Universitat de Girona

PHOTODYNAMIC THERAPY AS AN ALTERNATIVE TO PROGESTOGENS IN ENDOMETRIAL CANCER GRADE 1A G1

MULTICENTER CLINICAL ANALYSIS

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"Donde quiera que se ame el arte de la Medicina, se ama también a la Humanidad"
Platón

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ABBREVIATIONS

ABBREVIATION	WORD
BMC	Body Mass Index
HNPCC	Hereditary Nonpolyposis Hereditary Colorectal Cancer
HRT	Hormone Replacement Therapy
POLE	Polymerase Epsilon
PJS	Peutz-Jeghers Syndrome
CNS	Central Nervous System
DNA	Deoxyribonucleic Acid
CRC	Colorectal Cancer
CEA	Carcinoembryonic Antigen
PMR	Pelvic Magnetic Resonance
CT	Computerized Tomography
FIGO	International Federation of Gynecology and Obstetrics
LVSI	Lymphovascular Space Invasion
EBRT	Chemotherapy and Radiotherapy
UID-LNG	Intrauterine Dispositive of Levonorgestrel
ART	Assisted Reproductive Techniques.
PDT	Photodynamic Therapy
ROS	Reactive Oxygen Species
FDA	Food and Drug Administration.
MTHPC	Metatetrahydroxyphenyl chloro
5-ALA	5-Aminolevulinic Acid
LED	Light-emitting Diode
HPV	Human Papilloma Virus
CIN	Cervical Intraepithelial Neoplasia
VIN	Vulvar Intraepithelial Neoplasia
VAIN	Vaginal Intraepithelial Neoplasia

ABSTRACT

BACKGROUND: Endometrial neoplasia is the most prevalent gynecological cancer in developed countries. Although diagnoses during the fertile age is less significant, the standard treatment is surgery. In case of reproductive desire and stage 1A G1/G2 endometrial carcinoma, an alternative treatment (oral progestogens) can be administrated. This treatment has a low response rate (57-75%), presents recurrences (11-50%) and various systemic side effects. On the other hand, photodynamic therapy has been used to detect and combat malignant lesions on the cervix, endometrium, vulva, vagina, breast and ovarian, because it reduces the adverse effects of conventional treatments.

OBJECTIVES: To compare treatment with oral progestogens and photodynamic therapy in stage 1A G1/G2 endometrial carcinoma without myometrial involvement in patients without associated genetic factors: remission rate, time to cure, recurrence rate, adverse effects, quality of life of patients and reproductive desire.

DESIGN:

This experiment scientific study is a multicenter, national, parallel-group, prospective, randomized, open label but blinded for the end-point evaluators (PROBE) clinical trial.

PARTICIPANTS:

This study includes all those patients under 40 years of age with a gestational desire, without associated genetic factors and who have been diagnosed with stage 1A G1/G2 endometrial cancer, without myometrial invasion or adnexal extension, in public or private hospitals in Spain.

METHODS:

A non-probabilistic consecutive sampling method will be followed in the Gynecology and Obstetrics Unit of each participating hospital. Once a sample of 430 patients has been recruited, they are randomly divided into two groups:

- Control group (group A): The patient will be treated with oral progestogens.
- Intervention group (group B): The patient will be treated with photodynamic therapy.

KEYWORDS:

Endometrial carcinoma, Photodynamic therapy, oral progestogens, side effects, quality of life, remission rate, recurrence rate, pregnancy rate.

BACKGROUNG

1. ENDOMETRIAL CANCER:

The endometrium is the lining that covers the uterine cavity and allows the implementation of the embryo after the fecundation. It is formed by a cylindrical epithelial layer supported by a cellular stroma with tubular glands. It is a hormonosensible tissue, that depends on estrogens and progesterone, that remodels cyclically during the childbearing age. Both hormones do an antagonistic function: the estrogen promotes the proliferation, and the progesterone stimulates its abruption and differentiation. An increment of the endometrial deposits can cause benign lesions, for instance the hyperplasia, or malignant, for example, the neoplasm (1,2,3,4).

1.1 Epidemiology:

Endometrial carcinoma is the fourth most prevailing neoplasm in women and the most frequent gynecological cancer, if it is excluded breast cancer, with an incidence of 13,6/100.000 (1).

At the time of the diagnosis, most of the patients (90%) are more than 50 years old, with an average of 63 years. Nevertheless, a reduced percentage of people (2,4-5%) are diagnosed before the age of 40 and wish to complete their reproductive desires. A small percentage (2-5%) are hereditary, and from all of them, 10% can be diagnosed <50 years. The community risk of developing endometrial cancer is around 2%, but when we relate it to familial syndrome, it increases to 50%(1).

The majority (80%) are diagnosed early (1st stage) and present a more than 95% survival rate in five years. However, the presence of a regional dissemination (68%) and a distance (17%) decreases the survival rate. The epidemiological data confirms that it is the second most mortal gynecological cancer, after the ovarian one (1,4, 5).

1.2 Risk factors:

Although it is not possible to prevent endometrial cancer, reducing the risk factors can decrease the probability of developing it (1,4).

Some personal and histopathic characteristics from the patients must be taken into consideration because they can determine the prognosis and the treatment of it. **In table 1** there is a summary of the associated factors (1,4,5):

Table 1: Risk factors associated in endometrial cancer.

Hormonal therapy: • Complementary hormonal treatment: The prolonged use (>5 years) of estrogens without opposition increases between 10 and 30 times the risk of having endometrial cancer.
Metabolic syndrome: • Elevated body mass index (BMC): >30. • Arterial hypertension. • Diabetes (dissenting risk factor). • Hypertriglyceridemia.
Gynecological factors: • Nulliparity and infertility (polycystic ovarian syndrome is the most important) • Early menarche (< 12 years). • Late menopause (≥55 years). • Anovulation. • Endometrial hyperplasia.
Selective modifiers of the estrogen receptors: • Patients with breast cancer that take tamoxifen in a preventive or therapeutic manner: increases the risk of endometrial cancer in postmenopausal patients for estrogenic effect. It has to be taken into consideration the doses and its time of application.
Genetic predisposition and family background: • Hereditary disorders: Lynch syndrome (Hereditary Nonpolyposis Hereditary Colorectal Cancer (HNPCC). • First-degree family background: The risk increases to 3.1%.
Tumors that produce oestrogens, granulosa cells and theca cells.
Age: Age average at 63 years old. For this reason it often appears in developed countries.
Pelvic radiotherapy previous to other neoplasms.

The most important etiological factor is the prolonged estrogenic exposition (endogenic or exogenic) without opposition of a gestagen because it produces endometrial proliferation. If a gestagen is added to the Hormone Replacement Therapy (HRT), we can counteract the proliferative effect on the endometrium, and at the same time, it decreases the endometrial hyperplasia and the endometrial cancer to a rate below the general population. Moreover, the prognosis improves if the patient develops endometrial cancer during the HRT (1,4).

1.3 Classification:

Classically, endometrial cancer has been classified based on its histological and clinical-pathological characteristics. The knowledge acquired in molecular biology makes it possible to create a new classification that can improve its identification. For that reason, nowadays scientists support the dichotomous classification. From an etiopathogenic point of view, there exist two endometrial carcinomas: Type I, or hormone dependent, and type II or not hormone dependent (1,6,7). Each one presents their own characteristics that are summarized **in table 2**:

Table 2: Histological classification of the endometrial cancer.

	Endometrial carcinoma (type I)	***Non-endometrioid carcinoma (type II)***
Generalities	It is the most common (80-90%). Preceded by hyperplastic lesions. Premenopausal and perimenopausal. Associated with hyperestrogenism and obesity. Scarcely invasive or not invasive. Infrequently genetic changes.	Less common (10-20%). Preceded by endometrial atrophy. Postmenopausal. Not associated with risk factors. Deep invasion of the myometrium. Genetic changes.
Histological characteristics	Glandular structure like normal endometrium and hyperplasia of the epithelial cylindrical cells with low/medium atypia.	Loss of glandular structure and cells with signs of atypia (large nuclei, prominent nucleolus and pleomorphic cells with abnormal mitoses).
Differentiation degree	Low histological degree: good prognose. Good differentiation (G1, G2). Stage I.	High histological degree: poor prognosis. Little cell differentiation (G3) Stage II-IV.

Associated mutations	It is associated with genetic alterations in PTEN, KRAS, FGFR2, CTNNB1, MSI, ARID1A and PIK3CA. It is also related to hypermethylation of the MLH1.	It is associated with mutations of P53, HER2, CDH.
Histological subtypes	Endometrioid Mucinous Villoglandular	Serous Clear cell Carcinosarcoma Undifferentiated

This classification presents some limitations because it does not make possible to predict the sensibility to immunotherapy (antiPDL-1) and does not bring prognostic information like the molecular classification, which makes able to stratify the endometrial carcinoma depending on the number of mutations and, independently, the histopathological typology. With the implementation of the molecular profile, it has been detected that the previous patterns were not feasible enough to establish a correct treatment. The same histological pattern can be caused by different molecular profiles (7,8,9,10).

Table 3: Molecular classification of endometrial cancer

Subtypes	*Characteristic*
POLE (polymerase Epsilon): ultramutated (5-7%).	They are usually high-grade endometrioid adenocarcinomas. High number of mutations: mutation of the Polymerase Epsilon (POLE). This gene is involved in DNA repair and replication. Good prognosis: one-year survival of practically 100%.
Microsatellite instability hipermutado (28-30%)	They are usually endometrioid adenocarcinomas. Mutation of DNA repair genes: MSH2, MSH3, MLH1 and PMS2. Intermediate prognosis: 75% survival at one year.
Low number of copies (39%)	They are usually endometrioid adenocarcinomas with increased expression of estrogen and progesterone receptors. There are no errors in DNA (deoxyribonucleic acid) repair proteins. Intermediate prognosis: 80% survival at one year.
High number of copies (23-26%)	They are usually serous carcinomas (it can also be clear cell, carcinosarcoma and some endometrioid). TP53 mutation: reduction of physiological cell apoptosis. Poor prognosis: 50% survival at one year.

The endometrial carcinoma can be also classified based on its degree of differentiation **(table 4)**, in which G1 and G2 are a lower degree, and G3 a higher one (serous, clear cells and carcinosarcoma) (1,7,8,9,10).

Table 4: Tumoral degree of differentiation. In front of a nuclear atypia that diverges from the architectural degree, the tumors increase their degree. Adapted to *ESMO-ESGO-ESTRO consensus conference on endometrial cancer: diagnosis, treatment and follow-up.*

	Architecture	***Nucleus***
G1	≤5% of the tumor formed by solid masses	Oval nucleus. Evenly distributed chromatin.
G2	6-50% of the tumor formed by solid masses	Nucleus with intermediate characteristics between G1 and G3.
G3	>50% of the tumor formed by solid masses	Large and pleomorphic nucleus, irregular, eosinophilic nucleolus.

1.4 Hereditary syndromes:

Most of the endometrial carcinomas are caused by spontaneous mutations. However, a small percentage present a genetical predisposition associated mainly to de Lynch syndrome (hereditary non-polypoid colon cancer). There are others, for example de Cowden syndrome, the Peutz-Jeghers syndrome (PJS), the Li-Fraumeni syndrome and the Muir-Torre syndrome. Most of them are considered 1st type, although the proportion of type II increases in terms of spontaneous endometrial cancer (5).

1.4.1 Cowden syndrome:

It is an autosomal dominant hereditary disorder with incomplete penetrance and a variable expressivity. It can be clinically characterized by the presence of lesions in the skin, hamartomas, CNS (central nervous system) affectation, and a risk of having breast carcinoma (25-50%), endometrial (5-28%), thyroid (3-17%), colon (9-16%) and genitourinary tract (34%). It appears due to a mutation in PTEN (tumoral gen suppressor) (5).

1.4.2 Peutz-Jeghers syndrome (PJS):

It is an autosomal dominant hereditary disorder that is characterized by the presence of gastrointestinal polyps and melanin mucocutaneous spots in nose, lips, oral mucosa and phalanges (5).

It appears due to a mutation in the suppressor gene of tumors STK11/LKB1. Complications can occur in benign and malign tumors in various digestive and gynecological organs (colorectal, stomach, small intestine, duodenum, pancreas, breast, cervix, ovaries, lungs and endometrium).

1.4.3 Lynch syndrome or the colorectal nonpolyposis hereditary one:

It is an autosomal dominant hereditary disorder associated with mutations in the genes in charge of the repair of the DNA (MLH1, MSH2, MSH6, PMS1 and PMS2). It is characterized by the early apparition (<45 years) of colorectal cancer and other associated cancers (endometrial, ovarian, stomach, small intestine, and urinary tract). Therefore, these patients present a major risk of developing endometrial cancer (40-60%) between 46 and 54 years. However, 18% are diagnosed before the age of 40 (5,12).

Bethesda criteria:

To remit the patient to a unity of genetic study it has to accomplish any of the following criteria **(Table 5):**

Table 5: Bethesda criteria. Adapted to *ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma.*

Individual that accomplish the criteria of Amsterdam II: - At least 3 family members in 2 successive generations with someone associated with hereditary nonpolyposis colorectal cancer (HNPCC). - One is a first-degree family member. - One cancer diagnosed before the age of 50.
Individuals with colorectal cancer (CRC) diagnosed before the age of 50.
Individuals with 2 or more cancers related to the HNPCC.
Individuals with a suggestive histology of microsatellite instability: lymphocyte infiltration, lymphocyte reaction Crohn type, mucinosa differentiation, signet ring cells or pattern of medular growth.
Individuals with colorectal cancer and a first-degree family member with CRC or a tumor related to HNPCC; one of them diagnosed before the age of 50.
Individuals with CRC and 2 or more family members of first and second degree with CRC or a tumor related to HNPCC, independently of the age.

1.4.3 MUIR-TORRE SYNDROME:

Is a rare dominant autosomal genodermatosis characterized by the apparition of sebaceous neoplasms and visceral malign (especially colorectal and endometrial). They appear mutations in the genes MLH1, MSH6 MSH2 and PMS2, in charge of the repair of the DNA. It is considered a phenotypic subtype of the Lynch syndrome (5).

Genetic determination:

In patients with hereditary nonpolyposis colorectal cancer (HNPCC) it is necessary to do a molecular study to confirm the microsatellite instability present in a 90% of the cases. After a positive molecular study, we have to track the mutations with the genetic study. Finally, it can be conducted in a direct sequence of the DNA (12,5).

Recommendations:

The risk of presenting colorectal cancer and endometrial cancer is about 80% and 40% respectively. The established measures in a gynecological level are:

- From the age of 30-35 years, it is recommended to do annual revisions (exploration, transvaginal ultrasound scans, and endometrial biopsies).
- In women over 40 with these mutations is questionable the surgical prophylactic treatment (hysterectomy and bilateral salpingo-oophorectomy) to prevent the ovaric cancer (9%) and the endometrial cancer (40%).

1.5 Clinic:

The cardinal symptom (90% of the patients) is the abnormal or irregular bleeding (5,6):

- In young patients (<45 years) it must be valued the persistence of bleeding, risk factors and the estrogen treatment (endogenous or exogenous) without the exposition of gestagens.

- In perimenopausal patients (45-55 years) it has to be considered the abundance, frequency and duration of the intermenstrual bleedings.

- In postmenopausal patients it has to be considered any bleeding or vaginal flux.

Other symptoms can appear less frequently, for instance vaginal purulent secretion, ache or abdominal discomfort, alteration in the intestinal transit, respiratory clinical and

constitutional syndrome (anorexia, asthenia, loss of weight). In front of asymptomatic patients, but with a suspicious vaginal cytology, it must be discarded an adenocarcinoma, atypical glandular cells and endometrial cells in people over 45 years.

