

PCOS 101

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This session will provide participants with an overview and update on the history, presentation, evaluation, treatment and long term health sequellae of women with Polycystic Ovary Syndrome.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a complex hormonal disturbance that affects the entire body and has numerous implications *for* general health. For far too long, PCOS has been in the closet, underestimated both in prevalence and importance. Now, with a better understanding of the spectrum of the disorder and armed with new treatment options, PCOS is starting to receive the attention it deserves. Interest, research and most importantly, recognition are increasing in a number of medical disciplines including gynecology, reproductive medicine, internal medicine, endocrinology, dermatology, genetics, pediatrics, radiology, and family medicine. Still, it is quite possible that we are still at the tip of the iceberg as we look at the consequences of PCOS on long-term health and disease.

It has been said that PCOS is the most common hormonal disturbance of premenopausal women and certainly is a leading cause of infertility. Depending on how the disorder is defined, from 5% to 30% of all women have some characteristic of PCOS. There are three broad reasons why PCOS patients seek medical care: 1) menstrual cycle disturbance and infertility 2) problems of appearance and self esteem arising from obesity and excessive hair growth, and 3) metabolic derangements, including abnormalities in blood fat (lipid) levels, insulin/glucose (sugar), and elevated blood pressure (hypertension). Often gynecologists, the health care provider to whom many women turn for help, have concerned themselves with only the first of these concerns and have been relatively insensitive to the latter two. Generalists have often failed to make, or understand, the relationship of the different faces of PCOS. A more holistic approach to PCOS is certainly warranted and can have a significant effect in altering quality of life.

HISTORY AND TERMINOLOGY

In 1935, Drs. Stein and Leventhal associated infrequent menstrual bleeding with larger than normal ovaries containing many small cysts. They designated this condition polycystic ovarian disease, since referred to as Stein-Leventhal syndrome. The term disease indicates a specific set of symptoms, or constant physical findings. In this first report of 7 women all had prolonged intervals between periods. Most had a male pattern of hair growth, but at least one patient was reported as "thin." The term disease now has been abandoned in favor of syndrome to reflect a grouping of symptoms, physical and laboratory findings. It must be realized that the term syndrome still might be too restrictive and that this condition is broad spectrum with a vast difference among patients.

The triad of PCOS has been most simply related to irregular menstruation, skin problems and obesity. Not all patients are obese. There seems to be a distinct group of thin PCOS patients that may have even more firmly entrenched hormonal and fertility problems. Some patients with abnormal hair growth have been given the diagnosis of idiopathic (no known cause) hirsutism, but on close examination most will have subtle abnormalities of their hormones or polycystic ovaries on ultrasound scan. Some researchers make the distinction between PCO-appearing ovaries on ultrasound and PCOS. Not all PCOS patients are infertile or have obvious menstrual cycle abnormalities. With pelvic ultrasound it has been found that approximately 20-39% of women of the reproductive age range *will* have polycystic appearing ovaries, some despite proven fertility and lack of other characteristic findings. How all this fits together is really unknown. There may be a central, yet to be found problem that may be the root of PCOS. Alternatively, PCOS can be a symptom of a variety of problems; much like a fever is a consequence of a number of diseases. Despite the designation of PCOS, the ovaries may not be the primary source of the problem, but since the designation of PCOS is well entrenched in the literature and medical practice, no better name has emerged. It is much less important what the disorder is called than that it is appropriately recognized.

MAKING THE DIAGNOSIS OF PCOS

In no other gynecological condition is the general medical history more important than in PCOS. Once one is familiar with the common symptoms and physical appearance of individuals

with PCOS, the diagnosis can be made in family members, coworkers and perhaps, even in the occasional passer-by. Despite this, it is surprising how often health care providers miss the diagnosis. A concern remains in making the diagnosis of PCOS. While much less common, even rare, several serious diseases can masquerade with the same general symptoms as PCOS. Luckily the more serious disorders are often easily separated, once the physician is aware of their possibility. A key point in the history, and one that is especially important in the exclusion of more serious problems, is the rapidity of symptom progression. The more dangerous problems are usually of more rapid onset and do not tend to occur in other family members. Some of the less common diseases that have findings similar to PCOS include hyper- and hypothyroidism, Cushing's syndrome, pituitary gland, adrenal and ovarian tumors. Virilization is a condition where male sexual characteristics emerge. It is very rare, but not impossible for the individual with PCOS to be virilized. Virilization always warrants immediate attention and thorough evaluation. Characteristics of virilization include deepening of voice, balding, increased muscle bulk, increased size of the clitoris, or marked hirsutism.

There are 3 different ways to make the diagnosis of PCOS: 1) clinically, by symptoms and physical findings, 2) hormonal testing, and 3) ultrasound. Many with PCOS will have abnormalities in all three, some only in two, and possibly only in one. Some may argue that findings in only a single category may not constitute PCOS. But, until we have PCOS better characterized, or find a different diagnosis for these patients, the diagnosis of PCOS should remain at last as a talking point. The most minor of apparent problems may have significant implications for future general health and well-being.

Clinical Findings

Menstrual disturbance

Obviously, a detailed menstrual history including menarche (onset of periods), pattern of menses (periods) in the past and changes in the number of days of flow, amount of flow and number of days between menses should be recorded. Often in PCOS patients, the menarche occurs at the usual age of 12-13 years. Some PCOS patients may start menstruating earlier. Not uncommonly, PCOS patients may first be seen by a physician for lack of menses. Any female who has not had menses by age 16 should be evaluated. The menstrual cycle may at first be regular, but by high school, cycles start to lengthen and may be skipped. Often during this time, oral contraceptives are started. The pill usually regulates the menstrual cycle and may give the false impression that all is well. Usually in the teenage years, the other symptoms of skin and weight problems also start to be seen. Some PCOS patients easily establish a pregnancy in these early years. Occasionally, birth control pills may even increase the chance of pregnancy by suppressing abnormal hormonal production. Often a gynecologist sees the PCOS patient when she is in her 20s after stopping the pill, and experiencing a cessation of her periods. Some PCOS patients have quite regular 28-day cycles, but the diagnosis should be highly suspected in individuals with cycle length over 35 days. Some patients have no bleeding unless some form of medication, usually a progestin, is given. In some there is excessive bleeding, or long periods of spotting. It is thought that the age of menopause in individuals with PCOS is about the same, age as in other women. While virtually never mentioned in medical publications, or recognized by physicians, it seems that chronic pelvic pain and premenstrual (PMS) symptoms are quite common. Given the chronically abnormal hormonal patterns, the capacity of hormones to alter body fluid and even the enlarged cystic ovaries, these findings should not be surprising.

