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Pathogenesis and Signaling Cascade Pathways in Polycystic Ovary Syndrome with Concern to Insulin Resistance and Hyperandrogenism

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Bhavik Gala[3], Vaishnavi Tanwade*[3], Ankita Dudhal[1], Aniket Narayankar[2]

3 B.pharm, Dr.D.Y. Patil College of Pharmacy, Akurdi. Maharashtra, India.

1 Assistant professor in pharmacology, Dr. D. Y. Patil College of Pharmacy, Akurdi, Maharashtra, India.

2 Assistant professor in pharmacology, Dr.Ashok Gujar College of Pharmacy, Solapur. Maharashtra, India.

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder characterized by hyperandrogenism and chronic anovulation. PCOS patients show a wide range of signs and symptoms and it is difficult to diagnose. Diagnostic Workups include hormonal evaluation of androgen level ultrasonographic examination of follicles. Insulin resistance is only seen in obese women with PCOS. PCOS is a unique dysfunction characterized by dehydroepiandrosterone sulfate (DHEA) hyperresponsiveness and hypersensitivity to Adrenocorticotropic hormone (ADH) exposure. Insulin infusion results in the potentiation of 17 alpha-hydroxylase and 17/20 lyase activity respectively to ACTH. Free Fatty acid overload has been implicated in hyperandrogenism. Increased cortisol is due to elevated 5 alpha RD have suggested eliciting ACTH hypersecretion. Dimethyl diguanide (DMBG) is frequently used to treat PCOS-afflicted women's reproductive problems. Forced over-expression of DENND1A.V2 in PCOS theca cells resulted in a PCOS phenotype of augmented CYP17A1 and CYP11A1 gene expression mRNA abundance. DMBG is an insulin-sensitizing drug for type 2 diabetics to regulate their blood sugar levels. In the endometrium of PCOS women, DMBG raises the concentration of a molecule that controls the expression of the insulin-dependent glucose transporter GLUT4. Insulin-induced testosterone production in theca cells is mediated through the insulin receptor substrate activating the CAMP pathway, which involves CYP17A1 and 17-alpha hydroxylase. YAP knockdown decreased FAH-induced aromatase and proposed a potential hyperandrogenic pathway.

INTRODUCTION

PCOS [Polycystic ovarian syndrome/disorder] is a heterogeneous disorder characterized by hyperandrogenism and chronic anovulation. PCOS patients show a wide range of signs and symptoms which make it difficult to diagnose.

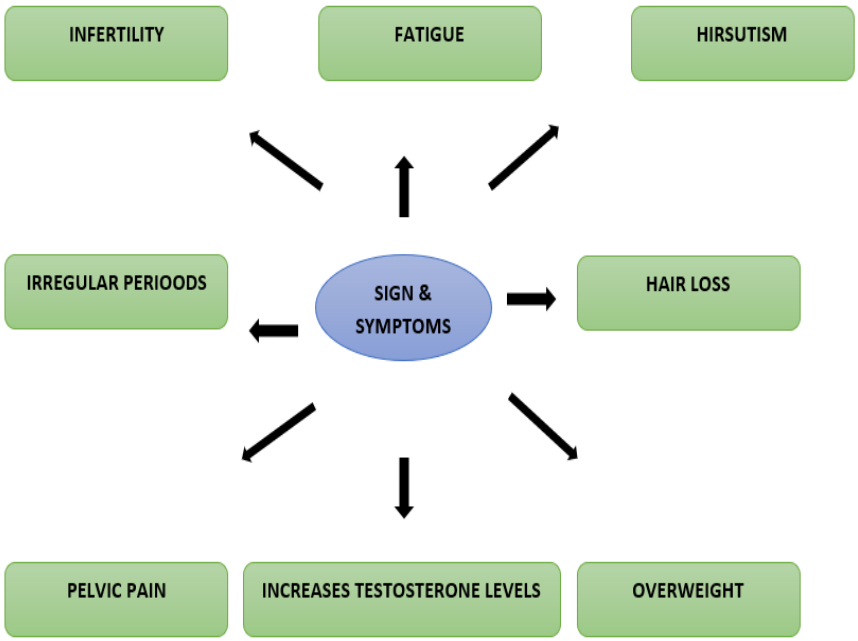

Figure no 1: Signs and Symptoms of PCOS/PCOD.[23]

Polycystic ovary syndrome (PCOS) is a prevalent, complex endocrine disorder characterized by polycystic ovaries, chronic anovulation, and hyperandrogenism leading to symptoms of irregular menstrual cycles, acne, and infertility.it is not reversed by the medication as compared to PCOD.

