HIRSUTISM

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Introduction to Hirsutism

The clinical definition of PCOS includes its dermatologic manifestations primarily hirsutism, as well as acne vulgaris and androgenetic alopecia (AA). These dermatologic features often provide early clinical clues to the presence of PCOS wherein treatment may improve quality of life as well as psychological well-being Ethnic differences in the number of hair follicles present and individual skin sensitivity of the pilosebaceous unit to androgens are major determinants of the presence of hirsutism, as well as acne and androgenic alopecia. The effects of androgens on the pilosebaceous units of the skin may vary by its anatomic location, producing pathophysiologic effects on hair growth and differentiation, sebaceous size and differentiation, sebaceous gland size and activity and follicular gland size and activity. Treatment modalities include hormonal therapy which may modulate androgen production and action as well as non-hormonal therapies directed to these dermatologic conditions.

HIRSUTISM

Hyperandrogenism, i.e., the finding of supranormal levels of circulating endogenous androgens mainly testosterone (T) and free or unbound testosterone, androstenedione, dehydroepiandrosterone (DHEA) and its sulfate (DHEAS), most frequently present as hirsutism. It is the most common manifestation of hyperandrogenism. This reflects racial and genetic differences in the hair follicle sensitivity to androgens with some women developing hirsutism in the setting of normal androgen levels, and other women to have no hirsutism in the presence of high serum androgens. This reflects the development of body hair

in a male pattern (sexual hair) skin distribution. The hair type present in androgen excess syndromes, including the most common entity, the polycystic ovary syndrome (PCOS), is coarse, thickened, pigmented and long, and is called terminal hair. It differs from vellus hair which is fine, soft, unpigmented and is nonandrogenic and present in non-male type skin areas. In PCOS, the hirsutism develops gradually and intensifies with weight gain with onset at puberty and several years later Some of these subjects may have a history of premature adrenarche or early pubarche, which may be an early sign of adrenal and/or hyperandrogenic dysfunction, which in a number of patients may be associated with a somewhat taller stature premenstrually, often with an advanced bone age in their preteens. The term hypertrichosis is applied to an excess of vellus hair, usually absence of hyperandrogenism, and most common in congenital or metabolic disorders (eg, hypothyroidism, anorexia nervosa, malnutrition, porphyria) or with the use certain drugs (eg, phenytoin, cyclosporine, minoxidil, diazoxide, penicillamine, glucocorticoids, androgenic medications, valproic acid) (1,2)

It appears that 5% of reproductive aged women in the general population are hirsute (3). There were no differences in the prospective prevalence study of hirsutism in a population of white and black women. (3). Alternatively studies stress the finding that Asian women in comparison to white women, hirsutism is generally uncommon, despite similarities in metabolic and endocrine abnormalities.(4,5) Thus in most Asian women hirsutism cannot be used to exclude the presence of a hyperandrogenic disorder.. Quantitation of the degree of hirsutism is indicated by a score of 6 to 8 on the Hatch modification of the Ferriman-Gallwey (FG) scale (6).Variations in score frequently depend upon ethnicity and racial location. Terminal hairs grow to greater than 5 mm in length in nine body areas: a) upper lip, b) chin, c) chest, d) upper abdomen (above the umbilicus), e) lower abdomen (a.k.a. male escutcheon, below the umbilicus), f) upper back, g) lower back, h) thighs (front and back), and i) upper arms (biceps area). Each area is assigned a score of zero (no detectable terminal hairs), 1 (minimum terminal hairs), 2 (more than minimum but not quite that of a man), 3 (that of a mildly hirsute man), and 4 (that of a hirsute man).The scale, however

does not measure the sideburn area, perineal areas, lower arms and lower legs, and is more difficult to assess in blond women (2)

