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POLYCYSTIC OVARY SYNDROME: A COMPLETE REVIEW FOR RISK FACTORS, DISEASE AND DIAGNOSIS MANAGEMENT

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ABSTRACT

Polycystic ovary syndrome (PCOS) is an endocrine-gynecology disorder affecting many women of childbearing age. Although a part of the involved mechanism in PCOS occurrence is discovered, the exact etiology and pathophysiology are not comprehensively understood yet. Androgen excess (male hormone excess), seen in 60-80% of girls and women with PCOS, is a key problem in the disorder and likely comes from ovaries in most women. The evidence suggests the several different external and internal factors which includes hyperandrogenism, insulin resistance, genetic, epigenetics and environmental factors. PCOS increases the risk of further complications like anxiety, depression, metabolic syndrome, cardiovascular diseases and type 2 diabetes mellitus, cardiovascular diseases. However, the symptoms can be successfully managed with proper medication and lifestyle interventions. In this review article, about PCOD are clearly explored. Physicians suggested to use anti androgen agents, insulin sensitizers, (combined) oral contraceptives, and ovulation inducers. According to United states food and drug administration (USFDA) there is no medication approved particularly for PCOD and all medications mentioned are off label used.

KEYWORDS: *PCOS, Anovulation, Hirsutism, Hyperandrogenism, External and Internal factors.*

INTRODUCTION

Polycystic ovarian syndrome is an endocrinal disorder affecting the women of reproductive (14-44) age. It is a complicated illness associated with metabolic psychological endocrinal disorganization affecting major public health concern. Anovulation is the most consequent condition that affects the female fertility. Women with pcos found that irregular menstrual cycle and hirsutism have the largest impact on QOL. However, the main etiology of this disorder is not completely understood.[1-2]

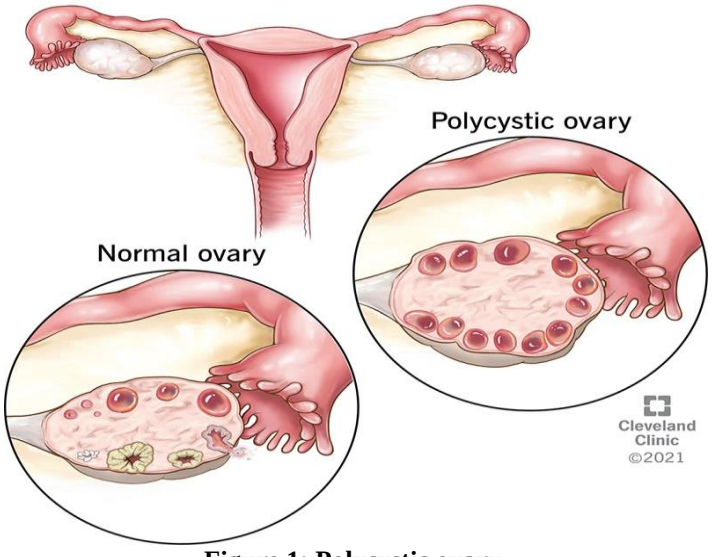

Figure 1: Polycystic ovary.

Etiology of PCOS

Some causes like hormonal changes can make the ovaries to produce multiple follicles and finally leads to formation of cysts. Obesity and amenorrhea are the precursors of this syndrome. It is affecting 1 in every 15 women world widely.[3] However, women can reverse this condition by modifying their lifestyle, pharmacologically manageable. so, our study states that number of people prone to PCOD in tertiary care hospital and finding the comparative treatment between medication and lifestyle modification.[4]

