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RESEARCH ARTICLE

GRANULOSA CELL DYSFUNCTION AND IMPAIRED OOCYTE MATURATION PLAY SIGNIFICANT ROLES IN POLYCYSTIC OVARY SYNDROME PATHOGENESIS

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Abstract

The polycystic ovary syndrome (PCOS) is an endocrine disorder that affects women of reproductive age worldwide. It is characterized by hyperandrogenism, ovarian dysfunction, and polycystic ovarian morphology.With a particular focus on granulosa cell dysfunction and abnormal oocyte maturation, this comprehensive review explores the intricate molecular mechanisms driving PCOS pathogenesis. PCOS is characterized by hormonal and metabolic disturbances caused by long non-coding RNAs (lncRNAs), microRNAs (miRNAs), and the insulin-like growth factor 1 (IGF1) signaling pathway.In this review, we discuss the dysregulation of certain lncRNAs, such as NEAT1, and miRNAs, including miR-29a-3p, in PCOS granulosa cells, as well as how these dysregulations affect cell proliferation, insulin sensitivity, and steroidogenesis. This study examines the interaction between non-coding RNAs and the IGF1 system, which reveals an intricate regulatory network involved in follicular development and ovarian function. These pathways are altered in expression and activity, which has implications for how oocytes mature and how fertility is affected.In addition, this review emphasizes the interconnected nature of granulosa cell dysfunction, oocyte maturation defects, and systemic metabolic disturbances in PCOS pathogenesis. Granulosa cells have the potential to be used as a research and therapeutic intervention focus, due to their accessibility and central role in ovarian function.Additionally, we propose future research directions using advanced technologies such as single cell sequencing and multi-omics technologies. According to the review, studies that focus on granulosa cells can help develop novel diagnostic markers, personalized treatment strategies, and potential PCOS-based therapies.In addition to providing insight into the molecular underpinnings of PCOS, this study sets the stage for future investigations aimed at improving diagnosis, management, and treatment.

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Introduction:-

Polycystic ovary syndrome (PCOS) affects the endocrine and metabolic systems of approximately five percent of women of reproductive age worldwide[1, 2]. Symptoms include menstrual irregularities, polycystic ovarian morphology, and hyperandrogenism. To diagnose PCOS, after the exclusion of other endocrine disorders, two out of these three features must be present, according to the Rotterdam criteria, established in 2003[3, 4].

The clinical presentation of PCOS is heterogeneous, with patients exhibiting a spectrum of symptoms. Menstrual disturbances often manifest as oligomenorrhea or amenorrhea, reflecting the underlying anovulation that is a hallmark of the syndrome. Hyperandrogenism may present clinically as hirsutism, acne, or male-pattern alopecia, or it may be detected biochemically through elevated serum androgen levels[5]. The polycystic ovarian morphology, typically assessed through transvaginal ultrasound, is characterized by the presence of 12 or more follicles measuring 2-9 mm in diameter per ovary and/or increased ovarian volume[6].

To fully appreciate the pathophysiology of PCOS, it is crucial to understand normal ovarian physiology. In the healthy ovary, folliculogenesis is a tightly regulated process involving the coordinated development of both the oocyte and its surrounding somatic cells[7, 8]. Granulosa cells play a pivotal role in this process, forming a bidirectional communication axis with the oocyte that is essential for normal follicular development and oocyte maturation[9]. These cells are responsible for steroidogenesis, particularly the production of estradiol, and they provide nutritional and regulatory support to the developing oocyte through gap junctions and paracrine signaling[10].

The importance of granulosa cells in ovarian function cannot be overstated. They are not only critical for hormone production but also for the creation of a microenvironment conducive to oocyte growth and maturation. It has been discovered that granulosa cells regulate meiotic arrest and resumption, as well as transcriptional activity and metabolism of the oocyte. Disturbances in granulosa cell function can therefore have far-reaching consequences for follicular development, ovulation, and ultimately, fertility[11-13].

In recent years, attention has turned to the role of non-coding RNAs in ovarian function and PCOS pathogenesis. These regulatory RNA molecules, which include long non-coding RNAs (lncRNAs) and microRNAs (miRNAs), have emerged as important modulators of gene expression at both transcriptional and post-transcriptional levels[14, 15]. Their involvement in various aspects of ovarian physiology, including folliculogenesis, steroidogenesis, and ovulation, has been increasingly recognized. Aberrant expression of specific non-coding RNAs has been implicated in the development of PCOS, offering new insights into the molecular underpinnings of the disorder[16-18].

Another key player in ovarian function and PCOS pathophysiology is the insulin-like growth factor 1 (IGF1) system. IGF1 and its associated proteins play crucial roles in follicular development, steroidogenesis, and oocyte maturation. Dysregulation of the IGF1 system has been observed in PCOS patients, potentially contributing to the hormonal and metabolic disturbances characteristic of the syndrome[19-21]. The interplay between IGF1 signaling and non-coding RNAs in the context of PCOS is an area of active investigation, promising to shed light on the complex regulatory networks underlying the disorder.

In exploring the pathophysiology of PCOS, it becomes clear that genetic, epigenetic, and environmental factors are all involved. The dysfunction of granulosa cells and abnormalities in oocyte maturation appear to be central to the development of PCOS, influencing both the reproductive and metabolic aspects of the syndrome[22]. It is crucial to understand these molecular processes to elucidate the pathogenesis of PCOS as well as identify potential therapeutic targets and develop more effective treatment strategies[23, 24].

The Granulosa Cells and Oocytes in PCOS

PCOS is characterized by a complex interplay of hormonal and metabolic changes that significantly impact granulosa cell function and oocyte maturation[25, 26]. Polycystic ovarian morphology, anovulation, and hyperandrogenism are hallmark characteristics of PCOS[27].PCOS is primarily characterized by hormonal imbalances, most notably hyperandrogenism and insulin resistance. The elevated androgen levels, particularly testosterone and androstenedione, are primarily due to increased production by the ovarian theca cells[28, 29]. This hyperandrogenism is often accompanied by insulin resistance and compensatory hyperinsulinemia, which further exacerbate androgen production through direct stimulation of ovarian androgen synthesis and by reducing sex hormone-binding globulin (SHBG) levels, thereby increasing free androgen concentrations[30].

