In the present paper we shall discuss adrenal androgen production in the context of polycystic ovary syndrome (PCOS). It appears to be well established that adrenal androgen production is abnormal in at least some patients with PCOS. Here we will discuss the evidence for abnormalities in adrenal androgen production, explore the underlying mechanisms and address the questions: are disturbances in adrenal androgen production primary or secondary phenomena? and, is there a role for treatment directed towards correction of adrenal androgen abnormalities in the management of PCOS?

The whole area surrounding PCOS and related conditions has been bedeviled by a lack of standardization in the definitions used. For this reason we will begin by defining the terms to be used in this paper and suggest a classification that may help to ensure that the topics under examination in this paper are delineated clearly.

Definitions

Polycystic ovary syndrome (PCOS)

Polycystic ovary syndrome is a clinical condition characterized by ovulation failure associated with oligomenorrhea or amenorrhea and frequently associated with hirsutism and/or obesity (1). Typically, PCOS presents in the decade between 15 and 25 years and comes to medical attention more than 1 year after the first signs or symptoms appear. It is not usually associated with frank virilization. The associated hormonal derangements include increased luteinizing hormone (LH) production, an increase in the LH/follicle-stimulating hormone (FSH) ratio, increased androgen concentrations in plasma (testosterone, androstenedione, dehydroepiandrosterone and its sulphate), normal or elevated oestradiol levels, elevated oestrone and suppressed sex hormone-binding globulin levels. Characteristically, the ovaries when seen macroscopically are enlarged, with lobular surfaces and peripherally distributed subcapsular cysts, while on microscopic examination atretic follicles, theca cell hyperplasia and a general increase in stromal tissue are evident.

Idiopathic hirsutism (IH)

Idiopathic hirsutism is characterized by the occurrence of hirsutism, i.e. the growth of male-type hair in a typically male distribution, in a woman who continues to menstruate regularly. The condition is usually associated with elevated androgen levels but gonadotrophin and oestrogen concentrations in blood are usually normal.

Screening studies performed in the general population employing ultrasound examination of the ovaries disclosed polycystic ovaries in approximately 25% of women (2). The subjects affected tend to have more menstrual abnormalities, to have more evidence of hirsutism and to have a higher body mass index than those subjects whose ovaries were not polycystic. However, some subjects demonstrating polycystic ovaries do not manifest any clinical abnormalities. Furthermore, when ultrasound examination was performed on patients with IH, approximately 85% of subjects demonstrated polycystic ovaries. These observations suggest that a continuum exists between entirely normal women at one end of the spectrum and those with full-blown PCOS at the other. Intermediate stages include the presence of cystic ovaries in otherwise normal women and the presence of IH with or without cystic ovaries. Therefore, the finding of a picture demonstrating cystic ovaries on ultrasound examination is not sufficient to establish a diagnosis of PCOS. Diagnosis of the syndrome requires the clinical manifestation of ovulation failure, usually associated with hirsutism, and does not require ultrasound demonstration of cystic ovaries.

Classification

Polycystic ovary syndrome may occur without evidence of any other clearly defined disorder. This appears to be the case in greater than 90% of patients with PCOS. However, in approximately 10% of patients with PCOS, largely depending on the ethnic group under evaluation, clearly defined disorders distinct from PCOS can be diagnosed where it is likely that these other conditions have given rise to abnormalities leading to the development of PCOS. These conditions include congenital adrenal hyperplasia, Cushing’s syndrome, androgen-secreting adrenal and ovarian tumours and hyperinsulinaemia associated with severe insulin resistance. Because of this, it is useful to classify PCOS as "primary" when it is not associated with any clearly definable separate diagnosis and as "secondary" where it is associated with relevant conditions as outlined...
Overview of hormonal abnormalities in PCOS