1.6 Diagnosis:

In order to do a correct diagnose, it is required a detailed anamnesis, focusing to the family background that could identify the risk factors associated to the Lynch syndrome (colon cancer, endometrial, and others). It is also necessary a general evaluation to analyze the comorbidities and/or the risk factors associated to endometrial cancer (hypertension, obesity and diabetes) and a gynecological exploration that includes inspection, colposcopy, vagino-abdominal tract, vagino-rectal tact, and palpitation of the ganglionic area (5,6). The first complementary test is the transvaginal ultrasound scan because it allows to measure the thickness of the endometrium **(Illustration 1)** and determine other findings (increased vascularization, heterogeneity, irregularity in the endometrial-myometrium junction line, fluid in the cavity or suspicious tumor). In the presence of any of these characteristics, a histological study (histotype and grade) will be necessary, through an endometrial biopsy (gold standard), to confirm the diagnosis.
The endometrial thickness changes according to age (fertile, premenopausal and postmenopausal). It is pathological if it measures 16 mm or more in reproductive age, 3-5 mm in postmenopausal and 8 mm in patients with HRT.
In a fertile patient, the endometrial thickness is 4-8 mm during the proliferative phase and 7-14 mm in the secretory phase.
This measurement is obtained from the endometrial-myometrium junction on the anterior face to the endometrial-myometrium junction on the posterior face(11,12,13).

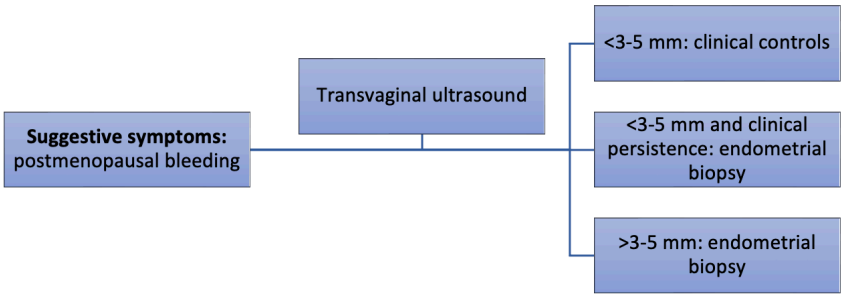

Illustration 4: Ultrasound protocol of endometrial cancer according to the clinic and the thickness of the endometrium.

At the time it is confirmed, other tests will be requested to determine the extension:

- Tumor markers: CA125 is useful depending on the histology. There are also other relevant markers, for example, the loss of expression of the PTEN, PAX-2, MLH1 and ARID1a. In front of a suspicion of an endocervix cancer, vimentin, CEA (Carcinoembryonic Antigen) and p16 must be included (7,8,9,10).
- Pelvic magnetic resonance (PMR): Enables the preoperational tumoral staging evaluating the locoregional extension of the tumor, presence of mass in the myometrium, the degree of infiltration, cervical affectation, endometrial width and adenopathies (13,14,15,16).
- Computerized tomography (CT): Evaluation of the adenopathies and distant metastasis (13,14,15,16).
- PET-TC: Enables the detection of node metastasis with a major sensibility and precision. It is used not only in the extension study, but also in the detection of the relapse (13,14,15,16).

It does not exist any agreement that determines the diagnosis of early endometrial cancer in asymptomatic risk women, except the hereditary ones, such as the Lynch syndrome. However, asymptomatic patients with risk factors (endometrial thickening) or positive finds in vaginal ultra-scanning (lack of homogeneity, increase of the vascularization) it is recommended to complete the diagnostic assessment of endometrial cancer.

1.7 Staging:

The two systems of staging used in endometrial cancer are the TNM and FIGO (International Federation of Gynecology and Obstetrics). These ones make possible to determine the localization, size, local extension and distant metastasis to establish the treatment **(Table 6):**

Table 6: Stating of endometrial cancer FIGO 2009. Adapted to *ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma.*

Stage	*Characteristics*
I	**Limited tumor to the uterine corpus.** • IA: Absence of myometrial invasion or <50%. • IB: Invasion of ≥ 50% of the myometrium.
II	**The tumor invades the cervical stroma, but does not extend outside the uterus.**
III	**Local-regional dissemination of the tumor.** • IIIA: The tumor invades the serosal layer of the uterine body and/or the annexes. • IIIB: Vaginal or parametrial metastasis. • IIIC: Metastatic ganglion pelvic affection and/or para-aortic. o IIIC1: Pelvic positive nodes. o IIIC2: Para-aortic positive ganglions or without positive pelvic nodes.
IV	**The tumor invades the bladder and/or rectal mucosa and/or distant metastasis.** • IVA: Invasion of the bladder and/or rectal mucosa. • IVB: Distant dissemination, including intra abdominal metastasis and/or metastatic inguinal nodes.

1.8 Prognostic factors:

The main prognosis factors (4,12) are reflected **in table 7:**

Table 7: Main prognosis factors of endometrial cancer

FIGO stage: It predicts the evolution of the patients with endometrial cancer.

Histological pathology: The endometrioid adenocarcinoma presents a good prognosis, unlike the serous carcinoma (aggressive) and the clear cell carcinoma (very aggressive).

Histological degree: Indicator of tumoral dissemination. A low-degree, has a better prognosis.

- **1st degree:** 94% of survival.
- **2nd degree:** 84% of survival.
- **3rd degree**: It has a major probability to invade the myometrium and produce metastasis in the pelvic and para-aortic nodes. Survival rate of 72%.

Myometrium invasion: If it is deep, it can be related to a short survival and a major probability of extrauterine dissemination, failure of the treatment and recurrence.

Presence of vascular lymphatic invasion: It determines the recurrence and mortality. Pelvic and para-aortic node metastases are frequent.

Annex affectation.

Distance of the tumor in the serous layer (outside) of the uterus.

Invasion of the uterine neck, age and molecular markers.

1.9 Treatment:

Although the endometrial cancer can't be prevented, it is necessary to inform the population about the clinic related to this pathology and promote a healthy lifestyle to reduce the risk of apparition: do regularly sport, maintain a healthy weight, control the arterial pressure and diabetes. The combination of oral contraceptive during a large period can also be associated with its reduction (11,13,16).

1.9.1 Surgical treatment:

It is important to effectuate a preoperative exploration to determine the surgical risk and if it exists a genesic desire. In addition, before surgery, an endometrial biopsy (histological study and molecular markers) and an extension study (transvaginal ultrasound scan, PMR and thoracoabdominal tomography) are required. Finally, to decide the surgical treatment, it is necessary to consider the stage of FIGO and the degree of differentiation (G1, G2 y G3). **In table 8**, the different therapeutic possibilities are shown:

Table 8: Surgical treatment in endometrial cancer.

	G1/G2	***G3***
Stage IA	Simple Hysterectomy. Evaluate the salpingo-oophorectomy depending on the risk of each patient and age. *(low preoperative risk)*	Hysterectomy + salpingo-oophorectomy + pelvic lymphadenectomy +/- para-aortic lymphadenectomy. *(medium preoperative risk)*
Stage IB	Hysterectomy + salpingo-oophorectomy + pelvic +/- para-aortic lymphadenectomy *(medium preoperative risk)*	Hysterectomy + salpingo-oophorectomy + pelvic + para-aortic lymphadenectomy *(high preoperative risk)*
Stage II	Hysterectomy + salpingo-oophorectomy + lymphadenectomy	
Stage III-IV	In this case, it will depend on the general state: - *Good general state:* cytoreductive surgery (resection of visible disease). - *Bad general state:* It is not possible to dry all the illness. Consider neoadjuvance with chemotherapy and/or radiotherapy.	

1.9.2 Adjuvant treatment:

The risk of relapse is determined by clinicopathological prognostic factors and it is necessary to determine the adjuvant treatment that each patient requires. **Table 9** describes the different risk groups and the adjuvant treatment that corresponds to each of them:

Table 9: New risk groups to guide adjuvant therapy use. FIGO 2009 staging used; molecular factors and tumor size were considered but not included. LVSI (lymphovascular space invasion).

Adapted to *ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma.*

Risk group	Description	Treatment
Low	Stage I endometrioid, grade 1-2, <50% myometrial invasion, LVSI negative.	Observation/Control
Intermediate	Stage I endometrioid, grade 1-2, ≥50% myometrial invasion, LVSI negative.	Brachytherapy
High-intermediate	Stage I endometrioid, grade 3, <50% myometrial invasion, regardless of LVSI status. Stage I endometrioid, 1-2, LVSI unequivocally positive, regardless of depth of invasion.	**Negative lymph node:** Brachytherapy. **Lymph node staging not performed**: • If there is lymphovascular invasion: external pelvic radiotherapy. • If there is no lymphovascular invasion: brachytherapy
High	Stage I endometrioid, grade 3, ≥50% myometrial invasion, regardless of LVSI status.	**Negative lymph node:** external pelvic radiotherapy or brachytherapy +/- chemotherapy. **Lymph node staging not performed**: external pelvic radiotherapy +/- chemotherapy.
	Stage II	**Negative lymph node:** • Grade 1-2: without lymphovascular invasion (brachytherapy). • Grade 3 or lymphovascular invasion: external pelvic radiotherapy + brachytherapy +/- chemotherapy. **Lymph node staging not performed**: external pelvic radiotherapy + brachytherapy +/- chemotherapy.
	Stage III endometrioid, no residual disease	Chemotherapy and radiotherapy
	Non endometrioid (serous or clear cell or undifferentiated carcinoma, or carcinosarcoma).	**Stage IA without lymphovascular invasion:** brachytherapy. **Stage IA with lymphovascular invasion/ Stage IB and II:** pelvic external radiotherapy +/- chemotherapy +/- brachytherapy **Stage III:** Chemotherapy and radiotherapy (EBRT)
Advanced	Stage III residual disease and stage IVA	Chemotherapy and radiotherapy (EBRT)
Metastasic	Stage IVB	Chemotherapy and radiotherapy (EBRT)

1.9.3 Relapse treatment:

The relapses appear in the first three years after the diagnosis, therefore, an early detection through a correct supervision enables to improve the prognosis (each 3-6 months the two first months; each 6-12 months the following five years).

In the examinations, it is necessary to ask for the clinic of the patient, do a complete exploration (ganglion chains, abdominal exploration) and a gynaecological exploration with a biopsy of the lesion. It is not recommended to do systemic image tests except in the III-IV stage.

The indicated treatment can vary: tumoral characteristics, free period of the disease, resectability, actual lesions, localisation, previous treatments, and general state. It is usually indicated to do radiotherapy except if the person has received it before (in that case, it is recommended to do surgery) and it can be added chemotherapy. We can also administer hormone therapy (tumors with hormone positive receptors) and immunotherapy (deficiency in repairing genes and/or mutation of POLE).

1.9.4 Medical treatment:

The patient with endometrial neoplasia requires invasive treatments like total hysterectomy and bilateral salpingo-oophorectomy to heal, being the pelvic and/or para-aortic lymphadenectomy necessary in more advanced cases. Surgical treatment is not always possible, so it is required to do an alternative treatment. The most relevant surgical contraindications include medical comorbidities (obesity), specific tumoral characteristics, medical background, and reproductive desire (17,18,19,20,21,22,23).

Before starting the fertility preservation treatment, it is necessary a diagnostic-therapeutic approach through a clinical study, general analytic with measure of the CA-125 and a study of the sample because the patient must achieve some criteria.

Some very important parameters are the histological degree, being one of the endometrial tumors with low degree (G1, good differentiated), positive progesterone receptors and without myometrial or cervical invasion who will be the candidates to preserve the fertility.

The study has to be completed with a transvaginal ultrasound scan and a magnetic resonance to know the extension in a myometrial level and annex organs because its affection will discard the possibility of a conservative treatment. The importance of long-term period follow-up and informed consent should be explained to the patient.

Nowadays, the treatment applied is the hormonal (high dose oral progesterone), such as the medroxyprogesterone acetate (100-800 mg for 4-14 months) or the megestrol acetate (40-160 mg/day). It can also be used local progestogens through an intrauterine dispositive of levonorgestrel (UID-LNG). This treatment is usually combined with periodic curettages every three months. In this moment, an endometrial sample is taken until the complete regression of the tumor.

Despite this data, a consensus has not been achieved regarding the best progestogen, the dose, the administration method, the duration and the supervision protocol that it has to be established.

Moreover, the response time to the hormonal therapy oscillates between the 57-75%, the index of recurrence is about a 11-50% and the risk of progression during the conservative treatment is about a 5-6%. Patients obtained a complete response in 9 months (range of 2-12 months) and the majority reappeared in 12 months (between the 8-48 months).

Its administration involves weight increase (between 3 and 7 kg), sickness, vomiting, diarrhea, alopecia, fluid retention, mammary alterations, mastalgia, irregular vaginal bleeding, altered menstrual flow, dysmenorrhea, amenorrhea, anxiety, asthenia, headache, skin rashes, dermatitis, acne vulgaris, melasma, anorexia, decreased libido, galactorrhea, fatigue, cervicitis, hirsutism, abdominal pain, leukorrhea, and vaginitis.

Abnormalities in blood coagulation or thromboembolic accidents are not frequent, except if the patient has a genetic predisposition or the dose administrated is high. Its establishment in patients with systemic problems (heart failure or kidney disease) can exacerbate the underlying pathology. More rarely, hepatic dysfunction, pulmonary embolism, retinal thrombosis, hypertension, biliary obstruction, jaundice and hyperglycemia may appear.

At the gynecological level, the most frequent risks are related to lack of effectiveness, risk of relapse and lack of diagnosis of ovarian lesions and lymph nodes. Myometrial invasion (9%), histologic changes, pelvic lymphatic metastases (3%), para-aortic (1.7%), and annexal malignancy disease (5%) may occur.

If, once the tumor has remitted, the patient does not wish to become pregnant, she should follow maintenance treatment with oral contraceptives or medroxyprogesterone acetate 150 mg intramuscularly, every 12 weeks, with periodic ultrasound evaluation of the endometrium. On the other hand, if the patient wishes to conceive, it may be spontaneous (if she has no history of infertility) or through assisted reproductive techniques (ART).

Studies confirm that 80-85% of the patients successfully conceived and none of the new-borns had congenital malformations. In addition, there is no evidence that treatment with progestogens worse the prognosis of the results obtained with ART.

Six weeks after the end of pregnancy, the endometrium should be reassessed. Postpartum hysterectomy as definitive treatment is a controversial issue and it should be agreed with the patient.

Experts recommend surgery due to the risk of recurrence of conservative treatment, although there is no evidence of residual tumor in any case.

2 PHOTODYNAMIC THERAPY OR PHOTOCHEMOTHERAPY:

2.1 Concept:

Photodynamic therapy (PDT) is a minimally invasive procedure that it is activated by the interaction between a specific wavelength (visible light) and a photosensitizer.

This photodynamic reaction based on the photooxidation of biological materials allow to improve wound healing, achieve an antimicrobial effect (infections) and destroy cancer cells.

Its operation requires dual selectivity because it depends on the capacity of the phosensitizer to accumulate in the pathological tissue and its activation by means of a light source applied to the affected tissue (1,24,25,26,27).

Its involvement in the medical field is expanding thanks to its simplicity, efficacy, effectiveness and safety. **Table 10** describes the advantages and disadvantages of PDT:

Table 10: Advantage and disadvantages of PDT.