Hair and skin problems

The skin manifestations associated with PCOS are possibly more common than either menstrual cycle irregularity, or obesity. Disorders of the skin in PCOS patients are related to an increase in level of male hormones (hyperandrogenism). This may be due to an absolute increase in androgen level, or an alteration in ratio of hormone levels. A third possibility is an exaggerated response of the skin to relative normal androgen levels. The end result of all three of these possibilities is the same and includes: acne, seborrhea, balding, hidradenitis suppurativa

(inflammation of the specialized sweat glands in the arm pit and groin), acanthosis nigricans (see below) and hirsutism.

Hirsutism is defined as an increase in amount and/or coarseness of hair distributed in the male pattern in a female. This is opposed to hypertrichosis, which is excessive growth of non-sexual hair. The issue of facial hair is usually self-evident, but a good screening test is the amount of hair between the umbilicus and pubic hair line. Other areas of male pattern hair growth include sideburns, lower neck, lower back and inner thighs. A faint moustache is quite common and may be more related to family trait and ethnic group than hormonal imbalance. The same can be said for occasional 'stray hairs around the breasts. Outside hirsutism, other manifestations of hyperandrogenism are often dismissed, or not recorded in the gynecologist's evaluation.

Acne and seborrhea occur quickly as androgens rise. Androgens increase sebum, which is a combination of skin oils and old skin tissue. Increased sebum causes plugging of skin pores. Bacteria that thrive on sebum are increased, resulting in inflammation. The inflamed skin pore is called a comedon. Closed comedones are whiteheads, while blackheads are open comedones. The black color comes not from dirt, but from the breakdown of keratin, a natural skin product. Increased male hormone levels also cause seborrhea. A particularly common skin condition and one not usually associated with hormonal alterations is dandruff. Contrary to what is generally believed, dandruff is caused by oily, not dry skin and is a variety of seborrheic dermatitis.

Many women complain of skin problems that wax and wane during the menstrual cycle. In regularly cycling women, the second half of the menstrual cycle is characterized by increased progesterone levels. Progesterone is a weak androgen and may create a situation of relative hyperandrogenism. Around the time of menstruation estradiol is decreased. Low levels of estrogen (hypoestrogenism) also create a situation of relative increase in androgens with resultant increased oiliness and inflammation of the skin.

One of the most distressing of hyperandrogenic skin disorders is alopecia (balding). The most androgen sensitive area of the scalp is the vertex, the highest point of the head. Frontal balding and anterior hairline recession is seen only in the more severe cases of androgen excess. As can be imagined, the mechanism for hair growth (and loss) has been extensively studied, but no unified theory has emerged.

A search for acanthosis nigricans (AN) should be a part of every physical exam of the PCOS patient. AN is usually described as a velvety, raised, pigmented skin change, most often seen on the back of the neck, axillae and beneath the breasts and is often seen in association with skin tags (acrochordons). Possibly the best description is that it looks like the affected area is dirty and would benefit from scrubbing. Obviously this is not the case. There is an association of this finding with simple obesity as well as other endocrine disorders and should always alert the clinician to a risk of diabetes, major lipid abnormalities, and hypertension. Although less common, it may be a warning signal of cancer.

Hidradenitis suppurativa is a hormonally related chronic, painful, disfiguring condition of boil-like abscesses in the groin and axillae that is often misdiagnosed as a problem of poor hygiene. The incidence of HS is increased in PCOS.

For androgens to have an effect on the skin they must bind together with an androgen receptor in the skin. There may be little, or no, physical evidence of hyperandrogenism despite very high androgen levels, if the androgen receptor is lacking or present in relatively low numbers. The number of androgen receptors varies among different ethnic groups and individuals. Northern European women with PCOS are more likely to be hairier than Asian women. A third requirement for androgen action in the skin, besides androgens and receptors, is a specific enzyme called 5 α -reductase. Testosterone must be converted to dihydrotestosterone (DHT) by this enzyme to exert its effect. Only sexual hair follicles contain the necessary enzymatic machinery for conversion of circulating androgens to DHT. A fair-skinned individual may have little excess hair growth despite high levels of testosterone, due to absence of the specific androgen receptor, or enzyme converting capacity, in the hair follicles. Another individual may be quite hirsute with no apparent abnormality in circulating hormones.

Obesity

Whether obesity is a cause of PCOS or obesity is a result of PCOS is unclear, but it seems that the latter is more likely. A distinction has been made between the lean and obese PCOS patient. The typical obesity of PCOS is described as centripetal, related to fat distribution in the center of the body, as opposed to the thighs and hips. This, apple opposed to a pear type of fat distribution clearly is associated with greater risk of hypertension, diabetes and lipid abnormalities. Certainly, many metabolic derangements improve with weight loss, but PCOS is not cured by weight reduction (or caused by obesity).

Almost always, individuals with PCOS gain weight very easily and lose it only with great effort. Everyone knows that some individuals consume large quantities of food and never gain weight while others work hard just to stay fat instead of severely obese. Vanity keeps some from weighing much more than they might, if only they were less vigilant. When seeking medical help for weight control, too often, the obese patient has been told to exercise more, or to eat less. Clearly, this over-simplification fails to take into account the high likelihood that individuals vary in the way their body utilizes calories. Some use calories less effectively, or store fat more easily. A key to the way the body uses energy is insulin. Insulin is a hormone released by the pancreas in response to the breakdown of food into sugars, proteins and fats by the digestive system. Insulin promotes the storage of fat to ensure a constant source of fuel, calories, ensuring the body's most efficient operation. As described in more detail below, PCOS increasingly has been linked to abnormalities of insulin and glucose metabolism. In the past, this may have been an adaptive advantage allowing survival against cold, or famine. Now, in part, a response to today's sedentary lifestyle, obesity has become a genetically related disease, which may be treated, but only with great personal conviction and effort. Certainly, weight loss can only be achieved when caloric expenditure exceeds caloric intake, but genetic, metabolic and environmental alterations make this a much more complex equation. Hopefully in the future, there will be relief, which is both more effective and less painful than our present treatment strategies.