PCOS has been defined by several phenotypes in adolescents and adults. The first description of PCOS was by Stein and Leventhal consisting of varying degrees of enlarged ovaries, obesity, hirsutism and chronic anovulation (7). An expert conference sponsored by the National Institute of Child Health (NICHD) of the NIH concluded that the definition of PCOS in order of importance were 1) hyperandrogenism and/or hyperandrogenemia, 2) menstrual dysfunction, and 3) the exclusion of other known disorders (8).In 2003 an International Rotterdam Conference required two of the three following findings: hyperandrogenism, chronic anovulation, and polycystic ovaries on ultrasonography (9).An Internationally composed Writing Task Force of the Androgen Excess and Polycystic Ovary Society in 2009, headed by Dr. Ricardo Azziz, defined the polycystic ovary syndrome as requiring 2 of the 3 following findings: hyperandrogenism either clinically and/or or biochemically ,ovarian dysfunction (oligo-anovulation and/or polycystic ovaries on ultrasound) (10).Exclusion of other androgen excess and related disorders such as nonclassical congenital adrenal hyperplasia (NCCAH), virilizing syndromes of the ovary or adrenal glands ,hyperprolactinemia, and Cushing's syndrome are mentioned in all reports. Parenthetically, NCCAH may mimic PCOS in most aspects, but 17-hydroxyprogesterone which is not increased in PCOS, could be measured in the early possible follicular phase of the menstrual cycle in hyperandrogenic PCOS women to exclude NCCAH.

Polycystic ovary syndrome is present in the majority of women with hyperandrogenism. In the presumptive diagnosis of PCOS, the above disease states have to be excluded. The presence of hypertrichosis is non-androgenic (see above in text), as is idiopathic hirsutism (IH)(2). The latter may be defined as mildly hirsute patients with regular yet frequent anovulatory menses and normal circulating androgen levels. A true definition of IH, however is still lacking since there may be antiandrogenic pharmacological response of the hirsutism A stricter definition of IH may include less than 15% of all hirsute women with many in this group probably having subtle PCOS

Testosterone is the key circulating androgen and arises from ovarian and adrenocortical secretion and metabolism of androstenedione and DHEAS.The main bioactive portion of T is freeT. In hirsute women the level of circulating free T may be elevated, while the total T remains normal. Hirsutism may result a result of the relatively low concentration of sex hormone binding globulin (SHBG) which determines the fraction of plasma T that is free or bound to albumin The levels of SHBG may be suppressed by elevated concentrations of circulating insulin resulting in normal T and elevated free T values (10).

Hirsutism is an important feature of PCOS, affecting 65-75% of patients with PCOS. In reviewing 18 publications (from 1983 through 2007), 4691 of 6281 afflicted women had a hirsutism prevalence of 74.7%, and 29.6% had an elevated total testosterone in 7 of the reports with an average of 29.6% in 1838 PCOS women (10). Of interest and commonly seen clinically are the magnitude of variations in results as with the 22 84% in the latter. Defining a syndrome brings the addition of commonality of findings a frequent help in making a presumptive diagnosis of a syndrome, and/or same disorder. The polycystic ovary syndrome may have similar morbidities such as insulin resistance and hyperinsulinism as well as type 2 diabetes mellitus. Furthermore, genetic factors may influence androgen concentrations as, for example, almost 50-% of sisters of PCOS subjects have elevated total or bioavailable T or free T concentrations (11), with 40% of sisters affected with PCOS, and 30-35% of mothers of a daughter with PCOS, also affected (12,13).

The interaction of the androgen level and the sensitivity of the hair follicle to the circulating androgen results in the presence and/or degree of hirsutism present. The pilosebaceous unit (PSU) response may result in formation of hair follicles or the formation of sebaceous glands (14).The response of the androgen receptor to androgens varies significantly within and among individuals. The tendency to develop facial hair hirsutism, which is most prevalent in the lower third of the face, including the chin and sideburns, suggests an enhanced sensitivity of the hair follicles in that area to androgens (14, 15).

