UNIVERSITAT DE GIRONA

"Dienogest versus Ethinylestradiol/Dienogest in patients with secondary dysmenorrhea due to clinical diagnosis of ovarian endometriosis"

A multicentric, prospective, controlled study

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ABSTRACT

TITLE

Dienogest versus Ethinylestradiol/Dienogest in patients with secondary dysmenorrhea due to clinical diagnosis of ovarian endometriosis.

BACKGROUND

Endometriosis is a common gynecological condition, affecting an estimated 10% of reproductive age women. Endometriosis can be a debilitating disease for women who experience painful symptoms such as dysmenorrhea, which may have a negative impact on the woman's quality of life. There is no cure for endometriosis; management consists of alleviating pain and other symptoms, reducing endometriotic lesions and improving quality of life. While dienogest is a specific treatment for endometriosis, combined oral contraceptives like ethinylestradiol/dienogest are used off-label for this pathology and contains estrogens despite the fact that endometriosis is an estrogen-dependent disease.

OBJECTIVES

The aim of the study is to evaluate the efficacy of dienogest in contrast to ethinylestradiol/dienogest in secondary dysmenorrhea due to clinical diagnosis of ovarian endometriosis in order to find out if dienogest is more effective in reducing dysmenorrhea, intake of analgesics and endometrioma's size, and in improving health-related quality of life compared to ethinylestradiol/dienogest.

DESIGN

A prospective, controlled, interventional and multicentric study. 264 patients from our reference ASSIR, will be divided in two groups, receiving with double-blind and a randomized distribution of the sample, dienogest or ethinylestradiol/dienogest during 1 year, for the management of secondary dysmenorrhea due clinical diagnosis of ovarian endometriosis.

KEY WORDS

Dysmenorrhea, Treatment, Endometriosis, Dienogest, Ethinylestradiol/Dienogest

INTRODUCTION

BACKGROUND

Endometriosis is a common, benign, estrogen-dependent and inflammatory disorder described as the presence of endometrial tissue (glands and stroma) at extrauterine sites. This endometrium is capable to grow, to infiltrate and even to disseminate in a similar way to the tumor tissue; nevertheless, malignant transformation is unusual**.** It's a chronic disease whose cause is unknown, although some genetic predisposition is proven (1–4)**.**

The most frequent locations affected by endometriosis are the ovaries and pelvic peritoneum, although it can be occasionally found in many other parts such as the bowel, bladder, stomach, lung, etc (5).

It is difficult to determine the prevalence of endometriosis because of the variety of the symptoms and their severity and because it may be asymptomatic. It's estimated to affect approximately 10% in reproductive age women although the percentage is higher in infertile women and those with chronic pelvic pain; between 30-80% and 20-50% respectively (5–7). In Spain, endometriosis is estimated to affect over a million women, and 170 million over the world (8).

This gynecologic pathology is associated with persistent pelvic pain and/or infertility, so it poses a significant public health problem. It not only affects health, well-being and quality of life of patients, but has also great impacts on daily life, work absenteeism and health care consumption (4).

The incidence is higher between 30-45 years, being uncommon in premenarcheal and postmenopause women (9). Incidence of endometriosis is believed to be increasing because of changes in women's lifestyle, such as the tendency to marry later and have fewer children. This life style change increases the number of times a woman menstruates and affects the incidence of endometriosis (10).

Endometriosis is considered a dynamic pathology with a percentage of evolution from 50% to 60%, a spontaneous regression from 10% to 20 % and without modification in the remaining 15-20% (11).

PHYSIOPATHOLOGY

ETIOLOGY

The pathophysiology of endometriosis is still unknown, although many theories have been described to address this issue (12,13):

- Retrograde menstruation (Sampson's theory): It's the oldest and most accepted theory. Suggests that endometrial cells dropped into the uterus during menstruation are transported through the fallopian tubes, entering and implanting on pelvic structures. Endometriosis seems to occur most commonly in the gravitationally dependent parts of the pelvis. Also, the incidence of endometriosis is increased in patients with mullerian anomalies or genital tract obstructions.
- Vascular and lymphatic spread (Halban's theory): suggests that endometrial cells can spread to ectopic locations via lymphatic and hematogenous spread, which explains the presence of endometriosis in distant sites outside the pelvis, including the brain, lung, lymph nodes, extremities, and the abdominal wall.
- Coelomic metaplasia (Meyer's theory): This theory proposes that the coelomic (peritoneal) cavity contains undifferentiated cells able of dedifferentiating into endometrial-type tissue. This seems to be logical, as cells from both the peritoneum and endometrium are the results from a common embryological precursor: the coelomic cell.

ALTERED HORMONAL MILIEU

Hormonal alterations may influence the ability of endometrial cells to proliferate, enclose to the mesothelium and avoid immune mediated clearance. Estrogens seem to have a causal relationship with endometriosis.

Endometriosis implants express aromatase and dehydrogenase of 17β-hydroxysteroid type 1 (17β-HSD 1), which are the enzymes that transform androstenedione to estrone and estrone to estradiol, respectively. Simultaneously, there is a deficiency of dehydrogenase of 17β-hydroxysteroid type 2 (17β HSD-2), which transforms estradiol to estrone, a less potent estrogen.

The consequence of this differential expression profile (17β HSD-1>17β HSD-2) is an increase in the locally bioavailable estradiol concentration. Estradiol stimulates the production of prostaglandin E2 (PGE2) which stimulates aromatase activity. These findings sustain the capacity of endometriotic lesions for estradiol biosynthesis, and justify treatments aimed at promoting a hypoestrogenic peritoneal environment (13,14).

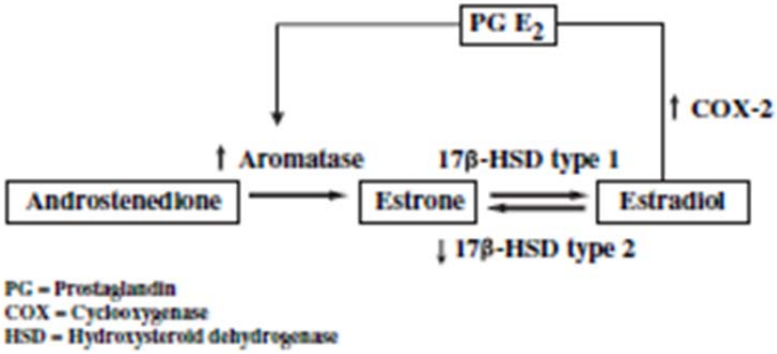


Figure 1 Pathophysiology of Endometriosis (15).

Estradiol produced by increased aromatase activity, raises the production of PGE2 due to the cyclooxygenase 2 (COX-2) stimuli in the endometrial cells originating a positive feedback, accentuating estrogenic effects on the production of endometriosis (*Figure 1*).

IMMUNE SYSTEM

Studies suggest that deficient cellular immunity results in an inability to recognize the presence of endometrial tissue in abnormal locations. There is evidence for altered humoral and cell-mediated immunity in the pathogenesis of endometriosis:

- Deficient cellular immunity may result in an inability to recognize the presence of endometrial tissue in abnormal locations.
- Natural killer (NK) cell activity may be reduced, resulting in decreased cytotoxicity to autologous endometrium.
- An increased concentration of leukocytes and macrophages in the peritoneal cavity and ectopic endometrium. These cells secrete cytokines (eg, interleukin-1, 6, and 8; tumor necrosis factors) and growth factors into the peritoneal fluid of women with endometriosis. It is uncertain whether this increase in leukocytes is the cause or effect of changes associated with endometriosis.

A survey of patients who are members of the Endometriosis Association found that these women had higher rates of autoimmune inflammatory diseases, hypothyroidism, fibromyalgia, chronic fatigue syndrome, allergies, and asthma, when compared with the general female population. If this association is confirmed in controlled studies, it provides support for the theory of altered immune surveillance in women who develop endometriosis (16–18).

RISK FACTORS (17,19)

Some increased risk factors are: early age at menarche, shorter menstrual cycle, hypermenorrhea, nulliparity, mullerian anomalies, Caucasian and Asian women, infertility, red hair, birth weight (<2'5 kg), diethylstilbestrol (DES) exposure, endometriosis in first degree relative, dioxin/polychlorinated biphenyl (PCB) exposure, diet high in fat and red meat, inmune disorders, high revised American Fertility Society score (rAFS), prior surgeries or medical therapy.

Some protective factors: multiple births, extended intervals of lactation, Increased Body Mass Index (BMI), increased waist-to-hip ratios, late menarche (after age 14 years), exercise, diet high in vegetables/fruits, Hispanic and black women.

CLASIFICATION AND LOCATION

CLASSIFICATION

The most used system was introduced by the American Society of Reproductive Medicine (ASRM), which classifies endometriosis depending on the location, the extent and the depth of endometriosis implants; presence and severity of adhesions; and presence and size of ovarian endometriomas. According to ASRM, there are four stages (*Table 1*): stage I (minimal), stage II (mild), stage III (moderate), stage IV (severe) (20). However this classification doesn't refer to pelvic pain or possible recurrences, and it doesn't have a prognostic value of fertility (16).

Stage	Disease	Description
I	Minimal	A few superficial implants
II	Mild	More and slightly deeper implants
III	Moderate	Many deep implants, small endometriomas on one or both ovaries, and some filmy adhesions
IV	Severe	Many deep implants, large endometriomas on one or both ovaries, and many dense adhesions, sometimes with the rectum adhering to the back of the uterus

Table 1 Stages of endometriosis (20)

LOCATION

The most common sites of endometriosis are, in decreasing order of frequency, the ovaries, anterior and posterior cul-de-sac, posterior broad ligaments, uterosacral ligaments, uterus, fallopian tubes, sigmoid colon, appendix, and round ligaments (18).

