**Estrogen and Growth Hormone and their Roles in Reproductive Function**

 Estrogen is the main hormone affecting growth, development, maturation and functioning of reproductive tract as well as the sexual differentiation and the behavior. Growth hormone is also important factor in sexual maturation and attainment of puberty. The impact of estrogen on growth hormone secretion has been reported in rodents and primates. However, the precise mechanism for the alterations in growth hormone secretion is not clearly known. Estrogen may possibility have a direct affect on growth hormone secretion via the binding to estrogen receptor-α due to its co-expression in growth hormone neurons in the medial preoptic area and arcuate nucleus. Estrogen may also have an indirect effect via the reducing insulin-like growth factor-1 feedback inhibition resulting with increased growth hormone secretion.

 Estrogen is an intra ovarian factor affecting the function of hypothalamus, pituitary, liver, skeleton and calcium homeostasis It is also a main reproductive hormone affecting growth, development, maturation and functioning of reproductive tract as well as the sexual differentiation and the behavior .It was hypothesed that exogenous estrogens enhance GH secretion and promote somatic growth.

Types of ESTROGEN:-

Estrogen is named for its importance in the estrous cycle. Animal body naturally produce three main forms of estrogen, which are estradiol17β (E2), Estrone (E1) and Estriol (E3). Estrone and estriol were firstly identified in the urine of pregnant women and this was followed by the identification of E2 in the follicular fluid of sow. Estradiol and estrone are formed, respectively, from testosterone and androstenedione by aromatase which catalyzes an aromatic hydroxylation of the A ring of C19 androgens. Estrone and estradiol are inter-converted by 17- hydroxysteroid dehydrogenase; both can be converted to estriol by 16α-hydroxylase, mainly in the liver . In the ovary, E2 is the most physiologically active type of estrogen produced by granulosa cells of pre-ovulatory follicles through the aromatization of thecal androgen by the granulose cells of growing follicles. In the testis, some E2 is produced by Sertoli cells through the aromatization of the androgen synthesized from the Leydig cells. Estrogen is also synthesized in extragonadal sites including the mesenchymal cells of adipose tissue and skin, osteoblasts and chondrocytes of bone, vascular endothelium and aortic smooth muscle cells as well as several sites in the brain, including the anterior hypothalamus and the medial basal hypothalamus brain, including the anterior hypothalamus and the medial basal hypothalamus

 **Estrogen receptors:**

Estrogens act via two types of receptors (ERα and ERβ), which are members of a large super family of proteins that function as ligand-activated transcription factors Both receptors have direct differentiative influences on reproductive organs and have similar binding affinity to estradiol .( Although, there are significant amino acid differences in the regions of these receptors that would be expected to influence transcriptional activity More recently, two Estrogen-Related Receptors, (ERRα/ERR1) and (ERRβ/ERR2) have also been characterized.

The presence of oestrogen receptors have been shown within the hypothalamus, pituitary, ovary, oviduct, uterus, cervix and vagina of **several species including human, sheep.**

**Effect of estradiol on reproductive function:**

Chromosomal sex is determined at the time of fertilization by the entry of an X or Y chromosome from the sperm pronucleus into the pronucleus of the oocyte (Marshall Graves, 2000). In accord to the chromosomal sex, gonads are formed. It was suggested that under the influence of the Y chromosome, the undifferentiated genital ridge develops into testis and in its absence, ovaries form by default. Therefore, the existence of two candidate genes (SRY and ZFY),[ former being confirmed as Testis Determining Factor (TDF), on the Y chromosome was predicted following the mutation analysis.

SRY= The Sex-determining Region Y (**Sry** in mammals but **SRY** in humans) is a gene found on Y chromosomes that leads to the development of male phenotypes, such as testes. The **Sry** gene, located on the short branch of the Y chromosome, initiates male embryonic development in the XY sex determination system.

ZFY=**Zinc finger Y-chromosomal protein** is a [protein](https://en.wikipedia.org/wiki/Protein) that in humans is encoded by the *ZFY* [gene](https://en.wikipedia.org/wiki/Gene) of the [Y chromosome](https://en.wikipedia.org/wiki/Y_chromosome).[[3]](https://en.wikipedia.org/wiki/ZFY#cite_note-pmid2497060-3)[[4]](https://en.wikipedia.org/wiki/ZFY#cite_note-entrez-4)

This gene encodes a [zinc finger](https://en.wikipedia.org/wiki/Zinc_finger)-containing protein that may function as a transcription factor. This gene was once a candidate gene for the testis-determining factor (TDF) and was erroneously referred to as TDF.

