Review of Literature

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2.1 Menstrual cycle: An overview

The female reproductive system, unlike the male, undergoes regular cyclic changes known as the menstrual cycle, which serves as the body's periodic preparation for ovulation and potential pregnancy. The most noticeable aspect of the female reproductive system is menstruation, or cyclic vaginal bleeding, which occurs alongside a series of coordinated hormonal shifts. Menstruation, also known as menarche when it first begins, typically starts around puberty with a median age of 12.4. Menstrual cycles cease at menopause, which has an average onset around age 51years (Pan and Li, 2019).

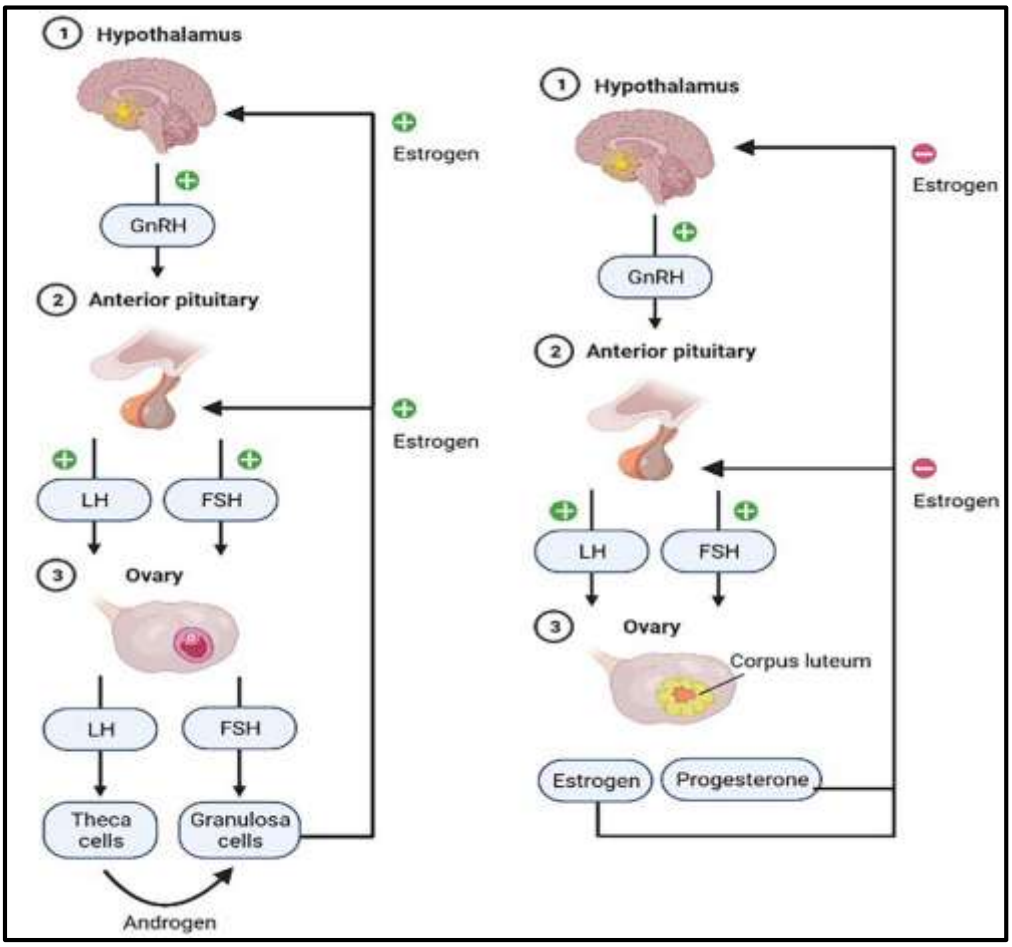
When discussing timing within the menstrual cycle, the first day of heavy menstrual flow is considered day 1. According to the International Federation of Gynecology and Obstetrics (FIGO), normal menstrual cycles should have consistent frequency, regularity, duration, and volume of flow. Normal menstrual frequency is defined as cycles occurring every 24 to 38 days. Infrequent menstruation is defined as cycle lengths longer than 38 days, while frequent menstruation refers to cycle lengths shorter than 24 days. Amenorrhea describes the complete absence of menstrual bleeding. Normal menstrual duration is defined as bleeding lasting 8 days or less while bleeding beyond 8 days is considered prolonged menses (Munro *et al.*, 2018).

The menstrual cycle comprises 2 distinct cycles—one within the ovary and another within the endometrium. The phases of the ovarian cycle include the follicular phase, ovulation, and the luteal phase. The endometrial cycle consists of the proliferative phase, the secretory phase, and the menstrual phase. Generally, the ovarian follicular phase corresponds to the menstrual and proliferative phases of the endometrium, while the luteal phase of the ovarian cycle corresponds to the secretory phase of the endometrial cycle (Thiyagarajan *et al*., 2024).

Hormones are secreted through both negative and positive feedback mechanisms to regulate the menstrual cycle. Hormonal regulation begins in the hypothalamus, where gonadotropin-releasing hormone (GnRH) is secreted in an increased, pulsatile fashion starting at puberty. GnRH is transported to the anterior pituitary, where it activates its G protein-coupled receptor, signalling the pituitary gland to release follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH and

LH then travel through the bloodstream to the ovaries, stimulating the production of sex steroid hormones from follicular cells (Thiyagarajan *et al*., 2024).

Figure 2.1 Negative and positive feedback mechanisms to regulate the menstrual cycle*



* Islam et al., 2022

The ovarian follicle contains 2 cell types responsible for hormone production—theca cells and granulosa cells. LH stimulates theca cells to produce progesterone and androstenedione by activating the enzyme cholesterol desmolase. Androstenedione then diffuses into the adjacent granulosa cells, where FSH stimulates the enzyme aromatase within the granulosa cells to convert androstenedione to testosterone and then to 17-β estradiol. Both 17-β estradiol and progesterone are secreted into the bloodstream and affect various tissues, including the uterus and pituitary gland. In the uterus, these hormones promote the growth and maturation of the endometrium. At the anterior pituitary, these sex steroid hormones provide negative feedback, reducing the secretion

of FSH and LH, which subsequently reduces the production of 17-β estradiol and progesterone by the ovaries (Harlow, 2018).

An exception to this negative feedback loop occurs around the time of ovulation. When a critical level of 17-β estradiol is reached, it provides positive feedback to the anterior pituitary, leading to a surge in FSH and LH production. Granulosa cells within the feedback system also produce inhibin B and activin, which inhibit and stimulate FSH release from the anterior pituitary, respectively. This feedback mechanism is regulated by the upregulation or downregulation of GnRH receptors on the anterior pituitary (Pepe *et al*., 2018).

