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# Nigerian Women Living in The United States are More Hirsute than Those Living in Nigeria.

A Thesis Submitted to the

Yale University School of Medicine

In Partial Fulfillment of the Requirements for the

Degree of Doctor of Medicine

By

Kikelomo Olorunrinu

2007

# Abstract

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## NIGERIAN WOMEN LIVING IN THE UNITED STATES ARE MORE HIRSUTE THAN THOSE LIVING IN NIGERIA

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This study was to determine if there exists a difference in the rate of hirsutism in genetically similar women in two different environments. 112 Nigerian women living in the U.S.A and 70 women living in Nigeria were surveyed. All women completed a pictorial survey scoring peripheral hair growth in 6 body areas from 0 (no significant hair growth) to 4 (severe hair growth). Total hirsutism score was calculated as a sum of individual scores. The survey also included demographic data, menstrual history, and data regarding use of hormonal treatments. Statistical comparisons between groups included t-test, nonparametric tests and chi-square test. Multiple regression analysis was carried out to identify independent predictors of peripheral hair growth. Women residing in U.S.A had a 31% higher total hirsutism score than those residing in Nigeria. This difference was not related to irregular menstrual cycle. To account for possible effects of age, B.M.I and differences in tribal origin, multiple regression analysis was performed. Location (living in U.S.A vs. Nigeria) remained the strongest predictor of total hirsutism score ( $P=0.02$ ); tribal origin was also significant ( $P=0.04$ ), while age and B.M.I had no independent predictive value ( $P>0.1$ ). It was concluded that this difference, is not explained by factors such as age, obesity and ethnic origin. We propose that this difference may be due to differences in environmental or lifestyle factors of the women.

# Acknowledgements

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I am grateful to the Office of Student Research for funding this project.

Dr. A. J. Duleba: Thank you for your unwavering support.

My family: Thank you for being my solid foundation. Dependable, like a rock, you have been here behind me all the way. I certainly would not be here without you.

OSK: Thank you for being my help, my unchanging, enthusiastic, perpetually optimistic encourager, one-man cheerleader, lover and friend.

Finally, and most importantly, to The King eternal, immortal, invisible, the only God, to You be honor and glory forever and ever. Without You, I am nothing.

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# Background

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Hirsutism is defined as the presence of terminal (coarse) hairs in females in a male-like pattern caused primarily by androgen excess <sup>1, 2</sup>. Non-androgenic causes of hirsutism are rare and include acromegaly, Cushing's syndrome, and certain drugs <sup>1</sup>. Androgenic causes account for approximately 75-80% of hirsutism cases. Regardless of the etiology of hirsutism, it is a constant psychosocial and aesthetic problem for the individual involved, in addition to the medical implications

Hair growth patterns are thought to be heritable, and hirsutism in particular with the corollary of PCOS is thought to be familial. In addition, body hair growth patterns differ across racial divides and even ethnic groups <sup>2</sup>. Consequently, in order to study the prevalence of hirsutism, it is necessary to evaluate genetically similar individuals, that is, distinct ethnic/ geographic groups so as to remove confounding variables. The degree of hirsutism is determined by a scoring system devised by Ferriman and Gallwey in 1961 <sup>3</sup>. In their landmark paper of 1961, they scored 12 body parts of in a group of Caucasian women. They defined hirsutism as a score of 8 or more. Several modifications have been proposed including one by Hatch et al <sup>4</sup>. A score of 6 or above on the modified Ferriman-Gallwey scale is required for a diagnosis of hirsutism <sup>1</sup>. Of recent, even a score above 3 is considered by statistical methods to be abnormal in a population study involving black and white women <sup>5</sup>. Not all women with unwanted or excess facial hair have hirsutism of identifiable cause. This type of hirsutism is termed 'idiopathic' <sup>1</sup>. However, Souter et al in 2004 found that even in women who do not meet the criteria for hirsutism, that is, with a score between 1 and 5 on a modified Ferriman-Gallwey scale, PCOS was observed in

50% of the study participants <sup>2</sup>. Thus, unwanted hair in a population of women should not be treated lightly as it may actually be of clinical significance. The scale was revised by Hatch et al in 1981 to include the parts of the body most sensitive to androgens<sup>6</sup>.

Hirsutism is the most commonly used clinical criterion for the diagnosis of hyperandrogenism <sup>8</sup>. It affects between 5-15% of women depending on definition and the way it is measured <sup>1</sup>. According to the 2005 estimate of the U.S.A census bureau, there are about 62 million women of reproductive age living in the United States <sup>9, 6</sup>. This means that between 3 and 9 million American women are affected. About half of these women also have underlying hyperandrogenism <sup>8</sup>. Conversely 70-80% of women with hyperandrogenism will have hirsutism <sup>2, 6</sup>.

Using the Hatch modified scale, with hirsutism defined as a score of 6 and above, 8% of the subjects had hirsutism in a prospective study involving 369 hirsute women<sup>10</sup>. Even in women with minimal hair growth, that is, a modified Ferriman-Gallwey (mF-G) score of 5 or less, up to 60% demonstrated hyperandrogenism, including some eumenorrheic subjects. One study found that statistically, working with mF-G scores of 633 black and white women in a multicenter study, a score of 3 or greater could be considered abnormal. Therefore a cut-off of 6 is not inappropriate <sup>1</sup>.

Attempts have been made to derive a population definition of hirsutism. Patterns of hair growth differ from one ethnic group or race to another. Questions have been raised about the validity of having a one-size-fits-all approach to defining hirsutism across race and ethnicity since the density of hair follicles and rate of hair growth varies by ethnicity <sup>8</sup>. Caucasians have the highest density of hair follicles per unit area, followed

by blacks then Asians. Consequently, racial and ethnic differences in the rates of hirsutism also exist<sup>11</sup>. For instance, Asian women may present with biochemical hyperandrogenemia, without obvious dermatologic manifestation of androgen excess<sup>8</sup>. The phenotypic expression of hyperandrogenism as hirsutism in females of Asian extraction is not as common or pronounced as in black and Caucasian females<sup>1</sup>. Only 20% of Japanese women with PCOS<sup>11</sup> exhibit hirsutism as opposed to 70-80% in blacks and whites<sup>1</sup>. Southern European, Mediterranean and Middle Eastern women have a genetic predisposition for some facial hair growth<sup>8</sup>. Generally, in Nigeria, Ibo women are known to have increased body hair.

### *Physiology of hair growth*

The unit of hair growth in the body is the pilosebaceous unit (P.S.U). The P.S.U is an epidermal appendage programmed from the embryonic stage to develop into a sebaceous gland or hair follicle<sup>12</sup>. Its structure is depicted in Figure 1. In humans, they are fully formed in the embryo at between 2 and 4 months *in utero*. The human body has two categories of hair types: sexual and non- sexual. Sexual hair is found in axillary, pubic, perineal, genital, upper lip and beard areas. Most facial P.S.Us in females are programmed to become sebaceous glands. Non sexual hair is found on the scalp, eyebrows, arms and legs. Hair also exists in three forms on the body: terminal, vellous and lanugo<sup>8, 1</sup>.



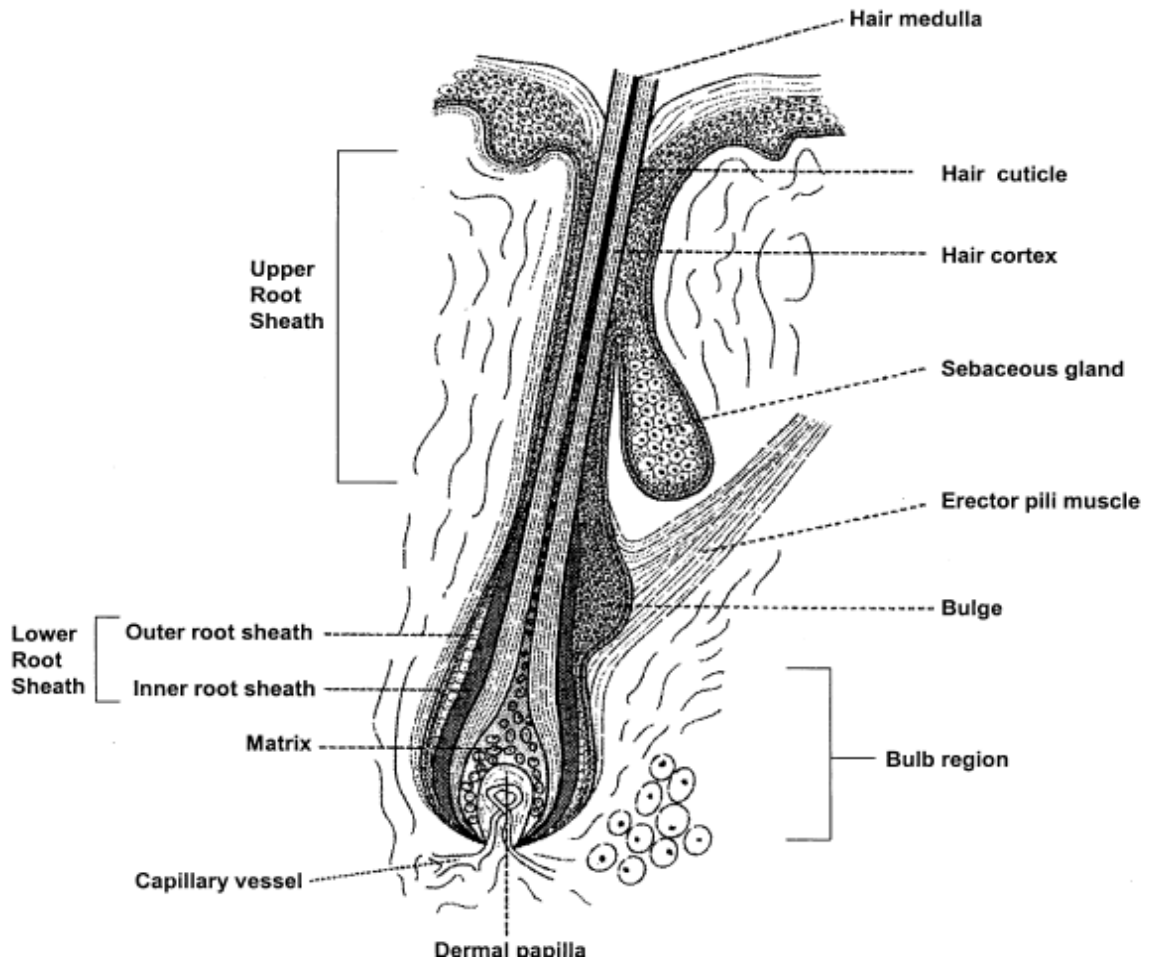


Figure 1. Anatomy of a pilosebaceous unit containing a terminal hair follicle. (Reprinted with permission from Sanchez LA, Perez M, and Azziz R. Laser hair reduction in the hirsute patient: A critical assessment. *Hum Reprod* 2002;8:169–81. ©European Society of Human Reproduction and Embryology. Reproduced by permission of Oxford University Press/Human Reproduction.) Azziz. *Hirsutism. Obstet Gynecol* 2003.

