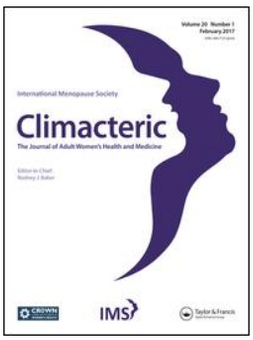

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REVIEW

Postmenopausal hyperandrogenism

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ABSTRACT

Postmenopausal hyperandrogenism is a state of relative or absolute androgen excess originating from the adrenal glands and/or ovaries clinically manifested by the presence of terminal hair in androgen-dependent areas of the body, and other manifestations of hyperandrogenism such as acne and alopecia or the development of virilization. In such circumstances, physicians must exclude the possibility of rare but serious androgen-producing tumors of the adrenal glands or ovaries. Worsening of undiagnosed hyperandrogenic disorders such as polycystic ovary syndrome, congenital adrenal hyperplasia, ovarian hyperthecosis, Cushing syndrome and iatrogenic hyperandrogenism should be considered for differential diagnosis. Elevated serum testosterone not only causes virilizing effects, but also will lead to hypercholesterolemia, insulin resistance, hypertension and cardiac disease. An ovarian androgen-secreting tumor, which is diagnosed in 1–3 of 1000 patients presenting with hirsutism, comprises less than 0.5% of all ovarian tumors. Adrenal tumors, including non-malignant adenomas and malignant carcinomas, are less common than ovarian tumors but cause postmenopausal virilization. Measurement of serum testosterone, sex hormone-binding globulin, dehydroepiandrosterone sulfate, androstenedione and inhibin B is necessary in postmenopausal women with the complaints and signs of hyperandrogenism. Some tests to discard Cushing syndrome should also be done. After an etiological source of androgen hypersecretion has been suspected, we recommend performing magnetic resonance imaging of the adrenal glands or ovaries. Medical management with gonadotropin-releasing hormone agonist/analogues or antagonists has been reported for women who are either unfit for surgery or in whom the source of elevated testosterone is unidentified.

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Introduction

After menopause, estrogen levels are reduced rapidly; however, androgen secretion declines gradually and is maintained until later stages of life [1]. Luteinizing hormone (LH) stimulation is the reason for androgen secretion in premenopausal and postmenopausal women [1]. A decrease in sex hormone-binding globulin (SHBG) together with a sharp decrease in estrogen levels causes an increase in free androgens [2].

High androgen levels adversely alter the lipid profile with a decrease in high-density lipoprotein, an increase in low-density lipoprotein and an increase in triglyceride levels [3]. The levels of advanced glycation end products and testosterone have been reported to be associated in postmenopausal women [4]. Moreover, a high testosterone to estradiol ratio was correlated with impaired insulin resistance and high blood pressure. Additionally, high testosterone levels in women were reported to link with increased risk of breast cancer and cardiac disease. Postmenopausal women with hyperandrogenemia had more evidence of coronary artery disease, as well as more metabolic syndrome, diabetes and obesity [5].

Because of these significant adverse effects on the health of postmenopausal women, a thorough evaluation and treatment are required in postmenopausal women who present with hyperandrogenism. However, the identification of that source often poses a clinical challenge [6]. Possible endogenous sources of the elevated androgen levels include ovarian hyperthecosis (OH) (i.e. hyperplasia of androgenic ovarian tissue) [7–9], ovarian tumors [10–12] and adrenal tumors [13]. Cushing syndrome is also a rare condition producing hyperandrogenism but is not associated with virilization.

The diagnosis of a cause of androgen excess in postmenopausal women may not always be straight-forward. A combination of clinical judgment accompanied with appropriate laboratory tests and imaging techniques should be used [1].

Even though normal androgen cut-off levels are not set for the menopausal period, it is widely presumed that the levels are below those of premenopausal women [14,15]. Meanwhile, patients with non-tumorous hyperandrogenism have higher androgen levels when compared with postmenopausal women who are non-hyperandrogenic [16]. For women with testosterone levels >100–140 ng/dl, tumorous hyperandrogenism should be suspected.

