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A REVIEW ON CAUSES, PREVENTION, TREATMENT AND CONSEQUENCES OF POLYCYSTIC OVARIAN SYNDROME

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Abstract:
Polycystic ovary syndrome (PCOS), characterized by hormonal imbalance and ovarian dysfunction, often starts during adolescence. Inconsistent diagnostic criteria, variable provider knowledge, and lack of consensus pose specific challenges for the care of women with PCOS. These factors encourage inaccurate diagnosis with both under and over diagnosis. This unfavorable diagnostic experience exasperates affected women and limits timely opportunities for intervention to minimize associated comorbidities, especially during the transition from pediatric to adult care. Recognition of these issues in the care of adolescents and women with PCOS inspired the development of the International Evidence-Based PCOS Guidelines, which emphasize the prevention, screening, and treatment of PCOS across the reproductive lifespan [8]. Diabetes, cardiovascular disease and cancer are also at the forefront of any risk assessment or comprehensive treatment strategy for these women. Lifestyle modifications including dietary changes, increased exercise and weight loss are appropriate first line interventions for many women with PCOS. Pharmaceuticals including metformin, lipid lowering agents and oral contraceptives should be tailored to the individual's risk profile and treatment goals [2].

Key Words: *PCOS, anovulation, hormonal imbalance, obesity*

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INTRODUCTION:

Polycystic Ovary Syndrome (PCOS) is one of the most frequent conditions, which affects both metabolic and reproductive systems. PCOS is best known for irregular menstrual Cycles, chronic anovulation, and hyperandrogenism [1, 2]. According to the Rotterdam criteria, the prevalence of PCOS. Is 10%, while the prevalence of polycystic ovaries is 28% [3]. The pathogenesis of this disorder is not clear yet although it probably has epigenetic origins; therefore, there is no single Effective treatment available for this disease [4, 5]. Different pharmaceutical treatments have been proposed for PCOS. However, they have disadvantages, such as adverse effects, low compliance of patients with long-term pharmaceutical treatments, low efficacy, and contraindications. Therefore, complementary treatments can be proper alternatives [6–9]. Today, oral contraceptives are the most Common options for the treatment of PCOS. They act by decreasing free androgens in the blood and suppressing the secretion of gonadotropins [10]. Our review will address the potential associations and possible interventions for obesity, cancer, type II diabetes, and cardiovascular disease in the Setting of PCOS.

Obesity:

Obesity has reached epidemic proportions in the United States and clearly contributes to the Morbidity seen with PCOS. In the United States, upper body fat distribution is highly Predictive of poor health, particularly diabetes and cardiovascular disease.(Lord, 2006) Mainly caused in women with BMIs of < 25 in 80% And 56% of these women, respectively. Obesity Increases one's lifetime risk of cancer and cardiovascular disease [2].

Cancer:

An increased risk for endometrial, ovarian and breast cancer in women with PCOS has been suggested. Clearly it has been associated with an increased risk for breast and endometrial Cancer in population based studies. (Legro, Barnhart, 2007) It is important to note that many Confounders including obesity, hyperglycemia and anovulation (unopposed estrogen) with Resultant infertility make it difficult to define the absolute risk of these neoplasms attributed To PCOS alone[2].

Diabetes:

PCOS is commonly associated with glucose metabolism abnormalities and is an independent Risk factor for the development of diabetes. Impaired glucose tolerance, measured by oral Glucose tolerance test, may approach 30–40% in obese populations with PCOS. Progression of insulin resistance without hyperglycemia to glucose intolerance and ultimately diabetes is variable but may occur in athird of those Affected within 2 – 3 years and exceed 50% within 10 years [2].

Cardiovascular risk:

Cardiovascular disease (CVD) is a major concern for women with PCOS, but a clear cause And effect relationship has not been established, nor can anyone state if events are even Elevated in this group of women compared to others. Several CVD risk factors have been Associated with PCOS including insulin resistance, type 2 diabetes mellitus, and possibly Hypertension [2]

CLINICAL FEATURES / SIGN & SYMPTOMS:

- The complexity of this condition does not refer to its name, there are many other conditions that are associated with this problem. PCOS patients have numerous cyst 8 mm in size in the sac of their ovary [7]
- More than 12 cysts are present in the ovary. About 70% of females are infertile because of this condition. As Discussed above in PCOS condition, the level of male hormones i.e. Androgen elevated causes hirsutism and acne [7].
- There is an Insulin resistance which leads to obesity and Type 2 Diabetes. This Problem leads to an irregularity in the menstrual cycle that results in infertility [7].
- 20% of females often experienced sleep apnea. Depression and anxiety are common [7]

DIAGNOSIS OF PCOS:

The guidelines endorsed use of the Rotterdam PCOS Diagnostic Criteria in adult women . Importantly, PCOS is a diagnosis of exclusion. Other disorders with similar clinical features need to be excluded from diagnostic consideration. For adult women, the Rotterdam criteria required fulfilling two of three findings [8]:

Oligo-anovulation
Clinical and/or biochemical Hyperandrogenism
Polycystic ovary morphology on ultrasound.

