissues – mainly the kidneys, the liver and the ovaries. The synthesis of the subunits are under individual genetic control, so that in early pregnancy, the free β subunit is secreted along with the intact molecule, and the α subunit predominates in late pregnancy. This forms the basis of the commercially available pregnancy test kits which measure βhCG. In normal pregnancy, it is rapidly secreted by the implanted placenta, reaches peak levels by the 10th–12th week and then declines [3]. Its main function is to enable and support pregnancy. Secreted by the syncytiotropho- blastic cells, it has a dual mechanism of action:

a. Through its action on its receptors on the ovary, it helps to maintain the corpus luteum, which then secretes progesterone to maintain pregnancy in the first trimester. The function of progesterone is to enrich the lining blood vessels of the uterus to help in the growth of the fetus [63].
b. In addition, as it is highly negatively charged, it probably repels maternal immune cells and, thus, protects the fetus. Also, trophoblastic invasion may be facilitated and peritrophoblastic immune tolerance maintained [64]. It is also secreted by trophoblastic tumors not only of the gonads but of other organs as well.

Clinical significance

Since the β subunit is secreted in early pregnancy, it is the basis of detection of pregnancy. It also allows for detecting continuation of pregnancy due to its typical pattern of rise upto the end of the first trimester and fall thereafter. Inflammatory conditions: hCG is secreted in duodenal ulcers as well as in inflammatory bowel disease, but in these conditions, its levels do not rise as markedly as in pregnancy.

Metastatic conditions: By virtue of its function in inducing enhanced vasculature and immune tolerance, hCG is known to promote tumorigenesis. It is secreted by several types of trophoblastic tumors like hydatiform mole, nonseminomatous testicular tumors, some biliary and pancreatic tumours, and, to a lesser extent, some bladder, renal, colorectal, lung, prostate and liver tumors. Hence, it is often used as a tumor marker, especially to monitor tumor volume and prognosis. Some tumors preferentially secrete one or the other subunit, e.g. neuroendocrine tumours secrete βhCG whereas carcinoid tumors secrete the α subunit [3]. In males and nonpregnant females, its serum concentrations are <5 mIU/ml. During pregnancy, these rise up to 500,000 mIU/ml by the end of the first trimester before declining. Similarly high levels are encountered in the presence of trophoblastic tumors, whereas in inflammatory conditions the rise is less remarkable [3].

Testosterone

Testosterone, a male sex hormone, is responsible for normal growth, development, maturation as well as maintenance of the male secondary sexual characteristics. It is produced by Leydig cells of testes and to a lesser extent, in adrenal cortex via peripheral conversion of dihydroepiandrosterone and androstenedione. In females, it is produced mainly by peripheral conversion of androstenedione [65]. Testosterone release is regulated by negative feedback control on the hypothalamus and pituitary gland by LH, a pituitary hormone. The synthesis of testosterone begins with the formation of pregnenolone from cholesterol via the action of the cholesterol side-chain cleavage enzyme. 98% of circulating Testosterone is protein-bound, mostly to Sex Hormone Binding Globulin (SHBG) or Testosterone Binding Globulin (TeBG) and in lesser amount to plasma albumin. The active or bioavailable form is the free testosterone and albumin bound testosterone [3].

Physiological function

In embryos, testosterone helps in the development of male phenotype. In adult males, it causes development of testis, scrotum, prostate, seminal vesicles and penis. Testosterone is also involved in male pattern distribution of hair as well as thickening and deepening of voice, and increase in body muscles and fat. Testosterone is an anabolic hormone responsible for increased protein synthesis and decreased protein breakdown. It also leads to the growth spurt seen in puberty and termination of linear growth by facilitating the fusion of the epiphyseal growth plate. It increases erythropoiesis by stimulating the production of erythropoietic stimulating factor [3].

Metabolism

Liver is the main site of testosterone metabolism. About 50% of testosterone is metabolized via the conjugation process into testosterone glucuronide, and to a lesser extent, testosterone sulfate. About 40% of testosterone is metabolized into 17 ketosteroids androsterone and eticholanone which gets further conjugated in liver. Testosterone is also hydroxylated and oxidized in the liver by cytochrome P450 enzymes. These metabolites, as well as a very small fraction of unchanged testosterone, are then excreted in urine [3].

Clinical significance

Serum testosterone helps in the diagnosis of a number of male endocrine abnormalities including infertility and testicular failure. In females, conditions like amenorrhea, infertility, PCOS, hirsutism, obesity and virilization can cause alteration in testosterone levels [3]. Beneficial outcomes were observed with testosterone treat-ment in symptoms of “low testosterone” like infertility, muscle wasting etc, as observed in a meta anaylsis by Huo *et al* [66]. However these results were in contrast to another meta analysis done by Jia *et al* [67] who showed that treatment with testosterone led to side effects such as increased incidence of prostate diseases, polycy- themia and decreased serum HDL.

Conclusion

Reproductive hormones are vital to both male and female reproductive health, governing everything from sexual development to fertility and pregnancy. Understanding these hormones' complex interplay is essential for diagnosing and treating reproductive disorders, ensuring that individuals can maintain their reproductive health throughout their lives. The careful balance of these hormones is key to optimal reproductive function, and modern medicine continues to advance in its ability to manage hormonal disorders through targeted therapies.

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