Laboratory Testing

Virtually all patients with PCOS will have at least subtle laboratory abnormalities. The reported results may be only on the upper limits of the normal range, showing only a tendency, not a discrete abnormality. Often a pattern will emerge after considering a group of tests together.

These subtleties may reveal dysfunction in the control mechanisms of the hypothalamus, pituitary, ovary and adrenal (HPOA axis) working collectively. In distinction, serious pathology may be more evident by a marked elevation, or suppression of a single test. Though the value of repeated blood testing for the same hormones could be questioned, it is recommended that each PCOS patient have an initial, relatively comprehensive evaluation and interpretation by an individual familiar with this testing. In the following list, normal levels will not be given because of the marked variations between laboratories and techniques.

Any level that is twice the upper or lower limit of normal is particularly important and may indicate a serious problem. The marginally elevated test is almost always dysfunctional, rather than pathologic. As a rule, endocrine testing, other than a pregnancy test, is probably best performed in the morning, soon after a spontaneous or induced menses. The days around ovulation or mid-cycle should be avoided. Hormonal evaluation in patients on oral contraceptives will often give misleading results with suppression of gonadotropin, ovarian steroid and SHBG levels. It is of limited value to determine these hormone levels in patients on the pill.

To have the greatest diagnostic value blood testing is best performed in the first 2-4 days after a period and with no food or drink after midnight the night before. Be aware that the normal ranges of blood tests vary greatly among different laboratories. Below is a basic outline of tests that may be included in PCOS evaluation:

- Fasting comprehensive biochemical panel- The designation for a group panel of blood tests that evaluate the body's overall metabolism, salt and fluid

balance. Various electrolytes (salts), fats, glucose and liver enzymes are measured. Overall these tests are used to evaluate the function of the liver and kidney. Some therapies used to control PCOS potentially have adverse effects and their use needs to be monitored periodically. This is a relatively inexpensive test obtained from a single blood sample.

- Lipid panel- A check of cholesterol types, and triglycerides.
- 2-hour glucose tolerance test (GTT) with insulin levels-The GIT can exclude diabetes and impaired glucose tolerance. It is much more sensitive than a single measure of glucose. A GIT should be considered on all PCOS patients who are over 120% of ideal weight, have first degree relatives with diabetes, have elevated serum lipid levels, or those having delivered an infant weighing over 9 pounds. The American Diabetic Association (ADA) has designated individuals with fasting glucose levels over 126 mg/dl, as diabetic. A new category is used to describe individuals with fasting levels 110-126 mg/dl, as having impaired glucose tolerance. The term Type 2 diabetes is used to describe insulin resistance that has resulted in elevated glucose levels and has replaced the older terminology of late, or adult onset. No distinction is made for insulin dependency. The ADA recommends a 2-hr. screening after a 75-gram glucose drink. High fasting insulin levels may be a marker of insulin resistance, but the diagnosis is made with more certainty by measuring insulin as a part of the GIT.
- The ratio of luteinizing hormone to follicle stimulating hormone (LH: FSH ratio, a measure of the health of the ovaries. Most pre-menopausal women have a ratio close to 1:1 with ESH values slightly greater than LH. The higher the LH: FSH ratio the greater the likelihood of PCOS. Levels of LH higher than FSH suggests PCOS. High ESH levels suggest the ovary is running out of eggs. Some doctors believe that an LH: FSH greater than 2:1 or 3:1 indicates PCOS.
- Androgens- Measurement of Total Testosterone and Sex Hormone Binding Globulin (SHBG) can be used to derive the *Free androgen Index* indicating how much androgen is being produced by the ovary and adrenal gland. Dehydroepiandrosterone sulfate (DHEAS) is a marker of the adrenal contribution to PCOS. These tests may help in evaluating type and response to different therapies. Some ethnic groups have a higher incidence of congenital adrenal hormone excess, a problem that is detected by measurement of 21-hydroxyprogesterone...
- Other tests. Thyroid-Stimulating Hormone (TSH). Many of the symptoms of thyroid problems are the same as those with PCOS. Since thyroid problems are so common, it is reasonable to measure TSH to exclude either the over- or under-active thyroid gland. Elevation in prolactin, a hormone that helps with milk production, is sometimes found in women with menstrual problems and it's measurement is common. Measurements of hemoglobin A1C is an excellent marker of long-term glucose blood glucose and how well diabetes is controlled. There is usually no reason to measure this in a PCOS patient unless diabetes or glucose intolerance is confirmed. As the net is cast wider and wider for PCOS and its potential metabolic consequences, there are more and more tests that can be ordered. Some of these tests are not easily available, some are experimental, most are costly and not reimbursed by insurance. While their results may add supportive evidence, they probably do not change management options.

Ultrasound

Sonography of the pelvis is warranted in virtually every potential PCOS patient. Evaluation should be performed by individuals experienced in judging ovarian and endometrial function. The finding of greater than ten (some say 8, others 12) cystic structures less than 10 mm in either ovary meets the generally established ultrasound criteria of PCOS. Often cysts of PCOS are located in a peripheral subcortical ring leading to the reference of a string of pearls. The PCOS ovaries are typically 1.5 to 3 times normal size with the normal ovarian volume generally considered to be about 8-12 ml. In some cases the ovary is virtually filled with small cysts. In other cases, it is heterogeneously dense with hardly any detectable microcystic changes. It must be remembered that any hyperandrogenic state may be manifested by the PCO-appearing ovary. Diffusely enlarged ovaries without discrete mass on ultrasound are often associated with insulin resistance.