When both ovulatory dysfunction and hyperandrogenism occur in the adult woman, ultrasound is not necessary for diagnosis. For the adolescent girl, diagnosis of PCOS requires both Ovulatory dysfunctions now clearly defined according to time post Menarche and persistent clinical or biochemical hyperandrogenism . Importantly, the guidelines advance the field by Highlighting that

ultrasound studies to assess for polycystic Morphology are not needed for this purpose until 8 years post Menarche due to a lack of sensitivity and specificityat this life stage [8].

- Clinical hyperandrogenism includes hirsutism and severe Acne. High-qualitytestosterone assays are essential to confirm Biochemical hyperandrogenism [8].
- Calculated free testosterone, free Androgen index, or calculated bioavailable testosterone can be used. Direct free testosterone assays should be avoided because these assays show poor sensitivity, reproducibility, and accuracy [8].
- Although commonly identified in affected women, obesity and Insulin resistance arenot diagnostic features. AMH, a member of the tumor growth factor-β family, is secreted by ovarian granulosa cells [8].
- The highest AMH secretion occurs, During the antral stage of folliculogenesis . Thisglycoprotein Hormone inhibits the transition of primordial to primary follicle; it Alsoinhibits follicle-stimulating hormone (FSH)-induced aromatase Expression impedingselection of a dominant follicle [8].
- Since serum AMH concentrations are elevated in women with PCOS, it has Been suggested that AMH concentrations could be used in place of ovarian ultrasound studies[8]
- However, at the present time, lack Of standardized assays and appropriate normativeranges Preclude the use of AMH for the diagnosis of PCOS in women Or adolescents[8]

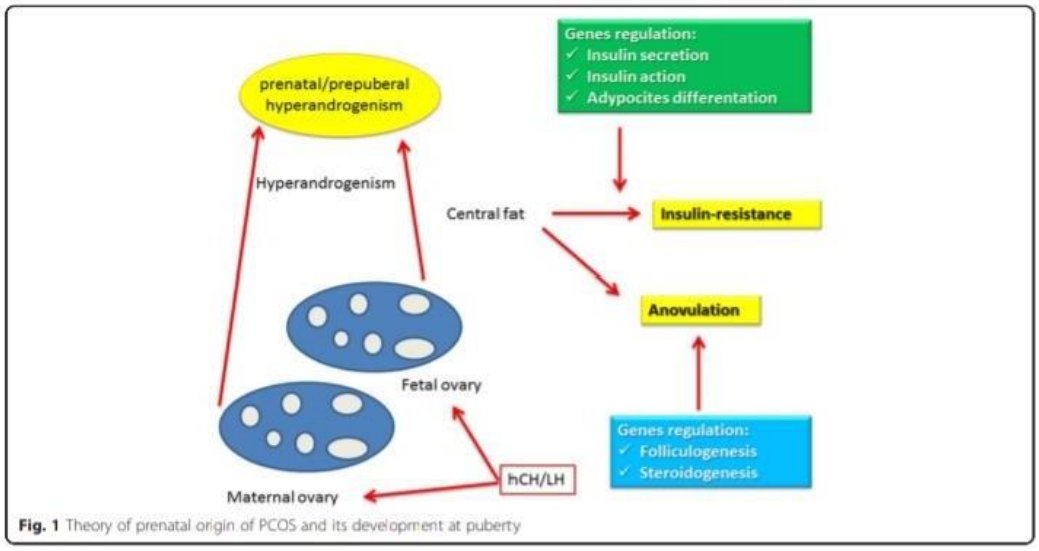

Fig. 1 Theory of prenatal origin of PCOS and its development at puberty

PCOS in the Adolescent….

- The Initial signs and symptoms of PCOS often emerge during adolescence.
- However, the diagnosis of PCOS in adolescent girls can be challenging because themajor clinical features, menstrual Irregularity, mild clinical hyperandrogenism, and polycystic ovary . Morphology, may be normal findings in adolescent girls during puberty.
- Pediatric, gynecologic, and adolescent medicine health care providers are thus confronted with the task of distinguishing features associated with normal maturationof the HPO axis.
- From early manifestations of a chronic health disorder. Other disorders associated withirregular menses and/or hyper androgenism also need to be excluded from diagnostic consideration.
- These disorders include Congenital Adrenal Hyperplasia, androgen-secreting tumors, Hyperprolactinemia, Thyroid dysfunction, Cushing's syndrome, Exogenous exposures, Lipodystrophy syndromes, and severe insulin resistance Syndromes [8].