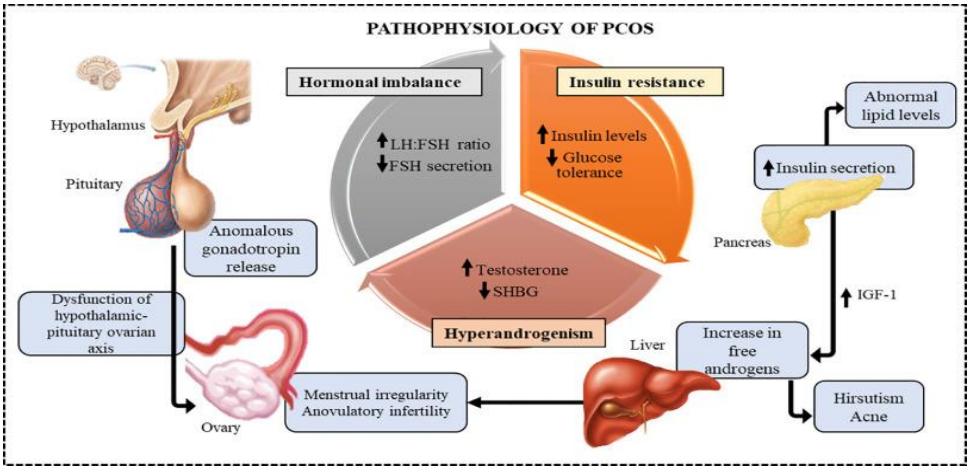

Figure 2: Brief insight into Polycystic Ovarian.

III.TYPES OF PCOS

Mainly four types are present: Insulin-resistant PCOS, Inflammatory PCOS, Hidden-cause PCOS, and Pill-induced PCOS.

Insulin-resistant PCOS

It is the most regular type of PCOS. This is caused by tobacco abuse, diabetes, environmental changes and obese. In these high levels of Insulin prevent ovulation and trigger the ovaries to create testosterone.[5]

As you are diabetic and your glucose tolerance was very high or not to be normal then u have increased level of insulin or obese, than u have might be a chances of PCOD.

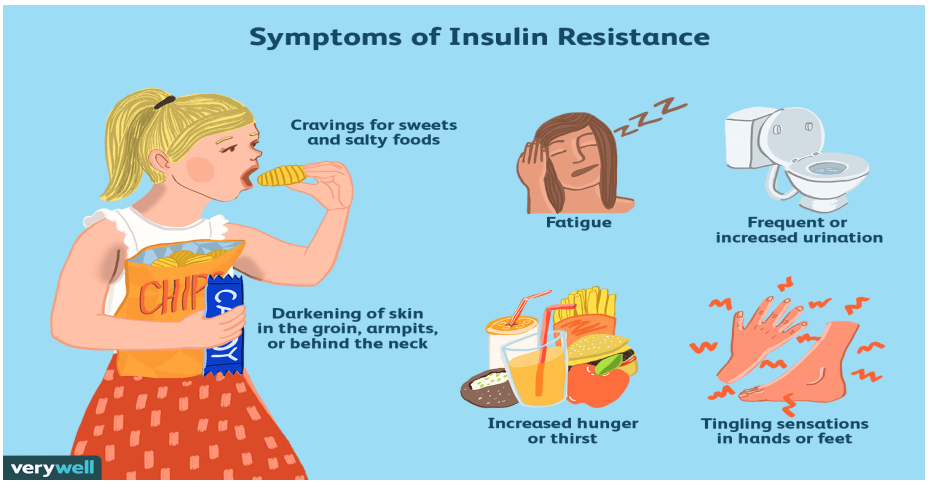

Figure 3: Diagnosing Insulin Resistance in Women with PCOS.

Pill-induced PCOS

It is a most regular type of PCOS. It ensures due to oral contraceptive pills that reduces ovulation. In most common adult female result anovulation due to excess usage of pills. Ovulation cannot come in adult females during years or months due to effect on pills.