CAUSES of PCOS

In short, the cause of PCOS is unknown. However, the story is starting to unravel and several important lines of evidence have emerged that offer clues about a central mechanism. The central question remains whether PCOS is a single entity. Is there only one, or are there many causes of PCOS? PCOS is a final common pathway of a variety of disorders and the diagnosis PCOS itself remains one of exclusion. Still, an important principle of medicine is that we always first attempt to link all physical complaints and clinical findings into a single disorder. Although thus far, we have not been able to do this with PCOS, it does not mean that we can not do so in the future,

Let's first look at several characteristics those individuals with PCOS universally tend to share--what binds not separates. We know that PCOS is inherited (see further explanation below). For the present, it also means that a cure is unlikely, so we must stick with trying to control, or correct, the abnormalities of PCOS. Elevated levels of male hormones (hyperandrogenism) also characterize PCOS. Hormones are natural chemicals that are released by the body into the bloodstream in very small quantities and have dramatic effects on distant sites throughout the body. As such, and in the case of PCOS, the entire body is affected by relatively small hormonal abnormalities. There is also the important observation that surgical removal of a portion of the ovary, wedge resection, restores menses and fertility in many PCOS patients. For this reason, it has been suggested that the ovary is the origin of the abnormality.

All estrogens, the female sex hormone, are made from androgens. It is only when androgens are present in abnormally large quantities, or the balance of estrogens to androgens is disrupted, do the unwanted effects of hyperandrogenism appear~ A large percentage of the androgens circulating in the bloodstream are produced in fat cells. A larger number of fat cells create a greater potential for androgen production. The remainder of androgen production normally is divided about equally between the adrenal gland and ovary. There may be adrenal and ovarian forms of PCOS depending from where the greater portion of androgens arise. In the ovary, androgens are produced in the smaller size follicles that characterize PCOS. That the ovary is filled with increased numbers of smaller follicles 4-10 mm, has led some to postulate that some factor blocking follicle development is the key to PCOS. The cells surrounding these follicles (theca cells) are sensitive to the higher amounts of LH also a characteristic of PCOS. LH stimulates androgen production. The smaller follicle has not developed the enzymatic machinery capable of converting these androgens to estrogens. Whether this is a specific block in the ovary, or a consequence of other factors outside the ovary is not known. A genetically acquired abnormality in steroid steroidogenesis, insulin resistance (see below) and/or hypothalamic-pituitary- ovarian axis abnormality probably act in concert as in the etiology of IPCOS. The degree of participation of each of these etiologies varies between patients. Regardless, the ovaries are arrested in a relatively static situation, a grid-lock, log-jam that prevents the eventful maturation of the follicles.

PCOS and insulin resistance

Insulin resistance (IR) is a condition whereby the body steadily becomes less responsive to the actions of insulin. A primary action of insulin is to regulate (lower) sugar (glucose) levels in the blood. In IR, blood sugar levels rise despite high levels of insulin and eventually type 2 diabetes results. This is in contrast to type 1 diabetes where the pancreas does not make sufficient insulin. Although the relationship of diabetes to other endocrine disorders is not new, only recently has the high preponderance of patients with PCOS with IR been recognized. It appears that hyperinsulinemia causes hyperandrogenism, rather than the reverse. The obese PCOS patient is more likely to have both IR and hyperinsulinemia, while the thinner individual does not show IR as often. In terms of general metabolism, insulin facilitates storage of calories and increases fat stores. In addition, hyperinsulinism and IR have been suggested as a root of many unrelated disorders, such as chronic fatigue syndrome, defects in the immune system, eating disorders, hypoglycemia, gastrointestinal disorders, depression and anxiety. Presently, there is considerable investigation on metabolic syndrome (Syndrome X) which is characterized by abnormal lipid levels, insulin resistance, and hypertension. Insulin resistance and hyperinsulinemia are considered to be significant risk factors in the development of atherosclerosis, hardening of the arteries. This predisposes PCOS individuals to increased risk of high blood pressure and stroke. Hyperinsulinemia results in an increase in both LH release and androgen production with subsequent alterations in follicle growth. Hyperinsulinemia is associated with androgen excess and a depressed level of sex steroid binding globulin (SHBG). IR has been associated with development of type 2 diabetes. In contrast to type 1 diabetes (previously called juvenile diabetes) where there is a pancreatic abnormality and low insulin production, with type 2 diabetes there is a strong family tendency to develop the disorder that is reminiscent of PCOS.

It's in the genes

It is a near universal finding that PCOS is genetic, but the heritage is complex. This genetic predisposition is not as simple as brown eyes or blue, but has a complex heritage. The tendency to develop PCOS may be of be inherited from either the mother's side, maternal origin, from the father's side, paternal origin, or from both sides. A paternal origin is equally likely, but often is overlooked. Also, various characteristic traits of PCOS may be passed down with varying degrees of severity. It is quite possible that PCOS is inherited as a small group of genes in which some are involved in glucose regulation and others in ovarian hormone production. Both groups may be necessary for an individual to develop PCOS. In addition, there may be the interaction of diet and other environmental factors that may worsen or improve the problems associated with PCOS. A particularly important point in the PCOS patient's history is whether family members have had similar problems. It is often distressing when a woman with PCOS learns that she may pass on the condition to her daughters, or through her son, to her granddaughters. Hopefully, with our new tools made available by molecular biology there may be significant advances in the genetics of PCOS during the next several years and in the future, PCOS may become a problem of the past.

PREGNANCY and PCOS

First trimester pregnancy loss is increased in PCOS. The major cause of this is probably poor egg quality and problems that were present at the time of fertilization. Many with PCOS have late ovulation, which has been linked with increased risk of miscarriage. Low progesterone levels are an indication of a pregnancy that is not doing well, but in most cases, low progesterone levels are not the cause of pregnancy loss. Ensuring timely ovulation is an important step in preventing pregnancy loss. It is clear that the risk of gestational diabetes and probably, pregnancy induced hypertension (PIH, toxemia, preeclampsia) is increased in pregnant women with PCOS. Some of this risk may be independently related to increased pre-pregnancy weight. There is evidence that weight loss and increased physical activity increases chance of pregnancy. The best method to ensure a healthy pregnancy is to enter pregnancy in optimum health. Pregnancy has a positive health benefit on breast and reproductive cancer. Spontaneous pregnancy sometimes follows a pregnancy that was achieved after a prolonged wait, or aggressive fertility therapy. All women contemplating a pregnancy should use folic acid supplements.

