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The nano-revolution in the diagnosis and treatment of endometriosis

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Endometriosis is a painful gynecological disease with a high prevalence, affecting millions of women worldwide. Innovative, non-invasive treatments, and new patient follow-up strategies are needed to deal with the harmful social and economic effects. In this scenario, considering the recent, very promising results already reported in the literature, a commitment to new research in the field of nanomedicine is urgently needed. Study findings clearly show the potential of this approach in both the diagnostic and therapeutic phases of endometriosis. Here, we offer a brief review of the recent exciting and effective applications of nanomedicine in both the diagnosis and therapy of endometriosis. Special emphasis will be placed on the emerging theranostic application of nanoproducts, and the combination of phototherapy and nanotechnology as new therapeutic modalities for endometriosis. The review will also provide interested readers with a guide to the selection process and parameters to consider when designing research into this type of approach.

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1. Introduction

Nanotechnology is the area of science and engineering in which nanoscale phenomena occur, and is gaining considerable worldwide attention in the field of medicine.[1,2] A large number of reports suggest that nanoparticles (NPs) have the potential to enhance conventional therapeutic modalities (*e.g.*, chemotherapy) and imaging modalities (*e.g.*, MRI) in order to detect (*e.g.*, photoacoustic imaging) and treat (*e.g.*, photothermal therapy [PTT] and magnetic hyperthermia) various diseases.[3,4] NPs are promising vehicles for the delivery of drugs and imaging agents to disease sites because they can be conjugated to drugs, antibodies, or other chemical compounds.[5,6] In particular, several studies have shown how NPs, with their low toxicity, high stability, and the possibility of conjugation with several biomolecules, could be used to deliver anti-inflammatory, antioxidant, anti-angiogenetic, or immunomodulating molecules at specific targets.[7–9] NPs are mainly designed to enhance stability, delivery efficiency, and targeted release length for molecules with limited bioavailability.[10–12] They are used to optimize the biodistribution of drugs to diseased organs, tissues, or cells to improve and target drug delivery. NPs can release drugs in response to a laser triggering photothermal effects, radiofrequency waves, and ultrasounds; for all these reasons, they have been investigated in combination with radiation physics for on-demand drug delivery.[13–15] With the rapid development of nanotechnology, several multifunctional nanoscale agents have been successfully synthesized, especially in the field of cancer therapies.[16–18] However, many researchers/experts agree that manipulating things at the nanometer level could be successful in tissue engineering and vaccine development and could pave the way for the development of diagnostic/therapeutic approaches and monitoring of other human diseases, which will revolutionize health care in the coming years.[19] A growing body of work clearly demonstrates that the "nanoscale revolution" has also laid its foundations in a complex disease,

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namely endometriosis. The endometriosis is an estrogen-dependent chronic gynecological disorder in which the endometrium tissue that normally lines the uterus forms lesions outside of the uterus and is one of the most disabling conditions for women of reproductive age, for which there are no side-effect-free therapies and for which early diagnosis is indispensable to limit the physical and psychological health damage associated with the progression of the disease.[20–22] Several reports have already shown that NPs could help treat endometriosis in animal models by localizing and removing painful and dangerous lesions in the ovaries, fallopian tubes and pelvis without the need for invasive surgery.[3,23] This is possible by exploiting the tendency of NPs to have a higher accumulation in tissue characterized by higher vascularization, such as the endometriotic tissue by the so-called enhanced permeability and retention (EPR) effect, or promoting the accumulation of NPs in endometriotic lesions by modifying their surface with targeting ligands that bind overexpressed receptors in endometriotic cells (the so-called active targeting).[24] Although nanomedicine for endometriosis is a budding field, this review intends to highlight the diagnostic and therapeutic importance of the application of NPs in endometriosis, and at the same time provide insights of interest to researchers aiming for new diagnostic/therapeutic approaches to address other diseases of the reproductive system, and finally represent a great hope for physicians and patients to address the challenges of endometriosis more effectively.

After a brief description of the disease, we provide an update on recent advances in nanomedicine in the diagnosis and treatment of this condition, concluding with a review of published work, showing how the combination of photothermal therapy with nanotechnology can achieve breakthroughs in the treatment of endometriosis. With regards to the latter, we focused on the selection of the laser device to be used and of the light treatment parameters, on which the outcomes of photothermal experiments depend.

2. Endometriosis – an overview

Endometriosis typically affects women and girls of reproductive age, with a prevalence ranging from 6% to 10%,[25] although it may sometimes be diagnosed also in menopause.[26] Endometriosis is responsible for pain symptoms and infertility, which can severely impact the quality of life of affected patients.[27,28] Endometriotic implants may be found in different sites. They are found most frequently on the pelvic peritoneum, ovaries, uterosacral ligaments, bowel, and rectovaginal septum. More rarely, they can be found in extra pelvic localizations, such as the diaphragm, umbilicus, pericardium, and pleura. The exact pathogenesis of endometriosis is still unknown, but several leading theories include retrograde menstruation, altered immunity, coelomic metaplasia, and metastatic cell spread.[29] Nevertheless, a unifying theory regarding the origin of endometriosis still remains elusive; in fact, the heterogeneity and differences among the three main classes of endometriosis presentation may suggest different multiple pathogenetic pathways.

There is increasing evidence to support the concept of endometriosis as a pelvic inflammatory condition. In women with endometriosis, the peritoneal fluid is remarkable for an increased number of activated macrophages and important differences in the cytokine/chemokine profile. The peritoneal microenvironment is notably rich in prostaglandins, and these mediators likely play a central role in disease pathophysiology, as well as clinical sequelae of pain and infertility.[30] In addition, hormonal alterations may influence the ability of endometrial cells to proliferate, establishing and maintaining implants. Long-appreciated clinically, the concept of endometriosis as an estrogen-dependent disorder is well supported by molecular evidence. A striking finding in endometriotic tissue relative to eutopic endometrium is the increased expression of the aromatase enzyme and decreased expression of 17β-hydroxysteroid dehydrogenase (17β-HSD) type 2. The sum consequence of this differential expression profile is a marked increase in the locally bioavailable estradiol concentration. Estradiol stimulates the production of prostaglandin E2, which further stimulates aromatase activity.[31]