If regular and normal comes before starting with the pills then this might be a sign of Pill-induced PCOS. Or if levels of LH are increased in the blood test, then this could be a sign too.[6,7]

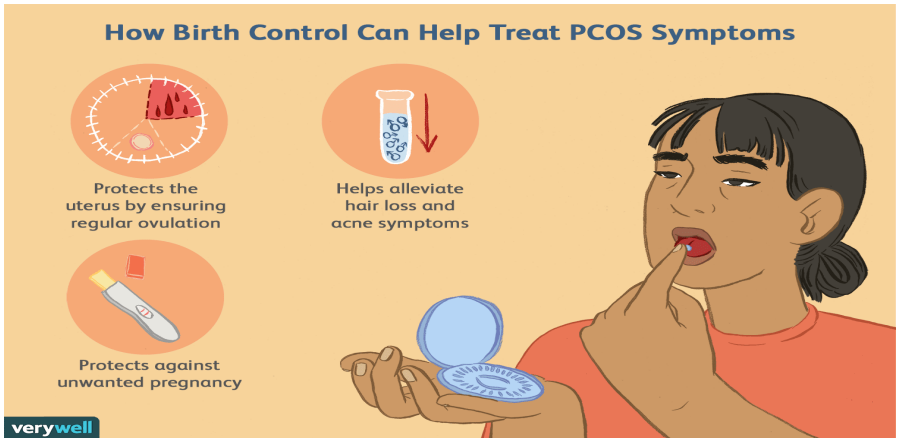

Figure 4: Using Birth Control to Treat PCOS.

Inflammatory PCOS

Inflammation is caused by pcos then ovulation gets decreased, cumbersome of hormones. Etiology of inflammation is mainly due to psychological changes, nature changes and dietary changes.[9-10]

Patients have complaints of sore head, contamination, hypersensitivity reactions then the hemoglobin test shows vitamin D reduction. Abnormal blood count changing of thyroid levels, might be having a chance of inflammatory PCOS.

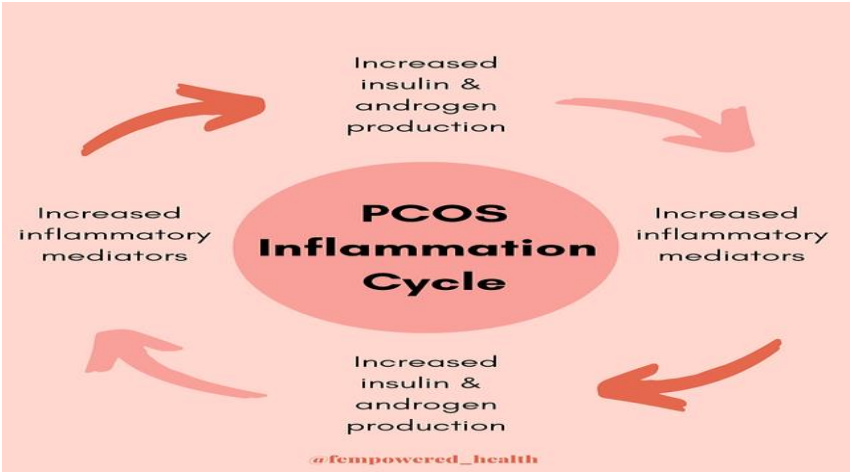

Figure 5: The Link between Inflammation and PCOS.

Hidden PCOS

It is rare type of PCOS. Etiology of PCOS is thyroid, abnormal levels of iodine, and diet of vegetarian due to lack of zinc.[8]

