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REVIEW



## Revisiting the physiological role of androgens in women

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### ABSTRACT

**Introduction:** Extensive research underlines the critical functions of androgens in females. Nevertheless, the precise mechanisms of their action are poorly understood. Here, we review the existing literature regarding the physiological role of androgens in women throughout life.

**Areas covered:** Several studies show that androgen receptors (ARs) are broadly expressed in numerous female tissues. They are essential for many physiological processes, including reproductive, sexual, cardiovascular, bone, muscle, and brain health. They are also involved in adipose tissue and liver function. Androgen levels change with the menstrual cycle and decrease in the first decades of life, independently of menopause.

**Expert opinion:** To date, studies are limited by including small numbers of women, the difficulty of dosing androgens, and their cyclical variations. In particular, whether androgens play any significant role in regulating the establishment of pregnancy is poorly understood. The neural functions of ARs have also been investigated less thoroughly, although it is expressed at high levels in brain structures. Moreover, the mechanism underlying the decline of dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) with age is unclear. Other factors, including estrogen's effect on adrenal androgen production, reciprocal regulation of ARs, and non-classical effects of androgens, remain to be determined.

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### KEYWORDS

Androgens; female physiology; fertility; hormones regulation; reproduction

## 1. Introduction

Androgens (from the Greek 'andro,' meaning male or man) are traditionally considered male sex steroid hormones responsible for the maintenance of male characteristics, while knowledge of roles of androgens in women is limited. However, it is now established that they play essential roles in women's physiology and are the most abundant sex hormones in females. Considering pg/ml as a unit of measurement, in women of reproductive age, while estrogens vary from 50 to 300, androgens and their precursors circulate in considerably greater levels: testosterone around 400, androstenedione around 2000, DHEA around 5000 [1].

Furthermore, several studies show that androgen receptors (ARs) are broadly expressed in several female tissues (urogenital tissue, mammary gland, nervous systems, bone, cardiovascular system, adipose tissue, and liver), where they mediate crucial functions and until recently were thought to be only targets of estrogen.

The limiting factors contributing to this 'knowledge gap' are the lack of more accurate laboratory methods for dosing androgens and the uncertainty of age and gender-specific reference range.

This review aims to highlight the most recent findings on the role of androgens in female physiology, which is to have a firm basis for investigating clinically relevant

situations of androgen insufficiency or excess throughout a woman's life (childhood, reproductive age and menopause).

Hyperandrogenism is a heterogeneous group of disorders characterized by elevated androgen levels that exhibit a typical phenotype. Signs and symptoms of excessive androgen secretion in women include hirsutism, acne, seborrhea, androgenic alopecia, and menstrual disorders [2].

The most common hyperandrogenic disorder in women of reproductive age is polycystic ovary syndrome (PCOS). The latter is a condition caused by an imbalance of sex hormones that can lead to menstrual cycle changes, ovarian cysts, difficulty conceiving, and other health changes, with approximately an 80–85% prevalence among women with androgen excess [3]. Other less frequent conditions include idiopathic hirsutism, androgenic drug intake, Cushing's syndrome, non-classical congenital adrenal hyperplasia (NCAH), acanthosis nigricans (HAIRAN), ovarian or adrenal androgen-secreting neoplasms (ASN), and hyperprolactinemia [4,5].

Studies on women suffering from gender dysphoria (female to male trans-sexual subjects) demonstrate the relevance of androgen effects in women: the long-term administration of androgens is associated with cardiovascular risk, malignancies, mental health problems such as depression and anxiety. However, future studies should aim to explore the long-term outcome of androgens treatment in transgender women [6].



### Article highlights

- Despite being the most abundant sex hormones in women, the potential role and precise mechanism of action of androgens in women is poorly understood
- The significant factors that contribute to this 'knowledge gap' include a) the difficulty of dosing androgens with standard laboratory methods, b) the difficulty of taking into account the diurnal and cyclical variations in androgen levels for blood sampling, and c) the uncertainty of what is considered normal in serum androgen levels in women of different ages
- Several studies show that androgen receptors (ARs) are broadly expressed in several female tissues (urogenital tissue, mammary gland, nervous systems, bone, cardiovascular system, adipose tissue, and liver), where they mediate crucial functions and, until recently, were thought to be only targets of estrogen
- Androgen levels change with the menstrual cycle and decrease in the first decades of life, independently of menopause
- Amongst the mechanisms that need further investigation, is the potential role of androgens in regulating pregnancy. Another topic to investigate is the function of AR in several structures of the CNS involved in cognitive processes. Furthermore, the molecular mechanisms behind decreasing DHEA and DHEAS levels with advancing age are also unclear
- Other factors, including estrogen's effect on adrenal androgen production, reciprocal regulation of ARs, and non-classical effects of androgens, remain to be determined

Today we also know that not only an excess of androgens, but also a reduction in androgen levels can cause various pathological conditions: a hypoandrogenic state is detrimental to cardiovascular, mental and sexual health. In this regard, the Endocrine Society recommends using testosterone in women only in the case of HSDD (hypoactive sexual desire disorder) [7]. However, the long-term safety of treatments with testosterone remains to be evaluated.

Androgen insufficiency, affecting not only postmenopausal women but also young women (for example when using

contraceptives), is an increasingly debated topic in recent years, especially for the absence of specific cutoffs for female hypoandrogenism.

## 2. Synthesis and androgen producing organs in women

### 2.1. Synthesis of androgens

Androgens, like all steroid hormones, originate from cholesterol, and they are also called 'C19 steroids' as they have 19 carbon atoms. Androgens can be divided, based on biosynthetic pathways, into two groups:

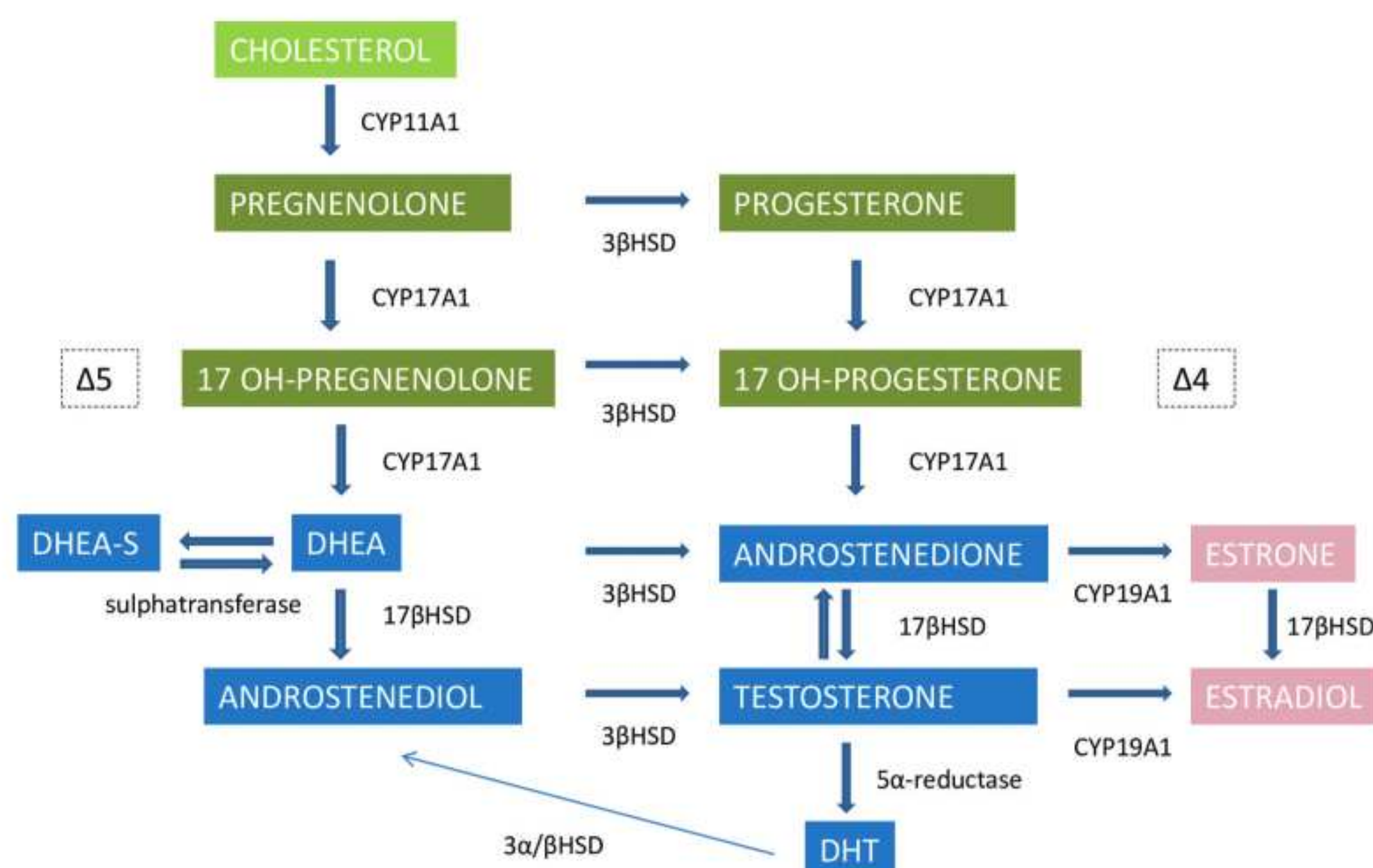
- C19- $\Delta$ 5-steroids derived from  $\Delta$ 5 pregnans. The progenitor of C19- $\Delta$ 5-steroids is dehydroepiandrosterone (DHEA) and its sulfate, dehydroepiandrosterone sulfate (DHEAS), which are interconverted by the steroid sulfatase (sulfotransferase).
- C19- $\Delta$ 4-steroids derived from  $\Delta$ 4 pregnans: androstenedione (A4) and testosterone (T).

The biosynthesis of androgens requires different enzymatic steps in succession [8,9], which we have summarized in Figure 1.

Based on their metabolic activity, there are three groups of endogenous androgens: precursors androgens (DHEA, DHEAS, and androstenedione), testosterone and its metabolites (such as dihydrotestosterone-DHT and androstenediol).

Testosterone and androstenedione are 'aromatizable androgens.' They are metabolized by aromatase to estrogens (estradiol-E2 and estrone-E1, respectively), which then interact with estrogen receptors (ER).

The enzymatic activity of aromatase and the conversion of circulating androgens into estrogens is clinically significant in women and men with aromatase deficiencies, and its regulation in tissues needs to be elucidated [10,11].



**Figure 1.** Biosynthesis and metabolism of androgens. Abbreviations: 3βHSD: 3β-hydroxysteroid dehydrogenase; 17βHSD: 17β-hydroxysteroid dehydrogenase; CYP11A1: P450ssc, 20,22 lyase; CYP17A1: P450c, 17,20 lyase; CYP19A1: P450 aromatase.



## 2.2. Sources of circulating androgens in women: 'endocrinology' and 'intracrinology.'

In women, the synthesis of androgens takes place in many tissues such as adrenal glands (reticular zone) and ovaries (theca cells of the ovarian follicle) which are considered classical steroidogenic organs. However, many peripheral tissues, including adipose tissue, skin, vagina, endometrial tissue, mammary gland, and nervous systems, are capable of synthesizing androgens [12–16].