There are several methods to diagnose endometriosis, such as laparoscopy, transvaginal ultrasound (TVUS), and magnetic resonance imaging (MRI).[32] Due to the heterogeneity of location and appearance of endometriotic lesions, these diagnostic tests are inadequate, and often lead to a delay in diagnosis, or even misdiagnosis.[33] In addition, available treatments, such as pharmacological and surgical approaches, help relieve the symptoms but cannot lead to a permanent cure.[34] Pain can be treated by excising peritoneal implants, deep nodules, and ovarian cysts, or inducing lesion suppression by abolishing ovulation and menstruation through hormonal manipulation with progestins, oral contraceptives and gonadotropin-releasing hormone agonists. Medical therapy is symptomatic, not cytoreductive, while surgery is associated with high recurrence rates. Although lesion eradication is considered a fertility-enhancing procedure, the benefit on reproductive performance is moderate. Assisted reproductive technologies represent a valid alternative. Surgical excision of endometriosis significantly ameliorates pain symptoms;[35] however, it may be associated with complications. Moreover, recurrence rates of pain symptoms after surgery are such as to require attention.[36] In addition, in the case of ovarian endometriomas, there is concern about the risk of damage to the ovarian reserve.[37] Faced with the paucity of treatment approaches, research has been focusing on nanotechnologies. Although their application in endometriosis is still to be considered innovative, the available reports suggest that NPs-based strategies can provide new tools for treating this disease.

3. Applications of nanotechnology in endometriosis

As stated in the Introduction section, in the field of endometriosis nanomedicine, the range of new diagnostic and thera-

peutic approaches is incredibly exciting.[3] As recently reviewed by Yuxue *et al.* nanomaterial-based strategies have a great impact in the treatment of endometriosis, such as nanomaterials alone, nanomaterial-based drug therapy, gene therapy, photothermal therapy, immunotherapy, and magnetic hyperthermia.[23] In general, what clearly emerges from the literature, and which the interested reader will find out in the following subsections, similarly to cancer field, are the nanotechnological approaches developed targeting specific features of endometriosis, while exploiting the enormous diagnostic, therapeutic and theranostic potential of certain types of NPs. Endometriosis and cancer share many pathophysiological features (*e.g.*, angiogenesis, reactive oxygen species (ROS) production, *etc.*), and some fundamental principles of cancer nanomedicine can be or have been adapted for the development of novel nanoparticle-based strategies for the treatment and imaging of endometriosis.[3] As with cancer nanotechnology, NPs differing in chemical composition (organic, inorganic and carbon-based) have been used for the diagnosis and therapy of endometriosis, by surface modification with specific targeting molecules and with/without drug loading (Table 1). Here, we set out to offer a summary of the enormous potential of nanotechnology as a diagnostic, therapeutic and theranostic approach in endometriosis by reporting some compelling results described in the literature. As regards therapy, given the great promise of PTT-nanomaterials, we highlight the results from PTT-nanomaterial combinatorial therapeutic approaches. To this end, we also discuss some of the characteristics of lasers to be considered during the experimental planning phase.

3.1 Molecular imaging and immunosensors: the promise of nanotechnology for endometriosis diagnosis

The diagnosis of endometriosis can be a lengthy procedure and it is complicated by the various mechanisms involved in the etiologies.[32] Several pre-clinical studies have explored the application of NPs for endometriosis diagnosis, with exciting up-front results (Table 1). Lee *et al.* presented a new diagnostic tool for the evaluation of experimentally-induced endometriosis.[38] They considered the role of ultrasmall superparamagnetic iron oxide (USPIO). USPIOs (size <50 nm) belong to the SPIO family, which have been approved by the US Food and Drug Administration (FDA) and European Commission as MRI contrast agent.[39] USPIOs possess a magnetic core composed of magnetite, maghemite or other insoluble ferrites which makes them ideal candidates for MRI.[40,41] MRI usually involves imaging in which the tissue contrast is weighted according to the *T*1 and *T*2 relaxation properties of the tissue.[42] In brief, *T*1-weighted images optimally show normal soft tissue anatomy and adipose tissue, while *T*2-weighted images optimally show fluid and pathological conditions.[43] USPIOs are considered *T*2 contrast agents and can therefore be used instead of gadolinium-based as they are less toxic and can increase magnetic susceptibility.[44] Taking advantages of low cost, biosafety and flexibility of surface modifications,[40,45–47] in the present work, USPIO were applied as contrast agent in MRI detection for the evaluation of ectopic uterine tissue (EUT). Since they are internalized by macrophages[48,49] that are abundant in the endometriotic lesions and peritoneum, it is could be a new diagnostic approach.[38,50] A few years later, Zhang *et al.* synthesized NPs modified with hyaluronic acid (HA) and magnetic iron oxide nanoparticles (Fe_3O_4 NPs).[51] In recent years, Fe_3O_4 NPs have gained increasing attention in various biomedical applications due to their magnetic properties.[52,53] In the proposed work, HA-Fe_3O_4 NPs was used as negative contrast agents for MRI in tumor cells over-expressing CD44 receptors. Since this receptor is over-expressed also in endometriotic cells,[54,55] they successfully applied this nanosystem also in *in vivo* imaging of endometriotic lesions in rats. Moreover, Simòn-Gracia *et al.* designed a nanovector based on silver NPs (AgNPs) functionalized with synthetic PL1 peptide (Fig. 1A).[56] Among the promising nanomaterials, AgNPs belong to inorganic materials and are increasingly used in biomedical field. They possess several properties, including optical, electrical, thermal, and high electrical conductivity.[57–59] AgNPs can be functionalized with ligand and homing peptides, but also labelled with a fluorophore that makes them brighter by increasing their fluorescence intensity.[57,58,60,61] Thanks to their low cytotoxicity, easy preparation, high stability, biocompatibility, and functionalization, in the work proposed by Simòn-Gracìa, AgNPs were used as tracker in cells and tissues by optical imaging. The AgNPs were synthesized according to the citrate method of Lee and Meisel[62] and functionalized with PL1, that is well internalized by endometriotic immortalized cell lines. It is possible to apply the nanosystem both in diagnostics (*e.g.*, guided surgery, imaging) as well as in the therapeutic field with the conjugation of a drug.[56] Marquardt *et al.* showed an imaging gold-fluorescein isothiocyanate (FITC) with photoacoustic (PA)-coupled NPs that can be used in deep endometriosis.[63] Gold nanoparticles (AuNPs) are one of the most widely investigated inorganic nanomaterials. The high surface area, unique size-dependent properties and precise tunability of NPs make them ideal candidate for multifunctional platform in biomedical application.[64–67] AuNPs application depend strongly upon their size and shape, and they may be controlled trough their synthesis methods.[68,69] Moreover, they exhibit a strong and tunable optical absorption resulting from the surface plasmon resonance (SPR) effect.[70] The SPR effect occurs when the free charges on the surface of AuNPs oscillate with the electromagnetic field, leading to an optical absorption that is several orders of magnitude higher than that of organic dyes.[64,71,72] In the present work, gold nanorods were coated with silica shells *via* the silica sol–gel process and attached them with a distal fluorescein tag (FITC) using simple silane chemistry.[73] Transmission electron microscopy (TEM) showed the distinctive rod structure of gold particles with a width of 12–14 nm and a length of 50–55 nm.[63] The major advantage was the increased signal penetration due to the fact that ultrasonic waves can spread further than normal light; they are emitted by thermoelastic expansion under near-infrared (NIR) light illumination (680–980 nm).[74–76]

