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Review on Polycystic Ovary Disease (PCOD)

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Abstract: *The research activity include the analysis of predisposing condition that increase the risk of PCOD due to genetic background and environmental factors such as endocrine disruptors and lifestyle. PCOD is a condion that affects womens ovaries the reproductive organ that produce progesterone and estrogen hormone that help in regulating menstrual cycle and also produce small amount of inhibition relaxin and male hormone called Androgen. Polycystic ovarian syndrome is a set of symptom related to an imbalance of hormone that can affect womens and girls at reproductive age.(6)*

Keywords: PCOD

I. INTRODUCTION

Between 5% -26% womens are affected by PCOD depending on diagnostic applied women throughout life span are at risk being affected by PCOD. Women from all region of the world including Australia, China, India, Greece, Netherland, Spain, U.K, and U.S have a reported cases of PCOD

Polycystic ovarian disease is a now days a commonly rising concern for gyanecologist PCOD is a condition that has multiple ovarian cyst and lots of hormonal and biochemical aberration(3)

Excess androgen production by ovary and adrenals interfere with growth of ovarian follicle and ovulation. The clinical of PCOD are menstrual abnormalities. Due to increasing obesity.

The PCOD is one of the most frequent endocrine disease in women at a reproductive age with prevalence of 9.13%in India (4)

A PCOD is associated with hyperinsulinemia it has a major metabolic as well as reproductrive morbidities (5)

In Ayurveda this condition not explained as a single disease entity but given under heading *Yonivyapada*(genital disorder) and *Artavadushti*(menstrual disorder)(3)

In PCOD there is *Nashtaartava* which means loss of both mensturation as well as ovulation (3)

Treatment of PCOD in modern science stresses more upon the management of obesity.

In medicinal therapy involves hormonal treatment which has various side effects of its own (6)

The diagnosis of PCOD based on existing clinical evidence oligo or ovulation, clinical and biochemical hyperandrogonesim and polycystic ovaries constitute the key of clinical feature on which diagnosis should be based

Poycystic ovary syndrome (PCOD) it's characterized by oligomennorrhoea, anovulation, infertility, hirsutism and obesity in young women having bilaterally enlarged and cystic ovaries

The principal of biochemical abnormalities in most patient are excessive (high amount) production of Androgen and low level of Follicle stimulating hormone(FSH). Current concept of pathogenesis of PCOD is the unbalanced release of FSH and LH by the pitutary gland.

FSH is inhibited to low levels by testosterone but the level of LH is sufficient to cause luteinisation of ovarian theca and granulosa cells which then secreate Androgen which appropriately produce an abnormal state of an ovulation (1)

The central morphological abnormality of PCOD is numerous cystic follicle cyst that enlarge the ovaries STROMAL HYPERTHECOSIS also called cortical stromal hyperplasia is a disorder of ovarian stroma most of seen in post.menopausal women but it overlap with PCOD in yonger women (2)

Pathophysiology of PCOD

PCOD in all stages is dominated by *kapha* leading to amenorrhoea as when *apana*is influenced by *pitta* it creates *artavartipraviriti.*

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Vishamaaharvihar causesagnimandya leading to apakwata of aadya rasa and formation of saam rasa which vitiates the arratva as well as causes kaphavridhi which further leads to srotorodhajanyaapachita-medhodhatuvridhi and vataprakopa causing obesity and amenorrhoea

The exact pathophysiology is not clearly understood. It may be discussed as hypothalamic pitutary compartment abnormality androgen excess anovulatuion ,obesity and insulin resistance long term consequences (3)

In normal women androgen production rate is high the result of adrenal and ovarian secreation and conversion from precursor in peripheral tissues, particularly the adipose tissue and skin(8)

The metabolic clearance rate of androgen may occur in both glandular and extraglandular tissue. Both production rate and metabolic clearance rate in female is depend on age and physiological status, all androgen exhibit a daily rhythm,less variable for androstenedione and testosterone than that of DHFA and Cortisol.(8)