While the ovary and adrenal glands contribute less to the amount of circulating active androgen, they produce significant levels of the inactive androgen precursors: DHEA, its sulfate ester DHEAS (only adrenal glands), and androstenedione, which are the most abundant released into the circulation [17].

This androgen production occurs under the pituitary stimulus of luteinizing hormone (LH) and adrenocorticotrophic hormone (ACTH), respectively.

On the other hand, most of the active androgens come from peripheral metabolism/conversion that produces 50% of the circulating testosterone, and this is a critical step for women.

This local control of androgen action by metabolic activation of precursors and subsequent inactivation has been termed '**intracrinology**' and was first conceptualized by Labrie [12,18,19].

The concept of intracrinology also underlines that a substantial amount of testosterone is metabolized from the inactive precursor DHEAS intracellularly in the target tissue, and it is not present in the peripheral blood. Similarly,

circulating concentrations of DHT are low, but this is largely due to local metabolism within target tissues at the site of action.

Different tissues can participate in the modulation of the circulating levels of androgens in relation to the quantity and activity of the enzymes available in the tissue, specifically to the ratio between 5 $\alpha$ -reductase (which transforms testosterone into DHT and androstenediol) and aromatase (which transforms  $\Delta$ 4 androgens into estrogens).




Peripheral tissues are able to metabolize and transform androgens into more or less active or completely inactive metabolites. Moreover, unlike the steroidogenic organs, peripheral tissues are not under the control of LH and ACTH, which are able to modulate enzymatic activity and secretion of a specific steroid in circulation.

The importance of androgen distribution and production in women is schematized in Figure 2, according to Simon JA et al. [20].

## 2.3. Peripheral steroidogenic tissue in women

The synthesis of androgens in women can take place in several peripheral tissues defined as follows:

- **The adipose tissue** is rich in aromatase which transforms  $\Delta$ 4 androgens into estrogens, and it has all the necessary enzymes for the activation of androgenic precursors and their subsequent inactivation for excretion, thereby regulating the local androgenic milieu. In female adipose tissue, aldo-ketoreductase 1C3 (AKR1C3, also

		ENDOCRINOLOGY		INTRACRINOLOGY			
				↓			
		Adrenal gland		Ovary		Periphery	
							
		Pre menopausal	Post menopausal	Pre menopausal	Post menopausal	Pre menopausal	Post menopausal
DHEAS		90%	90%	0%	0%	10%	10%
DHEA		60%	60%	10%	10%	30%	30%
A4		50%	70%	40%	20%	10%	10%
T		25%	10%	25%	50%	50%	40%

**Figure 2.** Sources of circulating androgens and their precursors in pre and post menopausal women. Contribution of the adrenal glands, ovaries, and peripheral conversion to the total circulating DHEAS, DHEA, A4 and Testosterone concentrations during pre and post-menopause. Following menopause, while the contribution of the adrenal glands, ovaries, and peripheral conversion to the total circulating DHEAS and DHEA concentrations remains essentially the same, the ovarian androstenedione contribution decreases from 40% to 20% and the ovarian testosterone accounts for 50% of total testosterone. Values come from Simon's study [20].



named 17 $\beta$ -HSD type 5, HSD17 $\beta$ 5) converts androstenedione to testosterone and interconverts estrogens and androgens [12].

- **Skin** has the capability to produce androgens both de novo from cutaneous cholesterol or using ovarian or adrenal circulating precursors, such as DHEA, through specific enzymatic activities. The pilosebaceous unit expresses key enzymes involved in the sex hormones synthesis, such as CYP11A1, CYP17A1, 3 $\beta$ HSD, and CYP19A1 [13]. However, the main precursor used to produce steroids is adrenal DHEAS. DHEAS is hydrolyzed to DHEA by the sulfatase located in sebaceous glands and dermal papilla cells in terminal hair follicles, whereas the enzymatic activity of 3 $\beta$ -HSD1 converts DHEA into androstenedione, and 17 $\beta$ -HSD3 converts androstenedione in testosterone [13].
- **Vulvovaginal tissue** is an androgen-target organ with the ability to synthesize androgens. It should be remembered that DHEA is transformed into both androgens and estrogens in the vagina [21,22]. A recent study has shown the ability of human vagina smooth muscle cells to synthesize androgens from the upstream precursor, DHEA. Increased expression of pro-androgenic steroidogenic enzymes (HSD3 $\beta$ 1/ $\beta$ 2, HSD17 $\beta$ 3/ $\beta$ 5), 5 $\alpha$ -reductase isoforms, and sulfotransferase mRNAs were detected in the vaginal tissue compared to the ovarian one. In addition, enzymes involved in androgen inactivation were less abundant in the vagina than in the ovaries [14].
- **Endometrial tissue** has a role in the local synthesis of androgens and signaling via intracrine mechanisms within the endometrium [23]. The expression and activity of androgen-metabolizing enzymes within the endometrium may represent a key mechanism for controlling steroid bioavailability within the tissue and regulation of endometrial functions. These enzymes include CYP11A1 and CYP17A1 [24], 3 $\beta$ HSD, that were detected in glandular epithelial cells in proliferative and secretory phase endometrial samples [25], 17  $\beta$ HSD and importantly aldo-keto reductase family 1 member C3 (AKR1C3; also known as 17 $\beta$ HSD5) that is the most efficient enzyme for the conversion of androstenedione to testosterone in the endometrium and it is localized into glandular and luminal epithelial cells throughout the menstrual cycle [26,27], CYP19A1, that is induced upon decidualization in endometrial stromal cells (ESCs). Following the induction of aromatase expression in decidualized ESCs, local estrogens regulate immune-mediated vascular remodeling by altering the function of uterine Natural killer (uNK) cells in early pregnancy [28].

Many functional processes in the endometrium, including cell proliferation, apoptosis, resistance to oxidative stress, and cell motility, are under the control of endocrine and intracrine androgens. Furthermore, processes such as decidualization are influenced by the biosynthetic enzymes of androgens. Thus, androgens can be considered key players during the onset of pregnancy, and androgen-metabolizing enzymes might become

therapeutic targets for the treatment of infertility associated with endometrial dysfunction [15].

- **Mammary gland** expresses enzymes involved in androgenic synthesis [8]. The epithelium lining the acini and ducts of the mammary gland is composed of two layers, an inner epithelial layer and an outer discontinuous layer of myoepithelial cells. By immunocytochemistry, 3 $\beta$ HSD is detected in the epithelial cells of acini and ducts as well as in stromal fibroblasts. Also, immunostaining for type 5 17 $\beta$ HSD gives similar results as those seen for 3 $\beta$ HSD, observed in epithelial, stromal cells, and in blood vessel walls [29].
- **Nervous system.** Neurosteroids, which include DHEAS, testosterone, and their metabolites, are synthesized in the central and peripheral nervous systems (CNS-PNS). Neurosteroids interact with non-sex hormone receptors and are able to influence excitability and neuronal function [16], and their synthesis plays a protective and restorative role in survival and neurodegeneration [30].

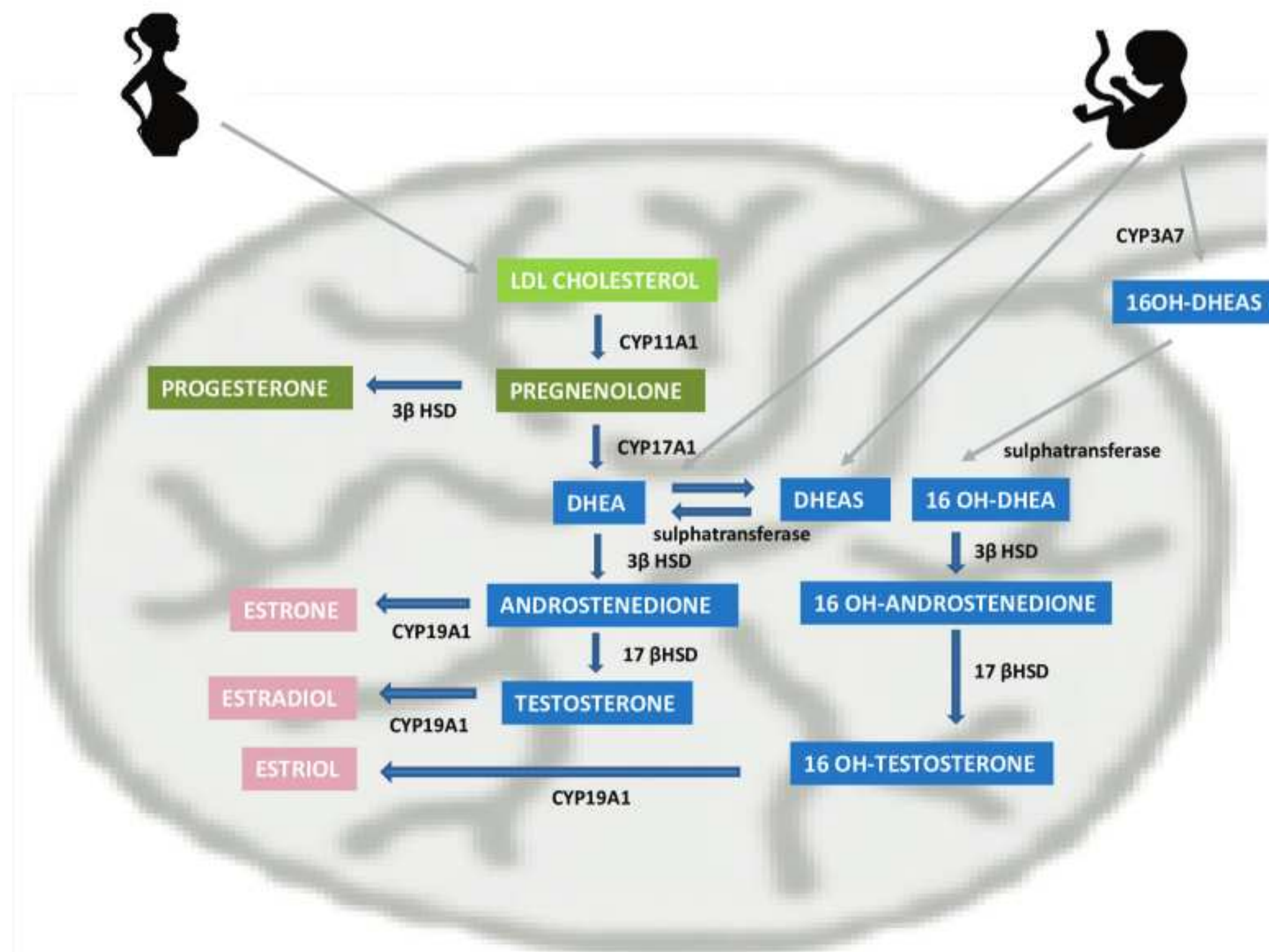
#### 2.4. Androgens biosynthesis in human placenta

Since the discovery of the fetoplacental unit [31], many previously unknown roles of the placenta have been investigated. The placenta is the major site of steroid hormone synthesis during pregnancy and is considered a 'classical steroidogenic organ,' along with the adrenal glands and ovaries. The primary role of the placenta is to synthesize and produce estrogen and progesterone, both necessary for the maintenance of pregnancy. It is known that androgens are the substrates for the synthesis of estrogen, thus having a fundamental role in placenta functions (Figure 3).

