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Cancer risk in polycystic ovary syndrome patients: Common treatments and future perspectives

Alfi Shahrin[1], Mahmuda Akter Mele[2] and Mohammad Zahirul Islam[3]*
[1]*Department of Pharmacy, East West University, Dhaka 1212, Bangladesh.*
[2]*College of Science and Engineering, James Cook University, Townsville, Queensland 4811, Australia.*
[3]*Department of Food Science and Biotechnology, Gachon University, Seongnam 13120, Republic of Korea*
**Corresponding authors' email address: zahirul@gachon.ac.kr (M.Z.I.)*

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Abstract. In women of childbearing age, polycystic ovarian syndrome (PCOS) is the most common endocrine and metabolic condition. Ovulatory dysfunction, clinical symptoms of hyperandrogenism, and multiple cystic ovaries are the hallmarks of PCOS. Women who have PCOS may have irregular insulin activity in addition to other difficulties such as pattern hair loss, acne, obesity, infertility, and hirsutism. An unhealthy lifestyle, hereditary causes, androgen exposures, and neuroendocrine factors are frequently the causes of PCOS. This results in an unbalanced hormonal state, hyperandrogenism, high insulin, and inflammation. Due to the overlapping metabolic and endocrine issues, PCOS patients' cancer risk has been the subject of debate for decades. This review article examines the relationship between PCOS and various types of reproductive cancers, focusing on the possible reasons for cancer in PCOS patients.

Keywords: *cancer, endocrine disorder, ovarian cancer, medicine, food and life style*

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1. Introduction

Polycystic ovarian syndrome (PCOS) is a complex disorder that involves aspects of both the metabolic and endocrine systems (Giudice, 2006). Most women with PCOS experience chronic anovulation, elevated levels of androgens in the blood, insulin resistance, and the growth of numerous tiny follicles on their ovaries (Witchel et al., 2019). Things like hyperinsulinemia and hypothalamic-pituitary-ovarian disturbances have a significant impact on the pathophysiology of PCOS (Balen, 2004). Ovarian dysfunction is an important part of the pathophysiology of PCOS. Hypersecretion of luteinizing hormone (LH), which is caused by too much gonadotrophin-releasing hormone (GnRH) pulsatility (Szeliga et al., 2022), affects both the ovaries' production of androgens and the maturation of oocytes. Disruption of the feedback system between the ovary, pituitary, and hypothalamus exacerbates gonadotropin abnormalities. Hyperinsulinemia requires the presence of both peripheral insulin resistance and abnormal beta-cell activity in the pancreas. According to Khan et al. (2019), a number of genetic abnormalities that frequently pass down through generations appear to be the root cause of PCOS's characteristics and its various symptoms. Environmental variables such as diet and lifestyle can also affect how the condition manifests itself in a person (Kshetrimayum et al., 2019).

Obesity, insulin resistance, hyperinsulinemia, and dyslipidemia are common metabolic abnormalities associated with this syndrome; however, these conditions are not included in the description of the syndrome because it is uncertain whether these factors are integral to the diseases (Moran & Teede, 2009). In addition, clinical features include irregular menstruation or amenorrhea, decreased or absent ovulation, elevated circulating androgen concentrations, and signs of hyperandrogenism.

Greater than fifty percent of women with PCOS have increased LH levels, and approximately seventy-five percent of women have insulin resistance and hyperinsulinemia with PCOS (Marshall & Dunaif, 2012).

PCOS-affected women also have an increased risk of progressing endometrial hyperplasia as well as endometrial cancer (Ding et al., 2018). Numerous PCOS symptoms can be treated with pharmaceuticals, including hirsutism, and acne with oral contraceptives; oligomenorrhea, infertility, and type II diabetes treatment with ovulation induction therapy; and metformin with clomiphene and letrozole (Legro et al., 2013). Moreover, PCOS is linked to a variety of health problems in women, some of which have been linked to reproductive malignancies. Despite the many data points on PCOS and gynecological malignancies, there appears to be a hole in the research describing the alliance between PCOS and the threat of developing each individual gynecological cancer. The purpose of this review is to provide further context for why PCOS increases the risk of gynecological malignancies in these individuals. Further, understanding the cause and pathophysiology of malignancies in women with PCOS. This review also gives information about the mechanisms of cancer development and the possible relationship with traditional medical treatment.