DIAGNOSTIC CRITERIA FOR PCOS:

<u>Adult Diagnostic Criteria (Rotterdam)[8]</u>

Otherwise, unexplained alternative phenotypes [8]:

1. Phenotype 1 (classic PCOS)
   a) Clinical and/or biochemical evidence of hyperandrogenism
   b) Evidence of oligo-anovulation
   c) Ultrasonographic evidence of a polycystic ovary[8]
2. Phenotype 2 (Essential NIH Criteria)

d) Clinical and/or biochemical evidence of hyperandrogenism
e) Evidence of oligo-anovulation[8]

3. Phenotype 3 (ovulatory PCOS)
   f) Clinical and/or biochemical evidence of hyperandrogenism
   g) Ultrasonographic evidence of a polycystic ovary[8]
4. Phenotype 4 (nonhyperandrogenic PCOS)
   h) Evidence of oligo-anovulation
   i) Ultrasonographic evidence of a polycystic ovary[8]

Adolescent Diagnostic Criteria[8]:

Otherwise, unexplained combination of

1. Abnormal uterine bleeding pattern
   a. Abnormal for age or gynecologic age
   b. Persistent symptoms for 1–2 yr
2. Evidence of hyperandrogenism[8]
   a. Persistent testosterone elevation above adult norms in Reliable reference laboratory is the best evidence.
   b. Moderate-severe hirsutism is clinical evidence of Hyperandrogenism[8]

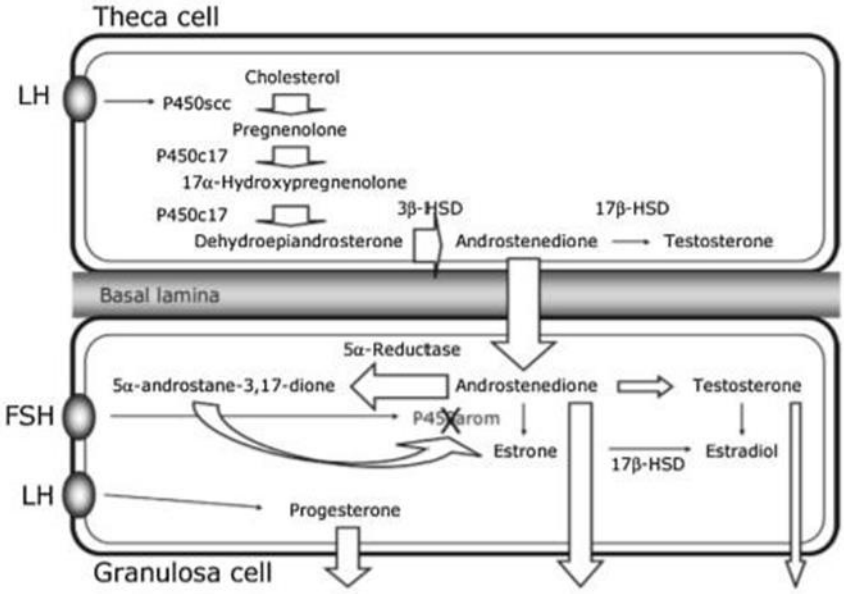

Fig. 4. effect of steroidogenesis enzyme and theca cells of an ovary.

ETIOLOGY OF PCOS:

- The genetic and environmental factor is responsible for the Etiology of this condition. Unhealthy lifestyle, diet or any infectious Mediators increase the risk of PCOS [7].
- Due to insulin resistance and its elevated level, the ovaries function disturbs that risesAndrogen level which leads to anovulation [7].
- The level of Gonadotropin-releasing hormone, follicular stimulating hormone (FSH),luteinizing-hormone (LH) and prolactin is also disturbed in Case of PCOS [7].
- Apart from the environmental factors, there are Genetic factors that are responsible for the etiology of PCOS.[7]
- Its cause involves candidate genes, SNP's. According to databases PCOS etiology involves 241 gene variations [7].
- Polymorphism or Any nucleotide change cause a defect in the transcriptional activity of agene that leads to PCOS[7]
- Mostly genes that encode for the Androgen receptor, Luteinizing Hormone receptors, Follicular Stimulating Hormone Receptors, Leptin receptors are responsible [7].
- Gene defect perturbs the biochemical pathway and leads to Dysfunction of an ovary. Polymorphism such as StAR polymorphs, FSHR polymorphism, FTO polymorphism, VD polymorphism, IR And IRS polymorphism, GnRHR polymorphism are found to be Involved in PCOS cause[7] .
- PCOS progression and severity Increases with the increase in insulin level as well as anandrogen. Hyperinsulinemia affects ovarian theca cells and raise androgen Level [7].

- This condition reduces the hepatic biosynthesis of SHBG and IGFBP-1. Elevated androgen level, on the other hand, stimulates Visceral adipose tissue (VAT) that generates free fatty acids (FFA's) which contributes in insulin resistance Fig. 2 . Genetic Predisposition with PCOS, a pathway describes hyperandrogenism Fig. 3.
- Fig. 4 depicts a pathway that describes how steroidogenesis Enzyme affect the theca cells of an ovary. 5ϱ-reductase activity Increased that elevates 5ϱ-androstane -3, 17 Dione concentrations and inhibit the activity of aromatase in the granulosa cells. In the case of PCOS, LH and progesterone are expressed in the granulosa Cells which results in high androgen level and reduced estrogen level [7].