Table 1 Summary NP-based approaches for endometriosis diagnosis and therapy

Type of NP	Cargo molecules	Target	Model/ concentration NP	Route of administration	Biological effect	Application	Ref.
USPIOs	—	Macrophages	Rats	Intravenously delivered *via* the tail vein	—	MRI	38
Fe_3O_4 NPs	HA	CD44	Rat 10 mg per kg	Intravenously delivered *via* the tail vein	—	MRI	51
AuNRs	—	Endometriotic lesions	Mice 0.06 mg Au mL^{-1}	Injected into peritoneal cavity	\	PA imaging	63
MWCN	Ab Anti-$_{CA19-9}$	CA19.9	Women blood	—	—	Immunosensor	77
AuNPs	Ab Anti-$_{CA125}$	CA125	Women blood	—	—	Lmmunosensor	81
AuNPs	Ab anti-HP	HP	Serum samples	—	—	Lmmunosensor	83
Nanoceria	—	OS marker; angiogenesis marker	Mice 0.5 mg/kg	Injection into the peritoneal cavity of the abdominal wall	Decreasing ROS, angiogenesis; endometrial glands and microvessels density	Therapy	88
PLGA	EGCG and DOx	OS marker; angiogenesis marker	Mice	Intravenously delivered *via* the tail vein	Decreasing OS, angiogenesis, and MMP activity	Therapy	91
PLGA	Copaiba oleoresin	—	ESCs, CESCs, EuESCs and EctESCs 0.3 mg per ml	Cell medium	Morphology alterations, necrosis, apoptosis	Therapy	96
PLGA	Anti-CTLA-4	CTL4	Mice	intravenously delivered *via* the tail vein	cell inhibition, proliferation, invasion	Therapy	99
PLGA	Anti-CCR5	CCR5	Mice	Intravenously delivered *via* the tail vein	Reduction of macrophages, IL-10, TGF-β	Therapy	100
PCL	Curcumin	\	Mice	Implanted nanosystem in the peritoneum	Reduction of endometrial glands, stroma, inflammatory cells, MMP-activity	Therapy	101
CaNPs	BML-111	\	Mice	Intravenously injected	Enhanced efferocytosis, reduced inflammation	Therapy	102
LDE	—	LDL receptor	Women	Injected intravenously	Cell internalization	Therapy	104
PEI–SA	HA/DNA and siRNA	CD44/beclin-1 gene	Mice	Intravenously injected	Regulation of autophagic activity	Therapy	106
Albumin-NPs	GOx	Neutrophils ($CD11b^+$ cells)	Mice	Intraperitoneally injected	Reduction of neutrophils	Therapy	108
HAuNS	TNYL peptides	EphB4	Mice 1.25 mg per ml	Intravenously injected	Inhibition of lesion growth, decreased levels of TNF-α and estradiol	PTT	128
PCL	SiNc	Vasculature of endometriotic grafts	Mice	*Via* lateral tail-vein injection	Apoptosis of endometriotIc lesions	Imaging and PTT	129
AgNPs	PL1/PL1-MMAE	TNC-C and Fn-EDB	12Z and HESC cells 0.3 nM	Cell medium	Guided surgery, imaging, viability suppressor	Imaging and therapy	56
MN	KDR	VEGFR-2	Mice	Intravenous injected with 200 μL of KDR-MN	MRI application, cell death	Imaging and therapy	107

Abbreviations: USPIOs, ultrasmall super magnetic iron oxide nanoparticles; MRI, magnetic resonance imaging; Fe_3O_4 NPs, magnetic iron oxide nanoparticles; HA, hyaluronic acid; CD, cluster of differentiation; AuNRs, gold nanorods; PA, photoacoustic imaging; MWCN, multi-walled carbon nanotubes; Ab, antibody; CA, carbohydrate antigen; AuNPs, gold nanoparticle; HP, haptoglobin; nanoceria, cerium oxide nanoparticles; OS, oxidant stress; ROS, reactive oxygen species; PLGA, poly(lactic-co-glycolic acid); EGCG, epigallocatechin gallate; Dox, doxycycline; MMP, metalloproteinase; ESCs, primary endometrial stromal cells; CESCs, ESCs obtained from patient without endometriosis; EuESCs, ESCs from eutopic endometriotic lesions; EctESCs, ESCs obtained from ectopic endometrium of patients with endometriosis; CTLA4, cytotoxic T-lymphocyte antigen 4; CCR5, C–C chemokine receptor type 5; TGF-β, transforming growth factor-B; PCL, poly ε-Caprolactone; CaNPs, calcium carbonate nanoparticles; LDE, lipid nanoparticle; LDL, low-density lipoprotein receptor; PEI, polyethyleneimine; SA, stearic acid; albumin-NP, albumin nanoparticles; GOx, glucose oxidase; HAuNS, hollow gold nanospheres; EphB4, Ephrin type-B receptor 4; TNF-α Tumor necrosis factor alpha; PTT, photothermal therapy; SiNC, dye silicon naphthalocyanine; AgNPs, silver nanoparticles; MMAE, monomethyl auristatin E; TNC-C, tenascin C domain C; Fn-EDB, fibronectin extra domain-B; 12Z cells, human immortalized endometriotic epithelial; HESC, human immortalized endometrial stromal HESC; MN, iron oxide magnetic; KDR, kinase insert domain receptor; VEGFR-2, vascular endothelial growth factor receptor 2; \: not reported.