2.2 Polycystic Ovarian Syndrome (PCOS): An emerging reproductive health issue

2.2.1 Prevalence of PCOS among young adult women Population

Polycystic Ovary Syndrome (PCOS) is a prevalent endocrine and metabolic disorder, affecting approximately 9.2% of women worldwide. The condition shows notable regional variability, with higher prevalence observed in South-East Asia (11.4%) and lower rates in the Western Pacific region (2.9%) (Laddad et al., 2019). PCOS predominantly affects women of reproductive age, particularly those between 20 and 24 years. Differences in prevalence are largely attributed to variations in diagnostic criteria, notably the Rotterdam, NIH, and International Evidence-based Guidelines.

According to Motlagh et al. (2022), PCOS continues to be a significant metabolic health concern among women of reproductive age, with a large proportion of cases remaining undiagnosed. This underscores the need for comprehensive awareness programs and effective interventions within healthcare systems. A study conducted among female students of the Navodaya Group of Institutions reported a 13.6% prevalence of PCOS based on the Rotterdam criteria, with 68 out of 500 participants aged 13–25 years exhibiting features such as hirsutism and oligomenorrhea (Pallavi & Harshitha, 2024).

Neven et al. (2024) presented a global analysis demonstrating PCOS prevalence of 9.8% using the Rotterdam criteria and 6.3% when assessed by the International Guidelines. Furthermore, findings from the Global Burden of Disease Study (2017) revealed a steady increase in incidence, with an age-standardized rate of 82.44 per

100,000 women and an overall rise of 1.45% since 2007. Approximately 1.55 million new cases and 0.43 million disability-adjusted life years were attributed to PCOS in 2017, particularly in regions with medium to high socio-demographic indices (Liu et al., 2024).

Within the Indian context, evidence from limited, primarily convenience-based studies indicates considerable variation in prevalence. A pilot cross-sectional study in Tamil Nadu reported a prevalence of 18% among adolescent females (Balaji et al., 2015), while Joshi et al. (2014) identified 22.5% prevalence using the Rotterdam criteria and 10.7% using the Androgen Excess Society criteria in an urban Mumbai cohort. Research among medical students in South India further indicated high PCOS occurrence accompanied by an increased incidence of mood disorders (Joseph et al., 2016). Vidya Bharathi et al. (2017) reported a 16% prevalence rate among community-dwelling women from both rural and urban regions of Chennai, highlighting the widespread nature of the syndrome.

Recent evidence from a national-level survey published in *JAMA Network Open* reported a PCOS prevalence of 7.2% based on NIH criteria and 19.6% using the Rotterdam criteria, with phenotype C being most predominant (40.8%) (Ganie et al., 2024). These findings collectively reaffirm the substantial burden of PCOS among Indian women and emphasize the imperative for standardized diagnostic approaches, enhanced public health awareness, and targeted management strategies to mitigate the associated metabolic and reproductive health complications.

2.2.2 Definition and Meaning of PCOS

One of the most prevalent endocrine system conditions affecting women of reproductive age is polycystic ovary syndrome (PCOS), also known as hyperandrogenic anovulation (HA) or Stein–Leventhal syndrome. This chronic and heterogeneous disorder manifests itself as menstrual dysfunction, infertility, hirsutism, acne, and obesity. It describes a condition where at least one ovary has an ovarian volume greater than 10 mL and at least one ovary has an estimated ten small cysts, with diameters ranging from 2 to 9 mm, develop (Singh *et a*l., 2023). The article "Global prevalence of polycystic ovary syndrome in women worldwide: a comprehensive systematic review

and meta-analysis" defines polycystic ovary syndrome (PCOS) as the most common endocrine disorder affecting women of reproductive age. PCOS is characterized by a combination of symptoms including irregular menstrual cycles, elevated androgen levels, and the presence of polycystic ovaries. The review emphasizes that PCOS can manifest in various ways, making it a heterogeneous condition (Salari *et al*., 2024).

According to Ndefo *et al* (2013), polycystic ovary syndrome (PCOS) is a complex condition characterized by elevated androgen levels, menstrual irregularities, and/or small cysts on one or both ovaries. The disorder can be morphological (polycystic ovaries) or predominantly biochemical (hyperandrogenemia). Hyperandrogenism, a clinical hallmark of PCOS, can cause inhibition of follicular development, microcysts in the ovaries, anovulation, and menstrual changes. PCOS is recognized as an important reproductive as well as metabolic disorder since it affects the ovaries, and 40 per cent of the affected women suffer from insulin resistance and are subsequently predisposed to developing T2DM (Jabeen *et al*., 2022). Again Witchel *and* co-workers (2019) added that it is a disorder primarily characterized by signs and symptoms of androgen excess and ovulatory dysfunction, which disrupts the Hypothalamic-Pituitary-Ovarian axis function.

As it is currently defined, PCOS most likely encompasses several distinct diseases with similar clinical phenotypes but different underlying pathophysiological processes. However, hyperandrogenism remains the syndrome's clinical hallmark. The clinical manifestations of PCOS often emerge during childhood or in the peripubertal years, suggesting that the syndrome is influenced by fetal programming and/or early postnatal events (Cioana *et al*., 2022). PCOS is often associated with severe insulin resistance as well as with defects in insulin secretion, and this appears to be related to the modulation of the activity of the key regulatory enzyme of androgen biosynthesis, cytochrome P450c17. In addition, hyperinsulinaemia inhibits the production of sex hormone-binding globulin, which increases the local availability of bioactive testosterone and works synergistically with increased levels of luteinising hormone to enhance androgen production. The PCOS phenotype results in androgen excess, oligo-anovulatory infertility, polycystic ovaries on ultrasound examination, insulin resistance and cardiometabolic disorders, with overweight/obesity and visceral adiposity occurring in 30–70% of PCOS women (Barrea *et al*., 2018).

PCOS occurs when the levels of particular hormones are out of balance. As a result, cysts or fluid-filled sacs, grow on the ovaries. Hair loss on the head, excessive hair growth elsewhere on the body (male hair growth), weight gain, depression, and fertility issues are associated symptoms (Safia *et al*., 2023). Currently, there are four commonly recognized phenotypes of PCOS: type A, polycystic ovary (PCO), chronic oligo-anovulation (OA) and hyperandrogenism (HA); type B, OA and HA; type C, PCO and HA; and type D, PCO and OA (Zhao *et al*., 2023).

2.2.3 Pathophysiology of PCOS

Polycystic Ovary Syndrome (PCOS) is a complex disorder with multifactorial pathogenesis, the mechanisms of which remain under investigation. Pathophysiological features include dysregulation of gonadotropin-releasing hormone (GnRH) resulting in elevated luteinizing hormone (LH) and reduced follicle-stimulating hormone (FSH), diminished ovarian follicular responsiveness to FSH, increased anti-Müllerian hormone (AMH), follicular arrest, and elevated secretion of testosterone, estradiol, and dehydroepiandrosterone (DHEA). Obesity, particularly abdominal fat deposition, predisposes to insulin resistance (IR) and metabolic abnormalities through adipocyte dysfunction occurring at a post-receptor level (Pellatt et al., 2007).