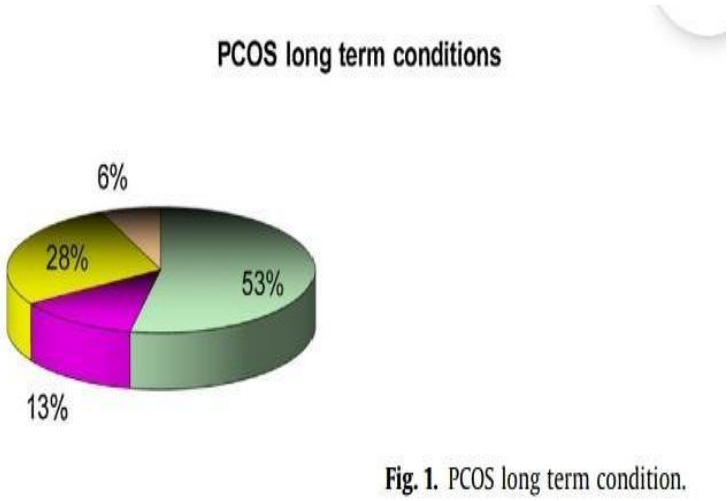

Fig. 1. PCOS long term condition.

Androgen Receptor Gene (AR):

This gene is present on chromosome Xq12 and has 11 exons, it Codes for more than 90 kb long protein that has total of three Functional domain . Androgen receptor AR is also linked with PCOS. X Inactivation disrupts androgen signaling pathway and Elevated. AR is an X linked gene and a single copy of X chromosome Perturbs the whole pathway. It is possible to conduct Genome- Wide Association for PCOS to identifythe novel mutations and other genetic variants that is associated with the cause of PCOS [7].

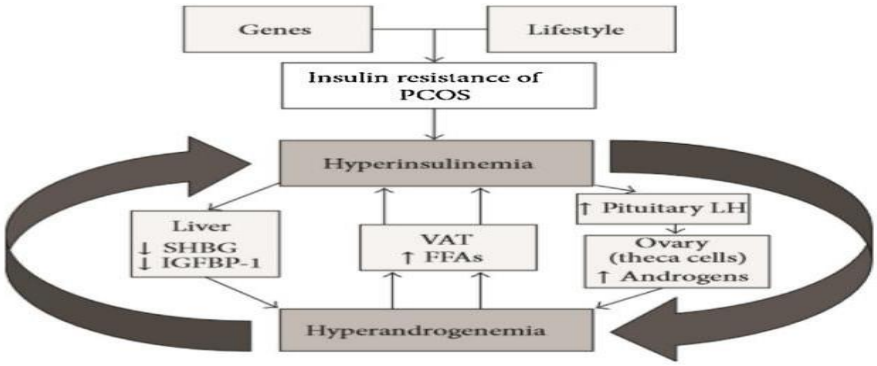

Fig. 2. how insulin resistance effects the ovarian theca cells and perturbs its functioning [18].

[7]

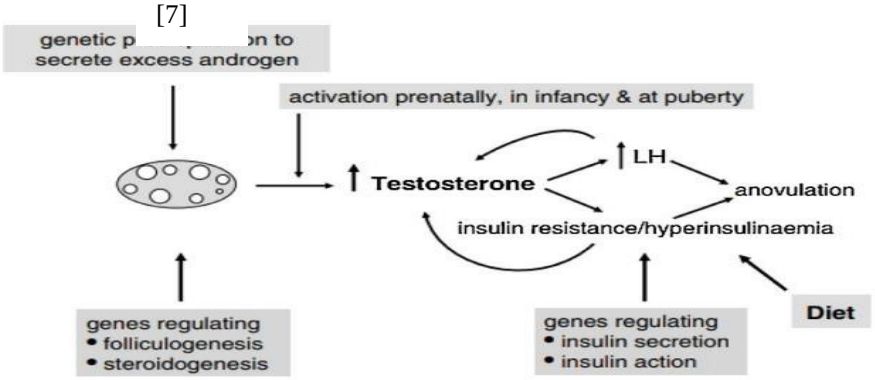

Fig. 3. A defect in the pituitary axis elates testosterone and LH. It also leads to insulin resistance. Together insulin resistance and high level of androgen subsidize in the pathway of anovulation [19].

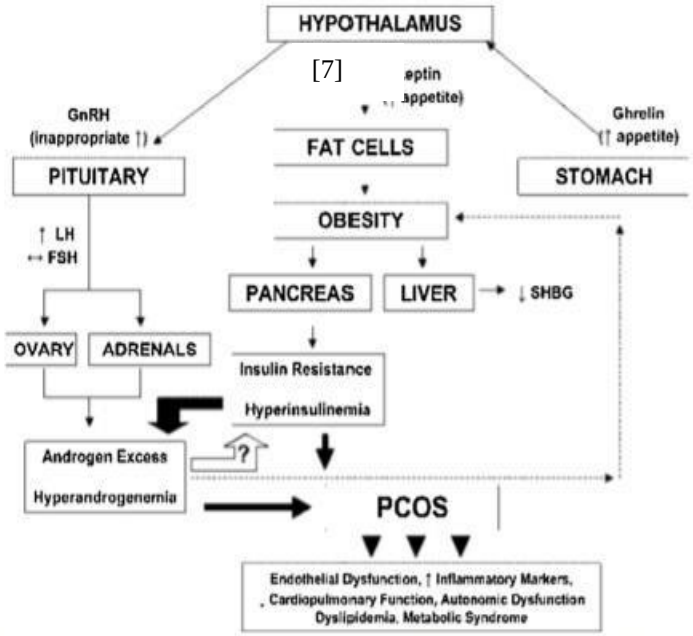

Fig. 5. Flowchart that illustrate how insulin resistance leads to elevated level of androgen. It also explains decrease level of androgen that can be possible by using drugs that prevents insulin resistance (55).