The hormonal milieu in PCOS includes hyperandrogenaemia, hyperoestrogenaemia and increased LH production giving rise to an increase in the LH/TSH ratio in peripheral blood. Controversy exists as to how this pattern of abnormality develops and several schools of thought exist (3–6). A primary abnormality may exist at the level of the hypothalamus–pituitary unit, characterized by an elevation in LH and suppression of FSH secretion. Under normal circumstances, an increase in FSH secretion occurring early in the follicular phase of the menstrual cycle is associated with maturation of the Graafian follicle and stimulation of aromatase activity in the granulosa cells, leading to oestrogen production. Oestrogen synthesis depends on the provision of substrate in the form of androgens from the theca cells that surround the follicle. Androgen production is under the control of LH. Where LH production is elevated, there is stimulation of the theca cells to produce excess androgens and if this is accompanied by suppressed FSH levels or a relative suppression of FSH levels, as occurs in PCOS, androgen production will be stimulated preferentially when compared to oestrogen production. This may be compounded by hyperinsulinaemia due to partial insulin resistance, because insulin acts as an LH surrogate in the ovary (5). The enzyme aromatase is also present in extra-ovarian sites, principally adipose tissue. The adipocyte is an important site of oestrogen production, particularly in obese subjects. While oestradiol arises mainly from the ovary, oestrone is mainly produced in adipose tissue (7). This probably occurs because of the higher circulating concentrations of androstenedione, the substrate of oestrone, than of testosterone, the immediate precursor of oestradiol.

Alternatively, abnormal gonadotrophin secretion may occur as a secondary event. For example, because oestrone levels are elevated in PCOS, it is possible that abnormal oestrogen feedback on the hypothalamus–pituitary unit leads to abnormal gonadotrophin secretion and the secondary abnormalities outlined above. In support of this theory is the observation that use of the anti-oestrogen cloxifenime citrate or a lowering in oestrogen production brought about by weight loss in obese subjects is associated with the induction of ovulation in some patients (1, 8). Therefore, excess peripheral oestrone production seen in obese subjects could be primary to the development of PCOS. Oestrone is derived from androstenedione, and androstenedione in turn arises in large part from the adrenal gland. It is also possible that elevated adrenal androgen production could contribute to the pathogenesis of PCOS by direct effects of androgens at the level of the hypothalamus–pituitary or on the ovary. In support of this concept are the observations that PCOS develops in association with conditions with clearly defined adrenal androgen overproduction, e.g. congenital adrenal hyperplasia (9) or androgen-secreting adrenal tumours (10). Furthermore, the uniquely adrenal steroid dehydroepiandrosterone sulphate (DHEAS) is found in elevated concentrations in plasma of some patients with PCOS (11). Animals given adrenal androgens develop a disorder equivalent to PCOS (12).

Adrenal abnormalities in PCOS

Production rates and catheterization studies

In the 1960s and 1970s it was clearly established that not only were androgen levels elevated but there were clear increases in the production rates of testosterone, androstenedione and dehydroepiandrosterone (DHEA) in PCOS subjects (13). The source of the androgen excess was then explored by a variety of catheterization studies that provided very inconsistent results, suggesting variously a predominantly ovarian origin, a predominantly adrenal origin or a mixed adrenal–ovarian origin. It is very likely that any patient with PCOS does have excess ovarian androgen production, in view of what is known about gonadotrophin secretion and the changes seen in the ovaries. The catheterization studies were associated with technical difficulties and faulty assumptions made in the calculation of androgen production (13). It was not always possible to catheterize both adrenal veins and ovarian veins, while steroid production from both organs is pulsatile rather than constant. In addition, these studies used sequential catheterization rather than simultaneous. In one study, androgen production was calculated from cortisol production by assuming parallel changes in glucocorticoids and androgens. This assumption cannot be sustained and it is not surprising that the results obtained were inconsistent.

Androgen response to adrenal stimulation

Over the years, several investigators have examined the androgen response to stimulation with various doses of ACTH. In general, elevated incremental responses of androstenedione and DHEA levels were noted in PCOS. In addition, 17-hydroxyprogesterone responses were excessive, although not to the levels seen in patients with even mild 21-hydroxylase deficiency. Furthermore, cortisol values were found to be excessively responsive to ACTH in some subjects with PCOS (14). This pattern was suggestive of a generalized hyperresponsiveness of the adrenal gland rather than that associated with an abnormality that could be localized to a specific enzymatic defect. The dose of exogenous ACTH frequently used in the stimulation of the adrenal
Aetiology of adrenal androgen overproduction in PCOS

Congenital adrenal hyperplasia

While congenital adrenal hyperplasia is a distinct disorder, late-onset or cryptic 21-hydroxylase deficiency has been described to account for greater than 30% to less than 1% of patients presenting with PCOS (15). As pointed out by New, the prevalence of congenital adrenal hyperplasia varies greatly from one ethnic group to another (15). The likelihood of encountering congenital adrenal hyperplasia is highest amongst Ashkenazi Jews, Eskimos and Mediterranean races. Affected subjects can be identified by finding markedly elevated 17-hydroxyprogesterone values in the early morning or by an extreme 17-hydroxyprogesterone response to stimulation with ACTH, clearly distinguishable from the much milder but still excessive response to ACTH seen in subjects with PCOS not associated with congenital adrenal hyperplasia (14). Cryptic congenital adrenal hyperplasia is clearly an important disorder to consider in the evaluation of patients presenting with PCOS from an ethnic background where the condition is common. In most populations in northern Europe the incidence of 21-hydroxylase deficiency is low and probably contributes little to the frequency of PCOS in such populations.