The interplay between hyperandrogenism and insulin resistance forms a self-perpetuating cycle. Hyperandrogenism, resulting from dysfunction of theca cells and/or altered hypothalamus-pituitary-ovarian axis activity, is amplified by elevated AMH concentrations. Excess androgens promote visceral adiposity and adipocyte abnormalities, while hyperinsulinemia secondary to IR stimulates theca cell androgen production and alters gonadotropin effects (Thong et al., 2020). The cumulative effect exacerbates metabolic and reproductive disturbances.

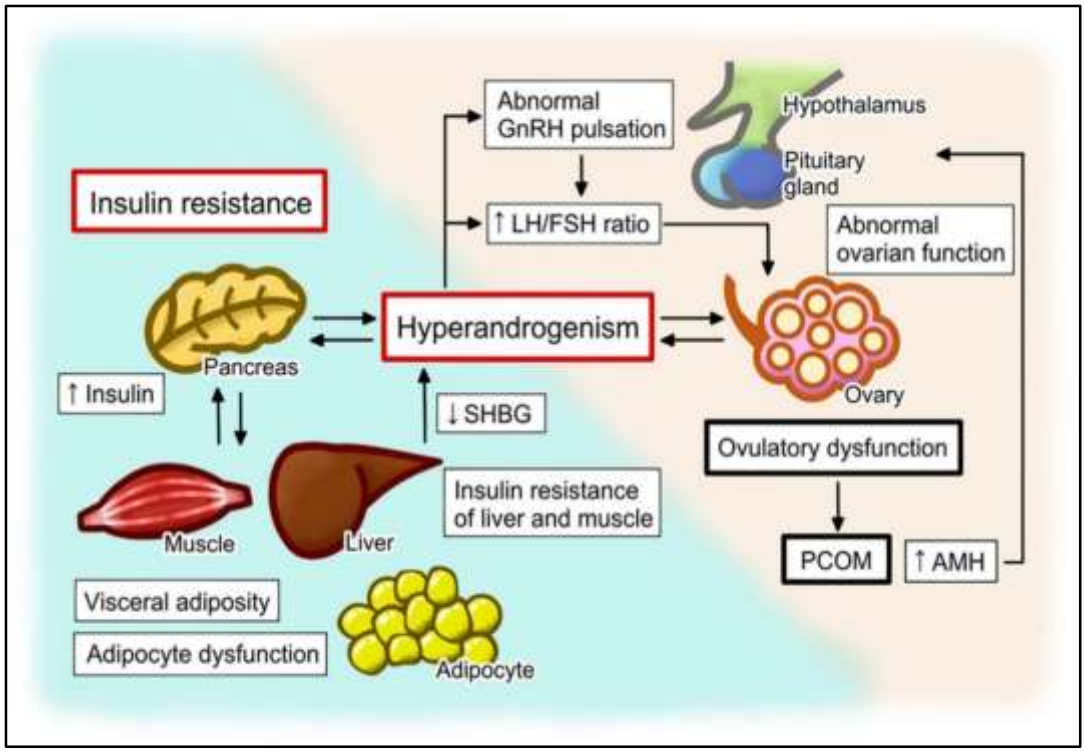
A characteristic feature of PCOS is disruption of the normal balance between androgen, AMH, and FSH, leading to follicular arrest. Elevated LH induces androgen synthesis by theca cells, but insufficient FSH limits conversion to estradiol, preventing the selection of a dominant follicle and causing chronic anovulation. Increased AMH production by granulosa cells inhibits early follicular transition, resulting in polycystic ovarian morphology. Follicles from PCOS ovaries may possess intrinsic differences

from normal ovaries (Lebbe & Woodruff, 2013). PCOS theca cells show persistently elevated androgen synthesis via increased CYP17A1 expression and activity, along with enhanced utilization of the "backdoor pathway" for steroidogenesis (Marti et al., 2017). Serum levels of 11-oxygenated androgens are substantially higher in PCOS compared to controls (O'Reilly et al., 2016).

Insulin resistance and hyperinsulinemia are observed across varying degrees of adiposity in PCOS and are linked to an increased risk of glucose intolerance and type 2 diabetes mellitus. The pathogenesis reflects the combined effects of genetic predisposition, environmental factors, and adaptive responses to energy surplus (Diamanti & Dunaif, 2012). IR in PCOS is tissue-specific: skeletal muscle, adipose tissue, and liver display metabolic resistance, whereas steroidogenic tissues such as the adrenal glands and ovaries remain insulin-sensitive (Ibáñez et al., 2017). Insulin also suppresses hepatic sex hormone-binding globulin (SHBG) synthesis, increasing free androgens, and may directly enhance ovarian steroidogenesis via activation of P450c17 and P450scc enzymes. In certain women, pancreatic beta cell dysfunction adds to the risk of carbohydrate intolerance (Torchen et al., 2014). Mechanisms contributing to IR include defective post-receptor activity, increased free fatty acids, cytokine release (TNF-α, IL-6, leptin, resistin), and abnormal fat distribution. Excess free fatty acids reaching the liver impair insulin action, while ceramide and diacylglycerol accumulation in skeletal muscle and liver further disrupts insulin signaling (Ibáñez et al., 2014; Badin et al., 2013).

A neuroendocrine hallmark of PCOS is altered secretion of LH and FSH, with increased LH levels, elevated LH:FSH ratios, greater pulse frequency or amplitude, and relatively low FSH. These changes affect steroidogenesis, follicular dynamics, and ovulatory function (Azziz et al., 2016). Kisspeptin-producing Kiss1 neurons, which regulate GnRH secretion, have been found to exhibit altered expression or reduced numbers in animal models of PCOS following excessive androgen exposure during critical developmental periods. Rodent studies of postnatal androgen exposure indicate persistent suppression of hypothalamic Kiss1 expression, implicating central neuroendocrine alterations in the etiology of PCOS (Brown et al., 2012).

Figure 2.2 Vicious Cycle of PCOS Pathophysiology*



* Harada, 2022

2.2.4 Clinical Manifestations of PCOS

2.2.4.1 Ovarian Dysfunction

PCOS is the most common cause of ovarian dysfunction, with a prevalence of 8-13 per cent in reproductive-aged women. The clinical and pathological hallmarks of PCOS include oligo/ anovulatory ovarian dysfunction, polycystic ovarian morphology, and clinical/biochemical hyperandrogenism. Follicular development frequently halts at the small antral stage in PCOS, preventing full maturation and ovulation. Hyperandrogenism, insulin resistance, Hypothalamic-pituitary-ovarian axis imbalance (LH>FSH), and chronic low-grade inflammation are major contributors to the pathophysiological changes observed in PCOS (Orisaka *et al*., 2023).

PCOS is characterized by excessive ovarian and/or adrenal androgen secretion. Intrinsic ovarian factors such as altered steroidogenesis and factors external to the ovary such as hyperinsulinemia contribute to excessive ovarian androgen production. Characteristic features include more growing follicles in women with PCOS than normal controls with premature growth arrest of antral follicles at 5 to 8 mm. The classic

ovarian phenotype of enlarged ovaries with string-of-pearl morphology and theca interstitial hyperplasia reflects androgen exposure; this morphology has also been observed in women with congenital adrenal hyperplasia (CAH) and female-to-male transgender individuals (Witchel *et al*., 2019).