The World Health Organization (WHO) data suggests that approximately 116 million women (3.4%) are affected by PCOS globally. The data on the prevalence of PCOS in India are scarce. An estimated one in five (20%) Indian women suffer from PCOS. Between 5% and 10% of women between 15 and 44 years.[23]

Here are some signs and symptoms of PCOS.PCOS can cause missed or irregular menstrual periods, excess hair growth, acne, infertility, and weight gain.PCOS is not easily detectable. Its sign and symptoms also do not get recognized. Women with PCOS are more likely to develop certain serious health problems. These include type 2 diabetes, high blood pressure,

problems with the heart and blood vessels, and uterine cancer. Women with PCOS often have problems with their ability to get pregnant (fertility).[1-4]

PATHOGENESIS:

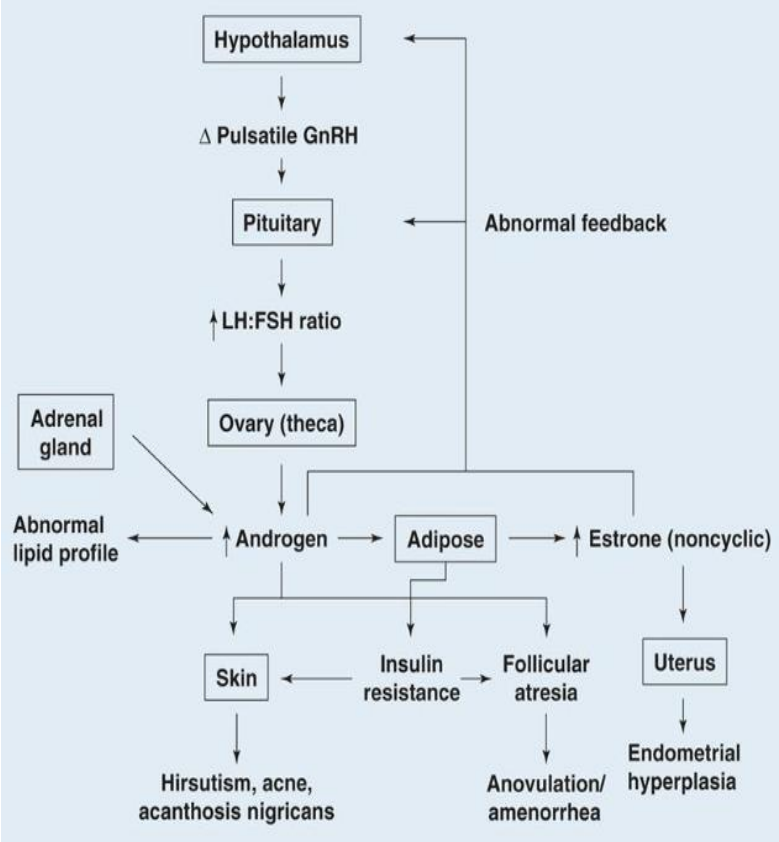

Figure no 2: Schematic Representation of PCOS PATHOGENESIS [4]

The pathogenesis of polycystic ovary syndrome (PCOS) is not precisely known. Several mechanisms have been suggested to play a role in the pathogenesis of PCOS, including hormonal imbalance, insulin resistance, and genetic inheritance.[5,6,15.]

INSULIN RESISTANCE

The disabled response of the body to insulin is insulin resistance. Insulin resistance and hyperinosemia are major features of women with PCOS. Impaired insulin leads to a drop in two protein binding factors growth factor binding protein (IGFBP1) and sex hormone binding globulin (SHBG). IGFBP binds to IGF1 and IGF2 [7]. Hyperinosemia leads to ovarian growth and conformation of ovarian excrescences.

