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Androgen-Secreting Adrenal and Ovarian Neoplasms

Michel Pugeat, Gérald Raverot, Ingrid Plotton, Aude Brac de la Perrière, Pascale Mirakian, Henri Déchaud, Nicole Berger, and Jean Louis Peix

SUMMARY

Androgen-secreting neoplasms (ASNs) are generally associated with rapidly progressive symptoms of hyperandrogenism, which result in various degrees of virilization. A plasma concentration of testosterone of more than 200 ng/dL (8.7 nmol/L) (or two to three times the upper normal range) with a normal dehydroepiandrosterone sulfate (DHEAS) level is highly suggestive of an ovarian ASN. The value of low dexamethasone suppression test is associated with high sensitivity but limited specificity in differential diagnosis of hyperandrogenism. Suppression of testosterone levels by administration of a progestogen or gonadotropin-releasing hormone agonist will not discriminate an ovarian ASN from hyperthecosis, but will strongly orientate the diagnosis to the ovarian origin of androgen excess. Ovarian and adrenal venous catheterization and sampling should be reserved for patients in whom the presence of a small ovarian tumor cannot be excluded on imaging studies and restrictive to expert unit.

The prognosis for ovarian ASNs is generally good, although some Sertoli and granulosa cell tumors can be aggressive and malignant, requiring surgery and chemotherapy. In postmenopausal women hysterectomy and bilateral salpingo-oophorectomy is the preferred treatment because of the high incidence of associated endometrial lesions. In young women in whom fertility is an issue, a unilateral salpingo-oophorectomy must be performed. In contrast, the prognosis of adrenocortical carcinoma is poor, but early surgical treatment can be life-saving. Mitotane (o,*p*'-DDD) is the recommended treatment for adrenal carcinoma in patients who cannot be cured by surgery.

Key Words: Androgen-secreting neoplasms; adrenocortical carcinoma; Sertoli–Leydig cell tumors; virilization; hirsutism.

1. INTRODUCTION

In women, acne and excess hair growth are generally associated with excessive androgen production *(1)*. Their prevalence is estimated to be 5–15% within the female population, with a likely genetic variability *(2)*. Although hirsutism and acne are not considered diseases *(3)*, the social prejudice of pilosebaceous male pattern is a frequent reason for a medical consultation. In practical medicine, consultation provides the opportunity to identify androgen disorders that require treatment and prevention, such as the polycystic ovary syndrome (PCOS) or 21-hydroxylase-deficient nonclassic adrenal hyperplasia (NCAH). The clinician should not misdiagnose the rare androgen-secreting neoplasm (ASN), which is potentially malignant and requires specific treatment. This chapter will review our current knowledge and propose a paradigm for laboratory investigation to identify adrenal and ovarian ASNs.

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2. BACKGROUND

2.1. Pathogenesis

2.1.1. Adrenal ASNs

The prevalence of adrenocortical carcinomas approximates two new cases per million of population per year (*see* ref. 4). In about 60% of cases *(5–7)* adrenocortical carcinoma produces hormones independently or in combination. The incidence of Cushing's syndrome or symptoms of excessive androgens is estimated to be approximately 30% and approximately 10%, respectively, and the incidence of combined excessive androgen and cortisol secretion is approximately 20%.

Hormone-secreting benign adrenal adenomas are rare; equally rare are hormonally silent or hormone-secreting adrenocortical carcinomas. Diffuse or nodular adrenocortical hyperplasia can be associated with genetic deficiency of cortisol synthesis or a part of the Carney's complex. The differentiation from benign to malignant adrenocortical neoplasms seems to occur via a multistep process that has been described within a tumor from one patient *(8)*. Local recurrence or distant metastasis cannot be predicted solely on the microscopic appearance of the tumor. However, histological classification and tumor–node–metastasis staging *(9)* and Weiss criteria *(10)* are currently used to suspect the malignancy of steroid-secreting adrenal tumor. A few cases of adrenocortical tumor have been described in patients with 21-hydroxylase deficiency *(11,12)*, but causality is unlikely. Indeed, adrenocorticotropic hormone (ACTH)-induced diffuse or nodular hyperplasia is polyclonal, in contrast to the monoclonal identity of most adrenal adenomas and carcinomas *(13,14)*.