Ovulatory dysfunction is one of the remarkable hallmarks of PCOS despite its heterogeneous nature. It has been reported that ovulatory dysfunction affects nearly 25% of couples. Ovulation disorders are classified into 3 categories by WHO as group I, II and III. Hypothalamic pituitary failure is said to be the cause of Group I. It has been found that nearly 10% of women with ovulatory dysfunction come under group I. Whereas, 85% of women with ovulatory dysfunction have group II disorder which arises due to the hypothalamic-pituitary-ovarian axis dysfunction. PCOS comes under group II ovulation disorders. Group III ovulation disorders include about 5% of women due to ovarian failure (ACOG, 2002).

2.2.4.2 Infertility

WHO (2023) states that PCOS can cause hormonal imbalances, irregular periods, excess androgen levels and cysts in the ovaries. Irregular periods, usually with a lack of ovulation, can make it difficult to become pregnant. PCOS is a leading cause of infertility. It is a chronic condition and can't be cured. However, some, symptoms can be improved through lifestyle changes, medications and fertility treatments. According to Cunha and Povoa (2021), Ovulation disorders are the cause of infertility in around 25 per cent of couples and PCOS is the major cause of anovulatory infertility, accounting for approximately 70 per cent of all cases. They added that women with PCOS may also have an increased risk of miscarriage and pregnancy complications such as gestational diabetes.

Non-ovulatory infertility accounts for approximately 30% of infertility, with PCOS accounting for 90% of these cases. Patients with PCOS are prone to ovulatory disturbance, which leads to infertility. They are also more likely to have poor pregnancy outcomes. In PCOS, many factors affect ovarian function. In addition, being overweight, having hyperandrogenemia, and having an elevated serum concentration of luteinising hormone (LH) can adversely affect fertility (Li *et al*., 2022). PCOS results from a vicious circle of androgen excess favoring abdominal and visceral adipose tissue

deposition, that induces insulin resistance (IR) and compensatory hyperinsulinemia, further facilitating androgen secretion by the ovaries and adrenal glands. This cyclical pathogenetic interaction between IR, hyperinsulinemia, and hyperandrogenism, in combination with hypothalamic-pituitary dysfunction, leads to further ovarian dysfunction that can result in anovulation and infertility (Escobar, 2018).

In PCOS patients, anovulation, a higher risk of spontaneous abortion, poor oocyte quality, raised blood LH concentration, and miscarriages linked to hyperinsulinemia all hurt fertility. With a higher risk of endometrial hyperplasia associated with ovulatory dysfunction and infertility, women with PCOS have less success getting pregnant and having children. The number of prior pregnancies has little bearing on the lower pregnancy rates associated with PCOS. Numerous international researches have repeatedly shown that PCOS is the main culprit in female factor infertility. Infertility was reported by 72 per cent of women with PCOS in a cross-sectional study, compared to 16 per cent of women without the disorder (Dar *et al*., 2024).

2.2.4.3 Hyperandrogenism

Hyperandrogenism, the hallmark feature of PCOS, is clinically manifested as hirsutism, acne, and alopecia. Excessive androgen production by ovaries as well as from adrenals contributes to hyperandrogenism. Abnormalities in the neuroendocrine system like increased pulse frequency of gonadotropin-releasing hormone, stimulating the pituitary for excessive production of luteinising hormone than that of follicle-stimulating hormone is seen in PCOS women. Excess LH stimulates ovarian androgen production, whereas a relative deficit in FSH impairs follicular development. The imbalance in LH: FSH causes proliferation of ovarian theca cells leading to increased steroidogenesis, and ultimately leading to hyperandrogenism in PCOS women (Ashraf *et al*., 2019).

Polycystic ovary syndrome (PCOS) is characterized by hyperandrogenism, resulting from abnormal ovarian or adrenal function that leads to excessive androgen production. This condition disrupts normal folliculogenesis, with excess androgens initially promoting the development of primordial and small antral follicles. The hypothalamus typically secretes gonadotropin-releasing hormone (GnRH) in a pulsatile manner, stimulating the pituitary gland to release luteinizing hormone (LH) and follicle-

stimulating hormone (FSH). In PCOS, increased LH stimulates androgen production in theca cells, while FSH facilitates the conversion of androgens to estrogens in granulosa cells, essential for follicle maturation. However, dysregulation of the hypothalamic-pituitary-ovarian axis leads to an imbalance in gonadotropin levels, characterized by an elevated LH/FSH ratio. This hormonal imbalance results in theca cell hyperplasia and the accumulation of follicular fluid, forming cyst-like structures that give the ovaries a "string of pearls" appearance. Additionally, increased androgen levels are linked to insulin resistance, suggesting a relationship between insulin action and hyperandrogenism in PCOS. Thus, understanding these mechanisms is crucial for addressing the reproductive and metabolic complications associated with PCOS (Mohammad *et al.,* 2023).

2.2.4.4 Metabolic Disorders

Polycystic ovary syndrome (PCOS) is one of the most common endocrine diseases among women of reproductive age and is associated with many metabolic manifestations, such as obesity, insulin resistance (IR) and hyperandrogenism. PCOS is closely linked to metabolic disorders such as obesity and insulin resistance (IR). A large proportion of women with PCOS are obese or overweight and exhibit IR with associated compensatory hyperinsulinemia. Of note, IR and hyperinsulinemia are metabolic traits that are also present in most lean women with PCOS. Hyperinsulinemia plays a prominent role in the development of some phenotypic features of PCOS and, together with β cell dysfunction, increases the risk of developing other metabolic abnormalities such as type 2 diabetes (T2D), hypertension, dyslipidemia, and cardiovascular diseases. Importantly, the prevalence of these metabolic comorbidities is high in women with this disorder, and the concurrence of overweight or obesity and PCOS exacerbates not only metabolic complications but also reproductive derangements associated with this endocrinopathy (Sanchez *et al.,* 2020).

IR and hyperinsulinemia are metabolic traits characteristic of lean and obese women with PCOS and are considered important components in the pathogenesis of this endocrinopathy. Hyperinsulinemia contributes to androgen-dependent anovulation through different mechanisms. Insulin enhances the stimulating effects of LH on

androgen production in ovarian theca cells. Insulin has been proposed to act as a co-gonadotropin and stimulate androgen biosynthesis in the ovary by activating P450c17 expression and activity in theca cells. Of note, theca cells in women with PCOS are more sensitive to the hyperandrogenic effects of insulin than those in healthy women. Despite peripheral IR, insulin sensitivity remains intact or maybe even enhanced in ovaries in women with PCOS. This observation suggests the presence of selective insulin resistance in PCOS that differentially affects the metabolic tissues and ovary (Rosenfield and Ehrmann., 2016).

