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Clinical Significance of 11-Oxygenated Androgens

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Abstract

Purpose of review—The adrenal gland is considered a source of weak androgens, such as dehydroepiandrosterone, dehydroepiandrosterone sulfate, and androstenedione. Emerging evidence proposes a set of 11-oxygenated 19-carbon (11oxC19) adrenal-derived steroids as clinically important androgens. Such steroids include: 11 β -hydroxyandrostenedione, 11-ketoandrostenedione, 11 β -hydroxytestosterone and 11-ketotestosterone. This review will discuss the synthesis, androgenic activity and clinical implications of the 11oxC19 steroids.

Recent findings—The clinical relevance of the 11oxC19 steroids resides in two key characteristics: 1. the synthesis of all 11oxC19 originates predominantly in the adrenal cortex; and 2. 11-ketotestosterone and its 5 α -reduced metabolite, 11-ketodihydrotestosterone are potent agonists of the human androgen receptor, similar to the classic androgens testosterone and dihydrotestosterone, respectively. Recent studies have demonstrated higher than normal circulating levels of 11oxC19 steroids in patients with 21-hydroxylase deficiency and in polycystic ovary syndrome. The 11oxC19 steroids are also thought to contribute to castration-resistant prostate cancer progression. Additionally, the 11oxC19 steroids might have clinical implications in adrenarche and postmenopausal women.

Summary—Future prospective studies are needed to establish the clinical utility of the 11oxC19 steroids for individualized patient care. Preliminary data suggest that these biomarkers hold promise to improve the evaluation and management of androgen excess disorders.

Keywords

adrenal; androgens; 11-oxygenated 19-carbon steroids; 11 β -hydroxyandrostenedione; 11-ketotestosterone; congenital adrenal hyperplasia; castration resistant prostate cancer; polycystic ovarian syndrome

Introduction

The testis is the principal source of androgens in adult males, and its primary product, testosterone (T), is the major active androgen in the circulation of normal men.

Consequently, T has been assumed to be the major androgen in the circulation for women

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and children as well. In contrast, the adrenal gland is viewed as a source of “weak androgens,” which are really precursors of active androgens. These other 19-carbon steroids become relevant starting with adrenarche in children of both sexes and remain so throughout life in females. Pathologically, the adrenal androgen production is particularly important in several disorders of androgen excess, such as congenital adrenal hyperplasia (CAH) and polycystic ovary syndrome (PCOS); in androgen-dependent tumors, primarily castration-resistant prostate cancer (CRPC); and rarely, in androgen-producing adrenal tumors. Dehydroepiandrosterone (DHEA), DHEA sulfate (DHEAS), and androstenedione (A4) have been considered the major adrenal-derived C₁₉-steroids and have been utilized in clinical practice to ascertain the adrenal contribution to androgen excess. Emerging evidence suggests that a set of 11-oxygenated C₁₉ (11oxC₁₉) adrenal-derived steroids are clinically important androgens, which will be discussed in this review, along with anticipated directions of investigation.

The adrenal cortex as a source of androgens

The major C₁₉ adrenal-derived steroids DHEAS, DHEA and A4 lack androgenic activity, but all serve as precursors for active androgens, including T and dihydrotestosterone (DHT), via 1–4 enzymatic steps. Indeed, patients with defective DHEA sulfation exhibit androgen excess [1], while steroid sulfatase deficiency leads to lower DHEA and T [2]. The efficient synthesis of DHEA requires the cofactor protein cytochrome *b*₅ (CYB5A, *b*₅), which greatly enhances the 17,20-lyase activity of 17 α -hydroxylase/17,20-lyase (P450 17A1), and the conversion of DHEA to A4 utilizes the enzyme 3 β -hydroxysteroid dehydrogenase type 2 (HSD3B2) in the adrenal. While these two proteins are co-expressed in the testicular Leydig cells and the ovarian theca cells, they are segregated in separate zones in the adrenal cortex: HSD3B2 in the zonae glomerulosa and fasciculata and *b*₅ in the zona reticularis [3, 4]. This enzymatic distribution favors the synthesis of DHEA, with limited production of the downstream C₁₉ steroids A4 and T. Adrenal DHEA is then efficiently sulfonated to DHEAS by the sulfotransferase 2A1 (SULT2A1), making DHEAS by far the dominant adrenal-derived C₁₉ steroid. It has been proposed that A4 and downstream C₁₉ steroids are synthesized at the interface between the zona fasciculata and zona reticularis [3]. The androgenic synthetic capacity of the adrenal gland might be further amplified if the typical zonation and segregation of HSD3B2 and *b*₅ are disrupted, as we have observed in patients with (CAH) [5].