In PCOD women with different obesity phenotypes, although there is evidence that in women with simple obesity, those with abdominal fat distribution have higher testosterone production rate, but not higher androstenedione, with respect to those with the peripheral phenotype(9)

Estrogen and progesterone production rate in women with PCOD have been poorly investigated,

The pathophysiology of PCOD involves primary defects in the hypothalamic pitutary axis, insulin secretion and action of ovarian function. The causes of PCOD is unknown PCOD has been linked to insulin resistance and obesity, insulin helps to regulate ovarian function, and ovaries respond to excess insulin by producing Androgen which can leads to anovulation.

Follicular maturation arrest is sign that an ovarian abnormality exist. Therapeutic intervention are designed to reduce insulin level and ovarian androgen production ultimately correcting sex-hormone binding globulin levels. Thecal cells of PCOD patient produce higher amounts of testosterone, progesterone, 17-hydroxy progesterone than in normal patient.

Obesity is not common comorbidity of PCOD but is not required for diagnosis. Clinical signs of PCOD include elevated LH and Gonadotropin releasing hormone (GnRH) levels, where as Follicular stimulating hormone (FSH) levels are muted and unchanged. As a result of increasing in Gonadotropin releasing hormone (GnRH), stimulate the ovarian thecal cells leads to produce more androgen. (13)

Significance of adrenal androgen production :-

The pathophysiological mechanism is responsible for increased androgen production by the adrenals in women with PCOD remains. Difficulty in obtaining viable and appropriate adrenal tissue has limited it vivtro study of human tissue, but long term culture is possible and the derivation of stem cell adrenal cortex tissue could significantly enhance studies of this important gland. It has been estimated that 25% of androstenedione and testosterone production of ovarian origin, 25% is adrenal origin and 50% is produced in peripheral tissues, while the adrenal cortex account almost uniquely for the synthesis of dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), As well that of androstenediol and 11-beta hydroxy androstenedione.

In women androgen serve as precursor of estrogen biosynthesis, which starts to decrease 3-4 years before menopause. At the same time basal serum levels of ovarian androgen decrease only slightly and remain relatively stable until menopause, while the decrease of adrenal androgen can already be observed after the age of 30 years compared with healthy subjects, women with previous PCOD have an increased adrenal capacity to secreate androgen that remains until after menopause

These result confirm the adrenals contribute significantly to hyperandrogenism in PCOD and similarly to ovarian androgen secreationcapacity,women with PCOD exhibit enhanced adrenal androgen production until their reproductive years(20)

Enzyme defects in PCOD :-

Are primary enzyme abnormalities in the steroidogenic pathway an important cause of PCOD?

On the basis of currently available evidence the answer to this is question is “NO”

The plausible candidate genes in genesis of hyperandrogenemia are CYP_{17} Because of evidence for a global increase in steroidogenic enzyme ativity in pco theca cells, CYP_{11a} .

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Case control family based studies have shown no clear evidence that varients in these genes contribute to pathogenesis of PCOD. Recent work has focused on metabolism of cortisol and adrenal androgen but although specific enzyme defects my be associated with a PCOD phenotype. In addition extraglandular synthesis of androgen particularlay in the adipose tissue has been found to be involved in the pathophysiology of PCOD.(20)

Classification of PCOD on their evidence :-

Initial analysis is patient suspected to suffer from PCOD should include serum determination of 17-Hydroxy progesterone, estradiol and follicle stimulating hormone, as well as LH, TSH and Prolactin level.

1)Oligo-or anovulation :-

Oligo and ovulation are always associated with menstrual irregularities. In oligo-anovulation ovulation occurs less than 8 ovulation per year. Therefore the intercycle interval should be exceed 35 Days. In case of ovulation is present no menstrual bleeding occurs hence the intercycle interval always excced 6 month or 183 Days.

The ovarian ageing has an impact on the length of intercycle interval since in some women a normal cycle length is increasing with increasing age (21)

2) Hyperandrogenism :-

The clinical indicator for hyperandrogenism is hirsutism, Acne seems a sensitive marker for hyperandrogenism.