Terminal hair is thick, pigmented, coarse, medullated and found on the scalp, eyebrows, pubis and axilla. Vellous hair is fine, non-medullated, non pigmented hair found on the apparently hairless parts of the body. Lanugo is soft, unmedullated hair on the surface of the fetus which is shed peri-partum<sup>1</sup>. In the pre-pubertal state in man, sexual hair exists in the vellous form. At puberty, under the influence of androgens, vellous hairs in sexual areas become terminal hairs. This important role of androgens was discovered in 1950 by

Hamilton, who found that males castrated before puberty did not develop axillary hair and beards while castration after puberty led to regression or reduction in axillary hair and beards<sup>13</sup>.

Hair follicles go through 3 stages in their life cycle: anagen is the stage of active growth and elongation; catagen is the shortening and transition stage between anagen and telogen; and telogen is the resting stage when the hair is shed<sup>1, 12, 14</sup>. The rate of hair growth depends on the duration of anagen, the percentage of time spent in anagen, the linear elongation rate of the hair follicle, the diameter of the hair (medullated hair is thicker than vellous; genetics also plays a role in hair thickness) and density of P.S.U.s.

#### *The role of Androgens on the P.S.U*

The growth and development of hair of sexual hair is largely dependent on androgens. Androgens are the most important determinant of the distribution of the different types of hairs on the body<sup>1</sup> (Figure 2 and Table 1). Testosterone and dihydrotestosterone (DHT) act on the androgen receptors (AR) found on the dermal papillae of the P.S.U to effect growth of the hair follicle<sup>12, 14</sup>. ARs belong to the steroid receptor family. They are ligand activated nuclear receptors with a DNA binding and ligand binding domains. Ligand binding leads to a conformational change in the receptor which leads to mRNA transcription.

Endocrine condition	Type of terminal hair					
	Eyelash	Scalp	Axial	Pubic	Abdominal/ chest	Facial
Normal child	+	+	-	-	-	-
Adult female androgens	+	+	+	+	-	-
Excess female androgens	+	+	+	+	±	±
Adult male androgens	+	+	+	+	+	+
5 $\alpha$ -Reductase II deficiency	+	+	+	+	-	-
Androgen receptor deficiency	+	+	-	-	-	-

Table 1. Distribution of terminal hair under endocrine conditions. From Stanczyk FZ. Diagnosis of hyperandrogenism: Biochemical criteria. Best Practice & Research Clinical Endocrinology & Metabolism. 2006;20(2):177-91.

Androgens not only increase the duration of time spent in anagen<sup>14</sup>, they also cause the medullation of vellous hair follicles, converting them to terminal ones. This process may take months to years of androgen exposure<sup>8</sup>. Since interaction of androgens and AR is necessary for conversion of vellous hair to terminal hair, it follows that hirsutism in females could be due to increased levels of androgens or increased AR sensitivity to androgens.<sup>8</sup> Paradoxically, under androgenic influence, scalp hair undergoes regression of vellous hair in men and women so genetically predisposed. Androgens also lead to enlargement and development of sebaceous glands leading to copious secretion of sebum. As such, the holy trinity of androgen excess in females is acne, hirsutism and male pattern alopecia<sup>15</sup>, most likely in that order depending on how elevated androgen levels are. The effects of androgen on hair growth in humans proceeds in a caudal-cephalad fashion with increasing levels of androgen<sup>12, 14</sup>. Figure 2 shows the stages of sexual hair development as it corresponds to increasing plasma T in the developing male.

It follows that rising levels of androgen in females would cause undifferentiated hair on the face, chest etc to undergo medullation and become sexual hair (see Figure 3).

Hyperandrogenism is diagnosed by measuring plasma free testosterone (T) derived from plasma total testosterone and SHBG. The higher the level of SHBG is, the lower the level of free T. The normal level of total T is 20-70ng/dl and free testosterone is 1-8pg/ml<sup>15</sup>. Routine testing for other androgens is of little clinical value in the evaluation of hirsutism except maybe to diagnose androgen secreting tumors and to confirm clinical suspicion of hyperandrogenism<sup>16</sup>.

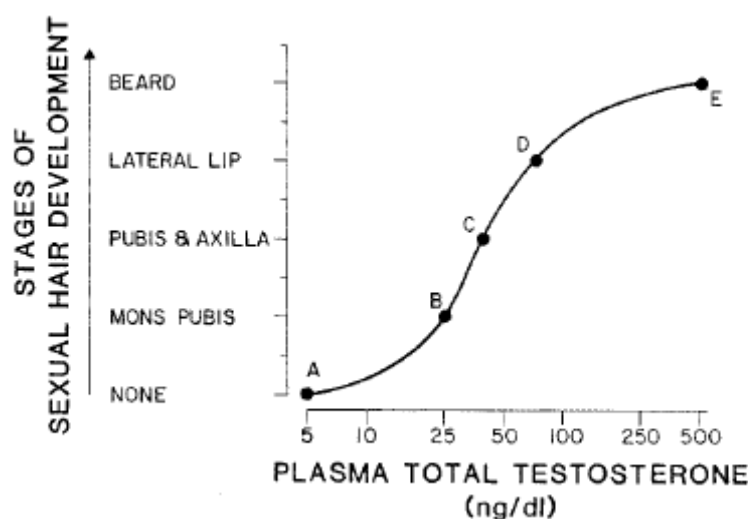


Figure 2. Relationship of stages of sexual hair development to testosterone as a representative plasma androgen. Note logarithmic scale for testosterone. A, Prepubertal; B, stage 3 pubic hair; C, stage 5 pubic hair; D, moderate hirsutism; E adult male. From R. L. Rosenfield: *Clin Endocrinol Metab* 15:341-362, 1986 (1) © W. B. Saunders

### *Mechanisms of Androgen Action*

Four principal androgens are secreted by the endocrine glands:

dehydroepiandrosterone sulfate (DHEAS), Dehydroepiandrosterone (DHEA),

androstenedione, and testosterone (T). These androgens are formed by well established

pathways in the ovaries and the adrenals as depicted in the figures below (Figure 4a and 4b). Almost all of the DHEAS produced in a woman is produced by the adrenals; the rest comes from the ovaries. It is the most abundant androgen in the human female <sup>15</sup>.

Contributions of the two glands to androgen production are shown in Table 2. T and DHT are carried in the blood unbound or bound to sex hormone binding globulin (SHBG) while DHEAS and DHEA and androstenedione are bound to albumin <sup>15</sup>. Only 1-2% of T and DHT in the body is unbound. This is the fraction available for biologic action <sup>12</sup>.

Androgen	Ovary	Adrenals
DHEA	20%	80%
DHEAS	0%	~100%
Androstenedione	50%	50%
Testosterone (T)	50-66%	33-50%

Table 2. Percentage contributions to the four major androgens from the ovary and the adrenals <sup>15</sup>.

Androgens can also be synthesized in the P.S.U itself <sup>12</sup>. In fact, skin is a major site of testosterone formation in the female <sup>14</sup>. DHEAS, DHEA and androstenedione are converted to T in the skin. The most potent androgen in the body, dihydrotestosterone (DHT), is formed in skin from T or androstenedione by 5 $\alpha$ - reductase (Figure 3 and 4b) <sup>15</sup>. The high potency of DHT is due to a higher affinity for the AR than T <sup>14</sup>.

5 $\alpha$ - reductase is a microsomal NADPH dependent enzyme with 2 isozymes. Type 2 is important for most androgen actions in sexual organs and deficiency results in male pseudohermaphroditism. The type 1 is the major isozyme in skin <sup>14</sup>.

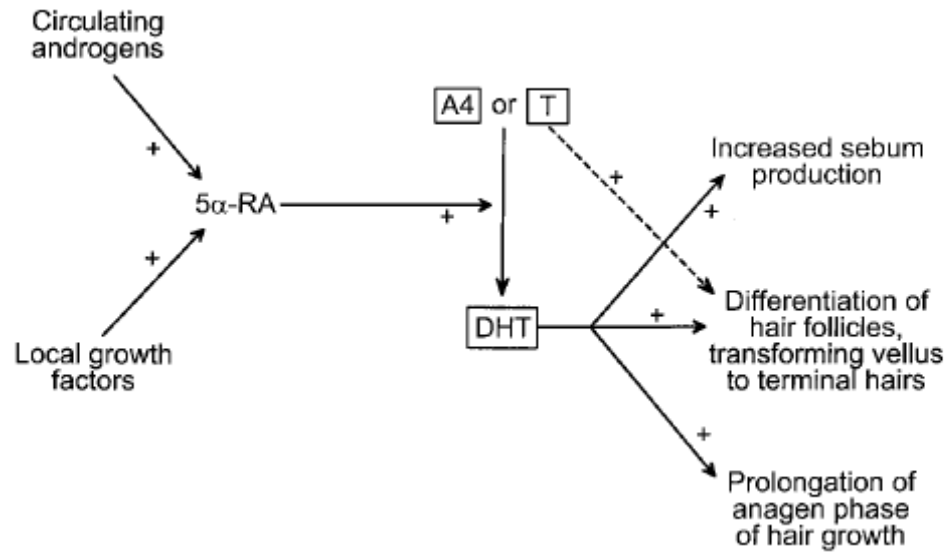


Figure 3. Effects of circulating androgens on cutaneous hair growth. From Azziz R, Carmina E, Sawaya ME. Idiopathic Hirsutism. *Endocr Rev.* 2000 August 1, 2000;21(4):347-62

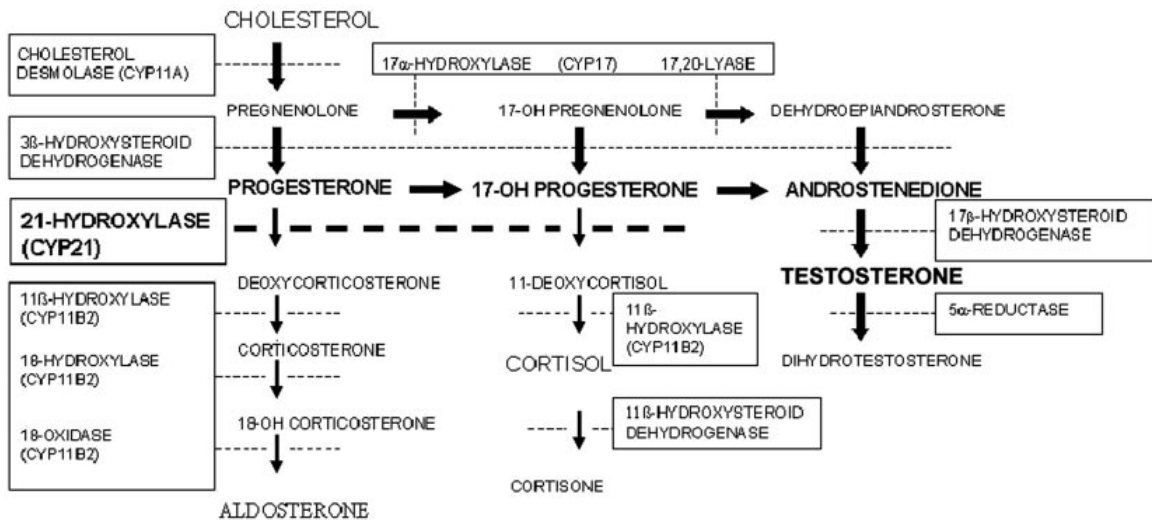


Figure 4a. Scheme of adrenal steroidogenesis. From New MI. Nonclassical 21-Hydroxylase Deficiency. *J Clin Endocrinol Metab.* 2006 November 1, 2006;91(11):4205-14

