CHAPTER 01

Polycystic Ovarian Syndrome (PCOS), Underlying Factors and Potential Treatments

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SUMMARY

Polycystic ovary syndrome (PCOS) is one of the most prevalent reproductive disorders in females during their reproductive age. Every one woman out of six is diagnosed with PCOS at her reproductive stage in USA. This chapter will assess the underlying reasons as well as potential treatment options against PCOS. There are several factors underlying the development as well as the progression of PCOS. These factors include hyperandrogenism, advanced glycation end products (AGEs), insulin resistance, obesity, and oxidative stress. Oxidative stress is considered one of the fundamental factors which directly damage the DNA. Furthermore, the imbalance in the levels of androgens in ovaries impairs follicular development. Recent advances in medical science have explored various therapeutic treatments to avert the onset of PCOS. The potential treatments include bariatric surgery, lifestyle modifications as well as use of metformin and aromatase inhibitors. Metformin regulates the production of insulin via downregulating its resistance. Lifestyle modification includes daily exercise, which reduces the body mass index (BMI) and ultimately regulate the process of ovulation. Aromatase inhibitors reduce the production of excessive estrogen levels, which mediate positive feedback to the pituitary glands. In response to this feedback, pituitary glands release FSH, ultimately regulating the process of ovulation. In conclusion, there are numerous factors behind the progression of PCOS however, potential treatment options can mitigate its potential adverse effects.

INTRODUCTION

Polycystic ovary Syndrome (PCOS) is one of the most common gynecological disorders among the female, which is characterized by hyperandrogenaemia, disrupted ovarian morphology, hirsutism, as well as ovulatory dysfunction (Stepto et al., 2013). This disorder affects approximately one female out of six during her reproductive age worldwide. The prevalence of this disease costs about 4 billion US dollars in the USA only (Azziz et al., 2005). There are different environmental factors such as those that contribute to being overweight in this multifaceted polygenic disorder. Numerous studies indicate that PCOS may be caused by innate anomalies in ovarian steroidogenesis and follicular formation. In addition to excessive ovarian androgen production and ovulatory dysfunction, this syndrome is linked to persistently rapid pulses of gonadotropin releasing hormone, an excess of luteinizing hormone, and insufficient secretion of follicle-stimulating hormone (FSH). Moreover, compensatory hyperinsulinemia boosts ovarian and adrenal) androgen production and increases androgen bioavailability by lowering levels of sex hormone-binding globulin. This is because many women with PCOS also have insulin resistance (Dumesic et al., 2015).

A plethora of literature demonstrated that PCOS is associated with cardiovascular disorders (Wild et al., 2010). Furthermore, it is observed that approximately 50-80% of women suffering from PCOS are obese (Dumesic et al., 2015). About 30-35% of women in the USA diagnosed with PCOS are reported to have impaired glucose tolerance. However, these conditions worsen due to different factors such as adiposity, the age of the patient as well as family history of diabetes (Ehrmann & Liljenquist, 1999). Another investigation documented that PCOS lowered the levels of high-density lipoproteins cholesterol and higher levels of triglyceride (Wild et al., 2011). Although the exact cause of PCOS is unknown, intrinsic anomalies in androgen production and secretion provide a probable explanation for this medical condition. Although irregularities in the synthesis of androgen by the adrenal glands have also been associated with the etiology, constitutive hypersecretion of androgen by ovarian theca cells has clearly been demonstrated (Tee et al., 2008). Thus, it makes sense to ask, "Is it a major contributing factor to PCOS that certain primary enzyme abnormalities in the steroidogenic pathway exist?" The data suggests that the answer to this question is most likely "no"w. Possible possibilities for the genesis of hyperandrogenemia include CYP17 (which codes for P450c17 and the related P450 reductase) and CYP11a

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(P450scc), which is linked to a widespread upsurge in steroidogenic enzyme activity in polycystic ovarian PCOS theca cells (Draper et al., 2006). Furthermore, the extra-glandular synthesis of different androgens in adipose tissues has been reported to be involved in the onset of PCOS. These androgens alter the normal activity of 5β-reductase, 11β-hydroxysteroid dehydrogenase and 5α-reductase (Stewart et al., 1990). Changes in these peripheral cortisol metabolism-related enzyme systems may trigger the neuroendocrine urge to enhance adrenal steroidogenesis, which in response may help to explain why some subgroups of PCOS-affected women produce more androgens (Gambineri et al., 2009).