The placenta uses two pathways for androgen synthesis. The first pathway involves the use of androgenic precursors of both maternal and fetal origin, mainly DHEAS and DHEA, that are then converted into androstenedione through 3 $\beta$ -HSD type 1 (3 $\beta$ -HSD-1) and then into testosterone through 17 $\beta$ HSD. These androgens are then aromatized into estrone (E1) and estradiol (E2), respectively, by CYP19A1 [32]. Furthermore, the fetal liver is able to produce 16-OH-DHEAS (through the CYP3A7) which, returning to the placenta, undergoes various enzymatic steps that lead to the production of estriol (E3) [24]. In fact, more than 90% of placental E3 derives from 16-OH-DHEAS of fetal origin [24].

The second pathway, recently discovered, begins with the use of maternal cholesterol, which, thanks to the gene expression of CYP17A1, leads to the placental synthesis of DHEA [33–35]. In particular, cholesterol is transferred to the mitochondria, where it is transformed into pregnenolone, thanks to CYP11A1. While the 3 $\beta$ -HSD type 1 (3 $\beta$ -HSD1) changes and modifies pregnenolone to produce progesterone, the placental CYP17A1 modifies pregnenolone to produce DHEA. Therefore, during pregnancy, sex steroid production is under the control of CYP19A1/CYP17A1 gene expression. The increased expression of CYP19A1, compared to CYP17A1, disfavours the accumulation of androgens in the placenta,





**Figure 3.** Androgens biosynthesis in human placenta. The human placenta utilizes both fetal adrenal precursor (mainly DHEAS) and maternal cholesterol to synthesize androgens (testosterone and androstenedione). These are then aromatized to estrone (E1) and estradiol (E2), respectively, by CYP19A1. In addition, the fetal liver is able to produce 16-OH-DHEAS (through the CYP3A7), which is the precursor of estriol (E3).

protecting the fetus from the adverse effects of these hormones during pregnancy. In fact, high levels of androgens during pregnancy are associated with preeclampsia, gestational diabetes mellitus, and PCOS [36].

### 3. Body circulation: androgen binding proteins

Steroids circulate in the blood in essentially three forms: free, loosely bound to albumin, and tightly bound to specific binding globulins, specifically for androgens, sex hormone-binding globulin (SHBG) [20].

Albumin binds androgens with limited specificity and low affinity. By contrast, SHBG binds androgens with high affinity and specificity and plays much more dynamic roles in controlling access of androgens to target tissues and cells.

According to the 'free hormone hypothesis,' only the free testosterone fraction is the biologically active fraction, able to diffuse into the cell and exert a biological effect, while the SHBG-bound steroids are not considered bioavailable [37]. Soon after, this hypothesis was questioned by various studies, which reported that SHBG-bound testosterone might be internalized into the cell through an endocytic process mediated by lipoprotein receptor-related protein-2 (LRP2) encoding for megalin [38].

Furthermore, it has been postulated that in many potential target tissues, including the epididymis, testis, prostate, skeletal muscle, and the liver of rats, SHBG may bind to an 'SHBG receptor' to form a complex that may exert an 'independent biological effect' [39,40]. However, the topic is still debated, and the mechanisms are incompletely understood.

Plasma proteins also regulate the non-protein-bound or 'free' fractions of circulating steroid hormones that are considered to be biologically active; as such, they can be viewed as the 'primary gatekeepers' of steroid action [41].

The SHBG has a different concentration in men than in women (respectively  $50 \pm 20$  and  $75 \pm 30$  nM/L).

In women, since the circulating levels of testosterone are only 1/10 of those present in men, SHBG binds about 75% and albumin 25%, while only <1% is completely free [42]. Also, the percentage of unbound steroids differs between androgens. Testosterone circulates bound to SHBG; in contrast, their precursors androstenedione, DHEA, and DHEAS are not strongly linked to SHBG [43]. Androgen binding affinities with SHBG do not change with age or menopause. The concentration of SHBG can have an impact on the unbound or bioavailable levels of circulating androgens [43].

Finally, plasma SHBG production by the liver varies during development and different physiological or pathophysiological conditions, and abnormalities in the plasma levels of SHBG or its ability to bind steroids are associated with a variety of diseases [44]. Several hormones can affect the hepatic secretion of SHBG: thyroid hormones and estrogen increase it, while androgens, cortisol, growth hormone (GH), and prolactin (PRL) reduce it [41].

### 4. Mechanism of action of androgens: the androgen receptor (AR), the genomic and non-genomic mechanism of action

Androgens exert their effects via a single receptor protein, the androgen receptor (AR), also known as nuclear receptor



subfamily 3, group C, member 4 (NR3C4) [45]. It is expressed in fetal tissues as early as eight weeks of gestation before an androgenic activity begins and is activated in a ligand-dependent manner [46].

AR-mediated transcriptional action occurs because steroid hormones cross the plasma membrane of target cells, cross the cytoplasm, and bind to the receptor in the nucleus, thereby inducing gene transcription [47–49]. In detail, when the ligand is absent, the AR resides in the cytoplasm; upon binding with its ligand, the receptor dimerizes and interacts with a specific sequence of DNA, leading to translocation into the nucleus, thus activating transcription [50,51].

AR has a modular structure composed of an N-terminal domain (NTD), a conserved DNA-binding domain (DBD), and a C-terminal ligand-binding domain (LBD) [52].

The first interactions between AR functional domains that have been analyzed were the NTD–LBD interaction (N/C interaction) and the dimerization of DBD, while the physiological relevance of LBD dimerization for AR functioning was recently demonstrated [53,54].

Surprisingly, in a recent study on male mice, it was shown that the N/C interactions in the AR are not essential for the development of a male phenotype under normal physiological conditions: the mutated mice show a normal male development, with normal male circulating androgen levels, body composition, and fertility [54].

Furthermore, recent studies have shown that LBD dimerization is crucial for developing of AR-dependent tissues. A mouse model with disrupted dimerization of the AR LBD demonstrated a feminized phenotype, characterized by the absence of male accessory sex glands, and decreased spermatogenesis [53]. *In vitro* studies revealed that the mutation in the LBD dimer interface also affects other AR functions such as DNA binding, ligand binding, and co-regulator binding [53].

The AR gene is located on the long arm of the X chromosome and is composed of eight exons. In exon 1 of the AR gene, a polymorphic CAG repeat sequence encodes traits of the AR transactivation domain [45]. The longer CAG repeat length is negatively correlated with the transcriptional activity of AR. The length of CAG repeats polymorphism results in lower testosterone production, thus influencing sexual function and fertility, cardiovascular risk, body composition, and bone metabolism [55–59].

Hormones can also act through non-genomic effects and interact with protein/receptor/ion channels of the plasma membrane [47,48]. However, the most consistent non-genomic effect of androgen exposure is a rapid change in  $\text{Ca}^{2+}$ , probably resulting from a binding to a cell surface receptor. This rapid androgen receptor-independent effect of androgens on intracellular  $\text{Ca}^{2+}$  has been shown in murine macrophages [60], neuroblastoma cells [61], and rat osteoblasts [62].

Furthermore, among the other non-genomic mechanisms of action, there is the induction of changes in membrane flexibility, the activation of a second messenger pathway, or the interaction with a membrane-bound AR [47].

Finally, as mentioned above, aromatizable androgens (such as testosterone and androstenedione) have a dual mechanism of action, as they interact both with the ARs and, following their aromatization in estrogens, with the estrogen receptor

(ER). Androgen aromatization deficiency or excess is involved in various clinical conditions such as estrogen-dependent breast cancer, metabolism, and bone health [11].

## 5. Target organs for androgens in women

Androgen receptors mediate crucial functions in several female tissues, such as the female genital system (ovary, endometrial tissue, vulvovaginal tissue), breast, skin, bone, muscle, adipose tissue, liver, platelets, blood vessels, immune system, kidney, and nervous system (Table 1).

### 5.1. Female genital system

#### 5.1.1. -Ovary

In addition to being one of the principal organs of steroidogenesis, the ovaries are also the target organ of androgens. Androgens have a crucial role in regulating ovarian function and fertility and in all phases of follicular development and ovulation.

Studies on animals have shown that the administration of androgens increases the expression of AR mRNA in the follicle [63] and is critical for activating of both ovulatory and primordial follicles [64,65].

In AR knock-out mice reduced reproductive abilities have been demonstrated [66,67]. In addition, Sen et al. showed that androgens regulate follicle-stimulating hormone (FSH) increase, leading to the ovulatory process [68].

Finally, some human studies also confirm these results highlighting a stage-specific expression of AR in human follicles [69]. Another study reported that low testosterone levels could cause inadequate ovulatory responsiveness [70].

#### 5.1.2. -Endometrial tissue

Androgens can control the physiological and pathophysiological conditions of the endometrium through AR-mediated pathways and indirectly as precursors of local estrogen synthesis [71]. Studies performed on human and rodent tissues show that AR expression changes significantly during the menstrual cycle [23,72,73]. Moreover, AR is differently expressed in estrogen- and progesterone-dominated proliferative phases. In the first phase, AR is expressed predominantly in stromal fibroblasts of the basal and functional layers. In the second one, AR expression is low in stromal fibroblasts and endometrial epithelial cells. Also, during menses and pregnancy, AR expression is different in endometrial epithelial cells; during menses, AR increases following progesterone withdrawal. In pregnancy, AR is detected in decidual stromal cells and in endothelial cells lining endometrial arteries in first-trimester decidua [74,75].

The different expression of AR mirrors the up-regulation by estrogens and the down-regulation in response to decreasing levels of progesterone [72,73].

Androgens via AR influence dynamic changes in endometrial tissue prior to the onset of the proliferative phase of the normal cycle and during tissue repair after menstruation and pregnancy [76,77].

For instance, androgens have an anti-proliferative effect on endometrial epithelial and stromal cells by antagonizing the bioactivity of estrogens [71].



**Table 1.** Target organs of androgens in women.

Organs	Actions	References
Genital system	<b>Ovaries:</b> Coordinate the ovarian function, stimulate the granulosa cells and oocytes, favoring follicular development and regulation of all phases of the follicular maturation. <b>Endometrial tissue:</b> Regulate the restoration of endometrial tissue integrity before the onset of the proliferative phase of the normal cycle. Induce an anti-proliferative effect in the human endometrium. Regulate the establishment of pregnancy. <b>Vulvo-vaginal tissue:</b> Essential for the integrity of vaginal tissue structure and for the neurovascular processes that regulate arousal and lubrication. They also modulate nociception, inflammation, and mucin secretion within the vagina.	[14,22,66,71,76,77,80,84,85]
Breast	Control breast epithelial growth (cell proliferation) directly by enhancing cellular growth and proliferation or, indirectly through their aromatization to estrogens. They are associated with increased breast cancer risk.	[86–89]
Skin	Regulate the growth of the hair follicle in all its phases, sebum production and secretion, and other physiological effects such as wound healing and cutaneous barrier formation.	[13,91]
Nervous System	Increase neuronal survival, stimulate neuronal differentiation and plasticity, and promote synaptic density and connectivity. In the CNS, they are responsible for regulation of the hypothalamic-pituitary-gonadal axis, reproductive behaviors, modulation of cognition, anxiety and other non-reproductive functions. In the PNS, they have trophic effects on motor neurons including enlargement of cell bodies and dendrites, extended life span, and enhanced recovery from damage.	[16,92–94,98,101,102]
Bone	Influence bone directly via interactions with ARs, and indirectly via binding to ER $\alpha$ and ER $\beta$ being aromatized in 17 $\beta$ -estradiol in adipose or different tissues. AR activation stimulates osteoblast proliferation and the blockade of osteoclast activity, inducing bone formation. Conversely, ER activation inhibits osteoclast proliferation and stimulates their apoptosis, resulting in the inhibition of bone resorption.	[103,104]
Muscle	Increase both the size and strength of skeletal muscle.	[108,109]
Adipose tissue	Induce abdominal and/or visceral adipose tissue accumulation. They may also encourage enlargement of the adipocyte.	[115,116]
Liver	Stimulate the synthesis of lipoproteins (LDL cholesterol) and triglycerides, increase insulin resistance/reduces insulin sensitivity and stimulate the synthesis of coagulation factors such as fibrinogen and ATIII.	[122,123,125]
Vessels and platelet	Induce vasodilatation, acting in both an endothelium-dependent and an endothelium independent way. They inhibit platelet aggregation and this effect is dependent on endothelial NO synthesis.	[126–129]
Immune System	Decrease antibody production, T cell proliferation, NK cytotoxicity, and stimulate the production of anti-inflammatory cytokines (immunosuppressive properties).	[133]
Kidney	It has been postulated for several years that testosterone induces erythropoietin kidney production. More recent studies have shown that the hematopoietic effect of testosterone does not appear to be mediated by stimulation of erythropoietin production	[139,141]

Evidence showed that long-term administration of testosterone and androstenedione in female to male trans-sexual individuals caused glandular atrophy, similar to that observed in post-menopause females [78,79].