Signs and symptoms

A minority of women with polycystic ovarian syndrome (PCOS) continue to experience persistent hyperandrogenism

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after the climacteric age [17] whether or not they were diagnosed prior to the menopausal transition. A history of postpubertal menstrual irregularity, androgen excess symptoms (oily skin, acne, hirsutism), weight gain and/or metabolic syndrome, and difficulty in conceiving a child, should suggest undiagnosed premenopausal PCOS [18,19]. The timing of acneform eruptions, whether during puberty, during the perimenopausal period or of sudden-onset appearance, is other knowledge of importance. The relative timeline coinciding with the onset of hirsutism and/or acne should be asked.

Hirsutism on the face and/or trunk together with loss of hair on their head are the main complaints of most postmenopausal women with hyperandrogenism. An increase in terminal hair growth, especially on the chin, upper lip and abdomen, is a diagnostic sign for hirsutism [20]. The severity of hirsutism can be measured by the Ferriman–Gallwey score [5], for which a score of 0–4 is assigned for each type of hair growth in nine body areas. In premenopausal women, hirsutism is diagnosed when a score >8 or sometimes >16 is summed (Figure 1) [21]. Nevertheless, the score in postmenopausal women has not yet been validated.

Differential diagnosis between progressive hirsutism and true virilization necessitates a detailed history. Virilization is a manifestation of a more profound hyperandrogenism that includes the combination of severe hirsutism together with anabolic appearance, lowering of the voice, male-pattern balding and clitoromegaly (>1.5 cm × 2.5 cm) [22]. Hair along the linea alba below the umbilicus is seen in up to 20% of women.

When a postmenopausal women is examined, the timing of menarche, history of irregular menses, history of premenopausal hyperandrogenism (i.e. acne and/or male-pattern hair loss, oily skin, hirsutism) and the timing of menopause should be documented. As obesity is so prevalent among postmenopausal women, the timing of any dramatic weight gain and loss must be noted.

Insulin resistance plays a role in the pathophysiology of OH. It was observed that women with OH had insulin resistance irrespective of obesity. It was speculated that hyperinsulinemia would induce stromal luteinization and stimulate the production of ovarian androgens [23]. A significant association between peripheral insulin levels and serum levels of testosterone, androstenedione and dihydrotestosterone collected in the ovarian veins was found. These findings were also shown by other researchers who demonstrated the link between OH and insulin resistance and alterations in fasting