UNDERLYING FACTORS OF PCOS

There are various environmental as well as genetic reasons underlying the onset of PCOS. The following are the most significant reasons behind the progression of PCOS in females.

Hyperandrogenism

Ovaries are considered as the pathophysiologic as well as fundamental core of PCOS. It is found that excessive generation of androgens in the ovaries is one of the major reasons behind the development as well as the progression of PCOS (Jonard & Dewailly, 2004). These androgens exert neuro-endocrine as well as paracrine effects on the hypothalamic-pituitary axis, leading to the onset of anovulation (Blank et al., 2009; Eagleson et al., 2000). Furthermore, these androgens trigger the development of small antra follicles during the primary and primordial stages of development (Vendola et al., 1998). The excessive production of these small follicles ultimately escalates the levels of anti-mullerian hormone (Pellatt et al., 2007; 2010). The increased production of anti-mullerian hormones averted the action of FSH, leading to the development of anovulation (Pigny et al., 2003). Moreover, these androgens augment the metabolic features during PCOS, ultimately increasing insulin resistance in these patients (Christakou et al., 2008) as illustrated in Fig. 1.

Insulin resistance

Dunaif et al. (1995) observed abnormally elevated serine phosphorylation and low tyrosine phosphorylation of the insulin receptor and its substrate IRS-1 in cultured cells derived from a sample of fourteen insulin-resistant women with PCOS, indicating impaired metabolic insulin signaling. However, 50% of the individuals that were investigated did not exhibit this particular aberration, despite the fact that they were also insulin resistant, indicating variability in the processes behind this occurrence. A similar investigation revealed that in cultured cells from PCOS women, mitogenic signaling of insulin was stimulated in contrast to metabolic signaling (Corbould et al., 2006). These results showed that greater insulin action—driven by insulin resistance-induced hyperinsulinemia—on non-metabolic pathways, notably androgen synthesis in the ovary, may be attributed to either this route or other mechanisms that are not inadequate and remain responsive to insulin (Diamanti-Kandarakis & Dunaif, 2012).

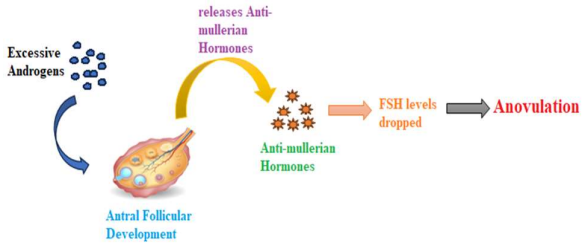

Fig 1. Hyperandrogenism induced Anovulation in PCOS female

It is revealed that insulin promotes the development as well as the progression of PCOS via triggering two primary pathways including PI-3K/Akt as well as MAPK which eventually enhances cell proliferation, growth, and differentiation (Munir et al., 2004; Zhang et al., 2016; Thattai et al., 2018). Human follicular cells contain high affinity as well as highly specific receptors which mediate the thecal cells to increase physiological effects. Insulin escalates the secretion of androstenedione from thecal cells (Cadagan et al., 2016). Furthermore, insulin directly upregulates the levels of human chorionic gonadotrophin which subsequently increases the levels of p450scc and CYP17 resulting in hyperandrogenism (Li et al., 2012). An investigation conducted by Feng et al. (2018) revealed that resistance to insulin reduced sex hormone binding protein expression in villous trophoblasts in humans which subsequently prevent the expression of mRNA of IRS-2, GLUT-4, IRS-1 as well as PI3Kp85α. It shows that sex hormone binding protein might be involved in PI3K/Akt stimulated insulin resistance. Moreover, escalated levels of insulin reduced this hormone which led to the onset of hyperandrogenism (Malini & George, 2018).