Similarly the presence of Alopecia androgenica appears to be a poor marker for hyperandrogenism. Nowithstandingthe assessment of free testosterone or free androgen index are the more sensitive method of determining Hyperandrogenemia. Measurement of other androgen like Dehydroepiandrosterone (DHEA) And in sulphated form as well as Androstenedione (AD) seem to a limited value. The assessment of hirsutism is rather subjective since most clinicians do not used standardized scoring method. Biochemical assessment of hyperandrogenemia might be hampered by the fact that normative data specially in Aldoscent women. Androgen are suppressed very rapidly due to exogenous hormone administration and may remain suppressed even after therapy has been discontinued.(21)

3)Polycystic ovaries :-

Polycystic ovaries (PCO) isnowdays defined as the presence of 12 or more follicles in each ovary measuring 2-9mm in diameter and an increased ovarian volume i.e more than 10 ml. Follicle distribution seems not of any value as an stromal echogenicity and subjective appearance of PCO.

The measurement of ovarian volume constituets a good subjective for stromal echogenicity. Ultrasound should be performed preferably through the transvagianal approach using state of the art equipment. Reguraly menstruating women and those having had a progestagenwithdrawlbleeding should be scanned on 3-5 Days in the early follicular phase. Ovarian volume should be determined using the simplified formula for a prolate ellipsoid, i.e. (0.5 length width thickness)

Follicular number should be estimated in both longitudinal and anterio-posterior cross section. The size of the follicles less than 10 mm should be expressed as the mean of diameter measured on two section.(21)

4) Leuteinizing hormone:-

Elevated leuteinizing hormone (LH) levels are frequently encountered in PCOD despite normal serum follicle stimulating hormone (FSH) concentration. Serum level of leuteinizing hormone (LH) above 95% of a normal women population can be found in upto 60% of women with PCOD, whereas the ratio of FSH/LH elevated in upto 95% of subjects.

Sets of data in WHO-2, infertile patient suggest that LH serum concentration are independent from timing in relation to bleeding in oligomenorrheic patient. Hyperinsulinaemia direct stimulate the gonadotropic cell which is related to hypersecreation of LH. The abnormalities in the production of intra-ovarian regulators of LH secretion rather than a primary hypothalamic defect are the cause of LH hypersecretion. The recent observation from large repeated miscarriage clinics show convincingly that initial LH levels are normal in these women (21)

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5)Insulin Resistance :-

Insulin resistance associated with reproductive abnormalities in women with PCOD. Insulin resistance inwomen with PCOD is seen in upto 50% of patient in obese and non-obese women. Insulin resistance is generally measured by fasting glucose ratio's which co-relate with dynamic test of insulin action instead criteria have been develop to define the metabolic syndrome which include insulin resistance centripetal obesity, hypertension, fasting hyperglycemia and dyslipidemia. Elucidate the intricate relationship between insulin resistance, the metabolic syndrome and PCOD both as far as treatment outcome and health hazard's are concerned (21)

CAUSES OF PCOD :-

The function of ovary is to produce and release egg, for fertilization with egg production it secreate few hormone necessary for the maturation of egg and to prepare uterus for implantation of fertilized egg. The hormone like oestrogen and progesterone are the prime female hormone, ovaries also secreatethe male hormone, i.e. Androgen

Any imbalance of these hormone cause PCOD condition.

i) Hyperinsulinemia :-

insulin is a hormone responsible for glucose metabolism and help the cells to utilize glucose for energy. In certain condition cells remain insensitive to insulin, this leads to increase in amount of insulin cause hyperinsulinemia. This hyperinsulinemia cause stimulate to ovary to secrete more androgen.

ii) Increased Amount of Androgen / Testosterone :-ovaries secrete very less amount of androgen, but it secretion was increased due to hyperinsulinemia or increased LH hormone level , it can adversely affect ovulation leads to PCOD condition.