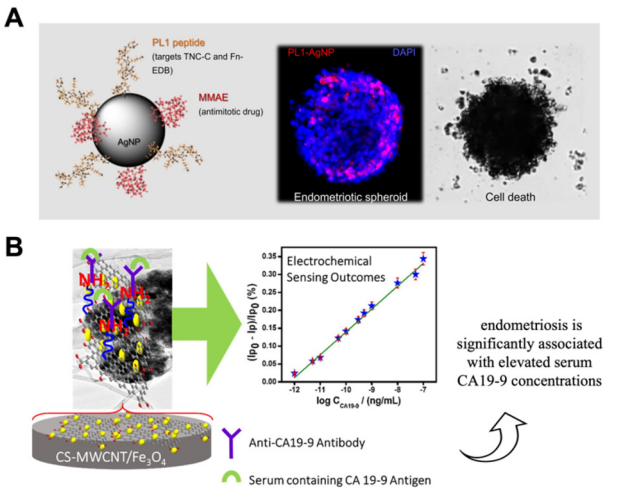

Fig. 1 Use in diagnosis of endometriosis. (A) Design of AgNPs with PL1 peptide that can be combined with MMAE. Confocal images show the internalization of PL1-AgNPs into Z12 cell spheroids. SEM images demonstrate the therapeutic capacity of the nanovector. Adapted with the permission of ref. 56. (B) Schematic representation of CS-MWCNT/Fe_3O_4 bio-nanocomposite based on electrochemical immunosensor for detecting CA19.9 antigen in endometriosis diagnostic applications.[77] Reprinted with permission from Elsevier (License number 5582481039205).

In a similar way, Ding *et al.* reported a (photoacoustic) PA imaging microscopy method for *in vivo* endometriosis mice models.[78] In the context of diagnosis, several diagnostic techniques are available for the preparation of NPs-based immunosensors. They are highly sensitive, and can be used for direct, non-invasive measurement of protein levels in the clinical sample, in comparison to ELISA and fluorescence tests.[79] They are receiving increasing attention because of their many advantages, such as cost-effectiveness, high sensitivity, and rapid results. Kalyani *et al.*[77] reported the first bio-nanocomposite immunosensor that showed high sensitivity for the detection of CA19-9 (tumor antigen 19-9),[80] a potential biomarker for endometriosis diagnosis (Fig. 1B).[77] The film of nanocomposite, composed of chitosan (CS), a linear polysaccharide polymer, multi-walled carbon nanotubes (MWCNT), and Magnetite (Fe_3O_4), was fabricated dropping the solution of CS-MWCNT-Fe_3O_4 on a glassy carbon electrode (GCE) surface.[77] In detail, CS has been shown to interact with MWCNTs to form stable dispersions; Fe_3O_4 has superparamagnetic property, biocompatibility, good electrocatalytic activity, and low toxicity and used as an attention-grabbing material for the immobilization of biomolecules. The CS capping MWCNT-Fe_3O_4 composite on the modified GCE enhances the stability of the electrode surface and effective immobilization of the antibody.[77] In this study, a monoclonal anti-CA19-9 antibody was immobilized on the composite modified electrode for label-free, selective, and sensitive capture of CA19-9 antigen. Antibodies are commonly used in immunosensors for antigen detection. Therefore, the proper immobilization of antibodies on the transducer surface is very important and is possible using micro/nanostructured composites. The sensing performance of the immunosensor was tested by detecting serum samples from endometriosis patients and validated using the enzyme-linked immunosorbent assay (ELISA). The results showed that this CA19-9 detection system showed high sensitivity and rapid detection of the CA19-9 biomarker, as well as being very accurate and precise, cost-effective and easier to perform than conventional techniques such as ELISA.[77] In a similar way, another group[81] proposed an immunosensor to detect CA125: a carbohydrate antigen irregularly produced in severe endometriosis.[82] This immunosensor is based on AuNPs and reduced graphene oxide (rGO) obtained through electrochemical deposition, an approach that facilitated the *in situ* reduction of GO and Au^{3+}. Interestingly, the fabricated immunosensor demonstrated, showed better results for the detection of CA 125 in endometriosis patient blood samples compared to the standard ELISA method (the calculated maximum Relative Standard Deviation (RSD) from the fabricated immunosensor was 6.6% while the maximum RSD value obtained from the standard ELISA kit was 7.3%).[81] The immunosensor proposed for the evaluation of glycoprotein haptoglobin (HP) is also based on Au/rGO hybrid film.[83] In cases of endometriosis, the *HP* gene and HP protein have abnormal levels in liver cells, and they are unusually glycosylated.[84] The anti-HP antibody was immobilized on the Au/rGO GCE *via* ethyl-*N*′-(3-dimethyl aminopropyl) carbodiimide hydrochloride–*N*–hydroxysuccinimide (EDC–NHS) coupling with the help of 1-mecaptoundecanoic acid (11-MUA).[83] Although negligible variation in the detection of HP in human serum plasma was detected compared to the standard ELISA method, the result clearly showed that the proposed detection platform has high sensitivity, selectivity, reproducibility, stability and reusability and could be used for the robust determination of the endometriotic HP biomarker in clinical laboratories.[83]