Obesity

Epidemiological data suggested that obesity is directly associated with PCOS and accounts for 38-88%. A meta-analysis has demonstrated that obese women had odds ratio of 2.77 for the onset of PCOS in contrast to non-obese females (Lim et al., 2012). During obesity, adipose tissues accumulate excessively which increases the levels of adipokines that regulate insulin resistance. Therefore, obesity is known as a chronic metabolic disorder which is associated with various impairments such as type 2 diabetes, insulin resistance, cardiovascular complications, atherosclerosis, anovulation, reproductive dysfunctions, PCOS as well as cancer (American Diabetes Association, 2021; Legro, 2012).

Metabolic syndrome is the term commonly used to describe the grouping of aforementioned risk factors. Many of the irregularities associated with metabolic syndrome are also found in PCOS, and it is possible that hyperinsulinemia and glucose intolerance are common etiology behind the development of metabolic syndrome and PCOS (American Heart Association, 2005). Numerous studies have established a connection between PCOS and metabolic syndrome (Ehrmann et al., 2006) on the basis of fact that metabolic syndrome is more common in women with PCOS (between 33 and 46%). Therefore, it was assumed that reducing the weight

would be beneficial to avert the effects of metabolic disorders on fertility in females. A study was conducted on 67 obese anovulatory infertile females for 6-month training to reduce weight. Interestingly, ovulatory function was restored in 90% of females who reduced their weight to 10 kg (Clark et al., 1998). In conclusion, obesity provides ground for the development of different metabolic disorders which results in the development as well as progression of PCOS.

Oxidative stress

Oxidative stress is considered as one of the major reasons behind the pathophysiology of PCOS. Oxidative stress occurs when reactive oxygen species (ROS) are excessively generated as compared to antioxidant enzymes in the body. However, the generation of ROS may be attributed due to several factors such as hyperglycemia or any environmental toxicants (González et al., 2006). Elevated levels of oxidative stress subsequently upregulated the generation of pro-inflammatory markers which lead to insulin resistance as well as various cardiovascular disorders (Victor et al., 2009). Free radicals directly attack pivotal macromolecules such as DNA, lipids and proteins which ultimately induce tissue damage (Murri et al., 2011).

Numerous studies have revealed that females suffering from PCOS have elevated levels of oxidative stress markers in the follicular fluid of oocytes (Liu et al., 2021). Excessive generation of oxidative stress in follicular fluid impairs the normal growth as well as the maturation of the ovary leading to development of infertility. Furthermore, ROS damages the DNA which may induce carcinogenesis or genetic impairments in ovaries (Ziech et al., 2011). It is evident ROS prompts cross-linking, strand breakage as well as point mutation in DNA thereby instigating endometrial cancer in PCOS patients. Moreover, oxidative stress accelerates the process of DNA methylation which inhibits the normal functions of tumor suppressor genes (Donkena et al., 2010). Therefore, elevated levels of oxidative stress might increase the onset of endometrial cancers in PCOS females. Additionally, excessive generation of ROS enhances hyperandrogenemia, obesity and insulin resistance which are linked with PCOS (March et al., 2010). It is reported that levels of oxidants in PCOS patients with a remarkable decrease in the activities of antioxidant enzymes were also observed (Couillard et al., 2005). To sum up, oxidative stress is the underlying behind the occurrence as well as progression of PCOS and its associated complications in females as depicted in Fig. 2.

