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Photodynamic Therapy in Endometrial Cancer: Current Evidence and Future Perspectives

Alicja Gruna[1], ORCID https://orcid.org/0009-0005-3729-4457

E-mail alicjagruna@gmail.com

[1]Uniwersytet Rzeszowski, Rzeszów, Subcarpathia, PL

Katarzyna Szalacha[1], ORCID https://orcid.org/0009-0009-0647-6441

E-mail kk.szalacha@gmail.com

[1]Uniwersytet Rzeszowski, Rzeszów, Subcarpathia, PL

Krzysztof Górecki[1], ORCID https://orcid.org/0009-0003-3242-8896

E-mail krzysiek.gorecki@onet.eu

[1]Uniwersytet Rzeszowski, Rzeszów, Subcarpathia, PL

Maciej Kozłowski[1], ORCID https://orcid.org/0009-0000-5135-9994
E-mail maciejkozlowski@icloud.com
[1]Uniwersytet Rzeszowski: Rzeszów, Subcarpathia, PL

Marcel Likus[1], ORCID https://orcid.org/0009-0008-7010-9542
E-mail marcel.likus8@gmail.com
[1]Uniwersytet Rzeszowski, Rzeszów, Subcarpathia, PL

Maria Lizner[1], ORCID https://orcid.org/0009-0005-9015-8120
E-mail: marysia.lizner@gmail.com
[1]Uniwersytet Rzeszowski: Rzeszów, Subcarpathia, PL

Michał Pawlików[1], ORCID https://orcid.org/0009-0005-3274-6346
E-mail: pawlikow01@gmail.com
[1]Uniwersytet Rzeszowski, Rzeszów, Subcarpathia, PL

Natalia Kobylarz[1], ORCID https://orcid.org/0009-0002-9819-8029
E-mail nk123396@stud.ur.edu.pl
[1]Uniwersytet Rzeszowski, Rzeszów, Subcarpathia, PL

Paulina Wyszkowska[1], ORCID https://orcid.org/0009-0008-2921-384X
E-mail paulwysz@gmail.com
[1]Uniwersytet Rzeszowski, Rzeszów, Subcarpathia, PL

Wiktor Marek[1], ORCID https://orcid.org/0009-0006-2562-2617
E-mail: wiktor5a@interia.pl
[1]Uniwersytet Rzeszowski, Rzeszów, Subcarpathia, PL

Corresponding author

Alicja Gruna, alicjagruna@gmail.com

Abstract

Background. Endometrial cancer is a common gynecologic malignancy with substantial biological heterogeneity. Photodynamic therapy (PDT) is a local treatment in which a photosensitizer, light and molecular oxygen generate reactive oxygen species and tumor injury. The accessibility of the endometrial cavity makes PDT a potentially attractive organpreserving approach.
Aim. To critically summarize current evidence on PDT in endometrial cancer, focusing on clinical and preclinical studies, photosensitizers, mechanisms, fertility-sparing applications, limitations and emerging strategies.
Materials and methods. A narrative literature review was conducted using PubMed/MEDLINE and additional bibliographic sources. Searches addressed PDT, endometrial cancer, photosensitizers, 5-aminolevulinic acid, hypericin, hematoporphyrin derivatives, radachlorin, nanoparticles, hypoxia and immunogenic cell death, with particular attention to publications from 2024–2026.
Results. Direct clinical evidence remains limited. Small clinical series and fertility-preserving reports suggest that PDT may achieve local responses in selected early-stage tumors. Preclinical studies demonstrate phototoxic effects of several photosensitizers, including hematoporphyrin derivatives, hypericin, 5-aminolevulinic acid/protoporphyrin IX and radachlorin. Current research focuses on tumor selectivity, light delivery, oxygen availability, nanocarriers and immunogenic cell death. No large randomized trials have established PDT as standard treatment.
Conclusions. PDT should currently be considered an investigational, potentially organpreserving modality rather than a replacement for surgery or systemic therapy. Its strongest rationale is in selected localized disease accessible to light. Future studies should address molecular risk classification, standardized hysteroscopic protocols, dosimetry, fertility outcomes, long-term surveillance and combinations with systemic therapies.

Key words: endometrial cancer, photodynamic therapy, photosensitizers, fertility preservation, hysteroscopy, molecular classification, immunogenic cell death, photodynamic diagnosis

1. Introduction

Endometrial cancer (EC) represents a heterogeneous group of malignant neoplasms arising from the endometrium. Its incidence has increased in many populations in parallel with population ageing, obesity and metabolic disease, although the biological determinants of individual tumors are considerably more complex than the traditional distinction between estrogen-related endometrioid tumors and non-endometrioid carcinomas. Contemporary classification increasingly integrates histopathology with molecular features, and the 2023 FIGO staging system incorporates molecular information into prognostic assessment. These developments are important when evaluating any emerging local therapy because a treatment that is potentially appropriate for a highly selected low-risk tumor cannot be extrapolated to aggressive or metastatic disease (Berek et al., 2023; Concin et al., 2025; Sakai et al., 2026; Bogani et al., 2026; Kumari et al., 2025; Anca-Stanciu et al., 2025).
For most patients with apparently localized EC, hysterectomy with appropriate staging remains the foundation of treatment. Depending on histology, stage, grade, lymphovascular space invasion and molecular profile, adjuvant radiotherapy and/or systemic treatment may be indicated. In advanced or recurrent disease, the therapeutic landscape has changed rapidly with the incorporation of immune checkpoint inhibitors and targeted combinations. The 2025 update of the ESGO-ESTRO-ESP guidelines further emphasizes risk-adapted management and the importance of molecular classification (Liang et al., 2025). Consequently, a potential role for photodynamic therapy (PDT) must be defined as complementary and highly selective rather than as a generic substitute for established oncologic treatment.