THERAPY for PCOS

Weight Loss

While dieting is certainly valuable, it is the most difficult of therapeutic regimens to administer. With weight loss there is often an improvement in endocrine parameters and sometimes return of regular menses. Plans that focus on behavioral modification and group involvement have been the most effective. Weight loss may improve general health and menstrual regularity, but may have little effect on hirsutism. Diet plans approved by the American Diabetes Association (ADA) are all excellent for PCOS. I believe that PCOS patients do better with weight staying off longer with low carbohydrate, low saturated fat approach rather than high protein diets. Regular physical activity is as important as calorie reduction. Weight loss should be slow, generally no more than one pound per week to one pound per month. Fad diets are discouraged. The emphasis must be on life-long changes.

Progestins

A progestin is a medication that mimics the action of progesterone. Progesterone is an ovarian hormone produced by the corpus luteum, the structure that forms from the ovarian follicle after ovulation and prepares the uterus for implantation. Unless a pregnancy intervenes the corpus luteum has a finite lifespan of 10-14 days. As it fails, progesterone levels fall. Menses, which is the bleeding accompanying the loss of the uterine lining, is the consequence of the withdrawal of progesterone support. As such, it is not the progestin, but its withdrawal, which results in menstruation. In the absence of ovulation, minimal progesterone is produced from the ovary and the interval between menses is lengthened (oligomenorrhea). While progestins may be used to regulate the menstrual cycle, they appear to be of little use in reduction of hair growth, or possibly metabolic derangements.

For a progestin to work, the uterus must first be primed with estrogen. In some PCOS patients the estrogen levels are not sufficient for the progestin to have an effect. If a progestin alone does not induce bleeding, a regimen first using estrogen then progestin may be tried.

Because of the nature of PCOS, there are the early stages of follicle development, but ovulation does not occur. The small follicles (cysts) of PCOS, while not producing near the amount of a pre-ovulatory follicle, do usually produce enough estrogen to stimulate the proliferation of the uterine lining. In absence of ovulation, the uterus is subject to unopposed estrogen stimulation. Left unchecked, this can lead to an overgrowth of the lining of the uterus (endometrial hyperplasia) and if unchecked, even uterine cancer. While uterine cancer is rare under age 40, most cases will occur in associations with PCOS. Progestins do little for the overall body health, but are used to cause regular withdrawal uterine bleeding and prevention of hyperplasia.

Oral Contraceptives

Oral contraceptives (OC) are a mainstay of treatment of PCOS in women who do not want to become pregnant. The estrogen component of OC increases sex steroid binding globulin (SHBG) which bind androgens in the bloodstream and prevent their effects. Increases in SHBG reduce the amount of circulating free testosterone. The progestational component of OC reduces the amount of LH released from the pituitary gland and therefore testosterone production from the ovary. Most OC contain the same estrogen, but in varied amounts. The major difference is in the progestin components. Some progestins are more androgenic and may have a more negative impact on glucose tolerance than others do. OC therapy should be individualized.

Corticosteroids

Steroids have the ability to suppress adrenal androgen production and may be useful in treatment of PCOS with an adrenal component. Overall, their use is better in theory than practice and they are often discontinued by patients because of unwanted side effects. The effectiveness of corticosteroids in the control of hirsutism is questioned and they should probably be considered third-line therapy. Some have reported an additive effect with

clomiphene and patients with elevated DHEAS may be candidates for a trial of therapy. Doses as low as 0.25 mg. of dexamethasone can be used chronically with little fear of overly suppressing adrenal function. Because of the higher cortisol levels at night, suppression therapy is probably better given at bedtime.

Anti-androgens

This group of medications can be used only when not attempting a pregnancy or without some form of adequate birth control. There is at least a theoretical, risk of feminizing the genitals of a male fetus. The value of the agents for PCOS patients is to improve the skin problems that occur with PCOS.

Spironolactone (Aldactone) is a diuretic used to treat hypertension. It has an idiosyncratic action as an anti-androgen and can reduce excessive hair growth by blocking the effects of androgen. It is the most widely prescribed anti-androgen in the United States. At high doses spironolactone blocks the metabolic pathway called the cytochrome P-450 system that affects the capacity of the ovary and adrenal glands to make androgens. It also alters the conversion of testosterone to dihydrotestosterone (DHT) by 5 α -reductase enzyme. Some patients have a surprisingly good response to therapy while others seem completely resistant. In some cases, especially when OC can not be used, it may represent first line therapy. The effects of OC therapy may be additive, as well as reducing a tendency of irregular bleeding seen in some patients using spironolactone.

Cyproterone acetate (CA) is a potent anti-androgen and weak progestin. CA is available only outside the United States. Its effectiveness in treatment of hirsutism is well substantiated. Most patients will report decreased hair growth and some patients become amenorrheic. While CA is usually well tolerated, its glucocorticoid activity may cause weight gain.

Flutamide (Eulexin) is a non-steroidal anti-androgen indicated for treatment of prostatic cancer. Its action is similar to spironolactone and cyproterone acetate in that androgen action is reversibly blocked at the androgen receptor. Flutamide is theoretically superior to cyproterone due to its absence of prednisone (steroid) like activity and to spironolactone because of its lack of alteration in kidney function. A majority of patients report the side effect of dry skin. Less common side-effects are hot flashes, increased appetite, headache, fatigue, and nausea. It is metabolized by the liver and fatal liver toxicity has been reported. While some have reported the drug as safe and superior to spironolactone, others report a similar efficacy and avoid its use due to its high cost and potential of serious liver damage.