Advanced glycation end products (AGEs) and PCOS

AGEs are one of the primary environmental factors behind various reproductive and metabolic impairments observed in the presence of PCOS (Diamanti-Kandarakis et al., 2012). AGEs, also referred to as the Maillard or browning reaction, are the endogenous consolidation of reactive molecular species generated through non-enzymatic reactions. This process occurs when free amino groups from proteins, lipids, or nucleic acids combine with the carbonyl group from carbohydrates (Piperi et al., 2012). Furthermore, AGEs are also consumed through fast food and their levels are observed to be high in PCOS patients (Garg & Merhi, 2015). It is documented that AGEs circulate in bloodstream and eventually deposited in various body tissues and adversely affect the normal physiology of deposited site. Moreover, the expressions of AGEs receptors also known as receptors for advanced glycation end products (RAGE) were upregulated in PCOS patients which indicates the presence of AGEs (Diamanti-Kandarakis et al., 2007).

Various researchers demonstrated that levels of AGEs and expressions of RAGE were escalated in ovaries which led to impairing the process of steroidogenesis as well as folliculogenesis in PCOS patients (Diamanti-Kandarakis et al., 2005). Any disruption in the process of steroidogenesis results in abnormal follicular growth and production of unnecessary androgens (Vlassara et al., 2002). Furthermore, AGEs stimulate the production of inflammatory cytokines as well as induce oxidative stress in ovarian tissues (Cai et al., 2002). The deposition of AGEs in ovarian tissues dysregulates the normal maturation of oocyte (Tatone et al., 2014). It is observed that accumulation of AGEs in ovarian tissues upregulate the expression of RAGE in granulosa cells of ovaries (Diamanti-Kandarakis et al., 2007). The aforementioned evidence reaffirms that AGEs play a significant role in disrupting the growth and maturation of oocytes via dysregulating ovarian function.

POTENTIAL TREATMENTS

Following are the therapeutic approaches to avert the development as well as progression of PCOS.

Bariatric surgery

Since few years, bariatric surgery has been considered as one of the successful treatments against PCOS (Malik, 2012). Bariatric surgery is divided into different categories such as gastric banding, Roux-en-Y gastric bypass and vertical sleeve gastrectomy (Wolfe et al., 2016). The use of bariatric surgery has been increasing since many years worldwide (Lazzati, 2023). Various investigations reported that 73.7% bariatric surgeries were carried out from 2014-2018 and majority of them were performed at reproductive age (Welbourn et al., 2019). However, National Institute for Health and Care Excellence guidelines warned the medical surgeons about the implications of this surgery when the BMI of a patient exceeds 35-40 kg/m^2 along with diabetes type 2 or obesity (NICE, 2016). Surprisingly, a data collected from 17 women with

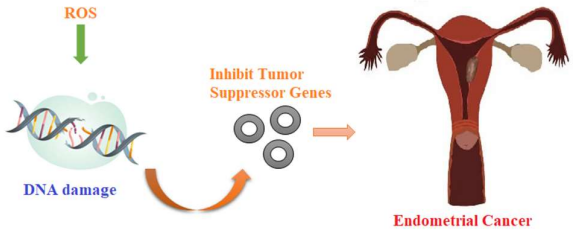

Fig 2. Oxidative stress led toward the onset of endometrial cancer

PCOS with mean BMI of 50.7 kg/ m^2 revealed that bariatric surgery resulted in significant recovery in insulin, resistance, BMI, hyperandrogenism as well as ovulation and hirsutism (Escobar-Morreale et al., 2005).

Lifestyle modifications

As discussed above obesity, insulin resistance and hyperinsulinemia are the basis of PCOS thereby weight reduction with different lifestyle modifications can mitigate the progression of PCOS during anovulatory infertility (Moran et al., 2006). It is documented that physical exercise can reduce body weight which ultimately downregulates insulin resistance as well as hyperinsulinemia in PCOS patients (Thyfault & Wright, 2016; Araújo-Vilar et al., 1997). Furthermore, regular exercise regulates the hormone levels in ovaries (Panidis et al., 2008). Various investigations executed on 533 PCOS patients elucidated that weight reduction regulates the normal ovulations in these patients (Jarrett & Lujan, 2017). Interestingly, Harrison et al. (2011) demonstrated that even moderate exercise without affecting overall body weight can improve the ovulatory cycle in PCOS patients. Moreover, different weight reducing medications exhibited additive effects which ultimately stimulate the onset of conception and ovulation (Kumar & Arora, 2014). Weight loss after bariatric surgery exerts beneficial effects during anovulatory infertility (Skubleny et al., 2016).

