## Role of Estrogen in Male Androgenetic Alopecia

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**Abstract :** Estrogen is traditionally involved in both female and male reproduction, besides various other biological systems involving the neuroendocrine, vascular, skeletal, and immune systems. Hair growth is affected by multiple factors that consist of transcription factors, cytokines and hormones. Androgenetic alopecia or male-pattern hair loss is a hereditarily determined progressive process that causes a gradual conversion of terminal hair into vellus hair. The most important factors involved in male baldness are characterized by androgens, genetic factors, and age. The 17β-estradiol inhibits, while the estrogen antagonist stimulates hair growth in both male and female. The alopecia results in a decrease in hair follicle size escorted by a decrease in the duration of anagen and an increase in the percentage of hair follicles in telogen with follicular miniaturization, which is the trademark of androgenetic alopecia. Estrogen inhibits hair growth, signifying that scalp hair growth might control the sex hormones. Among the various types of estrogen, the estradiol acts on hair follicle cycling by delaying the initiation of anagen and by prolongation of duration of telogen. Estradiol has found to modulate hair growth, playing primarily as hair growth inhibitor.

**Keywords:** Androgenetic alopecia, Follicular miniaturization, Anagen, Estrogen, Estradiol

## Introduction:

Hormones are chemicals secreted by the endocrine glands which are carried to the targeted organs. (1) Estrogen is conventionally considered as female sex hormone. It is made from cholesterol within the body. Hormones facilitate communication between cells around the entire body. Cells that have receptors for estrogen have functions which are activated or deactivated by it. The estrogen act as a key and estrogen receptors as a lock and thereby together they make your body systems work.(2) Estrogen is primarily a female sex hormone but also observed in men, trans-women, children. They are produced in fat tissues, bones, skin, liver, and adrenal gland (3). In adult men, estrogen is produced in the testes (4). Estrogen not only helps to control the menstrual cycle and in childbearing. Estrogen also has other functions: Keeps cholesterol in control, protects bone health for both women and men (3), Affects your brain (cognitive function like mood), bones, heart, skin, and other tissues. (4,5). Testosterone is the most significant hormone to male sexual development and function. But estrogen requires to be in equilibrium with testosterone which helps to control sex drive, the ability to have an erection, and the production of sperm. Testosterone naturally decreases as men age, while estrogen increases. This isn't much to be concerned about unless estrogen levels are abnormally high. This can be a risk factor for conditions like diabetes and certain forms of cancer.

## Types of estrogens:

These types have different functions across the body over different life stages. The four types of estrogen includes:

1. **Estrone (E1):** Produced principally in body fat, nevertheless also found in the ovaries and placenta. It is a type weak estrogen.

2. **Estradiol (E2):** This is the most active type of estrogen, which is the type involved in the menstrual cycle. This type of estrogen binds very strongly to estrogen receptors.

3. **Estriol (E3):** This is the main estrogen of pregnancy. This type of estrogen is primarily made and secreted from the placenta (with help from the foetus) about five weeks after implantation. It is also a weak estrogen (6).

4. **Estetrol (E4):** This type of estrogen is only produced during pregnancy from the liver of the foetus (7).

Most of the estrogen in your body is estradiol, and is made in the ovaries. However, estrogen are also produced in other areas of the body, including fat tissues, bones, skin, liver, and adrenal glands (1). As people enter menopause, these other sources increase estrogen synthesis and become more influential in the body (8).

