Review

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Polycystic ovary syndrome and adverse pregnancy outcomes: Potential role of decidual function

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SUMMARY Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting fertility and mental health among women of reproductive age. In addition to anovulation and hyperandrogenism, patients also experience metabolic issues, such as insulin resistance, obesity, and dyslipidemia, as well as chronic low-grade inflammation throughout the body. Recent studies have shown that even with assisted reproductive technology to treat anovulatory issues, patients with PCOS still have higher rates of adverse pregnancy outcomes and abortion compared to normal pregnancies. These findings suggest that PCOS may impair the endometrium and disrupt the onset and maintenance of healthy pregnancies. Decidualization is a crucial step in the process of healthy pregnancy, during which endometrial stromal cells (ESCs) differentiate into secretory decidual stromal cells (DSCs) regulated by hormones and local metabolism. This article comprehensively reviews the pathological processes of PCOS and the mechanisms involved in its impaired decidualization. In addition, we explore how PCOS increases the incidence of adverse pregnancy outcomes (APO). By gaining a better understanding of the adverse effects of PCOS on pregnancy and its specific mechanisms, we hope to provide a theoretical basis for reducing APO and improving the live birth rate among women with PCOS.

Keywords polycystic ovary syndrome, decidualization, adverse pregnancy outcomes, insulin resistance, inflammation

1. Introduction

Polycystic ovarian syndrome (PCOS) is the most prevalent reproductive endocrinopathy affecting women of reproductive age, with a predicted prevalence of 6%-10%, based on diagnostic criteria (*1*). PCOS is known for causing fertility-related challenges such as decreased fecundity, anovulation or oligo-ovulation, reduced oocyte competence, and impaired endometrial receptivity (*1-3*). The increased risk of adverse pregnancy outcomes and iatrogenic ovarian hyperstimulation syndromes are linked to PCOS patients' greater prevalence of assisted reproductive technologies (ARTs) (*4*). Additionally, pregnant women with PCOS are more likely to experience pregnancy- and neonatal-related problems (*5,6*). Research has shown that pregnant women with PCOS experience a 3 to 4 times higher incidence of gestational hypertension (GHTN), pre-eclampsia (PE), and gestational diabetes mellitus (GDM) compared to healthy women (*6-8*). Studies showed greater risk of miscarriage, preterm delivery, and intrauterine growth restriction (IUGR) among women who experience these adverse pregnancy outcomes (*9*). These unfavorable effects are thought to be caused by PCOS-affected women's aberrant hormone levels and metabolic malfunction. Previous systematic reviews and meta-analyses have linked PCOS in pregnancy with higher fasting blood glucose (FBG) levels, decreased levels of high-density lipoprotein (HDL), and high levels of serum androgen (*10,11*). As pregnancy progresses, mothers experience a natural increase in insulin resistance (IR) and androgen levels to supply energy to the growing fetus (*12*) and regulate critical processes during pregnancy and childbirth (*13*). However, in women with PCOS, the imbalance of beneficial and adverse effects of endocrine changes can lead to pathological alterations, resulting in an overexpression of metabolic pathways and potentially causing adverse outcomes for the pregnancy, fetal growth, and neonatal health (*14*).

Establishing the maternal-fetal interface as well as sustaining and growing the placenta depend on the decidualization of endometrial stromal cells (*15*). Due

to the heterogeneous phenotype of PCOS patients and multiple confounding factors, the pathogenic mechanisms of PCOS for adverse pregnancy outcomes are difficult to identify with precision. However, new literature reports progressively point to negative effects of PCOS on endometrial stromal cell decidualization impairment during the first trimester of pregnancy. This review summarizes current knowledge on PCOS-related decidualization impairment and discusses the role of decidualization in adverse pregnancy outcomes for women with PCOS.

2. The impact of PCOS on pregnancy

2.1. PCOS

PCOS is a complex and heterogeneous disease. The Rotterdam criteria requires the presence of at least two out of three features: oligo- or anovulation, hyperandrogenism (HA), and polycystic ovary morphology observed *via* ultrasound (*16*). The condition is lifelong and can have origins in fetal life, often being associated with intrauterine growth retardation or post-term birth (*17*). PCOS is characterized by reduced reproductive capacity and endocrine disturbances. The former includes infertility and adverse pregnancy outcomes, and the latter involves alteration in the levels of sex hormones as well as their stimulating hormones and clinical or laboratorial metabolic disorders such as IR, type II diabetes, dyslipidemia and a higher risk of cardiovascular disease. We hypothesized that the hormonal and metabolic disorders presented in PCOS patients may be the intrinsic pathological factors causing pregnancy disorders. We focus on the decidualization process in particular since it is essential for the creation and maintenance of pregnancy. And the specific molecular mechanisms of which will be described in detail later.

2.2. Pathogenic factors of PCOS

HA is a defining characteristic of PCOS, contributing to hormonal dysregulation and the development of small follicles in the ovaries. IR is a common metabolic disturbance in PCOS, characterized by impaired insulin sensitivity and elevated insulin levels. HA and IR influence each other, exacerbating PCOS symptoms. The interplay between IR and HA serves to accelerate the progression of PCOS symptoms in affected women (*18*). IR has been shown to contribute to androgen excess in PCOS through various mechanisms, including the upregulation of Gonadotropin-releasing hormone (GnRH) expression and enhancing the stimulating effects of Luteinizing hormone (LH) (*19*), inhibition of Sex Hormone-Binding Globulin (SHBG) release from the liver (*20*), and upregulation of aldo-keto reductase type 3 (*AKR1C3*), increasing adipose tissue testosterone production (*21*). Contrarily, the HA found in PCOS patients has been demonstrated to alter the phosphorylation patterns of Akt and protein kinase C (PKC), as well as reduce the production of the proteins glucose transporter type 4 (GLUT4) and insulin receptor substrate 1 (IRS-1) associated to tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6) (*22-24*). Obesity and dyslipidemia are closely linked to PCOS, with obesity playing an integral role in its development. Dyslipidemia, characterized by abnormal lipid levels in the blood, promotes IR. Dyslipidemia in PCOS is characterized by the impaired inhibition of free fatty acid (FFA) release in response to insulin, increasing levels of low-density lipoprotein cholesterol (LDL-C)/triglycerides (TG) with decreasing high-density lipoprotein cholesterol (HDL-C) (*25*). PCOS is also recognized as a chronic low-grade inflammatory disease, with elevated levels of inflammatory markers. HA and IR stimulate the inflammatory pathway, leading to oxidative stress and chronic inflammation.

In summary, PCOS is characterized by hyperandrogenism, IR, obesity-related dyslipidemia, and chronic inflammation. These factors interact and contribute to the pathophysiology of this syndrome (Figure 1).

2.3. The impact of PCOS on pregnancy outcomes

PCOS and its manifestations potentially infer high-risk pregnancies, leading to a series of adverse maternal outcomes (*26*). The two main adverse maternal outcomes are hypertensive disorders during pregnancy (HDP) and GDM. Meta-analyses have reported higher risks for GDM and HDP in women with PCOS, especially PE compared to normal controls (*27,28*). Studies have shown that GDM is independently associated with PE in singleton pregnancies, and we speculate that there may be a common pathogenic factor of GDM and PE in women with PCOS.

The effects of PCOS on fetal growth have been linked to meconium aspiration, very preterm birth, and low Apgar scores (< 7) at five minutes (*29*). Large for gestational age (LGA) and small for gestational age (SGA) infants were more likely to be born to moms with PCOS. Animal experiments have demonstrated that IR and hyperinsulinemia are able to cause increased fetal size (*30*). It is also suspected to lead to higher LGA birth risk in human with PCOS. Although some studies have not detected fetuses with IUGR in PCOS patients (*31*), others have claimed that women with PCOS had higher rates of IUGR and SGA than women without the condition who are the same age and body mass index (BMI) (*28*). The decrease of nutrients such as amino acids required by the fetus due to placental malperfusion may be one of the causes.

HDP may stem in part from the direct and indirect effects of insulin on vasoconstriction (*32*). In addition, insulin stimulates various growth factors promoting

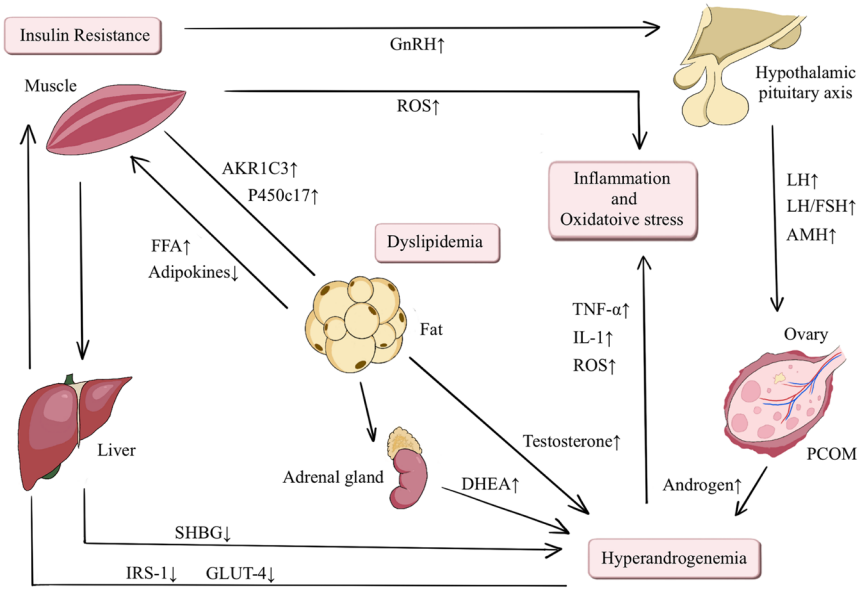

Figure 1. Characteristic manifestations of PCOS and their interaction. Hyperandrogenemia may be due to insulin resistance and dyslipidemia that induces the production of additional androgens through a variety of mechanisms (*e.g.*, increased hypothalamic-pituitary-gonadal axis release, increased adipose tissue and adrenal gland synthesis), which can in turn exacerbate insulin resistance. In addition to directly or indirectly acting on adrenal androgen production, lipid metabolism disorders can also promote insulin resistance through up-regulation of fatty acids (FFA) and down-regulation of Adipokines. In addition, hyperandrogenemia, lipid metabolism disorders, chronic inflammation and oxidative stress in patients with insulin resistance and PCOS are also closely related and mutually reinforcing.

thrombosis and fibrosis as well as up-regulates blood pressure response to sodium intake (*33,34*). Hormonal imbalance and HA may also play a role here. Animal experiments demonstrated that testosterone-treated mice exhibited increased vascular resistance and hypertension (*35*).

Placental dysfunction caused by impaired maternal-fetal interface is widely known as a vital cause of pregnancy complications and adverse fetal outcomes (*36*). Therefore, we hypothesized that the characteristic manifestations of PCOS, such as IR, HA, abnormal lipid metabolism and inflammation may contribute to adverse pregnancy outcomes (APO) by influencing decidualization, one of the most essential parts in maternal-fetal interface.

3. Impaired decidualization in adverse pregnancy outcomes

PCOS is commonly associated with APO, leading to greater use of ART compared to women without PCOS (*29*). APO refers to a range of short- and long-term complications related to pregnancy and delivery that impact both the mother and the fetus. APOs related to maternal PCOS include preeclampsia, gestational diabetes, gestational hypertension, and recurrent miscarriage. The process of becoming pregnant is intricate and irreversible, involving a number of separate steps, such as implantation, decidualization, placentation, and ultimately, birth. Any interference with these processes can result in adverse pregnancy outcomes. In humans, decidualization is initiated not by the blastocyst signal but by the menstrual cycle, and it occurs simultaneously with the development of the fertilized egg. Decidualization not only plays a critical role in implantation but also regulates placentation, making it of utmost importance during pregnancy. This review aims to examine and summarize the relationship between impaired decidualization and APO, as well as the specific mechanisms involved (Figure 2).

4. The role of PCOS in decidualization impaired APO

4.1. The role of decidualization in the progress of pregnancy

Decidualization of the human endometrium is the process of remodeling post-ovulation in preparation for pregnancy. This procedure includes vascular remodeling, the development of secretory uterine glands, and the influx of specialized uterine natural killer cells (uNKs) (*37,38*). More specifically, human endometrial stromal cells (ESCs) undergo morphological and functional differentiation known as decidualization (*39*). It is initiated mainly by hormones, particularly estrogen estradiol (E2) and progesterone (P4) secreted by the corpus luteum post-ovulation. In pregnancy, trophoblast cells produce human chorionic gonadotropin (hCG), which helps maintain progesterone levels. A regulatory loop is then established between hormones such as relaxin and corticotropin-releasing hormone (CRH), along with hCG, to increase intracellular

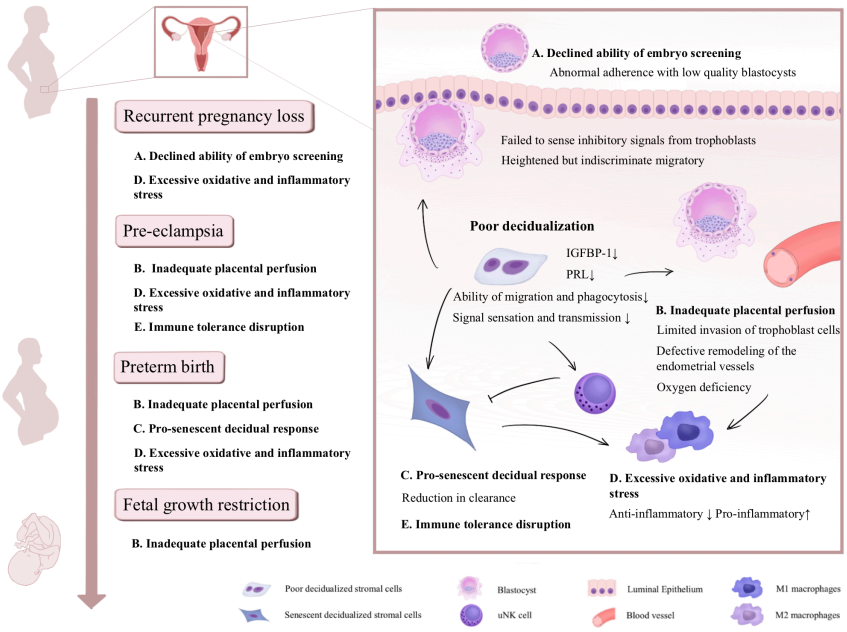

Figure 2. The role poor decidualization played in adverse pregnancy outcome in women with PCOS. Endometrial stromal cells with imperfect decidualization in the maternal-fetal interface have adverse effects on the normal physiology of surrounding cells, including embryonic trophoblast cells, immune cells, *etc*. Resulting in declined ability of embryo screening, inadequate placental perfusion, pro-senescent decidual response, excessive oxidative and inflammatory stress and immune tolerance. These phenomena affect the mother and fetus at different periods respectively, contributing to adverse pregnancy outcomes.

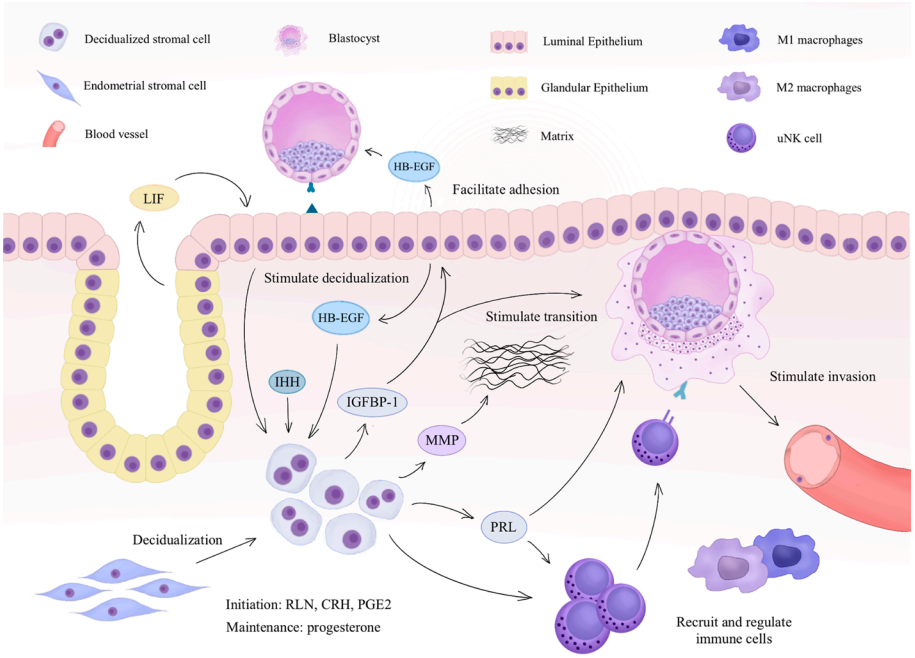

Figure 3. Communication between decidualized stromal cells and other cells in maternal-fetal interface. Successful decidualization is regulated by multiple factors, including contact between blastocyst and epithelium, changes in hormone levels and other factors in the body. At the same time, normal decidualized stromal cells (DSCs) also promote the invasion of blastocyst trophoblast cells and vascular reconstruction through multiple ways, such as promoting stromal decomposition, promoting endometrial NK cell recruitment and recognition of blastocyst.

cyclic adenosine monophosphate (cAMP) levels and promote decidualization. Prolactin (PRL) and insulin-like growth factor binding protein 1 (IGFBP1), which have been frequently employed as markers of decidual cells, are examples of particular molecules secreted by decidualized ESCs (Figure 3).

4.2. The regulation of dysdecidualization in APO

In addition to discrete events like implantation, decidualization, placentation, and childbirth, pregnancy is a difficult, irreversible process. Interference in any of these steps may lead to adverse pregnancy

outcomes. Decidualization in humans is initiated not by the blastocyst signal but the menstrual cycle (*15*). Decidualization of the endometrium and the development of the fertilized egg go on simultaneously and it is not only related to implantation but also regulates placentation, which plays an extremely essential role during pregnancy. Therefore, the purpose of this review is to study and summarize the relationship between impaired decidualization and APO and the specific mechanisms involved. Recurrent pregnancy loss (RPL) is considered a disease as compared to sporadic pregnancy loss. Although embryo aneuploidy is a common cause of pregnancy loss, studies have shown that RPL patients with PCOS have a decreased rate of embryo aneuploidy, suggesting a potentially greater role for endometrial disorders in RPL (*40*).

Numerous studies have established a link between PRL and deficient endometrial decidualization, with reduced expression of decidualization markers, including PRL, tissue factor (TF), and signal transducer and activator of transcription 5 (Stat5), detected in such patients. However, it is yet unclear how PRL affects the expression of IGFBP-1 (*41-43*). Studies on the mechanism of improper decidualization leading to RPL primarily focus on two aspects: reduced embryo screening ability and premature, excessive oxidative and inflammatory stress. Women with RPL often show prolonged, heightened inflammatory endometrial reactions which may be linked to defective endometrial vessel remodeling and disrupted oxygen supply (*44,45*). In women with RPL, all genes in the interleukin 8 (IL-8) pathway are upregulated, while those in the interleukin 1 (IL-1) pathway are downregulated (*46*). Oxidative and inflammatory stress, such as heightened tumor necrosis factor α (TNF-α) and nucleotide oligomerization domain (NOD)-like receptor thermal protein domain associated protein 3 (NLRP3) secretion, can induce stromal cell senescence and deplete endometrial mesenchymal stem cells (eMSCs) (*47-49*). RPL has also been linked to a variety of genes, intracellular signaling pathways, and metabolic dysregulation (*50-53*).

4.3. The relationship between PCOS pathological factors and dysdecidualization

Numerous studies have yielded compelling evidence supporting the association between PCOS characteristics and adverse pregnancy outcomes, irrespective of the phenotype, including metabolic and hormonal disorders and the ensuing inflammatory response (*54*). Of these factors, endometrial factors have been increasingly cited, with a greater emphasis on decidualization. To address this topic, our review focuses on investigating the mechanisms through which PCOS directly affects the differentiation and function of endometrial stromal cells by disrupting endocrine balance. Additionally, epithelial cell growth and the attraction of immune cells can both be negatively impacted by a number of variables, leading to epithelial-mesenchymal communication disorders that ultimately undermine ESC decidualization. The above content is an important elaboration of our review.

4.3.1. Insulin resistance impairs the energy uptake in ESC through the insulin signaling pathway

The impairment in insulin signal pathway contributes to the improper decidualization of women with PCOS by downregulating the expression of variety of important secretion factors. Neff *etc*. has reported a reduced expression of IR stimulated by hyper-insulinemic conditions led to impaired decidualization (*55*). Insulin receptor substrate 2 (IRS2) induced by progesterone bridges receptor tyrosine kinases such as insulin-like growth factor 1 receptor (IGF1R) and IR to downstream phosphoinositide 3-kinase (PI3K)/AKT and mitogen-activated protein kinases (MAPK) pathways. EDCs with abnormal PI3K/AKT and MAPK activation had less glucose transporter type 1 (GLUT1) and GLUT4 accumulating in the cell membrane, which may lead to an energy deficiency during decidualization considering an obviously increased uptake in decidual stromal cells (DSCs) and a booming necessity of energy during decidualization (*56*). Thus, IR and declined progesterone in women with PCOS are supposed to have negative impact on MAPK and PI3K/AKT signal pathway. IGFBP1, bone morphogenetic protein 2 (BMP2), Wnt family member 4 (WNT4), and heart and neural crest derivatives expressed 2 (HAND2) (but not PRL) expression in human ESC has been reported to be dramatically reduced by IRS-2 loss. IGFBP1 and PRL expression were considerably reduced after treatment with an ERK1/2 (member of the MAPK pathway) inhibitor, and the activation of known extracellular regulated protein kinases 1/2 (ERK1/2) target genes FOS, mitogen- and stress-activated kinase 1 (MSK1), signal transducerand activator of transcription 1 (STAT1), and signal transducerand activator of transcription 3 (STAT3) was also blocked, which verified the importance of MAPK pathway in decidualization (*57*). Increased nuclear accumulation and forkhead box O1 (FOXO1) transcriptional activity require PI3K/AKT activation, which is exhibited to promote decidual procession by increasing PRL promoter activity (*58*).

Insulin resistance is also found significantly up-regulated Prokineticin 1 (PROK1) mRNA and protein levels in human decidualized endometrial stromal cells through hypoxia-inducible factor-1α (HIF1α) and PI3K pathways, which impacted trophoblast migration and invasion as well as endometrial stromal cell migration (*59*).

4.3.2. Elevated androgens and increased androgen receptor expression in PCOS patients may disrupt the decidualization

In uterus of normal pregnant women, the abundance of

androgen receptor (AR) in pregnancy phase is down-regulated, but for PCOS, AR is reported overexpressed both in endometrium epithelial and stromal cells compared to fertile controls (*60*). This upregulation of AR' s expression may be attributed to the chronic elevation of estrogen and androgens in women with PCOS (*61*). Numerous researches have shown endometrial androstenedione concentrations in women with PCOS are three times greater than in normal women and dramatically promote cell proliferation in ESC cultures because AR is colocalized with Ki-67. Androgen and progesterone work together to promote PRL secretion, and can be inhibited by the specific AR competitive inhibitor flutamide. *In-vitro* experiments showed a decreased proliferation of ESC cells collected from both PCOS patients and normal pregnant women treated with dihydrotestosterone (DHT), which can be partially compensated by treatment with dexamethasone (*60*). And the decreased expression of PRL has also been exhibited, suggesting that ESC decidualization was impaired.

A recent study found that melanoma-associated antigen 11 (MAGEA11), a cAMP-induced AR coregulator, was delayed in up-regulation and expressed less in ESC cells from PCOS patients. Furthermore, AR chromatin immunoprecipitation research revealed that Krüppel-like factor (KLF)-9 and 13 transcription factors (KLF9/KLF13) are both important targets of androgen receptor. Researchers postulated that aberrant MAGEA11 expression may induce delayed or incorrect decidualization by interfering with normal signal transduction from AR to the target KLF9/13 and its downstream component *BMP2*. Furthermore, the promyelocytic leukemia zinc finger transcription factor (PLZF)-related pathway may play a role in the poor decidualization process. AR overexpression and activation appear to mediate mis-expression of these transcriptional regulators required for transcriptional programming (*62*).

The up-regulation of B-cell lymphoma-2 (*Bcl-2*) in PCOS samples with hyperandrogenemia showed signs of early apoptosis and delayed cell cycle. And a higher p27 protein expression also shows that cell cycle regulation may be compromised (*63*). Apoptosis is delayed in PCOS; overexpression and hyperactivation of AR may be the cause of this. Gene ontology analysis showed that AR targets were primarily involved in processes linked to the positive control of cell death.

4.3.3. Disorders of lipid metabolism may directly affect the synthesis and breakdown of cellular lipids required during decidualization

Lipids and their derivatives are increasingly being identified to be crucial in the decidualization of endometrial stromal cells in research. Cholesterol-derived steroid hormones E2 and P4 are essential for the maintenance of decidualization of stromal cells. Up-regulated by E2 and stimulated by P4, the progesterone receptors (PGRs) directly activate transcription factors such as FOXO1 and homeobox A10 (HOXA10), which leads to the procession of decidualization and the secretion of DSCs markers such as IGFBP-1 and PRL (*64-66*). E2 and P4 expression in the circulation and estrogen receptor (ER) and PGR observed in the endometrium of PCOS patients are both vary from that in normal women. More intriguingly, the findings showed that a subset of PCOS-affected women had ESCs that showed a reduced decidualization response to E2P4 therapy, which is also called "progesterone resistance" (*67*).

Adipocytes synthesize and secrete adipokines, such as leptin and adiponectin. Leptin is involved in the pro-inflammatory process, while adiponectin has protective effects such as anti-inflammatory and increasing insulin sensitivity. Some studies have found that the level of circulating adiponectin is decreased in PCOS patients, and there is abnormal expression of adiponectin system genes in granulosa cells (*68,69*). Investigators have identified adiponectin expression in endometrial ESCs of PCOS patients and reported that adiponectin is a component of correct endometrial decidualization and embryo implantation (*70*). Adiponectin treatment of stromal cells was found to up-regulate the expression of leukemia inhibitory factor (*LIF*) and glutathione peroxidase 3 (*GPX3*), and down-regulate the expression of interleukin 15 (*IL-15*) and mucin 1 (*MUC1*), indicating that the presence of adiponectin promotes stromal cell decidualization and is anti-inflammatory and anti-oxidative and creating a favorable endometrial environment (*71*). In addition, adiponectin can inhibit the excessive invasion of trophoblast cells, the effect of which may be related to the decreased activity of matrix metalloproteinase 2 (MMP-2) and matrix metalloproteinase 9 (MMP-9) and the up-regulated expression of tissue inhibitor of metalloproteinase 3 (*TIMP-3*) mRNA, a tissue inhibitor of metalloproteinases in ESCs (*72,73*). Therefor we can conclude that the decreased expression of adiponectin in PCOS patients has an adverse effect on decidualization of ESCs.

Additionally, high levels of advanced glycation end products (AGEs) affect the function of endometrial epithelial cells and endometrial stromal cells, stress endoplasmic reticulum (ER) in ESCs and impair decidualization, compromise the implantation of blastocyst mimics, and inhibit trophoblast invasion (*74*).

4.3.4. Imbalance of pro- and anti-inflammatory factors interferes with signal transduction, apoptosis and cell cycle regulation in ESC

Inflammation is prevalent in women with PCOS: Serum levels of TNF-α, IL-1, IL-6 and IL-18, adhesion molecules, follistatin and C-reactive protein (CRP) were widely observed elevated. Microarray analysis revealed

that ESCs in women with PCOS showed upregulation of inflammatory genes (*C4A/B*, *CCL2*, *ICAM1*, *TNFAIP3*) (*75,76*). Inflammation is closely related to metabolic disorders, immune cell dysfunction and even oxidative stress, and leading to a definite disruption on decidualization procession. In addition, some inflammatory cytokines themselves can directly damage the decidualization process of ESCs through Intracellular pathways.

TNF-α was significantly increased in PCOS patients. On the one hand, TNF-α levels interfere with the insulin signal pathway by lowering adiponectin signaling and GLUT-4 protein, which in turn interferes with the activation of the *IRS-1* gene in the ESCs of PCOS women. This will further exacerbate the disruption of insulin signaling pathway, which is especially common in obese PCOS women (*69,77*). On the other hand, infertile PCOS patients with increased levels of the inflammatory cytokines TNF-α and IFN-α increase NF-κB and STAT1 protein recruitment to osteopontin (OPN) and CD44 promoters. This overexpression of NF-κB p65 (Rel A) is positively correlated with serum insulin levels and hyperandrogenism in overweight PCOS women (*78*). Thus, we can infer that TNF-α could profoundly damage decidualization by promoting IR and HA decidua.

It has been found that the cytotoxic cytokine IL-1β blocks human ESCs differentiation and automatically upregulates its synthesis and secretion through independent signaling pathways. Uterine gap junction protein connexin 43 (Cx43) and two other ESCs differentiation markers: PRL and vascular endothelial growth factors (VEGF) are inhibited by IL-1β activation. This may be handled through the ERK1/2 and p38 MAPK cascades. Furthermore, IL-1β has been suggested to inhibit the expression of estrogen receptor-α, progesterone receptor-a and progesterone receptor-b in ESCs (*79*).

Studies have demonstrated that PCOS patients' endometrium expresses more IL-6 and IL-8, which may be due to the influence of insulin and androgen (*80*). These inflammatory factors secreted by the DSCs plays the chemotaxis of white blood cells (WBC) in endometrium, coordination of sertoli cell invasion, and so on. But do these cytokines have an effect on the differentiation of ESCs themselves? A recent study found *in vitro* experiment that the addition of IL-6 and IL-8 to ESCs cells derived from PCOS patients did not affect their decidual morphology or reduce the expression of their secreted production IGFBP-1. This may imply IL-6 and IL-8 have no significant effect on decidualization of endometrial ESCs from PCOS patients (*81*).

Excepting the upregulation of inflammatory factors, the downregulation of anti-inflammatory factors is also be found in PCOS patients. A pro-survival factor called stoniocalcin-1 (STC-1) shields tissues from stresses including inflammation and hypoxia. In the nonpregnant state, *STC-1* gene expression is restricted to the uterine luminal epithelium, while during implantation, *STC-1* gene expression is observed to be exhibited and increased in DSCs in the superficial layer of endometrium (*82*). Expression of *STC-1* is found reduced in women with PCOS when facing stress that may cause deficits, possibly because of a diminished STC-1 response to stressors in ESCs of PCOS patients (*83*). This reflects that STC-1 may affect the decidualization of ESCs in PCOS patients through inflammation and oxidative stress pathways. A recent study constructing endometrial organoids reported that treatment of ESCs *in vitro* with STC-1 alone had no effect on decidualization (84) (Figure 4). We suggest more future experiments are needed to verify this conclusion.

5. Conclusions and prospects

PCOS is a global health concern with serious and long-term adverse effects on the physical and mental health of women in their reproductive age, studies have found woman with PCOS suffering a higher rate of APO. However, the study of the increased incidence of APO in PCOS patients is still in its early stages, with multiple essential pathological mechanisms yet to be uncovered and clinically verified. Decidualization plays a crucial role in pregnancy and any dysfunction leading to poor decidualization can result in catastrophic adverse pregnancy outcomes. Through our review of recent literature, we have discovered that decidualization of stromal cells in PCOS patients is not only impacted by low progesterone levels caused by ovulation disorders, but also influenced by changes in biochemical and metabolic signals, such as hyperandrogenism, obesity, IR, and hyperinsulinemia. These pathological processes impair decidualization of endometrial stromal cells at the cellular signaling and gene expression levels mediated by cytokines, inflammatory factors, and oxidative stress. Dysfunctional secretion and phagocytosis further contribute to poor function and excessive pro-senescence, resulting in various APO, including RPL, preterm birth (PTB), PE, and IUGR. It is apparent that the changes in biochemical and metabolic signals caused by PCOS not only affect stromal cells, but also impact other components of the endometrium, including epithelial cells and immune cells. These effects may directly impair decidual function or indirectly damage stromal cell decidualization through intercellular crosstalk. However, space limitations prohibit us from exploring this aspect in this review. Similarly, due to the wide range of biochemical and metabolic signal changes and types of APO associated with PCOS, we have focused on discussing 4 representative features and diseases. Furthermore, the subject of PCOS and its impact on decidualization and APO is still a topic of debate, and the effects and outcomes may vary depending on the patient's phenotypic presentation and pathophysiological processes. Therefore, in this review, we have not

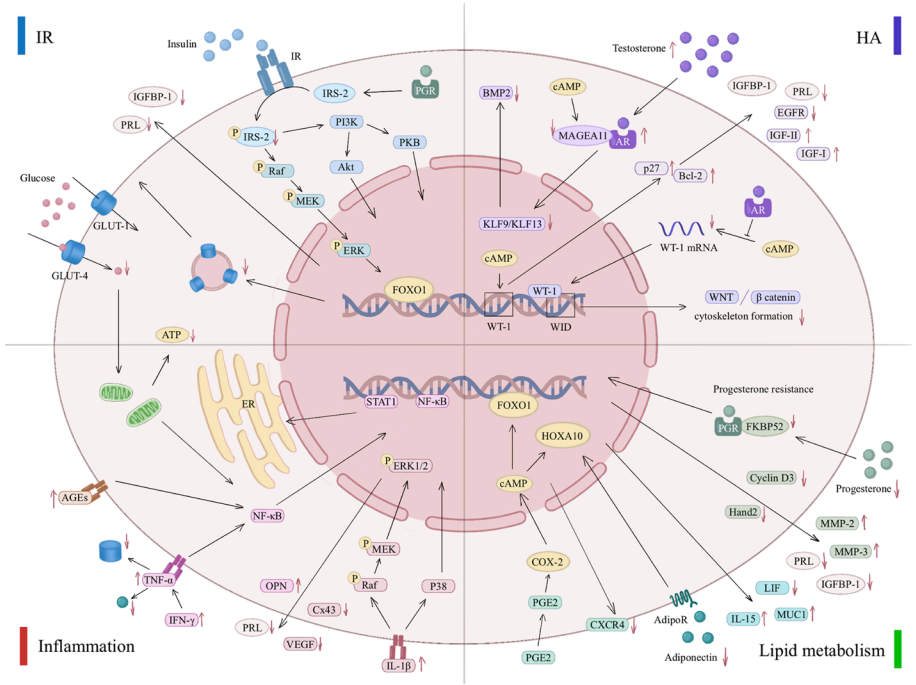

Figure 4. Mechanism of poor decidualization caused by PCOS. IR (insulin resistance) affects ESC decidualization through pathways such as insulin receptor MAPK and reduced glucose transport, shown in blue in the upper left box. HA (hyperandrogenemia) affecting receptor cofactors MAGEA11 and WT-1 pathways, which are highlighted in purple in the upper right box. The inflammatory NF-κB pathway as well as inflammatory cytokines and oxidative stress are highlighted in red at the lower left corner. The mechanisms of lipid disorders are highlighted in green in the bottom right box.

differentiated between different PCOS phenotypes.

Our aim was to link PCOS to APO through decidualization, which is a novel approach to our knowledge. We have outlined a range of signaling pathways and cytokines that could serve as potential therapeutic targets for the treatment of PCOS or improving live birth rates for pregnant PCOS patients. Our summary of the pathological mechanisms linking gynecological endocrine diseases and adverse obstetric outcomes may assist clinicians in gaining a better understanding of the impact of PCOS on pregnancies, and pave the way for further in-depth research in this field.

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