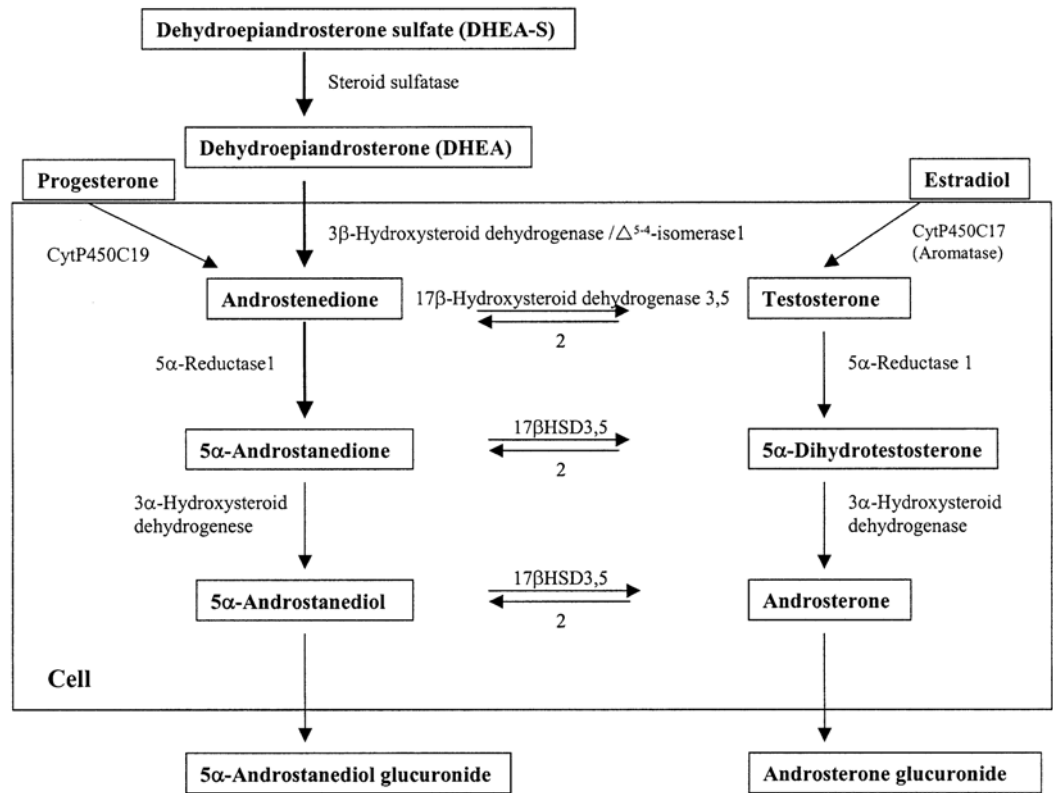


Figure 4b. Synthesis of T and DHT from DHEAS and DHEA, also showing metabolism of T and DHT to glucuronides.

Hairs from balding scalp have more ARs in the dermal papilla than hair from non-balding scalp<sup>12</sup>. Therefore, the dermal papilla may be responsible for the effects of androgens on the P.S.U.

The biologic effects of androgens are determined by the rate of metabolism or degradation to less androgenic compounds. At the site of action, for instance, testosterone is converted to estrogen in the hair follicle by aromatase. The heterogeneity of cutaneous manifestation of androgen excess has been attributed to differences in metabolism of androgens at the P.S.U and differences in AR sensitivity to androgens<sup>12</sup>.

Group	TEBG (nM)	Steroid	Total steroid concentration (ng/dl)	Free steroid (%)	Free steroid concentration (ng/dl)
Normal women	40	Testosterone	49	1.4	0.7
		DHT	16	0.6	0.1
		Androstenedione	123	8.3	10.8
Moderate hirsutism	23	Testosterone	85	2.6	2.2
		DHT	14	1.4	0.2
		Androstenedione	274	8.2	22.5
Normal men	25	Testosterone	810	2.7	22.0
		DHT	58	0.1	0.8
		Androstenedione	114	9.5	10.8

Data from Rosenfield et al (1984).

Table 3. Average plasma levels of the major androgens and testosterone binding globulin (TEBG) in normal and hirsute individuals

Table 3 indicates that hirsute women seem to have higher levels of androgen and androgen concentration. Women with cryptic hyperandrogenism, that is, high levels of androgens and no cutaneous manifestation may have higher rates of androgen metabolism, degradation and inactivation, or less sensitive ARs. Women with normal androgen levels and hirsutism may have hypersensitive ARs, or slow/impaired metabolism/degradation of androgens. There is also the possibility that hirsute women convert T to DHT at a higher rate. Stanczyk et al carried out a series of studies testing this hypothesis by measuring  $5\alpha$  reduced metabolites in serum and skin. They found that levels of  $3\alpha$  –androstenediol and androsterone conjugates were higher in hirsute women than in normal women<sup>15</sup>. Furthermore, the conversion rates of T to DHT and T to  $3\alpha$  –androstenediol in genital skin of hirsute women is intermediate between than for normal women and men. Serum levels of  $3\alpha$  –androstenediol glucuronide was also found to be elevated in hirsute women<sup>14</sup>. Whereas, men and non-hirsute women express predominantly type 2 isozymes of  $5\alpha$ - reductase in genital skin, hirsute women seem to express predominantly type 1 isozymes<sup>15</sup>. These findings have been countered by other



researchers who say that androgen conjugates are more likely a marker of adrenal steroid production than skin metabolism<sup>14</sup>. Nevertheless, whether elevated levels of conjugates are due to differential skin metabolism of androgens in the skin, or increased steroidogenesis from the adrenals, the fact remains there is a measurable difference.

### *Effects of Non-androgenic Hormones on the P.S.U*

Growth Hormone (GH), insulin, glucocorticoids and estrogen may play a role in P.S.U growth in man. Growth hormone seems to be synergistic with androgens in promoting hair growth and is probably responsible for the hirsutism seen in acromegalic patients. In addition, the waxing and waning of acne during adolescence corresponds more to the rise and waning of GH than androgens<sup>14</sup>. Furthermore, Zachmann and Prader<sup>17</sup> showed that GH deficient boys are sub-normally responsive to T (Figure 5). Sex hormones also stimulate the production of GH. The growth hormone spike during puberty is due to a response to rising estrogen/testosterone levels<sup>18</sup>. Stress and exercise are also known to stimulate release of GH. GH is diabetogenic; increasing the rate of lipolysis, thereby increasing levels of free fatty acids and also raising insulin levels<sup>18</sup>. IGF-1 is thought to potentiate the effects of GH.

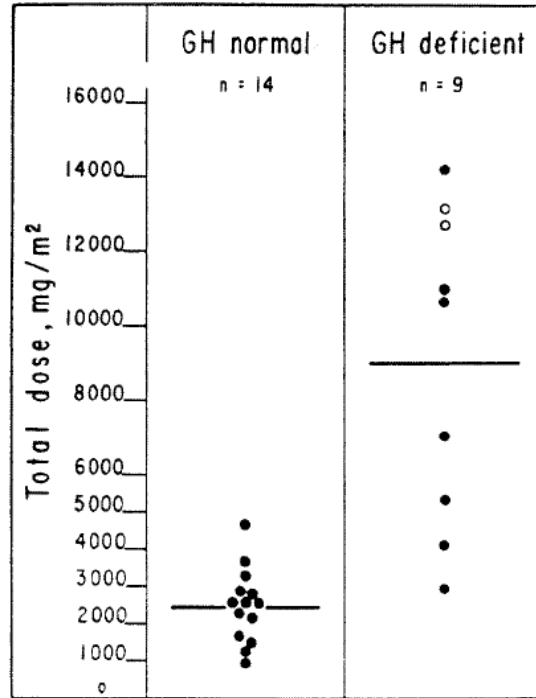


Figure 5. Comparison of the total cumulative testosterone dose needed to induce axillary hair growth in 23 boys with and without GH deficiency. The mean total dose of testosterone (lines in figures) needed to induce axillary hair growth was significantly higher in the GH-deficient group as compared with the non-GH-deficient group. The open circles represent two patients who did not develop axillary hair despite 2.2 and 3.7 yr of testosterone treatment from M. Zachmann and A. Prader: J Clin Endocrinol Metab 30:85-95, 1970 (181). © The Endocrine Society.

Insulin's effects on the P.S.U is evidenced by the fact that hair growth can be accelerated in DM I sufferers when insulin is supplemented. Insulin acts as a growth factor in keratinocytes or dermal fibroblasts cells, hence the development of acanthosis nigricans in hyperinsulinemic, insulin resistant states <sup>11</sup>. Moreover, insulin deficient hair follicles enter a premature catagen phase *in vitro*. <sup>14</sup>

Cortisol, a glucocorticoid, also seems to have an effect on the P.S.U because Cushing's syndrome may result in hypertrichosis <sup>19</sup>.

The role of estrogens in P.S.U growth and development is largely unclear. Estradiol is thought to weakly inhibit 5 $\alpha$  reductase. Hairs from balding areas of scalp have less aromatase than hairs from non-balding areas of scalp. Furthermore, a condition

known as telogen effluvium, in which several hairs simultaneously enter telogen is common after pregnancy or after withdrawal of oral contraceptives<sup>12, 14</sup>. Paradoxically, pubic hair increases in hypogonadal females when puberty is induced by physiologic doses of estradiol alone<sup>14</sup>

Other hormones that may play a role in P.S.U growth include prolactin and thyroid hormone. Prolactinemia is marked by hirsutism which may be mediated by increased adrenal androgen production. Hyperthyroidism leads to diffuse hair loss and hypothyroidism leads to dry and brittle hair.

