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REVIEW ARTICLE

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Pathophysiological roles of chronic low-grade inflammation mediators in polycystic ovary syndrome

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Abstract

Polycystic ovary syndrome (PCOS) is the most common hormonal imbalance disease in reproductive-aged women. Its basic characteristics are ovulatory dysfunction and ovarian overproduction of androgens that lead to severe symptoms such as insulin resistance, hirsutism, infertility, and acne. Notwithstanding the disease burden, its underlying mechanisms remain unknown, and no causal therapeutic exists. In recent years, further studies showed that inflammation processes are involved in ovulation and play a key role in ovarian follicular dynamics. Visceral adipose tissue can cause inflammatory response and maintenance of the inflammation state in adipocytes by augmented production of inflammatory cytokines, monocyte chemoattractant proteins, and recruitment of the immune cell. Therefore, the PCOS can be related to a low-grade inflammation state and inflammatory markers. Investigating the inflammatory processes and mediators that contribute to the commencement and development of PCOS can be a critical step for better understanding the pathophysiology of the disease and its treatment through inhibition or control of related pathways. In the present review, we discuss the pathophysiological roles of chronic low-grade inflammation mediators including inflammasome-related cytokines, interleukin-1β (IL-1β), and IL-18 in PCOS development.

KEYWORDS

chronic low-grade inflammation, IL-18, IL-1β, inflammasome, polycystic ovary syndrome

1 | INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common hormonal imbalance with an unknown etiology in reproductive-aged women. The National Institute of Health (NIH) provided the first definition of PCOS in 1990. According to this criterion, the disorder involves a combination of oligo-anovulation and clinical or biochemical signs of hyperandrogenism (Lujan, Chizen, & Pierson, 2008). Another definition mentioned by the Rotterdam consensus in 2003 is based on showing at least two sets of the following characteristics: oligo-and/or anovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovaries (Jalilian et al., 2015). The imbalance of estrogen and progesterone levels may be involved in the growth of ovarian cysts. Secretion of estrogen in PCOS women is specified by chronic secretion without the cyclic pattern that complements the ovulatory cycle. Serum estradiol (E_2) levels may vary in PCOS women. In contrast, serum levels of estrone (E_1) are frequently higher than that of E_2. In addition, serum progesterone levels are low in PCOS women. However, it has been described that 17-hydroxyprogesterone values are significantly elevated in women with PCOS (Velija-Asimi, 2013).

The main characteristics of PCOS are hyperandrogenism, polycystic ovary morphology, and ovulatory dysfunction, which is associated with hirsutism, metabolic disturbances including obesity and insulin resistance (found in 60–80% of women with PCOS). Fertility

disorders, cardiovascular problems, psychological effects on the quality of life (including anxiety and depression), and endometrial cancers have been observed in many PCOS patients (Carmina, Oberfield, & Lobo, 2010). Recent findings have revealed that inflammation processes are involved in ovulation and play an important role in ovarian follicular dynamics. Of note, the visceral adipose tissue is linked to the development of inflammation. Along the same lines, abdominal obesity is more common among women with PCOS. Visceral adipose tissue by augmented production of inflammatory cytokines, monocyte chemoattractant proteins (MCPs), and recruitment of the immune cell, leads to an inflammatory response, maintaining the inflammatory state in adipocytes (Deligeoroglou et al., 2012). Therefore, PCOS can be related to a low-grade inflammation state and inflammatory markers. Moreover, many factors such as obesity, insulin resistance, genetic factors, and lifestyle could contribute to the development of the PCOS. Investigating the inflammatory processes and factors that contribute to the onset and development of these processes in PCOS may be a vital step for better understanding the pathophysiology of the disease and treatment through inhibition or control of related pathways. In the present review, we discuss the role of chronic low-grade inflammation in PCOS as summarized in Figure 1.

2 | EPIDEMIOLOGY OF PCOS

According to the NIH and Rotterdam criteria, 6 –10% of women were affected by PCOS. This makes PCOS one of the most common disorders and endocrinopathies in women of reproductive age (15–49 years; Broekmans et al., 2006). PCOS frequency may be higher in women younger than 35-year old (Koivunen et al., 1999). The prevalence of PCOS has been reported differently in different parts of the world. The prevalence of hirsutism seems to be higher among South Asian patients living in the United Kingdom, compared with PCOS women of European descent living in the same location (Azziz et al., 2004; Wijeyaratne, Balen, Barth, & Belchetz, 2002). Screening of an unselected population in the Southwestern United States estimated the incidence of PCOS to be approximately 4% (Knochenhauer et al., 1998). The occurrence of PCOS was studied in teenage girls and adolescents in Iran. The disease was observed in 11.34% of teenage girls and demonstrated an estimated incidence of 11% in adolescents (Asgharnia, Mirblook, & Ahmad Soltani, 2011). According to the AEH and NIH criteria, the prevalence of PCOS in Iran is reported to be about 8%. The rate has been obtained and is estimated to be 15.2%, based on Rotterdam criteria (Mehrabian, Khani, Kelishadi, & Ghanbari, 2011).

3 | PATHOPHYSIOLOGY OF PCOS

Over the last decade, several hypotheses have been proposed about PCOS development. PCOS reflects the interactions among numerous genes and proteins influenced by epigenetic and environmental factors. Although in the pathogenesis of PCOS, the ovary is fundamental, neuroendocrine and metabolic dysfunctions play a key role in the pathophysiology of PCOS. The association of PCOS with hyperandrogenism, hyperinsulinemia, and insulin resistance is well-known. Furthermore, in recent years, more studies have directed their focus on the critical role of chronic low-grade inflammation in PCOS development (Nardo, Patchava, & Laing, 2008).

3.1 | Insulin resistance

Insulin resistance is a usual feature of PCOS affecting 50–70% of women affected by the disease. Insulin resistance alone does not fully account for the development of type 2 diabetes mellitus (T2DM) in patients with PCOS. The β-cell defect may be the primary abnormality in PCOS (Tsilchorozidou, Overton, & Conway, 2004). The action of insulin is mediated through a protein tyrosine kinase receptor. A possible mechanism for insulin resistance in affected women appears to be related to excessive serine phosphorylation of the insulin receptor. It seems that serine phosphorylation of the insulin receptor substrate-1 (IRS1) and insulin receptor substrate-2 (IRS2), leads to inhibition of signaling. Also, the auto-phosphorylation of insulin receptor leads to decreased expression of glucose transporter type 4 (GLUT-4), which is the insulin-sensitive glucose transport protein. Hyperinsulinemia results in an increased risk for many diseases including, type 2 diabetes (T2D), hypertension, dyslipidemia, endothelial dysfunction (ED), atherosclerosis, and cardiovascular diseases (Bednarska & Siejka, 2017). The association between hyperinsulinemia and hyperandrogenism revealed a positive correlation between increasing insulin and androgen levels. Hyperinsulinemia augments the androgen production in PCOS. Insulin may act through both direct and indirect pathways: directly, as a gonadotropin augmenting luteinizing hormone activity through stimulation of ovarian receptors of insulin and insulin-like growth factors (Ranjithkumar et al., 2019) and indirectly, by enhancing the amplitude of serum LH pulses. The structure of the insulin receptor and the insulin-like growth factor 1 (IGF-1) receptor are similar. Hence, insulin cross-reacting with the IGF-I receptor. IGF-I by augmenting the theca cell androgen response to LH activation of IGF-I receptors via insulin leads to increased androgen production in theca cells. It has been shown that insulin exerts specific actions on steroidogenesis through its receptor in both granulosa and theca cells (Tsilchorozidou et al., 2004). Actual evidence pointing to the insulin-mediated increase of ovarian cytochrome P450c17a activity can be considered as an additional mechanism of insulin action in PCOS women. Also, an increased level of glucose causes defects in the secretory capacity of insulin and damages the pancreatic beta cells during long-term exposure, resulting in the activation of inflammasome (Zhou, Tardivel, Thorens, Choi, & Tschopp, 2010). Taken together, these findings indicate the performance of the insulin-signaling pathway to be a major contributor to the onset and development of PCOS.

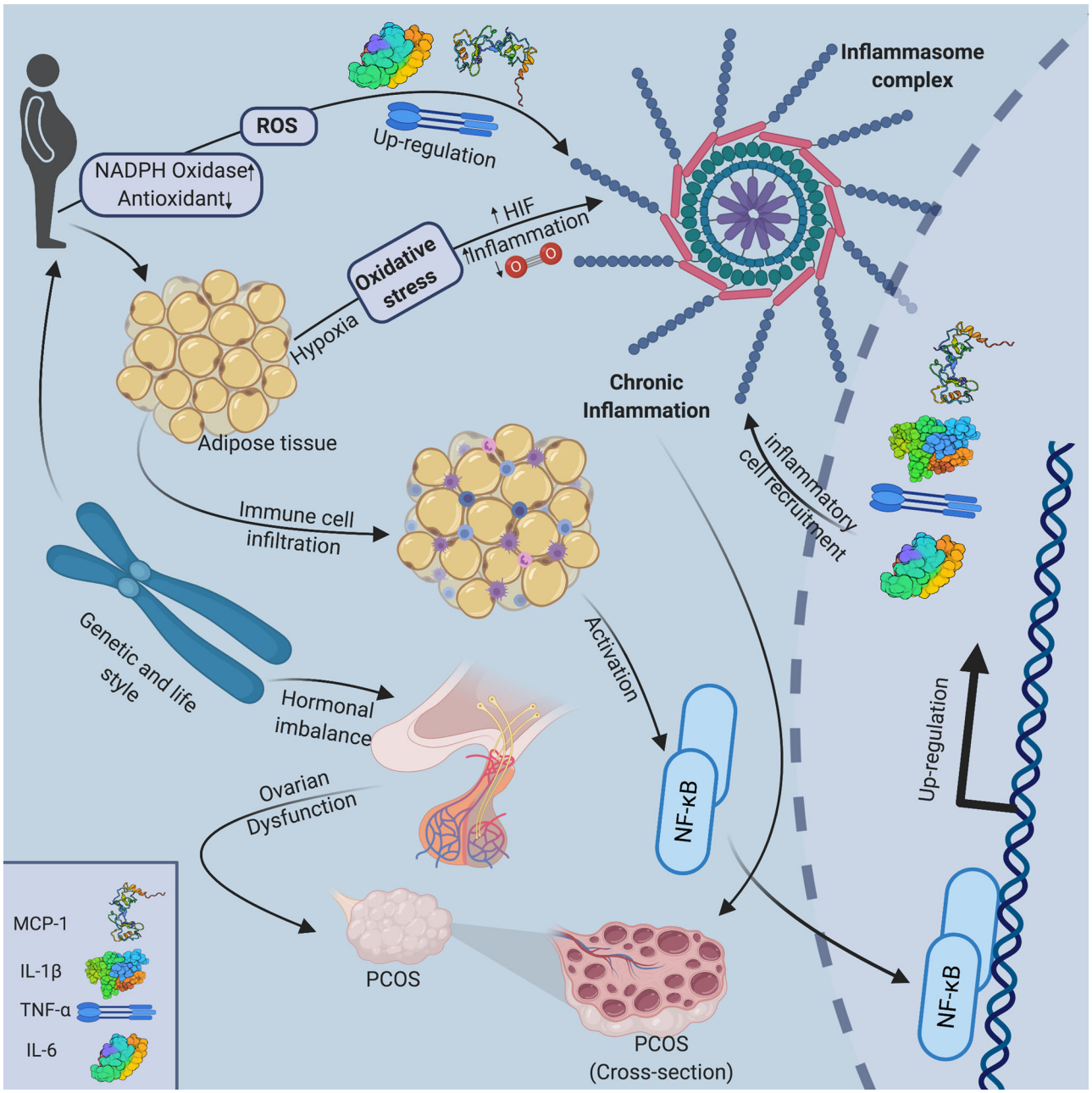

FIGURE 1 Schematic representation of inflammatory mediators and related factors that are involved in the development of PCOS. The figure demonstrates how chronic low-grade inflammation and PCOS are linked. In addition, genetic and lifestyle may lead to the alteration of hormonal disorders, and co-occurrence of obesity along with its side effects, which usually follow an increase in visceral adipose tissue, increased oxidative stress in cells, and subsequent recruitment of the inflammatory cells. In addition, hormonal alteration may have affected the ovulation process, and fertilization. Created with BioRender.com (https://www.rcsb.org/structure/3NJ5; PDB ID: 3NJ5; Cheng et al., 2011, PDB ID: 1DOM; Handel & Domaille, 1996; PDB ID: 2L3Y; Veverka et al., 2012). IL-1β, interleukin-1β; MCP-1, monocyte chemoattractant protein-1; NADPH, Nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor-κB; PCOS, polycystic ovary syndrome; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-α

3.2 | Defect in androgen synthesis

Ovarian hyperandrogenism is mainly attributed to the steroidogenic defect of theca cells in the PCOS. In this disorder, increased LH and insulin levels can amplify the intrinsic abnormality of theca steroidogenesis. Impaired gonadotropin dynamics may lead to abnormal androgen production. This defect in PCOS contributes to excessive androgen production. Moreover, excess production of LH leads to an enhancement in androgen synthesis of theca cells. It has been shown that elevated LH levels can be caused by impaired negative feedback on LH secretion because of excessive androgenic actions affecting the hypothalamic–pituitary axis (Jonard & Dewailly, 2004).

Moreover, the FSH levels, which have been mentioned, are reduced when affected by LH, diminishing the stimulation of aromatase. This results in a decreased conversion of androgen to estrogen and induces ovarian androgen excess, which accelerates the production of small and immature ovarian follicles as cysts (Haisenleder, Dalkin, Ortolano, Marshall, & Shupnik, 1991). So, as briefly mentioned, impairment in the production of the androgen by triggering a cascade can contribute to the emergence of the PCOS.

3.3 | Chronic low-grade inflammation

During recent years, an increasing number of studies have focused on the effects of chronic low-grade inflammation in PCOS. Some investigations have suggested that in some aspects, PCOS-related inflammation may depend on visceral adipose tissue (Garruti et al., 2009). This is a crucial point, taking into account that in PCOS, insulin resistance-related glucose ingestion can induce an inflammatory response that increases nuclear factor-κB (NF-κB) activation and oxidative stress. It has been made clear that oxidative stress has an important role in chronic low-grade inflammation and can be significantly augmented in PCOS by expression of pro-inflammatory cytokines (Park et al., 2009). It is conceivable to hypothesize that alteration in gene expression of pro-inflammatory cytokines, in turn, plays a role in the development of the PCOS. Considerable evidence indicates that some polymorphisms in the inflammation-related genes encoding tumor necrosis factor-α (TNF-α), TNF receptor 2 (TNFR2), and interleukin-6 (IL-6) are associated with hyperandrogenism and PCOS. Along the same lines, inflammatory factors including high sensitivity C-reactive protein (hsCRP), IL-1β, IL-18 as well as WBC count have shown increased levels in PCOS (Escobar-Morreale, Calvo, Villuendas, Sancho, & San Millan, 2003). On the other hand, more detailed studies showed WBC count to be one of the most important inflammatory variables that was affected by the increase of high body mass index (BMI) fatty acid. Moreover, obesity, metabolic syndrome, and insulin resistance have been reported to increase inflammatory mediators (D. H. Kim, Noh, et al., 2008). Increasing evidence proposes that subclinical inflammation is a part of metabolic syndrome. Some features of metabolic syndrome, including visceral obesity, are correlated with low-grade inflammation. Several studies pointed out that different components of the metabolic syndrome are correlated to inflammatory markers including CRP, fibrinogen, and white cell count. hsCRP levels tend to be increased in subjects with insulin resistance and obesity. On the other hand, dyslipidemia, hypertension, low insulin sensitivity, and abdominal obesity tend to increase levels of CRP. In addition, glucose and macronutrient intake leads to inflammatory changes. In contrast, insulin displays anti-inflammatory effects (Dulloo & Montani, 2012; Esser, Legrand-Poels, Piette, Scheen, & Paquot, 2014; Paoletti, Bolego, Poli, & Cignarella, 2006).

Some natural events in the female body can also contribute to exacerbating the effects of inflammatory factors. Accordingly, it has been demonstrated that the WBC count may be affected by IL-1β and TNF-α levels (Liu et al., 2018). Considerable evidence indicates in the ovulation process, adequate amounts of reactive oxygen species (ROS) regulate the normal physiologic process, but an increase in ROS production alters the physiologic ovarian dynamics, and adversely affects reproductive functions. Unbalanced ROS production stimulates the inflammation signaling pathways, leading to cystic ovarian disorder and failure to normal ovulation (Boots & Jungheim, 2015). Another important mediator in chronic low-grade inflammation is CRP. CRP is an acute-phase protein produced in hepatocytes by stimulation of IL-6. Furthermore, positive correlations were found between the CRP level and central adipose tissue. The evidence obtained thus far indicates that CRP is increased in PCOS-affected women (Boulman et al., 2004). Keeping in these results in mind, considering the close relationship between chronic low-grade inflammation and PCOS, investigating the inflammation signaling can provide strong future insights regarding controlling PCOS and its treatment.

3.3.1 | Old players of chronic low-grade inflammation in PCOS

Interleukin-6

IL-6 is one of the major pro-inflammatory cytokines playing a key role in acute and chronic inflammation (Kaplanski, Marin, Montero-Julian, Mantovani, & Farnarier, 2003). IL-6 is an endocrine cytokine produced by various cells, such as mononuclear cells and adipose tissue cells. It also regulates the hepatic synthesis of CRP. IL-6, by recruitment of immune cells, leads to the persistence of inflammatory states. The level of IL-6 cytokine is closely associated with obesity, insulin resistance (IR), and cardiovascular diseases (Vgontzas et al., 2006). The serum level of IL-6 in women with PCOS is reported to be higher compared to healthy women. Obese women with PCOS have a higher level of IL-6 compared to nonobese women with PCOS. A high BMI leads to an augmentation of the level of IL-6. Also, it has been observed that the IL-6 level was related to the levels of insulin resistance (IR) and androgen (Lin et al., 2011). The secretion of IL-6 in adipocytes has been found to be associated with the size of the adipocyte. Therefore, following a weight increase, IL-6 is secreted more (Hotamisligil, 2006). Elevated IL-6 levels can be seen in the development of clinical coronary heart disease. A recent study showed an increase in IL-6 level is associated with ovary dysfunction (DESHPANDE, CHAPMAN, MICHAEL, DESHPANDE, & CHANG, 2000). It has been shown that IL-6 gene polymorphisms play a role in increasing the risk of insulin resistance with PCOS (Fernandez-Real et al., 2000). However, Walch. et al showed − 174G/C polymorphism of the IL-6 gene promoter is not associated with the initiation of PCOS (Walch et al., 2004). The evidence obtained thus far indicates that IL-6, as an inflammatory cytokine, positively correlates with obesity in PCOS women. According to the increased level of IL-6 in PCOS subjects, it is expected that further studies will suggest considerable ways to diminish its bad effects.

Tumor necrosis factor (TNF-α)

TNF-α as a pro-inflammatory cytokine is produced by many immune and nonimmune cells such as epithelial cells, endothelial cells, fibroblast cells, monocytes, and macrophages. However, it is mainly produced by adipose tissue macrophages. Following the increase of visceral adipose tissue, adipose tissue, as an endocrine organ augments the production of adipokines and TNF-α secretion (Fernández-Real & Ricart, 2003). Also, a recent study showed a possible link between insulin resistance and dyslipidemia (Kershaw & Flier, 2004). TNF-α showed a stimulatory effect on the expression of IL-6 in adipocytes (Rotter, Nagaev, & Smith, 2003). In animal models, observations have shown the soluble TNF-a receptor is able to decrease insulin resistance (Hotamisligil, Shargill, & Spiegelman, 1993). Actually, serine phosphorylation of IRS1 and reduction of GLUT-4 gene expression lead to disruption of insulin signaling (Stephens & Pekala, 1991). The level of TNF-α cytokine in the serum of women with PCOS was reported to be higher than that in healthy women. A high level of TNF-α can stimulate the proliferation of theca intra cells and lead to hyperplasia of follicles as well as increase their number. The mechanism of TNF-α is through the activation of the JNK pathway. TNF-α levels in the follicular fluid (FF) of PCOS patients are also higher than those of non-PCOS women (Amato et al., 2003). TNF-α reduces progesterone production by inhibiting the expression of genes involved in the production of progesterone, causing reduced ovulation. Also, Yamamoto et al. (2015) uncovered the TNF-α roles in the cell death of granulosa cells in apoptosis and autophagy. TNF-α affects thecal and granulosa cell steroidogenesis and luteal regression through inhibition of adenylyl cyclase (Terranova, 1997). A recent study illustrated pentoxifylline has anti-TNF-α properties, which through decreasing inflammation exerts protective effects on ovarian cells (Rezvanfar et al., 2015). It seems that it has been somewhat effective so far by targeting pro-inflammatory cytokines. However, further studies are required to indicate the effect of anti-inflammatory drugs on the complication of PCOS.

3.3.2 | The inflammasome complex mediators may be new players in PCOS

The inflammasome is a multimeric complex localized within the cytoplasm of the cell, and is assembled in response to danger signals such as cholesterol and calcium phosphate crystals, ATP, high mobility group box1, oxidative stress, heat-shock proteins, and pathogens (Christgen & Kanneganti, 2019). The innate immune cells, via pattern recognition receptors (PRRs), identify specific structures of pathogens known as pathogen-associated molecular patterns (PAMPs), as well as damaged cells that release to danger-associated molecular patterns (DAMPs). PRRs can be divided into membrane and intracellular subtypes, according to the location of cell receptors. Membranous PRRs are membrane proteins that include C-type lectin receptors (CLRs) and Toll-like receptors (TLRs), and can detect PAMPs and DAMPs. Other sources of PRRs are intracellular, including NOD-like receptor (NLR), RIG-I-like receptor, and ALR (Hashem et al., 2018; Nouri, Karkhah, Mohammadzadeh, & Sankian, 2016). The identification of inflammatory ligands by PRRs triggers the recruitment of an apoptosis-associated speck-like protein, containing a caspase recruitment domain (adipose tissue-derived stem cell [ASC]) protein that recruits caspase-1 in the inflammasome complex. The ASC has two domains: the pyrin domain and a caspase recruitment domain, which causes assembly of the inflammasome complex. Inflammasome complexes are classified into canonical and noncanonical categories. Canonical inflammasomes comprise NLRP1, NLRP3, NLRC4, AIM2, and PYRIN, and noncanonical inflammasomes comprise, NLRP6, NLRP12. In general, the formation of the inflammasome leads to the change of inactive procaspase-1 into an active cysteine protease enzyme caspase-1, which subsequently activates the pro-inflammatory cytokines, IL-1β and IL-18 (Abais, Xia, Zhang, Boini, & Li, 2015; Saadi et al., 2020). Most of the canonical inflammasomes have three components including a sensor component, an adaptor component, and an effector component. Sensor molecules include the NLRs and AIM2-like receptors (ALRs). The most common adaptor protein is ASC. The effector component is caspase-1. The effector component of noncanonical inflammasome includes caspase-1 and caspase-5 (Lu & Wu, 2015).

IL-1β and IL-18 as inflammasome products in PCOS

The exact mechanism by which stimulants can activate the inflammasome is still unknown. However, so far, studies have shown that the inflammasome is activated by release of oxidized mitochondrial DNA, DNA and RNA viruses, mitochondrial ROS, changes in intracellular calcium levels, potassium efflux (reduction in intracellular potassium), pore-forming toxins, excessive levels of ATP, uric acid crystals, silica, aluminum hydroxide, and asbestos. Recent observations showed ASCs from obese subjects are able to activate the NLRP3 inflammasome. Also, the gene expression of the NLRP3 inflammasome and caspase-1 in obese subjects was found to be higher than in lean subjects. Also, measurements of NLRP3 and IL-1β proteins are markedly high in T2D subjects (Esser et al., 2013; Munoz-Planillo et al., 2013). Other results showed gene expression of IL-1β, IL-18, and NLRP3 were increased in visceral adipose tissue of metabolic disorders subjects. Recent studies have showed that the dysregulation of inflammasome activity plays a role in many diseases such as, cancer, metabolic diseases, and some neurodegenerative diseases (Esser et al., 2013; Rostamtabar et al., 2020).

IL-1β roles in PCOS

IL-1β as an inflammatory cytokine plays an important role in ovulation and fertilization, by regulation of steroidogenesis. Considerable evidence indicates that the PCOS is an inflammatory syndrome. Further data confirmed its association with increasing of IL-1β levels (Zafari Zangeneh, Naghizadeh, & Masoumi, 2017). The IL-1 family has 11 member proteins (IL-1F1 to IL-1F11), whose first members are, IL-1a (newly named IL-1F1) and IL-1 β (IL-1F2). IL-1β is a potent pro-inflammatory cytokine, and is secreted by monocytes, macrophages, and epithelial cells. The signaling pathway in the IL-1 family involves

the IL-1 receptor (IL-1RI and IL-1RII) and the activation of MAPK kinases, myeloid differentiation primary response gene 88 (MYD88), IL-1 receptor-associated kinase 4 (IRAK4), transcription factors NF-κB, and activator protein (AP-1; Sims et al., 2001). It has been observed that in cases with PCOS, the level of IL-1β and expression of the receptor are increased (Kolbus et al., 2007). Studies showed that increased levels of glucose could lead to increased expression of IL-1β. Also, insulin is able to stimulate IL-1β production by macrophages through glucose metabolism (Dror et al., 2017). Studies demonstrated that IL-1β leads to the triggerring of follicle rupture in the absence of gonadotropin in the rabbit ovary (Takehara, Dharmarajan, Kaufman, & Wallach, 1994). IL-1β leads to an increased production of progesterone and PGF2a in rat follicles. A recent study showed mRNA expression of IL-1β in the theca layer to be higher than stromal cells (Ono et al., 1997). It has been demonstrated that IL-1β plays a role in the ovulatory process by increasing hyaluronic acid and proteoglycan biosynthesis (Kokia, Hurwitz, Ben-Shlomo, Adashi, & Yanagishita, 1993). Studies showed the expression of IL-1β in granulosa cells increases under the influence of gonadotropins. Also, the role of IL-1β has been confirmed in follicle maturation (Martoriati & Gérard, 2003). Taken together, these findings indicate that due to the dysregulation of ovulation, production of IL-1β in most PCOS subjects is increased.

IL-18 roles in ovulation and PCOS

The IL-18 family includes the IL-18 and IL-18-binding proteins (IL-18BP). The structure of IL-18 is similar to the IL-1 family. The role of IL-18 has been confirmed in the pathophysiology of inflammatory diseases. In humans, the IL-18 induces the Th1 response that produces interferon-γ (IFN-γ). IL-18 is synthesized from a precursor molecule and is subsequently cleaved by caspase-1 before or during release from the cell (Olee, Hashimoto, Quach, & Lotz, 1999). It has been indicated that IL-18 might be produced by adipose tissue. Hence, the level of IL-18 is increased in women with obesity and insulin resistance. Also, it seems that hyperandrogenism is a crucial factor for increasing IL-18 levels. IL-18 is also a pro-inflammatory cytokine and is a risk marker for cardiovascular disease (Escobar-Morreale, Botella-Carretero, Villuendas, Sancho, & San Millan, 2004). Studies showed IL-18 levels are increased in overweight, diabetes, and PCOS. Veronika Günther et al. reported a clear correlation between serum levels of IL-18 and BMI (Gunther et al., 2016). It has been shown that ovulation is a quasi-inflammatory process, which is associated with increased vascular infiltration, cyclooxygenase 2 (cox-2), and an increase in the expression of inflammatory cytokines (Bartlett, Sawdy, & Mann, 1999). Tsuji et al. confirmed the role of IL-18 in the process of ovulation. Indeed, they discovered that the expression of IL-18 and its receptor were increased in mature ovaries. Also, they observed IL-18 expression in the corpus luteum. It has been observed that IL-18 and IL-18R are involved in ovulation, due to this, administration of anti-inflammatory drugs has inhibited ovulation in mice (Tsuji et al., 2001). Also, other studies showed IL-18 levels in FF correlate with the response to ovarian stimulation, and play a significant role in successful pregnancy after IVF treatment (Gunther et al., 2016). The findings of a recent study indicate that IL-18 plays an important role in follicular dynamics. In conclusion, it is suggested that the therapeutics taking effect via neutralizing excess IL-18 activity in ovarian dysfunction be further developed.

3.3.3 | Other inflammatory cytokines and chemokines may be involved in PCOS

IL-17 in PCOS

IL-17 is an inflammatory cytokine associated with inflammatory diseases. It consists of six members from IL-17A to IL-17F (IL-17A, IL-17B, IL-17C, IL-17D, and IL-17E [IL-25]). Members of the IL-17 family are predominantly produced by Th17 cells. But, IL-17E is produced by Th2 cells and promotes the activity of the Th2 pathway. IL-17A, as a prototype member of the IL-17 family, leads to the recruitment of immune cells and induces expression of chemokines, affecting the inflammatory state by producing IL-6 and IL-8 (CXCL8) cytokines (Shabgah, Fattahi, & Shahneh, 2014). In accordance with what has been said, obesity may correlate with low-grade systemic inflammation and infiltration of macrophages in adipose tissue, and increase in pro-inflammatory markers. IL-17, in adipose tissue macrophages, plays a role in the development of the inflammatory state via stimulating the secretion of IL-1β, TNF-α, and IL-6. IL-17A is able to exert a role in inflammatory processes by affecting the adipogenesis and glucose metabolism (Shin, Shin, & Noh, 2009). Recent studies have illustrated that IL-17A and IL-17F levels in PCOS patients were elevated. Increase in the TNF-α level can promote IL-17A production. Moreover, IL-17E levels were decreased in PCOS subjects in comparison with healthy subjects. Furthermore, inflammation in gingiva correlated with IL-17A level in PCOS patients (Ozcaka et al., 2012). It has been reported that IL-17A, as a pro-inflammatory cytokine, may be related to infertility in PCOS subjects (Ozcaka et al., 2012). To date, it seems that there has not been much research on the effect IL-17 on PCOS. Nonetheless, it is expected that the combination of drugs from inflammatory cytokines will be taken on the path of treating this disease.

IL-33 in PCOS

IL-33, as a novel cytokine, is involved in the pathogenesis of PCOS. It seems to be closely linked to oxidative stress. The findings of a recent study imply a significant role of IL-33 in follicular dynamics and fertilization. It is a member of the IL-1 family, which is expressed in epithelial cells, endothelial cells, and high endothelial venules, following inflammatory conditions (Moussion, Ortega, & Girard, 2008). Involvement in suppression of tumorigenicity 2 (ST2), a member of IL-1 receptor family, was defined as due to the IL-33 receptor, and resulted in the induction of signaling, and recruitment of MyD88 and NF-κB and/or MAPK. ST2 has two forms, soluble ST2 (sST2) and trans-membrane receptor (ST2L; Tago et al., 2001). Tissue damage, oxidative stress, high free fatty acids, and inflammation can lead to the release of the active form of IL-33. The IL-33 was able to reduce lipid uptake in adipocytes via downregulation of several

metabolic genes. Furthermore, it is likely that IL-33 mediates the production of Th2 cytokines and activation of macrophages with the M2 phenotype in adipocytes, and in turn, these have a protective impact on obesity and diabetes (Kakkar & Lee, 2008). IL-33 levels are elevated in women with PCOS, and this seems to be higher in most PCOS women with hyperandrogenism. So far, no studies have been performed on the IL-33 cytokine to reduce its effects in patients with PCOS. Further research aiming to understand the role of IL-33 in the PCOS is warranted.

Chemokines (MCP-1 and MIF) involved in PCOS

It seems that in PCOS, chemokines, as well as their role in the ovulation process have been extensively studied. Chemokines are proteins that are produced in response to inflammatory signals, and lead to the recruitment of monocytes, neutrophils, and lymphocytes in the target sites. Chemokines are classified into four subfamilies such as CXC, CC, CX3C (neurotactin), and C (Rollins, 1997). The MCP-1 is a member of the CC Chemokines family. MCP-1 (CCL2) is produced by a diversity of cell types, and acts as a potent factor for monocyte recruitment to the target site of inflammation (Deshmane, Kremlev, Amini, & Sawaya, 2009). IL-8 is a member of the CXC chemokine family and is mainly involved in neutrophil recruitment and migration. Studies have illustrated that MCP-1 may be involved in follicular dynamics (Dahm-Kähler, Runesson, Lind, & Brännström, 2006). IL-1 in FF exerts a significant role in the ovulatory process. Also, MCP-1, with the recruitment of monocytes and macrophages in FF, acts as a potent source of IL-1 production, and could be involved in the regulation of ovulation process (Takehara et al., 1994). In the chronic inflammatory state, the level of inflammatory markers including, MCP-1, macrophage inflammatory protein-1β (MIP-1β), and pro-inflammatory cytokines IL-1β, IL-6, TNF-α, and IL-18 were significantly increased (Zirlik et al., 2007). Given that the PCOS is associated with the chronic inflammatory condition, it is expected to be associated with the elevation of these inflammatory markers (Dahm-Kähler et al., 2006). The increase of obese tissue is associated with hypoxia and thereby augments the expression of MCP-1 and plasma level of MCP-1. It is believed that in obese PCOS patients, hypoxia may be a key factor that is involved in the development of the inflammatory pathways. Also, the hyperglycemic condition followed by insulin resistance is associated with overexpression of MCP-1. It is expected that the inflammation process can be more activated by the increase of glucose level in the PCOS cases with insulin resistance.

3.3.4 | Other inflammation mediators

Adipokines (leptin, adiponectin, vaspin, resistin, visfatin, omentin-1, and chemerin)

Adipocytes act as a dynamic endocrine organ and secrete many adipokines such as leptin, adiponectin, resistin, vaspin, visfatin, omentin-1, chemerin, lipocalin-2, and pro-inflammatory cytokines (e.g., TNF-α and IL-6). Given that PCOS is mostly associated with obesity, adipokines are likely to be involved in the pathogenesis of the disease. Leptin is mainly produced by white adipose tissue and shows pro-inflammatory properties. Its concentration in the plasma is linked to the storage of adipose tissue, and following increase of adipose tissue, the expression of leptin is increased. In fact, the main role of leptin is the control of food intake. Studies also showed that mutation in the gene of leptin and its receptor causes obesity (Fantuzzi, 2005; Oswal & Yeo, 2010). A recent study demonstrated BMI to be linked to the leptin level, and leptin concentration in women with PCOS was higher than healthy subjects (Sepilian, Crochet, & Nagamani, 2006). An increase in the level of leptin in the blood is a potential risk factor for the development of metabolic syndrome. In cases affected by both insulin resistance and PCOS, insulin leads to augmented leptin secretion via increase in androgen production. Indeed, the concentration of testosterone is linked to leptin expression (Brzechffa et al., 1996). Recent studies have disclosed a positive correlation between the IL-6 and TNF-α level with leptin concentration (Shen, Sakaida, Uchida, Terai, & Okita, 2005). Additionally, some studies suggested pro-inflammatory cytokines such as TNF-α and IL-1β lead to upregulated leptin expression (Iikuni, Lam, Lu, Matarese, & La Cava, 2008). In PCOS, it is expected that due to the increase in pro-inflammatory cytokines and chronic inflammation, leptin levels are increased. Adiponectin shows anti-inflammatory properties by decreasing the expression of inflammatory mediators (Ouchi & Walsh, 2007). Adiponectin is negatively correlated with the volume of adipose tissue. Moreover, an increase in adiposity is associated with downregulation of adiponectin (Groth, 2010). Some studies showed that regardless of obesity, the expression of adiponectin in subjects with PCOS is lower than healthy subjects (Carmina et al., 2008). It seems that an increase in the androgen concentration and insulin resistance status in PCOS is correlated with low adiponectin levels. Nonetheless, further studies are needed to evaluate adiponectin roles in the PCOS disease.

Vaspin is another adipokine with anti-inflammatory effects. It has been shown to correlate with body mass index (BMI) and increases the serum vaspin level in obesity. Given most subjects with PCOS are obese, they are expected show increased levels of its expression and contribute to the pathogenesis of the disease. Recent studies of obesity in cases with T2D have shown that vaspin levels in obese subjects with T2D are higher than normal subjects (Youn et al., 2008). Vaspin has a protective role in the development of atherosclerosis through inhibition of NF-κB activation and decrease in expression of adhesion molecules in the endothelium (Jung et al., 2014). Vaspin also plays a role in insulin sensitivity and its properties decrease insulin resistance. Indeed, increase in vaspin expression may present as desensitivity to insulin (Q. Li et al., 2008). Studies have suggested that the PCOS status positively correlates with increased vaspin concentration (Cakal, Ustun, Engin-Ustun, Ozkaya, & Kilinç, 2011). Another study showed that there was no correlation between PCOS and vaspin levels (Guvenc, Var, Goker, & Kuscu, 2016). However, the effect of vaspin in the pathogenesis of PCOS has not been clearly specified, and further studies are needed to determine the effects of this hormone on adipose tissue and metabolism.

In addition to the adipose tissue, resistin is produced by monocytes and macrophages. Pro-inflammatory mediators such as IL-1β,

IL-6, and TNF-α induce the expression of Resistin in the monocytes and macrophages. In PCOS, the expression of pro-inflammatory cytokines is increased, and it is likely that these cytokines are associated with augmented levels of resistin. Moreover, a recent study demonstrated that increase in androgen levels, specially testosterone, shows a positive correlation with resistin (Smitka & Marešová, 2015). Resistin plays an important role in the pathogenesis of T2D, cardiovascular diseases, rheumatoid arthritis, and PCOS by stimulation of the NF-κB pathway (McTernan et al., 2002; Spritzer, Lecke, Satler, & Morsch, 2015). Recently, it has been reported that the serum levels of resistin were linked to adipose tissue. Moreover, these levels were found to be higher in obese or overweight subjects with PCOS compared with lean subjects (Escobar-Morreale et al., 2006). In contrast, another study illustrated a lack of correlation between obesity and resistin levels (Panidis et al., 2004). Nevertheless, with discrepancies in the results in mind, further studies on the role of this hormone in PCOS are needed.

Visfatin is another adipokine associated with the upregulation of inflammatory mediators and low-grade inflammation. It has also been suggested that visfatin positively correlates with the adipose tissue and BMI. Increased Visfatin levels link to obesity, metabolic syndrome, T2DM, and PCOS. Visfatin, by stimulating the expression of MCP-1, leads to an increase in inflammatory macrophage in adipose tissue. Several studies demonstrated visfatin exerts a significant role in the development and progression of atherosclerosis (S. R. Kim, Bae, et al., 2008). Considering the fact that the increase of the androgen level as well as obesity is present in many PCOS subjects into account, an increase in visfatin levels is conceivable (Plati et al., 2010). Recent studies showed serum visfatin levels may be elevated in obese PCOS subjects (Dikmen, Tarkun, Canturk, & Cetinarslan, 2011). Several reports have suggested that visfatin is expressed on granulosa cells and is additionally involved in the regulation of the ovarian function. Visfatin, independent of the BMI and total testosterone ratio, may be involved in the pathogenesis of PCOS and is an intrinsic characteristic of PCOS (Y. Sun et al., 2015). According to recent research, to better understand the effect of this adipokine on the pathogenesis of PCOS, further studies are needed.

Another adipokine is omentin that, in addition to adipocytes, is expressed in the ovaries and heart. Its plasma levels were decreased in obesity-related diseases such as diabetes, metabolic syndrome, atherosclerosis, and PCOS (Ozgen et al., 2019). In adipocytes, it is involved in insulin function via the stimulation of glucose uptake by insulin. The obesity status is associated with the downregulation of omentin expression, and thereby the plasma concentration of omentin was decreased (Moreno-Navarrete et al., 2010). The omentin exerts anti-inflammatory effects by the inhibition of COX-2 expression and NF-κB activation (Yamawaki et al., 2011). It is expected that with anti-inflammatory drugs, it can be taken to control inflammation.

Chemerin is another adipokine with pro-inflammatory effects. Chemerin is predominantly produced by adipose tissue, and its receptors (ChemR 23, CMKLR1) are expressed on adipocytes, dendritic cells, macrophages, and endothelial cells (Ozgen et al., 2019). Chemerin leads to the development of the inflammation state by recruitment of immune cells (Wittamer et al., 2003). Studies have shown omentin is implicated in the processes of follicular steroidogenesis, and leads to ovarian dysfunction. The serum chemerin levels seem to be increased in PCOS (Wang et al., 2012). A recent report has suggested that obese PCOS subjects show a higher concentration of chemerin compared with obese subjects without PCOS (Guzel et al., 2014). It is hoped that further studies on the role of adipokines in the pathogenesis of PCOS lead to new therapeutic approaches through relying on them to reduce the inflammatory pathway.

