

---

## Review of Literature

The review of literature for the present study “**Impact of Nutrition interventions on the symptoms of Polycystic ovarian syndrome among women of reproductive age (20-45 years)**” is presented under the following headings:

### **A. An overview of menstrual cycle**

- a) Phases of the menstrual cycle
- b) Hormonal Regulation of different phases of menstrual cycle
- c) Follicular Arrest – A condition of polycystic ovaries and hormonal imbalance

### **B. Polycystic ovarian syndrome (PCOS) –A common reproductive health concern for women**

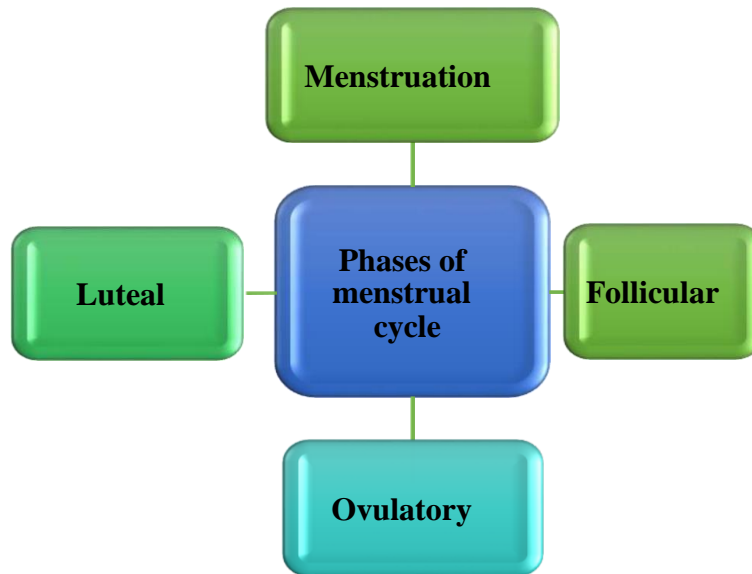
- a) History and definition
- b) PCOS and Reproductive Health
- c) Epidemiology
- d) Diagnostic criteria
- e) Classification
- f) Predisposing factors
- g) Pathophysiology
- h) Complications
- i) Signs and Symptoms

### **C. Management of Polycystic Ovarian Syndrome**

- a) Medical care and support
- b) Life style modification
- c) Nutrition intervention
- d) Nutrition Education
- e) Psychological management
- f) Adoption of Physical activity

**A) An overview of the menstrual cycle**

The menstrual cycle is the monthly series of changes a woman's body goes through in preparation for the possibility of pregnancy. The menstrual cycle is the monthly cycle of follicle and egg maturation, release of an egg (ovulation), and preparation of the uterine lining for pregnancy. Normal menstrual cycle is 28 days although normal cycle varies between 22-36days and last two to seven days (Richards, 2018).



**Figure 2 - Phases of menstrual cycle**

**a) Phases of the menstrual cycle**

**Phase I –Menstruation**

First phase Menstruation is the elimination of the thickened lining of the uterus (endometrium) from the body through the vagina. Menstrual fluid contains blood, cells from the lining of the uterus (endometrial cells) and mucus. The average length of a period is between three days and seven days

**Phase II –Follicular phase**

The 2<sup>nd</sup> phase of the cycle is Follicular phase, starts on 1<sup>st</sup> day of menstruation until the beginning of the ovulation (day 14). FSH (Follicle stimulating Hormone) and LH (Luteinising hormone) are released from the pituitary gland during this phase to stimulate the ovaries. Ovaries produce oestrogen and stimulate maturation of 15-20 eggs inside a small cystic area called follicle. Increased oestrogen causes FSH secretion being reduced so that follicle stimulation stops–feedback mechanism. This increase in FSH will stimulate

the granulosa cells of the ovaries to recruit several follicles from each ovary. One or two eggs in the follicle become dominant and continue secretion of oestrogen. These follicles will complete maturation, and only one Graafian follicle will go through ovulation during that cycle (Thiyagarajan, 2021)

### **Phase III – Ovulatory Phase**

Ovulatory phase occurs at the midpoint of the menstrual cycle. Oestrogen production from the dominant follicle leads to a sharp rise in LH secretion, causing the dominant follicle to release its egg. The egg is swept into the Fallopian tube by thin structures on the ends of the tubes known as fimbriae. At this time, the cervix produces an increased amount of thin mucus that assists sperm in the passage into the uterus (Jones 2008)

### **Phase IV - Luteal phase**

Luteal phase of menstrual cycle begins at ovulation (egg release). After the egg is released, the empty follicle turns into a cystic mass of cells called the corpus luteum. The corpus luteum then produces progesterone, a hormone that makes ready the lining of the uterus for implantation of a fertilized egg. If an egg has been fertilized, the fertilized egg travels down one of the fallopian tubes into the uterus and implants in the uterine lining tissue. If fertilization of an egg has not occurred, the lining of the uterus eventually breaks down and is shed resulting in menstrual bleeding. The luteal phase lasts 10-16 days. The luteal phase is very consistent but follicular phase is much more variable (Dickerson *et al.*, 2013)

### **b) Hormonal Regulation of different phases of menstrual cycle**

The menstrual cycle is regulated by the coordinated functions of the hypothalamus, pituitary, ovaries, and endometrium. The pulsatile secretion of gonadotrophin releasing hormone from the hypothalamus stimulates the anterior pituitary to secrete follicle stimulating hormone (FSH) and luteinizing hormone (LH), which in turn stimulates the development of ovarian follicles and the production of ovarian steroids. A negative feedback mechanism is crucial for its control and regulation. During the follicular phase, the recruited follicle prepares for ovulation. After the LH surge and ovulation, the luteal phase begins. The follicular and luteal phases correspond to the proliferative and secretory phases of the endometrium, which develops during the proliferative phase and is maintained during the secretory phase to prepare for implantation of the fertilized embryo. The endometrium is shed during menses in the early follicular/proliferative phase, and the cycle continues. (Comasco, and Sundström, 2015) and are discussed in the following pages

**i) Role of Follicle Stimulating Hormone**

FSH is produced in the pituitary gland, a small area near the hypothalamus. In the early follicular phase, overall FSH secretion increases slightly, stimulating growth of recruited follicles, stimulates the follicles to ripen several eggs, at the same time the recruited ovarian follicles release oestrogen (estradiol) for the process of reproduction. Increased production of estradiol stimulates LH and FSH synthesis but inhibits their secretion. During the late follicular phase (2<sup>nd</sup> half of the follicular phase), the follicle selected for ovulation matures and accumulates hormone-secreting granulosa cells its antrum enlarges with follicular fluid, reaching 18 to 20 mm before ovulation. FSH levels decrease; also, developing follicles produce the hormone estradiol, which inhibits FSH secretion (Thiyagarajan, 2021).

**ii) Role of Oestrogen**

Oestrogen promotes the development and maintenance of endometrial lining of the uterus and aids fluid and electrolyte balance in the body (Marjoribanks, et.al.,2015) Oestrogen levels rise and fall twice during the menstrual cycle. Oestrogen Prepares the follicle for the release of an egg and thus starts rising soon after menstruation and reaches peak during the mid-follicular phase, high levels of estradiol (oestrogen) trigger LH secretion by gonadotropins (positive feedback) and then drop precipitously after ovulation. This is followed by a secondary rise in oestrogen levels during the mid-luteal phase and peak around mid-ovulation period and falls just before the start of next menstruation at the end of the menstrual cycle (Jones, 2008)

**iii) Role of Progesterone**

The corpus luteum secretes primarily progesterone in increasing quantities, peaking at about 25 mg/day 6 to 8 days after ovulation. Levels of circulating progesterone is high during the luteal phase. Progesterone stimulates development of the secretory endometrium (womb lining) for the implantation of egg. Because progesterone is thermo genic, basal body temperature increases by 0.5° C for the duration of this phase and also prepares mammary glands for milk production (Witchel,2019)

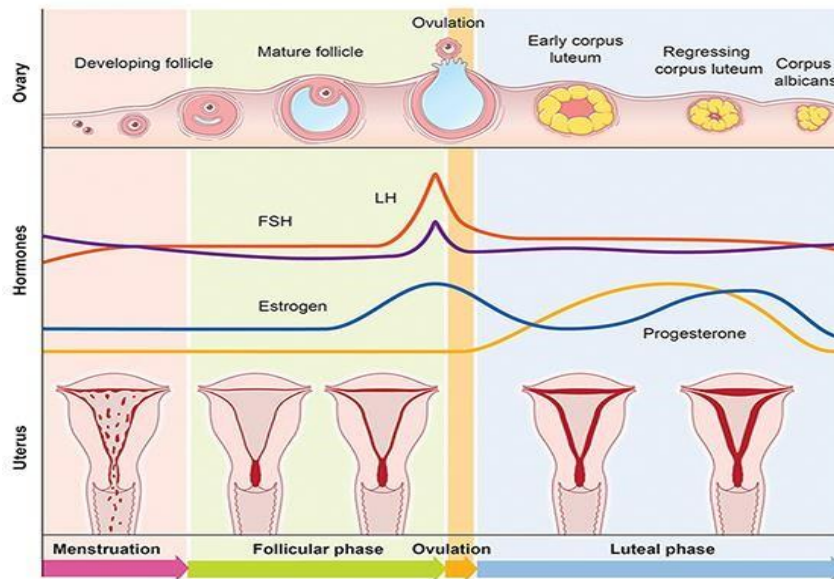
**iv) Role of Luteinising Hormone**

Develops the follicles, triggers ovulation and stimulates production of other hormones necessary for the post ovulatory stage of menstrual cycle. The LH surge stimulates enzymes that initiate breakdown of the follicle wall and release of the now

mature ovum within about 16 to 32 hours. The LH surge also triggers completion of the first meiotic division of the oocyte within about 36 hours (Witchel,2019)

**iv) Role of Gonadotropin-releasing hormone (GnRH),**

It is produced in the hypothalamus region in brain. GnRH stimulates the release of two additional hormones that are crucial for reproduction: follicle-stimulating hormone and luteinizing hormone. (Witchel,(2019)

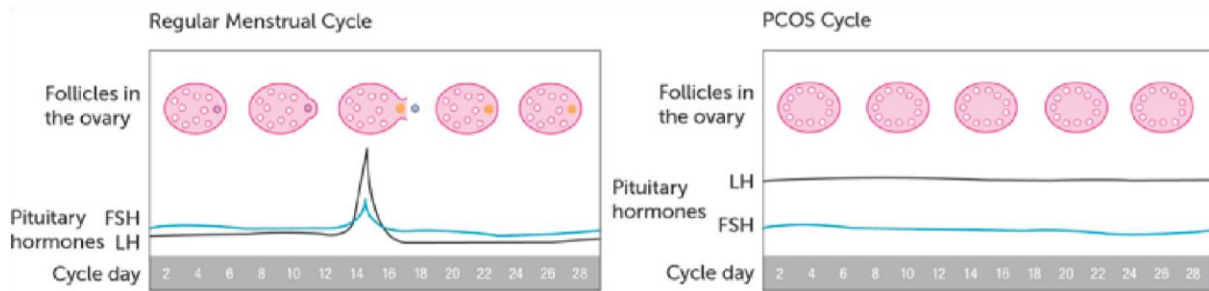


Source: Tortora G (2017).