### *Differential Diagnosis of Hirsutism*

Hirsutism should be distinguished from hypertrichosis. Hirsutism is specifically in a male pattern and involves excessive sexual hair. Hypertrichosis is generalized excessive hair growth that may be due to therapeutic drugs such as glucocorticoids, phenytoin, minoxidil or cyclosporine. Other causes include metabolic diseases such as anorexia nervosa and physical irritation of skin. These changes are not due to androgen excess<sup>16</sup>. Moreover, the resulting hair is usually vellous<sup>1</sup>.

The causes of hirsutism can be divided into three categories: non androgenic causes, those due to androgen excess, and idiopathic hirsutism. The most common hyperandrogenic cause of hirsutism in women of reproductive age is polycystic ovarian syndrome (PCOS) but its diagnosis is primarily one of exclusion. PCOS accounts for 70-80% of cases of hirsutism<sup>11</sup>. In fact PCOS is almost synonymous with hirsutism and hyperandrogenism in women<sup>21</sup>.

Other androgenic causes include non-classic adrenal hyperplasia (NCAH), androgen secreting tumors, hyperandrogenic, insulin resistance and acanthosis nigricans (HAIRAN) syndrome, Cushing's syndrome, androgenic or therapeutic drug intake and hyperprolactinemia<sup>8,1</sup>. In a study involving 873 patients with signs of androgen excess, Azziz et al found that the prevalence of androgen secreting tumors was 0.23%, CAH 0.69%, NCAH 1.06%, HAIRAN 3.78%, idiopathic hirsutism 4.68%, hyperandrogenism with hirsutism 6.75%, and PCOS 82.02%<sup>21</sup>.

NCAH, a mild form of adrenal hyperplasia caused by a mutation on the CYP21 gene resulting in 21 $\beta$ -hydroxylase deficiency, results in accumulation of the precursors progesterone and 17 hydroxyprogesterone. These are ultimately converted to androstenedione leading to hyperandrogenism (see Figure 4a)<sup>22, 23</sup>. In the U.S.A, the disorder affects 0.05-0.1% of the general population and 1-10% of hyperandrogenic women with the highest incidence in Ashkenazi Jews, 1:27<sup>22, 23</sup>. The data on NCAH on blacks is quite sparse, but the incidence of NCAH in blacks seems to be less than in whites<sup>24</sup>. The classic form of adrenal hyperplasia presents at birth with virilized genitalia in the female, or impaired aldosterone synthesis. With NCAH, females are asymptomatic at birth but develop symptoms related to androgen excess later in life. Symptoms include premature pubarche, accelerated linear growth, advanced bone age, short adult height, severe cystic acne, temporal baldness, infertility, menstrual irregularities, an ovulation and hirsutism. In a study of 28 women with known NCAH, 39% had isolated hirsutism<sup>23</sup>.

HAIRAN syndrome is characterized by ovulatory dysfunction, insulin resistance, hyperinsulinemia and hyperandrogenism. Affected individuals also have acanthosis nigricans, a cutaneous marker for insulin resistance characterized by increased growth of

the epidermal layer in skin folds such as the back of the neck, the ante-cubital, groin and axillary areas. The lesions are thickened, rough, and velvety gray-brown. This condition is linked to the metabolic syndrome, obesity, diabetes mellitus type II and increased cardiovascular risk.<sup>11</sup> Diagnosis is made by clinical and laboratory criteria: fasting glucose and insulin levels, glucose tolerance tests and androgen level assays<sup>1</sup>.

Androgen secreting tumors are generally very rare in women with hirsutism, between 1/300 to 1/1000 hirsute women<sup>1</sup>. Serum androgen levels tend to be very high (total T > 150ng/l or DHEAS > 8000ng/l) and ultrasound or physical exam finding of pelvic or abdominal mass should raise a high suspicion for tumor.

Other conditions that need to be ruled out in hirsutism include thyroid dysfunction, use of exogenous steroids or contact with persons who use exogenous steroids, prolactinemia and acromegaly. Other possible sources of exposure to androgens involve the use of topical androgen preparations possibly by partners of the opposite sex. Virilization in pre-pubertal girls from exposure (by passive contact) to topical androgen preparations of male caregivers has been documented<sup>26</sup>. However, hirsutism in these cases would be sudden and pronounced.

When all the aforementioned disease conditions have been ruled out, a diagnosis of PCOS or idiopathic hirsutism (IH) should be considered. In 2003, the ASRM/ESHRE revised the diagnostic criteria for diagnosis of PCOS (Table 4)<sup>27</sup>.

---

<b>1990 Criteria (both 1 and 2)</b>
<b>1. Chronic anovulation and</b>
<b>2. Clinical and/or biochemical signs of hyperandrogenism and exclusion of other etiologies.</b>
<b>Revised 2003 criteria (2 out of 3)</b>
<b>1. Oligo- or anovulation,</b>
<b>2. Clinical and/or biochemical signs of hyperandrogenism,</b>
<b>3. Polycystic ovaries and exclusion of other etiologies (congenital adrenal hyperplasia, androgen-secreting tumours, Cushing's syndrome)</b>

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Table 4. Revised Diagnostic criteria for PCOS. Note: Thorough documentation of applied diagnostic criteria should be done (and described in research papers) for future evaluation. 2003 Rotterdam PCOS consensus. Fertil Steril 2004

In a Finish longitudinal study involving 196 women complaining of oligomenorrhea and/ or hirsutism, polycystic ovaries were found in 70.4% of women with both symptoms and in 18.4% of women with hirsutism compared with 18.2% of normal controls. 37.3% of the all women with either hirsutism or oligomenorrhea had polycystic ovaries, more than double the percentage in normal controls<sup>28</sup>. Chronic anovulation used to be a required criterion for PCOS. Consequently, eumenorrheic women with signs of androgen excess and no other disease process were diagnosed with IH. Studies have shown that even in eumenorrheic women with signs of androgen excess, PCOS may be present. Approximately 40% of eumenorrheic women are actually an-ovulatory and have PCOS, not IH<sup>1</sup>. Hirsute women who claim to have regular periods should be evaluated further for ovulatory dysfunction. Azziz et al found that in a study of 228 women with minimal unwanted facial hair (mF-G of 1-5), one third of the women with regular menstrual cycles were found to be an-ovulatory after day 22-24 progesterone levels were found to < 4ng/dl<sup>1</sup>.

From personal observation and anecdotal evidence, Nigerian women who have moved to the U.S.A complain of hirsutism mostly in the form of facial hair than the ones who live in Nigeria. This may be because of more awareness of facial hair in a culture where facial hair is considered unsightly. However, hair growth in a male pattern by a female is stigmatized in Nigeria as well, so bias is unlikely to be to cause of this

difference. Till date, many studies have been done to decipher the etiology of hirsutism. However, so far, no studies have examined the rates of hirsutism in genetically similar women who live in different environments.

**Abbreviations:** AR androgen receptor, B.M.I Body Mass Index, CAH Classic Adrenal Hyperplasia, DHEAS Dihydroepiandrosterone Sulfate , DHEA Dihydroepiandrosterone, DHT Dihydrotestosterone, DM Diabetes Mellitus, E<sub>2</sub> Estradiol, FDA Food and Drug Administration, FSH Follicle Stimulating Hormone, HAIRAN HyperAndrogenic, Insulin Resistant Acanthosis Nigricans, HDL High Density Lipoprotein, IGF-1 Insulin Like Growth Factor-1, GH Growth Hormone, LH Luteinizing hormone, mF-G modified Ferriman-Gallwey, NADPH Nicotinamide Adenine Dinucleotide PHosphate, NCAH Non Classical Adrenal Hyperplasia, PCOS PolyCystic Ovarian Syndrome, PSU PiloSebaceous Unit, T Testosterone, SHBG Sex Hormone Binding Globulin, TbA Trenbolone Acetate, TBOH trenbolone, WHR Waist-to-Hip ratio,

# Statement of Purpose

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## Hypothesis:

Women living in the U.S.A are more likely to be hirsute than women living in Nigeria most likely due to environmental exposures. The null hypothesis is that location will not affect the rates of hirsutism of Nigerian woman living here or in Nigeria.

## The specific aims of the study

The study aims to demonstrate that given a shared genetic heritage, environmental factors may play a larger role in the development of androgen excess (using hirsutism as a marker) than thought before.



# Methods

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The study was approved by the Human Investigations committee of The Yale University School of Medicine as HIC#0611001976. Subjects were recruited online by sending emails to webmasters of “listservs” or mailing lists for Nigerian students and professionals. These lists mostly serve as a forum for discussion and information for Nigerians who share a common academic, tribal, social or religious bond. To participate, subjects had to be:

- Born in Nigeria of Nigerian parents
- Live in the U.S.A or Nigeria
- If in the U.S.A must have lived there for 3 yrs or more
- Must be older than eighteen years of age

Participants logged on to an independent online

(<http://www.freeonlinesurveys.com>) site to complete a questionnaire. They scored six body parts: the upper lip, the chin, the chest, the upper abdomen , the lower abdomen and the thigh based on the following pictorial scale taken from Azziz et al: <sup>1</sup>

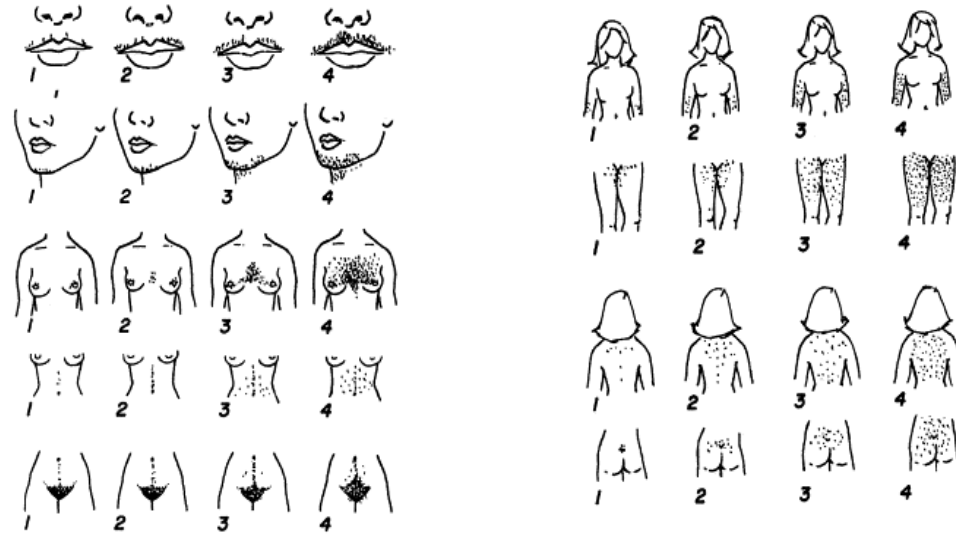


Figure 6. Visual method of scoring hair growth in women, modified from the system originally reported by Ferriman and Gallwey in 1961. Each of the nine body areas depicted is scored from 0 (absence of terminal hairs) to 4 (extensive terminal hair growth), and the scores in each area are summed for a total hair growth score. Hair growth scores of 6 to 8 or greater are generally considered to represent hirsutism. (Adapted with permission from Hatch R, Rosenfield RL, Kim MH, Tredway D. Hirsutism: Implications, etiology, and management. *Am J Obstet Gynecol* 1981;140:815–30 Azziz. *Hirsutism. Obstet Gynecol* 2003

Each participant also answered questions concerning her age, menstrual history (length of menstrual cycle, cycle regularity, and period length), height, weight, tribal origin, and use of hormonal medications. In addition, women in the U.S.A provided the length of time they had spent living in the U.S.A and the Nigerian residents indicated if they had ever lived in the U.S.A for more than 3 years at a stretch. A score of  $\geq 6$  was designated as a cut-off for hirsutism based on work done by Azziz et al. Statistical tests were performed to determine compare means in both locations. Sas® JMP program was used to calculate ANOVA to determine equivalence of the factors age, B.M.I, cycle and period length from the 2 locations. Chi<sup>2</sup> tests were used to compare the factors hormone use and cycle regularity across both locations. Multivariate analysis in form of multiple regression and effect tests was used to determine independent predictors of hirsutism score.