Cyclophilin A (CyPA)

CyPA is a member of the immunophilin family and is secreted from various cell types in inflammatory conditions. Oxidative stress, ED, and a high level of C-reactive protein (CRP) may augment the expression level of CyPA (Ramachandran & Kartha, 2012). It has been reported that CyPA plays a critical role in the development of atherosclerosis by induction of MCP-1 and recruitment of monocytes. A recent study suggested that an increased expression of CyPA is able to induce TNF-α, IL-8, IL-6, and IL-1β expression. Evidence suggested CyPA increases the proliferation of vascular smooth muscle cells (VSMCs) and accelerates atherosclerosis (Payeli et al., 2008). Chronic hyperglycemia in diabetes is associated with the pro-inflammatory state. Increased ROS correlates with high expression of CyPA. It seems that PCOS subjects with insulin resistance have higher CyPA levels and, expression of NF-κβ was elevated in them (S. Sun et al., 2014). Given that PCOS is associated with chronic low-grade inflammation, CyPA expression is expected to increase in PCOS. Recent studies have shown that in spite of the positive correlation between hsCRP level and PCOS, the CyPA level in PCOS patients not increased (Usta, Taskin, Baykan, & Adali, 2018). This suggests that further research may be needed to evaluate the correlation between CyPA and PCOS.

Endothelial/vascular dysfunction mediators in PCOS

Chronic inflammation is closely linked to ED, cardiovascular disease (CVD), coronary artery disease, and PCOS. Studies have disclosed the role of metabolic syndrome, hypertension, hypercholesterolemia, high levels of lipoprotein (LDL), and hypertriglyceridemia in the development of CVD. Endothelin-1 (ET-1) has many biological activities and is mainly produced by the endothelin-converting enzyme-1 (ECE-1). Recent reports have suggested ECE-1 is highly expressed in the luteinizing granulosa and theca interna cells, representing the significant role of ET-1 in ovarian dynamics (Yoshioka et al., 1998). It has been demonstrated that ET-1 is involved in the pathogenesis of PCOS (Diamanti-Kandarakis, Spina, Kouli, & Migdalis, 2001). ET-1 plays a critical role in the development of an inflammatory state by increase in intercellular adhesion molecule-1 (ICAM-1) expression on endothelial cells. In PCOS subjects, ET-1 concentration is increased independent of being overweight. Moreover, this indicates the role of ET-1 as an intrinsic characteristic of PCOS. In insulin resistant subjects with PCOS, the hyperglycemic status has been found to be

associated with the overproduction of ROS, and related to modified gene expression and upregulation of ET-1 (Matsumoto, Kobayashi, & Kamata, 2008). Inflammatory mediators such as CRP, oxidative stress, TNF-α and IL-6 are major contributors to chronic inflammation and lead to an increased expression of soluble ICAM- and vascular cell adhesive molecule-1 (Habas & Shang, 2018). Moreover, given the high expression of several adipokines including, resistin, chemerin, and visfatin in PCOS, the expression of soluble cellular adhesion molecules are increased (Mariana Cornelia, Eniko Csilla, Gizella Tusa, & Eniko, 2018). It is expected that according to studies on the role of adhesive molecules in the spread of inflammation, using drugs targeting adhesion molecules can reduce inflammation and control the activation of inflammatory pathways.

NF-κB and peroxisome proliferator-activated receptor-γ (PPARγ) signaling in PCOS

PCOS is considered as a pro-inflammatory state and is associated with an increased expression of the NF-κB transcription factor. Activation of NF-κB signaling is amplified by many stimulants including oxidative stress, hyperglycemia, hyperinsulinemia, chemical agents, hormones, and inflammatory cytokines. In PCOS, cases with increased levels of pro-inflammatory cytokines including TNF-α, IL-1, IL-6, and IL-18 NF-κB expression are stimulated (González, Rote, Minium, & Kirwan, 2006). Recent evidence suggested NF-κB pathway signaling in PCOS cases with insulin resistance and hyperglycemia is further activated compared to PCOS patients without insulin resistance. Also, obesity, especially in visceral adipose tissue, plays a significant role in activating the NF-κB pathway (Kriketos et al., 2004). Hyperglycemia and excess visceral adipose tissue lead to an increased stimulation of ROS, which are able to trigger the NF-κB activation and increase the transcription of the inflammatory cytokines genes. NF-κB also by stimulating the expression of enzymes involved in the inflammatory process, results in development of inflammation. Recent studies have shown that in obese PCOS subjects, the NF-κB expression was more than than in lean subjects (Malin, Kirwan, Sia, & Gonzalez, 2015). In addition, both NF-κB and AP-1 by the increase in the M1 phenotype macrophage, augment the inflammatory state in adipose tissue (Chandra, 1997). It is expected that a combination of anti-inflammatory drugs from inflammatory cytokines and the regulation of the NF-κB pathway are effective steps towards controlling PCOS.

Another transcription factor is PPARs and acts in adipogenesis, lipid metabolism, and inflammation. PPARγ is a member of the nuclear receptor superfamily and known as NR1C3. It is mainly expressed iin adipose tissue and acts in lipid metabolism. Obesity is associated with an increase in free fatty acids (FFA) which increase the expression of PPARγ (Guilherme, Virbasius, Puri, & Czech, 2008). A recent study showed knock out of the PPARγ gene is positively correlated with insulin resistance (Kosteli et al., 2010). Studies have also disclosed that PPARγ is affected by diet and high-fat nutrition as well as being linked to an increase in the activation of PPARγ, and thereby weight gain (Ryan et al., 2011). Given that human granulosa cells play a vital role in the maturation of oocytes, it seems that the expression of PPARγ in these cells plays an effective role. It is also effective in expressing the IGF gene in ovarian granulosa cells in the steroidogenesis process, and plays a critical role in follicular dynamics (Kokosar et al., 2016). Another study illustrated gene polymorphisms in the PPAR-γ gene are correlated with PCOS occurrence. However, the role of PPARγ in PCOS has not been fully understood (Dasgupta et al., 2012). A recent study has illustrated the expression of PPARγ in PCOS cases is lower than in healthy cases, hypothesizing that an increase of LH and testosterone leads to the decrease of PPARγ level in ovarian granulosa cells. Indeed, an abnormal regulation between PPARγ and LH levels may be linked to the development of PCOS (Cao, Maowulieti, & Yu, 2019). Nonetheless, nonsteroidal anti-inflammatory drugs (NSAIDs) and thiazolidinediones (TZDs) seem to show beneficial clinical effects in reducing inflammation by targeting PPARγ (Lehmann et al., 1995). The discovery of the effect of PPARγ on the pathogenesis of this disease needs further research.

Matrix metalloproteinase-2 (MMP-2) and MMP-9 in PCOS

Other factors including MMP-2 and MMP-9 are the most common components of the extracellular enzymes in the tissue remodeling of the ovary and vascular matrix. Followed by the breakdown of the follicle wall and expulsion of the oocyte, the level of TNF-α is increased, leading to the expression of MMP-2 (gelatinase A) and increasing its activity (Creemers, Cleutjens, Smits, & Daemen, 2001; Gottsch, Van Kirk, & Murdoch, 2000). Increased circulating levels of MMP-2 and MMP-9 (gelatinase B) may be linked to the abnormal follicular dynamics and development of cardiovascular disease in PCOS subjects (Lewandowski et al., 2006). On the other hand, a recent study by Gomes et al. disclosed the circulating concentrations of MMP-2 and MMP-9 in PCOS patients were lower than the healthy control subjects (Gomes et al., 2011).

3.4 | Oxidative stress and antioxidants in PCOS

The term oxidative stress is defined as an augmentation of ROS, in which the balance of oxidation and antioxidants is altered and the amount of oxidant species increases. Mounting evidence points out that oxidative stress may be observed in many disorders such as obesity, diabetes, PCOS, and metabolic syndrome-related disease. The obtained evidence indicates that PCOS is associated with an imbalance between oxidant and antioxidant in favor of the oxidant. This eventually leads to oxidative stress conditions. Many factors are involved in the development of oxidative stress including, adipose tissue, defects in mitochondrial metabolism, fatty acid oxidation, and hyperglycemia (Murri, Luque-Ramirez, Insenser, Ojeda-Ojeda, & Escobar-Morreale, 2013). In PCOS patients with insulin resistance, the expression and activity of NADPH oxidase and inducible nitric oxide synthase (iNOS) are increased followed by hyperglycemia. It seems that increased ROS generation is more significant in obese cases of PCOS compared to lean subjects. Although oxidative stress has a detrimental effect, it plays an important role in the regulation of ovulation and follicular dynamics,

and is also known to be involved in cellular processes via the activation of protein kinases and transcription factors (Miyamoto et al., 2010). There are numerous reports that indicate the ROS modulates the process of ovulation. But, PCOS is associated with the decrease of antioxidants and maintenance of the oxidative status and inflammatory state. Generally, antioxidants play a role in the reduction of ROS, which stimulate the activation of inflammation signaling and improve the management of PCOS by scavenging of ROS. Also, intriguingly, recent studies have shown that antioxidants, by reducing the damage caused by free radicals on oocytes, cell maturation, and other physiological mechanisms in female fertility, may be involved in fertility of PCOS women. Moreover, it has been discovered that gradual use of oral antioxidant supplementations modulates the side effect of insulin excess and generation of free radicals by increasing insulin sensitivity, indicating that they play a role in the improvement course of PCOS (Amini, Tehranian, Movahedin, Ramezani Tehrani, & Ziaee, 2015; Mohammadi, 2019). *N*-Acetyl-cysteine as an antioxidant plays an important role in the PCOS via increasing insulin sensitivity and induction of ovulation (Gayatri, Kumar, & Kumar, 2010). It is also demonstrated that melatonin, as an effective factor, may be able to promote of oocyte's quality and improved reproduction (Eryilmaz et al., 2011). Although numerous studies have been conducted to uncover the role of antioxidants in the ovulation process, they have been relatively effective. However, further investigation is required in the future.

3.5 | microRNAs (miRNA) and PCOS

miRNA are noncoding RNA molecules that interfere in the regulation of gene expression. miRNAs are present in human body fluids including serum and FF (Sang et al., 2013). Expression of miRNA-132 (miR-132) in adipocytes induces the expression of IL-8 and MCP-1 (Strum et al., 2009). miR-144 and miR-513a-3p expression was also observed in oocyte maturation, and was upregulated in woman with PCOS (Haouzi et al., 2012). In addition, miR-27 is involved in the inflammatory process via activation of the NF-κB pathway and oxidative stress. miR-27 also plays a role in lipid metabolism by induction of lipoprotein lipase (Chen, Yin, Zhao, Fu, & Tang, 2012). Also, other studies demonstrated gene expression of miR-32, -34c, -135a, -18b, and -9 are increased in the PCOS subjects (Roth et al., 2014). miR-93 is involved in insulin resistance and development of the disease via downregulation of GLUT-4 gene expression in adipose tissue of subjects with PCOS, and has been suggested to be a biomarker for the diagnosis of PCOS (Sathyapalan, David, Gooderham, & Atkin, 2015). Furthermore, miRs are involved in normal ovarian function through the regulation of granulosa cells proliferation (Xu, Zhang, Tong, & Liu, 2015). miRNAs have been shown to play important roles in ovarian follicular dynamics and pathophysiology of PCOS (Xu et al., 2015). The difference in miRNAs expression pattern has been established between PCOS and health subjects, but so far, they have not been utilized in prognostic or diagnostic assays.

4 | TREATMENT AND FUTURE INSIGHT

Most drugs for the treatment of PCOS act through increasing insulin sensitivity and the reduction of insulin levels. Insulin sensitizer drugs like metformin lead to increased insulin sensitivity by inhibition of hepatic glucose production and a decrease in glucose uptake. Metformin, by decreasing insulin levels, reduces the activity of cytochrome P450c-17α, causing a decrease in androgens' synthesis, and hence, decreasing levels of androgens in plasma (Nestler & Jakubowicz, 1996). Metformin also plays an anti-inflammatory role by inhibiting phosphorylation of IκB and activating NF-κB (S.-N. Li et al., 2009). Recent studies suggest that treatment with metformin cannot significantly increase ovulation and the likelihood of pregnancy in infertile women with PCOS (Sahin, Yirmibeş, Keleştimur, & Aygen, 2004). Metformin leads to an increase in insulin sensitivity by upregulation of the let-7 family miRs (Frost & Olson, 2011). Also, let-7 miRs may protect PCOS patients against inflammation (Coleman et al., 2013). Hence, in the future, scientists should further focus on drugs that interfere with inflammation mediators such as cytokines and chemokines, which are involved in development of PCOS.

5 | CONCLUSION

Although ovulation is a semi-inflammatory state, uncontrolled inflammation can lead to the development of PCOS. However, the role of inflammatory factors including inflammasome-related cytokines (IL-1β and IL-18), along with IL-6 and TNF-α, is well-established. Nevertheless, other inflammatory factors are also quite effective in the development of PCOS. It is hoped that these inflammatory mechanisms will become more prominent, and in the future, more attention will be directed towards stopping these pathways through designing new therapies.

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CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

M. R., S. E., M. T., and H. N. performed the systematic search, and interpreted the results. All authors drafted the manuscript and collected the relevant literature. K. S. made the figures and illustrations; H. N. designed and supervised this study.

DATA AVAILABILITY STATEMENT

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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