What are 11oxC₁₉ steroids? – Origins and androgenic activity

All 11oxC₁₉ steroids are synthesized with the contribution of the cytochrome P450 11 β -hydroxylase (P450 11B1), an enzyme predominantly expressed in the adrenal gland, where it catalyzes the last step in cortisol synthesis (Figure 1). P450 11B1 also utilizes A4 and T as substrates, yielding 11 β -hydroxyandrostenedione (11OHA4) and 11 β -hydroxytestosterone (11OHT), respectively [6]. Studies of adrenal-vein serum samples have demonstrated that 11OHA4 is the most abundant unconjugated C₁₉ steroid product of the human adrenal gland and that its synthesis is further enhanced by cosyntropin administration [7]. Smaller amounts of 11OHT, 11-ketoandrostenedione (11KA4), and 11-ketotestosterone (11KT) are also made in the adrenal gland, but the synthesis of 11KA4 and 11KT predominately occurs in

periphery, via 11 β -hydroxysteroid dehydrogenase type 2 (11 β HSD2). As shown by Storbeck and colleagues [8], 11KA4 is a much better substrate than 11OHA4 or A4 for the enzyme aldo-keto reductase 1C3 (AKR1C3/17 β -hydroxysteroid dehydrogenase type 5), which is expressed both in the adrenal zona reticularis and peripheral tissues. Although it has been proposed that 11KT might be a direct product of the testicular Leydig cells and ovarian theca cells, P450 11B1 expression in the gonads is insignificant compared with the adrenal cortex [9], and 11OHA4 is a poor substrate for 17 β -hydroxysteroid dehydrogenase type 3 (17 β HSD3), the testicular isoenzyme responsible for conversion of A4 to T [8]. Furthermore, 11KT concentrations are similar in adrenal vein samples and in peripheral serum of men and women, despite significantly higher circulating T in men [5, 9], suggesting that the gonadal-derived T is not an important source of 11OHT or 11KT. Additionally, only trace amounts of 11oxC19 steroids are detected in patients with primary adrenal insufficiency [5].

Although the capacity of the human adrenal to synthesize 11OHA4 has been recognized since the early 1970s [10], a significant contribution of 11oxC19 steroids to human androgen biology has been generally dismissed. Although the dogma that T and DHT are the dominant androgens in human beings has prevailed, this paradigm applies only to normal men. In contrast, the importance of 11oxC19 steroids as androgens in other species has been firmly established. The testes of teleost fishes produce little T, because a P450 11B1 homolog is highly expressed in fish testis. Instead, 11KT is the major androgen synthesized and the androgen responsible for spermatogenesis. Recent studies have demonstrated that 11KT is also a potent agonist of the human androgen receptor (AR, NR3C4). Rege and colleagues used an MDA-kb2 cell model expressing the human AR and found that the maximum androgenic activity of 11KT was indistinguishable from that of T, with an EC₅₀ only 5-fold higher than T [7]. The maximal androgenic activity of 11OHT was lower and EC₅₀ higher than those values for 11KT. In a recently optimized *in vitro* reporter system specific for the human AR and without the confounding presence of glucocorticoid, mineralocorticoid or progesterone receptors, 11KT was again confirmed to be a potent androgen, and 11OHT was less potent [11]. In contrast, 11KA4 and 11OHA4 had minimal androgenic activity in both systems. Similar results were observed using a human AR reporter system derived from COS-1 cells [8]. A potential limitation of these heterologous systems is that intracellular steroid metabolism from endogenous mammalian enzymes in these cells could influence results, unlike yeast-based reporter systems lacking this background metabolism [12]. Furthermore, Storbeck and colleagues showed that the 5 α -reduced metabolite of 11KT, 11keto-dihydrotestosterone (11KDHT), had similar androgenic activity as DHT, which is considered the most potent endogenous androgen [8]. The androgenic activity of 11 β -hydroxydihydrotestosterone (11OHDHT) was superior to that of 11OHT, but below that of 11KT.