Multiple types and locations often coexist in the same patient. Four different endometriosis phenotypes can be distinguished according to whether the endometriotic lesions are located (4):

- Ovarian endometrioma (OMA): Ectopic endometrial tissue within the ovary. OMA is the most common site of endometriosis, affecting 55% of patients with endometriosis (6,21). OMA seems to be the most frequently diagnosed variant of endometriosis, maybe because of the relative ease and accuracy in detecting this phenotype with the ultrasound.
- Superficial peritoneal endometriosis (SUP): ectopic endometrial tissue in peritoneum.
- Deep infiltrating endometriosis (DIE): ectopic endometrial tissue infiltrating to a depth of at least 5mm beneath the peritoneal surface.
- Adenomyosis: endometrial stroma and glands in the myometrium.

DIAGNOSIS EVALUATION

Diagnosis based on symptoms can be difficult due to overlap with other processes and symptomatic variability. This leads to underdiagnosis or bad labeling of the process. The delay in the diagnosis of endometriosis is frequent; in Spain it's estimated a delay of 8 years (22). Diagnosis options include:

- History: the history should include the presence and severity of symptoms, concerning about the impact of symptomatology on quality of life, since this helps to guide treatment decisions.
- Physical examination: physical examination during menstruation helps to make the diagnosis. The combination of a fixed, retroverted uterus, adnexal and uterine tenderness, pain with movement of the uterus, pelvic masses or nodularity along the uterosacral ligaments indicates a high probability of endometriosis (20).
- Laboratory evaluation: levels of CA125 are elevated in malignant gynecologic disorders and it can also be raised in endometriosis, especially in moderate-severe endometriosis. Nevertheless CA-125 levels don't have value as a diagnostic tool (9), although it can be useful for the assessment of endometriosis progression.
- Imaging studies: ultrasound is the first-line study for pelvic imaging. Other imaging techniques include nuclear magnetic resonance or computerized axial tomography.
- Complementary methods: cistoscopy, colonoscopy, contrasted studies, bronchonscopy, etc. Gonadotropin-releasing hormone (GnRH) analogues can be useful for diagnosis with the aim to avoid diagnostic laparoscopy.
- Laparoscopy: currently is the gold standard for the diagnosis of endometriosis. A definitive diagnosis is made with biopsy and histological demonstration of ectopic endometrial tissue. A diagnosis made by visual inspection of lesions is also considered satisfactory. If surgery is proceeding for diagnosis, we ask for the consent for surgical treatment at the same time if necessary.

Because a reliable nonsurgical diagnosis of endometriosis is possible and should be pursued, although laparoscopy is the gold standard, the SEGO (Sociedad Española de Ginecología y Obstetricia) recommends history and physical examination plus transvaginal ultrasound (TVS) as a first-line diagnostic modality, which is correct in 78-87% of cases (9); leaving laparoscopy whenever it's indicated for therapeutic purposes (23). Summarizing, diagnosis of endometriosis in primary care is predominantly clinical.

SYMPTOMS

Clinical manifestation of endometriosis is diverse and there may be an overlap with other pathologies such as irritable bowel syndrome or pelvic inflammatory disease. Therefore, it can lead to a delay of several years in the definitive diagnosis. Besides, 15-30% of patients with endometriosis are asymptomatic and endometriosis may be diagnosed incidentally with a finding of an ovarian endometrioma on imaging or endometrial lesions at time of surgery for another indication (5).
In symptomatic women, most common symptoms are:

- Pain in form of dysmenorrhea, chronic pelvic pain, dyspareunia, dysuria, dyschezia.
- Infertility in reproductive-age women.

Intensity of the symptoms is not related, in some cases, to the anatomical extent of the disease, except in DIE. In addition to these symptoms, women with endometriosis may have other non-gynecological symptoms such as digestive, vesicular or pulmonary symptoms, abdominal or back pain, bleeding (rectal bleeding, hemoptysis), etc. Generally, symptoms are more intense during the menstrual period and improve after menopause and during gestation (17,18).

The disease is also associated with an increased prevalence of depression, reduction in sexual satisfaction, disrupted personal relations, and loss of work leading to substantial economic cost (12).

Dysmenorrhea is the most common symptom of endometriosis and can seriously affect the quality of life of women and their mental and emotional health (24). When associated with endometriosis, it's a dull or crampy pelvic pain that interferes with daily activity, and typically begins one to two days before menses and then persists throughout menses, sometimes for several days afterward. Associated general symptoms, such as nausea, vomiting, lumbago, diarrhea, and headache are also common (10,17) .

The prevalence of dysmenorrhea reported in the literature varies considerably. A greater prevalence was generally observed in young women, with estimates ranging from 67% to 90% for those aged 17–24 years (25).

TREATMENT

At the present, there is no causative treatment for endometriosis, so the real objectives of the treatment are the reduction or elimination of symptoms and/or fertility improvement.

Management of endometriosis can be expectant, medical or surgical, depending on the patient's choice, age, childbearing desire, previous treatments, nature or severity of symptoms, location and severity of the disease; so it's difficult to generalize the actions, being necessary and individualized attention.
Medical therapies control but do not cure the disease, therefore long periods of pharmacologic management may be needed until pregnancy desire or, sometimes, physiologic menopause.

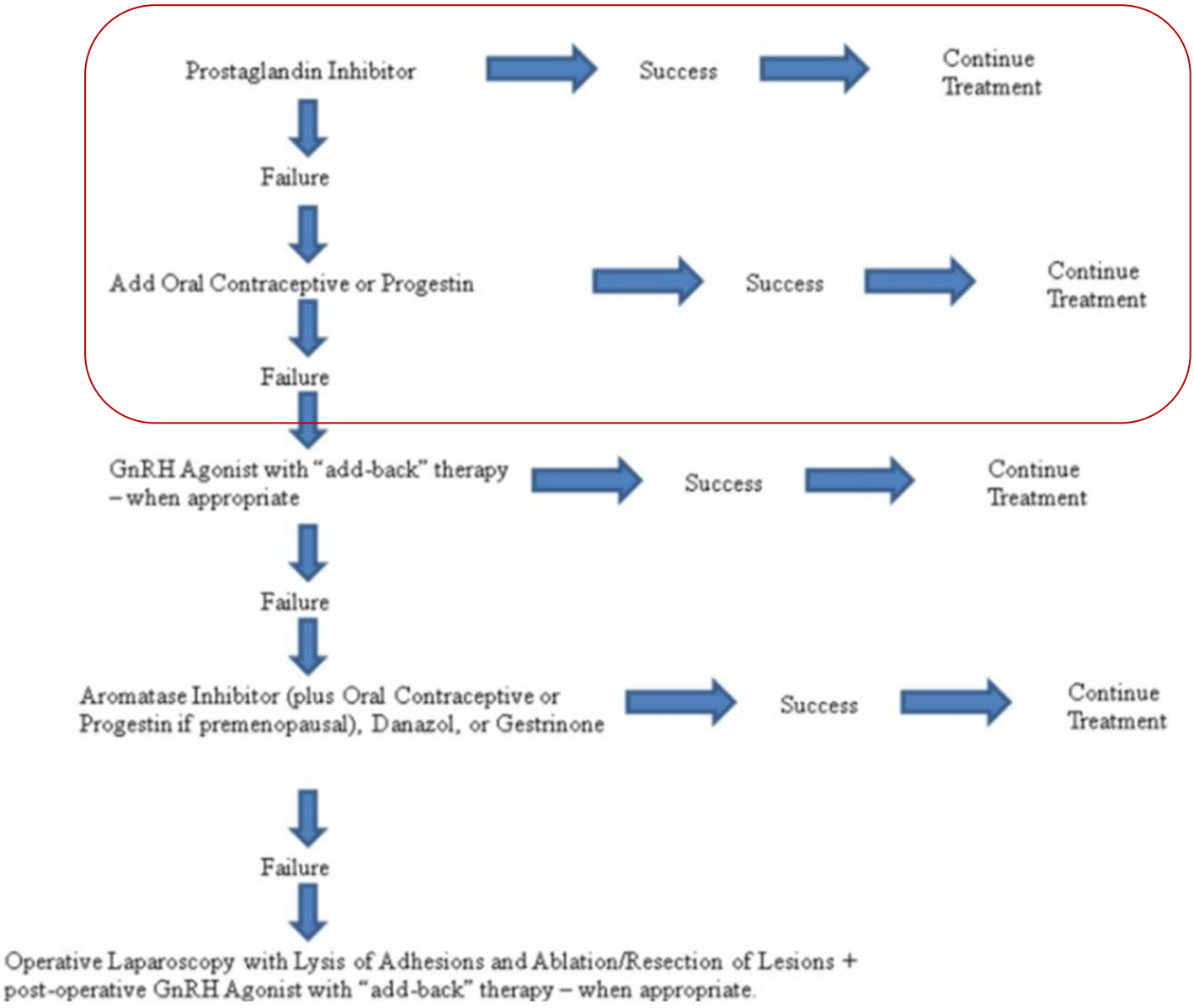
Medical treatment reduces or disappear symptoms in the majority of the patients, although recurrences are common if it is interrupted.
According to the ASRM, ''endometriosis should be viewed as a chronic disease that requires a life-long management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures'' (23).

Main therapeutic procedures include medical or surgical treatments, alternative treatments like acupuncture and a combination of treatments (11):

MEDICAL TREATMENT**:** it's offered first, reserving surgery for resistant or recurrent cases.

- Pain: treatment of pain is divided in first and second line therapy. It includes analgesics, mostly nonsteroidal anti-inflammatory drugs (NSAIDS), and hormonal treatment (Algorithm 1). The most effective medical therapy is the hormonal treatment. Because dysmenorrhea is one of the most common complaints in women with endometriosis, many of the hormonal agents aim to cause amenorrhea. Medications used in endometriosis are (6) (Annex 1):
    - Hormonal
        - Combined Oral Contraceptives
        - Progestins
        - GnRH agonists
        - Gestrinona
    - Non-hormonal
        - Prostaglandin Inhibitors
        - Aromatase Inhibitors
        - Danazol

- Subfertility: in patients with endometriosis and associated infertility, assisted reproductive technology (ART), like in-vitro fertilization (IVF) or intrauterine insemination, are recommended according to age, infertility duration, severity and extent of disease, surgical history, ovarian reserve markers and the ART previously done. It is recommended the use of GnRH analogues between 3-6 months before IVF, enhancing gestation probability x4.