PDT is based on three components: a photosensitizing agent, light of an appropriate wavelength and molecular oxygen. After accumulation of the photosensitizer in the target tissue, irradiation generates reactive oxygen species (ROS), particularly singlet oxygen, which can damage cellular membranes, mitochondria, proteins and nucleic acids. Tumor destruction may result from direct cell death, microvascular injury and activation of antitumor immunity (Kwiatkowski et al., 2018; Allison & Moghissi, 2013; Hamblin, 2020; Kessel, 2019; Acroyd et al., 2001; Dougherty et al., 1978). The spatial restriction of light activation provides a distinctive form of selectivity: systemic administration of the photosensitizer does not necessarily cause cytotoxicity throughout the body because tissue injury is concentrated in the illuminated field.

The endometrial cavity is an unusual but attractive anatomical target for PDT. Hysteroscopy can provide direct visualization of focal lesions and potentially allow precise light delivery. This feature has generated interest in fertility-preserving treatment for carefully selected young women with early-stage disease, particularly when the tumor is confined to the endometrium and the patient strongly wishes to preserve reproductive potential. The published clinical experience, however, is small and heterogeneous, and the available data cannot establish equivalence with standard conservative hormonal treatment or definitive surgery (Choi et al., 2013; Colombo et al., 2016; Żołyniak-Brzuchacz et al., 2024; Son et al., 2020).

The purpose of this review is therefore not to present PDT as an established treatment, but to critically examine where the method currently stands. Particular attention is paid to direct evidence in EC, the molecular and cellular mechanisms of PDT, the characteristics of photosensitizers, hysteroscopic and fertility-preserving applications, limitations of current studies, and future strategies involving nanotechnology, oxygen modulation and immunotherapy. A critical distinction is maintained between evidence generated directly in endometrial cancer and evidence extrapolated from other tumor models, especially cervical cancer and experimental solid tumors.

2. Research materials and methods

This manuscript was prepared as a narrative review with a structured literature-search strategy. PubMed/MEDLINE was searched using combinations of the following terms: (“endometrial cancer” OR “endometrial carcinoma” OR “uterine cancer” OR “endometrium”) AND (“photodynamic therapy” OR “photodynamic treatment” OR PDT OR “photodynamic diagnosis”) and additional combinations involving “photosensitizer”, “5-aminolevulinic acid”, “protoporphyrin IX”, “hypericin”, “hematoporphyrin”, “Photofrin”, “radachlorin”, “nanoparticle”, “hypoxia”, “immunogenic cell death” and “fertility preservation”. The search was updated to 11 August 2026.

Priority was given to studies directly investigating endometrial carcinoma, followed by clinical and translational studies in gynecologic oncology and recent mechanistic reviews relevant to the future development of PDT. Publications from 2024–2026 were specifically screened to capture developments in molecular classification, contemporary endometrial cancer treatment, photosensitizer development, hypoxia-responsive nanotechnology and PDTinduced immunogenic cell death. Seminal studies were retained when they provided foundational information not replaced by newer work.

For each relevant study, the following variables were considered: study type, tumor model, photosensitizer, light source or wavelength when reported, major biological endpoint, clinical endpoint, treatment setting, and principal limitation. Evidence was then grouped into: (1) direct clinical evidence in endometrial cancer; (2) in vitro and animal evidence in endometrial cancer; (3) evidence from other gynecologic malignancies that may inform translation; and (4) general PDT technology with potential relevance to EC.

Because the literature is characterized by small case series, in vitro studies and substantial protocol heterogeneity, a quantitative meta-analysis was not considered appropriate. Treatment response rates from individual historical reports are presented descriptively and should not be interpreted as pooled efficacy estimates.

2.1. Biological basis of photodynamic therapy

PDT is a photochemical treatment rather than a conventional thermal or ionizing radiation technique. Following administration, a photosensitizer undergoes selective or preferential localization in tumor tissue. Absorption of a photon promotes the molecule to an excited singlet state, followed by intersystem crossing to a longer-lived triplet state. The triplet photosensitizer can participate in Type I and/or Type II photochemical reactions. Type I reactions involve electron or hydrogen transfer and produce radical species, whereas Type II reactions transfer energy directly to molecular oxygen and generate singlet oxygen. In many clinically used PDT systems, singlet oxygen is a major cytotoxic mediator (Kwiatkowski et al., 2018; Allison & Moghissi, 2013; Hamblin, 2020; Kessel, 2019; Acroyd et al., 2001; Dougherty et al., 1978; Oniszczuk et al., 2016).

The biological consequences depend strongly on subcellular localization. Photosensitizers associated with mitochondria may trigger mitochondrial permeability transition and apoptosis; localization in lysosomes can cause lysosomal membrane permeabilization; and plasma membrane-associated photosensitizers can rapidly disrupt membrane integrity. Vascular localization adds a second mechanism by producing endothelial damage, platelet activation and microvascular thrombosis. The final response is therefore determined by the photosensitizer, dose, light fluence, irradiance, oxygenation and tissue architecture rather than by the photosensitizer dose alone.
Three major mechanisms of tumor control can be distinguished. First, direct tumor-cell killing occurs through apoptosis, necrosis or other regulated cell-death pathways. Second, PDT can damage the tumor-associated vasculature, limiting oxygen and nutrient supply. Third, PDT can stimulate an immune response against tumor-associated antigens. The latter mechanism has become increasingly important in modern PDT research because dying cells may expose or release danger-associated molecular patterns such as calreticulin, ATP and HMGB1, promoting dendritic-cell activation and subsequent antitumor immunity
(Mishchenko et al., 2024; Liu et al., 2024; Catanzaro et al., 2025; Zheng et al., 2024).