Women frequently witness PCOS (hirsutism, acne, and alopecia), irregulate menstrual cycles, and biochemical differences associated with elevated testosterone situations, advanced

dehydroepiandrosterone (DHEA), androstenedione (ASD), reduced SHBG, and the Binding Protein Insulin Related Growth Factor (IGFBP). These changes are linked to insulin and hyperinsulinemia resistance.

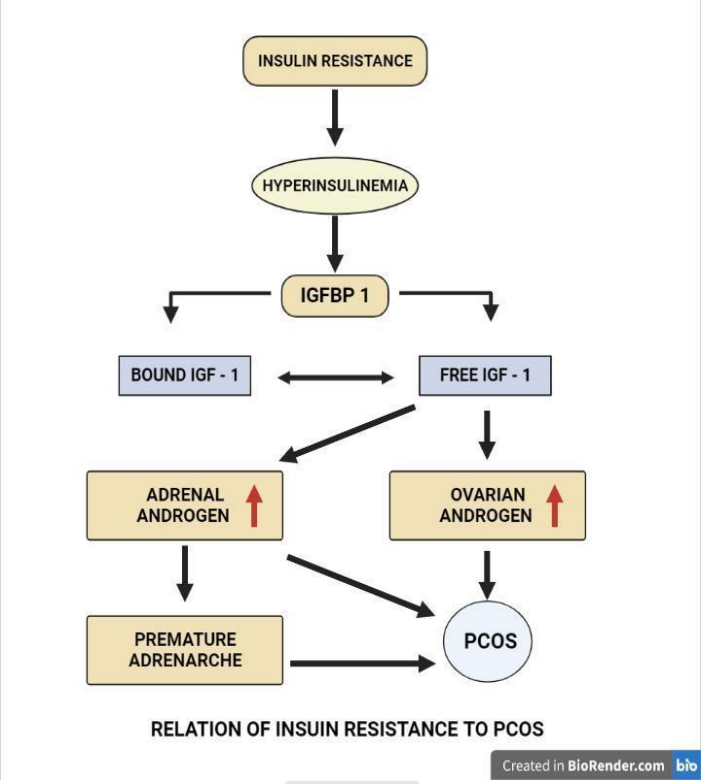

Figure no 3: Relation of Resistance to PCOS[8]

The action of insulin on the ovary through IGF-1 receptor. The action of insulin on the ovary uses inositol glycol, activated by phosphorylation of a receptor at tyrosine level in the tissue. Insulin stimulates theca cell proliferation, increased secretion of androgen, and increased cytochrome p450 expression of LH and IGF -1 receptor.[8]

Excess androgens increase the expression of lipolytic β3-adrenergic receptors on visceral adipose tissue (VAT) [14] which favors the release of free fatty acids (FFA) contributing to insulin resistance and hepatic gluconeogenesis leading to a prediabetes/insulin-resistant state. An MTNR1B mutation can delay the conflation of insulin and produce rapid levels of blood glucose. Hepatic insulin resistance, defined as increased post-absorptive glucose conflation and dropped perceptivity to insulin-intermediated inhibition of endogenous glucose production, is only seen in obese women with PCOS when compared to healthy women of equivalent body weight.[9,20]