[7]

Follicular stimulating hormone receptor (FSHR):
Cytogenic location of FSHR is at chromosome 2p16.3 and it has Total of 14 exons. This geneencodes a protein named as G coupled Receptors and plays an important role in gonad development. The disturb hormonal levels effects endocrine reproductive System. Apart fromother hormones imbalance level of FSH also Responsible for PCOS severity. FSH is encodedby Follicular Stimulating Hormone receptor. Follicular and ovary functioning Disturbs due toany abnormality present in FSHR. Based on Statistical analysis and RFLP using restriction enzymes Eam11051, a Great difference was observed among healthy and affected Individual in a study conducted in the North of Iraq[7].

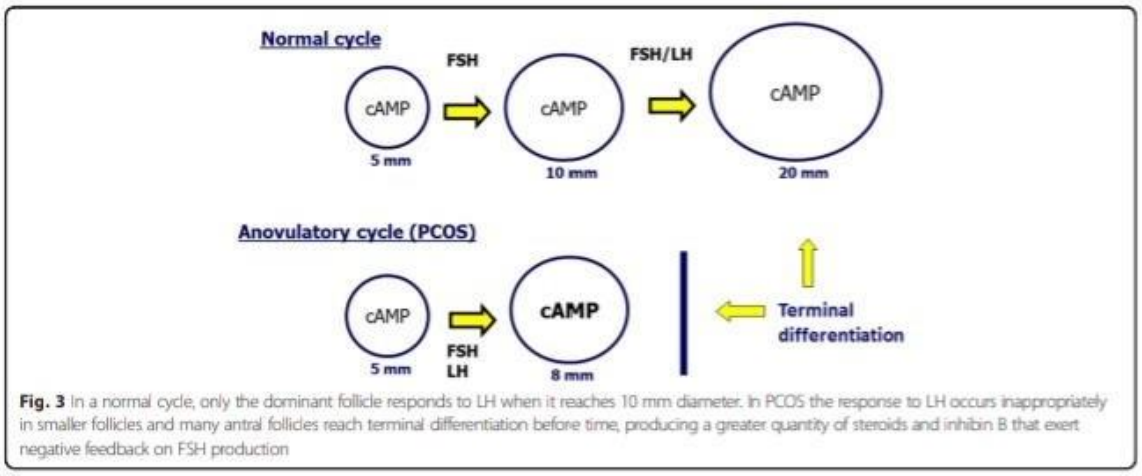

Fig. 3 In a normal cycle, only the dominant follicle responds to LH when it reaches 10 mm diameter. In PCOS the response to LH occurs inappropriately in smaller follicles and many antral follicles reach terminal differentiation before time, producing a greater quantity of steroids and inhibin B that exert negative feedback on FSH production

PATHOPHYSIOLOGY:

- The pathogenesis of PCOS is complex and multifactorial, Including genetic, environmental, and transgenerational Components.[4]
- These sources drive the underpinnings of un-Balanced hypothalamus-pituitary- ovarian axis signaling, Promoting ovarian and adrenal hyperandrogenism [4].
- The Syndrome is also burdened with insulin resistance that is Worsened by hyperandrogenism-related adipose tissue Accumulation and dysfunction with lipotoxicity and oxidative stress [4].
- Thus, the full clinical spectrum of the Syndrome involves metabolic, reproductive, and psychological impairments.
- In addition to genetic factors, environmental factors likely also play a role.
- The link between Obesity and the prevalence of PCOS is highly correlated; Among women with body mass index (BMI) <25 kg/m2, the Prevalence is 4.3%, and in women with BMI > 30kg/m2 It Is 14%, although selection bias may play a role in assessment.
- Neuroendocrine link to PCOS Women with PCOS present with gonadotropin- releasing Hormone (GnRH) neuronal network dysfunction and in-Creased pulse amplitude for pituitary activity, shown as High serum luteinizing hormone levels and high ovarian Androgen response, most likely relating to decreased responsiveness to steroid hormone negative feedback[4,8]
- Different animal models have successfully been able to Recapitulate the hyperandrogenism driven neuroendocrine pathology of PCOS and other centralmechan-Isms involved .
- Recently, aberrant neuroendocrine Signaling was linked with adipose tissue dysfunction in A murine model , whereas other studies have pro-Posed high anti- Müllerian hormone (AMH) promoting GnRH neuron activation and PCOS onset .
- Given the Central role of hyperandrogenism and obesity in the impairments in neuronal circuitry and the high prevalence of psychological distress among women with PCOS, the Central dysfunction most likely involves larger and more Complex neuronal networks than previously recognized Genetic factors The genetic factors andfamilial clustering are described in the early PCOS literature however, as more genetic data has started to accumulate, it has become obvious that the syndrome harbors multigenetic background.
- Indeed, the genome-wide association studies have identified a total of 19 risk gene loci for PCOS located in the neuroendo- crine, metabolic, and

reproductive pathwayswith the reproductive and metabolic populations segregating in a recent unsupervised clustering analysis.

