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Review Article

Hormonal and Genetic Controls of Hirsutism: Link Between hyperprolactinemia, Polycystic ovary syndrome and Hirsutism

Zainab Zamil Gataa Allami [1, *], Maytham A. Dragh[1], Salah H. Faraj[1], Rana S. Jawad [2]

[1] Department of Biology, College of Science, University of Misan, Maysan, Iraq.

[2] Department of Biology, College of Science, Mustansiriyah University, Baghdad, Iraq.

*Corresponding author

Email: zainabzamil@uomisan.edu.iq

DOI: 10.21608/jmals.2024.372239

Abstract:

The definition of hirsutism is when a woman has dark, thick hair that resembles men on her neck, face, chest, and in between thighs. The pathophysiology of hirsutism has been linked to some causes, such as genetic and hormone factors. It has been demonstrated that several such variables contribute to the development of hirsutism. The development of effective hyperprolactinemia for hirsutism diseases has relied on an understanding of the physiological roles and mechanistic functionalities of prolactin and hyperprolactinemia in hirsutism disease. Prolactin was reported to be effective through its action on DHEA and DHEA sulfate levels. The prolactin hormones have been effect described on the hepatic synthesis of SHBG, simulating the actions of LH, and increasing both ovarian testosterone and adrenal DHEA-S production. The presented review aims to offer the most recent research on the possible roles of hormones and genes, their impacts on hirsutism, and the function of Reactive oxygen species (ROS) in the pathophysiology of polycystic ovary syndrome (PCOS).

This review examines hormonal and genetic in human hair growth disorder. A focus is made on disorders of well-established genetic and hormonal origin. Such as hirsutism. Reviewed confirms that a complex interaction between hormones, genes, and ROS may underlie the differential of PCOS and hirsutism between patients and the healthy.

Keywords: hyperprolactinemia, Polycystic ovary syndrome, ROS, Hirsutism

INTRODUCTION:

An excessive amount of hair development in females that resembles that of males is referred to as hirsutism [1]. A medical disorder that affects women's physical appearance is called hirsutism, the condition is characterized by excessive hair development in parts of the body where women typically have little hair, such as the chest, face, and belly [2], as illustrated in the fig. (1-1) [3, 4, 5].

Hirsute women encounter psychosocial problems despite using various coping mechanisms, which could be the cause of poor mental health [2]. The most prevalent endocrine condition affecting women is hirsutism, which affects between 5 and 15% of all women and puts a great deal of stress on them [6]. For women in various cultures, having too much hair is a serious problem since even a small amount of hair is considered unattractive. The ladies feel "unfeminine" and "unusual" as a result. It has generally been demonstrated that females find the growth of dark hairs on their upper lip and chin to be more upsetting, which is why they seek medical

Received: April 14, 2024. Accepted: July 3, 2024. Published: July 15, 2024

attention [7]. Strong familial and genetic prevalence of endocrine abnormalities leading to hirsutism could explain the variation across various populations (Ahmeda et al., 2013) [8]. An enhanced sensitivity of hair follicles to androgens or an overabundance of androgens can lead to hirsutism [9]. As illustrated in Figure (1-2), hirsutism might be majorly categorized into non-androgenic and androgenic types [10].

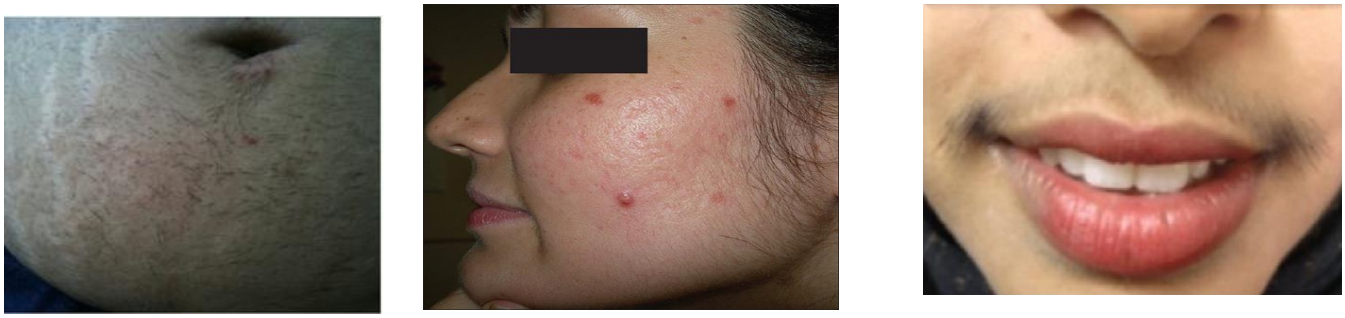

Figure (1-1) Hirsutism on the abdomen and some areas of the face (Mustache and beard) [3, 4, 5].

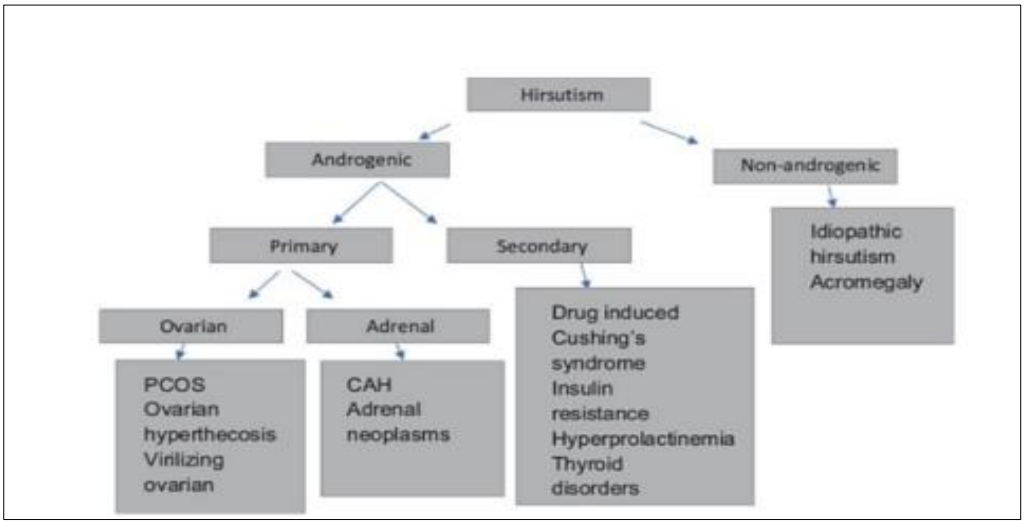

Figure (1-2) Diagram illustrates the classified of hirsutism [10]

Individuals exhibiting an excess of hair on their body could be classified as having hirsutism or hypertrichosis, based on the gender of the afflicted individual and the distribution features. Any sex and age group can have hypertrichosis, and the extra hair can appear anywhere on the body. However, only females have hirsutism, and the extra hair is usually seen in androgen-dependent areas. Hypertrichosis can have a variety of causes, including genetic, endocrine, and physiological conditions; on the other hand, hirsutism is primarily puberty-related and androgen hormone-influenced, with causes ranging from benign to malignant ovarian, pituitary, or adrenal disorders [11]. Between 60 and 80 percent of hirsute females have elevated levels of androgen [12, 13].

Genetic Basis of Prolactin and hyperprolactinemia:

The prolactin gene encodes the large polypeptide hormone known as human prolactin [14]. The human genome has a single prolactin-encoding gene on the chromosome 6. Prolactin gene has a size of 10.215kb and it consists of 5 exons and 4 introns. Two distinct promoter regions control the prolactin gene's transcription. Extrapituitary expression is driven by a more upstream (distal) promoter region, whereas pituitary-specific expression is directed by a proximal 5,000bp region [15, 16]. A mature polypeptide has a molecular mass of about 23kDa and is made up of 199 amino acids which could change during post-translation. Numerous physiological processes in the body are facilitated by prolactin, most notably the ones related to the development of mammary glands, lactation, and female reproductive activities throughout pregnancy [14]. Prolactin affects several aspects of hair growth in a clinically significant way [17]. The anterior pituitary gland secretes and produces prolactin in a pulsatile way. It is essential to many reproductive processes, including lactation. Human prolactin release is dependent upon physiological conditions and is subject to variation in response to various stimuli. A common endocrinological condition, hyperprolactinemia can have pathological, physiological, or idiopathic causes. Pituitary hypersecretion is linked to elevated prolactin levels, which are also associated with prolactinomas and using psychotropic drugs [18]. One of the reasons for hirsutism is hyperprolactinemia [19]. In 1975, it was first reported that hyperprolactinemia and hirsutism were related [20]. Numerous hormones have a significant impact on both the structure and the hair cycle of a hair follicle. Also, the hair follicle cycle is split into three primary unique phases: catagen, anagen, and telogen [21], as shown in Figure (1-3) [21].

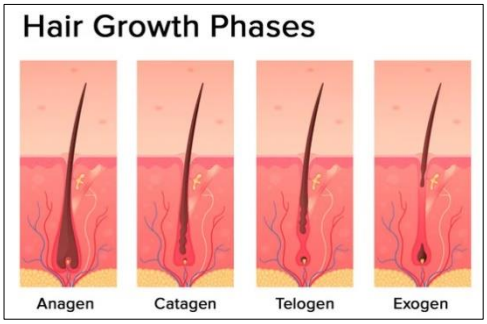

Figure (1-3) Stages of hair growth [21].

Hormones play a major role in hair follicle formation as well as the hair cycle because of their strong relationship to hair growth [22]. There is a connection between hirsutism and hyperprolactinemic conditions. The idea that certain patients with hyperprolactinemia have increased levels of DHEA and DHEA sulfate has been supported by numerous research. More recent research indicates that hyperprolactinemia could raise free testosterone concentrations via lowering SHBG levels, even though it is implausible that prolactin might directly stimulate adrenaline androgen production. As previously mentioned, obesity, idiopathic hirsutism, and hyperprolactinemia are the three disorders for which SHBG was linked to the pathophysiology. Although there is no question about SHBG's involvement in hirsutism pathogenesis, its relative importance has not yet been established [23].

Evidence points to hyperprolactinemia as a potential cause of abnormal androgen production [24]. Hyperprolactinemia occurs most commonly due to a pituitary adenoma or medications such as antipsychotics/ dopamine receptor blockers. The exact mechanism through which elevated prolactin causes hirsutism is not understood. However, it is believed that prolactin decreases hepatic synthesis of SHBG, simulates the actions of LH, and increases both ovarian testosterone and adrenal DHEA-S production. Galactorrhea and amenorrhea are common signs in those affected. In addition, some patients with a pituitary adenoma might experience visual field changes, depending on the size of the tumor. Treatment of adenomas is usually surgical resection. Offending medications are discontinued and, in some cases, dopamine agonists such as bromocriptine and cabergoline were utilized to offset high levels of prolactin [25].

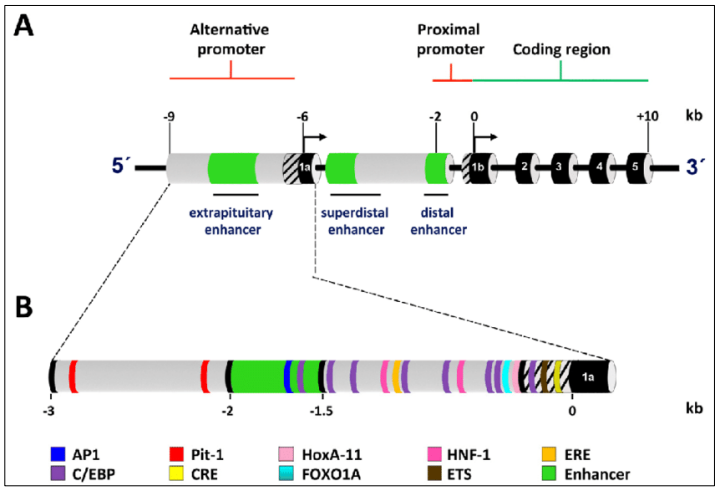

Figure (1-3) Schematic representation of the human PRL gene [26]

There are multiple ways in which hyperprolactinemia can lead to hirsutism. The concentration regarding plasma-free (unbound) testosterone is increased by prolactin, which also suppresses the hepatic synthesis related to sex hormone-binding globin [13, 27]. In hirsutism, the most reliable endocrinologic result is an increase in the levels of plasma-free testosterone [13, 28]. Additionally, prolactin promotes the synthesis of testosterone and works in concert with luteinizing hormone. Prohormone dehydroepiandrosterone sulphate is formed by the adrenal glands in response to hyperprolactinemia [13, 29]. In peripheral tissues like fat, this prohormone is converted to testosterone [13, 30].

Correlation between Hyperprolactinemia and Hirsutism:

Prolactin affects androgen synthesis in three ways:

1. Stimulates production of adrenal androgen DHEAS. In hyperprolactinemic women, either dexamethasone or bromocriptine reverses the androgen abnormalities, suggesting that a synergistic effect exists between prolactin and ACTH.

2. Depresses SHBG due to the direct effect on liver production of this globulin.

3. Hypoestrogenism, which is associated with hyper-prolactinemia, also reduces the SHBG levels. However, there is a protective effect against hirsutism by a decrease in the 5 alpha-reductase activity in hyper-prolactinemic females [31].

Polycystic ovary syndrome (PCOS):

One prevalent heterogeneous condition that is referred to as a syndrome is polycystic ovary syndrome (PCOS). A phenotypic, or group of clinical characteristics, is referred to as a "syndrome." Clinical indicators of androgen excess, high blood androgen concentrations, infertility, and irregular menses are among the distinctive characteristics of the PCOS phenotype [32]. The multifaceted, heterogeneous, complicated genetic, metabolic condition, and endocrine known as PCOS is defined by chronic anovulation, polycystic ovaries, and clinical and biochemical signs of hyperandrogenism. It has a severe detrimental effect on the body's metabolism and physiology because it can progress into a metabolic syndrome that can lead to dangerous long-term consequences like endometrial hyperplasia, T2DM, IR, CVD, abdominal obesity, hyperinsulinemia, dyslipidemia, and hypertension. Significant reproductive, biochemical, and metabolic dysfunction might result from the primary endocrine abnormalities, including the dysregulation of gonadotropin-releasing hormone (GnRH) pulse generator to feedback inhibition by the ovarian steroids, leading to luteinizing hormone (LH) hypersecretion, reduced follicle-stimulating hormone (FSH), and ovarian stromal–thecal hyperactivity, leading to ovarian hyperandrogenism. The pathophysiology of the syndrome has been linked to numerous candidate genes, including those involved in gonadotropin and gonadal hormone action, insulin action and secretion, steroid hormone biosynthesis and metabolism, and obesity and energy regulation [33]. A complex altered hormone profile is linked to PCOS; up to 25–30% of PCOS women have functional moderate hyperprolactinemia [34]. Research found that the insulin resistance phenomenon was the cause of the elevated levels of prolactin in PCOS patients [35]. According to a different theory, PCOS promotes relative hyperestrogenemia, which leads to hyperprolactinemia [36]. Some experimental investigations have demonstrated that the action of estrogen causes an increase in prolactin release [37]. Additionally, it was proposed that women with PCOS may have an acceleration of GnRH pulsatility. This phenomenon could be linked to the rise in LH and fall in dopaminergic tone, both of which lead to hyperprolactinemia [38].

Genetic Basis of PCOS:

Numerous genetic variables that either indirectly or directly impact the ovaries control PCOS evolution [39]. The way such condition manifests in females is mostly determined by a few genes, which both regulate and impede the action of different metabolic/hormonal processes. The development of PCOS is brought on by aberrant gene regulation at a genetic level, which results in a variety of post-translational changes in protein products. PCOS is linked to all of the genes/mutations that either indirectly or directly impact ovaries, as Figure (1-4) [40] illustrates. To identify the causing mutation or gene, numerous research across several families were carried out; nevertheless, up till now, no real penetrance regarding a single gene mutation was documented. Every mutation or gene linked to familial aggregation exhibits limited penetrance and is linked to disease-causing factors such as hormonal, covariant, or environmental factors.

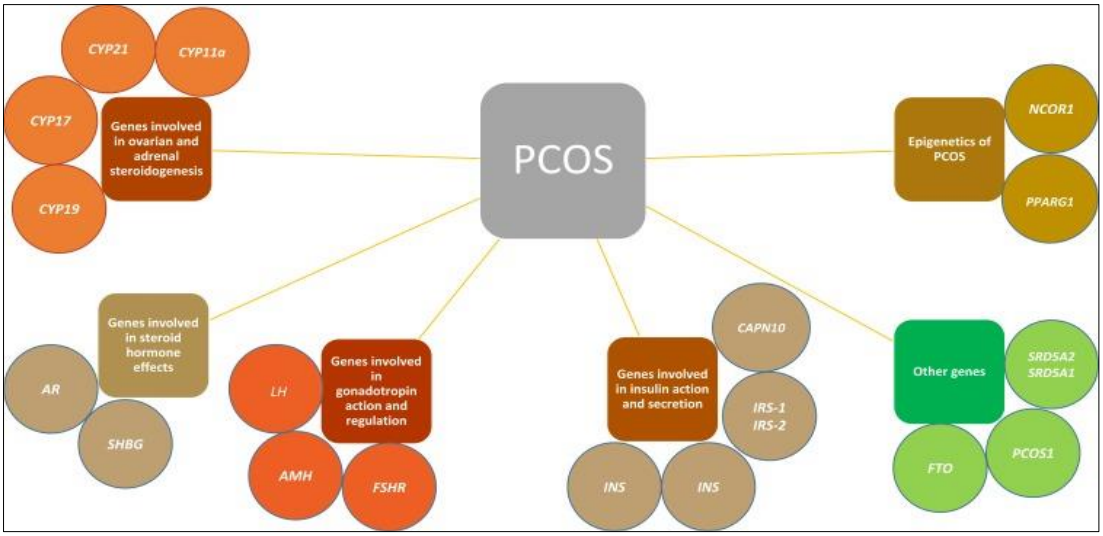

Figure (1-4) Summary of genes involved in PCOS highlights the complexity of the disease [40].

There were reports of tissue-specific epigenetic controls in female PCOS patients, including enhancer-binding activity, histone modifications, transcription factor binding patterns, DNA methylation, and promoter activity. According to Figure (1–5) [39], overexpression regarding DENND1A (DENN/MADD domain containing 1A) in PCOS female theca cells plays a major role in increased progestin and androgen synthesis [41]. In androgenized rats, hyperexpression of androgen receptors throughout fetal development results in certain CpG sites from the promoter region of GATA-6 (-520) and STAR (-822) genes having hypomethylated DNA. Those genes are crucial for steroidogenesis, which modifies the epigenetic environment and causes PCOS [42]. Numerous genes with different DNA methylation statuses in PCOS and normal females have been identified by GWAS research. For example, altered gene expression was found in PCOS patients for the LHCGR gene, which codes for LH receptors, the LMNA gene for Lamin A/C, the FST gene for follistatin, the EPHX1 gene, and the PRARGC1A gene for peroxisome proliferation, which codes for epoxide hydrolase. It should be highlighted that no single gene methylation alteration causes the disease; rather, these changes encode for basic physiological processes, like follicular growth, insulin control, steroidogenesis, inflammation, and glucose metabolism [43]. Syndromic conditions are caused by a change in their methylation state.

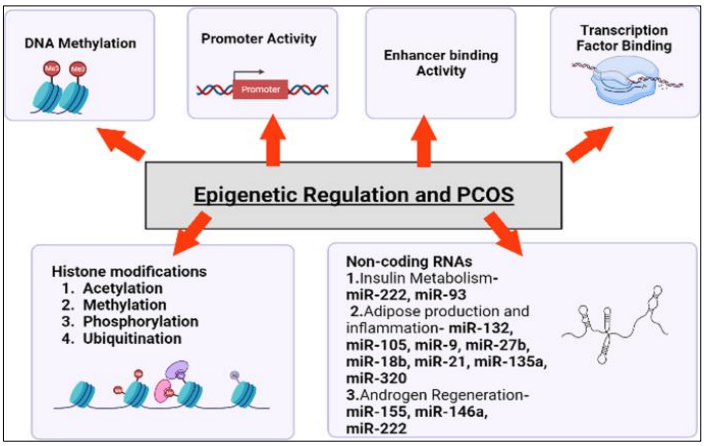

Figure (1-5) Diagram that shows different epigenetic regulations modulating PCOS in females. The figure has been generated with the use of BioRender software [39].

The progression of PCOS is controlled by some environmental factors that either indirectly or directly affect the ovaries. Dietary habits and sedentary lifestyles, for example, can deteriorate the reproductive cycle by causing irregular menstruation, a decrease in obesity, physical activity, menstrual cycle impairment, and other issues. These factors can also have an impact on PCOS modulation and prevalence. PCOS manifestation has been observed throughout development, as evidenced by the existence of a 2-3-fold rise in Anti-Mullerian hormone (AMH) in female PCOS patients. This biomarker serves as a diagnostic tool for tracking PCOS pathophysiology [39, 44], as illustrated in Figure (1-6).

Correlation between ROS and PCOS:

The term "oxidative stress" describes the unbalance between oxidants and antioxidants which causes abnormal redox conditions in cells. This leads to the formation of free radicals and peroxides, which can harm various cell constituents, such as lipids, proteins, nucleic acids, carbohydrates, and other compounds. Reactive oxygen species (ROS) and Reactive nitrogen species (RNS) are the two main types of radicals. Hydrogen peroxide (H2O2), hydroxyl radical, and superoxide radical are among ROS [45,46,47]. It is still unclear, nonetheless, how oxidative stress contributes to the PCOS pathogenesis. According to studies, oxidative stress may have a role in PCOS by altering steroidogenesis in ovaries, which raises androgen levels, interferes with follicular growth, and leads to infertility [48]. Ovarian disorders may arise as a result of elevated ROS levels. Beyond antioxidant capacity, increased ROS production from drinking and aging could cause OS and oxidative damage to proteins, DNA, and lipids [49, 50]. Figures 1–7 illustrate how oxidative damage and aberrant signaling pathways ultimately show up in age-related ovarian dysfunction, PCOS, ovarian endometriosis, and ovarian cancer [50].

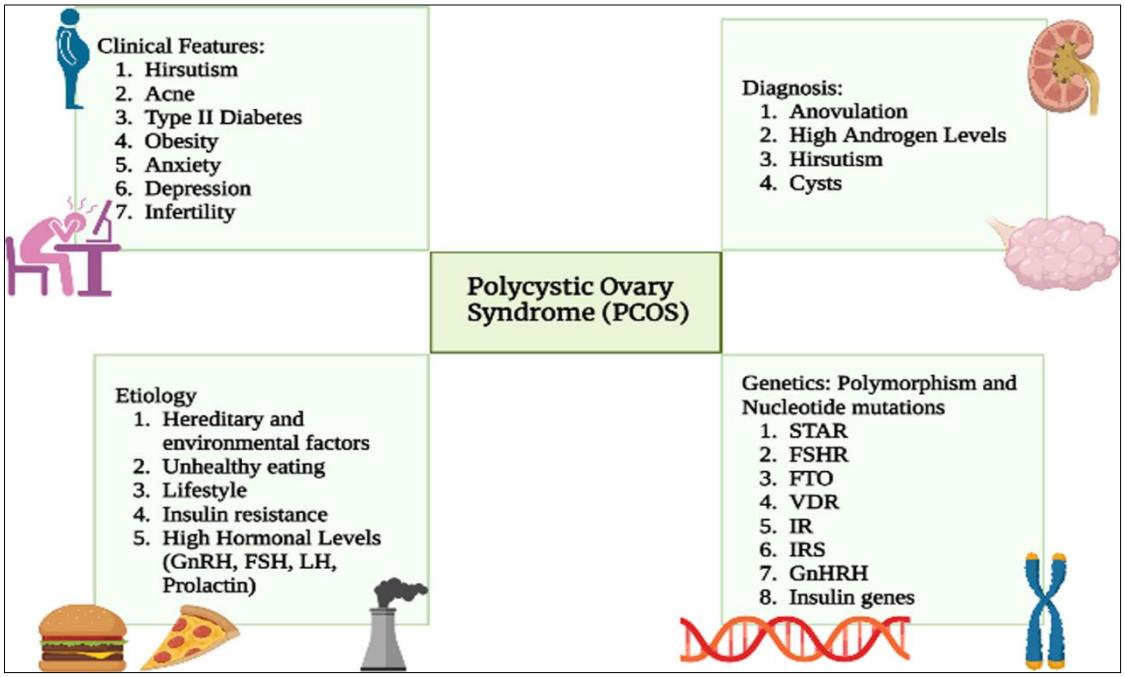

Figure (1-6): Summary of the main features related to PCOS, like diagnosis, clinical features, genetics, and etiology involved. The figure was generated with the use of BioRender software [39].

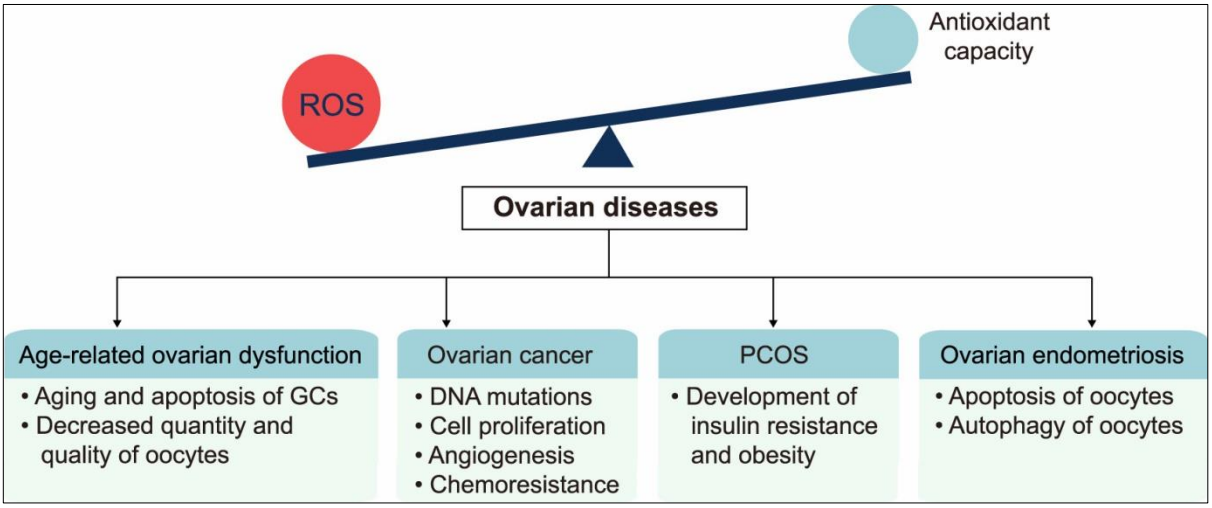

Figure (1-7): The imbalance between ROS generation and the antioxidant defense system affects ovarian diseases, such as ovarian cancer, age-related ovarian dysfunction, ovarian endometriosis, and PCOS [50].

Relation Between Polycystic ovary syndrome and Hyperprolactinemia:

Hypothesis for explaining a physiopathological link between PCOS and HPRL

1. Dopamine may be able to reduce LH secretion, according to certain research [51]. Therefore, it was postulated that a reduction in dopaminergic tone, which in turn might cause an increase in prolactin, could be the primary cause of the high LH levels that are observed in PCOS women [52]. Concerning the impact of dopamine agonist or inhibitor medication on LH levels in PCOS women, on the other hand, there are contradictory findings (Steingold et al., 1986) [53].
2. According to another theory (Azziz et al., 2016) [36], PCOS promotes relative hyperestrogenemia, which leads to hyperprolactinemia. Some experimental investigations have demonstrated that the action of estrogen causes an increase in prolactin release [54]. Additionally, it was proposed that women with PCOS may have an acceleration of GnRH pulsatility. This phenomenon could be linked to the rise in LH and fall in dopaminergic tone, both of which lead to hyperprolactinemia [38].

Nevertheless, there was no proof that PCOS women who profit from pituitary desensitization with the GnRH-agonists had lower prolactin levels [55, 56].

Conflicts of Interest:

The authors declare no conflict of interest.

Fund:

No funds, grants, or other support were received.

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