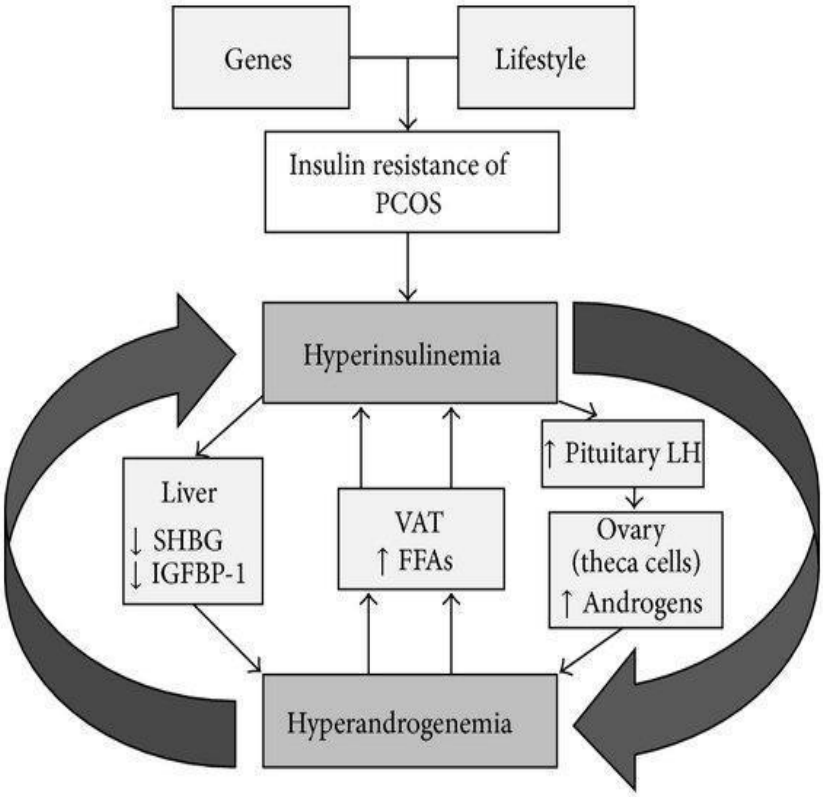

Figure 4: The Vicious Cycle Between Hyperinsulinemia and Hyperandrogenemia Underlying PCOS Development[24]

HYPERANDROGENISM:

Women with PCOS have elevated levels of LH/FSH ratio. High levels of LH then reduced the production of FSH. GnRH causes an increased level of production of LH. Role of FSH is to recruit ovarian follicles and stimulate growth [2-5] mm follicles whereas a large one [6-8] increases E2 and inhibits B in a normal person. People with PCOS have accumulated antral follicles that differentiate early and undergo premature growth arrest. [22,23]

LH also activates premature meiotic processes, damaged oocyte quality, and altered opioid tone found in these patients. Kisspeptin excitatory element is an important regulator of GnRH neurons which helps in production such as brain sex differentiation, puberty onset, ovulation, and gonadotropin secretion.[25]

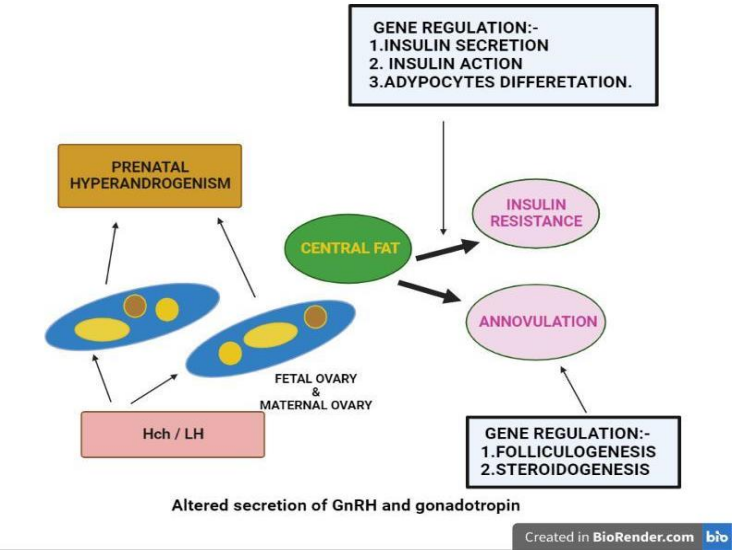

Figure no 5: Altered Secretion of GnRH and Gonadotropin[22]

Functional adrenal hyperandrogenism (FAH) coexists with functional ovarian hyperandrogenism (FOH).

Functional adrenal hyperandrogenism (FAH) in PCOS is a unique dysfunction characterized by dehydroepiandrosterone sulfate (DHEA) hyperresponsiveness and hypersensitivity to Adrenocorticotropic Hormone (ACTH) of DHCA. ACTH stimulation elicits selective Dehydroepiandrosterone (DHEA) and Human placental lactogen (17-HPL) hyper response in PCOS persons. Border-specific stereogenic abnormalities concerning high dose ACTH relative possible by PCOS patients have increased capacity of abnormal secretion.[11,12]

FAH is reflected in high Dehydroepiandrosterone sulfate (DFAS) levels attributed to exaggerated adrenalin. Stereogenic Functional Adrenal Hyperandrogenism (FAH) concerning Adrenocorticotropic Hormone (ACTH) connect with 17-20 lyase hyperactivity and overactivity of early enzymatic step common to adrenal zona reticularis and ovarian steroidogenesis.

