THERAPY OF ENDOCRINE DISEASE

Treatment of hirsutism in the polycystic ovary syndrome

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Abstract

Hirsutism is a common medical complaint among women of reproductive age, and it affects the majority of women with the polycystic ovary syndrome (PCOS). Increased rate of androgen production and its availability in tissue represent the main pathophysiological mechanisms responsible for hirsutism. In addition, androgens may be generated *de novo* in the hair follicle; therefore, circulating androgen levels do not quantify the real exposure of the hair follicle to androgens, as a quota is locally generated. Hirsutism is a clinical sign and not a disease in itself; its presence does not therefore necessarily require treatment, particularly in mild-to-moderate forms, and when an affected woman does not worry about it. Physicians should decide whether hirsutism is to be treated or not by evaluating not only the severity of the phenomenon but also the subjective perception of the patient, which does not necessarily correspond to the true extent of hair growth. In any case, a physician should manage a woman with hirsutism only on the basis of a diagnosis of the underlying cause, and after a clear explanation of the efficacy of each therapeutic choice. Cosmetic procedures and pharmacological intervention are commonly used in the treatment of hirsutism and are discussed in this paper. Importantly, there are different phenotypes of women with hirsutism and PCOS that may require specific attention in the choice of treatment. In particular, when obesity is present, lifestyle intervention should be always considered, and if necessary combined with pharmacotherapy.

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Introduction

Hirsutism is the medical term that refers to the presence of excessive terminal (coarse) hair in androgen-sensitive areas of the female body (upper lip, chin, chest, back, abdomen, arms, and thighs). It should be differentiated from virilisation, which refers to the concurrent presentation of hirsutism with a broad range of signs suggestive of androgen excess, such as ambiguous external genitalia, increased muscle mass, acne, balding, deepening of the voice, breast atrophy, amenorrhea/oligomenorrhea, and increased libido, varying with age. All these signs and symptoms may differ in their clinical presentation according to the patient's age. Hypertrichosis is hair growth that is abnormal for the age, sex, or race of an individual, or for a particular area of the body, which should be

differentiated from hirsutism (1). The different underlying pathologic conditions responsible for hirsutism are summarised below.

Epidemiology of hirsutism

Hirsutism is a common medical complaint among women of reproductive age (2). Its prevalence in adults ranges from 3 to 15% in Blacks and Whites (3, 4, 5, 6), but is somewhat lower in Asians (1–3%) (7). Recent epidemiological surveys have added data concerning hirsutism restricted to adolescence and youth and demonstrated that this condition may be frequent from the post-menarchal years, with a prevalence ranging from

8 to 13% (8, 9, 10). The most common cause of hirsutism is represented by the polycystic ovary syndrome (PCOS). A recent report by the Androgen Excess-PCOS Society reviewed 18 studies from 1983 to 2007, involving 6281 women with PCOS, and found that 74.7% of women were presented with hirsutism (11). In these women, hirsutism often tends to be more severe in the presence of obesity, particularly the abdominal phenotype (12, 13, 14). Interestingly, although the presence of hirsutism does not fully predict ovulatory dysfunction, some studies found that it may predict the metabolic sequelae (14, 15) or failure to conceive with infertility treatment (16) in women with PCOS.

Etiology of hirsutism

Functional causes account for most of the cases of hirsutism. Other than PCOS, they also include idiopathic hyperandrogenaemia (17) and idiopathic hirsutism. The PCOS, which is the most common cause of hirsutism, is characterised by the combination of hirsutism and/or biochemical hyperandrogenism with anovulatory cycles and/or polycystic ovarian morphology (PCOM) (11). Idiopathic hyperandrogenism is characterised by the presence of hirsutism or biochemical hyperandrogenaemia, or both, but normal ovulatory cycles and normal ovarian morphology (18). Idiopathic hirsutism is characterised by hirsutism in the presence of normal androgens, ovulatory cycles, and normal ovaries (18). Less common but important causes of hirsutism may be present (2) (see paragraph on Differential diagnosis).

Pathophysiology of hirsutism

There are three structural types of hair on the human body: lanugo is a soft hair that covers the skin of the foetus, but disappears soon after the birth; vellus is a soft hair, usually non-pigmented and with a diameter <0.03 mm covering much of the body in men and women; terminal hair is longer, pigmented, and coarser in texture and with different extents of expression in men and women. In particular, females have terminal hairs only in the eyebrows, eyelashes, scalp, pubis, and axillae (1). Hair arises from a complex and highly dynamic structure, the hair follicle, that consists of several components and has a rhythmic growth cycle. The hair follicle growth cycle is made up of three major phases: anagen (a stage of rapid growth), telogen (a stage of relative quiescence), and catagen (apoptosis-mediated regression) (1). Hirsutism follows an alteration in the hair follicle cycle, in particular

a prolongation of the anagen phase with a consequent transformation of vellus into terminal hairs. This alteration appears under the effect of androgens that are triggered and involved in the regulation of sexual hair growth. Androgens involved in the regulation of hair follicles are testosterone and dihydrotestosterone (DHT), which may be generated via a *de novo* synthetic pathway from cholesterol, and/or via a shortcut pathway from circulating DHEA-S (19). Cutaneous testosterone may come from the circulation, principally synthesised in the adrenals and ovaries, and/or may be locally generated, as hair follicles are equipped with all the necessary enzymes for the biosynthesis and metabolism of androgens (19). DHT is almost entirely synthesised locally in a step catalysed by the enzyme 5 α -reductase (20). Therefore, circulating androgen levels do not quantify the real exposure of the hair follicle to androgens, as a quota is locally generated. Furthermore, cutaneous androgen effects also depend on the local expression and activity of the androgen receptor (18). This justifies why the severity of hirsutism is not always correlated with circulating androgen concentrations.

Key points in the diagnosis of hirsutism

The diagnosis of hirsutism is based on the quantification of the problem and on the definition of the aetiology. The quantification of hirsutism can be obtained by a physical exam through the use of subjective and objective methods. The establishment of the most probable aetiology is based on clinical history (age of onset and rapidity of progression), hormone profile and, in some cases, on genetic analysis. Apart from the degree of hirsutism, the most important clinical feature to be aware of is the recent onset and rapid progression of hair growth, which is consistent with a tumoural cause or with a drug interference. By contrast, the onset of mild to moderate hirsutism around the time of puberty or in young adult age often has a benign cause, the most common being represented by PCOS.

Physical examination

The quantification of hirsutism by objective methods, such as photographic evaluations, weighing of shaved or plucked hairs and microscopic measurements, is reliable. However, the complexity and high cost of these methods limit their use in clinical practice (21), although they could be a desirable option in the future. Subjective methods have the advantage of being easy, convenient,

cheap, and fast, although they are subject to some large inter-observer variation that can be reduced by trained physicians (21). The modified Ferriman-Gallwey score (mFG) is the most commonly used method (22), but at least three open questions related to the interpretation of the mFG score still remain. They include: i) which cut-off value should be used to diagnose the presence of hirsutism; ii) how to interpret hirsutism predominantly localised on the face with respect to that localised on the trunk or arms; and, finally, iii) the interpretation that should be given to the presence of terminal hairs selectively on the face. The Androgen Excess and Polycystic Ovary Syndrome Society recently issued recommendations regarding the cut-off value of the mFG score to be applied (11). The Society recommends adapting the cut-off to the race and ethnicity of the population to which it is applied and, if this value is unavailable, using a cut-off value of eight or above for White, Black and South-East Asian women, and a cut-off of three or above for Far-East Asian women (23). Given the importance of the topic in both clinical practice and scientific research, how to define hirsutism should require more intensive attention, and, possibly, the development of objectively quantitative methods to avoid subjective variability. In addition, other factors should be considered in defining cut-off points, including age (i.e. paediatric vs adult age) and, as reported above, how the presence of terminal hairs selectively on the face should be evaluated with respect to body hair.

Hormone profile

Although the diagnosis of hirsutism does not necessarily reflect high levels of circulating androgen, the investigation of androgen blood levels may nonetheless be extremely useful to define the aetiology of hirsutism. Notably, the present assay performance of the analytical methods commonly used to measure androgens has to be seriously taken into account for the correct interpretation of the results, because their specificity and accuracy may be poor, particularly for some androgens (17OH-progesterone, androstenedione, DHEA) and for low circulating concentrations, particularly in the female range (<1 ng/ml) (23). Liquid chromatography combined with tandem mass spectrometry (LC-MS/MS) is a recent technique displaying good precision, sensitivity and high accuracy for measuring androgen levels in females throughout all stages of life, with the advantages of high throughput and the low cost required for the analysis (24, 25, 26). Therefore, it represents a convenient and reliable assay when androgen measurement in females is

required, provided that a reference normal range is determined in house, by using a carefully selected healthy non-hyperandrogenic control female population (23). In addition, by using LC-MS/MS it is possible to measure important steroids such as 11deoxycortisol, and deoxycorticosterone (DOC) that cannot be measured with immunoassay methods and that are triggers for the diagnosis of uncommon forms of classic and non-classic congenital adrenal hyperplasia. Due to the numerous advantages of this technique, LC-MS/MS has recently been introduced in laboratories in critical fields that strongly rely on the reliability and rapidity of the measurement, such as newborn screening for congenital diseases including classic congenital adrenal hyperplasia (27). By using LC-MS/MS in the differential diagnosis of hirsutism, an enormous improvement in the sensitivity and specificity of the measured analytes, specifically testosterone and androstenedione, can be achieved. In fact, this method has highlighted the limits of currently used immunoassays, particularly when applied to women in whom circulating androgens are much lower with respect to men (24, 25). In a recent paper, we have produced reference values for many androgens in large and well-defined groups of healthy normal late-adolescent (aged 16–19 years) and premenopausal women (25). In these women ($n=133$), we found that testosterone blood levels, a key index of hyperandrogenaemia in women with PCOS, never exceeded 0.55 ng/ml, whereas in postmenopausal women ($n=53$) the highest values were 0.45 ng/ml. Accordingly, reference values for androstenedione did not exceed 2.2 and 1.0 ng/ml respectively. An additional product of the aforementioned study was the definition of specific late adolescent reference values in both the follicular and luteal phases of the cycle (25, 28).