Algorithm 1 Treatment algorithm for pain associated with endometriosis (26)

Because the main objective of our study is the improvement of dysmenorrhea, we will focus on treatment of pain:

First-line treatment of pain

Initial treatment includes analgesics, mainly nonsteroidal anti-inflammatory (NSAIDS) drugs, combination estrogen/progestin contraceptives, or progestin-only contraceptives. Only estrogen/progestins and progestins have safety/tolerability/cost profiles that allow long-term use; both compounds induce atrophy of eutopic and ectopic endometrium and have antiinflamatory and proapoptotic properties (23,27).

- **Analgesics:** NSAIDS are the most commonly used first-line treatment for endometriosis. The release of prostaglandins (PGs) in ectopic endometrial cells is involved in the pathogenesis of endometriosis. NSAIDS interfere with the function of the enzyme cyclooxigenase type 1 (COX-1) and cyclooxigenase type (COX-2), inhibiting the production of PGs, which are involved in the genesis of endometriosis-associated pain. However, there is inconclusive evidence to demonstrate whether or not they are effective in relieving pain associated with endometriosis (27,28). A major limitation to the long-term use of NSAIDS drugs is their significant gastrointestinal, cardiovascular and renal, among others, side effects.

- **Combined oral contraceptives (COCs):** COCs are hormonal treatments containing synthetic estrogen and progestin. They are used next if pain relief has not been achieved, and they may be used alone or in combination with NSAIDs (29). Despite there are no differences between cyclic and continuous administration in terms of side effects and metabolic profile, women are usually counseled to take COCs in cyclic use (intake for 21 days of active pill plus 7 days of placebo) , and in case of inefficacy, continuous use (intake of only active pill without hormone-free interval). COCs are widely used to treat the symptoms of endometriosis, although they are not approved for this indication in the majority of countries because of the absence of supportive trial evidence (30–32).

- ***ETHINYLESTRADIOL/DIENOGEST (EE/DNG)***

EE/DNG is a COCs with an anti-androgenic effect whose estrogenic component is ethinylestradiol (EE) and whose progesterone component is dienogest (DNG).
Its main mechanism of action is the inhibition of ovulation and changes in vaginal secretion. The anti-androgenic effect of the combination of EE and DNG is based on the reduction of serum androgen levels.

Mechanism of action of EE/DNG:

- Estrogen and progesterone causes suppression of gonadotropins via a negative feedback on GnRH in the hypothalamus.
- Prevents ovulation.
- Causes endometrial atrophy.
- Relieves pain by thinning of endometrial lining and causing regression of the endometriotic implants, especially in continuous use.

The effect of progestin prevails over the effect of estrogen, so most of these actions are realized by DNG.
On the other hand, EE is a very powerful oral synthetic estrogen. Given alone, EE has a proliferative effect on the epithelial tissues of the female genital organs, which includes both the glands and stroma of eutopic and ectopic endometrium. EE affects the parameters of lipid and carbohydrate metabolism, hemostasis, renin-angiotensin-aldosterone system and serum-binding proteins. Estrogen dose correlates with efficacy, adverse events and numerous side effects.
Nevertheless, COCs in continuous use have proven to be effective for reduction pain-related symptoms, as well as in decreasing the ovarian endometrioma size and improving QoL. It also has beneficial effects on hair and skin (27,33).

At the moment, it is not clear whether the efficacy of DNG in the treatment of pain associated with endometriosis could be eliminated by the addition of an estrogenic component (31, 33,34).

Side effects: the most common (1 of 10 patients) frequently reported side effects during treatment are breast pain, discomfort or tenderness, and headache. Some of the uncommon (1 of 100 patients) side effects are weight gain, headache, migraine, irregular menstrual periods, nausea/vomiting, acne, hyper/hypotension. The risk of thrombosis is rare (1 of 1.000 patients) but severe, and it's associated more with EE dose than with the progestin type contained (34).

- **Progestins**: Progestin therapy is frequently used for patients with symptomatic endometriosis, and is typically considered when COCs are contraindicated, lead to intolerable side effects, or fail to improve pain. While COCs are used off-label for endometriosis, DNG (*Visannette* ®) is a specific and approved treatment for endometriosis.

- ***DIENOGEST*** (***Visannette*** ®)

DNG is the most recent member of the synthetic progestogen family acting as a specific progesterone receptor agonist.
It's a derivative of 19-nortestosterone that combines the pharmacological properties of 19-nortestosterone derivatives with those of natural progesterone derivatives. It shows a high selectivity for the progesteron receptors and a powerful progestinic effect on the endometrium.
DNG combines several beneficial effects, apart from the high specificity for the progesterone receptor, like negligible binding affinities for estrogen, androgen, glucocorticoid and mineral-corticoid receptor.
Its anti-androgenic properties cause minimal changes in serum lipid profile and carbohydrates metabolism.

Mechanism of action of DNG:

- Decreases estrogen levels in endometriotic tissue, through inhibition of aromatase and 17β-HSD type 1 in stromal cells, therefore, suppresses the trophic effects of estradiol both in eutopic and ectopic endometrium.
- Increases apoptosis of endometriotic cells.
- Reduces the production of pro-inflammatory cytokines by endometriotic stromal cells.
- Decreases the production and release of estradiol-induced angiogenic factors such as vascular endothelial growth factor and stromal cell-derived factor in endometrial stromal cells.

When administered in continuous use, DNG leads to a hypoestrogenic and hypergestogenic endocrine environment, producing first the decidualization of endometrial tissue, followed by atrophy of the endometrial lesions. That's the reason why will assess the evolution of OMA in our study.

In our study, the dose of DNG will be 2mg, as DNG doses of 2 and 4 mg/day have been studied and they suggested a more favorable pharmacologic profile for the 2 mg dose: on one hand, this dose seems able to suppress estrogen levels sufficiently to inhibit endometriotic lesion growth; on the other hand, it is adequate to prevent hypoestrogenic side effects, such as bone mineral loss (27,29,36,37).

Side effects: the most common (between 1 and 10 of 100 patients) side effects are weight gain, depressed mood, headache or migraine, nausea/vomiting, acne, back pain, breast pain. Some of the uncommon side effects (between 1 and 10 of 10.000 patients) are anemia, anxiety, hypotension, nonspecific circulatory problems, breathing difficulties, tinnitus, diarrhea, hirsutism (37).

Second-line treatment of pain

In endometriosis, a drug is considered as second-line when use is subject to failure or intolerance of previous first-line treatments. Second-line drugs consist of GnRH analogs, gestrinone, danazol and aromatase inhibitors. Due to their side effects, they should be prescribed to women for whom other treatments have proven ineffective.

SURGICAL TREATMENT: each type of endometriosis (OMA, SUP and DIE) has its own indications. The general indications for surgery include (7):

- Failure of medical therapy to ameliorate symptoms.
- Women who decline or have contraindications to medical therapy.
- Need for a definitive diagnosis of endometriosis (for example: if empirical treatment with first-line therapies fails, a definitive diagnosis is preferred prior to treating with therapies difficult to tolerate and/or have potential adverse effects).
- Exclude malignancy in an adnexal mass.
- Treatment of infertility in selected women.
- Obstruction of the urinary tract or bowel.

JUSTIFICATION

Endometriosis is a common disease with a difficult management due to its chronic and recurrent nature. There is no cure for endometriosis; it requires a treatment plan with the objective of maximizing the use of medical treatment and avoiding repeated surgical procedures since recurrence after surgical intervention is common.
The treatment is mainly aimed at alleviating pain and other symptoms, reducing endometriotic lesions, and improving quality of life.

The symptoms of endometriosis impact on many aspects of a woman's life, including work, education, relationships, and social functioning. As symptoms become more severe, quality of life (QoL) is further reduced. Endometriosis also impacts on mental health, with depressive symptoms and anxiety. Impairment in quality of life represents a substantial economic burden to patients, families and society.

A study published in 2012 showed that delays in diagnosis, high rates of hospital admission, surgical procedures, and incidences of comorbid conditions contribute to make endometriosis a more costly public health problem than other chronic conditions such as migraine or Crohn's disease. It arises predominantly from productivity loss, and is predicted by decreased quality of life, with an average annual cost per patient around 10.000 euros (38).

Because dysmenorrhea is the most common gynecologic complaint in patients with endometriosis (24,39,40) and endometriosis is one of the main causes of secondary dysmenorrhea, it's important to study which treatment improves the best both symptom and disease.

Several medical treatments are adopted to treat endometriosis. Among them, analgesics, combined oral contraceptives and progestins may be used as first-line therapy for endometriosis-related pain symptoms like dysmenorrhea.

Analgesics are the most commonly used first-line treatment for endometriosis, although clinical trial evidence to support the efficacy of these agents in endometriosis is lacking.

While combined oral contraceptives are widely used to treat the symptoms of endometriosis, although they are not approved for this indication, Dienogest is a progestin specifically investigated for endometriosis treatment.

Despite accumulating evidence suggests that Dienogest has a favorable safety profile, a systematic review (41) found a lack of studies comparing Dienogest with first-line therapy, such as progestins and estrogen–progestogen combinations, including Ethinylestradiol/Dienogest.

Furthermore, endometriosis is an estrogen-dependent pathology and many experts opine estrogen should be avoided for its treatment (36,42).
In patients with endometriosis, it's still unknown if the administration of estrogens should be completely avoided or it could be permitted in low dosages.

Studies with Dienogest proved to be effective for reducing dysmenorrhea, endometriotic lesions and consumption of analgesics, in adittion to improve quality of life (32,35,39). What it's not clear whether the efficacy of Dienogest in the treatment of pain associated with endometriosis could be eliminated by the addition of an estrogenic component.

In conclusion, the aim of the study is to compare at our reference ASSIR [1](Atenció a la Salut Sexual I Reproductiva) Dienogest with Ethinylestradiol/Dienogest in women with secondary dysmenorrhea due to ovarian endometriosis clinical suspicion, to asses if progestin only-pills are a better option than adding estrogen to the treatment. Taking advantage of our following study, it will be useful to assess if progestin-only pills are more effective at reducing analgesia consumption and endometriotic lesions, as well as at improving quality of life.

