Polycystic Ovarian Syndrome
Chiaoling Sua-Lao, M.D.

INTRODUCTION

Polycystic ovarian syndrome is the most common endocrine disorder in females. Prevalence rates vary depending on the diagnostic criteria used. It ranges from 15-20% universally [1]. The clinical presentation commonly includes oligoovulation or anovulation, hyperandrogenism (clinical or biochemical) and the presence of polycystic ovaries. The etiology of this heterogenous condition remains obscure and the variability in phenotype expression continues to render the clinical care and research concerning this disease challenging.

There is no universally accepted definition of PCOS. The following table shows the recommended diagnostic schemes for PCOS [2].

Table 1. Recommended Diagnostic Schemes for Polycystic Ovary Syndrome by Varying Expert Groups

Signs and Symptoms*	National Institutes of Health Criteria† 1990 (both are required for diagnosis)	Rotterdam Consensus Criteria 2003‡ (two out of three are required for diagnosis)	Androgen Excess Society§ 2006 (hyperandrogenism plus one out of remaining two are required for diagnosis)
Hyperandrogenism‖	R	NR	R
Oligoamenorhhea or amenorrhea	R	NR	NR
Polycystic ovaries by ultrasound diagnosis		NR	NR

All diagnostic approaches require more than one sign or symptom. PCO alone is a nonspecific finding and is noted in women with no endocrine or metabolic finding. So, conditions like hyperprolactinemia, disorders of thyroid glands, and non-classic congenital adrenal hyperplasia should be excluded before a PCOS diagnosis can be made. Metabolic disorders like insulin resistance and obesity are commonly seen in PCOS. But they are not included in the diagnostic criteria.

In 2012, an independent party in an international workshop reviewed the diagnostic schemes and recommended that Rotterdam criteria be adopted with specific identification of phenotype. These four phenotypes are listed below in order of decreasing clinical severity, which also correspond to decreasing specificity of the milder phenotypes [3].

Table 2. Diagnostic Criteria for PCOS

Adult Diagnostic Criteria (Rotterdam)

Otherwise unexplained alternative phenotypes:

1. Phenotype 1 (classic PCOS)[a]
   a. Clinical and/or biochemical evidence of hyperandrogenism
   b. Evidence of oligo-anovulation
   c. Ultrasonographic evidence of a polycystic ovary
2. Phenotype 2 (Essential NIH Criteria)[a]
   a. Clinical and/or biochemical evidence of hyperandrogenism
   b. Evidence of oligo-anovulation
3. Phenotype 3 (ovulatory PCOS)[a]
   a. Clinical and/or biochemical evidence of hyperandrogenism
   b. Ultrasonographic evidence of a polycystic ovary
4. Phenotype 4 (nonhyperandrogenic PCOS)
   a. Evidence of oligo-anovulation
   b. Ultrasonographic evidence of a polycystic ovary

ETIOLOGY

The exact etiology of PCOS is unclear. It is currently thought to emerge from a complex interaction of genetic and environmental traits. Hyperandrogenism is the central concept of PCOS etiology.

Proof of the genetic origin of hyperandrogenism in PCOS is performed by familial aggregation and twin studies as well as identification of dependent genetic variance associated with PCOS susceptibility. All these account for the similar prevalence rates among various ethnic and racial groups.

Environmental factors may be congenital or acquired. They include intrauterine factors such as androgen exposure, poor prenatal nutrition, and even toxic changes during embryonic development and early stages of female gonadal differentiation. Obesity is a major postnatal factor influencing the PCOS phenotype. Insulin resistance is common in this disease condition.

PCOS is a syndrome with different characteristics. Therefore, different pathways may be involved in its etiology with hyperandrogenism being the final common pathway [4].

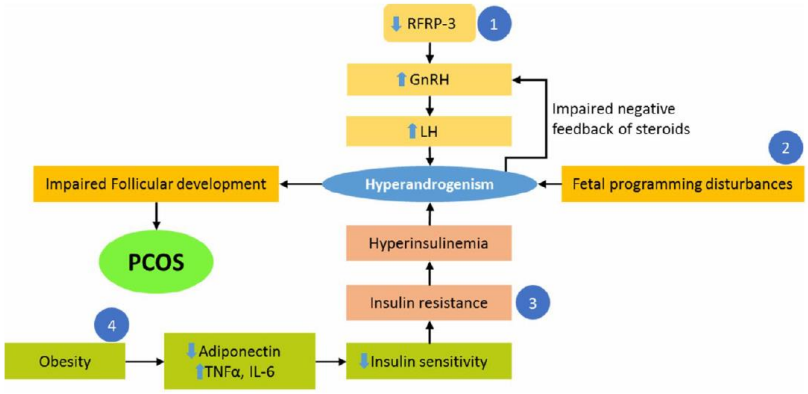

Figure 1. The pathophysiological pathways that presumed to mediate polycystic ovary syndrome (PCOS) formation are expressed. Four different pathophysiological pathways lead to PCOS. Abbreviation: RFRP-3, arginine-phenylalanine-amide (RFamide) -related peptide 3; GnRH, gonadotropin releasing hormone; LH, luteinizing hormone; TNFα, tumor necrosis factor-α; IL-6, Interleukin-6

(Discussion of Figure 1.)