There are two main types of estrogen in men: estrone and estradiol. The amounts are measured in picogram per millilitre (pg/ml). The typical averages of each are: (9)

|  | Estrone | Estradiol |
|---|---|---|
| Prepubescent male | Undetectable–16 pg/ml | Undetectable–13 pg/ml |
| Pubescent male | Undetectable–60 pg/ml | Undetectable–40 pg/ml |
| Adult male | 10–60 pg/ml | 10–40 pg/ml |

However, estradiol, the prime form of estrogen, also plays a critical role in male sexual function. Estradiol in men is essential for modulating libido, erectile function, and spermatogenesis. Estrogen receptors, as well as aromatase, the enzyme that converts testosterone to estrogen, are abundant in brain, penis, and testis, organs important for sexual function. Particular form of estrogen known as estradiol is exclusively key to male sexuality. (10)

**Male Androgenetic alopecia (maga):**

Male androgenetic alopecia (MAGA) is a therapeutic challenge as our current knowledge of the complete spectrum of the biomolecular mechanisms underlying this condition remains uncertain. (11) MAGA specially when premature and severe may have significant psychosocial effects. (12) Hair also provides physical protection of scalp from sun damage to reduce the risk of skin cancers, an important consequence of baldness. (13) Androgenetic alopecia (AGA), or male-pattern hair loss (MPHL), is a hereditarily determined progressive process that causes a gradual conversion of terminal hair into vellus hair. The prevalence increases with advancing age; but, the age of onset and rate of progression are variable. (14, 15) The morbidity of MPHL is mainly psychological and differs from person to person. In the etiology of MAGA, the most important factors involved are characterized by androgens, genetic factors, and age. (16) MAGA is histologically indistinguishable, (17) suggesting shared biomolecular mechanisms. This condition is a result of altered hair follicle cycling and miniaturization, which lead to the transformation of the terminal to vellus hair follicles and the production of shorter, finer hair shafts. At the cellular level, follicle miniaturization is thought to be caused by a reduction in dermal papilla volume, resulting from a reduction in cell number per papilla. (18)

MAGA generally occurs after puberty, with its frequency and severity increasing with age. (19) Even though MAGA is a benign condition, it has an important impact on the patients' quality of life. Hair is associated with an individuals' identity. Hair loss is associated with stress, low self-esteem, reduced satisfaction with body image, depression, and anxiety. (20, 21) Furthermore bald men perceive themselves as older as and less attractive than others. (22)

**Etiology:**

The hair follicle (HF) cycle is characterized by a period of follicle growth (anagen), followed by regression and remodeling (catagen), and lastly by a resting period (telogen). A group of very specialized mesenchymal cells, known as dermal papilla, resides at the bottom of the epithelial follicle,