The oxygen requirement is also one of PDT's principal limitations. Solid tumors can contain hypoxic regions, and oxygen consumption during irradiation can further reduce local oxygen availability. Consequently, a treatment that works efficiently in an oxygenated cell culture may be less effective in a poorly oxygenated tumor. Recent experimental work has therefore focused on oxygen-generating or oxygen-sparing nanoparticles, modulation of mitochondrial respiration, and photosensitizers capable of Type I photochemistry that may be less dependent on oxygen availability (Birhan et al., 2025; Xu et al., 2024; Zhao et al., 2025; Zhang et al., 2025; Ren et al., 2025).
The physical characteristics of the light source are equally important. Longer wavelengths generally offer greater tissue penetration than shorter wavelengths, although penetration remains limited by optical absorption and scattering. In the endometrial cavity, the superficial and anatomically accessible location of many early lesions could reduce one of the major limitations encountered in deeply situated tumors. Hysteroscopic guidance may additionally permit circumferential or focal illumination and direct treatment of a visible lesion. Nevertheless, light dosimetry must be standardized because inadequate irradiation can leave viable tumor cells, while excessive fluence can damage normal endometrium.
PDT therefore possesses a potentially useful combination of spatial precision and biological selectivity. At the same time, its efficacy depends on a chain of conditions—adequate photosensitizer delivery, appropriate intracellular localization, sufficient oxygen, effective light penetration and correct timing. Any clinical protocol for EC must account for the entire chain rather than treating PDT as a single pharmacological intervention.

2.2. Endometrial cancer in the era of molecular classification

The clinical context in which PDT might eventually be used has changed substantially since the first endometrial PDT studies. Choi et al. (2013) reported a retrospective cohort of 16 patients with endometrial cancer treated with PDT. The treatment protocol consisted of intravenous administration of the photosensitizer at a dose of 2 mg/kg, followed by light irradiation 48 h later. A 630-nm red laser was used to illuminate both the endometrial cavity and the endocervical canal. This study represents one of the early clinical applications of PDT in endometrial cancer and provides a relatively well-defined treatment protocol for this approach. The TCGA framework identified four molecular groups POLE ultramutated, mismatch-repair deficient/microsatellite instability-high (MMRd/MSI-H), copy-number low and copy-number high which have distinct biological behavior and prognostic implications. In routine practice these categories are approximated using POLE sequencing and immunohistochemical or molecular assessment of mismatch-repair proteins and p53, with additional clinicopathological information (Berek et al., 2023; Concin et al., 2025; Sakai et al., 2026; Bogani et al., 2026; Kumari et al., 2025; Anca-Stanciu et al., 2025).
The 2023 FIGO staging system incorporates molecular classification and recognizes that two tumors with the same anatomical stage can have markedly different biological behavior. POLE-mutated tumors may have exceptionally favorable prognosis, whereas p53-abnormal tumors are generally associated with aggressive behavior. MMRd/MSI-H tumors are particularly relevant to immunotherapy because of their increased neoantigen burden. These differences should matter when designing trials of PDT. A local treatment intended for fertility preservation should not enroll biologically aggressive tumors simply because the anatomical disease appears limited.
The current treatment landscape also establishes an important comparator. For advanced or recurrent EC, randomized trials have demonstrated clinically meaningful benefits from combining platinum-based chemotherapy with immune checkpoint inhibition in appropriately selected populations. RUBY established the efficacy of dostarlimab plus carboplatinpaclitaxel, with particularly pronounced benefit in dMMR/MSI-H disease, and later analyses have confirmed durable benefit in this molecular subgroup (Powell et al., 2024; Powell et al., 2025; Powell et al., 2026; Auranen et al., 2024). NRG-GY018 similarly demonstrated the importance of pembrolizumab added to chemotherapy, while DUO-E provided evidence for durvalumab-based strategies with or without olaparib in selected advanced disease (Makker et al., 2022; Mirza et al., 2023; Westin et al., 2024).

These advances make it increasingly difficult to justify an experimental local therapy in advanced disease without a compelling biological rationale. Conversely, they strengthen the rationale for studying PDT in a different clinical niche: small, localized, endometriumconfined tumors in patients for whom preservation of fertility or avoidance of radical treatment is an important objective. In such patients, the relevant question is not whether PDT can replace immunotherapy or chemotherapy, but whether a carefully controlled local intervention can eradicate selected disease while preserving uterine anatomy and reproductive potential.
Molecular classification could also become a biomarker for PDT response. Tumors with different mutational landscapes may differ in oxidative stress responses, apoptosis pathways, antioxidant capacity, immune infiltration and susceptibility to immunogenic cell death. At present, however, there is insufficient direct evidence to recommend a specific molecular subtype for PDT. Future prospective trials should collect molecular data prospectively rather than treating molecular classification as an optional exploratory variable.

2.3. Direct clinical evidence for PDT in endometrial cancer

The direct clinical literature on PDT for EC is remarkably small. One of the earliest clinical experiences in gynecologic oncology reported PDT for recurrent gynecologic malignancies, including endometrial adenocarcinoma. The series by Corti and colleagues included a small number of endometrial cancer cases and demonstrated that local responses could be achieved without treatment-related mortality, while also emphasizing that the method remained investigational (Corti et al., 1995). Because the cohort was small and clinically heterogeneous, the study cannot provide a modern estimate of efficacy.
More directly relevant to fertility preservation is the long-term study by Choi et al., which evaluated young women with early-stage endometrial cancer treated with Photofrin-based PDT. Sixteen patients younger than 35 years with early-stage disease were included. PDT was used as a primary treatment in most patients and as treatment for relapse in others after hormonal therapy. Complete remission was reported in 12 women, although some subsequently experienced recurrence. Importantly, a proportion of patients achieved pregnancy, mainly with assisted reproductive technologies. The report demonstrated the conceptual feasibility of treating selected endometrial lesions while preserving reproductive potential (Choi et al., 2013).
The interpretation of this study requires caution. The sample size was small, patient selection was highly specialized, treatment protocols were not standardized according to contemporary molecular risk groups, and the study predates the current understanding of fertility-sparing eligibility. In addition, complete remission after a local treatment is not equivalent to long-term oncologic safety. For a fertility-preserving therapy, the relevant endpoint should include durable complete response, hysterectomy-free survival, recurrencefree survival, time to recurrence, obstetric outcomes and the safety of subsequent pregnancy.
A further case report described conservative management of a young woman with lowgrade endometrial stromal sarcoma using surgery followed by hematoporphyrin derivativemediated PDT and adjuvant letrozole. The patient remained without radiographic evidence of recurrence for many years and subsequently achieved a twin pregnancy after in vitro fertilization (Choi et al., 2018). This case is clinically interesting but should not be extrapolated to endometrial carcinoma because endometrial stromal sarcoma has different biology and treatment principles.
The clinical evidence therefore supports feasibility rather than efficacy. PDT can be delivered to the endometrium, can produce complete local responses in selected cases, and has been followed by successful pregnancies in a limited number of patients. What is missing is a prospective, multicenter, molecularly stratified study with predefined eligibility criteria, standardized photosensitizer and light parameters, histologic confirmation of response, systematic imaging and long-term follow-up.