Finasteride (Proscar, Propecia) is not a true anti-androgen, but since it is an alternative to anti-androgen therapy, it is described here. Finasteride is an inhibitor of 5 α -reductase activity and was initially indicated for use in the management of benign prostatic hypertrophy. Now it has been approved and received the most publicity for its capacity to thwart male pattern baldness in some men. Since its action is directed at the point of production of the active skin androgen dihydrotestosterone, the drug shows promise in the treatment of hirsutism. The dose of 5 mg. daily is usually prescribed. Finasteride is questionably as effective as spironolactone. The safety profile and tolerance appears to be very good. Despite the pregnancy warning and high cost, the theoretical advantages and excellent tolerance may make this a drug to consider.

Vaniqa (eflornithine) does not inhibit the production or action of androgens but interferes with an enzyme found in the hair follicle needed for hair growth (ornithine decarboxylase). It is a cream used twice daily and only on the face. About one in three patients have reported marked improvement. Some improvement is seen in about another one-third, but this is also about the improvement when women used a cream containing no active ingredient (placebo). Improvement is gradual and may not be evident for 2 months and may take as long as six months. If there is no improvement in six months, use is discontinued. Less than one percent of the active ingredient is absorbed into the body. Side effects are rare and usually limited to skin sensitivity. Use in pregnancy

should be avoided and while the risks are unknown, use in those attempting a pregnancy should be discouraged.

Fertility Promoting Drugs

In PCOS, the normal mechanisms of hypothalamic-pituitary-ovarian (HPO) axis and therefore, follicle growth and ovulation are disturbed. Fertility drugs are commonly used in an attempt to temporarily override the problem and facilitate ovulation. The traditional fertility agents, clomiphene citrate CC (Clomid, Serophene) and various preparations of injectable gonadotropins, both create a super-physiologic situation where an extra push is given for follicular development. All fertility drugs increase the stimulation of the ovary by increasing the concentration of gonadotropins available to stimulate the ovary. CC causes a release of the body's own gonadotropin stores and indirectly stimulates the ovaries, while the injectable gonadotropins stimulate the ovaries directly. One of the drawbacks of all fertility drugs is that they tend to work in only one cycle (month). The developing follicle may take as long as three months (cycles) to go through the entire process of growth and maturation. For the PCOS patients, this means that the follicle and its egg have progressed through its early stages of growth in an abnormal hormonal environment that may contribute to poorer egg quality despite aggressive stimulation.

Clomiphene citrate (CC) probably is the first-line therapy in PCOS patients who want to become pregnant. In comparison, it is quite safe, inexpensive, easy to use and offers chance of pregnancy in the initial months of use. It works by a pharmacological trick that promotes the release of the pituitary gland's own storage of gonadotropins (FSH and LH); CC is not a hormone, but a synthetic anti-estrogen. As such, it fools the body's regulatory mechanisms into perceiving that more estrogen is needed. This challenge is met by gonadotropin release and hopefully a breakdown in the barriers to successful follicle growth with resultant ovulation. However, this antiestrogenic action is a double edge sword and extends to other target organs such as the lining of the uterus (endometrium) and cervix. CC retards endometrial development and may decrease the possibility of implantation of the embryo. CC also markedly decreases the amount and quality of cervical mucus, which may impede sperm transport. Some investigators have proposed a detrimental affect of CC on the follicle, egg, or embryo, but this is much less well substantiated. Still, it is clear that many more patients on CC will ovulate than will get pregnant.

Except under very specific circumstances, CC therapy should not be used over six months. Over 70% of pregnancies are achieved during the first 3 months of use. In the first 3 cycles an expectation of 5-25% is not unreasonable. The risk of twins is reported at 5-10%. Triplets and greater are uncommon (<1%) when used in the prescribed way. Ovarian hyperstimulation is also uncommon and may be more related to stimulation of residual cysts from the previous cycle rather than multiple cystic development in a current cycle. There is generally reported to be a cumulative pregnancy rate of about 30% after six cycles. Some additional success has been reported in using clomiphene after several cycles of oral contraceptives have "leveled the field" with regular cycles.

It is probably good advice to have a baseline ultrasound scan performed before the first CC cycle. This will usually exclude ovarian cysts and some other pelvic abnormality that may complicate therapy or make it less effective. Some form of exam, ultrasound or bimanual (pelvic) should be performed each time CC is used, although this may be modified depending on the particular circumstances.

Insulin altering drugs Results now seem conclusive that metformin can improve ovarian function and increase fertility. Metformin may be used before other fertility agents are tried or in combination with them. See below.

Leptosome (Femara) Letrozole belongs to a group of drugs known as aromatase inhibitors. While indicated for long term treatment of breast cancer, when letrozole is used

in a short time regimen similar to clomiphene, it may promote normal follicle and ovulation. The cost of letrozole is comparable to clomiphene and like clomiphene, the risk of hyperstimulation is low with usually no more than 2 mature follicles produced. Letrozole is rapidly cleared from the bloodstream and it appears to have a high safety profile. The reported side effects are much less than clomiphene and the negative effects of clomiphene on the cervical mucus and uterine lining are avoided. The jury is still out about their effectiveness in PCOS and especially in those that have failed to have follicle development of clomiphene.

Gonadotropin Injections Initially, gonadotropins for use as fertility agents were extracted from the urine of post-menopausal women who produce large quantities of these hormones. A major change in the way gonadotropins were obtained was made possible by genetic engineering and recombinant DNA technology. Here, specific cells that produce massive amounts of absolutely pure hormone are cultured in the laboratory. This type of production has obvious advantages of purity, but at present, the disadvantage of higher cost.

Although there are many claims, to date, no specific formulation or product has emerged as superior for controlled ovarian stimulation. Some patients respond better to one drug, but it has been impossible to predict this in advance. The amount of gonadotropin to be given is determined by expected and previous response. The amount of drug needed may be difficult to predict in advance.

Gonadotropin injections have three major disadvantages. First, they are injections. While relatively simple and painless as injections go, they are inconvenient. Second, their cost ranges from \$40-80 per ampule and usually 5-40 ampules are used in each cycle. And third, they carry a significant risk of ovarian hyperstimulation and multiple pregnancies. It is usually suggested that the twinning rate is about 20% and larger order pregnancies occur in about 5% of cycles. While cyst formation and abdominal enlargement is common, some patients develop ovarian hyperstimulation syndrome (OHSS). Here large amounts of fluid are leaked from the ovaries and can represent a medical emergency.