1) Abnormal HPO Axis

   The increase in frequency and magnitude of GnRH and subsequent LH secretion is the most important pathophysiological feature of PCOS. Effective mechanisms for increasing pulse frequency and amplitude of LH in PCOS are not well understood. Four hypotheses have been suggested.

   a. Defective GnRH pulse generator that reduces the activity of gonadotropin inhibitory hormone (GnIH) known as RFRP-3. RFRP-1 and RFRP-3 neuronal cell bodies are located in the dorsomedial nucleus of the human hypothalamus that inhibit GnRH pulses [5].
   b. Hyperinsulinemia elevates the GnRH activity or increases the pituitary responsiveness of the gonadotropins to GnRH.
   c. Low levels of progesterone from anovulation eventually remove the influence of negative feedback at the level of the hypothalamus.
   d. Hyperandrogenism in itself blunts all the negative feedback circuits (estrogen, progesterone, cortisol feedbacks).

2) Fetal Programming Disturbances

   Fetal exposure to androgens during development may also lead to PCOS phenotypes in adulthood.

   a. Mother has PCOS. Placenta has defective aromatase and sex hormone binding globulin (SHBG) activity resulting in increased passage of androgens to the fetus [6, 7].
   b. Fetal undifferentiated ovary is the source of excess androgen production [8].
   c. Malformation of androgen producing tissues including the adrenals as is seen in CAH with defective 21 alpha hydroxylase enzyme
   d. HPO axis disorder during embryonic development [8]

3) Insulin Resistance

   Hyperinsulinemia increases the secretion of androgens with different effects on the ovary, adrenals, pituitary, LH receptor, SHBG, insulin growth factor binding protein (IGFBP), etc.

4) Obesity

DISCUSSION

NORMAL ANDROGEN PHYSIOLOGY

Central to the pathophysiology of PCOS is hyperandrogenemia. It is imperative that everyone must understand the normal androgen physiology before one can fully comprehend PCOS.

Under normal circumstances, the ovaries and adrenal glands contribute equally to male hormone production. Half of the testosterone in the circulation comes directly from the two endocrine organs – adrenals and ovaries. The other half arises from peripheral conversion of androstenedione.

Androgens are secreted in response to their respective trophic hormones – LH and ACTH. Androgen production is NOT UNDER direct negative feedback regulation of the HPO/HPA axis in the female. Intraglandular (adrenals and ovaries) paracrine and autocrine mechanisms modulate androgen response to trophic hormone stimulation.

OVARIAN STEROIDOGENESIS

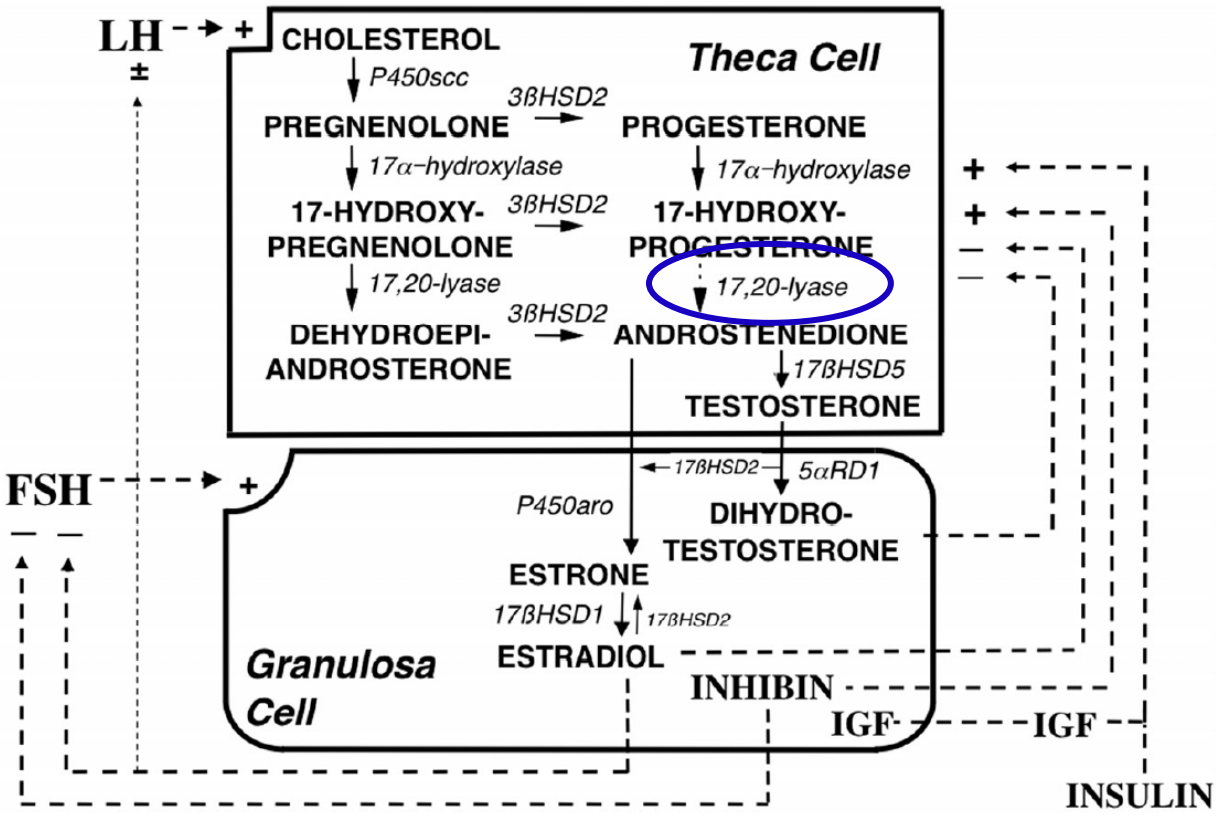

Figure 2. Depiction of the organization and regulation of the major steroid biosynthetic pathways in the small antral follicle of the ovary according to the 2-gonadotropin, 2-cell model of ovarian steroidogenesis.