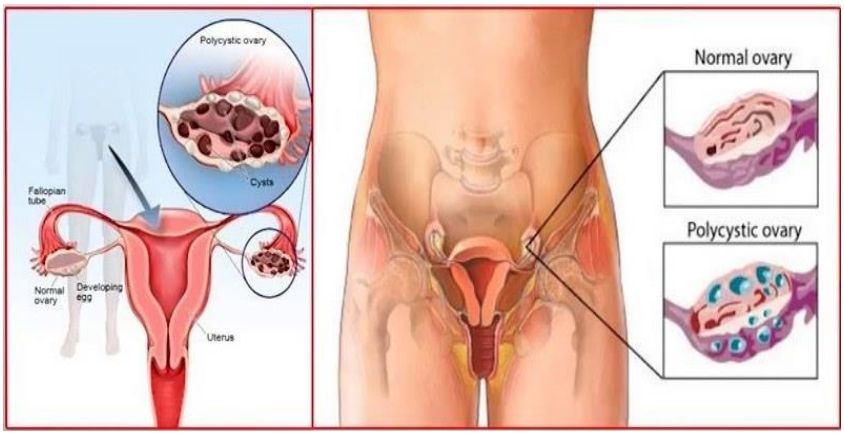

Figure 6: Polycystic Ovary Syndrome (PCOS) - Reproductive Solutions Ja.

IV. MECHANISM

It involves excessive androgen production and decrease aromatization. Exact pathophysiology is not known. It may be diccussed under the following

1. Hypothalamic pituitary compartment abnormality
2. Androgen excess
3. Anovulation
4. Obesity and insulin resistance long term consequences

Hypothalamic-Pituitary Compartment in PCOS

Increased pulse frequency of GnRH leads to increased pulse frequency of LH. Leptin (a peptide, secreted by fat cells and by the ovarian follicle), insulin resistance and hyperandrogenemia are responsible for this, GnRH is preferential to LH rather than FSH.[11] Increased pulse frequency and amplitude of LH results in tonically elevated level of LH. FSH level is not increased. This is mainly due to the negative feedback effect of chronically elevated estrogen and the follicular inhibin. Increased free estradiol due to reduced sex hormone binding globulin (SHBG) bears positive feedback relationship to LH. The LH: FSH ratio is increased.[12-13]

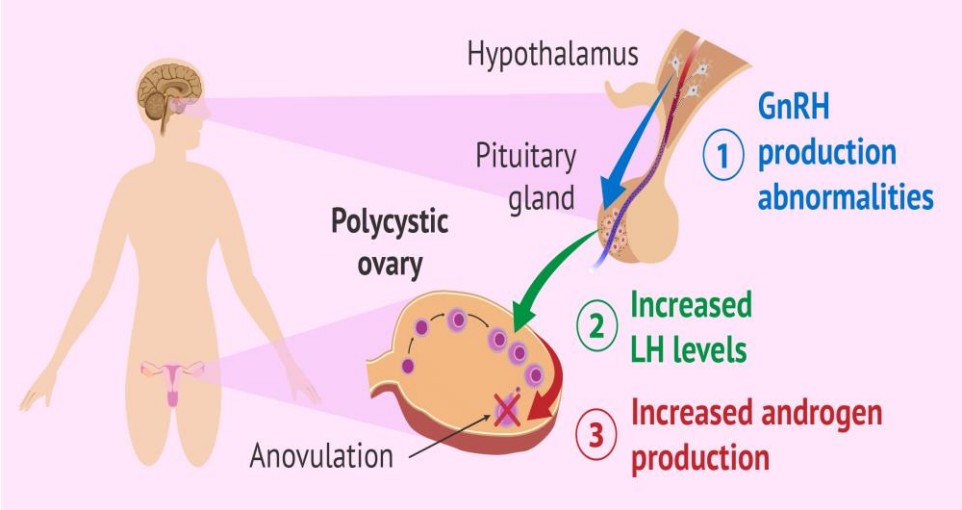

Figure 7: Hypothalamic-pituitary dysfunction in PCOS.

Androgen Excess

Abnormal regulation of the androgen forming enzyme (P450 C 17) is thought to be the main cause for excess production of androgens from the ovaries and adrenals. The principal sources of androgens are

(A) Ovary
(B) Adrenal
(C) Systemic metabolic alteration.

A. Ovary produces excess androgens due to
(i) Stimulation of theca cells by high LH
(ii) P450 C17 enzyme hyperfunction
(iii) Defective aromatization of androgens to estrogen
(iv) Stimulation of theca cells by IGF-1 (insulin growth factor-1)

B. Adrenals are stimulated to produce excess androgens by (i) stress (ii) P450 C17 enzyme hyperfunction (iii) associated high prolactin level (20%).