[1] Our reference ASSIR is the ASSIR Gironès-Pla de l'Estany, which includes the population of Girona, Sarrià de Ter, Celrà and Banyoles.

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HYPOTHESIS

- Dienogest treatment in patients with clinical diagnosis of ovarian endometriosis will be superior in reducing dysmenorrhea compared to ethinylestradiol/dienogest.

- Dienogest treatment in patients with clinical diagnosis of ovarian endometriosis will decrease the intake of analgesia compared to ethinylestradiol/dienogest combined pills.

- Dienogest treatment in patients with clinical diagnosis of ovarian endometriosis will improve the health-related quality of life compared to ethinylestradiol/dienogest combined pills.

- Dienogest treatment in patients with clinical diagnosis of ovarian endometriosis will be superior in reducing endometrioma's size compared to ethinylestradiol/dienogest combined pills.

OBJECTIVES

MAIN OBJECTIVE

The principal aim of this project is:

- To evaluate the efficacy of dienogest compared to ethinylestradiol/dienogest, both in continuous use, in reducing dysmenorrhea in women with a clinical diagnosis of ovarian endometriosis in the reference centers included in the ASSIR Gironès-Pla de l'Estany.

SECONDARY OBJECTIVES

- To evaluate if dienogest is superior in reducing the use of analgesia compared to ethinylestradiol/dienogest.

- To evaluate if dienogest is superior in improving the health-related quality of life compared to ethinylestradiol/dienogest.

- To evaluate if dienogest is superior in reducing endometrioma's size compared to ethinylestradiol/dienogest.

METHODS

STUDY DESIGN

The study will be prospective, multicentric, controlled and randomized. The intervention model will be parallel assignment in 2 groups and the masking will be double blind. Each patient will be randomly assigned in a ratio 1:1 to receive monophasic COC (ethinylestradiol 0'03mg plus dienogest 2 mg) or monophasic progestin (dienogest 2 mg). Treatment will begin on the first day of the menstrual cycle and the treatment period will have a fixed time of 48 weeks for all patients. During treatment, a follow up period every 3 months will be performed.

The COC and the progestin will be prepared by the manufacturer in 28-day blister packs and will appear identical. The use of analgesic agents are allowed, but other hormonal treatments for pain or vaginal bleeding are prohibited.

STUDY POPULATION

This is a multicenter study; the sample will be extracted from all the patients who fulfill the inclusion criteria.

INCLUSION CRITERIA

- Patients consulting for moderate dysmenorrhea and a clinical diagnosis of ovarian endometriosis.
- Age ranging from 18 to 35 years.
- VAS scale ranging from 4 to 6.
- Understanding and accepting the purpose of this study signing the informed consent.

EXCLUSION CRITERIA

- Other causes of secondary dysmenorrhea.
- Endometriomas > 4 cm.
- < 18 and > 35 years.
- Gestational desire at the time of the treatment.
- Smokers.
- Mild and severe dysmenorrhea (VAS scale < 4 and > 6).
- Need for primary surgical treatment of endometriosis.
- Abnormal findings on gynecological examination other than endometriosis.
- Contraindications of estrogens and progestin.
- Hypertension.

SAMPLE SELECTION

The selection of the population will be performed as a consecutive non-probabilistic sample of women with a clinical diagnosis of ovarian endometriosis complaining for moderate dysmenorrhea. We will select the patients who fulfill the criteria as they consult to the doctor. Patients will be given all the information and the information sheet (Annex 2). Then, they will be asked to participate in the study and will have to sign the informed consent (Annex 3).

SAMPLE SIZE

Accepting an alpha risk of 0'05 and a beta risk of 0'20 in a bilateral contrast, with a reason between the samples equal 1 and an anticipated drop-out rate of 10%, we will need 132 patients in each group to achieve a difference statistically significant, with 264 patients in total.

STUDY INTERVENTIONS

Patients who respect inclusion and exclusion criteria will receive one of those followings therapies for secondary dysmenorrhea due to clinical diagnosis of ovarian endometriosis:

- Ethinylestradiol/Dienogest 0'3mg/2mg
- Dienogest 2mg

STUDY VARIABLES

DEPENDENT

Dysmenorrhea

The main dependent variable of this study is dysmenorrhea, defined as painful menstruation. Patient's dysmenorrhea will be evaluated at months 0, 3, 6, 9 and 12 employing a 10 cm visual analog scale (VAS). VAS grades dysmenorrhea in four groups:

- Absent: 0 cm
- Mild: 1 to 3 cm
- Moderate: 4 to 6 cm
- Severe: 7 to 10 cm

During the study, patients scoring their dysmenorrhea > 6 will be excluded because of the need of carry out more tests. It will be measured at the screening and at each visit of the patient. This main variable is an ordinal categorical variable.

Analgesia consumption: Analgesia consumption is defined as the quantity of days a patient will consume analgesics during one cycle. The use of analgesics will be scored as:

- None: none analgesic use
- Mild: take analgesics for 1 day
- Moderate: take analgesics for 2 days
- Severe: take analgesics for ≥3 days.

It will be evaluated at months 0, 3, 6, 9 and 12. This variable is an ordinal categorical variable.

Health-related quality of life (HR-QoL): HRQoL is defined as a patient's perceived physical and mental health overtime. It will be measured at months 0, 3, 6, 9 and 12 with the Short Form Health Survey (SF-36), a generic questionnaire which includes 36 items. According to the Rand group punctuation, the answers will be transformed on a scale of 0 to 100 where 0 is the worst and 100 the best state of health. HRQoL is a discrete quantitative variable.

Endometrioma's size: OMA will be diagnosed with the ultrasound as will be explained on execution plan section. Endometrioma's size is defined by the three-dimensional diameters (longitudinal, transverse and anteroposterior) and the volume, both of them measured with the ultrasound. It will be measured at months 0, 6 and 12. Both diameters and volume are a continuous quantitative variable.

INDEPENDENT VARIABLE

Drug administered: EE/DNG or DNG

Ethinylestradiol / Dienogest: 1 tablet daily of Ethinylestradiol / Dienogest 2mg will be taken without any break, taken preferably at the same time each day with some liquid as needed. Tablets must be taken continuously without regard to vaginal bleeding. When a pack is finished the next one should be started without interruption. In the event of missed tablet(s), the missed dose should be taken as soon as it is remembered and the normal schedule should be resumed.

Dienogest: 1 tablet daily of Dienogest 2mg will be taken without any break, taken preferably at the same time each day with some liquid as needed. Tablets must be taken continuously without regard to vaginal bleeding. When a pack is finished the next one should be started without interruption. The efficacy of dienogest may be reduced in the event of missed tablets, vomiting and/or diarrhea if occurring within 3-4 hours after tab taking. In the event of missed tablet(s), the patient should take 1 tab only, as soon as she remembers, and should then continue the next day to take the tab at her usual time.

COVARIABLES

- **Age**: from 18 to 35 years old. We will collect this variable as a discrete quantitative variable. It will be expressed in years.
- **Socioeconomic status**: it will be evaluated by asking for two variables:
  - Studies: latest completed studies
    - Without studies or incomplete primary education.
    - Secondary education or professional training.
    - University.
  - Occupation: Active worker, home related work, student, retired, incapacitated, unemployed, other situation. For retired and unemployed patients we will ask for the last occupation they had (open question).

  Then we will assess their socioeconomic status as low, medium or high. This variable is an ordinal qualitative variable.

- **Comorbidities**: such as depression, irritable bowel syndrome, interstitial cystitis, diabetes, etc. It will be an open question. We will collect this variable as a nominal qualitative variable.

METHODS OF DATA COLLECTION

The data will be collected during the first and the following visits. At each visit, doctors will provide patients with questionnaires (Annex 4) which will include:

- VAS scale for rating dysmenorrhea.
- SF-36 scale for rating HR-QoL.
- Use of analgesics scale for rating the intake of analgesic pills.

On the first, third and fifth meeting, doctors will also realize an ultrasound to patients in order to assess OMA. Maximum diameter of the OMA will be measured by ultrasound, and the total volume will be obtained by calculating the three-dimensional diameters on a longitudinal and sagittal scan.
Doctors will write the observations on the questionnaire of each patient. All data should be introduced to a computer database after each appointment in order to have two copies of the questionnaire. Data will be collected by the gynecologists, who will be previously taught and trained so to know the questionnaire, the methodology of collecting data and how and when each item should be collected.

ENROLLMENT AND RANDOMIZATION PROCESS

All patients consulting for dysmenorrhea with suspected OMA at our reference ASSIR will be assessed to participate in the study. After it has been verified that they are

eligible per inclusion and exclusion criteria, they will be enrolled in the study once have read the information sheet and signed the informed consent. Enrolled participants will be randomly assigned at a 1:1 ratio between DNG versus EE/DNG by using cards in sequentially numbered, sealed opaque envelopes. Each patient will be assigned an identification number obtained by a number code generator to maintain personal data confidentially. Subjects withdrawn from the study will not be replaced.

EXECUTION PLAN AND SCHEDULE EVENTS

1. Screening/Meeting nº 1: At the first visit on gynecologic center, the gynecologist will perform on the patient:

- Anamnesis: asking for classical symptoms such as dysmenorrhea, dyspareunia, dyschezia, dysuria, lower back or abdominal discomfort and chronic pelvic pain (non-cyclic abdominal and pelvic pain); other symptoms like vesicular, digestive or pulmonary; family history of endometriosis; abnormal irregular bleeding; chronic fatigue or infertility.
- Physical examination: examination will include an assessment to determine the position, size and mobility of the uterus. A rectovaginal examination may be necessary to palpate the uterosacral ligaments and rectovaginal septum. Signs suggesting endometriosis are a fixed, retroverted uterus, adnexal and uterine tenderness, pain with movement of the uterus, pelvic masses or nodularity along the uterosacral ligaments. In our study, the most important sign will be the adnexal masses discovered, which suggests OMA.