In the 2-cell 2-gonadotropin theory of ovarian steroidogenesis, LH stimulates androgen formation within the theca cell. FSH regulates estradiol biosynthesis from androgen inside the granulosa cells. Estradiol at physiologic levels suppress LH via long-loop negative feedback. But with increased levels of estradiol, LH can be stimulated under certain circumstances (i.e. LH surge during ovulation). Androgen formation in response to LH appears to be modulated by intraovarian feedback at the levels of 17-hydroxylase and 17,20-lyase (enzyme cytochrome P450c17A1) which are expressed only in the theca cells. The relative quantity of androstenedione formation from 17 hydroxyprogesterone (17OHP) in the intact follicle is probably small. And this small amount of androstenedione crosses over to the granulosa cell and is converted to estradiol via the aromatase enzyme. Note that aromatase is present only in the granulosa cell. But androstenedione is preferentially metabolized to dihydrotestosterone rather than estradiol in

small ovarian follicles prior to the main follicle selection by FSH. Estradiol on the other hand is primarily formed from androstenedione and not from testosterone. Modulation of all these enzymatic activities occur locally. Androgens and estradiol inhibit while inhibin, insulin, and IGF-1 stimulate 17-hydroxylase and 17,20-lyase activities [9].

ADRENAL STEROIDOGENESIS

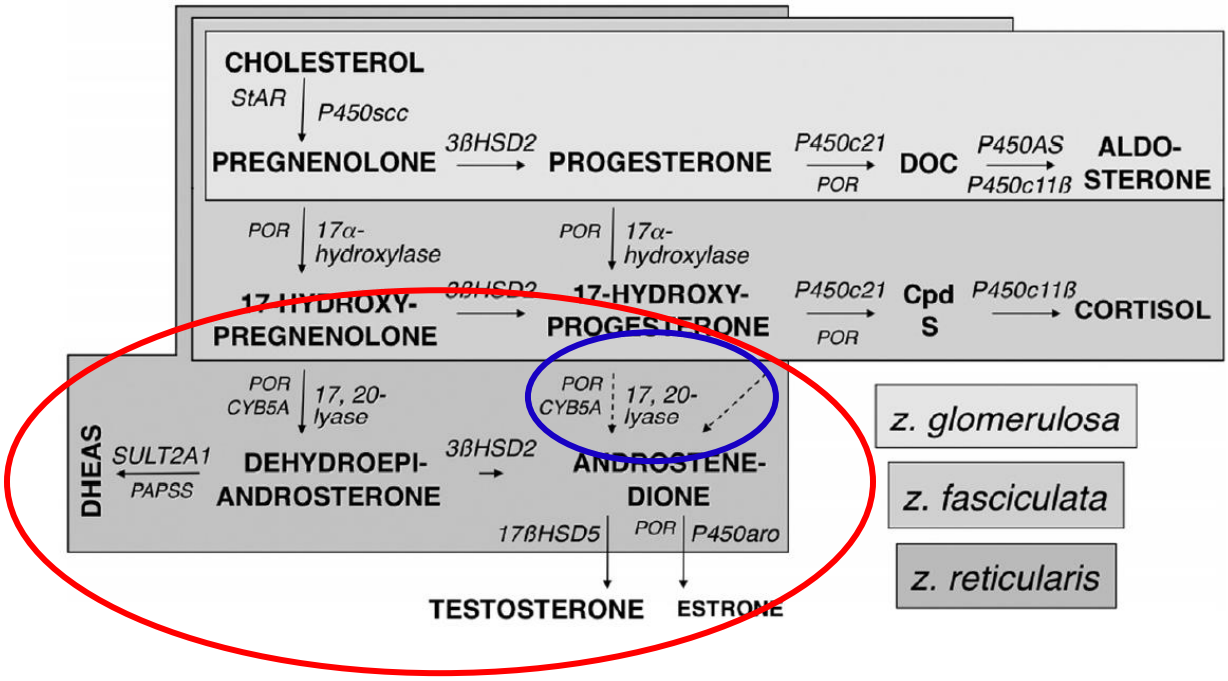

Figure 3. Depiction of the organization of the major steroid biosynthetic pathways in the adrenal cortex.

There is marked similarity between the synthetic capacities of the zona reticularis and that of the ovarian theca cells. Sulfotransferase 2A1 is uniquely expressed in the zona reticularis and rapidly converts DHEA to DHEAS. Whereas the 3 beta hydroxysteroid dehydrogenase enzyme (3βHSD) which converts DHEA to androstenedione is low in activity. Therefore, the main androgen product in the adrenals is DHEAS and not the sex hormones. But there exists a unique expression of cytochrome *b*5 which acts a cofactor enhancing the 17,20-lyase activity contributing to the small amount of sex hormone production in the adrenals. Insulin also stimulates the activities of 17,20-lyase [10].