Disrupted control of adrenal androgen production

The overall control of adrenal androgen production has not been defined (16). Clearly, adrenal androgens respond to stimulation with ACTH. However, while ACTH and cortisol levels remain fairly constant throughout life, androgen levels change independently. Up to the end of the first decade of life, circulating adrenal androgen levels are low. Through the second decade, adrenal androgens characterized by DHEAS continue to rise, plateau through the third, fourth and fifth decades and commence to fall then approximately in the sixth decade of life. Furthermore, conditions such as stress and anorexia may bring about a lowering of androgen levels while cortisol levels are normal or elevated. In subjects with Cushing’s disease or ectopic ACTH production where ACTH levels are elevated, androgen values are very variable, stretching through the spectrum from suppressed to elevated values (17). In patients with partial hypopituitarism or following treatment with exogenous glucocorticoids, androgen values tend to be suppressed preferentially. All of these observations suggest that the association between androgen production and ACTH is complex. It is possible that an additional factor is also involved. This factor has been designated tentatively cortical androgen-stimulating hormone (CASH). Its identity has not been defined but the possibility that it may be a fragment derived from proopiomelanocortin (POMC) has much to recommend it. Proopiomelanocortin is also the parent molecule of ACTH and differential processing of POMC to ACTH and CASH at various stages of life and under various circumstances could explain the changes observed. This possibility is certainly consistent with the variability in glucocorticoid and androgen levels seen in states of ACTH excess where POMC processing is known to be variable and abnormal, e.g. Cushing’s disease and the ectopic ACTH syndrome. In response to treatment with dexamethasone, preferential suppression of androgens occurs in IH and in congenital adrenal hyperplasia where 17-hydroxyprogesterone values continue to be markedly elevated while androgens are suppressed (18). Potential candidates for the role of CASH include β-endorphin, whose levels have been reported to increase at the time of adrenarche (the onset of adrenal androgen secretion) and to fall in later years (19). Plasma β-endorphin levels have been reported to be elevated in PCOS (20). Parker and co-workers have suggested that another POMC fragment, the joining peptide, may preferentially stimulate adrenal androgens (21). A recent report indicates that joining peptide and β-endorphin can interact with ACTH in stimulating cortisol and androgen secretion in human adrenal cells in vitro, in a manner that favours androgen production, consistent with the changes occurring at the time of adrenarche (22). This of course assumes that POMC processing is changed in such a way as to alter the relative secretion of ACTH, β-endorphin and joining peptide under physiological conditions and that this may be disrupted under pathological circumstances. It is possible, therefore, that excessive production of CASH, irrespective of its identity, could give rise to
adrenal androgen hypersecretion and contribute to the development of PCOS.