- In line with this, Mendelian randomization analyses suggest a causal link betweenPCOS and variants associated with BMI, fasting insulin, menopause timing, depression, and male-pattern balding.
- From all genes of interest, the gene loci with the most potential, namely THADA, FSHR, INS-VNTR, and DENND1A, would require validation in the future. Interestingly, the clinically validated PCOS cases have similar genetic profile to the self-reported ones, allowing data generation in the future also through less burdensome and more inexpensive means.
- Known genetic risk alleles account for less than 10% of PCOS heritability; therefore, other etiological factors also must be considered. Transgenerational transmission of PCOS Animal studies and human data show the syndrome having transgenerational origins, with a 5-fold higher risk for daughters born to mothers with PCOS for inheriting the syndrome.
- In a murine model, prenatal androgen excess alone can predispose to transgenerational transmission of PCOS. Early androgen exposure may in- crease susceptibility to the syndrome. Longer anogenital distance (AGD) has been shown ininfant girls born to PCOS mothers, and daughters of PCOS mothers have higher metabolic and androgenic risk.
- Maternal testosterone in women with PCOS was found to be a predictor of infant AGD .
- The mechanism through which the daughters are exposed to hyperandrogenism re- mains elusive, although AMH could be one of the players. Interestingly, a recent study showed that mice subjected to high levels of AMH at late pregnancy produced PCOS offspring with high luteinizing hormone pulsatility and in- creased androgen levels.
- The mechanism was thought to transit via AMH effect on aromatase activity in the placenta, promoting hyperandrogenism. Even though AMH levels have been reportedto be high in the second and third trimesters in women with PCOS, the role of AMH on transgenerational transmission in humans. Warrants further studies [4,8].

PREVENTION:

- There is no proven way to prevent PCOS, but you can take small steps to reduce yoursymptoms. For example, eating nutritious foods, exercising regularly, and managing your weight can help you avoid the effects of PCOS [12].
- Polycystic ovarian syndrome, sometimes called polycystic ovarian disease, is a condition in which there are higher levels of male hormones in women [12].
- Polycystic ovarian disease has many causes but PCOS treatment has only two main forms [12].
- PCOS treatment includes a healthy diet and certain health supplements and herbs [12].
- Here are the two main ways you can prevent PCOS happening and reoccurring and they are Diet and Eat equal amounts of protein and carbohydrates [12].
- One of the major causes of polycystic ovarian disease is insulin resistance. It has been said by doctors that if you balance the two of these, the chances of insulin resistance and polycystic ovarian disease are much reduced [12].
- Also avoid processed carbohydrates as they cause a spike in protein levels. Instead, eat spelt, quinoa and millet among other foods [12].
- Eat foods low on the glycemic index [12].
- Foods low on the glycemic index includes walnuts, apples, beans and asparagus. The reason you should eat foods with a low glycemic index is because they reduce glycemic load and therefore do not produce a sudden spike and then a dip in blood sugar levels that foods like pancakes, white potatoes and scones do [12].
- Eat a high-fiber diet. There are two ways that fiber decreases the chances of PCOS. The first is that it helps digest sugars so insulin spikes are reduced. The second is that it helps in estrogen metabolism [12].
- Eat often.Eating only three or four times a day causes an imbalance in the estrogen metabolism. Eating five or even six times a day allows for your estrogen metabolism to improve [12].
- Two major causes of PCOS are obesity and of course hormonal imbalances. Certain fatty acids actually help in weight loss and also regularize the body's metabolism [12].
- Quit coffee: Coffee is the best way to increase estrogen levels and contract PCOS. Therefore, it is crucial that you quit coffee long before you start worrying about pregnancy [12].

TREATMENT:

Lifestyle Modification:

In overweight and obese PCOS women and adolescents, exercise and calorie-restrictive dietsare

the best first-line interventions for weight loss and IGT. Different studies have shown thathirsutism can improve as well as regulation of the menstrual cycle and ovulation. Low- carbohydrate diets have been used, hoping that these will have a better effect on hyperinsulinism, but studies have shown no difference in outcomes with low-carbohydrate diets [13].

Hormonal Contraceptive:
First-line treatment for menstrual abnormalities, hirsutism, and acne is a hormonal contraceptive, either oral contraceptive, patch, or vaginal rings. The Endocrine Society does not favor any choice over another. The progestin component decreases LH levels, indirectly decreasing ovarian androgen production and increasing sex hormone-binding globulin.