Furthermore, androgens play a crucial role in regulating the onset of pregnancy and, specifically, the decidualization process of endometrial stromal cells (ESCs).

Studies in rodents show that insufficiency and an excess of androgens can interfere with embryo implantation [80]. However, in humans, such mechanisms are still poorly studied.

### 5.1.3. -Vulvovaginal tissue

The vagina is both a synthesis and an androgen-target organ. Androgens play an essential role in the differentiation of the vagina and in maintaining trophic and functional actions in postnatal life.

In the vagina, the ubiquitous expression of AR, both in proximal and distal regions, in epidermal keratinocytes and dermal fibroblasts suggests the importance of androgens in maintaining trophism and functionality [29,81].

Reduction of AR expression in vaginal tissue has been shown to induce vaginal morphological changes such as

atrophy, reduction, and thinning of the epithelium, smooth muscle, and collagen fibers [82,83].

It has been shown that testosterone acts not only on the non-vascular smooth muscle, favoring the integrity of the vaginal structures but also on the vascular smooth muscles, regulating the mechanisms of lubrication and arousal. In addition, it is also involved in inflammatory and nociception mechanisms within the vagina [84].

Moreover, DHEA has beneficial effects on the three layers of the vaginal wall (epithelium, muscle, and collagen fiber), and this provides support for the use of androgen therapy in sexual arousal disorders or in genito-urinary syndrome in post-menopausal women [14,22,85].

## 5.2. Breast

Androgens play a crucial role in breast cell proliferation, directly and indirectly, through their aromatization into estrogen [86].

Regarding their direct action, androgens stimulate apocrine mammary cells to increase the epidermal growth factor (EGF) synthesis, which stimulates cell proliferation, activating Erb2



receptors, resulting in the growth of ER-negative/AR-positive tumors [86].

Several studies have shown a positive correlation between circulating androgen levels and breast cancer in postmenopausal women [87–90].

### 5.3. Skin

The skin constitutes a critical peripheral steroidogenic tissue and an androgen-target organ.

ARs are present in sebocytes, keratinocytes, inflammatory cells (mainly macrophages), and fibroblasts. Androgens regulate the growth of the hair follicle in all its phases, sebum production and secretion, and other physiological effects such as wound healing and cutaneous barrier formation [13].

Androgens are the primary regulators of human hair growth. After puberty, they promote the transformation of vellus follicles, producing tiny, unpigmented hairs to terminal ones, forming more prominent pigmented hairs in many areas, e.g. the axilla [91].

### 5.4. Nervous system

The nervous system is a place of steroidogenesis and a target of androgenic action. Androgens can increase neuronal cells' survival, stimulation differentiation, and plasticity [92–94].

ARs are abundantly expressed both in the CNS and in the PNS.

#### a) Central nervous system (CNS)

In recent years the number of functions attributed to androgens in CNS has steadily increased, from the regulation of the hypothalamus-pituitary-gonadal axis and reproductive behavior to the modulation of cognition, anxiety from stress, and other non-reproductive functions (reinforcement sensitivity and competitive drive) [95–98].

In the CNS, ARs are found mainly in the hypothalamic areas and precisely the diagonal band of Broca, the mamillary nucleus, the preoptic area, and the pituitary peduncle [21].

ARs induce trophic factor release, which supports neurogenesis [99,100], and several neuroprotective pathways involved in cognitive function [72].

Notably, since 1952 it has been known that the loss of androgenic precursors, DHEA/DHEAS, in adult life is associated with neuropsychiatric disorders (e.g. schizophrenia, depression). Moreover, CNS indirectly modulates effects on, among others, bone and adipose tissue, as shown in the following paragraphs.

#### b) Peripheral nervous systems (PNS)

In the PNS, ARs are expressed in the brainstem and spinal cord [101]. A study showed that AR inhibition leads to the degeneration of motor neurons, with a reduction in their survival [102]. Conversely, activation of AR is associated with trophic effects, with extended lifespan and improved recovery from damage.

### 5.5. Bone tissue

Current evidence suggests that circulating androgens and estrogens protect bone tissue and structure.

Experimental data suggest that androgens influence bone directly via interactions with ARs and indirectly after being aromatized in estradiol, via binding to ER $\alpha$  and ER $\beta$  in the adipose or in different tissues.

For instance, activation of AR stimulates osteoblast proliferation and the blockade of osteoclast activity, leading to bone formation. In the same way, ER activation inhibits osteoclast proliferation and stimulates their apoptosis, inhibiting bone resorption [103,104].

In addition, DHEA inhibits skeletal catabolism through IL-6 blockage and stimulates osteoanabolic insulin-like growth factor 1 (IGF-1)-mediated mechanisms [105].

Studies in bone tissue have shown that exposure to glucocorticoids induces the expression of ARs and the production of androgens, resulting in a bone mineral density (BMD) increase [106].

Finally, it is interesting to underline that androgen effects on bone are indirect through the CNS, where the ARs are also abundantly expressed. In this regard, a study conducted on male mice concludes that androgen, through the AR expressed on neurons, protects cortical bone from age-related involution, restraining the loss of cortical thickness by virtue of medullary expansion [107].

### 5.6. Muscle

Androgens increase muscle size and strength [108]. This anabolic effect is not only explained by the activation of the myocyte AR, but is also the combined result of many genomic and non-genomic actions [109]. Women with PCOS and higher androgen levels have greater muscle mass and better competitive performance [110,111].

Postmenopausal women receiving testosterone enanthate significantly improved lean body mass, chest-press power, and full stair-climb power [112]. In addition, the combination of estrogens and androgens proved to be better than estrogen therapy alone on muscle mass and strength, without significant side effects [113]. In older women, a synthetic androgen, oxandrolone, improved muscle mass and performance after resistance training [114].

### 5.7. Adipose tissue

Adipose tissue is both an important peripheral steroidogenic tissue and an androgen-target organ. Androgens are key modulators of body fat distribution in both men and women. Importantly, androgens are responsible for accumulating of adipose tissue, especially at the visceral and abdominal levels. It seems that they are also accountable for the increase in the volume of adipocytes [115,116]. This distribution of body fat results from the local transformation of steroids by enzymes specifically expressed in adipose tissue, underlining the fundamental role of intracrinology.

*In vitro* studies showed that testosterone inhibits adipose stem cell (ASC) differentiation into preadipocyte and also reduces early-stage preadipocytes differentiation to adipocytes [117].

Also, androgens through the CNS regulate food intake, thus having an indirect effect on adipose tissue. A study on mice



showed that DHT treatment caused leptin resistance and increased appetite behavior (hyperphagia) in females, leading to obesity [118].

Interestingly, androgens have opposite effects on lipid accumulation in the liver (hepatosteatosis) of males compared to females.

Some studies show that androgens protect against males' hepatosteatosis or nonalcoholic fatty liver disease (NAFLD) [119,120].

On the other hand, other studies report that androgens significantly influence lipid metabolism in the female liver, causing more lipid accumulation and other signs of biochemical dysfunction (impaired glucose tolerance and resistance to leptin) [118,121].

### 5.8. Liver

Androgens act on the liver in different ways like:

- stimulating the synthesis of lipoproteins (LDL cholesterol) triglycerides [122] and increasing insulin resistance or reducing insulin sensitivity. The mechanisms of how androgens induce hyperinsulinemia and insulin resistance are not clear. Hyperandrogenemia in a DHT-treated female mouse model induces whole-body insulin resistance, possibly through activation of the hepatic AR [123]. On the other hand, we know that insulin resistance stimulates androgen synthesis in the ovary and lowers the amount of free testosterone accessible to the body, which inhibits the development of SHBG in the liver. These results demonstrate that insulin resistance can contribute to hyperandrogenemia [116,124].

- stimulating the synthesis of coagulation factors, such as fibrinogen and ATIII [125].

### 5.9. Platelet and vessels

Several studies indicate that androgens can increase Thromboxane A2 (TXA2) receptors to activate platelets, one of the central mechanisms responsible for hemostasis and atherosclerotic processes [126].

However, more recent studies have shown that testosterone can inhibit platelet aggregation with a mechanism dependent on nitric oxide (NO) synthesis [127,128]. Furthermore, testosterone plays a role in blood vessels, acting as a potent vasodilator, both in an endothelium-dependent and an endothelium-independent way. The former mechanism assumes that testosterone leads to the increased synthesis of NO [128,129]. The second endothelium-independent relaxation mechanism has been demonstrated in isolated rabbit coronary arteries and aorta [130].

Moreover, testosterone was positively correlated to brachial artery flow-mediated dilation in postmenopausal women [131].

The final effect of testosterone on the cardiovascular system depends on the amount of circulating hormone: physiological levels of androgens are possibly beneficial for the cardiovascular system. An optimal range of testosterone may exist for cardiovascular health in women, with an increased risk of coronary heart disease at low levels of testosterone

overall and at high levels of the bioavailable fraction of testosterone [132].

### 5.10. Immune system

Sex hormones can regulate several processes in the immune system, and ARs are detected in many different hematopoietic cells. It would appear that androgens play an immunosuppressive role, and some studies show that androgen deprivation therapy can induce expansion and increase the T-cell response [133].

This feature could be responsible for gender dysmorphisms in autoimmune, infectious, and tumor processes.

Women, whose circulating levels of androgens are certainly lower than men, would seem more likely to develop autoimmune diseases, while they are relatively less susceptible to infections and tumors than men.

Relative reductions in DHEA and DHEAS have been noted in subjects with systemic lupus erythematosus, HIV and autoimmune deficiency syndrome, sepsis, and trauma. This ability to regulate immune function has raised interest in the therapeutic potential of DHEA as a treatment for immunological abnormalities [134].