Advantage	Disadvantages
• Highly selective cytotoxic effects: localized and minimally invasive (few side effects). • Simple and painless technique (performed on an outpatient). • It allows to combine treatments: chemotherapy, ionizing radiation and surgery. • It allows treating superficial lesions or accessible cavities. • Good healing. • Low potential to cause DNA mutations. • Preserve the anatomy and function of the affected organ (less destruction of surrounding tissues): relevant to preserve fertility. • It has low systemic toxicity. • Repeated application at the site of action.	• First-generation photosensitizers cause skin photosensitivity. • It is difficult to predict the clinical reaction of each individual because it depends on different variables: absorption of the photosensitizer in the tissues, metabolism of the agent and penetrance of the applied light. • The hydrophobic properties of photosensitizers limit their therapeutic effect. • Deep treatments are a limitation.

2.2 Mechanism of action:

Specific cell death is caused by three harmless components: photosensitizer, light source and molecular oxygen. To improve this selectivity, the concentration of photosensitizer must be increased in the pathological tissue and irradiation limited to a specific area.

Initially, a photosensitizer, substance sensitive to light, is administered systemically (intravenously or orally) or topically and it is selectively absorbed/accumulates in tumor cells over a period of time.

Once the bioavailability time has elapsed, the affected tissue is irradiated with a certain wavelength and a dose to produce cell death of the cancer cells that they have previously absorbed the photosensitizer (1,26,27,28).

When the photosensitizer absorbs light in the form of photons, it passes from a fundamental or basal state, called the singlet state, to a first excited singlet state (short duration) because an electron is driven to a higher energy orbital. Later, the excited electron goes into an excited triplet state (with longer half-life). In that state, it increases the interaction with surrounding molecules and enhances the phosensitizing potential as a therapeutic agent.

Once in a high-energy state, light energy is transferred to the oxygen contained in the affected tissue, generating reactive oxygen species (ROS) that cause cytotoxic effects and, therefore, somatic cell death. That is, it transforms light energy into chemical reactions, generating ROS that cause cell death **(Illustration 2).**

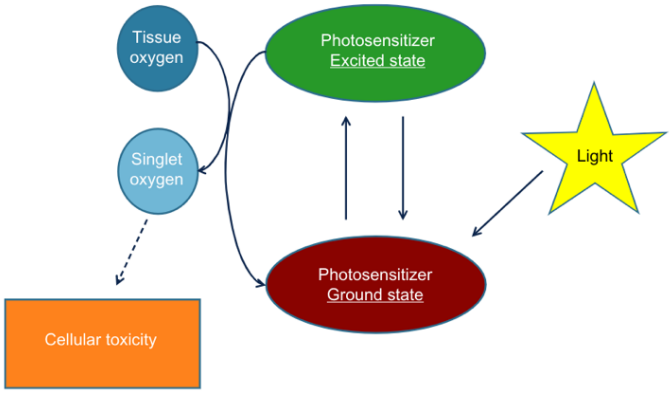

Illustration 5: Schema of a photochemical reaction during photodynamic therapy. The photosensitizer absorbs photons and goes from a ground state to an excited state. This procedure will end up causing cellular cytotoxicity.

There are two mechanisms of energy transfer:

- **Type I reaction:** the excited photosensitizer interacts with a biological substrate and generates anionic or cationic radicals that interact with cellular oxygen to produce reactive oxygen species such as superoxide anion radical, hydroxyl radical and hydrogen peroxide.
- **Type II reaction:** energy is transferred directly to molecular oxygen that emits excited singlet oxygen (the most prevalent ROS in PDT).

High concentrations of ROS trigger a cellular cytotoxic response (necrosis and apoptosis), interrupt vascularization (ischemia) and trigger an inflammatory/immune antitumoral response (production of interleukin 1-beta, interleukin 2, tumor necrosis factor alpha) (1,24,25,26).

To minimize damage to surrounding tissues, the duration and depth of the light source and the capture selectivity must be modified. This selectivity is conditioned by the absorption of the photosensitizer in the target tissues, the metabolism of the agent and the penetrance of the light source.

2.3 Photosensitizers:

Photosensitizing agents are natural or synthetic (non-toxic) substances that contain different photoactive components, that is, substances that are excited by a certain wavelength and trigger intracellular reactions, generating reactive oxygen species.

They are characterized by selectively accumulating in pathological tissues (malignant and premalignant cells) and not being toxic if a light source is not applied. They are effective both diagnostically and therapeutically.

The first to be used were those derived from natural systemic hematoporphyrins, such as, sodium porfimer (Photofrin®) which was the first to be clinically approved.

Conceptually, intravenous hematoporphyrin is an endogenous porphine formed in the heme biosynthetic pathway. It is characterized by presenting good efficacy as a photodynamic agent and localizing in tumor cells. A more important side effect is prolonged skin photosensitivity caused by slow elimination (6 weeks) and low intensity of absorption. To reduce it, patients should be protected from sunlight and artificial light for 6-10 weeks.

Second-generation photosensitizers are a large group of synthetic compounds created to improve the pharmacokinetic properties of the previous group, accelerating the elimination of pathological tissues and reducing treatment time. Therefore, they can be administered on an outpatient and decrease skin photosensitivity (<2 weeks).

They are subdivided into two subgroups, porphyrin (chlorins, bacteriochlorins, phthalocyanines, porphycenes and texaphyrins) and non-porphyrin (anthraquinones such as hypericin, phenothiazines, xanthenes and cyanines).

There are endogenous photosensitizers, such as, 5-aminolevulinic acid (ALA) and methyl aminolevulinate (MAL), which are precursors of protoporphyrins IX (heme group metabolite).

ALA is an endogenous mitochondrial metabolite that is generated from two substrates (glycine and succinyl coA) and the enzyme ALA synthetase.

Through biochemical reactions, ALA will end up forming protoporphyrin IX and, with the enzyme ferrochelatase (catalyzes the insertion of iron into protoporphyrin IX), will give rise to the heme group.

Its formation will take place in the mitochondria, although it rapidly diffuses to other intracellular membranes. Therefore, it's necessary an "occlusion time" for the drug to metabolize and accumulate protoporphyrin IX before light activation **(Illustration 3).**

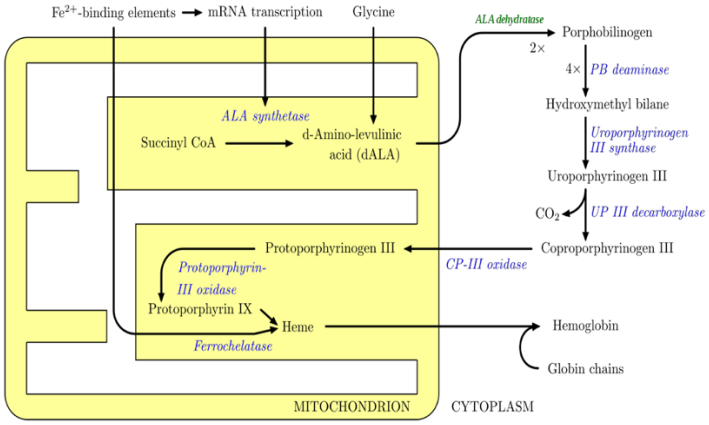

Illustration 6: Heme synthesis. *Photodynamic therapy and the development of metal-based photosensitisers.*

Currently, third-generation photosensitizers have appeared, characterized by increasing solubility, bioavailability, absorption, distribution, metabolism, excretion and decreased toxicity thanks to the use of different transport systems called nanoparticles (these are called nanophotosensitizers) (27,28,29,30).

The characteristics of the photosensitizers will determine the therapeutic results obtained with PDT. Some have been approved by the European Union and the FDA (food and drug administration) with various clinical indications and using different wavelengths **(Table 11):**

Table 11: Types of photosensitizers and their clinical application

Compound	***Brand***	***Wavelength***	***Use***
Sodium polymer	Photofrin®	630-632 nm	Bladder, esophageal, lung, gastric and cervical cancer. Cervical dysplasia.
Benzoporphins	Verteporfin®	690 nm	Basal cell carcinoma Choroidal neovascularization associated with macular degeneration and myopia.

Metatetra (hydroxyphenyl) chloro (mTHPC)	Foscan®	652 nm	Squamous cell cancer of the head and neck, breast, gastrointestinal and pancreas
Tin ethyletiopurpurin	Purlytin®	660 nm	Macular degeneration associated with age. Skin and prostate cancer. Kaposi's sarcoma.
Lutetium Texaphyrin	Lutrin® Antrin® Optrin®	732 nm	Breast cancer, basal cell carcinoma, melanoma and treatment of vascular diseases.
Boronated porphyrin	BOPP®	628 nm	Brain cancer
Hypericin	VIMRxyn®	600-1000 nm	Glioblastoma, basal cell carcinoma, psoriasis, warts
5-ALA (5-aminolevulinic acid)	Levulan®	630-635 nm	Actinic keratosis, basal cell carcinoma, Bowen's disease, psoriasis, acne
Palediporfin	Tookad®	753 nm	Prostate adenocarcinoma

2.4 Light sources:

To activate the photosensitizer, it is essential that the light spectrum coincides with the maximum absorption spectrum of the photosensitizer (it usually extends between 600 and 1300 nm) to generate ROS and produce a cytotoxic effect. Depending on the wavelength applied to the tissues, a different penetrating power will be achieved: a wavelength of 630 nm is required to penetrate 0.5 cm of the tissue; 700 nm for 1.5 cm **(Illustration 4 and 5).**

The first to be used were non-coherent light (tungsten lamps, quartz halogen, xenon arc, metal halide and phosphor-coated sodium lamps), which are safe, easy to use and suitable for treating large areas. These had several drawbacks: difficult to dose, low light intensity and significant thermal effect (28,29,30,31).

Light-emitting diodes (LEDs) are other systems used in PDT that require little power to produce irradiations at different wavelengths. Currently, the most used are lasers that produce high-energy monochromatic light at a specific wavelength for each photosensitizer.

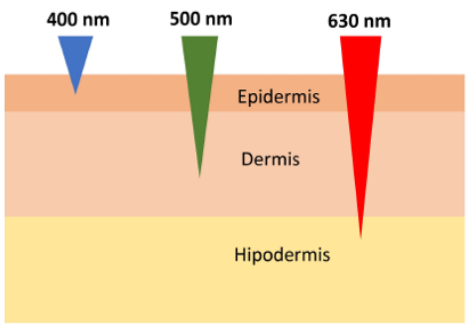

Illustration 4: Light penetration depth as a function of wavelength.

Illustration 5: Laser used in PDT.

2.5 Effectiveness in gynecology:

In the field of gynecology, PDT has been used to detect and combat premalignant and malignant lesions of the cervix, endometrium, vulva, vagina, breast and ovarian.

In the cervix, it allows to eliminate the human papilloma virus (HPV) and cervical intraepithelial neoplasias (CIN). One study used 2 mg/kg Photofrin® and 630 nm red light to treat CIN II/III with a 96% response rate. Through PDT, the adverse effects of surgery are avoided, maintaining sexual function and fertility.

It can also be used in invasive lesions, but in this case, intravenous photosensitizers should be used, which are characterized by causing skin sensitivity because topical photosensitizers do not penetrate deeply (30,31,32,33,34).

In the vulva and vagina, lesions that are susceptible to photodynamic therapy are warts, lichen, Paget's disease, vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VAIN). A study with Photofrin reported a 71% elimination of carcinoma in situ of the vulva/vagina. Other studies use of Foscan® in recurrent vulva-vaginal cancer.

Finally, PDT has been implemented in benign and malignant endometrial lesions, endometriosis and adenomyosis, obtaining significant results. Preclinical studies in animal models have implemented the systemic ALA photosensitizer with low-power light exposure (50-100 J/cm2) and short duration (10 minutes) for the ablation of endometriotic explants, destroying 60-81% of the total.

On the other hand, adenomyosis is treated with laparoscopic surgery (adenomyomectomy), a technique that can cause uterine rupture during pregnancy.

PDT has been highly effective in diagnosis and treatment due to increased absorption of 5-ALA in adenomyosis tissues.

In benign and malignant lesions, the results have also been promising. The PDT is effective, using a hematoporphyrin derivative (Photofrin®), as primary and secondary (after administration of progestogens) conservative treatment for recurrences in women under 35 years of age and early endometrial carcinoma was confirmed.

Different studies obtained significant and comparable results to hormonal therapy because complete remission was achieved in 75% of patients and 33% had recurrences. In addition, after a second course of PDT, statistics improved: reduction in recurrences and remission of patients who had not responded to the first course of PDT.
The probability of successful pregnancy after the application of PDT and using assisted reproductive techniques was also studied (57% fulfilled their reproductive desire).
Therefore, the potential of photodynamic therapy as a conservative treatment of stage 1A G1/G2 endometrial carcinoma has been demonstrated in cases of fertility preservation, surgical risk and recurrence thanks to its selectivity for tumor cells, low mutagenic capacity and few side effects. It is also effective in reducing the rate of relapses, metastasis and high rate of reproductive desire (35,36,37).

Some studies propose a multimodal treatment as an alternative to the use of progestogens, that is, the combination of three procedures: a hysteroscopic approach with tumor removal, the use of PDT to eradicate the remaining tumor and suppress recurrences with adjuvant medical treatment. In one study, PDT was administered as primary treatment, followed by progestogens for 6 months and recurrences were observed after 99 months and twin pregnancy by in vitro fertilization.
Other studies have combined PDT with chemotherapy, obtaining greater cytotoxicity and ROS production (increase in apoptotic and necrotic cells), while the concentration of superoxide anion and hydroxyl radical remained stable.
In conclusion, PDT is an innovative technique with great potential and a promising future in the gynecological field, especially in the conservative treatment of benign and malignant endometrial lesions. Its effectiveness will correlate with the investigation of new topical and systemic photosensitizers; therefore, improved photosensitizers are being investigated.

JUSTIFICATION

Endometrial neoplasia is the most prevalent gynecological cancer in developed countries, after breast cancer, with an average age of 63 years. Even so, there is a small percentage (2.4-5%) that is diagnosed during the fertile age (before the age of 40). Although most patients are diagnosed early (stage 1), the standard treatment is surgery. In case of reproductive desire, an alternative treatment based on oral progestogens is offered. This treatment has a low response rate (57-75%), significant recurrence (11-50%) and a high percentage of gestational success but it presents several systemic side effects: weight gain, gastrointestinal symptoms, alopecia, mastalgia, dysmenorrhea or amenorrhea, skin rashes, galactorrhea, cervicitis, etc. More rarely, hepatic dysfunction, pulmonary embolism, retinal thrombosis, hypertension, biliary obstruction, jaundice and hyperglycemia may appear.

On the other hand, photodynamic therapy is a medical procedure that uses photosensitizing drugs and visible light to eliminate unwanted cells, improve wound healing and obtain an antimicrobial effect. Initially, it was used to treat different dermatological pathologies but, currently, the FDA has approved its use to treat other benign and malignant lesions that affect the esophagus, lung, prostate, bladder, etc.

In gynecology, PDT has been used to detect and combat premalignant and malignant lesions on the cervix, endometrium, vulva, vagina, breast and ovarian, because it reduces the adverse effects of conventional treatments: hormonal treatment or surgery. The delay of motherhood and the scientific evidence that some factors associated with infertility are also associated with endometrial cancer increase its appearance in fertile patients who have not fulfilled their gestational desire. For this reason, this study aims to compare the hormone treatment versus PDT, analysing different parameters: remission rate, recurrence rate, adverse effects and pregnancy rate (conventional or assisted reproductive therapy) after the application of both treatments.

At the interhospital level, the machinery necessary to implement photodynamic therapy is feasible in different Spanish hospitals because its use has expanded in dermatology services. Only by administering the appropriate photosensitizer at a certain wavelength can it be applied in the gynecological filed reducing the cost of prolonged pharmacological treatment, the hospital care burden (by causing fewer side effects, patients require fewer medical visits) and improving medical conditions.

