

MINI-REVIEW

The role of progesterone in ovarian cancer from pathogenesis to personalized therapy: an updated mini-review

Iara Fernandes^{1,†}, Rita Coelho^{2,*†}, Margarida Figueiredo-Dias¹, Ricardo Roque²¹Faculty of Medicine, Gynecology
University Clinic, University of Coimbra,
3000-548 Coimbra, Portugal²Medical Oncology Department,
Portuguese Institute of Oncology of
Coimbra, 3000-075 Coimbra, Portugal***Correspondence**4126@ipocoimbra.min-saude.pt
(Rita Coelho)

† These authors contributed equally.

Abstract

Ovarian cancer is the most lethal gynaecologic malignancy, with high-grade serous ovarian carcinoma representing the most prevalent and aggressive subtype. Despite advances in surgery and chemotherapy, recurrence remains high, highlighting the need for novel therapeutic approaches. Progesterone plays a dual role in ovarian cancer, acting both as a potential tumour suppressor and, in specific genetic contexts, as a carcinogenic factor. While hormone therapy remains underutilized, emerging evidence supports its relevance in selected patient populations. This narrative review aims to explore the physiological and pathological roles of progesterone in ovarian cancer and its potential as a therapeutic target, to identify future research opportunities, focused on molecular stratification to optimize endocrine strategies and integrate hormonal biomarkers into clinical decision-making.

Keywords

Ovarian cancer; Progesterone; Hormonal therapy; PR receptors

1. Introduction

Ovarian cancer (OC) is the most aggressive gynaecological malignancy and the fifth leading cause of cancer-related death among women worldwide, with approximately 300,000 new cases diagnosed each year [1]. It typically presents at an advanced stage due to vague and nonspecific symptoms, such as abdominal distension and urinary urgency, which contribute to diagnostic delays. This late presentation, combined the lack of effective early detection biomarkers and limited understanding of resistance mechanisms to current therapies, results in a poor prognosis, with 5-year survival rates for advanced-stage disease ranging between 30% and 40% [2, 3].

Epithelial OC (EOC), particularly high-grade serous ovarian carcinoma (HGSOC), is the most common histological subtype, accounting for nearly 70% of all EOC cases. Approximately 80% of patients are diagnosed at an advanced stage, often with extensive peritoneal dissemination. Although most cases are sporadic, pathogenic variants in BReast CAncer gene 1 (*BRCA1*) and BReast CAncer gene 2 (*BRCA2*) are recognised as major hereditary risk factors, albeit with incomplete penetrance [4, 5].

In recent decades, sex hormones—particularly progesterone—have attracted increasing interest in OC research. Progesterone plays essential roles in ovarian physiology and modulates key processes involved in carcinogenesis and tumour progression, such as apoptosis, cell survival, and invasiveness, indicating its potential as a therapeutic target [6]. This review explores the multifaceted

roles of progesterone in OC pathogenesis and progression and evaluates emerging evidence supporting its therapeutic relevance.

2. Methods

This narrative review was based on a non-systematic search of the PubMed database, using combinations of the Medical Subject Headings (MeSH) terms: “Progesterone”, “Gonadal Steroid Hormones”, “Ovarian Neoplasms”, and “Therapeutics”. The primary search was limited to articles published in English between 2014 and 2025. Additionally, a backward citation search was conducted to identify earlier relevant publications referenced within the selected articles, thereby broadening the scope of the review. A total of 39 key articles were selected based on their relevance to the physiological, molecular, and therapeutic roles of progesterone in OC. Articles were subjectively assessed for scientific quality and contribution to the field. As a narrative (non-systematic) review, several limitations must be acknowledged, including potential selection bias, limited reproducibility, and the possibility of excluding pertinent studies not captured by the chosen search strategy.

3. Progesterone: more than a sex hormone in women's health

3.1 Production and physiology of progesterone

Progesterone, the “pregnancy hormone”, plays a pivotal role in maintaining gestation by suppressing myometrial contractions and promoting endometrial receptivity through angiogenesis and cellular proliferation (Fig. 1). It is also critical in breast development, particularly in promoting lobuloalveolar maturation during puberty and pregnancy [7]. During the first ten weeks of pregnancy, progesterone—produced by the corpus luteum under the influence of human chorionic gonadotropin (hCG) stimulation—maintains elevated levels; thereafter, the placenta sustains its levels until term [7].

Hormone replacement therapy (HRT) in postmenopausal women has been shown to influence the risk of developing EOC. Notably, combined estrogen-progestin regimens are associated with a lower increase in EOC risk compared to estrogen-only therapies. Recent data from the Women’s Health Initiative (WHI) reinforce this distinction, suggesting that the addition of progesterone mitigates the carcinogenic potential of unopposed oestrogen on the ovarian epithelium [7].