Gonadal hormone secretion is under the control of chromosomal sex, which, in turn, controls the phenotype of non-gonadal tissue. The hormonal regulation of sexual differentiation of the mammalian reproductive system was established in the late 1940s by Jost. **In his study, testes were removed from fetal male rabbits, inducing a female phenotype at birth. In contrast, transplantation of testis into female embryos induced a male phenotype.** The early fetus has the potential to be either male or female and possesses not only an undifferentiated gonadal ridge, but also ‘precursors’ for both Mullerian and Wolfian ducts. Once the testis are formed, they secrete Mullerian Inhibitory Substance (MIS), which induces regression of the Mullerian duct and they also produce testosterone, which stimulates development of the Wolfian duct. In the absence of testis and thus, MIS and testosterone, the Mullerian duct develops and the Wolfian duct regresses. Thus, it was established that male sexual development requires hormonal control and that the female reproductive system develops in the absence of these hormones (Jost *et al*., 1973). Other studies have confirmed that estrogen has no effect on mullerian duct formation. Because, treatment of the pregnant mice with Diethylstilboestrol (DES) did not affect Müllerian duct formation in female embryos (Newbold and McLachlan, 1982). However, **the presence of estrogen receptors in both male and female mice from gestational day 10 and later (Gorski and Hou, 1995) indicate that estrogen has role in reproductive tract development and functioning. According to a study, in mutant mice lacking responsiveness to estradiol by disrupting the estrogen receptor gene by gene targeting showed abnormal reproductive tract development**.

**It was also noted that the males were infertile (Lubahn *et al*., 1993). Experimental inhibition of the formation or action of estrogen in the female chicken and Japanese quail embryos** can result in almost complete phenotypic sex-reversal, such as formation of testis-like ovaries, development of male secondary sex characteristics, lack of oviductal development and male-like growth of the cloacal gland in response to testosterone (Elbrecht and Smith, 1992). The sex differences in the morphological and functional phenotype of the body and brain underlie gender identity, sexual orientation, sexual behavior and differences in certain non-reproductive behaviors. In most mammals, the principal hormone masculinizing the brain is testosterone. However, testosterone is the principal hormone causing brain musculinisation, but its metabolite, oestradiol, acting on estrogen receptors α and β (ERα and β) control separate aspects of differentiation. ERα is primarily involved in masculinization, while ERβ mediates defeminization of sexual behaviors, but not masculinization (Kudwa *et al*., 2006).

Estrogen also acts as an intra-gonadal factor and has negative and positive feedback influences on the hypothalamic-pituitary axis to regulate gonadotrophin secretion. It has been known for many years that estrogen has a direct influence on folliculogenesis. Oestradiol-17β (E2) and its analogues have both proliferative and differentiative effects on somatic cells of follicles (Findlay *et al*., 2001). It stimulates the proliferation of granulosa cells in follicles and serves to facilitate the actions of Follicle Stimulating Hormone(FSH) and Luteinizing Hormone (LH) (Richards, 1980). Thus, it permits follicle growth because, increase in follicle size is due directly to an increase in granulosa cell number and not due to the antrum formation (Goldenberg *et al*., 1972). Estrogen is also responsible for facilitating the differentiation of granulosa cells including the induction of receptor systems for FSH, LH and prolactin and it can influence post-receptor mechanisms. There is a strong consensus that both ERα and ERβ are expressed in granulosa cells of preantral and antral follicles (Drummond *et al*., 1999). Esrogen Recptor-α Knockout (ERKO) female mice are acyclic, infertile and possess hyperemic ovaries devoid of corpora lutea (Couse and Korach, 1999). Folliculogenesis is arrested at the antral stage with large secondary follicles becoming cystic and hemorrhagic within 3 weeks of birth. In contrast, Estrogen Receptor-Β Knockout (BERKO) females have small ovaries, some arrested follicular development and their fertility is compromised with reduced numbers of offspring per litter, consistent with the reduced number of corpora lutea observed . Estrogen is also synthesized in the male reproductive system and it is found in high concentrations in rete testis and seminal fluids. Both estrogen receptors (ERα and ERβ) are found in various regions of the male reproductive tract. It was reported that estradiol (E2) induces spermatogenesis in gonadotropin-deficient hypogonadal (*hpg*) mice (Allan *et al*., 2010). It was concluded that E2-induced spermatogenesis in hypogonadal (*hpg*) mice involves an ERα-dependent neuroendocrine mechanism increasing blood FSH and Sertoli cell function (Allan et *al*., 2010). The main breakthrough in this field was brought forth by estrogen receptor knockout mice. Phenotypically, these mice have significant alteration in testes histology, spermiogenesis and they suffer from infertility (Eddy *et al*., 1996).