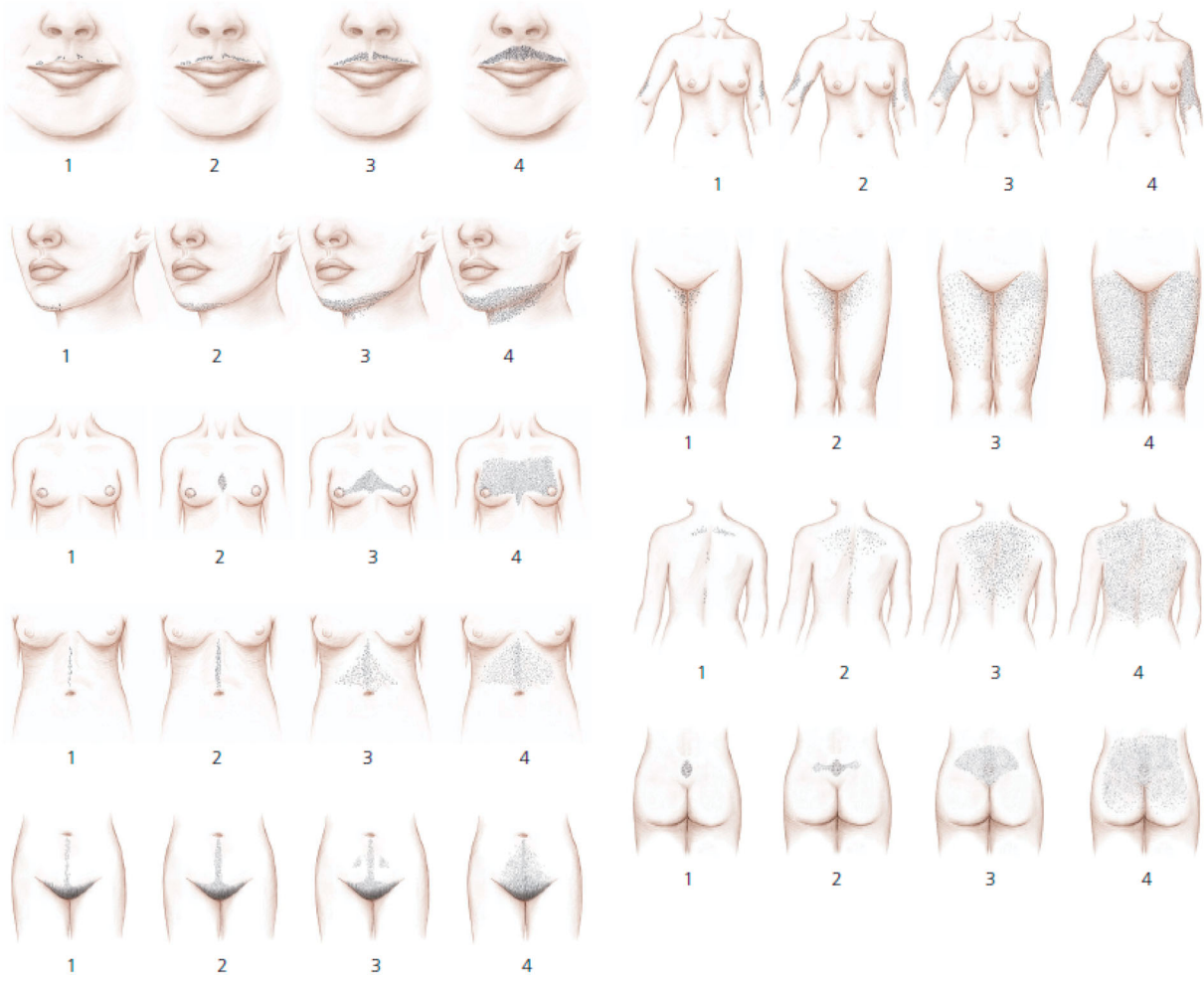

Figure 1. Ferriman–Gallwey hirsutism scoring system. A score of 1–4 is given for nine areas of the body. A total score <8 is considered normal, a score of 8–15 indicates mild hirsutism and a score >15 indicates moderate or severe hirsutism. A score of 0 indicates the absence of terminal hair [72].

Table 1. Differential diagnosis and presentation of androgen excess in postmenopausal women [5].

Diagnosis	*Presentation in postmenopausal women*
Polycystic ovarian syndrome	Past history of anovulatory cycles Elevated testosterone, dehydroepiandrosterone sulfate (DHEAS) Pelvic ultrasound A1C/glucose tolerance test Fasting lipids
Obesity-induced hyperandrogenic anovulation	Past history of regular menses before weight gain, then threshold weight Elevated testosterone and/or DHEAS
Hyperthecosis	Past history of anovulatory cycles, very high testosterone, modest DHEAS Pelvic ultrasound
Androgen-secreting ovarian or adrenal tumor	Past history of regular menses Rapid onset of virilizing symptoms Very high testosterone, DHEAS
Cushing syndrome	Elevated urine free cortisol and/or abnormal 1 mg dexamethasone suppression Pituitary: normal to elevated adrenocorticotrophic hormone (ACTH), elevated DHEAS Adrenal: suppressed ACTH and DHEAS
Congenital adrenal hyperplasia	Elevated 17-hydroyprogesterone baseline (classic) Elevated 17-hydroxyprogesterone after ACTH stimulation (non-classical)
Iatrogenic	Elevated testosterone, dehydroepiandrostenedione, DHEAS, androstenedione Luteinizing hormone (LH)/follicle stimulating hormone (FSH) may or may not be suppressed

glucose [24]. However, many women with OH did not show signs of hyperandrogenism during their reproductive life [19].

The differential diagnosis and presentation of androgen excess in postmenopausal women are presented in Table 1. The two most important causes of ovarian androgen excess in postmenopausal women are OH and virilizing ovarian tumors (VOTs) [19]. Adrenal tumors tend to be malignant and produce androgens (mainly testosterone and dehydroepiandrosterone sulfate [DHEAS]) and many steroid precursors, either exclusively or in association with cortisol, resulting in a clinical phenotype of mixed androgen and cortisol excess. Approximately 25% of patients present with a combination of virilization and hypercortisolism, whereas <10% present solely with virilization [25]. Cushing syndrome has been reported in 30–40% of patients with adrenocortical tumors. Thirty-eight percent of adrenal tumors are non-functional.

Hyperandrogenism of non-tumorous origin

Hyperthecosis is a severe form of PCOS in which elevated gonadotropins are suspected to contribute in postmenopausal women. Peripheral estrogen as well as androgen production are increased. Hence, these women often are at risk for endometrial hyperplasia and carcinoma [9]. Women with hyperthecosis are at risk for metabolic complications of type 2 diabetes and hyperlipidemia [9].