HYPOTHESES

Main hypothesis:

Photodynamic therapy (PDT) shows no inferiority in the curative management of stage 1A G1/G2 endometrial cancer in patients under 40 years of age with gestational desire after three and six months compared to standard pharmacological treatment with oral progestogens.

Secondary hypotheses:

- PDT reduces treatment time, quickly achieving complete remission of stage 1A G1/G2 endometrial carcinoma in patients under 40 years with reproductive desire compared to established medical treatment.
- Being a minimally invasive and local procedure, PDT generates fewer adverse effects than standard medical treatment and, therefore, improves quality of life, in young patients (<40 years) with endometrial cancer stage 1A G1/G2 and desire to preserve fertility.
- PDT has a recurrence rate not inferior to standard treatment with oral progestogens in young patients (<40 years) with endometrial carcinoma stage 1A G1/G2 after eight, twelve, sixteen and twenty months.
- PDT allows pregnancy rates not inferior to pharmacological treatment, spontaneously or with assisted reproductive techniques (ART), six months after starting treatment, in young patients (<40 years) with endometrial neoplasia stage 1A G1/G2 and desire to preserve fertility.

OBJECTIVES

Main objective:

To confirm the non-inferiority of photodynamic therapy (PDT) with respect to pharmacological treatment based on oral progestogens in the curative response of stage 1A G1/G2 endometrial cancer in patients under 40 years with reproductive desire after three and six months after diagnosis through a pathological study with endometrial biopsy.

Secondary objectives:

- To assess the durability of both conservative treatments (PDT and oral progestogens) to obtain a complete response in young patients (<40 years) with stage 1A G1/G2 endometrial neoplasia and desire to preserve fertility.
- To study whether the symptoms are reduced and, therefore, the quality of life of patients (<40 years old) treated with PDT instead of administering oral progestogens in endometrial carcinoma stage 1A G1/G2 and gestational desire is improved.
- To compare the adverse effects caused by PDT with respect to standard medical treatment in young patients (<40 years) with stage 1A G1/G2 endometrial cancer and a desire to preserve fertility.
- To record the recurrence rate of both treatments (PDT and oral progestogens) in young patients (<40 years) with endometrial carcinoma stage 1A G1/G2 and reproductive desire after eight, twelve, sixteen and twenty months.
- To compare the rate of patients with fulfilled reproductive wishes through spontaneous pregnancy or assisted reproductive techniques (ART) six months after starting treatment with PDT or pharmacological treatment in young patients (<40 years) with stage 1A endometrial neoplasia. G1/G2 and desire to preserve fertility.

MATERIALS AND METHODS

Study design:

This experimental scientific study is a multicenter, national, parallel-group, prospective, randomized, open label but blinded for the end-point evaluators (PROBE) clinical trial. In this case, the very nature of the intervention prevents it from being hidden from the participants and health professionals, therefore, a blind evaluator is used (both the investigator who analyzes the histological response and the statistician).

PROBE studies carry lower cost and greater similarity in clinical practice, so the results are easily applicable to routine medical care. In addition, this type of study has the maximum scientific evidence (high internal validity) because the same results are obtained when the conditions are repeated.

The design of this study allows comparing both conservative treatments

Study population:

This study includes all those patients under 40 years of age with a gestational desire, without associated genetic factors and who have been diagnosed with stage 1A G1/G2 endometrial cancer, without myometrial invasion or adnexal extension, in public or private hospitals in Spain. All the patients them must be informed of the importance of gynecological follow-up and of the side effects and risks of recurrence or progression of both treatments.

Patients previously treated with surgery (hysterectomy and bilateral salpingo-oophorectomy) or progestogens as conservative therapy and also those who have not signed the informed consent are excluded.

Study subjects:

INCLUSION CRITERIA:

- Young patients (<40 years) with reproductive desire or preservation of fertility.
- Diagnosis of endometrial carcinoma that must meet the following characteristics:
    - Stage 1A: The tumor must be limited to the uterine body and without myometrial invasion.
    - G1/G2 (low grade).

- Progesterone receptor positive.
- Endometrial carcinoma (type I)

- Negative extension study by pelvic magnetic resonance imaging, computed tomography and PET-CT.
- Sign informed consent in writing.

EXCLUSION CRITERIA:

- Patients with a genetic syndrome related to endometrial cancer (Cowden, Peutz-Jeghers, Muir-Torre and Lynch syndrome) or other genetic factors.
- Serious systemic pathologies related to the cardiovascular and renal system (heart failure, kidney failure, previous thromboembolic accidents).
- Previous treatment of endometrial cancer by surgery or progestogens.
- Patients diagnosed before the start of the study.
- Patients previously diagnosed and treated with radiotherapy or chemotherapy for another neoplasm.
- Patients treated with tamoxifen preventively or therapeutically.
- Patients who have not signed the informed consent.

Withdrawal and replacement of patients:

Whenever possible, patients should be attempted to complete the study unless there is a valid reason.

Patient lost to follow-up: When the investigator tries to contact the patient to assess her health status and the patient does not attend scheduled visits. If the patient does not attend two visits or the investigator cannot contact her, it will be considered a loss of the study. A record of the loss of the patient should be kept during follow-up with her documents along with the reason.

Situation to stop the trial: The inefficiency of the implemented therapeutic procedure (photodynamic therapy or hormonal treatment) after six months would force the study to end to avoid aggravating the clinical stage of endometrial cancer and standard surgical treatment would be implemented.

Study setting:

This study is designed to be multicenter and, therefore, it requires the participation of different Spanish reference hospitals to obtain significant results due to the low incidence (2.4%-5%) of stage 1A G1/G2 endometrial carcinoma in patients under 40 years of age with reproductive desire.

A national study is proposed where the diagnosis can be made in any center that has a Gynecology and Obstetrics Service of the Public or Private National Health System. Next, the patient will be informed of both the available therapeutic possibilities and the research project (if she wishes to preserve fertility). To participate in the study, the patient must go to the reference hospital in the same Autonomous Community, where one of the two treatments will be randomly administered, and follow-up will continue.

All the hospitals that have been invited to participate have the PDT machinery in the dermatology service.

In addition, as has been mentioned, for greater logistical effectiveness, each autonomous community will have a reference hospital that will promote the treatment and follow-up of participating patients. The following diagram shows the list of health centers participating in the study **(Illustration 6):**

- Hospital Universitario Reina Sofía, Córdoba **(Andalucía)**
- Hospital Universitario Miguel Servet, Zaragoza **(Aragón)**
- Fundación Hospital Jove, Gijón **(Asturias)**
- Hospital Universitario Son Espases, Palma de Mallorca **(Islas Baleares)**
- Complejo Hospitalario Universitario de Canarias, Santa Cruz de Tenerife **(Canarias)**
- Hospital Universitario Marqués de Valdecilla, Santander **(Cantabria)**
- Complejo Asistencial Universitario de León **(Castilla y León)**
- Hospital General Universitario de Ciudad Real, Ciudad Real **(Castilla-La Mancha)**
- Hospital Universitario Doctor Josep Trueta, Girona **(Cataluña)**
- Hospital La Fe, Valencia **(Comunidad Valenciana)**
- Hospital Universitario de Badajoz, Badajoz **(Extremadura)**
- Complexo Hospitalario Universitario de Coruña, La Coruña **(Galicia)**
- Hospital Universitario de la Paz, Madrid **(Comunidad de Madrid)**

- Hospital General Universitario Reina Sofía, Murcia **(Región de Murcia)**
- Complejo Hospitalario de Navarra, Pamplona **(Navarra)**
- Hospital Universitario de Cruces, Barakaldo, Bizkaia **(País Vasco)**
- Hospital de San Pedro, Logroño **(La Rioja)**

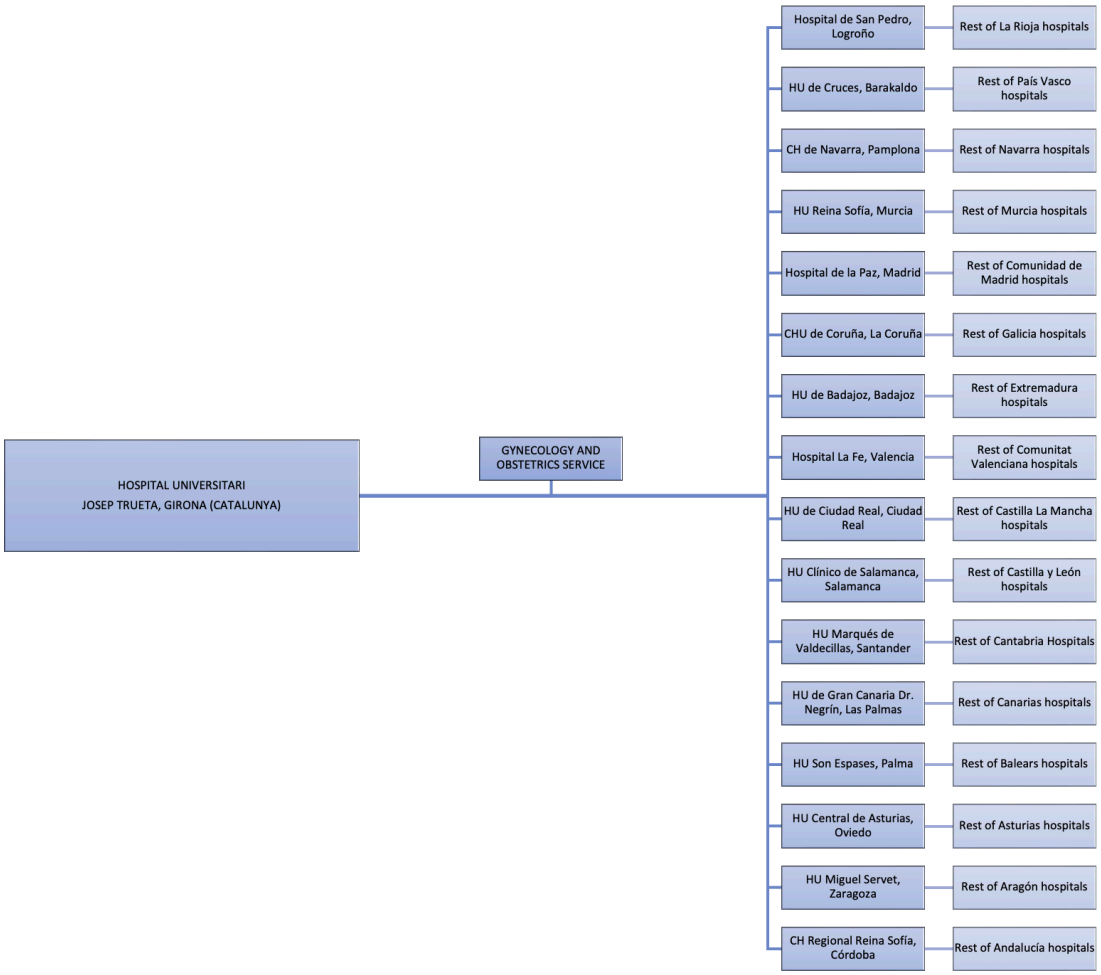

Illustration 6: Diagram of the reference hospitals participating in the study. Most have already participated in other previous scientific studies, so their operation is known.

The project's coordinating center is the **Hospital Universitari Doctor Josep Trueta (Girona)**, with the participation of the same hospital's dermatology and gynecology-obstetrics service. In this same center, a gynecologist will be assigned as **coordinator** of the entire project, who will collect the data obtained at the histopathological level, analyze the results and coordinate the rest of the participating centers, improving communication between them.

The figure of a **principal investigator** (gynecologist) in each reference hospital will also be necessary.

Its function will be to manage the rest of the hospitals in the region, administer the randomized treatment to the patients and collect the data in the same reference center which will be analyzed by the coordinator.

The participation of all the specialists in gynecology in Spain will be essential, since they will oversee informing the patients of the study and proposing their participation, with the corresponding follow-up.

This study should include other **collaborators**: a **dermatologist**, an expert in the use of photodynamic therapy; a **pathologist**, in charge of analyzing the endometrial biopsies obtained both in the diagnosis and in the follow-up of the patients and, finally, a **radiologist** for the staging of the endometrial cancer prior to the start of the study. In addition, a statistician distributes the sample into two groups and evaluates the data obtained.

Evaluation of the results:

The data analysis includes the following results:

- **Complete remission:** absence of adenocarcinoma or endometrial hyperplasia.
- **Partial remission:** development of endometrial hyperplasia.
- **Persistent disease:** histopathologic confirmation of residual endometrial carcinoma.

Sampling:

SAMPLE SELECTION:

A non-probabilistic consecutive sampling method will be followed in the Gynecology and Obstetrics Unit of each participating hospital. All those patients who meet the inclusion criteria and wish, will be offered to collaborate in the study.

SAMPLE SIZE:

We estimated the sample size using the GRANMO software. In a unilateral contrast (one-sided test), accepting an alpha risk of 0.05 and a beta risk of 0.2, with a moderate difference for non-inferiority compared to complete tumor remission, we will need a sample of 196 subjects for each study group, that is, 392 patients in total.

Assuming a drop-out rate of 10%, we will need 215 subjects per group, that is, a total of 430 women under 40 years of age with reproductive desire and stage 1A G1/G2 endometrial carcinoma.

This sample will be distributed among the participating hospitals in proportion to the number of patients in each of them.

ESTIMATED TIME OF RECRUITMENT:

Considering that the design of this clinical trial is multicenter and that the number of patients, in the different participating hospitals in Spain, is approximately 430, we estimate a sis months of recruitment to be able to enroll the required number of participants (430 women). If the sample size is not reached in this period, the recruitment time will be extended.

Randomization:

Once the informed consent is signed, each participant will be randomly assigned to a group (control or intervention) using software that reduces selection bias. The collaboration of an external statistician is required, who does not know the treatment of any of them. Treatment groups are divided into two:

- **Control group (group A):** The patient will be treated with oral progestogens (standardized therapy) until complete remission of the tumor (a maximum of 6 months).
- **Intervention group (group B):** The patient will be treated with PDT, through one or two sessions.

Masking techniques:

This study is designed to be an open label but blinded for the end-point evaluators (PROBE), that is, both the gynecologist and the patient know the treatment they are receiving (oral progestogens or PDT) but the coordinator and the statistician are blinded, so that they analyze the results without being informed of the treatment that each of the groups has received.

Therefore, the blinding of this study is not possible because both the specialist and the patient have knowledge of the treatment they administer or receive (pharmacological or PDT).

Variables:

INDEPENDENT VARIABLE:

The independent variable of this study is the type of intervention that is being carried out:

- **Group A:** pharmacological treatment based on oral progestogens.
- **Group B:** photodynamic therapy (PDT).

Group A, called the control group, is given standardized medical treatment while group B, called the intervention group, is given photodynamic therapy. The two variables will be expressed as a percentage of patients with respect to the total sample, being symmetrical in both groups. It is a dichotomous qualitative variable.

OUTCOME OR DEPENDENT VARIABLES:

Main outcome:

- **Complete remission of the endometrial tumor:** it is the main variable of the study. Tumor remission will be evaluated through clinical controls, ultrasound and endometrial biopsies at 3 and 6 months after the start of treatment and will be recorded in the medical record.

  The initial date is established as the day the patient attends the Obstetrics and Gynecology service to undergo hormonal treatment or photodynamic therapy.

  The main outcome is divided into two categories:

  - **Positive malignant histology:** presence of endometrial tumor.
  - **Negative malignant histology**: absence of endometrial tumor.

Secondary outcome:

- **Treatment time:** The time elapsed from the start of therapy until tumor remission is diagnosed, on the date of the pathology anatomy report. It will be measured in **days** and will be recorded in the patient's clinical history.
- **Genetic desire:** Pregnancies successfully achieved through spontaneous gestation or assisted reproductive therapy are assessed. The data will be recorded in the patient's clinical history. We will express this variable as dichotomous:

- **Fulfilled reproductive desire.**
- **Unfulfilled reproductive desire**

When the results of this study are measured, **percentages** as the unit of measurement.