C. Systemic metabolic alteration
(i) Hyperinsulinemia causes
(a) Stimulation of theca cells to produce more androgens.
(b) Insulin results in more free IGF-1. By autocrine action, IGF-1 stimulates theca cells to produce more androgens.
(c) Insulin inhibits hepatic synthesis of SHBG, resulting in more free level of androgens. Features suggestive of insulin resistance are: BMI > 25 kg/m 2, Acanthosis nigricans and waist to hip ratio > 0.85. (ii) Hyperprolactinemia: In about 20% cases, there may be mild elevation of prolactin level due to increased positivity of GnRH or due to dopamine deficiency or both. The prolactin further stimulates adrenal androgen production.

Abnormal regulation of the androgen forming enzyme P450 C17 is thought to be the main cause for excessive production of androgens from the ovaries and adrenals.[14] The principal sources of androgens are Ovary, adrenal, systemic metabolic alteration. Ovary produces excess androgens due to:

1. Stimulation of theca cells by high LH
2. P450 C17 enzyme hyperfunction
3. Defective aromatization of androgens to estrogen
4. Stimulation of theca cells by IGF-1(insulin growth factor-1)

Anovulation

Because of low FSH level, follicular growth is arrested at different phases of maturation (2–10 mm diameter). The net effect is diminished estradiol and increased inhibin production. Due to elevated LH, there is hypertrophy of

theca cells and more androgens are produced either from theca cells or stroma. There is defective FSH induced aromatization of androgens to estrogens. Follicular microenvironment is therefore more androgenic rather than estrogenic. Unless there is estrogenic follicular microenvironment, follicular growth, maturation and ovulation cannot occur.[15-16] There is huge number of atretic follicles that contribute to increased ovarian stroma (hyperthecosis). LH level is tonically elevated without any surge. LH surge is essential for ovulation to occur.

Gonadotropin hormones are namely follicle stimulating hormone (FSH) and luteinizing hormone (LH) which are produced by the pituitary gland which is produced as a response to gonadotropin-releasing hormone (GnRH) that is secreted by the hypothalamus.

Ovulation is controlled by two hormones. FSH role is stimulation of the growth of follicles into eggs in which LH action is the release of the eggs. PCOS is a group of symptoms that take interferes with ovulation and ovaries. PCOS mainly have the three following features namely: irregular periods, elevated androgen levels and the cysts which are fluid-filled sacs in the ovaries.[17]

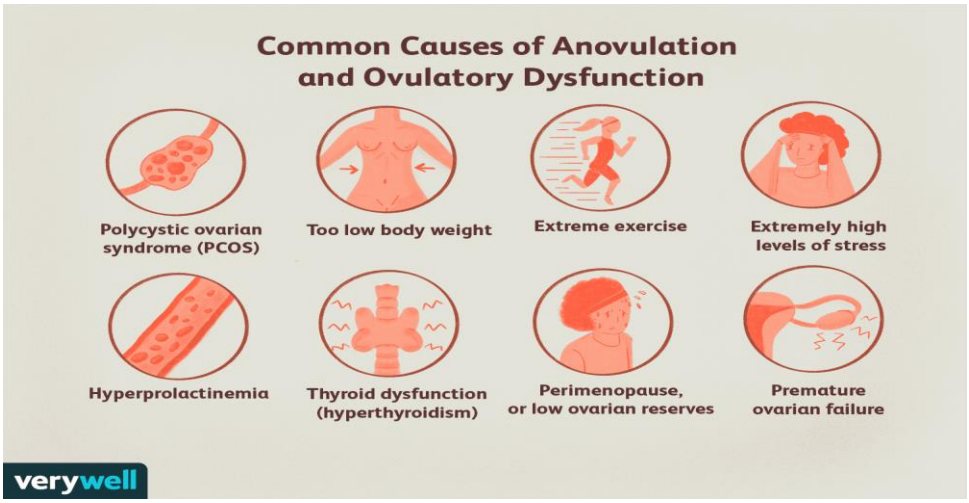

Figure 8: Anovulation and Ovulatory Dysfunction.