OH, which resembles the clinical manifestations and metabolic sequel of PCOS, is mainly diagnosed in postmenopausal women [26]. Women with OH have a long history of slowly progressive hyperandrogenism, which might often result in virilization. The women have markedly increased serum testosterone levels (>150 ng/dl) in the absence of other elevated androgens. Their gonadotropin levels are high [27,28]. Ultrasound examination will most often show big ovaries bilaterally, when compared to normal postmenopausal ovaries [26,29].

Severe insulin resistance and hyperinsulinemia occur in most of the patients. These will increase ovarian androgen production and cause skin tags, central obesity and acanthosis nigricans.

Since no definite criteria for PCOS in postmenopausal women are currently available, diagnosis of PCOS in this group is not defined [30]. However, age-based criteria for the definition of PCOS have been proposed [31]. LH and/or insulin [32] stimulate androgen production by the theca cells, which causes the androgen excess in PCOS. Some women with PCOS also have elevated DHEAS levels, showing adrenal androgen excess [33]. Even though clinical and laboratory features of PCOS tend to improve in the perimenopausal period [17], the androgens originating from both ovaries and adrenal glands persists as elevated during early postmenopause [16]. Androgens stay increased until the late menopausal period but do not exceed the premenopausal levels [34]. Other androgens such as androstanediol glucuronide have been implicated in the development of hirsutism, but data that show their effect is lacking in postmenopausal women with PCOS [35]. These patients have a long history of hirsutism and they tend to ameliorate with ageing.

In cases of obesity-induced hyperandrogenism, menstrual cycles that were initially regular become irregular by the time premenopausal women gain weight. Signs of hyperandrogenism then develop. But there is no elevated LH/follicle stimulating hormone (FSH) ratio frequently seen in PCOS. Besides, the ovaries are often cystic [5].

The prevalence of hirsutism in women with non-classical congenital adrenal hyperplasia (CAH) increases with age. In addition, the severity of hyperandrogenism may increase in postmenopausal women [36]. On the contrary, hyperandrogenism improves with aging in women with PCOS [17]. Moreover, patients with adrenal hyperplasia may also have hyperinsulinemia and insulin resistance. These might adversely affect the metabolic profile during the postmenopausal period [37]. Due to the long-term treatment with glucocorticoids, the majority of postmenopausal women with CAH usually have the mild phenotype. On the other side,

postmenopausal patients with classic CAH who were inadequately treated might have symptoms and/or signs of hyperandrogenism [1].

Growth hormone hypersecretion may induce ovarian hyperandrogenism. Moreover, the increased insulin-like growth factor 1 levels together with hyperinsulinemia might stimulate ovarian testosterone production [38]. Additionally, SHBG levels are negatively linked with growth hormone levels, which can contribute to elevated free androgen levels [1].

Some drugs might cause iatrogenic hyperandrogenism. For instance, testosterone or dehydroepiandrosterone (DHEA) supplementation for the treatment of menopausal and androgen-deficiency-related symptoms may cause hyperandrogenism. Similarly, the antiepileptic drug valproic acid has also been found to stimulate ovarian androgen biosynthesis directly [39].

Hyperandrogenism of tumorous origin

Ovarian tumors that present with hyperandrogenism include ovarian thecomas, Sertoli cell tumors, Leydig cell tumors and steroid cell tumors not otherwise specified [5].

The androgen-secreting ovarian tumors mostly arise from the sex cord cells that surround the oocytes. However, some might also originate from the stroma. Sex cord–stromal tumors (SCSTs) comprise 5–8% of all ovarian neoplasms [1]. SCSTs account for nearly 90% of all functioning ovarian neoplasms. Patients often present with clinical manifestations of excessive estrogen or androgen production. Ovarian SCSTs either behave in a clinically benign fashion or have low malignant potential. Complete surgical resection is the mainstay of treatment. The vast majority of SCSTs are confined to one ovary at presentation, and few patients will require postoperative therapy. The overall prognosis of ovarian SCSTs is excellent – primarily due to early diagnosis and curative surgery [40].

These tumors can occur at any age, but the peak incidence occurs in postmenopausal women just beyond 50 years. One-third of tumors produce estrogen, progesterone, testosterone or other androgens. Excessive tumor-induced estrogen production may result in postmenopausal bleeding [40].