### 5.11. Androgens and female sexual function

For women, the correlation between circulating androgens and sexual desire is still a matter of debate today. In fact, it is well-known that women's sexuality is influenced by various biological, psychological, and social factors. Moreover, apart from the complex multidimensional nature of sexual desire across the reproductive lifespan, the correlation between measurements of testosterone and specific signs and symptoms has been difficult because most available assays are unreliable [135]. However, despite this, it is believed that androgens play an independent role in women's arousability and pleasure as well as intensity and ease of orgasm [136]. Moreover, the androgen milieu and sexual desire in women seem to be tightly linked because they both decline with age.

As we have seen, there are multiple ways androgens target the brain regions (hypothalamic, limbic, and cortical) involved in sexual function and behavior. Testosterone appears to play a key role in the motivational components of women's sexuality. Data obtained with liquid chromatography tandem-mass spectrometry (LC-MS/MS) found a significant positive association between testosterone levels and sexual desire, arousal and masturbation in both women of reproductive age and in perimenopause women [109].

In a cross-sectional study including 560 healthy women aged 19–65 years, free testosterone and androstenedione were statistically significantly correlated with sexual desire [137]. Discordant results were reported from a community-based cross-sectional study of 18 to 75-year-old women, in which it was not observed a significant correlation between serum levels of free testosterone or androstenedione and sexual function. However, an association was found between low DHEAS and low sexual responsiveness, low arousal, pleasure, and orgasm in women aged > 45 years [138].



### 5.12. Kidney

It has been postulated for several years that testosterone induces erythropoietin kidney production

[139]. This concept has been considered a scientific dogma based on animal and small human studies [139,140]. However, more recent studies have shown that the hematopoietic effect of testosterone does not appear to be mediated by stimulation of erythropoietin production [141].

## 6. Androgens and female pubertal development

During intrauterine life, the fetal adrenal cortex produces DHEA and DHEAS, a substrate for the placental production of estrogen and androgen. However, after birth, the adrenal cortex of the fetus undergoes involution, and the concentrations of DHEA and DHEAS decrease.

During childhood, around 8–9 years, the reticular area of the adrenal cortex produces increased amounts of androgenic precursors, which leads to numerous physiognomic changes. This phase is a fundamental stage of sexual maturation and takes the name of 'adrenarche' [142]. Adrenarche is probably a progressive maturation process from early childhood [143]. A study investigating serum DHEAS levels during childhood and adolescence showed that serum DHEAS was markedly age-dependent [144]. Below seven years of age, DHEA values remain around 0.5–1  $\mu\text{mol/L}$ , and then progressively increase from 8 years onwards for both sexes, with values around 12–13  $\mu\text{mol/L}$  (in mid-late teenage males and women).

From a clinical point of view, when DHEAS values exceed 40–50  $\mu\text{g/dL}$  (1.08–1.35  $\mu\text{mol/L}$ ), the development of apocrine glands, sebaceous glands, and pubic and axillary hair occurs (pubarca).

In addition to producing androgen precursors (DHEA, DHEAS), the adrenal cortex is also a potential source of steroid compounds with strong androgenic bioactivity such as testosterone, 11 $\beta$ -hydroxytestosterone, and 11-ketotestosterone, which seem to be the main responsible for the phenotypic changes during adrenarche [145–147].

Adrenal androgens act on the sebaceous glands, leading to comedogenic acne, on the apocrine glands bringing changes in the composition of sweat (with adult-type armpit odor), independently of gonadotropins, as well as on bone mass,

the central nervous system, the immune system, and metabolism [148].

Overall, the pre-pubertal DHEA/DHEAS surge plays a crucial role in modulating early brain development, perhaps by prolonging brain plasticity during childhood to allow the pre-adolescent brain to adapt and re-wire in response to new and ever-changing social challenges [149].

## 7. How androgen levels vary in the menstrual cycle

Circulating concentrations of androgens undergo variations throughout the menstrual cycle, exceeding those of estrogens [150,151]. Testosterone is at its lowest concentrations in the early follicular phase of the cycle, rises to a mid-cycle peak, and the luteal phase concentrations are higher than those in the early follicular phase [152]. In the menstrual period, plasma concentrations of testosterone are relatively high, whereas estrogen and progesterone levels progressively decline [153].

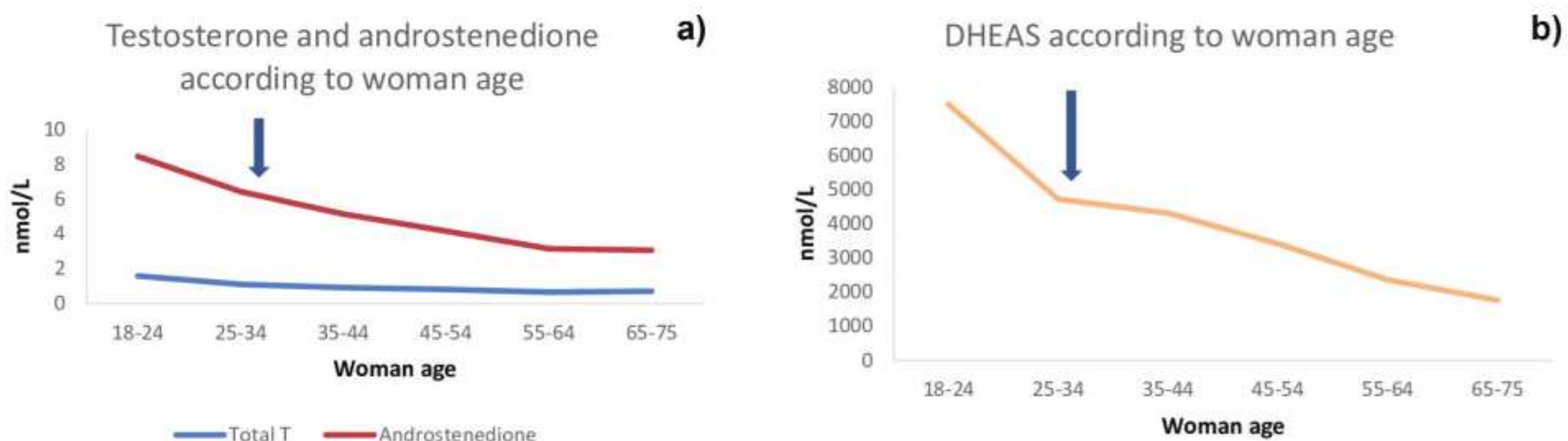
Total and free testosterone levels peak at midcycle, coincident with E2, E1 and SHBG levels and follicular development, whereas DHT did not change. These data support the hypothesis that the changes in testosterone across the cycle may reflect changes in SHBG and estrogen [151].

According to a study that used the LC-MS/MS method and a 2nd generation automated immunoassay, the elevation of mid-cycle testosterone concentrations is statistically significant, although not clinically relevant since the day-to-day variation is higher and independent of the menstrual cycle [154,155].

Regarding androstenedione, some studies showed no significant variation during the menstrual cycle [156]. However, other studies report a fluctuation similar to testosterone for androstenedione during the menstrual cycle phases [157]. Instead, DHEAS levels do not significantly vary during the menstrual cycle [150,156].

## 8. How androgen levels vary according to women's age

The serum androgen levels decline steeply in the early reproductive years, with flattening out during middle age (around 40 years old) and a slight tendency to increase in the following years [158] (Figure 4). Natural menopause does not appear to



**Figure 4.** Androgen levels according to woman age. These results indicate that the serum androgen levels (testosterone and androstenedione in A and DHEAS in B) decline with age largely independent of menopause, with flattening out during middle age (around 40 years old) and a slight tendency to increase in the following years. Values come from Davison's study [157].



affect this process, despite the concomitant sharp drop in estradiol levels. Interestingly, total testosterone, free testosterone, DHEAS, and androstenedione decline greater in the earlier than the later decades of age. Indeed, compared to premenopause, DHEA secretion drops by an average of 60% after menopause [159]. For instance, the levels of DHEA in a woman, 30 or 40 years old, decrease by half those of 20 years old [160]. In addition, ovarian androstenedione at the time of menopause is reduced more drastically than testosterone, modifying the relative contribution of the ovary to the production of systemic androgens.

Finally, as far as testosterone quantity is concerned, it does not suffer a precipitous decline at the time of menopause, but its production decreases slowly over the 5 to 10 years following the last menstrual period [161]. However, although ovarian testosterone production does not change significantly at the time of menopause, circulating testosterone concentrations are reduced because the availability of its precursors is also decreased.

Therefore, the overall equilibrium is a reduction of all androgens during the menopausal transition.

So, most importantly, after menopause, DHEA becomes the sole source of both estrogens and androgens [162,163]. DHEA is transformed directly within the cells into small amounts of estrogen and androgen to minimize systemic exposure to these hormones [164].

In addition to the general reduction of androgens, the contribution of each source for circulating androgen also changes before and after menopause [20](Figure 2).

Following menopause, while the contribution of the adrenal glands, ovaries, and peripheral conversion to the total circulating DHEAS and DHEA concentrations remain the same, the ovarian androstenedione contribution decreases from 50% to 20%, and the ovarian testosterone accounts for 50% of total testosterone [43,165,166].

## 9. Conclusion

DHEAS, DHEA, androstenedione, testosterone, and DHT in women are present with decreasing concentration levels. Specifically, DHEAS, DHEA, and androstenedione can be transformed intracellularly into small amounts of active androgens. On the other hand, the same precursors, when inactive, can maintain low contractions within the tissues. This local hormonal control, activation, and inactivation mechanism has been termed 'intracrinology.'

The central message of this review is that androgens play essential roles in women's physiology. They act in different target organs, directly, by binding to the ARs, or indirectly, after their aromatization into estrogens.

Androgens in women are essential for reproductive competency, sexual function, cardiovascular health, appropriate bone remodeling, muscle tone, and mass and brain function. In particular, androgens seem to play a beneficial role in follicular development and regulating pregnancy establishment and maintenance. Physiologically, the androgen levels in women change with the menstrual cycle and, unlike estrogens, are reduced already in the first decades of life, largely

independent of menopause. This decrease with aging is due to reduced production rather than altered metabolism.

Most importantly, after menopause, DHEA becomes the exclusive source of both estrogens and androgens.

Overall, the picture emerging from our investigations is that physiological levels of androgens are essential for women's health throughout life. Changes in the availability of circulating androgens may impact the regulation of numerous physiological processes.

In this context, diagnosis of androgen deficiency or excess in women is of clinical relevance because restoring physiological levels of androgens is essential in the prevention and treatment of many diseases.

## 10. Expert opinion

From a clinical perspective, this review provides physiological data of androgen action in women that are an essential basis for further investigation into female androgen insufficiency or excess.

To unravel the distinctive pathological effects of androgens in women, it is necessary to deeply understand their physiological actions in the various tissues under normal conditions. As we have seen, androgens are known to regulate many processes in female physiology, but the potential role and precise mechanism of action in some of them are poorly understood. The significant factors that contribute to this 'knowledge gap' include;

1. The difficulty of dosing androgens with standard laboratory methods,
2. The difficulty of taking into account the diurnal and cyclical variations in androgen levels for blood sampling, and
3. The uncertainty of what is considered normal in serum androgen levels in women of different ages and, in particular, the absence of specific cutoffs for female hypoandrogenism.

Since the bias mentioned above influences the studies on this topic, it would be necessary to perform prospective, longitudinal studies on larger populations [158].