3.2 Emerging therapeutic and theranostic nanotechnology approaches in endometriosis

Although endometriosis is a complex disease and the underlying mechanisms still elusive, there are distinctive features that can be harnessed for the development of selective and targeted therapeutic strategies, including NPs.[85] For example, it has been shown that there is a positive association between oxidative stress (OS) and endometriosis, just as excessive endometrial angiogenesis is believed to be a critical mechanism in the pathogenesis of this disease.[86,87] Chaudhury *et al.* obtained successful outcomes in the mitigation of endometriosis using regenerative cerium oxide NPs (nanoceria).[88] Nanoceria, characterized by the co-existence of fully oxidized Ce^{4+} and fully reduced Ce^{3+}, has attracted much attention due to its ability to act as a scanner of free radicals (especially superoxide radical and hydrogen peroxide) in biological systems. The authors showed that injection of nanoceria (a single dose of 0.5 mg per kg body weight) into the peritoneal cavity of the abdominal wall significantly mitigated the endometrial lesions induced in mice model by decreasing oxidative

stress lower OS parameter such as ROS, lipid peroxidation (LPO) and total antioxidant capacity (TAC) and inhibiting angiogenesis lower expression of vascular endothelial growth factor (VEGF) and adrenomedullin (ADM) as compared to a known antioxidant (*N*-acetyl cysteine; NAC- a dose of 250 mg per kg body weight thrice a week for 15 days)[88] This model also showed a promising reduction in endometriosis-related negative effects on oocyte quality, which is a critical factor for pregnancy success.[88] Poly(lactic-*co*-glycolic acid) (PLGA) is one of the most effective biodegradable polymeric NPs. It has been approved by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for use in drug delivery systems due to its controlled and sustained release properties, low toxicity, and biocompatibility with tissues and cells.[89] The Extracellular matrix degradation play also an important role the pathogenesis of endometriosis.[90] Singh *et al.* developed a dual drug-loaded PLGA NPs that combines the anti-angiogenic and antioxidant properties of epigallocatechin gallate (EGCG) and the matrix metalloproteinase inhibitory activity of antibiotic doxycycline (Dox)[91] in order to improve and reduce the limitations when they are used in their native forms. The novelty of this nanosystem is given by the delivery of two different agents (Dox and EGCG) in a single vehicle: the dual agent-NPs was more efficient at reducing levels of metalloproteinase (MMPs) and angiogenic factors in mice with endometriosis than single drug-loaded NPs. Another further confirmation of efficacy by Dox-EGCG NP compared to the Dox NPs and EGCG NPS-treated groups and drugs alone was the significant reductions in endometrial gland and micro vessel density. Moreover, treatment with Dox-EGCG NPs in mice with endometriosis, seemed to be favorable in terms of the number and quality of oocytes.[91] A few years later, De Almeida Borges *et al.* developed a PLGA NPs loaded with copaiba oleoresin (COPA), obtained from Copaifera landgroffii.[92,93] COPA is chemically defined as a solution of diterpene acids in an essential oil. The diterpene (the β-caryophyllene) in COPA possess anti-inflammatory and antitumorigenic activity[94] and it is able to cause regression of endometrial implants in a rat model of endometriosis without affecting fertility.[95] The authors hypothesized that the administration of COPA in lamellar silicate nanocomposites could increase the potential of its therapeutic effects by enhancing the pharmacological efficacy of COPA and reducing its distribution in other tissues. From the *in vitro* investigation, resulted that COPA was released from the nanocomposite in a delayed manner, a finding associated with reduced viability and proliferation of endometriosis cell cultures than untreated controls.[96] PLGA NPs were also studied as a delivery method for certain antibodies, such as the anti-CTLA-4 antibody (the main suppressive immune checkpoint)[97] and the anti-CCR5 antibody (C–C chemokine receptor type 5).[98] Anti-CTLA-4/PLGA NPs were reported to constantly release anti-CTLA-4 antibodies providing a greater inhibition of ectopic endometrial cell proliferation and invasion in a mouse model than anti-CTLA-4 alone.[99] Anti-CCR5/PLGA bioconjugate showed a significant reduction in macrophage, IL-10, and TGF-β levels, with an associated reduction in the proliferation and invasion capacity of ectopic endometrial cells compared to anti-CCR5 alone.[100] Furthermore, many studies have investigated the potential role and molecular mechanisms of curcumin in endometriosis by suppressing angiogenesis, oxidative stress, inflammation, and controlling cell proliferation, apoptosis, invasion, and attachment. For example, Boroumand *et al.* designed a curcumin-loaded nanofiber to target endometriosis in the peritoneum of mice. The authors investigated nanofibers of poly ε-caprolactone (PCL) and polyethylene glycol (PEG) polymers loaded with curcumin as an implantable anti-endometriosis scaffold capable of continuously releasing curcumin onto endometriotic implants. PCL is a biodegradable, biocompatible polymer that makes it a more reasonable choice for an implanted scaffold. The release of curcumin from this nanosystem was approximately of 23% during 30 min, 35% at 24 h, and 50% at 30 days compared to the curcumin alone; in addition, curcumin was more stable in the nanosystem than alone.[101] Similarly, a group of researchers proposed an acid-sensitive calcium carbonate NP (CaNP) with BML-111, which is an anti-inflammatory agent.[102] Among different inorganic materials, calcium carbonate NPs offer many advantages, including bioavailability, low cost, safety, biocompatibility, pH sensitivity and slow biodegradability. They can be combined with drugs to achieve various treatments, including chemical therapy, gene therapy, phototherapy and immunotherapy.[102,103]

This nanosystem promoted apoptosis of endometriotic stromal cells, increased the uptake of apoptotic cells by macrophages (a process called efferocytosis), and reduced inflammation by decreasing cytokine secretion.[11] Another preliminary nanotechnological approach consisted of an artificial lipid emulsion (LDE) with LDL-receptor-like characteristics. Bedin *et al.* showed preliminary results in which they found a high uptake of labelled LDE by the topical endometrium, which can be used as a nanosystem.[104] Another mechanism of endometriosis that can be studied regard the autophagy process, in which Beclin-1 play an essential positive regulatory role.[105] Zhao *et al.* devised a hyaluronic acid (HA) (PEI-SA/DNA) as a tool for Beclin-1 gene delivery and consequent Beclin-1 upregulation within endometrial lesions. (Fig. 2A). In details, (PEI-SA/DNA) HA can reach CD44, which is overexpressed in the lesion tissue and internalized by endometrial cells.[55] It resulted in an enhanced autophagy and inhibition of endometriotic pathogenesis and progression. From these preliminary data, the nanosystem appears to be sufficient to promote autophagy induction and, to some extent, mediate therapeutic efficacy *in vivo*.[106]

A recent article described a new therapeutic approach using neutrophils as a target.[108] Here, Zhu *et al.* designed a glucose oxidase-loaded bovine serum albumin NP (BSA-GOx-NP) that is internalized by neutrophils *in vivo*. Albumin nanoparticles can be synthesized using various approaches[109] and can be exploited for active and passive targeting[110] and in controlled drug delivery. Moreover, they have been approved by FDA for clinical use.[108] The enzymatic activity and cytotoxicity of GOx