Metformin

Metformin is a synthetic anti-hyperglycemic drug that is used to regulate type 2 diabetes mellitus. Metformin demonstrated marvelous results in improving menstruation, reducing androgen levels as well as enhancing ovulation (Sam & Dunaif, 2003). Metformin is reported to reduce body weight which ultimately enhances metabolic functions while metformin. After a few hours of its intake, metformin ceases the production of hepatic glucose although it reduces the levels of intestinal glucose uptake as well as escalates the insulin sensitivity (Grundy, 2002). Furthermore, metformin increases the process of ovulation in PCOS women through different pathways such as by reducing androgen formation, proliferation of thecal cells, insulin levels as well as growth of endometrial layers. Metformin potentially inhibits the process of gluconeogenesis in ovaries which subsequently decreases the synthesis of androgens (Harborne et al., 2005).

Different dose regimens have been approved to increase patient tolerance toward the drug. Metformin initially started from 500mg per day after meals. After 7 days the dose can be increased to 1000 mg and similarly 1500 mg on 3rd week of consecutive treatment. The clinical physician recommends the target dose of 1500-2500mg per day or 500-850mg thrice a day. It is revealed that if some patients don't respond to 1500mg per day then the dose should be increased to 2000 mg per day for better results. General side effects include diarrhea, nausea and vomiting as well as dizziness. The oral intake of metformin is regarded as teratogenic thereby strictly prohibited during the pregnancy period (Glueck et al., 2002).

Aromatase inhibitors

Various sorts of aromatase inhibitors such as letrozole and anastrozole are widely used to induce ovulation (Table 1). These drugs are highly potent and reversible in their action. Unlike other drugs, letrozole has a life of 45 hours while anastrozole has 5-7 days. However, letrozole has gained more attention as compared to anastrozole (Badawy et al, 2009). Letrozole is used in various reproductive impairments such as for the treatment of gonadotropins related complexities. Aromatase inhibitors were taken into consideration to induce ovulation because of their ability to selectively block androgen-to-estrogen passage, which lowers the concentration of estrogens and causes the pituitary to produce positive feedback that increases FSH and optimizes ovulation. Letrozole has the benefit of not having any peripheral antiestrogenic effects on the endometrium while promoting the growth of monofollicles (Carroll & Palmer, 2001). Due to potential teratogenicity, Novartis Pharmaceuticals (Basel, Switzerland) has advised against using letrozole for ovulation induction; however, a comparison with clomiphene did not show an increase in the incidence of major or minor malformations (Badawy et al., 2009).

Table 1. Causes and potential treatment options to avert PCOS

Causes	Treatment Option	References
Hyperandrogenism	Aromatase Inhibitors	Badawy et al., 2009
Insulin resistance	Metformin	Grundy, 2002
Obesity	Lifestyle modifications	Jarrett & Lujan, 2017
Oxidative stress	Increase uptake of flavonoids	Shi et al., 2019
Advanced glycation end products	Aromatase inhibitors	Carroll & Palmer, 2001

CONCLUSION

PCOS is a gynecological problem affecting females at reproductive age which is increasing day by day. Different factors such as insulin resistance, imbalance in levels of androgens, oxidative stress, AGEs and obesity are the major factors behind the progression of PCOS. However, potential therapeutic approaches such as use of metformin, aromatase inhibitors, bariatric surgery and lifestyle modifications can reduce the risk of getting this disorder. Nevertheless, further research is indispensable to find out the clinical basis as well as treatment for PCOS.

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