Amongst the mechanisms that need further investigation, is the potential role of androgens in regulating pregnancy. In this perspective, some therapies, such as selective AR modulators, could be used to improve reproductive outcomes. Another topic to investigate is the function of AR in several structures of the CNS involved in cognitive processes. Furthermore, the molecular mechanisms behind decreasing DHEA and DHEAS levels with advancing age are also unclear. Therefore, more studies are needed to elucidate the selective reduction of the adrenal reticular zone, responsible for the production and secretion of androgens, with increasing age.

Finally, existing data do not permit an evaluation of the reciprocal regulation between androgens and estrogens, mainly their receptors and transcription factors. The remedy to this unsatisfactory state of affairs will develop more effective therapeutic protocols for managing androgen insufficiency or excess.

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## References

- Lobo RA. Androgens in postmenopausal women: production, possible role, and replacement options. *Obstet Gynecol Surv.* 2001;56(6):361–376.
- Lee AT, Zane LT. Dermatologic manifestations of polycystic ovary syndrome. *Am J Clin Dermatol.* 2007;8(4):201–219.
- Ehrmann DA. Polycystic ovary syndrome. *N Engl J Med.* 2005;352(12):1223–1236.
- Azziz R, Sanchez LA, Knochenhauer ES, et al. Androgen excess in women: experience with over 1000 consecutive patients. *J Clin Endocrinol Metab.* 2004;89(2):453–462.
- Carmina E, Rosato F, Janni A, et al. Extensive clinical experience: relative prevalence of different androgen excess disorders in 950 women referred because of clinical hyperandrogenism. *J Clin Endocrinol Metab.* 2006;91(1):2–6.
- T'Sjoen G, Arcelus J, Gooren L, et al. Endocrinology of transgender medicine. *Endocr Rev.* 2019;40(1):97–117.
- Davis SR, Baber R, Panay N, et al. Global consensus position statement on the use of testosterone therapy for women. *J Clin Endocrinol Metab.* 2019;104(10):4660–4666.
- Labrie F, Luu-The V, Bélanger A, et al. Is dehydroepiandrosterone a hormone? *J Endocrinol.* 2005;187(2):169–196.
- Labrie F. Extragonadal synthesis of sex steroids: intracrinology. *Ann Endocrinol.* 2003;64(2):95–107.
- Carreau S, Wolczynski S, Galeraud-Denis I. Aromatase, oestrogens and human male reproduction. *Philos Trans R Soc Lond B Biol Sci.* 2010;365(1546):1571–1579.
- Czajka-Oraniec I, Simpson ER. Aromatase research and its clinical significance. *Endokrynol Pol.* 2010;61(1):126–134.
- Schiffer L, Arlt W, O'Reilly MW. Understanding the role of androgen action in female adipose tissue. *Front Horm Res.* 2019;53:33–49.
- Ceruti JM, Leirós GJ, Balaña ME. Androgens and androgen receptor action in skin and hair follicles. *Mol Cell Endocrinol.* 2018;465:122–133.
- Cellai I, Di Stasi V, Comeglio P, et al. Insight on the intracrinology of menopause: androgen production within the human vagina. *Endocrinology.* 2021;162(2). DOI:10.1210/endo/bqaa219
- Gibson DA, Simitsidellis I, Saunders PT. Regulation of androgen action during establishment of pregnancy. *J Mol Endocrinol.* 2016;57(1):R35–47.
- Vegeto E, Villa A, Della Torre S, et al. The role of sex and sex hormones in neurodegenerative diseases. *Endocr Rev.* 2020;41(2):273–319.
- Schiffer L, Arlt W, Storbeck KH. Intracrine androgen biosynthesis, metabolism and action revisited. *Mol Cell Endocrinol.* 2018;465:4–26.
- Labrie C, Belanger A, Labrie F. Androgenic activity of dehydroepiandrosterone and androstenedione in the rat ventral prostate. *Endocrinology.* 1988;123(3):1412–1417.
- Labrie F. Intracrinology. *Mol Cell Endocrinol.* 1991;78(3):C113–8.
- Simon JA. Estrogen replacement therapy: effects on the endogenous androgen milieu. *Fertil Steril.* 2002;77(Suppl 4):S77–82.
- Sourla A, Flamand M, Bélanger A, et al. Effect of dehydroepiandrosterone on vaginal and uterine histomorphology in the rat. *J Steroid Biochem Mol Biol.* 1998;66(3):137–149.
- Berger L, El-Alfy M, Martel C, et al. Effects of dehydroepiandrosterone, Premarin and Acolbifene on histomorphology and sex steroid receptors in the rat vagina. *J Steroid Biochem Mol Biol.* 2005;96(2):201–215.
- Gibson DA, Simitsidellis I, Cousins FL, et al. Intracrine androgens enhance decidualization and modulate expression of human endometrial receptivity genes. *Sci Rep.* 2016;6(1):19970.
- Huhtinen K, Saloniemi-Heinonen T, Keski-Rahkonen P, et al. Intra-tissue steroid profiling indicates differential progesterone and testosterone metabolism in the endometrium and endometriosis lesions. *J Clin Endocrinol Metab.* 2014;99(11):E2188–97.
- Rhee HS, Oh SH, Ko BJ, et al. Expression of 3 beta-hydroxysteroid dehydrogenase and P450 side chain cleavage enzyme in the human uterine endometrium. *Exp Mol Med.* 2003;35(3):160–166.
- Rizner TL, Penning TM. Role of aldo-keto reductase family 1 (AKR1) enzymes in human steroid metabolism. *Steroids.* 2014;79:49–63.
- Catalano RD, Wilson MR, Boddy SC, et al. Comprehensive expression analysis of prostanoid enzymes and receptors in the human endometrium across the menstrual cycle. *Mol Hum Reprod.* 2011;17(3):182–192.
- Gibson DA, Greaves E, Critchley HO, et al. Estrogen-dependent regulation of human uterine natural killer cells promotes vascular remodelling via secretion of CCL2. *Hum Reprod.* 2015;30(6):1290–1301.
- Pelletier G, Luu-The V, Têtu B, et al. Immunocytochemical localization of type 5 17beta-hydroxysteroid dehydrogenase in human reproductive tissues. *J Histochem Cytochem.* 1999;47(6):731–737.
- Garcia-Ovejero D, Azcoitia I, DonCarlos LL, et al. Glia-neuron crosstalk in the neuroprotective mechanisms of sex steroid hormones. *Brain Res Brain Res Rev.* 2005;48(2):273–286.
- Diczfalusy E. Endocrine functions of the human fetoplacental unit. 1964. *Am J Obstet Gynecol.* 2005;193(6):2024. discussion 2025.
- Pasqualini JR. Enzymes involved in the formation and transformation of steroid hormones in the fetal and placental compartments. *J Steroid Biochem Mol Biol.* 2005;97(5):401–415.
- Loganath A, Peh KL, Wong PC. Evidence for the biosynthesis of DHEA from cholesterol by first-trimester human placental tissue: source of androgens. *Hormone Metab Res.* 2002;34(3):116–120.
- Escobar JC, Patel SS, Beshay VE, et al. The human placenta expresses CYP17 and generates androgens de novo. *J Clin Endocrinol Metab.* 2011;96(5):1385–1392.
- Noyola-Martínez N, Halhali A, Zaga-Clavellina V, et al. A time-course regulatory and kinetic expression study of steroid metabolizing enzymes by calcitriol in primary cultured human placental cells. *J Steroid Biochem Mol Biol.* 2017;167:98–105.
- Noyola-Martínez N, Halhali A, Barrera D. Steroid hormones and pregnancy. *Gynecol Endocrinol.* 2019;35(5):376–384.
- Mendel CM. The free hormone hypothesis: a physiologically based mathematical model. *Endocr Rev.* 1989;10(3):232–274.
- Hammes A, Andreassen TK, Spoelgen R, et al. Role of endocytosis in cellular uptake of sex steroids. *Cell.* 2005;122(5):751–762.
- Porto CS, Lazari MF, Abreu LC, et al. Receptors for androgen-binding proteins: internalization and intracellular signalling. *J Steroid Biochem Mol Biol.* 1995;53(1–6):561–565.
- Krupenko SA, Krupenko NI, Danzo BJ. Interaction of sex hormone-binding globulin with plasma membranes from the rat epididymis and other tissues. *J Steroid Biochem Mol Biol.* 1994;51(1–2):115–124.
- Hammond GL. Plasma steroid-binding proteins: primary gatekeepers of steroid hormone action. *J Endocrinol.* 2016;230(1):R13–25.
- Keovil BG, Adaway J. Assessment of free testosterone concentration. *J Steroid Biochem Mol Biol.* 2019;190:207–211.
- Longcope C, Franz C, Morello C, et al. Steroid and gonadotropin levels in women during the peri-menopausal years. *Maturitas.* 1986;8(3):189–196.