Insulin resistance in PCOS affects approximately 65-70% of patients, with rates varying depending on the diagnostic criteria used. This metabolic dysfunction extends beyond its reproductive implications, predisposing PCOS patients to type 2 diabetes, dyslipidemia, and cardiovascular disease[31]. Recent studies have also highlighted the role of adipokines, such as leptin and adiponectin, in modulating insulin sensitivity and androgen production in PCOS patients[32, 33].

Folliculation and oocyte maturation require the function of granulosa cells, and their dysfunction plays a significant role in PCOS pathophysiology. In PCOS, granulosa cells exhibit altered steroidogenesis, characterized by increased androgen production and decreased aromatase activity. This shift in steroidogenic enzyme expression and activity results in an androgen-dominant follicular microenvironment, which is detrimental to follicular development and oocyte maturation.

Recent transcriptomic and proteomic analyses have revealed significant alterations in gene expression profiles of granulosa cells from PCOS patients[34]. These changes affect multiple cellular processes, including steroidogenesis, cell proliferation and apoptosis, oxidative stress response, and inflammation. For instance, there is an upregulation of genes involved in androgen synthesis and downregulation of those involved in estrogen production. Additionally, dysregulation of genes involved in cell cycle control and survival potentially contributes to the increased number of small antral follicles characteristic of PCOS.

The oocyte plays an active role in follicular development, and its maturation is critical for successful ovulation and fertilization. In PCOS, oocyte maturation is often impaired, leading to reduced oocyte quality and developmental competence. Several abnormalities have been observed in PCOS oocytes, including mitochondrial dysfunction, epigenetic alterations, increased oxidative stress, and meiotic abnormalities.

Mitochondrial dysfunction in PCOS oocytes often manifests as altered mitochondrial distribution and reduced ATP production, potentially compromising their developmental potential. Studies have reported aberrant DNA methylation and histone modification patterns in PCOS oocytes, which may affect gene expression and embryo development. Increased levels of reactive oxygen species (ROS) have been observed, potentially leading to DNA damage and reduced oocyte quality. Some research has also reported higher rates of meiotic spindle abnormalities and chromosomal misalignment in PCOS oocytes[35-37].

The bidirectional communication between granulosa cells and the oocyte is crucial for normal follicular development and oocyte maturation. In PCOS, this delicate interplay is disrupted, contributing to follicular arrest and anovulation. Key aspects of this disruption include altered paracrine signaling, impaired gap junction communication, disrupted metabolic coupling, and premature luteinization.

The expression of oocyte-secreted factors such as growth differentiation factor 9 (GDF9) and bone morphogenetic protein 15 (BMP15) is often dysregulated in PCOS, affecting granulosa cell function and follicular development. Studies have reported reduced expression of connexin 43, a key component of gap junctions, in PCOS granulosa cells, potentially limiting the transfer of nutrients and regulatory molecules between the oocyte and surrounding cells[38].

The altered metabolic environment in PCOS, characterized by hyperinsulinemia and increased androgen levels, can disrupt the metabolic cooperation between granulosa cells and the oocyte, affecting oocyte energy metabolism and maturation. Some studies have suggested that PCOS granulosa cells may undergo premature luteinization, potentially contributing to follicular arrest and anovulation.

Understanding these complex interactions and their perturbations in PCOS is crucial for developing targeted therapies aimed at improving ovarian function and fertility outcomes in affected individuals. Future research focusing on the molecular mechanisms underlying these disruptions may provide new insights into PCOS pathogenesis and potential therapeutic interventions.

Long Non-coding RNAs in PCOS Pathogenesis

Long non-coding RNAs (lncRNAs) have emerged as crucial regulators of gene expression in various biological processes, including ovarian function. These RNA molecules, typically longer than 200 nucleotides, do not encode proteins but play essential roles in transcriptional and post-transcriptional regulation. In recent years, the

involvement of lncRNAs in the pathogenesis ofPCOS has garnered significant attention from researchers worldwide.

LncRNAs participate in multiple aspects of ovarian physiology, including folliculogenesis, steroidogenesis, and ovulation. They exert their regulatory functions through diverse mechanisms, such as chromatin modification, transcriptional regulation, and post-transcriptional modulation of mRNA stability and translation. In the context of PCOS, several lncRNAs have been found to be dysregulated, potentially contributing to the hormonal imbalances and metabolic disturbances characteristic of the syndrome.

Numerous studies have reported altered expression profiles of lncRNAs in ovarian tissues, granulosa cells, and even in the circulation of PCOS patients compared to healthy controls. For instance, lncRNAs such as HOTAIR, H19, and SRA have been found to be differentially expressed in PCOS ovarian tissues[39-41]. These dysregulated lncRNAs are thought to influence various pathways implicated in PCOS pathogenesis, including insulin signaling, androgen synthesis, and inflammatory responses.

One lncRNA that has garnered particular attention in PCOS research is the Nuclear Enriched Abundant Transcript 1 (NEAT1). NEAT1 is an essential component of nuclear paraspeckles and has been implicated in various cellular processes, including gene expression regulation and stress response. In the context of PCOS, NEAT1 has been found to be significantly upregulated in granulosa cells of PCOS patients compared to healthy controls[39].

The elevated expression of NEAT1 in PCOS granulosa cells has been associated with several key aspects of the syndrome's pathophysiology. Firstly, NEAT1 has been shown to modulate steroidogenesis by influencing the expression of key steroidogenic enzymes. Overexpression of NEAT1 leads to increased expression of enzymes involved in androgen production, such as CYP17A1, while simultaneously decreasing the expression of aromatase, which is responsible for converting androgens to estrogens. This shift in steroidogenic enzyme expression contributes to the hyperandrogenic state characteristic of PCOS.

Furthermore, NEAT1 has been implicated in the regulation of granulosa cell proliferation and apoptosis. Studies have demonstrated that NEAT1 can promote granulosa cell proliferation and inhibit apoptosis, potentially contributing to the increased number of small antral follicles observed in PCOS ovaries. This effect is thought to be mediated, at least in part, through the interaction of NEAT1 with various microRNAs and its influence on cell cycle regulators.

NEAT1 also plays a role in modulating insulin signaling in granulosa cells, a crucial aspect of PCOS pathogenesis given the prevalence of insulin resistance in affected individuals. Elevated NEAT1 levels have been associated with impaired insulin-stimulated glucose uptake and altered expression of insulin signaling components in granulosa cells. This connection between NEAT1 and insulin signaling provides a potential link between the reproductive and metabolic aspects of PCOS.

The molecular mechanisms through which NEAT1 exert its effects in PCOS are complex and multifaceted. One key mechanism involves the ability of NEAT1 to act as a competitive endogenous RNA (ceRNA), sequestering microRNAs and thereby modulating their regulatory effects on target mRNAs. For instance, NEAT1 has been shown to interact with miR-146a, a microRNA involved in regulating inflammation and insulin sensitivity. By sequestering miR-146a, NEAT1 can indirectly influence the expression of genes involved in these processes.

Additionally, NEAT1 can interact with various proteins, including transcription factors and chromatin modifiers, to regulate gene expression at the transcriptional level. In PCOS granulosa cells, NEAT1 has been found to interact with the transcription factor FOXO1, influencing its activity and thereby affecting the expression of genes involved in cell cycle regulation and apoptosis.

Increasing understanding of NEAT1's role in PCOS pathogenesis has provided new therapeutic avenues. Strategies aimed at modulating NEAT1 expression or disrupting its interactions with target molecules could potentially ameliorate some of the hormonal and metabolic disturbances associated with PCOS. However, given the complex regulatory networks involving NEAT1 and other lncRNAs, further research is needed to fully elucidate their roles and develop targeted therapies (Figure 1).

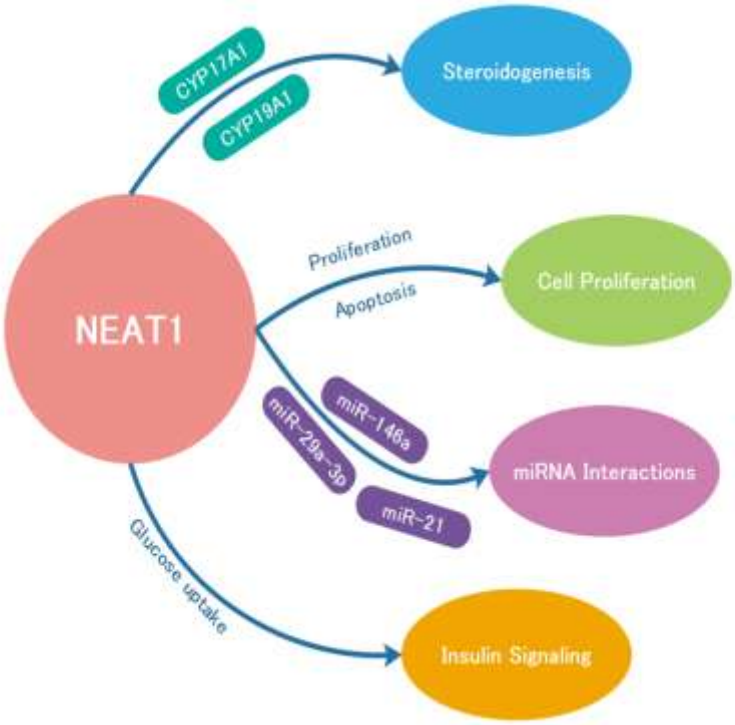

Figure 1:- The role of NEAT1 in PCOS pathogenesis

MicroRNAs in PCOS Development

MicroRNAs (miRNAs) have emerged as critical regulators of gene expression in various biological processes, including those involved in ovarian function and the pathogenesis of PCOS. These small, non-coding RNA molecules, typically 20-25 nucleotides in length, play crucial roles in post-transcriptional regulation of gene expression by binding to complementary sequences in target mRNAs, leading to their degradation or translational repression.

The biogenesis of miRNAs is a complex process that begins in the nucleus with the transcription of primary miRNA (pri-miRNA) by RNA polymerase II. The pri-miRNA is then processed by the Drosha-DGCR8 complex to form precursor miRNA (pre-miRNA), which is exported to the cytoplasm. In the cytoplasm, the pre-miRNA is further processed by Dicer to generate mature miRNA. The mature miRNA is then incorporated into the RNA-induced silencing complex (RISC), where it guides the complex to its target mRNAs.

In the context of ovarian physiology, miRNAs have been shown to regulate various aspects of folliculogenesis, steroidogenesis, and ovulation. They are involved in controlling granulosa cell proliferation and apoptosis, modulating hormone responsiveness, and regulating the expression of key enzymes involved in steroid hormone synthesis. The intricate balance of miRNA expression is crucial for normal ovarian function, and perturbations in this balance have been implicated in the development of ovarian disorders, including PCOS.

Numerous studies have reported altered miRNA expression profiles in PCOS patients compared to healthy controls. These differences have been observed in various tissues and bodily fluids, including ovarian tissue, follicular fluid, granulosa cells, and serum. The dysregulation of miRNAs in PCOS is thought to contribute to the characteristic features of the syndrome, such as hyperandrogenism, insulin resistance, and chronic anovulation.

One miRNA that has garnered significant attention in PCOS research is miR-29a-3p. This miRNA has been found to be differentially expressed in the follicular fluid and granulosa cells of PCOS patients. Studies have shown that miR-29a-3p plays a crucial role in regulating steroidogenesis and insulin sensitivity in granulosa cells, two key processes that are dysregulated in PCOS[42].

In the context of steroidogenesis, miR-29a-3p has been shown to target the mRNA of steroidogenic acute regulatory protein (StAR), a key rate-limiting enzyme in steroid hormone synthesis. Overexpression of miR-29a-3p in granulosa cells leads to decreased StAR expression and consequently reduced progesterone production[43]. This finding provides a potential mechanism for the altered steroidogenic profile observed in PCOS ovaries.

Furthermore, miR-29a-3p has been implicated in the regulation of insulin signaling in granulosa cells. It has been shown to target the insulin receptor substrate 1 (IRS1) mRNA, a crucial component of the insulin signaling pathway. Elevated levels of miR-29a-3p in PCOS granulosa cells may contribute to insulin resistance by reducing IRS1 expression and attenuating insulin signal transduction.

The effects of miR-29a-3p extend beyond steroidogenesis and insulin signaling. This miRNA has also been shown to influence granulosa cell proliferation and apoptosis, potentially contributing to the increased number of small antral follicles characteristic of PCOS ovaries. Additionally, miR-29a-3p has been implicated in the regulation of extracellular matrix remodeling, a process that is crucial for follicular development and ovulation.

The regulatory networks involving miR-29a-3p and other miRNAs in PCOS pathogenesis are complex and involve multiple feedback loops and interactions with other regulatory molecules, including long non-coding RNAs and transcription factors. For instance, the expression of miR-29a-3p itself is regulated by various factors, including hormones and metabolic signals, adding another layer of complexity to its role in PCOS development.

Other miRNAs have also been implicated in PCOS pathogenesis, each with its own set of target genes and regulatory functions. For example, miR-27b has been shown to regulate testosterone synthesis by targeting 17β-hydroxysteroid dehydrogenase type 3, while miR-93 has been implicated in the regulation of glucose metabolism and insulin sensitivity in PCOS.

There are several potential diagnostic and therapeutic applications of miRNA dysregulation in PCOS, thanks to a growing understanding of its role. Circulating miRNAs in serum or plasma have been proposed as potential biomarkers for PCOS diagnosis and prognosis. Moreover, strategies aimed at modulating the expression or activity of specific miRNAs, such as miRNA mimics or inhibitors, are being explored as potential therapeutic interventions for PCOS.

It is still unclear how miRNAs impact PCOS development despite significant advancements in understanding the role of miRNAs. The precise mechanisms by which altered miRNA expression contributes to the various clinical manifestations of PCOS are still being elucidated. Additionally, the potential of miRNA-based therapies for PCOS treatment requires further investigation, including assessments of efficacy, safety, and delivery methods.

As research in this field continues to advance, it is likely that our understanding of the roles of miRNAs in PCOS will deepen, potentially leading to novel diagnostic tools and targeted therapies for this complex endocrine disorder. The intricate regulatory networks involving miRNAs underscore the complexity of PCOS pathogenesis and highlight the need for comprehensive, system-level approaches to fully unravel the molecular underpinnings of this syndrome.

IGF1 Signaling in PCOS Pathogenesis

IGF1 plays a crucial role in ovarian physiology and has been implicated in the pathogenesis of PCOS. The IGF1 system is a complex network comprising IGF1, its receptor (IGF1R), IGF binding proteins (IGFBPs), and IGFBP proteases. This intricate system regulates various aspects of ovarian function, including folliculogenesis, steroidogenesis, and oocyte maturation[6, 44].

In the context of normal ovarian physiology, IGF1 acts as a potent stimulator of granulosa cell proliferation and differentiation. It enhances the responsiveness of granulosa cells to follicle-stimulating hormone (FSH), thereby promoting follicular development and estradiol production. IGF1 also plays a role in theca cell function, stimulating androgen production in concert with luteinizing hormone (LH)[45, 46]. The bioavailability and activity of IGF1 are tightly regulated by IGFBPs, which can either inhibit or potentiate IGF1 actions depending on the specific IGFBP and the cellular context[46-48].

In PCOS, the IGF1 system is often dysregulated, contributing to the hormonal and metabolic disturbances characteristic of the syndrome. Several studies have reported altered levels of IGF1 and IGFBPs in the serum and follicular fluid of PCOS patients compared to healthy controls[46, 49]. While the exact nature of these alterations can vary between studies, a common finding is an increase in bioavailable IGF1, often due to decreased levels of IGFBP-1 and increased IGFBP protease activity[46, 50, 51].

The increased bioavailability of IGF1 in PCOS has significant implications for ovarian function. In granulosa cells, excess IGF1 signaling can lead to premature luteinization and arrest of follicular development, contributing to the characteristic polycystic ovarian morphology seen in PCOS[46, 52-54]. IGF1 also enhances the stimulatory effect of LH on theca cell androgen production, potentially exacerbating the hyperandrogenism associated with PCOS[46, 55-57].

At the molecular level, IGF1 signaling is mediated primarily through the IGF1 receptor, a tyrosine kinase receptor that shares significant homology with the insulin receptor. Upon ligand binding, the IGF1R undergoes autophosphorylation and activates several downstream signaling cascades, including the phosphatidylinositol 3-kinase (PI3K)/Akt pathway and the mitogen-activated protein kinase (MAPK) pathway[46, 58, 59]. These pathways regulate various cellular processes, including metabolism, proliferation, and survival.

In the context of PCOS, altered IGF1 signaling can have profound effects on granulosa cell function. Enhanced IGF1 signaling has been shown to increase the expression of LH receptors on granulosa cells, potentially contributing to premature luteinization[46, 60, 61]. It also modulates the expression of steroidogenic enzymes, influencing the balance between androgen and estrogen production. Furthermore, IGF1 has been implicated in the regulation of aromatase activity, a key enzyme in the conversion of androgens to estrogens, which is often dysregulated in PCOS[46, 62].

The effects of IGF1 on oocyte maturation in PCOS are complex and not fully elucidated. In normal physiology, IGF1 promotes oocyte maturation and enhances oocyte developmental competence. However, in the context of PCOS, where IGF1 signaling is often dysregulated, these beneficial effects may be altered. Some studies have suggested that excessive IGF1 signaling may contribute to accelerated oocyte maturation, potentially leading to the release of immature or poor-quality oocytes[46, 63, 64].

The interplay between IGF1 and insulin signaling is particularly relevant in PCOS, given the high prevalence of insulin resistance in affected individuals. IGF1 and insulin can bind to each other's receptors, albeit with lower affinity, and their downstream signaling pathways share several components[46, 65]. In the context of hyperinsulinemia, which is common in PCOS, insulin can act through the IGF1 receptor to further amplify IGF1-like signaling in ovarian cells[26, 46, 66].

Recent research has also highlighted the potential crosstalk between IGF1 signaling and non-coding RNAs in PCOS pathogenesis. Several miRNAs have been identified as target components of the IGF1 signaling pathway, potentially modulating its activity in ovarian cells[46, 67, 68]. For instance, miR-145 has been shown to target the IGF1 receptor, while miR-21 can regulate the expression of programmed cell death 4 (PDCD4), a downstream effector of IGF1 signaling[69]. The complex interplay between IGF1 signaling and these regulatory RNAs adds another layer of complexity to our understanding of PCOS pathophysiology[69].

The therapeutic implications of targeting the IGF1 system in PCOS are an area of active research. Strategies aimed at modulating IGF1 bioavailability or signaling, such as the use of IGF1R inhibitors or agents that increase IGFBP levels, have shown promise in preclinical studies. However, given the fundamental role of IGF1 in normal physiology, any therapeutic interventions would need to be carefully tailored to avoid unintended consequences[70].

IGF1 appears to sit at the nexus of multiple pathways implicated in PCOS pathogenesis as our understanding of its role in PCOS pathogenesis continues to develop. To unravel the underlying mechanisms of PCOS, integrated approaches are needed to consider the complex interactions between IGF1 signaling, gonadotropin action, steroidogenesis, and metabolic regulation (Figure 2).

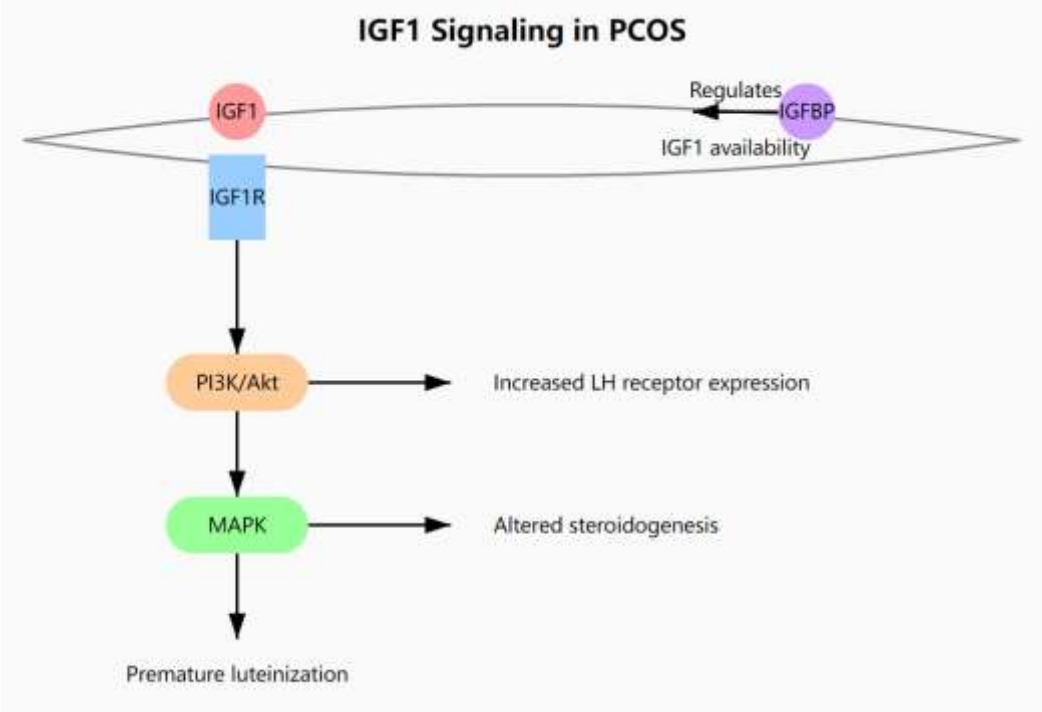

Figure 2:- IGF1 Signaling in PCOS.

Integrated Molecular Mechanisms in PCOS

Multiple molecular pathways play a role in the pathogenesis of PCOS, including lncRNAs, miRNAs, and growth factors like IGF1. These interconnected pathways collectively contribute to the hallmark features of PCOS, including disrupted follicular development, hyperandrogenism, and metabolic disturbances. Understanding the intricate relationships between these molecular players is crucial for elucidating the underlying pathophysiology of PCOS and identifying potential therapeutic targets.

At the core of PCOS pathogenesis lies the dysregulation of granulosa cell function and oocyte maturation. The regulatory networks involving lncRNAs, miRNAs, and IGF1 converge on these cellular processes, influencing various aspects of ovarian function. For instance, the lncRNA NEAT1, which is upregulated in PCOS, has been shown to modulate granulosa cell steroidogenesis and proliferation. This effect is mediated, in part, through its interaction with specific miRNAs, creating a complex regulatory circuit that fine-tunes gene expression in granulosa cells.

The interplay between NEAT1 and miRNAs exemplifies the concept of ceRNA networks in PCOS. NEAT1 can act as a molecular sponge, sequestering miRNAs such as miR-146a and miR-21, thereby modulating their regulatory effects on target mRNAs. This mechanism adds an additional layer of complexity to gene regulation in PCOS, as changes in the expression of one RNA species can have ripple effects throughout the entire network.

miRNAs play a central role in these regulatory networks, targeting multiple components of signaling pathways implicated in PCOS. For example, miR-29a-3p, which is often dysregulated in PCOS, targets the mRNA of StAR and IRS1. By modulating the expression of these key proteins, miR-29a-3p influences both steroidogenesis and insulin signaling in granulosa cells. The fact that a single miRNA can impact multiple pathways underscores the interconnected nature of PCOS pathogenesis.

The IGF1 signaling pathway intersects with these RNA-based regulatory networks at multiple points. IGF1R expression can be modulated by specific miRNAs, such as miR-145, which is often downregulated in PCOS. This downregulation may contribute to enhanced IGF1 signaling, further exacerbating the hormonal imbalances characteristic of the syndrome. Moreover, IGF1 signaling can influence the expression of certain lncRNAs and miRNAs, creating feedback loops that reinforce the dysregulated state in PCOS.

The consequences of these integrated molecular mechanisms on follicular development and anovulation in PCOS are profound. The altered expression of lncRNAsand miRNAs, combined with dysregulated IGF1 signaling, can lead to premature luteinization of granulosa cells, impaired response to FSH, and arrested follicular development. These cellular changes manifest as the polycystic ovarian morphology and chronic anovulation that are hallmarks of PCOS.

Furthermore, the regulatory networks involving lncRNAs, miRNAs, and IGF1 extend beyond the ovary, influencing systemic metabolic processes that are often disturbed in PCOS. For instance, altered expressions of specific miRNAs in adipose tissue and skeletal muscle can contribute to insulin resistance, a common feature of PCOS. The crosstalk between these systemic metabolic disturbances and ovarian dysfunction creates a self-reinforcing cycle that perpetuates the PCOS phenotype.

Systems biology approaches are necessary to fully understand the pathogenesis of PCOS due to its complexity of integrated molecular mechanisms. These intricate regulatory networks are being mapped with unprecedented detail thanks to high-throughput technologies, including RNA sequencing and proteomics. These efforts are revealing new nodes of regulation and potential points of therapeutic intervention.It is becoming increasingly evident that effective treatments for PCOS will require multi-targeted approaches as our understanding of integrated molecular mechanisms continues to advance. Therapies that can modulate multiple components of these regulatory networks simultaneously may hold the key to addressing the diverse manifestations of PCOS more effectively than current treatments.

In addition to shedding light on PCOS' pathophysiology, integrated molecular mechanisms provide insight into fundamental aspects of ovarian biology and hormone regulation. The advancement of research in this field should lead to improved diagnostic markers, prognostic indicators, and therapeutic strategies for PCOS and related disorders soon.

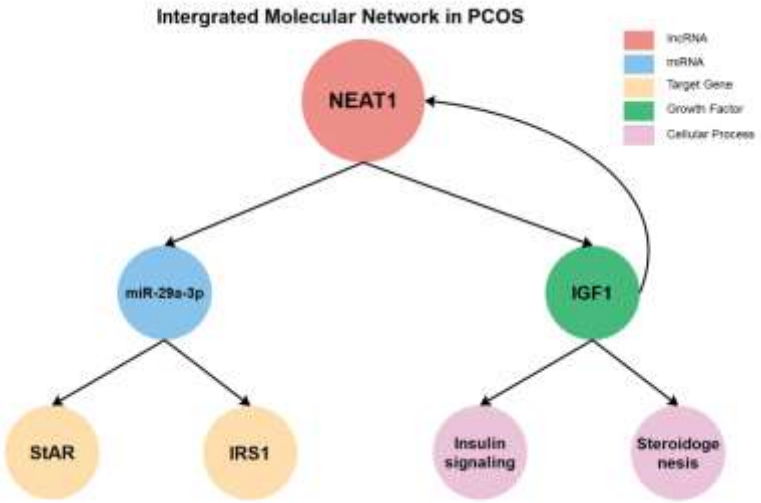

Figure 3:- Integrated molecular network in PCOS.

Conclusions:-

The interactions between lncRNAs and miRNAs in granulosa cells, as well as the IGF1 signaling pathway, have been unresolved despite significant advancements in understanding PCOS. These regulatory networks should be unraveled and in vitro models that simulate PCOS ovarian environment should be developed in the future. It may be possible to develop new diagnostic markers and therapeutic targets by integrating multi-omics data and advanced technologies such as single-cell sequencing. It is possible to develop more tailored and effective PCOS treatment strategies by focusing on granulosa cells.

Declarations

Consent for publication

Not applicable.

Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests
The authors declare that they have no competing interests.

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Authors' contributions
Conceptualization, LN.H. and W.C.; methodology, W.C.; software, W.C.; validation, Q.X., YM.Q., and YH.F.; formal analysis, LN.H. and W.C.; investigation, YH.F., Q.X. and L.H.; resources, J.L. and X.R.; data curation, X.R.; writing- original draft preparation, LN.H.; writing- review and editing, W.C.; visualization, LN.H.; supervision, W.C. and J.L.; project administration, LN.H, and W.C.; funding acquisition, LN.H, and W.C. All authors have read and agreed to the published version of the manuscript.

References:-

1 Zhang J, Zhang H, Guo B et al. Melatonin attenuates hepatic oxidative stress by regulating the p62/lc3 autophagy pathway in pcos. Endocr Connect. 2024:
2 Kumar A, Nazim A, Maheshwari M et al. Efficacy of metformin-cabergoline compared to metformin monotherapy for management of pcos with hyperprolactinemia: A systematic review and meta-analysis. Clin Med Insights Endocrinol Diabetes. 2024; 17: 11795514241280028
3 Shrivastava R, Patel S, Mishra S et al. Effect of yoga and naturopathy on sleep quality and pain in pcos patients with primary dysmenorrhea: A case series. Integr Med (Encinitas). 2024; 23: 29-32
4 Liu X, Wang F, Wang X et al. Impact of body mass index and polycystic ovary syndrome (pcos) subtypes on periodontal health in chinese women with pcos and periodontitis. Gynecol Endocrinol. 2024; 40: 2405097
5 Jabarpour M, Amidi F, Aleyasin A et al. Randomized clinical trial of astaxanthin supplement on serum inflammatory markers and er stress-apoptosis gene expression in pbmcs of women with pcos. J Cell Mol Med. 2024; 28: e18464
6 Sahin E, Eraslan Sahin M, Kirlangic MM et al. Effects of different pcos phenotypes on placental three-dimensional power doppler indices and placental volume during the first trimester. Placenta. 2024; 154: 176-183
7 Motahari Rad H, Mowla SJ, Ramazanali F et al. Characterization of altered micrornas related to different phenotypes of polycystic ovarian syndrome (pcos) in serum, follicular fluid, and cumulus cells. Taiwan J Obstet Gynecol. 2022; 61: 768-779
8 Juliawan IMP, Suwana FP, Annas JY et al. High sucrose and cholic acid diet triggers pcos-like phenotype and reduces enterobacteriaceae colonies in female wistar rats. Pathophysiology. 2022; 29: 344-353
9 Kargar Godaneh M, Rahimi S, Abizadeh M et al. Insulin ameliorates folliculogenesis in an experimental model of pcos mice. Int J Fertil Steril. 2023; 17: 22-27
10 Hashemian Z, Afsharian P, Farzaneh P et al. Establishment and characterization of a pcos and a normal human granulosa cell line. Cytotechnology. 2020; 72: 833-845
11 Cosar A, Ozcan P, Tanoglu FB et al. Comparative effects of the antioxidant glutathione with metformin and diane-35 on hormonal, metabolic, and inflammatory indicators in a dhea-induced pcos rat model. Gynecol Endocrinol. 2024; 40: 2302086
12 Namli Kalem M, Anadol E, Kalem Z et al. A rat study on the pten expression in ovarian tissue in pcos and folliculogenesis. Sci Rep. 2023; 13: 20774
13 Merhi Z, Mouanness M, Wang R et al. Intraovarian platelet-rich plasma administration induced spontaneous ovulation in an anovulatory woman with pcos. JCEM Case Rep. 2023; 1: luad038
14 Tu M, Wu Y, Wang F et al. Effect of lncrna malat1 on the granulosa cell proliferation and pregnancy outcome in patients with pcos. Front Endocrinol (Lausanne). 2022; 13: 825431
15 Guo H, Li T, Sun X. Lncrna hotairm1, mir-433-5p and pik3cd function as a cerna network to exacerbate the development of pcos. J Ovarian Res. 2021; 14: 19

16 Huang X, Pan J, Wu B et al. Construction and analysis of a lncrna (pwrn2)-mediated cerna network reveal its potential roles in oocyte nuclear maturation of patients with pcos. Reprod Biol Endocrinol. 2018; 16: 73
17 Lin H, Xing W, Li Y et al. Downregulation of serum long noncoding rna gas5 may contribute to insulin resistance in pcos patients. Gynecol Endocrinol. 2018; 34: 784-788
18 Huang X, Hao C, Bao H et al. Aberrant expression of long noncoding rnas in cumulus cells isolated from pcos patients. J Assist Reprod Genet. 2016; 33: 111-121
19 Shah A, Dodson WC, Kris-Etherton PM et al. Effects of oral contraception and lifestyle modification on incretins and tgf-ss superfamily hormones in pcos. J Clin Endocrinol Metab. 2021; 106: 108-119
20 Szczuko M, Zapalowska-Chwyc M, Drozd A et al. Changes in the igf-1 and tnf-alpha synthesis pathways before and after three-month reduction diet with low glicemic index in women with pcos. Ginekol Pol. 2018; 89: 295-303
21 Prado Correia LE, de Almeida BC, de Jesus Simoes M et al. Igf-1r and leptin expression profile and the effects of metformin treatment on metabolic and endocrine parameters in pcos mice. Biomed Res Int. 2017; 2017: 9058307
22 Sudhakaran G, Priya PS, Jagan K et al. Osteoporosis in polycystic ovary syndrome (pcos) and involved mechanisms. Life Sci. 2023; 335: 122280
23 Kebapcilar AG, Tatar MG, Ipekci SH et al. Cornea in pcos patients as a possible target of igf-1 action and insulin resistance. Arch Gynecol Obstet. 2014; 290: 1255-1263
24 Shokeir T, El-Kannishy G. The effects of laparoscopic ovarian drilling on flow mediated dilation in women with pcos: Relationship with insulin resistance and igf-i. Minerva Ginecol. 2014; 66: 209-218
25 Heidarzadehpilehrood R, Pirhoushiaran M, Binti Osman M et al. Unveiling key biomarkers and therapeutic drugs in polycystic ovary syndrome (pcos) through pathway enrichment analysis and hub gene-mirna networks. Iran J Pharm Res. 2023; 22: e139985
26 Li S, Li Y, Yan X et al. Malat1 expression in granulosa cells in pcos patients with different phenotypes. Sci Rep. 2024; 14: 5019
27 Wang T, Xiong X, Xiao N et al. The therapeutic effect of anti-cd19 antibody on dhea-induced pcos mice. Int Immunopharmacol. 2024; 130: 111711
28 Li X, Lin Y, Cheng X et al. Ovarian ferroptosis induced by androgen is involved in pathogenesis of pcos. Hum Reprod Open. 2024; 2024: hoae013
29 Yang L, Yang Y, Han X et al. Grim19 deficiency aggravates metabolic disorder and ovarian dysfunction in pcos. BiochimBiophys Acta Mol Basis Dis. 2024; 1870: 167063
30 Serra L, Estienne A, Bongrani A et al. The epoxiconazole and tebuconazole fungicides impair granulosa cells functions partly through the aryl hydrocarbon receptor (ahr) signalling with contrasted effects in obese, normo-weight and polycystic ovarian syndrome (pcos) patients. Toxicol Rep. 2024; 12: 65-81
31 Smirnov VV, Beeraka NM, Butko DY et al. Updates on molecular targets and epigenetic-based therapies for pcos. Reproductive sciences. 2023; 30: 772-786
32 Nanda D, Chandrasekaran SP, Ramachandran V et al. Evaluation of serum mirna-24, mirna-29a and mirna-502-3p expression in pcos subjects: Correlation with biochemical parameters related to pcos and insulin resistance. Indian J Clin Biochem. 2020; 35: 169-178
33 Rotterdam EA-SPcwg. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (pcos). Human reproduction (Oxford, England). 2004; 19: 41-47
34 Daghestani MH, Alqahtani HA, AlBakheet A et al. Global transcriptional profiling of granulosa cells from polycystic ovary syndrome patients: Comparative analyses of patients with or without history of ovarian hyperstimulation syndrome reveals distinct biomarkers and pathways. J Clin Med. 2022; 11:
35 Zhu L, Han CS, Cao ZL et al. Confocal microscopic analysis of the spindle and chromosome configurations of in vitro-matured oocytes from different types of polycystic ovary syndrome patients. GynecolObstet Invest. 2015; 80: 179-186
36 Vieira RC, Barcelos ID, Ferreira EM et al. Spindle and chromosome configurations of in vitro-matured oocytes from polycystic ovary syndrome and ovulatory infertile women: A pilot study. J Assist Reprod Genet. 2011; 28: 15-21
37 Barcelos ID, Vieira RC, Ferreira EM et al. Comparative analysis of the spindle and chromosome configurations of in vitro-matured oocytes from patients with endometriosis and from control subjects: A pilot study. Fertil Steril. 2009; 92: 1749-1752
38 Kotipalli RSS, Patnaik SS, Kumar JM et al. Biochanin-a attenuates dhea-induced polycystic ovary syndrome via upregulation of gdf9 and bmp15 signaling in vivo. Life Sci. 2023; 326: 121795

39 ElMonier AA, El-Boghdady NA, Fahim SA et al. Lncrna neat1 and malat1 are involved in polycystic ovary syndrome pathogenesis by functioning as competing endogenous rnas to control the expression of pcos-related target genes. Noncoding RNA Res. 2023; 8: 263-271
40 Meng J, Chen X, Wang H et al. Porcine granulosa cell transcriptomic analyses reveal the differential regulation of lncrnas and mrnas in response to all-trans retinoic acid in vitro. Anim Biosci. 2024:
41 Meng J, Zhao Y, Lan X et al. Granulosa cell transcriptomic study reveals the differential regulation of lncrnas and mrnas related to follicle development in goat. ReprodDomest Anim. 2022; 57: 967-979
42 Ding CF, Chen WQ, Zhu YT et al. Circulating micrornas in patients with polycystic ovary syndrome. Hum Fertil (Camb). 2015; 18: 22-29
43 Chen J, Zhu Z, Xu S et al. Hdac1 participates in polycystic ovary syndrome through histone modification by regulating h19/mir-29a-3p/nlrp3-mediated granulosa cell pyroptosis. Mol Cell Endocrinol. 2023; 573: 111950
44 Siddiqui MH, Beg A, Dixit R et al. Role of vitamin d and leptin levels in pcos in young women: A family medicine perspective. J Family Med Prim Care. 2024; 13: 2612-2615
45 Attia GM, Almouteri MM, Alnakhli FT. Role of metformin in polycystic ovary syndrome (pcos)-related infertility. Cureus. 2023; 15: e44493
46 Sankhwar P, Jaiswar SP, Yadav S et al. Beneficial effects of a novel fenugreek seed extract (trigonellafoenum-graecum, furocyst(r)) in women with polycystic ovary syndrome (pcos): A follow-up compliance clinical investigation. J Am Nutr Assoc. 2023; 42: 691-699
47 Ben Salem A, Ezzidi I, Ben Abdennebi H et al. Interleukin 10 (il-10) gene variants and haplotypes in tunisian women with polycystic ovary syndrome (pcos): A case-control study. Mol Biol Rep. 2023; 50: 8089-8096
48 Bezerra Espinola MS, Lagana AS, Bilotta G et al. D-chiro-inositol induces ovulation in non-polycystic ovary syndrome (pcos), non-insulin-resistant young women, likely by modulating aromatase expression: A report of 2 cases. Am J Case Rep. 2021; 22: e932722
49 Al-Awadi AM, Babi A, Finan RR et al. Adipoq gene polymorphisms and haplotypes linked to altered susceptibility to pcos: A case-control study. Reprod Biomed Online. 2022; 45: 995-1005
50 Fedeli V, Catizone A, Querqui A et al. The role of inositols in the hyperandrogenic phenotypes of pcos: A re-reading of larner's results. Int J Mol Sci. 2023; 24:
51 Fighera TM, Dos Santos BR, Spritzer PM. Lean mass and associated factors in women with pcos with different phenotypes. PLoS One. 2023; 18: e0292623
52 Emanuel RHK, Docherty PD, Lunt H et al. Comparing literature- and subreddit-derived laboratory values in polycystic ovary syndrome (pcos): Validation of clinical data posted on pcos reddit forums. JMIR Form Res. 2023; 7: e44810
53 Escobar-Morreale HF, Martinez-Garcia MA, Insenser M et al. Serum metabolomics profiling by proton nuclear magnetic resonance spectrometry of the response to single oral macronutrient challenges in women with polycystic ovary syndrome (pcos) compared with male and female controls. Biol Sex Differ. 2023; 14: 62
54 Escobar-Morreale HF, Martinez-Garcia MA, Insenser M et al. Serum metabolomics profiling by proton nuclear magnetic resonance spectroscopy reveals sexual dimorphism and masculinization of intermediate metabolism in women with polycystic ovary syndrome (pcos). Biol Sex Differ. 2023; 14: 21
55 Jethaliya H, Gajjar N, Patel V et al. Efficacy of myo-inositol on anthropometric, metabolic, and endocrine outcomes in pcos patients: A meta-analysis of randomized controlled trial. Reprod Sci. 2022; 29: 2282-2298
56 Ji L, Jin L, Shao MJ et al. Levonorgestrel-releasing intrauterine system effects on metabolic variables in pcos. Gynecol Endocrinol. 2023; 39: 2208667
57 Jiang X, Liu R, Liao T et al. A predictive model of live birth based on obesity and metabolic parameters in patients with pcos undergoing frozen-thawed embryo transfer. Front Endocrinol (Lausanne). 2021; 12: 799871
58 Meczekalski B, Niwczyk O, Kostrzak A et al. Pcos in adolescents-ongoing riddles in diagnosis and treatment. J Clin Med. 2023; 12:
59 Melo V, Silva T, Silva T et al. Omega-3 supplementation in the treatment of polycystic ovary syndrome (pcos) - a review of clinical trials and cohort. EndocrRegul. 2022; 56: 66-79
60 Nawrocka-Rutkowska J, Szydlowska I, Jakubowska K et al. Assessment of the parameters of oxidative stress depending on the metabolic and anthropometric status indicators in women with pcos. Life (Basel). 2022; 12:
61 Nawrocka-Rutkowska J, Szydlowska I, Jakubowska K et al. The role of oxidative stress in the risk of cardiovascular disease and identification of risk factors using aip and castelli atherogenicity indicators in patients with pcos. Biomedicines. 2022; 10:
62 Nayeem J, Islam MMT, Deeba F et al. Insulin resistance and insulin secretory defect among bangaleepcos women: A case-control study. BMC EndocrDisord. 2024; 24: 207

63 Kurowska P, Dawid M, Oprocha J et al. Spexin role in human granulosa cells physiology and pcos: Expression and negative impact on steroidogenesis and proliferationdagger. Biol Reprod. 2023; 109: 705-719
64 Lacey H, Attersley-Smith S, Stone S et al. Quality of life improvements after bariatric surgery in reproductive age women with and without pcos: A cohort study. Minerva Obstet Gynecol. 2023; 75: 251-259
65 Lewandowski K, Gluchowska M, Garnysz K et al. High prevalence of early (1st trimester) gestational diabetes mellitus in polish women is accompanied by marked insulin resistance - comparison to pcos model. Endokrynol Pol. 2022; 73: 1-7
66 Li R, Mai T, Zheng S et al. Effect of metformin and exenatide on pregnancy rate and pregnancy outcomes in overweight or obese infertility pcos women: Long-term follow-up of an rct. Arch Gynecol Obstet. 2022; 306: 1711-1721
67 Zheng P, Lu Y, Tang Y et al. Effect of hypoglycemic drugs on kisspeptin expression in the hypothalamic arcuate nucleus of pcos rats. Diabetes Metab Syndr Obes. 2023; 16: 2717-2732
68 Zhou YY, Wu YQ, Chong CJ et al. Irpexlacteus polysaccharide exhibits therapeutic potential for ovarian fibrosis in pcos rats via the tgf-beta1/smad pathway. Heliyon. 2023; 9: e18741
69 Naji M, Nekoonam S, Aleyasin A et al. Expression of mir-15a, mir-145, and mir-182 in granulosa-lutein cells, follicular fluid, and serum of women with polycystic ovary syndrome (pcos). Arch Gynecol Obstet. 2018; 297: 221-231
70 Cai G, Ma X, Chen B et al. Microrna-145 negatively regulates cell proliferation through targeting irs1 in isolated ovarian granulosa cells from patients with polycystic ovary syndrome. Reprod Sci. 2017; 24: 902-910.