Additionally, some progestins have been shown to have direct antiandrogenic properties as a direct inhibitor 5 alpha-reductase activity to prevent the conversion of free testosterone to itsmore potent form, 5 alpha-dihydrotestosterone. For this reason, they are highly effective for symptoms of hyperandrogenism and controlling the menstrual cycle [13].

Screening for contraindication for hormonal contraceptives should be done in all patients. Women 35 or older who smoke more than 15 cigarettes daily, uncontrolled hypertension greater than 160/100, uncontrolled diabetes with severe peripheral vascular disease are considered absolute contraindications. The United States Medical Eligibility Criteria For Contraceptive Use are a valuable tool when multiple comorbidities are present. Patients withdiabetes and without vascular complications do not have any contraindication to use hormonal contraceptives [13].

Regarding the metabolic effect of hormonal contraceptives, higher estrogen activity increasesHDL cholesterol and decreases LDL cholesterol. No impact on body weight and fat distribution between PCOS and healthy women.

Oral contraceptive initial dosing of 20 mcg of ethinyl estradiol combined with a progestin with antiandrogenic properties such as desogestrel and drospirenone or with neutral effects like norethindrone acetate. Progestin with antiandrogenic properties has been shown to have a higher risk of venous thromboembolism (VTE). If hyperandrogenic symptoms are not controlled completely with this initial dose, ethinyl estradiol can be increased to 30 to 35mcg [13].

Metformin:
Endocrine Society recommends starting metformin in PCOS patients with DM2 or IGT whofail lifestyle modifications. It decreases progression from IGT to DM2. Metformin also improves menstrual cycles, abnormal waist to hip ratio, and vascular markers in non-obese women with PCOS [13].

Metformin is also second-line therapy for menstrual irregularities in patients with a contraindication for hormonal contraceptives. It is commonly used in the adolescent as monotherapy, and it helps restore normal menses, weight loss, and reduce insulin resistance. Even though it should not be used primarily to treat clinical hyperandrogenism, it can mildly improve androgen excess symptoms [13].

Infertility Treatment:
First-line therapy for infertility in PCOS patients is clomiphene citrate. This is a selective estrogen receptor modulator (SERM), competitive inhibitor of estrogen receptors (ERs), andhas mixed agonist and antagonist activity [13].

Clomiphene enhances fertility and ovulation, especially by its effect on the hypothalamus, where it binds for a prolonged period to estrogen receptors and depletes them, blocking the negative feedback inhibition effect of circulating endogenous estrogen. This results in the pulsatile release of a hypothalamic gonadotropin-releasing hormone (GnRH), promoting thesecretion of FSH and LH and indirectly stimulating ovulation [13].

New evidence for estrogen modulators such as letrozole has shown that it can be used in ovulatory infertility. This is an aromatase inhibitor that blocks estrogen synthesis, reducing negative estrogenic feedback at the pituitary. A National Institute of Health founded a double-blind, multicenter trial that reported that letrozole, compared to clomiphene, was associated with higher live-birth and ovulation rates among infertile women with polycystic ovary syndrome. Additional studies regarding relative teratogenicity need to be done, but future guidelines can change after this new evidence [13].

Metformin is suggested as an adjuvant treatment for infertility, helping prevent ovarian hyperstimulation syndrome in a patient undergoing in vitro fertilization. It has shown higher benefits in obese patients. After pregnancy is confirmed, it is now allowed for patients withdiabetes or glucose intolerance to continue the medication as a treatment for sugar control, but attention should be given to avoid maternal

gastrointestinal disturbances [13].

Treatment for Hyperandrogenism:
Clinical hyperandrogenism requires long-term treatment and takes several months beforeeffects are evident.

Cosmetic interventions should be initiated while medications start working. These can bebleaching and temporary hair removal methods, using galvanic or blended electrolysis for localized areas with the experienced operator, using laser photo-epilation for generalized hirsutism [13].

Pharmacological interventions include topical eflornithine for face hirsutism which can be an expensive treatment with potentially serious side effects if the body absorbs it.

First-line treatment of hirsutism is low-dose neutral or antiandrogenic oral contraceptives which effectively lowers androgens level and effect. Additionally, contraceptive properties are beneficial when combined with antiandrogenic drugs because the latter requires reliablecontraception as they are highly teratogenic. Mild hirsutism can be treated OCP alone [13].

Adjuvant antiandrogen administration can be done for moderate, severe hirsutism and mild hirsutism without adequate hair growth control after 6 months to 1 year of OCP. As those drugs have similar efficacy, androgen excess and the PCOS Society suggest prescribing finasteride, cyproterone acetate, which is not available in the United States, or spironolactone, instead of flutamide when an antiandrogen is needed, due to potential side effects like hepatotoxicity. They act by blocking androgens effects over the hair follicle; finasteride also has inhibition of 5 alpha-reductase [13].

Spironolactone is the most common adjuvant anti-androgen medication prescribed after OCP; it is a nonselective mineralocorticoid receptor antagonist and suppresses testosterone levels.