The Sertoli–Leydig cell tumors (androblastomas) account for $<$0.5% of all ovarian tumors. Approximately one-quarter of these tumors present after menopause [41]. Virilization is found in at least one-third of the patients [42]. The Sertoli–Leydig cell tumors are generally unilateral with a relatively large size. The tumor is mainly confined to the ovary at the time of diagnosis. Staging is described similarly to that of other ovarian cancers [41].

Frank virilization occurs in 35% of patients and another 10–15% have some clinical manifestations related to androgen excess [40]. An elevated testosterone/androstenedione ratio suggests the presence of an androgen-secreting ovarian tumor, usually a Sertoli–Leydig cell tumor [40]. Surgical removal results in an immediate drop in androgen levels and, over time, partial to complete resolution of signs of virilization. The majority (97%) of Sertoli–Leydig cell tumors are stage I at diagnosis. The mortality rate for patients presenting with greater than stage I disease approaches 100% [40].

Pure Leydig cell tumors occur in postmenopausal women, are usually benign, are unilateral and secrete testosterone [40]. Pure Sertoli cell tumors [43] account for less than 5% of all SCSTs. Two-thirds of cases produce estrogen. The majority of these tumors are well differentiated and cured with surgery alone.

Primary granulosa cell tumors account for 2–3% of all ovarian tumors and are mostly found during the sixth decade of life [44]. Granulosa cell tumors mainly secrete estrogens leading to postmenopausal bleeding, endometrial hyperplasia and endometrial carcinoma; however, $>$10% may secrete androgens and cause virilization [44].

Granulosa cell tumors comprise 70% of ovarian SCSTs. Adult-type tumors account for 95% of all granulosa cell tumors. The average age at presentation is 52 years. Adult granulosa cell tumors are low-grade malignancies that demonstrate indolent growth. The majority are unilateral and 90% are confined to the ovary at diagnosis [40]. The 10-year survival for stage I disease is approximately 90%. Fifteen to 25% of stage I tumors will eventually relapse. The median time to documented relapse is 6 years. These indolent tumors usually progress slowly thereafter, and the median length of survival after recurrence is another 6 years [40].

Androgen secretion may also result from ovarian metastases from neuroendocrine tumors, and other malignancies [1].

In almost 50% of patients with Cushing syndrome, adrenal androgen excess will be the reason for hirsutism [45]. Furthermore, SHBG reduction will increase the free androgen levels resulting in endogenous hypercortisolism [45]. In women with adrenocorticotropin-dependent Cushing syndrome, signs of hyperandrogenism are usually mild when compared to women with Cushing syndrome secondary to adrenal carcinomas. Women with adrenal adenomas do not show signs of hyperandrogenism [1].

Functioning adrenal tumors secrete androgenic prohormones (DHEA and DHEAS, rarely testosterone), glucocorticoids and/or estrogens [46,47] The androgen-secreting tumors of adrenal origin affect mostly women at perimenopause or postmenopause. Their incidence is 1–2 cases/million population per year. They are usually malignant, yet benign tumors have also been reported [48]. Virilization and hypercortisolism is seen in approximately 25% of patients. Meanwhile, less than 10% of women will present with virilization alone [49].

Differential diagnosis between ovarian hyperthecosis and virilizing ovarian tumor

The differential diagnosis between an adrenal cause and an ovarian one must be done in the clinic and laboratory before resorting to images. This is to avoid misdiagnosis in the event of an adrenal incidentaloma. In the case of ovarian tumor, inhibin B is usually elevated and DHEAS and cortisol secretion is normal. In adrenal tumors, apart from

testosterone, DHEAS and, frequently, cortisol are hypersecreted, giving a cushingoid appearance, although there are exceptions to this rule. After the biochemical differential diagnosis has been carried out, for imaging, since they can be very small, the choice is magnetic resonance imaging (MRI). Selective adrenal and ovarian sampling is rarely necessary and its availability is very scarce.

Studies have looked at whether serum testosterone, FSH and LH levels would differ between patients with VOTs and OH, but an overlap in serum testosterone and gonadotropin concentrations between the two groups was noticed [19]. Consequently, a high serum testosterone cut-off value >315.5 ng/dl for differentiating VOT from OH has a sensitivity and specificity of only 77% and 91%, respectively [23]. Furthermore, the cut-off value for the serum FSH level has been studied for the differential diagnosis between ovarian tumor and non-tumorous sources of postmenopausal androgen excess. Cut-off values of ≤35 IU/l (sensitivity 90%, specificity 92%) and <22.3 IU/l (sensitivity 77%, specificity 86%) were defined [23,27].

Even though ovarian volume ≥4.0 cm^3 in the postmenopausal period was considered pathological and marked asymmetry of the ovaries was suggestive of an ovarian tumor [28], sonographically normal ovaries in patients with ovarian androgen excess may still harbor VOTs or OH [50]. Neither the presence of nodules or cysts on ovarian imaging confirms VOTs, and nor does the absence of such lesions rule out VOTs. Even MRI might miss VOTs [23]. Just as unilateral ovarian enlargement may indicate either OH or a VOT, so might bilateral ovarian enlargement indicate OH, with or without VOTs [19].

Women with OH typically present with a long history of slowly progressive hyperandrogenism, often resulting in virilization. Their hormonal profile is characterized by markedly increased serum testosterone levels (>150 ng/dl) in the absence of other elevated androgens, accompanied with high gonadotropin levels [9,26]; ultrasound examination usually reveals bilaterally bigger than normal postmenopausal ovaries (mean size 7.7 ± 2.3 vs. 2.3 ± 0.01 ml, respectively) [26,29]. In the majority of patients, severe insulin resistance and hyperinsulinemia occur, enhancing ovarian androgen production and leading to clinical manifestations such as central obesity, skin tags and acanthosis nigricans [51].

Diagnostic evaluation of postmenopausal hyperandrogenism

The diagnosis of postmenopausal hyperandrogenism should be based on clinical suspicion, detailed history and physical examination [1]. PCOS and non-classical CAH are clinically evident before the menopause. In these conditions, hirsutism and/or alopecia might worsen during the perimenopausal and early postmenopausal period [5]. These are mostly associated with relative hyperandrogenism. Attention should be given to clitoromegaly (clitoral size >1.5 cm × 2.5 cm) and other signs of virilization should always direct toward OH or an androgen-secreting ovarian neoplasm even if symptom progression is not rapid [52]. An algorithm for the diagnostic evaluation is summarized in Figure 2.

Laboratory tests

Testosterone and DHEAS are the primary hormonal tests measured [20]. An accurate and specific assay, such as mass spectrometry, is the best choice for assessing serum total testosterone concentrations. Some direct radioimmunoassays and chemiluminescence assays available in specialty laboratories provide results comparable to the new generation of liquid chromatography/mass spectrometry methods. Norms are standardized for early morning, when levels are the highest [22]. Assessing free testosterone levels using high-quality testosterone and SHBG or equilibrium dialysis assays with well-defined reference intervals is the single most useful, clinically sensitive marker of androgen excess in women if the serum total testosterone is normal in the presence of moderate or severe hirsutism. However, since this procedure is time consuming, an indirect parameter of free testosterone, the free androgen index, can be obtained as the quotient 100 × testosterone / SHBG [53].

In most cases of hirsutism, albumin levels are within a narrow physiologic range and thus do not significantly affect the free testosterone concentration. Therefore, in conditions that maintain physiologic albumin levels, the calculated free testosterone level can be estimated by measuring the total testosterone as well as the SHBG level. This method has good reliability in individuals with normal albumin levels when compared with equilibrium dialysis. This method provides a rapid, simple and accurate determination of the total and calculated free testosterone level as well as the concentration of SHBG [53].

If the testosterone level is less than 200 ng/dl then thyroid function tests, the prolactin level and the 17-hydroxyprogesterone level should be checked. Testing for Cushing syndrome should be considered.

When evaluating the significance of hyperandrogenism, the fact that both ovarian and adrenal androgens decline with age [54] should be taken into consideration. If the early-morning 17-hydroxyprogesterone value is >170–200 ng/dl, a corticotropin stimulation test will give definitive diagnosis. When the 17-hydroxyprogesterone value is ≤1000 ng/dl, a heterozygote carrier of 21-hydroxylase deficiency is confirmed and a 17-hydroxyprogesterone value >1000 ng/dl indicates late-onset adrenal hyperplasia [22].

For the assessment of Cushing syndrome, 24-h urinary free cortisol, 1 mg overnight dexamethasone suppression and salivary free cortisol levels can be measured [46,47]. Two consecutive collections are recommended with creatinine determination. Normal urinary free cortisol should range from 30 to 80 mg/day. The overnight dexamethasone suppression test is a cortisol determination at 08:00 am after the patient has been given 1 mg of dexamethasone at 11:00 pm the previous night. The measurement of the 08:00 am adrenocorticotropic hormone (ACTH) level is useful, since its suppression suggests adrenal hypersecretion of cortisol.