## Results

A total of 186 women entered the study. Four women were excluded from the final statistical analysis: one woman residing in Nigeria for a standing diagnosis of PCOS, and three women residing in the U.S.A cohort because they had not lived in the U.S.A for up to 3 years. Of the 183 left, 112 live in the U.S.A and 71 live in Nigeria. Four of the women living in Nigeria had spent between 4 and 11 years living in the U.S.A. Women taking the survey from the U.S.A had lived in the country for between 3 and 33 years. Mean age of all participants was  $27.4 \pm 6$  (SEM 0.44, minimum 18, maximum 57) and B.M.I was  $24.5 \pm 5.1$  (SEM 0.37, minimum 7, maximum 46). 23.32% of the women in the U.S.A and 12.5% of the women living in Nigeria had a score of 6 or more. Tables 6 and 7 summarize the modified Ferriman- Gallwey scores and demographics of the subjects. Of overweight or obese women, 17 had modified Ferriman-Gallwey scores of 6 or greater. Of these, 23 (32%) live in Nigeria 48 (43%) live in the U.S.A (Table 6)

B.M.I	Weight Status	Nigeria %	U.S.A %
Below 18.5	Underweight	13	5
18.5 – 24.9	Normal	55	52
25.0 – 29.9	Overweight	21	30
30.0 and Above	Obese	11	13

Table 5. Distribution of weight categories in Nigeria and the U.S.A

		Nigeria		P-value	U.S.A	
		Mean mF-G score $\pm$ S.D	S.E.M		Mean mF-G score $\pm$ S.D	S.E.M
	<b>Age</b>	29.07 $\pm$ 4.92	0.58	0.002	26.32 $\pm$ 6.37	0.60
	<b>B.M.I</b>	23.79 $\pm$ 5.26	0.62	0.13	24.95 $\pm$ 4.90	0.46
<b>Body Part Score</b>	<b>Upper Lips</b>	0.25 $\pm$ 0.50	0.06	0.006	0.47 $\pm$ 0.61	0.06
	<b>Chin</b>	0.32 $\pm$ 0.67	0.08	0.003	0.71 $\pm$ 1.00	0.09
	<b>Chest</b>	0.20 $\pm$ 0.43	0.05	0.2	0.27 $\pm$ 0.63	0.06
	<b>Upper Abdomen</b>	0.42 $\pm$ 0.71	0.08	0.15	0.54 $\pm$ 0.79	0.07
	<b>Lower Abdomen</b>	1.39 $\pm$ 1.03	0.12	0.15	1.56 $\pm$ 1.11	0.10
	<b>Thighs</b>	0.51 $\pm$ 0.63	0.07	0.02	0.77 $\pm$ 0.92	0.09
	<b>Total mF-G score</b>	3.10 $\pm$ 2.77	0.33	0.005	4.32 $\pm$ 3.34	0.32
	<b>Menstrual History</b>	<b>Period Length (days)</b>	4.37 $\pm$ 1.01	0.12	0.14	4.67 $\pm$ 1.50
<b>Cycle (days)</b>		28.11 $\pm$ 3.17	0.38	0.63	27.83 $\pm$ 4.26	0.40

Table 6. Summary of descriptive statistics classified by location. S.D = Standard Deviation, S.E.M = Standard Error of Mean, mF-G = modified Ferriman Gallowey Score.

	Nigeria		U.S.A	
Is cycle regular?	% of Total	N	% of Total	N
NO	21%	15 of 71	21%	23 of 112
YES	79%	56 of 71	79%	89 of 112
<b>Post menopausal</b>				
YES	0 of 71		2 of 112	
<b>Hormone use</b>				
NO	93%	66 of 71	89%	100 of 112
YES	7%	5 of 71	11%	12 of 112
<b>Tribe</b>				
Ibo	13%	9 of 71	21%	24 of 112
Yoruba	62%	44 of 71	69%	77 of 112
other	25%	18 of 71	10%	11 of 112

Table 7. Characteristics of survey participants by location

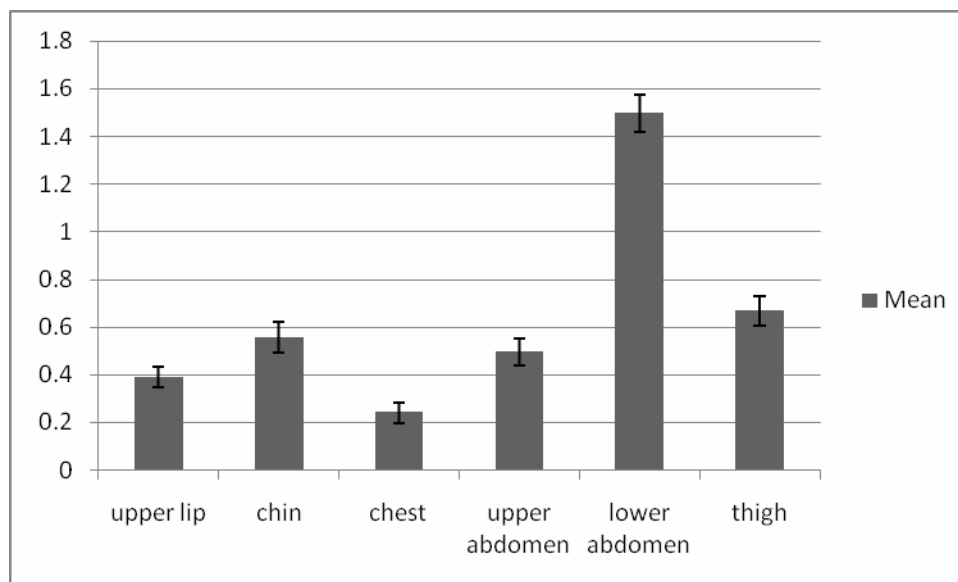


Figure 7. Average contribution of the 6 scored body parts to total score. The lower abdomen, followed by the thighs were highest in both locations.

### Multiple Regression and Effect Tests

Effect of Individual factors					
Source	Nparm	DF	Sum of Squares	F Ratio	Prob > F
Tribe	2	2	64.64014	3.2774	0.04
Location	1	1	64.97742	6.6268	0.0108
Age	1	1	56.52342	5.7373	0.0176
B.M.I	1	1	4.593591	0.4531	0.5017
Cycle regularity	1	1	0.158678	0.0156	0.9007
Hormone use	1	1	56.04753	5.6875	0.0181

Table 8. Effects of tribe, location, age, B.M.I, cycle regularity and hormone use as individual factors.

Only tribe, location, age and hormone use had significant effects on total score when considered as individual predictive factors. However in both locations, the number of women on hormonal medications were few (Table 7) and comparable. Time spent in the U.S.A was not an independent predictor of total score ( $P= 0.388$ ) for the women in both location. The women on hormonal medications, in this case mostly different types of oral contraceptives, had lower average total scores than women who were not taking hormonal medications.

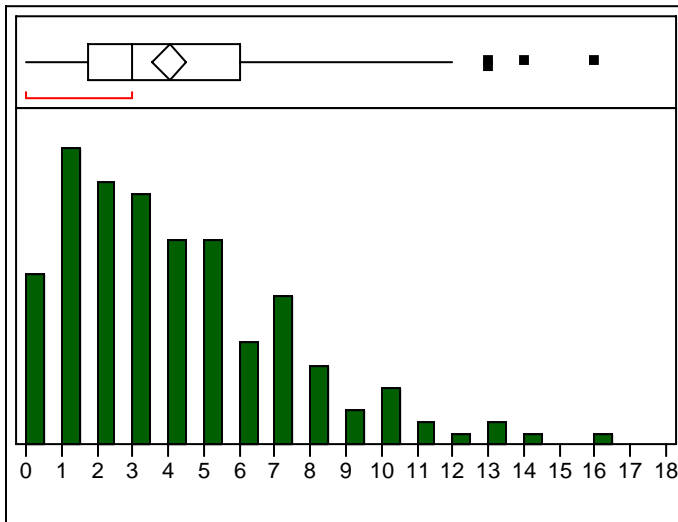


Figure 8. Total mF-G score distribution of women who denied hormone use.

On the other hand, women who were on hormonal medications, though few, had a median score of 1, and less than 10% had a total score of 6 or more. Mean total score was  $2.11 \pm 1.37$  (S.E.M 0.57)

The median scores for women not on hormonal medications was 3, the maximum score was 16 and 25% of them had total scores that were 6 or greater. Mean was  $4.02 \pm 3.2$  (S.E.M= 0.25)

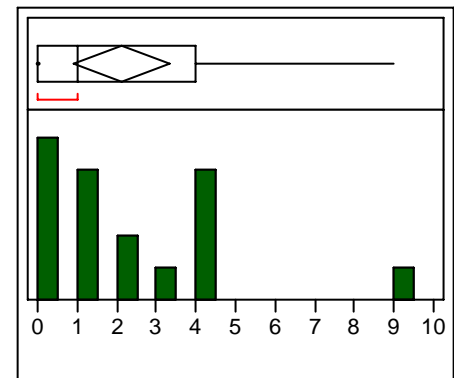


Figure 9. Total mF-G score distribution of women on hormonal medications.