Another limitation is that many older reports used photosensitizers and light-delivery systems that are no longer representative of current PDT technology. Modern agents can have improved tumor selectivity, deeper activation wavelengths, faster clearance and more controllable photophysics. Therefore, the historical clinical evidence may underestimate the potential of contemporary PDT, but it also cannot be used to infer that newer agents are clinically effective. A new generation of trials is required.

2.4. Preclinical evidence in endometrial cancer

Preclinical studies provide broader evidence base than clinical investigations. Human endometrial carcinoma cell lines have been exposed to several classes of photosensitizers, demonstrating that malignant endometrial cells can be selectively or preferentially damaged after light activation.
Early work by Raab and colleagues investigated responses of human endometrial and ovarian carcinoma cell lines to PDT, establishing that endometrial tumor cells could be photodynamically injured (Raab et al., 1990). Subsequent work examined the relationship between PDT and extracellular matrix or receptor biology. Ziółkowski and colleagues evaluated epithelial tissue derived from patients with endometrial cancer and explored the role of

laminin and epidermal growth factor receptor in PDT-related effects (Ziółkowski et al., 1999). These studies were important because they moved the field beyond simple observations of cell death toward a mechanistic understanding of tumor-cell susceptibility.

Hypericin has attracted particular attention because of its strong photodynamic activity and intracellular localization. Varriale et al. showed that low-energy presensitization of hypericinloaded human endometrial carcinoma cells modified gene expression, cell-cycle behavior and photo-tolerance (Varriale et al., 2002). Schneider-Yin et al. subsequently reported enhanced phototoxicity of hypericin and 5-aminolevulinic acid-induced protoporphyrin IX in human endometrial cancer cells under non-coherent white light (Schneider-Yin et al., 2009). These findings suggest that the photosensitizer and cellular metabolic state can substantially modify the photodynamic response.

5-Aminolevulinic acid (5-ALA) is particularly attractive because it is a precursor rather than a permanently retained photosensitizer. After administration, it enters the heme biosynthetic pathway and can result in intracellular accumulation of protoporphyrin IX. Because PpIX is photoactive and its intracellular concentration can be influenced by tumor metabolism, 5-ALA has been extensively investigated in other cancers. Its relatively short duration of photosensitivity compared with some first-generation systemic photosensitizers is potentially advantageous for fertility-preserving applications, although the optimal route of administration and intrauterine exposure for EC remain unresolved.

Radachlorin-mediated PDT has also been evaluated in the human endometrial adenocarcinoma cell line HEC-1-A. Kim et al. reported anticancer effects following Radachlorin activation, supporting the feasibility of chlorin-based photosensitization in endometrial carcinoma models (Kim et al., 2024). However, in vitro cytotoxicity is only an initial proof of concept. The key translational questions are tumor-selective accumulation, light penetration through the uterine cavity, normal endometrial toxicity, pharmacokinetics, reproductive safety and long-term recurrence.

The 2024 review devoted specifically to PDT in EC summarized these experimental studies and concluded that most evidence remains preclinical. A further 2024 report described in vitro PDT investigations in EC and highlighted the continuing interest in combining cell culture models with different photosensitizers (Żołyniak-Brzuchacz et al., 2024). These publications are important because they show that the field is still active, but they also make clear that the evidence base is not yet comparable with that supporting established EC treatments.

A major opportunity is to develop models that reproduce the tumor microenvironment more faithfully. Conventional two-dimensional cell cultures cannot adequately represent hypoxia, extracellular matrix, stromal cells, vascular structures or immune interactions. Threedimensional organoids, patient-derived xenografts and ex vivo tissue models could help determine whether the promising cytotoxicity observed in monolayer cultures persists under more realistic conditions. For an endometrial application, organoid models should also incorporate normal endometrial cells and, where possible, patient-specific molecular subtypes.

Table 1. Evidence base for photodynamic therapy in endometrial cancer

Evidence level	Typical evidence	Main findings	Key limitations
Clinical	Small series, case reports, fertilitypreservation cohort	Local complete responses and pregnancies have been reported in selected patients	Small sample sizes, historical protocols, selection bias, no randomized comparison
In vitro	Endometrial carcinoma cell lines	Phototoxicity demonstrated with hematoporphyrins, hypericin, 5-ALA/PpIX and Radachlorin	Cell lines do not reproduce tumor microenvironment or pharmacokinetics
Translational	PDD, hysteroscopy, nanotechnology	Potential for lesion mapping, targeted illumination and improved photosensitizer delivery	Most evidence indirect or from other tumor types

Mechanistic	ICD, hypoxia, ROS biology	PDT can induce direct cytotoxicity, vascular injury and immune activation	Clinical relevance of immune effects in EC remains unproven

Source: Authors' own elaboration based on Choi et al. (2013), Corti et al. (1995), Raab et al. (1990), Ziółkowski et al. (1999), Varriale et al. (2002), Schneider-Yin et al. (2009), Kim et al. (2017), Żołyniak-Brzuchacz et al. (2024), Mayor and Lele (2016), Matoba et al. (2018), Shanazarov et al. (2024), Carobeli et al. (2024), Bartusik-Aebisher et al. (2025), and mechanistic literature by Mishchenko et al. (2024), Liu et al. (2024), Catanzaro et al. (2025), Han et al. (2024), Zheng et al. (2024), Birhan et al. (2025), Xu et al. (2024), Zhao et al. (2025), Zhang et al. (2025), and Ren et al. (2025).