**DR ALI SHALASH SULTAN**

**21/10/2018**

**Human chorionic gonadotropin** (**hCG**) is a [hormone](https://en.wikipedia.org/wiki/Hormone) produced by the [placenta](https://en.wikipedia.org/wiki/Placenta) after [implantation](https://en.wikipedia.org/wiki/Implantation_%28human_embryo%29).[[1]](https://en.wikipedia.org/wiki/Human_chorionic_gonadotropin#cite_note-pmid19171054-1)[[2]](https://en.wikipedia.org/wiki/Human_chorionic_gonadotropin#cite_note-pmid10235686-2) The presence of hCG is detected in some [pregnancy tests](https://en.wikipedia.org/wiki/Pregnancy_test) ([HCG pregnancy strip tests](https://en.wikipedia.org/wiki/HCG_pregnancy_strip_test)). Some [cancerous tumors](https://en.wikipedia.org/wiki/Cancer) produce this hormone; therefore, elevated levels measured when the patient is not pregnant may lead to a cancer diagnosis and, if high enough, [paraneoplastic syndromes](https://en.wikipedia.org/wiki/Paraneoplastic_syndrome), however, it is not known whether this production is a contributing cause, or an effect of [carcinogenesis](https://en.wikipedia.org/wiki/Carcinogenesis). The pituitary analog of hCG, known as [luteinizing hormone](https://en.wikipedia.org/wiki/Luteinizing_hormone) (LH), is produced in the [pituitary gland](https://en.wikipedia.org/wiki/Pituitary_gland) of males and females of all ages.[[1]](https://en.wikipedia.org/wiki/Human_chorionic_gonadotropin#cite_note-pmid19171054-1)[[3]](https://en.wikipedia.org/wiki/Human_chorionic_gonadotropin#cite_note-pmid1695224-3)

Regarding [endogenous](https://en.wikipedia.org/wiki/Endogeny_%28biology%29) forms of hCG, there are various ways to categorize and measure them, including total hCG, C-terminal peptide total hCG, intact hCG, free β-subunit hCG, β-core fragment hCG, hyperglycosylated hCG, nicked hCG, alpha hCG, and pituitary hCG. Regarding pharmaceutical preparations of hCG from [animal](https://en.wikipedia.org/wiki/Animal) or [synthetic](https://en.wikipedia.org/wiki/Chemical_synthesis) sources, there are many [gonadotropin preparations](https://en.wikipedia.org/wiki/Gonadotropin_preparations), some of which are medically justified and others of which are of a [quack](https://en.wikipedia.org/wiki/Quackery) nature. As of December 6, 2011, the United States [Food and Drug Administration](https://en.wikipedia.org/wiki/Food_and_Drug_Administration) has prohibited the sale of "[homeopathic](https://en.wikipedia.org/wiki/Homeopathy)" and [over-the-counter](https://en.wikipedia.org/wiki/Over-the-counter_drug) hCG [diet](https://en.wikipedia.org/wiki/Dieting) products and declared them [fraudulent](https://en.wikipedia.org/wiki/Fraud) and illegal.[[4]](https://en.wikipedia.org/wiki/Human_chorionic_gonadotropin#cite_note-MedPage20111206-4)[[5]](https://en.wikipedia.org/wiki/Human_chorionic_gonadotropin#cite_note-5)[[6]](https://en.wikipedia.org/wiki/Human_chorionic_gonadotropin#cite_note-6)**Contents**

Structure[[edit](https://en.wikipedia.org/w/index.php?title=Human_chorionic_gonadotropin&action=edit&section=1)]

Human chorionic gonadotropin is a [glycoprotein](https://en.wikipedia.org/wiki/Glycoprotein) composed of 237 [amino acids](https://en.wikipedia.org/wiki/Amino_acid) with a [molecular mass](https://en.wikipedia.org/wiki/Molecular_mass) of 36.7 [kDa](https://en.wikipedia.org/wiki/KDa%22%20%5Co%20%22KDa), approximately 14.5 αhCG and 22.2kDa βhCG.[[7]](https://en.wikipedia.org/wiki/Human_chorionic_gonadotropin#cite_note-Canfield_1987-7)

It is [heterodimeric](https://en.wikipedia.org/wiki/Heterodimer), with an α (alpha) [subunit](https://en.wikipedia.org/wiki/Protein_subunit) identical to that of [luteinizing hormone](https://en.wikipedia.org/wiki/Luteinizing_hormone) (LH), [follicle-stimulating hormone](https://en.wikipedia.org/wiki/Follicle-stimulating_hormone) (FSH), [thyroid-stimulating hormone](https://en.wikipedia.org/wiki/Thyroid-stimulating_hormone) (TSH), and β (beta) subunit that is unique to hCG.