and these cells are considered to provide the signal that initiates anagen and command the bulge follicular stem cells to proliferate. The matrix cells multiply and differentiate into the inner root sheath cells and then finally differentiate into the mature hair fiber. The follicle enters catagen, and after deterioration of the lower follicle, the follicle enters and remains in telogen until the dermal papilla signals the bulge stem cells to divide, and the hair follicle cycle begins again. (23)
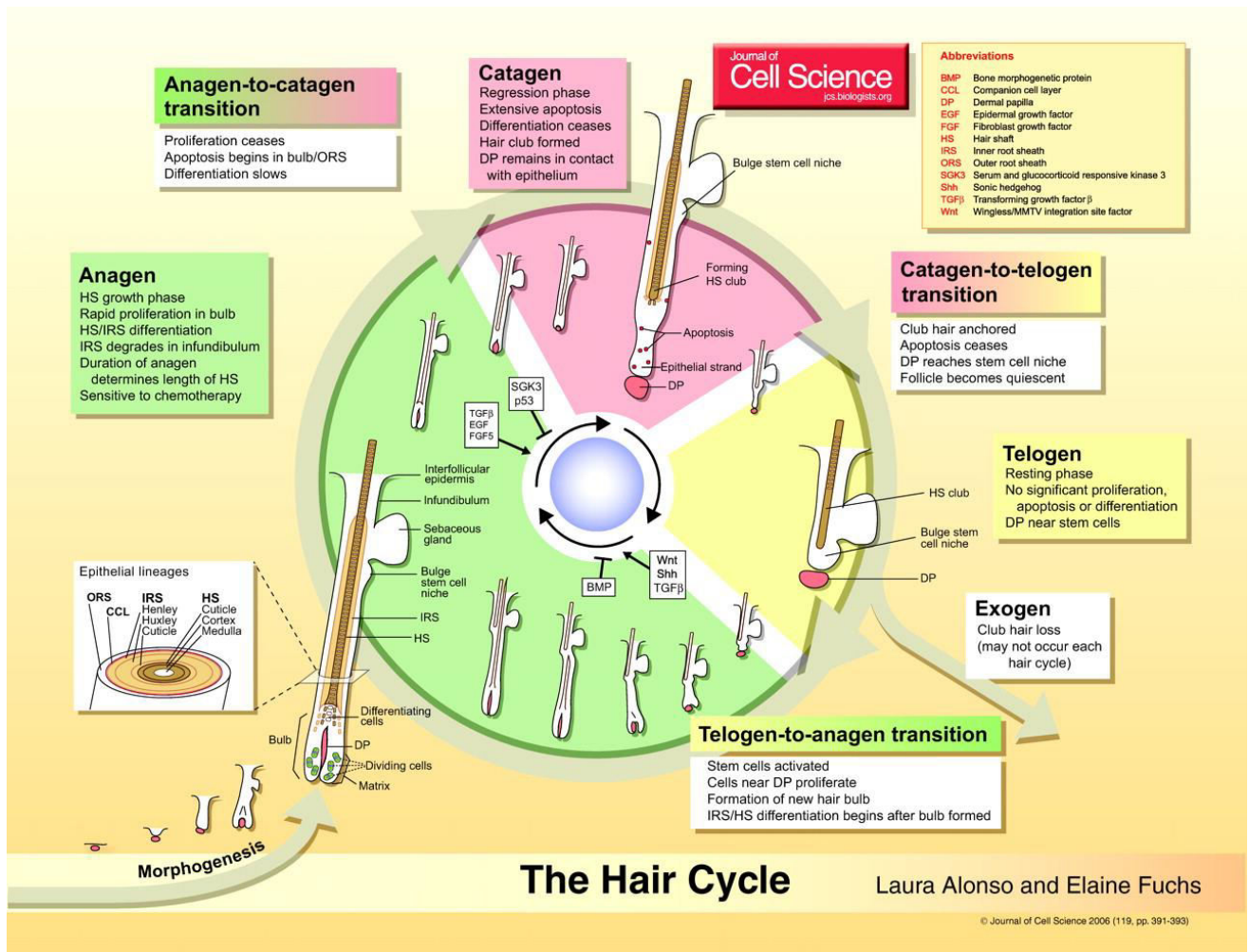


Figure 1: The Hair Cycle (24)

Hair growth is affected by multiple factors that consist of transcription factors, cytokines and hormones. Several studies established that 17β-estradiol inhibits, while the estrogen antagonist stimulates hair growth in both male and female. Estrogen acts by means of estrogen receptor (ER) and there are two ER, denoted ERα and ERβ. (25) These ER belongs to a super family of ligand-activated transcription factors, comprising receptors for steroids, thyroid hormones, retinoids, prostanoids, and vitamin D. Estrogen action depends on various mechanisms of confounding complexity, involving not only the two receptors but also additional, non-ER-related proteins. For example, both ERα and ERβ activate transcription on classical estrogen response elements. On the other hand, in the presence of

17β-estradiol, ERα is an activator, whereas ERβ is an inhibitor at activating protein-1 sites. Also, ERα's transactivation potency is down-regulated by wild-type ERβ in an 17β-estradiol dose-dependent manner. Additionally, one ERβ splice variant, called ERβ ins, which has an extra 18-amino acid in-frame sequence flanked by exons 5 and 6 of wild type ERβ, may act as a dominant-negative regulator of ERα, free of the 17β-estradiol concentration. (26) Using an immunohistochemical approach, it was found that estrogen receptor immunoreactive protein is expressed in the nuclei of the dermal papilla cells and that topical with 17β-estradiol arrests follicles in telogen, whereas topical treatment with the ER antagonist causes the telogen follicle to enter anagen and initiate hair growth. These results specify that an ER pathway within the dermal papilla regulates the telogen-anagen transition of the hair follicle. (23)

Estrogen treatment causes premature onset of catagen, characterized by apoptosis of precortex cells all the way through up-regulation of TGF β2. Subsequently, expression of the anagen chalone, bone morphogenetic protein (BMP4) increases and the estrogen induced telogen will be maintained. Although the long-lasting estrogen treatment causes alopecia, the hair follicle stem cells (HFSCs) were not ablated. Besides, the dermal papillae (DP) cells showed no involution of their signature gene expressions after estrogen treatment. This recommended that the potential of DP cells to induce hair regrowth was set aside. Based on these results, the estrogen induced hair cycle retardation is reversible. TGF β2 functioned as an estrogen downstream effector to activate premature onset of catagen, and then BMP4 increased. The up-regulation of BMP4 may further function to prevent anagen transition and maintain telogen. (27)

Estrogens prevent skin aging by influencing skin thickness, skin wrinkling, and skin moisture. Skin appendages, such as hair, are also influenced by estrogens. High systemic estrogen levels delay the anagen phase of the hair follicle, and the falling estrogen levels cause this excess number of anagen follicles go in telogen phase concurrently, sometimes resulting in clinically major hair loss. Androgenetic alopecia is a dihydrotestosterone (DHT)-mediated process, characterized by constant diminish of androgen-sensitive hair follicles. Undeniably, it is frequently treated with systemic antiandrogens such as cyproterone acetate in women, or steroidogenic enzyme inhibitors such as finasteride in men. The ability of estrogen to modify androgen metabolism in dermal papillae of hair follicle showed that estradiol diminishes the amount of DHT in human hair follicle by inducing aromatase activity. The induction of aromatase activity increases the translation of testosterone to estradiol, thereby decreasing the amount of testosterone accessible for the conversion to DHT which might make clear the beneficial effect of estrogen treatment of AGA. In contrast to ER-α, ER-β is extensively expressed in the hair follicle with strong staining in dermal papilla cells and in the bulge region of the outer root sheath. These results provide confirmation that estradiol mediates its effects on hair follicle through direct regulation of specific cells and suggest an important role of estrogens in

regulation of hair growth. (28)

Because the most common hair growth disorders encountered represent disorders of HF cycling, it was of chief interest to illuminate how exogenous ER agonists and antagonists affect HF cycling in vivo. Earlier studies focused on the influence of 17β-estradiol on telogen and subsequent anagen development, while it remained to be firm whether and how 17β-estradiol affects catagen development under physiological conditions. It was hypothesized that 17β-estradiol should be a strong catagen inducer. For quantifying the results, quantitative histomorphometry of catagen development in anagen HFs was applied, whereas the macroscopic spreading of anagen/catagen waves was evaluated with a recently developed planimetric assay. (26)

Androgens are recognized as key regulators of normal human hair growth and the requirement for sexual hair and sebaceous gland development. However, estrogens also very much alter hair growth in humans by binding to high-affinity ER. Studies have revealed that prototypic ER agonist, 17β-estradiol, after topical application, is a very effective hair growth inhibitor in mice. This hair growth-inhibitory activity reported in mice significantly contrasted with the apparently hair growth-stimulatory topical 17β-estradiol therapy long practiced in many countries for the treatment of female pattern androgenetic alopecia and the hair loss induced by therapy with aromatase inhibitors, which lower serum and tissue 17β-estradiol levels. This recommended that 17β-estradiol effects on the mammalian hair follicle were likely to be complex, and species dependent. Estrogens are able to modify androgen metabolism within distinct subunits of the hair follicle decreasing the amount of 5α-dihydrotestosterone formed after incubation with testosterone. Since aromatase, the enzyme that converts testosterone to 17β-estradiol was found at many of the sites of ER and androgen receptor expression, the equilibrium between 17β-estradiol and androgen levels serves to modify 17β-estradiol and androgen action in their target cells. Also, many of the growth and transcription factors, cytokines, and hormones that are presently recognized to control hair growth are themselves modulated by estrogens. (29)


**Pathophysiology**

In androgenetic alopecia, large terminal hairs are shed and are replaced by small vellus hairs. Three areas of the scalp are affected preferentially: temples, vertex scalp and mid-frontal scalp (Figure 1). Within these areas, the process is strictly patterned. Bitemporal hair loss starts at the anterior hairline and moves posteriorly over the scalp. Hair loss over the vertex scalp begins centrally and radiates outwards circumferentially. (14)
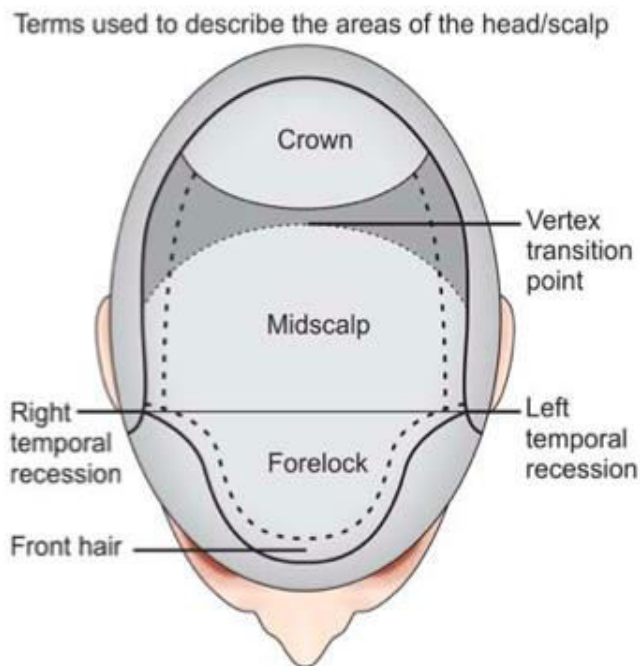
**Figure 2- Areas of the head/scalp**

Irrespective of age, balding scalps have a reduced density of terminal hair follicles than normal people of the same age. (30) Those aged 30–90 years with normal hair are reported to possess 459 follicles per cm2, compared with 306 in male pattern hair loss. (31) Due to the substantial thinning of the subcutaneous adipose layer, total scalp thickness is reduced. The progressive miniaturization of hair follicles in MAGA is revealed within the histopathologic changes. (32) Terminal hairs become vellus-like, and hair roots retreat upwards so that many miniaturized hair bulbs are found within the mid or papillary dermis. The position of the original terminal follicle is indicated by a follicular streamer extending from the subcutaneous tissue up the course of the follicle to the miniaturized hair. MAGA is hence characterized by reduced terminal hairs and increased follicular streamers and vellus-like hairs. (33, 34)

Anatomy of normal scalp hair with growth

Hairs are invaginations of the epithelial layer of the skin which grow from follicles. Normally, an adult scalp contains 100,000 follicles. (35) The maximum number of hair follicles is present at birth and as the head enlarges the concentration of scalp hair follicles decreases. Recent biopsy data suggest that the estimated 700–750 follicles per cm2 at birth decreases to approximately 318 per cm2 in adult life. (32, 36) Each hair has the cortex, containing elongated cells surrounded by a cuticle of overlapping flattened cells. (37, 38) Thick hairs may have a central medulla. Hair cells are produced from a matrix of specialized epidermal cells that surround a small invagination of the dermis at the base of the follicle, known as the dermal papilla. (39) Melanocytes in the bulb hair add pigment to newly formed cells. There are two basic types of human hair: vellus and terminal. Vellus hairs are fine and

hypopigmented, scarcely visible, have no obvious arrector pili muscle and never contain a medulla, while terminal hairs are pigmented and relatively coarse. (30)

Hair-follicle cycling and signaling molecules controlling hair growth

The hair-growth cycle:

The hair follicle is subject to constant turnover in the course of continuous cycles through various stages of proliferation (anagen), involution (catagen), and resting (telogen), with regeneration in the successive hair cycle.