In vitro fertilization (IVF) The *American Society for Reproductive Medicine* states "in vitro fertilization for infertility, not solvable by other means, is considered ethical." IVF is increasingly being used for treatment of PCOS. The major factor limiting even greater use of assisted reproduction is its high cost. IVF offers several distinct advantages that may make it more cost-effective than it might seem initially. Perhaps the largest benefit, a desire shared by both clinician and patient, is to evaluate the capacity of the oocyte to be fertilized. As expected, the chance of fertilization failure is higher in PCOS patients than in patients with anatomic abnormalities. Lack of fertilization in one cycle does not necessarily prove that by altering the stimulating regimen, or timing, that fertilization will fail in subsequent cycles. It may be more the environment in which the oocyte develops than the oocyte itself. An additional advantage is that a more aggressive approach can be taken toward ovarian stimulation. With PCOS, hyperstimulation is somewhat less of an issue because the preovulatory size follicles are aspirated and a limited number of embryos are replaced. Not only does this decrease the chance of multiple pregnancies, it reduces the risk of more pronounced cystic change. Many PCOS patients either over-stimulate, or under-stimulate, with gonadotropin therapy. The use of GnRH analogs and gonadotropins in conjunction with IVF may maximize control and ensure the greatest chance of pregnancy in any one cycle.

Surgical therapy

In the past, ovarian wedge resection, a procedure whereby a portion of the ovary is removed and the ovary sewn back together, resulted in a significant reduction in LH and androgen production, reestablishment of regular menses in over 75% of patients and a pregnancy rate of about 60%. However, pelvic adhesive disease, which was often severe, occurred in about 30% of patients. There is probably no longer an indication for wedge resection by laparotomy, although electrosurgical incisions, or ovarian drilling, has become relatively common place.

Success rates of microcautery vary by operator and, while adhesion formation may be considerably less, it is still common. A fine cautery needle is used to make 4-20 punctures on each ovary. Alternatively, lasers have been used for the same effect with the possible disadvantage of greater surface injury and scar tissue formation. Laparoscopic outcomes seem somewhat less effective than traditional wedge resection. Usually ovarian dulling is reserved for fertility therapy and may be especially useful when there has been an exaggerated response to fertility drugs.

The mechanism by which surgical therapy works is not known. It is unclear whether it is surface destruction and thinning of the cortex or reduction of ovarian mass which causes the procedure to be effective. Long term effects are largely unknown. Earlier menopause due to partial destruction of the oocyte pool is a theoretical risk. Surgical intervention should not be considered first line therapy in treatment PCOS. If hysterectomy is performed for other reasons, it may be justified to remove the ovaries as well. The value of removal of ovaries has not been studied in enough detail to make a comment on the usefulness of this procedure.

Cosmesis

The physical removal of unwanted hair is a useful, even necessary, adjunctive therapy. Medical therapy may significantly slow hair growth, but usually will not completely stop it. Permanent reduction in unwanted hair can be accomplished by electrolysis or laser therapy. These therapies destroy the hairs regeneration mechanism. Contrary to popular belief, shaving and plucking does not induce faster or coarser hair growth. However, it is painful and can cause significant inflammation, infection and scarring. If possible, medical therapy should be the first line therapy.

Laser is now much favored over electrolysis, but beware that all lasers are not the same and there can be big differences in cost between laser centers. Laser therapy works best on individuals with fair skin and dark hair.

Insulin Altering Agents

The association of PCOS and insulin resistance is described above. By treating the insulin resistance, PCOS may be also treated, possibly reversed while preliminary studies have been very encouraging, there is much to be learned. A major benefit of these medications is that the entire spectrum of problems arising in PCOS appears to be improved. Additionally, this appears to be accomplished at relatively low risk, inconvenience, and cost. It should be noted that since these medications are currently approved solely for the treatment of diabetes, they must be considered experimental for sole treatment of PCOS. But then, there is no therapy that is approved for the treatment of PCOS, only its symptoms. It is still very unsettled which PCOS patient many derive benefit from these medications. With some PCOS patients these medications have successfully restored normal menstruation and fertility even in the absence of the insulin resistance. They may be a useful alternative when other therapies have failed, or benefit appears to exceed risk. The primary drug of choice because of its safety profile is metformin. Rosiglitazone (Avandia) and pioglitazone (Actos) are usually second line drugs used when metformin can not be tolerated, or is ineffective in reducing insulin levels. At least some weight loss is common with metformin, while the "glitazones" have been reported to cause weight gain, at least in diabetics.

Metformin (Glucophage) an FDA advisory subcommittee voted unanimously in March 1994 that Metformin be approved for the treatment of insulin resistance and type 2 (insulin resistant) diabetes that cannot be controlled by diet alone. It had the strong endorsement of the American Diabetes Association and is presently used in over 80 countries. By September 1996 over one million U.S. patients had been prescribed the medication. Now there are as many as 10 million patients on the drug. Metformin enhances the bodies sensitivity to insulin and inhibits glucose production from the liver without the risk of hypoglycemia. It does not lower blood glucose levels, but acts to improve the body's sensitivity to insulin. There is new evidence that suggests that metformin may also have a direct activity on androgen production

by the ovary. Metformin use in some with PCOS have shown weight loss, improved lipid profiles, lowering of blood pressure, lowered androgen levels, increased sensitivity to clomiphene, restoration or improvement in menstruation, pregnancy and improved pregnancy outcome. About 50% of PCOS patients taking metformin note improvement in well being and energy level. Results from a large scientific trial studying men and women at high risk for type 2 diabetes indicated that metformin may postpone or prevent the development of diabetes. Of note, the effect of metformin use was not as strong as that seen in another group that significantly altered their diet and exercise. Overall, metformin appears to have an excellent safety profile. While those with higher insulin levels and/or altered glucose tolerance are most likely to benefit, there have been anecdotal reports of restoration of normal cycles in individuals with normal laboratory values. While metformin appears to be a safe drug, its use remains off label and should be monitored by a physician experienced in its use. Below are listed common precautions.