Androgen levels should always be measured in all women with hirsutism, irrespective of its extent. In fact, as discussed above, the present methods for detecting and quantifying hirsutism are largely subjective, which implies potential over- or underestimation. In addition, it has been shown that testosterone blood levels only partially (although significantly) correlate with the mFG score, and high testosterone blood levels can also be found in women with low or moderately severe hirsutism scores (23).

In all patients with hirsutism related to PCOS, following the AE-PCOS guidelines for the assessment of metabolic status, including lipids, the glucose–insulin system (29) and the cardiovascular risk factors (30), should be recommended. In fact, it has been widely demonstrated that, particularly in the presence of excess body fat, the prevalence of insulin resistance and the metabolic

syndrome is significantly higher in women with PCOS than in their non-affected counterparts, matched for BMI (13).

Additional diagnostic procedures

PCOS is the most common cause of hirsutism in adolescent and premenopausal women; therefore, the diagnosis of PCOS should always be considered in hirsute women. The first step is to exclude any other potential cause of androgen excess and hirsutism (see above) by appropriate clinical judgment and laboratory analyses. In some cases, adrenal and/or ovarian morphology should be investigated by appropriate imaging techniques (magnetic resonance or computed tomography). The presence of a hyperandrogenic pattern can be defined by both clinical and biochemical markers, as summarised in the previous paragraph. According to the current guidelines for the diagnosis of PCOS, ovarian dysfunction can be analogously evaluated by both clinical and morphological or biochemical parameters. Menses abnormalities, particularly oligo- and amenorrhoea, are very common in these women (more than 80%) (11). Typically, the majority of these women have chronic anovulation, although the pattern of ovulatory performance may change with increasing age (31). The recognition of a typical PCOM by ultrasound (possibly transvaginal) represents one of the three cardinal criteria in the definition of PCOS, although it largely depends on the available technologies and subjective evaluation by the operator. Although the consensual threshold to define a normal ovary from PCOM has been defined according to the presence of 12 or more follicles of 2–9 mm in diameter, it is possible that this limit is destined to change in a short time, due to the continuing improvement of modern technologies, able to detect follicles <2 mm in diameter (32). On the other hand, in the last years a growing number of studies have shown that serum anti-Müllerian hormone (AMH), measured by an appropriate assay, might be a more sensitive and specific biomarker of the ovarian dysfunction typical of PCOS (32).

Genetic analysis

Genetic analyses are warranted when classic and non-classic congenital adrenal hyperplasia are strongly suspected as causes of hirsutism or virilisation. Genetic analysis for identification of mutations of the genes involved is informative for the index case (type and severity of the disorder) and for future prenatal diagnosis (33, 34).

Differential diagnosis

Hirsutism is a marker of excessive tissue exposure to androgens and, therefore, always deserves to be investigated. Various disorders enter into the differential diagnosis, some more frequent (PCOS, idiopathic hirsutism, idiopathic hyperandrogenism), others more rare (non-classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency, hyperprolactinaemia, hypothyroidism, drugs, gestation) and others very occasional (androgen-secreting tumours, Cushing's syndrome, acromegaly, non-classic adrenal hyperplasia not due to 21-hydroxylase deficiency) (23). However, all these causes must be taken into account in the correct approach to a patient who complains of hirsutism. In addition, a correct medical approach to hirsutism assumes the need to exclude whether it accompanies signs of virilisation or, alternatively, it is isolated. All patients presenting with hirsutism should be firstly subjected to a careful evaluation of their clinical history and a thorough physical examination. Age of onset and rapidity of progression are key factors that should be investigated. Functional causes or non-classic congenital adrenal hyperplasia, in fact, almost always shows a peripubertal onset and a slow progression over time and are generally not associated with signs of virilisation. In contrast, androgen-secreting tumours can manifest at any age with sudden onset and rapid progression and are usually associated with signs of virilisation. Functional forms of hirsutism (PCOS, idiopathic hirsutism, idiopathic hyperandrogenaemia) must be considered and dealt with only after androgen-secreting tumours and the other forms have been excluded. At this point, measurement of major androgens (particularly testosterone) in serum, assessment of ovulatory function and ultrasound evaluation of ovaries are essential for the differential diagnosis between the three forms. The laboratory analyses needed to identify other causes of hirsutism (see above) are beyond the scope of this article and many recent reviews (23, 34) and textbooks are available (35).

The role of obesity

Obesity *per se* is a condition of sex hormone imbalance in women. A significant decrease in production rate and blood levels of sex hormone-binding globulin (SHBG) is inversely correlated with body weight and particularly with the expansion of visceral fat, due to the inhibitory action of higher insulin concentrations (36). The decrease in the concentration of SHBG in blood results in an

increase in circulating SBG-bound steroids, specifically testosterone (37), although an increase in their production rate may occur, particularly in those with the abdominal obesity phenotype (38). Interestingly, blood concentrations of androgens are paralleled to those observed in the fat tissue, specifically the visceral fat (39). Therefore, a condition of 'relative functional hyperandrogenism' is associated with excess body fat and particularly with central adiposity in women (40).

Obesity has multiple negative effects on the pathophysiology and clinical expression of PCOS, which are complex and not completely understood (13). In obese women with PCOS, maternal obesity seems to predispose to the susceptibility to develop androgen excess (41). Obesity is also associated with increased testosterone levels in adolescent girls presenting with stigmata of PCOS (42). It is possible that the ability of obesity to worsen the androgen balance is related to the associated insulin resistance and hyperinsulinaemia, which may be directly responsible for an increased ovarian steroidogenesis (43, 44, 45). The impacts of obesity on the phenotype of PCOS are multiple and involve both the expression of hyperandrogenism and ovarian dysfunction. Several studies have demonstrated that obese women with PCOS have a worsened hyperandrogenaemic pattern, characterised by low SHBG and high testosterone blood levels compared with their normal weight counterpart. Accordingly, obesity has been found to be associated with worsened hirsutism scores (13).

Management of hirsutism

Hirsutism is a clinical sign and not a disease in itself. Therefore, its presence does not necessarily require treatment, particularly in its mild-to-moderate forms and when an affected woman does not worry about it. Cultural and social conditions may offer another point of view that should also be carefully taken into consideration. In addition, many women who complain of hirsutism are endocrinologically normal and do not manifest metabolic alterations. Physicians should therefore decide whether hirsutism is to be treated or not by evaluating not only the severity of the phenomenon but also the subjective perception of the patient, which does not necessarily correspond to the true extent of hair growth. In any case, a physician should manage a woman with hirsutism only on the basis of a diagnosis of the underlying cause, and after a clear explanation of the efficacy of each therapeutic choice. Importantly, the woman's perspective can vary according to age, therefore the treatment can be managed

differently during childhood, adolescence, youth and adult age of postmenopause. Usually, however, treatment targeted at ameliorating hirsutism directly is also necessary. However, it is worth mentioning that treatment does not always have to include pharmacological intervention. Hair grows in cycles, and it therefore takes months for an individual hair follicle to proceed through catagen, anagen and telogen phases. All systemic treatments reduce the anagen phase, in particular, by reducing testosterone effects, therefore enough follicles have to pass through the anagen phase before a significant effect can be observed. In any case, all pharmacological treatments can have the same efficacy in all women, who should therefore be advised on the potential long-term treatment and on the potential combination of different drugs and/or cosmetic procedures. Unfortunately, almost all studies investigating the potential efficacy of drugs on hirsutism lasted for a maximum of 6–12 months, so it is unclear how long any systemic treatment should be prolonged (43). Nonetheless, it is very common in clinical practice to meet women who have been treated for many years or decades, without attending any structured follow-up. In many cases, women say that hirsutism has been completely eliminated and they are afraid to discontinue their treatment in case it returns.

Cosmetic procedures

Cosmetic measures may be particularly effective as individual therapy in controlling mild and localised hirsutism. In addition, they may be recommended as an adjuvant to pharmacological therapy in cases of clinically moderate to severe hirsutism, according to each woman's wishes. Techniques of actually removing the hair may be categorised into depilatory methods or epilatory methods.

Depilatory methods

Mechanical and chemical methods for the treatment of hirsutism have been summarised in many scientific reviews in the last years (46). There is evidence that these methods can be convenient for the patients, although multiple treatments are often needed and the individual responsiveness must be taken into consideration. It should be considered that these methods still include manual and electrical shaving, although an increased number of hirsute women seem to not accept these procedures easily (47) and are frightened of side effects, such as hair growth or pigmentation (48).

Chemical depilatories can also be used, but in some cases they may be associated with unpleasant side effects (49). On the other hand, depilation still represents one of the most common procedures and it is essentially without risk, although it may be painful. Shaving may also be used, although it obviously requires continuous treatment; however, if added to pharmacological therapies it may no longer be needed (33).

Epilatory methods

For patients who seek permanent remedies for hirsutism, there are three widely available options: electrolysis, thermolysis and laser treatment. These methods provide a longer efficacy than depilatory ones, because some forms may cause permanent damage of the follicle (1). As expected, individual preferences (often due to economical reasons) are critical in selecting the most appropriate procedure. Electrolysis and the newer methods, such as laser therapy and intense pulse light, are folliculitic treatments that may result in permanent amelioration of hirsutism in the treated area (50, 51). This technique destroys the base of the hair follicle without causing a scar on the surface. However, it is operator-dependent and may be associated with local side effects (52). In the last decade, laser techniques became very popular, mostly because of the growing improvement of the technologies and the professional skilfulness of dermatologists (53). The main advantages of lasers over electrolysis are related to their rapid effectiveness and, in most cases, the relative permanence of hair removal (1). However, it should also be considered that a recent Cochrane review of hair removal methods found little evidence of effectiveness for some of these techniques, although alexandrite and diode lasers were able to reduce hair by ~50% in a few months (52, 54). Notably, at present, long-term efficacy on hair removal has not been reported, which justifies the frequent need for multiple therapeutic sessions. In addition, it should be considered that there are no long-term follow-up studies.