**Figure 3: Level of hormones in different phases of menstrual cycle**

**c) Follicular Arrest – A condition of polycystic ovaries and hormonal imbalance**

Poly Cystic Ovarian Syndrome is a condition with LH levels are often high when the menstrual cycle starts. LH levels are higher than FSH levels. Because the LH levels are already quite high, there is no LH surge. Without this LH surge, ovulation does not occur, and periods are irregular. Thus, the entire process of maturation goes haywire. PCOS ovaries contain 2-3 times the number of small primary follicles measuring 2-5 mm with more recent studies suggesting up to six times the normal number. Too many primordial follicles were forced from the resting phase to become primary follicles, driven by high testosterone levels. Insulin acts indirectly by increasing testosterone levels but also directly on the ovary to promote this transition from primordial to primary follicle. There are too many primary follicles, but no single dominant follicle is selected to continue growing (Dewailly 2004). These large numbers of small follicles don't shrivel up when they're supposed to, eventually becoming cystic and then visible as polycystic ovaries. This failure of maturation of the follicles is called follicular arrest.



**Figure 4: Comparison of Regular Menstrual Cycle VS PCOS Cycle**

Source :Richards 2018

**B. Polycystic ovarian syndrome (PCOS) –A common reproductive health concern for women**

**a) History and definition**

Polycystic Ovarian syndrome is a common but often misunderstood condition. According to the Hormone Health Network, (2016) PCOS affects an estimated 7 to 10 per cent of women of childbearing age. PCOS was first recognized as a clinical entity in 1930's. The first description of PCOS was done by Drs Stein and Leventhal in 1935. At that time, it was named as Stein–Leventhal syndrome. The disorder was present in seven women who presented with amenorrhea, enlarged bilateral polycystic ovaries, along with obesity, most of them also displayed hirsutism (Azziz *et al.*,2016). This complex heterogeneous disorder includes the presence of signs such as clinical or biochemical hyperandrogenism, ovulatory dysfunction (oligo- or anovulation) and polycystic ovary morphology. Diagnosis is established in the absence Cushing syndrome, congenital adrenal hyperplasia, androgen-producing tumours and hyperprolactinemia. (Diamanti and Dunaif 2012).

**b) PCOS and Reproductive Health**

One of the main aspect of women's health is the reproductive health. Most of the women are multitasking, and many times not taking care of their health. Reproductive health service is very much necessary to ensure the health and safety of women in employment. As per the recent studies by Sivapriya *et al.*, (2018) premenstrual symptom is found among 40 per cent women in the Reproductive age group. Polycystic ovarian syndrome (PCOS), the heterogeneous syndrome having several reproductive and metabolic irregularities affecting 4-18 % of women. (Moran,2011 and Sirmans *et al.*, (2014). The WHO estimates 3.9 % of primary infertility in India among 25-49years of women and 16.8 per cent among 15-49 years (Moran *et al.*,2010).

Young women are most concerned with fertility and cosmetic symptoms such as acne or hirsutism. Women with PCOS are at increased risk of endometrial cancer. Among the reproductive age women 90-95 per cent of patients undergoing treatment for infertility have PCOS that itself is the main reason for anovulatory infertility (Teede, 2018). During the treatment course of infertility only those people came to know about PCOS. Biochemical hyperandrogenism along with elevated levels of Luteinizing hormone and reduced levels of follicle stimulating hormone are the common biochemical presentation in PCOS (Haqq *et al.*, 2014). Many women with PCOS notice that as they enter their late 30's and early 40's their menstruation become more regular in association with reduced ovarian volume and androgen production. Women should also focus on their metabolic health, preventive care and psychological health.

### **c) Epidemiology of PCOS**

The choice of diagnostic criteria correctly estimates its prevalence. The World Health Organization estimates that it affects 116 million women worldwide as of 2010 (3.4% of the population). Global rate of prevalence highly variable, ranging from 2.2% to as high as 26%. One community-based prevalence study using Rotterdam criteria (2003), Vos *et al.*, (2012) found that about 18% of women had PCOS and that 70% of them were previously undiagnosed (Vos *et al.*, 2012). Prospective study among adolescent girls in India aged between 15-18 years from college of South India revealed a prevalence of 9.13% (Nidhi *et al.*, 2011). The studies done by Joshi *et al.*; 2014 confirmed 22.5% prevalence among young women in Mumbai. A recent study done in Kolkata reported that 28 % of college students were at high risk of PCOS (Chatterjee and Bandyopadhyay, 2020). The study conducted by George and Malini (2014) in Central Travancore region reported that the prevalence of PCOS among females in the age group of 21-35 years as thirty three per cent due to their unhealthy dietary pattern and lifestyle changes. The socio economic studies carried out in these patients revealed that they belong to high income families and have a high intake of dietary sugar. Even then PCOS patients from South India did not report glucose impairment and exhibited increased blood cholesterol levels and high BMI (Varghese *et al.*, 2015). The proportion of PCOS was higher in urban population in comparison to rural counter parts

### **c) Diagnostic criteria**

The Endocrine Society advises clinicians to diagnose PCOS using the Rotterdam criteria (2003)

Table I Diagnostic criteria for PCOS

	NIH (1990) and Zawadzki <i>et al.</i> , (1992)	ESHRE/ASRM (Rotterdam) (2003)	AE-PCOS (2006) Azziz, <i>et al.</i> , (2009)	NIH (2012)
<b>Findings</b>	Hyperandrogenism (HA) Oligo Anovulation (OA)	Hyperandrogenism (HA) Ovarian Dysfunction (OD) Polycystic Ovarian Morphology (PCOM)	Hyperandrogenism (HA) Plus Ovarian Dysfunction (OD) Or Polycystic Ovarian Morphology (PCOM)	Hyperandrogenism (HA) Ovarian Dysfunction (OD) Or Polycystic Ovarian Morphology (PCOM)

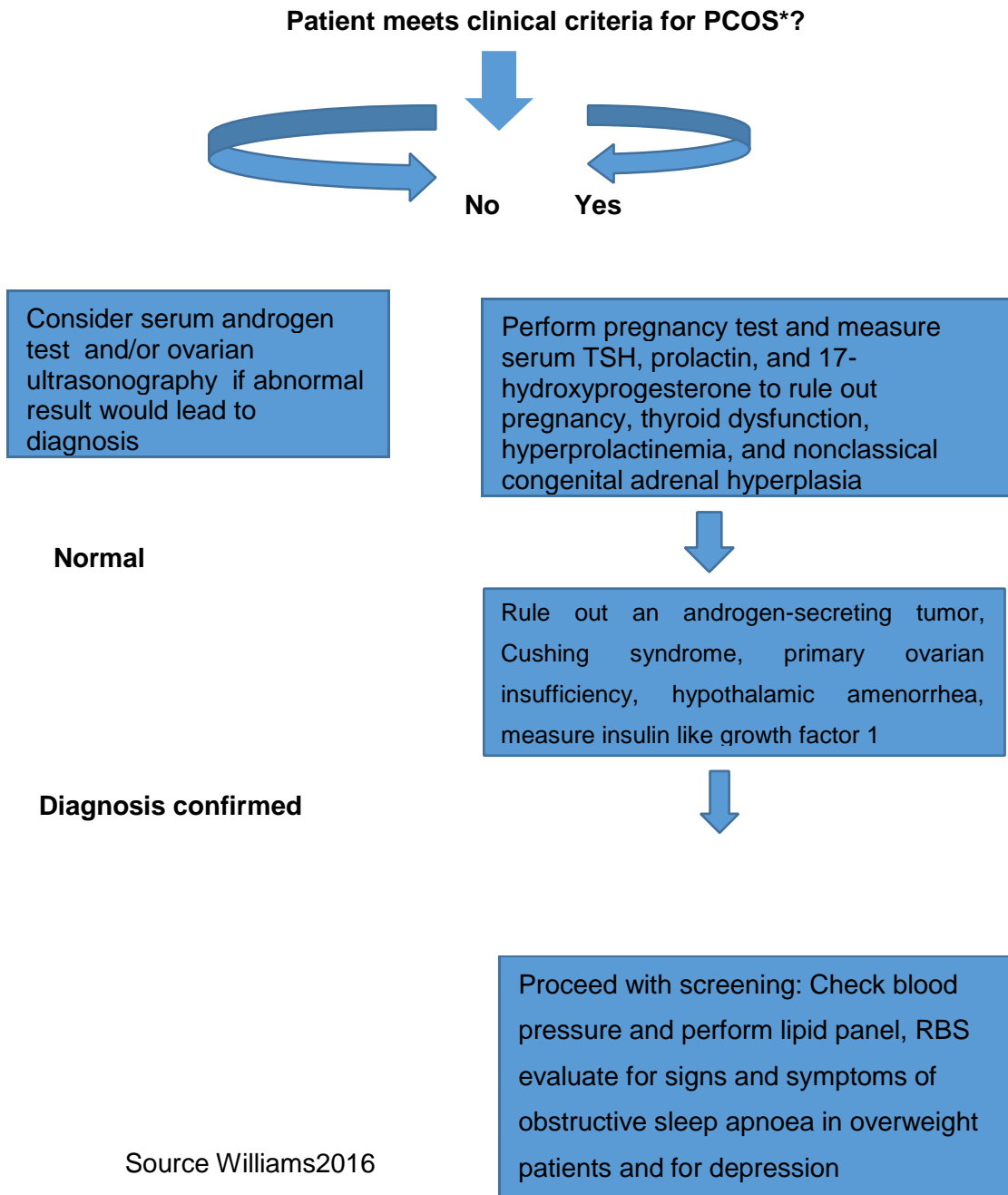
Although recommendation differ across guidelines, Rotterdam consensus workshop held in Rotterdam on 2003 under the sponsorship of European Society of Human Reproduction and Embryology (ESHRE)/ American Society for Reproductive Medicine ASRM (2004), confirmed the diagnosis require at least 2 of the following findings

- Oligo-ovulation or anovulation
- Clinical and/ or biochemical signs of hyperandrogenism (without Cushing’s syndrome, congenital adrenal hyperplasia, thyroid abnormalities, androgen-secreting tumours and hyperprolactinemia)
- Polycystic ovarian morphology (PCOM) detected on ultrasound (Rotterdam ESHRE/ASRM(2004))

National Institute of Health criteria, (1990) insisting on both of the findings hyperandrogenism and Oligo-anovulation might be without polycystic ovaries. In 2009, the androgen excess Society (AE-PCOS) stated that androgen excess is the principal hallmark of the disorder; therefore, the diagnosis should be based on the presence of hyperandrogenism plus ovarian dysfunction (Legro *et.al*, 2013). Twelve years later, in 2012, the broader classification of the Rotterdam criteria (2003) together with specification of phenotypes included as the tools (Evidence-based Methodology Workshop on PCOS, sponsored by NIH). The specification of the phenotypes as follow: 1) Clinical and/or biochemical hyperandrogenism (HA) + Ovarian Dysfunction (OD), that include oligo- or anovulation; 2) HA + PCOM; 3) HA + OD + PCOM and 4) OD + PCOM (Table 1). This phenotypic classification would improve research and clinical practice for patient

management according to the risk of co-morbidities, such as metabolic syndrome, T2D and cardiovascular disorder.