The above lines of evidence illustrate two important characteristics of 11oxC19 steroids, which promote them as promising biomarkers and clinically important mediators of adrenal androgen excess: 1. 11oxC19 steroids originate almost exclusively from the adrenal cortex; and 2. 11KT and 11KDHT are potent androgens in humanized systems. We will now explore some of the clinical implications of 11oxC19 steroids in specific disorders, including CAH, PCOS, CRPC, and adrenarche.

CAH

CAH represents a heterogeneous group of autosomal recessive defects in cortisol biosynthesis [13]. Due to the impaired cortisol production, the negative feedback to the pituitary gland and hypothalamus is reduced, promoting chronic adrenocorticotropin (ACTH) elevation. In turn, the ACTH rise stimulates steroidogenesis, and along with the specific enzymatic blockage, leads to accumulation of products derived from the accessible pathways. In the case of 21-hydroxylase (P450 21A2) deficiency (21OHD), which is the most prevalent form of CAH, the adrenal glands produce excessive amounts of androgens [14]. The disease spans a wide spectrum of clinical presentations, which is determined in great part by the degree of enzymatic impairment. Severely affected individuals with minimal residual P450 21A2 activity have cortisol deficiency and are said to have classic 21OHD, and these girls also present with virilized external genitalia from prenatal androgen excess. Patients with milder or nonclassic forms of 21OHD are able to produce normal amounts of cortisol, but nonclassic 21OHD patients also exhibit adrenal-derived androgen excess and can present with premature pubarche, rapid somatic growth, hirsutism, acne or subfertility.

Despite the profound clinical manifestations and abundant biochemical evidence of androgen excess in 21OHD, the contributions of specific androgens and pathways of their synthesis at various stages of life remain elusive. The characteristic adrenal C₁₉ steroids, DHEAS and DHEA, are often paradoxically low in patients with classic 21OHD, even with under-treatment [15]. We have recently shown that pregnenolone sulfate is approximately 3-fold higher in patients with classic 21OHD than in sex- and age-matched unaffected individuals, whereas DHEAS and DHEA are 6- to 7-fold lower [5]. Peripheral metabolism of adrenal-derived DHEAS and DHEA, therefore, cannot account for the androgen excess of 21OHD. Kamrath and colleagues provided evidence for the direct adrenal production of the 5 α -reduced androgen androsterone via the “backdoor pathway” during the first year of life, consistent with adrenal-derived androsterone as the source of DHT (Figure 2) in the developing fetus [16], as also observed in P450-oxidoreductase deficiency [17]. In this study, the contribution of adrenal-derived androsterone, however, was not observed in older children or adults receiving treatment [16]. A more recent study of adults with classic 21OHD analyzed urinary steroid metabolites during conventional glucocorticoid treatment and found a significant contributions from the “backdoor pathway” to the total androgen burden, whereas excretion of 11 β -hydroxyandrosterone, a major metabolite of 11OHA4, was highly variable [18].