Spironolactone also has additional benefits regarding the risk of CVD compared to OCP. Combinations of spironolactone with metformin were superior to monotherapy with either drug regarding improved menstrual cycles, glucose during OGTT, assessed by the area underthe curve, and testosterone levels[2,3,6].

Metformin alone or other insulin sensitizers are not considered target treatment for hirsutism due to no consistent evidence showing superior effect than placebo [13].

Additional Insulin Sensitizing Treatment in PCOS
GLP-1 agonists:
GLP-1 agonists bind to the GLP-1 receptor and stimulate glucose-dependent insulin releasefrom the pancreatic islets. They have a longer half-life than our bodies GLP-1 because of resistance to degradation by the enzyme dipeptidyl peptidase 4 (DPP-4). Data shows that GLP-1 secretion was significantly lower in obese compared with lean women with PCOS [13].

Treatment with GLP-1 agonist was associated with decreased BMI and testosterone and improved ovulation rate in obese women with PCOS [13].

DPP4 inhibitors:
DPP4 inhibitors decrease the degradation of incretins, therefore, increasing glucose- dependent insulin release. In patients with type 2 diabetes, they are considered weight neutral.New data suggest that in obese women with PCOS, DPP4 inhibitors have beneficial effects in weight loss and lower blood glucose levels. It prevented weight gain in women who were transitioning from GLP-1 agonists [13].

Evidence suggests that the effect of DPP4 inhibitors on the weight of women with PCOS is based on increasing growth hormone, which is reduced in patients with PCOS. These, in turn,decrease visceral fat mass. Data is still limited, and it is considered experimental [13].

SGLT2 inhibitors:
SGLT2 inhibitors increase urinary glucose secretion, improves weight loss and cardiovascular risk in patients with type 2 diabetes. Limited data in obese patients shows promising data for weight loss and fat mass reduction with treatment with SGLT2 inhibitors compared to metformin, but its effect on hormonal and metabolic parameters was similar.

More data is needed to implement this medication in clinical practice. Peroxisome proliferator-activated receptor gamma (PPARg) agonist

In PCOS, PPARg agonist treatment improved hormonal and metabolic outcomes but had anadverse effect on weight. It can be superior in patients with NAFLD compared to metformin [13].

Myoinositol:
Myoinositol is an over-the-counter food supplement that increases insulin sensitivity. Compared with placebo improved insulin sensitivity in women with

PCOS without significant effect on BMI. Data is limited, and its use has been mostly applied as fertility treatment of PCOS or when metformin is not tolerated, given it has fewer gastrointestinalside effects [14].

Herbs and supplements:

- **Liver oil**:- Cod liver oil is crucial in helping weight loss and balancing hormones which is why you must incorporate this either in your diet or take it by itself as a supplement.
- **Liquorice root**:-A licorice root is crucial for maintaining proper hormone production andrelease and also leads to better liver health and healthy insulin levels.
- **Cinnamon**:-Cinnamon is a crucial herb to help regulate insulin and prevent insulinresistance.
- **Omega**:- Finally, omega-3 and omega-6 help in reducing inflammation. However, you must note that women always have low-grade inflammation in their bodies.

Consequences:

There is currently no cure for PCOS, and it does not go away on its own. Even after menopause, women with PCOS often continue to have high levels of androgens as well as insulin resistance. This means that the health risks associated with PCOS are lifelong. If polycystic ovary syndrome is left untreated, the syndrome may lead to serious, life-threatening illnesses such as :

- **Cardiovascular diseases:** PCOS risk factors like being overweight or having insulin-resistant diabetes or higher blood pressure are associated with cardiovascular disease. Studies suggest that women with PCOS have a twice as likely risk of a future cardiovascular event, like a heart attack or stroke.
- **Type 2 diabetes:** More than half of women with PCOS develop type 2 diabetes by the age of 40. Gestational diabetes (diabetes when pregnant) which puts the pregnancy and baby at risk and can lead to type 2 diabetes later in life for both mother and child. Heart diseased women with PCOS are at higher risk and women risk increases with age.
- **Endothelial Cancer:** Women with a condition called PCOS have abnormal hormone levels such as higher androgen and estrogen levels and lower levels of progesterone. The increase in estrogen relative to progesterone can increase a women's chance of getting endothelial cancer.
- **Uterine cancers:** The major reason PCOS increases the risk of endometrial cancer is the prolonged exposure of the endometrium to unopposed estrogen caused by anovulation. This prolonged exposure can cause endometrial hyperplasia and may lead to uterine cancer.
- **Stroke:** PCOS is associated with significant increased risk of store, while there is no consistent evidence to indicate that PCOS influences all cause death outcomes. Increased BMI is an important contributor to the relationship between PCOS and stroke risk [2,4,7,8].

CONCLUSION:

Apart from environmental factors, many candidate genes are involved in the etiology of the PCOS, Alteration in the metabolic Pathway due to a defect in the gene leads to the progression of PCOS and ovary dysfunction. The severity can only be reduced when followsproper precautionary measures i.e. weight loss, healthy diet and recommended medications [7].

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