DENN Domain Containing 1A is expressed in zona reticularis and theca cells.[13]

Insulin infusion results in the potentiation of 17 alpha-hydroxylase and 17/20 lyase activity respectively to ACTH. Free Fatty acid overload has been implicated in hyperandrogenism.[25]

Intra-adrenal end-product inhibition of 3-Beta–hydroxysteroid dehydrogenase (3BHD) activity by cortisol might play a role in increasing adrenocortical DHEA secretion.

Increased cortisol is due to elevated 5 alpha RD have suggested eliciting ACTH hypersecretion which maintains cortisol level.[10,11,12]

ANDROGEN IS CALCULATED BY THE FORMULA:

$$FAI = [TT/SHBG]\ 100$$

Where,

FAI= free androgen index

TT= total testosterone

SHBG= sex hormone binding globulin.

Synthesis of androgen done by microsomal P450e17 which catalyzes 17-20 lyase activity. Women with PCOS show inhibition of 17-20 lyase activity. Administration of GnRH in PCOS women increases 17-20%.[16,17,19.]

MUTUAL ACT OF IR AND HA ON OVARIES AND ADRENAL GLANDS:

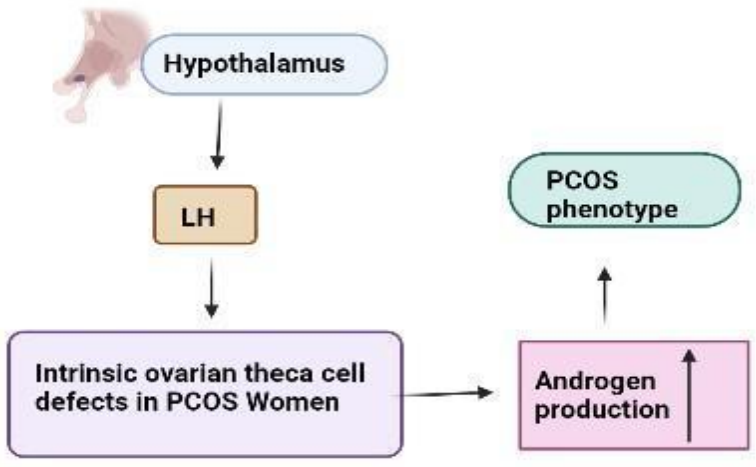

Figure no 6: Mutual Act of IR and HA on Ovaries and Adrenal Glands [14]

The ca cell defect accounts for excess androgen production stereogenic secretory pattern. The ca cell over-expresses most steroidogenic enzymes, particularly P450C17 and LH receptors.

Theca cell presents in follicles of polycystic ovaries of women, basal, CAMP, stimulated pregnenolone, progesterone, DHEA metabolism increased in PCOS theca cell.

CAMP stimulated CYP11A, CYP17A1 expresses augmented in PCOS theca cell. DENN1A encodes proteins associated with Claritin-coated pits. Forced over-expression of DENND1A.V2 in normal theca cells resulted in PCOS phenotype of augmented CYP17A1 and CYP11A1 gene expression mRNA abundance, androgen bioassay. Urinary excretion of DENAP1A.V2 RNA in PCOS women increased as compared to normal women.[14]

SIGNALING PATHWAY IN PCOD

INTERRUPTED INSULIN SIGNALING PATHWAY:

Anovulation, insulin resistance, and defective insulin signaling are all clinical manifestations of PCOS that are directly related to increased androgen production. Western blotting was used to analyze the expression of PI3, insulin resistance substrate [IRS-2], and insulin signaling.