2.5. Photosensitizers and treatment parameters

The clinical translation of PDT depends heavily on photosensitizer selection. Firstgeneration hematoporphyrin derivatives established the clinical feasibility of PDT but were associated with prolonged cutaneous photosensitivity and relatively limited tissue penetration. Second-generation agents, including chlorins, bacteriochlorins, phthalocyanines and related compounds, have been developed to improve absorption characteristics, tumor localization and clearance (Kwiatkowski et al., 2018; Mayor & Lele, 2016; Matoba et al., 2018; Shanazarov et al., 2024; Carobeli et al., 2024).

For EC, the most relevant historical photosensitizers include hematoporphyrin derivatives, Photofrin, hypericin, 5-ALA/PpIX and Radachlorin. Their properties differ substantially. Photofrin has a long clinical history, but its prolonged photosensitivity is inconvenient for young patients. Hypericin has strong photochemical activity, but its formulation, pharmacokinetics and optimal light parameters require careful control. 5-ALA is metabolically converted to PpIX and offers a potentially shorter systemic photosensitivity window, but PpIX production is influenced by cellular metabolism and ferrochelatase activity. Radachlorin and other chlorin-based agents may offer favorable red-light activation characteristics.

Table 2. Photosensitizer classes relevant to endometrial cancer research

Agent/class	Activation	Potential advantages	Main limitations	Evidence in EC
Hematoporphyrin derivatives / Photofrin	Red light	Historical clinical experience; established PDT platform	Prolonged photosensitivity; older pharmacology	Clinical series; fertilitypreservation cohort
Hypericin	Visible light	Strong phototoxicity; experimental mechanistic data	Lipophilicity; formulation and pharmacokinetic issues	In vitro endometrial carcinoma studies
5-ALA → PpIX	Blue/red activation of PpIX	Metabolic precursor; relatively short photosensitivity window	Variable PpIX accumulation; dosing not standardized in EC	In vitro endometrial cancer studies
Radachlorin / chlorins	Red light	Favorable photophysical properties; potentially deeper penetration	Clinical EC data absent or very limited	In vitro HEC-1-A study
Next-generation nanoformulations	Red/NIR depending on platform	Targeting, oxygen modulation, combination therapy	Manufacturing, safety, translation	Mostly indirect evidence from other cancers

Source: Authors' own elaboration based on Kwiatkowski et al. (2018), Oniszczuk et al. (2016), Varriale et al. (2002), Schneider-Yin et al. (2009), Kim et al. (2017), Mayor and Lele (2016), and Matoba et al. (2018).

The optimal wavelength is determined by the absorption spectrum of the photosensitizer and the desired tissue penetration. Red and near-infrared wavelengths generally penetrate tissue more effectively than blue or green light. For the endometrium, however, depth is less problematic than in many solid tumors because lesions are frequently superficial and accessible hysteroscopically. This creates an opportunity to use precise local light delivery rather than relying solely on deep tissue penetration.

Dosimetry is an underappreciated source of variability. Photodynamic efficacy depends on photosensitizer concentration, tissue oxygenation, fluence, irradiance and timing. Two studies that both describe "PDT" may therefore be biologically incomparable if these parameters differ. Future EC trials should report all components of the treatment protocol and should use reproducible dosimetry, preferably with intra-procedural assessment of light delivery and, where technically possible, oxygenation or photosensitizer fluorescence.

The current generation of photosensitizer research also explores targeting ligands and nanocarriers. Nanoparticles may improve solubility, protect photosensitizers from premature degradation, alter biodistribution and facilitate tumor accumulation. In other cancers, nanoplatforms are being engineered to release oxygen, respond to hypoxia,

or combine PDT with chemotherapy and immunotherapy (Birhan et al., 2025; Xu et al., 2024; Zhao et al., 2025; Zhang et al., 2025; Ren et al., 2025; Bartusik-Aebisher et al., 2025; Chen et al., 2025). These strategies remain experimental in EC but are highly relevant to future development.
An ideal photosensitizer for fertility-preserving EC would combine strong tumor selectivity, activation at a tissue-penetrating wavelength, rapid clearance, low systemic toxicity, minimal reproductive toxicity and compatibility with hysteroscopic light delivery. It should also retain efficacy under the relatively hypoxic conditions that may exist in a tumor.
No currently studied agent has definitively met all these criteria.