  Blood pressure will be evaluated since hypertension is a contraindication for both treatments. A pregnancy test will be realized in order to discard pregnancy.
- Ultrasound: in our study, we will focus on OMA. The appearances of endometriomas can be quite variable. There are 3 types of ovarian endometriomas (Image 1) defined by ultrasound features:
    - Type 1: Typical homogeneous pattern with low echogenicity and thick wall, which are the most frequent and easy to diagnose by ultrasound.
    - Type 2: heterogeneous mixed echogenicity and intra-cystic content
    - Type 3: homogeneous anechoic

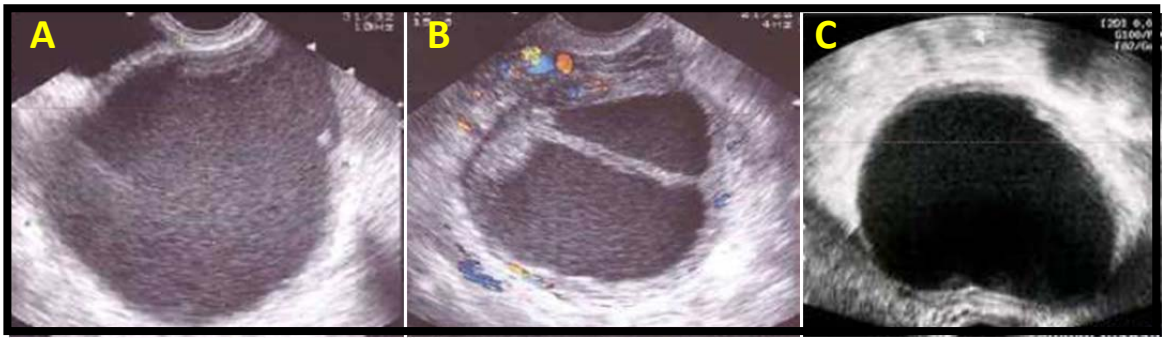


Image 1. Ovarian endometriomas: type I (A), type II (B) and type III (C).

Any unilocular cyst larger than 10 mm mean diameter with typical characteristics of regular wall, homogeneously low-level echogenicity (so-called ground glass appearance) of the cyst's content and poor capsular vascularization will be considered as an endometrioma.

After these 3 steps, the doctor will consider if the patient meet inclusion and exclusion criteria. Those patients who meet the criteria must be informed about the current study by the explanation of the gynecologist and corresponding patient's information sheet. After this, in the same visit, if the patient accepts enters on the study, she must read the information sheet and sign the informed consent. Once we have informed consent signed, the patient can enter on our database. Each patient will be assigned an identification number obtained by a number code generator. Then, the doctor will give the questionnaire to the patient. Next, the doctor will give her the treatment, explaining to take 1 tablet per day, the possible adverse effects, warnings and precautions. The treatment will contain three packs with 28-day blisters per pack, so the doctor will schedule a medical appointment every three months. After the visit, the doctor must complete the section of endometrioma's size located at the end of the questionnaire.

2. Follow up period:

- Phonecall: after 1 month of the screening, the doctor will call the patient in order to ask her about tolerance, adverse effects, doubts and adherence to treatment.
- Meeting nº 2: at 3rd month of treatment, the patient will come to medical consultation for therapy control. The doctor will give her another 3 packs with 28-day blisters and the questionnaire without performing an ultrasound. The doctor will schedule a medical appointment at three months and write information on database.
- Meeting nº 3: at 6th month of treatment, the patient will come to medical consultation for therapy control. The doctor will give her another 3 packs with 28-day blisters and the questionnaire. An ultrasound will be performed in order to assess OMA size. The doctor will schedule a medical appointment at three months and write information on database.
- Meeting nº 4: at 9th month of treatment, the patient will come to medical consultation for therapy control. The doctor will give her another 3 packs with 28-day blisters and the questionnaire without performing an ultrasound. The doctor will schedule a medical appointment at three months and write information on database.
- Meeting nº 5: At 12th months of treatment, the patient will come to medical consultation for an overall assessment. The doctor will perform an anamnesis, physical examination, an ultrasound and give the patient the questionnaire for the last time.

DESCRIPTIVE ANALYSIS

IBM SPSS Statistics will be the software package that will be used for statistical analysis. To manage computed data, Microsoft Excel tool will be used. We will considerate all variables statistically significant if p value <0.05.

In the case of response variables Dysmenorrhea and Analgesia consumption, we will construct two contingency tables, where, in columns we will place the response variables, and in rows, the "standard treatment" (EE/DNG) and "new" treatment (DNG). We will stratify these contingency tables by the covariates' value. In case of quantitative covariates we will categorize them into quartiles.

In the case of response variables Health-related quality of life (HR-QoL) and Endometrioma's size, we will summarize them using means (standard deviation) or median (interquartile range), when the histogram is symmetrical (normal distribution) or asymmetric (non-normal distribution), respectively. We will stratify this descriptive analysis according to treatment and the values of the covariates of interest. In the case of quantitative covariates, we will categorize them into quartiles.

Bivariate analysis:

- In the case of response variables Dysmenorrhea and Analgesia consumption we will contrast the null hypothesis of equality of proportions (among two treatments), using Chi Square tests.
- In the case of response variables Health-related quality of life (HR-QoL) and Endometrioma's size we will contrast the null hypothesis of equality of means (among two treatments) using the t-Student test (when the histogram is symmetrical) or U of Mann-Whitney (when the histogram is asymmetrical).

In both cases we will stratify for the values of the covariates of interest. In the case of quantitative covariates, we will stratify them into quartiles.

Multivariate analysis:

The relationship between dysmenorrhea-treatment and analgesia consumption-treatment could be adjusted in a multinomial logistic regression controlling the covariates. In the other hand, the relationship between HRQoL-treatment and endometrioma's size-treatment could be adjusted in a Poisson regression controlling the covariates; nevertheless, to facilitate the analysis we will categorize all the dependent variables into Yes-No:

- Reduction of dysmenorrhea: Yes-No
- Reduction of analgesia consumption: Yes-No
- Improvement of HRQoL: Yes-No
- Reduction of endometrioma's size: Yes-No

Then, the relationship between response variables and treatment will be adjusted in a logistic regression controlling the covariates.

For controlling possible losses (as lack of adherence) we will reweight the sample adequately (Re-Weighting → matching the % of the variables of interest).

Discussion: if the interventional study is successful, we will take the steps to register it as a clinical trial.

ETHICAL ASPECTS

The study follows the declaration of Helsinki involving ethical principles for Medical Research involving Human subjects. Prior to starting the study, this protocol will be presented to Clinical Research Ethics Committee (CEIC) of Hospital Universitari Dr. Josep Trueta (HUDJT) for its aprroval.

It will be performed according to the Spanish Laws related to clinical trial:

"Ley 29/2006 de26 de julio, de garantías y uso racional de los medicamentos y productos sanitarios:

- *RD 223/2004 de 6 de febrero: ensayos clínicos con medicamentos*
- *RD 1591/2009 de 16 de octubre y 1616/2009 de 26 de octubre: investigación con productos sanitarios"*

It will be registered in the European Clinical Trials Database (EUDRA-CT). Informed Consent will be obtained from each patient. The patients enrolled in the study will find all the information about the purpose of the study, the treatment groups, visits to the center, interruption and withdrawal, benefits and risks, compensation for damages and the confidentiality notice in the information sheet; all the information will be also thoroughly explained by the investigators. Important information included is that "**Dienogest alone is not licensed as a method for contraception, and sexually active women should use an additional non-hormonal contraceptive method".**
The data collected for the study will be always treated and used anonymously preserving the confidentiality of the patients.

As it is now recommended, the study will be registered with an International Standard Randomized Controlled Trial Number (http://www.controlled-trials.com) and submitted to ClinicalTrials.gov (http://clinicaltrials.gov).
The information will be confidential, guaranteeing the anonymity of the patients involved in the study under the Organic Law of Data Protection 15/1999.

The investigators have no conflicts of interest.

STUDY LIMITATIONS

- The side effects of the study drugs can impair the blinding process and induce a procedure bias. However most of side effects are similar and don't have to suppose a real limitation.

- The high cost of DNG, since it's a relatively new drug commercialized in March of 2013, nevertheless when the patent expires the price will be more affordable.

- The possibility of inter- and intra-observer differences in the measurement of the endometrioma by ultrasound, which can interfere in our final results. For that reason, we decided that, in order to reduce differences in the estimation of the endometrioma and the assessment of its reduction, endometrioma will be measured twice by two gynecologists, choosing then the most repeated value.

- Data collection may be another limitation as 14 study members are involved in it. To avoid mistakes and missing data, all members will be previously trained to collect data correctly.

- Lack of adherence and lost to follow-up may be a limitation in the study but we expect it will be minimum as we scheduled the meetings for the treatment year.

- The study will be performed in a small Health Area of Catalonia with a small number of patients which may be difficult to extrapolate to other regions or countries. However, randomization of patients increases reliability to extrapolate outcomes to other regions or countries.

WORK PLAN

PERSONNEL OF THE RESEARCH TEAM

The research team involved in the study will be composed by:

- 1 general coordinator: Raquel Marañés.
- The 14 gynecologist included in the ASSIR Gironès-Pla de l'Estany.
- 1 statistical specialist.

STUDY STAGES

The study will be performed in 3 years, and it will be composed of 4 stages, which are explained below:

- **Stage 1: Coordination (3 months)**
  - Obtaining the ethical approval from the Clinical Research Ethics Committee (CEIC). The general coordinator of the study will be responsible of this activity.
  - Informative meeting. The general coordinator will explain all the objectives to the rest of the research team. Information sheet and informed consent will be designed. The final protocol will be presented, the chronogram of the study will be done and tasks will be distributed.
  - A second research team meeting will take place in order to review all the protocol steps and clarify any possible doubt before the start of the clinical trial.
  - Database elaboration. The statistical specialist will be in charge to create a database in order to ease data extraction and data management.
- **Stage 2: Study conducted (24 months)**
  - Consecutive and non-probabilistic recruitment of patients during 1 year in order of appearance and random distribution of the drugs of the study will be performed by the doctors. Recruitment and intervention of the patient will start the same day. Data will be introduced in the database after each appointment. Follow up period will last 1 year per patient.
  - The general coordinator will supervise the study, maintain a good quality of data base and make sure all the information of each patient is correctly introduced in the data base.
- **Stage 3: Data analysis and interpretation (3 months)**
  - Statistical analysis. Data will be analyzed using the appropriate statistical tests by the statistical specialist.
  - Interpretation and discussion of the results. The results will be interpreted and discussed by the general coordinator, the gynecologists and statistical specialist.