A4 and, in women, T are routinely used as biomarkers of 21OHD control; however, these steroids correlate poorly with clinical findings of androgen excess in patients with 21OHD [19, 20]. A4 and T are also synthesized in the gonads, explaining at least in part their poor clinical utility in adolescents and adults with 21OHD. Might 11oxC₁₉ steroids be important androgens in 21OHD? We have found that all 11oxC₁₉ steroids are 3 to 4-fold higher in treated patients with classic 21OHD of both sexes than in age- and sex-paired controls [5]. Furthermore, 11KT is twice as high as T in women and poorly controlled men with 21OHD. Indeed, in the same study we showed that 11KT correlates directly with T in females with 21OHD, but 11KT and T tend to correlate inversely in male patients [5]. Similarly, in a more

recent study of 114 patients with classic 21OHD ages 2 to 67 years (median, 15; 59% younger than 18), we confirmed a direct correlation between T and all four 11oxC19 steroids in females of all Tanner stages. In this study, we found that T correlated positively with all 11oxC19 steroids in boys of Tanner stages 1–2 but negatively in males who reached Tanner stage 5. These findings suggest that, in poorly controlled post-pubertal males with 21OHD, 11KT is the major adrenal-derived androgen responsible for gonadotropin suppression and poor testicular production of T [5]. The ratio of 11KT/T could serve as an excellent clinical indicator of disease control in patients with 21OHD, particularly in post-pubertal males.

While the dynamics of the 11oxC19 steroid synthesis remain to be determined in prospective trials, our recent cross-sectional study of patients with classic 21OHD suggests that these steroids also reflect long-term disease control [21]. Of the 23 steroids measured, the four 11oxC19 steroids and 21-deoxycortisol, which are all P450 11B1 products, showed the tightest correlations with adrenal volume as assessed by computed tomography. The 11oxC19 steroids were also found to be significantly higher in male patients with testicular adrenal rest tumors (TART) than in those without TART of similar ages. The 11oxC19 steroids did not correlate with TART size, but in the subset of patients who had both testicular ultrasound and abdominal imaging, the median adrenal volume was higher in patients with TART than in those without. Thus, it remains unclear if the higher 11oxC19 steroid concentrations in the former group simply reflect a larger adrenal tissue mass capable of producing 11oxC19 steroids.

PCOS

PCOS is a common endocrinopathy, affecting up to 10% of women of reproductive age. Unlike 21OHD, which is a monogenic disease with autosomal recessive inheritance, PCOS is likely a heterogeneous condition, and its pathogenesis remains poorly understood. Complex genetic and epigenetic factors are thought to interact in the development of PCOS and its phenotypic expression [22]. PCOS and nonclassic 21OHD have several common phenotypic features and are difficult to distinguish clinically. Despite heterogeneity and controversy, clinical and/or hormonal evidence of androgen excess is the major defining feature of PCOS. Additional manifestations of PCOS include ovarian dysfunction, manifest as oligo- or anovulation with or without ultrasound evidence of polycystic ovaries, and features of the metabolic syndrome, such as insulin resistance, obesity, dyslipidemia and nonalcoholic steatohepatitis in various combinations.

The ovary was originally regarded as the primary source of androgen excess in PCOS. It has been now recognized for over two decades that the adrenal gland also contributes to the androgen pool in many patients with PCOS. While gonadal steroidogenesis is under the regulation of gonadotropins, ACTH is the primary driver of androgen synthesis from the zona reticularis of the adrenal cortex. Dynamic studies conducted in women with PCOS have demonstrated that some androgen production persists when the pituitary-gonadal axis is suppressed with gonadotropin-releasing hormone agonists and that the circulating androgens can also be lowered with exogenous glucocorticoids [23, 24]. In addition, women with PCOS mount an exaggerated adrenal steroidogenesis response to cosyntropin,

indicating alterations in adrenal steroidogenic for these patients [25]. Numerous studies have reported elevated serum concentrations of DHEA and DHEAS in women with PCOS, albeit with variable frequency, supporting the idea that an adrenal steroidogenic derangement exists in a subset of PCOS patients.