2.1.2. Ovarian ASNs

Ovarian cancer is the sixth most common cancer among women. The annual incidence rates differ according to geographic area, with a high rate in Scandinavia (15/100,000) and a low rate in Japan (3/100,000). Ovarian cancer may derive from coelomic epithelium, stromal (e.g., granulosa) cells, and germ cells, the latter almost always arising in children and young adults during the first decades of life. The 2003 World Health Organization (WHO) histological classification of sex cord-stromal, Sertoli-stromal, and steroid cell tumors is depicted in Table 1. This classification encompasses most ASNs that are well differentiated and benign, although some intermediate or poorly differentiated tumors can be malignant and aggressive.

The vast majority of epithelial ovarian cancers are sporadic, whereas 5–10% are estimated to be inherited. The breast–ovarian cancer syndrome is the most common inherited type and has been linked to germline mutations in the *BRCA1* tumor-suppressor gene *(15)*. No heritability has been reported for ovarian ASN. Interestingly, one study reported that a heterozygous inactivating mutation (F591S) located in the sixth transmembrane domain of the gene encoding follicle-stimulating hormone (FSH) receptor was found in 9 of 13 patients with sex cord tumors (69%) and 2 of 3 ovarian small cell carcinomas, but not in a control population *(16)*. In contrast, no evidence for a role for activating mutations or polymorphisms of FSH receptors was subsequently reported in 15 granulosa cell tumors *(17)*. This discrepancy suggested that the F591S mutation, which was observed in young patients, might be a distinct subgroup of granulosa cell tumors *(17)*.

Significant concern has been focused on the risk of epithelial ovarian cancer after treatment of infertility *(18,19)*. Several cases of ovarian cancer were reported in infertile women receiving infertility drugs. In one study, granulosa cell tumors were the most common ovarian tumor in infertile women receiving clomiphene citrate and gonadotropin *(20)*. It has been proposed that gonadotropins might be associated with the development of ovarian tumors. One hypothesis is that after ovulation, the mitotic activity required to repair the ovarian epithelium increases the likelihood of genetic abnormalities, such as mutations of the *p53* gene, which leads to malignant transformation *(21)*. However, women with increasing parity have been found to have a strong protection against epithelial ovarian cancer (*see* ref. 22). Therefore, this "repetitious ovulatory activity" or "gonadotropins" hypothesis in relation to ovarian carcinogenesis remains to be elucidated.

Table 1
World Health Organization 2003 Histological Classification Including Most Ovarian Androgen-Secreting Tumors

Sex cord stromal tumors	Sertoli stromal cell tumor
Granulosa stromal cell tumors	Sertoli–Leydig cell tumor group (androblastomas)
Granulosa cell tumor group	Well differentiated
Adult granulosa cell tumor	Of intermediate differentiation
Juvenile granulosa cell tumor	Variant with heterologous element
Thecoma-fibroma group	Poorly differentiated (sarcomoid)
Thecoma, not otherwise specified	Variant with heterologous element
Typical	Stromal Leydig cell tumor
Luteinized	Retiform
Fibroma	Variant with heterologous element
Cellular fibroma	Sex cord stromal tumors of mixed or unclassified type
Fibrosarcoma	Sex cord tumor with annular tubules
Stromal tumor with minor sex cord elements	Gynandroblastoma (specific components)
Sclerosing stromal tumor	Sex cord stromal tumor, unclassified
Signet-ring stromal tumor	Steroid cell tumors
Unclassified (fibrothecoma)	Stromal luteoma
	Leydig cell tumor group
	Hilus cell tumor
	Leydig cell tumor, nonhilar type
	Leydig cell tumor, not otherwise specified
	Steroid cell tumor, not otherwise specified
	Well differentiated
	Malignant

Adapted from ref. *14a*.