The choice of these procedures is obviously only partly dependent on the doctor's advice, and many patients may consult a doctor after these procedures have been performed. Epilatory techniques could be reserved for cases with moderate-to-severe hirsutism. In any case, when possible, the doctor should inform the patient of the balance between cosmetic procedures, especially epilatory methods and pharmacological therapies, particularly when they are combined.

Topical medication

In cases of mild hirsutism localised on the face, an alternative to the cosmetic approach is the topical application of a 13.9% eflornithine cream. Eflornithine is an irreversible inhibitor of L-ornithine decarboxylase, which is involved in the regulation and differentiation of the hair follicle (55). Topical administration of eflornithine may reversibly slow facial hair growth in many hirsute women (56), but it does not remove hair. Although its systemic absorption is very low, it may cause skin irritation. There are several other side effects (stinging, burning, tingling, and erythema), which seem to partly depend on individual sensitivity, that should be considered.

Oestrogen–progestin compounds

A systemic pharmacological approach is usually required when hirsutism is moderate to severe and/or it is widespread. Drugs that are safer and more cost-effective are oestrogen–progestin compounds (EPs). Their efficacy is mainly justified by the ability of progestin to suppress luteinising hormone (LH) levels, and thus production of ovarian androgen, and by the ability of oestrogen (specifically ethinylestradiol) to increase SHBG, thus reducing bioavailable free androgens (57). Moreover, EPs induce a moderate reduction in adrenal androgens, probably through a direct interaction with adrenal steroid synthesis (58). In addition to these effects, which are common to all EPs, some progestins have antiandrogenic properties, due to their antagonising effects on the androgen receptor (cyproterone acetate, drospirenone, dienogest) and due to the inhibition of 5 α -reductase activity (cyproterone acetate, clormadinone acetate, 'third-generation' progestins (desogestrel, gestodene, norgestimate), drospirenone and dienogest) (57). Specifically, cyproterone acetate, the oldest product used for its antiandrogenic properties, also has a weak glucocorticoid agonist capacity. It is commonly associated with ethinylestradiol, to favour ovarian suppression. For this reason, it is usually placed in the family of EPs. For many decades, it has represented the commonest pharmacological choice for treating hirsutism, particularly in women with PCOS (57, 59). The combination with ethinylestradiol provides specific benefits in favouring the suppression of the gonadotropin drive and in increasing the synthesis of SHBG by the liver.

Older reports, mostly relative to high-dose EPs, have shown a 60–100% response to the efficacy of those compounds in reducing hirsutism (57). The same results

seem to be achieved with lower dosage EPs. In a systematic review of nine studies using cyproterone acetate to treat hirsutism in different regimens, either dosed at 2 mg associated with ethinylestradiol or at 25–100 mg, all resulted in a subjective improvement of hirsutism both in patients with PCOS and with idiopathic hirsutism when compared with placebo (59). A comparative study of an EP containing 0.15 mg desogestrel plus 30 µg ethinylestradiol with an EP containing 2 mg cyproterone acetate plus 35 µg ethinyl-estradiol demonstrated a similar efficacy of the two formulations in reducing hirsutism in a group of adolescents with PCOS (60). Similar efficacy in reducing hirsutism was also observed in comparing drospirenone/ethinylestradiol with 2 mg cyproterone acetate/35 µg EE pills (61, 62). However, drospirenone/ethinylestradiol pills are more efficacious in reducing hirsutism when compared with a formulation containing 2 mg chlormadinone acetate and 30 µg EE (63).

Concern was raised by some scientists that the efficacy of EPs in the treatment of hirsutism might be limited by the coexistence of obesity that occurs in ~50% of women with PCOS. Accordingly, it was demonstrated in one study that obese PCOS women failed to show improvement in hirsutism after 6 months of EP treatment when compared with a group of lean PCOS women who significantly improved this parameter. In addition, lean PCOS patients had a dramatic decrease in serum testosterone and androstenedione concentrations, whereas obese patients decreased only serum testosterone levels and not as markedly as their lean counterpart (64). However, these results were not confirmed by other studies (65, 66, 67), where the treatment of obese and non-obese PCOS patients was followed by a significant and similar reduction in hirsutism, though a direct comparison between the two populations was not performed. In addition, a recent placebo-controlled randomised study, enrolling only obese PCOS patients, showed that EPs may be effectively used to reduce hyperandrogenaemia and its clinical manifestations also in this subgroup of patients (68).

Therefore, although all EPs are efficacious in reducing hirsutism, probably more in lean than in obese subjects, EPs containing a progestin with antiandrogen properties are preferable for the treatment of hirsutism because they are more efficacious.

Antiandrogens

In cases of moderate to severe forms of hirsutism not responsive to EPs or, alternatively, when EPs are

contraindicated, the use of antiandrogens alone or combined with EPs is indicated. Antiandrogens (androgen receptor blockers – flutamide, spironolactone – and 5 α -reductase inhibitors – finasteride, spironolactone) are, in fact, the most effective drugs currently available for hirsutism (69). Several randomised controlled trials support the use of antiandrogens for hirsutism (69). Flutamide, finasteride, and spironolactone all ameliorate hirsutism more than placebo and insulin-sensitisers, both in PCOS and in idiopathic hirsutism. Furthermore, the combination of antiandrogens and EPs is more effective than EPs alone in improving hirsutism (23).

Whether antiandrogens should be recommended according to the extent of hirsutism has never been investigated. However, there are very few studies indirectly establishing a scale of efficacy of the different antiandrogens. In general, they did not provide evidence for a significant difference in efficacy among flutamide, finasteride and spironolactone, with some exceptions (23). In any case, the lowest effective dose should be recommended, particularly if a long-term treatment is planned. This has usually been suggested by all review articles published in the field, although it should also be considered that in many cases the dose is decreased after a first 3–6-month period at higher doses. The case of flutamide has been considered with particular attention, in both adolescents (70) and adult (71) women with PCOS, due to its potential negative effect on liver function. In adolescents, it has been reported that side effects can be easily avoided if low doses are administered (generally lower than 125 mg/day). A recent review article has reported that at these low doses hepatic dysfunction is extremely rare, whereas long-term efficacy on hirsutism is preserved (72). Antiandrogens should not be given to pregnant women as there is a risk of feminisation of male foetuses and should only be prescribed to women using secure contraception.

Combined treatment with EPs and antiandrogens

In order to increase the efficacy of the pharmacological treatment of hirsutism, several randomised controlled studies have been performed to investigate the potential combined efficacy of oral contraceptives with antiandrogens. One study (73) found no significant difference after 1 year of treatment with ethinylestradiol + drospirenone alone or combined with cyproterone acetate (100 mg/day) or spironolactone (100 mg/day). Intriguingly, another study (74) investigating the efficacy of

ethinylestradiol+dospirenone added to cyproterone acetate (12.5 mg/day) or metformin (1500 mg/day) found that metformin favoured some significant benefit of selected cardiovascular risk factors; by contrast, cyproterone acetate abolished this positive effect, at least in normal weight women with PCOS. Another study (75) reported that a 9-month treatment with ethinylestradiol+cyproterone acetate (2 mg/day) was significantly more effective than finasteride alone in decreasing the mFG score. However, an additional study by the same research group found that finasteride added to ethinylestradiol+cyproterone (2 mg/day) could achieve a double-positive efficacy on hirsutism improvement (76). The same results were obtained by another study, in which spironolactone (100 mg) had been added to ethinylestradiol+cyproterone acetate (2 mg/day) for 1 year (77). From the clinical perspective, these data suggest overall that both finasteride and spironolactone, if added to oral contraceptives containing small doses of cyproterone acetate, could provide some additional significant clinical benefit in the treatment of hirsutism in women with PCOS. On the other hand, it should be recognised that further long-term studies are needed, possibly involving women with specific phenotypes of PCOS (e.g. classic vs non-classic forms) and possibly considering the impact of excess body weight and that of metabolic abnormalities, chiefly insulin resistance and glucose intolerance states, on the outcomes.

Metformin

Metformin has pleiotropic actions on several tissues sensitive to the primary effect of insulin or affected by insulin resistance, such as the liver, the skeletal muscles, the adipose tissue, the endothelium and the ovaries (78). Apart from its action on classic insulin-sensitive tissues, metformin also has a direct effect at ovarian level (78, 79). Its beneficial effects are partly based on the alleviation of excess insulin. It has been clearly demonstrated that insulin directly regulates ovarian steroidogenesis at different steps, therefore synergising the action of the LH. In particular, *in vitro* studies have shown that metformin may reduce CYP17 activity and directly suppress androstenedione production rates in the theca cells. In addition, metformin may decrease the follicle-stimulating hormone (FSH)-stimulated granulosa cell steroidogenesis in both experimental animals and in women with PCOS (80).

Based on what is summarised earlier, the efficacy of metformin on androgen and, indirectly, on hirsutism has been investigated (71). In women with PCOS, the majority

of studies have demonstrated that metformin may improve not only fasting and glucose-stimulated insulin but also testosterone and LH levels (81). Some other studies have also reported that the degree of hirsutism was attenuated, although this does not represent a common and significant finding (11). Although mechanistic studies on all potential mechanisms responsible for metformin effects on the gonadal axis do not provide conclusive information, it is nonetheless generally accepted that the effects of metformin on hyperandrogenism may depend on the decrease in circulating insulin and improved insulin sensitivity, increased SHBG levels, which in turn decrease bioavailable free testosterone and, possibly, decreased insulin-like growth factor 1 (IGF1), due to increased IGF1-binding protein 1 (81). A recent systematic review and meta-analysis of randomised controlled studies on metformin or thiazolidinediones, alone or combined with EP compounds or antiandrogens, has been published (82). A total of 16 trials out of 348 candidate studies, most of which had been performed in women with PCOS, were considered eligible for the aim of this work. The final conclusion was that insulin sensitisers only produce minor effects on hirsutism with respect to placebo, and much more if compared with EP compounds or antiandrogens. Therefore, metformin should not be used in the treatment of hirsutism in hyperandrogenic women, particularly those with PCOS.