Recognizing that many women with PCOS have mixed ovarian and adrenal components of androgen excess, investigators have long tried to identify biomarkers, which could distinguish between the two sources. Owing to its adrenal-specific origin, 11OHA4 has been proposed to be such a biomarker since the late 1980s and early 1990s, but results have been inconsistent. Some [26], yet not all studies [27, 28] have reported elevations of 11OHA4 in women with PCOS as compared to controls. These discrepant results can be explained by variability in the immunoassays used, but also by the heterogeneity of the groups studied. The ratio between A4 and 11OHA4 has been found to be elevated in women with PCOS and lower in women with nonclassic 21OHD, demonstrating a more consistent adrenal component of androgen excess in nonclassic 21OHD than in PCOS [28, 29]. Advances in steroid assays that have occurred in recent years, particularly the implementation of liquid chromatography/tandem mass spectrometry (LC-MS/MS), have allowed not only more accurate quantitation of key steroids but also the simultaneous measurement of multiple biomarkers from small biological samples [30, 31].

In a recent study of 114 women with PCOS and 49 healthy controls, LC-MS/MS and gas chromatography/tandem mass spectrometry (GC-MS/MS) were employed to measure traditional and 11oxC19 androgens in peripheral serum and in 24 h urine collections, respectively [32]. The serum concentrations of all four 11oxC19 steroids, 11OHA4, 11KA4, 11OHT and 11KT, were significantly higher in women with PCOS than in controls, as was the urinary excretion of 11 β -hydroxyandrosterone, a major metabolite of 11OHA4. In PCOS women, A4, 11OHA4 and 11KA4 represent a greater fraction of total androgens than in controls. Interestingly, 11OHA4 and 11KA4, but not 11OHT or 11KT, correlated significantly albeit weakly with markers of insulin resistance, including BMI, fasting glucose and HOMA-IR. Thus, 11OHA4 and 11KA4 might also serve as biomarkers for increased metabolic risk in women with PCOS. Surprisingly, however, no significant differences in any of the 11oxC19 steroids were noted between lean and obese women with PCOS, presumably due to insufficient statistical power for subgroup analysis. The lack of correlation between 11OHT and 11KT with BMI might also constitute a surprise, given a positive correlation between BMI and T. The authors remark that T can be synthesized in adipose tissue from A4 via the AKR1C3, while 11OHA4 is a poor substrate for peripheral AKR1C3 [8]. Furthermore, while 11KT could derive from 11KA4, the authors propose that the expression of 11 β HSD type 1 in adipose tissue favors the reduction of 11KA4 to 11OHA4 [32].

Castration-resistant prostate cancer (CRPC)

Androgens promote prostate cancer progression, and the initial therapy for advanced disease relies on surgical (bilateral orchiectomy) and/or medical castration, using gonadotropin-releasing hormone (GnRH) agonists or antagonists, with or without anti-androgens. Circulating T declines drastically following androgen deprivation therapy, but the cancer

eventually progresses in most patients, and this stage is clinically referred to as CRPC. The abundance of DHT in recurrent prostate cancer tissue is preserved despite suppression of serum T [33], and the adrenal gland remains an important source of DHT precursors after castration. Ablation of adrenal-derived androgens with the P450 17A1 inhibitor abiraterone acetate improves survival in CRPC [34, 35], which illustrates the clinical significance of residual androgen biosynthesis during GnRH agonist/antagonist therapy. Adrenal A4 is a preferred substrate as compared to T for 5 α -reductase type 1 (SRD5A1), the dominant isoenzyme in CRPC, and A4 is thus funneled to DHT via 5 α -androstane-3-one (5 α -dione) [36].

Beyond T and DHT, other androgens might be involved in CRPC progression. The adrenal gland produces 11OHA4 at higher rates than A4, but both have minimal androgenic activity [7]. Storbeck and colleagues showed that the LNCaP androgen-dependent prostate cancer cell line metabolizes 11OHA4 to 11KT and 11KDHT, steroids that bear similar androgenic activity as T and DHT, respectively [8]. Recently, du Toit and colleagues assessed, for the first time, the presence of 11oxC19 steroids in two CRPC tissue samples and in the peripheral serum of other two patients with CRPC. The most abundant C₁₉ steroid in the prostate tissue of both patients was 11OHA4, while the other steroids demonstrated variable concentrations [37]. In the peripheral serum of the two patients with CRPC studied, concentrations of 11KT and 11KDHT were considerably higher than those of T and DHT, respectively.