2.2. Diagnosis

2.2.1. History and Symptoms

Virilization is defined as the development of male secondary sex characteristics, including enlargement of the clitoris (transverse diameter >10 mm), deepening of the voice, marked growth of facial and body hair, acne and seborrhea, and male-pattern balding. However, although hirsutism with menstrual irregularity is generally associated with PCOS or less frequently with NCAH *(23)*, in less than 1% isolated hirsutism may be the presenting symptom of an ASN. Therefore, this diagnosis must be ruled out in any patient with apparently simple hirsutism *(3)*.

There are some specific clinical expressions of ASNs, such as age of presentation, progression of symptoms, and size of the tumor. In prepubertal females, because of their relatively large volume, ovarian tumors are often easily palpable and can be identified by computed tomography (CT) scanning and pelvic ultrasonography. Isosexual precocious puberty in girls, defined by early development of the secondary sexual characteristics before the age of 8 years, with breast development and pubic and axillary hair growth followed by menarche, has been described in both ovarian and adrenal ASNs. However, heterosexual precocious puberty with appearance of sexual hair not accompanied by breast development as a result of predominant androgen effects is highly suggestive of an ASN. In adult premenopausal women, rapidly progressive symptoms of virilization are highly suggestive of tumoral hyperandrogenism.

Secondary amenorrhea or extreme oligomenorrhea is reported in most but not all premenopausal patients with an ASN. These symptoms may be masked by the use of oral contraceptives, which may

also decrease androgen secretion by the ovarian tumor. After the discontinuation of oral contraceptives, secondary amenorrhea accompanied by a rapid virilization is therefore one possible clinical finding.

In postmenopausal women, a long history of clinical hyperandrogenism cannot exclude the presence of an ovarian ASN. In most cases facial hirsutism with frequent shaving, male-pattern baldness, increased muscular development, and some deepening of the voice can be associated with a slowly growing Leydig (or hilus) cell tumor. Clitoromegaly, with an enlarged phallus diameter (>10 mm), is usual but sometimes difficult to identify. In contrast, a history of non-insulin-dependent diabetes and of infertility, with or without irregular menstrual cycles, late menopause, abdominal obesity, and acanthosis nigricans, is more suggestive of hyperthecosis and either PCOS or the Hyperandrogenic-insulin resistant-acanthosis nigricans (HAIR-AN) syndrome.

Adrenal androgen-secreting adenomas have been reported in both pre and postmenopausal women *(24)*. Some are human chorionic gonadotropin (hCG) or gonadotropin dependent. In contrast, androgen-secreting adrenocarcinomas are gonadotropin independent. They can secrete androgens exclusively *(25)* or in association to cortisol.

Symptoms of hypercortisolism (Cushing's syndrome) indicate an adrenal ASN in a patient with virilization, but can be observed in rare steroid cell tumors of adrenocortical type *(26)*. Combined symptoms of Cushing's syndrome and virilization are highly indicative for the diagnosis of secreting adrenal carcinoma. Cushing's syndrome is usually recognizable, with proximal muscle wasting, striae, and thin skin, although the presence of central obesity, glucose intolerance, and hypertension causes some confusion with PCOS.

2.2.2. Laboratory Investigation

2.2.2.1. Basal Measurement of Androgens

Screening for ASNs is generally achieved by the measurement of basal testosterone and dehydroepiandrosterone sulfate (DHEAS) plasma concentrations. In most ovarian ASNs, testosterone level is more than 200 ng/dL and DHEAS is within the normal range for age. Unfortunately, these cutoff values cannot guarantee the diagnosis in all cases *(27,28)*. Indeed, 20% of ovarian ASNs have total testosterone levels of below150 ng/dL *(15)*, although conversely testosterone levels greater than 150 ng/dL are extremely uncommon in patients with PCOS, the most common cause of hyperandrogenism in premenopausal women *(23)*. Moreover, while a normal DHEAS level is unlikely to be associated with an adrenal ASN *(29)*, a high DHEAS level can be observed in premenopausal patients with functional hyperandrogenism (30) and in a few ovarian steroid cell (lipid cell) or Sertoli–Leydig cell tumors *(31,32)*.