* The [α (alpha)](https://en.wikipedia.org/wiki/Chorionic_gonadotropin_alpha) [subunit](https://en.wikipedia.org/wiki/Protein_subunit) is 92 amino acids long.[[8]](https://en.wikipedia.org/wiki/Human_chorionic_gonadotropin#cite_note-urlGlycoprotein_hormones_alpha_chain_precursor_-_Homo_sapiens_(Human)-8)
* The β-subunit of hCG gonadotropin (**beta-hCG**) contains 145 amino acids, encoded by six highly homologous [genes](https://en.wikipedia.org/wiki/Gene) that are arranged in tandem and inverted pairs on [chromosome 19q](https://en.wikipedia.org/wiki/Chromosome_19)13.3 - *CGB* ([*1*](https://en.wikipedia.org/wiki/CGB1), [*2*](https://en.wikipedia.org/wiki/CGB2_%28gene%29), [*3*](https://en.wikipedia.org/wiki/CGB3), [*5*](https://en.wikipedia.org/wiki/CGB5), [*7*](https://en.wikipedia.org/wiki/CGB7), [*8*](https://en.wikipedia.org/w/index.php?title=CGB8&action=edit&redlink=1))[[9]](https://en.wikipedia.org/wiki/Human_chorionic_gonadotropin#cite_note-urlChoriogonadotropin_subunit_beta_precursor_-_Homo_sapiens_(Human)-9)

The two subunits create a small [hydrophobic](https://en.wikipedia.org/wiki/Hydrophobic) core surrounded by a high surface area-to-volume ratio: 2.8 times that of a sphere. The vast majority of the outer amino acids are [hydrophilic](https://en.wikipedia.org/wiki/Hydrophilic).[[10]](https://en.wikipedia.org/wiki/Human_chorionic_gonadotropin#cite_note-pmid8202136-10)

Function

Human chorionic gonadotropin interacts with the [LHCG receptor](https://en.wikipedia.org/wiki/LHCG_receptor) of the ovary and promotes the maintenance of the [corpus luteum](https://en.wikipedia.org/wiki/Corpus_luteum) during the beginning of [pregnancy](https://en.wikipedia.org/wiki/Pregnancy). This allows the corpus luteum to [secrete](https://en.wikipedia.org/wiki/Secretion) the hormone [progesterone](https://en.wikipedia.org/wiki/Progesterone) during the first trimester. Progesterone enriches the [uterus](https://en.wikipedia.org/wiki/Uterus) with a thick [lining](https://en.wikipedia.org/wiki/Endometrium) of [blood vessels](https://en.wikipedia.org/wiki/Blood_vessel) and [capillaries](https://en.wikipedia.org/wiki/Capillary) so that it can sustain the growing [fetus](https://en.wikipedia.org/wiki/Fetus)[[*citation needed*](https://en.wikipedia.org/wiki/Wikipedia%3ACitation_needed)].

Due to its highly negative charge, hCG may repel the immune cells of the mother, protecting the fetus during the first trimester[[*citation needed*](https://en.wikipedia.org/wiki/Wikipedia%3ACitation_needed)]. It has also been hypothesized that hCG may be a placental link for the development of local maternal [immunotolerance](https://en.wikipedia.org/wiki/Immune_tolerance)[[*citation needed*](https://en.wikipedia.org/wiki/Wikipedia%3ACitation_needed)]. For example, hCG-treated endometrial cells induce an increase in T cell [apoptosis](https://en.wikipedia.org/wiki/Apoptosis)(dissolution of [T cells](https://en.wikipedia.org/wiki/T_cell)). These results suggest that hCG may be a link in the development of peritrophoblastic immune tolerance, and may facilitate the [trophoblast](https://en.wikipedia.org/wiki/Trophoblast) invasion, which is known to expedite(enhanced) fetal development in the endometrium.[[11]](https://en.wikipedia.org/wiki/Human_chorionic_gonadotropin#cite_note-11) It has also been suggested that hCG levels are linked to the severity of [morning sickness](https://en.wikipedia.org/wiki/Morning_sickness) or [Hyperemesis gravidarum](https://en.wikipedia.org/wiki/Hyperemesis_gravidarum) in pregnant women.[[12]](https://en.wikipedia.org/wiki/Human_chorionic_gonadotropin#cite_note-pmid10636378-12)

Because of its similarity to [LH](https://en.wikipedia.org/wiki/Luteinizing_hormone), hCG can also be used clinically to induce [ovulation](https://en.wikipedia.org/wiki/Ovulation) in the [ovaries](https://en.wikipedia.org/wiki/Ovary) as well as [testosterone](https://en.wikipedia.org/wiki/Testosterone) production in the testes. As the most abundant biological source is women who are presently pregnant, some organizations collect urine from pregnant women to extract hCG for use in [fertility treatment](https://en.wikipedia.org/wiki/Assisted_reproductive_technology). Human chorionic gonadotropin also plays a role in [cellular differentiation](https://en.wikipedia.org/wiki/Cellular_differentiation)/proliferation and may activate [apoptosis](https://en.wikipedia.org/wiki/Apoptosis)/