The sacs in the ovaries are the immature follicles that are never prone to ovulation. Thus, lack of ovulation completely affects the hormonal levels in the body. Elevated androgen levels disrupts the regular monthly cycles. Environmental determinants, genetic alterations and genetic alterations are also one of the underlying causes of hormonal imbalance.[18]

Obesity and Insulin resistance

Obesity and Insulin resistance Obesity (central) is recognized as an important contributory factor. Apart from excess production of androgens, obesity is also associated with reduced SHBG. It also induces insulin resistance and hyperinsulinemia which in turn increases the gonadal androgen production.[19] PCOS is thought to have a dominant mode of inheritance as about 50% of first-degree relatives have PCOS. Etiology of insulin resistance is unknown. Mutations of the insulin receptor gene in the peripheral target tissues and reduced tyrosine autophosphorylation of the insulin receptor, is currently thought to be an important cause. Increased central body fat leads to android obesity.

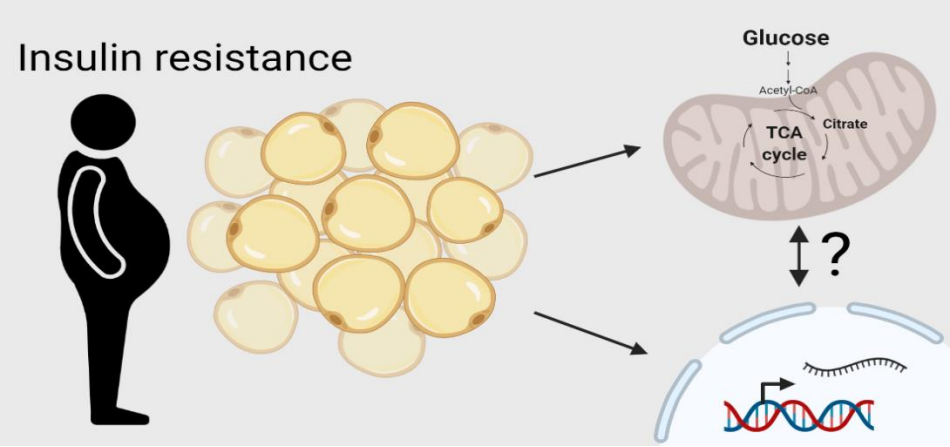

Figure 9: Unhappy fat: New clues on how obesity drives metabolic dysfunction.

Long-term consequences

It occurs in a patient suffering from PCOS includes: The excess androgens (mainly androstenedione) either from the ovaries or adrenals are peripherally aromatized to estrone (E1). There is concomitant diminished SHBG. Cumulative excess unbound E2 and estrone results in a tonic hyper estrogenic state. There is endometrial hyperplasia.

V. Clinical Manifestations

- PCOS causes many symptoms based on adult female however, the patients having pcos have different clinical manifestations but some clinical manifestations under the following:
- **Irregular menses**
- It involves high bleeding, missed periods, irregular cycles. Periods occurs at the starting stage of menarche; some patients have regular years for some years but they become irregular after some years this may be sign to pcos.
- **Over expression of hormones [androgens]**
- Androgens play major role in the pcos, male hormone releases excessively during pcos condition
  - Over blackness and excessive hair, called **hirsutism**, on the chin, upper lip, around the breasts, and on the midline of the abdomen
  - Male-pattern baldness (receding hairline)

Common symptoms of PCOS

- Irregular periods or no periods but occurs heavy flow
- Hirsutism i.e., growth of hair on the face, back, chest or butt
- Pimples
- Loss of hair
- Difficulty in conceiving
- Pain in the pelvic area
- Fear and sadness

VI. Diagnosing PCOS

Abdomen exam: look over reproductive organs for mass, width and other changes

Blood tests: Hormone levels can be examined by blood tests. And other levels like cholesterol, Tolerance of glucose.