The basal androgen levels in one premenopausal and five postmenopausal patients presenting with virilization are depicted in Table 2 *(31)*. This limited experience and review of the literature suggests the following:

1. Small ovarian tumors can demonstrate episodic secretion of androgens; therefore, repeated androgen measurements for diagnosis may be required, notably in postmenopausal women presenting symptoms of virilization.
2. Postmenopausal women have the highest incidence of ovarian ASNs. In normal postmenopausal women, the plasma concentrations of androgens are considerably lower than in normal premenopausal women, and therefore androgen concentrations must be interpreted accordingly *(31)*.
3. Circulating levels of precursors of testosterone, Δ^4-androstenedione, and 17α-hydroxyprogesterone (17-OHP), as well as estradiol should be measured, because some ovarian secreting tumors may predominantly secrete testosterone precursors or estradiol, being either androgenic, estrogenic, or even both.
4. The 17-OHP concentrations were increased in all patients in our study, with the exception of one woman, who presented with a Leydig (hilar) cell tumor (patient 2, Table 2). An increased 17-OHP plasma concentration may also be suggestive of 21-hydroxylase deficiency, and therefore an ACTH test should be performed. On rare occasions, 21-hydroxylase deficiency has been reported in patients with Leydig cell or lipid ovarian tumor *(11,12,33)*. We found one patient with virilization and hyperthecosis (patient 5, Table 2) who had a 17-OHP concentration as high as 6289 ng/dL 60 minutes after intravenous ACTH. The diagnosis of homozygous 21-hydroxylase-deficient NCAH was confirmed subsequently by genetic molecular analysis.

Table 2
Basal Plasma Concentrations of Testosterone (T), Δ4-Androstenedione (A4), 17α-Hydroxyprogesterone (17-OHP), and Dehydroepiandrosterone Sulfate (DHEAS) in Six Women Presenting Symptoms of Virilization

Case	Age (yr)	T (ng/dL)	A4 (ng/dL)	17-OHP (ng/dL)	DHEAS (μg/dL)	Final diagnosis
1	77	706[a]	340[a]	350[a]	88	Granulosa cell tumor
2	66	310[a]	420[a]	53	202	Leydig (hilar) cell tumor
3	68	300[a]	215[a]	157[a]	202	Bilateral hyperthecosis
4	62	234[a]	233[a]	350[a]	90	Bilateral hyperthecosis
5	62	235[a]	132[a]	534[a]	39	Bilateral hyperthecosis + 21-hydroxylase deficiency (nonclassic)
Range for normal, Postmenopausal		16–32	31–75	12–103	35–210	
6	24	655[a]	512[a]	663[a]	273	Sertoli–Leydig cell tumor
Range for normal, premenopausal		12–43	45–230	16–85	60-295	

[a]Higher than normal range for age.

2.2.2.2. Gonadotropin Levels

Gonadotropin measurements are not required for the screening of patients with virilization. They are usually within the normal range, whether pre- or postmenopausal *(31)*. To date, no evidence of gonadotropin suppression by the excess androgens of functioning ASNs has been reported.

2.2.2.3. Suppression Tests of Androgen Secretion

Several suppression tests have been proposed for the evaluation of patients with suspected ASNs:

1. Dexamethasone-suppression test: This is the classic method for diagnosing adrenal ASNs. It has been claimed that an adrenal ASN is unlikely if the DHEAS level is within the normal range after dexamethasone administration *(29)*. The value of a 48-hour low-dose (2 mg) dexamethasone-suppression test has been evaluated in the differential diagnosis of hyperandrogenism in 211 hyperandrogenic women *(34)*. Testosterone suppression (>40% reduction or normalization) was associated with 100% sensitivity and 88% specificity in distinguishing patients with ovarian and adrenal ASNs from patients with nontumorous hyperandrogenism.
2. Gonadotropin-suppression test: This test can be achieved by the administration of a progestogen or long-acting gonadotropin-releasing hormone agonist (GnRHa). Progestogens can suppress androgens in patients with virilizing ovarian tumors, an effect probably mediated through gonadotropin suppression. GnRHa administration has also been reported to decrease plasma gonadotropin and androgen levels in patients with hyperthecosis or Leydig cell ovarian tumors. However, androgen suppression by a GnRHa will not discriminate hyperthecosis from ovarian secreting tumors, as shown in Table 3, although it will serve to indicate that the ovaries are the source of the excessive androgen secretion in a virilized patient *(31)*. These findings would need further investigation. Indeed, ovarian ASNs which are poorly differentiated or have luteinizing hormone receptor mutations may have androgen secretion independent of gonadotropins.