**Diagnostic criteria algorithm for PCOS**



The diagnostic work up starts with history and physical examination. History of weight changes, skin changes such as hirsutism, acne, androgenic alopecia, acanthosis nigricans, biochemical hyperandrogenism as evidenced by total, free testosterone, Dehydroepiandrosterone sulphate (DHEAS), skin tags and oligo anovulation is considered.

(Rotterdam, 2003) and (Legro, *et al.*, 2013). Ovulatory dysfunction refers to oligomenorrhea (cycles more than 35 days apart but less than 6 months apart) or amenorrhea (Absence of menstruation for six to 12 months after a cycle pattern has established (Woolcock *et al.*, 2008). The definition of PCO morphology was suggested as 12 or more follicles in one ovary, each follicle measuring 2-9 mm in diameter and/or volume of the ovary >10ml on ultrasonography. (Dewailly *et al.*, 2014)

#### **e) Classification of PCOS**

The presentation of PCOS can be classified into four phenotypes as per (Rotterdam 2003 criteria. Phenotype A: Hyperandrogenism +Ovulation Dysfunction +Polycystic ovarian Morphology on ultrasound (HA +OD + PCOM) ; phenotype B:hyperandrogenism +Ovarian Dysfunction, but normal ovaries on ultrasound (HA+OD);.Phenotype A and B are the classic PCOS types .Increased insulin levels and insulin resistance including metabolic syndrome and menstrual dysfunction, obesity, metabolic syndrome are very common among these phenotypes .Phenotype C also known as “Ovulatory PCOS” presented with Hyperandrogenism+Polycystic ovarian morphology on ultrasound but without ovulation dysfunction ( HA +PCOM).Compared to classic PCOS phenotypes the ovulatory types have intermediate levels of serum testosterone, insulin , lipid profile , hirsutism score and metabolic syndrome. Phenotype D also known as “Nonhyperandrogenic PCOS” reported with Ovulation dysfunction and polycystic ovarian morphology on ultrasound, but without clinical or biochemical evidence of hyperandrogenism (OD + PCOM) (Wołczyński *et.al.*, 2012) .Most of the patients with non-hyperandrogenic PCOS rarely have endocrine and metabolic dysfunction, the prevalence of metabolic syndrome among them is also very low (Guastella *et al.*, 2010).

PCOS Women in the reproductive age have two times high risk for hospital admission,gestational diabetes ,pre-eclampsia , foetal macrosomia at the time of pregnancy(Qin *et al.*,2013 and Hart,2015).Rate of prevalence of menstrual dysfunction and prevalence of PCOS phenotype A was higher among the hospitalized PCOS patients compared with general cases of PCOS in the community)

**f) Predisposing factors**

**i) Genetic factors -Family history of PCOS.**

Incidence of hypertension and Cardiovascular diseases is double among the mothers of women of reproductive age with PCOS when compared to mothers of those women without PCOS. Fathers of women of reproductive age with PCOS have double risk for heart disease and 4 times high risk for cerebro vascular accidents when compared to fathers of reproductive age women without PCOS (Davies, *et al*, 2011). Studies reported by Tan *et al*, (2010) focused on the association of insulin resistance and particular genes (INSIG2 and MC4R) and role of TCF7L2 SNP on development of NIDDM and continuous weight gain of around 1.56 kg /m<sup>2</sup> in PCOS subjects. PCOS is an autosomal dominant inheritance trait, the prevalence among first degree relatives is 55-60%. While all disease ultimately comes down to genetic tendencies and the influence of environmental factors, a very strong genetic basis is widely accepted as being likely for PCOS. Genetic predisposition has been shown that PCOS may be inherited. Approximately 40% of women with a family history of PCOS will have a condition. Approximately 35 per cent of mothers and 40 per cent of sisters of women with PCOS are affected. Clearly the familial pattern of PCOS with affected mothers and daughters implies a role for genetic factors (Miller, 2001)

**ii) High Maternal Androgen:**

Prenatal exposure to increased androgens poorly because of controlled maternal congenital adrenal hyperplasia, Androgen secreting tumours considered as a risk factor for Low birth weight/small for gestational age, premature adrenarche in infants (Smith *et al.*, 2010)

**iii) Endocrinal factors: Insulin Resistance**

Onset of type 1 diabetes mellitus before menarche, insulin resistance and obesity are common endocrine problems in PCOS. Insulin resistance is more commonly seen among 50-80% of PCOS women. Decreased insulin activation, due to increased serine phosphorylation and decreased tyrosine phosphorylation is the ultimate reason for IR. IR is seen among 50–80% of women with different phenotypes of PCOS in different races (Rosenfield, 2020). Dysbiosis of gut micro flora can contribute to IR and potential mechanisms involved are endotoxemia, some gut-brain peptides, hyperandrogenism and some abnormal metabolites (He, *et al.*, 2020). Mitochondrial dysfunction, endoplasmic reticulum stress and oxidative stress were also found to play a role in IR (Peng, *et al.*, 2020)

**iv) Obesity in PCOS**

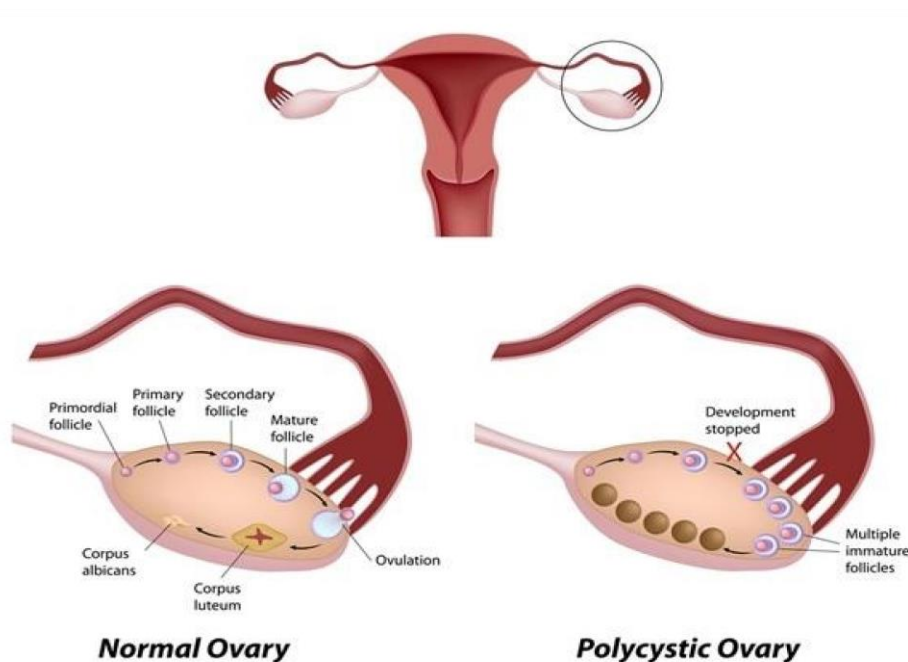
Obesity, especially abdominal obesity, is a common manifestation of PCOS, and the prevalence depends on geographic location and ethnicity (Bil *et. al*, 2016)

**v) Drugs: Anti-epileptic drugs**

The neuroendocrine changes associated with PCOS is induced by the use of Valproic acid (VPA), a branched short-chain fatty acid derived from valeric acid, is used to treat epilepsy. It increases GABA levels by interfering with GABA degradation pathways, signalling GnRH secretion such as LH pulse frequency leading to increased androgen production (DeFazio *et al.*, 2002).

**g) Pathophysiology**

The complex pathophysiology of PCOS is contributed by genetic, environmental, hormonal disturbances and several other factors. The main factors include obesity, ovarian Dysfunction and hypothalamic- pituitary abnormalities (Usadi and Legro, 2012). Several authors have explained different factors that contribute to PCOS pathology.



**Figure 5: Normal Ovary and Polycystic Ovary**

(Source: Smith,2021)

In India, the prevalence is increasing gradually PCOS has become an epidemic in most of the metro cities because of the lifestyle pattern, change in the diet habits, adoption of restaurant eating .All these are the reasons for hormonal imbalance .The impact of increased LH pulse amplitude and frequency and insulin has the major role in

hyper androgenism in PCOS, leading to irregular pattern of Hypothalamic Gonadotropin releasing hormone (GnRH) secretion further causing subfertility and pregnancy complications Goldenberg *et al.*, (2008) and Boomsma *et al* (2008) .The major symptoms are amenorrhea, oligomenorrhea dysfunctional uterine bleeding, acne , hirsutism , obesity etc.

### **i) Steroidogenesis Ovarian Axis**

ACTH or adreno corticotropic hormone produces androgen from the adrenal glands and LH or luteinizing hormone contribute the synthesis of androgen in ovaries (Handa, *et al.*, 2015). In normal course LH stimulate the ovarian theca cells to produce androgen which in turn converted into oestrogen by by CYP19A1 (P450aromatase), in granulosa cells (Rosenfield,*et al*, 2016) . Steroidogenesis in the ovary involves both theca and granulosa cells. The theca cells produce ovarian androgens, which are converted to oestrogens in the granulosa cell due to the actions of FSH-stimulated aromatase. Androgen promote aromatase expression and, ultimately, LH/chorionic gonadotropin receptor (LHCGR) expression in granulosa cells. As a follicle matures, androgens appear to inhibit the proliferation and promote apoptosis. (Harlow, 1988). An alteration in gonadotropin-releasing hormone secretion results in increased luteinizing hormone (LH) secretion. Women with PCOS have an increase in both the LH pulse frequency and amplitude, resulting in increased 24-hour secretion. This increase in LH secretion is thought to occur as a result of increased frequency of hypothalamic gonadotropin-releasing hormone (GnRH) pulses, which increases the synthesis of androgens.