Ultrasound: Look over ovaries and thickened lining. The transducer emits sound waves that are Translated into images on a computer screen.

Tests you may have include

- Prolactin level
- Pregnancy test.
- Lipid/cholesterol levels
- LH (luteinizing hormone) and FSH (follicle stimulating hormone) levels.
- Testosterone level

VII. Treatment

The treatment of PCOS is mainly included as follows:

- Weight loss,
- Dietary changes,
- Medications to treat acne and excessive hair growth
- Medications to improve insulin sensitivity,
- Fertility therapy

i) Medications

To regulate your periods, the physician might recommend the following

- **Combined birth control pills:** These are the pills that contains both progestin and estrogen which decrease androgen production and regulates the estrogen. Hormonal regulation can decreases the risk of endometrial cancer and corrects irregular bleeding and also excessive hair growth, acne.
- **Progestin therapy:** Taking progestin for 10 to 14 days for every 1 to 2 months can regulate your periods and protect against endometrial cancer. This progestin therapy doesn't improve androgen levels and won't prevent pregnancy.
- To help you ovulate so that you can become pregnant, your physician provider might recommend
- **Clomiphene.** This oral anti-estrogen medication is taken during the first part of your menstrual cycle.
- **Letrozole (Femara).** This breast cancer treatment can work to stimulate the ovaries.
- **Metformin.** Usually this medicine is for type 2 diabetes that you take by oral route that improves insulin resistance and lowers insulin levels. If you don't become pregnant using clomiphene, your provider might recommend adding metformin to help you ovulate. If you have pre-diabetes, metformin can slow the progression to type 2 diabetes and help with weight loss.
- **Gonadotropins.** These are injectable hormones.
- To improve acne and reduce excessive hair growth, the following are recommended:
- **Birth control pills.** These pills decreases the androgen production, leading to reduce of excessive hair growth and acne.
- **Spironolactone (Aldactone).** This medication blocks the effects of androgen on the skin, which includes excessive hair growth and acne. Spironolactone can cause birth defects, so effective birth control is needed while taking this medication. This medication isn't recommended if you're pregnant or planning to become pregnant.
- **Hair removal.** Laser hair removal and electrolysis are two options for removing hair.
- **Acne treatments.** Medications, including pills and topical creams or gels.

ii) Lifestyle Modification and Non-Pharmacological Approaches

- **Weight Loss**
  - Due to excessive production of androgens leads to weight gain in women with PCOS especially in the abdominal area. Many studies shows that even a 5% to 10% weight loss can regulates the regular

menstruation cycle. The women who are obese, the best way is to get normal body mass index (BMI).

- **Diet**
  - An ideal diet should be low in saturated fats and carbohydrates and rich in fibers. Patients should also be aware that foods with a high glycemic index for prevention, chips, fries, cookies, cakes, white rice, and some fruits such as pineapple or watermelon are actual examples.

There is a carbohydrate classification considering the blood glucose response they cause within 2 h: low and high glycemic index carbohydrates. Low glycemic index carbohydrates are at the top of our agenda; they include foods and vegetables like broccoli, raw carrot, lentils, soy, breakfast cereals, whole-grain bread, etc.

- **Exercise**

Physical activity and exercise plays a vital role in weight reduction. Insulin sensitivity can be improved by physical activity. The American Heart Association (AHA) recommends approximately 2 hrs. 30min of moderate or 1 hr. 15 min of vigorous and intense exercise per week. Several studies show that exercise, with or without being on a diet, can resume ovulation in women with PCOS. Exercise can affect ovulation through modulation of the hypothalamic-pituitary-gonadal (HPG) axis.[20]

- **Acupuncture**

In china for more than 3000 yrs.' acupuncture is a fundamental part of CAM (Complementary and alternative medicine). It is a kind of sensory stimulation in which thin needles are placed into the skin and muscles. Acupuncture improves clinical manifestations of PCOS by activating somatic afferent nerves of the skin and muscles, modulating somatic and autonomic nervous system activity and endocrine/metabolic functions.