2.2.2.4. Nonsteroid Markers of Ovarian Secreting Tumors

hCG-producing ovarian tumors are of the germ cell type and do not secrete androgens, although some may be associated with minor symptoms of hyperandrogenism and slightly increased androgen levels.

Table 3
Total Testosterone (T), Androstenedione (A4,) and 17α-Hydroxyprogesterone (17-OHP) Levels in Five Women With Ovarian Androgen-Secreting Tumors, at Baseline, After Administration of a Long-Acting Gonadotropin-Releasing Hormone Agonist (GnRHa),[a] and Following Surgery

	T (ng/dL)			A4 (ng/dL)			17-OHP (ng/dL)		
	Basal	GnRHa	Postsurg	Basal	GnRHa	Postsurg	Basal	GnRHa	Postsurg
1	706	3	3	340	16	5	350	18	10
2	310	5	7	420	23	31	53	19	77
3	300	24	19	215	94	77	157	ND	ND
4	234	26	36	233	98	189	103	92	49
5	655	13	15	512	86	50	430	112	16

[a]D-Trp-6-GnRH, 3.75 mg im, monthly.
ND, not determined.

α-Fetoprotein (AFP) is generally expressed by germ cell ovarian tumors containing yolk sac elements. It has been reported that some Sertoli–Leydig cell tumors also express AFP, with immunostaining within Leydig and/or Sertoli cells or within heterologous elements (hepatoid cells) *(35)*. Of well-documented AFP-secreting Sertoli-Leydig cell tumors, 20–30% have a malignant prognosis. Thus, the measurement of AFP may be useful in detecting recurrence and/or metastasis in these cases.

Inhibin serum concentration was found to be high in three postmenopausal women with granulosa cell tumors. Furthermore, among 209 patients, inhibin was high in 92% of the mucinous, 17% of clear-cell, 15% of undifferentiated, and 19% of all the other ovarian carcinomas *(36)*. The measurement of serum inhibin levels is a useful diagnostic aid when monitoring for recurrence following surgery. The assays are applicable for postmenopausal women, when inhibin is physiologically low, and when studies are underway to assess its use in premenopausal women *(37)*.

The anti-Müllerian hormone (AMH) serum concentration, also known as müllerian-inhibiting substance was found to be very high in one patient with an ovarian sex cord tumor with annular tubules. The serum concentration of AMH correlated with the recurrence and/or the metastasis of the tumor throughout the patient's evolution *(38)*. AMH has been shown to be a specific marker of Sertoli and granulosa cell origin in ovarian tumors *(39)*. A highly sensitive AMH assay has been proposed for the monitoring of patients with granulosa cell tumor *(40)*.

2.2.3. Imaging Techniques

Adrenocortical tumors can be visualized by various radiological techniques, although ultrasound can only delineate an adrenal mass larger than 2 cm in diameter. Because of the adipose tissue that surrounds them, the adrenal glands are easily visible by CT scan, which can detect adrenal nodules smaller than 5 mm *(4)*. Magnetic resonance imaging (MRI) can provide additional information regarding the invasion of an adrenocortical carcinoma into blood vessels. However, it remains to be further documented whether MRI can distinguish between malignant tumors and nonfunctioning adenomas by comparing the ratio of the signal intensity of each type of adrenal mass to that of liver.

