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A Review on Pregnancy Complications in Women with Polycystic Ovary Syndrome

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ABSTRACT: Polycystic ovary syndrome (PCOS) is a common infertility disorder, affecting a significant proportion of the global population. This syndrome has been one of the most controversial entities in gynecological endocrinology for many years. Both genes and the environment contribute to PCOS. Obesity, exacerbated by poor dietary choices, and physical inactivity, worsens PCOS in susceptible individuals. PCOS is a complex and heterogeneous disorder characterized by hyperandrogenemia, hyperinsulinemia, insulin resistance, and chronic anovulation. Many candidate genes have been identified to be one of the causes of PCOS. Different studies have been carried out to find the genetic correlation of PCOS. It is essential to carry out such studies that identify the clear cause of PCOS and its genetic association and hormonal disbalance. Currently, PCOS is considered a polygenic trait that might result from the interaction of susceptible and protective genomic variants and environmental factors, during either prenatal or postnatal life.

KEYWORDS: Polycystic ovary syndrome, Genetics, Preeclampsia, Hypertension, Gestational diabetes mellitus, Preterm delivery, Metformin, Hyperandrogenism, Oligoanovulation.

I. INTRODUCTION

Polycystic ovary syndrome (PCOS) affects 6%-15% of women of reproductive age worldwide and is characterized by hyperandrogenism, ovulatory dysfunction and polycystic ovarian morphology. Polycystic ovary syndrome (PCOS) is a condition in which the ovaries produce an abnormal amount of androgens, male sex hormones that are usually present in women in small amounts. The name polycystic ovary syndrome describes the numerous small cysts (fluid-filled sacs) that form in the ovaries. Polycystic ovaries contain a large number of harmless follicles that are up to 8mm (approximately 0.3in) weight gain. Post conception, PCOS women are at increased risk for early pregnancy loss (EPL). After having successfully passed the first trimester, they commonly encounter later pregnancy complications gestational diabetes mellitus like (GDM), pregnancy-induced hypertension in size. The reproductive issues with PCOS mainly start with anovulatory cycles leading to subfertility, irregular periods, hirsutism and (PIH), preeclampsia, preterm delivery, and birth of small for gestational age (SGA) infant. It is estimated that between five to 10 percent of U.S. women of childbearing age have PCOS. That's about 5 million women, which makes the condition one of the most common hormonal endocrine disorders among women of reproductive age. Overweight is also a major cause. Weight loss can be very effective in lessening many of the health conditions associated with PCOS. Sometimes weight loss alone can restore hormone level to normal, causes many of the symptoms to disappear or become less severe. Healthy food habits and exercise helps to combat the weight gain. It is now clear that the majority of hirsute women with regular menses have polycystic ovaries. The normal functioning of hormones plays an important role in the ovary functioning and regulation of the menstrual cycle that maintains fertility. India has witnessed about 30% rise in polycystic ovarian syndrome (PCOS) cases in the last couple of years. Lack of knowledge and lifestyle changes are considered to be the major factor leading to this phenomenon. There is a need to increase awareness among women so as to avoid major cases of fertility problems in the future. [1]-[2]

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POLYCYSTIC OVARY SYNDROME

A disorder develops during puberty and characterized by enlargement of ovaries with fluid filled sac (cysts) and tendency to have high levels of male hormone (androgen). It is also called as STEIN LEVENTHAL SYNDROME. It is chronic anovulation and excess activity ovaries that involves ovarian dormancy or primary insufficiency.
It's a common endocrinal disorder which may include reproductive, endocrine and metabolic alterations characterized by hypothalamic - pituitary - ovary axis dysfunction. It is characterized by Oligominorrhoea, anovulation, hirsutism and obesity in young women. [2]