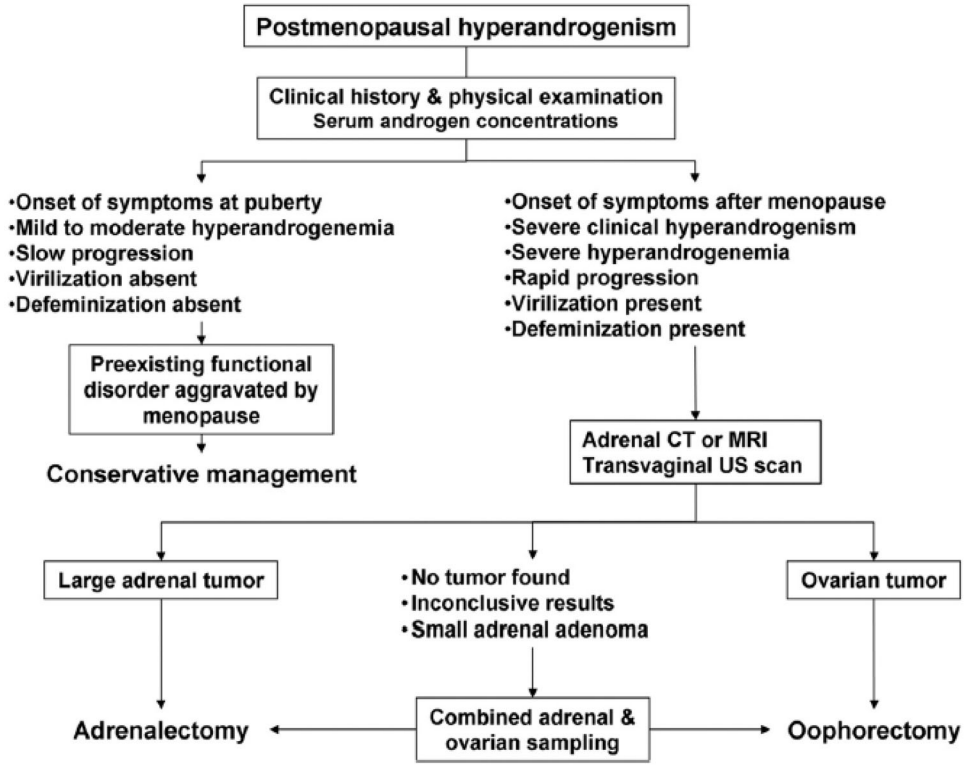

Figure 2. Diagnostic algorithm for the investigation of hyperandrogenism in women after menopause [73]. CT, computed tomography; MRI, magnetic resonance imaging; US, ultrasound.

Total testosterone levels >200 ng/dl should prompt a work-up for ovarian or adrenal tumors and DHEAS levels greater than twice the upper limit of normal should prompt evaluation for adrenal neoplasm. Both should be measured in the presence of virilization. For most laboratories, the upper limit of the DHEAS level is 350 μg/dl [55,56]. A random sample suffices because the level of variation is minimized due to the long half-life of this sulfated steroid. A normal level essentially rules out adrenal disease, and moderate elevations are a common finding in the presence of PCOS and obesity. As a general guideline, a DHEAS level of over twice the upper limit of normal, 700 μg/dl (20 nmol/l), indicates the need to rule out an adrenal tumor or Cushing syndrome [55,56]. Some centers suggest a 2-day to 5-day low-dose dexamethasone suppression test in these situations [57]. Failure of suppression of the initial testosterone, androstenedione or DHEAS elevations will indicate an ovarian source [5]. However, a testosterone or DHEAS suppression test with dexamethasone has not proven to be an effective method in the differential diagnosis.

Furthermore, administration of gonadotropin-releasing hormone (GnRH) analog has been shown to normalize elevated testosterone levels in patients with hyperandrogenism of ovarian origin. However, the distinction between androgen-secreting tumors and OH is not possible [58]. Unfortunately, neither of these tests will determine the reason for the hyperandrogenism.