**Enzyme induction**

Variable rates of metabolic clearance of cortisol without changes in androgen clearance would result in maintenance of physiological plasma cortisol levels because of compensatory adjustments in ACTH secretion. Variable ACTH levels with constant androgen clearance will result in fluctuating androgen levels while cortisol levels are steady. Theoretically, alterations in cortisol clearance could explain the changing cortisol/androgen ratio seen in physiological and pathological settings. The fluctuations in adrenal androgen levels do not appear to be under any direct feedback control. The physiological role of adrenal androgens has not been defined and may merely be vestigial. However, adrenal androgen production may be important during fetal life. Furthermore, adrenal androgens are responsible for the normal stimulation of pubic and axillary hair growth in women, they protect normal bone density and may contribute to libido in women. The biological effect of androgens depends on the prevailing androgen level plus the number and affinity of androgen receptors (23). Therefore, there is likely to be great variation in androgen effect in women because adrenal androgens are in large part produced as a by-product of cortisol synthesis and are not matched with androgen receptor availability or affinity, as occurs when a feedback system operates. It has been proposed that in PCOS excessive cortisol metabolism could give rise to lowering of cortisol values and thereby to stimulation of ACTH production, which returns cortisol levels to normal but causes elevation in androgen levels. Several potential candidate enzymes involved in cortisol clearance exist. One such enzyme is 5α-reductase. A recent report suggests that this enzyme is overactive in some subjects with PCOS (24). 5α-Reductase is particularly relevant because it is involved not only in the clearance of cortisol but in the transformation of testosterone to the most biologically active androgen in most tissues, 5α-dihydrotestosterone. Another candidate enzyme is 11β-hydroxysteroid dehydrogenase, which is responsible for the conversion of cortisol to cortisone. Rodin et al. recently demonstrated that subjects with PCOS have increased urinary excretion of metabolites of cortisone when compared to those of cortisol and they also demonstrate excessive androgen production (25). These findings were interpreted to indicate an increase in 11β-hydroxysteroid dehydrogenase activity, leading to increased cortisol clearance, a fall in cortisol concentrations in blood and a compensatory increase in ACTH secretion to bring cortisol levels back to normal while increasing androgen levels. Thus, increased cortisol clearance occurring in PCOS may be associated with an adrenal gland more active than normal and possibly hyperresponsive to stimulation and associated with hyperandrogenaemia. Whether induction of enzymes involved in cortisol metabolism is primary to PCOS or occurs as a consequence of the associated hormonal disturbances has not been established. It should be noted, however, that increased 5α-reductase activity was not confirmed by Rodin et al. (25) and, in contrast, increased activity of the 11β-hydroxysteroid dehydrogenase enzyme was not observed by Stewart et al. (24).

Barnes and Rosenfeld have suggested that the enzyme responsible for the production of 17-hydroxyprogesterone, i.e. 17-hydroxylase, and the enzyme responsible for the conversion of 17-hydroxyprogesterone to androstenedione, i.e. 17.20-lyase, are excessively active in both the ovaries and the adrenal glands in PCOS (4). These enzymes are closely related components of the cytochrome 17-P-450 enzyme system, and it is possible that the same enzyme catalyses both activities. This suggestion that cytochrome 17-P-450 is induced in PCOS is based on the observations that there are excessive 17-hydroxyprogesterone and androgen responses when the adrenal is stimulated with ACTH or when the ovary is stimulated using the GnRH analogue naloterin to bring about gonadotrophin release and thereby stimulation of the ovary. If the cytochrome 17-P-450 enzyme system is indeed induced, it appears that 17-hydroxylase is relatively more active than 17,20-lyase because 17-hydroxyprogesterone accumulates. However, other investigators have been unable to confirm dysregulation of any component of the cytochrome 17-P-450 system (26).

**Epilepsy and anticonvulsant drugs**

Patients with epilepsy and on treatment with anticonvulsant drugs have a high incidence of PCOS. The precise cause of this is unknown. In patients with menstrual disturbances, polycystic ovaries are more common in those treated with valproate than in those patients receiving carbamazepine. Valproate is associated with elevated plasma DHEAS, elevated free testosterone and normal sex hormone-binding globulin (SHBG) levels, whereas carbamazepine, which causes more marked induction of liver steroid-metabolizing enzymes than valproate, is associated with elevated plasma SHBG and little change in free testosterone (27). It is possible that valproate has unidentified mechanisms that stimulate adrenal androgen production with secondary development of PCOS.

**Role of anovulation in the evolution of PCOS**

It has been reported recently that abnormal gonadotrophin secretion in patients with PCOS may be corrected by cyclical treatment with progesterone (28). It is possible that any disorder giving rise to anovulation while oestrogen levels are normal or
Impact on ovarian androgens and oestrogens on adrenal function

One possibility for the occurrence of disturbed adrenal function in hyperandrogenaemic patients is the effect of hyperandrogenaemia of ovarian origin on adrenal enzyme activity. A number of studies have now examined the impact of grossly elevated androgen levels, much in excess of those occurring in PCOS, on adrenal activity in women. The findings have been inconsistent and where an impact was observed it was modest (29–31). It appears unlikely that the relatively mild androgen excess observed in patients with PCOS would have a consistent impact on adrenal androgen production. Similarly, high oestrogen levels may also increase adrenal androgen secretion by enhancing 17,20-lyase activity (32).