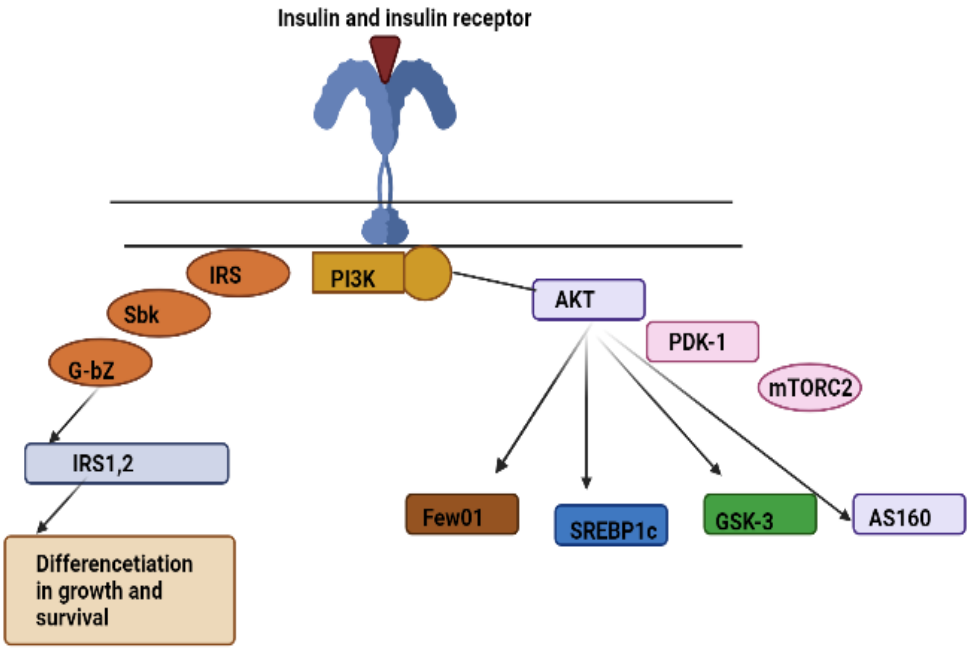

Figure no 7: Insulin Pathway with Errors in PCOS [20]

Dimethyl diguanide (DMBG) is frequently used to treat PCOS-afflicted women's reproductive problems.

As a result of DMBG therapy, the expression of IRS-2 and PI3K in PCOS ovarian cells increases. Additionally, PCOS-related ovary expression of PDK-1 and MTOR (mammalian target of rapamycin) declines. Protein kinase B1AK1 (PI3K) signaling is connected to the formation of follicles, androgen production, obesity, and insulin resistance.

Through its receptor and interaction with gonadotropin, insulin affects the ovary and controls steroidogenesis. Metabolic resistance to insulin action is impaired by the PI3K pathway, other functions are increased by the MAPK pathway, and insulin target tissues are affected.

Through its receptor and interaction with gonadotropin, insulin affects the ovary and controls steroidogenesis. Insulin resistance arises when the PI3K pathway, which is involved in metabolic resistance to insulin action, is weakened, when the MAPK pathway is increased, and when the ovary's insulin target tissue is present. Inhibition of PI3K in the ovary results in lessened downstream signal activation, which affects how insulin-induced glucose absorption is affected. Tyrosine residues are phosphorylated by insulin to form a bond with the insulin receptor. When PI3K and phosphorylated tyrosine on the IRS molecule interact, PI3, 4, and 5 diphosphates are phosphorylated to create PIP3, which activates PDK-1.

DMBG is an insulin-sensitizing drug for type 2 diabetics to regulate their blood sugar levels. In the endometrium of PCOS women, DMBG raises the concentration of a molecule that controls the expression of the insulin-dependent glucose transporter GLUT4.

PATHWAYS RESPONSIBLE FOR HYPERANDROGENISM

Cholesterol is created by theca cells in the ovary acting on l LH. The androgen is produced by this cholesterol. Women produce 5 different forms of androgen.

1.Dehydroepiandrosterone (DHEA)

2.sulphate of dehydroepiandrosterone (DHEAS)

3.Androstenedione-A4

4.Testosterone

5. Dihydrotestosterone (DHT)

Androgen is produced in PCOS in the manner listed below Pathway

1. GPCR/CAMP/PKA

2. PI3K/AKT Pathway

3. MARK

GPCR MECHANISM

Two different forms of GPCR have connected to the G protein-coupled receptor in the cell membrane stereognosis.

- The ACTH hormone stimulates steroidogenesis in the adrenal gland via the melanocortin 2 receptor (MCIR). By attaching to MC2R, this ACTH triggers the manufacture of androgen by generating cyclic adenosine monophosphate (CAMP) and activating protein kinase A (PKA).
- FSH /LH receptor

The FSH and LH hormones are produced by these receptors. Steroidism is mediated by FSH and LH via the CAMP pathway.