Progesterone deficiency is implicated in infertility, largely due to impaired endometrial receptivity, increased risk of miscarriage, and preterm birth as a result of insufficient suppression of myometrial activity. Additionally, unopposed oestrogen action—secondary to low progesterone—elevates the risk of endometrial cancer [6]. Studies using progesterone receptors (PR) knockout mice (PRKO)—genetically engineered to completely lack PR—have confirmed the essential role of pro-

gesterone signalling in reproduction. Such mice exhibit: (1) anovulation; (2) endometrial hyperplasia with inflammation; (3) impaired mammary gland development; and (4) diminished sexual behaviour [7].

3.2 Cell signaling pathways of progesterone

Progesterone exerts its effects through a complex network of nuclear and membrane PR [8] that are highly sensitive to the local cell-signalling environment and the availability of substrates and cofactors [6, 9], regulating a multitude of cellular processes in target tissues.

The best-characterised PRs belong to the steroid hormone nuclear receptor superfamily [9]. Although encoded by a single gene (PGR), alternative promoter usage and splicing generate several functional isoforms [9]. The two major isoforms are PR-A (PRA) and PR-B (PRB), both of which possess DNA- and ligand-binding domains [7]. However, the PRB isoform contains a unique N-terminal region essential for activating transcription of genes associated with progesterone’s proliferative and differentiating actions [6]. In contrast, PRA functions as a dominant-negative regulator of PRB and interacts with other hormonal pathways, such as oestrogen receptors, thereby playing a critical role in coordinating hormonal responses in reproductive tissues, including normal uterine development [6]. PR isoforms also feature distinct activation function domains (AF1, AF2 and AF3), enabling complex interactions with co-regulators and transcriptional machinery, with AF3 being exclusive to PRB [6].

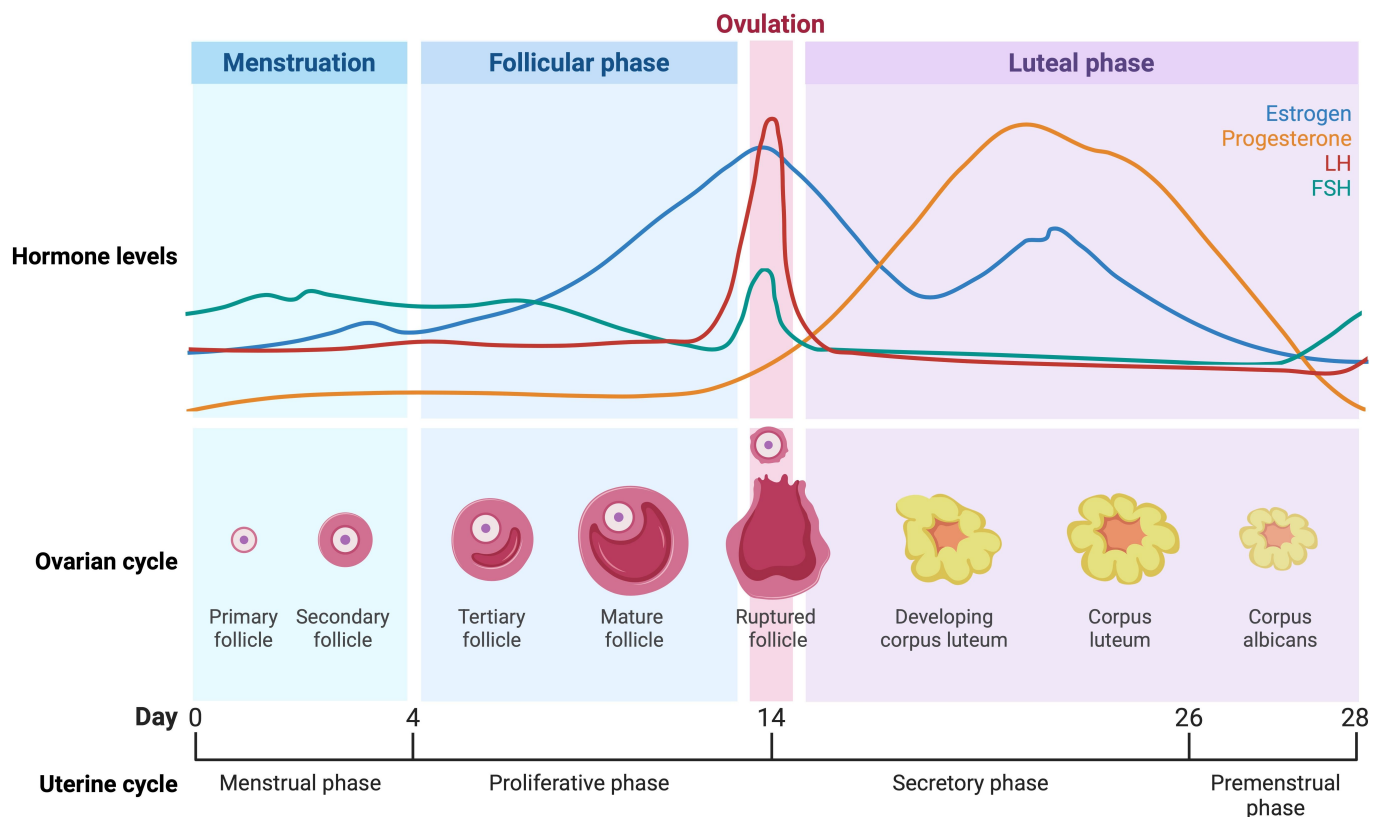


FIGURE 1. Hormonal fluctuations and folliculogenesis during the human menstrual cycle, illustrating changes in estrogen, progesterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH), alongside corresponding ovarian and uterine phases. Figure created with BioRender.com by the authors.