Very high serum testosterone (>150–200 ng/dl) and/or DHEAS (>600 μg/dl) levels are more in favor of an ovarian androgen-secreting tumor and an adrenal tumor, respectively [59]. Similarly, high testosterone levels may also be found in women with OH. Nevertheless, it might not be possible to differentiate one from the other. Besides, raised androgen levels other than testosterone will be more in favor of a tumor. However, these cut-off values have been obtained from series that have included both premenopausal and postmenopausal hyperandrogenic women and their predictive value varies considerably [57].

Serum AMH and inhibin B measurements can be used for detecting ovarian granulosa cell tumors in postmenopausal women [60].

Radiologic evaluation

A pelvic ultrasound or MRI is useful in women with elevated testosterone levels to evaluate the ovary. As most tumors are quite small, however, the expertise of the ultrasonographer may influence detection [5] Ovarian volume $\geq$4.0 cm^3 was considered an increased ovary size in postmenopausal women [28]. The presence of ovarian asymmetry was defined as the largest ovary size greater than or equal to twice the smallest ovary size. This finding would suggest the presence of an ovarian tumor [61].

MRI may be more sensitive and specific than ultrasonography in the identification of ovarian tumors. It has shown a positive predictive value of 78% and a negative predictive value of 100% in a study evaluating postmenopausal women with and without tumorous hyperandrogenism [27].

MRI showed good sensitivity (83%), specificity (80%) and accuracy (82%) in a group of hyperandrogenic women for the differential diagnosis of VOT. The characteristic MRI image of VOT was a solid nodule with a hypointense signal

on T1 with enhancement after contrast. On the contrary, in patients with hyperthecosis, the ovarian characteristic MRI image was a bilateral enlargement of the ovary with a hypointense signal on T2 and T1 without enhancement after contrast [23].

Although adrenal tumors are less common than ovarian, they are usually of large size exhibiting distinct radiological features and can easily be identified with computed tomography or MRI [62].

A high frequency of adrenal incidentalomas can be misdiagnosed as the cause of hyperandrogenism [62]. Normal DHEAS, a normal dexamethasone suppression test, an unsuppressed ACTH and normal inhibin B make an adrenal etiology very unprovable.

Treatment

Once the diagnosis of ovarian or adrenal tumors, hyperthecosis, iatrogenic causes, CAH or pituitary tumor has been made, medical and/or surgical treatment of the primary condition is planned.

Hyperandrogenism related to OH can be treated either by bilateral oophorectomy or GnRH analogs. Hyperandrogenism-related symptoms and co-existing metabolic abnormalities will improve [26,58]. Postmenopausal women with androgen-secreting ovarian neoplasms typically undergo surgical treatment because such tumors are diagnosed with early-stage disease. When patients have comorbidities preventing them from surgery or when there is no radiologically confirmed tumor, GnRH analogs can be administered [58].

Some ovarian [26,63–67] and adrenal [13] testosterone-producing tumors are reported to be gonadotropin-responsive. Administration of either GnRH agonist or antagonist in these cases decrease testosterone levels dramatically. However, GnRH agonists [26,64,66] or antagonist [63,65,67] are mostly used to confirm ovarian sources of excess testosterone production, but not as a long-term treatment option.

Medical treatment options for hyperandrogenism include the use of anti-androgens, which include androgen receptor blockers, such as flutamide and spironolactone, as well as 5α-reductase inhibitors, such as finasteride. These have been shown to be effective in ameliorating hirsutism associated with non-tumorous causes of hyperandrogenism, including PCOS [68].

Adrenal androgen-secreting tumors are mainly malignant and life-threatening. Adjuvant treatment with mitotane and chemotherapy may be needed for patients with extensive disease [69].

Sequelae of hyperandrogenism

Normalization of androgen levels is seen after surgical oophorectomy in patients with ovarian androgen-secreting tumors [70]. The risk of breast cancer along with the risk of endometrial cancer is reduced [71].

Conclusion

Measurement of testosterone, SHBG, DHEAS, androstenedione and inhibin B is necessary in postmenopausal women with the complaints and signs of hyperandrogenism. Some tests to discard Cushing syndrome should also be done. After an etiological source of androgen hypersecretion has been suspected, we recommend performing MRI of the adrenal glands or ovaries, according to the clinical suspicion.

Surgery remains the main curative treatment, particularly for adrenal androgen-secreting tumors, and may be substantiated with adjuvant therapy [1]. GnRH agonists can be used in patients with ovarian hyperandrogenism with no obvious tumors at imaging and/or who are unfit for surgery [58].

Potential conflict of interest No potential conflict of interest was reported by the authors.

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