iii) Increased level of LH hormone:-

Leuteinizing hormone (LH) is a secreted by Anti-pitutary gland. The function of this hormone is help to ovulation and development of corpus luteum, when this hormone level is increased in blood it can stimulate excessive production of Androgen in females, that cause hormonal imbalance.

iv) Increased prolactin level:-

Prolactin is a hormone again secreted by pitutary and help mainly for milk secretion. The increased level of prolactin cause decrease oestrogen hormone level that cause imbalance in hormonal level.(22)

The exact cause of PCOD is still unknown it is a hormonal disorder and various reason contribute to it.

Some factor as follow:-

- Heredity
- Obesity
- High levels of inflammation
- High production of male hormone
- Unhealthy lifestyle
- Poor diet
- Lack of proper nutrition
- Pollution

Excess insulin

SIGN AND SYMPTOM:-

Sign and symptom of PCOD often develop around the time of the first menstrual period during puberty.

The symptom as follow:-

A)Irregular periods:-

Infrequent and prolonged menstrual cycles are the most common sign of PCOD.

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E.g:- In PCOD women the menstrual cycle below 9 cycles per year the time between two cycle is more than 35 days and abnormality heavy periods. In normal women menstrual cycle ranges between 10-12 cycles per year.

B)Excess Androgen :-

Increased level of male hormone may result in physical sign. Such as excessive facial and body hair and occasionally severe acne and male pattern haldness.

C) ***Polycystic ovaries:-***

Ovaries might be enlarged and contain follicles that surround eggs. Polycystic ovary was defined as an ovary with 12 or more follicles measuring in 2-9mm in diameter or increased in ovarian volume.

D)Acne:-

PCOD messes with hormones and result in various facial problems like acne. Excessive amount of male hormone in the body lead to acne.

Some women suffer from severe cystic acne due to PCOD.

E)Weight gain :-

In PCOD, high levels of insulin and male hormone are produced in the body. This leads to sudden weight gain in women. Fat deposit in the lower abdomen is a common symptom in PCOD.

F)Oily skin :-

Due to hormonal imbalance the skin also goes for a toss. It produce excessive amounts of serum and causes acne.

G)Heavy bleeding :-

Since the periods are irregular the build-up of the uterine wall (Endometrium layer) is more, during menstrual cycle when progesterone decreasing that cause breaking of endometrium layer it's leads to bleeding.

Hence more endometrium layer leads to heavier bleeding when menstrual cycle happens.

H)Hair thinning :-

Most women with PCOD suffer from hair thinning on the crown some even suffer complete hair loss. This is due to hormonal imbalance in the body.

I)Diabetes :-

Women suffering from PCOD are at a higher risk of developing diabetes due to high insulin level.

J)Skin darkening :-

Darkening of the skin on the neck or around the privates part is a common symptom of PCOD.

COMPLICATION :-

1)Infertility :-

PCOD reduce the frequency of ovulation in women, it delays the menstrual cycle and causes menstrual problem. All this can lead to infertility problems when women tries to get preganant.

2)Diabetes :-

PCOD causes the insulin resistance in the body if PCOD is not treated timely. It can cause diabetes.

3)Heart disease :-

PCOD leads to an increase in blood pressure. It can cause irregular heart-beat and other heart related problems.

4)Endometrial cancer :-

Endometrium is the inner lining of the uterus. In PCOD cause delays ovulation and this increase the chances of endometrial cancer.

5)Depression :-

Due to hormonal imbalance, many women suffering from depression during PCOD.

DIAGNOSIS :-

There is the no test to definitively diagnose PCOD your's doctor is likely to start with a discussion of your medical history, including your menstrual periods and weight changes, a physical exam will include checking for signs of excessive hair growth, insulin resistance, and acne

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Doctor recomandation some following test:-

1)A Pelvic Exam :-

The doctor visually and manually inspect your reproductive organ for masses growth or other abnormalities.