Insulin is the main hormone in charge of both lipogenesis and glucose homeostasis. Insulin serves as a mitogenic hormone in addition to having an impact on the metabolism of carbohydrates, fats, and proteins. Insulin receptors, which are present in many tissues of the HPO axis, mediate the activities of insulin. Insulin potentiates the corresponding trophic hormones in steroidogenic tissues, such as the ovary and the adrenal cortex, to encourage steroidogenesis. As insulin directly mimics the action of LH and indirectly raises GnRH, hyperinsulinemia is the primary cause of excessive androgen production. Sex hormone binding globulin (SHBG), a key circulatory protein that regulates testosterone levels, is decreased by insulin. Therefore, lower SHBG levels would lead to higher levels of free androgens, which cause clinical symptoms of PCOS, such as hirsutism, alopecia, and acne. Numerous studies have shown that lowering insulin resistance will ultimately result in reduced androgens and an improvement in the disease condition (Singh *et al.,* 2023).

Women with PCOS often exhibit dyslipidemia, with the level of low-density lipoprotein (LDL) cholesterol and triglycerides, and decreased high-density lipoprotein (HDL) cholesterol. This lipid profile increases the risk of cardiovascular disease (Chen and Pang, 2021).

2.2.4.5 Psychological Features

The intersection of PCOS and mental health is complex, with individuals often grappling with heightened risks of depression and anxiety. The hormonal imbalances characteristic of PCOS can contribute to mood disturbances, amplifying the risk of depressive symptoms and anxiety disorders. Beyond the physiological factors, the emotional toll of managing a chronic condition, coupled with societal pressures and

potential fertility concerns, can further contribute to the heightened prevalence of depression and anxiety among those with PCOS (Dewani *et al*., 2023). The prevalence of anxiety and depressive disorders among women with PCOS ranges from 28 per cent to 39 per cent for anxiety and 11 per cent to 25 per cent for depression (Chaudhari *et al*., 2018).

PCOS has profound effects on body image and self-esteem, as individuals may contend with physical symptoms such as weight gain, acne, and hirsutism. Societal beauty standards often exacerbate these challenges, perpetuating unrealistic expectations that can be particularly distressing for individuals with PCOS. The visible manifestations of the syndrome can lead to a negative self-perception and, in some cases, contribute to the development of eating disorders. A comprehensive understanding of the impact of PCOS on body image is essential for implementing supportive interventions that address both the physical and psychological aspects of well-being (Alur-Gupta *et al*., 2019).

The psychosocial impact of PCOS extends to interpersonal relationships, with potential ramifications on both romantic and familial connections. Fertility concerns, a common worry for individuals with PCOS, can strain relationships and contribute to emotional distress. The challenges associated with fertility treatments, coupled with the uncertainty surrounding conception, can further intensify the strain on relationships. Acknowledging and addressing the emotional toll on both individuals and their partners is crucial for providing holistic support and fostering open communication within relationships affected by PCOS (Zangeneh *et al*., 2012). The results of the study conducted by ZareMobini and co-workers showed that some women with PCOS feared and were concerned about developing chronic illnesses, such as diabetes and hypertension. Due to its chronic nature and various symptoms, PCOS affects the patients' different aspects of life (ZareMobini *et al.,* 2018).

2.2.5 Diagnosis of PCOS

In 1935, Stein and Leventhal first characterized what is now known as PCOS among a case series of seven women with a combination of hirsutism, obesity, amenorrhea and bilateral enlarged polycystic-appearing ovaries on surgical and pathologic evaluation (Stein and Leventhal, 1935). Since then, several diagnostic

criteria have been proposed which variably include a combination of oligo-amenorrhea, hyperandrogenism and changes in ovarian morphology, as now assessed by pelvic ultrasonography.

In 1990, the first attempt to produce a clinical definition of PCOS was completed by the National Institute of Child Health and Human Development, in which PCOS was defined by the presence of both clinical and/or biochemical signs of hyperandrogenism and oligo- or chronic anovulation (Zawadski and Dunaif, 1992). Ultrasonographic evidence of polycystic ovaries was reported as suggestive of PCOS, but not necessarily diagnostic, which conflicted with the leading practice in the United Kingdom and much of Europe at the time, whereby polycystic ovaries on ultrasound were viewed as the "defining feature of PCOS" (Balen and Michelmore,2002).

This debate continued until 2003, when 27 PCOS experts met in Rotterdam, the Netherlands, at a conference sponsored by both the European Society of Human Reproduction (ESHRE) and American Society for Reproductive Medicine (ASRM), and produced a joint consensus statement commonly known as the "Rotterdam Criteria" (Rotterdam, 2004). These criteria broadened the phenotypic expression of PCOS to include any two out of the three key characteristics of PCOS: oligo-amenorrhea, hyperandrogenism, and polycystic-appearing ovarian morphology on ultrasonography. In doing so, the prevalence of PCOS, in some studies, increased as much as three times compared to diagnosis using the 1990 NIH criteria (Deswal *et al.,* 2020). Furthermore, the use of these criteria allowed for the diagnosis of PCOS without hyperandrogenism, which had previously been viewed as the primary defect by the 1990 NIH criteria.

Since the 2003 Rotterdam criteria, all proposed criteria have included ovarian morphology with varying degrees of importance. In 2006, the Androgen Excess Society (AES) again made hyperandrogenism central to the diagnosis of PCOS, while affirming the relevance of ovarian morphology in the diagnosis of this syndrome (Azziz *et al*., 2006). The AES guidelines required the presence of hirsutism and/or biochemical hyperandrogenism, as well as either oligo-anovulation and/or polycystic-appearing ovarian morphology (PCOM) for the diagnosis of PCOS (Azziz et al., 2006). Thus, the "most mild" phenotype of PCOS (oligo-anovulatory women with polycystic ovarian morphology and without hyperandrogenemia) was excluded.

The presence of multiple classification systems resulted in clinical confusion and was viewed as delaying scientific progress in our understanding of PCOS. Thus, in 2012, the NIH held an evidence-based methodology workshop on PCOS, in which experts on PCOS again recommended the use of the broader 2003 Rotterdam criteria, while specifically identifying sub-phenotypes within these criteria of (1) androgen excess and ovulatory dysfunction, (2) androgen excess and PCOM, (3) ovulatory dysfunction and PCOM, and (4) androgen excess, ovulatory dysfunction and PCOM (NIH, 2013), The Rotterdam criteria continues to be the most widely used and accepted criteria for PCOS and were once again unanimously supported in the 2018 International Evidence-Based Guideline for the Assessment and Management of PCOS . Now it is recommended to use the modified Rotterdam criteria in which PCOS may be diagnosed if any two of the following are present: (1) clinical or biochemical hyperandrogenism, (2) evidence of oligo-anovulation, (3) polycystic appearing-ovarian morphology on ultrasound, with exclusion of other relevant disorders (Teede *et al*.,2018).

Table 2.1 Features of diagnosing PCOS.

Features	Recommended Diagnosis	Considerations
Biochemical Hyperandrogenism	Elevated total or free testosterone, or calculated indices of free testosterone (FAI, BioT). DHEAS and ANSD can be considered	High-quality assays should be used for the evaluation of analytes
Clinical Hyperandrogenism	A modified Ferriman–Gallwey score of ≥4 to ≥8	The threshold level should be considered in the context of patient ethnicity
Oligo-anovulation	Oligo-amenorrhea (cycles >35 days apart or <8 menses a year)	If highly suspicious for PCOS, but does not have oligo-amenorrhea, consider serum progesterone or luteinizing hormone assessment
Polycystic ovarian morphology	≥20 follicles per ovary in either ovary ≥10 cm^3 ovarian volume	Based on transvaginal ultrasonography with a transducer frequency ≥ 8 MHz

Criteria based on the modified 2003 Rotterdam criteria. FAI—free androgen index, BioT-bioavailable testosterone, DHEAS—dehydroepiandrosterone sulfate, ANSD-androstenedione.

2.2.6 Complications of PCOS

2.2.6.1 Early Term Complications

Infertility is a widely disputed problem affecting patients suffering from polycystic ovary syndrome (PCOS). As a serious dysfunction, it frequently occurs in PCOS patients. It is, therefore, important to devote more attention to pregnancy in PCOS sufferers. According to various data, the risk of miscarriage in PCOS women is three times higher than the risk of miscarriage in healthy women. Unfortunately, the risk of most frequent pregnancy pathologies is also higher for PCOS patients, such as gestational diabetes (GD), pregnancy-induced hypertension and pre-eclampsia, and small for gestational age (SGA) children. Impaired glucose tolerance and GD in pregnant PCOS patients occur more frequently than in healthy women (Katulski *et al*., 2015).

A quadruple increase in the risk of pregnancy-induced hypertension linked to arterial wall stiffness has also been observed in PCOS patients. The risk of pre-eclampsia, the most severe of all complications, is also four times higher in those suffering from PCOS. Pre-eclampsia is also more frequent in patients presenting additional risk factors accompanying PCOS, such as obesity or GD. At that point, it should be mentioned that PCOS patients are under 2.5 times more at risk of giving birth to SGA children than healthy women. It appears that SGA can be linked to insulin resistance and insulin-dependent growth dysfunction. Therefore, PCOS pregnant women are patients of special obstetrical care (Gilbert *et al*., 2018).

Recently, the risk of preterm delivery has increased twofold and more in PCOS patients, even if confined to hyperandrogenic subjects (Naver *et al*., 2014). Neonates born to women with PCOS had a twofold increased risk for admission to the neonatal intensive care unit and their mortality was increased by threefold (Qin *et al*., 2013). Albeit the first published meta-analysis found no difference in the risk of small-for-gestational-age neonates (Boomsma *et al*., 2006), the most recent one found an almost twofold increased risk of small-for-gestational-age and no risk of large-for-

gestational-age neonates (Kjerulff *et al*., 2011). Two recent studies confirmed an increased risk of small-for-gestational-age of four and twofold and half in neonates of women with PCOS, whereas another study showed no effect of PCOS on the risk of small-for-gestational-age (Naver *et al*., 2014).

2.2.6.2 Long-term Complications

As reported by the main scientific societies, women with PCOS present an increased prevalence of classic risk factors for cardiovascular disease (CVD) such as hypertension, dyslipidemia, diabetes, and obesity and nonclassic risk factors such as C-reactive protein (CRP), homocysteine, and tumour necrosis factor-α.PCOS at any age is characterised by greater odds for elevated CVD risk markers and these elevated markers can occur without obesity but are magnified with obesity (Palomba *et al*., 2015).

With the current evidence, the connection between PCOS and cardiovascular disease seems to be strengthening. Since obesity and components of MS mediated the association between CVD and PCOS, this emphasises the importance of prevention and treatment of obesity, hypertension, and dyslipidemia in women with PCOS even those under the age of 40 years (Meri-Maija *et al*., 2023).

Dyslipidemia is very common in PCOS patients, which is present in 70% of patients in the United States (US) with different patterns. Most often it is represented by hypertriglyceridemia and low high-density lipoprotein (HDL) cholesterol levels and small dense low-density lipoprotein (LDL) cholesterol particles (also called atherogenic lipoprotein phenotype), similar to that found in type-2 diabetes mellitus (T2DM) and typical for the states of IR. In contrast, the increased LDL cholesterol in PCOS is less dependent on body weight and may be partially related to the hyperandrogenism (Essah *et al*., 2008). Higher non-HDL cholesterol, frequent in women with PCOS, reflects altered ApoB/A1 ratios, an important risk factor for CVD (Valkenburg *et al.,* 2008).

At present, based on the most recent meta-analysis, women with PCOS of all ages seem to be at an increased risk of endometrial cancer. In particular, the risk of endometrial cancer may be even higher in the premenopausal subgroup of women with PCOS, while overall the risk of ovarian and breast cancer was not significantly

increased (Barry *et al*., 2014). PCOS women with amenorrhea are at greater risk for endometrial hyperplasia and cancer; therefore, ESHRE/ASRM Consensus Workshop Group has established proper endometrial surveillance with ultrasound and/or biopsy to assess endometrial thickening in women who experience extended periods of amenorrhea, based on clinical suspicion and presentation, and in these women periodic progestogen withdrawal is also recommended, at least four episodes per year (Fauser *et al*., 2012).

PCOS is associated with insulin resistance and may also coexist with type II diabetes. In the meta-analysis, which covered the population of patients aged 8.9 to 75 years with type II diabetes, the incidence of PCOS in the group <25 years was 18 per cent (Long *et al*., 2022). Non-Alcoholic fatty liver disease (NAFLD) is a common subject of research into the complications of PCOS. It was shown that teenagers with PCOS complicated by NAFLD accounted for 37.5 per cent of the respondents, and those with coexisting obesity and lower SHBG were more predisposed to the development of NAFLD. In another study, the prevalence of NAFLS in adolescents with PCOS was found to be 19 per cent, not significantly different from the prevalence in adolescents without PCOS (Urbano *et al*., 2022).

2.3 Preventive Measures for minimising the consequences of PCOS

2.3.1 Dietary Management in PCOS

To date, various dietary regimes have been developed to reduce the symptoms and further hormonal imbalances occurring due to PCOS. A summary of nutrients' distribution for PCOS patients was described by Kamran and colleagues which included a hypocaloric, high fiber, high protein, high PUFA, low carbohydrates, low GI, low GL, and low-fat diet. Reduction in calories from 500 kcal to 1000 kcal for a period of 6 months and reduction of 7–10 per cent of body weight is recommended, optimum caloric intake would be 1200–1400 kcal per day including 40 per cent of calories from carbohydrates, 30 per cent from protein while 30 per cent of fat and major part of fat should be from omega-3 polyunsaturated fatty acid. This diet altogether represents a major impact on weight reduction, insulin management, and PCOS amelioration (Kamran *et al*., 2017).

Dietary goals should target excess weight and insulin resistance. A low-fat, plant-based diet causes weight loss and reduces insulin resistance, which affects 50-70% of women with PCOS (Hahn *et al*., 2005). This is particularly important because insulin tends to reduce sex hormone-binding globulin (SHBG) and increase free testosterone concentrations. Low-fat, high-fibre diets reduce circulating androgens, increase SHBG, and effectively address dyslipidemia (elevated triglycerides, low HDL) and elevations of C-reactive protein and homocysteine (In Bernard, 2023).

Diets high in fruits, vegetables, whole grains, and legumes also reduce oxidative stress and inflammation. These may be involved in PCOS for several reasons. First, a genetic basis exists for the inflammation found in PCOS, with polymorphisms for proinflammatory cytokines (e.g., tumour necrosis factor, interleukin-6) being found independent of obesity and in association with insulin resistance. Second, a systematic review and meta-analysis found that several markers of oxidative stress were altered in women with PCOS, independent of obesity (Kandaraki *et al*., 2011).

One of the key nutrients in a diet that emphasizes whole grain intake, legumes, and nuts in place of refined carbohydrates is inositol hexaphosphate (Ip6, phytic acid). In clinical trials, inositol has been shown to improve insulin action, decrease androgen levels, and improve ovulatory function in both lean and obese women with PCOS. The benefits of metformin in PCOS appear at least partly due to increasing inositol availability (In Bernard, 2023). The effects of soluble dietary fibre on SCFAs were demonstrated. Fermentable fibre has positive metabolic benefits on the gut microbiome with the subsequent release of SCFAs. Diets with a low GI may influence appetite-regulating hormones including ghrelin and glucagon. Low-GI meals reduced ghrelin and increased glucagon in women with PCOS (Hoover *et al*., 2021).

The research showed that the vast majority of women with PCOS consume an improperly balanced diet, involving deficiencies in fiber, omega 3, calcium, magnesium, zinc, and vitamins (folic acid, vitamin C, vitamin B12, and vitamin D). An excess of nutrients was also noted in sucrase, sodium, total fats, saturated fatty acids, and cholesterol (Szczuko *et al*., 2016). In the case of most vitamin B, the increase in its supply with the diet led to the expected result in the form of its increased level in the plasma of women with PCOS. This effect was not observed for vitamin B3, and the

levels of B2 and thiamine were not as satisfactory as in the case of the other, related vitamins (Szczuko *et al*., 2021). Women with PCOS may be treated with metformin, which normalizes glycemia, but its chronic intake is additionally associated with deficiencies in thiamine and cobalamin. Therefore, it is a good idea to supplement with thiamine, which, by activating transketolase, contributing to the inhibition of mechanisms damaging blood vessels, reducing the risk of cardiovascular diseases (Eshak and Arafa, 2018).

Supplementation of vitamin D increases insulin synthesis and release, increases insulin receptor expression, and increases insulin response to glucose transport. Vitamin D indirectly influences carbohydrate metabolism by normalizing extracellular calcium and parathyroid hormone concentration. It also affects the expression of the genes of the metabolic pathways affecting systemic inflammation by inhibiting the synthesis of pro-inflammatory cytokines, which may contribute to the occurrence of IR. Women with PCOS receiving 20,000 IU of cholecalciferol weekly benefited from improved carbohydrate metabolism. Decreases in fasting glucose, triglycerides, and estradiol were observed (Szczuk *et al*., 2021).

Current results showed that myo-inositol is as effective as metformin in improving the clinical and metabolic profile of women with PCOS and the metabolic disorders associated with diabetes. However, the administration of metformin is associated with side effects that are not experienced with inositol. Inositol increases insulin sensitivity, normalizes androgens in the blood, improves glycemia, and affects numerous features of metabolic syndrome (Saleem and Rizvi, 2017).

The research, and the available literature, show that supplementation with zinc and selenium to counter deficiencies may be indicated in the case of at least some patients with PCOS. Due to intracellular signaling and structural functions, zinc plays a role in lipid and glucose metabolism and fertility. Low zinc intake in obese people is associated with hyperinsulinemia, increased low-grade inflammation, and a worsened lipid profile. In addition, zinc ions can act in an insulin-mimetic manner in adipocytes, stimulating lipogenesis and glucose transport through the translocation of glucose transporter 4 (GLUT4) to the plasma membrane. Zinc deficiency may play a significant role in the pathogenesis of PCOS and may be a prognostic marker of PCOS. Studies

showed that the average serum zinc levels of PCOS patients are significantly lower compared with healthy controls (Nasiadek *et al*., 2020).

Selenium is associated with a lower level of CRP. It has anti-inflammatory and antioxidant properties (Coskun *et al*., 2013). Finally, it is necessary to supplement the omega-3 fatty acids, which tend to be lacking in the diet of PCOS women. However, with a balanced diet, supplementation can be regarded as a seasonal intervention (Michael *et al*., 2019). Polyunsaturated fatty acids (PUFAs) enhance the reproductive performance in PCOS by increasing the expression of steroidogenesis enzymes, which are related to hormone secretion and ovarian functions, and the protein levels of CYP51, CYP19, StAR, and 3β-HSD (Ma et al., 2019). In summary, supplementing the diet is an individual subject that requires dietary consultation with the patient, and active participation and compliance are desirable for the overall improvement of the metabolic equilibrium. A properly balanced diet and a healthy lifestyle should be the first element of PCOS therapy.

2.3.2 Exercise and stress management on PCOS

The most preferred and effective method of treatment of PCOS is lifestyle modification. Weight loss is an important treatment strategy. Physical exercise can be used as an independent treatment for PCOS women to appraise all PCOS phenotypic characteristics (Harrison *et al*., 2011). Possible factors that are responsible for obtaining the expected response of exercise include genes, age, and hormonal status of the individual. Lifestyle changes, including physical activity modification, can be recommended as an early management strategy to reduce PCOS-related comorbidities, as it decreases insulin resistance, enhances metabolic and reproductive characteristics, and enhances self-esteem (Jiskoot *et al.*, 2017).

Australian guidelines for the management of PCOS recommend at least 150 min of moderate-level exercise each week (Tay *et al.,* 2020). Aerobic exercise can enhance glycemic control while providing a beneficial impact on sexual function and quality of life. Physical activity is beneficial for PCOS women's reproductive health because it lowers the risk of developing metabolic syndrome and its associated clinical symptoms (Kaczmarek *et al*., 2016). In addition to enhancing reproductive and self-esteem in

PCOS women, physical activity has positive effects on mental health (Banting *et al*., 2014) and (Lopes *et al*., 2018).