A commonly asked question is what happens to the peri-and postmenopausal woman with PCOS. Androgen production in postmenopausal PCOS women decrease as a result of ovarian aging and decreased production by the adrenal glands. The prevalence of the dermatologic features of hirsutism and acne thus diminish with age. The menstrual cycles tend to become regular with age in women with PCOS (as hyperandrogenism partially resolves before the menopause in women with PCOS (16, 17). Ovarian volume and follicle number decrease with age in women both with and without PCOS, and the typical ultrasonographic ovarian features frequently normalize as the menopause nears [17, 18]. Aging may further be associated with increased risk of insulin resistance and metabolic disturbances. Therefore, these age-related changes may affect the observed incidence and complications of PCOS (19). Hyperandrogenism and chronic anovulation are the primary disturbances in younger women with PCOS; whereas, obesity, insulin resistance, and metabolic disturbances are predominant in older women with PCOS. The deterioration of insulin resistance during the reproductive life of women with PCOS appears to be mainly attributable to the increased obesity. Therefore, if body weight could be controlled properly, younger hyperandrogenic PCOS women might reduce their risk of insulin resistance and metabolic disturbances later in life.

Lack of controlled studies remains in the literature regarding the history of CVD and mortality, well into the postmenopausal age of women with PCOS (61-79 years), compared to unafflicted women controls. Dahlgren studied 35 women with PCOS (61-79 years) and 95 similar aged controls, both groups were studied prospectively after an initial exam 21 years previously. PCOS women had a higher prevalence of hypertension ($P = 0.008$) and higher triglyceride levels ($P = 0.012$) than controls. Myocardial infarction, stroke, type 2 diabetes mellitus, cancer, and mortality prevalence, however, was similar in the two cohorts with similar body mass index (20). The well-described cardiovascular/metabolic risk profile in pre- and perimenopausal PCOS women did not result in an evident increase in cardiovascular events during the postmenopausal period Possibly risk factors increased with age in controls similar to those found in the PCOS women.

Differences in conclusions have been published (13), but the important findings above (20) distinctly warrant investigators to further study in detail well-aged PCOS together with defined control subjects.

MANAGEMENT OF HIRSUTISM, ACNE, ALOPECIA IN ANDROGENIC DISORDERS

A) Androgen receptor blockers:

Spironolactone:

It is the role of the physician to define the role of treatment to the patient and note the patient's goals and expectations. Women should be aware that drug therapy is unlikely to totally eliminate hair growth. What may be anticipated is less coarse hair, slower growth, a change in the volume of the hair, and a lighter pale grey color perhaps in 4-6 months. . In PCOS, controlling the androgen overproduction of male hormones and stabilizing the disease is an essential first step prior to the use of these drugs for androgen effects on the hair follicle which include acne, hirsutism and alopecia. Spironolactone (SPA) is the most commonly used androgen blocker in the U.S.A., and an aldosterone antagonist related to progestins. It is relatively effective in the treatment of all the dermatological signs of PCOS (22). In addition to being an aldosterone antagonist, it competes with dihydrotestosterone (DHT) for binding to the androgen receptor, although its effect for the latter is minimal compared to DHT.It also has several other effects which include a moderate local 5-alpha reductase activity (5RA), blocking conversion of T to DHT in dermal papilla cells, and consequentially the androgenic effect of DHT on the hair follicle. Spironolactone also demonstrates competition with androgens for binding to SHBG. Steroidogenesis of androgens by an effect on

enzymatic pathways may occur, by using large doses of SPA greater than 200 mg daily, but this may yield significant side effects. For moderate to severe hirsutism gradual increased doses of 150-200 mg SPA daily appear necessary. Its progestational activity may also reduce gonadotropin-releasing hormone (GnRH) and luteinizing hormone (LH), thereby attenuating the LH effect on androgen steroidogenesis (4).

Spironolactone likely is the most commonly used androgen blocker in the U.S.A., and is an aldosterone antagonist related to progestins. It is relatively effective in the treatment of all the dermatological signs of PCOS (listed above).The relative absence of SPA on insulin resistance while reducing serum T makes it more likely that T has no effect on insulin resistance. In addition to being an aldosterone antagonist, it competes with dihydrotestosterone (DHT) for binding to the androgen receptor, although its effect for the latter is minimal compared to DHT.It also has several other effects which include a moderate local 5-alpha reductase activity, blocking conversion of T to DHT in dermal papilla cells, and consequentially the androgenic effect of DHT on the hair follicle. Spironolactone also demonstrates competition with androgens for binding to SHBG. Steroidogenesis of androgens by an effect on enzymatic pathways may occur, by using large doses of SPA greater than 200 mg daily, but this may yield significant side effects. Its progestational activity may also reduce GnRH and luteinizing hormone (LH), thereby attenuating the LH effect on androgen steroidogenesis (4).

Monotherapy of hirsutism with an antiandrogen alone, as SPA, although somewhat helpful in affecting terminal hairs is only partially effective. Clinical observation may note a change in the volume of the hair, and a lighter color which often is only minimally seen on close examination. The dosage of SPA is 100 to 200 mg daily, given in 2 divided doses. Spironolactone may induce hyperkalemia and should be used cautiously in patients with renal impairment. Serum potassium should be monitored in patients who are also taking a drospirenone OCP, because of its antialdosterone effect. Hypotensive episodes and dizziness are relatively frequent and the patient should be well hydrated in hot weather with the addition of extra salt Intermenstrual spotting may occur in almost half of the women taking SPA as monotherapy. Breast discomfort, dry skin

and gastritis are also noted in some women on this drug. As with other antiandrogens, SPA has the potential for teratogenicity (specifically, inadequate masculinization of male genitalia) and is recommended together with a nonandrogenic oral contraceptive to avoid its effect on masculine genital development during pregnancy. The patient should be informed of contraceptive measures during its administration, and wait 3-5 months after stopping SPA prior to attempting conception.

……**Flutamide**

Flutamide is a pure nonsteroidal androgen-receptor blocker and the most potent drug in the treatment of hirsutism (23,24).While doses of 250-500mg daily are used, doses of 250 mg daily (or less, 125 mg) as a single dose daily may be effective . Frequent tests of liver markers in the serum must be performed frequently. There is no disagreement in the literature of the potential of serious hepatotoxicity, and some deaths with the use of this drug, which considerably lessens the use of flutamide in clinical practice.

Diane-35 (containing cyproterone acetate and ethinyl estradiol)

Although it is not approved by the U.S. Food and Drug Administration (FDA), cyproterone acetate (CPA) is a potent progestin and antiandrogen reducing androgen action in view of its competitive binding with the androgen receptor (25). It is effective when combined with an estrogen such as ethinyl estradiol in the form of Diane-35. It may be obtained in Canada and many other countries including those in Europe. CPA blocks the binding of the active androgen DHT at the receptor site of the hair follicle as well as other hormonal effects in the synthesis of androgens in the ovary, with some effect on the release of LH by the pituitary gland in view of its progestin property. There are conflicting and no conclusive data as yet indicating a more effective antiandrogen treatment of Diane-35 when compared to the combined use of OCP and spironolactone. Some common side effects of Diane-35 include light-headedness, fluid retention, weight gain and rare reports of adrenal insufficiency. The risks of venous thromboembolism (26) are no more frequent than the use of third generation

combined oral contraceptives (27). The latter study used 2mg cyproterone acetate combined with 35 ug ethinyl estradiol (Dianette in the U.K.).

B) Other Hormonal Treatments of Hirsutism, Acne and Alopecia

5-alpha -reductase inhibitors:

As increased 5α-reductase activity is considered a pathogenetic mechanism of hirsutism (28), selective enzyme inhibition has been proposed as a rational medical approach to this condition as well. Peripheral androgen production and particularly the conversion of T to the most potent endogenous androgen DHT by 5-α reductase (5AR), enhances target tissue androgen activity and is differentially expressed as 2 isoenzymes. The type 2 isoform is mostly predominant in the prostate and some hair bearing regions, while the type 1 isoform is mostly present in the skin, particularly in sebaceous glands and acne-prone areas (29).
Finasteride (Proscar), strictly considered, is not an antiandrogen, because it does not act directly at the androgen receptor site. It is a potent competitive inhibitor of the type 2 isoenzyme of 5-α reductase and blocks 70% of the conversion of T to DHT (30, 31) after 6 months of use. Side effects are minimal and the associated use of an oral contraceptive is mandatory as with any antiandrogen therapy. The effective dosage in women is 2.5 to 5 mg taken once daily. A study of postmenopausal women with 1 mg finasteride demonstrated no improvement of alopecia compared to controls. Most investigators, however, use the 5 mg daily treatment dosage of finasteride. A controlled double-blind study of 6 months of treatment indicated that the effectiveness of finasteride in treating hirsutism was equal to that of spironolactone as well as flutamide, and was devoid of serious side effects. (32). This observation was refuted by another study demonstrating the effectiveness of flutamide to be superior to that of finasteride (33)However, there is no clear opinion as yet on the efficacy of finasteride on hirsutism of women with moderate to high FG scales of hirsutism. It appears to be useful in idiopathic hirsutism (34), and its effect on androgenic alopecia appears to be variable. An interesting study was made in 40 non-androgenic normal postmenopausal women with androgenetic alopecia. After 6 months of 5 mg finasteride daily for 6 months, improvement was noted in34 of the 42 women, with minimal further improvement at 18 months of treatment (35).

Dutasteride (Avodart) is a competitive inhibitor of both type 1 and 2 isoenzymes of 5-α reductase. It is 3 times more potent in blocking type 1 5AR than finasteride. Its half-life is 5 weeks, unlike 5-8 hours of finasteride (31). Dutasteride blocks 90% of conversion of T to DHT. There are only several papers to date of the effect

of dutasteride on androgenic alopecia but it has been shown to moderately effective in several studies (36, 37). A study noted that 2.5mg dutasteride was more effective then 5.omg finasteride in treatment of male alopecia (31, 38). Clinical observation by the author has noted stabilization and or some regrowth of hair in almost 50% of PCOS women with 0.5mg dutasteride for 6 months while on an oral contraceptive. There are no studies as yet for the effect of dutasteride on hirsutism.
In view of the effect of 5ARs, the shift of T to aromatization of estrogens should be a factor in the consideration and use of these drugs in women with a prior history of breast cancer and those with a close family member with breast cancer.

↵Metformin, Rositaglone and Pioglitazone: Insulin Sensitizers

Metformin is used primarily for increasing insulin sensitivity which also results in a decrease of the bioavailability of androgens via SHBG. The usual daily dosage of the drug is 1000mg with food, at a12 hour interval with the second 1000mg dosage The 2000 mg daily is the preferred dosage of metformin in women with PCOS. Initial side effects which include bloating, nausea and moderate diarrhea usually are minimized after a gradual increased dose to 2000mg daily at weekly increments. The initial complaints are somewhat less after the first 8 weeks of therapy. A 500 ug B12 tab is taken daily at any time while on metformin to minimize any level of B12 absorption by the metformin which may lead in varying degrees over time to early features of pernicious anemia. A direct effect on ovarian theca cells reducing their androgen production is also an additional feature. Clinically, however, the effect on hirsutism is modest and inconsistent (39, 40) While few studies have shown monotherapy to be minimally effective, most papers have not seen significant improvement. A Cochrane Group meta-analysis comparing metformin and oral contraceptive treatment of hirsutism in women with PCOS did not show any significant clinical difference between the two (41).

The available thiazolidinediones, insulin sensitizers rosiglitazone and pioglitazone, in addition to reducing circulating androgens indirectly by

reducing insulin levels, also have a direct effect on the androgen production of the ovaries and adrenals(42) Rosiglitazone 4mg/ daily administered to PCOS women as monotherapy for 6 months had a 39% effect of FG scores, while metformin alone, had a 19% improvement.(43)) Pioglitazone alone,45 mg/daily, also had an effective reduction of FG score of 30% in subjects with PCOS while there was a 30% reduction as well with metformin treatment(44)
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STATINS

In vitro studies have demonstrated that statins reduce theca cell androgen production, decrease cell proliferation, and induce apoptosis. Statins inhibit proliferation of the human theca-interstitial cells irrespective of the availability of cholesterol both in normal and PCOS ovaries (45). Results of a 6 month trial demonstrating the effects of simvastatin and metformin on PCOS noted that simvastatin is superior to metformin, as evidenced by improvement of both reproductive and cardiovascular features of the syndrome. For the first time it was shown that simvastatin improves menstrual regularity, reduces ovarian volume, and induces progressive improvement of biochemical and clinical features of hyperandrogenism. (46) Another studied the use of a statin 6-12 weeks (less than 6 months than above paper) on the menses of 244 women with PCOS and found no improvement was noted in menses, hirsutism, or acne (47). What they did agree was the reduction of serum T and lipid profiles, other than HDL, high-sensitive C-reactive protein (CRP), fasting insulin and HOMA-IR. There is a need for further research to be performed with large sample sizes and well-designed methods to assess clinical outcomes.