2)Blood Test :-

Patient blood may be analyzed to measure hormone levels. This testing can exclude possible causes of menstrual abnormalities or androgen excess that mimics PCOD.

You might have additional blood testing to measure glucose tolerance and fasting cholesterol and triglyceride levels.

3)An Ultra-sound :-

Doctor should checks the appearance of your ovaries and the thickness of the lining of your uterus.

A wandlike device (Transducer) is placed in your vagina (Transvaginal ultra-sound) the transducer emits sound waves that are translated into images on a computer screen.

If you have diagnosis of PCOD your doctor might recommended additional test for complication, Those test can include as follow:

a) periodic checks of blood pressure, glucose, tolerance, and cholesterol and triglyceride levels

b) screening for depression and anxiety

c) screening for obstructive sleep apnea.

TREATMENT APPROCHES FOR PCOD

PCOD treatment focuses on managing your individual concern, such as infertility hirsutism, acne or obesity.

Specific treatment might involve lifestyle changes or medication

1)Life style and home remedies:-

Maintain healthy weight :-

Some helpful tips for loasing weight with PCOD as Follow:-

i)Reduce carbohydrate intake :-

lowering your carbohydrate consumption may help manage PCOD due to carbohydrate impact on insulin level. A low glycemic diet may benefit women with PCOD. The glycemic index (GI) is a measurement of how quickly a particular food raises blood sugar. A women followed by a low GI diet for 12 weeks. Their measures of insulin sensitivity were significantly better during the low GI phase.

ii) Eat enough protein :-

Protein helps stabilize blood sugar and increase feelings of fullness after a meal. 57% women with PCOD were given either high protein diet more than 40% of calories from protein and 30% from fat a standard diet consisting of less than 15% protein and 30% fat.

iii) Eat healthy fat :-

healthy fat in your diet help you feel more satisfied after meal, as well as tackle weight loss and other symptom of PCOD.

iv) Exercise regularly :-

Exercise is a well known strategy to improve weight loss .

Ayurvedic treatment / Herbal therapy :-

Shatavari

Synonym:-shatmuli

B.S:-Aspargusracemosus

Family:-Aspargaceae / Liliaceae

For medicinal purpose shatavari root are used

Chemical constituent :-

Aspargamine A

Shatavarins

Polycyclic alkaloid

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Effect of shatavarin on PCOD :-

Shatavarin is an herb that helps to balance the hormone which are impaired in PCOD, maintsin hormone level, maintain HPO-Axis , and maintain ovarian plexus. Also it prevent the production of new cyst and even prevents the remmision of the disease. Shatavri helps to maintain the duration of the menstural cycle (3-7 days) and interval of the mensturalcycle (28-35 days) and blood flow during menses. It improves the uterine and ovarian health, its also called as female tonic, prepration available In market as SHATAVARI GULAM.

2)The varunacrataevanurvala is an effective herb help in the clearance of channel which reduce cyst.

3)Strotasshuddhi:- is a required and herbs like punarnava, kapphar medicine are advised

4*) Ashwagandha*

Synonym:-Indian ginsing , withania root

B.S:-WithaniaSomnifera

Family :- Solanaceae

Chemicals:- withaferin, withaferin-A, are steroidal chemical present.

Ashwagandha can help reduce PCOD symptom by lowering stress and cortisol.

Allopathic Approches for PCOD :-

i)To maintain Anovulation :-

Clomiphene citrate :-The drug of choice for inducing ovulation in PCOD is clomiphene citrate. A dose of 50mg/day for 5 days is given after 1st 5 days treated there if ovulation occurs but no pregnancy result continue these dose for subsequent cycle.(13) If ovulation does not occur after the first cycle, these dose may be increased to 100mg daily for 5 days at least 30 days after the previous course of therapy. Not more than 6 treatment cycle should be tried.(14) clomiphene citrate binds to both ER alpha & ER beta act as pure estrogen antagonist in all human tissues. It includes Gn secretion in women by inhibition of pituitary, the amount of LH/FSH released at each secreatory pulse is increased ovulation occurs.

Adverse Effect :-

Multiple pregnancy

Hot flashes

Vertigo

Dermatitis

Risk of ovarian tumor

Cautionly use with lower dose in women with enlarged ovary(14)

ii) To control hyperandrogenism :-

Spironolactone

Flutamide

Finasteride

Are the anti-hyperandrogenism drug are worked in PCOD by decreasing androgen level. Thereby reducing the signs and hirsutism and Acne. These anti-androgen may also improve lipid level which can be elevated in patient with PCOD.(15)

a)Spironolactone:-

it's a steroid, it show diuretic action also, it works anti-androgen also at a dose 25mg, 100mg, twice a daily. It most commonly used anti-androgen because of its safety, availability, and low cost,contraceptiveis recommended when patient are using anti-androgen for the treatment of PCOD.(16)

Adverse effect:-

Drowsiness, ataxia, mental confusion, epigastric distress and loose motion

Gynacomestia, libido in men erectile dysfunction

b)Flutamide:-

it's a non steroidaldrug , it's a active metabolite

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2-Hydroxyflutamide compitatively blocks androgen action on accessary sex organ as well as on pituitary. It increase LH secretion by blocking of feedback inhibition.

Adverse effect:-

Gynecomastia
Breast tenderness
Libido in men
Liver damage
Long treatment

iii) Anti-Dibeticagent:-

Anti-dibetic drugs can be used to improve fertility and decrease insulin resistance and reduce circulating androgen levels. Some ant-dibetic drug used in PCOD treatment like Metformin. The role of metformin for the treatment of infertility with PCOD.

Metformin :-

It's a anti-dibetic drug, metformin enhance insulin mediated glucose uptake and disposal in skeletal muscle and fat. Thus the insulin
resistance exhibited by Type-2 dibetes it overcome which is responsible for PCOD.

Adverse Effect:-

Abdominal pain
Anorexia
Bloating
Nausea
Metallic taste
Mild diarrhoea
Tiredness

Contraindication :-

Metformin contraindicated in renal failure because risk of lactic acidosis.(17)
Metformin has been found to improve ovulation and fertility in some infertile women with polycystic ovary. These benefit is observed irrespective of the glycemic status of the women, due to mitigation of insulin resistance and lowering of circulating insulin levels. A combination of metformin and clomiphene may be tried after individual therapies fail.

iv) Gonadotropins:-

Human menopausal gonadotropin and FSH can also be used to induce ovulation if clomiphene and metformin therapy fails.(13) Gonadotropins might be more effective than clomiphene for inducing ovulation. The comparative expenses and easy of administration of clomiphene favored. Clomiphene is a first line therapy for fertility in PCOD. Low dose of FSH was used in this study because in high doses are increased risk of multiple pregnancies.(18) inadequate gonadotropin secretion result in amenorrhea which leads to PCOD in women.(17)

V) Aromatase inhibitor :-

Letrozole :-

Letrozole is an aromatase inhibitor approved for patient with hormone responsive breast cancer it also has been studied for the induction of ovulation in PCOD.(19) In phase-2 dose finding study, a 5-day regimen of various doses of letrozole as compared with clomiphene 50mg/day. Arotamase inhibitor may be consider for patient with clomiphene resistance

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or for that women who are not candidates for clomiphene or gonadotropin because the risk of congenital abnormalities associated with the class of medication.(19)

vi) Oral contraceptive:-

women with PCOD who do not wish to become pregnant may consider oral contraceptive, the mechanism of action for oral contraceptive in the treatment of PCOD is primarily through regulation of menstural periods. Oral contraceptive also reduce hirsutism, acne and androgen levels.

Estrogen and progestin combination are primarily oral contraceptive used in treatment of hirsutism and acne associated with PCOD. Some newer oral contraceptive contain anti-androgenic action such as drosperenone and dienogest. These drug are more effective for treating androgenic symptom as compared with older formulation.(13)

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