Beyond their classical genomic roles, PRs also mediate non-genomic signalling. PRB, in conjunction with oestrogen receptor alpha ($ER\alpha$) and the non-receptor tyrosine kinase c-Src of the Src family, participates in rapid signal transduction at the cell membrane [6]. There is also evidence that unliganded nuclear PRs can interact with DNA and regulate gene expression. In some models, unliganded PRs silence genes via nucleosome-inhibitory complexes such as heterochromatin protein 1 (HP1)-lysine-specific demethylase 1 (LSD1) [6]. Conversely, upon ligand binding, nuclear receptors undergo conformational changes that trigger signalling pathways leading to histone phosphorylation (e.g., trimethylation of lysine 9 on histone H3 (H3K9me3)), enabling thus enabling the activation of progesterone-regulated genes [6].

In addition to nuclear receptors, progesterone and synthetic progestins exert their functions through membrane receptors that modulate the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) signalling pathways [10]. Membrane PRs, a group of seven-transmembrane proteins with high progesterone affinity, regulate oocyte maturation, follicular development and uterine contractions during labour [11, 12].

A third class of progesterone-binding proteins includes the PR membrane components Progesterone receptor membrane component 1 (PGRMC1) and progesterone receptor membrane component 2 (PGRMC2), which interact with heme and cytochrome P450 enzymes, playing roles in chemoresistance and cell division [8, 13]. However, their role as true signalling receptors remains controversial. PGRMC1 may act as a scaffold protein that stabilises membrane PRs and promotes their downstream signalling, rather than directly transducing progesterone binding [14].

4. Oncogenic pathways in ovarian cancer

4.1 Histological and molecular classification

OC is both molecularly and histopathologically heterogeneous [3]. Tumours are classified into epithelial, mesenchymal, germ-cell, and sex-cord stromal types, reflecting their pathophysiology and clinical behaviour [2]. EOC accounts for approximately 90% of all cases [3], subdivided into high-grade serous (HGSOC), low-grade serous (LGSOC), endometrioid, mucinous and clear-cell. HGSOC is the most common (70%) and aggressive subtype, typically diagnosed after menopause, with a median age of 63 years [2, 3].

4.2 Emerging theories of HGSOC origin

HGSOC was historically thought to originate from the ovarian surface epithelium (OSE) [15], based on the “incessant ovulation theory” [16]. This hypothesis suggested that repeated cycles of ovulatory rupture and repair trigger chronic inflammation and DNA damage, thereby increasing the risk of malignant transformation [16]. However, mounting molecular and pathological evidence now supports the secretory epithelial cells (SECs) located in the secretory epithelium of the fimbrial end of the fallopian tube (SEF), particularly those forming serous tubal intraepithelial carcinomas (STICs), as

the principal site of origin [16]. This is further supported by epidemiological data linking physiological states associated with fewer ovulations, such as pregnancy or oral contraceptive use, to a lower risk of OC [4, 6].

Recent studies have identified precursor lesions (STICs) in the SEF of women with *BRCA1/2* mutations who underwent prophylactic salpingo-oophorectomy [4, 5]. These lesions, which frequently harbour tumour protein p53 (TP53) mutations, are believed to arise decades before the diagnosis of HGSOC. A recognised earlier alteration is the so-called “p53 signature”, a cluster of morphologically normal secretory cells with strong p53 immunostaining, now regarded as a potential early diagnostic marker for HGSOC [17].

4.3 Epigenetic and molecular drivers

Epigenetic alterations may play a pivotal role in OC oncogenesis. Mechanisms such as DNA methylation and histone modifications can contribute to the silencing of tumour suppressor genes, including *BRCA1* [5]. Additionally, other precursor molecular changes in the SEF may contribute to the evolutionary cascade, such as loss of expression of the paired box gene 2 (*PAX2*), an important regulator of epithelial homeostasis [18]. This alteration has been observed even earlier within benign lesions known as secretory cell outgrowths (SCOUTs), which may eventually progress to STICs (Fig. 2). Over-activation of oestrogen receptor signalling sustains proliferation of SCOUTs.

Emerging evidence highlights specific histone modifications, particularly H3K9me3, as key events in early HGSOC development. This epigenetic mark is associated with transcriptional repression of tumour suppressor genes such as *BRCA1* and *CDH1*. Aberrant H3K9me3 enrichment promotes genomic instability and epithelial-to-mesenchymal transition. Dysregulation of related enzymes, including methyltransferase suppressor of variegation 3-9 homolog 1 (*SUV39H1*) and lysine demethylase 4 (*KDM4*) demethylases reinforces its role in malignant transformation and underscores histone methylation as a potential therapeutic target [14].

The SEF appears particularly susceptible to malignant transformation. This vulnerability is linked to its stem cell-like properties and exposure to follicular fluid during ovulation [1, 18], which exhibits genotoxic characteristics, as it contains reactive oxygen species (ROS), insulin-like growth factor 2 (*IGF2*), transforming growth factor beta ($TGF-\beta$), and norepinephrine, that, when in contact with the SEF during ovulation, promote its malignant transformation [5, 17]. These compounds directly damage DNA and act as key activators of signalling pathways, such as the insulin-like growth factor 1 receptor (IGF-1R)/protein kinase B (AKT), promoting cell proliferation and survival [2]. Benign conditions such as endosalpingiosis and ovarian cortical inclusion cysts have also been associated with the origin of HGSOC, as they promote the presence of an inflammatory and carcinogenic microenvironment.

From a molecular standpoint, deregulation of the Wnt signalling pathway (Wnt)/ β -catenin signalling in the SEF also appears to be a relevant mechanism in the initiation of HGSOC through STIC formation, particularly in carriers of germline

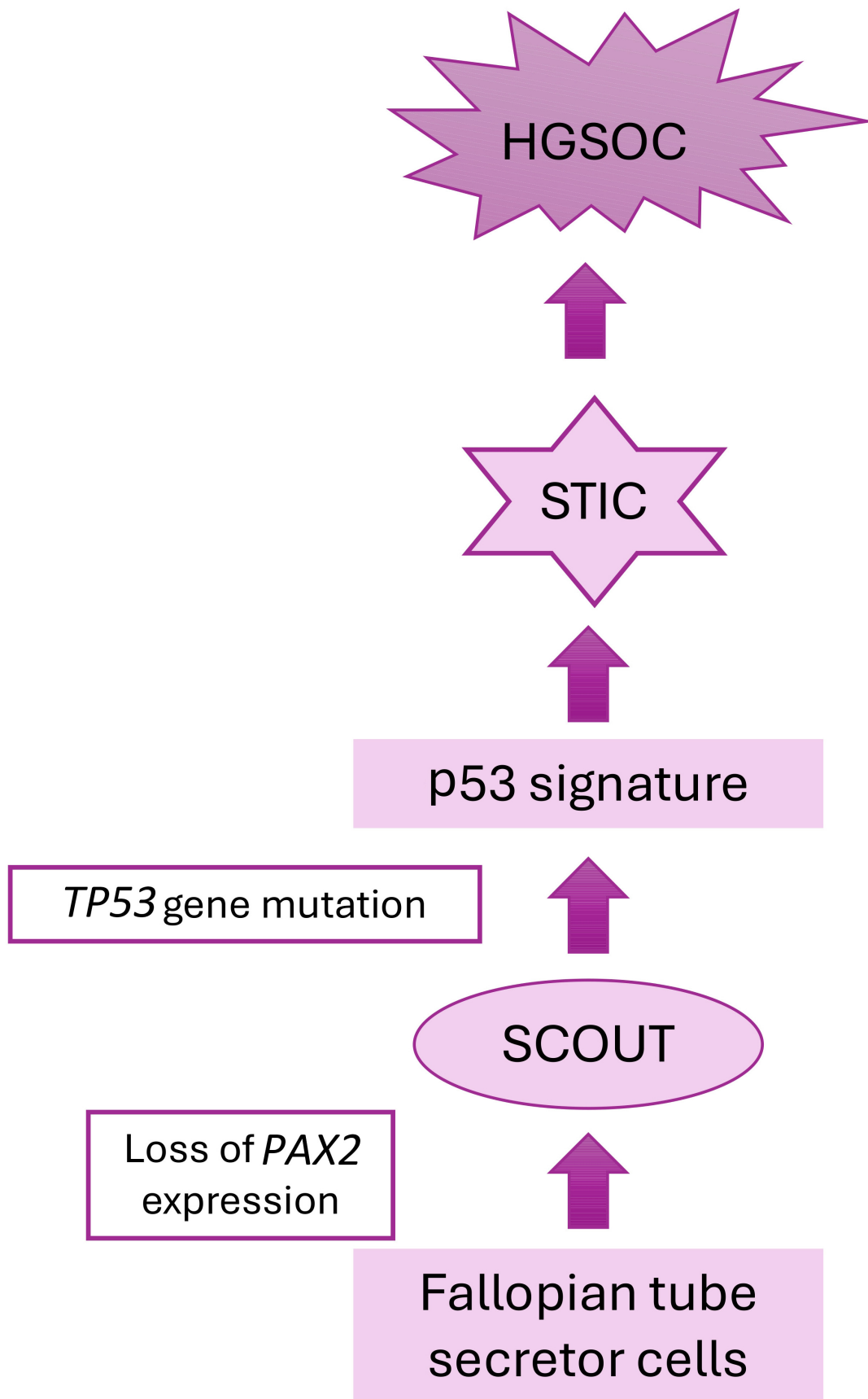


FIGURE 2. Sequence of oncogenesis in high grade ovarian serous carcinoma. HGSOC, high-grade serous ovarian carcinoma; SCOUT, secretory cell outgrowths; STIC, serous tubal intraepithelial carcinoma; *TP53*, tumour protein p53 gene; *PAX2*, paired box gene 2. Figure created by the authors.

BRCA1/2 mutations. This signalling pathway plays a key role in regulating proliferation, differentiation, migration, and stem cell renewal, and its abnormal activation is therefore expected to contribute to the development of preneoplastic lesions [19].

4.4 Tumor microenvironment and immune modulation

The tumour microenvironment is also a key player in the carcinogenesis of OC [20]. It includes cancer-associated fibroblasts (CAFs), immune cells, endothelial cells, extracellular matrix (ECM) components, and steroid hormones [2]. CAFs can remodel ECM, releasing tumour necrosis factor- α (TNF- α), interleukin 6 (IL-6), interleukin 8 (IL-8) to boost angiogenesis and cancer survival [13], and promote epithelial-mesenchymal transition (EMT), facilitating metastasis [7]. Immune cells display an immunosuppressive phenotype [2, 4] such as M2 macrophages and regulatory T cells, which aid tumour immune evasion [2]. Overexpression of vascular endothelial growth factor (VEGF) fosters abnormal vasculature and metastasis, while hypoxia also drives EMT and promotes OC aggressiveness [2].

4.5 Progesterone and ovarian cancer interplay

4.5.1 Protective and regulatory functions of progesterone

Progesterone is widely recognized for its protective role against the development of EOC [21], primarily through its anti-proliferative and pro-differentiation effects on the ovarian and fallopian tube epithelium. Elevated progesterone levels during pregnancy [20, 22] and the prolonged use of combined oral contraceptives (COCs) [6, 20] which suppress ovulation and induce a progestogenic environment, are associated with a reduced risk of EOC [7]. However, the association between breastfeeding and increased progesterone levels has been mischaracterised; in reality, lactation is linked to suppression of the hypothalamic-pituitary-ovarian axis rather than elevated circulating progesterone concentrations [23].

Physiologically, during the menstrual cycle, progesterone counteracts estrogen-driven epithelial proliferation. The oestrogen-dominant follicular phase promotes cell proliferation, whereas the luteal phase, characterised by elevated progesterone levels, supports terminal differentiation and apoptosis, thereby limiting the risk of malignant transformation. This hormonal balance is essential for preserving tissue homeostasis and preventing the emergence of premalignant lesions. Prolonged exposure to unopposed oestrogen—such as during the use of oestrogen-only HRT or in the context of uninterrupted ovulatory cycles—can disrupt this balance and increase the risk of ovarian carcinogenesis. While nulliparity is associated with a higher lifetime number of ovulatory cycles, it should not be viewed as a directly hyperoestrogenic state but rather as a reproductive pattern that leads to cumulative hormonal exposure over time [7].

4.5.2 Molecular mechanisms and signaling pathways

As previously discussed, progesterone acts mainly through its nuclear (PRA and PRB) and membrane receptors, which regulate the expression of genes involved in apoptosis, cellular senescence, and intracellular signaling. Activation of the nuclear PR, especially the PRB isoform [20], induces the transcription factor forkhead box protein O1 (FOXO1), which in turn upregulates cyclin-dependent kinase inhibitor 1A (*CDKN1A*), the gene encoding p21—a key protein for ensuring accurate DNA repair during the cell cycle. This mechanism promotes cellular senescence and inhibits uncontrolled proliferation [6], both of which are crucial for cancer prevention.

Progesterone-activated membrane receptors are responsible for rapid cytotoxic responses, including the induction of the pro-apoptotic protein Bcl-2-associated X protein (BAX) in OC. Additionally, progesterone has been shown to inhibit the Wnt/ β -catenin signalling pathway [19], which is closely associated with HGSOC development. In experimental models, progesterone suppresses this pathway and thereby limits the progression of precursor lesions into HGSOC, contributing to its protective role against carcinogenesis [17]. Progesterone also reduces tumour cell migration by modulating the phosphorylation of proteins such as focal adhesion kinase (FAK) and proto-oncogene tyrosine-protein kinase Src, both of which are essential regulators of cell polarity and motility [20].

Emerging evidence suggests that progesterone may also interact with other therapeutic agents and endogenous molecules, enhancing its modulatory effects on the tumour microenvironment. For example, the combination of calcitriol and progesterone exerts synergistic effects in inducing apoptosis and inhibiting tumour cell proliferation in experimental models [24]. Furthermore, progesterone regulates the expression of members of the α disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) protein family, which modulate ECM remodelling, angiogenesis, invasion, and metastasis—further reinforcing its therapeutic potential [25].