Additional mechanisms proposed to contribute to CRPC progression include AR gene amplification and activating AR mutations within CRPC cells. Intratumoral metabolism can activate or inactivate key steroids and thus regulate AR activation via a pre-receptor mechanism [38]. Steroids can be inactivated via 3 α -hydroxysteroid dehydrogenases (3 α HSD), and/or by conjugation, such as the sulfation or glucuronidation reactions carried out by sulfotransferase and uridine 5'-diphospho-glucuronosyltransferase (UGT) enzymes, respectively. In an *in vitro* model provided by two androgen-dependent prostate cancer cell lines (LNCaP and VCaP), 11KT and 11KDHT were metabolized to inactive products significantly more slowly than T and DHT, respectively [39]. Furthermore, du Toit and colleagues showed that while most T was conjugated to T-glucuronide by 48 h in the LNCaP cells, 11KT and 11KDHT were only poorly glucuronidated [37]. These findings suggest that intracellular 11KT and 11KDHT remain available to activate AR longer than T and DHT. Indeed, using the same cell lines, Pretorius and colleagues showed that 11KT and 11DHT activate the expression of endogenous AR-regulated genes (*KLK3*, *TMPRSS2* and *FKBP5*) and induced cellular proliferation [39].

Adrenarche

Adrenarche is clinically defined as the appearance of axillary and pubic hair in children, which typically begins around age 8. Because adrenarche is independent of puberty and does not occur in children with androgen insensitivity, adrenarche is regarded as the onset of adrenal-derived androgen production [40]. These phenotypic changes correlate temporally with the development of the adrenal zona reticularis and a rise in circulating DHEAS concentrations. Although previously considered a developmental phenomenon unique to late

childhood, careful analysis of urinary steroids in young children demonstrate a logarithmic rise in serum DHEAS from birth [41]. DHEAS is the traditional biomarker of adrenarche and is assumed to be the precursor of the androgen(s) that cause the phenotypic changes of adrenarche, but 11oxC19 steroid might participate in these changes. One small study found that serum 11OHA4 concentrations rose from 2.5 to 6.4 nmol/L during childhood in both boys and girls, consistent with 11OHA4 as a biomarker of adrenarche [42]. Emerging evidence from preliminary studies have confirmed these earlier findings using mass spectrometry assays and suggest that 11oxC19 steroids are relevant androgens during adrenarche [43]. Large cross-sectional and longitudinal studies are necessary to determine the contribution of 11oxC19 steroids to normal, delayed, and premature adrenarche.

Conclusions and future directions

The biologic significance of 11oxC19 steroids is not limited to fish reproduction and extends to human physiology and disease states. Recent studies implicate 11oxC19 steroids as significant if not the dominant adrenal-derived androgens in human beings, with complex peripheral metabolic pathways and specific properties that enhance their functions as androgens and androgen precursors. With an androgenic potency comparable with that of T and DHT, respectively, 11KT and 11KDHT are likely to be recognized as important androgens in several clinical scenarios. Furthermore, 11OHA4 and 11KT might best reflect the adrenal contribution to the circulating pool of androgens. In contrast to T and A4, 11oxC19 steroids remain stable or increase after menopause [44]. In fact, 11OHA4 and 11KT have been shown to be more abundant than their respective precursors, A4 and T, even in healthy women [5, 32]. These findings challenge the canonical view, which maintains T as the cornerstone in the clinical evaluation of hyperandrogenism and DHEAS as the most relevant biomarker of adrenal androgen production.