44. Baldassarri M, Picchiotti N, Fava F, et al. Shorter androgen receptor polyQ alleles protect against life-threatening COVID-19 disease in European males. *EBioMedicine*. 2021;65:103246.
45. Brinkmann AO. Molecular basis of androgen insensitivity. *Mol Cell Endocrinol*. 2001;179(1–2):105–109.
46. Galani A, Kitsiou-Tzeli S, Sofokleous C, et al. Androgen insensitivity syndrome: clinical features and molecular defects. *Hormones (Athens)*. 2008;7(3):217–229.
47. Foradori CD, Weiser MJ, Handa RJ. Non-genomic actions of androgens. *Front Neuroendocrinol*. 2008;29(2):169–181.
48. Lorigo M, Mariana M, Lemos MC, et al. Vascular mechanisms of testosterone: the non-genomic point of view. *J Steroid Biochem Mol Biol*. 2020;196:105496.
49. Lucas-Herald AK, Alves-Lopes R, Montezano AC, et al. Genomic and non-genomic effects of androgens in the cardiovascular system: clinical implications. *Clin sci*. 2017;131(13):1405–1418.
50. Tirabassi G, Biagioli A, Balercia G. Bone benefits of testosterone replacement therapy in male hypogonadism. *Panminerva Med*. 2014;56(2):151–163.
51. Heinlein CA, Chang C. The roles of androgen receptors and androgen-binding proteins in nongenomic androgen actions. *Mol Endocrinol (Baltimore, Md)*. 2002;16(10):2181–2187.
52. Brinkmann AO, Faber PW, van Rooij HC, et al. The human androgen receptor: domain structure, genomic organization and regulation of expression. *J Steroid Biochem*. 1989;34(1–6):307–310.
53. El Kharraz S, Dubois V, van Royen ME, et al. The androgen receptor depends on ligand-binding domain dimerization for transcriptional activation. *EMBO Rep*. 2021;22(12):e52764.
54. El Kharraz S, Dubois V, Launonen KM, et al. N/C interactions are dispensable for normal in vivo functioning of the androgen receptor in male mice. *Endocrinology*. 2022;163(9):9.
55. Ibáñez L, Ong KK, Mongan N, et al. Androgen receptor gene CAG repeat polymorphism in the development of ovarian hyperandrogenism. *J Clin Endocrinol Metab*. 2003;88(7):3333–3338.
56. Tirabassi G, Cignarelli A, Perrini S, et al. Influence of CAG repeat polymorphism on the targets of testosterone action. *Int J Endocrinol*. 2015;2015:298107.
57. Zhang T, Liang W, Fang M, et al. Association of the CAG repeat polymorphisms in androgen receptor gene with polycystic ovary syndrome: a systemic review and meta-analysis. *Gene*. 2013;524(2):161–167.
58. Tirabassi G, Delli Muti N, Corona G, et al. Androgen receptor gene cag repeat polymorphism regulates the metabolic effects of testosterone replacement therapy in male postsurgical hypogonadotropic hypogonadism. *Int J Endocrinol*. 2013;2013:816740.
59. Francomano D, Greco EA, Lenzi A, et al. CAG repeat testing of androgen receptor polymorphism: is this necessary for the best clinical management of hypogonadism? *J Sex Med*. 2013;10(10):2373–2381.
60. Wunderlich F, Benten WP, Lieberherr M, et al. Testosterone signaling in T cells and macrophages. *Steroids*. 2002;67(6):535–538.
61. Estrada M, Uhlen P, Ehrlich BE. Ca<sup>2+</sup> oscillations induced by testosterone enhance neurite outgrowth. *J Cell Sci*. 2006;119(4):733–743.
62. Lieberherr M, Grosse B. Androgens increase intracellular calcium concentration and inositol 1,4,5-trisphosphate and diacylglycerol formation via a pertussis toxin-sensitive G-protein. *J Biol Chem*. 1994;269(10):7217–7223.
63. Hampton JH, Manikkam M, Lubahn DB, et al. Androgen receptor mRNA expression in the bovine ovary. *Domest Anim Endocrinol*. 2004;27(1):81–88.
64. Hickey TE, Marrocco DL, Amato F, et al. Androgens augment the mitogenic effects of oocyte-secreted factors and growth differentiation factor 9 on porcine granulosa cells. *Biol Reprod*. 2005;73(4):825–832.
65. Magamaga MPS, Zengyo M, Moniruzzaman M, et al. Testosterone induces activation of porcine primordial follicles in vitro. *Reprod Med Biol*. 2011;10(1):21–30.
66. Gill A, Jamnongjit M, Hammes SR. Androgens promote maturation and signaling in mouse oocytes independent of transcription: a release of inhibition model for mammalian oocyte meiosis. *Mol Endocrinol (Baltimore, Md)*. 2004;18(1):97–104.
67. Kimura S, Matsumoto T, Matsuyama R, et al. Androgen receptor function in folliculogenesis and its clinical implication in premature ovarian failure. *Trends Endocrinol Metab*. 2007;18(5):183–189.
68. Sen A, Prizant H, Light A, et al. Androgens regulate ovarian follicular development by increasing follicle stimulating hormone receptor and microRNA-125b expression. *Proc Natl Acad Sci U S A*. 2014;111(8):3008–3013.
69. Guo J, Zhang Q, Li Y, et al. Predictive value of androgens and multivariate model for poor ovarian response. *Reprod Biomed Online*. 2014;28(6):723–732.
70. Rice S, Ojha K, Whitehead S, et al. Stage-specific expression of androgen receptor, follicle-stimulating hormone receptor, and anti-Müllerian hormone type II receptor in single, isolated, human preantral follicles: relevance to polycystic ovaries. *J Clin Endocrinol Metab*. 2007;92(3):1034–1040.
71. Simitsidellis I, Saunders PTK, Gibson DA. Androgens and endometrium: new insights and new targets. *Mol Cell Endocrinol*. 2018;465:48–60.
72. Mertens HJ, Heineman MJ, Theunissen PH, et al. Androgen, estrogen and progesterone receptor expression in the human uterus during the menstrual cycle. *Eur J Obstet Gynecol Reprod Biol*. 2001;98(1):58–65.
73. Marshall E, Lowrey J, MacPherson S, et al. In silico analysis identifies a novel role for androgens in the regulation of human endometrial apoptosis. *J Clin Endocrinol Metab*. 2011;96(11):E1746–55.
74. Milne SA, Henderson TA, Kelly RW, et al. Leukocyte populations and steroid receptor expression in human first-trimester decidua; regulation by antiprogesterone and prostaglandin E analog. *J Clin Endocrinol Metab*. 2005;90(7):4315–4321.
75. Critchley HO, Saunders PT. Hormone receptor dynamics in a receptive human endometrium. *Reprod Sci*. 2009;16(2):191–199.
76. Massafra C, Gioia D, De Felice C, et al. Effects of estrogens and androgens on erythrocyte antioxidant superoxide dismutase, catalase and glutathione peroxidase activities during the menstrual cycle. *J Endocrinol*. 2000;167(3):447–452.
77. Cousins FL, Kirkwood PM, Murray AA, et al. Androgens regulate scarless repair of the endometrial “wound” in a mouse model of menstruation. *FASEB J*. 2016;30(8):2802–2811.
78. Perrone AM, Cerpolini S, Maria Salfi NC, et al. Effect of long-term testosterone administration on the endometrium of female-to-male (FtM) transsexuals. *J Sex Med*. 2009;6(11):3193–3200.
79. Tuckerman EM, Okon MA, Li T, et al. Do androgens have a direct effect on endometrial function? An in vitro study. *Fertil Steril*. 2000;74(4):771–779.
80. Diao HL, Su RW, Tan HN, et al. Effects of androgen on embryo implantation in the mouse delayed-implantation model. *Fertil Steril*. 2008;90(4):1376–1383.
81. Bertin J, Dury AY, Ouellet J, et al. Localization of the androgen-synthesizing enzymes, androgen receptor, and sex steroids in the vagina: possible implications for the treatment of postmenopausal sexual dysfunction. *J Sex Med*. 2014;11(8):1949–1961.
82. Traish AM, Vignozzi L, Simon JA, et al. Role of androgens in female genitourinary tissue structure and function: implications in the genitourinary syndrome of menopause. *Sex Med Rev*. 2018;6(4):558–571.
83. Simon JA, Goldstein I, Kim NN, et al. The role of androgens in the treatment of genitourinary syndrome of menopause (GSM): international society for the study of women’s sexual health (ISSWSH) expert consensus panel review. *Menopause*. 2018;25(7):837–847.
84. Maseroli E, Vignozzi L. Testosterone and vaginal function. *Sex Med Rev*. 2020;8(3):379–392.
85. Comeglio P, Cellai I, Filippi S, et al. Differential effects of testosterone and estradiol on clitoral function: an experimental study in rats. *J Sex Med*. 2016;13(12):1858–1871.
86. Secreto G, Girombelli A, Krogh V. Androgen excess in breast cancer development: implications for prevention and treatment. *Endocr Relat Cancer*. 2019;26(2):R81–r94.



87. Dorgan JF, Stanczyk FZ, Kahle LL, et al. Prospective case-control study of premenopausal serum estradiol and testosterone levels and breast cancer risk. *BCR*. 2010;12(6):R98.
88. Kaaks R, Rinaldi S, Key TJ, et al. Postmenopausal serum androgens, oestrogens and breast cancer risk: the European prospective investigation into cancer and nutrition. *Endocr Relat Cancer*. 2005;12(4):1071–1082.
89. Yu H, Shu XO, Shi R, et al. Plasma sex steroid hormones and breast cancer risk in Chinese women. *Int J Cancer*. 2003;105(1):92–97.
90. Muscogiuri G, Barrea L, Feola T, et al. Pancreatic neuroendocrine neoplasms: does sex matter? *Trends Endocrinol Metab*. 2020;31(9):631–641.
91. Randall VA, Hibberts NA, Thornton MJ, et al. The hair follicle: a paradoxical androgen target organ. *Hormone Res*. 2000;54(5–6):243–250.
92. Heberden C. Sex steroids and neurogenesis. *Biochem Pharmacol*. 2017;141:56–62.
93. Leranth C, Petnehazy O, MacLusky NJ. Gonadal hormones affect spine synaptic density in the CA1 hippocampal subfield of male rats. *J Neurosci*. 2003;23(5):1588–1592.
94. Marron TU, Guerini V, Rusmini P, et al. Androgen-induced neurite outgrowth is mediated by neuritin in motor neurones. *J Neurochem*. 2005;92(1):10–20.
95. Edinger KL, Frye CA. Intrahippocampal administration of an androgen receptor antagonist, flutamide, can increase anxiety-like behavior in intact and DHT-replaced male rats. *Horm Behav*. 2006;50(2):216–222.
96. Hermans EJ, Bos PA, Ossewaarde L, et al. Effects of exogenous testosterone on the ventral striatal BOLD response during reward anticipation in healthy women. *NeuroImage*. 2010;52(1):277–283.
97. Edinger KL, Frye CA. Testosterone's analgesic, anxiolytic, and cognitive-enhancing effects may be due in part to actions of its 5 $\alpha$ -reduced metabolites in the hippocampus. *Behav Neurosci*. 2004;118(6):1352–1364.
98. Mhaouty-Kodja S. Role of the androgen receptor in the central nervous system. *Mol Cell Endocrinol*. 2018;465:103–112.
99. Louissaint A Jr., Rao S, Leventhal C, et al. Coordinated interaction of neurogenesis and angiogenesis in the adult songbird brain. *Neuron*. 2002;34(6):945–960.
100. Wu Y, Zhao W, Zhao J, et al. Identification of androgen response elements in the insulin-like growth factor I upstream promoter. *Endocrinology*. 2007;148(6):2984–2993.
101. Simerly RB, Chang C, Muramatsu M, et al. Distribution of androgen and estrogen receptor mRNA-containing cells in the rat brain: an in situ hybridization study. *J Comp Neurol*. 1990;294(1):76–95.
102. Banks WA. Brain meets body: the blood-brain barrier as an endocrine interface. *Endocrinology*. 2012;153(9):4111–4119.
103. Bianchi VE, Bresciani E, Meanti R, et al. The role of androgens in women's health and wellbeing. *Pharmacol Res*. 2021;171:105758.
104. Mohamad NV, Soelaiman IN, Chin KY. A concise review of testosterone and bone health. *Clin Interv Aging*. 2016;11:1317–1324.
105. Zhou S, Glowacki J. Dehydroepiandrosterone and bone. *Vitam Horm*. 2018;108:251–271.
106. Notelovitz M. Androgen effects on bone and muscle. *Fertil Steril*. 2002;77(Suppl 4):S34–41.
107. Jardí F, Kim N, Laurent MR, et al. Androgen receptor in neurons slows age-related cortical thinning in male mice. *J Bone Miner Res*. 2019;34(3):508–519.
108. Hwang AC, Liu LK, Lee WJ, et al. Association of androgen with skeletal muscle mass and muscle function among men and women aged 50 years and older in Taiwan: results from the I-Lan longitudinal aging study. *Rejuvenation Res*. 2013;16(6):453–459.
109. Dubois V, Laurent M, Boonen S, et al. Androgens and skeletal muscle: cellular and molecular action mechanisms underlying the anabolic actions. *Cell Mol Life Sci*. 2012;69(10):1651–1667.
110. Douchi T, Yamamoto S, Oki T, et al. Serum androgen levels and muscle mass in women with polycystic ovary syndrome. *Obstet Gynecol*. 1999;94(3):337–340.
111. Berman S. Androgens and athletic performance of elite female athletes. *Curr Opin Endocrinol Diabetes Obes*. 2017;24(3):246–251.
112. Huang G, Basaria S, Travison TG, et al. Testosterone dose-response relationships in hysterectomized women with or without oophorectomy: effects on sexual function, body composition, muscle performance and physical function in a randomized trial. *Menopause*. 2014;21(6):612–623.
113. Dobs AS, Nguyen T, Pace C, et al. Differential effects of oral estrogen versus oral estrogen-androgen replacement therapy on body composition in postmenopausal women. *J Clin Endocrinol Metab*. 2002;87(4):1509–1516.
114. Mavros Y, O'Neill E, Connerty M, et al. Oxandrolone augmentation of resistance training in older women: a randomized trial. *Med Sci Sports Exerc*. 2015;47(11):2257–2267.
115. Tchernof A, Brochu D, Maltais-Payette I, et al. Androgens and the regulation of adiposity and body fat distribution in humans. *Compr Physiol*. 2018;8(4):1253–1290.
116. Sørensen AE, Udesen PB, Wissing ML, et al. MicroRNAs related to androgen metabolism and polycystic ovary syndrome. *Chem Biol Interact*. 2016;259(Pt A):8–16.
117. Chazenbalk G, Singh P, Irge D, et al. Androgens inhibit adipogenesis during human adipose stem cell commitment to pre-adipocyte formation. *Steroids*. 2013;78(9):920–926.
118. Kanaya N, Vonderfecht S, Chen S. Androgen (dihydrotestosterone)-mediated regulation of food intake and obesity in female mice. *J Steroid Biochem Mol Biol*. 2013;138:100–106.
119. Zhang H, Liu Y, Wang L, et al. Differential effects of estrogen/androgen on the prevention of nonalcoholic fatty liver disease in the male rat. *J Lipid Res*. 2013;54(2):345–357.
120. Völzke H, Aumann N, Krebs A, et al. Hepatic steatosis is associated with low serum testosterone and high serum DHEAS levels in men. *Int J Andrology*. 2010;33(1):45–53.
121. Bohdanowicz-Pawlak A, Lenarcik-Kabza A, Brona A, et al. Non-alcoholic fatty liver disease in women with polycystic ovary syndrome - clinical and metabolic aspects and lipoprotein lipase gene polymorphism. *Endokrynol Pol*. 2014;65(6):416–421.
122. Schooling CM. Testosterone and cardiovascular disease. *Curr Opin Endocrinol Diabetes Obes*. 2014;21(3):202–208.
123. Andrisse S, Feng M, Wang Z, et al. Androgen-induced insulin resistance is ameliorated by deletion of hepatic androgen receptor in females. *FASEB J*. 2021;35(10):e21921.
124. Ding H, Zhang J, Zhang F, et al. Resistance to the insulin and elevated level of androgen: a major cause of polycystic ovary syndrome. *Front Endocrinol (Lausanne)*. 2021;12:741764.
125. Aydılek N, Aksakal M. Effects of testosterone on lipid peroxidation, lipid profiles and some coagulation parameters in rabbits. *J Vet Med A, Physiol, Pathol, Clin Med*. 2005;52(9):436–439.
126. Halushka PV, Matsuda K, Masuda A, et al. Testosterone regulation of platelet and vascular thromboxane A<sub>2</sub> receptors. *Agents and Actions Suppl*. 1995;45:19–26.
127. Campelo AE, Cutini PH, Massheimer VL. Testosterone modulates platelet aggregation and endothelial cell growth through nitric oxide pathway. *J Endocrinol*. 2012;213(1):77–87.
128. Karolczak K, Konieczna L, Kostka T, et al. Testosterone and dihydrotestosterone reduce platelet activation and reactivity in older men and women. *Aging (Albany NY)*. 2018;10(5):902–929.
129. Kelly DM, Jones TH. Testosterone: a vascular hormone in health and disease. *J Endocrinol*. 2013;217(3):R47–71.
130. Yue P, Chatterjee K, Beale C, et al. Testosterone relaxes rabbit coronary arteries and aorta. *Circulation*. 1995;91(4):1154–1160.
131. Montalcini T, Gorgone G, Gazzaruso C, et al. Endogenous testosterone and endothelial function in postmenopausal women. *Coron Artery Dis*. 2007;18(1):9–13.
132. Laughlin GA, Goodell V, Barrett-Connor E. Extremes of endogenous testosterone are associated with increased risk of incident coronary events in older women. *J Clin Endocrinol Metab*. 2010;95(2):740–747.