- **Recurrence rate:** It is evaluated at eight, twelve, sixteen and twenty months after the initiation of treatment. To study this variable, a anatomopathological report is necessary, in which the previous remission of the tumor is recorded. In addition, the patient must undergo clinical and ultrasound controls and, if recurrence is suspected (abnormal uterine bleeding and/or suggestive ultrasound parameters: endometrial thickness >16 mm, increased vascularization, heterogeneity, irregularity in the endometrium-myometrium junction line, fluid in the cavity or suspicious tumor), an endometrial biopsy and a pathological study to confirm the diagnosis. The data obtained will be recorded in the patient's clinical history. It is a dichotomous variable:
    - **Presence of recurrences.**
    - **Absence of recurrences.**
- **Quality of life:** To measure the quality of life and degree of satisfaction of the patients, they will be administered the QLQ-C30 (37,38) questionnaire **(Annex 2),** developed and provided by the EORTC. It is made up of 30 questions or items:
    - Five functional subscales: physical, occupational, cognitive, emotional and social.
    - Three symptomatic subscales: fatigue, pain, nausea and vomiting.
    - Global quality of life
    - Additional symptoms: dyspnea, loss of appetite, sleep disturbances, constipation and diarrhea.

  Each individual item is added and divided by the number of items that make up the same scale. The scores obtained through the questionnaire are standardized to obtain a score between 0 and 100 according to the formulas and instructions provided in the EORTC QLQ-C30 Scoring Manual **(Annex 3).**

  High scores on global health and functional scales represent an improvement in quality of life, while a high score on symptom scales represents a high level of

symptoms and poorer quality of life. Patients must complete this questionnaire on the same day of the intervention (prior to its administration), 3, 7, 14, 30 and 90 days after treatment.

- **Adverse effects (4,5):** The presence or absence of the following symptoms will be determined through a directed anamnesis at 3, 7, 14, 30 and 90 days after treatment **(Annex 4):**
    - Weight increase: it will be significant when it is greater than 3 kg, if it is not the initiative of the patient herself (diet, physical exercise, etc.).
    - Gastrointestinal symptoms: nausea, vomiting, diarrhea and abdominal pain.
    - Alopecia
    - Gynecological clinic: breast abnormalities, mastalgia, irregular vaginal bleeding, changes in menstrual flow, dysmenorrhea, amenorrhea, galactorrhea, cervicitis, hirsutism, leukorrhea and vaginitis.
    - General disorders: asthenia, headache, rashes, skin sensitivity, dermatitis, acne vulgaris, melasma and anorexia.
    - Mood changes: anxiety, decreased libido and fatigue.
    - Others: hepatic dysfunction, pulmonary embolism, retinal thrombosis, hypertension, biliary obstruction, jaundice, and hyperglycemia.

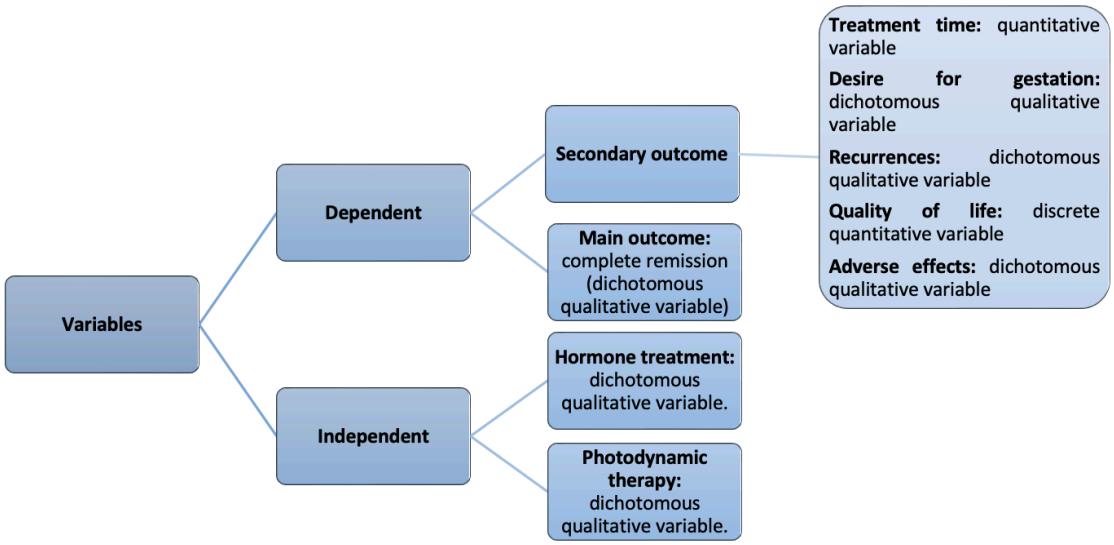

Illustration 7: Variable type

COVARIABLES:

All possible covariates have been defined to describe characteristics of the patients (4,5) and identify possible risk factors **(Table 12).** Most of them are evaluated during the patient's first visit to the reference center through a data collection **(Annex 5).**

- **Weight (overweight and obesity):** It is a risk factor for endometrial cancer because it is related to hormonal changes. The adipose tissue can convert androgens to estrogen and, if estrogen levels increase, the risk of endometrial cancer increases. It can be classified into different categories according to the body mass index (BMI):
    - **<18,5:** Underweight.
    - **18,5-24,9:** Healthy.
    - **25-29.9:** Overweight.
    - **30 or more:** Obesity.
- **Arterial hypertension:** The hypertension is a risk factor for endometrial cancer because it causes hyperestrogenemia. The main problem is that the hypertension is related to lifestyle factors and medical conditions, such as diet, BMI, physical activity, and others. It is possible that this association causes confounding factors. There are 2 categories:
    - **<140/90:** Not hypertension.
    - **≥ 140/90:** Hypertension.
- **Diabetes:** Type 2 diabetes mellitus is an important risk factor and a common comorbidity in women with endometrial cancer.

  The insulin resistance and the resultant hyperinsulinemia promotes endometrial carcinogenesis and its progression by the direct pro-proliferative and anti-apoptotic effect to insulin and insulin growth factor (IGF-1) on endometrial cells.

  The serum glucose is measured by a blood test:
    - **The plasma glucose level is normal:** between 60 and 99 mg/dl.
    - **Prediabetes:** between 100 and 125 mg/dl.
    - **Diabetes:** ≥ 126 mg/dl.
- **Tobacco consumption:** Smoking reduce the risk of endometrial carcinoma through different antiestrogenic mechanisms. First, smokers tend to be thinner than non-smokers (less conversion of androstenedione to estrogen).

Other mechanisms would be to change the metabolism of estrogens to favor the production of 2-hydroxyestrone (anticancer and increases circulating progesterone). It can be classified into different categories:

- **Smoker:**
  - Person who consumes 1 or more cigarettes every day.
  - Person who has quit smoking for less than a year.
- **Former smoker:** person who has not consumed tobacco for more than 1 year.
- **Non-smoker:** person who has not smoked.

- **Alcohol consumption:** The different studies confirm the association of endometrial cancer with consuming ≥ 2 alcoholic drinks/day. This association was observed for all types of alcoholic drinks because it is associated with an increase endogenous estrogen. The total intake of alcohol was expressed in grams/day. It was categorized into 4 categories:
  - **Non-drinkers:** 0 g/day.
  - **< 1 drink/day:** >0 to <12 g/day.
  - **1 to <2 drinks/day:** 12 to <24 g/day.
  - **≥2 drinks/day:** ≥24 g/day.
- **Infertility:** the ovulatory disorders (polycystic ovarian syndrome) are related to endometrial cancer. The prolonged anovulation and consequent release of estrogen unopposed by progesterone may increase the development and growth of endometrial cancer. This variable is qualitative nominal dichotomous.
- **Early menarche (<12 years):** Having more menstrual cycles raises the risk of endometrial cancer, such as, starting menstrual periods (menarche) before age 12. This variable is qualitative nominal dichotomous.
- **Number of relatives with endometrial cancer:** It will be a quantitative discrete variable.
- **Origin:** The incidence of endometrial cancer changes by origin. This variable will include five groups between: African, Asian, Caucasian, Latin-American, and others.

- **Oral contraceptives:** It is a protective factor against endometrial cancer (risk is reduced by at least 30%, with a greater risk reduction the longer oral contraceptives were used):
    a) **3 or more years of use:** 30% lower risk.
    b) **After 10 years of use:** 80% lower risk.
- **Estrogens:** The estrogen exposure (endogenous or exogenous) without opposition from a progestin because it increases mitotic proliferation of endometrial cells, DNA replication errors and somatic mutations. This variable is qualitative nominal dichotomous.
- **Reproductive factors:** It has been seen that nulliparous women have a higher risk of endometrial cancer because these patients present more menstrual cycles associated with absence of pregnancy and lactation and subsequent uninterrupted exposure to estrogens for prolonged periods.
  It can be classified into two categories:
    - **Nulliparity:** The woman has never given birth to a child or has never carried a pregnancy.
    - **Multiparity:** The woman has given birth to a child or has carried a pregnancy.
- **Hospitals:** It is a polytomous qualitative variable. It is an important covariable in multicenter study because there are variations in the application of the same treatment. To reduce reproducibility defects, the coordinator will do a formation before treatment.

Table 12: Covariables

Variable	Description	Instrument of measure	Categories
Weight	Quantitative continuous but categorized as polytomous qualitative	Body mass index (BMI). Anamnesis: data collection sheet (Annex 5)	**<18,5:** Underweight **18,5-24,9:** Healthy **25-29.9:** Overweight **30 or more:** Obesity.
Arterial hypertension	Quantitative continuous but categorized as dichotomous qualitative	Sphygmomanometer (Annex 5)	**<140/90:** Not hypertension **≥ 140/90:** Hypertension
Diabetes	Quantitative continuous but categorized as polytomous qualitative	Blood test (Annex 5)	**60 and 99 mg/dl:** normal **100 and 125 mg/dl:** prediabetes. **≥ 126 mg/dl:** diabetes.

Tobacco consumption	Qualitative nominal	Anamnesis: data collection sheet (Annex 5)	**Smoker** **Former smoker** **Non-smoker**
Alcohol consumption	Qualitative polytomous	Anamnesis: data collection sheet (Annex 5)	**Non-drinkers:** 0 g/day. **< 1 drink/day:** >0 to <12 g/day. **1 to <2 drinks/day:** 12 to <24g/day. **≥2 drinks/day:** ≥24 g/day.
Infertility	Qualitative nominal dichotomous	Anamnesis: data collection sheet (Annex 5)	**Yes/No**
Early menarche (<12 years)	Qualitative nominal dichotomous	Anamnesis: data collection sheet (Annex 5)	**Yes/No**
Number of relatives	Quantitative discrete	Anamnesis: data collection sheet (Annex 5)	**1,2,3**
Origin	Qualitative polytomous	Anamnesis: data collection sheet (Annex 5)	**African, Asian, Caucasian, Latin-American and Others**
Oral contraceptives	Quantitative discrete but categorized as polytomous qualitative	Anamnesis: data collection sheet (Annex 5)	**<3 years** **3-10 years** **>10 years**
Estrogens	Qualitative nominal dichotomous	Anamnesis: data collection sheet (Annex 5)	**Yes/No**
Reproductive factors	Qualitative nominal dichotomous	Anamnesis: data collection sheet (Annex 5)	**Nulliparity/Multiparity**
Hospitals	Polytomous qualitative variable.	Anamnesis: data collection sheet (Annex 5)	**Study hospitals (Illustration 5)**

Methods of measurement:

This study requires different complementary tests to evaluate the results obtained after treating patients with photodynamic therapy or oral progestogens.

ANAMNESIS AND MEDICAL HISTORY:

It will provide information on the patient characteristics. If the information does not appear in the clinical history, it will be specifically asked through data collection sheet **(Annex 5).** Also, the anamnesis allows to assess the presence or absence of symptoms after treatment (side effects, **Annex 4**).

EORTC QLQ-C30:

This questionnaire allows to determine the quality of life of the patient. It is composed of 30 items: functional, symptomatic, global quality of life and other symptoms.

The scores are standardized using the formulas and instructions provided in EORTC QLQ-C30 Scoring Manual **(Annex 3).**

TRANSVAGINAL ULTRASOUND:

It is an essential technique to diagnose endometrial cancer (remission and recurrence) by determining different characteristics that it could indicate malignancy:

- **Endometrial thickness**: measurable, not measurable and not visible.
- **Tumor:** defined or undefined.
- **Tumor volume**
- **Endometrial-myometrial junction**: regular, irregular, interrupted, undefined.
- **Myometrium:** fibroid present and adenomyosis.
- **Endometrial morphology:**
    - Uniform: hyperechogenic, hypoechogenic and isoechogenic.
    - Non-uniform: homogeneous (regular cystic areas and irregular cystic areas) and heterogeneous (without cystic areas, regular cystic areas and irregular cystic).
- **Bright edge**
- **Endometrial midline appearance:** linear, non-linear, irregular and not defined/seen.
- **Vascular pattern:**
    - No vascularity, sparse vascularity, moderate vascularity and abundant vascularity.
    - No flow, single vessel (without branching and with branching), multiple vessels (focal origin and multifocal origin), scattered vessels and circular vessels.

ENDOMETRIAL BIOPSY AND HISTOLOGICAL STUDY:

Endometrial biopsy is a simple and effective office-based procedure that samples the endometrium to allow for direct histological evaluation and confirm the diagnosis.

It is essential that the fertile women have a negative pregnancy test, and she signs an informed consent. Also, if it is possible, the examination will be scheduled in the first phase of the cycle because the endometrium will be more tinner.

To begin the procedure, the patient should be undressed from the waist down and remain covered with a sheet to maintain modesty. The first part of the procedure is non-sterile: the patient is first placed in the lithotomy position and a bimanual examination is done to determine the uterine size and position of the uterus. Then, the speculum can be inserted to allow for cervical visualization.

Once visualized, the cervix can be anesthetized and cleansed by spraying a 20% benzocaine spray for 5 seconds and then applying and iodine solution. In this moment, it is appropriate to don sterile gloves.

Before inserting the uterine sound, the cervix should be stabilized by placing a tenaculum on the anterior lip of the cervix. This allows the provider to straighten the uterocervical angle. The uterine sound is then inserted an average depth of 6 to 10 cm into the uterus. The provider can discern that the sound is fully inserted when feeling resistance from the fundus. One common complication is that the uterine sound will not pass through the internal cervical, in this case, it is necessary use the cervical dilators.

Once achieving adequate dilation and determining the uterus depth, the sampling pipelle can be inserted. The pipelle should be advanced until resistance is encountered. This resistance should be at the same depth as the sounding of the uterus. Once the pipelle is in the uterine cavity, the internal piston of the catheter is fully withdrawn, creating suction at the tip of the catheter.

This suction, accompanied by inward and outward movement of the tip, allows for sample collection. This movement must be completed with a 360-degree twisting motion to reach all four quadrants of the endometrium. The pipelle is now removed and the collected tissue sample is placed in a formalin solution. Finally, the tenaculum should be removed and bleeding controlled by pressure (with cotton swabs or a sponge). If bleeding persists, use silver nitrate sticks to cauterize the site (11).

If the results are inconclusive, the endometrial biopsies can also be obtained by **hysteroscopy:**

Once the patient is placed in the gynecological position, a vaginal speculum is inserted and the cervix and vagina are cleaned with an antiseptic solution. Small caliber hysteroscopes (4 mm or less) are used to avoid dilating the cervix.