- **Stage 4: publication and dissemination of the research findings (6 months)**
  - Publication of the results by the general coordinator and the 14 ginecologists. Articles will be written and we will also attempt to publish them in a journal of gynecology.
  - Dissemination of the findings. We will attempt to assist to conferences about endometriosis to present the results.

CHRONOGRAM

		2018				2019				2020			
ACTIVITY	**TASK**	Jan-Mar	Abr-Jun	Jul-Sep	Oct-Dec	Jan-Mar	Abr-Jun	Jul-Sep	Oct-Dec	Jan-Mar	Abr-Jun	Jul-Sep	Oct-Dec
COORDINATION PHASE	Research team meeting												
	Ethical approval from the clinical research ethics committee												
	Database elaboration												
STUDY CONDUCTED	Recruiting and randomization												
	Intervention and data collection												
	Supervision of the clinical trial												
DATA ANALYSIS AND INTERPRETATION	Review of data collected from appointments												
	Statistical analysis												
	Interpretation and discussion of the results												
PUBLICATION AND DISSEMINATION OF RESEARCH FINDINGS	Publication of the resuts in a gynecologyc journal												
	Scientific diffusion at gynecologic meetings and conferences												

BUDGET AND AVAILABLE MEANS TO CARRY OUT THE PROJECT

The budget encompasses all the possible expenses that will be needed to accomplish this study. Most of the procedures are already performed in the reference centers included in the ASSIR Gironès-Pla de l'Estany and most of the required staff already works in them, so the procedures are included in their daily duties. These tasks are counted as zero expenses. The first ultrasound is included in the daily routine, although the other two will have to be included in the budget. We will hire a statistical specialist in order to randomize and code patients, do data quality control and statistical analysis. The estimated salary will be 30€ per hour and approximately 18 hours of statistical support will be needed. Then, the estimated cost will be 540€. A manufacturer will be necessary for getting both treatments with an identical appearance. Each treatment will contain three packs with 28-day blisters each pack.

Personnel costs	*Cost*
- Manufacturer	300€
- Statistical specialist: 30€/h x 6h/ week x 3 weeks	540€
Material expenses	
- COC (EE/DNG): 4'71€ x 48 weeks x 132 patients	29.842'56€
- Visannette® (DNG): 53'70€ x 48 weeks x 132 patients	340.243'2€
- Transvaginal ultrasound: 31€ x 2 x 264 patients	16.368€
- Phonecall: 0'13€ min x aprox 3 min x 264	102'96 €
- Questionnaires photocopies 0'03€ x 7 pages x 264 patients	55'44€
- Information sheet and inform consent photocopies	
o 0'03€/unit x 7 pages x 264 patients	55'44€
o 0'03€/unit x 264 patients	7'92€
Publication and dissemination costs	
- Approximated cost of publication at SEGO	1.000€
Trial insurance	XXXXX €
Total study costs	388.515'52€

ANNEX 1: *PHARMACOLOGIC OPTIONS IN THE TREATMENT OF PAIN ASSOCIATED WITH ENDOMETRIOSIS* (26)

Agent	Route	Side-Effects
Oral Contraceptive Agents	Oral	Mild nausea, vomiting, weight gain
Progestins	Oral, Injection, or Intrauterine	Breakthrough bleeding, breast tenderness. Some have unfavorable effects of bone mineral density and lipid profile, some have androgenic side-effects
GnRH Agonists	Injection or Intranasal	Symptoms of a hypoestrogenic state(hot flushes, mood irritability, vaginal dryness, sleep disturbances, and decreased bone mineral density)
Aromatase Inhibitors	Oral	Ovarian stimulation in pre-menopausal women
Danazol	Oral	Weight gain, fluid retention, breast atrophy,acne, oily skin, hot flushes, hirsuitism, and unfavorable changes in the lipid profile
Gestrinone	Oral	Unfavorable changes in the lipid profile, weight gain, hirsuitism, seborrhea, and acne
Prostaglandin Inhibitors	Oral	Unfavorable gastrointestinal side-effects

ANNEX 2: *INFORMATION SHEET FOR PARTICIPANTS*

"Dienogest vs Dienogest/Etinilestradiol en uso continuo en pacientes con dismenorrea secundaria a la sospecha clínica de endometriosis ovárica"

Estudio multicéntrico, doble ciego, aleatorizado en 2 grupos: un grupo será tratado con dienogest (DNG) y el otro con Etinilestradiol/Dienogest (EE/DNG) en pacientes con dismenorrea secundaria a la sospecha clínica de endometriosis ovárica.

Código de Protocolo:	EudraCT:
Nombre del investigador Principal: Datos de contacto:	Centro:

Nos dirigimos a usted para informarle sobre un ensayo clínico en el que se le invita a participar. El estudio ha sido aprobado por el Comité Ético de Investigación con medicamentos correspondientes y la Agencia Española del Medicamento y Productos Sanitarios, de acuerdo a la legislación vigente, el Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos.

Nuestra intención es tan sólo que usted reciba la información correcta y suficiente para que pueda evaluar y juzgar si quiere o no participar en este ensayo. Para ello lea esta hoja informativa con atención y nosotros le aclararemos las dudas que le puedan surgir después de la explicación. Además, puede consultar con las personas que considere oportuno.

Debe saber que su participación en este estudio es voluntaria y que puede decidir no participar y retirar el consentimiento en cualquier momento, sin que por ello se altere la relación con su médico ni se produzca perjuicio alguno en su tratamiento.

PROPÓSITO

El propósito principal del estudio es evaluar si el DNG es más eficaz para la reducción de la dismenorrea comparado con el EE/DNG. Este estudio también pretende determinar si el DNG es más eficaz en la reducción de la toma de analgésicos y el tamaño del endometrioma, además de ser más efectivo en la mejora de la calidad de vida.

GRUPOS DE TRATAMIENTO

Se espera aproximadamente la participación de 264 pacientes en 4 centros de estudio.
Habrá dos grupos de tratamiento, y se compararán los resultados de cada grupo de tratamiento para averiguar qué tratamiento funciona mejor. Para asegurarnos de que los grupos de tratamiento son similares, al comienzo del estudio será asignada de forma aleatoria a uno de los dos grupos, lo que significa que ni usted ni el doctor

podrán escoger el grupo de tratamiento. Usted tiene la misma probabilidad de estar en cada uno de los grupos de tratamiento.

Para evitar que sepa qué tratamiento se le ha proporcionado, ambos tratamientos tendrán la misma apariencia y forma de administración.

Los grupos de tratamiento de este estudio son:

- Grupo 1: Alrededor de 132 pacientes. Dienogest 2mg, 1 comprimido por día, todos los días.
- Grupo 2: Alrededor de 132 pacientes. Etinilestradiol/Dienogest 0'03mg/2mg, 1 comprimido por día, todos los días.

Recibirá el medicamento del estudio por hasta 48 semanas (aproximadamente 12 meses). Ni usted ni el médico o personal del estudio sabrán si está recibiendo DNG o EE/DNG. Sin embargo, en una emergencia, podemos averiguar qué tratamiento está recibiendo.

VISITAS AL CENTRO

Durante el estudio, usted vendrá al centro alrededor de 5 visitas por un período de aproximadamente 12 meses. La primera visita será una visita de selección para ver si cumple con las condiciones para participar en el estudio. Si cumple las condiciones para participar en el estudio, se le ofrecerá la posibilidad de participar, y se le proporcionará la Hoja de información para la paciente y la Hoja de consentimiento informado. Si decide participar, será asignada a uno de los grupos de tratamiento y se le facilitará el medicamento.

Durante el estudio, visitará el centro cada 3 meses. Si tiene graves síntomas de dismenorrea o cambios significativos en su salud que pueden estar relacionados con el uso del medicamento, pueden ser necesarias visitas adicionales.

Durante el estudio, las siguientes pruebas se realizarán en algunas o todas las visitas: anamnesis, exploración física, ecografía y cuestionario a rellenar por usted.

INTERRUPCIÓN Y RETIRADA

Puede decidir suspender su participación en el estudio en cualquier momento. Antes de hacerlo, debe discutir su decisión con el médico del estudio. El tratamiento con el medicamento del estudio se interrumpirá si:

- Tiene deseo gestacional
- Tiene síntomas de una reacción alérgica al medicamento del estudio
- Muestra signos de deterioro de la función hepática
- Tiene una razón médica para suspender el medicamento del estudio
- No sigue las reglas del estudio

El médico del estudio puede decidir suspender la participación en este estudio en cualquier momento También retire su participación en este estudio por cualquiera de las siguientes razones: el médico del estudio decide que continuar no es lo mejor para usted o que es necesario por razones médicas, usted no sigue las reglas del estudio.

BENEFICIOS

Esperamos que su participación en el estudio sea beneficiosa. Los resultados del estudio pueden ayudar en el futuro a personas con una afectación similar a la suya.

RIESGOS

Si cree que está teniendo una reacción alérgica a la medicación (desarrolla ronchas, dificultad para respirar, hinchazón de la cara, mareos u otros síntomas) debe contactar con el médico del estudio o buscar atención médica inmediatamente

➔ ***RIESGOS DEL DIENOGEST (VISANNETTE)***

Las reacciones adversas más frecuentes (afecta entre 1 y 100 de cada 100 usuarias) son aumento de peso, humor depresivo, trastornos del sueño, nerviosismo, pérdida de interés por el sexo o humor inestable, dolor de cabeza o migraña, náuseas, dolor abdominal, flatulencias, hinchazón del abdomen o vómitos, acné o pérdida de vello, dolor de espalda, molestias en las mamas, quiste ovárico o sofocos, sangrado uterino/ vaginal, incluyendo manchado, debilidad o irritabilidad.

ADVERTENCIAS Y PRECAUCIONES

No debe tomar anticonceptivos orales de ninguna forma (en comprimido, parche, sistema intrauterino) mientras toma Visannette.

