INTRODUCTION

Hirsutism is the presence of terminal (coarse) hairs in females in a male-like pattern, affecting between 5-10% of women ***(Agrawal, 2013).***

For clinical and therapeutic purposes, hirsutism can be classified into eight categories; hirsutism of pituitary origin, hirsutism of adrenal origin, hirsutism of ovarian origin, constitutional hirsutism, hepatic hirsutism, hirsutism due to ectopic hormone production, iatrogenic hirsutism and hirsutism due to peripheral failure in converting androgens into estrogens ***(Camacho-Martínez, 2008).***

Hirsutism is caused by increased androgenicity in the pilosebaceous system resulting in increased growth of terminal hairs. Hirsute patients have increased dermal activity of the enzyme 5α-reductase, which is responsible for conversion of testosterone to the more powerful androgen; dihydrotestosterone (DHT) ***(Aziz, 2000).*** High DHT levels increase terminal hair growth and therefore, 5α-reductase inhibitors can be used for the treatment of hirsutism ***(Glintborg et al., 2009).*** Individual variations in dermal 5α-reductase activity may explain the often near normal testosterone levels and the lack of correlation between circulation testosterone levels and clinical hirsute manifestations ***(Aziz, 2000).***

Hirsutism is a clinical sign and is not a disease by itself, and its presence does not necessarily require treatment. However, perception of having male-type pattern body hair, irrespective of its objective severity, may have profound adverse effects on the psychological wellbeing of women with even mild hirsutism. Therefore, the subjective perception of the patient, and not only the absolute extent of hair growth, should guide physicians in deciding whether hirsutism should be treated or not ***(Escobar-Morreale, 2010).***

The goals of the correct management of hirsutism are to ameliorate the hirsutism and reproductive complaints, to prevent and/or treat the possible associated metabolic derangements and, if possible, to treat the underlying cause ***(Escobar-Morreale, 2010).***

Cosmetic measures include mechanical hair removal with the help of shaving, plucking, waxing, depilatory creams, electrical epilation, and laser hair removal. Systemic therapies directed at hirsutism can be divided into those that decrease ovarian or adrenal androgen production and those that inhibit androgen action in the skin. The systemic therapies include: oral contraceptives (OC), gonadotropin releasing hormone analogs, glucocorticoids, antiandrogens (spironolactone, flutamide, finasteride, cyproterone acetate), and insulin sensitizers (metformin, troglitazone, and rosiglitazone) ***(Al Robaee et al., 2008).***

Aim of the Work

The aim of this essay is to provide an updated review on hirsutism.

Chapter One
ANATOMY AND TYPES OF HAIR

Macroscopic and microscopic structures of the hair

Hair is a derivative of the epidermis. Externally, hair is thin, flexible tubes of dead, fully keratinized epithelial cells, whereas inside the skin, it is a part of individual living hair follicles, cylindrical epithelial downgrowths into the dermis, and subcutaneous fat, which enlarge at the base into the hair bulb surrounding the mesenchymal derived dermal papilla ***(Randall and Botchkareva, 2009).***

From a macrostructural point of view, hair varies in length, diameter, color, and cross-sectional shape among the different ethnic groups and among individuals ***(Kelly et al., 2000).*** Hair has two separate structures: the follicle in the skin and the hair shaft, which is visible on the body surface. The hair shaft consists of a cortex and cuticle cells, and in some cases, a medulla in the central region. The medulla is the central part of the hair, whereas the cortex, which represents the majority of the hair fiber composition and plays an important role in the physical and mechanical properties of hair, is the peripheral part and is made up of approximately 50–60% of macrofibrils, which consist of rods of microfibrils embedded into a matrix ***(Wolfram, 2003).***

The hair shaft cuticle covers the hair from the root to the tip of the epidermis and is formed by flat overlapping cells ***(Gurden et al., 2004).*** The integrity and properties of the cuticle layer have an important role in protecting the cortex from physical and chemical insults and in maintaining the hair in a clean and disentangled state and have a great impact on its appearance ***(Swift, 1999).*** The follicle is the essential growth structure of hair. From the outermost aspect of the follicle, the histological structures are **(Figure 1)**:

1- **Outer root sheath (ORS),** which has been identified as a reservoir of multipotent stem cells, i.e., keratinocyte and melanocyte stem cells, and contains keratinocytes. The ORS forms a distinct bulge area between the insertion of the arrector pili muscle and duct of the sebaceous gland ***(Oshima et al., 2001; Randall and Botchkareva, 2009).***

Adjoining the ORS on the dermal side is a basket-like arrangement of two orthogonally arrayed layers of collagen fibers, the glassy layer ***(Rogers, 1957).*** Known as the dermal sheet ***(Rogers, 2004).***

2- **Inner root sheath (IRS)** consists of three layers: Henle's layer, Huxley's layer, and cuticle layer. The IRS cuticle layer adjoins the cuticle of the hair shaft, anchoring the hair shaft to the follicle. Inner root sheath cells produce keratins and trichohyalin that serve as an intracellular cement giving strength to the IRS to support and mold the growing hair

shaft, as well as guide its upward movement. The IRS separates the hair shaft from the ORS ***(Randall and Botchkareva, 2009).***

The hair bulb is the portion of the follicle, which actively produces the hair. It encloses the follicular dermal papilla, dermal papilla cells, mucopolysaccharide-rich stroma, nerve fibers, and a single capillary loop. The follicular papilla is believed to be one of the most important drivers to instruct the hair follicle to grow and form a particularly sized and pigmented hair shaft; moreover, it is an essential source of growth factors (keratinocyte growth factor, bone morphogenetic protein, hepatocyte growth factor, insulin-like growth factor, stem cell factor), critical for hair growth and melanogenesis ***(Peus and Pittelkow, 1996; Randall and Botchkareva, 2009)*** **(Figure 1).**

The hair bulb can be divided into two regions: a lower region of undifferentiated cells and an upper region in which the cells became differentiated. A line across the widest part of the papilla separates the two regions at the critical level (Auber's line). Below the Auber's line lies the matrix, or germination center of the follicle, where every cell is mitotically active, and the dermal papilla. From the matrix, cells move to the upper part of the bulb, where they increase in volume and become elongated vertically ***(Randall and Botchkareva, 2009).***

Above the bulb, the upper hair follicle is composed of two anatomical parts: the infundibulum and the isthmus **(Figure 2)**. **The infundibulum** is a funnel-shaped structure filled with sebum, a product of the sebaceous gland; it extends from the surface of the skin to the sebaceous duct, serves as a reservoir, and provides an interface for interactions with hair follicle-associated cell populations. In detail, in the upper part, called the acroinfundibulum, the epithelium is continuous with the keratinized epidermis and is covered by an intact, rather impermeable stratum corneum; this barrier is interrupted in the lower follicular infra-infundibulum, as the differentiation pattern switches from epidermal differentiation to a tricholemmal differentiation pattern. Only few differentiated corneocytes remain, and the invagination of the epidermis in the infundibulum must be considered as highly permeable ***(Blume-Peytavi and Vogt, 2011).*** **The isthmus** completes the upper part of the hair follicle, and it extends from the duct of the sebaceous gland to the exertion of arrector pili muscle (***Randall and Botchkareva, 2009; Wosicka and Cal, 2010).***

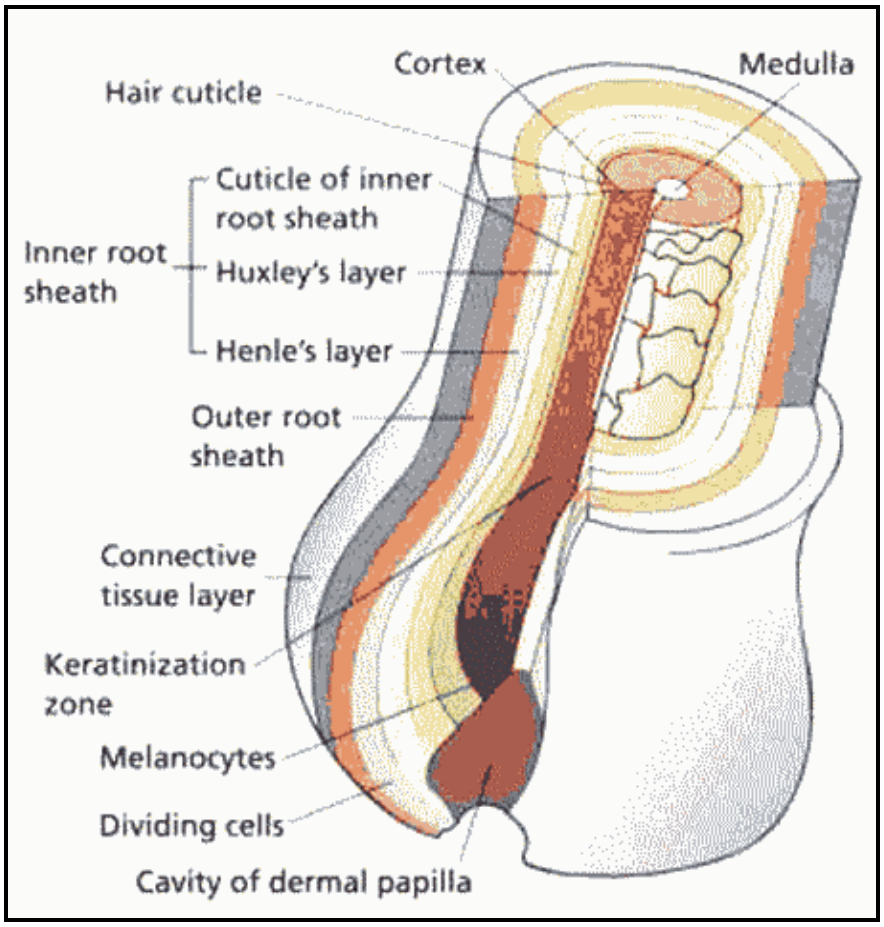

Figure (1): Structure of the hair ***(Schlake, 2007).***

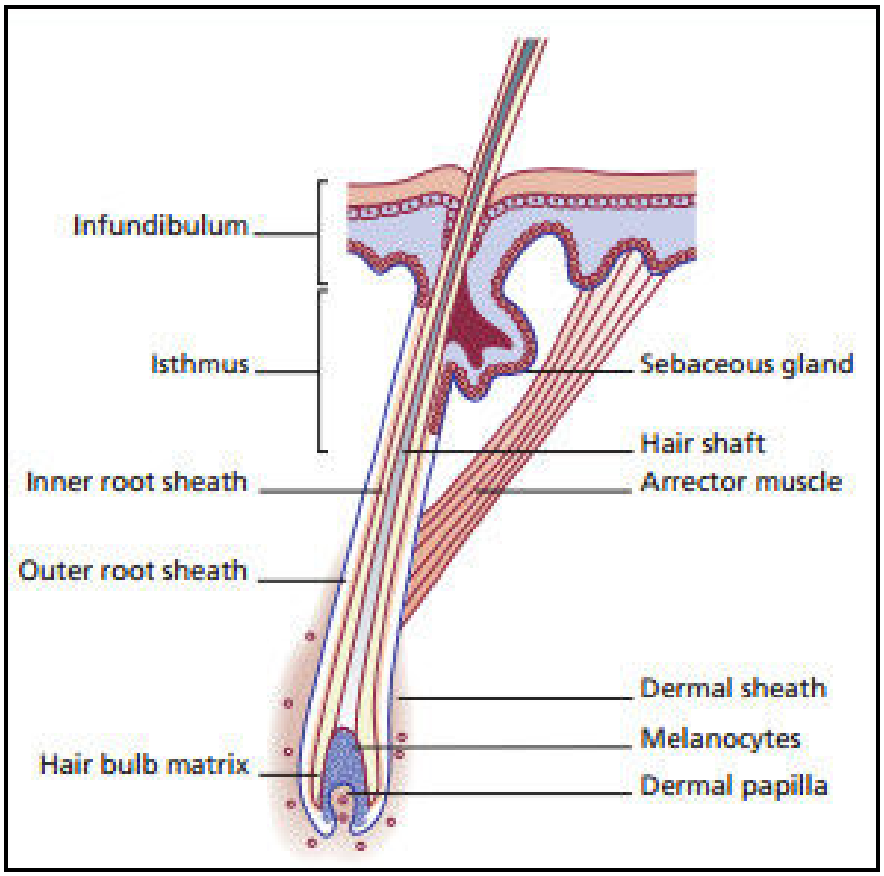

Figure (2): Structure of hair follicle ***(Poblet et al., 2002).***

Types of hair

There are three types of hair. They vary regarding the time of appearance, the location and the pigment content. They are:

A. Lanugo hair:

It is soft and fine, usually un-pigmented and without a medulla. This hair is found on the fetus and is usually shed

about the eighth month of gestation with the vellus and terminal hair replacing it ***(Slee et al., 2007).***

B. Vellus hair:

It is also soft and un-medullated and may be pigmented. It is short, rarely exceeding 2cm in length, small in diameter approximately 30 micrometers. It replaces lanugo hair in the postnatal period and is spread over the entire body surface ***(Grossman, 1999).***

C. Terminal hair

It is larger, coarser, medullated and contains more pigments. It is longer up to 100 cm and coarser, approximately 60 micrometer. It replaces vellus hair at specific sites of the body. During puberty, vellus hair is replaced by terminal hair in the axillary, pubic and beard (males) regions. Eyebrows and eyelashes are considered terminal hair despite their short length ***(Mofid et al., 2008).***

The hair follicle growth cycle

The hair follicle functions as a stem cell repository containing cells of multiple cell lineages ***(Kligman, 1959; Paus and Foitzik, 2004).*** To some extent, the molecular oscillator system responsible for hair cycling is autonomous, as demonstrated by persistent hair cycling following transplantation to a different skin site. The presence of these

stem cells is crucial to continued hair follicle cycling ***(Ebling, 1988).***

Hair follicles pass through three major growth phases. These three phases are anagen (a stage of rapid growth), telogen (a stage of relative quiescence) and catagen (apoptosis-mediated regression) **(Figure 3).** Following regression of the epithelial column during catagen, the dermal papilla relocates to lie near the bulge ***(Schneider et al., 2009).*** The physical proximity of these two structures promotes stem cell activation and initiation of a new hair cycle. Following activation, the stem cells leave the bulge and proliferate downward to generate the outer root sheath ***(Hsu et al., 2011).*** During anagen, rapidly proliferating progenitor cells in the bulb generate the hair shaft and its surrounding inner root sheath, and the distance between the bulge and dermal papilla increases. The duration of the anagen phase governs the hair cycle length in different body regions. Scalp follicles have the longest anagen phase, and most normal scalp follicles are in the anagen phase ***(Randall, 2008).*** Although often not obvious, seasonal alterations occur in the human hair cycle with more hair shedding during the autumn months ***(Randall, 2008).***

Please check figure **:[١MA]Comment** numbers in text (presence and their correspondence to figures) and under the figures

Checked **:[٢MA]Comment**

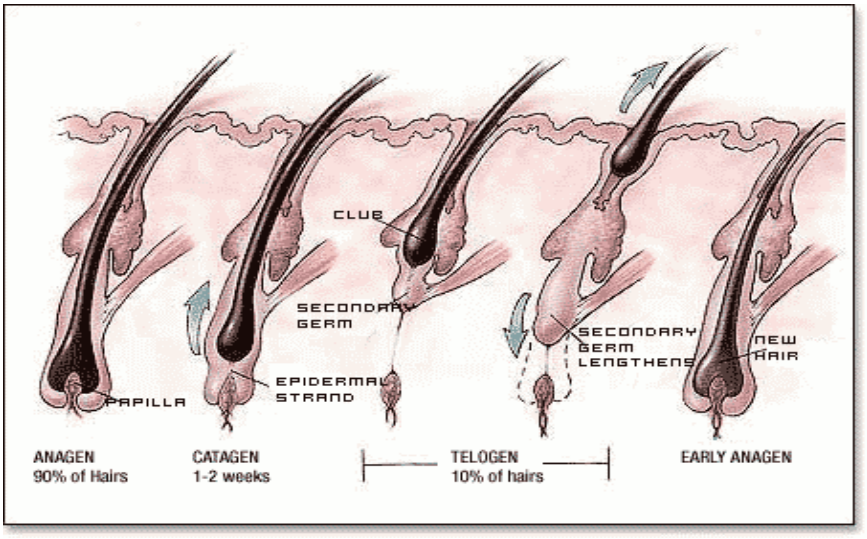

Figure (3): Hair growth cycle ***(Schneider et al., 2009).***

Androgen Biosynthesis

Androgens may be generated via a *de novo* synthetic pathway from cholesterol to testosterone and dihydrotestosterone (DHT), and/or via a shortcut pathway from circulating dehydroepiandrosterone-sulfate (DHEAS). The *de novo* synthesis of androgens requires four 'upstream' proteins, including steroidogenic acute regulatory protein, cytochrome P450 cholesterol side-chain cleavage enzyme, cytochrome P450 17α-hydroxylase/17, 20-lyase and steroid 3β-hydroxysteroid dehydrogenase, which are responsible for the early steps of androgen synthesis from cholesterol to dehydroepiandro-sterone. Additional 'downstream' enzymes, including 17β-hydroxysteroid dehydrogenase and 5α-reductase, catalyze the conversion of androstenedione into testosterone and,

subsequently, to DHT, amplifying its androgenic effects ***(Chen and Zouboulis, 2009).***

The major androgens in the serum of normal cycling women are DHEAS, dehydroepiandrosterone, androstenedione, testosterone and DHT, in descending order of serum concentrations ***(Burger, 2002).*** Testosterone and DHT bind to the androgen receptor to promote changes in gene transcription. Dehydroepiandrosterone, DHEAS and androstenedione do not bind to the androgen receptor and can be considered to be pro-hormones ***(Burger, 2002).***

Sulfotransferase, principally sulfotransferase 2A1, catalyzes the conversion of dehydroepiandrosterone to DHEAS in the adrenal cortex. Steroid sulfates can be hydrolyzed to the native steroid by steroid sulfatase. Circulating testosterone in women originates mostly (50%) by peripheral conversion of other steroids, the rest coming in equal parts (25%) from the ovaries and the adrenals ***(Longcope, 1986).*** Of note, the most active androgen, DHT, is synthesized locally in androgen target tissues in a step catalyzed by the enzyme 5α-reductase, and its circulating levels are very low ***(Longcope, 1986).***

Adrenal pubertal maturation, adrenarche, is characterized by increasing DHEAS concentrations. The physical manifestation of adrenarche is pubarche, the development of sexual hair. Adrenarche, a phenomenon limited to a fewer higher primate species, is associated with increased 17,20-lyase

activity of cytochrome P450 17α-hydroxylase/17–20 lyase, decreased 3β-hydroxysteroid dehydrogenase type 2 activity and increased expression of cytochrome b5 ***(Auchus and Rainey, 2004).*** This change in DHEAS synthesis is independent of the hypothalamic–pituitary–gonadal axis ***(Sklar et al., 1980; Counts et al., 1987).*** While adrenocorticotropic hormone (ACTH) plays a permissive role, the molecular events triggering the onset of adrenarche remain uncertain ***(Miller, 2009).***

Onset of adrenarche prior to age 8 years in girls, premature adrenarche, can precede the development of PCOS in some, but not all, girls. In addition to the effects of circulating androgens on the growth of sexual hair, human sebaceous glands and hair follicles are equipped with all the necessary enzymes for biosynthesis and metabolism of androgens ***(Thiboutot et al., 2003).*** Therefore, circulating androgen levels may not reflect local androgen concentrations at the pilosebaceous unit ***(Chen and Zouboulis, 2009).*** Furthermore, cutaneous androgen effects also depend on the expression of the androgen receptor in the pilosebaceous unit ***(Chen and Zouboulis, 2009).***

In sebaceous glands, androgen receptor immunoreactivity is detected only in the basal, early differentiated sebocytes. Conflicting data exist regarding the exact pattern of androgen receptor expression in human hair follicles, especially concerning expression in occipital scalp. Androgen receptor

expression is found mainly in the dermal papilla but is absent in the keratinocytes of outer root sheath (including the bulge regions supposed to contain the hair stem cells) and those of the inner root sheaths. On the other hand, higher levels of androgen receptor immunoreactivity are found in the dermal papilla cells from balding hair follicles when compared with non-balding scalp ***(Escobar-Morreale, 2012).***

Androgen receptor (AR):

Androgens are well known to control the development and functions of the reproductive system in both males and females ***(Yeh et al., 2002; Kimura et al., 2007).*** The major circulating androgen is testosterone, which is mainly produced by Leydig cells in the male testis, while adrenal glands are also capable of secreting testosterone, but at a much lesser degree. Testosterone can be metabolized by 5α-reductases into a more potent androgen, 5 α -dihydrotestosterone (DHT). Both testosterone and DHT can bind to androgen receptor, but DHT has tenfold higher affinity to AR compared to testosterone ***(Chen et al., 1998).***

In sebocytes, sweat glands and dermal papilla cells, the circulating androgenic pro-hormones, dehydroepiandrosterone (DHEA) and androstenedione, can be converted into testosterone and DHT. These potent androgens subsequently regulate dermal physiology through an intracrine or paracrine manner ***(Zouboulis et al., 2007).***