. In February 2012, the Food and Drug Administration released changes to statin safety label to include that statins have been associated with increases in hemoglobin A1C and fasting serum glucose levels. This has

stirred much debate in the medical community. Estimate for new onset diabetes from statin treatment is approximately one in 255 patients over four years. Statins may accelerate progression to diabetes via molecular mechanisms that impact insulin resistance and cellular metabolism of carbohydrates. It remains clear that the benefit of statin therapy outweighs the risk of developing diabetes (48). Two meta-analyses published since 2012 unequivocally support statins for primary prevention. Data from the Cholesterol Treatment Trialists' Collaborators demonstrated a 9% reduction in all-cause mortality and a 25%reduction in major vascular events A 2013 Cochrane review corroborated these findings including a 14% reduction in all-cause mortality and a 25% reduction in cardiovascular disease events with statin therapy despite an 18% increase in incident diabetes (49). The vast majority of experts suggest that the cardiovascular benefit of statins for primary prevention far outweigh reported harms.

C) BIRTH- CONTROL- PILLS (BCPs)

Combination oral BCP have been traditionally used in the management of PCOS. These pills contain estrogen (almost exclusively ethinyl estradiol) and a progestin. Over the last few decades, the daily dose of estrogen has been reduced from 50 µg to 20 to 35 µg. Newer progestins have been developed with an emphasis on greater progestogenic and less androgenic effects, and include norgestimate, desogestrel, and drospirenone. In Europe and other parts of the world, BCPs containing norethisterone and the antiandrogen cyproterone acetate are also available.

OCPs are often used alone or in combined treatment of PCOS with antiandrogens and other drugs. The latter combination frequently is an initial therapeutic option used in PCOS patients with acne, hirsutism or AA. Additional forms of BCP also include transdermal and vaginal estrogen-progestin contraceptive preparations. They also reduce the prevalence of functional ovarian cysts and reduce their number if high-dose BCPs are administered. Ovarian volume does decrease with

BCP treatment and higher-dose pills have been associated with reduced prevalence of ovarian cysts. Parenthetically, use of low-dose BCPs does not substantially reduce the risk of functional ovarian cysts (50). Non-hirsutism benefits of BCP of course include contraception, and cycle management.

The mechanisms whereby these contraceptives reduce serum androgens in hirsutism, acne, and alopecia are 1) Inhibition of LH secretion by estrogen reducing LH-dependent ovarian androgen production; 2) Increased liver synthesis of SHBG by estrogen, decreasing circulation freeT; 3) Inhibition of adrenal androgen secretion.

Regular menses are usually achieved with BCP treatment. Unopposed estrogen stimulation of the endometrium in anovulatory PCOS increases the risk of endometrial hyperplasia and cancer. BCPs have been shown to reduce the risk of endometrial cancer in the general population and are considered to be protective of the endometrium in PCOS. The use of BCPs in PCOS provides an acceptable method of contraception which allows the use of other agents, such as the antiandrogen spironolactone, and others which are contraindicated in pregnancy. Many clinicians prefer the use of low dose20 ug ethinyl estradiol formulations, when clinically indicated, in women over age 35-40 years.

The discovery of the central role of insulin resistance in PCOS makes the clinician re-assess traditional; management of this disorder which may have untoward long-term consequences in some women (51). Both lean and obese women with PCOS most often have insulin resistance with the former having an intrinsic unique defect and role in PCOS while obese PCOS women have a combination of the unique defect and IR secondary to the IR related to adiposity (52). The latter has generated interest and concern regarding possible exacerbation of these effects by medications used in the treatment of PCOS, such as BCPs. Even in the absence of PCOS, the long-term vascular effects of BCPs have been under scrutiny. A meta-analysis of the association of low-dose BCP with vascular events found an increased risk (odds ratio, 2.01) of myocardial infarction and stroke (53). Even third-generation low-dose BCPs carried an increased risk of ischemic stroke. Another area of concern relates to the metabolic effects of BCPs. Results of

epidemiologic studies have been discordant with respect to BCPs and diabetes mellitus risk. One long-term study showed a 10% increased risk after 12 years of follow-up in those who had used high-dose BCP (54). Two other studies had negative results (55, 56).