Potential side effects of EP compounds, antiandrogens and metformin

Potential side effects of EP compounds and antiandrogens in patients with hirsutism and PCOS may represent a hallmark for effective treatment and may interfere with the choice of the specific therapeutic drug. However, in general the side effects of the compounds discussed above are relatively acceptable, mild and reversible, with some exceptions.

Metformin can favour gastrointestinal side effects in ~10–15% patients, which often necessitate a lower dose and may resolve within a few days. It is rarely necessary to discontinue the drug. Vitamin B12 deficiency has been reported in anecdotic cases, with very rare reports of megaloblastic anaemia. In any case, renal dysfunction, organ hypoxia and alcohol abuse represent contraindications for metformin use (79).

EP compounds may be associated with an increased risk of thromboembolism, irrespective of the progestin used (83). Although there is evidence that this side effect does not occur more frequently in women with PCOS,

there are however inconclusive data on the potential risk represented by excess body weight and age. This could be important, as women with PCOS often start treatment in the adolescent age and continue it for a long period of time. Metabolic abnormalities are relatively uncommon, which fits with the potential protection of EPs against cardiovascular events. A recent systematic review and meta-analysis focused on the risk of venous thromboembolism and cardiovascular risk factors and events in women taking drospirenone added to ethinylestradiol, supporting the concept that long-term use of this drug may be associated with higher risks, compared with both no treatment or levonorgestrel combined with ethinylestradiol (83). This event should therefore be taken into account when planning a treatment including drospirenone.

Antiandrogens may conversely represent a matter of some concern. In the previous paragraph, the potential hepatotoxicity of flutamide was highlighted; however, there are no data on the potential contribution of specific metabolic factors, including obesity, non-alcoholic fatty liver disease or the metabolic syndrome. At present, age and the dose of flutamide appear to represent potential risk factors, although adequate scientific information is still lacking (72).

Finasteride appears to possess very limited potential for side effects, except for some concerns related to its potential teratogenicity, which implies that it should not be administered to women wishing to become pregnant.

Spironolactone alone has been associated with menses abnormalities, such as menorrhagia or polymenorrhea (83, 84, 85). It seems to be metabolically neutral, although its effects on bone metabolism requires further investigation. Due to its potential capacity to increase potassium levels in blood, it should be avoided in the presence of even modest kidney dysfunction, even if at the current doses used in hirsute PCOS women it has been observed very rarely.

Lifestyle intervention and weight loss

In the presence of excess weight or obesity, women with PCOS should always be treated in order to achieve weight loss, which is often associated with metabolic benefits and a significant improvement in menses and ovulation rates (86). A systematic review was conducted of the published medical literature to identify studies evaluating the lifestyle treatment of PCOS (defined as dietary, exercise or behavioural treatment with the aim of inducing weight loss in overweight or obese women with PCOS with or

without anti-obesity pharmacological agents (85). Most of studies employ various forms of dietary restriction with resultant weight reduction of <5 to >15% over starting body weight and variation in the number of patients, with several studies including very few patients. With respect to androgens, most studies demonstrated reductions in either total or free testosterone and some demonstrated reductions in adrenal androgens (85). SHBG was improved in all of the longer term studies, with only one very-short-term intervention failing to show improvement (86). Clinically, improvements in hirsutism were documented in a number of studies (87, 88, 89). Menstrual function and ovulation improved in all the studies reporting this endpoint. As expected, metabolic improvements were seen in all studies in which these were measured (86). There is currently no evidence that modifying dietary macronutrient composition offers additional benefits over conventional dietary approaches for weight loss, and further research is needed. By contrast, there is emerging evidence suggesting that exercise offers additional benefits to dietary energy restriction for reproductive features of PCOS, particularly on responders in terms of weight loss; however, no data on hirsutism are available. A meta-analysis investigated the efficacy of lifestyle intervention on biochemical hyperandrogenism and, separately, on hirsutism (89). A greater reduction was achieved in endpoint total testosterone (MD -0.27 nmol/l, 95% CI -0.46 to -0.09 ; 144 participants, five trials, $P=0.004$) for lifestyle treatment compared with minimal treatment, but there was no evidence of effect for endpoint SHBG (MD 2.29 nmol/l, 95% CI -0.12 to 4.70 ; 144 participants, five trials, $P=0.06$) and endpoint FAI (MD -0.06 , 95% CI -1.34 to 1.22 ; 132 participants, four trials, $P=0.93$). In addition, the authors found a greater reduction in endpoint mFG (MD -1.19 , 95% CI -2.35 to -0.03 ; 132 participants, four trials, $P=0.04$) for lifestyle treatment compared with minimal treatment. It is worth mentioning that a recent study supported the concept that long-term treatment of obesity with lifestyle intervention may not only significantly improve features of PCOS in more than 80% of affected obese women but also that a full recovery of categorical features can be achieved, including hirsutism, in one-third of them (90).

Obesity has been shown to have a negative impact on the efficacy of treatment of hirsutism with different drugs. In a systematic review, Koulouri & Conway (91) reported that a significant reduction of hirsutism was found for flutamide, spironolactone, cyproterone acetate combined with ethinylestradiol and other oral contraceptive pills, thiazolidinediones, finasteride and

metformin, but not for placebo. However, the reduction in the mFG score in response to treatment was negatively associated with BMI ($r = -0.38$; $P = 0.004$). Thus, these findings suggest that in overweight and obese women with hirsutism and particularly in those with PCOS, appropriate lifestyle advice should always be associated with a pharmacological therapy for a successful treatment programme.

Bariatric surgery

Given the disappointing results of diet-based approaches, interest in bariatric surgery for the treatment of grade II or III obesity is increasing worldwide. A meta-analysis of the effects of bariatric surgery in more than 22 000 procedures found an average weight loss of more than 50%, associated with the complete resolution or improvement of diabetes, hyperlipidaemia, hypertension and obstructive sleep apnoea in more than 60% of the patients (92). The Sweden Obesity Study is a long-term large prospective study (93) that has repeatedly confirmed that weight loss, and metabolic and cardiovascular benefits together with a significant decrease in mortality for all causes were maintained 10 years after the bariatric surgery procedure. Although PCOS is a highly prevalent disorder that is frequently associated with obesity (94), very little is known of it in women presenting with morbid obesity. A recent study by Escobar-Morreale *et al.* (95) aimed at prospectively estimating the prevalence of PCOS in morbidly obese women and evaluating changes in the PCOS phenotype induced by the marked and sustained weight loss after bariatric surgery, adds some useful and relevant information in this field. They found a very high prevalence of PCOS (35%) and, most importantly, that after a sustained weight loss, all features defining the phenotype, including hirsutism and hyperandrogenaemia, menses irregularities and anovulation, insulin resistance and metabolic derangements, may be completely resolved after bariatric surgery in all women. Two additional studies published in the last years found that bariatric surgery may have an important albeit not universal benefit on hirsutism in massively obese women with PCOS. One study (96) found that in 20 women with severe obesity and PCOS, a Roux-en-Y gastric bypass significantly ameliorated menses and conception rates in most, and resolved hirsutism in 29% of them. A second study (97) reviewed the outcomes of 24 massively obese women diagnosed with PCOS who had undergone elective laparoscopic gastric bypass surgery and found that all but one were hirsute before surgery but 12 (52%) had complete

resolution at a mean follow-up of 8 ± 2.3 months, six (25%) had moderate resolution at a mean of 21 ± 18 months, three had minimal resolution at 34 ± 14 months and, finally, two women reported no change in their hirsutism at 32 ± 7 months. Overall, these studies confirm that in selected cases, obese women with PCOS can be cured and the phenotype can be completely resolved. However, given the very high association of PCOS with obesity, long-term multicentre and prospective studies should be performed to confirm these promising findings.

Choice of treatment according to age and the phenotype

The topic related to the best treatment according to the patient's age is still a matter of debate and some controversy. In addition, there are no studies focusing on the specific drug treatment for clinical hyperandrogenism, specifically hirsutism, in adolescent and adult women with PCOS. Therefore, the doctor's choice is often based on his/her clinical experience and scientific background.

Adolescent girls

Hirsute adolescent girls often complain of their condition, and therefore require prompt attention in order to avoid psychological distress. In the presence of mild hirsutism, cosmetic procedures may be effective and sufficient. If excess weight or obesity is present, appropriate lifestyle intervention should be promptly provided after a careful investigation for the presence of eating disorders, which are not uncommon in these patients. The use of EPs in early adolescence is controversial, and few data exist as a guide. Moreover, the best EP for adolescents and appropriate duration of therapy is uncertain (98). Many support the symptom-driven approach, whereas others support an approach targeting the underlying reproductive/hormonal and metabolic abnormalities associated with PCOS (99). Finally, there are no adequately powered, randomised, double-blind, placebo-controlled trials on the treatment of hirsutism in adolescents with PCOS. The goals of treating hyperandrogenism and providing contraception prompt the use of EPs as the mainstay of therapy for adolescents with PCOS (100, 101), which appear to be reasonably acceptable, particularly in adolescents with severe hirsutism. In addition, benefits such as normal menses and decreased acne and hirsutism are typically of the greatest importance to an adolescent. As no guidelines exist yet, when appropriate on the basis of clinical history and physical examination, EPs (including progestins with

antiandrogenic properties) can be added for a long period of time, provided an adequate follow-up programme is planned. If lifestyle intervention is effective, therapeutic strategies could be modified. By contrast, psychological support should be planned when poor compliance and behavioural aspects, including poor quality of life, are present.

Normal weight hirsute women with PCOS

Normal weight women with hirsutism may represent a specific target for the long-term use of EPs and/or antiandrogens. In these women, an EP containing drospirenone or cyproterone acetate may be an appropriate first choice (91), provided no risk factors for thrombosis are present. If little progress has been achieved after several months, additional antiandrogens could be added. As reported in a previous section, all antiandrogens have been found to provide the same efficacy in the treatment of hirsutism in women with PCOS. Spironolactone can be safely added to EPs (23, 101) and low-dose-flutamide has been found to improve hirsutism in the long term (23, 69). In fact, a large retrospective study on 414 premenopausal women with hirsutism of different aetiopathogeneses (69) showed a marked improvement after 12 months' treatment with flutamide compared with basal values, with a maximum effect observed after 2 years. In this study, doses were tapered yearly by reducing them (250, 125 and 62.5 mg/day) over time. No important side effects were observed but a few patients had to forsake the study in the first 6 months of treatment because of the mild increases in the level of aminotransferases in the liver. Although available studies on the treatment with EPs and/or antiandrogens have provided sufficient data on their efficacy and tolerability, most of them suffer from some heterogeneity of the cohort included (in relation to their BMI) and rarely exceed 1 year in treatment duration. Therefore, more long-term multi-centre studies should be performed, with careful selection of the phenotype. Finally, there is some evidence that extended-cycle EPs (vs cyclic therapy) may offer greater hormonal suppression and prevent rebound ovarian function during the pill-free interval (102). However, their efficacy in the treatment of hirsutism should be investigated.

Obese hirsute women with PCOS

Obese women with hirsutism are often affected by PCOS. As mentioned earlier, treatment should firstly include

lifestyle intervention, possibly planned for a long period of time, in order to promote effective weight loss. In those with massive obesity, bariatric surgery should be considered, provided specific contraindications are present. In this way, hirsutism may improve without the need for specific drugs. In fact, effective suppression of hair growth is unlikely without weight loss (89). On the other hand, there is sufficient evidence that metformin may help in achieving metabolic benefits, may decrease androgen blood concentrations and, possibly, reduce visceral fat (103). In selected cases, metformin may slightly improve hirsutism (88). Antiandrogens can also be added, particularly in the presence of severe hirsutism. In fact, long-term treatment with antiandrogens has been shown to significantly amplify hair loss and, additionally, to increase insulin sensitivity independently of the amount of weight loss (104).

Hirsute women with PCOS seeking pregnancy

Hirsute women with PCOS in the fertile age seeking pregnancy represent a specific target for weight loss if excess weight or obesity is present, as it has been clearly demonstrated that chances to improve ovulatory rates and become pregnant are significantly increased. Similar findings have been observed in massively obese women with PCOS after bariatric surgery (see above). In all women with PCOS, either normal weight or overweight/obese, pharmacological treatment should be avoided, except metformin, which has been found to significantly improve fertility rates in the long term. As reported above, this is particularly relevant for antiandrogens. For psychological reasons, adequate cosmetic procedures could be recommended to women wishing to improve their appearance.

Hirsute women with PCOS and menopause

For women with PCOS approaching the menopause or in postmenopausal years, there is no evidence-based treatment or specific treatment that has been investigated in clinical trials. Apart from cosmetic procedures, there is evidence that mild hirsutism can benefit from oestrogen replacement therapy, possibly combined with antiandrogenic progestins (91). In cases presenting with severe hirsutism of non-neoplastic origin or due to ovarian stromal hyperplasia, the use of gonadotropin-releasing analogues can be recommended (105). Particular care should be taken in cases of rapidly worsening hirsutism in postmenopausal women, which can be a marker of an androgen-secreting ovarian tumour (106).

Hirsute women with PCOS and glucose intolerance states

A specific condition refers to how to manage hirsutism in women with PCOS who present with impaired glucose tolerance or diabetes. If obesity is present, a lifestyle programme with a structured follow-up is mandatory. With respect to the treatment of hirsutism, the use of EPs containing progestin with antiandrogenic properties can be considered. In fact, the impact of EPs on carbohydrate metabolism in PCOS women is still unclear because available studies are small and short-term, and they utilise varying methodologies to assess endpoints. Studies, mostly cross-sectional, on healthy postmenopausal women have found some derangement in insulin sensitivity and increased glucose response to a glucose load during EP use, although these results varied according to the oestrogen dose and the type of progestin used (107). In fact, the residual androgenic activity of the progestin contained in the EP formulation may influence glucose metabolism more than the dose of ethinylestradiol (108). With respect to PCOS, a Cochrane meta-analysis concluded that EPs do not have a significant effect on glucose tolerance, although this conclusion was based on limited and low-quality evidence (108). Available data from long-term studies performed on healthy women are promising, because EPs use did not result in an increased incidence of type 2 diabetes either in the general population (109) or in women with a history of gestational diabetes (110, 111). Recently, the American Diabetes Association along with the Centre for Disease Control concluded that EPs are not contraindicated in women with diabetes without vascular complications (112, 113). Importantly, it should be noted that available studies on this topic have shown that the impact of EPs on body weight and fat distribution is similar between healthy women and women with PCOS, and that BMI and the waist-to-hip ratio (WHR) were unchanged (114) or occasionally improved, independent of coexistent obesity (103). Therefore, given the ability of EPs to suppress ovarian steroidogenesis, they can be safely used in hirsute women with PCOS and diabetes, provided a strict follow-up is planned to monitor the cost/benefit balance. A recent long-term prospective study (mean follow-up 16.9 years) planned to investigate the risk of type 2 diabetes in women with PCOS (115) found that, among 249 of them without diabetes at baseline, 16.9% (42 women) developed type 2 diabetes during the follow-up, with an incidence rate of 1.05 person-year. The age-standardised prevalence of type 2 diabetes was 39.3% in the whole group of PCOS, therefore significantly higher than that reported in the national

general female population with similar age (5.8%). The most important predictive factors were an increase in BMI during the follow-up period, as well as the persistence of low SHBG blood levels over time. During the follow-up period, metformin was taken for a long-time in 71.4% women with PCOS who developed diabetes vs 23.1% ($P<0.001$) in those who did not. Interestingly, both diabetic and non-diabetic PCOS women had similar values of SHBG at baseline, whereas those who did not become diabetic at follow-up had a twofold increase in SHBG with respect to diabetic PCOS women at follow-up. These data indirectly support the concept that available EPs do not worsen glucose homeostasis and may suggest a potential benefit in the prevention of type 2 diabetes in obese women with PCOS. Therefore, much more research should be performed on the potential role of EPs on metabolic issues in women with PCOS.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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References

- Wendelin DS, Pope DN & Mallory SB. Hypertrichosis. *Journal of the American Academy of Dermatology* 2003 **48** 161–179. (doi:10.1067/mjd.2003.100)
- Escobar-Morreale HF. Diagnosis and management of hirsutism. *Annals of the New York Academy of Sciences* 2010 **1205** 166–174. (doi:10.1111/j.1749-6632.2010.05652.x)
- Asuncion M, Calvo RM, San Millan JL, Sancho J, Avila S & Escobar-Morreale HF. A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. *Journal of Clinical Endocrinology and Metabolism* 2000 **85** 2434–2438. (doi:10.1210/jc.85.7.2434)
- Sagsoz N, Kamaci M & Orbak Z. Body hair scores and total hair diameters in healthy women in the Kirikkale Region of Turkey. *Yonsei Medical Journal* 2004 **45** 483–491.
- DeUgarte CM, Woods KS, Bartolucci AA & Azziz R. Degree of facial and body terminal hair growth in unselected black and white women: toward a populational definition of hirsutism. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 1345–1350. (doi:10.1210/jc.2004-2301)
- Sanchón R, Gambineri A, Alpañés M, Martínez-García MÁ, Pasquali R & Escobar-Morreale HF. Prevalence of functional disorders of androgen excess in unselected premenopausal women: a study in blood donors. *Human Reproduction* 2012 **27** 1209–1216. (doi:10.1093/humrep/des028)
- Cheewadhanarak S, Peeyananjarassri K & Choksuchat C. Clinical diagnosis of hirsutism in Thai women. *Journal of the Medical Association of Thailand* 2004 **87** 459–463.

- 8 Noorbala MT & Kefae P. The prevalence of hirsutism in adolescent girls in Yazd, Central Iran. *Iranian Red Crescent Medical Journal* 2010 **12** 111–117.
- 9 Hickey M, Doherty DA, Atkinson H, Sloboda DM, Franks S, Norman RJ & Hart R. Clinical, ultrasound and biochemical features of polycystic ovary syndrome in adolescents: implications for diagnosis. *Human Reproduction* 2011 **26** 1469–1477. (doi:10.1093/humrep/der102)
- 10 Gambineri A, Prontera O, Fanelli F, Repaci A, Di Dalmazi G, Pagotto U & Pasquali R. Epidemiological survey on the prevalence of hyperandrogenic states in adolescent and young women. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** 1641–1650. (doi:10.1210/jc.2012-3537)
- 11 Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, Janssen OE, Legro RS, Norman RJ, Taylor AE *et al.* The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. *Fertility and Sterility* 2009 **91** 456–488. (doi:10.1016/j.fertnstert.2008.06.035)
- 12 Wild RA, Vesely S, Beebe L, Whitsett T & Owen W. Ferriman Galloway self-scoring I: performance assessment in women with polycystic ovary syndrome. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 4112–4114. (doi:10.1210/jc.2004-2243)
- 13 Carmina E. The spectrum of androgen excess disorders. *Fertility and Sterility* 2006 **85** 1582–1585. (doi:10.1016/j.fertnstert.2006.02.069)
- 14 Gambineri A, Pelusi C, Vicennati V, Pagotto U & Pasquali R. Obesity and the polycystic ovary syndrome. *International Journal of Obesity and Related Metabolic Disorders* 2002 **26** 883–896. (doi:10.1038/sj.ijo.0801994)
- 15 Ozdemir S, Ozdemir M, Gökemli H, Kiyici A & Bodur S. Specific dermatologic features of the polycystic ovary syndrome and its association with biochemical markers of the metabolic syndrome and hyperandrogenism. *Acta Obstetrica et Gynecologica Scandinavica* 2010 **89** 199–204. (doi:10.3109/00016340903353284)
- 16 Rausch ME, Legro RS, Barnhart HX, Carson SA, Diamond MP, Carr BA, Schlaff WD, Coutifaris C, McGovern PG, Cataldo N *et al.* Predictors of pregnancy in women with polycystic ovary syndrome. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 3458–3466. (doi:10.1210/jc.2009-0545)
- 17 Unluhizarci K, Gokce C, Atmaca H, Bayram F & Kelestimur F. A detailed investigation of hirsutism in a Turkish population: idiopathic hyperandrogenemia as a perplexing issue. *Experimental and Clinical Endocrinology & Diabetes* 2004 **112** 504–509. (doi:10.1055/s-2004-821307)
- 18 Azziz R, Carmina E & Sawaya ME. Idiopathic hirsutism. *Endocrine Reviews* 2000 **21** 347–362. (doi:10.1210/er.21.4.347)
- 19 Thiboutot D, Jabara S, McAllister JM, Sivarajah A, Gilliland K, Cong Z & Clawson G. Human skin is a steroidogenic tissue: steroidogenic enzymes and cofactors are expressed in epidermis, normal sebocytes, and an immortalized sebocyte cell line (SEB-1). *Journal of Investigative Dermatology* 2003 **120** 905–914. (doi:10.1046/j.1523-1747.2003.12244.x)
- 20 Longcope C. Adrenal and gonadal androgen secretion in normal females. *Clinics in Endocrinology and Metabolism* 1986 **15** 213–228. (doi:10.1016/S0300-595X(86)80021-4)
- 21 Yildiz BO, Bolour S, Woods K, Moore A & Azziz R. Visually scoring hirsutism. *Human Reproduction Update* 2010 **16** 51–64. (doi:10.1093/humupd/dmp024)
- 22 Hatch R, Rosenfield RL, Kim MH & Tredway D. Hirsutism: implications, etiology, and management. *American Journal of Obstetrics and Gynecology* 1981 **140** 815–830.
- 23 Escobar-Morreale HF, Carmina E, Dewailly D, Gambineri A, Kelestimur F, Moghetti P, Pugeat M, Qiao J, Wijeyaratne CN, Witchel SF *et al.* Epidemiology, diagnosis and management of hirsutism: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome Society. *Human Reproduction Update* 2012 **18** 146–170. (doi:10.1093/humupd/dmr042)
- 24 Legro RS, Schlaff WD, Diamond MP, Coutifaris C, Casson PR, Brzyski RG, Christman GM, Trussell JC, Krawetz SA, Snyder PJ *et al.* Total testosterone assays in women with polycystic ovary syndrome: precision and correlation with hirsutism. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 5305–5313. (doi:10.1210/jc.2010-1123)
- 25 Fanelli F, Belluomo I, Di Lallo VD, Cuomo G, De Iasio R, Baccini M, Casadio E, Casetta B, Vicennati V, Gambineri A *et al.* Serum steroid profiling by isotopic dilution-liquid chromatography–mass spectrometry: comparison with current immunoassays and reference intervals in healthy adults. *Steroids* 2011 **76** 244–253. (doi:10.1016/j.steroids.2010.11.005)
- 26 Janse F, Eijkemans MJC, Goverde AJ, Lentjes EGWM, Hoek A, Lambalk CB, Hickey TE, Fauser BC & Norman RJ. Assessment of androgen concentration in women: liquid chromatography–tandem mass spectrometry and extraction RIA show comparable results. *European Journal of Endocrinology* 2011 **165** 925–933. (doi:10.1530/EJE-11-0482)
- 27 Balsamo A, Rinaldini D, Marsigli A, Monti S, Bettocchi I & Baronio F. Screening e diagnosi dell'iperplasia surrenale congenita: dalle vecchie alle nuove tecnologie. *Ligand Assay* 2012 **17** 1–10.
- 28 Fanelli F, Gambineri A, Belluomo I, Repaci A, Diana Di Lallo VD, Di Dalmazi G, Mezzullo M, Prontera O, Cuomo G, Zanotti L *et al.* Androgen profiling by liquid chromatography – tandem mass spectrometry (LC–MS/MS) in healthy normal weight ovulatory and anovulatory late adolescent and young women. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** 3058–3067. (doi:10.1210/jc.2013-1381)
- 29 Salley KE, Wickham EP, Cheang KI, Essah PA, Karjane NW & Nestler JE. Glucose intolerance in polycystic ovary syndrome – a position statement of the Androgen Excess Society. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 4546–4556. (doi:10.1210/jc.2007-1549)
- 30 Wild RA, Carmina E, Diamanti-Kandarakis E, Dokras A, Escobar-Morreale HF, Futterweit W, Lobo R, Norman RJ, Talbott E & Dumesic DA. Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 2038–2049. (doi:10.1210/jc.2009-2724)
- 31 Pasquali R & Gambineri A. Polycystic ovary syndrome: a multifaceted disease from adolescence to adult age. *Annals of the New York Academy of Sciences* 2006 **1092** 158–174. (doi:10.1196/annals.1365.014)
- 32 Dewailly D, Gronier H, Poncelet E, Robin G, Leroy M, Pigny P, Duhamel A & Catteau-Jonard S. Diagnosis of polycystic ovary syndrome (PCOS): revisiting the threshold values of follicle count on ultrasound and of the serum AMH level for the 250 definition of polycystic ovaries. *Human Reproduction* 2011 **26** 3123–3129. (doi:10.1093/humrep/der297)
- 33 Loriaux DL. An approach to the patient with hirsutism. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 2957–2968. (doi:10.1210/jc.2011-2744)
- 34 Balsamo A, Baldazzi L, Menabò S & Cicognani A. Impact of molecular genetics on congenital adrenal hyperplasia management. *Sexual Development* 2010 **4** 233–248. (doi:10.1159/000315959)
- 35 Nimkarn S, Lin-Su K & New MI. Steroid 21 hydroxylase deficiency congenital adrenal hyperplasia. *Pediatric Clinics of North America* 2011 **58** 1281–1300. (doi:10.1016/j.pcl.2011.07.012)
- 36 Pasquali R. Obesity and androgens: fact and perspectives. *Fertility and Sterility* 2006 **85** 1319–1340. (doi:10.1016/j.fertnstert.2005.10.054)
- 37 Samojlik E, Kirschner MA, Silber D, Schneider G & Ertel NH. Elevated production and metabolic clearance rates of androgens in morbidly obese women. *Journal of Clinical Endocrinology and Metabolism* 1984 **59** 949–954. (doi:10.1210/jcem-59-5-949)
- 38 Kirschner MA, Samojlik E, Drejka M, Szmál E, Schneider G & Ertel N. Androgen–estrogen metabolism in women with upper body versus