Gastrointestinal disturbance Gastrointestinal (GI) upset and a tendency toward looser stools or more frequent bowel movements are reported in at least 1/3 of users. These problems are much more common in the initial month of use and can be decreased by starting at lower doses and taking the medications less frequently. GI problems are most often experienced after a meal rich in fats or sugars. If there is recurrent vomiting or persistent diarrhea, a physician should be consulted. The extended release variety (Glucophage 3CR) may have fewer GI side effects.

Generalized feeling of unwellness It seems that about 30-40% of patients on metformin really feel better. They may have mild GI effects; overall the energy level is increased and their appetite is decreased. They appear to almost be addicted to the drug. Another 30-40% are more in the take it or leave it category. They see or feel advancement in some areas, maybe a little decline in others, and often no real change one way or the other. A third group of 10-20% feel poorly on metformin with a number of varied complaints. Common sense would dictate that the medication be stopped in this group.

Blood Monitoring Metformin is cleared from the body by the kidneys. One half the drug has been removed in 6 hours and another 50% in the next 6 hours. If there is a reduction in kidney function, the clearance of metformin is slowed and can build up in the body. Renal (kidney functions) is tested by measurement of blood urea nitrogen (BUN) and creatinine levels in the blood and repeated yearly. A complete blood count (CBC) and comprehensive biochemistry panel including tests for liver and kidney function should be drawn at onset of therapy and at least yearly.

Lactic acidosis Lactic acidosis is a potentially fatal disorder that has been reported to complicate a small number of cases of metformin use. The reported incidence of lactic acidosis is 3/100,000 using the drug for one year. Some have argued that there is no risk in healthy individuals and that the problem only occurs in those already compromised by other illnesses and/or medication use. For now we should be vigilant. The symptoms of lactic acidosis are hyperventilation, slow and erratic pulse, weakness, muscle pain, sleepiness, and feeling of extreme unwellness. It will not just happen; there will be warning signs. There is some fear that if we no longer consider it a possibility and fail to inform our patients, then the one case might occur that could be prevented.

X-ray dye Metformin should be stopped at the time of, or just prior to a procedure using X-ray dye containing iodine. The kidneys clear X-ray dye and rare cases of diminished kidney function have occurred because of the dye. Since the kidney clears metformin, it could cause a build-up of metformin and potentially increase the risk of lactic acidosis. The procedures that use iodinated dye include the hysterosalpingogram (HSG) in evaluation of infertility, intravenous pyelogram (VIP) often to exclude a kidney stone or evaluate the urinary tract for recurrent infection and abnormalities, evaluation for gall bladder disease (cholangiogram), and tests to evaluate for blood clots, coronary artery function (angiogram), and CT / MRI scans. Metformin can be safely started in 48 hours if there have been no problems with the procedures.

Surgery The same rationale for withholding metformin before procedures using X-ray dye can be said for surgery. Metformin should be discontinued until a regular diet and fluid intake has resumed.

Alcohols use a social drink or two should pose no problems, but since alcohol may worsen lactic acid metabolism, excessive intake should be avoided.

Liver disease Again it's the lactic acid problem. Metformin is not metabolized by the liver but individuals with markedly altered liver (hepatic) function may be at increased risk of lactic acidosis.

Exercise and dehydration Prolonged aggressive exercise may cause of buildup of lactic acid. Aggressive exercise routines should be discussed. Kidney function can also be altered by dehydration. Metformin should be withheld if there is not adequate fluid intake.

Vitamin absorption Use of metformin may alter the body's capacity to absorb vitamins from the digestive system, specifically vitamin B-12. Daily multivitamin with increased calcium supplementation is a good idea.

Metformin use in Pregnancy It must be emphasized that the risk in pregnancy is unknown, but it is thought to be low. Metformin has been given a class B rating by the Federal Drug Administration (FDA), indicating expected safety, but with insufficient data to identify a harmful effect. Studies in laboratory animals have not shown an alteration in fertility, an increase in rate of pregnancy loss, or birth defects. Some physicians suggest that metformin be stopped as soon as a pregnancy is established, others at 8-12 weeks. Very few are recommending use throughout pregnancy. The medication has been used in a relatively small number of pregnant patients with no apparent adverse events on the mother or fetus. Several small studies have shown that metformin may reduce the possibility of miscarriage. A pregnancy test should be performed with breast tenderness, or other subjective signs of pregnancy. It appears that use in pregnancy is increasing. In the future, these drugs potentially could be used in pregnancy to prevent, or treat gestational diabetes. It is important to note that maternal diabetes has been associated with increased rates of early pregnancy loss and birth defects. Metformin is excreted in milk and use during nursing is questionable.

“Glitazones Rosiglitazone” (Avandia) Pioglitazone (Actos)

The above three drugs are thiazolidinedione class of agents and are often commonly referred to a glitazones. These drugs have been approved by the FDA for treatment of type 2 diabetes unresponsive to diet. Glitazones improve insulin sensitivity. Like metformin and different from the other anti-diabetic drugs, the glitazones do not cause hypoglycemia. Glitazones bind to DNA in the nucleus (PPAR, peroxisome proliferator-activated receptors) in the nucleus of target tissues of insulin action such as fat, muscle and the liver and promote insulin action, or decrease insulin resistance. Rezulin (troglitazone), another similar drug, was removed from the market by reports of liver damage and even death. There has been no substantiated evidence of liver toxicity with rosiglitazone and pioglitazone. Glitazones increase the number of fat cells (adipocytes) in the body. This may, in part, account for the minor weight gain seen in some individuals as opposed to weight loss often seen, at least initially, with metformin.

The side effects are few and mild with the most of common fluid retention. At least in diabetes, there is a weight gain of 2-10 pounds. This is thought to be evidence of improved metabolism.

Treatment during mid-late gestation was associated with fetal death and growth retardation in rats and rabbits when over 4 times the usual human dose was given. There was no increase in birth defects even at very high doses. There is insufficient information to determine positive or negative effects in human pregnancy and most advise against use in pregnancy.