By theca cells and results in thecal hyperplasia causing enhanced production of androgen, disruption, aberrant follicle development and follicular atresia. Increased LH, in turn, leads to an increase in androgen production by the theca cells within the ovary. Abnormal development of follicles in the early stages of follicular growth is the contributing factor for ovarian aspects of PCOS.(Franks,2018).PCOS ovaries have primordial to growing follicles with increased number of 2-4mm follicles (Homer,2019) .AMH serves as an agent responsible for depletion of primordial follicles and selection of maturing follicles .AMH is significantly higher in women with PCOS due to an increased rate and number of antral follicles facilitating the follicular arrest in PCOS (Kushnir*et al.*,2017.) The growing follicle is exposed to an atypical environment with increased LH, insulin, androgen, and Antimullarian hormone (AMH) concentrations accompanied by insufficient FSH concentration. In PCOS, activity of enzyme Cytochrome P450 c17 (CYP17), which converts progesterone to 17-hydroxyprogesterone and from

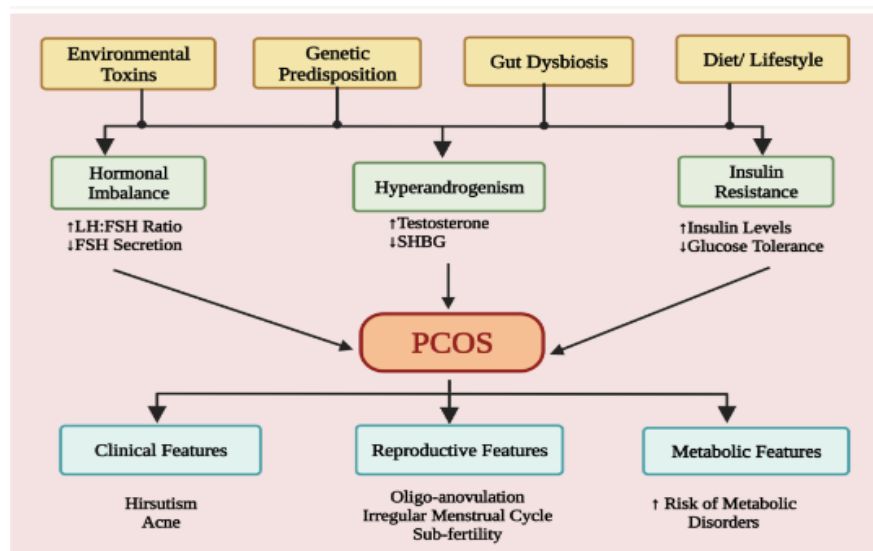
17- hydroxyprogesterone to androstenedione (A4) is exaggerated and a decreased activity of CYP19A1 also favours androgen production. (Yang, *et al.*, 2015)

**ii) Steroidogenesis - Adrenal Axis**

Hyperandrogenism in PCOS can also be contributed by adrenal axis. Adrenal cortex produces Dehydroepiandrosterone (DHEA), androstenedione (A4) and in minor extent testosterone (T) through steroidogenic pathway (Schiffer, *et al.*, 2017). DHEA could be sulfated through DHEA sulfotransferase and released to the circulation as DHEA sulfate (DHEAS). DHEAS is the best marker of adrenal androgen precursor production as most of which is produced in the adrenal cortex. Among non-obese women all these androgen precursors are found higher compared to obese women with PCOS (Moran, 2015). Moreover, adrenal hyperandrogenism in women with PCOS has been associated with reduced insulin sensitivity and increased blood pressure. (Alpanes, *et al.*,2015)

**iii) Neuro endocrine Axis**

Hypothalamic neurons secrete kisspeptin, neurokinin B, and dynorphin along with GnRh neurons that are generators for concomitant GnRH secretion, subsequent gonadotropin secretion and ovarian oestrogen production, GnRH in discrete pulses that travel through the median eminence to the pituitary gonadotrophs, resulting in pulsatile LH and FSH secretion (Casoni, 2016). Increased GnRH pulse frequency increases LH pulse frequency and decreases FSH pulse frequency further leading to increased androgen production modulating the HPO axis (Hill, *et al.*, 2018).



**Figure 6 proposed pathophysiology and features of PCOS**

(Source: Journal of Clinical Medicine 2023)

The relation between diet, as a modifiable environmental factor, and components of the female reproductive axis in reversing PCOS has biological plausibility(Figure6). PCOS puts women at increased risk of Metabolic syndrome, Cardiovascular Diseases, Type-2 Diabetes, and also mental health problems such as depression and anxiety.(Mirmasoumi 2018). Although the main mechanism leading to the pathogenesis of PCOS remains unclear, Insulin Resistance and Obesity seem to play a key role. Hyperinsulinemia caused by Insulin Resistance leads to hyperandrogenemia through excess production of androgens by Theca cells in the ovaries and also reduces the synthesis of Sex Hormone Binding Globulins (SHBG) by the liver cells. It is now well-known that adipose tissue, specifically visceral fat, is associated with Insulin Resistance, Diabetes, and pro-inflammatory states. Adipocytokines such as adiponectin and leptin, secreted by adipose tissues are involved in the pathogenesis of PCOS (Mamaghani 2009).

#### **iv) Insulin resistance and Hyperinsulinaemia**

Insulin resistance with compensatory hyperinsulinemia is commonly seen among PCOS subjects. In PCOS, activity of enzyme CYP17 is activated in the presence of insulin and favours the conversion of progesterone precursors to androgen in adrenals and ovaries (Schiffer, 2017). Insulin increases free androgen availability and IGF concentration in the ovary, by decreasing the synthesis of sex hormone-binding globulin (SHBG) and insulin-like growth factor binding protein (IGFBP-1) by the liver. This in turn stimulating the production of androgen via stimulation of IGF receptor. Adiponectin, and hormone considered as insulin sensitizer (Ziemke, 2010), has also been related to the pathophysiology of PCOS. Adeponectin is found in decreased amounts in obese PCOS compared to normal ones. A defective secretion of adiponectin due to androgen excess has been reported. The adiponectin level is decreased in obese PCOS patients compared to weight matched controls (Chen,2014), Insulin resistance in PCOS women strongly predicted by a high waist circumference, size and number of circulating adipocytes (Manneras-Holm, *et al.*,2011)

#### **h) Complications**

Polycystic ovarian syndrome is a heterogenous multifaceted disorder imparting reproductive, metabolic and psychological consequences for short and long term if left untreated. PCOS women has high risk for Gestational Diabetes Mellitus, pregnancy induced hypertension, preeclampsia, endometrial cancer. Many obese women with PCOS have features of metabolic syndrome, which increases the risk of cardiovascular disease,

hypertension, and type 2 diabetes mellitus (Yu, *et al.*, 2016). Patients with PCOS are also presented with non-classical cardiovascular risk factors including mood swings, depression anxiety, obstructive sleep apnoea etc. (Palomba *et al.*, 2015)

**i) Infertility**

Several PCOS comorbidities seemed to contribute to infertility. In particular, insulin resistance (Tian *et al.*, 2007) and obesity (Jungheim *et al.*, 2009) were independently related to an increased risk of abortion and to reduced pregnancy and live-birth rates. The guidelines of the Endocrine Society-appointed Task Force of Experts (Lergro *et al.*, 2013) suggested that PCOS is a risk factor for infertility only in the presence of oligoanovulation.

**ii) Ovulatory dysfunction**

Ovulatory dysfunction refers to oligomenorrhea (cycles more than 35 days apart but less than six months apart) or amenorrhea, absence of menstruation for six to 12 months after a cyclic pattern has been established (Woolcock *et al.*, 2008)

**iii) Obstetric complications**

The risk of pregnancy induced hypertension is 12.7% and preeclampsia 8% respectively among PCOS patients. The most commonly found complication among PCOS is Gestational Diabetes mellitus with incidence of around 14.7% (Palomba, 2014) among reproductive age women and 22% in women with PCOS (Wilde, 2014). Among PCOS subjects the prevalence of gestational diabetes, impaired glucose tolerance and type 2 diabetes is significantly increased to 5-fold in Asia and is exacerbated by obesity (Teede *et al.*, 2018). The risk of preterm delivery was increased twofold and more in PCOS patients. Neonates born to women with PCOS had a twofold increased risk for admission to the neonatal intensive care unit (Qin, *et al.*, 2013) and their mortality was increased of threefold (Boomsma *et al.* 2006). Endocrine Society guidelines for the diagnosis and treatment of PCOS (Legro *et al.*, 2013) declared that women with PCOS are at increased risk of pregnancy complications and recommended preconceptional assessment of BMI, blood pressure, and oral glucose tolerance. Increased prevalence of hypoglycaemia, perinatal death, gestational diabetes (GDM), preeclampsia, pregnancy-induced hypertension (PIH), preterm delivery, caesarean delivery and miscarriage among women with PCOS were reported (Yu *et al.* 2016). Artificial reproductive Technologies (ART) helped PCOS women for higher ovarian hyper stimulation syndrome compared with non PCOS women during fertility treatments.

**iv) Cardio Vascular Diseases**

At any age, PCOS subjects have greater odds for elevated CVD risk markers and more magnified with obesity. The classic risk factors include hypertension, elevated lipid profile, and Type 2 diabetes mellitus. On classical risk factors were C reactive protein , homocysteine , tumour necrosis factor(TNF $\alpha$ ) etc (Toulis *et al.*,2011).Obese PCOS subjects had higher cholesterol , LDL cholesterol ,Triglycerides and significantly lower levels of HDL cholesterol compared to non-obese PCOS woman( Karla *et al.*, 2013) .Symptoms of chronic inflammation such as oxidative stress, and impaired fibrinolysis are increased with higher prevalence of CVD( Murri, *et al.*, 2013) .Those with a higher prevalence of CVD are were more likely to experience moderate-to- severe depression and anxiety symptoms,( Barry, 2011) low self-esteem, negative body image and psychosexual function compared to healthy women. Hyper homocysteinemia in PCOS patients can be corrected and long-term consequences can be prevented with treatment with folic acid. (Aversa *et al.*, 2020)

**v) Metabolic co-morbidities of PCOS**

PCOS has metabolic implications including Insulin resistance (Behboudi Gandevani *et al* 2016), dyslipidaemia (Toulis *et al.*, 2011) and abnormal glucose metabolism (Traub, 2011). Obese people have presented with more of these symptoms. Among PCOS subject's Subclinical hypothyroidism was associated with decreased HDL-C levels and increased TG levels hyperandrogenism was associated with decreased HDL-C levels, and no differences in the lipid profile (Yang, *et al.*, 2016). PCOS affects the healthy lifestyle and health related quality of life of affected women.