The era of customized biomarkers is emerging and is likely to evolve rapidly in the coming years. The application of mass spectrometry to steroid profiling has highlighted the importance of several previously neglected metabolites, amongst which the 11oxC19 steroids discussed here constitute only one such example. To further establish the clinical utility of 11oxC19 steroids, multiple research questions remain to be answered: Do these 11oxC19 steroids have a circadian rhythm? What fractions are free and protein-bound? What are their dynamic changes with glucocorticoid therapy as compared with established biomarkers? How do they correlate with clinical evidence of androgen excess, such as hirsutism, acne or infertility? Do they have bone or sexual health benefits in postmenopausal women? Carefully designed and replicated clinical studies are necessary to implement these and other under-appreciated steroid biomarkers in patient care protocols.

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Key points

- The adrenal gland produces a unique set of 11-oxygenated 19-carbon (11oxC19) steroids with the contribution of cytochrome P450 11 β -hydroxylase (P450 11B1), a key enzyme in cortisol synthesis, which is predominantly expressed in the adrenal gland.
- The 11oxC19 steroids include 11 β -hydroxyandrostenedione (11OHA4), 11-ketoandrostenedione (11KA4), 11 β -hydroxytestosterone (11OHT) and 11-ketotestosterone (11KT). In women, 11OHA4 and 11KT are more abundant than their precursors, androstenedione (A4) and testosterone (T).
- 11KT and its 5 α -reduced metabolite, 11-ketodihydrotestosterone (11KDHT) are strong agonists of the human androgen receptor, with potencies similar to the classic androgens T and dihydrotestosterone (DHT), respectively.
- The 11oxC19 steroids are likely to emerge as clinical biomarkers of adrenal androgen excess.
- Further studies are needed to determine how to best utilize clinical measurements of 11oxC19 steroids in patients with 21-hydroxylase deficiency, polycystic ovary syndrome, and castration-resistant prostate cancer, as well as in children with premature adrenarche and postmenopausal women.

Figure 1.

Adrenal androgen synthesis.

Preg, pregnenolone; 17OH-Preg, 17-hydroxypregnenolone; DHEA(S), dehydroepiandrosterone (sulfate); A-diol, androst-5-ene-3 β ,17 β -diol; A4, androstenedione; T, testosterone; 11OHA4, 11 β -hydroxyandrostenedione, 11KA4, 11-ketoandrostenedione; 11OHT, 11 β -hydroxytestosterone; 11KT, 11-ketotestosterone; StAR, steroidogenic acute regulatory protein; CYP11A1, cholesterol side-chain cleavage; HSD3B2, 3 β -hydroxysteroid dehydrogenase type 2; CYP17A1, 17 α -hydroxylase/17,20-lyase; CYB5A, cytochrome *b5* type A; CYP11B1, 11 β -hydroxylase; AKR1C3, 17 β -hydroxysteroid dehydrogenase type 5; HSD11B2, 11 β -hydroxysteroid dehydrogenase, type 2; SULT2A1, sulfotransferase 2A1.

Figure 2.

Adrenal steroidogenic pathways in 21-hydroxylase deficiency.

DHEA, dehydroepiandrosterone; A4, androstenedione; T, testosterone; 11OHA4, 11β-hydroxyandrostenedione, 11KA4, 11-ketoandrostenedione; 11OHT, 11β-hydroxytestosterone; 11KT, 11-ketotestosterone; DHT, dihydrotestosterone; 11OHDHT, 11β-hydroxydihydrotestosterone; 11KDHT, 11-ketodihydrotestosterone; HSD3B2, 3β-hydroxysteroid dehydrogenase/isomerase type 2; CYP17A1, 17α-hydroxylase/17,20-lyase; CYB5A, cytochrome *b*₅ type A; CYP11B1, 11β-hydroxylase; AKR1C3, 17β-hydroxysteroid dehydrogenase type 5; HSD11B2, 11β-hydroxysteroid dehydrogenase, type 2; SRD5A1/2, 5α-reductase, types 1 and 2; AKR1C2,4, aldo-keto reductase types 1C2 and 1C4; HSD17B6, 17β-hydroxysteroid dehydrogenase type 6.