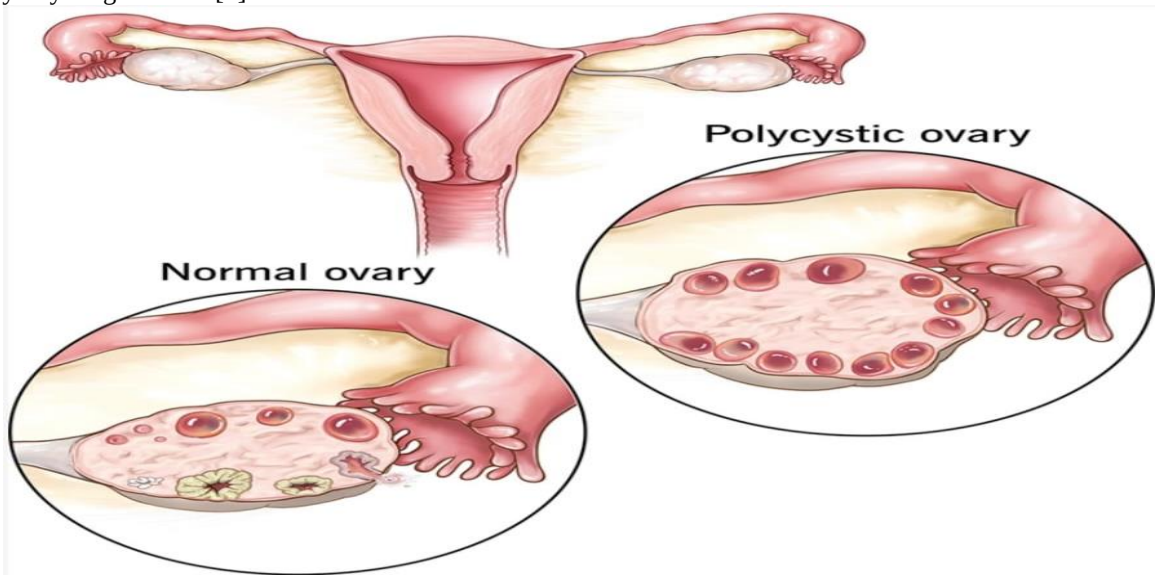

Fig: 1 Polycystic Ovary Syndrome

TYPES OF POLYCYSTIC OVARY SYNDROME

There are 4 types of PCOS each require different types of treatment:

A. Insulin resistance PCOS
B. Adrenal PCOS
C. Inflammatory PCOS
D. Post-pill PCOS

A. INSULIN-RESISTANT PCOS

It occurs in 70% cases of PCOS. This condition is called due to the insulinoma means cell become numb to the effect of insuline.

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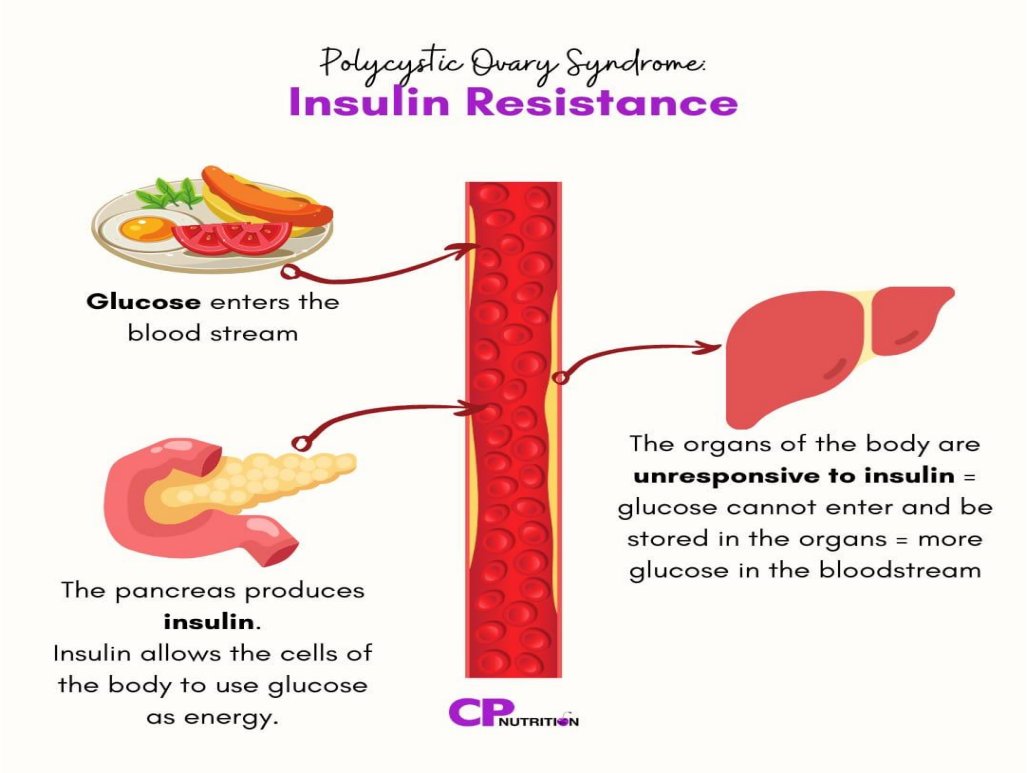

Fig: 2 Insulin Resistance PCOS

Insulin-resistant PCOS happens when your cells don't respond to insulin. Insulin is a hormone that regulates glucose, or your blood sugar.

When working properly, insulin helps turn the sugar from your food into energy or stores it for energy later. But with insulin resistance, your body isn't able to use the sugar as energy, so it builds up in your cells and causes high blood sugar.

As a result, your insulin level can increase, causing PCOS-related symptoms.

The symptoms of this conditions are weight gain, sugar cravings and fatigue. Regular exercise and movement can help to treat this condition. Stress and sleep well can helpful.

B. ADRENAL PCOS

It accounts around 10% of PCOS cases this mainly occurs in masive stressful periods. This type of PCOS marked indicators of high levels cortisol and DHEA (another type of androgen from adrenal gland). Adrenal PCOS happens when the adrenal glands (which are located on top of your kidneys) make too many hormones. Typically, the adrenal glands make hormones like cortisol (the stress hormone) and norepinephrine (adrenaline). When your adrenal glands make too many hormones, you may be at risk for higher androgen levels, which can produce PCOS symptoms. Managed stress, get enough sleep each night, avoid high intensity exercise, avoid caffine, can help to treat this type of PCOS.

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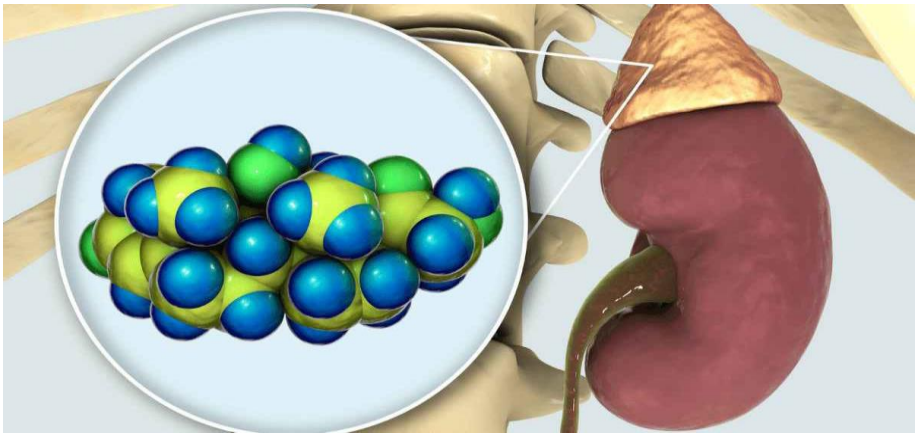

Fig: 3 Adrenal PCOS

C. INFLAMMATORY PCOS

This type of PCOS mainly causes due to chronic inflammation which causes ovaries to make excess testosterone, that's result into issues with ovulation and physical symptoms.

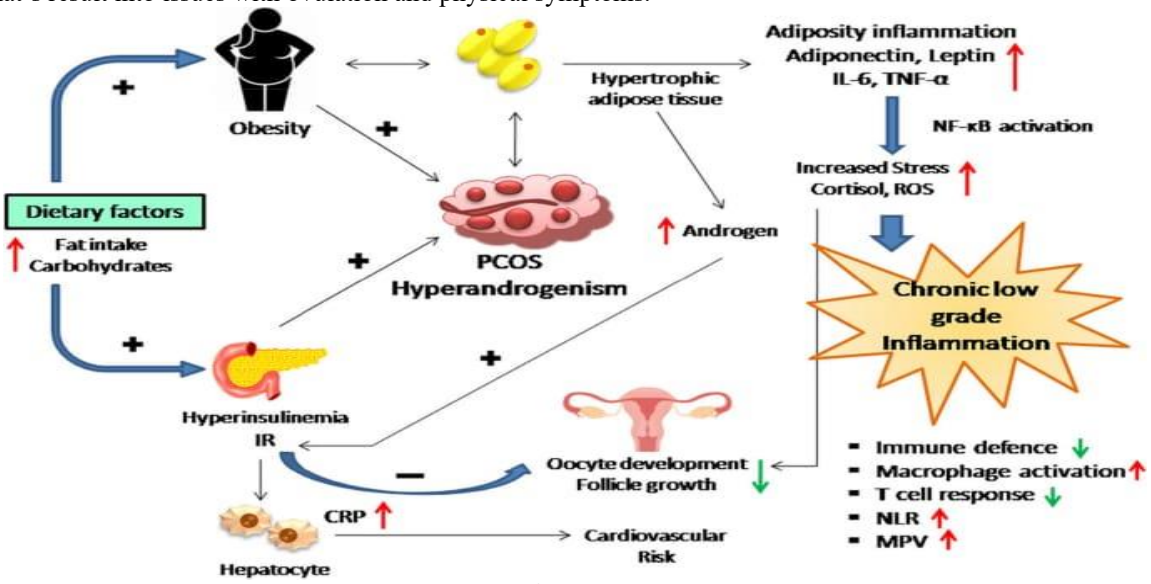

Fig: 4 Inflammatory PCOS

Inflammatory PCOS have chronic low-grade inflammation. This means that people with this type have high blood levels of C-reactive protein, a protein your liver makes when there's inflammation in your body. Inflammation can raise both your androgen and insulin levels, causing PCOS symptoms to occur.

Headache, joint pain, skin issues, IBS symptoms of this type which occur due to inflammation.

D. POST-PILL PCOS

This type of PCOS seen in women after stop taking oral contraceptive pills. Oral contraceptive pills (e.g., birth control) can cause post-pill PCOS. Specifically, oral contraceptive pills manipulate estrogen and progesterone hormones to prevent pregnancy. In some cases, when you stop taking those pills, your ovaries may make more androgen than usual. Symptoms like excess hair growth, acne, irregular periods. Low stress, good sleep, nutrients can help to treat this condition. [3]

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Fig: 5 Post pill PCOS

II. EPIDEMIOLOGY

- Polycystic ovary syndrome is a common endocrine disorder in women of reproductive age, with a prevalence of 4- 21% depending on the diagnostic criteria used.
- The global disease burden seems to be increasing at a high rate. In 2019, an age per 100 000 population were reported based on data from 204 countries, representing increases of 30.4% and 29.5%, respectively, since 1990.
- The rising incidence, and accompanying morbidity, emphasises the importance of recognising polycystic ovary syndrome as an international public health priority.
- Up to 70% of affected women remain undiagnosed worldwide.
- With a prevalence of 4-12% up to 10% of women were diagnosed with PCOS during gynecologic visits.
- The World Health Organization (WHO) data suggests that approximately 116 million women (3.4%) are affected by PCOS globally.
- Worldwide it affects 4%-20% (8-40 crore) of women.
- In India, it affects 3.7%-22.5% (1.3-7.9 crore) of women.
- In the United states, an estimated 5-6 million women have PCOS. [4]

III. ETIOLOGY

The exact etiology of PCOS or PCOD is yet to be explicated nevertheless there is noticeable inherent resistance towards insulin, even if the women are slender.
Hyperinsulinemia (increase in insulin level), which increases the production of androgen; there is a decrease in protein binding, which ultimately increases the level of free androgen. Due to the above-mentioned hormonal imbalance, there are noticeable alterations in the appearance of the ovary, disturbing its function and hurts fertility.
Insulin resistance concerning PCOS is further worsened by obesity. Obesity is having a two-directional relationship with PCOS, with women gaining weight regularly, exacerbates PCOS occurrence and its severity. PCOS reacts well to exercise and having a change in the dietary plan, both of which reduce insulin resistance.
Some features highlighted by findings that androgen secretion is stimulated by insulin via ovarian theca, which suppresses (SHBG) sex hormone-binding globulin and, thus, enhances free circulating testosterone. However, insulin resistance is not considered a universal feature of PCOS.
Both genes and the environment contribute to PCOS. Obesity, exacerbated by poor dietary choices and physical inactivity, worsens PCOS in susceptible individuals. The role of other environmental modifiers such as infectious agents or toxins are speculative.
Genetic factors are strongly implicated in PCOS, although the exact etiology is unknown.
For instance, a significant proportion of mother and siblings of PCOS-affected women share the same morphological features on ultrasound. Furthermore, evidence points to the autosomal transmission of the implicated genetic sequences. It's possible that a gene, or set of genes, prevents follicular maturation and makes the ovary vulnerable to insulin stimulated androgen secretion. [5]-[6]

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IV. PATHOPHYSIOLOGY

Polycystic Ovary Syndrome (PCOS), the pulsatile release of gonadotropin-releasing hormone (GnRH) from the hypothalamus is often disturbed in polycystic ovary syndrome (PCOS), leading to the hypersecretion of luteinizing hormone (LH) by the pituitary gland, which induces ovulary dysfunction and hyperandrogenism. This disturbed secretion of LH is thought to occur early in puberty and is related to the disturbed inhibition of GnRH secretion by progesterone. Although serum follicle-stimulating hormone (FSH) levels are generally normal, follicles seem to be more resistant to FSH for women with PCOS than in controls. This effect might be due to increased levels of intra-ovarian anti-Müllerian hormone (AMH). Notably, genetic and epigenetic variants contribute considerably to most of these alterations. Environmental factors contribute somewhat less, most by exacerbating insulin resistance and dysregulated gonadotropin secretion.

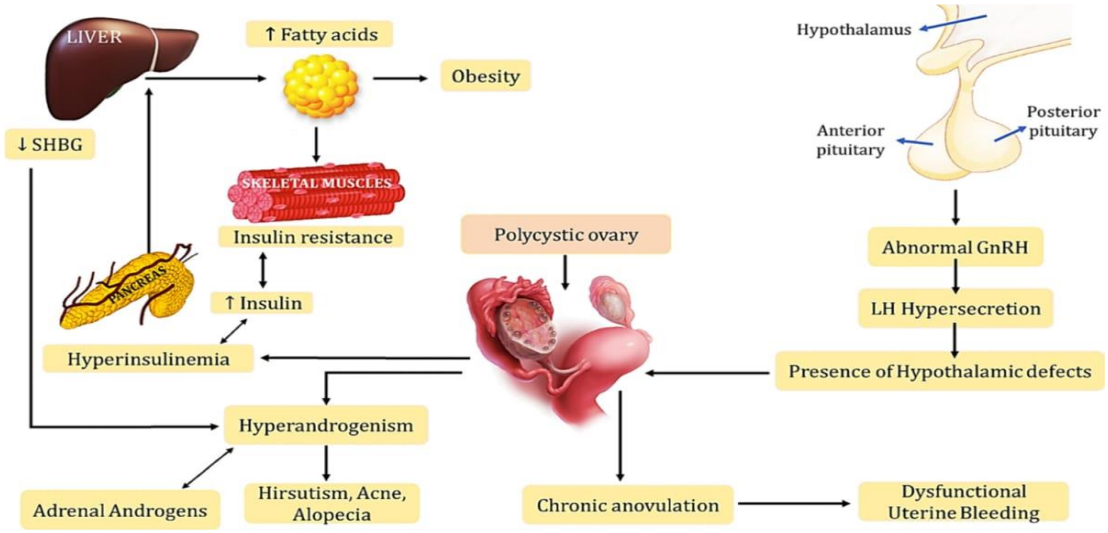

Fig:6 Pathophysiology of PCOS

Across the globe, PCOS affects between 8% and 20% of women of reproductive age annually, according to the diagnostic criteria. The pathophysiology of these condition is influenced by alterations in steroidogenesis, ovarian folliculogenesis, neuroendocrine function, metabolism, insulin production, insulin sensitivity, adipose cell activity, inflammatory factors, and sympathetic nerve function.

The high consumption of carbohydrates, hyperinsulinemia, hyperandrogenemia, persistent low-grade inflammation of the four key contributors to pathophysiological alterations in PCOS. [7]-[8]

V. SYMPTOMS

There are many symptoms which are contributed to PCOS. Such as:

- Excessive body hair growth
- Insomnia
- Acne
- Irregular periods
- Diabetes mellitus
- Acanthosis
- Seborrhea
- Infertility
- Hirsutism
- Alopecia

A. HIRSUTISM

It is excessive growth of hair on a woman's face and body. In this case, there is a condition of unwanted hair growth in women mainly on the face, chest, and back, just as males.

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B. ACNE
It is a chronic skin condition that causes the spots and pimples. It mainly occurs when oil and dead skin cells clog the hair follicles which leads to the formation of whiteheads, blackheads, pimples, cysts, etc. They mainly occur on the face, shoulders, back, neck, chest, upper arms.
C. ALOPECIA
It is the condition in which there is sudden hair loss which leads to baldness and in this condition, there is also thinning of hair.
D. ACANTHOSIS
It is skin condition when there are dark velvety patches in the body folds and body creases like underarms and neck. The affected skin can become thicken and blackened.
E. SOBORRHEA
It is a condition when there are patches and red skin mainly on the scalp. There may be yellow plaques on the scalp. It is also a chronic inflammatory disease.

F. INFERTILITY

It is an inability to conceive after a long period with unprotected sex.

G. INSOMNIA (OR) SLEEPING DISORDER

Women with PCOS reports for the poor sleep or insomnia. There are a number of factors which leads to poor sleep but the PCOS is associated with the sleep disorder called sleep apnea. In the case of sleep apnea person, stops breathing for some duration during sleep.

H. IRREGULAR PERIODS

It is a problem with menstrual cycles. It is a condition when there are delayed, missed, or more bleeding patterns. It further leads to the problem in the reproductive system. With PCOS, there is a correlation to a low level of androgen with advancing age in women. [9]

VI. PREGNANCY COMPLICATIONS RELATED TO PCOS

A. MULTIPLE PREGNANCY

Multiple complications pregnancies in prenatal increased morbidity observed in fertility treatment with special regards to women with PCOS affected by an ovulatory infertility. Most complications are caused due to preterm delivery. Multiple pregnancies are also related to obstetric and neonatal complications. Twin pregnancies increased 10-fold risk in newborn and 6-fold risk in premature delivery.

B. PREGNANCY INDUCED HYPERTENSION AND PRE-ECLAMPSIA

The PCOS pregnancies lead to increase the maternal obesity. The meta-analysis gives the result of 3-4 folds increase the risk of pre-eclampsia it is similar to the pregnancy hypertension (PIH). In induced PCOS pregnancies the 50% of women's cause the pre-eclampsia as compared to the normal one. In the pre-eclampsia which increase the blood pressure after the 20th week of pregnancy. Pre-eclampsia damage the mother's organs are kidney, liver, and brain. The pre-eclampsia is not treated on time leads to cause the eclampsia.

C. GESTATIONAL DIABETES MELLITUS
The gestational diabetes is one of the diabetes which pregnant women get 40 to 50% of gestational diabetes complicates the PCOS pregnancies. GDM caused due to the adequate pancreatic β-cell functioning in PCOS women. Treating the GDM which reduces the maternal and neonatal complications. The risk of GDM is three times higher with PCOS women. The pregnant women with PCOS having the gestational diabetes mellitus (GDM) whose baby having the greater risk of causing the type- 2 diabetes mellitus later in life.

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D. MISSCARRIAGE

PCOS women are at risk of first trimester miscarriage. This is because of early pregnancy loss (EPL) occurs in 30-50% of PCOS women compared with 10-15% of normal women. There are various mechanisms of EPL which includes obesity, insulin resistance, impaired fibrinolysis hyperandrogenism, and endometrial dysfunction. Reoccurrence or spontaneous pregnancy loss in PCOS which occurs in nearly 50% of total pregnancies is a frequent obstetric complication.

E. CAESAREAN RISK

The women with PCOS also lead to increase complication deliveries as in caesarean compared with normal deliveries or deliveries of women's without PCOS. Due to the hormonal in in women with PCOS the size of embryo also gets increased and hence the risk of C section or caesarean delivery gets increased twice as compared to normal women. The infants with caesarean delivery of women with PCOS can also susceptible towards the risk of shoulder dystocia (condition in which baby's shoulder get stuck during labour) due to larger size of infant.

F. CONTINUOUS PRETERM DELIVERY /PRENATAL DELIVERY

The prenatal deliveries can do worst effect on infant as well as mother with PCOS compared to mother without PCOS. This can be further leads to GDM, obesity and other maternal issues. Prenatal deliveries can indicate adverse effects due to poor development of oocyte, embryo quality and intrauterine environment. The prenatal delivery of women with PCOS having GDM history can leads to develop fetal macrosomia resistant into altered glucose metabolism and disturbed uterine blood flow. [10]

VII. RISK FACTORS

- Diabetes
- 4-7 times of higher risks of Heart attacks
- High Lipids
- High Cholesterol
- Sleep Apnea
- Infertility
- High rate of Miscarriages
- Obesity which can also leads to low self-esteem and depression

A. HIGH ANDROGEN AND INSULIN LEVELS

Androgen and insulin are hormones, which are chemical messengers that control different functions in your body. Having high androgen levels, insulin levels, or both could increase your risk of developing PCOS. Insulin controls the way the food you eat is converted to energy, and it influences metabolism and body weight. High insulin levels increase your risk of PCOS and insulin resistance, a condition that changes the way your body responds to insulin.

B. FAMILY HISTORY OF PCOS

Hormone imbalance and other genetic factors that influence PCOS can be passed from one generation to another, although these links aren't well-understood. Women with a family history of Type 2 diabetes may also be at increased risk for PCOS.

C. LIFESTYLE HABITS

Lifestyle factors alone don't cause PCOS, but they can work with genetic and environmental factors to increase your risk. These factors may include:
Being obese or overweight.
Having poor eating habits.

D. OBESITY

Obesity is a chronic recurrent multifactorial neurobehavioral disease in which an increase in body fat contributes to adipose tissue dysfunction and biomechanical effects of adipose tissue on surrounding tissues with the development of metabolic and psychosocial health consequences. [11]

VIII. DIAGNOSIS

Diagnosis is the main purpose to detect or to identify the disease by seeing their symptoms, or by performing many tests.

A. APPEARANCE

Diagnosis of PCOS occurs by seeing the appearance of ovaries like in case of PCOS there are polycystic ovaries due to having more than 12 follicles present in it which cause enlargement of the ovary.

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B. MEDICAL HISTORY

To diagnose PCOS doctors may check a patient's medical history like is there any person already having the same problem in the patient family.

C. SYMPTOMS

The person with PCOS is more prone to mental health problems like depression, anxiety because it is a chronic disease with increase male hormone i.e. testosterone causing problems and this hormone during pregnancy having reported increasing the risk of neurodevelopmental disorders.

D. PELVIC EXAM

During a pelvic exam, check your reproductive organs for masses, growths or other changes.

E. BLOOD TEST

Blood tests can measure hormone levels. This testing can exclude possible causes of menstrual problems or androgen excess that mimic PCOS. You might have other blood testing, such as fasting cholesterol and triglyceride levels. A glucose tolerance test can measure your body's response to sugar (glucose).

F. ULTRASOUND

An ultrasound can check the appearance of your ovaries and the thickness of the lining of your uterus. A wand-like device (transducer) is placed in your vagina. The transducer emits sound waves that are translated into images on a computer screen.

G. HORMONAL BLOOD TEST

These tests are used to check the level of hormone in our body. The most important hormonal test to check whether women may have hyperandrogenism is tested for androgens like testosterone and free androgen index. There are many other tests performed to detect the hormonal level, which may affect mensuration and ovulation. [12]

IX. TREATMENT

Since there isn't a cure for PCOS that addresses all clinical manifestations and cures the hormone imbalances that cause it, medical care solely focuses on treating specific symptoms in conjunction with lifestyle modifications.

A. Diet Regimen

A diet plan works to control weight while lowering the long-term risk of PCOS. Cardiovascular illness, type 2 diabetes, etc.

B. The following products should be avoided

- Nicotine, caffeine, alcohol, and the addictive substance in each.
- Products made from soy: they prevent ovulation.
- Normal testosterone processing is limited by milk protein, which results in level syndrome.
- Red meat and dairy items are high in saturated fats, which boost the synthesis of estrogen.
- High glycemic index food, such potatoes and white rice.

C. The following products should be consumed

- Whole grains: red rice, ragi.
- Rich in vitamins, minerals and nutrients are green leafy vegetables.
- Dry fruits-fig, dates.
- Whole fruits with low glycaemic index: pears, apples, grapes, oranges, and plums.

PHARMACOLOGICAL MANAGEMENT

*Clomiphene citrate**:***

For PCOS patients, it is the first-line medication for inducing ovulation. The oestrogen receptor antagonist increases the availability of FSH by interfering with the oestrogen signalling pathways negative feedback. Follicle growth is a result of elevated FSH. It includes the first phase of the menstrual cycle. Additionally, infertility is treated using it.

Metformin:

Insulin sensitizing medications, including metformin and troglitazone, work to counteract some hyperandrogenic symptoms by lowering the concentrations of both free and total testosterone. It promotes ovulation, lessens insulin resistance-related issues, and controls abnormally high testosterone levels. It brings back fertility, ovulation, and the menstrual cycle. Pregnancy-related conditions such gestational diabetes and gestational hypertension are less common when this occurs.

Flutamide:

It was suggested as a substitute for spironolactone, which works by blocking the androgen receptor. Pure non- steroidal antiandrogens work in a dose-dependent manner to block the androgen receptor, although they are not more effective than spironolactone.

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Glucocorticoids:
To induce ovulation, prednisone and dexamethasone have been utilized. Patients with PCOS who have elevated adrenal androgen may benefit from taking low doses of dexamethasone (0.25-0.5mg) before bed.
Gonadotropins:
When clomiphene citrate is no longer effective, it is used as a second line of treatment. With the carefully regulated injection of FSH4, it promotes follicle growth, maintains ovulation, and begins treatment with modest dosages.
N-Acetyl cysteine:
It contains antioxidants needed by the body to produce glutathione, which reduces oxidative stress and keeps hyperinsulinemia from occurring.
Surgery:
Laparoscopic ovarian drilling [LOD] is a procedure used to eliminate androgen-producing tissues in women who do not respond to clomiphene treatment. Re-establishing hormonal balance and making corrections in ovarian activity. Treatment options for hirsutism and acne include suppressing hyperandrogenism.
Isotretinoin:
Isotretinoin works by altering the cell cycle, cell differentiation, survival, and apoptosis. This action reduces sebum production, preventing blockage of pores and the growth of acne-causing bacteria. It can also reduce the formation of comes down by reducing hyper keratinization. The side effects of Isotretinoin include dry skin, conjunctivitis, dry mucous membranes, cheilitis, itching, joint and muscle pain, and mood changes in adolescence. [13]

X. CONCLUSION

It is obvious from the review that PCOS could be a complex condition. The central instrument is troublesome to get it and state. Subsequently no treatment can be claimed as an enchantment bullet because it targets the clinical side effects instead of curing the disorder. Elective drugs such as home grown or therapeutic plants ought to be considered by knowing their instrument of activity. Assist examination with respect to pathophysiology and drugs acting on it ought to be done for extemporizing the standing result on patient's health. And libbing way of life seem ease the PCOS related indications.

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