What is Polycystic Ovary Syndrome? PCOS is an endocrine disorder that is characterized by insulin resistance, hyperandrogenism, obesity, and ultimately infertility. Today, PCOS is considered one of the most common endocrine disorders. It generally affects 1 out of 10 women in their fertile age. The diagnosis of PCOS patients is very complex, since it is a multiform syndrome. That is reason because a diagnostic of exclusion has been established. This means that for women to be treated as a PCOS patient, they must show hyperandrogenism and ovulatory dysfunction. [1] When excessive amounts of androgens are secreted into the body, it is usually evident by the presence of acne, hirsutism (excessive production of hair), or frontal alopecia (lack of hair in the frontal area.) Hyperandrogenism is caused by the impairment in gonadotropin releasing hormone (GnRH) secretion that supports luteal hormone (LH) secretion. Insulin sensitivity is decreased in PCOS patients. This creates insulin resistance and growth of compensatory hyperinsulinemia. PCOS patients also tend to have higher levels of adipose tissue in the abdominal area due to the excessive production of androgens and the insulin sensitivity. This adipose tissue focuses on the abdominal area. It increases the risk of carbohydrates intolerance, and it develops abdominal obesity which can cause miscarriages and infertility. PCOS patients with higher body mass index (BMI) are more predisposed to have menstrual PCOS, but most of these treatments only focus on the symptoms and not in the root of the syndrome. Such is the case of Metformin, which has been able to fight many of the symptoms but has not been able to eradicate the syndrome. PCOS is a syndrome that affects not only the women that have this disorder, but her family as well.
It has been recognized that androgens are produced by both ovaries and the adrenals. A higher percentage of androgens are produced by the ovaries and the rest is produced by the adrenals. For this reason it is important to know how androgens are produced in a healthy person. In the adrenals, androgens such as dehydroepiandrosterone, DHEA, and androstenedione are produced by the zona fasciculate and zona reticularis. Androgen synthesis is achieved with the help of P450c17 enzyme. This enzyme is the responsible for steroid differentiation by converting progesterone to its C17 hydroxylated analogs and by blocking the pathways to the androgens. [3] P450c17 enzyme also regulates the ratios of 17α-hydroxylase, which converts pregnenolone to 17-hydroxypregnenolone, 17-OH pregnenolone, and 17, 20-lyase which converts 17-OH pregnenolone to DHEA. [9] Each has a higher activity rate depending on the area in which they are placed. 17α-hydroxylase is most expressed in the zona fasciculate, while 17, 20-lyase is mostly expressed in the zona reticularis. Zona fasciculate and zona reticularis are tissue regions that compose the adrenal cortex. This equilibrium between the zonas is essential for the production of DHEA and androstenedione. In the ovary, androgen production is achieved in the LH thecal cells. Thecal cells are the responsible for the production of both 17α-hydroxylase and 17, 20-lyase. P450c17 enzyme also helps with the production of DHEA and androstenedione in the ovaries. A healthy woman should produce 60% of androgens in the ovaries and 40% in the adrenals. In PCOS patients the ovarian production of androgen is suppressed by GnRH. This has been confirmed, by studies where the mutation of P450c17 enzyme is the responsible for this shift on the androgen ratios in the ovaries [7]. To compensate for the loss of androgens, adrenal over produces androgen. This shifts the ratio from the ovaries to the adrenals.

Almost 70% of women with PCOS display insulin sensitivity. Both hyperinsulinemia and insulin resistance promote hyperandrogenism. Although obesity is not related to hyperglycemia, this condition is proinflammatory since it generates reactive oxygen species (ROS). Nuclear factor-κB (NF-κB) is a transcription factor composed of DNA-binding subunits p50 and p65. NF-κB is present in the cytoplasm when mononuclear cells (MNC) is at rest, but when MNC is activated, NF-κB is transformed into inhibitory-κB(I-κB). The increment in MNC sensitivity to hyperglycemia in PCOS is still not known [4]
PCOS patients show increments in the percent level of testosterone and androstenedione. DHEA activates NF-κB, p65, p105, TNF-α, IL-1β RNA. It also reduces the percent change in fasting and glucose-challenged inhibitory-κB (I-κB) protein. Since androgen is not found at regular levels in PCOS patients, hyperandrogenemia starts and sensitizes MNC to glucose.

A study has shown not only that hyperandrogenism causes acne, hirsutism, and alopecia, but also is related to insulin sensitivity. In PCOS patients, mononuclear cells, MNC, are pre-activated by hyperandrogenism. The pre-activation of MCN has being observed by the increment of reactive oxygen species, ROS, and the activation of nuclear factors κB, NFκB. Hyperandrogenism not only pre-activates MCN, but also increases the sensitivity to glucose for PCOS patients. Contrary to women with PCOS, women without the syndrome do not show sensitivity to hyperglycemia or any inflammatory reaction to glucose intake.

The high correlation of circulating androgens with molecular markers of oxidative stress and inflammation increases the chance that women with PCOS have hyperandrogenemia. The induction of hyperandrogenism in ovulating women with normal weight will explain the relationship between normal levels of androgens and PCOS.

For the experiment, two groups of normal weight ovulating women without PCOS were chosen. To the first group small dosages of androgen were given. This was done to increase the circulating levels of androgen to the ones observed in women with PCOS. The second group was used as a control group. They were given placebos to keep their androgen levels normal. To the testing group, oral dosages of DHEA were administered. As a result, the glucose ingestion, ROS, NFκB and TNFα were increased. TNFα is part of RNA MNC.
The image above is divided into two sections. The first section represents the electrophoretic mobility shift assay, EMSA, bands from the two study groups. EMSA measures the affinity of protein-DNA or protein-RNA interaction. These bands show the quantity of NFkB in nuclear extract from MNC before and after the intake of either placebos or DHEA. Two samples were collected, one at fasting stage (empty stomach), and after two hours (a post glucose intake.) This graph shows a slight rise of the post glucose intake for the women that have taken DHEA, but not on for the women taking placebos.

As for the second section of the image, a densitometric quantitative analysis is shown. This test is based on the measurement of optical density of light sensitive materials. This analysis measures the percentage of NFkB is activated in both groups before and after glucose intake. For the first graph, left, a sample of women that have taken placebos and DHEA was taken with an oral glucose tolerance test, OGTT. The second graph, right, shows a comparison on the percent change in activated NFkB in the before and after the intake of placebos or DHEA. For the women that took placebos a decrease in the percentage change in activated NFkB was revealed. Also, the group of women that took DHEA showed an increment on the percent change, according to the graph. This gives a positive conclusion that the levels of androgen in women are related to the levels of activated NFkB. Implying that, although hyperandrogenism is one of the main characteristics of PCOS, is also the progenitor of the disorder’s glucose-stimulated inflammation.

More than 50% of PCOS patients are overweight. Adipose tissue not only works as energy storage, but also as one of the largest endocrine organs. One of the properties of adipose tissue is the maintenance of reproductive functions. Androgens are modulator for the adipocyte functions and the circulation of adipose tissue. [6]

The excess of hyperinsulinemic androgen is linked to overweight PCOS patients. This plays an important role in the metabolic symptoms of the PCOS patients. According to an experiment done by the department of endocrinology, the subcutaneous adipose tissue in the abdominal area is associated with anovulation. P450c17 enzyme and 5α-reductase are the responsible for the conversion of...
testosterone/androstenedione to estradiol/estrone, and testosterone/dihydrotestosterone (DHT). In PCOS patient the synthesis of estrone, estradiol and DHT decreased accordingly with the BMI. 5α-reductase2 was found in PCOS women. The receptors of androgen and estrogen (AR and ER) do not describe a significant difference in PCOS patients, but the levels of leptin were positively connected to AKR1C2 are negative connected to 5α-reductase2. These results indicate that the levels of leptin are negatively interconnected to the levels of DHT. Sex steroid enzymes levels are significantly increased in SAT of PCOS confirming the imbalance of estrogen, androgen and progesterone are directly related to the adipose tissue.