Androgen-secreting ovarian neoplasms can be visualized by transabdominal pelvic ultrasonography when tumor size is larger than 6–8 cm in diameter, although differentiation from normal ovarian structure is inaccurate. Transvaginal ultrasonography is able to detect neoplasms 1–3 cm in size and allows reproducible measurement of the ovaries, and thus it is more useful than pelvic ultrasonography in locating ovarian tumors. However, because stromal hyperthecosis mimics an ASN sonographically, caution is advisable. CT scanning has limited value in the diagnosis of ovarian

ASNs. In contrast, iodomethyl-norcholesterol scanning has been found to be useful in identifying ovarian tumors larger than 2 cm in size *(26)*.

2.2.4. Selective Venous Catheterization

Selective venous catheterization is an invasive technique that is not easy to perform and that carries a risk of intracorporeal hemorrhage and thrombosis. Its accuracy is operator-dependent and varies greatly according to the anatomical variability of the venous system *(41)*. However, in skillful hands, ovarian and adrenal vein catheterization is helpful in the preoperative assessment of virilized women to locate the source of excessive androgen production in patients suspected of having an ASN *(27,32,41)*.

2.2.5. Exploratory Laparotomy

Exploratory laparotomy is an invasive method of diagnosing ovarian ASNs, during which tumors can be located by elementary palpation. However, because ASNs can be associated with the development of typical polycystic-like ovaries *(42)*, direct ultrasonography of both ovaries during laparotomy will help identify the tumor *(31)*. Alternatively intraoperative measurement of testosterone in serum samples taken from each ovarian vein has also been useful in identifying small Leydig cell tumors *(43)*.

An ovarian ASN should be treated by ovariectomy. In addition, hysterectomy in postmenopausal women may be indicated when an endometrial lesion (e.g., endometrial hyperplasia/carcinoma) is suspected *(44)*. In our experience, three of four postmenopausal patients with an ASN or hyperthecosis had associated endometrial pathology, with subclinical adrenocarcinoma in one case *(31)*.

3. CONCLUSIONS/SYNOPSIS

Androgen-secreting neoplasms are generally associated with distinct clinical features and presentations, and are associated with rapidly progressive symptoms of hyperandrogenism that generally result in various degrees of virilization. The patient's history and clinical presentation are strong predictors for ASNs. A plasma concentration of testosterone greater than 200 ng/dL (8.7 nmol/L) (or two to three times the upper normal range) with a normal DHEAS level is highly suggestive of an ovarian ASN. A combined increased testosterone of greater than 200 ng/dL (8.7 nmol/L) with an elevated DHEAS level of more than 600 µg/dL (16.3 µmol/L) is highly suggestive of an adrenal ASN. Suppression and stimulation testing has a high degree of sensitivity, albeit low specificity, for the diagnosis of ASNs and is generally of limited value in the diagnosis of these neoplasms. Ovarian and adrenal venous catheterization and sampling should be reserved for patients in whom the presence of a small ovarian tumor cannot be excluded on imaging studies and restrictive to expert unit. The prognosis of ovarian ASNs is generally good, although some Sertoli and granulosa cell tumors can be aggressive and malignant, requiring surgery and chemotherapy. Alternatively, the prognosis of adrenocortical ASNs, namely carcinomas, is poor, although early surgical treatment can be lifesaving.

4. FUTURE AVENUES OF INVESTIGATION

Our understanding of the pathogenesis of ASNs has undergone major advances during the past decade. The identification of molecular defects in the hereditary syndrome responsible for adrenocortical tumors has guided the search for a candidate gene mutation in sporadic tumors *(46,47)*. Much remains to be done to identify relevant molecular alteration that will open new avenues for treatment.

Human ovarian ASNs are a potential model for studying theca cell steroidogenesis. From an autonomous Sertoli-Leydig cell tumor, a human ovarian theca-like cell culture model has been developed, found to be appropriate for the study of the molecular mechanisms regulating steroidogenesis *(48)*. A pluripotential model for human adrenocortical studies has been developed, the NCI-H295R cell line *(49)*, which is widely used for understanding the mechanism(s) of multidrug resistance of steroid-secreting adrenocortical carcinoma and adrenocortical physiology in general *(50)*.