Once the external cervical orifice has been visualized, the hysteroscope will be introduced into the cervical canal, which will be opened with the help of a distending gas or liquid until it reaches the uterine cavity. When the uterine cavity is accessed, samples of the endometrium are obtained. If access to the internal cervical orifice is not technically possible, paracervical anesthesia (5 ml of 1% mepivacaine) is administered to dilate the cervix (11).

Intervention:

In this study, the total population (430 patients) will be divided into two groups:

- **Control group (A):** administration of oral progestogens.
- **Intervention group (B):** administration of photodynamic therapy.

The purpose of both treatments is the remission of endometrial carcinoma grade 1A, without myometrial involvement, low grade (G1/G2) without genetic risk factors.

HORMONAL TREATMENT (PROGESTOGENS):

The hormonal treatment that will be administered to group A is medroxyprogesterone acetate (Provera ®) oral (500 mg/day for 6 months).

During this interval, two endometrial samples should be obtained: at three and six months. Six months after starting treatment, if the tumor has remitted, the patient can fulfill her reproductive wish (although she must continue with follow-up)(20,21).

PHOTODYNAMIC THERAPY:

PDT is a simple technique, and it can be performed without anesthesia as it does not cause pain or bleeding. It is divided into two clinical phases:

- On a first visit, a photosensitizer is administered, specifically sodium porfimer (Photofrin®), which is a derivate from natural hematoporphyrins. Porfimer sodium (2 mg/kg) is diluted with 5% dextrose or saline solution before intravenous administration. The mean clearance time of the drug is 40-50 hours in most tissues, for this reason, exposure to light stimulus is usually carried out 48 h after administration of the porfimer (when the difference in density between malignant and normal cells is greater).
- On a second visit (48 hours later), red laser light (630-635 nm) is applied to the endometrial cavity to activate the action of the photosensitizer on the cells.

In this case, the laser used is OPO-YAG, which allows the selective destruction of malignant cells with hardly any effect on normal tissues.

To apply the light inside the uterus, an endoscope will be necessary. Once placed inside the vagina, a guidewire will be inserted through its working channel to reach the uterine cavity. A balloon is advanced over this guide, specially designed for PDT (it has a translucent cylindrical window).

Then, the guide is removed and a catheter equipped with a light-emitting device will be introduced through the internal channel to the balloon window. Finally, the balloon will be inflated in the endocervical canal to flatten its walls and the light stimulus will be applied with a predetermined wavelength.

The photosensitizer captures the light energy and activates, moving to a higher energy state. From this state, the photosensitizer transfers light energy to oxygen in the cells. When the cellular oxygen receives this energy transfer, a reactive oxygen is generated that is tremendously toxic for the cancer cells and ends up destroying it. Meanwhile, the photosensitizer returns to its original state to receive a second photon of light and start the cycle again.

The effects of PDT usually appear after 12-24 hours of procedure.

After the administration of the treatment, the patient is followed up with imaging tests and endometrial biopsies (pipelle biopsy or hysteroscopy) at 3 and 6 months. If after 6 months the tumor has not remitted, surgical treatment should be indicated (23,24,25,26,27).

Data collection and follow-up:

This study is a multicenter clinical trial, so that, the participants come from different public or private centers in Spain. All the patients must meet the inclusion criteria and none of the exclusion criteria. These data are obtained through:

- **Clinical history:** provides information on serious systemic diseases, genetic factors or syndromes related to endometrial cancer, previous neoplastic diagnoses and treatments carried out.

  Apart from the patient's medical history, it includes:

  - Reason for the gynecological consultation: abnormal bleeding (usually).

- Directed anamnesis: genetic wish fulfilled.
- Gynecological examination: includes ultrasound evaluation of the endometrium with characteristics of malignancy.
- Endometrial biopsies: with pipelle or hysteroscopy.

- **Pathological anatomy report:** Through the histological study, the diagnosis is confirmed. In the case of the participants, a low-grade (G1/G2) endometrioid carcinoma **(Annex 1).**
- **Other tests:** PMR and PET-CT allow staging of endometrial carcinoma. In this case, stage 1A without myometrial involvement.

If you have all these characteristics, the patient can participate in the study.

First visit:

After informing the patient at her usual center, she is transferred to the reference hospital of her Autonomous Community.

In the first visit, the following tasks will be carried out:

- Both treatments will be explained (medical procedure, adverse effects and percentage of remission, recurrences, and pregnancy), phases of the study (specifying the temporality) and confidentiality. The therapeutic failure six months after the beginning of the treatment, will cause the end of their participation and the establishment of the standard surgical treatment.

  If the patient agrees to be part of the study, she will be given the information sheet **(Annex 6)** and the informed consent document **(Annex 7).**
- Analyze the clinical history and a directed anamnesis to collect all covariates **(Annex 5).**
- Performing a physical examination that includes the determination of blood pressure and a blood test.

Randomization:

Once the study is explained, the patients will be randomized into two groups:

- **Control group (A):** administration of oral progestogens.
- **Intervention group (B):** administration of photodynamic therapy.

Before starting treatment, the quality-of-life questionnaire must be completed (QLQ-C30, **Annex 2).**

Screening strategy:

Once the treatment has been applied, a follow-up must be carried out in the Gynecology and Obstetrics department of the different reference hospitals of each Autonomous Community:

- Control the adverse effects of the patient through a directed anamnesis **(Annex 4)** and the quality of life through the QLQ-C30 **(Annex 2)** at 3,7,14,30, and 90 days after treatment.
- Verify tumor remission after 3 months by clinic, transvaginal ultrasound and anatomopathological study of endometrial biopsies.
    - If the tumor has remitted, continue with the follow-up at six, eight, twelve, sixteen and twenty months.
    - If the tumor has not remitted, continue pharmacological treatment for 6 months in the control group or apply another PDT session in the intervention group.
- Verify tumor remission or recurrence after 6 months through clinical symptoms, transvaginal ultrasound and anatomopathological study of endometrial biopsies.
    - If the tumor has remitted, continue the follow-up at eight, twelve, sixteen and twenty months: clinical symptoms, transvaginal ultrasound and, if recurrence is suspected, anatomopathological study of endometrial biopsies.
        - The patient can fulfill her pregnancy wish spontaneously or through assisted reproduction techniques.
    - If the tumor has not regressed, refer the patient for standard surgical treatment.

All the data will be collected in SAP database that will be managed by the coordinator of the Hospital Universitari Josep Trueta and his assistant. In addition, to improve the blinding of this study, the identity of the patients will be coded to analyze the results statistically. Therefore, the main coordinator, his assistant and the statistician are blinded.

The duration of the entire study is 3 years, from the collection of information to the publication of the results in scientific journals. The timing is specified in the chronogram.

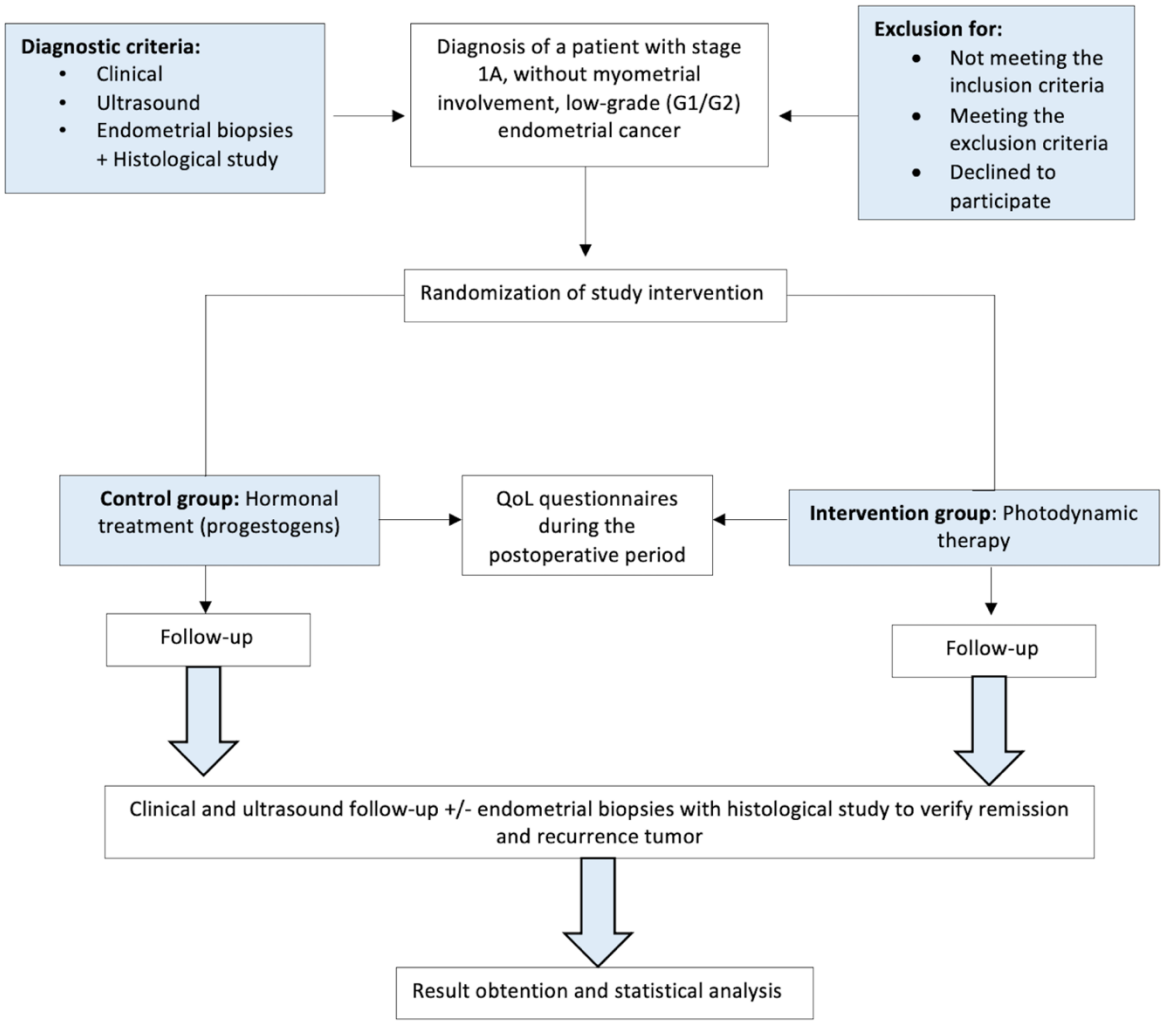

Illustration 8: Flow chart

STATISTIC ANALYSIS

The statistical analysis will be performed by a blinded statistician, using the IBM SPSS Statistics 28.0.1.1 (SPSS Windows®). For all results, we will consider the statistical significance at a value of $p<0,05$, defining a confidence interval of 95%.

Descriptive analysis:

The qualitative dependent variables (complete tumor remission, reproductive desire, presence or absence of recurrences and adverse effects) will be summarized using proportions (percentages).

On the other hand, the number of adverse effects, treatment time and quality of life score are discrete quantitative variables. They will be summarized using medians and interquartile range.

These analyses will be stratified by intervention and control groups. Additional stratification will be done for the covariates.

We will be drawn the survival curves of treatment time using the Kaplan-Meier estimates. This analysis will be also stratified by intervention and control groups and by the covariates.

Bivariate inference:

The difference of the proportions of the dependent qualitative variables between the intervention and the control groups will be tested using the chi-squared test or the Fisher's exact test, if the expected number of cases in a cell will be lower than 5.

The difference of medians of the dependent discrete variables between the intervention and the control groups will be tested using the Mann-Whitney's U test. The difference of the survival curves will be tested using the log-rank test.

These analyses will be stratified by the covariates.

Multivariable analysis:

The effectiveness of the intervention on the qualitative dependent variables will be assessed in logistic regressions controlling for the covariates.

In the case of discrete dependent variables, the multivariate model will be Poisson regression, again adjusting for covariates.

The association of the intervention on time of treatment will be assessed in a Cox regression, controlling for the covariates.

WORK PLAN AND CHRONOGRAM

The activities developed in this clinical trial will be divided in the following stages:

STAGE 0: STUDY DESIGN (October 2022-November 2022)

- **Activity 1:** Bibliographic research about endometrial cancer (risk factors, classification, diagnosis and therapeutic management).
- **Activity 2:** Protocol elaboration including objectives, hypothesis, variables and methodology.

STAGE 1: ETHICAL EVALUATION AND STUDY APPROVAL (December 2022-Febrery 2023)

- **Activity 3:** Protocol submission to the CEIC of the Hospital Universitari Doctor Josep Trueta and it will be adapted to the CEIC contributions. Once approved, the protocol must be accepted by the CEIC of the reference hospitals.
- **Activity 4:** A liability insurance will be contracted.

STAGE 2: COORDINATION AND FORMATION (February 2023- March 2023)

- **Activity 5:** The research team from each participant hospital choose a principal investigator who will communicate with other centers and apply both treatments for the duration of the study and will organize the tasks from his hospital.
- **Activity 6:** The main coordinator belonging to Hospital Universitari Doctor Josep Trueta will establish the first meeting between all participant centers main researchers.
- **Activity 7:** To reduce reproducibility bias, the main coordinator will organize a virtual workshop to explain the therapeutic procedures to the main investigators of the reference hospitals.

STAGE 3: DATA COLLECTION AND FOLLOW-UP (March 2023-May 2025)

- **Activity 8:** Patient recruitment will be performed by a consecutive sampling in every hospital participating in the trial. Only patients meeting inclusion criteria and not meeting exclusion criteria will be included in the sample: young patients (<40 years) must be diagnosed with stage 1A endometrial carcinoma, without involvement of the myometrium, low stage G1/G2 and gestational desire.
- **Activity 9:** The patients will travel to the reference hospital to be informed in detail about the study.

In this visit, the covariates (diabetes, arterial hypertension, tobacco, alcohol) will be studied through the medical history and complementary examinations. Finally, the patient will be randomly assigned to one of the groups of intervention.

- **Activity 10:** The intervention will be performed: hormonal treatment or photodynamic therapy. Before treatment, the patient must fill out a QoL questionnaire and sign the informed consent (risks of disease recurrence or progression and adverse effects).
- **Activity 11:** Follow-up visits will be carried out periodically:
    - **The first 3 months** (3,7,14, 30 and 90 days after treatment), the principal researchers evaluate the quality of life (through QLQ-C30 questionnaire) and adverse effects (through anamnesis). To avoid displacing patients, they will be completed virtual or by phone.
    - **Three months after the treatment:** the principal researchers visit the patients to determinate if the tumor has remitted (at 3 and 6 months after treatment). To confirm tumor remission, a physical examination, transvaginal ultrasound and endometrial biopsy are performed.
    - **Six months after treatment:** After informing the patient about the risks, if there is no tumor after 6 months of treatment, the patient can fulfill her desire to become pregnant.
    - **Eight months after treatment:** the principal researchers study the recurrences that could appear at 8,12, 16, 20 months.

  The follow-up visits should last 48 months because recurrences can appear during this period, but the financing of this study will end after 3 years.
- **Activity 12:** Specialists will record the information collected from the different variables in every visit in the patient's clinical chart and the study database.

  The virtual questionnaires will be sent to the investigator assistant, and he/she will be deposited in the virtual study database.

STAGE 4: DATA ANALYSIS AND INTERPRETATITON (March 2024-June 2025)

- **Activity 13:** Statistical analysis of the obtained data will be performed by a statistician who will be masked for intervention groups.

He/she will perform an intermediate analysis once half of the sample's data has been collected (March 2024) to identify any situation that could stop the trial (the recurrence of the tumor will require surgical removal).

Final statistical analysis will be performed when all the data has been collected (July 2025).

- **Activity 14:** The final statistical analysis will be interpretated by the coordinator and the mains investigations of each participant hospital. Then, discussion and conclusions from the previous analyses will be elaborated.

STAGE 5: PUBLICATION AND DISSEMINATION OF THE RESEARCH FINDINGS (July 2025-September 2025).

- **Activity 15:** Presentation of the results to the National Congress of Gynecology and Obstetrics.
- **Activity 16:** Presentation of the results on the European Academy of Gynecology and Obstetrics.
- **Activity 17:** Publication of the results in scientific journals.

Table 13: Chronogram

TASKS		2022		2023						2024				2025			
		OCT-NOV	DEC	JAN	FEB	MAR	ABR-AUG	SEP	OCT-DEC	JAN-FEB	MARCH	APR-AUG	SEP-DEC	JAN-MARCH	APR-MAY	JUN	JULY-SEP
S0	A1: Bibliographic research																
	A2: Protocol elaboration																
S1	A3: CEIC																
	A4: Insurance																
S2	A5: Coordinators designation																
	A6: 1st meeting																
	A7: Online formation																
S3	A8: Recruitment																
	A9: Inform and assign																
	A10: Intervention																
	A11+A12: Follow-up and data collection																
S4	A13: Statistical analysis																
	A14: Final analysis																
S5	A15: National Congress																
	A16: European Academy																
	A17: Scientific journals																

ETHICAL AND LEGAL CONSIDERATIONS

This clinical trial will be performed respecting human rights and the basic ethical principles of Beauchamp and Childress, and the principles gathered in the World Medical Association Declaration of Helsinki of *"Ethical Principles for Medical Research Involving Human Subjects"* (1964, last reviewed on 2013) (39,40).

The **justice** principle will be taken into consideration since every woman meeting the inclusion and not meeting the exclusion criteria will be asked to enroll on the trial, without any discrimination. The patient autonomy principle will be respected as it will be completely voluntary and only those signing the informed consent will participate in the trial. Also, patients will have the necessary time to decide if they want to participate or not and will have all the information of the clinical trial (Annex), so that they can choose knowing what to expect from it. **Non-maleficence** principle is expected to be respected according to the available bibliography, as it exists enough evidence that the use of PDT doesn't imply a patient's infratreatment. Finally, the principle of **beneficence** will be respected by reducing the adverse effects caused by hormonal treatment.

This protocol has also been developed according to the Spanish legal precepts of *Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos, los Comités de Ética de la Investigación con medicamentos y el Registro Español de Estudios Clínicos; Ley 14/2007, de 3 de julio, de Investigación Biomédica; and Ley 41/2002, de 14 de noviembre (Ley de Autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica).*

Before the start of the study, its protocol will be submitted to the Clinical Research Ethics Committee (CEIC: Comitè Ètic d'Investigació Clínica) of Hospital Universitari Doctor Josep Trueta from Girona for its evaluation and approval, taking in consideration all their suggestions and adding them to the protocol. After the ethical committee approval, the protocol will be sent to the investigator of each participant hospital to get their approval and reconfirm their participation. Only after all these entities have approved our study protocol, the clinical trial will be carried out.

All members from each research team of every participating hospital will need to sign a statement indicating their approval of the final protocol and their commitment with the ethics aspects of the research.

The confidentiality of the patients will be respected according to the Spanish law *"Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales"*.

All patient's data will be registered by a numeric code assigned to each of them to preserve their anonymity. Patients will also have the right to modify or erase their personal data. All the information obtained will be completely confidential and only used for the purpose of research.

Finally, all data will be published with transparency. Unfavorable events or data won't be excluded.

No conflicts of interest are declared by the investigators in charge of this study.

STUDY LIMITATIONS

Throughout the design process of this clinical trial protocol, some limitations have been detected and will be taken into consideration at the time of the statistical analysis:

- As this trial is **open labeled** because of the impossibility to mask patients and gynecologist, it can lead to a **detection bias**. To minimize this possible bias, the statistician (who evaluates the results) and coordinator (collect histopathological data and he/she manages the data obtained in the reference hospitals) will be masked.
- Being a multicentric trial, in which the intervention (PDT) is operator dependent, there is a risk of **variability.** Although at the beginning of the study a virtual workshop to unify the techniques of main investigators, there is the possibility of **inter and intravariability** not only between hospitals but also between professionals from the same hospital. In addition, all hospitals selected to participate in this study are referral hospitals with similar capabilities and resources to achieve common results.
- The consecutive non-probabilistic recruitment method used for sample selection in this trial may lead **to selection bias** as it is not the perfect method to obtain a representative sample of the population. However, due to the low incidence of young patients with stage 1A G1/G2 progesterone receptor-positive endometrial carcinoma, designing it differently would not be as beneficial. To minimize this bias, the intervention will be randomized to distribute patients between equitable groups.
- This study is a clinical trial that measures two very different treatments: PDT, an operator-dependent procedure and progesterone hormone treatment, which depends on patient compliance. In this study can appear a **compliance bias** if the patient abandons the treatment.
- Due to the **prospective** format of the clinical trial, there is a risk of withdrawals during the 2 years of the follow-up period. This risk has been assessed at the time of the sample size determination with a 10% of drop-out rate. Therefore, the sample size has been increased to be able to cover for those who will potentially drop-out the clinical trial.

Furthermore, to avoid withdrawals, telephone calls will be made to patients by the research team when detecting their absences on the follow-up visits and will encourage them to pursue in the study.

- To study the recurrences that appear in both groups of patients, after treatment, it would be necessary to follow up for 48 months, but **financing** is limited to 3 years.
- The clinical trial lacks **external validity** because it is difficult to extrapolate the results obtained in similar ambient but not identical. Being a multicenter study, its external validity is improved.
- The statistical analysis has reduced the **confounding bias**, which appears during the evaluation of the results. A confounding factor acts as an independent risk factor. To reduce this bias, covariates have been established.
- **Side effects:** This study intends to study the adverse effects that appear with the establishment of both treatments through a directed anamnesis. Some adverse effects are not included in the questionnaire because they are very infrequent, so they will not be recorded in the final results of this study.

FEASIBILITY

This study is feasible for different reasons:

- It will be carried out by different health professionals who work in the reference centers medical in Spain:
    a) The main coordinator is a gynecologist who work at the Hospital Universitario Josep Trueta for years. Together with her assistant, she will collect information from the reference centers and facilitate communication between them.
    b) The principal investigators (gynecologists) and pathologists are also work in the reference centers.
    c) Dermatologists are medical specialists who use PDT more frequently. So that, they can solve problems that may appear.

    The gynecologists will be trained before the study to unify knowledge and avoid bias.
- The machinery used in photodynamic therapy is available in the dermatology service of the different reference hospitals.
- The complementary tests used to diagnose remissions and recurrences are common medical procedures in the daily clinical practice of the hospital's gynecology and obstetrics service.
- The SAP systems are a structured database where all clinical information of a patient can be uploaded with all the data required for the study.
- Although it is a multicenter clinal trial, the patients will undergo treatment and follow-up at a hospital in their own Autonomous Community.
- Any aggravation of the cancer is avoided by constant controls. In addition, if remission is not obtained at 6 months, the patient should remove from the study and standard surgical treatment applied.
- There are previous in vitro, animal and clinical studies that certify the efficacy of photodynamic therapy in this type of cancer.

CLINICAL AND HEALTHCARE IMPACT

Although stage 1A endometrial carcinoma, without myometrial invasion, low grade (G1/G2) and without genetic involvement is rare, its appearance requires surgical removal of the uterine cavity, fallopian tubes, and ovaries.

If this neoplasm is diagnosed in young patients (<40 years) with a desire to become pregnant, conservative treatment should be instituted.

Currently, oral progestogens are used. They are a drug that causes multiple side effects, worsening the patient's quality of life and causing recurrences (30-40%) a few months. In addition, it usually responds months after its establishment, so the patient must go to the gynecologist several times to study the remission of the tumor and treat the side effects that it is causing. Therefore, its establishment increases the public cost: prolonged and financed hormonal treatment, increased demand for care to carry out periodic check-ups and treat the symptoms presented by the patient and a greater number of sick days.

For years, PDT has been used to treat skin lesions and carcinomas of the prostate, breast, lung, esophagus, etc. This technique has shown great efficacy due to its selectivity against malignant cells, reduction of adverse effects (minimally invasive) and reduction of remission time. Its use allows costs to be reduced for different reasons: it is available this machinery in other services; therefore, it is only necessary to buy the photosensitizer and the endoscope. In addition, it is an outpatient technique that allows the tumor to be remitted in two clinical sessions and avoids the systemic adverse effects of hormonal treatment, reducing care work and sick days.

Topical photosensitizers have been investigated in recent years to improve the efficacy and reduce the photosensitivity of systemic photosensitizers. This has made it possible to expand the therapeutic field of TDF. At the gynecological level, topical photosensitizers such as 5-ALA are being used.

For all these reasons, we encourage hospitals that do not have TDF to invest in its purchase and ambulatory use.

If the objectives of this study are achieved, further research is needed to one day avoid surgical treatment of these patients.

STUDY BUDGET:

PERSONNEL EXPENSES

The main research team is composed by physicians (gynecologists and pathologists) pertaining to the study hospitals, therefore, the coordinator of Hospital Trueta and the principal investigators will not incur an additional cost.

In this study, a part-time research assistant must be hired who will work for 20€/h, during approximately 150 hours. This will cost 3.000 euros. He/she will take care of typewriting the results of questionnaires filled in by patients and doctors, as well as scanning the signed informed documents to bring up to date our databases.

A statistician expert will also be hired to randomize and code patients, as well as to perform the final statistical analysis from the data collected. His/her salary will be 30€/hour, during approximately 50 hours. This will cost 1.500€.

INSURANCE POLICY

When performing an invasive clinical trial, it is necessary to take out health insurance to cover any possible adverse effect that may result from the participation of patients in the study. Its estimated cost is 45.000€.

EXECUTION EXPENSES

Material for the bibliography research hasn't represented an additional expense.

Also, the monitoring of patients by ultrasound and endometrial biopsies, with their subsequent histological study, are part of the routine treatment of the Gynecology and Obstetrics Service, so they will not add any cost.

Moreover, photodynamic therapy will suppose a decrease in costs as it is a technique minimally invasive that causes fewer side effects and therefore, reduces the number of care visits and sick leave. As the machine is available in the dermatology service of the different reference hospitals, only the systemic photosensitizer (sodium polymer or Photofrin®) and the endoscope should be purchased.

A 70 kg patient requires 0.14 kg of photosensitizer. Considering that 430 patients participate and each 20 kg of photosensitizer costs 329 euros, the total is 987 euros.

Execution expenses are composed by the printing of the Information Forms for patients, the Informed Consent forms, the QoL questionnaires, and the Data Collection Sheets **(Annexes 2-7).**

TRAVEL AND COORDINATION EXPENSES

During this clinical trial, eight meetings will be realized between the coordinator and the main investigators of each reference hospital.

At the first meeting, the objectives, the type of study, the required sample, and the medical procedures to be performed will be explained.

At the second meeting, the principal investigators from each reference hospital will receive virtual formation on PDT. The rest will be follow-up meetings.

Nevertheless, all meetings between coordinator and main investigations of different hospitals will be telematic via videoconference, so no travel expenses are expected.

PATIENT DISPLACEMENT

Patients must travel from their place of residence to the reference hospital in their Autonomous Community.

It has been estimated about 100 km per visit and a payment of 130 euros for each journey. Considering that a first information visit, 1 or 2 treatment visits and 6 more follow-up visits are required for 430 patients, the budget reaches 503.100 euros. To reduce the cost, they can take advantage of each trip by transferring 4 patients in the same taxi (125.775 euros).

In addition, neither of the two treatments prevent the patient's own movement by means of her own vehicle or public transport. This would be an alternative to reduce the costs of this study.

CONFERENCE EXPENSES

In order to disseminate the results of our clinical trial to the scientific community, we will attend national and international congresses. Two researchers will participate in the national congress with the final statistical analyses and discussion. Its admission fee is estimated on 500€ per person. Accommodation and diets are estimated on 500€ per person. Therefore, we approximate a cost of 2.000€.

Two of the researchers will also present our results and discussion to the international congress. Its admission fee is estimated in 500€ per person and the costs of travel, accommodation and diets are estimated on 1.000€ per person. Thus, we approximate a cost of 3.000€.

PUBLICATION EXPENSES

Once our study has ended, and the extraction and interpretation of results has been performed, we will publish it as a journal article. We must preparation of the Open Access (1.800€).

All expenses are summarized in the following **Table 14:**

Table 14: Budget

ÍTEM	AMOUNT	COST	SUBTOTAL
Coordinator assistant	150 hours	20€/hour	3.000€
Statistician	50 hours	30€/hour	1.500€
Insure policy	1	45.000€/trial	45.000€
Photosensitizer	3	329€/package	987€
Endoscope	17	120€/unit	2.040€
Photocopies	12	0,03€/page	154,8€
Patient displacement	100 km	130€/trip	125.775 €
National Congress	2	1.000€/participant	2.000€
International Congress	2	1.500€/participant	3.000€
Publication	1	1800€	1800€

The total budget is approximately 185,256.8 €.

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ANNEXES

Annex 1: Pathology report

DATOS DEL PACIENTE

NUHSA: DNI:

NOMBRE:

EDAD:

SEXO:

SOLICITUD ESTUDIO DE ANATOMÍA PATOLÓGICA

CENTRO PETICIONARIO:

SERVICIO REMITENTE:

MEDICO REMITENTE:

TIPO DE PACIENTE:

PRIORIDAD: FECHA DE SOLICITUD:

TIPO DE MUESTRA: ☐ BIOPSIAS ☐ CITOLOGÍAS

ÓRGANO:

DATOS CLINICOS:

NUMERO DE MUESTRAS:

DATOS ADICIONALES:

FIRMA:

Annex 2: QLQ-C30 Questionnaire

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____
Your birthdate (Day, Month, Year): _____
Today's date (Day, Month, Year): 31 _____

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Annex 3: QLQ-C30 Scoring Manual

General principles of scoring

The QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales, three symptom scales, a global health status / QoL scale, and six single items. Each of the multi-item scales includes a different set of items - no item occurs in more than one scale.

All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level.
Thus a **high score for a functional scale** represents a *high / healthy level of functioning*,
a **high score for the global health status / QoL** represents a *high QoL*,
but a **high score for a symptom scale / item** represents a *high level of symptomatology / problems*.

The principle for scoring these scales is the same in all cases:

1. Estimate the average of the items that contribute to the scale; this is the *raw score*.

2. Use a linear transformation to standardise the raw score, so that scores range from 0 to 100; a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms.

Coding of the scoring procedure is presented in Appendix 3 for three major statistical packages.

Technical Summary

In practical terms, if items $I_1, I_2, \ldots I_n$ are included in a scale, the procedure is as follows:

Raw score
Calculate the raw score
$RawScore = RS = (I_1 + I_2 + \ldots + I_n)/n$

Linear transformation
Apply the linear transformation to 0-100 to obtain the score S,

Functional scales: $$S = \left\{1 - \frac{(RS-1)}{range}\right\} \times 100$$

Symptom scales / items: $$S = \{(RS-1)/range\} \times 100$$

Global health status / QoL: $$S = \{(RS-1)/range\} \times 100$$

Range is the difference between the maximum possible value of *RS* and the minimum possible value. The QLQ-C30 has been designed so that all items in any scale take the same range of values. Therefore, the range of *RS* equals the range of the item values. Most items are scored 1 to 4, giving *range* = 3. The exceptions are the items contributing to the global health status / QoL, which are 7-point questions with *range* = 6, and the initial yes/no items on the earlier versions of the QLQ-C30 which have *range* = 1.