The effect of BCPs on carbohydrate metabolism in normal individuals was reviewed by Godsland (57) and can be briefly summarized as follows. Estrogens impair insulin sensitivity and carbohydrate tolerance in a dose-dependent manner while progestins with androgenic properties may also impair insulin action. Progestins also modify insulin half-life and estrogen elimination. The literature on the effect of BCPs on carbohydrate metabolism in PCOS is conflicting. This is not particularly surprising given the genetic and anthropometric heterogeneity of the patient population, the variability of the BCPs studied with regard to estrogen dose and type of progestin, and the effect of other factors such as puberty, the degree of androgenicity of the woman, and the androgen-lowering effect of the pill. Thus, studies have shown improvement (presumably from lowering of androgens), no effect, deterioration, or the development of frank diabetes (58-61). For example, the effect of BCPs may be exacerbated by the insulin resistance associated with puberty in adolescents, by weight gain and inactivity, and, conversely, may be ameliorated by weight loss. Therefore, in the management of PCOS patients and their androgenic symptoms, weight control and physical activity should be encouraged at each visit.

The concomitant use of agents such as metformin, that favorably modify carbohydrate metabolism, may be of benefit in certain subgroups, such as the obese, adolescents, and those with weight gain, especially when there is a family history of T2DM. However, there is no strong support in the medical literature for the potential benefits of co-treatment with metformin In relation to hyperandrogenism, the estrogen component of BCPs ,however enhances hepatic production of SHBG, thereby reducing free androgen availability. BCPs also reduce luteinizing hormone concentrations, reducing the drive to ovarian androgen production and thus circulating androgens. Adrenal androgen secretion may also be reduced.

A considerable literature has been available assessing the effect of BCP on cardiovascular outcomes in women with PCOS. One should take into consideration the presence of hypertension, endothelial dysfunction, and a a baseline insulin resistance in women who are already at risk for type 2 diabetes mellitus, and other multiple risk factors for cardiovascular disease. The fact that BCP may increase their relative risk for type 2 diabetes mellitus and possibly CVD by using BCP should individualize their use. A population-based, case controlled study of 248 women between the ages of 18-49 years reported a two-fold increased risk of myocardial infarction among women using a variety of BCP (62). Regarding diabetes mellitus risk, prospective clinical trials demonstrate a 31-35% prevalence of impaired glucose tolerance (IGT) and a 7.5-10.0 prevalence of type 2 diabetes mellitus (T2DM) in women with PCOS (63, 64).A study of 101,073 women in the Nurses' Health Study II reported over an 8-year time span the conversion rate to T2DM in oligomenorrheic women was 2-fold greater than for eumenorrheic women regardless of BMI. It appears that oligomenorrhea is an independent predictor of type 2 diabetes (65)

The androgenic symptoms that may be attenuated somewhat by BCP treatment include hirsutism, and acne. Overall, 70% to 80% of women with androgen excess demonstrate hirsutism. Reduction of free androgens with BCP treatment reduces newer hair growth and slows the growth of terminal hairs already present. It may take 6 months or longer for this effect to become manifest.

Treatment of acne is often most satisfactory, and the Food and Drug Administration has approved several BCPs for this indication. With 6 to 9 months of use, inflammatory acne lesion counts are reduced by 30% to 60%, with improvements in 50% to 90% of patients (66). BCPs may be especially useful in the subset of women with deep-seated acne nodules of the lower face and adult women who relapse following isotretinoin (Accutane) therapy.

While there are no extensive trials on the use of BCPs in alopecia, they are commonly used in this context as a co-treatment .BCPs as monotherapy are not useful in arresting mild to moderate alopecia or hirsutism. Therefore, BCPs are preferably combined with an antiandrogen to achieve a better response.

Topical Therapy: Chin Hirsutism

Eflornithine hydrochloride cream (**Vaniqa**) is used topically for lower facial hirsutism. It inhibits hair growth, and is not a depilatory. Continuous use is necessary to prevent regrowth (67) It is not a depilatory and is used twice daily at least 8 hours apart only to chin and nearby unwanted hair-growth .A more rapid response in noted when compared to laser treatments (68).Improvement should be noted in 4-8 weeks. Local acneform and inflammatory changes may occur as a result of the cream.

The clinical response to antiandrogens is only partially effective for hyperandrogenism, and direct removal of unwanted terminal hair with **laser photothermolysis** and/or a variety of **electrolysis** techniques is recommended.

Topical Therapy Alopecia

Minoxidil (Loniten) (**Rogaine** Solution) has a metabolite, minoxidil sulfate which stimulates hair growth in the dermal papilla.It tends to shift anagen to telogen hairs due to its its increased cutaneous blood flow and dilatation. The "women's" 2% Rogaine is applied twice daily to affected areas of alopecia, while the 5% is applied once or twice daily depending on the concern of the patient. A distressing side effect, particularly if used in excess, or use of the 5%% Rogaine solution, is the development of hirsutism in a number of women which can also be distressing to the patient. (69) It must be used uninterruptedly for an effect to have a significant effect, and cessation of treatment will cause loss of the new scalp. However, it appears to be a useful potential adjunct in regrowth of hair p after a hair transplant. It is a Category C and the patient must be advised

A Brief Treatment Guide Used by Most Clinicians Treating the Dermatological Manifestations of PCOS:*

*author's recommendation

ACNE

Mild- : **BCP with 15 or 35ug Ethinyl estradiol daily (EE)**

Moderate **BCP 15 or 35 EE together with at least 50 mg spironolactone BID**

Severe……..BCP 35EE with at least 150 mg spironolactone-200 mg daily

ALOPECIA (AA)

Premenopausal mild to moderate…. BCP-35EE with 150-200mg spironolactone

If unsuccessful after 6-8 months, may add finasteride 5 mg daily.

Premenopausal severe-…….. BCP only 20ug EE in women under 35-40 yr, with dutasteride 0.5 mg daily. Add spironolactone 100 mg bid if no response after 6 months.

Postmenopausal AA mild and often physiological (rule out TE)…….No hormonal treatment frequently or 50-100 mg spironolactone and/ or minoxidil

Postmenopausal .moderate- Spironolactone 100-150 mg daily. ……Add finasteride 5 mg daily. If no response on patient's demeanor, Minoxidil prn.

Postmenopausal .severe- Spironolactone !50 mg daily, dutasteride 0.5 mg daily, minoxidil 5% if no significant hyperhidrosis

HIRSUTISM

Treatment as in alopecia in premenopausal women to age 35.

Postmenopausal hirsutism women usually have had dermal laser or electrolysis treatment by then. In some with recurrences one may use spironolactone 150-200 mg daily in divided dose, and if needed 0.5 mg dutasteride. Some may prefer to use eflornithine cream daily only.

The following are some hair care procedures and ways to improve scalp hair for everyone. Many of these listed below have been modified from the book (Philip Kingsley, Hair: Aurum Press, 2003).

1) It is vital that the hair be shampooed daily, and rinsed fully.

2) Conditioning the hair removes tangles, with particular attention to the ends of the hair.

3) Avoid insufficient rinsing, and minimize tangling with a wide-toothed comb.

4) Use of a brush with sharp bristles should be avoided. Smooth combs are preferable.

5) Undefined stresses, hormonal medications (androgenic-like oral contraceptives and a number of other medications possibly may be associated with hair loss).

6) Blow drying should be done with the dryer about 6 inches away. As the hair starts to dry reduce the heat gradually. It is necessary to avoid blow drying hair from damp to dry to avoid hair damage, brittleness, and split ends.

7) Rollers have to be used carefully, and not tightly. Pins and clips are also to be used cautiously, and never on while sleeping.

8) If elastic bands and barrettes are used at all, they must not be tight. They may cause traction alopecia. Similarly, pulling the hair too tightly from the forehead may also lead to severe hair breakage.

9) A habit of compulsively touching hair and pulling it (trichotillomania) should be seriously addressed.

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