Vitamin D deficiency in women with PCOS had significantly lower HDL-C level compared to non-vitamin D deficient women. Vitamin D deficiency was negatively correlated with Triglycerides positively correlated with HDL-C .The majority of retrieved reviews reported worse insulin sensitivity and glucose tolerance in women with compared to women without PCOS(He *et al.*, 2020).. Non-Alcoholic Fatty Liver Disease (NAFLD) is more prevalent in women with PCOS which was increased in women with compared to those without PCOS (Ramezani *et al.*, 2014). The first-degree relatives of PCOS women have higher prevalence of IR hyperinsulinaemia, CVD, hypertension at younger ages below 40years. Male have higher metabolic risk and female have endothelial dysfunction (Norman *et al.*, 1996).

**vi) Metabolic syndrome**

As per the studies of Chandrasekaran and Sagili (2018) Metabolic syndrome affects 33% of women with polycystic ovarian syndrome. Spandana *et al.*,2017, reported

that 21.3 per cent of prevalence of PCOS with a maximum number of prevalence in the age group of 31-35 years (52.9%). The risk factors for metabolic syndrome included the android obesity, hypertension, atherogenic dyslipidaemia and insulin resistance. (Chandrasekaran and Sagili 2018). Excess testosterone and insulin plays the central role in PCOS and metabolic syndrome among obese women (Spandana *et al.*, 2017)

**vii) Android Obesity**

Obesity is more prevalent among PCOS subjects. Obesity is the major metabolic concern in PCOS women up to 61% of prevalence with central distribution of adipose tissue compared with the non PCOS woman. It increases the risk for metabolic dysfunction including Insulin resistance. The number of obese and overweight women was found to be high as 75% in previous studies (Kalra *et al.*, 2006). Greater adiposity was related to hyperandrogenism associated with chronic anovulation (Wild *et al.*, 2010).

**viii) Atherogenic Dyslipidaemia**

Insulin resistance in the fat tissues leads to increased transfer of free fatty acids from adipose tissues to liver and synthesis of more VLDL causing elevation of TG, apolipoprotein B and decreased HDL. These alterations results in atherogenic dyslipidaemia (Chandrasekaran and Sagili 2018)

**ix) Hyperinsulinemia/insulin resistance**

Hyperinsulinemia in combination with pancreatic beta cell dysfunction results in an increased risk of many disorders including impaired glucose tolerance test (IGT), Diabetes Mellitus and classic cardiovascular risk factors including atherosclerosis, endothelial dysfunction, and cardiovascular diseases. Insulin also stimulates the theca cells of the ovary to produce excessive testosterone, which is responsible for the clinical symptoms of hyperandrogenism such as acne, hirsutism and alopecia (Traub *et al.*, 2011)

Women with PCOS have low levels of the carrier proteins SHBG. Insulin is the major regulator of SHBG production in the liver. The higher the insulin, the lower the SHBG production. A predictable inverse relationship between insulin and SHBG indicates that insulin controls SHBG synthesis. Human studies have confirmed that high insulin indeed increases androgen levels and decreases SHBG production.

**x) Hypertension**

Blood pressure measured in sitting position in PCOS patients. Among obese individuals, increased levels of insulin and free fatty acids and endothelial dysfunction leads to development of hypertension usually with systolic BP above 140mmhg and diastolic BP above 85mmhg (Wu *et al.*, 2020)

**xi) Type 2 Diabetes Mellitus**

Metabolic syndrome contributes to a five-fold increase in type 2 diabetes risk in PCOS, and PCOS has been identified as a significant non-modifiable risk factor up to 16% of women with PCOS convert to IGT per year (Norman *et al.*, 2001). Women with baseline IGT have a 2% risk of progressing to diabetes type II per year, and over 6 years this risk may be as high as 54 %. (Legro *et al.*, 2015).

**xii) Risk for Cancer**

Since the PCOS is characterised by reproductive and metabolic alteration involving hormonal and metabolic pathogenic mechanisms, it is associated with cancer risk among women especially endometrial, ovarian and breast cancer. Endometrial proliferation is marked by Insulin resistance, obesity oligomenorrhea and prolonged exposure to oestrogen in anovulation. Women of all ages are at increased risk of endometrial cancer with higher prevalence among premenopausal group of women (Barry *et al.*, 2014)

**xiii) Inflammation**

The role of inflammation in PCOS has been the subject of a number of studies chronic low-grade inflammation induces insulin resistance and plaque formation in the arteries. Genetic abnormalities, high BMI and high Glycaemic index diet are the inducers of proinflammatory cytokines, inflammation markers (CRP, ferritin, leukocyte TNF- $\alpha$ , IL-6) (Aubuchon *et al.*, 2014)

**xiv) Psychological risk**

PCOS patients are the risk categories exhibiting a lot of psychological disturbances. There are evidence based studies represent PCOS patients are at high risk for developing psychological disturbances and reduced quality of life as some may have features of obesity, hirsutism, irregular menstruation and infertility. The prevalence of depression is four times higher in PCOS women than the general population, with increased severity of symptoms these women are also more likely to develop anxiety. (Dokras, *et al.*, 2011)

**xv) Sleep disturbances and disorders**

Obstructive sleep apnoea and sleep disturbances are seen frequently among PCOS patients. Changes in hormone cortisol and melatonin secretion is affecting the hypothalamic –pituitary adrenal function causing hyperandrogenism. Lack of physical activity, Anxiety and depression is common as the psychological pathway is affected. Compromise in the cardio metabolic health and uncontrolled type 2 diabetes is the main reason for sleep disturbance (Fernandez, *et al.*, 2018)

PCOS subjects have 30-fold higher risk for Obstructive sleep apnoea (OSA), day time sleepiness is also high among them. Insulin resistance is the main predictor for sleep apnoea IR has emerged as a principal predictor of sleep apnoea with increased CVD. Women should be screened for and counselled about snoring, daytime somnolence and fatigue, and offered interventions when necessary (Vgontzas *et al.*, 2005)

**i) Signs and Symptoms**

**i) Oligomenorrhea and Amenorrhea**

In PCOS, the main menstrual problems are anovulation and oligo-ovulation. Menstrual cycles may be completely absent (amenorrhea) or may last longer than usual (oligomenorrhea). Irregular menstrual cycles are caused by the failure of ovulation. The prevalence of oligomenorrhea in obese was 66.7 % and 60% in non-obese with infertility around 44.68%. One of the main diagnostic criteria of PCOS is Oligomenorrhea, which is a highly predictive marker (Ramanand *et al.*, 2013). Oligomenorrheic women had a higher chance of type 2 diabetes of around two fold compared to eumenorrheic women (Solomon *et al.*, 2001). The prevalence of menstrual irregularities among obese as 79.2% and non-obese as 44 per cent only (Majumdar *et al.*, 2009). Oligomenorrhea was defined as a delay in menstruation for >35 days to 6 months. The intervals of menstrual cycle continuously shorter than 20 days or >45 days in girls >2 years after menarche, < 21 or > 35 days or < 8 cycles per year (Teede 2018). Secondary amenorrhea was defined as an absence of menstrual cycles more than 6 months (Spandana *et al.*, 2017) Anovulation is absence of ovulation in post menarche and premenopausal stage (Soni *et al.*, 2018)

**ii) Anovulatory infertility**

The complexity and diversity of both underlying pathology as well as clinical manifestations renders difficulty in defining better predictors of PCOS. Normal ovulation results in regular menstrual cycles (28\_35 day's cycle). Anovulation is the pathognomic feature of PCOS and results in irregular menstrual cycles. Therefore, persistent menstrual irregularities (resulting from anovulation) seem to be better predictors compared to biochemical parameters

**iii) Hyper Androgenism- (Hirsutism or excessive amounts of dark, course hair)**

Hirsutism is the excessive growth of thick, dark terminal hair in women where hair growth is normally absent. Modified Ferriman Gallwey Score (FG) used for scoring and quantifying and to grade hirsutism. A score of 0 (none) to 4 (severe) in nine areas of the body is assigned with a maximum possible score of 36. Scores < indicate mild hirsutism,

4-7 indicate moderate hirsutism,  $\geq 8$  indicate severe hirsutism (Muthukumar *et al.*, 2021). Clinical hyperandrogenism was defined using a modified Ferriman-Gallaway (FG) Score for evaluating and quantifying hirsutism in women using nine body areas (upper lip, chin, chest, upper and lower abdomen, thighs, upper and lower back and upper arm). Study by affirmed that Hirsutism was the most predominant clinical hyperandrogenic marker, and it was present in 54.54% of the PCOS cases with a mean Ferriman-Gallway Score of  $8.6 \pm 2.17$  (Spandana *et al.*, 2017)

**iv) Acanthosis Nigricans.**

Acanthosis Nigricans is dark patches of skin which usually appear on the neck or the armpits which are thick and velvety texture which may itch or may have an odour. PCOS subjects are more prone to this condition and affected areas are skin folds, armpits, groin, neck, elbows, knees, knuckles, Lips palm, and soles of feet. These are also indications for pre diabetes. (Gruber *et al.*, 1999)

**v) Alopecia or hair loss**

Androgenic/central alopecia may also be presented as female pattern hair loss in some patients with PCOS In women with androgenic alopecia the hair follicles remain alive. Hair loss is characterised by loss of hair density at frontal and vertex region of the scalp resulting in short thin hair. The prevalence was about 7% in the study conducted by (Spandana *et al.*, 2017)

**vi) Acne**

Acne can be presented as two forms of lesions that are non-inflammatory (closed and open) and inflammatory lesions (papules, nodules pustules, along with pigmentary changes. Acne can be graded as mild, moderate, and severe forms of acne, based on the number and types of inflammatory lesions. A description of the location and type of acne lesions according to the age group as described by the Indian Acne Association (IAA). Among the different variants of acne, the SAHA syndrome (seborrhoea, acne, hirsutism, alopecia) denotes acne specific to endocrine abnormality of a subject. When diagnosing PCOS in adolescents, acne, a common and transient feature should not be interpreted in isolation, as is the case with androgenic alopecia (Alsulaimani, 2020)

**vii) Hormonal disorders**

Testosterone is produced normally in both the ovaries and the adrenal gland. Other than androgens, the adrenal gland also produces other hormones, including cortisol, adrenalin, and aldosterone. The ovaries and adrenal glands contribute equally to testosterone production. In women with PCOS the ovary is the key source of excessive

testosterone production Elevated Testosterone levels ,high S levels, elevated LH/FSH ratio, elevated androstendione (androgen) levels, AMG (anti Mullerian hormone) levels seen among PCOS patients .SHBG Hormones do not circulate freely and travel around the bloodstream bound up with other proteins that accompany them to their proper destination. SHBG is the protein designed to work with testosterone. Testosterone in high levels starts to exert its masculinizing effects on the neighbouring organs because it is not getting to its proper destination causing acne, excessive facial hair and male pattern baldness. The total amount of testosterone might be the same, but the lack of carrier protein, SHBG allows excessive effect of these androgen. (Yang *et al.*, 2015)

#### **viii) Insulin resistance**

Insulin resistance plays the central role in regulating metabolic pathway. The varying Insulin sensitivity is due to the varying pattern in the insulin sensitivity in the peripheral tissues and in the ovarian cortex. Post-binding defect in the insulin signalling pathway is due to the abnormal serine phosphorylation of the insulin receptor (Diamanti 2012).

#### **ix) Polycystic ovarian morphology**

Polycystic ovary morphology as defined by ESHRE/ASRM consensus criteria is as at least one ovary with  $\geq 12$  follicles of 2–9mm (between day 2-5 of cycle) or ovarian volume  $> 10\text{mL}$  in the absence of a cyst or dominant follicle  $> 10\text{ mm}$ , established with ultrasound examination of ovaries. Polycystic ovarian morphology is more prevalent in younger ages below 35 years as the USG appearance will normalize with advancing age (Spandana, *et al.*, 2017).

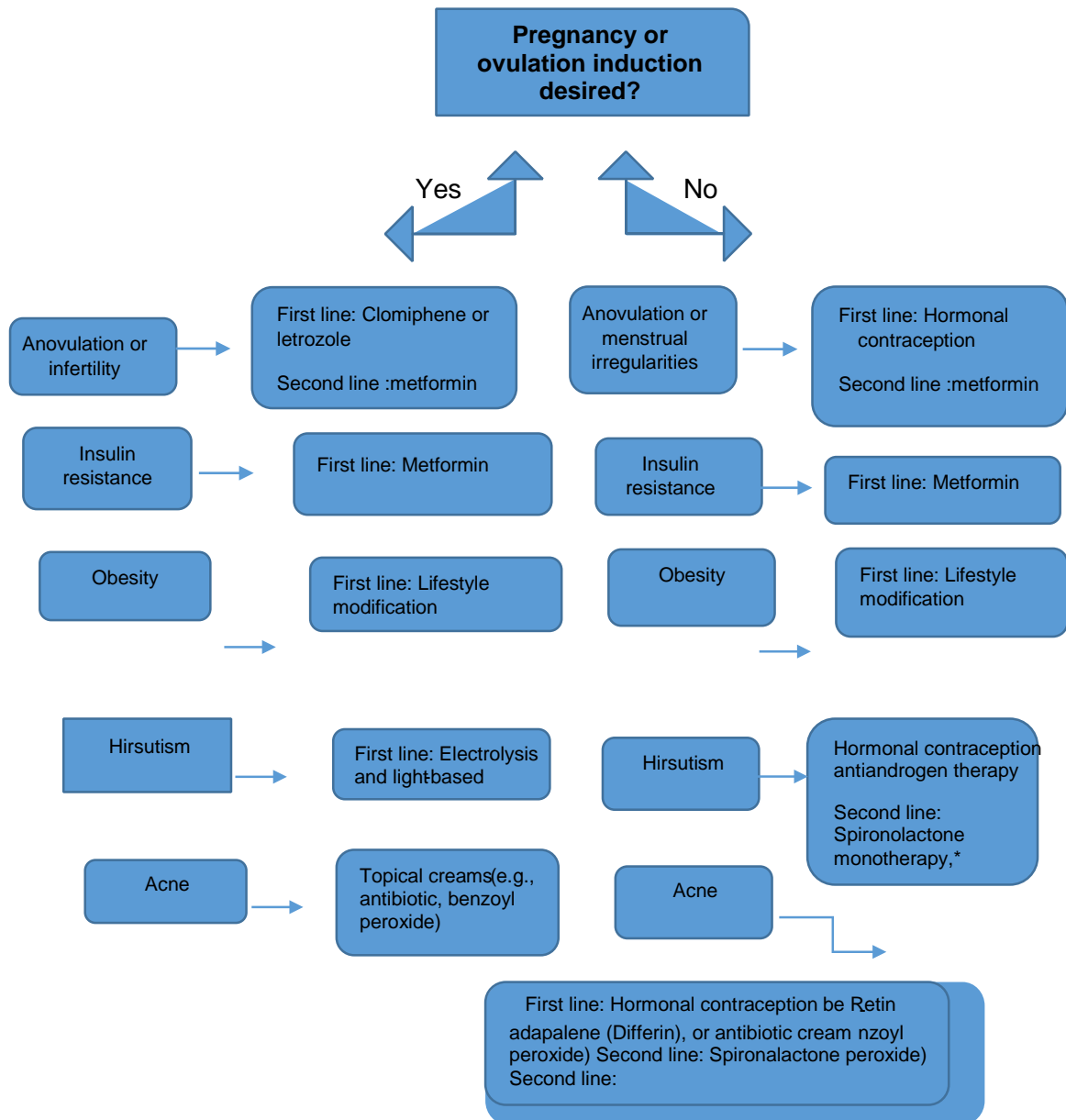
### **C) Management of Polycystic Ovarian Syndrome**

Goals of treatment include reducing insulin resistance, correct anovulation, PCOS treatment goals depends on the physical symptoms. The main goals include

- i) Control of symptoms
- ii) Management of weight
- iii) Management of Fertility issues
- iv) Minimize long term complications of PCOS

#### **i) Medical management of metabolic issues**

Metformin is commonly used for the treatment of weight, hormonal and metabolic outcome. Long term use may cause low vitamin B12 levels. Metformin may offer greater benefit in high metabolic risk groups including those with IGT, diabetes mellitus or high-risk ethnic groups (Teede *et al.*, 2018)



Source :Williams et al (2016)

### a) Medical care and support

The goal of medical management is to treat infertility, regulating oligo anovulation, protection of endometrium, reducing insulin resistance, control hyperandrogenic features. Holistic approaches are required and pharmacological therapy in PCOS needs to be considered alongside education, lifestyle and other options including cosmetic therapy and counselling. (Soni *et al.*, 2018)

**ii) Medical management of Infertility and Menstrual irregularity**

COCP is the first line management for hyper androgenism and menstrual irregularity among PCOS subjects. Clomiphene or letrozole (Femara) recommended for ovulation induction. Clomiphene Citrate treatment is the first choice for ovulation induction. This drug is an oestrogen receptor modulator (it can act as an oestrogen agonist or antagonist) and its mechanism of action is controversial but can be explained as follows. In physiological menstrual cycles, low levels of oestrogen promote negative feedback in the hypothalamus and pituitary gland and inhibit the endogenous secretion of gonadotropin during the early follicular phase. When CC is administered in this phase of the cycle, it competes with oestrogen for its receptors in the hypothalamus and pituitary, which will block the negative feedback mechanism. Consequently, increased levels of endogenous gonadotropins are released and the dominant follicle is recruited (follicle that has the highest number of follicle-stimulating hormone (FSH) receptors) between the sixth and ninth day of the menstrual cycle. Letrozole Aromatase inhibitors (AI) (Mitwally, *et al.*, 2011) which have the biggest impact in higher live birth rates and ovulation rates. Hormonal contraceptives are the initial medication in patients not seeking pregnancy and also to alleviate symptoms of hyperandrogenism acne hirsutism etc( Rosner,*et al.*, 2010).Some studies showed the role of metformin in regularising menstrual cycles ( 50-70%)but Oral contraceptives reported superior to metformin in regulating menses and lowering androgen levels( Moghetti, *et al.*, 2000).Chronic anovulation treated with progesterone/ progestin-containing oral contraceptives, or the levonorgestrel-releasing intrauterine system (Mirena) reduced the risk of endometrial hyperplasia (Bayer *et al.*, 2013)

In combination with the COCP, metformin should be considered in women with PCOS for management of metabolic features where COCP and lifestyle changes do not achieve desired goals. In combination with the COCP, metformin may be most beneficial in high metabolic including those with diabetes risk factors, impaired glucose tolerance or high-risk ethnic groups ovulation rate and menstrual cycles appear to improve with inositol in women with PCOS (Pundir, *et al.*,2018). D- Chiro inositol is effective in reducing the risk of GDM (Crawford *et al.*,2015) and regulating metabolic, hormonal imbalance the inositol stereoisomers, myo-inositol (MI) and D-chiro-inositol (DCI), are hexahydroxycyclohexanes, with the same molecular formula as glucose (Unfer *et al.*, 2016).