2.6. Hysteroscopy, local treatment and fertility preservation

The anatomical accessibility of the uterine cavity is one of the strongest arguments for studying PDT in EC. Hysteroscopy allows direct visualization of the lesion, targeted biopsy, resection of visible tumor and potentially controlled illumination of the treatment field. This could enable a multimodal conservative strategy in which hysteroscopic resection reduces tumor volume and PDT targets residual microscopic or superficial disease.
The rationale resembles other organ-preserving approaches in oncology: treatment intensity is adapted to disease biology and extent, while preservation of function is considered an explicit therapeutic endpoint. In EC, fertility-sparing management has traditionally relied mainly on high-dose progestins, with or without a levonorgestrel-releasing intrauterine system, combined with rigorous hysteroscopic and histologic surveillance. PDT could theoretically complement rather than replace hormonal therapy by directly damaging residual malignant cells.
However, the threshold for adopting a local ablative therapy in a fertility-preserving setting must be high. Patients must be selected using contemporary criteria, including young age, desire for fertility, well-differentiated endometrioid histology, disease limited to the endometrium, absence of myometrial invasion and absence of extrauterine disease. Molecular classification should increasingly be incorporated into selection. Tumors with p53 abnormalities or other features associated with aggressive biology should not be considered suitable merely because imaging shows apparently superficial disease (Sakai et al., 2026; Bogani et al., 2026; Kumari et al., 2025; Anca-Stanciu et al., 2025; Liang et al., 2025).
The published fertility-preservation experience with PDT is encouraging but insufficient. Pregnancy after PDT has been reported, including successful pregnancies after conservative treatment. Nevertheless, the number of exposed patients is too small to estimate reproductive safety. A future trial should distinguish oncologic response from reproductive outcome. Important reproductive endpoints include return of normal endometrial morphology, menstrual function, time to conception, implantation, miscarriage, preterm birth, placental disorders and neonatal outcomes.
There is also a biological question concerning the normal endometrium. Even if PDT is selective for malignant cells, treatment-induced inflammation or stromal remodeling could theoretically affect implantation. Conversely, if PDT preserves the tissue architecture better than extensive resection or radiotherapy, it could ultimately prove favorable for fertility. These hypotheses require dedicated reproductive studies rather than assumptions based on the general safety of PDT.
A rational clinical pathway could therefore be conceived as: molecular and histologic eligibility assessment → hysteroscopic mapping and biopsy → maximal removal of visible tumor where appropriate → standardized PDT of the tumor bed → continued progestin-based management when indicated → repeated hysteroscopy and biopsy → strict surveillance → definitive surgery after completion of childbearing or if conservative treatment fails. This remains a research concept and should not be presented as a current standard of care.

2.7. Photodynamic diagnosis and theranostic approaches

PDT is closely related to photodynamic diagnosis (PDD), in which a fluorescent photosensitizer or precursor is used to identify abnormal tissue. The ability to combine diagnosis and therapy may be particularly valuable in endometrial disease because hysteroscopy already provides a direct optical route to the endometrial cavity.
A review of gynecologic photodynamic applications reported that PDD under hysteroscopy could help distinguish endometrial cancer and hyperplastic or secretory endometrial tissue, while earlier clinical PDT reports suggested that fertility could be preserved in selected patients (Matoba et al., 2018). The concept is attractive because the same biological phenomenon-preferential accumulation of a photoactive compound - could potentially be used first to map disease and then to guide treatment.
Fluorescence - guided PDT could reduce one of the major weaknesses of conventional local treatment: uncertainty about treatment boundaries. In a future theranostic workflow, hysteroscopy could identify fluorescent tumor areas, map the lesion, quantify fluorescence intensity and guide light delivery. This approach could also enable repeated assessment of the same area during follow-up.

The development of theranostics is particularly relevant to molecularly heterogeneous EC. Fluorescence alone is not equivalent to molecular targeting, but photosensitizers can potentially be linked to ligands directed at tumor-associated receptors or antigens. Such approaches remain experimental, yet they could improve the therapeutic index by increasing photosensitizer concentration in tumor cells relative to normal endometrium.
The main barriers are technical standardization, reproducibility and the absence of validated fluorescence thresholds for endometrial lesions. Prospective studies should compare fluorescence-guided mapping with histopathology and evaluate sensitivity, specificity and interobserver variability. If validated, PDD could become a valuable companion technology even before PDT itself becomes a standard treatment.

2.8. PDT and the tumor immune microenvironment

The immunological consequences of PDT provide an important bridge between local therapy and contemporary systemic treatment. PDT can induce immunogenic cell death (ICD), characterized by the exposure or release of danger-associated molecular patterns, including calreticulin, ATP and HMGB1. These signals can facilitate dendritic-cell maturation, antigen presentation and activation of tumor-specific T cells (Mishchenko et al., 2024; Liu et al., 2024; Catanzaro et al., 2025; Zheng et al., 2024).
This mechanism has particular relevance to EC because the tumor's immune phenotype varies substantially across molecular subtypes. MMRd/MSI-H tumors are generally more immunogenic and show strong responses to immune checkpoint inhibition. It is therefore reasonable to hypothesize that a local treatment capable of increasing antigen release and inflammatory signaling could complement checkpoint blockade. This hypothesis is biologically plausible but not yet clinically established in EC.
Recent experimental studies have focused on engineering PDT to maximize ICD. Nanomaterial-based PDT can be designed to improve tumor accumulation, generate ROS efficiently and stimulate immune activation. Other approaches use photosensitizers that release nitric oxide or otherwise reduce oxygen consumption, thereby preserving oxygen for ROS production and enhancing immunogenic cell death under hypoxic conditions (Birhan et al., 2025; Xu et al., 2024; Zhao et al., 2025; Zhang et al., 2025; Ren et al., 2025; BartusikAebisher et al., 2025; Chen et al., 2025). A 2024 study demonstrated that oxygen-economized PDT using nitric-oxide-releasing photosensitizers could enhance ICD, illustrating a broader direction for next-generation PDT (Xu et al., 2024).
The potential combination with immune checkpoint inhibitors should nevertheless be approached carefully. PDT can produce acute local inflammation, but not every photodynamic regimen induces a clinically meaningful systemic immune response. The magnitude and quality of immune activation depend on the photosensitizer, subcellular localization, treatment intensity and tumor microenvironment. A combination trial would therefore require mechanistic biomarkers rather than simply combining two active treatments.
In EC, a rational translational strategy could test whether PDT increases tumor-infiltrating lymphocytes, dendritic-cell activation, interferon signaling or other immune biomarkers. Molecular subgroup analysis could determine whether the effect is strongest in MMRd/MSIH tumors or whether PDT can make otherwise less immunogenic tumors more responsive to checkpoint inhibition. These questions are particularly relevant in recurrent localized disease, where systemic therapy may be indicated but local control remains clinically important.