ADAM AND EVE THEORY

In small antral follicles, theca cells produce androgens in response to LH. But granulosa cells do not do so because they do not express cytochrome P450c17A1, which to reiterate, possesses the activities of 17-hydroxylase and 17,20-lyase. Androgens diffuse from theca cells to granulosa cells. In the presence of FSH, when the follicle is destined is mature, the androgen is converted to estrogen by aromatase. This enzyme is encoded by the gene CYP19A1.

HOMOLOGOUS DESENSITIZATION TO LH

The expression of theca steroidogenic enzymes depends upon LH stimulation in a dose-response relationship. However, as LH rises, desensitization of ovarian responses to LH begins. This occurs via recycling of LH receptors as seen in animal studies and in part via down regulation of 17,20-lyase activity. Thus, more of the precursor 17OHP is produced compared to the sex hormones. This is what usually occurs in normal ovaries. But insulin and IGF stop the normal desensitization process leading to increased 17,20-lyase activity. The reaction hence proceeds to excessive androgen production. Insulin was initially thought to act through IGF-1. But recent studies showed that it acts via its own insulin receptor [11].

ROLES OF INSULIN AND ANDROGEN IN FOLLICULOGENESIS

Normal thecal androgen production supports antral follicle growth and development. It first upregulates the granulosa cell expression of FSH receptors then augments the FSH induction of LH receptors on the granulosa cells. Granulosa cells become sensitized to both FSH and LH followed by luteinization. Insulin amplifies the luteinization process.

Androgen excess stimulates proliferation of small antral follicles causing follicle maturation arrest and premature luteinization of the granulosa cells, ultimately presenting with PCOM.

REGULATION OF PERIPHERAL ANDROGEN PRODUCTION

Peripheral formation of testosterone primarily occurs in liver, skin and fat. Skin and fat express 17 beta hydroxysteroid dehydrogenase 5 (17βHSD5) and P450aro (aromatase) required for the conversion of androstenedione to testosterone and estrone respectively. Adipose tissue is an important site for the generation of sex steroids and inflammatory enzymes. Insulin potentiates these activities by upregulating the gene expression of 17βHSD5. In the liver, insulin instead downregulates 17βHSD5 but potentiates 5 alpha reductase, thereby converting testosterone to the more potent dihydrotestosterone.

Sex hormone binding globulin (SHBG) of hepatic origin binds serum androgen and estrogen delivering them to target tissues and liver for clearance from circulation. Estrogen increases SHBG while androgen, obesity, insulin resistance, and hypothyroidism decrease SHBG [12, 13]. Monosaccharide excess itself, via inflammatory cytokine signals, mediates the SHBG response to obesity [13, 14].

THE HYPOTHESIS OF PCOS AS FUNCTIONAL OVARIAN HYPERANDROGENISM REVISITED [15]

Hyperandrogenism is the central mechanism in PCOS. Polycystic ovarian syndrome was hypothesized to result from functional ovarian hyperandrogenism (FOH) due to dysregulation of androgen secretion back in 1989 to 1995. This hypothesis was revisited subsequently by Rosenfield et al (2011). In their study, they functionally categorized PCOS patients according to whether the source of androgen excess is primarily the ovaries, adrenal glands, or both. Tests used were GnRH antigen test or HCG test, dexamethasone androgen suppression test (DAST), and ACTH test. The study measured the respective

androgen excess, namely 1) 17OHP 2) testosterone and 3) DHEA. Remember that 17OHP and testosterone predominantly come from the ovaries while DHEA is from the adrenal glands. The study concluded that the common denominator of the great majority (87%) of PCOS patients is FOH. Two-thirds of these 87% of PCOS cases have 17OHP hyperresponsiveness to GnRH antigen stimulation. Two-thirds of the remaining PCOS patients have FOH detectable by DAST in which testosterone remains elevated after suppression of adrenal androgen production. The remaining 13% of the PCOS subjects had negative results from both GnRH antigen test and DAST. They were then subjected to the ACTH test. Of the 13% PCOS patients, about 5% have isolated functional adrenal hyperandrogenism (FAH), which is DHEA excess. And the last 8% of the PCOS cases have mild symptoms and lack evidence of steroid secretory abnormalities. Most of these 10% are obese comprising the atypical group of PCOS patients.

