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Roles of estrogen and its receptors in polycystic ovary syndrome

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Polycystic ovary syndrome (PCOS) is an endocrine disorder characterized by abnormal steroid hormone levels in peripheral blood and poor-quality oocytes. In the ovary, androgen is produced by theca cells, and estrogen is produced by granulosa cells. Androgen is converted to estrogen in granulosa cells, with cytochrome P450 aromatase as the limiting enzyme during this process. Estrogen receptors (ER) include ER alpha, ER beta, and membrane receptor GPR30. Studies have demonstrated that the abnormal functions of estrogen and its receptors and estradiol synthesis-related enzymes are closely related to PCOS. In recent years, some estrogen-related drugs have made significant progress in clinical application for subfertility with PCOS, such as letrozole and clomiphene. This article will elaborate on the recent advances in PCOS caused by abnormal expression of estrogen and its receptors and the application of related targeted small molecule drugs in clinical research and treatment.

KEYWORDS

estrogen, estrogen receptor, ovary, polycystic ovary syndrome, estrogen signaling

1 Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine-metabolic disorder characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology (PCOM), affecting about 9%–18% of reproductive-aged women (Mykhalchenko et al., 2017). Women diagnosed with PCOS often exhibit endocrinal abnormalities, including hirsutism, insulin resistance, and obesity (Rotterdam Eshre/asrm-Sponsored PCOS consensus workshop group, 2004; Shrivastava and Conigliaro, 2023), followed by increased risk for type 2 diabetes (DM2), cardiovascular disease, and cancers of reproductive organs (Lizneva et al., 2016). The most common clinical marker of hyperandrogenism is hirsutism (Escobar-Morreale et al., 2012), which is measured by the extent of terminal hair growth in male-like areas according to the modified Ferriman–Gallwey score (Yildiz et al., 2010; Escobar-Morreale et al., 2012). What's more, overweight and obesity play a critical role in the development of PCOS, and weight management can markedly relieve the symptoms of hyperandrogenism, metabolic dysfunction, and ovulatory dysfunction, even with only 5% body weight loss (Kiddy et al., 1992; Holte et al., 1995; Barber et al., 2019). In addition, familial clustering studies provided strong evidence for genetic contribution to the etiology of PCOS. There is a 30%–50% risk of developing PCOS in women who have a first-degree relative

diagnosed with PCOS (Kahsar-Miller and Azziz, 1998; Legro et al., 1998; Kahsar-Miller et al., 2001; Moore and Campbell, 2017). Many studies identified a set of susceptibility loci and variants in genes involved in androgen biosynthesis (*CYP11A1*, *CYP17A1*, *CYP19*, *HSD17B5*, and *HSD17B6*), androgen activity (*AR*, *SHBG*, *SRD5A1*, and *SRD5A2*), insulin signaling (*INSR*, *IRS1*, and *IRS2*), folliculogenesis (*FSHR*, *LHCGR*, and *AMHR2*) and estrogen receptors (*ESR1* and *ESR2*) (Ibanez et al., 2003; Echiburu et al., 2008; Pusalkar et al., 2009; Unsal et al., 2009; Gu et al., 2010; Chen et al., 2011; Dolfin et al., 2011; Ramos cirilo et al., 2012; Shi et al., 2012; Kosova and Urbanek, 2013; Cui et al., 2015; Hayes et al., 2015; Silva et al., 2015; Azziz et al., 2016; Zhao et al., 2016; Moore and Campbell, 2017). Although enormous progress has been made in identifying PCOS loci and candidate genes, the role and function of these genes in PCOS remain unclear.

Steroidogenesis is a fundamental human hormone metabolism process involving cytochrome P450 and hydroxysteroid dehydrogenase enzymes to produce androgens and estrogens (Bondesson et al., 2015). Endocrinal disorder, especially high serum androgens, is thought to be the critical factor of PCOS. In the ovary, granulosa cells convert androgens to estrogens, and estrogen functions are mainly mediated through estrogen receptors (ERs). Three estrogen receptors have been identified in different tissues and intercellular locations: estrogen receptor alpha (ERα), estrogen receptor beta (ERβ), and the G-protein coupled estrogen receptor (GPER) (Gibson and Saunders, 2012; Yu et al., 2022). Studies in human and rodent animals have demonstrated disruption in estrogen signaling is highly related to PCOS, which makes estrogen and ERs a potential target in clinical treatment (Ryu et al., 2019). In non-human primates, it is reported that naturally hyperandrogenic female rhesus monkeys exhibit traits typical of women with PCOS (Abbott et al., 2017). Thus, anti-estrogen clomiphene citrate and aromatase inhibitor letrozole have become the first-line drug therapy to induce ovulation in PCOS treatment, and both drugs achieved good pregnancy outcomes (Legro et al., 2014; Roque et al., 2015). Here, we briefly review the roles of estrogen and its receptors in the pathogenesis and treatment of PCOS.

2 Polycystic ovary syndromes: definition and diagnosis

PCOS is a highly prevalent and heterogeneous disorder in women. The prevalence of PCOS ranges from 9% to 18% in reproductive-aged women due to different diagnostic criteria (March et al., 2010; Yildiz et al., 2012; Bozdag et al., 2016), which makes it the most common endocrine and metabolic disorder in women (Conway et al., 2014; Escobar-morreale, 2018). PCOS was first described by Stein and Leventhal in 1935, with the clinical characterization of oligo-amenorrhea, hirsutism, acne, obesity, and polycystic ovaries (Stein and Leventhai, 1935; Azziz and Adashi, 2016; Rosenfield and Ehrmann, 2016). Furthermore, patients with PCOS also demonstrate disorders, including insulin resistance (IR), increased risks for type II diabetes (DM2), and cardiovascular disease (Norman et al., 2001; Deugarte et al., 2005; Krentz et al., 2007; Lizneva et al., 2016; Chen and Pang, 2021). Thus, PCOS has become a prominent health issue of reproductive women, which seriously influences their physical and moral integrity. Three sets of diagnostic criteria for PCOS have been developed over the past three decades (Table 1) (Zawadzki et al., 1992; Rotterdam, 2004; Azziz et al., 2006a; Teede et al., 2023).

3 Estrogens and estrogen receptors

3.1 Steroidogenesis of estrogens

Steroidogenesis refers to a complex biochemical reaction in which steroids are generated from cholesterol under the action of hydroxysteroid dehydrogenase (HSD) and cytochrome P450 enzymes. As typical steroid hormones, sex hormones can be divided into androgen and estrogen (Moravek et al., 2015). Despite the different functions of androgen and estrogen, they are structurally similar and can be transformed from each other in the body. In addition, a certain proportion of the two sex hormones exist in balance in both men and women.

Similar to other steroid hormones, estrogen has many target tissues, which not only affect the growth, differentiation, and function of organs such as the ovary, uterus, and breast, but also play a role in the nervous system, cardiovascular system, and bone tissue (Nilsson and Gustafsson, 2011). Three major estrogens are produced through steroidogenesis, namely, estrone (E1), estradiol (E2), and estriol (E3) (Caiazza et al., 2015).

The biosynthesis of estrogens is shown in Figure 1, and the synthesis process is also linked to each other. In the first stage of steroidogenesis, cholesterol is converted to androstenedione under the action of CYP11A1, CYP17A1, and 3β-HSD. Among them, CYP11A1 catalyzes the cleavage of the cholesterol side chain and the conversion to pregnenolone. Furthermore, with the activity of l7, 20 carbon chain lyase, CYP17A1 catalyzes the l7α-hydroxylation of pregnenolone and progesterone. As for 3β-HSD, which is known as 3β-hydroxysteroid dehydrogenase, controls critical steroid hormone-related reactions in the adrenal cortex, gonads, placenta, liver, and other peripheral target tissues and affects all types of steroid hormones (Rasmussen et al., 2013). In the second stage, androstenedione is converted to E1 by aromatase CYP19A1, which is known as estrogen synthase and is specifically expressed in large antral and preovulatory follicles (Stocco, 2008). During the antral follicle growth, estrogen production results from follicle stimulating hormone (FSH)-dependent activation of aromatase (Dewailly et al., 2016).

On the other hand, androstenedione is converted to testosterone by 17β-HSD and is further converted to E2 by aromatase catalysis. Known as a group of enzymes, l7β-HSD are widely distributed in various tissues of the human body, including steroid hormone secretion tissues such as the placenta and ovary, and also distributed in other tissues such as fat and skin, breast, endometrium, liver, and other tissues (Vihko et al., 2001; Hilborn et al., 2017). In addition, the transformation between E1 and E2 is also catalyzed by l7β-HSD.

E3 is a steroidal estrogen produced by the human placenta and is derived from dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) (Legrain et al., 2000), which are the most abundant steroid hormones in human blood circulation. Origin from the adrenal glands of the fetus and the mother, DHEAS and DHEA can

TABLE 1 Diagnostic criteria for PCOS.

	NIH 1990	Rotterdam 2003	AE-PCOS society 2006	International evidence-based guideline 2023
Criteria	1. hyperandrogenism 2. anovulation	1. hyperandrogenism 2. oligo or anovulation 3. polycystic ovarian morphology	1. hyperandrogenism 2. oligo or anovulation 3. polycystic ovarian morphology	1. hyperandrogenism 2. ovulatory dysfunction 3. polycystic ovaries on ultrasound; and in 2023, alternatively anti-Müllerian hormone (AMH) can be used instead of ultrasound
Criteria required	1 and 2	1 and 2/1 and 3/2 and 3/1 and 2 and 3	1 and 2/1 and 3/1 and 2 and 3	1 and 2/1 and 3/2 and 3/1 and 2 and 3

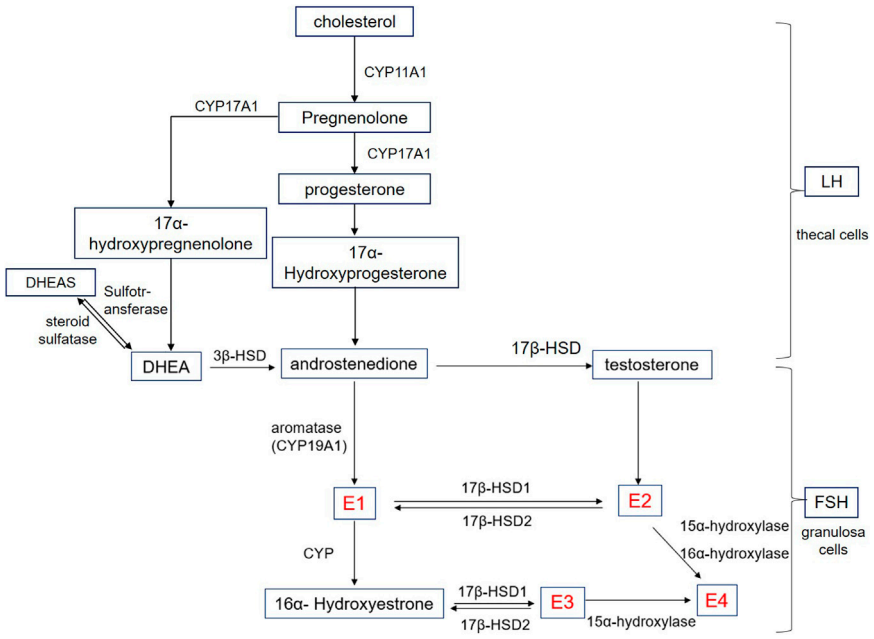

FIGURE 1
Schematic representation of estrogen biosynthesis. E1: estrone; E2:17β-estradiol; E3: Estriol; E4: Estetrol; Cyp: Cytochrome P450; HSD: Hydroxysteroid dehydrogenase; HEAS: Dehydroepiandrosterone sulfate; DHEA: Dehydroepiandrosterone; LH: Luteinizing hormone; FSH: Follicle stimulating hormone.

be converted to each other by steroid sulfatase and sulfotransferase, respectively. In addition to the three estrogens, estetrol (E4) can only be produced by the fetal liver. Both E2 and E3 are the substrates for E4 biosynthesis. Of these, E2 requires 15α and 16α hydroxylases, while E3 requires only 15α hydroxylase (Warmerdam et al., 2008). In humans, E4 is the end product of steroid metabolism, and cannot be metabolized to E3 or E2, nor is there any other active product produced (Visser and Coelingh Bennink, 2008).

Among all the above, E2 is the main estrogen secreted by the female ovaries and the most abundant and effective endogenous estrogen in women before menopause. The first step of E2 synthesis occurs in the thecal cells where cholesterol is converted to androstenedione under the action of luteinizing hormone (LH). The second step refers to androstenedione entering into granulosa cells through the basement membrane. Following this, the third step occurs in granulosa cells where estrogen is synthesized by converting androstenedione to E2 under the action of FSH, which produces aromatase during development. Finally, the formed E2 is secreted into the follicular fluid and blood. In addition, the inactivation process occurs in the liver where E2 converts to E1 and E3, which combine with glucuronic acid and excrete from the urine. Among them, E1 has the strongest activity, while E2 and E3 are 10% and 1% of E1, respectively (Wang and Roy, 2008).

3.2 Estrogen receptors

Estrogen exerts physiological effects by binding to the estrogen receptor (ER), which is localized in the cell membrane, cytoplasm, or nucleus (Tang et al., 2019). Thus, two categories are divided according to the location: one is the nuclear estrogen receptor (nER), and the other is the membranous estrogen receptor (mER). The representative of the former includes estrogen receptor α (ERα) and estrogen receptor β (ERβ) (Paterni et al., 2014), which are located in the nucleus and regulate the transcription of downstream target genes specifically by binding to its ligand. In recent years, nER can also be found located in the cell membrane or cytoplasm, and is called the membranous component

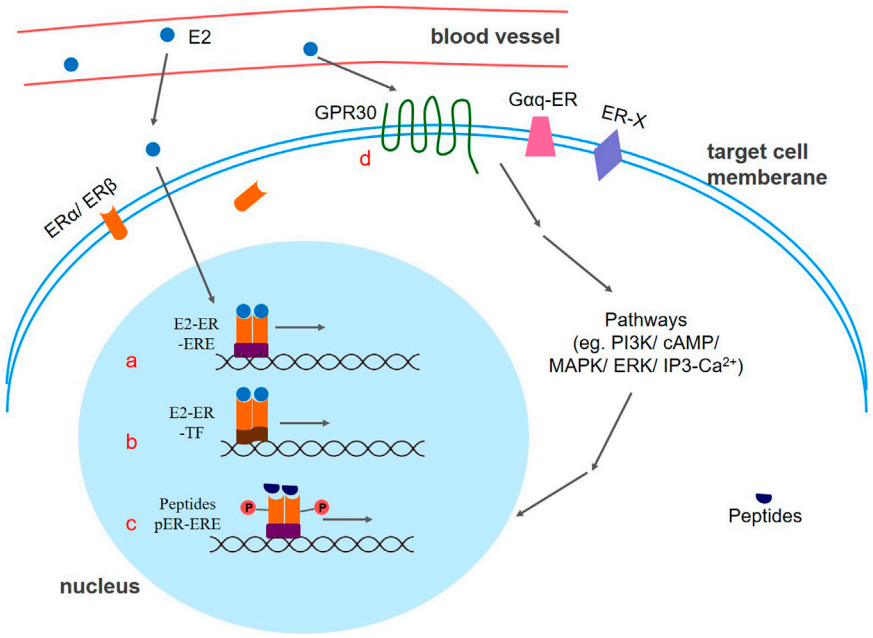

FIGURE 2
Different patterns of estrogen receptor signaling. (a) Classic ERE genomic pattern: The E2-ER complex acts as a transcriptional activator that promotes gene expression. (b) ERE independent genomic pattern. E2 activated ER binds with other classes of transcription factors, thereby regulating gene expression. (c) Ligand independent genomic pattern. Peptides such as EGF, and IGF-1 can activate estrogen receptors to express target genes. Phosphorylation of estrogen receptors may be the key factor. (d) mER-mediated signaling pathway. E2-mER mediated signal transduction causes a rapid regulation effect of the cellular response. E2:17β-estradiol; ER: estrogen receptor; GPR30: G protein coupled estrogen receptor; ERE: estrogen response element; TF: transcription factor; P: phosphate group.

of the classical nuclear receptor. Except that, G protein coupled estrogen receptor (GPER), ER-X, and Gαq-ER are included in mER as well, which can rapidly regulate intracellular signal cascade reaction by binding to ligands (Heldring et al., 2007).

ERα and ERβ were first identified in 1962 (Hewitt and Korach, 2002) and 1996 (Kuiper et al., 1996), respectively. From the view of tissue distribution, ERα is mainly found in tissues that are commonly thought to have estrogen effects, such as the uterus, breast, placenta, liver, central nervous system, cardiovascular system, and bone tissue where the expression of E2 response genes are induced as well (Matsuzaki et al., 1999). However, ERβ mainly distributed in the prostate, testis, ovary, pineal gland, thyroid gland, parathyroid gland, pancreas, gallbladder, skin, urethra, lymphoid tissue, and red blood cells where ERα expression is rare or undetectable (Lau et al., 2000). What's more, ERα and ERβ are co-distributed in the breast, epididymis, adrenal gland, hypothalamus, and tonsils (Paramanik et al., 2018).

In addition to the classical nuclear receptor for estrogen, a G-protein coupled receptor, GPR30 was identified in the ER-positive breast cancer cell line MCF-7 in 1997 (Tskitishvili et al., 2017), also known as G protein coupled estrogen receptor (GPER). The *GPER* gene is located on the 7th autosomal short arm p22.3 and is composed of four transcriptional splice variants, encoding 375 amino acids. As a seven-transmembrane signaling protein, GPER is widely distributed in a variety of tissue cells without specificity, such as neuroglia and vascular endothelium. Besides, its main functional area is not only located in the cell membrane but also in the nucleus, Golgi, or endoplasmic reticulum, which can bind E2, glucocorticoids, mineralocorticoids, and vitamin D receptors (Prossnitz and Barton, 2011; Prossnitz and Barton, 2014). In 2005, it was first demonstrated that E2 was competitively bound to GPER (Revankar et al., 2005). Subsequently, DHEA was found to have an antagonistic effect on GPER (Niro et al., 2012). In recent years, a large number of studies have shown that GPER regulates various physiological functions of cells in normal organs such as the uterus, ovary, and breast. At the same time, its abnormal expression plays a role in the occurrence and development of gynecological diseases and other tumors as well (Prossnitz and Barton, 2023).

3.3 ER signaling

There are two main types of estrogen receptor signaling pathways (Figure 2). One is Nuclear-Initiated Steroid Signaling (NISS), the genomic mode of action, which includes the classical Estrogen Response Element (ERE) genome pattern, ERE independent genomic pattern, and ligand independent genomic pattern. The other is Membrane Initiated Steroid Signaling (MISS), a non-genomic mode of action, which activates the MAPK pathway, the PI3K/AKT pathway, the cAMP/PKA pathway, and the Ca^{2+} pathway.

3.3.1 Classic ERE genomic pattern

Similar to other nuclear receptor superfamily members, nER contains five functional regions: the DNA binding region (DBD),

the ligand binding region (LBD), the hinge region, and two transcriptional activation regions (AF1 and AF2 regions) (Wu and Loverde, 2019). Usually, nER is in an inactive state, and exists as an oligomer complex binding with heat shock protein Hsp90 in the cytoplasm. When E2 appears and binds to the AF2 domain, nER is activated and dimerized with Hsp90 releases, thereby exposing the dimerized surface and the DBD region, which could bind the DNA reaction element ERE to the target gene. To stabilize the binding, the DBD monomer of the nERs needs to bind to two-half arms of the ERE. After ER allosteric, a hydrogen bond network is formed between the ERE and amino acid residue of the receptor to achieve selective contact of the bases. Furthermore, different cofactors are recruited to the ER-ERE complex site, thereby realizing the transcriptional regulation mechanism of different ERE genes. Thus, the estrogen-ER complex acts as a transcriptional activator that promotes gene expression (Cunningham et al., 2014; Jacquot et al., 2017). In addition to estrogen, ER ligands also include Selective Estrogen Receptor Modulators (SERMs) and Selective Estrogen Receptor Downregulators and/or Degraders (SERDs), which exerts agonism or antagonism through ERα phosphorylation.

3.3.2 ERE independent genomic pattern

Even if the promoter region does not carry an ERE, estradiol can also affect the expression of related genes (Maneix et al., 2015). In this case, E2-activated ER does not bind directly to DNA but rather binds by interacting with other classes of transcription factors, thus regulating gene expression. For example, nER can bind to the AP-1 site on DNA by interacting with Fos and Jun. In addition, the ERα-Ap1 complex can also bind to the GC-rich promoter sequence. It is worth noting that ERα activates the transcription after binding to estrogen at the AP-1 site, while ERβ inhibits it. However, the antagonists tamoxifen and raloxifene become potent transcriptional agonists after binding to ERβ at the AP-1 site (Paech et al., 1997).

3.3.3 Ligand independent genomic pattern

In addition to estrogen, peptides such as EGF (epidermal growth factor), IGF-1 (insulin-like growth factor-1), and 8-bromo-cAMP can also activate ERs to express target genes (Ueda et al., 2006). It is reported in the literature that a key factor in this process may be caused by phosphorylation of ERs by kinases in cells (Legrain et al., 2000). Both ERα and ERβ are phosphorylated by MAPK, but the phosphorylation sites are different. The 118th serine in the ERα AF-1 region is phosphorylated by MAPK (mitogen-activated protein kinase) after receiving EGF, resulting in the binding of the p68 RNA helicase, known as the ERα-specific coactivator, to the receptor, which finally activates the target gene (Kato, 2001). Similarly, MAPK can also phosphorylate the activation region of the ERβ N terminus, allowing the receptor to bind to the p160 coactivator SRC-1 in a ligand-independent manner and finally interact with the ERE, attenuating the transcriptional activity of ERα (Tremblay and Giguere, 2001).

3.3.4 mER-mediated signaling pathway

Compared to the classical nER-mediated slow "genomic effect", mER-mediated signal transduction is fast and cannot be inhibited by proteins and RNA synthesizers, so it is also called a fast "non-genomic effect." That is, the binding of estrogen to ER can induce a change in the conformation of the binding site, and this conformational change can cause aggregation of some accessory proteins, thereby causing a rapid regulation effect of the cellular response.

When GPER is activated by a ligand such as estrogen or G-1, the associated G protein is first activated, and the Gαβγ heterotrimer is dissociated into Gα and Gβγ to function separately. The dissociated G protein activates or inhibits the downstream effector molecule, and changes the content and distribution of the second messenger in the cell, which acts on the corresponding target molecule through PI3K (Liu et al., 2015), Cyclic adenosine monophosphate (cAMP) (Li et al., 2010), MAPK (Filardo et al., 2002; Albanito et al., 2008), IP3-Ca^{2+} (Furuyama et al., 2014) and other pathways to exert physiological effects. For instance, Gα can activate adenylyl cyclase (AC), which induces cell signaling of second messengers such as cAMP, increases calcium ion expression, and activation of ERK signaling pathway, or enhances mitochondrial autophagy through the ERK1/2 signaling pathway. Besides, Gβγ can activate tyrosine kinase to phosphorylate, which activates matrix metalloproteinases, thereby rapidly activating ERK and other signaling pathway-associated kinases. Multiple modes of action of GPER described above have overlapping signaling pathways that mediate independent rapid intracellular signal transduction.

Apart from GPER, Gαq-ER and ER-X are newly discovered mERs, and the mechanism of signal transduction is not fully understood. Estrogen activates Gαq by binding to the receptor, then activates PLC and hydrolyzes PIP2 out of DAG to activate PKC, which subsequently activates cAMP and PKA, finally opening the potassium channel of the membrane to induce corresponding biological effects (Qiu Jronnekleiv and Kelly, 2008). Studies suggest that ER-X-mediated estrogen regulation involves the MAPK-ERK1/2 signaling pathway, and activation of ERK1 and ERK2, which is important for neuronal survival and growth.

4 Role of estrogen and ERs in PCOS

Estrogen and ERs exert a variety of physiological activities, including reproductive, immune, cardiovascular, endocrine, aging, and neurological diseases. The abnormal expression of estrogen and ERs is closely related to PCOS in various aspects.

4.1 Role of estrogen and ERs in the endometrium of PCOS

The endometrial changes in patients with PCOS vary with the level of estrogen secreted by the ovaries (Palomba Spiltonen and Giudice, 2021). When the follicles always develop immaturely, and the ovaries continue to secrete a small amount of estrogen. The endometrium of patients with PCOS is impaired progesterone response (Albaghdadi and Kan, 2021; Hamza et al., 2021). The endometrium without progesterone undergoes different degrees of hyperplasia, even the occurrence of endometrial cancer. Studies have been made to detect the expression levels of ERα and ERβ in the endometrium of patients with PCOS. Results showed that the

expression of ERα mRNA and protein in the endometrium of patients with PCOS was higher than that of normal women. However the expression of ERβ was not significantly changed, suggesting that the sensitivity of PCOS intimal to estrogen stimulation is increased (Quezada et al., 2006). It is considered that PCOS intima is directly stimulated by long-term estrogen without progesterone, which may be one of the reasons for the increase of ERα expression (Gregory et al., 2002; Matthews and Gustafsson, 2003). Increased expression of ERα was observed in the endometrium of PCOS, indicating that the endometrium is more sensitive to estrogen stimulation and may affect the normal function of the mid-secretory endometrium (Giudice, 2006). However, there is little research on the expression and significance of GPER in the endometrium of infertile women, especially in PCOS patients. In summary, estrogen and some receptors play an important role in the pathogenesis of PCOS endometrium, which can be the basis for developing new drugs to alleviate the symptoms.

4.2 Role of estrogen and ERs in hyperandrogenemia of PCOS

Excessive androgen synthesis in the ovarian thecal cells is one of the most important features of PCOS. Hyperandrogenism participates in the pathogenesis of anovulation and may cause anovulatory infertility. And too much testosterone in serum in patients with polycystic ovary syndrome can scent into estrogen, and the ERs play a role. It has indeed been suggested that indirect, possibly ER, effects of androgens are important modulators of the reproductive characteristics of PCOS (Aflatounian et al., 2020). As mentioned above, estrogen plays an important regulatory role in the synthesis of androgen in thecal cells. It was found that the expression of *CYP17A1* in ERα-deficient follicles was significantly increased and a large amount of androstenedione was secreted after culturing wild-type follicles and ERα-deficient follicles *in vitro* (Taniguchi Fcouse et al., 2007). The results showed that ERα can reduce the production of androgen in thecal cells by inhibiting the expression of *CYP17A1*, and plays a key role in the regulation of ovarian androgen synthesis and ovarian function. Therefore, the abnormal expression of ERs in the follicles leads to changes in the estrogen sensitivity of thecal cells, which matters in the pathogenesis of ovarian hyperandrogenemia.

4.3 Role of estrogen and ERs in ovarian PCOS

The main pathological changes in the ovary in PCOS patients were bilateral ovarian enlargement and pearl-like cystic follicles. It was found that ERα KO adult mice display polycystic ovary, increased expression of LH receptors in ovarian follicular cells and granulosa cells, and increased concentration of serum LH, androgen, and estradiol levels (Couse et al., 2003), which indicates abnormal expression of ERα plays an important role in PCOS ovarian disease. In addition, studies showed that follicular granulosa cells in ERβ KO mice were less sensitive to gonadotropin response, and aromatase expression in granulosa cells was decreased, leading to an elevated androgen level (Couse et al., 2005). The results demonstrate that ERβ mediated estradiol actions may be the key factor responsible for maintaining differentiation of ovarian granulosa cells and the ovulation function, and lack of ERβ will destroy preovulatory follicles and finally lead to the phenotype of ovulation dysfunction. αβERKO mice ovaries demonstrate a unique morphology of the supportive-like cell, with no pre-ovulation follicles or corpus luteum formation, and granulosa cell stratification, which indicates that both subtypes of nERs are essential to maintain normal ovarian function in females. Moreover, studies have shown that GPER, along with estrogens can inhibit oocyte meiosis and mediate oocyte maturation in zebrafish (Pang and Thomas, 2010). Except, GPER has proved to be a mouse oocyte-specific estrogen membrane receptor, which can regulate oocytes to undergo meiosis again and inhibit the maturation of follicles (Li et al., 2013).

4.4 Role of estrogen and ERs in the metabolism of PCOS

Metabolic dysfunction is one of the most common phenotypes of PCOS, among which, insulin resistance is commonly seen in PCOS patients. The relationship between PCOS and IR was first reported in 1980, showing that obese women with PCOS have an increased insulin response compared with obese controls (Burghen et al., 1980). What's more, Z. Douma recently discovered that the *ESR1* gene suggested correlations with a metabolic profile of PCOS by haplotype analysis. They found that four haplotypes reconstructed in the *ESR1* gene were highly associated with PCOS and one of these is consistent with insulin resistance in haplotype trend regression (Douma et al., 2020). Estrogen actions in pancreatic islet β-cells regulate insulin secretion and estrogen deficiency contributes to metabolic dysfunction prone to obesity, the metabolic syndrome, and DM2. And GPER mediates E2-stimulated pancreatic β-cell insulin (Sharma and Prossnitz, 2011; Mianowska et al., 2020). Significantly modified metabolic and endocrine features can be found in PCOS patients by using insulin-sensitizing drugs, which may demonstrate that insulin resistance plays an important role in the etiology of PCOS (Holte et al., 1995; Azziz et al., 2001; Barber et al., 2006). Meanwhile, IR, along with the subsequent hyperinsulinemia increased the risk for impaired glucose tolerance and DM2 in PCOS patients (Jayasena and Franks, 2014; Azziz, 2018). Moreover, hyperinsulinemia leads to hyperandrogenism, which further aggravates the syndrome. In addition, a study demonstrated that ERα actions confront obesity and metabolic dysfunction by mitochondrial function in adipocytes (Zhou Zmoore et al., 2020). Adipocytes express aromatase, resulting in intracrine estrogen synthesis. And GPER contributes to estrogen-dependent proliferation and lipid metabolism (Chaturantabut et al., 2019). In recent years, there have also been some findings on the increased risks of PCOS with dyslipidemia, hypertension, and other cardiovascular diseases (Azziz et al., 2006b; Cobin, 2013). Estrogen serving as a cardioprotective agent is mediated by ERα, Erβ, and GPER signaling pathways to maintain cardiovascular homeostasis (Knowlton and Lee, 2012; Aryan et al., 2020; Visniauskas et al., 2023). Thus, cardiovascular risk factors should be assessed in patients with PCOS. Perhaps estrogen and Ers are not directly related to the development of PCOS, but they are involved in the

metabolic phenotype of complications of the syndrome. Therefore, genes encoding for ESRs may become valuable markers for metabolic features of PCOS at the clinical scale.

4.5 Role of estrogen and ERs in immune regulation of PCOS

PCOS is characterized by chronic low-level inflammation, hormonal imbalance, and immune dysregulation (Luan et al., 2022; Shamsi et al., 2022). Abnormalities in the immune system are significant directions that have recently been studied extensively for their role in PCOS (Franks and Hardy, 2006; Su et al., 2018; He et al., 2020). The function of the immune system exhibits exceptional sexual dimorphism, as shown by the active role of estrogen/ER signaling in the development, differentiation, and function of innate and adaptive immune cells (Chakraborty et al., 2023). Dendritic cells (DCs), as key antigen-presenting cells in the immune system, present antigens to different receptors on different immune cells to activate innate and adaptive immune responses (Lindquist et al., 2004; Geissmann et al., 2010). Furthermore, DCs induce a positive ovulatory response by affecting the expansion of the cumulus-oocyte complex, ovum release from the ovarian follicle, formation of a functional corpus luteum, and enhanced lymphangiogenesis (Cohen-Fredarow et al., 2014). According to a study by O. Fainaru et al., the maturity of DCs is correlated positively with ovarian function determined by the synthesis of estrogen response to gonadotropins (Fainaru et al., 2012). However, a study has shown that PCOS patients have a decreased percentage of CD11c+ HLA-DR + DCs in follicular fluid and there is a positive correlation between serum estrogen level and HLA-DR expression (Zhang et al., 2017). These studies indicate the declination of serum estrogen levels in PCOS patients may lead to dysfunction of DC maturation, thereby affecting the inflammatory response and resulting in the failure of follicle development.