The main components of PCOS infertility are gonadotropic dysfunction and insulin resistance. When PCOS patients are overweight, the chances of a healthy pregnancy are minimal. The reproductive outcome is expected to be adverse in pregnant women and their fetuses when women are both PCOS patients and overweight. Hyperandrogenism and metabolic state increases with the weigh to the women. This creates more irregular menstruations and less ovulatory cycles. As a result, the rates of pregnancy decrease.

For the following experiment three different groups were studied. The levels of androstenedione and testosterone of overweight PCOS, lean PCOS, and control patients (without PCOS) were determined by serum androstenedione/testosterone measurement. This test measures the level of sex hormones in the blood. With the help of radioimmunoassay, antigens are made radioactive and mixed with known quantities of antibodies for the antigen. These two bind with each other. Then, the serum of the patient with unknown quantities of antigens is added to the mix. This creates a competition between the known and unknown antigen as the binding agent. The bind antigens are separated from the unbind ones left in the supernatant. Using gamma counter, a standard curve is generated to measure the amount of antigens in the patient and therefore known the levels of androstenedione and testosterone in each patient. [8][9]
The image below shows the impact of obesity in pregnant women and its result in both metabolic and hormonal factors. [10] The values of testosterone and androstenedione are shown in the box and whiskers plots. The line in the middle of each box corresponds to the median. Upper and lower limits of each box indicate 75 and 25 percentiles. The whiskers (above and below) show the upper and lower closest values. The levels of testosterone are greater in overweight PCOS patients than the lean PCOS patients and controls. Also, the testosterone levels were considerably greater in lean PCOS patients than in control patients. No difference is seen for androstenedione for any group. This establishes that the levels of testosterone are the ones that affect pregnancy and not androstenedione.

Metformin has been considered an aid to control insulin resistance. It is recommended to greater part of PCOS patients that are overweight and glucose intolerant. Metformin is recommended for a short period time. It is not recommended for long periods of time or as permanent medication. Yet, Metformin reduces the synthesis of hepatic glucose, inhibiting the gluconeogenesis. Metformin also reduces the levels of androgens in PCOS patients, and regulates menstrual cycles. This improves the ovulation of PCOS patients and as a result their fertility. [11] Usually, Metformin is combined with Clomiphene since this product can be use in long terms. This is used for patients that have high levels of insulin resistance. Metformin helps PCOS patient to respond faster to the Clomiphene treatment. Together, Metformin and Clomiphene, help regulate levels of insulin as well as the fertility levels in PCOS patients.

Polycystic Ovary Syndrome, PCOS, is a very common endocrine disorder, and with it brings many symptoms that affect women’s daily activities. PCOS patients that suffer hyperandrogenism over produce testosterone, estrogen, androgen and progesterone. These different hormones help modify the regular process of ovulation, metabolic synthesis, and insulin synthesis. Also, PCOS causes insulin sensitivity that can
develop into insulin resistance, hyperglycemia, and even diabetes. Carbohydrates intolerance together with hyperandrogenism, are one of the main causes for low-grade inflammation in PCOS patients. Although obesity has been demonstrated to be independent to insulin resistance, it is still another symptom present in PCOS patients. Women with PCOS have a difficult time when it comes to pregnancy. Especially if PCOS patient are overweight this becomes more difficult. Drugs treatments such as Metformin serve as support for those women that want to start a healthier path. Treatments are still developing, more and more drugs are created in order to exterminate this disorder. Even though a final cure has not yet been found, studies and investigation are developing in the quest to find the overall mechanism of the disorder. This will lead to the right treatment where not only the symptoms are treated but the disorder as well.

References:


