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PI3K/AKT Signaling in Ovarian Health and Disease: From Follicle Activation to Pathogenesis

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Abstract

The PI3K/AKT signaling axis is a key cellular mechanism that coordinates external signals for cell survival, proliferation, metabolism, and differentiation. In the ovary, fine-tuning of this network is critical for folliculogenesis, granulosa cell survival, steroidogenesis, corpus luteum function, and oocyte maturation. Disruption of this balance, either in the form of hypoactivity or hyperactivity, plays a central role in the pathogenesis of a wide range of ovarian diseases. Novel therapeutic approaches targeting this pathway are diverse, ranging from PI3K isoform-specific inhibitors and direct AKT inhibitors (such as afuresertib) to dual mTORC1/2 inhibitors (such as sapanisertib). Natural compounds and nanodrug delivery systems are also complementary options. On the one hand, inhibition of this pathway in hyperactive conditions has yielded promising results; On the other hand, activators such as SC79 could be used to preserve fertility in patients with premature ovarian insufficiency (POI). However, achieving ideal treatment faces obstacles such as the need for more precise isoform targeting, overcoming drug resistance, ensuring specific delivery to ovarian tissue, and identifying reliable biomarkers to predict treatment response. Ultimately, a deeper understanding of the molecular mechanisms regulating this axis will pave the way for precision medicine approaches to diagnose, prevent, and treat a wide range of ovarian disorders.

Keywords: PI3K/AKT signaling pathway, Ovary, Polycystic ovary syndrome, Premature ovarian insufficiency, Endometriosis, Ovarian cancer, Targeted therapy

Introduction

Ovarian diseases comprise a heterogeneous spectrum of pathological disorders that severely affect women's health from reproductive age to menopause. This broad group includes several diseases, including polycystic ovary syndrome (PCOS), a common endocrine disorder; endometriosis, a chronic inflammatory disease; premature ovarian insufficiency (POI), a disease that impairs reproductive function at a young age; and ovarian cancer, the most malignant tumor of the female reproductive system. Global epidemiological findings indicate that the prevalence of PCOS has increased from approximately 36.7 million cases to nearly 69.5 million cases between 1990 and 2021, and this upward trend is expected to continue until 2050 (1-4). Although the incidence of ovarian cancer is lower than that of other malignancies, it has the highest mortality rate among female cancers due to delayed diagnosis and aggressive clinical course, and the five-year survival rate of patients is still reported to be less than 50%. The burden of this disease is expected to increase significantly in the coming decades, especially in low- and middle-income countries. On the other hand, endometriosis affects approximately 10–15% of women of reproductive age and is usually associated with chronic pelvic pain and infertility, while POI, defined as cessation of ovarian function before the age of 40, has profound consequences on fertility, mental health, and quality of life of sufferers (5). Despite decades of extensive study, the exact etiology of these disorders remains incompletely understood. Available therapeutic approaches often have limited efficacy and are associated with side effects. In addition, in many cases, especially in endometriosis, reliable biomarkers for early diagnosis are not available. These shortcomings highlight the need to delve deeper into the molecular underpinnings and pathophysiology of ovarian diseases (6,7).

Assessment at the cellular level shows that the phosphatidylinositol-3-kinase/protein kinase B (PI3K/AKT) signaling axis plays a crucial role in translating extracellular signals into the cell's ultimate fate. The binding of growth factors, hormones, or cytokines to tyrosine kinase receptors or G protein-coupled receptors usually initiates activation of this signaling cascade. Following this event, the PI3K enzyme converts phosphatidylinositol (4,5)-bisphosphate (PIP_2) to phosphatidylinositol (3,4,5)-triphosphate (PIP_3) in the

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plasma membrane (8). Subsequently, the accumulation of PIP3 in the membrane leads to the recruitment of the AKT protein to the membrane surface, where it is fully activated through two sequential phosphorylation steps: first at Thr308 by phosphoinositide-dependent kinase (PDK1) and then at Ser473 by the mTORC2 complex. Activated AKT then phosphorylates a wide range of downstream targets, including mTOR, FOXO transcription factors, glycogen synthase kinase 3β (GSK3β), and BAD, thereby regulating fundamental processes such as cell proliferation, survival, metabolism, angiogenesis, and cell growth. It is worth noting that the tumor suppressor gene PTEN tightly controls the activity of this signaling pathway; this gene effectively inhibits this axis by dephosphorylating PIP3. In addition, other layers of regulation, including posttranslational modifications such as ubiquitination, methylation, SUMOylation, and O-GlcNAcylation, also play a role in intensifying or modulating the duration and intensity of AKT activation (9). Given the remarkable complexity of this signaling network, even minor disturbances in its function can have widespread and multifaceted consequences in ovarian tissue, where the processes of cell proliferation, differentiation, and steroidogenesis must be carried out in precise and systematic coordination throughout the reproductive cycle (10,11).

From a physiological perspective, the PI3K/AKT signaling pathway plays a pivotal role in maintaining the functional homeostasis of the ovary. During follicular development, AKT activation ensures continued follicle survival and maturation by stimulating granulosa cell proliferation and inhibiting apoptosis. In addition, this signaling pathway prevents premature activation of primordial follicles by phosphorylating the transcription factor FOXO3a and subsequently translocating it from the nucleus to the cytoplasm, thus playing a key role in preserving ovarian reserve. Furthermore, the PI3K/AKT axis acts as a link between metabolic status and reproductive function; Thus, through this pathway, insulin, while increasing glucose absorption through the GLUT4 transporter, also enhances the expression of enzymes involved in steroidogenesis, thus providing synergy between energy metabolism and ovarian hormone secretion (10,12,13).

Despite the critical importance of this pathway in ovarian homeostasis, its dysregulation is pivotal in the pathogenesis of a wide range of ovarian diseases. In PCOS, insulin resistance and chronic hyperinsulinemia lead to excessive activation of the PI3K/AKT axis. The consequences of this event are increased androgen production in theca cells, impaired granulosa cell function, and arrest of normal follicular development, ultimately leading to hyperandrogenism and anovulation. In the meantime, drugs such as metformin and inositols have partially improved the metabolic disorders and reproductive outcomes of these patients by modulating this signaling pathway. In contrast, in POI, decreased activity of the PI3K/AKT axis—often due to increased PTEN expression, genetic mutations affecting components of this pathway, or damage from chemotherapeutic agents—leads to premature activation of primordial follicles and, subsequently, an accelerated decline in ovarian reserve. It is worth noting that experimental studies have shown that pharmacological stimulation of this signaling pathway can play a protective role against deterioration of ovarian function and, under certain circumstances, help preserve fertility (14-16).

In the pathophysiology of endometriosis, chronic and sustained activation of the PI3K/AKT signaling axis promotes cell survival, angiogenesis, and resistance to apoptosis in ectopic endometriotic lesions. Recent evidence suggests that macrophage-secreted factors, including SPP1, promote lesion growth and spread through activation of the FAK/PI3K/AKT axis. In ovarian oncology, genetic alterations such as mutations in the PIK3CA gene, increased AKT protein expression, or loss of PTEN tumor-suppressor function lead to persistent activation of this signaling pathway. This in turn promotes tumor growth, metastatic invasion, and resistance to chemotherapeutic agents. In this regard, recent clinical trials of targeted inhibitors such as afuresertib (an AKT inhibitor) and sapanisertib (a dual mTORC1/2 inhibitor) have shown promising results and offer a new perspective in the treatment of this malignancy (17,18).

Accordingly, this review aims to provide a comprehensive and up-to-date overview of the role of PI3K/AKT signaling in four major ovarian diseases, namely PCOS, premature ovarian failure (POI), endometriosis, and ovarian cancer, with particular emphasis on recent advances. First, the molecular structure and physiological functions of this pathway in ovarian biology will be described. Then, the mechanisms of dysregulation of this axis and their contribution to the onset and progression of diseases will be explored in detail, integrating evidence from human genetics, tissue studies, animal models, and clinical studies. Finally, the latest targeted therapeutic approaches against this pathway will be reviewed, along with future perspectives, including ovarian-specific drug delivery systems, the discovery of predictive biomarkers, and the design of combination therapy regimens to overcome drug resistance.

Molecular Basis of the PI3K/AKT Pathway: Molecular On–Off Switches

The PI3K/AKT signaling pathway is one of the most fundamental communication networks in eukaryotic cells, integrating and coordinating diverse cellular responses to external stimuli. This axis is a key regulator of cellular homeostasis, as it can simultaneously control fate-determining processes, including survival, proliferation, differentiation, migration, metabolism, and programmed cell death. In fact, PI3K/AKT can be considered a dynamic

switch that switches the cell between growth and rest, survival and death, or proliferation and differentiation, depending on physiological or pathological conditions. In ovarian tissue, the proper functioning of this system requires precise temporal and spatial monitoring to ensure that events such as activation of primordial follicles, follicular maturation, ovulation, steroid hormone production, and maintenance of the follicular reserve proceed without disruption. Any disruption of the balance in the activity of this axis—whether it's sustained increase or abnormal inhibition—can contribute to the genesis and course of many ovarian diseases. In this section, the molecular structure of the PI3K/AKT pathway, its most important regulatory layers, and its tissue coordinates in the ovary are reviewed (8,9,19) (Figure 1). The major molecular components of the PI3K/AKT signaling pathway, together with their principal biological functions in ovarian physiology, are summarized in Table 1.

Core Components of the Pathway: Architecture of a Multilayered Molecular Switch

The starting point of this chain is the enzyme phosphatidylinositol-3-kinase (PI3K), which consists of two subunits: a catalytic (p110) and a regulatory (p85). In mammals, PI3K is classified into three main classes, of which class IA plays the most important role in transmitting signals from tyrosine kinase receptors and is most closely associated with ovarian function and disease. This class includes the catalytic isoforms p110α, p110β, and p110δ, along with several regulatory subunits such as p85α, p85β, and p55γ. The initial event in the activation of this pathway is the binding of ligands such as insulin, insulin-like growth factor (IGF), follicle-stimulating hormone (FSH), luteinizing hormone (LH), vascular endothelial growth factor (VEGF), and a wide range of cytokines to cell surface receptors. This binding results in autophosphorylation of the receptors and recruitment of mediator proteins, such as IRS, which subsequently bind to phosphorylated tyrosine residues via the SH2 domains of the p85 regulatory subunit. This binding removes the constitutive inhibition of PI3K and activates the enzyme. Activated PI3K converts PIP_2 to PIP_3, which is considered the major second messenger of this pathway (19).

PIP_3 provides a platform for binding at the plasma membrane, facilitating the assembly of PH-domain proteins, including AKT and PDK1. The association of these molecules allows for sequential phosphorylation and full activation of AKT. Recent structural studies have shown that binding of AKT to PIP_3 induces significant conformational changes in the protein, separating the PH domain from the kinase domain, a change that prepares the catalytic site for phosphorylation and activation of the enzyme (9).

AKT, also known as protein kinase B (PKB), comprises three isoforms, AKT1, AKT2, and AKT3, which, although structurally similar, exhibit significant differences in biological function. Each isoform has a PH domain at the amino terminus, a serine/threonine kinase domain in the middle, and a short regulatory region at the carboxyl terminus. Full activation of AKT requires two independent

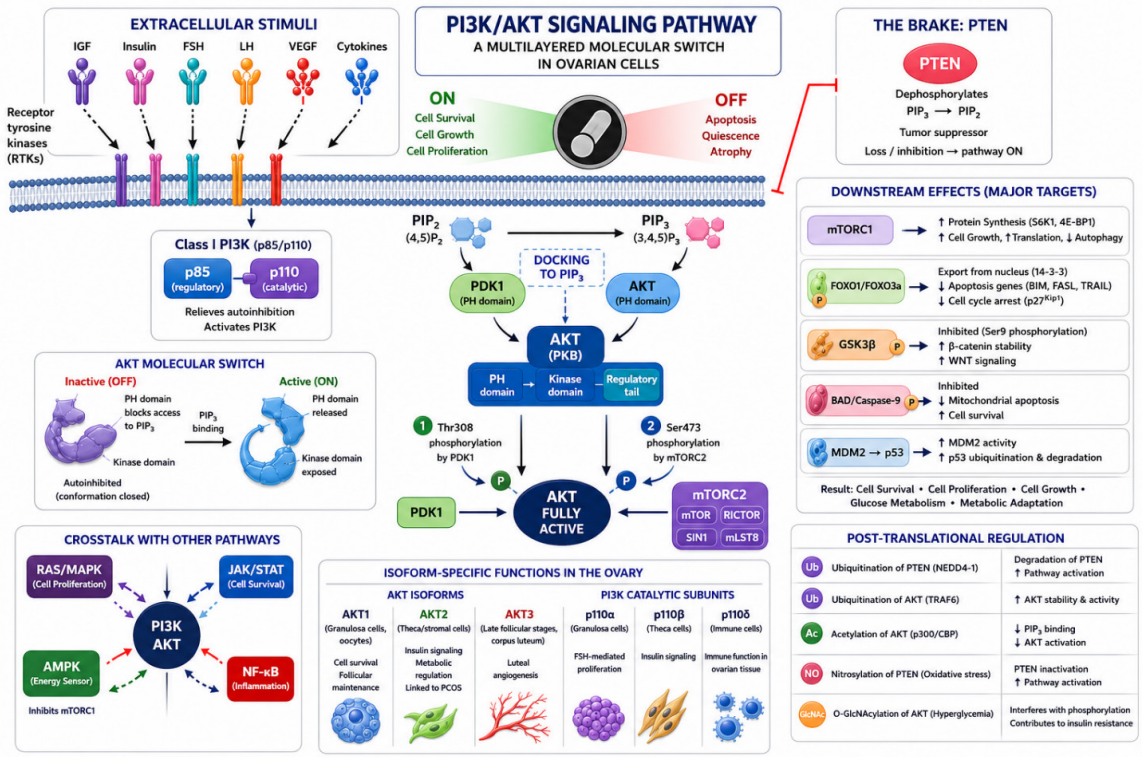

Figure 1. Molecular Basis of the PI3K/AKT Pathway: Molecular On–Off Switches.

Table 1. Core Components of the PI3K/AKT Pathway and Their Functions

Pathway Component	Type	Main Function	Ovarian Disorder–Related Alteration
PI3K (class IA)	Enzyme (p85/p110 heterodimer)	Converts PIP_2 to PIP_3	Activating *PIK3CA* mutations in ovarian cancer, endometriosis
PTEN	Phosphatase (tumor suppressor)	Converts PIP_3 back to PIP_2 (pathway off-switch)	Loss of function in PCOS, endometriosis, ovarian cancer
AKT (AKT1, AKT2, AKT3)	Kinase (Ser/Thr)	Phosphorylates downstream targets (survival, growth, metabolism)	Increased phospho-AKT in PCOS, endometriosis, ovarian cancer; decreased in POI
PDK1	Kinase	Phosphorylates AKT at Thr308	Less studied; involved in drug resistance
mTORC1	Kinase complex	Promotes protein synthesis, cell growth, inhibits autophagy	Hyperactivation in ovarian cancer and endometriosis
FOXO (FOXO1/ FOXO3a)	Transcription factor	Induces apoptosis, cell-cycle arrest	Phosphorylation and nuclear exclusion when pathway is active

phosphorylation steps: first, PDK1 phosphorylates the Thr308 residue in the activation loop, which strongly increases AKT kinase activity; then, the mTORC2 complex (including mTOR, RICTOR, SIN1, and mLST8) phosphorylates Ser473, ensuring structural stability and maximal enzymatic activity of AKT. The absence of either phosphorylation significantly reduces the function of this kinase (8).

Crystallographic and cryo-electron microscopy studies have shown that AKT is in an autoinhibitory state in the absence of stimulatory signals; In this way, the PH domain interacts with the kinase domain and prevents PIP_3 from binding and accessing the Thr308 site. Only after binding to PIP_3 does this closed structure open and provide the basis for phosphorylation by PDK1 and mTORC2. This feature is considered one of the most important mechanisms for inhibiting the inappropriate activation of the PI3K/AKT pathway (20).

Downstream Consequences: Switching Key Cellular Processes on or Off

Once activated, AKT phosphorylates more than fifty downstream substrates across multiple cellular compartments—including the nucleus, cytosol, plasma membrane, and mitochondria. Major downstream targets include:

- mTORC1: AKT activates mTORC1 by phosphorylating and inhibiting TSC2 and by suppressing PRAS40. Activated mTORC1 stimulates protein synthesis through phosphorylation of S6K1 and 4E-BP1, leading to increased cellular growth, enhanced protein translation, and inhibition of autophagy (21).
- FOXO transcription factors (FOXO1 and FOXO3a): AKT phosphorylates FOXO proteins at conserved residues, promoting their binding to 14-3-3 proteins and export from the nucleus to the cytoplasm. This process suppresses transcription of FOXO-dependent genes involved in apoptosis (e.g., BIM, FASL, TRAIL), cell-cycle arrest (p27Kip1), and metabolic regulation (22).
- GSK3β: Phosphorylation of GSK3β at Ser9 by AKT inhibits its kinase activity, preventing degradation of substrates such as β-catenin and thereby promoting WNT-mediated cell proliferation and differentiation.
- BAD and CASP9: AKT phosphorylates the pro-apoptotic protein BAD and procaspase-9, suppressing mitochondrial apoptosis pathways and promoting cell survival.
- MDM2 and p53: AKT can phosphorylate MDM2, enhancing its ability to ubiquitinate and degrade the tumor suppressor p53—a mechanism particularly relevant in ovarian cancer.

The principal negative regulator of this pathway is the phosphatase and tensin homolog (PTEN), a tumor suppressor that dephosphorylates PIP3 back to PIP2, thereby terminating PI3K signaling. Loss of PTEN function—through mutation, deletion, epigenetic silencing, or post-translational inhibition—effectively locks the pathway in an activated state. Such alterations are frequently observed in ovarian cancer, particularly in endometrioid and clear cell subtypes, and have also been reported in severe forms of PCOS and experimental models of ovarian insufficiency (23).

Interaction of PI3K/AKT With Other Signaling Pathways

The PI3K/AKT pathway does not act alone but is part of an intricate intracellular network that is closely functionally linked to other signaling cascades (24,25):

The most prominent of these interactions is the RAS/MAPK pathway, which is activated through tyrosine kinase receptors and the GRB2 and SOS proteins. Since RAS can also directly activate PI3K, there is a significant convergence between these two pathways. This feature is considered one of the main reasons for resistance to targeted therapies, as inhibition of one of these pathways is usually accompanied by compensatory activation of the other pathway (26).

In addition, cytokines such as IL-6 interact with the PI3K/AKT pathway via the JAK/STAT axis, thereby increasing cell proliferation and survival. The AMPK pathway, as a sensor of cellular energy status, limits the

anabolic effects of AKT under energy-deficient conditions by inhibiting mTORC1. AKT also promotes NF-κB activation and increased expression of inflammatory genes through activation of the IKK complex.

Functional Properties of PI3K and AKT Isoforms in the Ovary

Although all three AKT isoforms are expressed in the ovary, evidence suggests that each of them plays a specific role. AKT1 is predominantly present in granulosa cells and oocytes and is essential for cell survival, follicular development, and maintenance of ovarian reserve. AKT2 is predominantly expressed in theca and stromal cells of the ovary and plays an important role in regulating metabolism and insulin response; genetic variants in this isoform have been linked to insulin resistance and an increased risk of PCOS. AKT3, although expressed more limitedly, is involved in the development of late folliculogenesis and angiogenesis in the corpus luteum (27-29).

Similarly, different PI3K isoforms have specific functions; p110α mainly regulates granulosa cell proliferation in response to FSH, p110β is the main mediator of insulin signaling in theca cells, and p110δ is mostly expressed in immune cells located in ovarian tissue (30,31).

Post-translational Regulation of the PI3K/AKT Pathway

The activity of the PI3K/AKT pathway is not only dependent on phosphorylation, and a wide range of post-translational modifications also play a role in regulating its function. Ubiquitination of PTEN by ligases such as NEDD4-1 leads to its degradation and increased pathway activity, while ubiquitination of AKT by TRAF6 enhances its kinase activity. On the other hand, acetylation of AKT by p300/CBP can reduce its ability to bind to PIP_3. Also, nitrosylation of PTEN under oxidative stress conditions inactivates this protein. In addition, increased O-GlcNAcylation under chronic hyperglycemia disrupts the normal phosphorylation of AKT and contributes to insulin resistance (32-34).

The PI3K/AKT signaling pathway, as a central molecular switch, plays a fundamental role in regulating ovarian cell survival, proliferation, growth, and metabolic adaptation. Extracellular stimuli, including insulin, IGF, FSH, LH, VEGF, and various cytokines, activate receptor tyrosine kinases (RTKs), leading to the activation of PI3K and the conversion of PIP_2 to PIP_3. PIP_3 then recruits PDK1 and AKT to the plasma membrane, providing the necessary conditions for full AKT activation; A process that is mediated by phosphorylation of Thr308 residues by PDK1 and Ser473 by the mTORC2 complex. Once activated, AKT coordinates important processes such as cell survival, protein synthesis, follicle growth, cell proliferation, and inhibition of apoptosis by regulating a wide range of downstream molecules, including mTORC1, the transcription factors FOXO, GSK3β, BAD/CASP9, and the MDM2/p53 axis. In contrast, PTEN, the most important negative regulator of this pathway, prevents excessive activation of the PI3K/AKT pathway by dephosphorylating PIP_3 to PIP_2, thereby maintaining the balance of intracellular signaling. Furthermore, the activity of the PI3K/AKT axis is tightly regulated by post-translational modifications and modulated by extensive interactions with other signaling networks, including RAS/MAPK, JAK/STAT, AMPK, and NF-κB. Furthermore, different AKT isoforms and PI3K catalytic subunits play distinct roles in the ovary, underscoring the complexity and critical importance of this pathway in ovarian development, folliculogenesis, steroidogenesis, ovarian cell survival, and ultimately the maintenance of homeostasis and health of the female reproductive system.

Physiological Role of the PI3K/AKT Pathway in the Ovary: Regulator of Cell Growth, Survival and Function

The ovary is a dynamic, highly active organ that undergoes numerous structural and functional changes throughout the menstrual cycle. These changes, from follicle growth and selection to ovulation, corpus luteum formation, and finally its dissolution, all require precise regulation of intracellular signaling networks, and the PI3K/AKT pathway plays a pivotal role in this regulation. Under normal conditions, this axis, by establishing a balance between growth, proliferation, survival, and programmed cell death, ensures that only follicles of desirable quality progress to maturity and that unsuitable follicles are eliminated through atresia. Any disruption in this balance—whether excessive activation or deficiency of the pathway's activity—can underlie many ovarian diseases. In this section, the physiological functions of this pathway at various stages of normal ovarian function are reviewed (35,36). A summary of the alterations in PI3K/AKT signaling and their pathological implications across major ovarian disorders is presented in Table 2 (Figure 2)

Folliculogenesis and Maintenance of the Ovarian Reserve

The pool of primordial follicles established during embryonic development determines a woman's ovarian reserve. These follicles remain dormant for years until local or systemic signals trigger their activation and entry into the growing follicle pool. A key regulator maintaining primordial follicle dormancy is the transcription factor FOXO3a. In primordial follicles, FOXO3a resides within the nucleus, where it suppresses transcription of genes required for follicular growth initiation. It is believed that inhibitory signals—potentially derived from surrounding stromal cells—maintain the PI3K/AKT pathway in an inactive state in these follicles (37).

The secretion of growth factors such as GDF9 and BMP15 from the oocyte accompanies the initiation of primordial follicle activation. After binding to tyrosine kinase receptors located on the oocyte membrane and granulosa cells, these molecules stimulate the PI3K

Table 2. Physiological Roles of PI3K/AKT in Different Stages of Ovarian Function

Ovarian Process	Role of PI3K/AKT	Key Molecular Mechanism	Consequence of Dysregulation
Primordial follicle quiescence	Inactive (low AKT)	Nuclear FOXO3a → represses growth genes	Premature activation → reserve depletion (POI)
Primordial follicle activation	Transient activation	AKT → FOXO3a phosphorylation → nuclear export	Initiation of follicle growth
Granulosa cell proliferation	Active (FSH-mediated)	AKT → BAD inhibition, mTORC1 activation	Follicular atresia if signaling is reduced
Steroidogenesis (granulosa)	Enhances aromatase (CYP19A1) expression	Phosphorylation of SF-1, CREB	Reduced estrogen → impaired follicle growth (PCOS)
Corpus luteum formation and survival	Active (hCG-mediated)	AKT → prevents luteal cell apoptosis	Premature luteolysis and luteal phase defect
Oocyte maturation	Essential for meiosis completion	AKT → regulation of oocyte spindle assembly	Chromosomal abnormalities, reduced oocyte quality

pathway and increase the level of PIP_3 production. In the next step, activated AKT phosphorylates the transcription factor FOXO3a, facilitating its exit from the nucleus into the cytoplasm. This translocation relieves the repressive effect of FOXO3a on the transcription of genes essential for follicular development, such as Kit Ligand and its receptor, and as a result, the follicle transitions from the primordial stage to the primary follicle (38,39).

Evidence from gene deletion studies in animal models shows that deletion of the FOXO3a gene leads to the simultaneous activation of almost all primordial follicles, resulting in rapid depletion of ovarian reserve and POI.

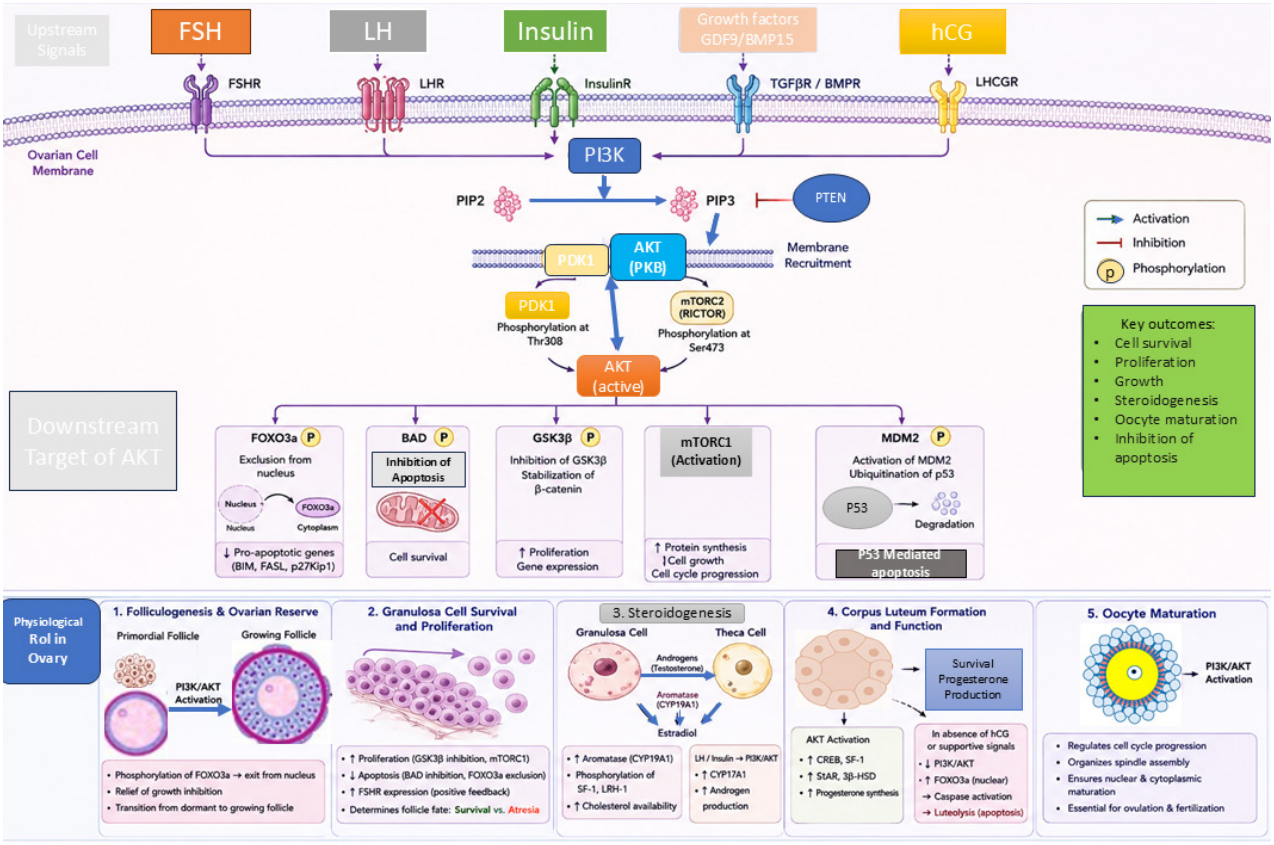

Figure 2. Central Role of the PI3K/AKT Axis in Ovarian Homeostasis and Related Diseases. This diagram illustrates the key role of the PI3K/AKT cascade in regulating ovarian growth, follicular development, cell survival, metabolism, and fertility. It also links disruption of this pathway to the pathogenesis of common ovarian diseases including PCOS, endometriosis, POI, ischemia-reperfusion injury, and ovarian cancer. Upstream, stimuli such as FSH, LH, insulin, oocyte factors (GDF9 and BMP15), and hCG bind to their receptors, activating PI3K, which converts PIP_2 to PIP_3, thereby facilitating the accumulation and activation of AKT at the membrane. Active AKT regulates the balance of survival and apoptosis and determines cell fate by phosphorylating targets such as FOXO3a, BAD, GSK3β, and mTORC1. In folliculogenesis, this axis determines whether primordial follicles remain quiescent or proliferate, and in granulosa cells, it prevents atresia by stimulating proliferation and inhibiting programmed cell death. In steroidogenesis, it controls the expression and activity of key enzymes, thereby regulating sex hormone synthesis. It also ensures the stability of the corpus luteum and progesterone secretion by maintaining the survival of luteal cells, and, when signaling decreases, it predisposes to luteolysis and apoptosis. Finally, this pathway prepares the oocyte for ovulation and fertilization by coordinating the cell cycle and nuclear-cytoplasmic maturation. In short, the fine-tuning of this cascade is crucial for maintaining normal female reproductive function.

In contrast, overexpression of PTEN, a natural inhibitor of the PI3K/AKT pathway, prevents the initiation of folliculogenesis and leads to the accumulation of quiescent follicles. Thus, the delicate balance between PI3K/AKT and FOXO3a activity acts as a two-state molecular switch that determines the fate of the follicle between remaining quiescent and entering the growth pathway (40,41).

Granulosa Cell Proliferation and Anti-apoptotic Signaling

After the onset of follicular development, granulosa cells enter a phase of rapid proliferation and form multiple layers around the oocyte. At this stage, FSH is recognized as the most potent stimulator of follicular growth. Binding of this hormone to its specific receptor (FSHR) on granulosa cells activates adenylyl cyclase via the classical pathway (i.e., through the Gs protein), increasing cAMP levels. However, recent studies have shown that FSH is also capable of activating the PI3K/AKT axis independently of the cAMP pathway (42,43).

Once activated, AKT recruits several downstream cascades in granulosa cells. On the one hand, by phosphorylating and inactivating BAD, it prevents the initiation of apoptosis. On the other hand, inhibiting GSK3β promotes β-catenin stability and increases the expression of genes involved in cell proliferation. In addition, mTORC1 activation increases the production of proteins necessary for cell cycle progression. Evidence suggests that the PI3K/AKT pathway also plays a role in regulating FSH receptor expression and, through a positive feedback loop, increases the follicle's sensitivity to this hormone.

In contrast, follicles that are moving towards atresia (degeneration) show a significant decrease in AKT activity. In these conditions, FOXO3a once again enters the nucleus and activates the transcription of proapoptotic genes such as BIM and FASL. Therefore, it can be said that the ratio of PI3K/AKT axis activity to the nuclear presence of FOXO3a is one of the most determining factors in the fate of granulosa cells - both survival and death (44).

The Role of PI3K/AKT in Ovarian Steroidogenesis

The production of steroid hormones is perhaps the most important functional achievement of the ovary; it is a delicate, coordinated process that results from the cooperation of two distinct cell populations: granulosa and theca cells. In response to FSH, granulosa cells convert androgens synthesized by theca cells into estradiol, the most important active estrogen in women, by activating the enzyme aromatase (CYP19A1). The PI3K/AKT axis plays a central role in regulating this process and, by coordinating hormonal signals with the enzymatic machinery of steroidogenesis, enables precise control of steroid hormone production. Numerous lines of evidence indicate that activation of this pathway increases aromatase expression and function, thereby enhancing estradiol synthesis. Conversely, disruption of this axis disrupts the coordination between hormonal signals and the activity of steroidogenic enzymes, disrupting normal ovarian steroidogenesis (45).

In theca cells, LH stimulates androgen synthesis by activating the PI3K/AKT pathway and increasing the expression of key enzymes such as CYP17A1. In addition, insulin signaling through its receptor activates this pathway and enhances androgen production in theca cells. This synergy explains the molecular basis of the association between hyperinsulinemia and hyperandrogenism, two prominent pathophysiological features frequently observed in PCOS (10).

Corpus Luteum: Formation, Function, and Regression

Following ovulation, the remaining granulosa and theca cells undergo luteinization, forming the corpus luteum, a transient endocrine structure responsible for progesterone production during early pregnancy. The PI3K/AKT pathway plays multiple roles during this stage (46,47).

During corpus luteum formation, AKT signaling supports the survival of differentiating luteal cells and prevents premature apoptosis. In the functional corpus luteum, AKT promotes progesterone synthesis by activating transcription factors such as CREB and SF-1, which regulate steroidogenic genes including steroidogenic acute regulatory protein (StAR) and 3β-hydroxysteroid dehydrogenase (3β-HSD) (48,49).

In the absence of pregnancy, corpus luteum regression (luteolysis) is associated with decreased PI3K/AKT signaling. Reduced AKT activity allows nuclear accumulation of FOXO3a and activation of caspase-mediated apoptotic pathways. Notably, human chorionic gonadotropin (hCG), produced during early pregnancy, prevents luteolysis by activating PI3K/AKT signaling in luteal cells, thereby maintaining corpus luteum function (50).

Oocyte Maturation

During the pre-ovulatory phase, the oocyte resumes meiosis and progresses to metaphase II. Multiple studies have demonstrated that activation of PI3K/AKT signaling within the oocyte is essential for both nuclear and cytoplasmic maturation. AKT regulates transcription factors such as FOXO3a, as well as proteins involved in regulating the spindle assembly checkpoint.

Experimental inhibition of PI3K in mouse oocytes prevents meiotic maturation and results in chromosomal abnormalities. Similar results have also been reported in human oocytes, highlighting the critical importance of this pathway in ensuring proper oocyte developmental competence (51).

Ovarian disorders associated with imbalance in the PI3K/AKT pathway

Under physiological conditions, the PI3K/AKT axis plays a fundamental role in the growth, survival, and

function of ovarian cells; however, in many ovarian disorders, this pathway is dysregulated. Importantly, the nature of this dysregulation—whether overactivation or underactivation—largely determines the type of disease that develops. Such imbalances can lead to impaired folliculogenesis, altered steroid hormone production, decreased oocyte quality, and abnormally increased cell survival or proliferation.

Increasing evidence from molecular, genetic, and clinical studies suggests that the PI3K/AKT axis plays a pivotal role in the pathogenesis of a wide range of ovarian diseases. In this section, four important diseases that are well-established to be associated with disruption of this pathway are reviewed, including PCOS, POI, endometriosis, and ovarian cancer. The principal genes, regulatory molecules, and signaling interactions involved in PI3K/AKT-mediated ovarian pathophysiology are summarized in Table 3.

The Role of the PI3K/AKT Pathway in Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is the most common hormonal disorder in women of reproductive age. It is characterized by three main clinical features: elevated androgen levels (hyperandrogenism), chronic anovulation or cessation of ovulation, and polycystic ovaries on ultrasound. Statistics show that approximately one in ten women of reproductive age has this syndrome. Although the exact cause of this disease is complex and multifactorial, recent studies have clearly shown that insulin resistance and aberrant activation of the PI3K/AKT pathway are among the most important molecular mechanisms behind ovarian dysfunction in these patients (36).

Insulin Resistance and Hyperinsulinemia: The Main Driving Force of PCOS

About half to seventy percent of women with PCOS experience some degree of insulin resistance, a phenomenon that is frequently observed even among non-obese patients. Under normal conditions, insulin, by binding to its receptor, activates the PI3K/AKT pathway and facilitates the entry of glucose into liver, muscle, and adipose cells by increasing the glucose transporter GLUT4. However, in women with PCOS, PI3K/AKT-dependent signaling in peripheral tissues is impaired; as a result, the cells' sensitivity to insulin is reduced, and to compensate for this deficiency and maintain blood sugar balance, the pancreatic β cells are forced to increase insulin secretion. This compensatory response ultimately leads to chronic hyperinsulinemia (52-54).

Interestingly, unlike surrounding tissues, ovarian cells typically maintain—or even become more responsive to—insulin, a phenomenon known as "selective pathway sensitivity." In such a situation, excess insulin in the blood can keep the PI3K/AKT pathway continuously active in the ovary, while other tissues in the body become effectively insulin resistant. The result of this dual situation is overstimulation of ovarian androgen production pathways, increased production of male hormones, and disruption of normal follicular development (13, 55).

Effect of PI3K/AKT on Theca Cells; Stimulation of Androgen Synthesis

Theca cells, the main source of androgen production in the ovary, synthesize testosterone and androstenedione. Insulin, through binding to its receptor and activating the PI3K/AKT axis, increases the expression of the key enzyme CYP17A1, thereby stimulating androgen

Table 3. Genetic and Epigenetic Alterations of the PI3K/AKT Pathway in Major Ovarian Disorders

Disorder	Gene / Protein	Alteration Type	Estimated Frequency	Functional Consequence
PCOS	AKT2	Polymorphism (increased insulin sensitivity)	~30-40% in some populations	Increased phospho-AKT in theca cells → hyperandrogenism
PCOS	PTEN	Reduced expression (miRNAs, methylation)	~20-30%	AKT hyperactivation in granulosa cells → impaired FSH response
POI	*PIK3R1* (p85α)	Loss-of-function mutation (autosomal dominant)	Rare (familial)	Reduced PI3K/AKT → premature follicle activation
POI	FOXO3a	Gain-of-function (phosphorylation-resistant) mutation	Rare	Persistent nuclear FOXO3a → arrested follicle growth
POI	PTEN	Heterozygous loss-of-function mutation	Rare (PHTS syndrome)	Transient AKT increase → rapid reserve depletion
Endometriosis	PTEN	Promoter hypermethylation, miR-21/222 silencing	>50%	PTEN loss → sustained AKT activation → survival and angiogenesis
Endometriosis	PI3K (p110α)	Overexpression (not mutation)	Common	Increased AKT signaling
Ovarian cancer (HGSOC)	*PIK3CA*	Activating mutations (exons 9, 20)	12-20%	Constitutive AKT activation → proliferation, chemoresistance
Ovarian cancer (endometrioid/clear cell)	PTEN	Deletion, mutation, methylation	30-50%	Loss of AKT inhibition → poor prognosis
Ovarian cancer (HGSOC)	*INPP4B*	Inactivating mutations	5-10%	Increased PIP_3 and phospho-AKT

production. In PCOS, chronic hyperinsulinemia leads to persistent activation of this pathway in theca cells, resulting in a dramatic increase in androgen levels. Evidence shows that theca cells isolated from PCOS patients exhibit higher phosphorylation of AKT (at Ser473 and Thr308) than those from healthy controls, even in the absence of insulin, suggesting an intrinsic defect in the regulation of this axis. Interestingly, specific inhibition of AKT with the drug miransertib in culture conditions reduced androstenedione production by about 40%, clearly confirming the direct role of this pathway in the development of hyperandrogenism (40).

Effects of PI3K/AKT on Granulosa Cells; Impaired Follicle Growth and Steroidogenesis

Under normal conditions, granulosa cells, guided by the hormone FSH, convert androgens synthesized in theca cells into estradiol using the enzyme aromatase (CYP19A1), a process crucial for normal follicular growth and ovulation.

However, in PCOS, excessive activation of PI3K/AKT disrupts this delicate coordination in two ways. First, hyperactive AKT reduces CYP19A1 gene expression and aromatase activity by phosphorylating transcription factors such as SF-1; as a result, androgens are not converted to estrogen and accumulate in the follicular environment. Second, AKT reduces FSH receptor expression by phosphorylating FOXO1 and expelling it from the nucleus, because FOXO1 is one of the positive regulators of this receptor. The consequence of these two disorders is a decrease in the responsiveness of granulosa cells to FSH and the cessation of follicle growth in the early antral phase, which ultimately leads to chronic anovulation - one of the hallmarks of PCOS (10).

Clinical Evidence and Targeted Therapeutic Strategies

As the role of PI3K/AKT in the pathogenesis of PCOS has become increasingly clear, modulation of this pathway has become a major therapeutic goal:

Metformin remains the most widely used drug in this field and indirectly inhibits PI3K/AKT activity by activating AMPK. In an animal model, chitosan nanoparticles containing metformin were able to reduce phosphorylated AKT levels by approximately 50% and reduce testosterone from 2.1 to 0.6 ng/ml (14).

Inositols (myo-inositol and D-chiro-inositol (DCI)) reduce insulin resistance and androgen production by modulating PI3K-dependent signaling. A 2025 meta-analysis showed that the use of these two compounds at a ratio of 40:1 increased the chance of spontaneous ovulation by approximately 2.5 times (56).

Natural compounds such as dragon's blood extract (Resina Draconis) have also been shown to reduce fasting glucose and testosterone in experimental models by inhibiting the PI3K/AKT/GLUT4 axis (14).

Direct AKT inhibitors such as miransertib reduced free testosterone by approximately 30%. They increased the number of ovulatory cycles from 0.2 to 1.1 cycles in a pilot study of 28 women with metformin-resistant PCOS. However, its use in women of childbearing potential remains cautious due to concerns about teratogenic effects (40,51).

The Role of the PI3K/AKT Pathway in POI

POI is a condition in which the ovaries lose their normal function before the age of 40. This disorder is characterized by three clinical features: cessation of menstruation for at least 4 months, elevated blood levels of the hormone FSH (more than 25 international units per liter), and a significant decrease in estradiol levels. Its prevalence is about 1% in women under 40 years of age and 0.1% in women under 30 years of age, and its complications go beyond infertility to include osteoporosis, cardiovascular disease, and psychological problems.

Interestingly, unlike PCOS, which is associated with excessive activity of the PI3K/AKT pathway, POI is usually characterized by reduced activity or dysregulation of this axis. This deficiency acts in one of two ways: either by causing premature activation and rapid depletion of primordial follicles or by increasing apoptosis (programmed death) of granulosa cells, both of which rapidly deplete ovarian reserve (57,58).

The Physiological role of PI3K/AKT in Maintaining Ovarian Reserve

Primordial follicles are normally quiescent for many years. The secret to this long-term quiescence is the presence of the transcription factor FOXO3a in the nucleus of the oocytes of these follicles, which, like a sentinel, inhibits growth-initiating genes and prevents premature activation. Under these conditions, the activity of the PI3K/AKT pathway is at its lowest level.

When a follicle is physiologically due to enter the growth cycle, paracrine signals from the oocyte and surrounding cells activate PI3K and initiate a chain of phosphorylations up to AKT. Activated AKT phosphorylates FOXO3a and expels it from the nucleus; In this way, transcriptional inhibition of growth genes is removed, and the follicle enters the developmental phase. This is a precise and calculated switch that activates only a limited number of follicles per cycle. But if this activation occurs inappropriately or excessively - for example, due to a disruption in the regulation of the pathway - a chain of primordial follicles wakes up simultaneously. This rush to start growth, although at first glance it seems beneficial, in practice means a rapid depletion of the limited ovarian reserve, and it is precisely this event that ultimately leads to premature ovarian failure (59).

Genetic alterations in the PI3K/AKT Pathway Associated With POI

Genetic studies in patients with POI have identified

several molecular alterations in key components of this pathway, each of which disrupts the delicate balance of ovarian reserve in some way:

- Inactivating mutations in PIK3R1: This gene encodes the p85α regulatory subunit. Its inactivating mutations disrupt PI3K activation and AKT phosphorylation. In these patients, POI is often associated with common variable immunodeficiency and insulin resistance. Animal models have also shown a reduction of primordial follicles of approximately 50% (60).
- Activating or phosphorylation-resistant FOXO3a mutations: Mutations that render FOXO3a resistant to phosphorylation or increase its activity prevent this factor from exiting the nucleus. As a result, FOXO3a remains persistently in the nucleus and represses follicular growth genes. This leads to reduced ovarian reserve, poor response to stimulation, and familial POI (61,62).
- Loss-of-function mutations in PTEN: Loss-of-function mutations in PTEN remove the natural brake on the PI3K/AKT pathway, leading to excessive activation and rapid follicular growth in the short term. However, this unbridled acceleration leads to the premature depletion of ovarian reserve and, in the long term, POI. This pattern is also seen in the PTEN hamartoma tumor syndrome and is associated with an increased risk of endometrial and ovarian cancers (63).

PI3K/AKT Dysfunction in Chemotherapy-Induced POI

Chemotherapy drugs such as cyclophosphamide, cisplatin, and doxorubicin are among the most important factors in the development of acquired POI in women undergoing cancer treatment. These compounds kill oocytes and granulosa cells by inducing DNA damage and activating cell death pathways. Experimental studies have shown that cyclophosphamide strongly reduces the level of phosphorylated AKT in granulosa cells, increases the nuclear accumulation of FOXO3a, and stimulates the expression of the proapoptotic genes BIM and PUMA (23).

Although primordial follicles are relatively resistant to direct damage from these drugs due to their lower metabolic activity, conditions that suppress AKT survival signaling lead to secondary activation and eventual gradual atrophy. This silent but continuous process gradually depletes ovarian reserve and leads to progressive ovarian failure (23,62).

Therapeutic Strategies Based on PI3K/AKT Activation

Given the critical role of PI3K/AKT in follicle survival, temporary, controlled activation of this pathway has been proposed as a promising approach to preserving fertility and treating POI. The most important of these strategies are reviewed below:

- **SC-79; a direct activator of AKT:** SC-79 is a drug that acts independently of PI3K and activates this kinase by increasing the phosphorylation of AKT at two key sites, Thr308 and Ser473. In animal models treated with cyclophosphamide, intraovarian injection of SC-79 rescued approximately 60% of primordial follicles, maintained AMH levels within the normal range, and significantly reduced granulosa cell death. Phase I human trials to investigate the efficacy of this drug in preserving fertility in women undergoing chemotherapy are planned for 2026 (64).
- **Hormones and growth factors:** hCG and IGF-1 exert protective effects on the ovary through physiological stimulation of the PI3K/AKT pathway. In a pilot study of women with breast cancer receiving cyclophosphamide, pretreatment with hCG reduced the incidence of ovarian failure from 50% to 25%. However, careful patient selection and screening are necessary because hCG receptors are present in some breast tumors (65).
- **Natural compounds and traditional formulations:** Some natural compounds have also shown promise in treating POI by activating this pathway. In a study of 120 women with idiopathic POI, the traditional Chinese formulation Tiaozhou Ziyin reduced mean FSH levels from 78 to 32 IU/L after 6 months of treatment and induced at least one spontaneous menstrual cycle in 24% of patients. Molecular studies confirmed increased phosphorylation of AKT and FOXO3a in granulosa cells (33,64). The flaxseed-derived compound secoisolariciresinol diglucoside also reduced cell death in a mouse model of cyclophosphamide-induced POI by activating PI3K/AKT (10).

PI3K/AKT Signaling in Endometriosis and Ovarian Endometriomas

Role of the PI3K/AKT pathway in endometriosis and ovarian endometrioma. Endometriosis is a chronic, estrogen-dependent inflammatory disease characterized by the presence of endometrial-like tissue (glands and stroma) outside the uterine cavity. Its most common and clinically significant manifestation is ovarian endometrioma, also known as the "chocolate cyst." It affects approximately 10–15% of women of reproductive age and is a major cause of chronic pelvic pain and infertility. What distinguishes endometriosis from many diseases is the extraordinary ability of ectopic endometrial cells to survive, implant, proliferate, and resist programmed cell death, even in the unfavorable environment of the peritoneal cavity. Increasing evidence suggests that persistent and aberrant activation of the PI3K/AKT pathway is one of the most important molecular mechanisms behind these invasive features (66,67).

Enhanced PI3K/AKT Signaling in Endometriotic Lesions

Several studies using immunohistochemistry and

Western blotting have consistently shown that the level of phosphorylated AKT (at sites Ser473 and Thr308) in endometriotic tissues, especially in ovarian endometriomas, is significantly higher than in normal endometrium. This sustained activation results from the simultaneous action of several molecular mechanisms (67).

One of the most important of these changes is the reduction of PTEN gene expression, the main brake on the PI3K pathway. Hypermethylation of the PTEN promoter region in endometriotic cells silences PTEN transcription, and a significant reduction in PTEN expression is observed in more than half of the samples examined. Furthermore, increased expression of microRNAs such as miR-21 and miR-222, which directly target PTEN mRNA, exacerbates the repression of this gene (68).

At the same time, increased expression of catalytic and regulatory subunits of PI3K (such as p110α and p85α) has also been reported to enhance AKT activation at downstream stages. On the other hand, the peritoneal inflammatory microenvironment, which is rich in proinflammatory cytokines such as IL-6, TNF-α, and IL-1β, further activates the PI3K/AKT pathway by binding to its receptors and amplifying survival and proliferation signals of aberrant cells (69).

Biological Consequences of PI3K/AKT Activation in Endometriosis

a. Resistance to Apoptosis and Increased Cell Survival

Eccentric endometrial cells display a remarkable resistance to anoikis (death due to detachment from the substrate) and oxidative stress-induced apoptosis. Studies have shown that pharmacological inhibition of PI3K with LY294002 increases the rate of apoptosis in these cells by three- to fivefold. Active AKT ensures survival in several ways: by phosphorylating and inactivating BAD, by increasing antiapoptotic proteins such as Bcl-2 and Survivin, and by phosphorylating FOXO1, which, upon exiting the nucleus, reduces transcription of death genes (66,69,70).

b. Stimulation of Angiogenesis

The growth of endometriotic lesions is highly dependent on the formation of new blood vessels. Active AKT increases the expression of VEGF by increasing the stability and activity of HIF-1α. VEGF concentrations are significantly higher in peritoneal fluid of women with endometriosis and correlate with disease severity. Animal studies have also shown that inhibition of PI3K/AKT significantly reduces vascular density in lesions (71).

c. Enhanced Inflammation and Positive Feedback Loops

Activation of AKT through NF-κB activation increases the expression of proinflammatory cytokines such as IL-6, IL-8, and TNF-α. These cytokines in turn activate PI3K/AKT, creating a vicious cycle of inflammation that promotes disease persistence and progression. This pathway also plays a role in the polarization of macrophages to the M2 phenotype, which is associated with the progression of endometriosis. A 2025 study showed that osteopontin (SPP1) secreted from M2 macrophages accelerates lesion progression through the FAK/PI3K/AKT axis; inhibition of SPP1 or FAK reduces AKT phosphorylation and increases cell apoptosis (72,73).

Ovarian Endometriomas: Distinct Molecular Features

Ovarian endometrioma is a specific manifestation of this disease, characterized by cysts containing degenerated blood. PI3K/AKT activity in the wall of these cysts is even higher than in peritoneal lesions. The hypoxic microenvironment resulting from repeated hemorrhages independently activates HIF-1α, which in turn stimulates PI3K/AKT. As a result, a cycle is formed in which hypoxia activates HIF-1α, HIF-1α increases angiogenesis and PI3K/AKT, and this chain ultimately leads to cyst growth and exacerbation of hypoxia (74,75).

Therapeutic Targeting of the PI3K/AKT Pathway in Endometriosis

Given the pivotal role of this pathway, inhibition of PI3K/AKT has become one of the most important therapeutic targets.

PI3K Inhibitors

The nonselective drug LY294002 has reduced lesion size by approximately 50–60% in animal models, but systemic toxicity has limited its clinical application. For this reason, more selective inhibitors such as Alpelisib (a specific p110α inhibitor) are being evaluated in preclinical stages (76).

mTOR Inhibitors

Downstream of this pathway, inhibition of mTOR with rapamycin and everolimus has also shown promising results in animal models, increasing apoptosis and reducing lesion volume. A 2024 phase II clinical trial in women with endometriosis refractory to hormonal therapies showed that three months of everolimus treatment reduced pain intensity and was well tolerated (77,78).

The Natural Compounds

Curcumin, resveratrol, and berberine have been shown to increase apoptosis and reduce angiogenesis in experimental models by simultaneously inhibiting PI3K/AKT and NF-κB. Resveratrol has shown significant antiangiogenic effects by reducing HIF-1α and VEGF (79).

The Role of the PI3K/AKT Pathway in Ovarian Cancer

Ovarian cancer is the most lethal malignancy of the female reproductive system. It owes this unfortunate status to two

features: late diagnosis in advanced stages and frequent resistance to chemotherapy. Despite all the therapeutic advances, the five-year survival rate for patients with advanced disease remains around 30%. Histologically, this cancer is divided into four main subtypes: the most common is high-grade serous carcinoma (HGSOC); next are low-grade serous carcinoma (LGSOC), endometrioid carcinoma, and clear cell carcinoma. Disturbances in the PI3K/AKT pathway are seen in more than half of ovarian cancer cases, but the type, frequency, and consequences of these disorders differ significantly in different histological subtypes. In this section, the role of this pathway in tumorigenesis, development of therapeutic resistance, and the molecular basis of targeted therapies are reviewed (25,80,81).

Prevalence of Genetic Alterations in the PI3K/AKT Pathway

Disorders of this pathway in ovarian cancer can occur at any point in the chain, from membrane-surface receptors to core components and downstream molecules (25).

One of the most common of these alterations is activating mutations in the PIK3CA gene, which encodes the p110α catalytic subunit. These mutations occur predominantly in exons 9 and 20 and are present in approximately 12–20% of HGSOC, while in endometrioid and clear cell carcinomas this figure reaches 20–40% (25).

Loss of PTEN function, the pathway's main brake, is also one of the most important mechanisms of activation. This alteration may occur as a homozygous deletion, an inactivating mutation, or promoter hypermethylation. In HGSOC, loss of PTEN function is relatively rare (5–10%), but in endometrioid and clear cell carcinomas, its frequency reaches 30–50%. Loss or deletion of PTEN is associated with a worse prognosis and resistance to platinum chemotherapy (82,83).

Amplification of AKT1 or AKT2 is less common (<5%), but these alterations are often more abundant in refractory tumors. Inactivating mutations in INPP4B (a PTEN-like phosphatase) have also been reported in 5–10% of HGSOC patients and are associated with increased AKT phosphorylation (84).

Notably, these genetic alterations often co-occur with other oncogenic abnormalities; for example, TP53 mutations in HGSOC and KRAS or BRAF mutations in LGSOC are commonly associated with PI3K/AKT activation. This broad interaction between the PI3K/AKT, RAS/MAPK, and DNA repair pathways provides a solid basis for combination therapies (85).

Functional Consequences of PI3K/AKT Activation

a. Increased Proliferation and Survival of Cancer Cells

Sustained activation of AKT, caused by PIK3CA mutations or loss of PTEN, promotes malignant cells to proliferate and survive indefinitely. AKT increases protein synthesis and cell growth by activating mTORC1 and, conversely, by phosphorylating and inactivating BAD and FOXO factors, thereby inhibiting apoptosis. In cell lines with PIK3CA mutations, AKT inhibition with the drug capivasertib can increase apoptosis by three to fivefold (86,87).

b. Increased Invasion and Metastatic Potential

PI3K/AKT activation stabilizes β-catenin by inhibiting GSK3β and increases the expression of EMT factors such as Snail and Twist. AKT also stimulates the expression of matrix-degrading enzymes (MMP2 and MMP9), which facilitate tumor cell migration. Clinically, tumors with high levels of phospho-AKT are more likely to metastasize to the peritoneum and develop carcinomatosis (88).

c. Chemotherapy Resistance

PI3K/AKT is one of the most important factors in resistance to platinum drugs and taxanes. AKT mediates this resistance in several ways: increased expression of ERCC1 to repair DNA damage, downregulation of the copper transporter CTR1 to limit the entry of platinum drugs, and inhibition of apoptosis even in the presence of extensive DNA damage. AKT phosphorylation is significantly higher in platinum-resistant tumors (89,90).

Clinical Trials Targeting the PI3K/AKT Pathway

Given the key role of this pathway, several inhibitors have entered clinical trials:

AKT Inhibitors

Capivasertib is one of the most promising options in platinum-resistant ovarian cancer. In the phase II PROFECTA-II study (2025), its combination with paclitaxel increased the response rate from 12 to 34% in patients with high phospho-AKT expression. The main side effects included rash, hyperglycemia, and diarrhea, and a phase III study is currently being designed (91-93).

Dual mTORC1/2 Inhibitors

sapanisertib, in combination with paclitaxel, improved progression-free survival in relapsed HGSOC in the DICE study (HR=0.66). Interestingly, this benefit was observed independently of the level of AKT phosphorylation, suggesting mechanisms of action beyond direct AKT inhibition (94-96).

PI3K Plus PARP Inhibition

The combination of Alpelisib (a specific PI3Kα inhibitor) with Olaparib is being investigated in patients with PIK3CA mutations, PTEN depletion, or homologous repair defects. PI3K/AKT inhibition, by reducing BRCA1/2 expression, induces a phenotype known as BRCAness, which increases sensitivity to PARP inhibitors. Early phase II results have reported a response rate of approximately 45% in platinum-resistant patients (97-99).

Dual PI3K/AKT and MEK Inhibition in LGSOC

Low-grade serous carcinoma often harbors KRAS or

BRAF mutations along with PI3K/AKT activation. The combination of MEK inhibitors (e.g., trametinib) and AKT has almost completely inhibited tumor growth in xenograft models. The efficacy of this strategy is being evaluated in the phase II study (25,100).

Predictive Biomarkers and Mechanisms of Resistance

Among the most important biomarkers proposed for response to PI3K/AKT inhibitors are phospho-AKT by immunohistochemistry, PIK3CA mutations, and PTEN depletion. However, none of these markers alone can accurately predict therapeutic response. For example, tumors lacking PTEN may respond to PI3K inhibitors but be resistant to AKT inhibitors due to AKT activation from independent pathways (e.g., PDK1). For this reason, the use of multigene molecular profiling to select appropriate patients has received increasing attention (101,102).

Acquired resistance to these inhibitors usually develops within 6 to 12 months after initiation of therapy. It is caused by factors such as secondary mutations in PI3K, compensatory activation of the MAPK pathway, and metabolic reprogramming of tumor cells. For this reason, developing combination strategies aimed at simultaneously inhibiting these escape pathways is one of the most important areas of current research in the treatment of ovarian cancer.

Role of the PI3K/AKT Pathway in Other Ovarian Disorders

In addition to the four major diseases reviewed in detail earlier—PCOS, POI, endometriosis, and ovarian cancer—growing evidence suggests that the PI3K/AKT pathway is involved in the pathophysiology of several other ovarian disorders. Although research in this area is still in its early stages, understanding this role could open new avenues for diagnosis and treatment. In this section, we discuss three other conditions: ovarian hyperstimulation syndrome (OHSS), functional cysts and benign tumors, and ischemia-reperfusion injury due to ovarian torsion.

Ovarian Hyperstimulation Syndrome

OHSS is an iatrogenic and unwanted complication resulting from ovarian stimulation in assisted reproductive treatments, particularly in vitro fertilization (IVF). This syndrome is characterized by marked ovarian enlargement, increased vascular permeability, and fluid accumulation in the abdominal and peri-pulmonary cavities. In severe cases, OHSS can be life-threatening due to thromboembolism or renal failure (103).

The hormone hCG, which is administered for final oocyte maturation, increases VEGF production, possibly through activation of the PI3K/AKT pathway in granulosa and endothelial cells. VEGF is the primary driver of increased vascular permeability in OHSS. Experimental studies have shown that PI3K inhibition with LY294002 significantly reduces serum VEGF levels and vascular permeability in mouse models (104). Polymorphisms in the AKT2 gene have also been reported to be associated with the severity of OHSS in women undergoing IVF.

Clinically, replacement of hCG with GnRH agonists to stimulate terminal oocyte maturation has reduced the incidence of OHSS; this effect is attributed in part to reduced activation of the PI3K/AKT/VEGF axis in granulosa cells. Cabergoline, a dopamine agonist that inhibits the VEGFR2 pathway, has also been shown to be effective in preventing OHSS and likely exerts its effects in part by modulating crosstalk with PI3K/AKT (105).

Functional Ovarian Cysts and Benign Tumors

Follicular and corpus luteum cysts are the most common functional ovarian cysts, which are usually benign and resolve spontaneously. However, some follicular cysts enlarge due to anovulation and continued growth, causing pelvic pain and discomfort.

Histopathological studies have shown that granulosa cells in stable follicular cysts have higher levels of phosphorylated AKT compared with normal follicles. This increase is likely due to decreased PTEN expression or enhanced FSH signaling. AKT activation, by inhibiting apoptosis, increases the long-term survival of cystic cells. In animal models, AKT inhibitors have been shown to reduce cyst size (23,106).

In benign ovarian tumors such as serous cystadenomas, mature cystic teratomas, and fibromas, alterations in the PI3K/AKT pathway have rarely been investigated. A small study in 2024 of 45 cystadenoma specimens showed slightly increased levels of phospho-AKT compared with normal ovarian tissue, but no PIK3CA mutations or PTEN deletions were observed. These findings suggest functional (not genetic) activation of the pathway, possibly through local growth factors. Given the benign nature of these tumors, PI3K/AKT inhibition currently has no established clinical utility (107).

Ovarian Torsion and Ischemia–Reperfusion Injury

Ovarian torsion is a gynecological emergency caused by the twisting of the ovary around its vascular base and, if not treated promptly, can lead to necrosis and loss of the ovary. Even after detorsion, ischemia-reperfusion injury occurs due to the massive production of free radicals and inflammatory mediators (108,109).

Several experimental studies have demonstrated a protective role of the PI3K/AKT pathway against reperfusion injury. In mouse models subjected to torsion and subsequent detorsion for 3 h, phosphorylated AKT levels decreased rapidly, and granulosa cell apoptosis increased. Preemptive administration of PI3K/AKT activators such as IGF-1 or SC-79 before detorsion reduced apoptosis and preserved follicle survival (110).

In addition, antioxidant compounds such as resveratrol and curcumin have been shown to reduce ovarian ischemia-reperfusion injury by activating PI3K/AKT and

inhibiting apoptotic pathways. A small clinical study in women undergoing detorsion reported that intraoperative intravenous administration of resveratrol reduced serum inflammatory markers including IL-6 and TNF-α and increased the proportion of viable follicles in ovarian biopsy specimens (111).

Therapeutic Targets: From Molecular Keys to Clinical Applications

A deeper understanding of the molecular mechanisms of the PI3K/AKT pathway and its role in ovarian diseases has paved the way for the development of drugs that directly target its components. Given the dual nature of this pathway—increased activity in PCOS, endometriosis, and ovarian cancer on the one hand, and decreased activity in POI on the other—therapeutic approaches are also divided into two main categories: inhibitors for conditions with hyperactivity, and activators for conditions with hypoactivity or impaired signaling. In this section, we review the most important therapeutic agents in this pathway, from preclinical studies to clinical trials. Current therapeutic agents targeting the PI3K/AKT signaling pathway, together with their mechanisms of action and clinical development status, are summarized in Table 4.

Inhibitors of the PI3K/AKT Pathway

PI3K Inhibitors

PI3K inhibitors are divided into two generations: first-generation nonselective (e.g., wortmannin and LY294002) and second-generation isoform-selective (e.g., idelalisib, which targets p110δ, and alpelisib, which acts against p110α) (112).

In ovarian cancer, alpelisib has been studied as a single agent or in combination with PARP inhibitors (e.g., olaparib) in phase II and III trials. Initial results suggest that patients with PIK3CA mutations or PTEN deficiency benefit most from this drug. However, metabolic side effects, such as hyperglycemia and skin rash, are major limitations of this class of drugs (113).

In endometriosis, inhibitors such as LY294002 have been shown to reduce lesion size and pelvic pain in animal models, but no human clinical trials have been conducted (114).

AKT Inhibitors

Several AKT inhibitors, such as capivasertib (AZD5363), afuresertib (GSK2110183), ipatasertib (GDC-0068), and miransertib (ARQ092), have shown promising antitumor effects in preclinical studies and clinical trials. However, most of these compounds are pan-AKT inhibitors that simultaneously target all three AKT isoforms, AKT1, AKT2, and AKT3. Although this approach can effectively silence the entire PI3K/AKT signaling network, it is associated with an increased risk of systemic side effects due to the different physiological roles of each isoform.

Importantly, the AKT2 isoform is the dominant isoform in insulin signaling and regulation of glucose homeostasis in tissues such as muscle, fat, and liver. Therefore, inhibition of this isoform is significantly associated with treatment-induced hyperglycemia, which is among the most common dose-dependent toxicities of pan-AKT inhibitors. This metabolic complication may limit the long-term use of these drugs, especially in patients with pre-existing insulin resistance or metabolic disorders (93). In contrast, AKT1 plays a major role in cell proliferation and survival, whereas AKT3 is involved in the growth of specific tissues and has been associated with the progression of some malignancies, including ovarian cancer. Such functional distinction between isoforms has prompted researchers to develop isoform-selective inhibitors to reduce systemic toxicity while maintaining therapeutic efficacy. Although highly selective inhibitors of AKT1 or AKT3 are still mostly in the preclinical stage and have not yet been routinely used in the clinic, this class of compounds is considered a promising strategic compound in the context of precision medicine. Future

Table 4. Clinical Trials of PI3K/AKT Pathway Inhibitors in Ovarian Disorders

Drug	Target	Disorder	Trial Phase	Key Results (as of 2025)	Common Adverse Effects
Afuresertib	AKT (non-selective)	Platinum-resistant ovarian cancer (HGSOC, high phospho-AKT)	Phase II (PROFECTA-II)	Increased ORR from 12% to 34%; PFS 3.8 → 7.1 months	Rash, hyperglycemia, diarrhea
Sapanisertib	Dual mTORC1/2	Recurrent ovarian cancer (HGSOC)	Phase II (DICE)	HR = 0.66 for PFS; response independent of phospho-AKT	Fatigue, stomatitis
Alpelisib + olaparib	PI3Kα + PARP	Ovarian cancer with *PIK3CA* mutation or PTEN loss	Phase II	ORR ~45% in platinum-resistant disease	Hyperglycemia, nausea, fatigue
Miransertib	AKT	Metformin-resistant PCOS	Phase I/II pilot	Free testosterone ↓30%; ovulation frequency increased	Mild GI; potential teratogenicity
Everolimus	mTORC1	Hormone-resistant endometriosis	Small phase II (2024)	Pain score (VAS) reduced from 8.2 to 4.5	Stomatitis, fatigue
SC-79	Direct AKT activator	Chemotherapy-induced POI	Preclinical (mouse)	Preserved 60% of primordial follicles	Not yet evaluated in humans

therapies based on selective regulation of AKT isoforms could improve the therapeutic index by reducing metabolic complications due to off-target effects and allow for personalized management of ovarian diseases (115,116).

mTOR Inhibitors

Rapamycin and its analogs (everolimus and temsirolimus), which inhibit mTORC1, have been investigated in ovarian cancer and endometriosis. In addition, dual mTORC1/2 inhibitors such as sapanisertib have shown more promising results.

In the phase II DICE trial (2025), the combination of sapanisertib with paclitaxel improved progression-free survival compared with paclitaxel alone in patients with recurrent ovarian cancer (HR = 0.66). Notably, response to therapy was not predicted by phospho-AKT levels, suggesting the presence of AKT-independent mechanisms of action (117,118).

Pathway Activators for Fertility Preservation and POI Treatment

Unlike cancer therapy, where pathway inhibition is the primary goal, conditions such as POI and chemotherapy-induced ovarian injury often require transient activation of the PI3K/AKT signaling pathway.

One direct approach is to use AKT activators. SC-79 is a specific AKT activator that increases phosphorylation at Thr308 and Ser473 without directly affecting PI3K (119).

In a mouse model of cyclophosphamide-treated ovarian cancer, intraovarian injection of SC-79 three days before chemotherapy preserved approximately 60% of primordial follicles and maintained normal AMH levels. Human studies in breast cancer patients undergoing chemotherapy are in preclinical design (120).

Natural Compounds and Nanoformulations

In recent years, research has placed increasing attention on plant and other natural compounds that can modulate the PI3K/AKT pathway. These compounds, with diverse mechanisms and often fewer side effects than chemical drugs, provide attractive options for the management of ovarian disorders:

Metformin, long recognized as a first-line drug in the treatment of PCOS, leads to partial inhibition of the PI3K/AKT pathway through indirect activation of AMPK and improvement of insulin resistance. Nanoformulation (metformin-chitosan) has been shown in animal models of PCOS to restore AKT/GLUT4 signaling in ovarian tissue and reduce hyperandrogenism (10).

Inositols (particularly myo-inositol and d-chiro-inositol) act as quasi-competitive modulators of PI3K. Evidence from multiple meta-analyses has shown that these compounds can improve ovulation and oocyte quality in women with PCOS (121).

Resina Dracunis (dragon's blood), a plant compound with a long history in traditional medicine, was shown in a 2025 study based on network pharmacology and experimental validation to inhibit the PI3K/AKT/GLUT4 pathway in PCOS-affected mouse ovaries and reduce fasting glucose and testosterone levels (14).

Resveratrol, berberine, and curcumin, three bioactive compounds with known anti-inflammatory and anti-apoptotic properties, have also shown beneficial effects in models of POI and PCOS. A significant part of these effects is exerted through modulation of the PI3K/AKT pathway (122).

The traditional formulation of Tiaozhou Ziyin, as well as secoisolariciresinol diglucoside (derived from flaxseed), has been shown to reduce granulosa cell apoptosis and restore normal estrous cycling in POI models by activating the PI3K/AKT pathway (64).

Conclusion

The PI3K/AKT signaling axis is not only one of the most important regulators of ovarian health, but also central to the pathogenesis of many disorders of this vital organ. As described in this review, dysregulation of this pathway has distinct pathological consequences depending on the direction of the alteration: hyperactivity is associated with PCOS, endometriosis, and ovarian cancer, whereas decreased activity is implicated in POI and ischemic injury.

This dichotomy has provided the basis for the design of targeted therapeutic strategies. On the one hand, inhibitors such as afuresertib have shown promising clinical efficacy in chemotherapy-resistant ovarian cancer. On the other hand, natural compounds and drugs such as metformin are considered safer options for PCOS and endometriosis. In POI, transient activation of the pathway with a compound such as SC-79 has significant potential to preserve fertility.

Overall, the PI3K/AKT pathway appears to provide a molecular bridge between ovarian health and disease. Successful translation of these fundamental findings into the clinical setting—through precision medicine and the development of novel drugs—has great potential to improve reproductive outcomes, reduce disease burden, and enhance the quality of life for women worldwide.

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Conflict of Interests
Authors declare that they have no conflict of interests.

Ethical Issues
Not applicable.

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