### Anagen

Histologically, anagen follicles are long and exact straight, but the follicles are angled to allow the hair coat to lie flat along the body surface. (40) The growth or anagen phase of human scalp hair lasts 2–7 years. During the anagen phase, the epidermal cells divide and grow, with a high metabolic activity rate. Keratinized hair is continuously produced. Hair length depends partly on the growth rate and on the duration of the anagen phase, which varies with age and hair type. On average, some 90% or more of scalp hairs are in the anagen phase at any one time. (32)

### Catagen

Catagen is the dynamic conversion between anagen and telogen. (41) At the end of the anagen phase, hair growth ends, and the catagen phase begins. Normally, the hair follicle becomes thinner, due to a volumetric reduction of the external root sheath by apoptotic cell death and only 1% of scalp hairs lasting for many weeks are seen in this phase. The melanocytes in the bulb stop producing melanin. (42-44) Thickening of the glassy membrane occurs, and the epidermal column lengthens, following the club hair towards the surface of the skin.

### Telogen

Following catagen, terminal scalp hair then enters the resting telogen phase for 3 months. The epidermal column shortens in this phase until it forms a small protuberance known as secondary germ. After continuation of the anagen phase, the secondary germ grows downwards and invaginates the dermal papilla, forming a new hair bulb. (37) The enhanced turnover of hair cycles and the relative lengthening of telogen lead to a corresponding increase in the number of telogen hairs and a decrease in anagen hairs. The proportion of telogen hairs increases from 5–10% to approximately 15–20%, (45) with a corresponding increase in hair shedding because telogen hairs are easily plucked or lost through combing and washing.

### Cellular and Molecular Mechanisms of Estrogen Action in human baldness

The hair follicle signifies a strangely attractive model for studying the control of physiological angiogenesis by a complex epidermal-mesenchymal interacting system in vivo. Still we are not aware of exactly what cellular or molecular mechanisms control these vascular changes. In addition to the two major recognized angiogenesis stimulators, vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) (46-48), processes of angiogenesis can usually be controlled by

hormonal changes, including changes in estrogen levels (49). E2 also stimu lates human hair follicle synthesis of VEGF. The ability of the hair follicle to metabolize estrogens has been confirmed by the localization of aromatase and 17bhydroxysteroid dehydrogenase expression within dermal papilla cells and keratinocytes of the outer root sheath. It is required to study the mechanisms by which estrogens may affect hair follicle growth and cycling. For the conversion of testosterone to E2, testosterone is converted to 19-hydroxytestosterone by a monooxygenase (EC 1.14.13.), then to 19-oxotestosterone, which is then converted to E2 by an oxidoreductase (EC 1.14.99.) (50) The only known pathway connecting testosterone to E2 is the cytochrome P-450 enzyme aromatase (EC 1.14.14.1, CYP19A1; ARO) pathway (Fig. 3). The fact that CYP19A1 (also known as aromatase or estrogen synthetase; ARO) transcripts with specific 5′-ends that were isolated from various tissues (with all transcripts belonging to the exon I variant) leading to the finding of tissue-specific promoter regulation. These are under a complex control of transcription factors in response to gonadotropins, IL-6, IL-11, and TNF-α. Because exon I is not translated, all proteins are therefore identical. The flexibility of the system is exemplified by the differential regulation displayed by the adipocyte ARO promoter, compared with its bone counterpart. (51) Remarkably, ARO activity was also found in human hair follicles (52,53), and ARO transcripts have been detected in cultured hair follicle fibroblasts and keratinocytes (54). The paracrine secretion of estrogen by hair follicle cells with ARO activity might be important for hair growth control. (55)