Supplementations

- Vitamin D supplement
- Resveratrol,
- α-lipoic acid,
- Omega-3,
- Berberine,
- Folic acid,
- Myoinositol (MI),
- D-chiro-inositol (DCI).
- **Vitamin D** is very effective especially in cold seasons of the year, just compensatory amount is suggested.
- **Resveratrol** is among the most recommended supplements for the treatment of PCOS. It is assumed to possess neuroprotective, cardioprotective, antioxidant, and anti-inflammatory effects. Its action is by inhibiting HMG-CoA reductase expression and activity, just like statins. Clinical use of this product has been shown to reduce insulin resistance and the risk of type 2 diabetes development.

Alpha-lipoic acid

Usually, women's lipid profile is improved by the two supplements namely omega-3and alpha-lipoic acid and insulin sensitivity through their anti-inflammatory and antioxidant properties.

- **Berberine** is a nutraceutical compound which have desirable and possible effects against insulin resistance and obesity & particularly against visceral adipose tissue (VAT).
- **Folic acid** is usually an agent given to PCOD those who are seeking fertility.
- **Myoinositol (MI):** It corrects hormonal imbalance, improves insulin resistance, ovulation, and overall ovarian function.
- **D-chiro-inositol** (DCI): it has widely used in clinical practice to induce ovulation in clinical practice to induce ovulation in women with polycystic ovary disease.

VIII. Risk Associated With PCOS

- PCOD is associated with the potential risk of cerebrovascular and cardiovascular events, type 2 diabetes mellitus (T_2D), impaired glucose tolerance (IGT), pregnancy related complications, endometrial cancer, venous thromboembolism, and gestational diabetes. Many of these metabolic and reproductive conditions arise from an intrinsic feature of PCOS-insulin resistance (IR).
- Cardiometabolic events, Dyslipidemia, Hypertension, Obesity, other risks
- Sympathetic nervous system dysfunction, chronic inflammation, oxidative stress, and vitamin D deficiency are emerging risk factors of PCOD.

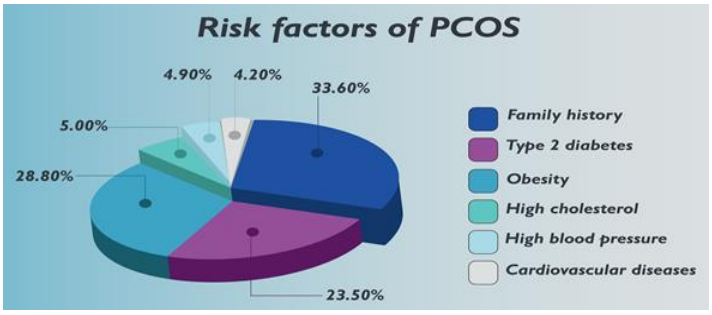

Figure 10: Risk Factors of PCOS

IX. CONCLUSION

Inspite of the mechanism of pcos is not completely understood, it is believed that different factors from epigenetic alterations to obesity, inflammation, and inactivity may leads to this syndrome. However, there is no exact medication for this syndrome, the common approach is to give some lifestyle modification and supplementary agents is symptomatic therapy, includes oral contraceptives, antidiabetics, or antiandrogens. The risk of pcos also very fastly occurs includes diabetes, cardiovascular problems, impaired glucose tolerance (IGT), pregnancy related complications, endometrial cancer, venous thromboembolism, and gestational diabetes. In this review article mechanism, symptoms, diagnosis, risks and management are clearly understood.

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