Table 3. Functional Classification of PCOS According to Source of Androgen Excess

PCOS Functional Type	Source of Androgen	GnRHag Test 17OHP Response	DAST Testosterone Response	ACTH test DHEA Response	Prevalence Among PCOS
PCOS-T	Primary FOH (typical FOH)	High[a]	High in 92.5%	High in 28% (associated FAH)	67%[b]
PCOS-A	Primary FOH (atypical FOH)	Normal[a]	High	High in 30% (associated FAH)	20%
	Primary FAH (isolated FAH)	Normal	Normal	High	5%
	PCOS without FOH or FAH (PCOS-A of obesity or idiopathic PCOS-A)	Normal	Normal	Normal	8%

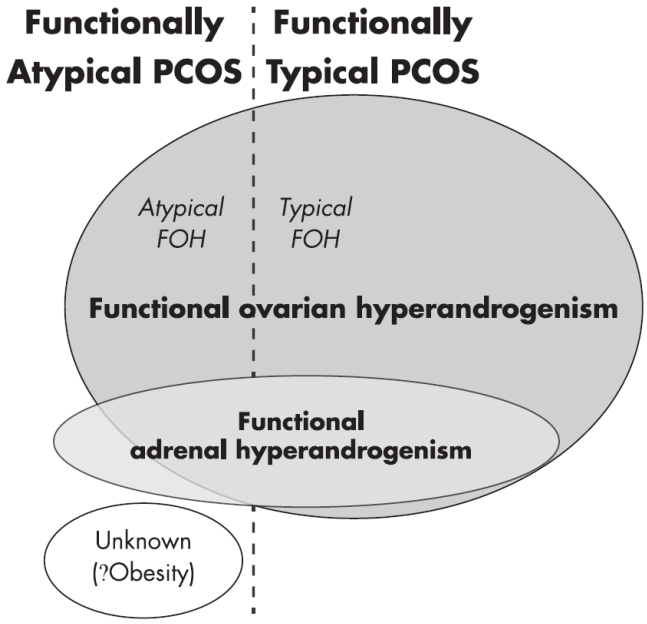

Figure 4. Relationship among sources of androgens in PCOS.

Theca cells from polycystic ovaries of classic PCOS patients are likewise subjected to long term in vitro cell culture, showing an intrinsic steroidogenic dysregulation typical of FOH. These cells overexpress most steroidogenic enzymes, particularly CYP450c17A1. On genetic screening using GWAS (Genome Wide Association Screening), an overexpression of DENND1A.V2 was identified to be located on the cell surface receptor site of theca cells. Stimulation of this protein produces characteristic PCOS phenotype. This enzyme is allegedly involved in protein trafficking, endocytotic processes, and receptor recycling

[16]. This study, though small and not randomized, tried to tell us that the fundamental defect in most PCOS patients is FOH which is an otherwise unexplained unique type of steroidogenic hyperactivity that disrupts the normal intraovarian hormonal function.

RELATIONSHIP OF METABOLIC DISORDERS TO PCOS

Metabolic syndrome is described as a cluster of hyperglycemia, central obesity, hypertension and dyslipidemia. It ordinarily results from the interaction of insulin resistance and obesity. Half of the adult PCOS have metabolic syndrome [17, 18, 19, 20, 21]. In 1/3 to 2/3 of PCOS cases, only obesity and insulin resistance are reported. Not only is insulin resistance common in PCOS, it is often in excess relative to the degree of adiposity. But insulin resistance is also found in non-obese PCOS women [22, 23, 24, 25, 26, 27]. Either it occurs intrinsically or acquired through exogenous obesity. The mechanism involves constitutive, very tissue specific post binding defects in receptor signaling. Intracellular serine kinases, instead of tyrosine kinases, account for the phosphorylation of the insulin receptors. This decreases the normal activation of the phosphatidyl inositol-3 kinase signaling pathway. Two main consequences occur in the absence of this pathway – 1) no glucose uptake into the skeletal and adipose tissues except visceral fat, 2) increased steroidogenesis in ovaries and adrenals via upregulation of the 17,20-lyase activity of CYP450c17 [23, 25, 27].

INSULIN RESISTANCE AND ADIPOST TISSUE BIOLOGY

Insulin stimulates adipogenesis, lipogenesis and inhibits lipolysis [28, 29, 30]. Studies on adipocytes from women with PCOS revealed impaired insulin sensitivity and reduced glucose transport which is the first step in lipogenesis [30, 31, 32, 33]. But in the visceral adipocyte lineage, this intrinsic defect is not present. Glucose can still enter and lipogenesis occurs. However, testosterone from ovarian, adrenal and peripheral sources causes impaired sensitivity of glucose transport to insulin in both abdominal and visceral adipocytes [23, 34, 35, 36, 37]. This data shows that there is a local negative feedback regulatory loop for visceral adipogenesis wherein the androgen formed by these adipocytes impairs the insulin-stimulated lipogenesis.

About half of the PCOS women have an abnormal degree of insulin resistance, selectively affecting tissue-specific metabolic but not mitogenic or steroidogenic insulin actions. The compensatory insulin-resistant hyperinsulinemia sensitizes ovarian theca cells to secrete androgen in response to LH and seems to have a similar effect on the adrenal androgenic response to ACTH. Insulin resistance is thus an aggravating factor in PCOS pathogenesis. The lipogenetic activity also contributes to the obesity of PCOS.

OBESITY AND PCOS

PCOS is the most common obesity related endocrine syndrome in females. One third or more of natural weight women with PCOS have abdominal obesity whereas obese PCOS women accumulate fat globally. Obesity plays roles in PCOS via insulin resistance and by generating testosterone from circulating androstenedione while suppressing gonadotropin production and decreasing SHBG.

Visceral fat contributes more to insulin resistance than abdominal wall fat. Catecholamines increase lipolysis in visceral fat. Free fatty acids from lipolysis are lipotoxic to the liver, thereby enhancing hepatic insulin resistance.