4.5.3 Clinical and molecular determinants of progesterone response

A meta-analysis by Luo *et al.* [26] (2017), involving over 3000 patients, confirmed that PR positivity is significantly associated with improved overall survival (OS) in OC. Additionally, transcriptomic analyses from The Cancer Genome Atlas suggest that elevated PR-B expression correlates with platinum sensitivity and prolonged survival in patients with HGSOC [27]. However, the efficacy of progesterone in preventing OC may be compromised by molecular alterations affecting the signalling pathways described above. Aberrant activation of the PI3K/AKT pathway impairs progesterone's suppressive effects in OC cells by promoting sustained phosphorylation and nuclear exclusion of the transcription factor FOXO1. This prevents FOXO1 from regulating pro-apoptotic and anti-proliferative genes, thereby promoting tumour progression [28]. These molecular alterations are illustrated in Fig. 3. This pathway is particularly relevant in advanced HGSOC, where progressive loss of PR expression and concomitant increase in PGRMC1 are associated with worse clinical

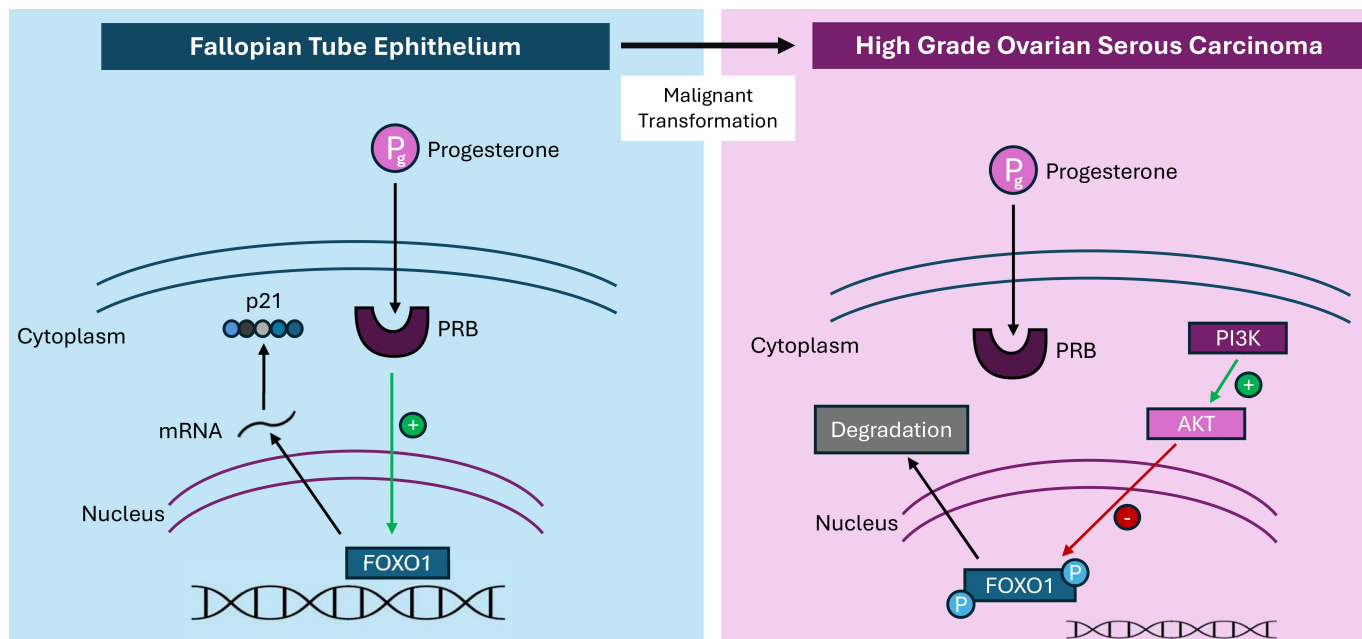


FIGURE 3. Schematic representation of how, during the malignant transformation of fallopian tube epithelium into high-grade serous ovarian carcinoma (HGSOC), aberrant activation of the PI3K/AKT signalling pathway leads to phosphorylation and nuclear exclusion of FOXO1, impairing its tumour suppressive activity. In normal epithelium, progesterone binds to the progesterone receptor isoform B (PR-B), activating transcription of genes such as p21, which inhibit cell proliferation via FOXO1 nuclear localization. PRB, progesterone receptor isoform B; FOXO1, transcription factor FOXO1; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; p21, cyclin-dependent kinase inhibitor 1A. Figure created by the authors.

outcomes [5, 22].

The heterogeneity among OC subtypes is also reflected in the variability of PRs expression. While high nuclear PR expression is typically seen in the endometrioid and serous subtypes, the mucinous and clear cell subtypes are characterised by lower expression, suggesting reduced sensitivity to progesterone. This heterogeneity reinforces the importance of an individualised therapeutic approach based on both molecular and hormonal profiling [6, 20].

A study by Matsuoka *et al.* [29] (2016) suggests that measurement of serum progesterone may be useful for risk stratification in mucinous OC, as postmenopausal women with mucinous OC have significantly higher progesterone levels than those with other OC. These findings indicate that progesterone may serve as a non-invasive biomarker for the pre-operative identification of mucinous tumours. Conversely, in OC subtypes with high nuclear PR expression, elevated progesterone levels are associated with more favourable clinical outcomes.

4.5.4 Controversies and dual role in BRCA-associated OC

In women with *BRCA1/2* mutations, the hormonal microenvironment may interact with defective DNA repair pathways, modifying progesterone's effects. Emerging evidence also implicates PI3K/AKT signalling in modulating PR activity, potentially converting progesterone's role from protective to oncogenic under specific molecular conditions [30]. This duality underscores the need to contextualize progesterone's effect based on receptor expression, genetic background, and downstream signalling environment.

These findings raise important questions about the contexts in which progesterone may switch from a protective to a tumour-promoting role. Further studies are warranted to delineate these scenarios, particularly in *BRCA1/2* mutation carriers, where defective DNA repair mechanisms may alter cellular responses to progesterone. This duality appears to be influenced by several factors, including the differential expression of PR isoforms (PR-A vs. PR-B), the presence of *BRCA1/2* mutations, and cross-talk with oncogenic signalling pathways such as PI3K/AKT. For example, *BRCA1*-deficient cells may respond differently to progesterone due to impaired DNA repair capacity, and PR-A predominance has been associated with pro-tumorigenic activity in certain models. Moreover, activation of the PI3K pathway may alter PR function, potentially shifting progesterone's effects from tumour-suppressive to oncogenic [31].

Despite progesterone's historically protective role in OC, recent studies have challenged this paradigm. They suggest that progesterone may promote HGSOC in specific contexts. Data from genetically engineered mouse models predisposed to HGSOC suggest that pharmacological inhibition of progesterone signalling significantly reduces tumour incidence and progression. These findings highlight both the complex and controversial role of progesterone in tumour initiation [32], and the current lack of robust clinical evidence regarding its therapeutic potential.

5. Hormonal therapy in ovarian cancer

5.1 Rationale and clinical relevance

To date, the treatment of OC remains one of the greatest challenges in gynaecologic oncology, with surgery representing the intervention with the greatest prognostic impact. As previously noted, most cases are diagnosed at an advanced stage, contributing to high recurrence rates even after maximal surgical efforts aimed at complete macroscopic tumour resection [33]. This underscores the urgent need to complement surgery with more effective systemic strategies.

The gold standard for OC treatment combines cytoreductive surgery with platinum-based (*e.g.*, carboplatin) and taxane-based (*e.g.*, paclitaxel) chemotherapy. In advanced-stage disease (stages III–IV), maintenance therapy with targeted agents such as poly (ADP-ribose) polymerase (PARP) inhibitors or anti-VEGF antibodies aims to prolong progression-free survival (PFS) and OS [34]. However, these treatments are not universally applicable across all OC subtypes. Despite recent advances, the majority of advanced HGSOE cases eventually relapse. In the absence of novel therapeutic approaches, patients are subjected to repeated chemotherapy cycles, leading to diminishing efficacy, shorter treatment-free intervals, and increasing cumulative toxicity over time [34].

Hormonal therapy in OC has historically been underutilised and inconsistently adopted, despite several potential advantages, including oral administration, affordability, and a favourable toxicity profile [34]. In recent years, it has garnered growing interest, particularly in histological subtypes with high expression of hormone receptors [34, 35]. Nevertheless, while oestrogen receptors—particularly ER α —are consistently expressed across EOC, PR expression is more heterogeneous [36, 37]. This variability may partly explain the differential clinical responses observed with progestin-based therapies [36, 37].

5.2 Hormonal agents targeting estrogen and progesterone pathways

In postmenopausal women, the primary source of oestrogen derives from the aromatase induced peripheral conversion of androgens. Accordingly, selective oestrogen receptor modulators (SERMs), such as tamoxifen, and aromatase inhibitors, including letrozole and anastrozole, have been investigated mainly in epithelial tumours with high ER α expression [38]. Tamoxifen, which competitively binds to ER α , has been used predominantly in chemotherapy-resistant disease, showing variable efficacy depending on hormone receptor expression. In the phase III Ovaresist trial, conducted in patients with platinum-resistant OC, the median PFS was 8.3 weeks with tamoxifen versus 12.7 weeks with chemotherapy. However, no significant differences in OS were observed, suggesting that tamoxifen may represent a less toxic alternative that does not compromise OS—particularly valuable in patients with limited performance status [38].

Aromatase inhibitors have demonstrated limited efficacy in LGSOC. In the phase II PARAGON trial, anastrozole was well tolerated and yielded a clinical benefit rate (CBR) of 64% at 3 months, which was maintained at 6 months, with a median PFS of 11.1 months in postmenopausal women with advanced ER/PR-positive LGSOC or borderline serous tu-

mours, supporting its role as a viable option in this setting [39]. A retrospective study by Gershenson *et al.* [40] analysed 89 hormonal regimens in 61 patients with recurrent LGSOC, reporting an objective response rate (ORR) of 9% and disease stabilisation in 61%, with a median PFS of 7.4 months—demonstrating modest but meaningful activity in indolent disease. More recently, the phase II Gynecologic Oncology Group (GOG)-3026 trial evaluated the combination of letrozole and the cyclin-dependent kinase 4/6 (CDK 4/6) inhibitor ribociclib in patients with recurrent LGSOC. The study reported an ORR of 23.5% and a median PFS of 19.1 months. At the time of data cutoff, median OS had not been reached, and results should be interpreted as preliminary pending longer follow-up [41].