The total E2 production rate of human males has been calculated and it ranges from 35 to 45 μg (0.0130−0.0165 μmol) per day, of which 15−20% originates from the testes. About 60% of circulating E2 is thought to arise from peripheral aromatization of testosterone, whereas 20% is formed by the reduction of estrone. Estrone is formed by peripheral aromatization of androstenedione, which partly derives from the adrenal glands and partly from the peripheral conversion of testosterone. In general, the testicular glands control circulating estrogen levels, as evident from their rapid decline after orchiectomy. (50)
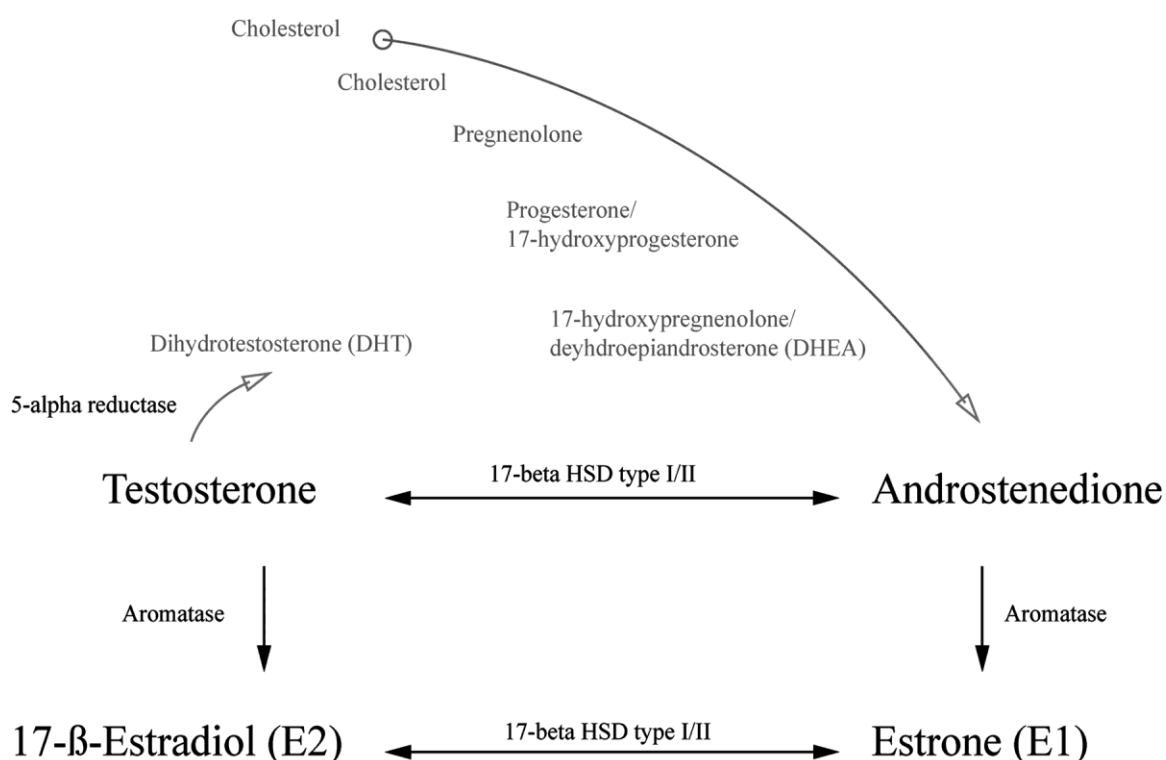
**Figure 2- General conversion of inactive hormonal precursors into active sex steroids.www.oup.silverchair-cdn.com**

**Conclusion:**

Understanding the hormonal regulation of human hair growth has important relevance to the clinician as the most common hair disorder i.e., Androgenetic alopecia is potentiated by androgen. Male androgenetic alopecia is a distinct clinical thing involving some underlying biomolecular mechanisms that lead to alteration in hair cycle development, follicular miniaturization and inflammation. Estrogen has been playing important role in hair growth. In the present work, we further explored the signalling mechanisms and elaborates that estrogen type estradiol cause the prematured catagen and subsequently sustained telogen. Thereby, the hair follicle proposes an investigation of this vital path of estrogen work and research.

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