133. Ben-Batalla I, Vargas-Delgado ME, von Amsberg G, et al. Influence of androgens on immunity to self and foreign: effects on immunity and cancer. *Front Immunol*. 2020;11:1184.
134. Hazeldine J, Arlt W, Lord JM. Dehydroepiandrosterone as a regulator of immune cell function. *J Steroid Biochem Mol Biol*. 2010;120(2–3):127–136.
135. Nappi RE. To be or not to be in sexual desire: the androgen dilemma. *Climacteric J Int Menopause Soc*. 2015;18(5):672–674.
136. Bachmann G, Bancroft J, Braunstein G, et al. Female androgen insufficiency: the Princeton consensus statement on definition, classification, and assessment. *Fertil Steril*. 2002;77(4):660–665.
137. Wählin-Jacobsen S, Pedersen AT, Kristensen E, et al. Is there a correlation between androgens and sexual desire in women? *J Sex Med*. 2015;12(2):358–373.
138. Davis SR, Davison SL, Donath S, et al. Circulating androgen levels and self-reported sexual function in women. *Jama*. 2005;294(1):91–96.
139. Rishpon-Meyerstein N, Kilbridge T, Simone J, et al. The effect of testosterone on erythropoietin levels in anemic patients. *Blood*. 1968;31(4):453–460.
140. Malgor LA, Valsecia M, Vergés E, et al. Blockade of the in vitro effects of testosterone and erythropoietin on Cfu-E and Bfu-E proliferation by pretreatment of the donor rats with cyproterone and flutamide. *Acta Physiologica, Pharmacologica Et Therapeutica Latinoamericana: Organo de la Asociacion Latinoamericana de Ciencias Fisiologicas Y [De] la Asociacion Latinoamericana de Farmacologia*. 1998;48(2):99–105.
141. Maggio M, Snyder PJ, Ceda GP, et al. Is the haematopoietic effect of testosterone mediated by erythropoietin? The results of a clinical trial in older men. *Andrology*. 2013;1(1):24–28.
142. Dumontet T, Martinez A. Adrenal androgens, adrenarche, and zona reticularis: a human affair? *Mol Cell Endocrinol*. 2021;528:111239.
143. Apter D, Pakarinen A, Hammond GL, et al. Adrenocortical function in puberty. serum ACTH, cortisol and dehydroepiandrosterone in girls and boys. *Acta paediatrica Scand*. 1979;68(4):599–604.
144. Babalola AA, Ellis G. Serum dehydroepiandrosterone sulfate in a normal pediatric population. *Clin Biochem*. 1985;18(3):184–189.
145. Rege J, Turcu AF, Kasa-Vubu JZ, et al. 11-Ketotestosterone is the dominant circulating bioactive androgen during normal and premature adrenarche. *J Clin Endocrinol Metab*. 2018;103(12):4589–4598.
146. Turcu AF, Nanba AT, Auchus RJ. The rise, fall, and resurrection of 11-Oxygenated androgens in human physiology and disease. *Hormone Res Paediatrics*. 2018;89(5):284–291.
147. Turcu AF, Nanba AT, Chomic R, et al. Adrenal-derived 11-oxygenated 19-carbon steroids are the dominant androgens in classic 21-hydroxylase deficiency. *Eur J Endocrinol*. 2016;174(5):601–609.
148. Bordini B, Rosenfield RL. Normal pubertal development: part II: clinical aspects of puberty. *Pediatr Rev*. 2011;32(7):281–292.
149. Greaves RF, Wudy SA, Badoer E, et al. A tale of two steroids: the importance of the androgens DHEA and DHEAS for early neurodevelopment. *J Steroid Biochem Mol Biol*. 2019;188:77–85.
150. Burger HG. Androgen production in women. *Fertil Steril*. 2002;77(Suppl 4):S3–5.
151. Rothman MS, Carlson NE, Xu M, et al. Reexamination of testosterone, dihydrotestosterone, estradiol and estrone levels across the menstrual cycle and in postmenopausal women measured by liquid chromatography-tandem mass spectrometry. *Steroids*. 2011;76(1–2):177–182.
152. Abraham GE. Ovarian and adrenal contribution to peripheral androgens during the menstrual cycle. *J Clin Endocrinol Metab*. 1974;39(2):340–346.
153. Burton KA, Henderson TA, Hillier SG, et al. Local levonorgestrel regulation of androgen receptor and 17 beta-hydroxysteroid dehydrogenase type 2 expression in human endometrium. *Hum Reprod*. 2003;18(12):2610–2617.
154. Bui HN, Sluss PM, Blincko S, et al. Dynamics of serum testosterone during the menstrual cycle evaluated by daily measurements with an ID-LC-MS/MS method and a 2nd generation automated immunoassay. *Steroids*. 2013;78(1):96–101.
155. Iannone M, Dima AP, Sciarra F, et al. Development and validation of a liquid chromatography-tandem mass spectrometry method for the simultaneous analysis of androgens, estrogens, glucocorticoids and progestagens in human serum. *Biomed Chromatogr*. 2022;36(5):e5344.
156. Salonia A, Pontillo M, Nappi RE, et al. Menstrual cycle-related changes in circulating androgens in healthy women with self-reported normal sexual function. *J Sex Med*. 2008;5(4):854–863.
157. Mushayandebvu T, Castracane VD, Gimpel T, et al. Evidence for diminished midcycle ovarian androgen production in older reproductive aged women. *Fertil Steril*. 1996;65(4):721–723.
158. Davison SL, Bell R, Donath S, et al. Androgen levels in adult females: changes with age, menopause, and oophorectomy. *J Clin Endocrinol Metab*. 2005;90(7):3847–3853.
159. Labrie F, Bélanger A, Cusan L, et al. Marked decline in serum concentrations of adrenal C19 sex steroid precursors and conjugated androgen metabolites during aging. *J Clin Endocrinol Metab*. 1997;82(8):2396–2402.
160. Zumoff B, Strain GW, Miller LK, et al. Twenty-four-hour mean plasma testosterone concentration declines with age in normal premenopausal women. *J Clin Endocrinol Metab*. 1995;80(4):1429–1430.
161. Burger HG, Dudley EC, Cui J, et al. A prospective longitudinal study of serum testosterone, dehydroepiandrosterone sulfate, and sex hormone-binding globulin levels through the menopause transition. *J Clin Endocrinol Metab*. 2000;85(8):2832–2838.
162. Labrie F, Martel C, Balser J. Wide distribution of the serum dehydroepiandrosterone and sex steroid levels in postmenopausal women: role of the ovary? *Menopause*. 2011;18(1):30–43.
163. Labrie F, Labrie C. DHEA and intracrinology at menopause, a positive choice for evolution of the human species. *Climacteric J Int Menopause Soc*. 2013;16(2):205–213.
164. Labrie F. Intracrinology and menopause: the science describing the cell-specific intracellular formation of estrogens and androgens from DHEA and their strictly local action and inactivation in peripheral tissues. *Menopause*. 2019;26(2):220–224.
165. Judd HL, Fournet N. Changes of ovarian hormonal function with aging. *Exp Gerontol*. 1994;29(3–4):285–298.
166. Adashi EY. The climacteric ovary as a functional gonadotropin-driven androgen-producing gland. *Fertil Steril*. 1994;62(1):20–27.