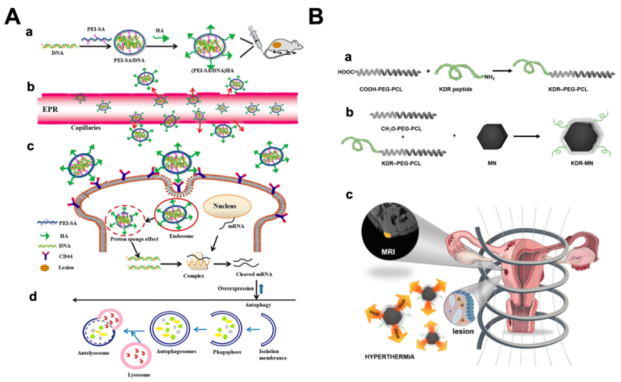

Fig. 2 Therapeutic application in endometriosis. (A) Schematic representation of autophagy process mediated by HA with Beclin-1 nanovector (PEI-SA/DNA): (a) after PEI-SA/DNA construction, (b) it is internalized through trough passive targeting (EPR effect), (c–d) and then binds the CD44 receptor. Finally, it enters the endometriotic cells. Adapted with the permission of ref. 106. (B) Schematic illustration of KDR-MN used as MRI contrast agents: (a and b) NPs were first prepared using PEG-PCL, KDR peptide and MN. (c) KDR-MN accumulation allowed MRI to detect the endometriotic lesion.[107] Reprinted with permission from Reprinted with permission from John Wiley and Sons (License number 5582490980873).

were preserved, inducing eutopic lesion apoptosis with undetectable side effects. The proposed nanosystem can be a promising tool in the inflammatory endometriosis microenvironment.[108]

The combination of diagnostics and therapy (the so-called theranostic) is also possible in the context of nanomedicine. For example, Simòn-Gracia *et al.*[56] tested the efficacy of AgNPs functionalized with synthetic PL1[111] both in endometriosis diagnostics (see above) and therapy. PL1 is able to recognize tenascin C domain (TNC-C) and fibronectin extra domain-B (Fn-EDB) on endometriotic cells and can be internalized (Fig. 1A). The study showed the ability of AgNPs loaded with the antimitotic drug monomethyl auristatin E (MMAE) to suppress the viability of endometriotic cells cultured in 2D, and as spheroids in a peptide-dependent manner.[56] Moreover, Park *et al.* devised iron oxide magnetic NPs (MN) coupled with a kinase insert domain receptor (KDR) able to accumulate in endometriotic lesions targeting vascular endothelial growth factor receptor 2 (VEGFR-2) (Fig. 2B).[107] In the study on KDR-MN, exposure to an alternating magnetic field (AMF) can result in it being heated to over 50 °C, causing cell death. In addition, the nanovector showed promising use as MRI contrast agents (before AFM) in endometriosis diagnosis.[107]

Taken together, all these examples make it clear that the increasing success of these therapies is due to their ability to induce cell death through key cellular mechanisms such as the induction of ROS generation mediated by NPs.

3.3 Combining nanotechnology with phototherapy

Recent efforts in nanomedicine have promoted the rapid development of light-induced theranostics based on versatile nanoagents with rich, light-induced functions, including near-infrared (NIR) to visible light conversion, photodynamic therapy (PDT), and photothermal therapy (PTT).[112] Here we discuss recent advances in the application of phototherapy in endometriosis (Table 1). In PTT, NIR light is converted into heat to induce local hyperthermia, thus exploiting the susceptibility of cells to denature their proteins and induce cell death (Fig. 3A).[113,114] NPs-based phototherapy involves the systemic or local administration of a nanosystem, followed by NIR laser irradiation (700 nm to 1350 nm). The ideal nanosystem should possess high absorption efficiency, photothermal conversion efficiency, low toxicity, and a good targeting ability.[115] Many NPs can be used as photothermal agents such as metal NPs, carbon nanomaterials, black phosphorus-based nanomaterials, and metal sulphide.[116] It is now understood that to improve photothermal performance, photothermal nanomaterials can be developed to be composed of a single or more components and can involve more than one photothermal conversion mechanism.[116,117] Among all, AuNPs have been the most widely used nanomaterials in PTT in recent decades. Due to special interactions with light, the free electrons of gold nanostructures undergo a collective, coherent oscillation process known as localized surface plasmon resonance.[118–120] The AuNPs can be designed and produced

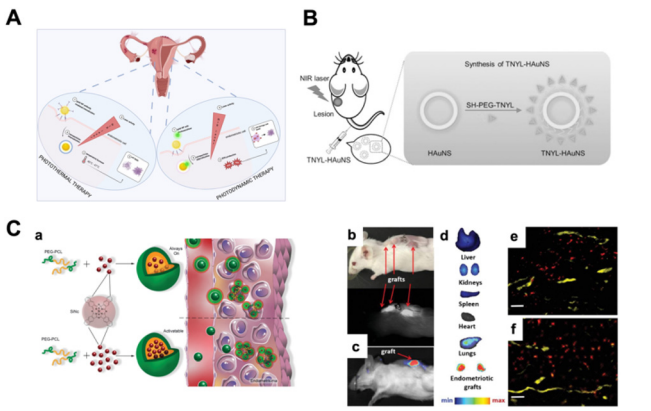

Fig. 3 Phototherapy in endometriosis. (A) Photothermal (PPT) and photodynamic (PDT) therapy. Briefly, when NPs are internalized and exposed to laser, in PTT, the increase in temperature leads to cell death, while in PDT, the PS favors the production of reactive oxygen species (ROS) that impact cell metabolism. Created with BioRender.com. (B) Set-up of PTT mediated by TNYL-HAuNS nanovector applied in a mouse model. Reprinted with permission from John Wiley and Sons (License number 5582490179408)[128] (C) (a) Schematic illustration of "always on" and "activable" SiNc-NPs. The difference is represented by the greater numbers of SiNc NPs in "activable" NPs in comparison to "always on" NPs in the hydrophobic core. This results in a generation of fluorescence only after internalization into endometriotic cells. (b, c, d, e and f) Illustration of endometriotic grafts 24 h after injection of "activable" SiNc-NP: (b and c) images of mouse bearing endometriotic grafts, and corresponding NIR fluorescence images; (d) NIR fluorescence images of resected tissue; (e and f) fluorescence microscopy images of endometriotic graft section. Red: NIR fluorescence generated by SiNc-NP. Yellow: blood vessels (anti-CD31 antibody). Scale bars are 50 μm.[129] Reprinted with permission from Copyright John Wiley and Sons (License number 5582490434492).

through different techniques, including chemical synthesis (*i.e.* Turkevich[121] and the Brust[122] methods, Seed-Mediated Growth[123] and Digestive Ripening)[124] and biological synthesis using biomass a plethora of organisms, ranging from bacteria to plants, algae, and fungi.[65] Considering AuNPs, in order to improve their photothermal effect, it was found useful to modify their organization as clusters or shells or similarly, combining them with different materials (*e.g.*, silica and graphene).[125] Moreover, a group of researchers show that the photothermal conversion efficiency of the flower-like-nanocopper sulphide was elevated by 50% in comparison to ordinary hexagonal sulphide NPs,[126] demonstrating the importance of NPs' morphology. Within the different strategies explored to enhance NPs-mediated PTT, the encapsulation of NIR responsive small molecules have shown to display promising results.[127] To further improve PTT and reduce side effects, nanomaterials must be functionalized to achieve site-specific PTT with protein denaturation, membrane disruption and irreparable damage leading to cell death.[120]

Considering the pathophysiological similarities between cancer and endometriosis, NP-based PTT could represent the ideal therapeutic strategy for endometriosis. However, the application of PTT combined with NPs in endometriosis is not as well explored as in cancer. To date, there are few articles in the literature dealing with this topic in endometriosis. In 2017, Guo *et al.* developed targeted EphB4 hollow gold nanospheres (HAuNS) for endometriosis therapy based on photothermia (Fig. 3B).[128] One of the mechanisms involved in both endometriosis and cancer is neovascularization, which is associated with overexpression of Eph receptors. To achieve the targeting effect, HAuNS was conjugated with TNYL peptides capable of binding (Ephrin type-B receptor 4) EphB4 receptors. In *in vivo* experiments under NIR light irradiation, TNYL-HAuNS significantly inhibited lesion growth by photothermal ablation without significant damage to normal tissue. However, congestive patients cannot be treated with this method, as EphB4 is also highly expressed in the uterus.[128] Moreover, Moses *et al.* designed a nanoplatform based on the dye silicon naphthalocyanine (SiNc) and polymeric NPs, which can be used for real-time near-infrared fluorescence imaging and photothermal therapy (Fig. 3C).[129] SiNc NPs are ideal candidate for PTT because they have shown strong absorption of NIR light and are able to generate both high NIR fluorescence and heat upon exposure to NIR light of relatively low power (>0.3 W cm^{-2}).[130–132] As these NPs have poor solubility and tend to aggregate in aqueous environments, the researchers applied a solvent evaporation approach to encapsulate SiNc molecules within the hydrophobic core of [methoxy poly(ethylene glycol)-*b*-poly(ε-caprolactone)] (PEG-PCL) polymer NPs. The aim of this work was to achieve high contrast during fluorescence imaging of endometriotic lesions: "always-on" fluorescent SiNc-NPs were remodeled to produce "activable" SiNc-NPs by increasing the amount of SiNc molecules from 0.5 to 6% SiNc per 1 mg PEG-PCL. In this way, the NPs were only activated once inside the endometriosis tissue. Both the *in vitro* and *in vivo* experiments demonstrated the validity of the system compared to SiNc alone.[129] Photodynamic therapy (PDT) involves light energy combining with a photosensitizing agent (PS) (Fig. 3A). PDT uses light and oxygen to stimulate the production of reactive oxygen species (ROS) by PSs, which leads to disorders in cell metabolism.[132] The photodynamic effect can be used both therapeutically and as a fluorescence-guided surgical procedure[133] (see above).[63] PDT combined with NPs is widely used in tumors,[134] but also as an antibacterial,[135] and can find applications in endometriosis treatment. A few years ago, a PS alone derived from 5-aminolevulinic called protoporphyrin IX was used in endometriosis.[136] The absence of a vehicle to deliver the PS led to a non-specified accumulation in nearby cells. In this case, if the authors had used a nanosystem delivery approach, there probably would have been a more targeted effect.[3]

The studies described above confirmed that NPs-based PTT can be useful in endometriosis and suggest that other NPs previously used in the field of oncology may be repurposed for PTT treatment of endometriosis. However, the technique has limitations due to its inadequate tissue penetration and the intensity of light required to activate the photosensitizers that are currently available.

3.4 Selecting laser parameters and the delivery approach

As a state-of-the-art approach, several light sources can be used for PDT and PTT studies.[137] The main parameters affecting the selection of the ideal light source are: emission wavelength, NPs absorption bandwidth, the required optical power, and the position of the surface to be irradiated.[138,139]

The correct emission wavelength must be chosen so as to maximize the interaction with the NPs used for the treatment, generally trying to match the NPs absorption peak.[132,140] Nevertheless, it is important to bear in mind that the light penetration in biological tissue is very low in the visible range (especially on the green/blue side of the visible spectrum), while it is significantly larger in the 800–1200 nm region (Fig. 4A).[141,142] Optical absorption and scattering are the two physical effects that limit light penetration at the different wavelengths, and they are both strongly dependent on the tissue composition; therefore, the 800–1200 nm range must only be considered to be a general reference. In this wavelength range, the absorption of water is much higher than that observed for blue light, but the main limitations are generally produced by blood (that strongly absorbs blue or green light) and by scattering. Several laser sources are usually available at this wavelength range, ranging from semiconductor lasers at 808 or 980 nm to solid-state lasers at 1064 nm (Nd:YAG laser) or to fiber lasers emitting around 1070 nm (Yb-doped fiber laser).[143–145] Another key aspect to be considered is the absorption bandwidth of the NPs to be used.[146] While working with a narrowband laser source (with an emission band narrower than 0.1 nm), it may be useful to carry out specific studies and to fully address the impact of wavelength selection. In practical applications where the NPs exhibit large absorption peaks (tens of nm), it may be convenient to use LED light sources instead of lasers. While LED sources have a larger emission