2. Pathophysiology of Polycystic Ovarian Syndrome (PCOS)

Ovarian malfunction and environmental variables both play roles in the pathophysiology (Figure 1) of PCOS. Androgens are present in serum in decreasing concentrations. These include dehydroepiandrosterone sulfate, dehydroepiandrosterone, dihydrotestosterone, testosterone, and androstenedione (Kanbour & Dobs, 2022). Neuroendocrine dysfunction is thought to lead to a difference in the hypothalamic-pituitary-ovarian axis in people with PCOS. This results in a greater number of gonadotropin-releasing hormone pulses occurring at regular intervals. Because of the increased rate of GnRH pulses, LH production is stimulated more than follicle-stimulating hormone (FSH) production. This leads to a rise in the LH: FSH ratio, which in turn induces hyperandrogenism in patients with PCOS (Ashraf et al., 2019). Moreover, ovarian granulosa cells are responsible for the production of anti-mullerian hormone, also known as AMH. In addition, GnRH release is controlled by AMH. In people with PCOS, a high level of AMH stimulates the production of LH through the AMH receptors on the hypothalamus and pituitary. This makes the ovarian cells release a lot of androgen. A low amount of FSH inhibits testosterone from converting to estrogen, which leads to an excess of androgen in the body. However, high levels of AMH restrict the synthesis of FSH receptors and aromatase in the granulosa cells. As a result, it encourages the direct and indirect release of AMH from granulosa cells, which is a result of the increase in testosterone (Ashraf et al., 2019).

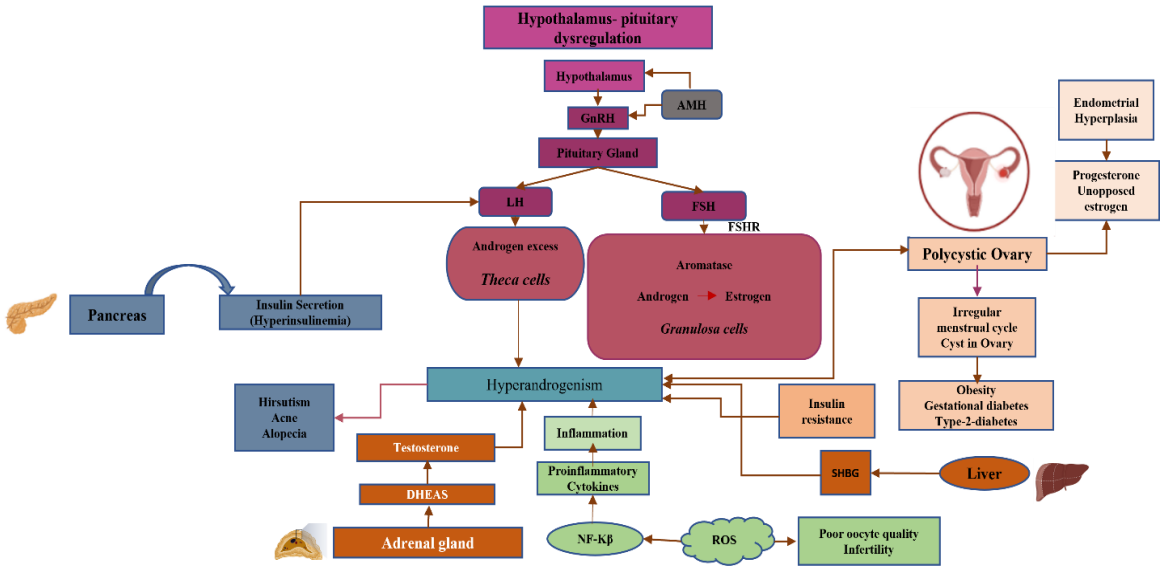

Figure 1. Pathophysiology of Polycystic Ovarian Syndrome (PCOS)

According to Franks and Hardy (2018), long-term exposure to acyclic LH causes ovarian cells to become overactive and stimulated, which results in the production of too much androgen. PCOS involves several hormones, including testosterone, androstenedione, LH, FSH, estrogen, progesterone, and insulin (Witchel et al., 2019). The activation of a sequence of enzymes in the ovary by LH controls testosterone synthesis. In PCOS, high testosterone levels result from the overexpression of steroidogenic enzymes and a rise in the number of microantral follicles (Dadachanji et al., 2018). Less testosterone is converted to estradiol and more testosterone is released into the circulation when aromatase enzymes are inhibited (Chan et al., 2016).

As described earlier, women with PCOS exhibit insulin resistance with compensatory hyperinsulinemia. Insulin stimulates androgen synthesis by acting on its receptors and interacting with LH (Baptiste et al., 2010). Conversely, in the presence of insulin, the liver creates less sex hormone-binding globulin, allowing for greater testosterone bioavailability. Follicle development stops, which leads to the hyperandrogenic phenotype and its symptoms, such as anovulation, hirsutism, acne, and androgenic alopecia (Witchel et al., 2019). Moreover, heart disease, diabetes, and other metabolic disorders are also more likely to develop (Dadachanji et al., 2018).