Proinflammatory cytokines arising from mononuclear cells (MNC) of adipose tissues mediate insulin resistance in PCOS. Androgens increase this inflammatory response after glucose and saturated fat ingestion [38, 39, 40, 41]. Abdominal adipocyte hypertrophy also triggers this inflammatory response [29].

Obesity is associated with suppression of serum gonadotropins independently of insulin resistance. The decreased gonadotropin secretion affects the follicular function. The accelerated metabolism of LH through sulfonation is the proposed mechanism [42].

Lastly, obesity itself can account for excess peripheral fat formation of testosterone independent of PCOS. But insulin also aggravates this by upregulating the enzyme 17βHSD-5 which converts androstenedione to testosterone.

SUMMARY

Polycystic ovarian syndrome is a heterogenous endocrine disorder characterized by oligo or anovulation, hyperandrogenism, and polycystic ovaries. There are four different phenotypes of PCOS but all have hyperandrogenism as their central etiology. Hyperandrogenism can be congenital or acquired and can arise from four different causes – abnormal HPO axis, fetal programming disturbances, insulin resistance, and obesity. Androgens may be exogenously supplied, produced by steroidogenic organs, or peripherally converted from fat. The key players in increasing circulating androgens include enzymes 17α hydroxylase, 17,20-lyase, 17βHSD5, and the SHBG protein. Androgen excess causes maturation arrest of the small antral follicles and premature luteinization of the granulosa cells, conferring the PCOM features and anovulation.

Rosenfield et al (2016) hypothesized that majority of the PCOS cases have functional ovarian hyperandrogenism as a result of dysregulated steroidogenesis. But more importantly, management of PCOS necessitates the understanding of the roles of insulin resistance and obesity in the pathogenesis of PCOS.

Insulin resistance can result from obesity or from an intrinsic defect in the phosphatidyl inositol-3 signaling pathway. This insulin resistance causes a compensatory hyperinsulinemia. Insulin then leads to hyperandrogenism by 1) upregulating 17,20-lyase activity 2) decreasing SHBG 3) sensitizing ovarian theca cells to secrete androgens in response to LH and 4) upregulating 17βHSD5 activity. Insulin also has an adipogenetic, lipogenetic property thereby contributing to obesity. Obesity, especially visceral fat, in turn promotes insulin resistance. This is aggravated by the inflammatory cytokines in the mononuclear cells of adipocytes. Other roles of obesity in PCOS include independent suppression of serum gonadotropins, and excess peripheral fat testosterone formation, and decreased SHBG.

In conclusion, this lecture highlights the magnitude of the involvement of obesity and insulin resistance in hyperandrogenism and PCOS. With this understanding, we can effectively justify proper diet and lifestyle modification as key approaches in the management of PCOS. We must then urge patients to eat

healthy, avoid food high in sugar and fat content, and engage in regular physical activities. The purpose of this lecture is to aid us physicians in properly guiding our patients as they face their PCOS condition. I hope we were able to achieve that today. Thank you and have a good day ahead.

REFERENCES

[1] Sirmans, S., & Pate, K. (2013). Epidemiology, diagnosis, and management of polycystic ovary syndrome. *Clinical Epidemiology*, 1. doi:10.2147/clep.s37559

[2] American College of Obstetricians and Gynecologists (2018). Polycystic ovary syndrome. ACOG Practice Bulletin No. 194. *Obstet Gynecol, 131,* e157-71

[3] Johnson, T., Kaplan, L., Ouyang, P., Rizza, R. (2013). National Institutes of Health evidence-based methodology workshop on polycystic ovary syndrome (PCOS). *NIH EbMW Report,* 1-14.

[4] Shaaban, Z., Khoradmehr, A., Jafarzadeh Shirazi, M.R., Tamadon, A. (2019). Pathophysiological mechanisms of gonadotropins– and steroid hormones–related genes in etiology of polycystic ovary syndrome. *Iran J Basic Med Sci*, *22*, 3-16. doi: 10.22038/ijbms.2018.31776.7646

[5] Ubuka, T., Morgan, K., Pawson, A. J., Osugi, T., Chowdhury, V. S., Minakata, H., … Bentley, G. E. (2009). Identification of Human GnIH Homologs, RFRP-1 and RFRP-3, and the Cognate Receptor, GPR147 in the Human Hypothalamic Pituitary Axis. *PLoS ONE*, *4*(12), e8400. doi:10.1371/journal.pone.0008400

[6] Nestler, J. E. (1987). Modulation of Aromatase and P450 Cholesterol Side-Chain Cleavage Enzyme Activities of Human Placental Cytotrophoblasts by Insulin and Insulin-Like Growth Factor I*. *Endocrinology*, *121*(5), 1845-1852. doi:10.1210/endo-121-5-1845

[7] Sir-Petermann, T. (2002). Maternal serum androgens in pregnant women with polycystic ovarian syndrome: possible implications in prenatal androgenization. *Human Reproduction*, *17*(10), 2573-2579. doi:10.1093/humrep/17.10.2573

[8] Fenichel, P., Rougier, C., Hieronimus, S., & Chevalier, N. (2017). Which origin for polycystic ovaries syndrome: Genetic, environmental or both? *Annales d'Endocrinologie*, *78*(3), 176-185. doi:10.1016/j.ando.2017.04.024