Table 1: Scoring the QLQ-C30 version 3.0

	Scale	Number of items	Item range*	**Version 3.0** Item numbers	Function scales
Global health status / QoL					
Global health status/QoL (revised)†	QL2	2	6	29, 30	
Functional scales					
Physical functioning (revised)†	PF2	5	3	1 to 5	F
Role functioning (revised)†	RF2	2	3	6, 7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F
Social functioning	SF	2	3	26, 27	F
Symptom scales / items					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14, 15	
Pain	PA	2	3	9, 19	
Dyspnoea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhoea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

* *Item range* is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.
† (revised) scales are those that have been changed since version 1.0, and their short names are indicated in this manual by a suffix "2" – for example, PF2.

For all scales, the *RawScore*, *RS*, is the mean of the component items:

$$RawScore = RS = (I_1 + I_2 + ... + I_n)/n$$

Then for **Functional scales**:

$$Score = \left\{1 - \frac{(RS - 1)}{range}\right\} \times 100$$

and for **Symptom scales / items** and **Global health status / QoL:**

$$Score = \{(RS - 1)/range\} \times 100$$

Examples:

Emotional functioning

$$RawScore = (Q_{21} + Q_{22} + Q_{23} + Q_{24})/4$$
$$\text{EF } Score = \{1 - (RawScore - 1)/3\} \times 100$$

Fatigue

$$RawScore = (Q_{10} + Q_{12} + Q_{18})/3$$
$$\text{FA } Score = \{(RawScore - 1)/3\} \times 100$$

Anexo 4: Adverse effects (directed anamnesis)

Marca la sintomatología que presenta después de la administración del tratamiento conservador del carcinoma endometrial 1A de bajo grado (G1/G2):

1) **¿Ha experimentado un incremento de peso de manera no voluntaria (sin dieta ni exceso de ejercicio físico)? Será significativo cuando sea superior a 3 kg.**
    a) Sí.
    b) No.
2) **¿Ha presentado algún síntoma gastrointestinal? Indique cuál/cuáles:**
    a) Náuseas.
    b) Vómitos.
    c) Diarrea.
    d) Dolor abdominal
3) **¿Ha presentado pérdida de cabello?**
    a) Sí.
    b) No.
4) **¿Ha presentado algún síntoma ginecológico? Indique cuál/cuáles:**
    a) Alteración en el tamaño mamario.
    b) Dolor en la mama.
    c) Sangrado vaginal irregular.
    d) Cambios en el flujo menstrual (cantidad, olor, etc).
    e) Dolor intenso en la menstruación
    f) No presencia de menstruación.
    g) Producción de leche materna sin presencia de embarazo.
    h) Síntomas de cervicitis: sangrado anómalo entre los periodos menstruales, dolor durante las relaciones sexuales y flujo vaginal anormal.
    i) Aparición de vello en nuevas localizaciones.
    j) Presencia de flujos vaginales abundantes antes de la menstruación.
    k) Secreción, picazón y dolor vaginal.

5) ¿Ha presentado algún otro síntoma? Indique cuál/cuáles:

a) Cansancio.
b) Dolor de cabeza.
c) Erupciones cutáneas.
d) Sensibilidad cutánea.
e) Picazón, hinchazón o/y enrojecimiento de la piel.
f) Acné.
g) Anorexia.
h) Aparición de parches oscuros en las zonas expuestas al sol.

6) ¿Ha presentado alteraciones del estado de ánimo? Indique cuál/cuáles:

a) Ansiedad.
b) Fatiga.
c) Disminución del deseo sexual.

7) ¿Ha presentado alguna otra complicación sistémica? Indique cuál/cuáles:

d) Disfunción hepática.
e) Embolia pulmonar.
f) Trombosis retinal.
g) Hipertensión.
h) Obstrucción biliar,
i) Ictericia.
j) Hiperglucemia.

*Para confirmar la pregunta 7 se requiere de un diagnóstico médico que, en caso de presentar síntomas, la paciente será visitada en cualquier hospital de España.

Anexo 5: Data collection sheet

Hoja de recogida de datos demográficos y epidemiológicos de las pacientes que participan en el estudio:

Hospital: _____

Fecha: _____

Marca con una cruz la opción más apropiada:

1. Código numérico asignado: _____

2. Fecha de nacimiento (día/mes/año): __/__/_____

3. Talla (expresado en centímetros):

4. Peso (expresado en kg):

5. Presión arterial (será registrada clínicamente mediante un esfingomanómetro):

a) <140/90

b) ≥ 140/90

6. Diabetes (se registrará a través de una analítica bioquímica):

a) 60-99 mg/dl

b) 100-125 mg/dl

c) ≥ 126 mg/dl.

7. Étnia:

a) africana

b) asiática

c) caucásica

d) latino-américa

e) otras

8. Hábito tabáquico:

a) No fumador

b) Exfumador: persona que no consume tabaco des de hace más de 1 año.

c) Fumador: persona que consume 1 cigarrillo/día o hace menos de un año que ha dejado de consumir.

9. Consumo de alcohol:

La equivalencia de gramos y alcohol= volumen (ml) x graduación bebida x 0,8/100. 10 gramos de alcohol son aproximadamente 1 cerveza o 1 copa de vino.

a) No consume alcohol: 0 g/día.

b) <1 bebida/día: >0 y <12 g/día.

c) 1 o < 2 bebidas/día: 12 y <24 g/día

d) ≥ 2 bebidas/día: ≥24 g/día.

10. Infertilidad:

a) Sí

b) No

En caso afirmativo, señala la causa (síndrome de ovario poliquístico, anovulación…):

_____

11. Primera menstruación antes de los 12 años:

a) Sí

b) No

12. Familiar con carcinoma de endometrio:

a) Sí

b) No

En caso afirmativo, qué familiar (madre, tía, abuela…):

_____

13. Uso de anticonceptivas orales:

a) Sí

b) No

En caso afirmativo, indica durante cuánto tiempo:

_____

13. Exposición a estrógenos sin oposición de progestágenos:

a) Sí

b) No

14. Número de embarazos finalizados o no finalizados:

a) Ninguno.

b) 1

b) 2 o más

Anexo 6: Clinical trial patient information sheet

HOJA DE INFORMACIÓN PARA EL PACIENTE SOBRE EL ENSAYO CLÍNICO

Nombre del estudio: *Terapia fotodinámica como alternativa a los progestágenos orales en el tratamiento del carcinoma endometrial 1A, G1/G2 en pacientes con deseo genésico.*

Centro asistencial:

Investigador principal:

Estimado/da,

Nos dirigimos a usted para proponerle participar en un estudio de investigación llevado a término por los Servicios de Ginecología y Obstetricia de varios hospitales de referencia de España.
Este estudio ha sido aprobado por el Comité de Ética e Investigación Clínica del Hospital Universitario Doctor Josep Trueta y por la Agencia Española del Medicamento y Productos Sanitarios.

Nuestra intención es que usted entienda el motivo por el que se realiza este estudio y qué implica formar parte, para que pueda decidir voluntariamente si desea participar. Por eso, le rogamos que se tome el tiempo necesario para leer detenidamente y comprender este resumen informativo sobre nuestro estudio. No es necesario que decida hoy su participación, y, en caso de que surja cualquier duda, nuestro equipo estará pendiente y le responderá, poniendo a su disposición toda la información necesaria.

DESCRIPCIÓN Y OBJETIVO DEL ESTUDIO

La neoplasia endometrial es el cáncer ginecológico más prevalente de los países desarrollados, por detrás del de mama, siendo la media 63 años. Aun así, hay un pequeño porcentaje (2,4-5%) que se diagnostica durante la edad fértil (antes de los 40 años). Aunque la mayoría son diagnosticadas precozmente (estadio 1), el tratamiento estándar es el quirúrgico. En caso de deseo genésico por parte de la paciente, se ofrece un tratamiento alternativo basado en progestágenos orales, los cuales presentan una tasa de respuesta reducida (57-75%), recurrencia significativa (11-50%) y un alto porcentaje de éxito gestacional.

Además, presentan varios efectos secundarios sistémicos: incremento de peso, síntomas gastrointestinales, alopecia, mastalgia, dismenorrea o amenorrea, erupciones cutáneas, galactorrea, cervicitis, etc. Más raramente puede ocasionar patologías sistémicas (disfunción hepática, embolia pulmonar, trombosis retinal…).

Por otro lado, la terapia fotodinámica es un procedimiento médico que utiliza medicamentos fotosensibilizadores y luz visible para eliminar células no deseadas, mejorar la cicatrización de heridas y obtener un efecto antimicrobiano. Inicialmente se usó para tratar diferentes patologías dermatológicas, pero actualmente la FDA ha aprobado su uso para tratar otras neoplasias y lesiones precancerosas que afectan esófago, pulmón, próstata, vejiga, etc. Des del punto de vista ginecológico, varios estudios confirman su eficacia en el tratamiento de lesiones endometriales benignas y malignas, disminuyendo los efectos adversos ocasionados por los progestágenos orales y mejorando o equiparando la tasa de respuesta y recurrencia.

Aunque la incidencia de pacientes jóvenes con cáncer de endometrio estadio 1A G1/G2 y deseo genésico es reducida, su tratamiento supone un reto. El retraso de la maternidad y la evidencia científica que algunos factores asociados a la infertilidad también se asocian con el cáncer de endometrio incrementa su aparición durante la edad fértil. Por este motivo, este ensayo clínico pretende comparar ambos, analizando diferentes parámetros, con el objetivo reducir el tiempo de visita, mejorar el posoperatorio, pronóstico y tasa de gestación de este tipo de pacientes.

METODOLOGÍA E INTERVENCIÓN

En este estudio participarán un total de 430 pacientes, las cuáles, serán distribuidas aleatoriamente en uno de los dos grupos del estudio, de igual tamaño (grupo A y B):

- A los pacientes del grupo A se les administrarán progestágenos orales.
- A los pacientes del grupo B se les administrará terapia fotodinámica.

Una vez cumplido el deseo genésico de la paciente, independientemente del grupo de estudio del que formen parte, deberá efectuarse la histerectomía más doble anexectomía. Este tratamiento será decidido por el comité multidisciplinar del centro hospitalario al que pertenezca, tal y como se procedería en caso de no participar en ningún estudio. Los pacientes serán seguidos por la Unidad de Ginecología y Obstetricia de cada hospital.

BENEFICIOS Y RIESGOS DEL ESTUDIO

El principal beneficio que se espera para las pacientes participantes de este estudio es reducir los efectos adversos ocasionados por el tratamiento hormonal administrado para preservar la fertilidad en pacientes jóvenes con carcinoma endometrial estadio 1ª, G1/G2, sin afectación miometrial ni presencia de factores genéticos asociados.

Por este motivo, proponemos un nuevo procedimiento mínimamente invasivo, la terapia fotodinámica, la cuál es utilizada en otros servicios médicos obteniendo exitosos resultados.
Además, para asegurar no perjudicar la salud de los pacientes participantes, seleccionamos a los individuos que pueden participar en el ensayo mediante criterios de inclusión y exclusión estrictos.
Para evitar la progresión tumoral hacia otros tejidos, si no remite el tumor 6 meses después de recibir el tratamiento, deberá desestimarse su participación en el estudio y efectuarse el tratamiento quirúrgico (histerectomía y salpingo-ooforectomía).

ALTERNATIVAS AL PROCEDIMIENTO

Si el paciente decide no participar en el ensayo clínico, será tratado mediante progestágenos orales (tratamiento estandarizado).
En referencia al seguimiento, el paciente que decida no participar en el estudio recibirá también la misma atención que aquél que sí participe, con las visitas de seguimiento y pruebas de imagen adecuadas.

CONFIDENCIALIDAD

Desde el principio de su participación en este estudio, todos los datos personales que se recojan serán gestionados y almacenados con total confidencialidad, ajustándose a la legislación actual de la Ley Orgánica 3/2018, de 5 de diciembre, de Protección de datos personales y garantía de los derechos digitales. Esta información será identificada con un número y sólo se utilizará con fines de investigación.
El acceso a la información sólo estará disponible para investigadores y otras autoridades sanitarias. El paciente tiene derecho a poder consultar la información recopilada sobre él y corregirla en caso de error. Garantizamos que ninguna información personal será publicada.

DIFUSIÓN DE LOS RESULTADOS

Cuando haya finalizado el estudio y se hayan extraído conclusiones, la intención es publicar estos resultados obtenidos en revistas científicas. De esta forma, otros centros asistenciales y pacientes en la misma situación podrán beneficiarse. Tal y como se ha comentado anteriormente, en estas publicaciones no constará ningún dato personal.

PARTICIPACIÓN Y COMPENSACIÓN ECONÓMICA

Los investigadores de este estudio no obtienen beneficio económico. Su participación como paciente en este estudio es estrictamente voluntaria, por lo que si decide participar no recibirá ningún tipo de compensación económica, pero tampoco le supondrá gasto alguno. En caso de no querer participar, tampoco le supondrá ningún cambio en cuanto a su atención médica por el equipo de especialistas.

Si usted decide participar, deberá firmar la hoja de consentimiento informado conforme da su aprobación.

También está usted en su derecho a salir del estudio si en cualquier momento de su transcurso así lo decide, no alterando esto tampoco su atención médica, aunque le pedimos que lo comunique a alguno de los profesionales del Servicio de Ginecología y Obstetricia del hospital de referencia donde se visitará.
Antes de decidir sobre su participación, usted está libre de pedir una segunda opinión a otros profesionales médicos si así lo requiere.

RESPONSABILIDAD Y SEGURO

Los promotores de este estudio tienen contratada una póliza de seguro para su realización, tal y como se establece en la legislación. En caso de perjuicio o detrimento de su salud como consecuencia de su participación en este estudio, se le proporcionará la correspondiente indemnización.

CONTACTO

En caso de cualquier duda antes, durante o después de la realización de este estudio, podrá ponerse en contacto siempre que lo necesite con:

_____

Anexo 7: Informed consent of the patient

DOCUMENTO DE CONSENTIMIENTO INFORMADO DE LA PACIENTE

Yo, _____, con documento de identificación personal (DNI/NIE) _____, declaro que:

- He recibido una copia de la hoja de información para el paciente
- He leído y entendido toda la información que aparece en la hoja de información para el paciente.
- He podido exponer cualquier duda que me haya salido, y me la han resuelto adecuadamente.
- Estoy de acuerdo con la cantidad de información que se me ha proporcionado.
- Comprendo que mi participación es voluntaria y no remunerada.
- Entiendo los potenciales riesgos y beneficios derivados de participar en este estudio.
- Comprendo que mis datos y pruebas serán confidenciales.

Además, comprendo que a pesar de haber firmado el consentimiento informado, puedo revocarlo en cualquier momento y que esto no supondrá un perjuicio en mi tratamiento ni en la asistencia sanitaria.

En consecuencia,

- Doy libremente mi conformidad a participar en el estudio *Terapia fotodinámica como alternativa a los progestágenos orales en el tratamiento del carcinoma endometrial 1A, G1/G2 en pacientes con deseo genésico.*
- Acepto que los investigadores del proyecto puedan ponerse en contacto conmigo en un futuro si se considera oportuno.

☐ Sí ☐ No

Firma del paciente **Firma del investigador**

Lugar y fecha: _____, ____ de _____ del año _____

REVOCACIÓN DEL CONSENTIMIENTO INFORMADO

Yo, _____, con documento de identificación personal (DNI/NIE) _____, revoco el consentimiento previamente firmado para la participación en el ensayo clínico: *Terapia fotodinámica como alternativa a los progestágenos orales en el tratamiento del carcinoma endometrial 1A, G1/G2 en pacientes con deseo genésico.*

Firma del paciente **Firma del investigador**

Lugar y fecha: _____, ____ de _____ del año _____