They are the two most abundant members of a family of nine stereoisomeric inositols, and are found widely in nature. Present in fruits and beans, the inositols are

incorporated into cell membranes as phosphatidyl-MI, which is a precursor of inositol triphosphate (InsP3) InsP3 is a second messenger for many hormones including insulin and follicle-stimulating hormone (FSH). Defects in this pathway can lead to impaired insulin signalling and cause insulin resistance. This is the rationale for the suggested use of inositols in the management of insulin resistance syndromes, including polycystic ovary syndrome (PCOS). Two inositols of physiologic interest are MI and DCI. The enzyme epimerase converts MI to DCI, maintaining a physiological ratio, which varies from tissue to tissue. A ratio of 40:1 is thought to be physiological for most tissue (Facchinetti *et al.*, 2016)

### **iii) Medical management of Hirsutism**

Hirsutism is the most troubling symptom among PCOS. The most effective first line therapy is oral contraceptives, second line spironolactone 100mg daily, flutamide 250mg twice daily. Electrolysis, lasers are also useful. Anti-androgen therapy with COCP's are considered for treatment of androgenic alopecia. Continuous treatment for atleast 6-12 months required for improving hirsutism and acne whenever COCP's are contraindicated Spironolactone (Aldactone) appears to have potential as a treatment for androgen-excess syndromes, including hirsutism. In both men and women, spironolactone decreases the rate of testosterone production and increases its metabolic clearance. Large studies have confirmed that women who are administered spironolactone exhibit no further progression in hair darkening and coarsening, a slowed growth rate of existing hair, and decreased hair shaft diameter (Van Zuuren, 2015)

### **iv) Medical management of Acne**

Hormonal contraceptives are first-line medications for treating acne associated with PCOS and can be used in conjunction with standard topical acne therapy (e.g., retinoid, antibiotics, benzoyl peroxide) or as monotherapy. Second line treatment included Anti androgens, spironolactone (Buzney 2014). Hyperinsulinemia alters the FSH to luteinizing hormone (LH) shift, preventing the selection of a dominant follicle. Myoinositol and D-Chiro inositol to have specific duties to perform. MI supports FSH signaling, whereas DCI is responsible for insulin-mediated testosterone synthesis. It is suggested that the inositols MI and DCI can reduce insulin resistance, improve ovarian function, and reduce androgen levels in women with PCOS. The effect of MI on ovarian function and oocyte quality is independent of its concentration in circulation. Inositol and associated molecules display inhibitory properties against 5- $\alpha$  reductase, COX-2, and lipase enzymes in addition to their antimicrobial and anti-inflammatory properties (Malvi *et al.*, 2019)

### **a) Lifestyle modification with PCOS**

Altering long term habits especially of eating and physical activity for making it a habitual adaptation and maintaining this new behaviour for long term is defined as lifestyle intervention. This is applicable in reducing metabolic risks such as impaired glucose tolerance, obesity management etc. Diet, exercise and appropriate drug therapy may prove to be critical in their management. In overweight women with hyperandrogenism and PCOS, weight loss decreases abdominal fat, hyperandrogenism and insulin resistance, and improves lipid profiles, menstrual cyclicity and fertility and risk factors for diabetes and cardiovascular disease. A multifaceted approach of modification of diet pattern, physical activity and behavioural therapy are the cornerstones of lifestyle intervention (Wadden and Butryn,2013).

A multidisciplinary team approach required for long term lifestyle modification including a gynaecologist, psychiatrist, dietician, physiotherapist and a nurse. Studies done by Clark et al 1998 concluded that it resulted in reduction of miscarriages from 75 % to 18%, restoration of ovulation from 60% to 67% improvement of pregnancy from 52% to 67 per centage (Clark *et al.*, 1998).

### **c) Nutrition Intervention**

Nutrition has been recognized as the most successful modifiable factor among the lifestyle intervention which imparts significant impact on insulin resistance, weight management and oxidative stress (Asemi *et al.*, 2015). Sedentary lifestyle, unbalanced diet less physical activity undoubtedly intensified the IR and Hyper insulinaemia along with increased weight gain. Change in lifestyle, especially dietary pattern is the first line management of polycystic ovarian syndrome. The limited number of studies explained the relationship of dietary patterns with symptoms of PCOS (Szczyko , 2021).

### **i) Diet pattern and PCOS Risk**

Several studies confirmed the relationship between diet pattern and risk for hypertension especially intake of sodium rich diet (Sacks *et al.*, 2001) .High glycaemic index foods has been associated with high incidence of Diabetes among PCOS women (Colditz *et al.*, 1992)but there .Excess consumption of trans fat increased the risk of CVD associated with elevated LDL cholesterol, TG and decrease in HDL Cholesterol ( Dhaka *et al.*, 2011 ).The energy and macronutrient intake of women using three day food record showed a significantly more saturated fat intake among US group of PCOS women compared to Italian counterparts (Carmina *et al.*, 2003).Comparison of energy and fat

intake among age and BMI matched PCOS and control group indicated PCOS group consumed more calories, fat and more servings of specific high Glycaemic index foods (Douglas *et al.*, 2006) (Lin, and Lujan, (2014).

#### **ii) Changes in eating pattern**

Increased fat and total energy intake observed during the luteal phase. The menstrual cycle increases energy expenditure alters energy and macronutrient intake among PCOS women leading to weight gain. Leptin produced by the adipocyte is reduced further causing trouble in normalising reproductive function and increased appetite. Increased ghrelin levels in patients with PCOS may lead to increased appetite and increased energy intake. PCOS subjects find it harder to lose weight even then with appropriate lifestyle intervention improved abdominal obesity and insulin sensitivity may occur without an overall change in body weight. Insulin Resistance resulted in fluctuation in blood glucose and insulin levels along with Carbohydrate craving accounted for difficulty in losing weight, leading to reactive hypo glycaemia (Farshchi, 2007).

#### **iii) Macronutrient intake in PCOS**

Modest weight loss of even (5%) had beneficial effects insulin sensitivity, and cardiovascular risk profile. Modest weight loss achieved in the short term may also improve hyperinsulinemia. Short periods of calorie restriction lead to decreased androgen levels, and this is sufficient in some patients to restore normal LH pulse frequency and amplitude with consequent restoration of normal menstruation. Some studies supporting the link between consumption of foods with a high glycaemic index and risk for T2DM. High carbohydrate dietary pattern may worsen the metabolic profile of weight loss. The prevalence of dysglycemia is significantly higher in women with PCOS compared to their healthy BMI-matched peers increased food and energy intake as a potential cause for PCOS mice exhibiting an increase in weight gain Studies proposed inverse associations between dietary components (total fat, SFA, total protein) and concentrations of circulating androgens (Mizgier 022)

#### **iv) Impact of Micronutrient intervention**

A favourable diet can improve PCOS health outcome (Kho and Lal 2020). Accordingly, the International Evidence-based Guidelines for the Assessment and Management of PCOS recommends lifestyle modifications, including dietary interventions, as the first-line therapy to manage PCOS. Most studies focus on the macronutrient constituent of the food, but now there is growing evidence that micronutrients also play an essential role in PCOS through beneficial effects on the undeveloped oocyte, Insulin

Resistance, hyperandrogenism and reduction of body fat. Large longitudinal observational studies concluded that multiple micro nutrient supplementation improved PCOS symptoms.(Gunalan 2018)

Some of the previous studies have inscribed the role of some micronutrients in insulin resistance and its improvement (Ni *et al.*, 2015). Supplementation obtaining omega-3 fatty acids and one unlabelled tablet containing folic acid, selenium, vitamin E, catechin, glycyrrhizin, and co-enzyme Q10 and Antioxidant intake in the diet, including  $\beta$ -carotene, zinc, selenium, Vitamin E and Vitamin C protects against free radicals there by preventing the adverse effects such as oxidative stress, damage of cellular membranes (Hager 2019, and Ruder *et al.*, 2009), .Recent studies explained the role of supplementation of Calcium and vitamin D for three months as it can reduce androgens by direct effect on the ovarian, adrenal steroid genesis pathway( Pal *et al.*,2018) . Carotenoids play important role in reducing oxidative stress (Kelishadi *et al.*,2010). Previous studies recommended  $\omega$ -3 rich diet for decreasing hirsutism, BMI, LH, testosterone, TNF- $\alpha$ , HOMA levels, and increasing (SHBG) in women with PCOS (Oner and Muderris, 2013). Selenium act as antioxidant, which protect against reactive oxygen species (ROS) signalling pathways and prevent free radicals' formation (Pal *et al.*, 2018). Zinc supplementation improves insulin resistance in PCOS women and has some favourable effects on metabolic risk factors including inflammatory markers (Pourteymour *et al.*,2010) Co administration of probiotic and selenium in PCOS subjects had beneficial effects on mental health parameters, abnormal hair growth, serum TT and MDA levels (Jamilian *et al.*, 2018). Even though Metabolic syndrome among PCOS subjects had no relationship with vitamin E intake (Wei *et al.*,2015) there was a protective effect of foods rich in vitamin E because of the antioxidant effect of vitamin E (Kim *et al.*,2017)

Dietary considerations to include food that have anti-inflammatory properties, may have a significant impact in reducing pathogenesis and metabolic problems in PCOS (Mina 2020).Clinical and epidemiologic studies suggest that dietary factors such as  $\omega$  -3 polyunsaturated fatty acids, antioxidant vitamins, dietary fibre, and L-arginine may play an important role in modulating inflammation and reducing inflammatory markers such as C-Reactive protein and Interleukin-6 (IL-6). Nuts and seeds are rich in unsaturated fatty acids, antioxidant vitamins (especially vitamin E), dietary fibre, and plant protein. Frequent seed consumption has been associated with reduced risk of cardiovascular disease and type 2 diabetes in prospective studies through mechanisms such as reduction of serum concentrations of total and low-density lipoprotein cholesterol and platelet aggregation,

increased antioxidant activity, and improved insulin sensitivity (Jiang 2006). Therefore, edible seeds such as flax seeds, pumpkin seeds, sesame and sunflower seeds can be tried as a dietary intervention in PCOS patients.

There is mounting proof that micronutrients, through their advantageous effects on developing oocytes, insulin resistance, hyperandrogenism, and body fat reduction, also play a critical role in PCOS (Farzana 2015). Any compound that can reduce androgens will be useful in PCOS. Several studies have conducted to find out the effect of seeds in PCOS. Flaxseeds provide lignans, omega-3 fatty acids, and fibre, which can aid with polycystic ovarian syndrome symptoms. ( Rizvi *et al*, 2021). Flaxseed supplementation led to a significant reduction in body weight, waist circumference, insulin concentration, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), Triglycerides (TG), CRP and IL-6 as per Mohammadi-Sartang *et al.* in a systematic review and meta-analysis of 45 randomized placebo-controlled trials( Haidari 2020) .Secoisolariciresinol Diglucoside (SDG) is the active compound in flaxseed, which has anti-inflammatory effects. SDG is the main lignan which will be converted into weaker form of estrogen by the action of gut bacteria and have anti- estrogenic effect. SDG could also affect the circulation levels of fat-oxidation related hormones, such as adiponectin, and increase fat oxidation in skeletal muscles (Mohammadi *et al* 2017). Flaxseed also contains a high amount of soluble fibre fermented to short-chain fatty acids (SCFA) (acetate, propionate, and butyrate) by intestinal bacteria. SCFAs can down regulate inflammatory pathways in the body and reduce the levels of inflammatory markers (TNF- $\alpha$ , CRP, and IL-6) (Rom *et al* 2018). Previous studies suggested that SDG in flaxseed could reduce visceral (abdominal) fat by down regulation of mRNA levels of sterol regulatory element-binding proteins that are involved in TG synthesis (Fukumitsu 2008, Kristensen 2013). A new clinical study from Duke University showed that daily flax seed supplementation (30g powder per day) could lower testosterone levels by up to 80% of PCOS patient

Sunflower seeds are a potent source of fibre, protein, healthy unsaturated fats, vitamin E, selenium, copper, zinc, folate, iron, and other phytochemicals. Sesame seeds have high concentration of a lignan compound, P3-sesaminol, that has strong anti-oxidant activity. The lignans present in these seeds help in improving insulin sensitivity by reducing glucose uptake speed and insulin release (Mamaghani 2009). They also detoxify the excess estrogen in follicular phase. Zinc and selenium help in increasing the production of progesterone in luteal phase (Abdalla 2020). Prebiotics are also present in the fibre content of the seeds. Prebiotics have also been shown to enhance microbial fermentation,

decrease appetite, and lower post-meal plasma glucose intake. In conventional medicine, sesame has been promoted as a beneficial treatment for oligomenorrhea, foetal abortion, and increasing sexual inclination. High concentrations of lignans and fatty acids found in sesame and sunflower seeds can help balance female hormone imbalances. During the luteal phase, lignans, a type of polyphenol in sesame are supposed to inhibit estrogen levels from increasing too much. Lignans seem to reduce the excess testosterone which plays a key role in the pathogenesis of PCOS

Nutraceuticals found in large quantities in pumpkin seeds include unsaturated fatty acids, such as palmitic, stearic, oleic, and linoleic acids (Rasheed et al., 2023), which are essential for many metabolic processes and help regulate the elevated insulin and cholesterol levels linked to PCOS. They are rich in nutrients and include a lot of beta-sitosterol, unsaturated fatty acids, and nutraceuticals, which help lower excess testosterone and treat PCOS symptoms like weight gain, acne, and hirsutism (Reddy et al, 2016). Sterol Regulatory Element Binding Protein-1 (SREBP1c) and peroxisome proliferator-activated receptor- $\alpha$  are two hepatic genes involved in lipid metabolism that can have their transcription altered by omega-3 fatty acids (Mani et al 2011). Eating a diet high in fibre can help lower blood pressure and improve cholesterol levels. It can also help lower insulin resistance, which can lead to type 2 diabetes mellitus and its problems if left untreated. However, to the best of our knowledge, no research has looked at how a combination of all these micronutrient rich seeds affects menstruation metabolic and hormonal markers of PCOS. The combination of seeds (flax, pumpkin, sunflower, sesame) contains high levels of other trace minerals (calcium, sodium, manganese, iron, zinc, and copper) as well as antioxidants, omega 3 and 6 fatty acids, protein, carbohydrates, fibre, zinc, potassium, phosphorus, and magnesium. These nutrients support female's normal progesterone levels hormonally.

**Table I(a) Literature review matrices**

<b>Intervention element</b>	<b>Process</b>	<b>Outcome</b>
Weight reduction in females with PCOS (Conte et al 215)	Two energy-restricted diets (6,000 kJ/day) + one exercise training per week (brisk walking and aerobic and stretching exercises)	Depressive symptoms decreased ( $p < 0.01$ ) and self-esteem increased ( $p < 0.05$ ) in HPLC group. No significant change in anxiety in either group

	12 weeks	
Diet and aerobic exercise = 18, Diet and combined exercise = 20 (Orio 2016)	Type: RT, aerobic, or mixed RT and aerobic Weekly frequency: five Moderate-to-vigorous intensity (60–80% HR max and 50–75% of 1RM) Time frame: 20 weeks	Decreases Fasting Insulin, LDL ,BMI Waist Circumference ,Waist Hip ratio Increases HDL
<b>Nutrition components</b>		
Flax seeds (Kristensen et al 2013)	(30g powder per day)	visceral (abdominal) fat, lower testosterone levels reduce the levels of inflammatory markers (TNF- $\alpha$ , CRP, and IL-6)
Flax seeds ,Pumpkin seeds, sesame seeds and sunflower seeds ( Rasheed et al 2023)	The recommended dosage for the follicular and luteal phases is 15 g of each seed mixture administered in two sets (pumpkin and flax in the Follicular phase followed by Sesame and sunflower seed in the Luteal phase). For 3months	Flax, pumpkin, sunflower, and sesame seeds are rich in antioxidants, omega 3 and 6 fatty acids, protein, carbs, fibre, zinc, potassium, phosphorus, and magnesium. They also contain high concentrations of other trace minerals, such as calcium, sodium, manganese, iron, zinc, and copper, which support females' normal progesterone levels and balance out fluctuating LH and FSH values, which are indicative of PCOS. Additionally, seed cycling raises blood levels of prolactin and TSH, which are related to weight gain in PCOS-affected females.
Sesame seeds (Wu 2006)	(50 grams) of sesame powder daily For 5 weeks in post-menopausal women	Reduces plasma total cholesterol (TC), LDL-C, the ratio of LDL-C to HDL-C
PCOS women were treated with seed cycling (flaxseed, pumpkin,	Phase One: During first phase, that lasts for 2 weeks, you consume a	Omega-3 is suggested in the treatment of PCOS by improving IR, high triglycerides,

sunflower and sesame seeds) (Irfan et al., 2021)	tablespoon of Flaxseed and pumpkin seeds each. Phase Two: During second phase, that also lasts for 2 weeks, sunflower seeds and sesame seeds for 3months	high LDL and low HDL levels improved and significantly reduced ovarian cysts
Pumpkin seed oil (2g/kg wt )Zeb and ahmed ,2017	30 rabbits 2 weeks	Decreased as well as improvements were seen in the serum cholesterol levels.

**d) Nutrition Education**

General principle of nutrition education is calorie restriction with appropriate intake of macro and micronutrients and adequate intake of dietary fibre and water.

**i) Principles of Anti-inflammatory Diets**

The principle dietary components of a proposed anti-inflammatory diet should be a low glycaemic-load diet low in omega-6 fatty acids but rich in EPA. The macronutrient composition of such a diet would provide about 150 g of carbohydrates (600Kcal) per day. It has been demonstrated that this level of calorie restriction is required to maintain weight loss. Calorie restriction at 1200 calories per day can reverse insulin resistance. One potential mechanism of this rapid effect of calorie restriction on insulin resistance may lie in the reduction of the NF-kappa B activation in hypothalamic neurons. Maintaining a calorie-restricted diet is primarily by increasing satiety by including more proteins (30% of total calories) to help stimulate the release of the satiety hormone PYY from the gut. The protein requirements would be approximately 100 g of protein per day coming from low-fat sources such as fish and chicken vegetarian protein sources like tofu or Imitation soybean meat products. (Batterham et al., 2006). The majority of carbohydrates should be coming from low glycaemic-load sources that would significantly lower the production of insulin. This can be achieved by consuming approximately 10 servings of non-starchy vegetables (200Kcal). A relatively rigid (but not total) exclusion of high glycaemic-load carbohydrates such as bread, pasta, rice, and potatoes. A significant increase in the consumption of polyphenols (found in vegetables and fruits), which are known to have anti-inflammatory benefits. Turmeric also enhances detoxifying capacity of xenobiotics. It contains water

soluble antioxidant “turmerin” which protects the membrane and DNA against oxidative injury (Djuric *et al.*, 2018).

**ii) Advance Glycation End products (AGE)**

Advanced glycation end products (AGEs) are a heterogeneous, complex group of compounds that are formed when reducing sugar reacts in a non-enzymatic way with amino acids in proteins and other macromolecules (Basta, *et al.*, 2015). The AGEs content of a diet depends on the nutrient composition (foods rich in protein and fat have the highest content) and on the way food is processed. AGEs formation can be rapidly accelerated by increasing the time and degree of exposure to heat and can be introduced into the body in heat-processed foods. (Koschinsky, *et al.*, 1997)

**e) Psychological management**

Mental health evaluation and supportive care is essential for PCOS subjects for maintaining their quality of life. PCOS creates an important psychological burden throughout the life-time of these women (Zare Mobini *et al.*, 2018). It was reported about 57% of PCOS cases have at least one mental disorder (Rodrigues *et al.*, 2012). High levels of androgens, acne, infertility, hirsutism, high body mass index, low body image, sexual problems and coping with the disease impair the mental health of them (Podfigurna *et al.*, 2015). Mental disorders including depression or anxiety have a negative impact on weight maintenance, increase ovulation and improve fertility (Deeks, *et al.*, 2010). Considering the importance of mental health, several techniques for relieving anxiety and depression are suggested including the Jacobson Muscle Relaxation Technique (JPMR) as adapted by Bushra *et al.*, (2018). Progressive muscle relaxation is an exercise that relaxes mind and body by progressively tensing and relaxation muscle groups throughout body.

**f) Adoption of Physical activities**

Adaptation of Physical activity is a key component of any lifestyle modification or weight maintenance regime. It can facilitate weight control through direct energy expenditure. (The American College of Sports Medicine recommends 200-300min ( $\geq 2000$ kcal) of moderate exercise per week to facilitate long-term maintenance of weight loss and prevent weight regain in overweight and obese adults. Studies by Mario *et al.*, (2017) defined that physical activity status as PA status number of steps ( $\geq 7500$  steps, active, or  $< 7500$  steps, sedentary). Active PCOS women presented lower waist circumference (WC) lower androgen levels compared to sedentary group. Some studies showed that 60–75 min of moderate-to-high intensity of physical activity daily promotes a

greater long-term (12 –18 months) weight loss compared with the conventional recommendation for optimum health. A realistic approach to exercise depends on the assessment of the patients current exercise habits, preferences regarding type of exercise, and inclination to undertake exercise. Regular, moderate-intensity aerobic exercise over a short period improves reproductive outcomes including ovulation and menstrual cycle regulation in addition to reducing weight and IR in young, overweight women with PCOS (Farshchi *et al.*, 2007).

By lowering stress hormones, decreasing inflammation, raising endorphin levels, and increasing endorphins, walking can improve stress resilience. Walking, aerobics, and strength training are good workouts for PCOS since they have been demonstrated to enhance the body's reaction to insulin. The authors of the Australian PCOS management guidelines recommend engaging in at least 150 minutes of physical activity every week (Teede *et al* 2011). Aerobic exercise is recommended as an efficient technique in the prevention and treatment of PCOS and is helpful in the management of PCOS (Elbandrawy 2022). Stress can impact one's physical health in addition to their mental health. The hypothalamus-pituitary-adrenal (HPA) axis, which is crucial for the body's response to stress, can be upset by consistently high cortisol levels. There is a strong association between the degree of felt stress and the symptoms of anxiety and depression, suggesting that mental health illnesses and stress confrontation have a common mechanism (Bergdahl 2022). Deep breathing, sometimes referred to as diaphragmatic breathing or belly breathing, eases tension, encourages relaxation, and heightens body awareness

Many studies proved that nutrition and diet care process including proper lifestyle modification and adaptation of physical activities provide a great support to women during treatment and throughout life by reducing the treatment related side effects, nutrition related health issues and also improving the quality of life.