5 Estrogen-related drugs in PCOS treatment

Routine management of PCOS includes lifestyle intervention, bariatric surgery, and drug treatment (Azziz et al., 2016; Reyes-Munoz et al., 2018; Franik Sle et al., 2022). Insulin resistance and estrogen metabolism are two typical targets of drug therapies. Metformin, a synthetically derived biguanide that was commonly used in the treatment of DM2, was used as an insulin-sensitizer drug in PCOS treatment. Metformin helps women in terms of decreasing body weight, serum insulin levels, and androgen concentrations (Naderpoor et al., 2015; Morley et al., 2017). Moreover, G-1, selective GPER agonists, increases glucose-stimulated insulin secretion in pancreatic islets of patients with DM2, while also suppressing glucagon and somatostatin secretion (Kumar et al., 2011). Combined (estrogen-progestin) oral contraceptives are the first-line medical treatment for menstrual discords and hyperandrogenism. It induces predictable withdrawal bleeding, offers reliable endometrial protection, and provides contraception (Teede et al., 2023). Clomiphene citrate (CC), an estrogen-receptor modulator, has been used for decades to induce ovulation (Misso et al., 2012). CC can increase ovarian stimulation and follicular development by blocking estradiol receptors in the hypothalamus. However, 15%–20% of PCOS patients remain anovulation after standard CC treatment, indicating CC resistance (Kurabayashi et al., 2006). Letrozole is an aromatase inhibitor and was first used to induce ovulation in 2001 in women exhibiting CC resistance (Mitwally and Casper, 2001). It blocks estrogen synthesis by inhibiting the enzyme aromatase, which can convert androgens to estrogens (Legro et al., 2014). Both CC and Letrozole are first-line drugs in PCOS treatment and there is much controversy over which therapy leads to a better clinical outcome. Legro et al. found that letrozole can achieve higher live birth and ovulation rates among PCOS women compared with CC (Legro et al., 2014). Nevertheless, Guang et al. demonstrated that the letrozole showed no advantages compared with CC in PCOS treatment (Guang et al., 2018). In a meta-analysis including seven prospective RCTs, Roque et al. found no differences in multiple pregnancy, miscarriage, and ovulation rates between Letrozole and CC groups and the letrozole group exhibited higher live birth and pregnancy rates in patients with PCOS (Roque et al., 2015). The 2023 International evidence-based guideline for the evaluation and treatment of PCOS recommends letrozole as the preferred first-line drug for infertility treatment, along with clomiphene plus metformin (Teede et al., 2023). Recently, several studies showed that melatonin, a neuroendocrine hormone secreted by the pineal gland, can mediate steroidogenesis, folliculogenesis, and oocyte maturation in the ovary (Talpur et al., 2017; Yu et al., 2019). Melatonin treatment can significantly decrease androgen and anti-mullerian hormone levels and by contrast, increase FSH levels after 6 months of melatonin treatment in PCOS patients (Tagliaferri et al., 2018). Additionally, it was found that melatonin had a positive impact on oocyte quality and *in vitro* culture of COCs from PCOS patients with melatonin can significantly increase the maturation rate of oocytes in PCOS patients (Yu et al., 2019).

6 Concluding remarks

PCOS is a common endocrine and reproductive disorder and metabolic dysfunction, especially hyperandrogenism is the upmost manifestation of the disease. Estrogens and ERs regulate the balance of steroidogenesis and play a significant role in the pathogenesis of PCOS. In this review, we detailed the biosynthesis of estrogens and the functions of ERs and ER signaling, trying to illuminate the essential role of estrogens and ERs in PCOS. Lastly, we reviewed estrogen-related drugs in PCOS treatment. This article exhibits a deep understanding of PCOS in the view of estrogen signaling, which may provide help in the drug screening and clinical management of PCOS.

Author contributions

YX: Writing–review and editing, Writing–original draft. ZZ: Writing–review and editing. RW: Writing–review and editing. SX:

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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