3. Carcinoma Risk of Polycystic Ovarian Syndrome (PCOS) Patients

In comparison to women without PCOS, those afflicted with this condition exhibit a threefold enhanced vulnerability to the development of endometrial cancer. Endometrial cancer is prevalent among PCOS-affected women, but the overwhelming majority will not develop the disease. It was determined that neither ovarian nor breast cancer was associated with PCOS (Ding et al., 2018). Moreover, when all other risk factors were taken into account, the study found no link between infertility and breast cancer (Lundberg et al., 2019).

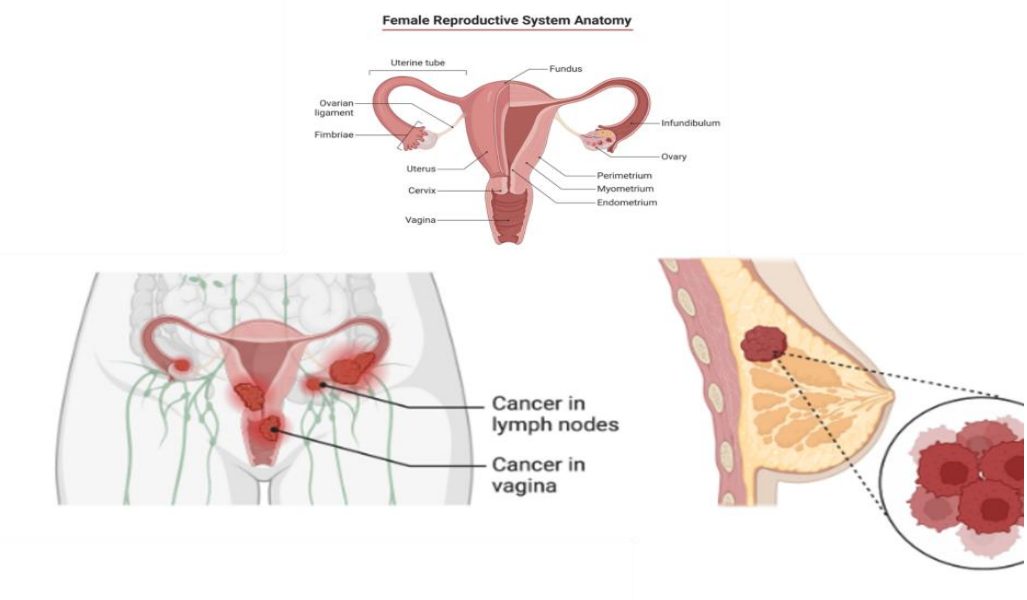

Figure 2. Progression of ovarian and breast cancer

3.1. Endometrial cancer

It has been of utmost importance to establish a safe and efficacious method for preventing endometrial cancer (EC) in women diagnosed with PCOS, considering the significant impact of this disease and the associated financial implications. Globally, it seems that there is an increasing trend in the occurrence of endometrial cancer (EC), particularly rising rates of obesity, which is a significant concern in PCOS cases (Shafiee et al., 2014). The projected increase is anticipated to range from 50% to 100% within the upcoming 20-year period (Legro et al., 2013; Kanbour & Dobs, 2022). Globally, it has been observed that endometrial cancer accounts for approximately 4% of all cancers in women, with a higher incidence among women who have reached menopause (Ashraf et al., 2019). In the United Kingdom, EC, also known as endometrial cancer, ranks as the fourth most prevalent form of cancer among women. In 2008, a total of 7,703 cases were reported, and unfortunately, this cancer

claims the lives of approximately 10,000 women annually in Europe (Franks & Hardy, 2018). PCOS has been linked to an increased risk of reproductive malignancies, particularly endometrial cancer (Harris & Terry, 2016). Particularly, endometrial carcinoma is more common in women who are overweight with PCOS, have never given birth, are above the age of 50, have infertility, hypertension, and diabetes, have difficulty ovulating regularly, or take estrogen supplements without getting their levels checked regularly.

Hyperinsulinemia causes an increase in endogenous estrogen production from progesterone and an increase in androgen synthesis in the adrenals and ovaries. In addition, visceral adipocytes contain aromatase enzymes, which can convert androgens to estrogens. Women who may not ovulate typically have lower amounts of progesterone than other women. Due to an increase in insulin-like growth factors, estrogens and androgens all increase mitotic activity. Endometrial hyperplasia and endometrial cancer are more likely to progress as a result of the effects of these alterations on endometrial proliferation and mutagenesis (Holm et al., 2012). However, the five-year chance of surviving endometrial cancer is 86%; this number may be increased with early identification (Haoula et al., 2012). According to the results of a cross-sectional study in Thailand including 52 patients, 19.2% of PCOS patients who presented with atypical menstrual patterns had abnormal endometrial pathology (Holm et al., 2012).

Endometrial tumors may be divided into two basic categories: endometrioid, which is considered Type I, and non-endometrioid, which is considered Type II, based on their histologic appearance (Harris & Terry, 2016). The claimed links between PCOS and endometrial cancer presumably stem from the Type I subtype, which accounts for 70–80% of all endometrial malignancies. For example, one study looked at the link between PCOS and endometrial cancer subtypes, and they found a higher link when only looking at Type I cases (Fearnley et al., 2010).

3.2. Ovarian cancer

Ovarian cancer is classified as the seventh most commonly diagnosed neoplasm in women globally (Reid et al., 2017). The risk of developing ovarian cancer has been associated with the hormonal fluctuations that occur during a woman's reproductive years as well as the cumulative number of ovulatory cycles experienced throughout her lifetime. The correlation between a decreased frequency of menstrual cycles and an elevated risk of carcinogenesis has been observed (Yang et al., 2016). Recent research (Jiao et al., 2019) has shown that ovarian tissue from women who have irregular menstruations has hypomethylated DNA and has the same miRNA and mRNA characteristics as ovarian tissue from women who have been diagnosed with ovarian cancer.

Adipose tissue, blood, and ovarian theca and granulose cells of PCOS women have all been discovered to have unusual DNA methylation and miRNAs, indicating the risk of ovarian cancer in this population (Chen et al., 2019). Nevertheless, the available clinical studies concerning the correlation between PCOS and ovarian cancer are relatively scarce. Furthermore, the patient cohort size in certain studies is exceedingly limited. Another issue pertains to the interplay of overlapping risk factors, namely obesity, dietary habits, tobacco use, and alcohol consumption. However, the available clinical studies regarding the correlation between PCOS and ovarian cancer are relatively scarce. Furthermore, the patient cohort size in certain studies is exceedingly limited. Another issue pertains to the interplay of overlapping risk factors, namely obesity, dietary habits, tobacco use, and alcohol consumption.

A certain hypothesis suggests that increased androgen levels in women with PCOS can enhance their chance of developing ovarian cancer (Figure 2) (Harris & Terry, 2016). Androgen receptors have been found in benign ovarian tumors, and higher androgen levels while pregnant are related to a 40–50% higher risk of tumors, suggesting that androgens have a contribution to the development of ovarian cancer (Butler et al., 2013). This means that when these hormones are overexposed, the chance of developing ovarian cancer increases (Harris & Terry, 2016). However, while the odds ratio was statistically significant in one study of older women, the elevated danger of PCOS was not statistically significant in the three investigations that identified ovarian cancer (Barry et al., 2014). There is evidence associating high body mass index with ovarian cancer, in addition to endometrial and breast cancer (Harris et al., 2017). In a recent Mendelian randomization study, the endometrioid histotype showed the highest negative connection between genetically induced PCOS and the progression of ovarian cancer. Table 1 summarizes past and present case studies of PCOS-related cancer patients.

Table 1. Past and present case studies of PCOS related cancer patients

Studied regions	Study types	Total cancer participants	Number of patients found with cancer-related to PCOS	Cancer types and Adjusted (HR/OR/SIR/RR)	References
USA, Japan, Australia, Europe	Systematic reviews	919	11	Ovarian (1.41) Breast (0.95) Endometrium (2.79)	(Barry et al., 2014)
United Kingdom	Systematic reviews	938	938	Endometrium (2.9)	(Haoula et al., 2012)
USA	Retrospective cohort	2560	5	Uterine corpus (1.28), Ovarian (0.42)	(Brinton et al., 2010)
Denmark	Cohorts	12070	85	Endometrium (3.9), Ovarian (1.8), Breast (1.1)	(Gottschau et al., 2015)
United Kingdom	Cross-sectional	128	11	Endometrium (1)	(Pillay et al., 2006)

Note. OR: Odds ratio; HR: Hazard ratio; SIR: Standardized incidence ration; RR: Relative risk

3.3. Breast cancer

Breast cancer represents the most prevalent form of cancer discovered among women, according to data compiled by a number of different organizations (Bray et al., 2018). It affects a staggering approximately million women annually and is responsible for the highest number of deaths associated with cancer. According to the statistics of the year 2018, it has been observed that a total of 627,000 individuals succumbed to breast cancer. This particular type of cancer is associated with approximately 15% of all cancer disease fatalities among women. The incidence of cancer tends to be higher in regions that have achieved higher levels of development. However, it is noteworthy that the rise in cancer rates is observable across nearly all regions worldwide. The intriguing matter at hand pertains to the correlation between PCOS and the prospect of developing breast cancer. The subject matter at hand pertains to certain facets of one's genetic makeup and the analysis of data through a meta-analysis approach. The idea may have been brought forward that genes linked to breast cancer are also shown to be dysregulated in people with PCOS. The genes hydroxysteroid dehydrogenase, high-mobility group box 2, platelet-derived growth factor receptor, and alpha polypeptide were identified as potential candidates (Xu et al., 2017).

Based on the available research, it has been suggested that there is currently no conclusive evidence establishing a definitive connection between PCOS and breast cancer. Nevertheless, certain studies have indicated a potential association between obesity in individuals with PCOS and an elevated susceptibility to breast cancer (Cooney & Dokras, 2018). Certain PCOS traits and outcomes have been associated with either an increasing or lower development of breast cancer in the past. Infertility caused by ovulatory disorders, for instance, has been linked to a lower risk of mammary gland cancer. While obesity lowers the progression of breast cancer in young women, it raises it after menopause (Beebeejaun et al., 2021).

Breast cancer has several different subtypes. Due to this, breast cancer rates, presentation, and survival rates vary greatly across racial and ethnic lines (Barańska et al., 2021). Several epidemiological studies (Table 1) have found a correlation between breast cancer and reproductive factors like getting the first period before the age of 12 and the last one after 55 (Figure 2). Several environmental factors have been linked to an increased possibility of breast cancer, such as wealth, obesity, poor diet, heavy alcohol use, insufficient exercise, and therapeutic exposure to ionizing radiation (Lee et al., 2019). Ovulatory dysfunction was not associated with an increased progression of breast cancer in large-scale research by Harris and Terry (2016). According to Barry et al. (2014) examination of prior data, the possibility of breast cancer in women with PCOS was similar to that of breast cancer in control women. Women with PCOS may not have a particularly reduced adjusted hazard ratio (aHR) for breast cancer in comparison to people who may not have PCOS (Ding et al., 2018). However, the current study has revealed that PCOS appears to play a significant role as a causal factor in the incidence of estrogen receptor-positive (ER-positive) breast cancer (Wen et al., 2021). This finding contributes to a deeper comprehension of the origins of breast cancer and offers insights into potential preventive measures.

Both estrogen and progesterone levels are highest in the course of the luteal phase of the menstrual cycle, which is skipped in anovulatory cycles. Women with fertility issues will have less relevance to luteal phase receptors throughout the course of their lives, which may account for the lower risk seen. This is because the proliferation of breast cancer cells is greater during the luteal phase. Thus, this result provided evidence for the hypothesis that PCOS might not have been shown to cause breast cancer.

4. Mechanisms of Carcinoma Development in Polycystic Ovarian Syndrome (PCOS) Patients

Many studies have been published about PCOS and the risk of cancer. Some of the features linked with the typical evolution of PCOS include hyperinsulinemia, high estrogen levels, and chronic inflammation. There is some evidence to suggest that these types of chronic diseases can be major factors in oncogenesis and the growth of cancer in PCOS (Mravec & Tibensky, 2020; Yau et al., 2017).

Hyperinsulinemia starts and tracks the progression of cancer right away. Inflammation, on the other hand, affects a number of pro-tumorigenic pathways that mostly lead to carcinogenesis and angiogenesis, making it easier for cancer cells to grow in certain places (Arcidiacono et al., 2012). Moreover, sympathetic hyperactivity has been identified as a risk factor for the advancement of cancer in women who have PCOS, according to recent studies. When the sympathetic nervous system is overactive, it sends out norepinephrine. A rise in norepinephrine levels acts like a molecular switch that makes tumors grow new blood vessels (Bauman & McVary, 2013; Mravec & Tibensky, 2020). In addition to this, having a low progesterone level is directly linked to a higher risk of endometrial cancer. Furthermore, several studies have found that having a lower progesterone level is a sign of hyperandrogenism, creating a connection between the two conditions (Papaioannou & Tzafettas, 2010).

A recent study found numerous PCOS-related genes (PRGs) that revealed substantial genomic abnormalities in endometrial, ovarian, and breast malignancies (Yumiceba et al., 2020). In addition, PTEN, ESR1, and TP53 were identified as cancer-causing genes in the case of endometrial cancer, whereas TP53 and PTEN were identified as cancer genes in the case of ovarian cancer, and NCOR1, ERBB2, ESR1, PTEN, AKR1C3, and TP53 were identified as cancer-related genes in the case of breast cancer (Yumiceba et al., 2020). The number of mutations found in endometrial cancer was greatest in the tumor suppressor gene PTEN, which was among the genes that were discovered. As a result, it is reasonable to assume that PCOS patients who have mutations in cancer driver genes might move towards developing cancer. These cancer driver genes are included in PRGs. Moreover, endometrial cancer is mainly divided into two distinct categories on the basis of clinical behavior and morphological features. Type I endometrial cancer is estrogen-related and has a favorable prognosis (Setiawan et al., 2013). Studies have shown that individuals with PCOS and endometrial cancer have elevated endometrial expression of insulin signaling-related genes. This was detected in the endometrium. Mutations in PTEN, CTNNB1, KRAS, and PIK3CA are a few examples of the typical genetic changes that are related to Type I endometrial cancer (Samarnthai et al., 2010).

However, there is a significant linkage between PCOS and ovarian cancer, and the underlying biological mechanism of this connection is still mainly a mystery (Zou et al., 2022). On the basis of its clinical behavior and the molecular genetics anomalies that it exhibits, ovarian cancer may be split into two distinct types (Toss et al., 2015). Examples of Type I tumors include lower-grade endometriosis, marginal serous tumors, lower-grade serous cancer, mucinous cancer, and transparent cell cancer. Moreover, type III ovarian cancer includes identical tumors, high-grade carcinomas, and carcinosarcomas. Cancers of the type II subtype are characterized by high levels of genetic instability. There is a connection between PCOS and the TP53 gene, which is shown to be predominantly mutated in higher-grade carcinoma (Yumiceba et al., 2020). For example, ovarian cancer in mice was not caused by a TP53 mutation by itself; however, it was found to be synergistically related to PTEN (Phosphatase and tensin homolog) loss (Perets et al., 2013). Both PCOS and breast cancer have been identified to have a correlation with an increased androgen level (Samarnthai et al., 2010). For example, PCOS individuals who have downregulated HSD17B4 and elevated PDGFRA can have an increased chance of progressing breast cancer (Samarnthai et al., 2010).

5. Common Treatments for Polycystic Ovarian Syndrome Patients

The available treatment options encompass a spectrum, ranging from modifications in one's lifestyle to the implementation of pharmacological interventions. This part of the review describes the common treatment for PCOS.

5.1. Lifestyle and foods

A sedentary lifestyle may potentially contribute to the development of PCOS and obesity. In order to maintain a high standard of living, it is imperative to engage in regular physical activity, effectively manage body weight, and incorporate the practise of yoga into one's lifestyle. PCOS can be effectively managed through the implementation of a calorie-restricted dietary regimen, the avoidance of nutritionally deficient foods, and the diligent practice of weight management techniques (Hajivandi et al., 2020). These supplements may serve as complementary therapy to alleviate the adverse effects of the medication.

The correlation between obesity and PCOS, as well as reproductive span, has been established. The decrease in fertility is observed in individuals with a high body mass index (BMI) (Dag & Dilbaz, 2015). The diminished likelihood of ovulation in PCOS results in an increased susceptibility to experiencing a miscarriage. A reduction in body weight helps prevent the occurrence of menstrual irregularities, type 2 diabetes, and cardiovascular disorders (Dag & Dilbaz, 2015). The avoidance of junk food, along with the consumption of a diet rich in high-fiber foods, fresh vegetables, fruits, and almonds, among others, can be beneficial in alleviating symptoms linked with PCOS such as seborrhoea, bloating, acne, and mood swings (Hajivandi et al., 2020). The regular practice of yoga and meditation has been observed to have a positive impact on orgasm, sexual satisfaction, libido, and fertility, as well as the maintenance of psychological wellbeing and body images (Conte et al., 2015).

5.2. Herbal remedy

Herbs have been regarded as companions for humanity throughout the ages. Numerous customary practices within households advocate the consumption of diverse herbal remedies for the amelioration of commonplace ailments. *Ocimum kilimandscharicum, Mentha piperita, Moringa oleifera, Curcuma longa, Hibiscus rosa-sinensis,* and other similar botanicals have demonstrated a favorable influence in alleviating PCOS and its related conditions (Rashid et al., 2022; Shahrin et al., 2022).

It has been observed that camphor basil (*Ocimum kilimandscharicum*) exhibits improved efficacy in treating reproductive defects in rats with PCOS. This treatment approach has shown potential for addressing the vascular, biochemical, and hormonal complications associated with PCOS (Khaled et al., 2019). The presence of curcumin in *Curcuma longa* has demonstrated its potential as a promising therapeutic agent for reducing hormonal imbalances, hyperandrogenism, and insulin resistance induced by obesity in individuals with PCOS (Chien et al., 2021; Shahrin et al., 2022).

However, the *Mentha piperita* plant contains a flavonoid known as Quercetin, which possesses numerous therapeutic potentials. These include its ability to combat cancer, act as an antioxidant, reduce inflammation, aid in weight management, and promote cardiovascular well-being. The rat model suffering from PCOS induced by Letrozole exhibited a reduction in ovarian diameter, the quantity of cysts, and bodyweight, along with improved corpora lutea, when quercetin was present (Jahan et al., 2018). The testosterone level was found to be reduced by Quercetin, exhibiting a comparable effect to the extensively employed medication, metformin. Recently, It has been demonstrated that quercetin has the ability to mitigate insulin resistance by triggering the phosphatidylinositol 3-kinase (PI3-K) pathway (Habiburrahman et al., 2023). Additionally, it has been observed to decrease testosterone levels, regulate LH secretion, and exert anti-inflammatory effects on the uterus.

5.3. Acupuncture

Acupuncture, a traditional form of sensory stimulation through needle intervention, has once again emerged as a significant approach in the field of reproduction (Wu et al., 2020). This particular technique possesses potential capabilities for addressing the hormonal imbalance that arises from PCOS. Acupuncture has proven to be an effective method for enhancing blood circulation to the reproductive parts of the body, thereby promoting optimal ovum quality, regulating the menstrual cycle, and facilitating ovulation.

According to numerous reports, it has been observed that the acupuncture technique has proven to be an effective treatment for women experiencing menstrual irregularities and imbalances in LH levels. Remarkably, this treatment has shown no detrimental impact on the rate of ovulation or the likelihood of a successful live birth (Wu et al., 2020). The combination of acupuncture and metformin has demonstrated efficacy in enhancing the ovulation rate and improving the homeostatic model assessment of insulin resistance in women afflicted with PCOS as compared to the use of metformin alone (Chen et al., 2022).

5.4. Oral contraceptives

Women with PCOS typically use combination oral contraceptives as a first-line therapy for monthly abnormalities if they are not trying to conceive (Rocca et al., 2015). The possibility of developing ovarian and endometrial malignancies is reduced in women who use combined oral contraceptives (Harris & Terry, 2016; Pollak, 2012). Moreover, users of combined oral contraceptives encountered a much lower risk of developing endometrial and ovarian cancer, and this protection lasts for decades after the last dose is taken (Iversen et al., 2018). Limiting endometrial cell proliferation as a factor and decreasing the number of ovarian cancer-causing ovulation events during a lifetime are the mechanisms responsible for this protective effect (Harris & Terry, 2016).

A study presents crucial new evidence indicating that the use of progestagen-only contraceptives, either presently or in the recent past, is linked to a minor elevation in the risk of developing breast cancer (Fitzpatrick et al., 2023). This risk does not seem to differ based on the method of administration and is comparable in magnitude to the risk related to combine hormonal contraceptives. Considering that the inherent risk of breast cancer escalates as one progress in age, the absolute surplus risk linked to the utilization of either form of oral contraceptive is projected to be comparatively lower in women who commence usage at a younger age as opposed to those who initiate at an older age. However, the potential risks associated with contraceptive use during the childbearing years must be carefully weighed against the corresponding benefits (Fitzpatrick et al., 2023).

Recent investigations also showed that the administration of combined oral contraceptive pills (COCP) has demonstrated an enhancement in the regularity of menstrual cycles when compared to the absence of medical intervention (Forslund et al., 2023). The observed results indicate a 100% improvement in cycle regularity with COCP treatment, while no medical treatment yielded a 0% improvement. However, it is important to note that the certainty of the evidence supporting these findings is relatively low. The COCP treatment might not demonstrate any significant variations in BMI or the development of hirsutism when compared to the placebo or lifestyle interventions (Forslund et al., 2023). It resulted in a lower weight compared to receiving no treatment, with a mean difference of -8.0 kg (95% confidence interval [CI]: -11.67; -4.33). Additionally, there was a slight enhancement in the quality of life, with a mean difference of 1.2 (95% CI 0.96; 1.44). It has been necessary to note that the certainty of the evidence supporting these findings was very low (Forslund et al., 2023).

5.5. Metformin

Metformin is a medication that can reduce insulin resistance, treat type 2 diabetes and, in particular circumstances, assist in regulating the menstrual cycle or stimulating ovulation in women who have PCOS. Metformin's potential cancer-preventive effects have been highlighted by several studies, and its anti-cancer actions have been demonstrated in experimental settings (Pollak, 2012). Moreover, Metformin's effects on cancer have been extensively examined, particularly breast cancer. For example, in 2014, researchers combined data from 13 studies and found that taking metformin increased the chance of developing breast cancer by a factor of 0.9 (95% confidence interval [CI]: 0.8–1.0) (Gandini et al., 2014). However, another study suggested that metformin users were shown to have no higher prognosis of breast cancer compared to sulfonyl urea and insulin users (Kowall et al., 2015). In general, epidemiological evidence comparing metformin and endometrial cancer has shown no link.

As opposed to breast and endometrial cancer, the association between ovarian cancer and metformin has received less attention. Metformin, on the other hand, has been shown to affect ovarian cancer cell proliferation both in vitro and in vivo, and interestingly, its usage is correlated with patient survival (Rattan et al., 2011). For instance, one observational study (among UK-based GPRD women) has demonstrated an opposite link between metformin and ovarian cancer risk, finding a lower progression of ovarian cancer with increased metformin usage (OR = 0.6, 95%; CI = 0.3 –1.3) (Bodmer et al., 2011).

5.6. Ovulation-induction therapies

Results from previous research examining the links between reproductive medications and hormone-related malignancies have been contradictory. Clomiphene, often known as Clomid, is a particular estrogen receptor modulator that helps the two ovaries produces more eggs. This property makes it an effective infertility treatment for PCOS. Clomiphene has a pro-apoptotic impact on breast carcinoma cell lines due to the fact that women who use clomiphene for infertility-related reasons have a lower chance of developing breast cancer (Elloumi-Mseddi et al., 2015). For example, in the majority of studies, Clomiphene users have not been shown to have a significantly increased risk of ovarian cancer.

The link between clomiphene and endometrial cancer is less well-known than its relationship with other hormone-related malignancies. Due to the chemical similarity between clomiphene and tamoxifen, a drug-related drug with a higher risk of endometrial cancer, it has been hypothesized that these are causally related (Harris & Terry, 2016). Less research has been conducted on clomiphene's association with cancers other than endometrial, ovarian, and breast cancer (Brinton et al., 2012).

An aromatase inhibitor called letrozole has recently gained attention as a potential supplementary therapy for women with anovulation problems (Burstein et al., 2019; Harris & Terry, 2016). Moreover, Letrozole is an augmentation treatment for postmenopausal women with hormone-receptor breast cancer, so it is reasonable to assume that it lowers the incidence of cancers connected to hormones. On the other hand, there is a lack of longitudinal data at this time, which prevents an effective

investigation of the connection between the uses of letrozole to treat ovulatory infertility and the progression of hormone-related cancer (Burstein et al., 2019).

6. Future Perspectives

Polycystic Ovary Syndrome (PCOS) remains a challenging condition, not only due to its uncertain underlying causes but also because of ongoing debates surrounding its diagnosis, treatment, and potential long-term effects. Our understanding of PCOS encompasses a wide range of factors, including but not limited to menstrual disorders, excessive androgen levels, and difficulties with fertility. The consideration of potential connections between PCOS and gynecological cancer risk is imperative, notwithstanding the contentious nature of these associations and the limited scope of relevant investigations. The correlation between PCOS and gynecological cancer remains a subject of debate within the medical community due to the scarcity of comprehensive research on this matter.

Indeed, as of the present moment, there exists a limited or nonexistent body of research establishing a connection between PCOS and the occurrence of cancer in the fallopian tubes, cervix, or vulva. According to current medical understanding, there is no evidence to suggest any connections between PCOS and breast cancer. The prevailing body of research and meta-analytical investigations suggest that PCOS may potentially elevate the likelihood of developing endometrial cancer. However, there are conflicting findings regarding the potential risk of developing ovarian cancer. Furthermore, it is imperative to take into account a genuine assessment of the impact of PCOS on the association with gynecological cancer. This assessment should also encompass the potential ramifications of the treatment modalities employed in these individuals, such as oral contraceptives, metformin, and ovulation induction medications. Generally, it would be advisable to conduct additional well-developed clinical studies in order to gain a more comprehensive understanding of the potential correlation between PCOS and the development of gynecological cancer.

7. Conclusions

Polycystic Ovary Syndrome (PCOS) has a diverse and intricate pathogenesis. PCOS affects a large percentage of women of childbearing age, yet it is difficult to diagnose since its etiology is unclear. Adolescent girls now make up a sizable portion of the PCOS population, joining reproductive-age women. Women with PCOS may experience reproductive and metabolic issues related to hyperandrogenism and insulin resistance. Ovarian and endometrial cancers are uncommon, which complicates efforts to learn more about them. This review suggested the risk of gynecological cancer, especially endometrial and ovarian cancer is more prevalent than breast cancer-related PCOS patients. However, more research is potentially needed to explore the process of progressing cancer in PCOS patients with respect to their medicinal therapy. The investigation of the underlying factors that lead to cancer-related disease in PCOS patients might require more attention. Therefore, the life-threatening cancer risk can be evaluated with more precision to combat cancer morbidity.

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ORCID

Alfi Shahrin: https://orcid.org/0000-0003-2116-8171
Mahmuda Akter Mele: https://orcid.org/0000-0002-7886-1228
Mohammad Zahirul Islam: https://orcid.org/0000-0001-7688-463X

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