2.9. Hypoxia, nanotechnology and next-generation PDT

Tumor hypoxia is a central challenge for conventional Type II PDT. Oxygen is consumed during ROS generation, and poorly oxygenated regions can therefore become progressively less responsive during illumination. Recent PDT research has addressed this problem through several complementary strategies: oxygen generation, oxygen storage, reduction of cellular oxygen consumption, Type I photochemistry, and intelligent light-responsive delivery systems (Birhan et al., 2025; Xu et al., 2024; Zhao et al., 2025; Zhang et al., 2025; Ren et al., 2025; Bartusik-Aebisher et al., 2025; Chen et al., 2025).
Oxygen-generating nanoparticles can use endogenous hydrogen peroxide to produce oxygen within the tumor. Other systems incorporate catalytic materials such as manganesecontaining compounds or enzymes. Hypoxia-responsive systems may change their structure or release cargo under low-oxygen conditions. These approaches are still largely experimental, but they are particularly interesting for tumors in which local oxygenation varies spatially.
Nanoparticle engineering may also solve the problem of photosensitizer solubility and nonspecific distribution. Encapsulation can improve pharmacokinetics and protect the photosensitizer until it reaches the target. Surface ligands can potentially direct particles to tumor-associated receptors. In the endometrial cavity, local administration could further reduce systemic exposure. A topical or intrauterine delivery strategy could theoretically provide high local photosensitizer concentration while limiting systemic photosensitivity, although safety and distribution would require rigorous investigation.

The 2025 literature includes several examples of hypoxia-responsive and oxygen-regulating PDT platforms, including light-activated nanoparticles and catalytic nanoformulations. These studies demonstrate that the field is moving from conventional photosensitizer/light combinations toward multifunctional systems that actively modify the tumor microenvironment (Birhan et al., 2025; Zhao et al., 2025; Zhang et al., 2025; Ren et al., 2025). Their relevance to EC is currently indirect because most have been tested in other tumor models. The translational value lies in the engineering principles rather than in any demonstrated clinical efficacy for endometrial tumors.
Future EC studies should therefore prioritize simplicity and clinical feasibility. A technologically complex nanoparticle may be scientifically impressive but difficult to translate into a hysteroscopic procedure. The best candidate platform may instead be a photosensitizer with favorable pharmacokinetics and a straightforward delivery method combined with a standardized light applicator. Translation should be driven by a clinically defined problem rather than by nanotechnology novelty alone.

3. Combination strategies

PDT can theoretically be combined with hormonal treatment, chemotherapy, radiotherapy, targeted therapy or immunotherapy. In EC, the most clinically relevant combinations should be selected according to disease biology and treatment intent.
Hormonal therapy is particularly relevant to fertility preservation. Progestins suppress estrogen-driven proliferation and can induce regression of selected low-risk endometrioid tumors. PDT could provide a complementary cytotoxic mechanism directed at residual malignant cells. A combined approach might therefore reduce the duration of exposure to high-dose hormonal treatment, although this hypothesis has not been tested prospectively.
Chemotherapy combinations have been studied extensively in other gynecologic cancers. A 2024 systematic review of PDT combined with chemotherapy in cervical cancer summarized evidence for synergistic effects in selected preclinical and clinical contexts (Carobeli et al., 2024). Such evidence should not be directly transferred to EC, but it supports the broader concept that PDT may sensitize tumor cells to other treatments.
Radiotherapy and PDT have mechanistic overlap because both can generate oxidative stress and damage tumor tissue. However, combined local toxicity and reproductive consequences would be major concerns in a fertility-preserving population. Any combination with radiation would therefore be more relevant to non-fertility-preserving local control than to conservative treatment.
Immunotherapy is arguably the most interesting future combination. The ability of PDT to generate tumor antigens and danger signals creates a biological rationale for combining local photodynamic treatment with immune checkpoint blockade. Modern EC therapy already relies on PD-1/PD-L1 pathway inhibition in several settings, particularly in dMMR/MSI-H disease. A localized PDT treatment might theoretically act as an in situ vaccine while checkpoint blockade prevents exhaustion of activated T cells (Mishchenko et al., 2024; Liu et al., 2024; Catanzaro et al., 2025; Zheng et al., 2024; Powell et al., 2024; Powell et al., 2025; Powell et al., 2026; Auranen et al., 2024; Makker et al., 2022; Mirza et al., 2023; Westin et al., 2024).
The combination should be tested in a stepwise fashion. Initial studies should establish safety and pharmacodynamic evidence of immune activation. Subsequent trials can evaluate objective response and progression-free survival. Because the local treatment volume is small, imaging and tissue biomarkers should be integrated whenever possible.

3.1. Limitations of the current evidence

The most important limitation is the small number of patients treated in published clinical studies. Much of the direct evidence comes from case reports, historical series and a small fertility-preservation cohort. Such studies can establish feasibility but cannot determine comparative efficacy, recurrence risk or long-term safety.
A second limitation is protocol heterogeneity. Different studies have used different photosensitizers, doses, administration routes, intervals between drug and light, wavelengths, fluence and treatment fields. Consequently, “PDT” does not represent a single standardized intervention. This prevents meaningful pooling of results.
Third, many clinical studies predate contemporary molecular classification. The biological risk of the included tumors was therefore not characterized according to POLE, MMR or p53 status. This is particularly important because the modern management of EC is increasingly biomarker-driven.
Fourth, the evidence base is vulnerable to publication bias. Positive case reports and unusual long-term successes are more likely to be published than unsuccessful attempts. The apparent response rates in early reports may therefore overestimate the true probability of durable disease control.

Fifth, fertility outcomes are underreported. A successful pregnancy in a small number of patients is encouraging, but it does not establish the absence of adverse effects on implantation, placentation or fetal development. Long-term obstetric follow-up should be a mandatory component of fertility-preserving PDT research.
Finally, there is a translational gap between in vitro efficacy and clinical therapy. Cell-line experiments are performed under controlled illumination and often with concentrations of photosensitizer that are difficult to achieve safely in vivo. They also lack the architecture and immune environment of a human tumor. For this reason, future studies should progressively move from two-dimensional cell cultures to organoids, ex vivo tissues, animal models and carefully designed early-phase clinical trials.