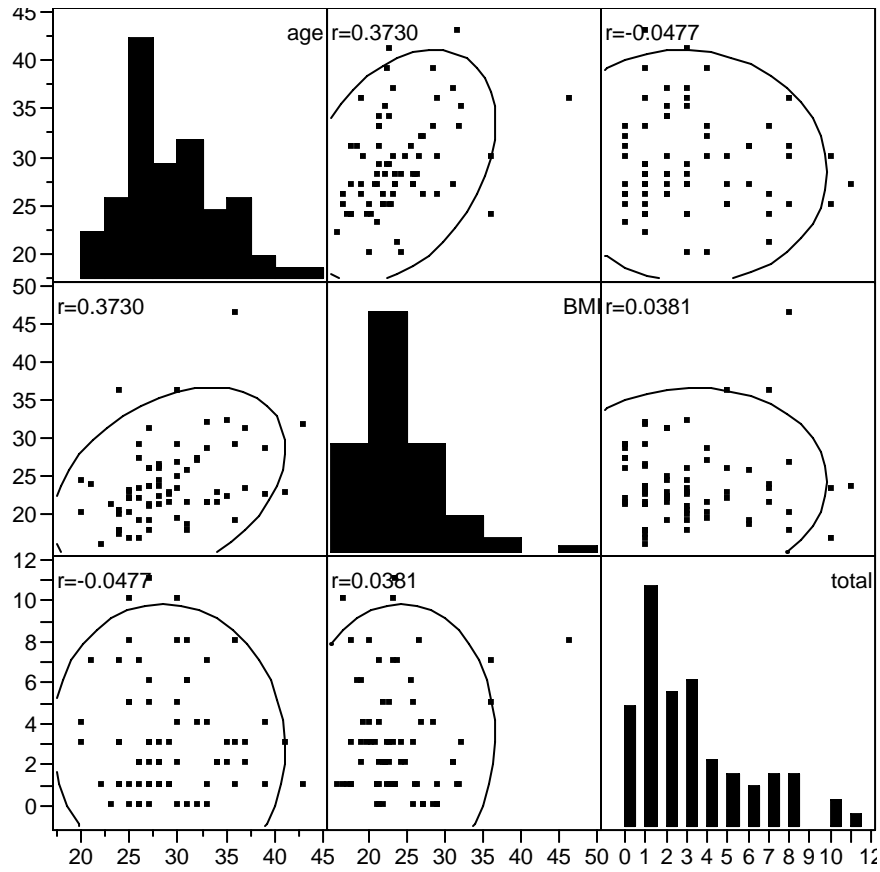


Figure10. Correlation between age, B.M.I and total scores of the women residing in Nigeria

In Nigeria, there was a positive correlation between mF-G score and B.M.I but a negative correlation of total score with age. (Figure 10). With women residing in the U.S.A, there was mF-G score was negatively correlated with both age and B.M.I (Figure 11).



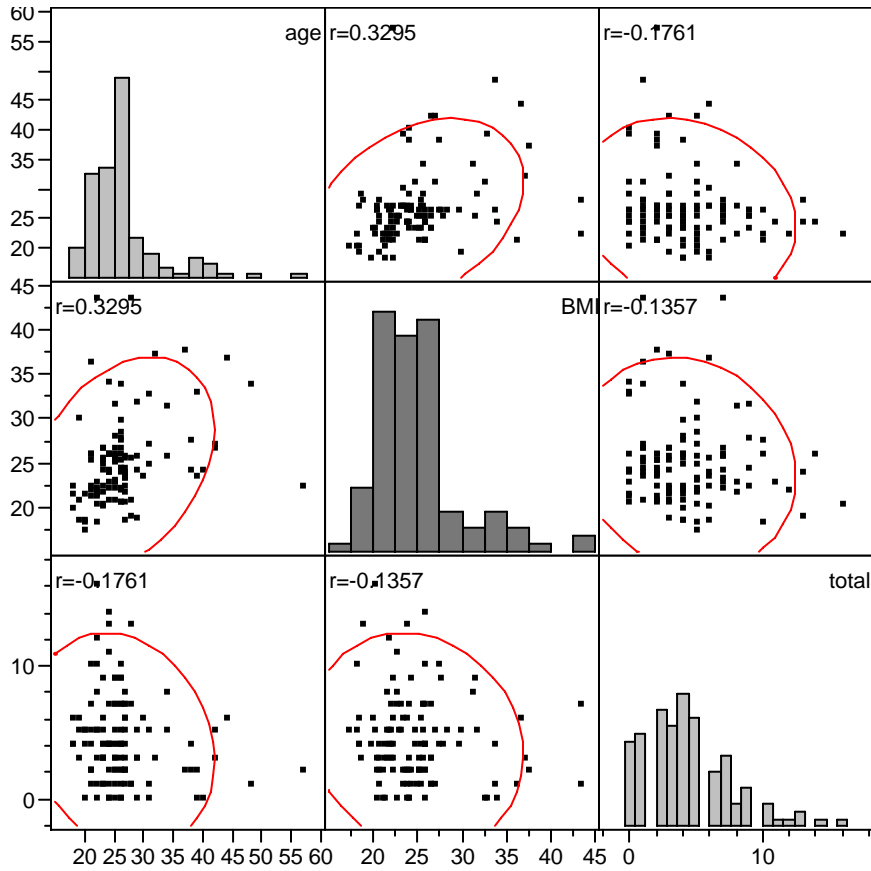


Figure 11. Correlation between age, B.M.I and total scores of women living in Nigeria

### Combined Effect Tests

The following tables show the results of the multiple regression model when several variables are evaluated simultaneously.

Source	Nparm	DF	Sum of Squares	F Ratio	Prob > F
Age	1	1	35.837531	3.9409	0.0487
Hormones	1	1	74.487406	8.191	0.0047
Tribe	2	2	60.933223	3.3503	0.0373
Location	1	1	50.26592	5.5275	0.0198

Table 9a. Effect tests of the most significant factors.

Hormone use was the most significant predictive factor followed by location, tribe and age respectively.

Source	Nparm	DF	Sum of Squares	F Ratio	Prob > F
Age	1	1	29.635867	3.1324	0.0785
Tribe	2	2	56.319206	2.9763	0.0535
Location	1	1	43.079331	4.5533	0.0342

Table 9b. Effect tests of age, tribe and location

Source	Nparm	DF	Sum of Squares	F Ratio	Prob > F
Age	1	1	25.50264	2.7933	0.0964
Tribe	2	2	63.163515	3.4592	0.0336
Location	1	1	52.988156	5.8039	0.017
Hormones	1	1	73.172233	8.0146	0.0052
B.M.I	1	1	2.759328	0.3022	0.5832

Table 9c. Effect tests of age, tribe, location, hormone use and B.M.I

Source	Nparm	DF	Sum of Squares	F Ratio	Prob > F
Oligomenorrhea	1	1	0.1269275	0.0125	0.9113
B.M.I	1	1	4.5618403	0.4475	0.5044

Table 9d. Effects of cycle regularity and B.M.I

Source	Nparm	DF	Sum of Squares	F Ration	Prob >F
B.M.I	1	1	7.61066601	0.803427	0.371288
Age	1	1	13.0724578	1.380006	0.241678
Location	1	1	53.1468204	5.610494	0.018931
Tribe	2	2	63.0439422	3.327647	0.038135