[9] Ehrmann, D. A. (1995). Polycystic ovary syndrome as a form of functional ovarian hyperandrogenism due to dysregulation of androgen secretion. *Endocrine Reviews*, *16*(3), 322-353. doi:10.1210/er.16.3.322

[10] Rosenfield, R. L. (2007). Identifying Children at Risk for Polycystic Ovary Syndrome. *The Journal of Clinical Endocrinology & Metabolism*, *92*(3), 787-796. doi:10.1210/jc.2006-2012

[11] Munir, I., Yen, H., Geller, D. H., Torbati, D., Bierden, R. M., Weitsman, S. R., … Magoffin, D. A. (2004). Insulin Augmentation of 17α-Hydroxylase Activity Is Mediated by Phosphatidyl Inositol 3-Kinase But Not Extracellular Signal-Regulated Kinase-1/2 in Human Ovarian Theca Cells. *Endocrinology*, *145*(1), 175-183. doi:10.1210/en.2003-0329

[12] Rosenfield, R. L., Moll, G.W. (1983). The role of proteins in the distribution of plasma androgens and estradiol. In: Molinatti, G., Martini, L., James, V., eds. *Androgenization in Women*. New York, NY: Raven Press; 25-45

[13] Pugeat, M., Nader, N., Hogeveen, K., Raverot, G., Déchaud, H., & Grenot, C. (2010). Sex hormone-binding globulin gene expression in the liver: Drugs and the metabolic syndrome. *Molecular and Cellular Endocrinology*, *316*(1), 53-59. doi:10.1016/j.mce.2009.09.020

[14] Simo, R., Barbosa-Desongles, A., Lecube, A., Hernandez, C., & Selva, D. M. (2011). Potential Role of Tumor Necrosis Factor- in Downregulating Sex Hormone-Binding Globulin. *Diabetes*, *61*(2), 372-382. doi:10.2337/db11-0727

[15] Rosenfield, R. L., & Ehrmann, D. A. (2016). The Pathogenesis of Polycystic Ovary Syndrome (PCOS): The Hypothesis of PCOS as Functional Ovarian Hyperandrogenism Revisited. *Endocrine Reviews*, *37*(5), 467-520. doi:10.1210/er.2015-1104

[16] McAllister, J. M., Legro, R. S., Modi, B. P., & Strauss, J. F. (2015). Functional Genomics of PCOS. *Obstetrical & Gynecological Survey*, *70*(9), 573-574. doi:10.1097/01.ogx.0000471341.33429.55
[17] Apridonidze, T., Essah, P. A., Iuorno, M. J., & Nestler, J. E. (2005). Prevalence and Characteristics of the Metabolic Syndrome in Women With Polycystic Ovary Syndrome. *Obstetrical & Gynecological Survey*, *60*(9), 589-591. doi:10.1097/01.ogx.0000175799.50780.34
[18] Coviello, A. D., Legro, R. S., & Dunaif, A. (2006). Adolescent Girls with Polycystic Ovary Syndrome Have an Increased Risk of the Metabolic Syndrome Associated with Increasing Androgen Levels Independent of Obesity and Insulin Resistance. *The Journal of Clinical Endocrinology & Metabolism*, *91*(2), 492-497. doi:10.1210/jc.2005-1666
[19] Leibel, N. I., Baumann, E. E., Kocherginsky, M., & Rosenfield, R. L. (2006). Relationship of Adolescent Polycystic Ovary Syndrome to Parental Metabolic Syndrome. *The Journal of Clinical Endocrinology & Metabolism*, *91*(4), 1275-1283. doi:10.1210/jc.2005-1707
[20] Nandalike, K., Agarwal, C., Coupey, S., Sin, S., Rajpathak, S., & Arens, R. (2010). Screening For Sleep Disordered Breathing And Excessive Daytime Sleepiness in Adolescent Girls With Polycystic Ovarian Syndrome. *D74. CLINICAL PRESENTATION AND EPIDEMIOLOGY OF SLEEP DISORDERED BREATHING*. doi:10.1164/ajrccm-conference.2010.181.1_meetingabstracts.a6554
[21] Rossi, B., Sukalich, S., Droz, J., Griffin, A., Cook, S., Blumkin, A., … Hoeger, K. M. (2008). Prevalence of Metabolic Syndrome and Related Characteristics in Obese Adolescents with and without Polycystic Ovary Syndrome. *The Journal of Clinical Endocrinology & Metabolism*, *93*(12), 4780-4786. doi:10.1210/jc.2008-1198
[22] Dunaif, A., Segal, K. R., Futterweit, W., & Dobrjansky, A. (1989). Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. *Diabetes*, *38*(9), 1165-1174. doi:10.2337/diabetes.38.9.1165
[23] Ciaraldi, T. P., Aroda, V., Mudaliar, S., Chang, R. J., & Henry, R. R. (2009). Polycystic Ovary Syndrome Is Associated with Tissue-Specific Differences in Insulin Resistance. *The Journal of Clinical Endocrinology & Metabolism*, *94*(1), 157-163. doi:10.1210/jc.2008-1492
[24] Rosenfield, R. L. (2001). Polycystic ovary syndrome and insulin-resistant hyperinsulinemia. *Journal of the American Academy of Dermatology*, *45*(3), S95-S104. doi:10.1067/mjd.2001.117430
[25] Diamanti-Kandarakis, E., & Dunaif, A. (2012). Insulin Resistance and the Polycystic Ovary Syndrome Revisited: An Update on Mechanisms and Implications. *Endocrine Reviews*, *33*(6), 981-1030. doi:10.1210/er.2011-1034
[26] Lewy, V. D., Danadian, K., Witchel, S. F., & Arslanian, S. (2001). Early metabolic abnormalities in adolescent girls with polycystic ovarian syndrome. *The Journal of Pediatrics*, *138*(1), 38-44. doi:10.1067/mpd.2001.109603
[27] Poretsky, L. (2001). Phosphatidyl-Inositol-3 Kinase-Independent Insulin Action Pathway(s) in the Human Ovary. *Journal of Clinical Endocrinology & Metabolism*, *86*(7), 3115-3119. doi:10.1210/jc.86.7.3115
[28] Kahn, C. R. (2003). Knockout Mice Challenge our Concepts of Glucose Homeostasis and the Pathogenesis of Diabetes. *Experimental Diabesity Research*, *4*(3), 169-182. doi:10.1155/edr.2003.169
[29] Rosen, E., & Spiegelman, B. (2014). What We Talk About When We Talk About Fat. *Cell*, *156*(1-2), 20-44. doi:10.1016/j.cell.2013.12.012
[30] Ciaraldi, T. P. (1992). Cellular mechanisms of insulin resistance in polycystic ovarian syndrome. *Journal of Clinical Endocrinology & Metabolism*, *75*(2), 577-583. doi:10.1210/jc.75.2.577
[31] Dunaif, A., Segal, K. R., Shelley, D. R., Green, G., Dobrjansky, A., & Licholai, T. (1992). Evidence for distinctive and intrinsic defects in insulin action in polycystic ovary syndrome. *Diabetes*, *41*(10), 1257-1266. doi:10.2337/diabetes.41.10.1257

[32] Ciaraldi, T. P. (1997). Cellular Insulin Resistance in Adipocytes from Obese Polycystic Ovary Syndrome Subjects Involves Adenosine Modulation of Insulin Sensitivity. *Journal of Clinical Endocrinology & Metabolism*, *82*(5), 1421-1425. doi:10.1210/jc.82.5.1421
[33] Marsden, P. J., Murdoch, A., & Taylor, R. (1994). Severe impairment of insulin action in adipocytes from amenorrheic subjects with polycystic ovary syndrome. *Metabolism*, *43*(12), 1536-1542. doi:10.1016/0026-0495(94)90013-2
[34] Corbould, A., & Dunaif, A. (2007). The adipose cell lineage is not intrinsically insulin resistant in polycystic ovary syndrome. *Metabolism*, *56*(5), 716-722. doi:10.1016/j.metabol.2006.12.021
[35] Corbould, A. (2007). Chronic testosterone treatment induces selective insulin resistance in subcutaneous adipocytes of women. *Journal of Endocrinology*, *192*(3), 585-594. doi:10.1677/joe.1.07070
[36] Corbould, A. (2008). Effects of androgens on insulin action in women: is androgen excess a component of female metabolic syndrome? *Diabetes/Metabolism Research and Reviews*, *24*(7), 520-532. doi:10.1002/dmrr.872
[37] Varlamov, O., White, A. E., Carroll, J. M., Bethea, C. L., Reddy, A., Slayden, O., … Roberts, C. T. (2012). Androgen Effects on Adipose Tissue Architecture and Function in Nonhuman Primates. *Endocrinology*, *153*(7), 3100-3110. doi:10.1210/en.2011-2111
[38] González, F. (2015). Nutrient-Induced Inflammation in Polycystic Ovary Syndrome: Role in the Development of Metabolic Aberration and Ovarian Dysfunction. *Seminars in Reproductive Medicine*, *33*(04), 276-286. doi:10.1055/s-0035-1554918
[39] González, F., Sia, C. L., Shepard, M. K., Rote, N. S., & Minium, J. (2014). The Altered Mononuclear Cell-Derived Cytokine Response to Glucose Ingestion Is Not Regulated by Excess Adiposity in Polycystic Ovary Syndrome. *The Journal of Clinical Endocrinology & Metabolism*, *99*(11), E2244-E2251. doi:10.1210/jc.2014-2046
[40] Shorakae, S., Teede, H., De Courten, B., Lambert, G., Boyle, J., & Moran, L. (2015). The Emerging Role of Chronic Low-Grade Inflammation in the Pathophysiology of Polycystic Ovary Syndrome. *Seminars in Reproductive Medicine*, *33*(04), 257-269. doi:10.1055/s-0035-1556568
[41] González, F., Sia, C. L., Bearson, D. M., & Blair, H. E. (2014). Hyperandrogenism Induces a Proinflammatory TNFα Response to Glucose Ingestion in a Receptor-Dependent Fashion. *The Journal of Clinical Endocrinology & Metabolism*, *99*(5), E848-E854. doi:10.1210/jc.2013-4109
[42] Wide, L., Eriksson, K., Sluss, P. M., & Hall, J. E. (2009). Serum Half-Life of Pituitary Gonadotropins Is Decreased by Sulfonation and Increased by Sialylation in Women. *The Journal of Clinical Endocrinology & Metabolism*, *94*(3), 958-964. doi:10.1210/jc.2008-2070