3.2. Proposed framework for future clinical trials

Future studies should be designed as prospective translational trials rather than retrospective case collections. A reasonable first population would consist of young patients with carefully selected, low-risk, endometrium-confined endometrioid carcinoma who desire fertility preservation and meet established conservative-treatment criteria. Molecular classification should be performed prospectively.
The intervention should be standardized. The protocol should define the photosensitizer, dose, route, drug-light interval, wavelength, fluence, irradiance, treatment field and criteria for retreatment. Hysteroscopic visualization should be used to document lesion size and location before and after treatment. If feasible, fluorescence-guided mapping could be incorporated.
Primary endpoints should include complete histologic response at a prespecified time point and treatment-related toxicity. Secondary endpoints should include recurrence-free survival, hysterectomy-free survival, time to recurrence, pregnancy rate and obstetric outcomes. Molecular and immunological biomarkers should be incorporated as exploratory endpoints.
A randomized design may initially be difficult because the eligible population is small and fertility-preserving hormonal therapy is heterogeneous. A multicenter single-arm phase II study with a predefined historical control could be an appropriate first step, followed by a randomized comparison against the contemporary conservative standard if sufficient preliminary efficacy is demonstrated.
Importantly, trials should include a predefined rescue strategy. Persistent disease, recurrence, progression, or development of high-risk molecular features should trigger definitive treatment according to current guidelines. PDT should never delay standard oncologic care.
An international registry would also be valuable. Because EC treated conservatively is relatively uncommon and PDT experience is even rarer, collaboration across centers would allow collection of standardized outcomes. Such a registry could define the natural history of PDT-treated disease and identify subgroups most likely to benefit.

4. Discussion

The evidence reviewed here supports a cautious but scientifically credible role for PDT research in EC. The strongest rationale is anatomical and clinical rather than purely technological. The endometrial cavity is accessible to hysteroscopy, allowing local visualization and potentially precise light delivery. In selected early-stage disease, preservation of the uterus may be clinically important, especially in young patients who wish to retain fertility.
Historical clinical reports demonstrate that complete local responses and pregnancies after PDT are possible. Preclinical studies provide biological support for phototoxic effects in endometrial carcinoma cells using several photosensitizers. Together, these findings justify further investigation. They do not, however, justify routine clinical use.
The current treatment landscape also changes the question that PDT must answer. Modern EC management is increasingly personalized, and advanced disease can be treated with chemotherapy-immunotherapy combinations that produce substantial improvements in outcomes. It would therefore be difficult to justify PDT as a primary systemic disease treatment. Its potential niche is more specific: local disease control, fertility preservation, or treatment of selected residual/recurrent lesions.
The molecular era provides an opportunity to make PDT research more precise. Instead of enrolling all early-stage EC patients, future trials could examine whether specific molecular groups show enhanced susceptibility to oxidative stress or stronger immune activation after PDT. The most plausible interaction with current therapy is the combination of local PDT with immune checkpoint blockade, but this remains hypothetical in EC.

The recent PDT literature also demonstrates that technological progress is accelerating. Photosensitizers are becoming more selective, nanocarriers can modify pharmacokinetics, and oxygen-regulating systems can address hypoxia. Importantly, recent research on ICD suggests that PDT can be more than a local cytotoxic treatment: it may stimulate systemic antitumor immunity (Mishchenko et al., 2024; Liu et al., 2024; Catanzaro et al., 2025; Zheng et al., 2024; Birhan et al., 2025; Xu et al., 2024; Zhao et al., 2025; Zhang et al., 2025; Ren et al., 2025). Whether this can be exploited clinically in EC is an important research question.

Nevertheless, technological complexity should not be mistaken for clinical progress. A highly sophisticated nanoparticle is only useful if it can be manufactured reproducibly, characterized pharmacologically, delivered safely, and integrated into a practical clinical procedure. The endometrial application offers an advantage because local delivery and hysteroscopic access may allow simpler approaches than those required for deeply located solid tumors.

The principal research priority is therefore standardization. Without standardized eligibility criteria, molecular characterization, photosensitizer dosing, light parameters and follow-up, the field will continue to generate isolated positive reports that cannot be compared. A consensus protocol developed by gynecologic oncologists, photomedicine specialists, pathologists and reproductive medicine experts would substantially accelerate progress.

Overall, PDT should be viewed as an investigational platform with several possible future applications rather than a single treatment. Its ultimate role may involve fertility preservation, local recurrence management, fluorescence-guided surgery, or combination photoimmunotherapy. The most likely successful pathway is not replacement of established treatments but integration of PDT into carefully defined multimodal strategies.

5. Conclusions

Photodynamic therapy represents a biologically plausible and technically attractive investigational approach to selected endometrial cancers. The method combines a photosensitizer, light and oxygen to generate cytotoxic reactive oxygen species and can additionally produce vascular and immunological effects. The accessibility of the endometrial cavity makes hysteroscopy-guided PDT particularly interesting for localized disease and fertility preservation.

Current evidence consists mainly of preclinical studies, small historical clinical series and limited fertility-preservation experience. Several photosensitizers including hematoporphyrin derivatives, hypericin, 5-ALA/PpIX and Radachlorin have demonstrated activity in endometrial cancer models. However, no randomized clinical evidence currently establishes PDT as a standard treatment for endometrial carcinoma.

The future of the field will depend on molecularly selected patients, standardized treatment parameters, improved photosensitizers, better management of tumor hypoxia, fluorescenceguided therapy and rational combinations with immunotherapy or hormonal treatment. Prospective multicenter trials with long-term oncologic and reproductive endpoints are required before PDT can be incorporated into routine endometrial cancer care.

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