Table 9e. Effect tests of B.M.I, age, location and tribe

*Distribution Plots*

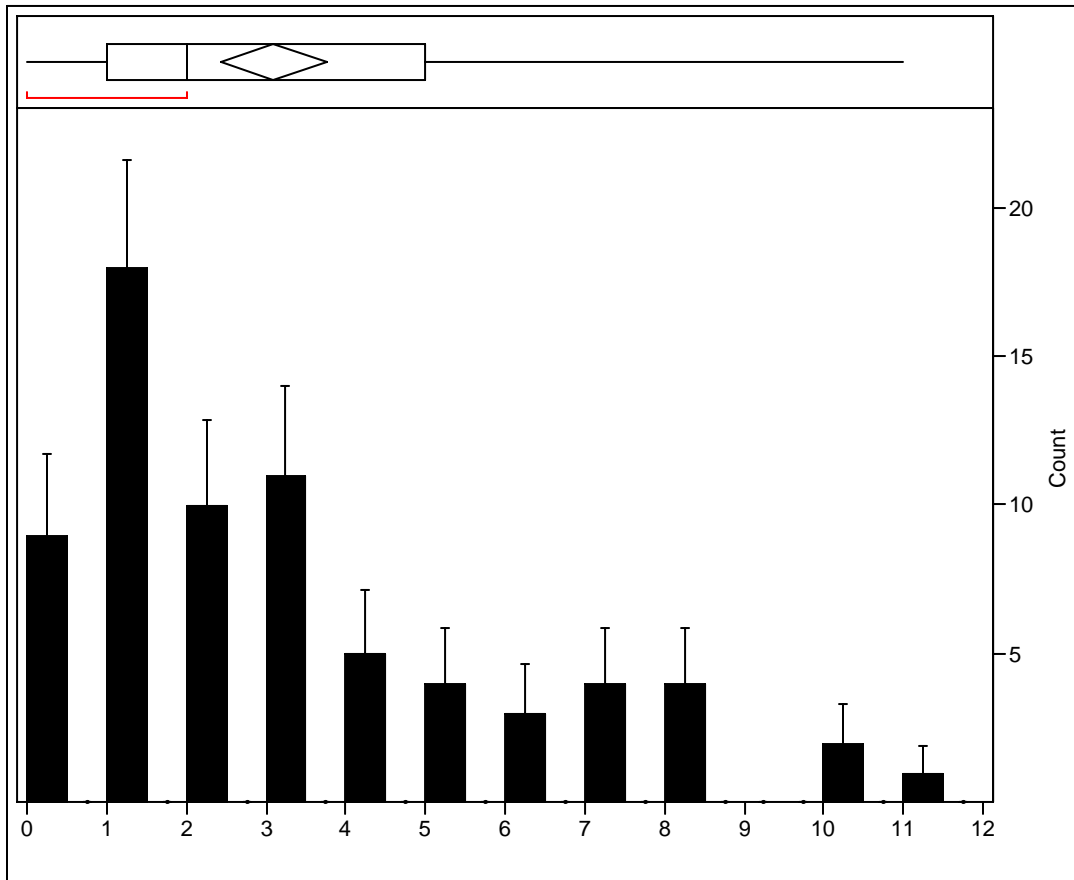


Figure 12. Distribution of mF-G scores of women living in Nigeria

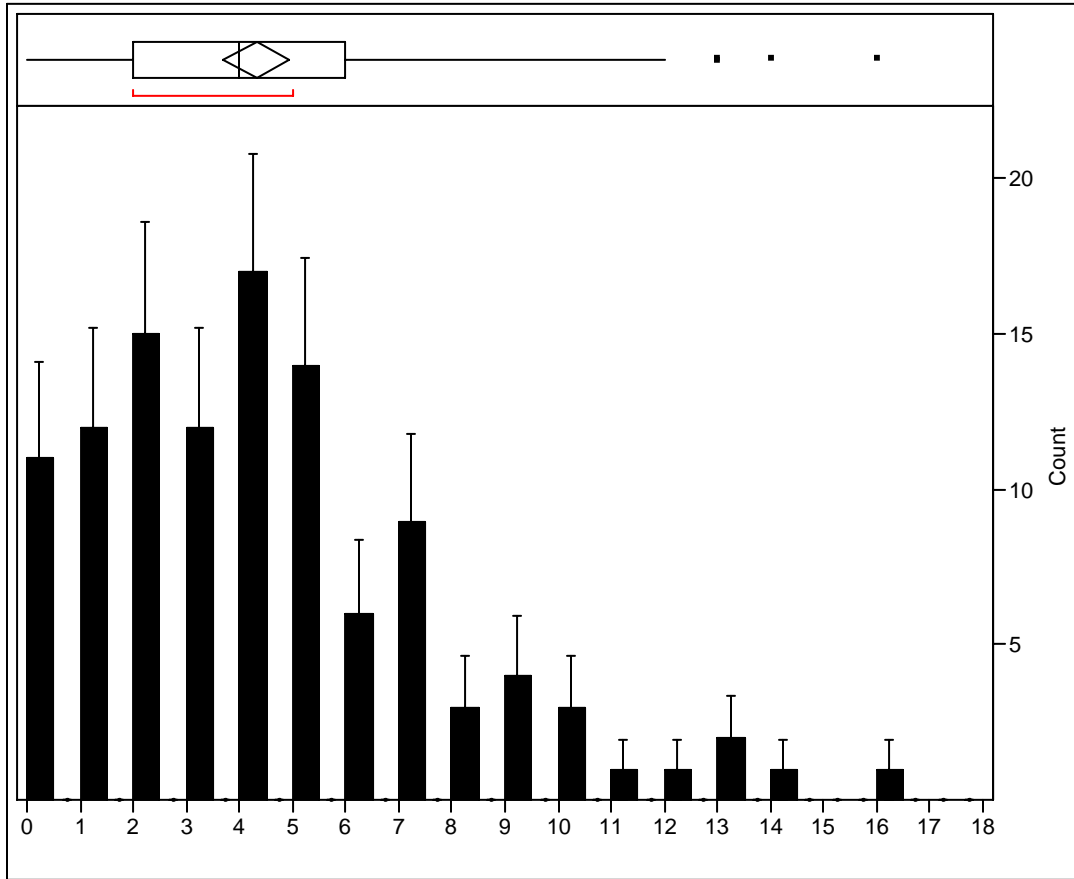


Figure 13. Distribution of mF-G scores of women living in the U.S.A

## Discussion

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The results show a significant difference in the rates of hirsutism between genetically similar women in dissimilar environments after correcting for age and B.M.I. There are many possible reasons for the observed difference.

The women from the U.S.A may have frankly higher levels of androgen, more sensitive ARs or lower rates of degradation/ clearance of the principal androgens. It is unlikely that the women residing in the U.S.A developed a different type of 5 $\alpha$ - reductase isozyme on migrating to the U.S.A, however, is it possible that they may have increased levels of 5 $\alpha$ - reductase metabolites due to other mechanisms, for example through environmental/toxicological effects such as diet or through topical cosmetics. The difference may also be caused to increased steroidogenesis in the adrenals possibly in relation to stress.

As for the diseases that constitute the differential diagnosis of hirsutism, it is possible that some of the subjects in this study have NCAH. However, with the low incidence in the black population and the relatively small number of participants in the study, this likelihood is very low. There is low likelihood of HAIRAN syndrome as the B.M.I of the women in Nigeria did not significantly differ from the women that live in the U.S.A. It was expected that the women in the U.S.A would have a higher average B.M.I because women who live in Nigeria would be expected to be more physically active than women residing in the U.S.A. Perhaps, due to the method employed in collecting data, we have selected for a certain type or class of woman. The average

participant in Nigeria lives in the city. She has a degree from a tertiary institution, has the financial means to afford the internet, or works for a company (usually a multi-national) that can provide internet access at work and probably works at a sedentary (office) job. Furthermore the level of physical activity in urban areas in Nigeria has decreased considerably because many people can now afford automobiles. Not only that, almost all places are now accessible via 'okada' which are motor scooters used for transport. The average person does not have to walk as much. Also, the women residing in Nigeria who took our study are also probably able to afford food with higher fat content, including foods from the fast food industry, one of the fastest growing segments of industry in Nigeria today.

As for the possibility that the women residing in the U.S.A are exposed to exogenous androgens, there is the occasional athletic woman who wants to improve lean muscle mass by body building and anabolic steroid use, but I doubt any of the women in this study fits that profile. The possibility of topical exposure from male partners using topical androgens exists since the U.S.A offers easier access to topical androgens via the internet and a more reliable postal system. Also related to topical exposure are hormonally active compounds in topical preparations and personal care cosmetics. A common practice among people of African descent is skin lightening (otherwise known as 'bleaching') using mostly topical glucocorticoids and/or hydroquinone. One documented side effect of skin lightening is hypertrichosis<sup>32</sup> amongst many more serious ones (e.g. cushingnoid features). This could have been mistaken by some of our subjects for hirsutism. There is no way to know which of the women bleach, however there seems to be no reason why Nigerian women living in the U.S.A may be more likely to 'bleach'

than the women in Nigeria. Besides, the women in the study are most likely well educated and are likely to know the deleterious side effects of 'bleaching'.

The most plausible source for steroid ingestion would be as part of a regular diet. Environmental androgens can act as precursors of naturally occurring biologically active androgens testosterone (T) and dihydrotestosterone (DHT) or result from anabolic steroid use in the livestock industry<sup>30</sup>.

Nigerians, by culture and upbringing are carnivores. It's hard to find a Nigerian vegetarian. Most Nigerians consume beef on a daily basis. Poultry, goats, sheep and turkey are mostly reserved for special occasions. However, with the rise of the fast food industry, poultry is becoming commonplace too. Meat is generally more costly than fresh vegetables; however, the average Nigerian family finds it more affordable to eat beef, not chicken. Meat constitutes a small part of the diet and is usually eaten at lunch and very rarely at dinner. That is to say, even though meat is consumed daily, it is consumed in small pieces/portions at a time. Frozen fish, which is much cheaper than fresh, especially mackerel (known as 'the corpse of Lagos') is also a regular part of many diets. Breakfast typically consists of a source of starch: fermented corn or millet gruel, bread, or yam, eaten with fried bean cakes, steamed ground beans (sort of like tamales but made of beans) or a tomato based sauce. It rarely includes meat, but may have some fish. The amount of meat eaten with every meal is considerably smaller than the portion of meat included with meals in the U.S.A. Butter and other dairy products such as cheese are consumed mostly by people of high socioeconomic class and are not a consistent part of the middle class diet. The exception is in Northern Nigeria where Hausa and Fulani women make curds from cow milk and drink fresh cow milk from their herds. The



change in diet when a woman moves from Nigeria to the U.S.A is therefore quite significant. She will consume more saturated fat, less fiber, more meat, more dairy products and a significantly larger portion size.

An Italian randomized case-control study on post menopausal women, the DIANA study, examined the effects of change in diet on the hormonal profile of 312 women with high plasma levels of T. The intervention group reduced their intake of meat, eggs and dairy products; increased their consumption of soy based products, substituted whole grain products for refined carbohydrates and reduced their intake of cooking fat and salt. The study found that the interventional group significantly reduced their weight, B.M.I, WHR, T, E<sub>2</sub> and increased their SHBG compared to controls. The changes were no longer significant after correcting for weight change, which showed that the observed differences may be due to weight loss<sup>46</sup>. As such, changing diets may as well explain some of the difference observed in our study.

In the U.S.A the use of natural and synthetic hormones is permitted in livestock, but not in Nigeria. Though poultry farming has been modernized in many areas, cattle-rearing is still practiced mainly by the Fulani tribe in northern Nigeria as it has been done for centuries<sup>31</sup>



Figure 14. Red Fulani (Rahaji) cattle grazing on open land, green grass; treeless hills behind. Mambilla Plateau, Nigeria. Copyright and Credit: www.tropix.co.uk / D. Davis

The Fulani are nomadic cattle herders, moving often to find pasture and water for their herds. Many live agrarian and subsistence lives; they do not have the financial means, nor the technical knowhow to administer hormones. Market ready cattle are transported live (by road) all over the country for slaughter and sale in regional meat markets.

The first steroid hormone used after approval by FDA in beef and sheep was diethylstilbestrol (DES) in 1954. It was banned in 1979 due to its carcinogenic potential. Since 1956, a number of synthetic and natural hormones have been approved for use including estradiol benzoate (EB) in 1956, melengestrol acetate in 1968, zeranol in 1969, trenbolone acetate in 1987, and bovine somatotropin in 1993 (for lactating cows). Testosterone was first use in concert with EB in 1958<sup>32</sup>. Hormones now commonly used in North America for raising livestock include synthetic steroids such as zeranol, trenbolone acetate, and melengestrol acetate and the naturally occurring ones such as estradiol 17 $\beta$ , testosterone, progesterone and bovine growth hormone<sup>33</sup>. The effects these steroids have on human consumers have been debated for a long time. In

fact, invoking the precautionary principle, the European Union banned both the use of growth promoting hormones in meat and the importation of hormone treated meat from the U.S.A and Canada<sup>32</sup>.

The evidence for interference of normal reproductive processes by xenobiotics used in raising livestock is not well established. Trenbolone acetate (TbA), a semi-synthetic androgen precursor, widely used in raising livestock to promote increase in muscle mass<sup>34, 35</sup> is also a potent anti-glucocorticoid and displays a high affinity for the progestin receptor in pigs<sup>30</sup>. The anabolic effect of TbA is 8-10 times stronger than testosterone<sup>36, 37</sup>. It is hydrolyzed into 17 $\alpha$ - and 17 $\beta$  trenbolone (TBOH) *in vitro*. 17 $\beta$  trenbolone is about as potent if not more potent than DHT in acting as an AR agonist<sup>36</sup>. The anabolic potency of the 17 $\alpha$  isomer is only about 5% of the 17 $\beta$  isomer. Studies have shown that these chemicals along with other pharmaceuticals in groundwater runoff or effluents from feedlots disrupt endocrine function in the wild<sup>30</sup>. In a study to determine the levels of TbA in the environment after use as growth promoters in livestock, the 17 $\beta$  isomer was found to have a half-life of 257 in liquid manure. Compared to liquid manure, the concentration of both isomers were 5-70 times higher in solid dung before storage<sup>37</sup>. In tissues, TbA metabolites bind with remarkable affinity to proteins and undergo biliary excretion. 90% of the TbA in implants given to heifers in one study could not be extracted with commonly used organic solvents suggesting that it was either water soluble or insoluble tissue-bound residue<sup>38</sup>.

Trenbolone (TBOH) resulting from the hydrolysis of TbA is the main metabolite found in meat and organs of treated cattle. Unchanged TbA can only be detected in fatty tissue<sup>35</sup>. The levels of 17 $\beta$ TbOH in uncooked bovine tissue in ascending order are

muscle, liver, kidney, and fat. Unlike T,  $17\beta$ -TbOH cannot be aromatized to estrogen and is not reduced by  $5\alpha$  reductase<sup>33</sup>. This is significant because non-muscular parts of the animal are used in many Nigerian delicacies, so the average Nigerian in the U.S.A may consume more offal, and by so doing, more TbA, than most.

Safe concentrations of T and  $17\beta$ -TbOH in human beings was determined by the USDA to be an exposure less than 1% of the daily synthesis in pre-pubertal human females and males respectively. For  $17\beta$ -TbOH this translates to a daily consumption of 102ng<sup>33</sup>. Trenbolone residues in meat from implanted cattle range from 0.01 to 0.3 mg/kg in most cases<sup>39</sup>. The level of TbA detected in livestock tissue is inversely proportional to the number of days, post implantation, preceding the slaughter of the animal.

Since TbA can accumulate in fatty tissue unchanged, and its metabolite  $17\beta$ -TbOH has a half life of about 8 months in the environment, it is possible that women in the U.S.A not only ingest TbA in meat, but also from the environment (in water). With such environmentally stable active metabolites- detectable for almost 8 months - and the ability of fat to serve as a TbA reservoir, there is the possibility of an accumulative effect. It would not be too far-fetched to suggest that women who consume meats so treated are at risk of accumulating increasingly physiologically significant amounts of this potent metabolite in fat especially since they will likely gain weight in the U.S.A. This could be likened to an endogenous TbA 'patch' steadily releasing low levels of  $17\beta$ -TBOH in the women who live in the U.S.A.

One argument against this hypothesis is the difference in routes of administration and clearance in humans and other mammals. In human meat ingestion, the route is oral and may subject the hormone to break-down by digestive enzymes; whereas, TbA in livestock is administered subcutaneously. One study showed that a dose of radioactively labeled trenbolone subcutaneously administered to a human volunteer was mostly (63%) excreted in the urine during the first 72 hours, with over half of the radioactivity present in glucuronides<sup>39</sup>, whereas, excretion in cows and rats are primarily biliary and fecal.

The significance of these findings extends beyond mere aesthetics. Hyperandrogenic women tend to cluster risk factors for reproductive site neoplasia<sup>44</sup>. Androgen excess has been shown to induce polycystic ovaries in female to male transsexuals<sup>45</sup>. Apart from decreased fertility, there is increasing evidence that hyperandrogenic patients may be at higher risk of metabolic and cardiovascular disease. PCOS, a disease characterized by excess androgen, is associated with dyslipidemia (generally reduced HDL) and increased C-reactive protein<sup>29</sup>. Hyperandrogenism is associated with elevated thromboxane B<sub>2</sub> and A<sub>2</sub> levels leading to the potential for increased platelet aggregation and vasoconstriction<sup>44</sup>. Lastly, hyperandrogenic women are predisposed to the accumulation of visceral fat typical of men. In a study of 10, non-obese, female-to-male transsexuals that had been ovariectomized receiving 250mg/day testosterone treatment. It was found that after about 3 years and in as little as 1 year after initiation of treatment, the women underwent a redistribution of fat depots with most of the deposition in the abdominal area even though muscle mass increased peripherally<sup>40</sup>. In another study, a case-control study comparing normal weight (B.M.I < 25), premenopausal, infertile women with either anorexia nervosa, primary infertility, or

PCOS with normal controls, women with PCOS showed the highest average serum levels of T and DHEAS. They also had average FDI (fat distribution index = upper body fat mass (kg)/lower body fat mass (kg)) >1 compared to women in other groups who had average FDI < 1 (P < 0.03)<sup>42</sup>. Increased visceral fat may predispose these women to the development of DM II<sup>44</sup>.

Some researchers have postulated that obesity results in increasing levels of circulating androgens and not vice versa<sup>43</sup>. Carmina provides an example of a patient who gained weight due to a stressful life event, increased her B.M.I by almost 6 and converted from ovulatory PCOS to classic PCOS<sup>29</sup>. Women in our study residing in the U.S.A may have conditions that fit into the PCOS spectrum such as ovulatory PCOS. Women with ovulatory PCOS do not have decreased fertility like in classic PCOS but are as likely to present with hirsutism and hyperandrogenemia as those with the classic variant. However, they are more likely to be of normal body weight and have regular menstrual cycles; and their serum insulin and glucose profile and B.M.I are intermediate between that of idiopathic hirsutism controls and classic PCOS<sup>29</sup>. As such, is it possible that the development of PCOS represents a continuum. The condition may start with idiopathic hirsutism, and due to environmental and genetic factors, progress to classic PCOS. It is possible that women already genetically predisposed to PCOS, who change environments from one where food is relatively scarce or at least consumed in moderation to one where food is more plentiful, cheaper and more calorific, combined with less likelihood of remaining physically active, may just be in the environmental milieu necessary to push them along the continuum. However from our results, being

both overweight and oligomenorrheic did not seem to be significant in determining mF-G score (Table 9d).

Carmina's findings also raise the possibility that stress may play a significant role in the observed differences. As discussed earlier, adrenal steroidogenesis may play a role in the development of hirsutism. It is not uncommon in Nigerian gatherings to hear people talk about how much more under stress they feel in the U.S.A than when they were in Nigeria. Many Nigerians here live relatively more socially isolated lives than they lived in Nigeria where family ties and societal connections are very close-knit. They also probably work longer hours and may not take care of themselves as well as they would have given more time on their hands. Chronic stress has been linked to both obesity and increased visceral fat stores and may play a part in the development of DM II. In chronically stressed individuals, hypercortisolemia results in increasing levels of LH and FSH leading to increasing levels of sex steroids, increasing central obesity and a host of other endocrine responses<sup>44</sup> (see figure 15).

This study has many limitations: Since the participants self-score themselves, their evaluations may have been biased. However, directly observing the women may not have been more productive because women use a variety of hair removal techniques. Many lifestyle factors such as smoking, physical activities and diet were not examined. The women were not asked about acne and alopecia, two other manifestations of androgen excess. Furthermore, the total score is largely dependent on what parts of the body are scored<sup>2</sup>. In Nigerian women according to our study, the scores from the upper abdomen were consistently the highest in both locations. In the Hassa study of Turkish women, the thigh was the highest contributor to total score<sup>2</sup>. B.M.I may not have been

sufficient to determine the fat distribution of the participating women; a waist-to-hip ratio may also have been helpful to determine cardiovascular risk. So would levels of LH, FSH and androgens. To find out the effects of the use of anabolic steroids in livestock, Nigerian immigrants in the UK, where use of anabolic growth aids in livestock is prohibited, could have been included. Ultrasound of the ovaries may have helped in ruling out PCOS and clarifying the reasons for the differences we observed.

In summary, there are many plausible reasons why genetically similar women in these two different environments exhibit a differential rate of hirsutism. Further research would be necessary to identify the most likely reasons.

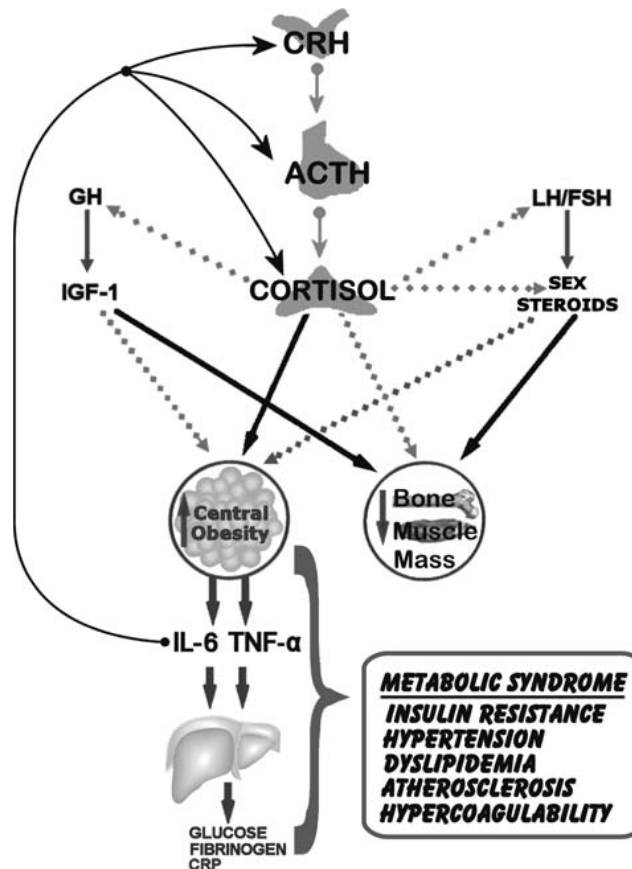


Figure 15. Schematic showing that stress may affect the secretion of sex hormones and central obesity. Schematic representation of the detrimental effects of chronic stress on adipose tissue, bone, and muscle metabolism, that may lead to clinical manifestations of the metabolic syndrome. Chronic HPA activation favors visceral obesity and lean body (muscle and bone) mass reduction. Hypersecretion of TNF- $\alpha$  and IL-6 is proportional to the accumulated adipose mass and induces the production of acute-phase reactants by the liver.



Reciprocally, the proinflammatory cytokines further stimulate the HPA axis activation, thus, forming a deleterious vicious cycle. CRH = corticotropin-releasing hormone; ACTH = adrenocorticotropic hormone; LH = luteinizing hormone; FSH = folliclestimulating hormone; GH = growth hormone; IGF-1 = insulin-like growth factor-1; TNF- $\alpha$  = tumor necrosis factor- $\alpha$ ; IL-6 = interleukin-6; CRP = C-reactive protein. Stimulation is represented by solid lines and inhibition by dashed lines. Ann. N.Y. Acad. Sci. 1083: 77-110 (2006). C\_2006 New York Academy of Sciences.

## Conclusion

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The regulation of hair growth in the human is both a fascinating and complex process. The results of this study suggest that changes in environmental factors of the women who live in the U.S.A may be responsible for observed differences in rates of hirsutism between Nigerian women in the U.S.A and the ones living in Nigeria. Having limited the possible contribution of genetic factors, environmental or lifestyle factors remain the most likely causes. Identifying the etiology of hirsutism involves ruling out several disease states involved with the regulation of sex hormones, adrenal function, and thyroid function. The most likely etiology epidemiologically is hyperandrogenism. The observed difference may not be trivial because of the association of hyperandrogenism with increased risk of cardiovascular diseases and neoplastic risk. The safety of the use of anabolic hormones in livestock needs to be re-examined as they may represent a reservoir of exogenous androgen. Stress is a factor in the development of obesity, hypercortisolemia, and possibly PCOS spectrum disorders. The observed changes may also be attributable to increased levels of stress.

It would be fascinating to compare the rates of PCOS in vegetarians to omnivores or the effect of switching from an omnivorous to a carnivorous diet on the progression of PCOS.

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