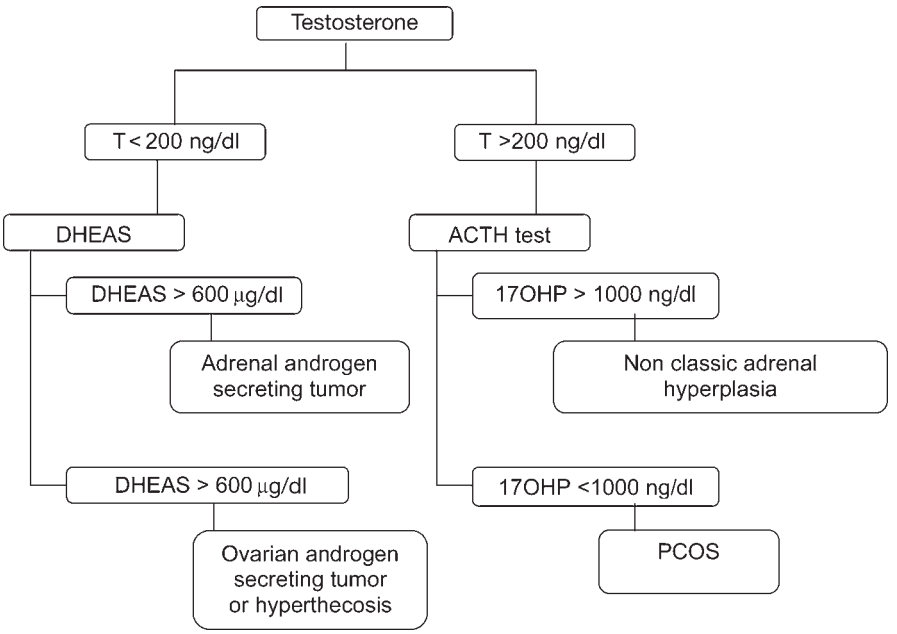

Fig. 1. Scheme of the laboratory investigation for identifying adrenal or ovarian androgen-secreting neoplasms in hirsute patients. T, testosterone;17-OHP, 17α-hydroxyprogesterone; DHEAS, dehydroepiandrosterone sulfate; ACTH, adrenocorticotropic hormone.

KEY POINTS

- Regardless of age of presentation, ASNs are generally associated with rapidly progressive symptoms of hyperandrogenism, which result in various degrees of virilization; secondary amenorrhea is common in premenopausal women.
- A plasma testosterone concentration of more than 200 ng/dL (or two to three times the upper normal range) with a normal DHEAS level is highly suggestive of an ovarian ASN. Combined increased testosterone greater than 200 ng/dL (8.7 nmol/L) with DHEAS greater than 600 µg/dL (16.3 µmol/L) is highly suggestive of an adrenal ASN (*see* Fig. 1).
- The value of the low dexamethasone suppression test in differential diagnosis of hyperandrogenism is associated with high sensitivity but limited specificity. Suppression of testosterone levels by administration of a progestagen or GnRHa will not distinguish an ovarian ASN from hyperthecosis, but will strongly orientate the diagnosis to the ovarian origin of tumoral testosterone level. Ovarian and adrenal venous catheterization and sampling should be reserved for patients in whom the presence of a small ovarian tumor cannot be excluded on imaging studies and restrictive to expert unit.
- The prognosis of adrenocortical carcinoma is poor, although surgical treatment can be life-saving. Mitotane (*o*,*p*'-DDD) is the only adrenal-specific agent available for treatment of adrenal carcinoma in patients who cannot be cured by surgery *(45)*.
- In postmenopausal women suspected of having an ovarian ASN, an abdominal hysterectomy and bilateral salpingo-oophorectomy is the preferred treatment because of the high incidence of associated endometrial lesions. In young women in whom fertility is an issue, only a unilateral salpingo-oophorectomy need be performed.
- Ovarian ASNs generally have a good prognosis, although some Sertoli and granulosa cell tumors can be aggressive, with malignant tumors requiring appropriate surgery and chemotherapy.

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