Hormonal therapy has also shown value in the maintenance setting following surgery and chemotherapy. In a retrospective study by Gershenson *et al.* [40] involving 203 patients with LGSOC treated with surgery and platinum-based chemotherapy, maintenance hormonal therapy was associated with significantly longer PFS (64.9 months) compared to controls (26.4 months). Although median OS was numerically longer (115.7 vs. 102 months), this difference was not statistically significant, and thus, hormonal maintenance remains a strategy validated only for delaying disease progression [42].

Progestins, such as megestrol acetate and medroxyprogesterone acetate, have been evaluated in patients with advanced or platinum-resistant OC, though clinical benefit has been limited [24]. Despite preclinical evidence of antiproliferative effects, their activity in this setting remains modest, and off-target hormonal receptor interactions may restrict their long-term therapeutic potential [42].

To enhance receptor specificity, selective PR modulators (SPRMs), including ulipristal, telapristone, and onapristone, have been developed. A phase II trial evaluated extended-release onapristone (50 mg twice daily) in PR-positive tumours, including LGSOC. Among four LGSOC patients, the median PFS was 4.4 months and CBR was 50%. Although no objective responses were recorded, the treatment was well tolerated [43].

5.3 Mechanisms of resistance and combinatorial approaches

Resistance to hormonal therapy remains a significant challenge, partly driven by the activation of oncogenic signalling pathways such as PI3K/AKT/mammalian target of rapamycin (mTOR) [2]. A phase II trial evaluating the combination of pimasertib (a mitogen-activated protein kinase (MEK) inhibitor) and voxalisib (a PI3K inhibitor) in recurrent LGSOC reported a median PFS of 9.9 months; however, the study was terminated early due to low response rates and poor accrual [44]. Preclinical studies have suggested that calcitriol may inhibit OC cell growth by modulating the Wnt/ β -catenin signalling pathway, thereby promoting cellular differentiation and apoptosis. Furthermore, co-administration with progestins may enhance therapeutic efficacy by suppressing the cytochrome P450 family 24 subfamily A member 1 (CYP24A1) enzyme, thereby prolonging calcitriol bioactivity. While promising, these findings still require validation in clinical trials [24].

5.4 Future directions and clinical integration

The integration of hormonal therapy into the treatment algorithm for OC is still evolving. Advances in the identification of hormonal biomarkers may enable better patient stratification, allowing the selection of those most likely to benefit from this approach, thereby maximising efficacy and reducing the risk of resistance. Despite current uncertainties, hormonal therapy appears to be a promising strategy for both the treatment and prevention of OC and warrants further investigation through clinical trials and translational research to confirm and optimise its role in clinical practice.

6. Conclusions

Progesterone exerts multifaceted effects in OC biology, influencing tumour growth, invasion, and cellular homeostasis through complex, receptor-mediated mechanisms. While its protective functions are often mediated via PR-B activation and suppression of oestrogen-driven signalling, these effects may be modulated or diminished by oncogenic pathways such as PI3K/AKT. The diversity of receptor expression across OC subtypes underscores the need for biomarker-guided therapeutic decisions, particularly in tumours like low-grade serous and endometrioid carcinomas, where hormonal strategies may offer low-toxicity benefit.

Despite encouraging results in selected settings, hormonal therapies remain underused, partly due to inconsistent methodologies and limited prospective validation. Progesterone and its analogues could represent promising candidates for therapeutic repurposing, especially given their established safety profile and accessibility. In parallel, a more refined understanding of PR isoform function—including PR-A, PR-B, and membrane-associated forms such as PGRMC1—may help explain variable responses and improve patient stratification.

These opportunities must be supported by well-designed clinical trials, harmonised biomarker assessment, and translational research to clarify progesterone's full therapeutic value in OC. Longitudinal studies are also needed to assess the sustained impact of progesterone signalling and its interactions with key oncogenic pathways. Harnessing the potential of progesterone will require not only scientific rigour, but also a shift in clinical mindset—towards more personalised, biology-driven treatment pathways in OC.

AVAILABILITY OF DATA AND MATERIALS

This narrative review is based on previously published studies that are fully referenced within the manuscript. No new datasets were generated or analysed. All data supporting the findings of this article are available from the cited literature.

AUTHOR CONTRIBUTIONS

IF and RC—participated in data collection and drafting and editing of the paper. MFD and RR—participated in the critical revision of the manuscript. All authors saw and approved the final version, and no other person made a substantial

contribution to the paper.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study is a narrative review of previously published literature and did not involve human participants or animals. Therefore, ethical approval and informed consent were not required.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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