PI3K/AKT PATHWAY

Due to disruption in this route, the female has increased androgen production and ovarian dysfunction.

PI3K is linked to insulin resistance, adipocyte differentiation, and androgen production, all of which have a significant impact on PCOS.

Insulin-induced testosterone production in theca cells is mediated through the insulin receptor substrate activating the CAMP pathway, which involves CYP17A1 and 17-alpha hydroxylase.

MAPK SIGNALING PATHWAY

Three routes make up the mitogen-activated protein kinase pathway: MEK1/2/ERK1/2, P38 MAPKS, and Jun-N-terminal (JNK). These three sub-pathways are related to PCOS and are involved in the metabolism of androgen and estrogen.

Granulosa cells are impacted by PCOS and the consequent downregulation of phosphor-ERK1/2 leads to the generation of androgen. Low STAR expression in GC decreases ERK activation. By controlling 3BHSD2 and STAR, CAMP and ERk crosstalk enhances androgen production.

HIPPO SIGNALING PATHWAY

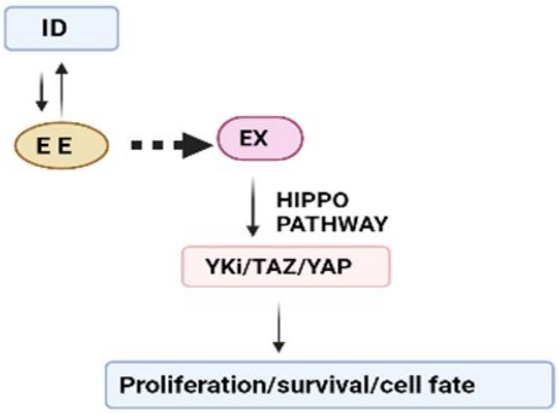

Figure no 8: Hippo Signaling Pathway[21]

According to evolution, mechanical tension brought on by an ovarian capsule that is thicker may be the cause of the folliculogenesis' stop. It appears that the ovary in PCOS loses the ability to control cellular proliferation and apoptosis, which may be related to the abnormal expression of the HIPPO pathway.[18,21.]

Compared to women without PCOS, PCOS women's ovaries are bigger. Granulosa cell tumor-affected ovaries express YAP more strongly. YAP knockdown decreased FAH-induced aromatase and proposed a potential hyperandrogenic pathway.

Steroidogenesis is regulated by the Hippo pathway in human granulosa cell tumor tissue. The hippo pathway and PCOS are related because PCOS is associated with a higher risk of insulin resistance.

To induce ovulation, metformin is used alone with certain estrogen receptor modifiers. The primary route cascade of insulin/IGF is regulated by YAP via PAK1 AKT signaling.

CONCLUSION

Epidemiological and preclinical research on humans suggests that several factors, including genetic, developmental, and epigenetic components, are implicated in the pathogenesis of PCOS.

It is commonly acknowledged that hyperandrogenism is the primary endocrine disturbance responsible for PCOS development and appearance.[24.]

According to the situation, early detection and treatment can stop PCOS's long-term effects.

Pharmacological treatments are used to treat PCOS-related metabolic problems. utilized TZP1 with metformin. GLP agonists, used alone or in combination with metabolic hormones, have the potential to treat PCOS and have qualities that reduce weight and have anti-diabetic effects.

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CONFLICT OF INTEREST:

The authors declare there is no conflict of interest.

ABBREVIATIONS

PCOS: - Polycystic Ovarian Disease

CVS: - Cardiovascular System

LH: - Luteinizing Hormone

FSH: - Follicle Stimulating Hormone

SHBG: - Sex hormone binding globulin

IGFBP: - Insulin-Like growth factor binding proteins

DHEA: - Dehydroepiandrosterone

ASD: - Androstenedione

VAT: - Visceral adipose tissue

FFA: - Free fatty acids

GnRH: - Gonadotropin-releasing hormone

FAH: - Functional adrenal hyperandrogenism

ACTH: - Adrenocorticotropic Hormone

CAMP: - Cyclic Adenosine Monophosphate

PDK: - Phosphoinositide-dependent kinase

MTOR: - Mammalian target of rapamycin

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