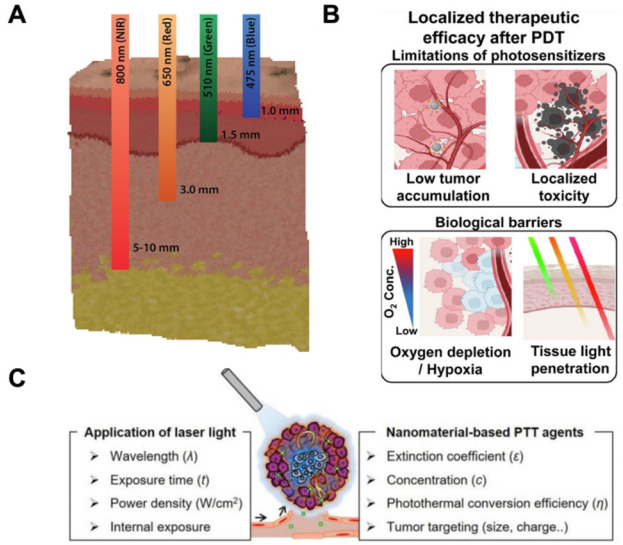

Fig. 4 Laser parameters for PTT and PDT applications: (A) schematic illustration of different light penetration in biological tissue depending on the laser emission wavelength; adapted with the permission of ref. 142. (B) Photodynamic nanomedicines enable highly localized PDT and can better overcome barriers.[151] Reprinted with permission from Elsevier (license number: 5582490789244) (C) schematic laser parameters to be used in PTT application. Adapted with the permission of ref. 152.

band, and their light is not coherent and cannot be as tightly focused as laser light, they may offer significant advantages in terms of reduced cost, higher efficiency in the electric-to-optical power conversion, and greater uniformity.

The required optical power is a fundamental aspect of their use and a key element for the light source.[147–149] A preliminary evaluation of the required power can be obtained simply by multiplying the required light intensity (in mW cm^{-2}) and the area of the surface to be treated (Fig. 4B and C). But it is important to consider that, in general, only a fraction of the emitted power can be confined with high homogeneity on the target surface, and thus it is useful to multiply the obtained power for a factor of between 2 and 5 to estimate the optical power required at light source output.[147–149] Another aspect that must be considered is the location of the surface to be irradiated, as this impacts on the power parameter. In fact, in the case of both PDT and PTT, the presence of targeted illumination produces a localized change within the tissue (*i.e.*, production of ROS/temperature increase) that will necessarily spread to the surrounding areas according to specific mechanisms of molecule diffusion/heat transfer.

Therefore, the maximum increase in ROS-concentration/temperature also critically depends on the environment around the treated area and on its level of "isolation" from surrounding tissues. As an example, considering the *in vivo* experiments carried out on subcutaneous lesions, it is to be expected that a higher intensity (roughly by a factor of 2 or 3) will be required to produce the same effects in deep tissues.[150,151] Finally, the position and the extension of the area to be treated can require specific tools to correctly guide light to the target. In the case of externally visible lesions, free-space light propagation (at least in the final section of the path) is probably the simplest alternative, while appropriate arrangements of optical fibers and catheters (with balloons if needed to extend the surface to be treated) could be the ideal choice when deep tissue treatments are necessary. Considering that the light-treatment of endometriotic lesions would require surgery (or laparoscopy), an interesting possibility is that offered by the development of bioresorbable optical fibers and implants, which could bring light to the tissues even for a few days following surgery, without any need for the implant to be removed.

4. Concluding remarks

Although nanomedicine for endometriosis is still in its infancy, it offers great hope to physicians and patients of a more effective management of the challenges of this disease. At the same time, it is of interest to researchers who are aiming to develop new diagnostic and therapeutic approaches to tackle other reproductive system diseases. Nanomedicine is one of the fastest-growing fields in translational medicine, and nanotechnological innovations may have implications not only in endometriosis research, but also in the study of other reproductive diseases,[85] *e.g.*, uterine fibroids, ovarian cancer, or microbial infections.[135] Nanomedicine could also be useful in the development of new treatment procedures, and in the identification of biological markers that could be applied in clinical practice to stratify the risk of disease recurrence or persistence, with a significant impact on disease management and decision-making approaches for personalized treatment and patient follow-up.[153,154] Due to similarities between cancer and endometriosis, some fundamental principles of cancer nanomedicine can be adapted to develop novel NPs-based strategies.[3] In general, data available in the literature demonstrate that these nanosystems can be optimized and functionalized in order to be applied in endometriosis. Summarizing the nano-approaches discussed in this review (Table 1), mainly inorganic NPs were applied in the diagnostic field, whereas organic NPs in the therapeutic area. Several studies functionalized nanomaterials to better achieve the target, but in same works the NPs alone were used to exploit their intrinsic characteristics. Many of the proposed literature evaluate the effectiveness of nanocarriers in animal models, such as rats and mice, and a few portion (10%) on 2D *in vitro* cell models.

However, in order to further facilitate their clinical application, there are still several issues and challenges that need to be overcome. Firstly, some of the trials involving nanomaterials are still at an early stage,[80] and most of these materials are not yet commercially available.[63,89] Secondly, a few NPs show potential toxicity, according to their size or shape and concentration.[88,89,91] Thirdly, some studies only described the absence of adverse effects on endometriotic tissue,[88] but nothing is known about the biodistribution of

NPs in other organs. Finally, results from studies on endometriosis using rat or mouse models may not be transferable to humans. Based on the 3R principles (refine, replace, and reduce), there are ethical and scientific reasons to support alternative non-animal-based models. In fact, animal models cannot always reproduce all the features of some diseases, and a non-animal-based model could better reproduce the human microenvironment.[155,156] A challenging 3D *in vitro* model has been proposed by Simon Garcia[56] and others.[157] A 3D model recreates the highly inflammatory microenvironment of endometriosis better than monolayer models since it includes different cell types and stimuli, allowing us to explore the cell complex while helping to reduce the number of animals used. In summary, more studies are needed to clarify the potential role of nanotechnology in diagnostic, therapeutic, and theranostic applications in endometriosis.

Conflicts of interest

The authors declare no conflict of interests.

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