Visannette NO es un anticonceptivo. Si desea prevenir el embarazo, deberá usar preservativos u otras precauciones anticonceptivas no hormonales.

Mientras toma Visannette, disminuye la probabilidad de que se quede embarazada porque Visannette puede afectar a la ovulación.

Visannette y la hemorragia uterina grave

Puede que la hemorragia uterina empeore con el uso de Visannette. Si la hemorragia es intensa y prolongada, ello puede derivar en una disminución de la cantidad de glóbulos rojos (anemia), que en algunos casos puede ser grave. En caso de anemia, debe consultar a su médico acerca de si debe dejar de tomar Visannette.

Visannette y los coágulos de sangre en las venas

Puede haber un aumento ligero aunque no significativo del riesgo de coágulos de sangre en las piernas (tromboembolismo venoso). Muy rara vez, los coágulos de sangre pueden causar discapacidades permanentes y graves o incluso pueden ser mortales. El riesgo de coágulos de sangre en las venas aumenta con la edad, si tiene exceso de peso (IMC > 30 kg/m2), si alguno de sus parientes próximos ha tenido un coágulo de sangre en la pierna, pulmón u otro órgano a una edad temprana (antes de los 50 años aproximadamente), si necesita una intervención quirúrgica, si ha sufrido un accidente grave o si ha de estar inmovilizada durante un periodo prolongado.

Visannette y los coágulos de sangre en las arterias

Hay pocas pruebas de una relación entre los preparados con progestágenos como Visannette y un aumento del riesgo de tener un coágulo de sangre, por ejemplo, en los vasos sanguíneos del corazón (ataque al corazón) o el cerebro (accidente cerebrovascular). En las mujeres con hipertensión, estos preparados pueden aumentar ligeramente el riesgo de accidente cerebrovascular. El riesgo de sufrir un coágulo de sangre en las arterias aumenta si fuma, especialmente si usted es mayor de 35 años, si tiene exceso de peso, si algún pariente próximo ha sufrido un ataque al corazón o un ictus a una edad temprana, o si tiene la tensión arterial elevada.

➔ ***RIESGOS DEL ETINILESTRADIOL/DIENOGEST***

Las reacciones adversas más frecuentes (1 de 10) son dolor de cabeza y dolor mamario. Reacciones adversas frecuentes (1 de 100) son vaginitis/vulvovaginitis, candidiasis vaginal o infecciones fúngicas vulvovaginales, aumento de apetito, humor depresivo, migrañas, mareos, hipotensión, hipertensión, dolor abdominal, nauseas, vómitos, diarrea, acné, alopecia, eritema, prurito, sangrado menstrual irregular, metrorragia, aumento del tamaño de las mamas, edema mamario, dismenorrea, sangrado vaginal, quistes ováricos, dolor pélvico, cansancio, variaciones en el peso corporal.

EFECTOS ADVERSOS GRAVES DEL ETINILESTRADIOL/DIENOGEST

Coágulos de sangre

El uso de un anticonceptivo hormonal combinado como etinilestradiol/dienogest, aumenta su riesgo de sufrir un coágulo de sangre en comparación con no usarlo. En raras ocasiones un coágulo de sangre puede bloquear vasos sanguíneos y provocar problemas graves. La recuperación de los coágulos de sangre no es siempre completa. En raras ocasiones puede haber efectos graves duraderos o, muy raramente, pueden ser mortales. El riesgo global de un coágulo de sangre perjudicial debido a etinilestradiol/dienogest es pequeño.

Los factores de riesgo para sufrir un coágulo de sangre en una vena o arteria son los mismos que los explicados con el uso de Visannette. Sin embargo, otros factores de riesgo añadidos para un coágulo de sangre en una arteria son: si usted o alguno de sus parientes próximos tiene un nivel elevado de grasa en la sangre (colesterol o triglicéridos), si padece migrañas, si tiene un problema de corazón (trastorno de las válvulas, alteración del ritmo cardíaco llamado fibrilación auricular) o si tiene diabetes.
El riesgo de presentar un coágulo de sangre aumenta cuantas más afecciones tenga.
Los viajes en avión (más de 4 horas) pueden aumentar temporalmente el riesgo de un coágulo de sangre, en especial si tiene alguno de los demás factores de riesgo enumerados. Es importante informar a su médico si sufre cualquiera de las afecciones anteriores, aunque no esté segura.
Si alguna de las afecciones anteriores cambia, informe a su médico.
Si alguna de las afecciones anteriores cambia, por ejemplo empieza a fumar, un pariente próximo experimenta una trombosis sin causa conocida o usted aumenta mucho de peso, informe a su médico

SEGURO

El promotor del estudio dispone de una póliza de seguros que se ajusta a la legislación vigente (Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos), que le proporcionará la compensación e indemnización correspondientes en caso de menoscabo de su salud o de lesiones que pudieran producirse en relación con su participación en el estudio.

Nº DE URGENCIA PARA PROBLEMAS DEL ENSAYO

En caso de que desee formular preguntas acerca del estudio o daños relacionados con el mismo, podrá contactar con el médico del estudio Dr. _____ en el número de teléfono _____

COMPENSACIÓN POR DAÑOS

Se ha contratado un seguro que cubre a todos los pacientes que participan en este estudio de acuerdo con el Real Decreto, del 6 de febrero. Este seguro le cubrirá si sufre daños relacionados con el estudio.
Debe informarle al médico del estudio inmediatamente si cree que ha sufrido daños por participar en este estudio. El seguro no cubre la progresión normal de su enfermedad ni ningún daño, lesión o complicación debido a una condición médica preexistente. Si tiene daños relacionados con el estudio, el médico decidirá qué atención médica necesita.

AVISO DE CONFIDENCIALIDAD

El tratamiento, la comunicación y la cesión de los datos de carácter personal de todos los sujetos participantes, se ajustará a lo dispuesto en la Ley Orgánica 15/1999, de 13 de diciembre de protección de datos de carácter personal. De acuerdo a lo que

establece la legislación mencionada, usted puede ejercer los derechos de acceso, modificación, oposición y cancelación de datos, para lo cual deberá dirigirse a su médico del estudio. Los datos recogidos para el estudio estarán identificados mediante un código y sólo su médico del estudio o colaboradores podrán relacionar dichos datos con usted y con su historia clínica. Por lo tanto, su identidad no será revelada a persona alguna salvo excepciones, en caso de urgencia médica o requerimiento legal.
En el caso de que se produzca esta cesión, será para los mismos fines del estudio descrito y garantizando la confidencialidad como mínimo con el nivel de protección de la legislación vigente en nuestro país.
El acceso a su información personal quedará restringido al médico del estudio, colaboradores, autoridades sanitarias (Agencia Española del Medicamento y Productos Sanitarios), al Comité Ético de Investigación Clínica y personal autorizado por el promotor, cuando lo precisen para comprobar los datos y procedimientos del estudio, pero siempre manteniendo la confidencialidad de los mismos de acuerdo a la legislación vigente. El acceso a su historia clínica ha de ser sólo en lo relativo al estudio.

OTRA INFORMACIÓN RELEVANTE:
Cualquier nueva información referente a los fármacos utilizados en el estudio que se descubra durante su participación y que pueda afectar a su disposición para participar en el estudio, le será comunicada por su médico lo antes posible.

Si usted decide retirar el consentimiento para participar en este estudio, no se añadirá ningún dato nuevo a la base de datos y, puede exigir la destrucción de todas las muestras identificables previamente obtenidas para evitar la realización de nuevos análisis.

También debe saber que puede ser excluido del estudio si el promotor o los investigadores del mismo lo consideran oportuno, ya sea por motivos de seguridad, por cualquier acontecimiento adverso que se produzca por la mediación en estudio o porque consideren que usted no está cumpliendo con los procedimientos establecidos. En cualquiera de los casos, usted recibirá una explicación adecuada del motivo por el que se ha decidido su retirada del estudio.

El promotor podrá suspender el ensayo siempre y cuando sea por alguno de los supuestos contemplados en el Real Decreto.
Al firmar la hoja de consentimiento adjunta, se compromete a cumplir con los procedimientos del estudio que se le han expuesto. Cuando acabe su participación recibirá el mejor tratamiento disponible y el que su médico considere el más adecuado para su enfermedad, pero es posible que no se le pueda seguir administrando la medicación objeto del presente estudio. Por lo tanto, ni el investigador, ni el promotor, adquieren compromiso alguno de mantener dicho tratamiento fuera de este estudio.

ANNEXE 3: *INFORMED CONSENT FOR PARTICIPANTS*

CONSENTIMIENTO INFORMADO

TITULO DEL ESTUDIO: Dienogest vs Etinilestradiol/Dienogest en pacientes con dismenorrea secundaria a la sospecha clínica de endometriosis ovárica.

Estudio multicéntrico, doble ciego, aleatorizado en 2 grupos: un grupo será tratado con Dienogest y el otro con Etinilestradiol/Dienogest en pacientes con dismenorrea secundaria por sospecha clínica de endometriosis ovárica.

Yo, _____*(nombre y apellidos).*

- He leído la hoja de información que se me ha entregado.
- He podido hacer preguntas sobre el estudio.
- He recibido suficiente información sobre el estudio.

He hablado con: _____*(nombre del Investigador)*

Comprendo que mi participación es voluntaria.

Comprendo que puedo retirarme del estudio:

1º Cuando quiera.
2º Sin tener que dar explicaciones.
3º Sin que esto repercuta en mis cuidados médicos.

Presto libremente mi conformidad para participar en el estudio.

Firma del Participante: Firma del Investigador:

Recibirá una copia de esta hoja de información al paciente y documento de consentimiento informado.

Centro: _____

Fecha: _____ de _____ de 20____.

ANNEXE 4: *PATIENT'S QUESTIONNAIRE FOR PARTICIPANTS*

CUESTIONARIO PARA LA PACIENTE

PROYECTO: Eficacia de DNG vs EE/DNG en pacientes con dismenorrea secundaria por diagnóstico clínico de endometrioma

Le agradecemos mucho que conteste a este cuestionario. La información que nos proporcione será tratada de modo absolutamente confidencial. Su elaboración será de gran utilidad para la realización de nuestro estudio. Por favor, conteste a todas las preguntas de la manera más precisa posible. No vacile en preguntar si tiene alguna duda.