- lower body obesity. *Journal of Clinical Endocrinology and Metabolism* 1990 **70** 473–479. (doi:10.1210/jcem-70-2-473)
- 39 Bélanger C, Hould FS, Lebel S, Biron S, Brochu G & Tchernof A. Omental and subcutaneous adipose tissue steroid levels in obese men. *Steroids* 2006 **71** 674–682. (doi:10.1016/j.steroids.2006.04.008)
 - 40 Pasquali R. The endocrine impact of obesity in eumenorrheic women. In *Androgen Excess Disorders in Women*, pp 455–462. Eds Azziz R, Nestler JE, Dewailly D. Philadelphia: Lippincott-Raven, 1997.
 - 41 Cresswell JL, Barker DJ, Osmond C, Egger P, Phillips DI & Fraser RB. Fetal growth, length of gestation, and polycystic ovaries in adult life. *Lancet* 1997 **350** 1131–1135. (doi:10.1016/S0140-6736(97)06062-5)
 - 42 McCartney CR, Blank SK, Prendergast KA, Chhabra S, Eagleson CA, Helm KD, Yoo R, Chang RJ, Foster CM, Caprio S *et al.* Obesity and sex steroid changes across puberty: evidence for marked hyperandrogenemia in pre- and early pubertal obese girls. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 430–436. (doi:10.1210/jc.2006-2002)
 - 43 Morales AJ, Laughlin GA, Bützow T, Maheshwari H, Bauman G & Yen SS. Insulin, somatotrophic, and luteinizing hormone axes in lean and obese women with polycystic ovary syndrome: common and distinct features. *Journal of Clinical Endocrinology and Metabolism* 1996 **81** 2854–2864. (doi:10.1210/jc.81.8.2854)
 - 44 Poretsky L, Cataldo NA, Rosenwaks Z & Giudice LC. The insulin-related ovarian regulatory system in health and disease. *Endocrine Reviews* 1990 **20** 535–582. (doi:10.1210/er.20.4.535)
 - 45 Diamanti-Kandarakis E & Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. *Endocrine Reviews* 2012 **33** 981–1030. (doi:10.1210/er.2011-1034)
 - 46 Koulouri O & Conway GS. Management of hirsutism. *BMJ* 2009 **338** 823–826. (doi:10.1136/bmj.b847)
 - 47 Richards RN, Uy M & Meharg G. Temporary hair removal in patients with hirsutism: a clinical study. *Cutis* 1990 **45** 199–202.
 - 48 Lynfield YL & MacWilliams P. Shaving and hair growth. *Journal of Investigative Dermatology* 1970 **55** 170–177. (doi:10.1111/1523-1747.ep12280667)
 - 49 Natow AJ. Chemical removal of hair. *Cutis* 1986 **38** 91–92.
 - 50 Richards RN & Meharg GE. Electrolysis: observations from 13 years and 140,000 hours of experience. *Journal of the American Academy of Dermatology* 1995 **33** 662–666. (doi:10.1016/0190-9622(95)91290-8)
 - 51 Haedersdal M & Wulf HC. Evidence-based review of hair removal using lasers and light sources. *Journal of the European Academy of Dermatology and Venereology* 2006 **20** 9–20. (doi:10.1111/j.1468-3083.2005.01327.x)
 - 52 Wagner R, Tomich J & Grande D. Electrolysis and thermolysis for permanent hair removal. *Journal of the American Academy of Dermatology* 1985 **12** 441–449. (doi:10.1016/S0190-9622(85)70062-X)
 - 53 Raulin C, Kimmig W & Werner S. Laser therapy in dermatology and esthetic medicine. Side effects, complications and treatment errors. *Der Hautarzt* 2000 **51** 463–473. (doi:10.1007/s001050051155)
 - 54 Haedersdal M & Gøtzsche PC. Laser and photoepilation for unwanted hair growth. *Cochrane Database of Systematic Reviews*, 2006 CD004684.
 - 55 Barman Balfour JA & McClellan K. Topical eflornithine. *American Journal of Clinical Dermatology* 2001 **2** 197–201. (doi:10.2165/00128071-200102030-00009)
 - 56 Wolf JE Jr, Shander D, Huber F, Jackson J, Lin CS, Mathes BM & Schrode K & Eflornithine HCl Study Group. Randomized, double-blind clinical evaluation of the efficacy and safety of topical eflornithine HCl 13.9% cream in the treatment of women with facial hair. *International Journal of Dermatology* 2007 **46** 94–98. (doi:10.1111/j.1365-4632.2006.03079.x)
 - 57 Vrbíková J & Cibula D. Combined oral contraceptives in the treatment of polycystic ovary syndrome. *Human Reproduction Update* 2005 **11** 277–291. (doi:10.1093/humupd/dmi005)
 - 58 De Leo V, Morgante G, Piomboni P, Musacchio MC, Petraglia F & Cianci A. Evaluation of effects of an oral contraceptive containing ethinylestradiol combined with drospirenone on adrenal steroidogenesis in hyperandrogenic women with polycystic ovary syndrome. *Fertility and Sterility* 2007 **88** 113–117. (doi:10.1016/j.fertnstert.2006.11.137)
 - 59 Van der Spuy ZM & le Roux PA. Cyproterone acetate for hirsutism. *Cochrane Database of Systematic Reviews*, 2003 CD001125.
 - 60 Mastorakos G, Koliopoulos C & Creatsas G. Androgen and lipid profiles in adolescents with polycystic ovary syndrome who were treated with two forms of combined oral contraceptives. *Fertility and Sterility* 2002 **77** 919–927. (doi:10.1016/S0015-0282(02)02993-X)
 - 61 van Vloten WA, van Haselen CW, van Zuuren EJ, Gerlinger C & Heithoecker R. The effect of 2 combined oral contraceptives containing either drospirenone or cyproterone acetate on acne and seborrhea. *Cutis* 2002 **69** (Suppl) 2–15.
 - 62 Batukan C, Muderris II, Ozelik B & Ozturk A. Comparison of two oral contraceptives containing either drospirenone or cyproterone acetate in the treatment of hirsutism. *Gynecological Endocrinology* 2007 **23** 38–44. (doi:10.1080/09637480601137066)
 - 63 Lello S, Primavera G, Colonna L, Vittori G, Guardianelli F, Sorge R & Raskovic D. Effects of two estrogestins containing ethinylestradiol 30 microg and drospirenone 3 mg and ethinylestradiol 30 microg and chlormadinone 2 mg on skin and hormonal hyperandrogenic manifestations. *Gynecological Endocrinology* 2008 **24** 718–723. (doi:10.1080/09513590802454943)
 - 64 Cibula D, Hill M, Fanta M, Sindelka G & Zivny J. Does obesity diminish the positive effect of oral contraceptive treatment on hyperandrogenism in women with polycystic ovarian syndrome? *Human Reproduction* 2001 **16** 940–944. (doi:10.1093/humrep/16.5.940)
 - 65 Morin-Papunen LC, Vauhkonen I, Koivunen RM, Ruokonen A, Martikainen HK & Tapanainen JS. Endocrine and metabolic effects of metformin versus ethinyl estradiol-cyproterone acetate in obese women with polycystic ovary syndrome: a randomized study. *Journal of Clinical Endocrinology and Metabolism* 2000 **85** 3161–3168. (doi:10.1210/jc.85.9.3161)
 - 66 Morin-Papunen L, Vauhkonen I, Koivunen R, Ruokonen A, Martikainen H & Tapanainen JS. Metformin versus ethinyl estradiol-cyproterone acetate in the treatment of nonobese women with polycystic ovary syndrome: a randomized study. *Journal of Clinical Endocrinology and Metabolism* 2003 **88** 148–156. (doi:10.1210/jc.2002-020997)
 - 67 Wu J, Zhu Y, Jiang Y & Cao Y. Effects of metformin and ethinyl estradiol-cyproterone acetate on clinical, endocrine and metabolic factors in women with polycystic ovary syndrome. *Gynecological Endocrinology* 2008 **24** 392–398. (doi:10.1080/09513590802217027)
 - 68 Hoeger K, Davidson K, Kochman L, Cherry T, Kopin L & Guzick DS. The impact of metformin, oral contraceptives, and lifestyle modification on polycystic ovary syndrome in obese adolescent women in two randomized, placebo-controlled clinical trials. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 4299–4306. (doi:10.1210/jc.2008-0461)
 - 69 Swiglo BA, Cosma M, Flynn DN, Kurtz DM, Labella ML, Mullan RJ, Erwin PJ & Montori VM. Clinical review: antiandrogens for the treatment of hirsutism: a systematic review and metaanalyses of randomized controlled trials. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 1153–1160. (doi:10.1210/jc.2007-2430)
 - 70 Ibáñez L & de Zegher F. Low-dose flutamide-metformin therapy for hyperinsulinemic hyperandrogenism in non-obese adolescents and women. *Human Reproduction Update* 2006 **12** 243–252. (doi:10.1093/humupd/dmi054)
 - 71 Paradisi R & Venturoli S. Retrospective observational study on the effects and tolerability of flutamide in a large population of patients with various kinds of hirsutism over a 15-year period. *European Journal of Endocrinology* 2010 **163** 139–147. (doi:10.1530/EJE-10-0100)
 - 72 de Zegher F & Ibáñez L. Therapy: low-dose flutamide for hirsutism: into the limelight, at last. *Nature Reviews. Endocrinology* 2010 **6** 421–422. (doi:10.1038/nrendo.2010.119)

- 73 Kelekci KH, Kelekci S, Yengel I, Gul S & Yilmaz B. Cyproterone acetate or drospirenone containing combined oral contraceptives plus spironolactone or cyproterone acetate for hirsutism: randomized comparison of three regimens. *Journal of Dermatological Treatment* 2012 **23** 177–183. (doi:10.3109/09546634.2010.519766)
- 74 Fruzzetti F, Perini D, Lazzarini V, Parrini D, Gambacciani M & Genazzani AR. Comparison of effects of 3 mg drospirenone plus 20 mg ethinylestradiol alone or combined with metformin or cyproterone acetate on classic cardiovascular risk factors in nonobese women with polycystic ovary syndrome. *Fertility and Sterility* 2010 **94** 1793–1798. (doi:10.1016/j.fertnstert.2009.10.016)
- 75 Sahin Y, Bayram F, Kelestimur F & Muderris L. Comparison of cyproterone acetate plus ethinyl estradiol and finasteride in the treatment of hirsutism. *Journal of Endocrinological Investigation* 1998 **21** 348–352.
- 76 Sahin Y, Dilber S & Kelestimur F. Comparison of Diane 35 and Diane 35 plus finasteride in the treatment of hirsutism. *Fertility and Sterility* 2001 **75** 496–500. (doi:10.1016/S0015-0282(00)01764-7)
- 77 Kelestimur F & Sahin Y. Comparison of Diane 35 and Diane plus spironolactone in the treatment of hirsutism. *Fertility and Sterility* 1998 **69** 66–69. (doi:10.1016/S0015-0282(97)00427-5)
- 78 Viollet B, Guigas B, Sanz Garcia N, Leclerc J, Foretz M & Andreelli F. Cellular and molecular mechanisms of metformin: an overview. *Clinical Science* 2012 **122** 253. (doi:10.1042/CS20110386)
- 79 Pasquali R & Gambineri A. Insulin sensitizers in polycystic ovary syndrome. In *Polycystic Ovary Syndrome: Novel Insight into Causes and Therapy*, pp 83–102. Eds D Macut, M Pfeifer, BO Yildiz & E Diamanti-Kandarakis. Frontiers of Hormone Research. Ed AB Grossman, Karger 2012.
- 80 Diamanti-Kandarakis E. Metformin: an old medication of new fashion: evolving new molecular mechanisms and clinical implications in polycystic ovary syndrome. *European Journal of Endocrinology* 2010 **162** 193. (doi:10.1530/EJE-09-0733)
- 81 Palomba S, Falbo A, Zullo F & Orio F Jr. Evidence-based and potential benefits of metformin in the polycystic ovary syndrome: a comprehensive review. *Endocrine Reviews* 2009 **30** 1–50. (doi:10.1210/er.2008-0030)
- 82 Cosma M, Swiglo BA, Flynn DN, Kurtz DM, Labella ML, Mullan RJ, Elamin MB, Erwin PJ & Montori VM. Clinical review: insulin sensitizers for the treatment of hirsutism: a systematic review and metaanalyses of randomized controlled trials. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 1135–1142. (doi:10.1210/jc.2007-2429)
- 83 Domecq JP, Prutsky G, Mullan RJ, Sundaresh V, Wang AT, Erwin PJ, Welt C, Ehrmann D, Montori VM & Murad MH. Adverse effects of the common treatments for polycystic ovary syndrome: a systematic review and meta-analysis. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** 4646–4654. (doi:10.1210/jc.2013-2374)
- 84 Moghetti P, Tosi F, Tosti A, Negri C, Misciali C, Perrone P, Caputo M, Muggeo M & Castello R. Comparison of spironolactone, flutamide, and finasteride efficacy in the treatment of hirsutism: a randomized, double blind, placebo-controlled trial. *Journal of Clinical Endocrinology and Metabolism* 2000 **85** 89–94. (doi:10.1210/jc.85.1.89)
- 85 Ganie MS. Comparison of spironolactone with metformin in the management of the polycystic ovary syndrome: an open-labeled study. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 2756–2762. (doi:10.1210/jc.2003-031780)
- 86 Moran LJ, Pasquali R, Teede HJ, Hoeger KM & Norman RJ. Treatment of obesity in polycystic ovary syndrome: a position statement of the Androgen Excess and Polycystic Ovary Syndrome Society. *Fertility and Sterility* 2009 **92** 1966–1982. (doi:10.1016/j.fertnstert.2008.09.018)
- 87 Van Dam EW, Roelfsema F, Veldhuis JD, Hogendoom S, Helmerhorst FM, Frolich M, Krans HM, Meinders AE & Pijl H. Increase in daily LH secretion in response to short-term calorie restriction in obese women with PCOS. *American Journal of Physiology. Endocrinology and Metabolism* 2002 **282** E865–E872.
- 88 Hamilton-Fairley D, Kiddy D, Anyaoku V, Koistinen R, Seppala M & Franks S. Response of sex hormone binding globulin and insulin-like growth factor binding protein-1 to an oral glucose tolerance test in obese women with polycystic ovary syndrome before and after calorie restriction. *Clinical Endocrinology* 1993 **39** 363–367. (doi:10.1111/j.1365-2265.1993.tb02378.x)
- 89 Moran LJ, Hutchison SK, Norman RJ & Teede HJ. Lifestyle changes in women with polycystic ovary syndrome. *Cochrane Database of Systematic Reviews* 2011. CD007506. (doi:10.1002/14651858.CD007506.pub3)
- 90 Pasquali A, Gambineri A, Cavazza C, Ibarra Gasparini D, Ciampaglia W, Cognigni GE & Pagotto U. Heterogeneity in the responsiveness to long-term lifestyle intervention and predictability in obese women with polycystic ovary syndrome. *European Journal of Endocrinology* 2011 **164** 53–60. (doi:10.1530/EJE-10-0692)
- 91 Koulouri O & Conway GS. A systematic review of commonly used medical treatments for hirsutism in women. *Clinical Endocrinology* 2008 **68** 800–805. (doi:10.1111/j.1365-2265.2007.03105.x)
- 92 Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrback K & Schoelles K. Bariatric surgery: a systematic review and meta-analysis. *Journal of the American Medical Association* 2004 **292** 1724–1737. (doi:10.1001/jama.292.14.1724)
- 93 Sjöström L, Narbro K, Sjöström CD, Karason K, Larsson B, Wedel H, Lystig T, Sullivan M, Bouchard C, Carlsson B *et al.* Effects of bariatric surgery on mortality in Swedish obese subjects. *New England Journal of Medicine* 2007 **357** 741–752. (doi:10.1056/NEJMoa066254)
- 94 Alvarez-Blasco F, Botella-Carretero JI, San Millán JL & Escobar-Morreale HF. Prevalence and characteristics of the polycystic ovary syndrome in overweight and obese women. *Archives of Internal Medicine* 2006 **166** 2081–2086. (doi:10.1001/archinte.166.19.2081)
- 95 Escobar-Morreale HF, Botella-Carretero JI, Alvarez-Blasco F, Sancho J & San Millán JL. The polycystic ovary syndrome associated with morbid obesity may resolve after weight loss induced by bariatric surgery. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 6364–6369. (doi:10.1210/jc.2005-1490)
- 96 Jamal M, Gunay Y, Capper A, Eid A, Heitshusen D & Samuel I. Roux-en-Y gastric bypass ameliorates polycystic ovary syndrome and dramatically improves conception rates: a 9-year analysis. *Surgery for Obesity and Related Diseases* 2012 **8** 440–444. (doi:10.1016/j.soard.2011.09.022)
- 97 Eid GM, Cottam DR, Velcu LM, Mattar SG, Korytkowski MT, Gosman G, Hindi P & Schauer PR. Effective treatment of polycystic ovarian syndrome with Roux-en-Y gastric bypass. *Surgery for Obesity and Related Diseases* 2005 **1** 77–80. (doi:10.1016/j.soard.2005.02.008)
- 98 Pfeiffer SM & Dayal M. Treatment of the adolescent patient with polycystic ovary syndrome. *Obstetrics and Gynecology Clinics of North America* 2003 **30** 337–352. (doi:10.1016/S0889-8545(03)00028-7)
- 99 Warren-Ulanch J & Arslanian S. Treatment of PCOS in adolescence. *Best Practice & Research. Clinical Endocrinology & Metabolism* 2006 **20** 311–330. (doi:10.1016/j.beem.2006.02.002)
- 100 Guttmann-Bauman I. Approach to adolescent polycystic ovary syndrome (PCOS) in the pediatric endocrine community in the U.S.A. *Journal of Pediatric Endocrinology & Metabolism* 2005 **18** 499–506.
- 101 Diamanti-Kandarakis E. PCOS in adolescents. *Best Practice & Research. Clinical Endocrinology & Gynaecology* 2010 **24** 173–183. (doi:10.1016/j.bpobgyn.2009.09.005)
- 102 Legro RS, Pauli JG, Kunselman AR, Meadows JW, Kesner JS, Zaino RJ, Demers LM, Gnutuk CL & Dodson WC. Effects of continuous versus cyclical oral contraception: a randomized controlled trial. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 420–429. (doi:10.1210/jc.2007-2287)
- 103 Pasquali R, Gambineri A, Biscotti D, Vicennati V, Gagliardi L, Colitta D, Fiorini S, Cognigni GE, Filicori M & Morselli-Labate AM. Effect of long-term treatment with metformin added to hypocaloric diet on body composition, fat distribution, androgen and insulin levels, in abdominally obese women with and without the polycystic

- ovary syndrome. *Journal of Clinical Endocrinology and Metabolism* 2000 **85** 2767–2774. (doi:10.1210/jc.85.8.2767)
- 104 Gambineri A, Patton L, Vaccina A, Cacciari M, Morselli-Labate AM, Cavazza C, Pagotto U & Pasquali R. Treatment with flutamide, metformin, and their combination added to a hypocaloric diet in overweight-obese women with polycystic ovary syndrome: a randomized, 12-month, placebo-controlled study. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 3970–3980. (doi:10.1210/jc.2005-2250)
 - 105 Martin KA, Chang RJ, Ehrmann DA, Ibanez L, Lobo RA, Rosenfield RL, Shapiro J, Montori VM & Swiglo BA. Evaluation and treatment of hirsutism in premenopausal women: an endocrine society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 1105–1120. (doi:10.1210/jc.2007-2437)
 - 106 Pelusi C, Forlani G, Zanotti L, Gambineri A & Pasquali R. No metabolic impact of surgical normalization of hyperandrogenism in postmenopausal women with ovarian androgen secreting tumours. *Clinical Endocrinology* 2013 **78** 533–538. (doi:10.1111/j.1365-2265.2012.04438.x)
 - 107 Santen RJ, Allred DC, Ardoin SP, Archer DF, Boyd N, Braunstein GD, Burger HG, Colditz GA, Davis SR, Gambacciani M *et al.* Postmenopausal hormone therapy: an Endocrine Society scientific statement. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** (7 Suppl 1) s1–s66. (doi:10.1210/jc.2009-2509)
 - 108 Lopez LM, Grimes DA & Schulz KF. Steroidal contraceptives: effect on carbohydrate metabolism in women without diabetes mellitus. *Cochrane Database of Systematic Reviews* 2009 CD006133. (doi:10.1002/14651858.CD006133.pub3)
 - 109 Rimm EB, Manson JE, Stampfer MJ, Colditz GA, Willett WC, Rosner B, Hennekens CH & Speizer FE. Oral contraceptive use and the risk of type 2 (non-insulin-dependent) diabetes mellitus in a large prospective study of women. *Diabetologia* 1992 **35** 967–972. (doi:10.1007/BF00401427)
 - 110 Skouby SO, Endrikat J, Düsterberg B, Schmidt W, Gerlinger C, Wessel J, Goldstein H & Jespersen J. A 1-year randomized study to evaluate the effects of a dose reduction in oral contraceptives on lipids and carbohydrate metabolism: 20 microg ethinyl estradiol combined with 100 microg levonorgestrel. *Contraception* 2005 **71** 111–117. (doi:10.1016/j.contraception.2004.08.017)
 - 111 Kjos SL, Peters RK, Xiang A, Thomas D, Schaefer U & Buchanan TA. Contraception and the risk of type 2 diabetes mellitus in Latina women with prior gestational diabetes mellitus. *Journal of the American Medical Association* 1998 **12** 533–538. (doi:10.1001/jama.280.6.533)
 - 112 American Diabetes Association. Preconception care of women with diabetes. *Diabetes Care* 2003 **26** (Suppl 1) S91–S93.
 - 113 Centers for Disease Control and Prevention (CDC) 2010 US medical eligibility criteria for contraceptive use, 2010. *Recommendations and Report: Morbidity and Mortality Weekly Report* 2010 **59** 1–86.
 - 114 Gallo MF, Lopez LM, Grimes DA, Schulz KF & Helmerhorst FM. Combination contraceptives: effects on weight. *Cochrane Database of Systematic Reviews* 2008 **4** CD003987. (doi:10.1002/14651858.CD003987.pub3)
 - 115 Gambineri A, Patton L, Altieri P, Pagotto U, Pizzi C, Manzoli L & Pasquali R. Polycystic ovary syndrome is a risk factor for type 2 diabetes: results from a long-term prospective study. *Diabetes* 2012 **61** 2369–2374. (doi:10.2337/db11-1360)

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