Skeletal muscle is known to play a crucial role in exercise-induced glucose uptake by stimulating the translocation of the glucose transporter type 4 (GLUT4) to the plasma membrane to promote glucose uptake. GLUT4 is regulated by insulin and belongs to a family of glucose transporter proteins that facilitate the transport of glucose across the plasma membrane (Huang *et al*., 2007). Studies have emphasised the role of adenosine monophosphate-activated protein kinase (AMPK), which can be activated through exercise in an intensity- and volume-dependent manner (Torma *et al.*, 2019), in regulating the post-exercise increase in glucose uptake and insulin sensitivity (Kjøbsted *et al*., 2019). Furthermore, it has been shown that after an acute bout of exercise, women with PCOS exhibit increased activation of skeletal muscle insulin signalling with changes in insulin gene expression and metabolic signalling similar to those in healthy women. However, the results of other studies have suggested that PCOS can impair the pathways through which exercise induces metabolic improvements (Stepto *et al*., 2020).

Among women with PCOS, exercise has been demonstrated to improve free androgen levels by increasing SHBG concentrations, which bind to circulating testosterone and regulate its bioavailability (Patten et al., 2022). Additionally, exercise can also lower hyperinsulinaemia (Kite *et al*., 2019), commonly present in women with PCOS, which may also impact androgen levels. In this regard, high insulin levels may inhibit the hepatic production of SHBG, increasing serum-free testosterone (Pugeat *et al.*, 1991). However, the precise mechanisms by which exercise modulates SBHG, including its effects on insulin levels, remain unclear. Exercise has also been found to positively affect ovarian function in individuals with PCOS. These improvements are linked to reduced hormonal imbalances and improvements in lean muscle mass and/or body fat, resulting in increased ovulation rates and regular menstrual cycles (Patten *et al*., 2022).

The effects of exercise on cardiometabolic health outcomes in PCOS have been investigated in various systematic reviews. The available evidence is consistent regarding exercise eliciting modest improvements in waist circumference (Breyley-

Smith *et al*., 2022), which is often used as a surrogate measure of visceral fat in clinical practice. However, lipid profiles and body weight have improved in some (Benham *et al*., 2018) but not all meta-analyses (Richards *et al*., 2021). Similarly, whilst fasting insulin appears to improve in most meta-analyses, fasting blood glucose does not.

Skeletal muscle mitochondrial function, which partly reflects substrate metabolism and energy production capacity, is impaired in those with insulin resistance and PCOS (Moreno-Asso *et al*., 2022). Exercise has been demonstrated to improve mitochondrial function and content, which can lead to improved metabolic health (Malamouli *et al.,* 2022). various meta-analyses have demonstrated that aerobic exercise, involving either moderate-intensity continuous training (MICT) or high-intensity interval training (HIIT), can improve cardiorespiratory fitness in women with PCOS by approximately one metabolic equivalent (~ 3.5 mL/kg/min) (Breyley-Smith *et al*., 2022). A cardiorespiratory fitness difference of one metabolic equivalent is associated with a 13 % risk reduction in all-cause mortality and a 15 % reduction in the incidence of cardiovascular disease (Kodama *et al*., 2009).

Exercise is known to be an effective strategy for improving symptoms of depression and anxiety (Singh *et al*., 2023) and QoL in various populations (Sabag *et al*., 2023). Whilst the effect of exercise on mental health outcomes and QoL has been relatively understudied in PCOS, available data suggests that those with PCOS who are more physically active report fewer symptoms of depression compared to their inactive counterparts (Banting *et al.,* 2014). Although it is currently unclear what type, intensity, or duration of exercise may be most effective for improving the abovementioned outcomes, preliminary evidence indicates that exercise may be an effective strategy for improving mental health outcomes in women with PCOS (Sabag *et al.,* 2024).

2.3.3 Medical care and alternative treatments for PCOS

Apart from nutritional interventions, oral contraceptives are recommended as first-line pharmacologic therapy in adolescents and adults to manage menstrual irregularities, hirsutism, and acne. Combined estrogen-progestin oral contraceptives also protect against endometrial hyperplasia (Shah *et al*., 2018).

Weight loss, physical activity, and metformin are usually necessary to reduce insulin resistance. Metformin is not recommended as a first-line therapy for cutaneous symptoms, ovulation induction, prevention of pregnancy complications, or treatment of obesity. It can, however, be used to help with many PCOS symptoms in women who have an insufficient response to dietary interventions, or who have contraindications to oral contraceptives. The use of thiazolidinediones is not recommended in PCOS patients due to safety concerns (Legro *et al*., 2013). Physical means of hair removal (e.g., electrolysis, laser treatment) may be necessary to treat hirsutism. If oral contraceptives are contraindicated or do not improve symptoms, acne is treated with topical or oral agents.

According to Nutrition Guidelines for Clinicians (2023), treatment of infertility is often necessary if the patient desires pregnancy. They detailed the points such as:

- Weight loss, even small reductions, and exercise may be beneficial.
- Assisted reproductive technologies (e.g., in vitro fertilisation) may be necessary.
- While not approved by the Food and Drug Administration for ovulation induction, letrazole is currently preferred given evidence of higher birth rates compared to clomiphene or metformin. Metformin is used as an adjuvant treatment in those undergoing in vitro fertilization to prevent ovarian hyperstimulation. While evidence suggests metformin can restore ovulation, and possibly promote weight loss by improving insulin resistance, its role in treating infertility is limited.
- Gonadotropin therapy can induce ovulation, but treatment regimens are complex and carry the risk of ovarian hyperstimulation syndrome.

In clomiphene-resistant PCOS women who are unable to comply with the close monitoring necessary for gonadotropin administration, bilateral laparoscopic ovarian surgery with monopolar electrocautery (multiple controlled perforation of the ovary) or laser is an acceptable alternative; both modalities confer similar results. Laparoscopic ovarian diathermy (LOD) is associated with lower multiple gestation rates than gonadotropins. In a Cochrane Database Systematic Review article, there was no

evidence of a difference in live birth rate and miscarriage rate in women with clomiphene-resistant PCOS undergoing LOD versus gonadotropin treatment. It appears to be more effective in patients with high LH, and significant reductions in LH and androgens have been shown following surgery. LOD restores menstrual regularity in 63%–85% of women, and the beneficial effects on reproductive outcomes seem to last for several years in many women (Rytz *et al*., 2022).

Based on the literature reviewed, Polycystic Ovary Syndrome (PCOS) is a prevalent and complex endocrine disorder affecting women of reproductive age worldwide. Its pathophysiology involves a multifaceted interplay of hormonal imbalances, including hyperandrogenism, insulin resistance, and abnormal gonadotropin regulation, leading to ovarian dysfunction and metabolic disturbances. The heterogeneity of PCOS, stemming from variations in diagnostic criteria (like Rotterdam and NIH guidelines) and diverse clinical presentations such as menstrual dysfunction, hirsutism, and polycystic ovaries, complicates its diagnosis and contributes to underdiagnosis. This highlights the critical need for increased awareness, standardized diagnostic approaches, and further research to address knowledge gaps and improve targeted management and intervention strategies, particularly dietary and lifestyle interventions, for young women affected by PCOS globally and in specific regions like India, where prevalence rates vary significantly.