Clinical considerations: significance of abnormal adrenal androgen secretion in PCOS

Sinister disorders associated with hirsutism and hyperandrogenaemia can usually be excluded from history alone. Patients with PCOS tend to present at the decade between 15 and 25 years, have a gradual development of hirsutism over years and do not demonstrate any evidence of virilization. When hirsutism or menstrual disturbances occur for the first time after 25 years of age, where the symptoms are rapidly progressive or if virilization is present, extensive evaluation for disorders such as adrenal or ovarian androgen-secreting tumours, Cushing’s syndrome or late-onset congenital adrenal hyperplasia is indicated (33). The physician who makes a clinical diagnosis of PCOS may undertake limited hormonal evaluation, e.g. measurement of testosterone levels, to exclude the extremely rare occult disorder and to provide a baseline against which the effect of intervention may be judged.

Means of identifying those patients with PCOS for whom excessive adrenal androgen production is the disorder initiating the sequence of events leading to PCOS or in whom adrenal androgen excess plays an important role in the cycle of events that maintains the PCOS state is not immediately obvious. The simple measurement of basal DHEAS levels is not reliable because patients demonstrating excessive responsiveness to ACTH and metyrapone and who subsequently respond to adrenal suppression frequently do not have elevated DHEAS levels (14). The most reliable form of evaluation is identification of an excessive androstenedione response to ACTH, or a testosterone and/or androstenedione response to metyrapone. Patients demonstrating such an abnormality respond well to treatment with physiological doses of glucocorticoids, given at night, when dexamethasone is useful because of its long biological half-life (14). On occasions, a trial of treatment with dexamethasone will be indicated for the hirsute patient who wishes to have both hirsutism and ovulation treated simultaneously. Only glucocorticoid suppression facilitates the resumption of ovulation and reduces androgen levels, which bring about a lessening of hirsutism. When used in an unselected group of patients with PCOS, glucocorticoid treatment is associated with a frequency of ovulation similar to that occurring in response to clomiphene citrate (34, 35). However, treatment with clomiphene citrate is more widely used to induce ovulation, although it is potentially associated with hyperstimulation syndrome and multiple births, events rarely seen in patients treated with adrenal suppression. Clomiphene citrate may be more appealing to the clinician because the time frame within which a response will be seen is well defined. In contrast, glucocorticoid treatment brings about a gradual normalization of hormonal abnormalities, after which spontaneous ovulation may occur. This is frequently seen within 4 months of the onset of treatment. Likelihood of response may be monitored by measuring free testosterone and gonadotrophin levels in the interim. Clinicians using glucocorticoid treatment, even in low dose, should be aware that weight gain is particularly likely to occur in obese subjects. Because PCOS is associated with obesity, this may prove to be a practical problem.

Summary

Secondary PCOS may occur in association with disorders characterized by adrenal androgen excess, e.g. congenital adrenal hyperplasia. Primary PCOS is associated frequently with more subtle abnormalities in adrenal androgen status. However, it has not been established that the mild adrenal androgen occurring in PCOS is causally involved in the development of PCOS, although adrenal hyperresponsiveness to stimulation appears to be characteristic of PCOS. It remains to be clarified whether this is due to excess stimulation of the adrenal by the putative CASH, which with ACTH probably coordinates adrenal androgen steroidogenesis, or whether adrenal hyperresponsiveness occurs as a consequence of increased cortisol clearance with compensatory hypersecretion of ACTH, which is associated with excessive adrenal androgen production. The possibility also exists that the enzyme system responsible for 17-hydroxyprogesterone production and its conversion to androgens is excessively active and may occur as a common defect in the adrenal and
ovaries as a consequence of a congenital disorder. For at least some patients, treatment with a nocturnal low-dose glucocorticoid is an effective form of treatment. Indeed, this is the only hormonal form of treatment for hirsutism that also facilitates fertility and pregnancy. It is possible that PCOS may occur as a consequence of any disorder in which anovulation is associated with normal or elevated oestrogen levels. For some patients with PCOS, mild adrenal androgen excess is probably primary to development of the disorder. Thus, a trial of treatment with low-dose glucocorticoid at night appears to be a reasonable option in susceptible patients who can probably be recognized by demonstration of an excessive androgen response to ACTH or metyrapone.

References
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Fig. 1. Schematic representation of interrelating hormonal abnormalities identified in polycystic ovary syndrome. The asterisks indicate sites where the initiating abnormality may arise. The figure assumes that some and not all abnormalities depicted will be operative in an individual patient. The arrows indicate the source from which a hormonal abnormality arises and the direction of the impact of that abnormality at an alternative site. CASH = cortical androgen-stimulating hormone.
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