Número de identificación (Código):

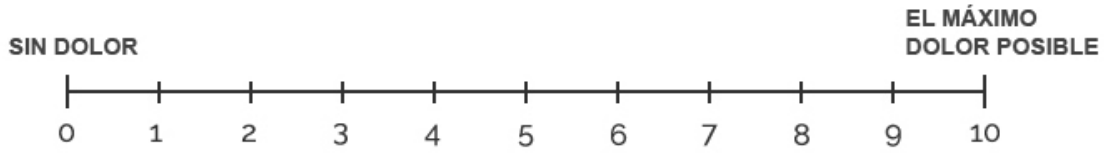
Fecha de nacimiento:

Email:

Teléfono:

Fecha:

Puntúe en la siguiente escala, en la que 0 supone ausencia de dolor y 10 el máximo dolor que pudiera imaginarse, como diría que es su dolor menstrual:



Marque con una cruz el número de días que consume analgésicos durante un período menstrual:

Ningún día	1 día	2 días	3 o más días
☐	☐	☐	☐

Cuestionario SF-36

INTRUCCIONES:

Las preguntas que siguen se refieren a lo que usted piensa sobre su salud. Sus respuestas permitirán saber cómo se encuentra usted y hasta qué punto es capaz de hacer sus actividades habituales.

Conteste cada pregunta tal como se indica. Si no está seguro/a de cómo responder a una pregunta, por favor conteste lo que le parezca más cierto

Marque una sola respuesta:

- En general, usted diría que su salud es:
    1. Excelente
    2. Muy buena
    3. Buena
    4. Regular
    5. Mala

- ¿Cómo diría que es su salud actual, comparada con la de hace un año?
    1. Mucho mejor ahora que hace un año
    2. Algo mejor ahora que hace un año
    3. Más o menos igual que hace un año
    4. Algo peor ahora que hace un año
    5. Mucho peor ahora que hace un año

Las siguientes preguntas se refieren a actividades o cosas que usted podría hacer en un día normal:

- Su salud actual, ¿le limita para hacer **esfuerzos intensos**, tales como correr, levantar objetos pesados, o participar en deportes agotadores?
    1. Sí, me limita mucho
    2. Sí, me limita poco
    3. No, no me limita nada

- Su salud actual, ¿le limita para hacer **esfuerzos moderados**, como mover una mesa, pasar la aspiradora, jugar a los bolos o caminar más de una hora?
    1. Sí, me limita mucho
    2. Sí, me limita poco
    3. No, no me limita nada

- Su salud actual, ¿le limita para **coger o llevar la bolsa de la compra?**
    1. Sí, me limita mucho
    2. Sí, me limita poco
    3. No, no me limita nada

- Su salud actual, ¿le limita para **subir varios pisos** por la escalera?
    1. Sí, me limita mucho
    2. Sí, me limita poco
    3. No, no me limita nada
- Su salud actual, ¿le limita para **subir un solo piso** por la escalera?
    1. Sí, me limita mucho
    2. Sí, me limita poco
    3. No, no me limita nada

- Su salud actual, ¿le limita para **agacharse o arrodillarse**?
    1. Sí, me limita mucho
    2. Sí, me limita poco
    3. No, no me limita nada

- Su salud actual, ¿le limita para caminar **un kilómetro o más**?
    1. Sí, me limita mucho
    2. Sí, me limita poco
    3. No, no me limita nada

- Su salud actual, ¿le limita para caminar **varias manzanas** (varios centenares de metros)?
    1. Sí, me limita mucho
    2. Sí, me limita un poco
    3. No, no me limita nada

- Su salud actual, ¿le limita para caminar **una sola manzana** (unos 100 metros)?
    1. Sí, me limita mucho
    2. Sí, me limita un poco
    3. No, no me limita nada

- Su salud actual, ¿le limita para **bañarse o vestirse por sí mismo?**
    1. Sí, me limita mucho
    2. Sí, me limita un poco
    3. No, no me limita nada

<u>Las siguientes preguntas se refieren a problemas en su trabajo o en sus actividades cotidianas</u>:

- Durante las 4 últimas semanas, ¿tuvo que **reducir el tiempo** dedicado al trabajo o a sus actividades cotidianas, a causa de su salud física?
    1. Si
    2. No

- Durante las 4 últimas semanas, ¿**hizo menos** de lo que hubiera querido hacer, a causa de su salud física?
    1. Si
    2. No

- Durante las 4 últimas semanas, ¿tuvo que **dejar de hacer algunas tareas** en su trabajo o en sus actividades cotidianas, a causa de su salud física?
    1. Si
    2. No

- Durante las 4 últimas semanas, ¿tuvo **dificultad** para hacer su trabajo o sus actividades cotidianas (por ejemplo, le costó más de lo normal), a causa de su salud física?
    1. Si
    2. No

- Durante las 4 últimas semanas, ¿tuvo que **reducir el tiempo** dedicado al trabajo o a sus actividades cotidianas, a causa de algún problema emocional (como estar triste, deprimido, o nervioso?
    1. Si
    2. No

- Durante las 4 últimas semanas, ¿**hizo menos** de lo que hubiera querido hacer, a causa de algún problema emocional (como estar triste, deprimido, o nervioso)?
    1. Si
    2. No

- Durante las 4 últimas semana, ¿no hizo su trabajo o sus actividades cotidianas tan **cuidadosamente** como de costumbre, a causa de algún problema emocional (como estar triste, deprimido, o nervioso)?
    1. Si
    2. No

- Durante las 4 últimas semanas, ¿hasta qué punto su salud física o los problemas emocionales han dificultado sus actividades sociales habituales con la familia, los amigos, los vecinos u otras personas?
    1. Nada
    2. Un poco
    3. Regular
    4. Bastante
    5. Mucho

- Tuvo dolor en alguna parte del cuerpo durante las 4 últimas semanas?
    1. No, ninguno
    2. Si, muy poco
    3. Si, un poco
    4. Si, moderado
    5. Si, mucho
    6. Si, muchísimo

- Durante las 4 últimas semanas, ¿hasta qué punto el dolor le ha dificultado su trabajo habitual (incluido el trabajo fuera de casa y las tareas domésticas)?
    1. Nada
    2. Un poco
    3. Regular
    4. Bastante
    5. Mucho

Las preguntas que siguen se refieren a cómo se ha sentido y cómo le han ido las cosas durante las 4 últimas semanas. En cada pregunta responda lo que se parezca más a cómo se ha sentido usted:

- Durante las 4 últimas semanas, ¿cuánto tiempo se sintió lleno de vitalidad?
  1. Siempre
  2. Casi siempre
  3. Muchas veces
  4. Algunas veces
  5. Sólo alguna vez
  6. Nunca

- Durante las 4 últimas semanas, ¿cuánto tiempo estuvo muy nervioso?
  1. Siempre
  2. Casi siempre
  3. Muchas veces
  4. Algunas veces
  5. Sólo alguna vez
  6. Nunca

- Durante las 4 últimas semanas, ¿cuánto tiempo se sintió tan bajo de moral que nada podía animarle?
  1. Siempre
  2. Casi siempre
  3. Muchas veces
  4. Algunas veces
  5. Sólo alguna vez
  6. Nunca

- Durante las 4 últimas semanas, ¿cuánto tiempo se sintió calmado y tranquilo?
  1. Siempre
  2. Casi siempre
  3. Muchas veces
  4. Algunas veces
  5. Sólo alguna vez
  6. Nunca

- Durante las 4 últimas semanas, ¿cuánto tiempo tuvo mucha energía?
  1. Siempre
  2. Casi siempre
  3. Muchas veces
  4. Algunas veces
  5. Sólo alguna vez
  6. Nunca

- Durante las 4 últimas semanas, ¿cuánto tiempo se sintió desanimado y triste?
  1. Siempre
  2. Casi siempre
  3. Muchas veces
  4. Algunas veces
  5. Sólo alguna vez
  6. Nunca

- Durante las 4 últimas semanas, ¿cuánto tiempo se sintió agotado?
  1. Siempre
  2. Casi siempre
  3. Muchas veces
  4. Algunas veces
  5. Sólo alguna vez
  6. Nunca

- Durante las 4 últimas semanas, ¿cuánto tiempo se sintió feliz?
  1. Siempre
  2. Casi siempre
  3. Muchas veces
  4. Algunas veces
  5. Sólo alguna vez
  6. Nunca

- Durante las 4 últimas semanas, ¿cuánto tiempo se sintió cansado?
  1. Siempre
  2. Casi siempre
  3. Muchas veces
  4. Algunas veces
  5. Sólo alguna vez
  6. Nunca

- Durante las 4 últimas semanas, ¿con qué frecuencia la salud física o los problemas emocionales le han dificultado sus actividades sociales (como visitar a los amigos o familiares)?
  1. Siempre
  2. Casi siempre
  3. Algunas veces
  4. Sólo alguna vez
  5. Nunca

Por favor, diga si le parece cierta o falsa **cada una** de las siguientes frases:

- Creo que me pongo enfermo más fácilmente que otras personas.
  1. Totalmente cierta
  2. Bastante cierta
  3. No lo sé
  4. Bastante falsa
  5. Totalmente falsa

- Estoy tan sano como cualquiera.
  1. Totalmente cierta
  2. Bastante cierta
  3. No lo sé
  4. Bastante falsa
  5. Totalmente falsa

- Creo que mi salud va a empeorar.
  1. Totalmente cierta
  2. Bastante cierta
  3. No lo sé
  4. Bastante falsa
  5. Totalmente falsa

- Mi salud es excelente.
  1. Totalmente cierta
  2. Bastante cierta
  3. No lo sé
  4. Bastante falsa
  5. Totalmente falsa

ENDOMETRIOMA/AS (información a rellenar por el médico)

Características:

Localización:

- Unilateral (derecho/izquierdo)
- Bilateral

Diámetros:

- Diámetro longitudinal
- Diámetro transversal
- Diámetro anteroposterior

Volumen: